I. Total Synthesis of Microcin SF608 and 
(±)-Gelsemoxonine

II. Novel Reagents for Amine Selective Bioconjugation

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Stefan Diethelm

Master of Science in Biology, ETH Zurich

born January 9, 1986

Citizen of Uttwil (TG)

Accepted on the recommendation of

Prof. Dr. Erick M. Carreira, examiner

Prof. Dr. Karl-Heinz Altmann, co-examiner

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Acknowledgments

As a student of biology who decides to work in total synthesis, I undertook an experiment with unclear outcome. Three fantastic scientists, Pierre Stallforth, Sascha Jauze and in particular Corinna Schindler, have accompanied me on this journey and have shared their passion for chemistry with me. I’m very grateful to Corinna, who has taught me not only the indispensable chemistry skills needed to master the total synthesis of a congested alkaloid natural product, but who also made me realize the importance of approaching such an endeavor with great initiative and even greater persistence.

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Abstract

Microcin SF608 (I) is a member of the aeruginosin serine protease inhibitors (Figure 1). This novel class of cyanobacterial non-ribosomal peptides exhibits a strong inhibitory activity against pharmaceutically relevant serine proteases such as thrombin or trypsin. The aeruginosins share a common 2-carboxy-6-hydroxyoctahydroindole (Choi) core fragment. We present a synthetic strategy towards microcin SF608. The Choi core of the natural product has been prepared using the intramolecular nucelophilic opening of oxabicyclo[2.2.1]heptane II promoted by the Lewis acid TMSOTf (Figure 1, box). The resulting product III could be readily converted into microcin SF608. Moreover, the reported synthesis features an unusual regioselective epoxide reduction mediated by Cp₂TiCl. Detailed mechanistic investigations have led to the hypothesis that an intramolecular hydrogen atom delivery is responsible for the regioselectivity observed. Furthermore, this transformation was found to be of general use for the directed reductive opening of various epoxide substrates.

Figure 1. Aeruginosin serine protease inhibitor microcin SF608 and key step towards its total synthesis.

Alkaloids isolated from the plant genus Gelsemium have been intriguing targets for synthetic chemists over more than 30 years due to their highly complex and compact structures. Only recently, gelsemoxonine (IV) has been isolated as a novel member of this natural product class (Figure 2). Its structure incorporates an unusual azetidine ring embedded in a compact polycyclic framework. Furthermore, a spiro-fused oxindole ring forms part of a series of six contiguous stereocenters arranged around the gelsemoxonine core. We herein document the total synthesis of this structurally intriguing gelsemium alkaloid. We have employed the acid mediated ring contraction of a spirocyclopropane isoxazolidine V to provide a highly substituted β-lactam product VI as a key transformation (Figure 2, box). The oxindole ring is constructed through a highly diastereoselective
reductive Heck reaction. Final introduction of the ethyl ketone functionality was achieved using a directed hydrosilylation protocol. Experimental studies on the key ring contraction have prompted us to propose a novel mechanistic scheme for this unprecedented transformation.

Figure 2. Gelsemoxoinine and key step towards its total synthesis.

Bioconjugative chemistry has emerged as a powerful tool for the modification of various classes of biomolecules. The coupling of two biochemical entities enables the construction of compounds exhibiting novel functional properties. This concept can be employed to study and characterize the function and behavior of biomolecules. We herein report a novel bioconjugative technique relying on the coupling reaction of aryl diazonium salt VII with amino groups on proteins and peptides furnishing amide products VIII (Figure 3). Notably, tyrosine residues and other electron rich aromatic rings, which have been previously reported to react with diazonium salts, are compatible with the system developed. The new technique allows for the direct coupling of numerous highly functionalized natural products to protein substrates.

Figure 3. Bioconjugative coupling of diazonium salts and proteins.
Zusammenfassung

Microcin SF608 (I) ist ein Vertreter der Familie der Aeruginisin Serin Protease Inhibitoren (Figur 1). Diese neue Klasse von nicht-ribosomalen Peptiden aus Cyanobakterien zeigt eine starke inhibitorische Wirkung gegenüber pharmazeutisch relevanten Proteasen, wie zum Beispiel Thrombin oder Trypsin. The Vertreter der Aeruginosin-Familie teilen eins gemeinsames 2-Carboxy-6-hydroxyoctahydroindol (Choi) Kernfragment. Wir haben eine synthetische Strategie zu Microcin SF608 entwickelt, wobei die Choi Kernstruktur über die nucleophile Öffnung eines Oxabicyclo[2.2.1]heptan Systems II synthetisiert wird (Figur 1, Kasten). Diese Reaktion basiert auf der Aktivierung des Oxabicyclischen Systems anhand der Lewi-Säure TMSOTf. Das resultierende Produkt III konnte in den Naturstoff Microcin SF608 überführt werden. Desweiteren beinhaltet unsere Synthesestrategie eine ungewöhnliche regioselektive Reduktion eines Epoxid-Intermediats mit Cp₂TiCl. Detailierte mechanistisch Studien führten zur Hypothese, dass eine intramolekulare Wasserstoff-Atom Donation für diese Regioselektivität verantwortlich ist. Wir konnten weiter feststellen, dass diese Transformation hat sich zur allgemeine Anwendung für die Reduction von Epoxiden empfiehlt.

Figur 1. Aeruginosin Serin Protease Inhibitor Microcin SF608 und Schlüsselschritt zur Bildung der 2-Carboxy-6-hydroxyoctahydroindol Kernsturktur.

Alkaloide die aus Pflanzen der Gattung Gelsemium isoliert werden, sind interessante Zielstrukturen für Totalsynthese seit über 30 Jahren aufgrund ihrer hoch komplexen und kompakten Struktur. Kürzlich wurde Gelsemoxonine (IV) als weiterer Vertreter dieser Naturstoff-Klasse isoliert (Figur 2). Die Struktur dieser Verbindung beinhaltet einen ungewöhnlichen Azetidin-Ring, der in das Polycyclische Gerüst von Gelsemoxonine eingebettet ist. Zusätzliche Merkmale dieses Alkaloids sind ein Spiro-Zentrum am Oxindol Ring sowie fünf weitere Stereozentren, die ein einer Reihe in der Kernstruktur angeordnet sind. Wir berichten über die Totalsynthese dieses Naturstoffs, basierend auf


**Figur 2.** Gelsemoxoamine und Schlüsselschritt zur Bildung des Azetidin Rings.

**Figur 3.** Bioconjugative Kopplung von Diazonium Salzen mit Proteinen.
Publications


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<td>$[\alpha]_D^T$</td>
<td>specific rotation at temperature $T$ at the sodium D line</td>
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<tr>
<td>Å</td>
<td>Ångstrom</td>
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<tr>
<td>Abn</td>
<td>azabicyclononane</td>
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<tr>
<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>acac</td>
<td>acetylacetonate</td>
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<td>ACC</td>
<td>aminocyclopropane carboxylic acid</td>
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<td>ACCO</td>
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<td>AIBN</td>
<td>2,2'-azobisisobutyronitrile</td>
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<td>anhydr.</td>
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<td>atm</td>
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<tr>
<td>BDE</td>
<td>bond dissociation energy</td>
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<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphtyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
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<tr>
<td>Boc</td>
<td>tert-butylcarbonyl</td>
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<td>Boc$_2$O</td>
<td>Di-tert-butyl dicarboxylate</td>
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<td>BOP</td>
<td>benzotriazolyl-N-oxytrisdimethylamino phosphonium hexafluorophosphate</td>
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<tr>
<td>bp</td>
<td>boiling point</td>
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<tr>
<td>bs</td>
<td>broad signal</td>
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<tr>
<td>BSA</td>
<td>N,O-Bis(trimethylsilyl)acetamide</td>
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<td>Bu</td>
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<tr>
<td>Choi</td>
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<td>CoA</td>
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<td>d</td>
<td>doublet, day</td>
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</tbody>
</table>
M: Molar, molecule ion
MAD: Methylaluminum bis(4-methyl-2,6-di-tert-butylphenoxide)
mb: millibar
mCPBA: 3-chlorperoxybenzoic acid
Me: methyl
MEM: 2-methoxyethoxymethyl
MEP: methylderythritol phosphate
MEPY: methyl 5-oxopyrrolidine-2-carboxylate
Mes: 2,3,6-trimethylphenyl
mg: milligram
MHz: Megahertz
MIC: minimum inhibitory concentration
min: minute
mL: milliliter
MoOPH: Vedej’s reagent, oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)
mp: melting point
mmol: millimole
MOM: methoxymethyl
MPPIM: methyl 2-oxo-1-(3-phenylpropanoyl)imidazolidine-4-carboxylate
Ms: methylsulfonyl
MS: molecular sieves
n: normal, unbranched alkyl chain
NBS: N-bromosuccinimide
NCS: N-chlorosuccinimide
nd: not determined
NHC: N-heterocyclic carbine
NHS: N-hydroxysuccinimide
NIS: N-iodosuccinimide
NMMO: N-methyl morpholine N-oxide
NMR: nuclear magnetic resonance
NOE: nuclear Overhauser effect
Ns: nosyl, 2-nitrosulfonyl
ν: vibration frequency in cm⁻¹
o: ortho
[O]: oxidation
p: para
PCC: pyridinium chlorochromate
PDC: pyridinium dichromate
PG: protecting group
pH: negative logarithm of hydrogen ion concentration
Ph: phenyl
Piv: pivaloyl, trimethylacetate
PMB: 4-methoxybenzyl
PMHS: poly(methylhydrosiloxane)
PPF: [(diphenylphosphino)ferrocenyl]ethylcyclohexylphosphine
ppm: parts per million
PPTS: pyridinium 4-toluenesulfonate
Pr: propyl
p-TSA: para-toluenesulfonic acid
py: pyridine
q: quartet
Q-Phos: 1,2,3,4,5-Pentaphenyl-1’-(di-tert-butylphosphino)ferrocene
quant.: quantitative
rac: racemic
recov.: recovered
Rf: retention factor
rt  room temperature
s  second, singlet
SAM  S-adenosyl methionine
sat.  saturated
SEM  2-(Trimethylsilyl)ethoxymethyl
SFC  supercritical fluid chromatography
S-Phos  2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t  triplet
t  tert
T  temperature
TBAB  tetra-n-butylammonium bromide
TBAC  tetra-n-butylammonium chloride
TBAF  tetra-n-butylammonium fluoride
TBDPS  tert-butylphenylsilyl
TBS  tert-butylmethylsilyl
TEMPO  2,2,6,6-tetramethylpiperidine 1-oxyl
TES  triethylsilyl
Tf  trifluromethanesulfonyl
TFA  trifluoroacetic acid
TFAA  trifluoroacetic acid anhydride
THF  tetrahydrofuran
TLC  thin layer chromatography
TMEDA  N,N,N',N'-tetramethylethylene diamine
TMG  1,1,3,3-tetramethylguanidine
TMP  2,2,6,6-tetramethyl piperidine
TMS  trimethylsilyl
TMU  N,N,N',N'-tetramethylurea
TPAP  tetra-n-propylammonium perruthenate
Tris  2,4,6-triisopropylphenylsulfonyl
triyl  triphenylmethyl
Ts  tosyl, 4-methylphenylsulfonyl
UV  ultraviolet
X-Phos  2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
18-crown-6  1,4,7,10,13,16-hexaoxacyclooctadecane
9-BBN  9-borabicyclo[3.3.1]nonane
Part I

Total Synthesis of Microcin SF608 via the Nucleophilic Opening of an Oxabicyclo[2.2.1]heptane
Introduction

Proteolytic enzymes, commonly referred to as proteases, have been found to be fundamental mediators of numerous important biological processes such as cell cycle regulation, cell differentiation and development or angiogenesis.\(^1\) Moreover, these enzymes are involved in various diseases such as cancers, Alzheimer’s disease, or inflammatory disorders.\(^2\) It is therefore not surprising that almost 2% of the human genome encodes for proteases.\(^3\) The involvement of these enzymes in many pharmaceutically relevant processes has stimulated the search for agents to intervene in these systems through the control of protease activity. In fact, numerous marketed drug molecules target proteolytic enzymes. Some of the most important examples include retroviral protease inhibitors for the treatment of HIV\(^4\) or hepatitis C\(^5\). Nature has invented a myriad of strategies for controlling the activity of such enzymes.\(^6\) The quest for secondary metabolites exhibiting inhibitory activity against pharmaceutically interesting proteases has led to the discovery of the aeruginosin family of serine protease inhibitors, a novel class of peptidic natural products.

18.1. Serine Proteases

Proteases, also called peptidases, are enzymes catalyzing the hydrolytic cleavage of one or more amide bonds in polypeptides of varying size. Proteases often cleave a peptide chain at a very distinct site depending on the peptide sequence. This allows us to accurately predict the peptide fragments produced by degradation of a protein by a specific protease. Peptidases are generally classified on the basis of their catalytic mechanism. Four major classes are known according to this categorization: aspartic, cysteine, metallo and serine proteases.

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The most extensively investigated serine proteases are the digestive enzymes trypsin and chymotrypsin. Most of the mechanistic and structural investigations were first undertaken with these enzymes.\(^7\) Serine proteases are characterized by a catalytic Ser residue in their active site.\(^8\) Together with catalytic Ser 195 (chymotrypsinogen numbering) two highly conserved amino acids, His 57 and Asp 102, form the catalytic triad of all serine proteases. As outlined in Scheme 1, the catalytic mechanism of serine proteases proceeds in two stages. In the first step, Ser 195 attacks the peptide bond of the substrate bound in the active site. The nucleophilicity of the serine OH is enhanced by deprotonation through the nearby histidine residue of the catalytic triad (base catalysis). Asp 102 assists this process by electrostatic catalysis as shown in intermediate 1. Upon nucleophilic attack of Ser 195 to the amide carbonyl group, a tetrahedral intermediate 2 is formed. This species is stabilized through hydrogen bonding to the protein backbone in the so called oxyanion hole. The tetrahedral intermediate then collapses leading to the cleavage of the C–N bond in the peptide substrate resulting in the formation of an acyl-enzyme species 3, whereby the C-terminal fragment of the substrate molecule is bound to the serine protease through an ester linkage to Ser 195. His 57 facilitates this

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\(^7\) For the first crystal structure of chymotrypsin, see: Matthews, B.W.; Singler, P.B.; Henderson, R.; Blow, D.M. *Nature*, 1967, **214**, 652-656.

process by protonation of the nitrogen leaving group. The N-terminal peptide fragment is therefore liberated and can leave the active site. In the second stage acyl-enzyme intermediate 4 is hydrolyzed, again through the assistance of the catalytic triad residues. His 57 deprotonates a water molecule coordinated within the active site. Nucloephilic attack of this water to the ester bond leads to the formation of a second tetrahedral intermediate 5. Again, this species is stabilized by hydrogen bonding in the oxyanion hole. Collapse of 5 assisted by acid-base catalysis through His 57 finally releases the carboxylic acid product (6). Only recently, low temperature X-ray crystallographic analysis and trapping experiments led to a more detailed understanding of this process.9

Proteolytic enzymes are generally produced as inactive precursor proteins called zymogens.10 Through the controlled activation of these zymogens, protease activity can be spacially and temporally regulated. This issue is of particular importance, as active proteases could endanger the metabolism of a cell by degrading native enzymes involved in essential processes, as well as other cell constituents. Zymogens are generally activated by proteolytic cleavage of an amino acid fragment. This process can be autocatalytic, meaning that the activated protease can activate its own zymogen thus leading to an amplification of the activation signal.

18.2. Blood Coagulation and Thrombosis

One of the most thoroughly investigated serine proteases is the enzyme thrombin, which plays a key role in blood coagulation. Upon injury of a blood vessel, a self-healing process is initiated, whereby the protein fibrin forms a dense insoluble network at the site of injury. Blood platelets are trapped in this net and aggregate to from a clot (thrombus). The whole processes is regulated and controlled by a complicated network of proteases called the blood coagulation cascade (Figure 1).11 The components of this cascade, the so called tissue factors, are initially present as inactive zymogens. Upon injury of the blood vessel, the first enzyme in this cascade is proteolytically cleaved and thereby activated (indicated by the suffix a). In a cascade of peptidase cleavage events, each protease activates its subsequent neighbor in the signal chain. Finally, prothrombin is converted to thrombin, which then activates fibrinogen to produce fibrin. Thrombin has a key role in this whole network, as it is involved in multiple feedback interactions with various activation factors (indicated by blue arrows in Figure 1).

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A defective execution of the coagulation cascade can lead to the uncontrolled formation of blood clots resulting in disease states such as thrombosis, heart attack or stroke. On the other hand, down-regulation of the blood coagulation cascade will lead to extensive bleeding as seen in haemophilia patients. It is therefore of high interest for medicinal purposes to be able to control blood coagulation. Thrombin has emerged as a key target to control blood clotting.

18.3. Aeruginosin Serine Protease Inhibitors

A drug screening program directed towards the identification of novel serine protease inhibitors led to the discovery of the aeruginosin family of natural products. To date, more than 30 members of this class of peptidic secondary metabolites have been isolated from different species of cyanobacteria. The first member of this natural product class was discovered by Murakami and co-workers during investigation into extracts from the marine cyanobacteria (green algae) *Microcystis aeruginosa*. In the course of these studies, aeruginosin 298A (7) was isolated and shown to exhibit potent inhibitory activity against various serine proteases (Figure 2). Structure elucidation revealed that aeruginosin 298A (7) contained an unprecedented 2-carboxy-6-hydroxyoctahydroindole (Choi) core fragment (8). Moreover, the natural product was composed of a dipeptide appendage including a hydrophobic amino acid (D-leucine) and a more polar N-terminal residue (D-hydroxyphenyllactic acid, Hpla). The carboxy terminus of the Choi core was attached to a reduced arginine residue (Argol).

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Figure 2. Aeruginosin serine protease inhibitors.

Soon after the isolation of aeruginosin 298A (7), a number of related natural products were isolated constituting a whole new family of aeruginosin serine protease inhibitors all sharing a common Choi core structure 8 (Figure 2, box). In particular, Murakami and co-workers reported the isolation of aeruginosin 98A (9) and aeruginosin 98B (10)\(^\text{15}\) in 1995 and four years later a series of novel aeruginosin members including aeruginosin 98C (11), 101 (12), 298B\(^\text{16}\) (13), 89A (14) and 89B (15) were isolated by the same group again from *Mycocystis aeruginosa*.\(^\text{17}\) Investigation of the secondary metabolites produced by algae cultures of *Oscillatoria agardhii* by researchers at Boehringer Mannheim GmbH led to the discovery of oscillarin (16).\(^\text{18}\) The structure of this compound could later be confirmed by X-ray crystallographic analysis of a thrombin-oscillarin complex.\(^\text{19}\) In 1997, the two


new aeruginosins 205A (17) and 205B (18) were isolated from the green algae *Oscillatoria agardhii.*\textsuperscript{20} The originally proposed structure of these two peptides was later revised based on the total synthesis of aeruginosin 205A\textsuperscript{21} and it was shown that a sulfated xylose residue was attached to the C(6) hydroxyl group of the Choi core. Moreover, a chloroleucine amino acid was part of the dipeptide side chain of aeruginosin 205A (17). Carmeli and co-workers isolated microcin SF608 (19) in 1999, incorporating a L-phenylalanine and a L-hydroxyphenyllactic acid (Hpla) residue along with an agmatidine (Agma) appendage at the Choi C-terminus.\textsuperscript{22} This is exceptional among the aeruginosins as all the other members of this family are composed of D-amino acids. With the isolation of aeruginosin EI461 (20) the first aeruginosin with a Choi core exhibiting opposite configuration at the ring fusion was isolated.\textsuperscript{23,24}

![Figure 3. Dysinosin-type aeruginosin serine protease inhibitors.](image-url)

In 2002 Quinn and co-workers reported the isolation of dysinosin A (21) as the first aeruginosin peptide from a marine sponges of the family *Dysideidae* (Figure 3).\textsuperscript{25} However, it seems most likely that the cyanobacterial symbionts (e.g. *Oscillatoria spongii*) associated with this sponge family are responsible for the production of this natural product rather than the sponge itself.\textsuperscript{26} Elucidation of the structure of dysinosin A (21) was achieved using 2D-NMR techniques and cocrystallization with thrombin. Interestingly, the Choi core of dysinosin A incorporates an additional hydroxyl group at C(5) in a *trans*-dioxial relationship with the C(6) alcohol. More recently, additional members of this subclass were isolated. Chlorodysinosin A (22) incorporates a 3-chloroleucine residue in the peptide side chain.\textsuperscript{27} In contrast, dysinosin C (23) and dysinosin D (24) have a valine at this position.\textsuperscript{28}

\textsuperscript{23} The structure of aeruginosin EI461 was later revised to compound 20 based on total synthesis: Valls, N.; Valrribera, M.; Carmeli, S.; Bonjojch, J. *Org. Lett.* 2003, 5, 447-450.
A third subclass of the aeruginosin serine protease inhibitors was discovered in 1997 by Harada and co-workers. From the cyanobacterium *Nodularia spumigena* the authors isolated the glycopeptide suomilide (25) (Figure 4). This novel natural product contains a 4-amino-5,7,9-tri-hydroxy-2-azabicyclononane-3-carboxylic acid (Abn) core fragment instead of the Choi residue found in the other aeruginosins. Furthermore, suomilide includes a dipeptide side chain incorporating an alloisoleucine and an O-sulfated methylglyceric acid residue similar to the side chain found in the dysinosins. Moreover, a 1-amidino-3-(2-aminoethyl)-3-pyrroline (Aaep) group is attached to the C-terminus of the Abn core. Two further members of this subclass, banyaside A (26) and banyaside B (27) were isolated in 2005 by Carmeli from the cyanobacterium *Nostoc* sp. A total synthesis of the originally proposed structure for banyaside B led to a proposed revision of the glycosylation site. It was suggested that glucose is linked to the C(9) alcohol of the Abn core as shown in Figure 4, rather than to the C(7) hydroxyl group as originally postulated.

\[ \text{Figure 4. Abn-core members of the aeruginosin family of serine protease inhibitors.} \]

### 18.4. Biological Activity of the Aeruginosins

The discovery of the aeruginosin peptides largely relied on activity guided isolation. The biological activity of the aeruginosins was further assayed through *in vitro* studies designed to evaluate their potential to inhibit serine proteases mainly using thrombin and trypsin as protein targets. Table 1 summarizes some of the most interesting results of these studies.

An intriguing characteristic of the aeruginosin serine protease inhibitors is their specificity to inhibit only a subset, or only a single peptidase, efficiently. The observation that aeruginosin 298B (13), lacking the guanidine containing C-terminal side chain, is completely inactive emphasizes the importance of this residue for biological activity (*vide infra*).

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Motivated by the high activity of the aeruginosins against the serine protease thrombin, researchers investigated the interaction between the natural products and the active site of thrombin. X-ray crystal structures of thrombin in complex with aeruginosin 298A (7), dysinosin A (21), oscillarin (16), and chlorodysinosin A (22) have been solved. These studies have enabled insight into the inhibitory mechanism of the aeruginosins. As shown in Figure 5, the guanidine moiety of the natural product forms a salt bridge with an aspartate residue in the S1 pocket of the enzyme in close proximity to the catalytic triad. This interaction is believed to play a key role in inhibiting the serine protease. Furthermore, interactions of the Choi core with the S2 pocket of the enzyme and the hydrophobic amino acid residue of the peptide with the S3 pocket help to stabilize the ligand-protein interaction.

**Figure 5.** A) Binding of aeruginosin protease inhibitors in the catalytic site of thrombin. X-ray crystal structure of a dysinosin A-thrombin complex; B) Ribbon diagram; C) Connolly surface representation. Adapted from ref. 12.

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**Table 1.** Inhibitory activity (IC\(_{50}\) values in μg/mL) of selected aeruginosins towards various serine proteases.\(^{12}\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Thrombin</th>
<th>Factor VIIa</th>
<th>Trypsin</th>
<th>Plasmin</th>
<th>Chymotrypsin</th>
</tr>
</thead>
<tbody>
<tr>
<td>aeruginosin 298A</td>
<td>0.3</td>
<td></td>
<td>1</td>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>aeruginosin 298B</td>
<td>&gt;100</td>
<td>-</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>aeruginosin 89A</td>
<td>0.03</td>
<td></td>
<td>0.4</td>
<td>0.02</td>
<td>&gt;10</td>
</tr>
<tr>
<td>aeruginosin 205A</td>
<td>1.5</td>
<td>-</td>
<td>0.07</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>aeruginosin 205B</td>
<td>0.17</td>
<td>-</td>
<td>0.07</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>oscillarin</td>
<td>0.018</td>
<td>2.5</td>
<td>0.024</td>
<td>&gt;260 (K(_i))</td>
<td>-</td>
</tr>
<tr>
<td>microcin SF608</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
<td>-</td>
<td>&gt;20</td>
</tr>
<tr>
<td>dysinosin A</td>
<td>0.029</td>
<td>0.206</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>chlorodysinosin A</td>
<td>0.0038</td>
<td>0.026</td>
<td>0.025</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>banyaside A</td>
<td>0.39</td>
<td>-</td>
<td>1.48</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

---


18.5. Biosynthesis of the Aeruginosins

Hemscheidt and Dittman have investigated the biosynthetic generation of the aeruginosin peptides based on genome analysis of the cyanobacterial strain \textit{Planktothrix agardhii} CYA126/8.\textsuperscript{34} The majority of cyanobacterial peptides are synthesized by non-ribosomal peptide synthases (NRPS).\textsuperscript{35} These modular enzyme assemblies are composed of several subunits responsible for the activation, coupling and processing of the amino acid components of the peptide natural product.\textsuperscript{36} Accordingly, PCR-based screening for NRPS’ in the genome of \textit{Planktothrix agardhii} led to the identification of a biosynthetic gene cluster composed of 19 open reading frames (ORF). Nine genes (\textit{aerA-I}) in this gene cluster were assigned to aeruginosin biosynthesis based on sequence similarity analysis with known biosynthetic enzymes. In particular, \textit{aerC-F} were proposed to be responsible for synthesis of the Choi peptide fragment. As outlined in Scheme 2, arogenate (28), available from the shikimic acid pathway, serves as a Choi precursor. AerC oxidizes alcohol 28 to give ketone 29. Intramolecular 1,4-addition of the amino group in 29 is then promoted through AerE. This step has to be enzyme catalyzed as the opposite diastereomer would be expected in the case of an acid or base mediated reaction (\textit{vide infra}). AerD further decarboxylates 30, followed by a reduction of unsaturated ketone 31 by AerF, to provide Choi core 8.

![Scheme 2. Proposed biosynthesis of the Choi core (8).](image)

Both, gene mutation and feeding studies confirmed that the Choi core is synthesized separately. The NRPS domain AerG then accepts the Choi amino acid and incorporates it into the growing peptide chain. Finally, release of the natural product from the NRPS is triggered by cleavage of the peptide-enzyme thioester linkage by the nucleophilic amino group of the agmatidine side chain.

18.6. Previous Total Syntheses of Aeruginosin Serine Protease Inhibitors

The potent bioactivity of the aeruginosin peptides has prompted numerous synthetic chemists to embark on the total synthesis of the aeruginosins and, in particular, their Choi core. This subchapter summarizes the approaches developed to access the 6-hydroxy-2-carboxyoctahydroindole core

fragment. The respective peptide side chains were generally attached to the Choi core by amide coupling reactions.

The first total synthesis of aeruginosin 298A (7) was reported by Bonjoch and co-workers in 2000.\textsuperscript{37} The strategy for preparation of the Choi core 32 relied on the use of L-tyrosine as a chiral precursor. As outlined in Scheme 3, Birch reduction of 33 using Li/NH\textsubscript{3} delivered enol ether 34. Hydrolytic liberation of the ketone and concomitant isomerization of the double bond enabled 1,4-addition of the amino group to occur. This biomimetic step delivered, after amine protection, a 1:1.8 mixture of endo and exo products 35 and 36, respectively. The undesired exo-isomer 36 could be isomerized to 35 by treatment with hydrochloric acid. Attempted reduction of the ketone functionality in benzyl-protected hydroindole 35 delivered the undesired alcohol diastereomer. However, a switch of the nitrogen protecting group to Boc followed by LS-Selectride reduction produced Choi core 32 with the correct alcohol stereochemistry. The authors speculated that the differential reactivity of the two ketones 35 and 37 towards reducing agents can be explained based on different conformations of the six-membered ring (Scheme 3, box). Benzyl derivative 35 adopts a boat-like arrangement leading to attack of the hydride nucleophile from the convex face of the molecule. With a bulky Boc-protecting group however, conformer 37 is preferred. This arrangement opens the concave side of the bicycle for attack of a hydride reagent. The same strategy was applied by the Bonjoch group for the total synthesis of aeruginosin 298B (13),\textsuperscript{38} microcin SF608 (19),\textsuperscript{39} and aeruginosin EI461 (20).\textsuperscript{40}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme3.png}
\caption{Synthesis of the aeruginosin Choi core by Bonjoch.}
\end{figure}

Shortly after Bonjoch’s first report, the Wipf group documented an alternative approach to aeruginosin 298A (7).\textsuperscript{41} Their synthesis started with the oxidative cyclization of Cbz-protected L-tyrosine 38 using PhI(OAc)\textsubscript{2} to furnish ketone 39 (Scheme 4).\textsuperscript{42} Subsequent benzoylation of the tertiary alcohol produced 40. In order to adjust the stereochemistry of exo-hydroindole 40, an isomerization step was needed. Accordingly, 40 was treated with NaHCO\textsubscript{3} leading to the formation of endo-isomer 41 via intermediate 42. S\textsubscript{N}2\textsuperscript{*}-type reduction of the benzoate group was achieved using

\begin{thebibliography}{99}
\end{thebibliography}
Zn/AcOH. The resulting alkene 43 was then hydrogenated and the ketone in 44 could be reduced with L-Selectride to give Choi core 45.

Scheme 4. Synthesis of the Choi core by Wipf and co-workers.

In 2002, Hanessian and co-workers reported the first total synthesis of dysinosin A.\(^\text{43}\) Their synthesis commenced with diastereoselective alkylation of glutamate derivative 46 (Scheme 5).\(^\text{44}\) Treatment of 46 with LiHMDS followed by addition of allyl bromide produced adduct 47. The reaction was suggested to proceed via transition states 48 and 49 (Scheme 5, box). These models were used to explain the exclusive approach of the electrophile from one side of the ester enolate. Conversion of ester 47 to pyrrolidinone 50 was achieved in 4 steps. Selective reduction of the amide carbonyl and protection of the intermediate hemiaminal delivered 51. Lewis-acid mediated allylation gave diene 52, which was subjected to ring-closing metathesis by Grubbs first generation catalyst. With hydroindole 53 in hand, introduction of the trans-diol moiety was now addressed. Epoxidation of the olefin produced 54 with complete stereoselectivity. The dysinosin Choi core 55 would now be


obtained by treatment of epoxide $54$ with CF$_3$CO$_2$H and water. Regioslective epoxide opening produced the desired diol $55$.

Scheme 6. Synthesis of the aeruginosin Choi core by Hannesian.

A related strategy was developed by Hanessian and coworkers for the total synthesis of oscillarin (16).$^{45}$ Alkene $56$ was prepared by an analogous route to the synthesis of $51$, as detailed above. Treatment of $56$ with SnBr$_4$ triggered an aza-Prins cyclization to give bromide $57$ via iminium intermediate $58$. SN$_2$ displacement of the bromide substituent by acetate then delivered Choi core $59$.

In addition to the total synthesis of oscillarin, Hanessian also reported the first synthesis of aeruginosin 205A (17) using this approach.$^{46}$ Alternatively, bromide $57$ can be treated with neat DBU to arrive at the dysinosin intermediate $53$. This strategy employed for the total synthesis of chlorodysinosin A (22) by the Hanessian group.$^{33}$

Scheme 7. Synthesis of aeruginosin Choi core $32$ by Shibasaki and co-workers.


Shibasaki and co-workers developed an approach to the aeruginosin core based on an enantioselective alkylation reaction (Scheme 7). Treatment of imine 60 with allyl bromide 61 in the presence of phase transfer catalyst 62, prepared from L-tartrate, produced amino ester 63 in 80% yield and 88% enantiomeric excess. In a similar sequence as previously employed by Bonjoch, acid promoted deprotection of acetal 63 was followed by olefin isomerization and 1,4-addition to provide a 2:1 mixture of exo- and endo-hydroindoles 35 and 36, respectively. Isomerization of the undesired exo-isomer was again carried out using hydrochloric acid. Finally, installation of a Boc carbamate on the hydroindole nitrogen and reduction of the C(6) ketone with LS-Selectride delivered Choi core 32. Attachment of a suitable peptide side chain enabled the total synthesis of aeruginosin 298A (7).

Recently, the Trost group applied a palladium catalyzed alkylation reaction for the synthesis of the Choi core of aeruginosin 98B (10) (Scheme 8). Their synthesis started with the preparation of ketoalcohol 64 from 4-methoxyphenol 65. Birch reduction followed by TIPS protection and dihydroxylation of the intermediate enol ether delivered 64. After silylation of the secondary alcohol, the ketone was converted into vinyl triflate 66 using Comin’s reagent. This intermediate now served as a suitable substrate for palladium catalyzed vinylation of serine-derived iodide 67, producing a diastereomeric mixture of alkenes 68 and 69. Conversion into allylic carbonates 70 and 71 now set the stage for the key palladium catalyzed cyclization. In the event, treatment of this mixture with palladium catalyst [(η^3-C₃H₅)PdCl]₂ and racemic ligand 72 delivered hydroindole 73 in 96% yield. Upon benzylation and olefin reduction, Choi core 74 was obtained in good yield.

Scheme 8. Synthesis of the Choi core by Trost and co-workers.

The only synthesis to date of the banyaside Abn core was reported by the Carreira group in 2008.\textsuperscript{51} The synthesis started with an enantioselective Diels–Alder reaction between furan (75) and bromoacrolein 76 using tryptophan-derived oxazaborolidine catalyst 77 (Scheme 9). Aldehyde adduct 78 was not isolated however, but directly subjected to an aldol reaction with the lithium enolate of ethylacetate, producing a diastereomeric mixture of alcohol 79. Treatment of this intermediate with KOt-Bu triggered a reaction cascade, which included initial formation of an epoxide by displacement of the bromide by the nearby alcohol. Epoxide opening through the ester enolate then delivered allylic alcohol 80. The oxazolidinone ring was closed by conversion of alcohol 80 into the corresponding primary carbamate 81 followed by aziridination of the unsaturated ester using a dimeric rhodium(I) catalyst. The resulting aziridine 82 was regioselectively opened using nosylamide to give 83. A protecting group switch from nosyl to a more nucleophilic benzylamine delivered 84. Treatment of this intermediate with NIS under irradiation with visible light led to the closure of the piperidine ring of the Abn core, forming endo-iodide 85. It was speculated that this reaction proceeds via an iodoamine intermediate, which is cleaved homolytically by light to produce a caged radical pair that adds to the double bond from the bottom face, resulting in a cis-arrangement of the amino and iodo substituents. A SmI\textsubscript{2} mediated opening of the oxabicycle 85 produced alkene 86. Finally, hydration of this olefin under Mukaiyama conditions followed by removal of the benzyl group gave Abn core 87.

\[ \text{Scheme 9. Synthesis of the aeruginosin Abn core by Carreira.} \]

18.7. Nucleophilic Opening of Oxabicyclo[2.2.1]heptanes

The synthesis of the Abn core presented in Scheme 9 relies on the S$_N$2'-type opening of oxabicyclic system 88. This transformation was achieved in two steps by initial attack of the nitrogen nucleophile to the olefin in 89 followed by the opening of the oxybridge to produce product 90 (Scheme 10). In the course of the synthetic studies directed towards the total synthesis of banyaside B, a direct conversion of amine 88 into secondary alcohol 90 was envisioned. Various attempts towards this end were evaluated. In particular, Lautens has reported the activation of oxabicycles towards nucleophilic attack using rhodium(I) catalysts. Application of such a protocol to aminoolefin 88 was therefore tested as outlined in Scheme 10. It was hoped that the rhodium catalyst might activate the hydrofuran ring to enable an S$_N$2' attack of the amino group onto the double bond as indicated in intermediate 89. Concomitant rupture of one C–O bond in the oxybridge would generate Abn precursor 90. However, when amine 88 was subjected to these conditions, unexpected octahydroindole 91 was obtained as the only product in 65% yield. It was speculated that Rh(I) promotes a direct nucleophilic oxybridge opening via S$_N$2 attack of the nitrogen substituent as shown for 92.

Scheme 10. Lewis-acid triggered nucleophilic opening of oxabicycle 88.

It is generally proposed that rhodium-catalyzed oxybridge opening reactions proceed via insertion of Rh(I) into the C–O bond of the oxabicycle. The resulting rhodium-allyl species then undergoes a nucleophilic allylation reaction to provide the product. For the direct nucleophilic attack observed for system 88 it seems more likely that rhodium is simply acting as a Lewis acid activating the substrate by coordination to the oxygen. Based on this hypothesis, a number of different Lewis acids were tested as promoters of this transformation. Indeed, the use of BBr$_3$ led to the production of hydroindole 91, albeit in low yield. However, when TBSOTf or TMSOTf were employed, the product was obtained in excellent yield (> 80%). Based on this finding, the generality of this reaction was

52. This work has not yet been published. For further details, see: ETH Diss. No. 18899.
53. For an overview, see: Lautens, M.; Fagnou, K.; Yang, D. J. Am. Chem. Soc. 2003, 125, 14884-14892.
Table 2. Selected substrates for the nucleophilic opening of oxabicyclo[2.2.1]heptanes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate 2" /></td>
<td><img src="image4.png" alt="Product 2" /></td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Substrate 3" /></td>
<td><img src="image6.png" alt="Product 3" /></td>
<td>91%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Substrate 4" /></td>
<td><img src="image8.png" alt="Product 4" /></td>
<td>89%</td>
</tr>
</tbody>
</table>

[a] Conditions: TMSOTf (4.0 equiv.), NEt₃ (5.0 equiv.), CH₂Cl₂, then HCl/MeOH.

evaluated. Table 2 summarizes some key results of this study. In particular, we found that hydroquinolines can be prepared with equal efficiency (entry 1). Moreover, amides were found to be potent nucleophiles in this reaction. Most importantly, the double bond in the oxabicyclic precursor was not essential for the transformation to occur (entry 2). Additionally, a peptide side chain attached to the amine nucleophile was tolerated (entry 3). Also primary amines could be used as substrates for the completely saturated system (entry 4).

Based on these results, we embarked on the total synthesis of microcin SF608 (19), an aeruginosin serine protease inhibitor incorporating a hydroindole core fragment. Our efforts towards this goal are presented in the following chapters.

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Synthetic Strategy towards Microcin SF608

The highly potent inhibitory activity of the aeruginosins towards pharmaceutically relevant proteases, such as thrombin, renders these natural products interesting targets for total synthesis. Moreover, the unprecedented structural features of the core fragments in these peptides offer fascinating opportunities to explore novel synthetic approaches.

During the synthesis of the banyaside Abn core, our group discovered a novel reactivity of oxabicyclic systems allowing to access highly functionalized hydroindole products (section 1.7.). This finding opened the intriguing possibility of developing a unified strategy towards the whole class of the aeruginosin serine protease inhibitors. In particular, we planned to establish allylic alcohol 80 as a common precursor to both the Abn core of the banyasides (87), as well as the Choi core (93) of the larger aeruginosin subclass (Figure 6, top).

*Figure 6.* Top: Divergent strategy for the synthesis of the Abn and Choi cores of the aeruginosins starting from common oxabicyclic building block 80. Bottom: Disconnection of microcin SF608 (19) into individual peptide fragments.
In order to implement this goal, we decided to embark on the total synthesis of microcin SF608 (19), an aeruginosin protease inhibitor incorporating a central Choi core fragment (8). As outlined in Figure 6 (bottom), microcin SF608 is further composed of two peptide appendages attached to the carboxyhydroindole amino acid residue. These side chains include a L-hydroxyphenyllactic acid (L-Hpla) (94), a L-phenylalanine (95) as well as an agmatidine (Agma) (96) component. Mircocin SF608 could thereby be assembled by combining the individual fragments through peptide coupling reactions. It was anticipated that the preparation of functionalized hydroindole fragment 8 would pose the greatest synthetic challenges. We ultimately opted for the application the nucleophilic opening of a suitable oxabicyclic precursor to access the hydroindole moiety of microcin.

![Scheme 11. Retrosynthetic strategy towards the microcin Choi core 97.](image)

As shown in Scheme 11, our retrosynthetic strategy towards the microcin Choi core 97 entails the preparation of late stage intermediate 98. Removal of the hydroxyl groups at C(5) and C(3a) would be required to arrive at the substitution pattern of the natural product. These two alcohol functional groups are remnants from the projected oxabicyclic cyclization precursor 99. Treatment of 99 with TMSOTf should trigger the nucleophilic opening of the oxybridge to generate the desired hydroindole product. In addition, hydration of the C(6)–C(7) double bond would be required to obtain triol 98. The key cyclization precursor 99 in turn could be prepared by α-amination of unsaturated ester 100. The planned route thus starts with common building block 100, the enantiomer of which was already employed for the synthesis of the banyaside Abn core.

![Scheme 12. Projected synthesis of cyclization precursor 101.](image)

As outlined in Scheme 12, our plan for the preparation of cyclization precursor 101 relied on a diastereoselective azidation of an ester enolate. We envisioned conversion of α,β-unsaturated ester 100 into lactone 102. The rigid tricyclic structure of 102 should thereby provide a useful platform for the face selective functionalization of the C(2) position. Based on molecular models, we reasoned that the
si-face of lactone enolate 103 is slightly more accessible for functionalization with a suitable electrophile than the opposite side of the molecule (Figure 7). We were hoping that this steric effect might control the diastereoselectivity of the projected carbonyl functionalization. Conversion of azidolactone 104 into oxabicycle 101 would then include lactone opening by an amine nucleophile followed by installation of the dipeptide side chain at the C(2) nitrogen.

**Figure 7.** Stereochemical analysis of the projected enolate azidation on lactone enolate 103 (MM2 energy minimized).

The two subsequent chapters report on the implementation of the synthetic plan detailed above leading to the total synthesis of microcin SF608 and to the establishment of a divergent access route to both, the Abn and the Choi core starting from the same oxabicyclic building block 100.
Preliminary Studies on the Nucleophilic Opening of Oxabicycles

The synthetic strategy towards microcin SF608, as detailed in the preceding chapter, entailed the use of the newly discovered nucleophilic opening of oxabicycles as a key step. The limited knowledge available on this transformation demanded a more intimate study of the reaction, in particular its functional group tolerance and its applicability for peptide substrates. We therefore set out to assess the characteristics of this transformation by studying a number of relevant model substrates.

3.1. Introduction of the C(2) Nitrogen Substituent by Enolate Azidation

Our synthetic strategy relied on allylic alcohol 100 as an easily accessible chiral building block for the preparation of the microcin Choi core. As outlined in Scheme 13, alcohol 100 was prepared in a two-step sequence according to the protocol reported earlier by our group.\textsuperscript{51} The synthesis started with an enantioselective Diels–Alder reaction between furan (75) and bromoacrolein (76).\textsuperscript{56,57}

\textsuperscript{55} The work described in this chapter was reported already in my Master thesis under the supervision of Corinna Schindler. For this reason, only the most relevant results from these studies are presented here.


\textsuperscript{57} Bromoacrolein was prepared on large scale (ca. 100 g per batch) and then stored at -80 °C until required. Bromoacrolein is highly irritant and should be handled with care.
According to a report by Corey and Loh, tryptophan derived oxazaborolidine 105 serves as a chiral catalyst to promote this cycloaddition via putative transition state 106.\textsuperscript{58} Aldehyde product 107 was not isolated but, directly treated with the lithium enolate of ethylacetate to provide bromoalcohol 108 in 63% yield and as an inconsequential 1.6:1 mixture of diastereomers at C(3). In a second step, treatment of 108 with potassium tert-butoxide effected the formation of intermediate epoxide 109, which underwent opening to yield α,β-unsaturated ester 100.

The projected functionalization of ester 100 in α-position to the carbonyl functionality now required reduction of the electron poor olefin, while retaining the endocyclic double bond of the oxabicyclic system. To this end, a copper-hydride mediated conjugate reduction protocol recently reported by Buchwald and co-workers was employed as depicted in Scheme 14.\textsuperscript{59} Treatment of unsaturated ester 100 with a copper-NHC catalyst,\textsuperscript{60} generated in situ from ligand 110\textsuperscript{61} and CuCl\textsubscript{2}, in the presence of KO\textsubscript{t}-Bu\textsuperscript{62} and poly(methylhydrosiloxane) (PMHS)\textsuperscript{63} produced lactone 102 in 62% yield. The in situ cyclization of the intermediate ester product to give lactone 102 may be promoted by KO\textsubscript{t}-Bu. Interestingly, conducting the reaction at 0 °C proved essential to avoid overreduction of the substrate and decomposition of the product.

\textbf{Scheme 14.} Conjugate reduction of allylic alcohol 100.

We next turned to introduction of the nitrogen substituent at C(2). This objective was achieved by azidation of the lithium enolate of lactone 102 following a procedure reported by Evans and Britton as outlined in Table 3.\textsuperscript{64} We initially encountered problems forming the enolate of 102 in ethereal solvents


\textsuperscript{60} The commercially available pre-synthesized copper-NHC catalyst can also be used, providing 102 in equal yield.


\textsuperscript{62} KO\textsubscript{t}-Bu proved superior to the originally reported NaO\textsubscript{t}-Bu as base.

\textsuperscript{63} More expensive Ph\textsubscript{3}SiH can also be used to provide product 102 in slightly higher yield.

such as THF or Et₂O, which was attributed to the poor solubility of 102 in these solvents. However, slow addition of a dilute solution of lactone 102 in CH₂Cl₂ to a precooled solution of LiHMDS at -78 °C efficiently provided the desired ester enolate 111. Treatment of 111 with trisopropylsulfonyl azide 112 (TrisN₃) followed by quenching with AcOH delivered desired azidolactone 104 in excellent yield (Table 3, entry 1). However, the product was obtained as an inseparable 1.2:1 mixture of diastereomers 104a and 104b. In order to improve this ratio to favor desired isomer 104a, we tested various different sulfonylazides as alternative azide donors. Changing the electronic properties of the arene ring did not affect the reaction outcome (113 and 114, entries 2 and 3). The use of benzylsulfonyl azide 115 also delivered the product as an equimolar mixture of diastereomers (entry 4). However, the use of (+)-camphor derived reagent 116 afforded a 1:2 diastereomeric ratio favoring the undesired isomer 104b (entry 5). Interestingly, enantiomeric sulfonyl azide 117 did not lead to inversion of the selectivity, but again produced 104a and 104b in equal amounts (entry 6).

Table 3. Azidation of lactone 102.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>dr (104a:104b)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Reagent 1]</td>
<td>1.2:1</td>
<td>81%</td>
</tr>
<tr>
<td>2</td>
<td>![Reagent 2]</td>
<td>1.2:1</td>
<td>55%</td>
</tr>
<tr>
<td>3</td>
<td>![Reagent 3]</td>
<td>1.2:1</td>
<td>75%</td>
</tr>
<tr>
<td>4</td>
<td>![Reagent 4]</td>
<td>1:1</td>
<td>68%</td>
</tr>
<tr>
<td>5</td>
<td>![Reagent 5]</td>
<td>1:2</td>
<td>58%</td>
</tr>
<tr>
<td>6</td>
<td>![Reagent 6]</td>
<td>1.1:1</td>
<td>60%</td>
</tr>
</tbody>
</table>

[a] Conditions: LiHMDS (1.5 equiv.), CH₂Cl₂, -78 °C; then reagent (1.3 equiv.), -15 °C; then AcOH/KOAc. [b] determined by crude NMR analysis, [c] reagent added at -45 °C.

Numerous bases were tested towards this end, generally leading to quantitative recovery of the starting material.

---

65 Numerous bases were tested towards this end, generally leading to quantitative recovery of the starting material.
3.2. Synthesis and Cyclization of a Bis-Amide Substrate

Microcin SF608 incorporates two peptide side chains attached to the central Choi core. We initially opted for the early introduction of these appendages in the cyclization precursor. Accordingly, we prepared a model substrate, which contained two amide bonds at the site of peptide attachment. As outlined in Scheme 15 (top), this was achieved by initial opening of lactone 104 by benzylamine affording amide 118 in 79% yield. Azide reduction under Staudinger conditions delivered amine 119 (73%). Installation of a second amide group was achieved through benzoylation to give bis-amide 120 in 76% yield.

Scheme 15. Preparation of cyclization precursor 120 (top) and TBSOTf-promoted nucleophilic opening of oxabicycle 120 (bottom).

Oxabicycle 120 was then subjected to treatment with TBSOTf as the Lewis acid promoter for nucleophilic oxybridge opening. Pleasingly, a cyclized product 121 was obtained in 50% yield. 2D NMR analysis of TBS protected derivative 122, in particular diagnostic HMBC correlations to the amide N–H, allowed assignment of its structure, revealing a hydroindoline scaffold (Scheme 15, box). Notably, only the 6-exo-tet product was obtained with complete selectivity. We speculate that the reaction proceeds via intermediate 123, whereby the oxybridge, as well as the amide, are activated by the silylating reagent. The O-silyl imidoester in 123 serves as a potent nucleophile by attacking the activated hydrofuran ring. The complete selectivity for hydroquinoline formation can likely be explained by the reduced steric hindrance around the reacting amide nitrogen compared to the C(2) nitrogen. Cyclization of the C(2) amide would produce the desired five-membered ring product.

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66 For the following model studies azidolactone 104 was used as a 1:1 diastereomeric mixture at C(2), as obtained from the azidation reaction.
68 We later discovered that the use of TMSOTf instead of TBSOTf generally leads to a higher product yield.
3.3. Synthesis of the Carboxyhydroindole Core of Microcin

The complete selectivity for hydroquinoline formation in systems incorporating two competing amide functionalities demanded the synthesis of a cyclization precursor harboring only one potential nitrogen nucleophile. As outlined in Scheme 16 (top), lactone 104 was reduced using NaBH₄ to produce an unstable primary alcohol intermediate in 67% yield.⁶⁹ Subsequent protection of the hydroxy group with TBDPSCI delivered silyl ether 124 in 94% yield. Staudinger reduction of the azide, followed by benzoylation gave adduct 125 incorporating only one amide nucleophile.

![Scheme 16. Preparation of cyclization precursor 125 (top) and nucleophilic opening of oxabicycle 125 (bottom).](image)

Treatment of 125 with TMSOTf in the presence of NEt₃ generated desired hydroindole product 126 via 5-exo-tet cyclization of intermediate 125, through an analogous mechanism to that proposed for cyclization of 120 (Scheme 15, bottom). Elaboration of the microcin Choi core still required introduction of a hydroxyl group at C(6), removal of the hydroxyl groups at C(5) and C(3a) as well as oxidation of the C(1) alcohol. The latter objective was carried out as outlined in Scheme 17. Conversion of diol 126 into its corresponding bis-acetate derivative followed by silylether cleavage gave primary alcohol 128. Oxidation of 128 to a carboxylic acid intermediate, followed by peptide coupling to benzylamine delivered carboxyhydroindole 129.

![Scheme 17. Synthesis of the microcin carboxyhydroindole core.](image)

Next, introduction of the C(6) hydroxyl group was attempted. Several approaches including hydroboration of the olefin, reductive transposition of the C(5) alcohol, followed by double bond

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⁶⁹ The instability of this alcohol intermediate could be explained by reaction of the azide with the strained olefin followed by further decomposition. Similar reactivity of oxabicycles was observed previously in our group (ETH Diss. No. 18899).
oxidation,\textsuperscript{70} metal mediated olefin hydration,\textsuperscript{71} or reductive epoxide opening failed to give the expected C(6) hydroxylated products. The inability to achieve this transformation, along with the lengthy route to access carboxyhydroindole 129, prompted us to design a revised synthetic strategy towards the microcin Choi core.

### 3.4. Conclusion

In summary, we have gained important insight into the nucleophilic opening of oxabicyclo[2.2.1]heptenes through model studies directed towards the preparation of the microcin Choi core fragment. As outlined in Scheme 18, we have discovered that bis-amide substrates such as 120 preferentially undergo a 6-exo-tet cyclization to provide hydroquinoline products. However, removal of the C(1) amide functionality allows for the synthesis of the desired hydroindole system 126.

Scheme 18. Differential opening of cyclization substrates 120 and 125.

Based on these model studies, we propose a revised synthetic scheme towards microcin SF608 as shown in Scheme 19. As we were not able to introduce the C(6) hydroxyl group after hydroindole formation, installation of this functionality before the key nucleophilic oxabicycle opening was

Scheme 19. Revised synthetic strategy towards the microcin Choi core.


envisioned. Furthermore, we planned to address the selectivity problems in the cyclization step by the use of primary amine substrate 130. The high nucleophilicity and the reduced steric hindrance of the amino group in 130 might override the inherent preference for hydroquinoline formation through cyclization of the amide nitrogen providing 131. We hoped to obtain secondary amine 132, which is amenable to peptide coupling, in order to introduce the dipeptide side chain of microcin SF608.

The successful implementation of this revised strategy towards the total synthesis of microcin SF608 is described in the following chapter.
Introduction of the C(6) Hydroxyl Group Through a Regioselective Epoxide Reduction

4.1. Titanium-Mediated Reductive Epoxide Opening

Based on the preliminary studies described in the previous chapter, we realized that introduction of the C(6) hydroxy group in the microcin Choi core would not be possible at a late stage in the synthesis. We therefore explored early installation of this alcohol functionality in an oxabicyclic precursor. This objective required the formal hydration of the endocyclic double bond. Such a transformation would have to account for both, regio-, as well as stereoselective functionalization of the C(6)–C(7) double bond. Hydroboration of this olefin seemed thereby a suitable strategy to meet these requirements. In particular, the use of chiral boron reagents might enable to control the regioselectivity of such an event. Accordingly, we evaluated several hydroborating reagents such as BH$_3$SMe$_2$, 9-BBN, (−)-Ipc$_2$BH or (+)-Ipc$_2$BH for their ability to convert alkene 102 into alcohol 133 upon oxidative workup (Scheme 20). However, in all of these cases a complex mixture of products was obtained.

Scheme 20. Unsuccessful hydroboration of alkene 102.

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72 For an overview covering alkene hydroboration, see: Brown, H.C. In *Hydroboration*; W.A. Benjamin Inc.: Reading; 1962.
An alternative strategy for the installation of the C(6) hydroxyl group could be drafted based on an intriguing observation made during the synthesis of the banyaside Abn core.\textsuperscript{77} In the course of this work, epoxide 134 needed to be converted into alkene 135 through deoxygenation, as outlined in Scheme 21. RajanBabu and Nugent reported in 1990 a protocol involving Cp\textsubscript{2}TiCl\textsubscript{2}\textsuperscript{78} as a stoichiometric reductant to convert epoxides into their corresponding olefins under very mild conditions.\textsuperscript{79,80} Surprisingly, when epoxide 134 was subjected to these conditions, secondary alcohol 136 was obtained as the sole product in 76% yield. Although RajanBabu and Nugent also had observed this transformation using their reagent system, the completely selective formation of only one regioisomeric alcohol 136 was unexpected.

Scheme 21. Regioselective reduction of epoxide 134 during studies directed towards the synthesis of the banyaside Abn core.

As shown in Scheme 22, the mechanism for this transformation originally proposed by RajanBabu and Nugent involves the titanium(III)-mediated homolytic rupture of one C–O bond of the epoxide substrate 137 to generate a carbon-centered radical intermediate 138 via intermediate 139. The more substituted C–O bond is cleaved preferentially; a characteristic initially attributed to the formation of a more stable radical intermediate.\textsuperscript{81} Reductive quenching of this radical should then deliver titanium-

Scheme 22. Generally accepted mechanism for the titanium(III)-mediated epoxide reduction.

\textsuperscript{77} This transformation was discovered by Corinna Schindler in the course of her PhD thesis: ETH Diss. No. 18899.

\textsuperscript{78} For all reactions reported here, Cp\textsubscript{2}TiCl was always prepared freshly from Cp\textsubscript{2}TiCl\textsubscript{2} and zinc powder.


alkoxide 140 and, upon aqueous workup, the observed product 141. Alternatively, addition of a second equivalent of the Ti(III) reagent produces unstable intermediate 142, which undergoes elimination of the titanium-alkoxide to give alkene 143. The product ratio 141:143 can thereby be influenced by changing the order of addition of substrate versus reagent, and therefore controlling the amount of titanium reagent available. In the case of epoxide 134, the mechanism outlined in Scheme 22 could not account for the exclusive formation of alcohol 136. In fact, both sides of the epoxide are sterically as well as electronically almost identical. Regardless of the origin of this unusual selectivity, this transformation could prove useful for the introduction of the C(6) alcohol in the Choi core as it provides the regioisomer required. We thus set out to implement this novel synthetic plan.

As depicted in Scheme 23, we prepared epoxylactone 144 in two steps from allylic alcohol 100. Selective oxidation of the strained endocyclic double bond in 100 was carried out with m-CPBA delivering epoxide 145 in 93% yield. The product was isolated as a single diastereomer consistent with reaction from the exo-face, as generally observed in oxabicyclic systems. Subsequent hydrogenation of the electron poor olefin in 145 delivered a mixture of ester 144 and ring-closed lactone 146. Pleasingly, addition of catalytic quantities of K$_2$CO$_3$ (5 mol%) to the reaction mixture led to complete cyclization of the product, providing lactone 144 in 78% yield.

Scheme 23. Preparation of epoxylactone 144.

We next turned our attention to the introduction of the C(2) nitrogen substituent. To this end, the previously established enolate azidation protocol was employed again (section 3.1). The poor solubility of the starting material 144 in ethereal solvents, and even in CH$_2$Cl$_2$, was even more pronounced than for the previously investigated substrate. We thus prepared a solution of lactone 144 in CH$_2$Cl$_2$ and then added this solution slowly to a precooled mixture of LiHMDS in CH$_2$Cl$_2$, according to the strategy used previously. The resulting solution of enolate 147 was then treated with various sulfonyl azides to produce azidolactones 148a and 148b (Table 4). Employing TrisN$_3$ again delivered the product in excellent yield (79%) but with essentially no diastereoselectivity (entry 1). We turned again to azidation reagents incorporating electron rich (entry 2) or electron poor (entry 3) aromatic rings. However, no beneficial change of the product ratio was observed. Changing the steric bulk of the sulfonyl azide also did not influence the diastereoselectivity either. In particular, 4-tert-

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82 Slow addition of substrate to Ti(III) preferentially produces alkene 143, whereas addition of Ti(III) to substrate gives alcohol 141.
83 For the preparation of 100, see previous chapter (section 3.1).
84 Addition of larger quantities of base led to partial decomposition of the product and reduced yield.
butylibenzenesulfonyl azide (149) as well as 1-naphthylsulfonyl azide (150) were evaluated (entries 4 and 5). We therefore turned back to the camphor-derived reagents. Subjecting enolate 147 to (+)-camphorsulfonyl azide delivered the product in a 5:1 ratio favoring the undesired diastereomer (entry 6). Similar to the observation made with the previously investigated substrate, the (–)-camphor enantiomer 117 did not invert the selectivity but led to the production of an equimolar mixture of 148a and 148b. We thus decided to use TrisN3, which provided the product in the best yield, and separated the two diastereomers.\textsuperscript{85}

**Table 4. Azidation of lactone 144.**

<table>
<thead>
<tr>
<th>Entry\textsuperscript{[a]}</th>
<th>Reagent</th>
<th>dr (148a:148b)\textsuperscript{[b]}</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
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<td>1.2:1</td>
<td>79%</td>
</tr>
<tr>
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<td><img src="image2" alt="Reagent 2" /></td>
<td>1:1.5</td>
<td>40%</td>
</tr>
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</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Reagent 5" /></td>
<td>1:1</td>
<td>57%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Reagent 6" /></td>
<td>1.5</td>
<td>51%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Reagent 7" /></td>
<td>1.1:1</td>
<td>62%</td>
</tr>
</tbody>
</table>

[a] Conditions: LiHMDS (1.5 equiv.), CH₂Cl₂, -78 °C; then reagent (1.3 equiv.), -15 °C; then AcOH/KOAc. [b] determined by crude NMR analysis, [c] reagent added at -45 °C.

The relative configuration of azide 148a could be determined by conversion into amide 151 and X-ray crystallographic analysis of this derivative (Scheme 24).

\textsuperscript{85} Partial recovery of the undesired diastereomer was possible as detailed below.
In order to access suitable precursors for the projected reductive epoxide opening, cleavage of the lactone ring in \(148a\) was required. The nucleophile employed in this reaction would ultimately have to be converted into the agmatidine side chain of the natural product. At this point, installation of a protected guanidine functional group did not seem advantageous due to the highly polar nature of such a substituent, along with its potential interference with various reactions on the way to microcin SF608. We thus decided to prepare an agmatidine surrogate, which could later serve as a handle to introduce the guanidine moiety. As outlined in Scheme 25, two different nucleophiles were evaluated as agmatidine surrogates. Boc-protected diaminobutane (152)\(^{86}\) would already incorporate a nitrogen substituent at the far end. However, we were worried about possible cleavage of the Boc-carbamate under the Lewis acidic conditions needed for nucleophilic opening of the oxabicycle.\(^{87}\)

We therefore also prepared TBDPS-protected aminobutanol (153).\(^{88}\) Both nucleophiles were employed in order to open lactone \(148a\) producing either carbamate 154 or silyl ether 155 in excellent yield.

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Subsequent conversion of the azide functionality into a Cbz carbamate was carried out following the previously established protocol to provide epoxides 156 and 157, respectively.

With the desired substrates in hand, we now turned to the projected epoxide reduction. In the event, carbamate 157 was treated with a solution of freshly prepared Cp₂TiCl (Scheme 26). To our delight, TLC analysis of the reaction indicated conversion into a single product. Isolation and characterization of this adduct suggested the formation of alcohol 158 as a single regioisomeric product. Only upon performing the reaction at considerably larger scale (0.3 mmol), the two byproducts 159 (5% yield) and 160 (4% yield) could be observed and isolated. However, closer spectroscopic and chemical investigation of alcohol 158 revealed that the C(2) stereocenter had epimerized completely under the reaction conditions. Most interestingly, the reisolated starting material, as well as the two side products 159 and 160, apparently did not suffer from such a C(2) epimerization. All these compounds were obtained as single diastereomers. These puzzling observations, along with the unclear origin of regioselectivity, prompted us to investigate this reaction more closely.


4.2. Studies on the Origin of Regioselectivity

Following the established mechanistic scheme of the titanium(III)-mediated epoxide reduction, two possible carbon-centered radical intermediates 161 or 162 could be formed upon treatment of epoxide 157 with Cp₂TiCl (Scheme 27). However, only reductive quenching of radical 161 leads to the formation of alcohol 158. As mentioned before, there is no obvious preference for the formation of radical 161 over its regioisomer 162 as both C–O bonds of the epoxide starting material are in essentially the same steric environment. Moreover, the substituents at C(3a) seem too remote to exert an electronic effect on the C(7) carbon.

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89 Spectroscopic characterization of 158 proved difficult due to rotamers in the NMR spectra. Various experiments, including high temperature measurements and chemical derivatization of 158, led to the conclusion that the C(2) stereocenter had epimerized.
Accordingly, we propose that radicals 161 and 162 exist in equilibrium with each other. In fact, computational and experimental studies indicated that the reductive opening of 1,2-disubstituted epoxides by Ti(III) is indeed reversible.\textsuperscript{81b} We further hypothesize that a Curtin–Hammett scenario must be operating whereby only one of the two rapidly equilibrating radical isomers, namely 161, is quenched efficiently by a reductant. In contrast, its regioisomer 162 should be much less reactive. We further reasoned that a directing effect, possibly exerted by the C(3a) alkyl substituent, might determine the choice for one reaction path over the other. In particular, this side chain could act as an internal quencher of radical 161 by intramolecular hydrogen atom delivery. In this case, the C–H bond strength of the hydrogen atom donating functionality needs to be sufficiently low to enable this process. In this regard, two R–H bonds in 158 can be considered as potential hydrogen atom sources: a) the donor-acceptor substituted tertiary C(2)–H or alternatively; b) the NH of the nearby Cbz carbamate. Although OH and NH groups are known to be very poor hydrogen atom donors due to the large heteroatom–H bond strength (85-110 kcal/mol for N–H), a number of recent reports have demonstrated that this bond strength can be considerably reduced by coordination of a Lewis acid, such as BE\textsubscript{3}\textsuperscript{90} or Cp\textsubscript{2}TiCl\textsuperscript{91}, to the heteroatom, thereby turning these functionalities into potent hydrogen atom donors. Initial molecular modelling of radical intermediate 161 indicated that the C(2)–H is not within good reach to the C(7) radical. However, the carbamate NH can be brought into perfect alignment with the SOMO of a carbon centered radical at C(7) in 161. In order to test this hypothesis, a number of deuteriation experiments were carried out on the rigid oxabicyclic system 163, which does not suffer from C(2) epimerization, thus simplifying spectroscopic analysis (Scheme 28).\textsuperscript{92}


\textsuperscript{92} The experiments presented in Scheme 28 were carried out by Corinna Schindler.
**Scheme 28.** Deuteration experiments on rigid epoxide 163.

When doubly deuterated carbamate \( d_2\)-163\(^{93} \) was subjected to the standard reaction conditions, C(7)-deuterated alcohol \( 164 \)\(^{94} \) was obtained (equation 1). Moreover, when deuterated THF was employed as solvent, no D-incorporation was observed in the product (equation 2). Similarly, quenching the reaction with D\(_2\)O did not lead to the production of deuterated 164. These experiments indicate that the hydrogen incorporated into C(7) is indeed delivered by the carbamate NH of the side chain. In order to further probe the reason for C(2) epimerization, epoxide 157 was subjected to similar deuteration studies (Table 5).

**Table 5.** Deuteration experiments on epimerizable epoxide 157.

<table>
<thead>
<tr>
<th>Entry(^{[a]} )</th>
<th>Additive (100 equiv.)</th>
<th>R</th>
<th>% [D] at C(2) in 165(^{[b]} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H(_2)O</td>
<td>H</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>D</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>D(_2)O</td>
<td>D</td>
<td>55%</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Conditions: Cp\(_2\)TiCl (2 equiv.), additive, THF, rt; \(^{[b]}\) determined by \(^1\)H-NMR; deuterium incorporation at C(7) could not be clearly determined due to overlapping peaks in the \(^1\)H NMR.

\(^{93}\) Prepared by stirring 163 in CD\(_3\)OD for 1h followed by removal of the solvent under high vacuum for several hours.

\(^{94}\) Determined by HiRes-MS analysis.
Deuterated epoxide 157 was subjected to treatment with \( \text{Cp}_2\text{TiCl} \) providing product 165. Although quantification of deuterium incorporation at C(7) was not possible due to overlapping signals in the \( ^1\text{H}-\text{NMR} \) spectrum, deuteration at C(2) could clearly be followed. Performing the reaction without any additives produced 165 with 35% D-incorporation at C(2) (entry 2). Upon addition of D\(_2\)O to the reaction mixture, a significant increase of deuterium incorporation was observed (55%, entry 3).

Based on the observations made so far, we speculated that C(2) epimerization might be a direct result of the hydrogen donation by the attached NH group. In particular, hydrogen abstraction from the carbamate NH would produce an intermediate nitrogen-centered radical. This reactive species would likely undergo a [1,2]-hydrogen shift to produce a more stable donor-acceptor substituted carbon-centered radical at C(2). Such a radical shift would thus result in epimerization at this carbon. Based on this hypothesis, we set out to further study this reaction with the intention of finding conditions to suppress C(2) epimerization.

**Table 6.** Optimization of the epoxide reduction in 157.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive (^{[a]} )</th>
<th>( 158a:158b )</th>
<th>Combined Yield ( 158a+158b^{[c]} )</th>
<th>Yield 160</th>
<th>Yield 159</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>1:1</td>
<td>70% (78% brsm)</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>H(_2)O</td>
<td>1.6:1</td>
<td>37% (71% brsm)</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>3</td>
<td>1,4-cyclohexadiene</td>
<td>1.4:1</td>
<td>50% (71% brsm)</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>4(^{[d]} )</td>
<td>1,4-cyclohexadiene</td>
<td>3:1</td>
<td>54% (75% brsm)</td>
<td>4%</td>
<td>5%</td>
</tr>
</tbody>
</table>

\(^{[a]} \) Conditions: \( \text{Cp}_2\text{TiCl} \) (2.0 equiv.), additive, THF, rt, 6h; \(^{[b]} \) 100 equiv. additive added; \(^{[c]} \) the reisolated starting material was not epimerized and retained (S)-configuration at C(2); \(^{[d]} \) reaction performed at 0 °C.

If a [1,2]-hydrogen shift were responsible for C(2) epimerization, addition of radical quenchers should suppress this reactivity. As presented in Table 6, we therefore evaluated the addition of external hydrogen atom donors to the reaction of 157. Performing the reaction in the presence of a large excess of water\(^{96} \) reduced the degree of epimerization affording alcohols 158a and 158b in a ratio of 1.6:1 (entry 2). A similar result was obtained when 1,4-cyclohexadiene was used as a radical quencher (entry 3). Finally, decreasing the reaction temperature to 0 °C led to a further reduction of


\(^{96} \) Water was reported to be an effective hydrogen atom donor under these conditions (ref. 91).
epimerization, producing product 158 in a diastereomeric ratio of 3:1 (entry 4). Notably, in all cases the two byproducts 160 and 159 were obtained in only minute quantities and, again, without any observable isomerization.

In order to gain further insight into the intriguing features of this transformation, we also prepared C(2) epimer 166 as epoxide opening substrate. As outlined in Table 7, a similar study to that with 157 was conducted. Interestingly, when 166 was subjected to the initially established reaction conditions without any additives, alcohol 167 was obtained as a 2:1 mixture of diastereomers at C(2) (entry 1). The regioselectivity of the reaction was however not affected and isomeric product 168 was again isolated only in trace amounts (4%) along with 5% of alkene 169. The dependency of the epimerization event on the substrate configuration therefore renders the possibility of a direct abstraction of the C(2)-hydrogen unlikely. Next, we conducted the same reaction again with varying amounts of hydrogen donor additives. Addition of 10 equivalents of water reduced the 167a:167b ratio to 3:1 (entry 2). The use of a larger excess of either water, or 1,4-cyclohexadiene, decreased the ratio even further to 7:1 or 12:1, respectively (entries 3 and 4). Interestingly, conducting the reaction at reflux led to complete epimerization of the C(2) stereocenter in product 167 (entry 5). This finding proved useful for the synthesis of microcin SF608, as it enabled partial recovery of the undesired C(2) epimer obtained in the azidation reaction (vide supra).

Table 7. Study of the regioselective epoxide reduction on substrate 166.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>167a:167b</th>
<th>Combined Yield 167a+167b</th>
<th>Yield 168</th>
<th>Yield 169</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>2:1</td>
<td>70% (78% brsm)</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>H2O[d]</td>
<td>3:1</td>
<td>60% (80% brsm)</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>3</td>
<td>H2O</td>
<td>7:1</td>
<td>51% (82% brsm)</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>4</td>
<td>1,4-cyclohexadiene</td>
<td>12:1</td>
<td>54% (75% brsm)</td>
<td>nd</td>
<td>1-2%</td>
</tr>
<tr>
<td>5[e]</td>
<td>-</td>
<td>1:1</td>
<td>75% (85% brsm)</td>
<td>nd</td>
<td>nd</td>
</tr>
</tbody>
</table>

[a] Conditions: Cp2TiCl (2.0 equiv.), additive, THF, rt, 6h; [b] 100 equiv. of additive added; [c] the reisolated starting material was not epimerized and retained (S)-configuration at C(2); [d] only 10 equiv. of H2O were added; [e] reaction performed at reflux; nd = not determined.

97 Prepared form azidolactone 148b using the chemistry used for the preparation of 157.
Substitution of the Cbz carbonyl group in 157 with an alkyl substituent would open the possibility of an alternative [1,2]-migration path. This should result in reduced epimerization at C(2). As outlined in Scheme 29, we prepared benzyl amine 170 and subjected it to Cp₂TiCl. Indeed, product 171 was obtained with excellent regioselectivity in a dr of 2.5:1 at C(2). Moreover, treatment of C(2)-epimer 172 under identical conditions provided alcohol 173 in a 7:1 ratio. These results are consistent with partial quenching of the nitrogen centered radical through a [1,2]-hydrogen migration from the benzyl substituent.

Scheme 29. Epoxide reduction of benzyl protected substrates 170 and 172.

Finally, we decided to probe the possible influence of the C(3a) hydroxyl group on the regioselectivity of the reaction. To this end, deoxygenated substrate 174 was prepared and subjected to the standard reaction conditions (Scheme 30). A mixture of regioisomeric alcohols 175 and 176 was obtained in a 5:1 ratio. The reduced selectivity observed for this substrate indicates some minor influence of the C(3a) hydroxyl group. This can either be explained by direct electronic control of the reaction, or by influence of the substitution at C(3a) on the conformational flexibility of the alkyl side chain harbouring the directing NH group.

Scheme 30. Evaluation of the influence of the C(3a) hydroxyl group.

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98 We were not able to use 171 in the synthesis of microcin SF608 as the benzyl protecting group proved very difficult to remove.
99 Removal of the C(3a) alcohol was achieved using the photochemical deoxygenation protocol described in the subsequent chapter.
Based on the observations made during these studies, we propose a detailed mechanistic rationale for both, the regioselective formation of alcohol 158, and the C(2) epimerization observed during this transformation. As depicted in Scheme 31, we hypothesize that treatment of epoxide 157 with Cp₂TiCl initially generates two rapidly equilibrating radical intermediates 161 and 162 by homolytic rupture of one oxirane C–O bond. In accordance with the Curtin–Hammett principle, only the C(7) radical 161 can undergo a rapid follow-up reaction, while isomer 162 undergoes slow intermolecular reductive quenching by the solvent THF. We further postulate that radical 161 is trapped through an intramolecular hydrogen atom donation by the nearby carbamate NH. This H-abstraction is enabled by coordination of the titanium complex to either the Cbz carbonyl group or directly to the nitrogen atom, thereby reducing the N–H bond strength. The resulting nitrogen centered radical 177 can then undergo a [1,2]-shift of a hydrogen atom to produce carbon-centered radical 178. This event results in loss of the stereochemical information at C(2). Alternatively, radical 178 could be generated by hydrogen abstraction from imidoester radical 179. Reductive quenching of 178 by a solvent molecule then generates product mixture 158a/158b. Alternatively, reaction of 178 with another equivalent of Cp₂TiCl would produce titanium enolate 180, which would give adduct 158a/158b upon aqueous workup. In the presence of an excess of a potent hydrogen atom donor however, the nitrogen centered radical 177 can be intercepted before H-migration can occur, thus leading to unepimerized product.

Scheme 31. Proposed mechanism for the regioselective epoxide reduction of 157.
Moreover, the efficiency of the [1,2]-shift likely depends on the conformation around the C(2)--N bond. Migration can occur only when an optimal orbital overlap between the SOMO of the nitrogen and the C(2)--H bond is ensured. The conformational preference and flexibility of the C(2)--N bond is influenced by a number of factors including the configuration at C(2), the reaction temperature as well as the substituents on the nitrogen.

4.3. Exploration of the Substrate Scope

The mechanistic hypothesis for regioselective reduction of epoxide 157, as detailed above, suggested that this transformation might have more general application. In particular, this reaction could prove useful for the selective opening of otherwise unbiased epoxides in the presence of a suitable intramolecular directing group. The reduction of substituted oxiranes is generally controlled by steric and electronic factors induced by the substituents attached. Moreover, the conditions employed (e.g. LiAlH₄, Li/NH₃) to effect these transformation are usually harsh and do not tolerate sensitive functional groups. A directed epoxide reduction using a Cp₂TiCl based protocol would therefore offer an attractive alternative to the so far known procedures and broaden the scope of epoxide substrates amenable to such reactions.

In order to explore the generality of our directed oxirane reduction, we set out to test various substrates under the previously established conditions. As outlined in Scheme 32, linear epoxides were investigated first. Treatment of Cbz carbamate 181 with freshly prepared Cp₂TiCl produced secondary alcohol 182, along with its regioisomer 183 in a ratio of 2:1 and in 31% combined yield. As OH groups have also been reported to serve as potent hydrogen atom donors in the presence of Lewis acids, epoxyalcohol 184 was prepared. Indeed, when 184 was subjected to the standard conditions, adduct 185 was isolated as a single regioisomer, albeit in low yield (12%). The low yields observed

![Scheme 32. Directed reductive opening of linear epoxide substrates.](image-url)
for these substrates might possibly be attributed to reaction of the ester groups with the titanium reagent. However, these initial observations suggested that OH groups are even more potent directing groups in Ti(III)-mediated oxirane reductions than carbamate NH’s.

We next evaluated cyclic epoxide substrates as outlined in Scheme 33. First, we prepared cyclohexane derivative 186 harboring a hydroxymethyl substituent trans to the epoxide ring. To our delight, treatment of 186 with Cp₂TiCl produced diol 187 in excellent yield (73%) and high regioselectivity (10:1) (equation 1). In contrast, extended cis-epoxide precursor 189 underwent unselective epoxide opening to give a mixture of alcohols 190 and 191 (equation 2). Interestingly, the corresponding trans-isomer 192 did not undergo any reaction when treated with Ti(III) (equation 3). It is not clear to us why this substrate does not react at all.

Scheme 33. Directed reductive opening of cyclic epoxide substrates.

The observation that directed epoxide reduction was only possible through delivery of the hydrogen atom trans to the breaking oxirane C–O bond suggested a more elaborate mechanistic scheme for this reaction than initially thought. Previously, mechanistic studies of the titanium-mediated epoxide opening suggested that this reaction can be described as a homolytic substitution at the oxygen atom of the breaking oxirane ring. Thereby, a carbon leaving group is homolytically displaced by the incoming titanium reagent. As outlined in Scheme 34, we speculate that the directed variant of this transformation, starting from epoxide 195, could be considered as a S₂H₂-type displacement of the C–O bond by a hydrogen atom at the carbon center as shown for transition state

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Introduction of the C(6) Hydroxyl Group Through a Regioselective Epoxide Reduction

Scheme 34. Proposed $S_{N}$2-type mechanism for the directed epoxide reduction.

196. Under these circumstances, titanium alkoxide 197 would be produced with inversion of the epoxide stereocenter. Generally, $S_{N}$2 reactions at carbon are relatively rare and are only possible with substrates harboring a weak C–X bond (whereas X is the leaving group). However, homolytic substitution reactions at cyclopropane rings have been observed. Mechanistic investigations into homolytic opening of trans-deuterated cyclopropane 198 with halide radicals have revealed that the reaction proceeds with complete inversion of configuration at the reacting carbon stereocenter as observed for the classical $S_{N}$2 substitution, thereby providing erythro isomer 199 as the only product (Scheme 35). In particular, a trigonal-bipyrudidal transition state 200 has been suggested to be operative leading to the production of radical 201.

Scheme 35. Homolytic substitution at cyclopropane 198 proceeds with inversion of configuration (ref. 108).

In a similar fashion, opening of the epoxide in 195 could occur by such a stereoinvertive substitution of an oxygen leaving group by the hydrogen atom. The geometrical requirements for such a Walden-inversion would not allow the directing group to come in from the face cis to the epoxide, as would be the case for substrates such as 189 (Scheme 33). Thus, unselective epoxide opening is observed for these substrates.

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105 As homolytic substitution has to compete with various side reactions involving the radical species (such as recombination), the $S_{N}$2 pathway needs to proceed easily enough to override these side reactions.


107 A $S_{N}$2 reaction at an epoxide has also been proposed: Gritter, R.J.; Wallace, T.J. J. Org. Chem. 1961, 26, 282-283.

4.4. Conclusion

In summary, we have synthesized oxabicycle 158a as a precursor for the key nucleophilic oxybridge opening as projected in our synthetic strategy towards microcin SF608. The concise route to 158a starts with allylic alcohol 100, which is first converted into rigid tetracyclic lactone 144 (Scheme 36). Enolate azidation of 144, followed by amide bond formation using agmatidine surrogate 153 and carbamate installation, produced epoxide 157 in excellent yield.

Scheme 36. Preparation of epoxide reduction precursor 157.

Cbz carbamate 157 now served as the substrate for a highly regioselective reduction of the epoxide functionality allowing installation of the C(6) hydroxyl group of the natural product. Extensive mechanistic investigations into the epoxide opening implied that the carbamate NH group in 157 serves as an intramolecular hydrogen atom donor. Thereby, a carbon-centered radical at C(7) is quenched by hydrogen delivery from the side chain. Furthermore, a [1,2]-hydrogen shift of nitrogen-centered radical 177 leading to epimerization of the C(2) stereocenter could be largely suppressed by

Scheme 37. Regioselective reductive opening of epoxide 157.
careful optimization of the reaction conditions. Investigation of the substrate scope revealed that this reaction might in fact be more general, enabling the regioselective reductive opening of various epoxide substrates guided by a NH or OH directing group.
Completion of the Total Synthesis of Microcin SF608

5.1. Nucleophilic Opening of the Oxabicycle

With a successful strategy for C(6)–OH introduction in hand, we now turned to the key nucleophilic opening of the oxabicylic framework. As outlined in the preceding chapter, different agmatidine surrogates were introduced in the oxabicycles so far prepared. As shown in Scheme 38, we first set out to elaborate N-Boc protected cyclization precursor 202. Application of the titanium-mediated epoxide reduction conditions to epoxide 156 delivered secondary alcohol 203 in 86% yield. We then evaluated various alcohol protecting groups to shield the newly generated hydroxyl group in 203. Notably, attempted installation of bulky silyl ether (TBDPS, TIPS), as well as a benzyl group, was not successful. Although we were able to protect 203 as a MOM ether, problems encountered in subsequent steps, in particular difficulties associated with removing this protecting group, led us to consider alternative options. In fact, treatment of alcohol 203 with acetic anhydride provided acetate 204 in excellent yield (98%). Subsequent reductive cleavage of the Cbz carbamate produced primary amine 202 as the projected cyclization precursor.


With amine 202 in hand, studies to explore its cyclization were undertaken. As outlined in chapter 3, of primary concern in this transformation was the choice between two possible nucleophiles for attack onto the bridgehead in 202: either the primary amine at C(2) could participate or alternatively, the amide nitrogen of the agmatidine side chain could compete to form a hydroquinoline system. To our surprise however, when 202 was treated with TMSOTf in the presence of

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109 The unoptimized conditions were used in this reaction. Therefore, the product was obtained as a 1:1 mixture of diastereomers at C(2).
triethylamine, no cyclization to 205 was observed (Scheme 39). The starting material was reisolated along with significant amounts of diamine 206 resulting from loss of the Lewis-acid labile Boc protective group. At this point, the observed outcome could not be explained in light of the model systems investigate so far (see sections 3.1. and 3.2.). We speculated, that the N-Boc group of the side chain might be responsible for this result, possibly by reacting with TMSOTf and generating triflic acid, which might inhibit the reaction by protonation of the amine.


To avoid this complication, we turned to a cyclization precursor lacking any functional groups on the side chain. Accordingly, we subjected carbamate 207 first to hydrogenolytic cleavage of the nitrogen protecting group and the resulting amine to the standard cyclization conditions (Scheme 40). Pleasingly, we were able to isolate hydroindole 208, although in low yield. Most of the material isolated was unreacted starting material. A possible explanation for the poor reactivity of the substrates so far investigated might be their high degree of substitution. This might limit the number of accessible conformers of the side chain, thus rendering adoption of the reactive conformation more difficult.

Scheme 40. Cyclization of model substrate 207.

According to this hypothesis, we envisioned to reduce the number of substituents on the oxabicyclic scaffold by removal of the C(3a) hydroxyl group, which was a remnant of the allylic alcohol starting material. Initially, protocols based on acid mediated activation of the tertiary alcohol (CF₃CO₂H, BF₃·OEt₂, ZnI₂) to generate a carbocation intermediate followed by reductive quenching (e.g. Et₃SiH, NaCNBH₃) were investigated. Under a variety of conditions tested, complex product mixtures resulted. This can likely be attributed to rearrangement events of the intermediate oxabicyclic carbocation. To circumvent problems associated with carbocation formation, we next turned our

attention to radical based deoxygenation strategies.\textsuperscript{111} Interestingly though, functionalization of the C(3a) hydroxyl group proved challenging. In particular, conversion into conventional deoxygenation precursors such as xanthates or thioester derivatives failed, leading to either recovery of starting material or complete decomposition when strong bases were employed (e.g. KH). We finally turned our attention to a scarcely used photochemical deoxygenation protocol originally reported by Saito and co-workers.\textsuperscript{112} This procedure relies on conversion of the alcohol into an activated $m$-CF$_3$ benzoate derivate. Irradiation of this species with UV light, in the presence of $N$-methylcarbazole, initiates an electron transfer from the electron rich carbazole to the $\pi$-system of the benzoate. The resulting aryl radical anion then undergoes protonation followed by fragmentation, ultimately leading to cleavage of the alcohol C–O bond.

In order to test this approach, benzoate 209 was synthesized by selective acetylation of the secondary alcohol in 158a with Ac$_2$O (Scheme 41). Treatment of the tertiary alcohol 210 with 3-trifluoromethylbenzoyl chloride (211) afforded ester 209 in 91% yield. When 209 was irradiated with UV light in the presence of $N$-methylcarbazole and 1,4-cyclohexadiene as hydrogen atom donor according to the reported procedure, desired deoxygenated product 212 was obtained in good yield of 68% (96% brsm). It is noteworthy that radical 213 resulting from fragmentation of intermediate 214 was quenched exclusively from the \textit{exo}-face of the bicyclic framework, thus ensuring complete retention of the stereochemistry at C(3a). Moreover, the cleanliness of our reaction is in stark contrast with previous observations, which reported that tertiary alcohol derived substrates are prone to

\begin{center}
\textbf{Scheme 41.} Photochemical deoxygenation of alcohol 158a.
\end{center}

\textsuperscript{111} For a review covering radical deoxygenation of alcohols, see: Hartwig, W. \textit{Tetrahedron}, 1983, 39, 2609-2645.

disproportionation, thus generating major amounts of an alkene side product.\textsuperscript{112a} Such a side reaction was not observed in our system. Finally, removal of the Cbz protecting group proceeded smoothly under hydrogenolytic conditions to give primary amine 215 in 93% yield.

As depicted in Scheme 42, amine 215 was subjected to the previously disclosed conditions for nucleophilic opening of the oxabicyclic system. To our great delight, treatment of 215 with TMSOTf/NEt\(_3\) cleanly produced a single product, which was identified to be doubly TMS-protected hydroindole 216. Notably, we did not observe any side products resulting from cyclization of the amide nitrogen (red in Scheme 42). As speculated before, the enhanced nucleophilicity of the amine nitrogen was able to completely override the system’s inherent preference for hydroquinoline formation. In order to fully complement the substitution pattern on the hydroindole core 216, installation of the dipeptide appendage on the sterically hindered secondary amine was required. Various reports suggested that TMS protected secondary amines exhibit an enhanced reactivity in peptide coupling reactions compared to the corresponding unfunctionalized amines.\textsuperscript{113} We therefore subjected silyl amine 216 to peptide coupling conditions involving various coupling partners. In all of these reactions, only unchanged starting material was recovered. This was surprising regarding the generally observed lability of N-silyl compounds. We surmise that the highly congested nature of the silylated amine in 216 renders this compound relatively inert.

![Scheme 42. Cyclization of amine 215.](image)

We thus set out to find conditions for silyl group removal prior to peptide coupling. As outlined in Table 8, numerous conditions were tested towards this end. Treatment of 216 with PPTS did not lead to any reaction of the starting material (entry 1). Although initial results using formic acid in a mixture of MeCN and water seemed promising, these conditions delivered the desired product 217 in varying yield (entry 2). On larger scale this reaction proved particularly irreproducible. We next turned to harsher conditions and invoked the use of HCl in MeOH as the acid promoter (entry 3). In this case however, loss of the TBDPS protecting group on the agmatidine side chain was observed. A similar result was obtained upon treatment of 216 with CF\(_3\)CO\(_2\)H in CH\(_2\)Cl\(_2\) (entry 4). In addition, partial loss of the acetate protecting group accompanied silyl ether cleavage. Subjecting 216 to a solution of

aqueous HF in MeCN also resulted in cleavage of the TBDPS protective group (entry 5). The use of HF-pyridine or TBAF did not only result in overall silyl deprotection, but was also accompanied by migration of the acetate group on C(6) to the C(5) hydroxyl producing a complex mixture of products (entries 6 and 7). We finally turned to a protocol involving fluorosilicic acid (H$_2$SiF$_6$) in the presence of triethylamine. These conditions are essentially neutral and should not harm any sensitive functionality in 216. Treatment of 216 with H$_2$SiF$_6$/NEt$_3$ at ambient temperature did not lead to any product formation. Warming the reaction mixture to 65 °C however, delivered desired adduct 217 in good yield (89% brsm) along with some mono-TMS protected starting material. After three rounds of deprotection the product was obtained in a total yield of 81%.

Table 8. Removal of silyl protecting groups on hydroindole 216.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPTS, MeOH</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>0.1% HCOOH, MeCN/H$_2$O</td>
<td>varying result (not reproducible)</td>
</tr>
<tr>
<td>3</td>
<td>HCl/MeOH, CH$_2$Cl$_2$</td>
<td>loss of TBDPS</td>
</tr>
<tr>
<td>4</td>
<td>CF$_3$CO$_2$H/CH$_2$Cl$_2$, 20:1</td>
<td>loss of acetate and TBDPS</td>
</tr>
<tr>
<td>5</td>
<td>aq. HF, MeCN</td>
<td>loss of TBDPS</td>
</tr>
<tr>
<td>6</td>
<td>HF-py, THF</td>
<td>loss of TBDPS, acetate migration</td>
</tr>
<tr>
<td>7</td>
<td>TBAF, THF</td>
<td>loss of TBDPS, acetate migration</td>
</tr>
<tr>
<td>8</td>
<td>H$_2$SiF$_6$, NEt$_3$, MeCN, rt</td>
<td>no reaction</td>
</tr>
<tr>
<td>9</td>
<td>H$_2$SiF$_6$, NEt$_3$, MeCN, 65 °C</td>
<td>minor loss of TBDPS, 89% brsm yield$^a$</td>
</tr>
</tbody>
</table>

[a] after 3 rounds of deprotection product 217 was obtained in a total yield of 81%.

5.2. Elaboration of the Microcin Choi Core

With a reliable route to hydroindole 217 in hand, we now turned our attention to the synthesis of the dipeptide coupling partner. As outlined in Scheme 43, carboxylic acid 218 was prepared by standard peptide chemistry. We decided to exclusively use hydrogenolytically cleavable protecting groups. This strategy would later enable a final deprotection of the natural product under mild conditions, possibly without the requirement of a purification step. Accordingly, lactic acid derivative

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115 Similar acetate migrations have been observed upon TBAF deprotection of silyl protecting groups. For example, see: Sadeghi-Khomami, A.; Blake, A.J.; Wilson, C.; Thomas, N.R. *Org. Lett.* 2005, 7, 4891-4894.

Completion of the Total Synthesis of Microcin SF608

219 was prepared following a literature procedure via diazotization of O-benzyl tyrosine 220.\(^\text{117}\) Diazotization reactions of amino acids are well known to proceed with retention of stereochemistry, possibly via intermediate 221.\(^\text{118,119}\) Treatment of 219 with trimethylsilyldiazomethane delivered methyl ester 222 in excellent yield. Benzyl protection was achieved by deprotonation of 222 using sodium hydride followed by alkylation of the resulting sodium alkoxide with benzylbromide to give 223 in 42% yield. Saponification of ester 223 produced acid 224, which was coupled to phenylalanine methyl ester, producing dipeptide 225 in 55% yield. The structure and configuration of 225 was confirmed by X-ray crystallographic analysis (Scheme 43, box). Finally, hydrolysis of the methyl ester furnished acid 218 in 96% yield.

**Scheme 43.** Synthesis of dipeptide 218 and Ortep representation of the X-ray structure of ester 225 (50% probability ellipsoids).

Unification of acid 218 with our microcin hydroindole core 217 was now attempted. Various coupling reagents generally used for sterically demanding amide bond forming reactions\(^\text{120}\) were tested to this end including EDC and PyBOP.\(^\text{121}\) In all these cases, however, epimerization at the C(2) stereocenter of the dipeptide substrate occurred, resulting in a diastereomeric product mixture.\(^\text{122}\) In order to avoid this epimerization event, we set out to test further coupling protocols on pyrrolidine as a model amine. As presented in Table 9, the use of the acid chloride derivative of dipeptide 226 as the reactive coupling partner resulted in complete isomerization of the C(2) stereocenter in 227 (entry 1). Generally, acid fluorides suffer much less from epimerization. Indeed, treatment of pyrrolidine with the acid fluoride derived from 226 led to a significant improvement of the diastereomeric ratio of


\(^{120}\) For a review covering peptide coupling reagents, see: Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606-631.


\(^{122}\) Such isomerization reactions are a well-known problem in peptide coupling reactions of sterically hindered amines (see also ref. 120).
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5.

product 227 (5:1, entry 2). Using the peptide coupling reagent DEPT\textsuperscript{123} to achieve linking of acid 226 with pyrrolidine led to a further improvement of this value (entry 3). Unfortunately, the conversion of this reaction remained low (55%). Finally, the use of HATU as activator restored full conversion while retaining the diastereomeric purity of the product (entry 4).

Table 9. Optimization of the peptide coupling to dipeptide 226.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Conditions</th>
<th>dr at C(2)</th>
<th>Conversion\textsuperscript{[a]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>DMAP, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>1:1</td>
<td>55%</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>NEt\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>5:1</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>OH</td>
<td>DEPT, i-Pr\textsubscript{2}NEt, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>7:1</td>
<td>55%</td>
</tr>
<tr>
<td>4</td>
<td>OH</td>
<td>HATU, i-Pr\textsubscript{2}NEt, CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>8:1</td>
<td>100%</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} based on peptide 226.

As outlined in Scheme 44, we next turned to application of this protocol to secondary amine 217. To our delight, treatment of 217 with acid 218 in the presence of HATU and Hünig’s base produced peptide 228 in 77% yield without any detectable epimerization at C(2) of the phenylalanine residue.

Scheme 44. Coupling of hydroindole 217 with dipeptide 218.

To access the natural product microcin SF608 (19), removal of the C(5) hydroxy group on the hydroindole core of 228 was required. Model studies suggested that this transformation can again be achieved using the photochemical deoxygenation protocol used before. Accordingly, alcohol 228 was treated with m-CF\textsubscript{3} benzylic chloride 211 to provide ester 229 in 59% yield (Scheme 45). Irradiation of this intermediate with UV light under the conditions established previously delivered the desired deoxygenated product 230. The conversion of this reaction was low (~50%) and could not be

Completion of the Total Synthesis of Microcin SF608 improved further. However, we were able to reisolate the unreacted starting material and resubject it to the reaction conditions. With 230 in hand, we had fully established the Choi core (red in Scheme 45) as it is found in microcin SF608 (19).

Scheme 45. Synthesis of the microcin Choi core by photodeoxygenation of the C(5) hydroxyl group.

Besides the monohydroxylated hydroindole fragment found in most aeruginosin serine protease inhibitors, a small subclass of these natural products, including the dysinosins, incorporates a slightly modified core fragment with a hydroxyl group at C(5). In contrast to the (R)-configured alcohol functionality found in peptide 228, the C(5) OH in the dysinosin Choi core has an (S)-configuration. In order to also access these aeruginosin members, inversion of the hydroxyl group in 228 would therefore be required. We decided to investigate this possibility as a proof of concept for being able to access all possible aeruginosin core fragments through one divergent synthetic strategy. Accordingly, alcohol 228 was subjected to Mitsunobu conditions (PPh₃, DEAD, p-nitrobenzoic acid). Unfortunately, no product could be obtained with this protocol. This can possibly be attributed to the poor accessibility of the concave face of hydroindole 228, making attack of any nucleophile onto an activated C(5) alcohol very difficult. We thus diverted our efforts towards an oxidation/reduction sequence. As outlined in Scheme 46, treatment of alcohol 228 with TPAP/NMO (Ley–Griffith oxidation)¹²⁴ gave ketone 231 in excellent yield (91%).¹²⁵ Reduction of 231 with sodium borohydride provided alcohol 232 as a single diastereomer in 63% yield. Hydride delivery only occurred from the convex face of the bicyclic system. Bis-hydroxyindole 232 harbors the Choi core found in the dysinosin-type aeruginosin serine protease inhibitors (blue in Scheme 46).

¹²⁵ Other oxidizing reagents such as Dess–Martin periodinone or PCC gave ketone 231 in significantly lower yield.
Scheme 46. Synthesis of the dysinosin Choi core by inversion of the C(5) hydroxyl group.

5.3. Completion of the Synthesis

For the completion of the total synthesis of microcin SF608, the last remaining task was conversion of the protected primary alcohol of the agmatidine surrogate in 230 to a guanidine functionality as found in the natural product. Again, we envisioned introduction of a guanidine moiety harboring

Scheme 47. Model studies for the installation of the guanidine group of the agmatidine side chain.
Completion of the Total Synthesis of Microcin SF608

hydrogenolytically cleavable protecting groups, thus facilitating the final deprotection and purification step. Various possible synthetic strategies to achieve this goal could be drafted. In order find the most efficient approach, we prepared model system 233. As outlined in Scheme 47, numerous strategies were investigated. We first converted the primary alcohol in 233 into a suitable leaving group. Conversion of alcohol 233 into iodide 234 proceeded smoothly under Appel conditions. Treatment of 234 with Cbz-protected guanidine 235 did not result in the nucleophilic displacement of iodide. Upon addition of sodium hydride to deprotonate the guanidine nucleophile, the major product isolated was pyrrolidine 236, resulting from intramolecular alkylation of the amide. Similarly, conversion of alcohol 233 into mesylate 237 (MsCl, NEt₃, 92%) followed by treatment with guanidine 235 in the presence of sodium hydride produced mainly cyclized adduct 236. Having mesylate 237 in hand, we next investigated a stepwise introduction of the guanidine moiety. Displacement of mesylate 237 with sodium azide produced 238 in 58% yield. Reduction of the azide group under hydrogenolytic conditions followed by treatment with triflylguanidine 239, developed by Goodman and co-workers, cleanly produced the desired product 240, albeit in moderate yield (39%). During our optimization, we discovered a report documenting the direct conversion of alcohols into bis-protected guanidine derivatives under Mitsunobu conditions. Application of this protocol to alcohol 233 indeed produced Cbz-carbamate 241 in excellent yield (73%). With two possible routes for guanidine introduction established, we tested its application in peptide 230.

Scheme 48. Attempted installation of the guanidine group under Mitsunobu conditions.

As depicted in Scheme 48, deprotection of the TBDPS group in 230 was carried out using TAS-F, an essentially neutral fluoride source which can be easily removed from the product by simple filtration over silica. The resulting primary alcohol 242 was then subjected to the previously disclosed Mitsunobu conditions. To our surprise, no product 243 was obtained in this reaction and the starting material was reisolated unchanged. We thus turned to the stepwise protocol established in the model system.

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127 A trace amount of the desired product was also isolated.
Completion of the Total Synthesis of Microcin SF608

As shown in Scheme 49, treatment of 242 with MsCl provided the corresponding mesylate, which was subjected to reaction with sodium azide in DMF. It proved necessary to increase the reaction temperature to 50 °C in order to achieve full conversion of the starting material. Subsequent cleavage of the acetate group delivered azidoalcohol 244. Staudinger reduction of 244 proceeded smoothly and produced the corresponding amine, which was directly treated with triflylguanidine 239 to give the desired product 245 in excellent yield (85%). Following our protecting group strategy, overall hydrogenolytic cleavage of all the protecting groups now remained in order to provide the natural product. Treatment of 245 with Pd/C under a hydrogen atmosphere indeed led to the cleavage of the all the protecting groups. As observed by LC-MS analysis of the reaction, the benzyl groups reacted more slowly than the Cbz groups on the guanidine. Simple filtration of the reaction mixture allowed isolated of microcin SF608 in excellent yield of 87% and in sufficient purity for detailed characterization. The NMR spectroscopic data of synthetic microcin SF608 was in good agreement with the previously reported data (Table 10). In particular, we were able to confirm the observation of Bonjoch and co-workers that the carbon and proton resonances at C(4) and C(5) of the Choi core should be reassigned as shown in Table 10. Moreover, the carbon signal at C(3) of the Hpla residue was originally reported to be at 30.7 ppm. We have found that this is probably a typographical error and the correct value should read 39.6 ppm (Table 10). Moreover, the IR and HiRes-MS data were in complete agreement with the reported spectra. The optical rotation measured for synthetic microcin ([α]_D = -30.7) was also in good agreement with the value reported by the isolation group ([α]_D = -19.1) and that reported by Bonjoch ([α]_D = -27.4).
Table 10. Comparison of the NMR spectroscopic data in d$_6$-DMSO for natural vs. synthetic microcin SF608 (19).

<table>
<thead>
<tr>
<th>Residue</th>
<th>Resonance</th>
<th>$^1$H natural$^a$</th>
<th>$^1$H synthetic$^b$</th>
<th>$^1$C natural$^a$</th>
<th>$^1$C synthetic$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agma</td>
<td>C-1</td>
<td>3.09 (q, $J = 5.5$ Hz, 2H)</td>
<td>3.12-3.03 (m, 4H)</td>
<td>38.0</td>
<td>38.0</td>
</tr>
<tr>
<td></td>
<td>C-2</td>
<td>1.47 (m, 2H)</td>
<td>1.51-1.34 (m, 7H)</td>
<td>25.9</td>
<td>25.8</td>
</tr>
<tr>
<td></td>
<td>C-3</td>
<td>1.36 (m, 2H)</td>
<td>1.51-1.34 (m, 7H)</td>
<td>26.3</td>
<td>26.3</td>
</tr>
<tr>
<td></td>
<td>C-4</td>
<td>3.11 (q, $J = 5.5$ Hz, 2H)</td>
<td>3.12-3.03 (m, 4H)</td>
<td>40.5</td>
<td>40.5</td>
</tr>
<tr>
<td></td>
<td>C-5</td>
<td>-</td>
<td>-</td>
<td>157.0</td>
<td>157.0</td>
</tr>
<tr>
<td></td>
<td>1-NH</td>
<td>7.88 (t, $J = 5.5$ Hz, 1H)</td>
<td>not identifiable</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4-NH</td>
<td>7.67 (t, $J = 5.5$ Hz, 1H)</td>
<td>not identifiable</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Choi</td>
<td>C-1</td>
<td>-</td>
<td>-</td>
<td>171.3</td>
<td>171.2</td>
</tr>
<tr>
<td></td>
<td>C-2</td>
<td>4.23 (dd, $J = 9.2$, 8.6 Hz, 1H)</td>
<td>4.25 (dd, $J = 9.8$, 8.1 Hz, 1H)</td>
<td>59.9</td>
<td>59.8</td>
</tr>
<tr>
<td></td>
<td>C-3</td>
<td>1.95 (m, 1H)</td>
<td>1.99-1.92 (m, 1H)</td>
<td>30.4</td>
<td>30.4</td>
</tr>
<tr>
<td></td>
<td>C-3a</td>
<td>1.82 (m, 1H)</td>
<td>1.87-1.80 (m, 1H)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>C-4$^{11}$</td>
<td>2.19 (m, 1H)</td>
<td>2.23-2.17 (m, 1H)</td>
<td>36.5</td>
<td>36.4</td>
</tr>
<tr>
<td></td>
<td>C-5</td>
<td>1.40 (m, 1H)</td>
<td>1.51-1.34 (m, 7H)</td>
<td>19.1</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>C-6</td>
<td>3.87 (bs-s, 1H)</td>
<td>3.88 (bs-s, 1H)</td>
<td>64.1</td>
<td>64.0</td>
</tr>
<tr>
<td></td>
<td>C-7</td>
<td>1.69 (bs-d, $J = 8.0$ Hz, 2H)</td>
<td>1.69 (bs-d, $J = 8.0$ Hz, 2H)</td>
<td>34.3</td>
<td>34.2</td>
</tr>
<tr>
<td></td>
<td>C-7a</td>
<td>4.41 (dt, $J = 9.1$, 7.3 Hz, 1H)</td>
<td>4.42 (dt, $J = 9.2$, 7.5 Hz, 1H)</td>
<td>54.6</td>
<td>54.4</td>
</tr>
<tr>
<td>Phe</td>
<td>C-1</td>
<td>-</td>
<td>-</td>
<td>169.6</td>
<td>169.5</td>
</tr>
<tr>
<td></td>
<td>C-2</td>
<td>4.69 (dt, $J = 7.3$, 5.5 Hz, 1H)</td>
<td>4.69 (dd, $J = 8.2$, 5.2 Hz, 1H)</td>
<td>50.5</td>
<td>50.5</td>
</tr>
<tr>
<td></td>
<td>C-3</td>
<td>2.78 (dd, $J = 13.8$, 8.0 Hz, 1H)</td>
<td>2.83-2.76 (m, 2H)</td>
<td>38.2</td>
<td>38.1</td>
</tr>
<tr>
<td></td>
<td>C-4</td>
<td>2.89 (dd, $J = 13.8$, 4.8 Hz, 1H)</td>
<td>2.89 (dd, $J = 14.0$, 5.0 Hz, 1H)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>C-5,5'</td>
<td>7.15 (d, $J = 7.2$ Hz, 2H)</td>
<td>7.17 (d, $J = 7.0$ Hz, 2H)</td>
<td>129.5</td>
<td>129.5</td>
</tr>
<tr>
<td></td>
<td>C-6,6'</td>
<td>7.23 (t, $J = 7.3$ Hz, 2H)</td>
<td>7.24 (t, $J = 2.0$ Hz, 2H)</td>
<td>128.1</td>
<td>128.1</td>
</tr>
<tr>
<td></td>
<td>C-7</td>
<td>7.19 (t, $J = 6.5$ Hz, 1H)</td>
<td>7.20 (t, $J = 2.3$ Hz, 1H)</td>
<td>126.4</td>
<td>126.4</td>
</tr>
<tr>
<td></td>
<td>NH</td>
<td>7.59 (d, $J = 8.2$ Hz, 1H)</td>
<td>not identifiable</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hpla</td>
<td>C-1</td>
<td>-</td>
<td>-</td>
<td>172.8</td>
<td>172.8</td>
</tr>
<tr>
<td></td>
<td>C-2</td>
<td>3.91 (bs-d, $J = 7.3$ Hz, 1H)</td>
<td>3.92 (dd, $J = 8.3$, 3.8 Hz, 1H)</td>
<td>72.3</td>
<td>72.2</td>
</tr>
<tr>
<td></td>
<td>C-3</td>
<td>2.42 (dd, $J = 13.9$, 8.3 Hz, 1H)</td>
<td>2.43 (dd, $J = 13.9$, 8.3 Hz, 1H)</td>
<td>30.7$^{12}$</td>
<td>39.6</td>
</tr>
<tr>
<td></td>
<td>C-4</td>
<td>2.70 (dd, $J = 13.9$, 3.4 Hz, 1H)</td>
<td>2.70 (dd, $J = 14.0$, 3.6 Hz, 1H)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>C-5,5'</td>
<td>6.90 (d, $J = 8.4$ Hz, 2H)</td>
<td>6.90 (d, $J = 8.5$ Hz, 2H)</td>
<td>130.3</td>
<td>130.2</td>
</tr>
<tr>
<td></td>
<td>C-6,6'</td>
<td>6.61 (d, $J = 8.4$ Hz, 2H)</td>
<td>6.61 (d, $J = 8.5$ Hz, 2H)</td>
<td>114.8</td>
<td>114.8</td>
</tr>
<tr>
<td></td>
<td>C-7</td>
<td>-</td>
<td>-</td>
<td>155.7</td>
<td>156.0</td>
</tr>
<tr>
<td></td>
<td>OH</td>
<td>5.48 (bs-s, 1H)</td>
<td>not identifiable</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

[a] measured at 500 MHz; [b] measured at 600 MHz; [c] measured at 125 MHz; [d] measured at 150 MHz.

$^{11}$ C(4) and C(5) of the Choi core were assigned incorrectly as already noted in ref. 39.

$^{12}$ The $^1$C-NMR shift for C(3) of the Hpla residue was originally reported to be 30.7 ppm. This is probably a typographical error (see text).
5.4. Conclusion

In conclusion, we have completed the total synthesis of the aeruginosin serine protease inhibitor microcin SF608 (19) as outlined in Scheme 50. The synthetic route relies on photochemical removal of the C(3a) hydroxyl group in diol 158a. The mild conditions employed for this transformation allow for preparation of cyclization precursor 215 in the presence of numerous sensitive functional groups. The key nucleophilic oxybridge opening was then realized using primary amine 215 as cyclization substrate. Treatment of 215 with TMSOTf/NEt$_3$ delivered hydroindole 216 as the only isomer observed. It is noteworthy that the high nucleophilicity of the amine in 215 completely overrides the inherent preference of the system for hydroquinoline formation observed during our prospecting studies. Finally, the natural product microcin SF608 (19) could be prepared from Choi core 216 by peptide coupling, removal of the C(5) hydroxyl group and installation of the guanidine moiety in the agmatidine side chain.

Scheme 50. Completion of the total synthesis of microcin SF608 (19).

We have further established a route towards the dysinosin-type Choi core through inversion of the C(5) alcohol in 228. With this strategy in hand, we are now able to access all core fragments of the aeruginosin natural products by a divergent synthetic route starting from oxabicyclic building block 100 as a common precursor.
Conclusion and Outlook

Microcin SF608 (19) is member of the aeruginosin family of serine protease inhibitors. This class of peptidic natural products exhibits a highly specific inhibitory activity against numerous pharmaceutically relevant proteases, including thrombin; the key player in the human blood coagulation cascade. The structure of the aeruginosins incorporates a 2-carboxy-6-hydroxyoctahydroindole core (Choi). We have developed a synthetic strategy towards microcin SF608 (19) relying on the nucleophilic opening of an oxabicyclo[2.2.1]heptane. As outlined in Scheme 51, the synthesis commenced with allylic alcohol 100, which is available through an enantioselective Diels–Alder reaction. Introduction of the C(6) hydroxy group of microcin was achieved through a regioselective epoxide reduction. Mechanistic studies have revealed that this reaction proceeds through hydrogen atom donation by the nearby carbamate NH. Alcohol 158a was further converted into primary amine 215. This intermediate served as a substrate for the central nucleophilic opening of the oxabicycle. Treatment of 215 with TMSOTf delivered hydroindole 216 as the sole product in excellent yield. Microcin SF608 (19) was accessed in 10 steps from this advanced intermediate.

Scheme 51. Total synthesis of microcin SF608 (19) relying on the nucleophilic opening of oxabicycle 215.
With the total synthesis of microcin SF608, we have developed a synthetic entry into the whole family of the aeruginosin protease inhibitors starting from common oxabicyclic precursor \(100\) (Scheme 52). In particular, we are now able to access all three core scaffolds of the aeruginosin protease inhibitors including the Abn core (87) of the banyasides,\(^{51}\) as well as the Choi core of the aeruginosin (93) and the dysinosin subclass (246).

Scheme 52. Divergent access to all core scaffolds of the aeruginosin family of serine protease inhibitors.

As presented in Figure 8, the nucleophilic opening of oxabicyclic systems harbors a great potential for the preparation of numerous natural products incorporating hydroindole core structures (247→248). In particular, alkaloids such as scabrosine ester A (249),\(^{133}\) galwesine (250),\(^{134}\) galanthine (251),\(^{135}\) tuberostemonine (252),\(^ {136}\) or ambine (253)\(^ {137}\) represent interesting targets for the application of this methodology.

Figure 8. Selected natural products containing a hydroxy hydroindole scaffold.

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Besides the total synthesis of microcin SF608 (19), we have conducted prospecting studies to establish the directed epoxide reduction employed in the synthesis as a more general strategy for the introduction of hydroxyl groups. As summarized in Scheme 53, we have found that this reaction is applicable to various substrate types. In particular, hydroxyl groups can serve as potent directing groups guiding the regioselectivity of the epoxide reduction as exemplified by the reaction of cyclohexane derivative 186. A more detailed study of this reaction will likely lead to a versatile tool for the manipulation of epoxides in the synthesis of complex target structures.

Scheme 53. Directed epoxide reduction.
Part II

Total Synthesis of (±)-Gelsemoxonine \textit{via} the Acid Mediated Ring Contraction of a Spirocyclopropane Isoxazolidine
Plants of the genus *Gelsemium* have been used by humans for thousands of years for medicinal purposes. In particular, the Southeast Asian species *Gelsemium elegans* bentham has found application in traditional Chinese and Japanese medicine as an analgesic and antispasmodic remedy, as well as for treatment of skin ulcers.\(^{138}\) During the past 150 years, these plants have been studied by chemists leading to the identification of a new class of tryptophan derived natural products; the gelsemium alkaloids.

### 7.1. Terpenoid Indole Alkaloids

Alkaloids can be classified on the basis of their amino acid nitrogen source. The tryptophan based alkaloids constitute one of the major alkaloid families. Besides a trytophane derived core scaffold, the carbon skeleton of these natural products generally contains fragments of polyketide, shikimate or terpenoid origin. The gelsemium alkaloids belong to the subdivisions of monoterpenoid alkaloids incorporating a C\(_{10}\) terpene fragment.

Indole alkaloids\(^{139}\) generally incorporate a tryptamine (255) fragment as key characteristic component. Terpenoid indole alkaloids additionally incorporate a C\(_9\) or C\(_{10}\) unit derived from the common monoterpane precursor secologanin (*vide infra*). This terpene fragment can undergo a series of rearrangements during natural product biosynthesis leading to the formation of different carbon skeletons. As outlined in Figure 9, the terpenoid indole alkaloids can be subdivided into three major classes according to their terpene pattern: 1) the Corynanthe-Strychnos type including corynantheine (256) (C\(_{10}\)) and strychnine (257) (C\(_9\)); 2) the Iboga type including catharanthine (258) (C\(_{10}\)) or ibogaine (259) (C\(_9\)) and 3) the Aspidosperma type represented by vindoline (260) (C\(_{10}\)). The C\(_9\) derivatives are generated by loss of one carbon unit from parent C\(_{10}\) precursor as indicated in Figure 9. This truncation event generally occurs through decarboxylation of an acid derivative.

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Figure 9. The three subclasses of monoterpenoid indole alkaloids.

Despite of the differing carbon skeletons of these alkaloids, they all share the common terpene precursor secologanin (261). Accordingly, the biosynthesis of terpene indole alkaloids starts with the monoterpenic geraniol (262), accessible through the MEP pathway (Scheme 54). Geraniol is first hydroxylated at the C(10) position by the cytochrome P450 dependent monooxygenase G10H. Conversion of 10-hydroxy geraniol 262 into loganin 263 proceeds through cyclization and further oxidation events. Through the action of another P450 enzyme, secologanin synthase SLS, loganin undergoes cyclopentane ring opening by a retro-Prins reaction. This transformation breaks up the regular terpene skeleton to generate the irregular secologanine pattern.

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142 Two pathways for the biosynthesis of the terpene starter units are known. Whereas animals employ the mevalonic acid (MVA) pathway for the synthesis of sterols, plants and bacteria generally rely on a different access route to terpenes starting from deoxyxylulose phosphate (MEP pathway). For a more detailed discussion, see: Dewick, P.M. In Medicinal Natural Products, 3rd edition; John Wiley & Sons Ltd: Chichester, 2009, pp.187-310.
Scheme 54. Biosynthesis of strictosidine (267), the universal precursor of all monoterpenoid indol alkaloids.

The enzyme SLS has been studied in detail and a mechanism involving radical intermediates has been proposed (Scheme 55). According to this hypothesis, loganin (263) is oxidized to radical 264 by the iron-oxo site in SLS. Two possible pathways (a or b in Scheme 55) could account for the subsequent cleavage of the C–C bond. Either radical intermediate 264 undergoes direct radical cleavage to form 265, which after further oxidation provides secologanin (261), or alternatively, radical 264 could first be oxidized to intermediate 266, which could generate secologanin through a retro-Prins reaction.

Scheme 55. Mechanistic hypothesis for the conversion of loganin into secologanin by SLS.

Incorporation of the monoterpane precursor into the alkaloid skeleton occurs through condensation of secologanin with tryptamine 255 (Scheme 54). The enzyme strictosidine synthase (STR) catalyzes a Pictet–Spengler type condensation between these two components through initial formation of an iminium intermediate. The product of this reaction is the natural product strictosidine (267), which serves as a universal precursor for all monoterpenoid indole alkaloids.

144 Tryptamine is generated by decarboxylation of tryptophan (see ref. 139)
7.2. Gelsemium Alkaloids

Three species in the plant genus *Gelsemium* (family of Loganiacea) have been described to date.\(^ {146} \) *Gelsemium sempervirens* ait. (yellow jasmine) and *Gelsemium rankinii* small are both indigenous to the southeastern United States, whereas *Gelsemium elegans* benth (chin.: Kou-Wen) can be found in China and Japan. All three species are highly toxic and have found use for medicinal purposes. The first isolation of gelsemine as the major component of these plants was reported as early as in 1870.\(^ {147} \) However, it was not until 1959 that the structure of this first gelsemium alkaloid could be elucidated.\(^ {148} \)

To date, an impressive number of monoterpenoid indole alkaloids have been isolated from *Gelsemium* plants. Based on their structure, these natural products can be subdivided into five classes (Figure 10). The sarpagine and koumine subclasses incorporate the indole ring from tryptophan. In contrast, the humantenine, gelsedine and gelsemine families include an oxindole moiety, which is biosynthetically derived from an indole ring (*vide infra*). Notably, the carbon skeletons of the individual subclasses can differ quite drastically as a result of major rearrangement events during the biosynthesis of these natural products.

![Figure 10. The five subclasses of the gelsemium alkaloids with representative members.](image)


\(^ {147} \) Wormley, T.G. *Am. J. Pharm.* 1870, 42, 1.

The gelsemium alkaloids generally contain highly congested polycyclic core structures in which a hydropyran ring as well as a saturated nitrogen heterocycle (either piperidine or pyrrolidine) are characteristic features. The oxindole moiety for the humantenine, gelsedine and gelsemine alkaloids is fused to the core through a quaternary spiro center. Moreover, the nitrogen of this oxindole ring is often present in oxidized form as an N-methoxy oxindole.

In 1991, Clardy and co-workers isolated gelsemoxonine, a novel oxindole alkaloid from *Gelsemium elegans* bentham. Based on NMR studies, the authors assigned structure 277 to this new compound (Figure 11). More than a decade later, Aimi and co-workers isolated the same natural product during detailed study of the constituents of *Gelsemium elegans*. However, a number of observations contradicted the original structural assignment. For instance, acetylation (Ac₂O, Py) of the natural product produced an unexpected diacetyl derivative. Moreover, an HMBC spectrum of gelsemoxonine was recorded at low temperature allowing for the detection of a sharp N₆⁻H signal. Clear correlation between this N₆⁻H proton and the carbons at C(14) and C(20) suggested an azetidine moiety as the central part of the natural product as shown for 278. Finally, X-ray crystallographic analysis confirmed this structural reassignment. This result was remarkable for several reasons. The C(14) hydroxyl group of gelsemoxonine is unusual among the *Gelsemium* alkaloids. Moreover, a ketone functionality has not been observed before in this natural product family. Most remarkably though, the polycyclic framework of gelsemoxonine incorporates a highly unusual azetidine, embedded within the core structure. These structural features along with the high functionalization pattern, the congested arrangement and the spiro-fused oxindole render gelsemoxonine an attractive target for total synthesis.

Figure 11. Originally proposed (277) and reassigned structure (278) of gelsemoxonine.

7.3. Biological Activity of the Gelsemium Alkaloids

The widespread use of *Gelsemium* extracts in traditional medicine, and the high toxicity of these plants, rendered an investigation of the biological activities of the plant components of particular interest. Accordingly, a number of studies evaluating the activity profile of the gelsemium alkaloids

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151 By now, other gelsemium alkaloids with C(14) hydroxyl groups and ketone functionalities have been isolated.
have been reported.\textsuperscript{152} Gelsenicine (274) was found to be the most toxic constituent of the \textit{Gelsemium} plants, with an LD\textsubscript{50} of 100-200 μg/kg in mice (Figure 12).\textsuperscript{152d} Moreover, gelsenicine was found to attenuate inflammatory and neuropathic pain in mouse model in concentrations well below the LD\textsubscript{50} value (2-10 μg/kg). Gelsemium alkaloids have also been reported to show potent antitumor activity \textit{in vitro}.\textsuperscript{153,152c} In particular, 14,15-dihydroxygelsenicine (279) (EC\textsubscript{50} 0.25μM), gelsedine (273) (EC\textsubscript{50} 0.35μM) and gelsemicine (280) (EC\textsubscript{50} 0.75μM) showed cytotoxicity towards A431 cells exceeding the activity of the antitumor agent cisplatin (EC\textsubscript{50} 3.5μM). Interestingly, although gelsemine (275) itself did not exhibit significant antitumor activity, the two gelsemine metabolites 4-N-demethylgelsemine (281) and 21-oxogelsemine (276) were found to have potent inhibitory effects on HepG2 and HeLa cells.

\textbf{Figure 12.} The most biologically active gelsemium alkaloids.

\subsection*{7.4. Biosynthesis of Gelsemium Alkaloids}

Biosynthetic access routes to the gelsemium alkaloids are largely speculative and based almost exclusively on the isolation of putative intermediates, analogous transformations proposed for related biogenetic routes and synthetic studies on the natural products. Neither have there been enzymes characterized or genes identified, which might be associated with gelsemium alkaloid biosynthesis. However, precursor labeling experiments have demonstrated that strictosidine (267) serves as a universal intermediate en route to gelsemine and related alkaloids.\textsuperscript{154} The subsequent section presents the most recent biogenetic hypotheses for the generation of the gelsemium alkaloids.


\textsuperscript{153} In particular, gelsemine showed toxicity leading to respiratory depression in mouse models (ref. 152c). Thus, \textit{in vivo} studies for antitumor activity are difficult to carry out.

7.4.1. Biosynthesis of the Sarpagine-Type Gelsemium Alkaloids

As apparent from the structure of the Sarpagine type gelsemium alkaloids, this subclass is most closely related to the universal terpenoid indole alkaloid precursor strictosidine (267). The proposed biosynthesis of the most prominent members of the Sarpagine division is outlined in Scheme 56. Accordingly, deglycosylation of strictosidine 267 produces enol 282. After formation of an intermediate iminium ion, a Mannich-type cyclization generates pentacyle 283 by formation of the carbon–carbon bond labeled in red. The C₉ indole alkaloid koumidine (269) is accessed by decarboxylation of the ester functionality followed by reduction of the aldehyde. After methylation of the quinuclidine nitrogen, the C(3)–N bond is cleaved, generating a benzylic carbocation, which is trapped by the adjacent primary alcohol to produce taberpsychine (268). Oxidation of the indole nitrogen leads to the formation of the natural product Nₓ-methoxy-19(Z)-anhydrovasinediol (284), the common precursor to all the other gelsemium alkaloid classes.

Scheme 56. Proposed biosynthesis of the sarpagine gelsemium alkaloids.

7.4.2. Biosynthesis of the Koumine-Type Gelsemium Alkaloids

The unique hexacyclic structure of koumine (270) was proposed to be generated from taberpsychine 268 (Scheme 57). Oxidation of the allylic C(18) position produces intermediate 285. This allylic alcohol is now susceptible to an Sₓ2’ displacement by the nucleophilic indole ring, as indicated in Scheme 57. Formation of the this new C–C bond generates koumine (270).

Scheme 57. Proposed biosynthesis of the koumine gelsemium alkaloids.
7.4.3. Biosynthesis of the Humantenine-Type Gelsemium Alkaloids

The humantenine type alkaloids incorporate an oxindole ring instead of the indole moiety derived from tryptamine. The oxindole ring is in fact accessed by oxidative rearrangement of an indole precursor, as depicted in Scheme 58. In particular, oxidation of \( N_{\text{a}}\)-methoxy-19(Z)-anhydrovobasinediol (284) triggers a ring contraction to produce the humantenine alkaloid rankinidine (272) (Scheme 58, top). As confirmed by synthetic studies on indole derivatives,\(^{155}\) indole rings 286 can undergo two different types of oxidative rearrangements (Scheme 58, bottom). Initial oxidation of the pyrrol portion generates a \( \beta \)-hydroxyindolenine 287. Two possible follow-up pathways are now possible. After hydration of the imine, the resulting hemiacetal is susceptible to C(2)-alkyl migration producing an oxindole product 288. Alternatively, C(3)-alkyl migration from intermediate 287 can produce indoxyl species 289. Both modes of reaction can be observed in biological systems,\(^{156}\) as well as in the laboratory.

![Scheme 58. Top: Proposed biosynthesis of the humantenine type gelsemium alkaloids. Bottom: Possible pathways for indole oxidation.](image)

**7.4.4. Biosynthesis of the Gelsedine-Type Alkaloids**

The biosynthesis of the gelsedine type alkaloids starts from the humantenine natural product rankinidine (272) (Scheme 59). In order to arrive at the carbon skeleton of the gelsedine alkaloids, the piperdine ring must be contracted to form a pyrrolidine. Several possible pathways have been proposed to account for the extrusion of one carbon from rankinidine (272). A widely accepted

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hypothesis involves formation of the aziridinium intermediate 290 through either oxidation of 272 to form the natural product 20-hydroxydihydrorankinidine (291) followed by displacement of the tertiary alcohol (path a). Alternatively, the double bond in 272 could be protonated and trapping of the intermediate carbocation would also produce aziridine 290 (path b). The strained heterocycle in 290 can be easily opened by water to provide gelselegine (292). In order to arrive at gelsenicine (274) and gelsedine (273), extrusion of one carbon is required. However, no mechanism has so far been proposed to account for the loss of the C(21) carbon from gelselegine (292).

Scheme 59. Proposed biosynthesis of the gelsedine gelsemium alkaloids.

No conclusive hypothesis concerning the biosynthesis of the gelsemine-type subclass has yet been proposed.
7.4.5. Proposed Biosynthesis of Gelsemoxonine

A route for the biosynthesis of gelsemoxonine (278) has been proposed invoking gelsenicine (274) as a precursor (Scheme 60). Oxidation of 274 would produce 14,15-dihydroxygelsenicine (279). Hydrolysis of the imine functionality would then give rise to primary amine 293. Displacement of the C(15) hydroxyl group would then allow for closure of the strained azetidine ring. The isolation of the natural product 14,15-dihydroxygelsenicine (279) from the same plant source as gelsemoxonine supports the biogenetic hypothesis presented.

Scheme 60. Proposed biosynthesis of gelsemoxonine (278).

7.5. Total Syntheses of Gelsemium Alkaloids

The gelsemium alkaloids have been the subject of extensive studies directed towards their synthesis. The unusual challenges associated with the construction of the polycyclic frameworks of these natural products have prompted the development of a variety of novel strategies and transformations. In particular, the natural product gelsemine has been in the focus of the synthetic community in the past decades, leading to several highly innovative approaches for its total synthesis. This chapter summarizes the strategies developed for the total synthesis of gelsemine and related gelsemium alkaloids, whereby particular consideration is given to the key bond formation events. Notably, the introduction of some key motifs present in most gelsemium alkaloids has been of continuous focus during these studies. This includes in particular: a) the formation of the quaternary C(7) spiro stereocenter at the oxindole ring, b) closure of the hydropyran ring, and c) construction of the highly conjugated carbocyclic framework including a saturated nitrogen heterocycle (a pyrrolidine ring in the case of gelsemine).

This chapter will not cover the huge array of model studies and approaches directed towards the partial synthesis of the gelsemine core structure.

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7.5.1. Total Syntheses of Gelsemine

Despite extensive efforts by numerous laboratories towards total synthesis of one of the most challenging of the gelsemium alkaloids known at the time, it was not until 1994 that the first total synthesis of racemic gelsemine was reported. In two consecutive publications, Johnson,\(^\text{159}\) as well as Hiemstra and Speckamp,\(^\text{160}\) reported independent syntheses of this natural product.

Johnson’s synthetic strategy relied on a photochemical [2+2] cycloaddition of triene 294 to produce cyclobutane derivative 295, as outlined in Scheme 61. This transformation allowed for construction of the crucial cis-arrangement of the vinyl group, masked as a tetrahydrofuran ring, and the hydrogen at the ring fusion. After closure of the pyran ring by haloetherification to give 296, the vinyl substituent was released by an unusual ether ring cleavage. In the event, phenyl trimethylselenide, promoted by ZnI\(_2\), opened the ether ring to deliver silyl ether 297 in 94\% yield. Remarkably, the hydropyran ring, as well as the methyl ester, were not affected under these conditions. 297 was further converted into \(\beta\)-ketoester 298. The cyclobutanone was then ring expanded to arrive at lactam 299. This intermediate now served as substrate for a highly challenging Mannich cyclization to forge the C(6)–C(5) bond of the gelsemine core. Treatment of 299 with CF\(_3\)CO\(_2\)H produced, via iminium intermediate 300, desired tricyclic ketone 301 in excellent yield of 74\%.

Scheme 61. Total synthesis of gelsemine core 301 by Johnson and co-workers.

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Introduction

Scheme 62. Completion of the total synthesis of (±)-gelsemine by Johnson and co-workers.

Tricycle 301 still required introduction of the oxindole ring system including the quaternary stereocenter at the ring fusion. To this end, a novel strategy for oxindole formation at sterically congested ketones was developed as depicted in Scheme 62. The protocol relied on the generation of a diradical using enol triazoles as radical precursor (Scheme 62, top).\textsuperscript{161} Irradiation of triazole 302 gave diradical 303. Recombination of this diradical from resonance form 304 allowed for construction of the quaternary spirocenter in oxindole product 305. Application of this strategy to triazole 306, derived from ketone 301, afforded a mixture of isomeric imino esters 307 and 308 in 36% yield. The minor isomer 308 could then be converted into (±)-gelsemine (275) by hydrolysis of the methyl ether to produce 21-oxogelsemine (276) (not shown) followed by DIBAL reduction of the amide.

Scheme 63. Total synthesis of (±)-gelsemine by Hiemstra and Speckamp.

The Hiemstra/Speckamp approach to gelsemine is outlined in Scheme 63. Mixed acetal 309 is generated in 6 steps, starting with a Diels–Alder cycloaddition between diene 310 and N-methylmaleimide 311. When intermediate 309 was treated with BF$_3$ etherate, a Mannich reaction similar to the one employed by Johnson, but this time between C(5) and C(16), produced bicycle 312 in 70% yield. Conversion of aldehyde 312 into amide 313 proceeded readily in 5 steps. After SEM protection, a Heck protocol as previously reported by Overman\textsuperscript{162,163} was employed to construct the

\textsuperscript{161} Photochemical generation of diradicals from triazoles has been previously investigated. In particular, see: Wender, P.A.; Cooper, C.B. \textit{Tetrahedron 1986}, 42, 2985-2991.
quaternary oxindole stereocenter present in 314. Notably, the spirocenter was formed with full selectivity for the desired isomer. The hydro.pyran ring of gelsemine was closed by oxymercuration followed by reduction of the C–Hg bond with NaBH₄ to produce 315. Finally, removal of the SEM group and reduction of the amide using AlH₃ delivered synthetic (±)-gelsemine (275).

Soon after the first reported total syntheses of gelsemine by Johnson and Hiemstra/Spec kamp, Hart reported an alternative strategy to access the natural product (±)-21-oxogelsemine (276), an intermediate in both of the previous syntheses.¹⁶⁴ The Hart approach started with a Diels–Alder reaction between N-methylmaleimide 311 and diene 316, much like the first transformation in the Hiemstra/Spec kamp synthesis (Scheme 64). The Diels–Alder product was further converted into phenylthiosulfide 317. This compound now served as a substrate for a highly efficient radical cyclization to provide pyrrolidinone 318 via radical intermediate 319. Introduction of the oxindole ring system was again achieved through a radical cyclization strategy. To this end, arylbromide 320 was treated under photochemical radical conditions to deliver the oxindole in 40% yield.¹⁶⁴ Elimination of the methylether delivered alkene 321. Ozonolysis of the double bond produced aldehyde 322, and after epimerization, this aldehyde was converted into hydropyran 323 through oxonium formation followed by reduction using Et₃SiH. The natural product (±)-21-oxogelsemine (276) could be accessed in a further three steps from 323.

Scheme 64. Total synthesis of (±)-21-oxogelsemine by Hart and co-workers.

¹⁶³ For a detailed discussion of this transformation, see section 13.2.2.
A very different access route to racemic gelsemine was reported in 1996 by Fukuyama.\textsuperscript{166} His synthesis commenced with an intramolecular cyclopropanation of diazoketoester 324 using Cu(acac)$_2$ to provide 325 (Scheme 65). This intermediate was further elaborated into oxindole 326. The iodine substituent on the aryl ring served to control the stereochemistry of the double bond in the olefination reaction. When 326 was heated to 90 °C in toluene, a divinylcyclopropane rearrangement occurred to give with complete stereoselectivity the spiro-fused oxindole 327. Conversion into acylchloride 328 now allowed for closure of the pyrrolidinone ring by treatment of this intermediate with silver salts. The resulting stable hemiacetal 329 was further converted into alcohol 330. Oxymercuration, as already seen in the Speckamp synthesis, provided hydropyran 331. This intermediate was readily elaborated into (±)-gelsemine (275).

![Scheme 65. Total synthesis of (±)-gelsemine by Fukuyama and co-workers.](image)

Soon after completion of their synthesis, the Fukuyama group reported a revised strategy towards gelsemine, now allowing for the enantioselective synthesis of the natural product (Scheme 66).\textsuperscript{167} The synthetic route started with diastereoselective Diels–Alder reaction between cyclopentadiene 332 and alkene 333 harboring a chiral oxazolidinone auxiliary. Bicycle 334 was then converted into epoxide

![Scheme 66. First enantioselective total synthesis of (+)-gelsemine by Fukuyama and co-workers.](image)


Treatment of 335 with the aluminum based Lewis acid MAD (336)\textsuperscript{168} initiated a rearrangement of the bicyclic framework to produce cyclopropane 337. After introduction of the oxindole to give 338 and conversion of the silyl ether into an enone, the divinylcyclopropane rearrangement already employed for the previous synthesis could be carried out to provide tetracycle 327. Conversion into (+)-gelsemine was achieved using similar chemistry as reported for the racemic synthesis.

Overman reported an alternative approach to racemic gelsemine relying on an aza-Cope/Mannich sequence to construct the core fragment of the natural product (Scheme 67).\textsuperscript{169} Again, initial Diels–Alder reaction with diene 339 and methylacrylate 340 delivered, after a few further transformations, bicycle 341. When 341 was treated with KH an aza-Cope rearrangement occurred, thus providing enamine derivative 342 after quenching the reaction with methylvchloroformate. After introduction of a bromine substituent, reaction of the enamine with CF\textsubscript{3}CO\textsubscript{2}H triggered a Mannich reaction via intermediate iminium ion 343 to generate tricycle 344. This ketone was then converted into enol ether 345. By employing a phosphine ligand free Heck protocol previously developed by Overman, oxindole 346 was accessed. Unlike in the synthesis reported by Speckamp, this transformation produced the undesired stereoisomer at the spiro-center. Therefore inversion of this stereocenter was needed later in the synthesis. First however, introduction of the C(17) substituent was achieved by

Scheme 67. Total synthesis of (±)-gelsemine by Overman and co-workers.

conversion of 346 into aziridine 347 followed by alkylation of the nitrogen and $S_N2$-type opening of the strained hetercyclic ring with cyanide. Removal of the acetal protecting group delivered alcohol 348. When 348 was treated with base, a retro-aldol/aldol sequence led to epimerization of the C(7) spiro-center, providing lactone 349 after aqueous workup. Racemic gelsemine (275) was accessed in two steps from this advanced intermediate.

Danishefsky reported a route which also relied on a divinylcyclopropane rearrangement to construct the carbocyclic core of gelsemine (275) (Scheme 68). The synthesis started with epoxide 350, which could be rearranged to cyclopropane aldehyde 351 using aluminum oxide. When aldehyde 351 was treated with phosphonate 352, olefination of the aldehyde took place immediately followed by the projected divinylcyclopropane rearrangement to provide diene 353. Conversion into oxetane 354 now allowed for closure of the pyrrolidine ring upon treatment of 354 with BF$_3$ etherate, generating alcohol 355. The quaternary oxindole stereocenter was set by Eschenmoser–Claisen rearrangement of allylic alcohol 356. This transformation provided hydroquinoline 357, which needed further ring contraction to arrive at the oxindole motif of gelsemine.

![Scheme 68. Total synthesis of (±)-gelsemine by Danishefsky and co-workers.](image)

Recently, Qin and co-workers reported an enantioselective synthesis of (+)-gelsemine (275). The strategy involved condensation of N-methoxyoxindole 358 with aldehyde 359, prepared in 20 steps from D-diethyl tartrate, to provide 360 (Scheme 69). This intermediate was then treated with LDA to effect addition of the nitrile enolate to the 1,4-acceptor, generating pyrrolidine 361. After inversion of the C(6) stereocenter, the resulting acetal 362 was treated with $p$-toluenesulfonylic acid. Oxonium ion 363 subsequently underwent ring closure to form hydropyran 364. This transformation parallels the

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epimerization step of the Overman synthesis. Conversion into the natural product (+)-gelsemine was then be achieved in 3 steps from 364. Although the authors suggest a biosynthetic pathway toward gelsemine, which parallels their strategy, no evidence whatsoever supports such a claim.

7.5.2. Total Synthesis of (+)-Koumine and (+)-Koumidine by Magnus

In 1990, Magnus reported a biomimetic approach to the gelsemium alkaloids koumidine and koumine. Indole derivative 365 could be accessed from natural L-tryptophan 366 in 13 steps (Scheme 70). Michael addition of the ketone enolate to the electron deficient alkyne delivered pentacycle 367 as a 5:1 mixture of E/Z double bond isomers. The minor Z-isomer of 367 could be converted into (+)-koumidine (269) by olefination of the ketone, followed by hydroboration/oxidation,

Scheme 70. Total synthesis of (+)-koumidine and (+)-koumine by Magnus and co-workers.

to introduce the primary alcohol. The access route to (+)-koumine involved a similar transformation of (E)-367 into allylic alcohol 368. Activation of the tertiary amine using methylchloroformate induced cleavage of the C(3)–N bond and generation of iminium intermediate 369. Intramolecular trapping by the adjacent primary alcohol produced hydropyran 370. The koumidine skeleton was accessed by displacement of the allylic alcohol in 371 under Mitsunobu conditions, delivering (+)-koumine (270) in 40% yield.

7.5.3. Total Synthesis of (–)-Koumidine by Cook

An alternative approach to (–)-koumidine (269) was reported by Cook (Scheme 71).\textsuperscript{173} The synthesis started with vinyliodide 372 prepared from D-tryptophan by a similar route as intermediate 365 in the Magnus route. Palladium catalyzed ketone vinylation delivered alkene 373 with complete retention of the double bond configuration. Intermediate 373 could be easily converted into (–)-koumidine (269), the natural enantiomer of this natural product.

\textbf{Scheme 71.} Cook’s approach to (–)-koumidine.

7.5.4. Total Synthesis of (+)-Gelsedine by Hiemstra

The only total synthesis of the gelsemium alkaloid gelsedine (273) to date was reported by Hiemstra and co-workers in 1999.\textsuperscript{174} This approach relied on a novel allene-terminated acyliminium cyclization of precursor 374, which was obtained in 5 steps from (S)-malic acid 375 (Scheme 72). Treatment of allene 374 with formic acid in the presence of sodium iodide produces bicycle 376 via iminium intermediate 377. Conversion into amide 378 now allowed for closure of the oxindole ring by a Heck reaction, again using Overman’s protocol,\textsuperscript{162} generating 379. This intermediate was elaborated into the natural product (+)-gelsedine (273) by a sequence including oxymercuration for hydropyran closure and installation of the ethyl appendage.

7.5.5. First Total Synthesis of (–)-Gelsemoxonine by Fukuyama

The first total synthesis of (–)-gelsemoxonine (278) was reported by Fukuyama in 2011, again relying on the divinylcyclopropane rearrangement previously employed as a key step in the synthesis of gelsemine. Enantioenriched acetate 380 was prepared in >99% enantiomeric excess by dynamic kinetic resolution of 381 (Scheme 73). Intermediate 380 was then further converted into oxindole 382 by cyclopropanation, acetal reduction and olefination to introduce the oxindole moiety. When this substrate was heated to 70 °C, divinylcyclopropane rearrangement gave tetracycle 383. Construction of the azetidine ring, a particular feature of gelsemoxonine, proved particularly challenging. Initially, isomerization of enal 384 produced ester 385 through a protocol involving formation of enol ether 386.

Scheme 73. Total synthesis of (–)-gelsemoxonine (278) by Fukuyama and co-workers.

and trapping of the resulting acylcyanide with allyl alcohol. Conversion into acid 387 was followed by a Curtius rearrangement to produce carbamate 388. The ethyl ketone substituent of the natural product was then introduced by initial synthesis of enamine 389 followed by treatment with Vilsmeyer reagent to produce chloraldehyde 390. Addition of the ethyl substituent and epoxidation of the unsaturated carbonyl system delivered intermediate 391. Azetidine ring formation could now be effected through a biomimetic transformation involving opening of the epoxide in 391 by a primary amine at C(5), thus producing (−)-gelsemoxonine (278).

7.6. Azetidines in Natural Products and Bioactive Compounds

In contrast to oxetanes, the corresponding nitrogen containing counterparts, the azetidines, are only rarely found in natural products. However, the rare examples of the azacyclobutane structural motifs are distributed over many secondary metabolite classes including alkaloids, terpenes or peptides. A representative set of azetidine containing alkaloids is given in Figure 13. In 1955, azetidine-2-
carboxylic azid (392) was isolated from a plant source as the first natural azetidine.\textsuperscript{177} Later it was discovered that this amino acid is incorporated into other natural products such as mugineic acid (393).\textsuperscript{178} More recently, larger azetidine containing peptides have been isolated, such as vioprolide A (394) and C (395).\textsuperscript{179} The polyoxine family of natural products incorporates an alternative azacyclobutane amino acid derivative as shown for polyoxin A (396).\textsuperscript{180} Penaresidin A (397) and B (398) were isolated from marine sponges and were proposed to be derived from sphingosine lipids.\textsuperscript{181} Azetidine rings are also found in a number of alkaloids with a highly complex overall structure. Okaramine B (399) is an indole alkaloid isolated from \textit{Penicillium simplicissimum} with potent insecticidal activity.\textsuperscript{182} The hexacyclic natural product calydaphninone (400) was isolated as a novel and unprecedented \textit{Daphniphyllum} alkaloid.\textsuperscript{183} Gelsemoxonine (278) represents another of these highly functionalized azetidine alkaloids. The biosynthetic formation of the azetidine rings in the aforementioned natural products is often not known and likely to be very different for each compound.

Besides the occurrence of azetidines in various natural products, this structural element has found widespread application in bioactive compounds and pharmaceuticals (Figure 14). Azelnidipine (401) is a potent calcium channel blocker and can be used for the treatment of hypertension.\textsuperscript{184} The β-lactam antibiotic tebipenem pivoxil (402) is marketed by \textit{Pfizer} in Japan. Another example of an azetidine containing bioactive substance is ABT-594 (403), which was identified in a screening program as a ligand of the nicotinic acetylcholine receptors.\textsuperscript{185} It has been shown, that this compound exhibits strong analgesic activity, surpassing well known opioids.\textsuperscript{186}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{bioactive_substances_401_402_403}
\caption{Bioactive substances incorporating an azetidine ring.}
\end{figure}

7.7. Chemical Synthesis of Azetidines

The chemical preparation of azetidines has been extensively investigated. This chapter summarizes the most common approaches for the synthesis of azacyclobutanes.

7.7.1. Ring Closure by Carbon–Nitrogen Bond Formation

The most widely used strategy for azetidine synthesis involves intramolecular nucleophilic displacement of a leaving group by a nitrogen in γ-position (Scheme 74, equation 1). Commonly employed leaving groups include halides, activated alcohols or epoxides. Similarly, azetidines can be accessed by double alkylation of a primary amine with a 1,3-dihalopropane derivate (eq. 2). Furthermore, cyclization of an amine to a double bond is possible by various modes of activation including formation of a halonium intermediate or activation by a metal species like palladium(0) (eq. 3). An alternative strategy relies on N–H bond insertion by a carbene species generated from a diazocarbonyl precursor (eq. 4).

Scheme 74. Preparation of azetidines by nitrogen-carbon bond formation.


7.7.2. Ring Closure by Carbon-Carbon Bond Formation

A less investigated strategy involves the formation of a carbon–carbon bond. This can be brought about through intramolecular displacement of a leaving group by a carbon nucleophile (Scheme 75, equation 1). Besides the use of halides and activated alcohols,\textsuperscript{190} 1,4-acceptors can also serve as the electrophilic functionality.\textsuperscript{191} Fused azetidine rings have also been obtained through irradiation of dihydropyridines (eq. 2).\textsuperscript{192} The highly strained double bond can be used for further functionalization. Another photochemical approach involves Norrish type II reaction of α-amino ketones (eq. 3).\textsuperscript{193} Upon irradiation, a diradical is generated, enabling hydrogen abstraction at a nitrogen substituent (not shown). Subsequent radical recombination gives rise to an azetidine product.

\begin{equation}
\begin{align*}
\text{X} & \quad \text{N} \quad \text{EWG} \\
\text{R} & \quad \text{N} \quad \text{EWG} \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{N} \quad \text{CO}_2\text{Me} & \quad \text{hv} \quad \text{[O]} \\
\text{N} \quad \text{CO}_2\text{Me} & \quad \text{RO}_2\text{C} \\
\text{R}_1 \quad \text{N} \quad \text{R}_2 & \quad \text{RO}_2\text{C} \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{R}_1 \quad \text{N} \quad \text{R}_2 & \quad \text{hv} \\
\text{R}_1 \quad \text{N} \quad \text{R}_2 & \quad \text{R}_2' \quad \text{OH} \\
\end{align*}
\end{equation}

\textbf{Scheme 75}. Preparation of azetidines by carbon–carbon bond formation.


\textsuperscript{191} Carlin-Sinclair, A.; Couty, F.; Rabasso, N. \textit{Synlett} \textbf{2003}, 726-728.

\textsuperscript{192} Krow, G.R.; Cannon, K.C. \textit{Heterocycles} \textbf{2004}, \textit{64}, 577-603.

7.7.3. Cycloaddition Reactions for Azetidine Formation

A few cycloaddition reactions have been reported for the construction of azetidine rings (Scheme 76). Allenyl esters can be treated with tertiary amines like DABCO in the presence of tosylimines to obtain a four membered ring product \textit{via} a stepwise ring closure (eq. 1).\textsuperscript{194} Another approach involves addition of an allyl silane to tosylimines (eq. 2).\textsuperscript{195} Trapping of an intermediate carbocation again leads to formation of an azacyclobutane.

\begin{equation}
\text{Scheme 76. Preparation of azetidines through cycloadditions.}
\end{equation}

Attracted by the unusual structure of gelsemoxonine, as well as the medicinal relevance associated with gelsemium alkaloids, and in particular with the gelsedine subclass, we decided to initiate a program aimed for the total synthesis of gelsemoxonine. Notably, despite the close biogenetic relationship between the gelsemium alkaloids, the core skeletons of these natural products differ significantly (Figure 15). As a consequence, synthetic approaches towards a new gelsemium alkaloid can only scarcely rely on previous studies conducted on other members of the gelsemium family. This fact offered additional opportunities for the discovery and exploration of novel strategies as well as reactions in the total synthesis of this fascinating natural product class.

The structure of gelsemoxonine (278) incorporates a dense array of functional groups including a secondary alcohol, a ketone, a secondary amine and a hydropyran ring, as well as an oxindole motif with a methoxy substituent on the amide nitrogen (Scheme 77, top). These functionalities are arranged as six contiguous stereocenters in a highly compact pentacyclic core. The most remarkable feature of gelsemoxonine is the azetidine ring, which is completely embedded in this framework. This azacyclo-
butane induces a severe strain on the whole system. Additional synthetic challenges include a quaternary stereocenter at the spiro-fused oxindole ring, as well as the fully substituted C(15) carbon, which forms part of the azetidine.

Our retrosynthetic analysis of gelsemoxonine initially focused on the construction of the densely functionalized carbon framework. However, the strain induced by the azetidine motif and the associated compactness of the pentacyclic gelsemoxonine core would render introduction of any substituent on the fully assembled ring system highly challenging. To address this constraint, we opted for the introduction of this ring strain at a late stage of the synthesis. Two possible strategies were considered as a means to implement this plan (Scheme 77, bottom). The first strategy involved retrosynthetic cleavage of the C(3)–C(7) bond of the natural product, leading back to a putative oxonium intermediate 404 (strategy A in Scheme 77). The nucleophilic character at C(7) could thereby be exploited to induce a ring closure by attack of an oxindole enolate onto the C(3) carbonyl. An alternative disconnection along the C(6)–C(7) bond would lead back to oxindole enolate 405. In this case, a C(7) nucleophile could displace a leaving group at C(6) to effect closure of the seven membered carbocycle.

In a model study, Kende and co-workers reported the implementation of an oxonium cyclization strategy for construction of the core of gelsedine (273) (Scheme 78). In the event, treatment of acetal 406 with a 1:1 mixture of TFAA and TFA produced hydropyran 407 in 53% yield. The product was obtained as a single diastereomer with the undesired (R) configuration at C(7), which was explained by oxonium intermediates 408 and 409. The authors surmised that steric repulsion between the pyrrolidine fragment and the oxindole ring in intermediate 408 (red arrow) renders this conformation less favored. However, cyclization can occur from conformer 409, accounting for the exclusive generation of 407.

Inspired by this report, we undertook molecular modeling studies on our projected intermediate 404. The analysis suggested that the azetidine alters the conformation of the ring system compared to the Kende model substrate, thus favoring formation of the desired (S)-conformer. This notion is exemplified by the two conformers depicted in Figure 16. In this case, the pre-(S)-conformer of oxonium species 410 seems preferred over pre-(R)-410 which suffers from steric repulsion between
the arene ring and the azetidine (as indicate by the arrow in Figure 16). Moreover, this repulsion forces the two reactive centers at C(3) and C(7) in pre-(R) 410 away from each other.\textsuperscript{196}

![Figure 16. Molecular models of possible conformers for oxonium species 410.](image)

In order to enable evaluation of both late stage strategies for construction of the seven membered carbocycle in gelsemoxonine, an efficient access to both intermediates 404 and 405 was required. To this end, we opted to establish a common precursor for the synthesis of these intermediates (Scheme 79). Such a universal strategy would have to account for differential functionalization at C(3) and C(6) of 404 and 405. For the introduction of the C(3) substituent we envisioned an approach involving C–H functionalization of an advanced intermediate. This could either be implemented on intermediate 411 by C–H oxidation at C(3) next to the ether bridge; a position well suited for facile C–H cleavage.\textsuperscript{197} Alternatively, the hydroxyl group at C(14) could serve as a handle for a directed oxidation of the adjacent methylene group in 412. For either strategy, we envisioned introduction of the C(6) substituent on a β-lactam precursor 413. Although azetidinones have been previously employed as precursors for the construction of saturated azacyclobutanes,\textsuperscript{198} application of such a strategy in the context of natural product total synthesis has not been investigated to date. Moreover, the high degree of functionalization on our projected β-lactam 413 would pose a delicate challenge for the implementation of such an approach.

![Scheme 79. Synthetic strategy for accessing 404 or 405 from a β-lactam presursor 413.](image)

\textsuperscript{196} After we had initiated our synthetic studies towards gelsemoxonine, a total synthesis of gelsemine employing a similar oxonium cyclization strategy was reported (ref. 171; section 7.5.1.).

\textsuperscript{197} For a discussion of C–H oxidation selectivity see section 9.3.

The synthesis of β-lactams has been extensively investigated due to their relevance in medicinal chemistry and as useful building blocks for organic synthesis.\(^{199}\) A schematic overview of the most common methods for azetidinone construction is given in Scheme 80. The traditional approaches include cycloaddition reactions as well as cyclizations of acyclic precursors. However, all of these strategies suffer from serious limitations when applied to the synthesis of highly functionalized β-lactams. These drawbacks include tedious preparation of cyclization precursors, limited substrate scope and, most importantly, the inability of many methods to construct the fully substituted C(15) carbon found in gelsemoxonine (indicated with red H’s in Scheme 80).

Scheme 80. Commonly employed methods for the construction of β-lactams.

In 2000, Cordero and Brandi reported an intriguing transformation for the synthesis of azetidinones (Scheme 81).\(^{200}\) The authors discovered that treatment of N-alkylated spirocyclopropane

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isoxazolidines 414 with protic acids induces a ring contraction to form β-lactam products 415. It was speculated that the reaction proceed under the extrusion of ethylene gas as a remnant of the cyclopropane ring.201

Scheme 81. Acid mediated ring contraction of spirocyclopropane isoxazolidines.

Although, the original report only included a few substrates, such as 416, with almost no functional groups present, we were curious if this unprecedented transformation could prove useful for the synthesis of our key β-lactam intermediate 413. Application of such a tactic for the formation of 413 would require isoxazolidine 418 as a cyclization precursor (Scheme 82). Construction of the fully substituted C(15) stereocenter was planned to be achieved through addition of a suitable nucleophile to oxime ether 419. Such a strategy would allow for the straightforward construction of the hydropyran ring present in the natural product by a nitrile oxide dipolar cycloaddition, starting from alkylidene cyclopropane 420.

Scheme 82. Synthetic strategy for the construction of key intermediate 413.

The subsequent chapters report on the successful implementation of this strategy leading to the total synthesis of gelsemoxonine (278).

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201 Although ethylene has never been detected, functionalization of the cyclopropane ring allowed for the isolation of the corresponding alkene derivative (ref. 200a).
9

Azetidine Construction and C(3) Functionalization Attempts

9.1. Spirocyclopropane Isoxazolidine Ring Contraction

The implementation of the synthetic strategy towards gelsemoxonine as outlined in the previous chapter entailed the initial construction of a suitably substituted alkylidencyclopropane starting material (chapter 8, Scheme 82). Any route to alkylidencyclopropanes such as allylic ether 421 has to meet with a number of synthetic challenges associated with this motif. For instance, the exocyclic double bond in 421 considerably enhances the strain associated with the cyclopropane ring. Based on experimental and computational studies, the strain energy of methylenecyclopropane has been estimated at 40.9 kcal/mol compared to 27.5 kcal/mol for the parent cyclopropane (29.8 kcal/mol for methylcyclopropane). This additional strain aggravates the difficulties associated with the construction of this ring and the introduction of the exocyclic double bond. Moreover, the increased reactivity of the olefin in 421 renders the system more prone to side reactions. Finally, the synthetic strategy towards 421 has to allow for the introduction of an ether functionality in the allylic position. To meet the aforementioned challenges, a variety of strategies were evaluated, as outlined in Figure 17.

![Figure 17. Strategies for the construction of alkylidencyclopropane 421.](image)

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A conventional approach to the alkylidenecyclopropane motif involves the olefination of carbonyl compounds 422 using phosphorous ylides204 such as 423, or related olefination reagents205 (Figure 17, route a). Alternatively, a Wittig reaction can be performed on the hemiacetal of cyclopropanone 424 using stabilized ylids such as 425 (route b).206 Another promising strategy to allylic ether 421 relies on the cyclopropanation of an allene such as 426, possibly using the allylic oxygen as a directing group (route c).207 The strained double bond in 421 could also be accessed by elimination of a leaving group208 or generation of an olefin from a bifunctionalized precursor 427, e.g. by Peterson olefination209 or thermal cyclorevision of a β-lactone210 (route d). An allylation approach using vinyl cyclopropanes 428 (X = OTs, OAc, Cl) and a variety of different nucleophiles, such as alkoxide 429, has also been reported (route e).211 A strategy involving closure of the cyclopropane ring after formation of the double bond could proceed from alkylmetal intermediates such as 430 (route f).212 Another powerful approach to alkylidenecyclopropanes is the isomerization of cyclopropene derivates 431 (route g).213 This route relies on the release of ring strain during the isomerization process (strain entropy of methylocyclopropene: 58.2 kcal/mol202a). Finally, a methylenecyclopropane rearrangement could be exploited to convert a methylenecyclopropane precursor 432 into an alkylidenecyclopropane product (route h).214

Several of the approaches presented above were investigated for the synthesis of 421.215 Most of these strategies suffered from low yields and competing side reactions, most likely as a result of the reactive alkylidenecyclopropane moiety in the product. We then turned our attention to the synthesis of two known building blocks 433 and 434, which could serve as an entry point for the construction of our projected starting material 421. As outlined in Scheme 83, both intermediates can be accessed starting from cyclopropanone hemiacetal 435. This compound was readily prepared by

215 Details not shown.
treatment of ethyl 3-chloropropionate 436 (commercially available or easily prepared from ethyl acrylate 437) with finely dispersed sodium metal in the presence of TMSCl.\textsuperscript{216} The silyl ether product 438 could be obtained in good yield on a 130 g scale.\textsuperscript{217} TMS deprotection using a catalytic amount of hydrochloric acid produced hemiacetal 435, which was easily purified on large scale by column chromatography and can be stored at -20 °C for several months. Allylic alcohol 433 was prepared from alcohol 435 by Wittig olefination using preformed ylide 439, followed by reduction of the intermediate ester 440.\textsuperscript{218,219} In addition to the low yield and poor scalability of the Wittig olefination, the volatility of allylic alcohol 433 presented a major drawback of this strategy. Alternatively, vinyl tosylate 434 was prepared by addition of vinyl Grignard to hemiactal 435,\textsuperscript{220} followed by tosylation of allylic alcohol 441 under optimized conditions. This protocol could be scaled up to allow convenient preparation of 100-200 g of 434.

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\begin{center}
\includegraphics[width=\textwidth]{scheme83.png}
\end{center}

Scheme 83. Synthesis of allylic alcohol 433 and vinyl tosylate 434 according to literature procedures.

Both building blocks were now evaluated as starting materials for the synthesis of a dipolar cycloaddition substrate. To this end, we envisioned introduction of a precursor functionality, which would allow for subsequent generation of a nitrile oxide, as postulated in our retrosynthetic plan. Nitrile oxides can be readily generated by oxidation of oximes or dehydration of nitroalkanes.\textsuperscript{221} Accordingly, we set out for the synthesis of dioxolane 442 by alkylation of allylic alcohol 433 with bromide 443 (Scheme 84). The desired product could indeed be obtained, albeit in very low yield. Alkylation attempts using other electrophiles were also met with failure.

\textsuperscript{217} Trimethylsilyl ether 438 is also commercially available from Aldrich or Acros Organics (735.- CHF/100 g).
\textsuperscript{219} Reduction of 440 was best performed using LiAlH\textsubscript{4}/AlCl\textsubscript{3} instead of DIBAL–H as reported in the literature.
We now turned our attention to a strategy involving formal $S_N2'$ addition of nucleophiles to vinyl tosylate 434. Salaün and de Meijere reported the allylic substitution of cyclopropanol derivatives like 434 using a Tsuji–Trost type protocol.\(^{211}\) We first tested addition of a sodium alkoxide species derived from nitroalcohol 444 to vinyl tosylate 434. When 434 was treated with Pd(dba)$_2$ and a premixed solution of sodium hydride and nitroalcohol 444 according to the reported procedure, alcohol 445 was obtained as the sole product in 45% yield (Scheme 84). In this instance, the $\alpha$-nitro carbon was preferentially deprotonated by sodium hydride and served as the nucleophile instead of the OH group. In order to circumvent this issue, dioxolane substituted sodium alkoxide 446\(^{222}\) was tested as nucleophile under identical conditions. To our delight, the desired allylic ether 442 could be isolated in excellent yield (82%).

![Scheme 84. Preparation of alkylidenecyclopropane 442.](image)

With allylic ether 442 in hand, we now turned to the elaboration of spirocyclopropane isoxazolidine 447 as precursor for the key ring contraction (Scheme 85). Direct conversion of 442 to oxime 448\(^{223}\) could be achieved by treatment of the dioxolane with hydroxylamine hydrochloride at elevated temperature.\(^{224}\) This protocol allowed to access the oxime without the generation of a potentially sensitive aldehyde intermediate.\(^{225}\) Subsequent dipolar cycloaddition was achieved by generating nitrile oxide intermediate 449 through treatment of 448 with bistrifluorobutyl oxide and tert-butyl hypochlorite\(^{226}\) to produce isoxazoline 450 in 64% yield.\(^{227}\) Various alternative protocols examined for the generation of nitrile oxide 449, such as NCS, Chloramine-T or diacetoxyiodobenzene, produced isoxazoline 450 in significantly lower yield. We now faced the task of introducing a surrogate for the ethylketone motif of the natural product. To this end, addition of an organometallic nucleophile to the electrophilic oxime ether carbon in 450 was investigated.

\(^{222}\) The corresponding alcohol was prepared in four steps from 1,3-propanediol.
\(^{223}\) 448 was obtained as an inconsequential mixture of oxime $E/Z$ isomers.
\(^{225}\) Attempted hydrolysis of dioxolane 442 under various acidic conditions indeed proved troublesome generating the desired aldehyde product only in low yield.
Traditionally, addition reactions to oxime ethers have proven challenging due to their low reactivity towards nucleophiles. Addressing this problem, Uno and Suzuki developed a protocol for the addition of organolithium derivatives to isoxazolines facilitated through activation of the imine by a Lewis acid.\(^{228}\) According to this procedure, isoxazoline \(450\) was treated with freshly prepared isoprenyllithium \(451\)\(^{229}\) in the presence of borontrifluoride etherate. In the event, the expected isoxazolidine \(447\) was produced in moderate yield and as a single diastereomer. This outcome indicates exclusive attack of the organolithium species from the convex face of bicyclic system \(452\). This selectivity is remarkable, as molecular models of \(452\) suggest an almost planar arrangement of the two rings. The terminal double bond in \(447\) could later serve as a handle to introduce the ketone functionality of the natural product by oxidative cleavage of this olefin. Despite the low yield of isoprenyl lithium addition, the concise route to contraction precursor \(447\) allowed for preparation of considerable quantities of this key intermediate.

With an efficient route to \(447\) secured, we now set out to test the key ring contraction to obtain the envisioned \(\beta\)-lactam intermediate. In the original report, \(N\)-alkyl substituted isoxazolidines were employed as the exclusive substrates.\(^{200}\) Accordingly, we prepared benzylamine \(453\) by alkylation of \(454\) as outlined in Scheme 86.\(^{230}\) When \(453\) was treated with equimolar amounts of \(p\)-toluenesulfonic acid according to the standard protocol, a single product was obtained. 2D NMR spectroscopic analysis of this product confirmed the formation of \(\beta\)-lactam \(455\) in 81% yield.

Scheme 85. Preparation of ring contraction precursor \(447\).

Scheme 86. Ring contraction of \(\text{N-benzyl spirocyclopropane isoxazolidine 453.}\)


\(^{229}\) \(451\) was prepared by addition of \(t\)-BuLi to 2-bromo-1-butene in \(\text{Et}_2\text{O}\).

\(^{230}\) Truncated isoxazolidine \(454\) had been prepared in the course of test reactions for addition of nucleophiles to isoxazoline \(450\). Its preparation was carried out in analogy to \(447\) by addition of isopropenyl lithium to \(450\).
Motivated by this result, we were curious if the reaction would proceed without a protecting group on the nitrogen. To this end, isoxazolidine 447 was treated with a number of different acids as outlined in Table 11.

When \( p \)-TsOH was used as the acid promoter, the desired unprotected \( \beta \)-lactam 456 was obtained in 39% yield (entry 1). Trifluoroacetic acid (TFA) produced the desired product in an excellent yield of 70% (entry 2). However, when the same reaction was conducted in refluxing toluene (110°C), the reaction produced a decompounding of the starting material completely decomposed (entry 3). A selection of acids with similar pK\(_a\) values to CF\(_3\)CO\(_2\)H were examined, but no further improvement of the yield could be achieved (entries 4-7).

Interestingly, when triflic acid was used, rearranged product 457 was obtained (entry 4). As outlined in Scheme 87, the formation of this product could be explained by two alternative mechanistic sequences. One rationale involves initial ring contraction to give \( \beta \)-lactam 456, followed by

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Yield of 456</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( p )-TsOH</td>
<td>39%</td>
</tr>
<tr>
<td>2(^{[b]})</td>
<td>CF(_3)CO(_2)H</td>
<td>70%</td>
</tr>
<tr>
<td>3(^{[c]})</td>
<td>CF(_3)CO(_2)H</td>
<td>decomp.</td>
</tr>
<tr>
<td>4</td>
<td>TIOH</td>
<td>20-30% of 457(^{[d]})</td>
</tr>
<tr>
<td>5</td>
<td>CCl(_3)CO(_2)H</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>MsOH</td>
<td>46%</td>
</tr>
<tr>
<td>7</td>
<td>2-chloropyridine-HCl</td>
<td>35%</td>
</tr>
</tbody>
</table>

[a] Conditions: acid (1.0 equiv.), MeCN, reflux, 6 h; \(^{[b]}\) 1.5 equiv. of acid; \(^{[c]}\) reaction conducted in refluxing toluene; \(^{[d]}\) see Scheme 87 for a mechanistic explanation; decomp. = decomposition.

Scheme 87. Mechanistic rationale for the reaction of isoxazolidine 447 to form 457.
protonation of the terminal double bond in 456. The resulting carbocation 458 could then rearrange through a [1,2]-shift of the C(15)-nitrogen substituent to produce 459. Subsequent loss of a proton then produces lactam 457. Alternatively, isoxazolidine 447 could first undergo nitrogen migration via carbocations 460 and 461 and ring contraction from intermediate 462 would also produce 457.

9.2. Introduction of the C(6) Methylene Substituent

After successful construction of β-lactam 456, introduction of the C(6) carbon by C1-extension at the lactam carbonyl group was required. Our objective was for the heterocyclic ring to remain intact during modification at the carbonyl group. This represented a substantial challenge considering the tendency of β-lactam rings to open readily when treated with nucleophiles. This reactivity can be explained by the severe ring strain associated with this motif. Moreover, only very few reactions manipulating the carbonyl group in β-lactams in order to obtain azetidine products have been reported in the literature. However, these transformations are generally limited to reductions by hydride reagents. Introduction of a carbon substituent adjacent to the nitrogen remained largely unexplored and would necessitate the development of a novel strategy. Scheme 88 presents the three approaches we investigated to achieve this goal.

Amide carbonyls are known to participate in olefination reactions. Thus, olefination of β-lactam 463 could produce highly strained enamine product 464 (Scheme 88, equation 1). Subsequent reductive modification of the double bond would then generate the desired azetidine motif. As depicted in equation 2, the β-lactam carbonyl group might be susceptible to a Corey–Chaykovsky epoxidation furnishing spiro-cycle 465, as the conjugation between the carbonyl and the nitrogen is hampered due to the ring geometry thus reducing the amide double bond character. In this context, the epoxidation of twisted amides has recently been reported. A third approach would exploit the enhanced nucleophilicity of a thiolactam derivative 466 (equation 3). Thioamides can participate in a

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231 A similar, but probably mechanistically different base mediated ring expansion of β-lactams has been observed: a) Alcaide, B.; Domínguez, G.; Martín-Domenech, A.; Plumet, J.; Monge, A.; Pérez-García, V. *Heterocycles* 1987, 26, 1461-1466; b) Alcaide, B.; Domínguez, G.; Martín-Domenech, A.; Martín, I.; Cativiela, C.; Mayoral, J.A.; Plumet, J. *Heterocycles* 1989, 29, 719-727.

232 An aziridinium intermediate could account for such a [1,2]-shift.


235 Reduced amide resonance character in β-lactams has been postulated based on computational studies: Glover, S.A.; Rossner, A.A. *J. Org. Chem.* 2012, 77, 5492-5502.

diverse set of transformations involving radical\textsuperscript{237} or carbene\textsuperscript{238} intermediates or addition of organometallic reagents\textsuperscript{239}. This would offer an alternative set of potential reaction pathways to access azetidine derivatives similar to 464. The strategies described were evaluated on azetidinone derivative 456 as outlined in Scheme 89.

Scheme 89. Attempts for the installation of the C(6) methylene substituent.

The olefination of azetidinones using dimethyltitanocene (Petasis reagent) has been investigated previously.\textsuperscript{240} It was observed that proper choice of the nitrogen protecting group is of crucial importance to ensure stability of the resulting enamine product. According to these reports, we converted lactam 456 into Boc carbamate 467. Treatment of 467 under Petasis olefination


delivered desired enecarbamate 468 in excellent yield. The electron-withdrawing substituent on the nitrogen rendered this intermediate stable enough to allow chromatographic purification. However, upon standing at ambient temperature, we observed slow hydrolysis of the strained heterocyclic ring to ketocarbamate 469.

In addition to the methyl substituted olefination reagent, Petasis and co-workers also reported the preparation of various titanocene derivatives including dibenzyltitanocene, allowing for the introduction of an aryl substituent in the product. This offered the possibility of the direct installation of an indole substituent at C(6), complementing the substitution pattern of gelsemoxonine. Preparation of titanocene derivative 470 was therefore envisioned. The synthesis of 470 would hence entail initial preparation of indole 471 incorporating a prefunctionalyzed C(3)-methyl group. Attempted synthesis of various derivatives of 471 resulted in decomposition of the respective starting material. This can most likely be explained by the system’s propensity to eliminate leaving groups at the C(3) methyl group furnishing imine 472, which further suffers from decomposition.

![Scheme 90](image)

Scheme 90. Projected indole Petasis reagent 470 (left) and proposed decomposition of substituted 3-methylindole derivative 471 (right).

Additional experiments were performed to implement alternative carbonyl functionalization strategies (Scheme 89). Treatment of imide 467 with the Corey–Chaykovsky reagent did not lead to the production of epoxide 473 but resulted in complete decomposition of the starting material. Next, thiolactam 474 was prepared by treatment of 467 with Lawesson’s reagent. However, subsequent reaction with the rhodium carbenoid derived from imine 475 did not result in the formation of desired product 476.

Due to our ability to directly install a substituted C(6) methylene group at the carbonyl functionality, we opted for functionalization of enecarbamate intermediate 468. Such a transformation would necessitate concerted reduction at C(5), along with concurrent manipulation at C(6). Hydroboration of olefin 468 would meet these requirements. As depicted in Scheme 91,

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244 Hydroboration of terminal enamine derivatives has been reported before. For a few examples, see: a) Borowitz, I.J.; Williams, G.J. J. Org. Chem. 1967, 32, 4157-4160. a) Tanaka, K.; Maesoba, T.; Sawanishi, H.
hydroboration of heteroatom substituted double bonds (477) can be accompanied by an undesired elimination involving the heteroatom substituent.\textsuperscript{246} Thereby, fragmentation of alkylborane intermediate 478 produces another olefin 479, which reacts further to provide product 480. This side reaction can be largely avoided by the use of 9-BBN as hydroborating agent. Moreover, under these conditions a number of sensitive functional groups are well tolerated.\textsuperscript{246,247}

\begin{center}
\begin{tikzpicture}

\node at (-1.5,0) {477}; \node at (0.8,0) {478}; \node at (2.8,0) {479}; \node at (5.2,0) {480};
\node at (0.7,-0.2) {$R_B-H$}; \node at (2.3,-0.2) {$HBR_2$}; \node at (4.7,-0.2) {$R_B-H$};
\node at (1.8,-0.5) {$X = O, NR$}; \node at (3.8,-0.5) {$X = H$};
\node at (0.4,-1.5) {Scheme 91. Competing side reaction in the hydroboration of heteroatom substituted double bonds.}
\end{tikzpicture}
\end{center}

This approach was applied to enecarbamate 468 as outlined in Scheme 92. Treatment of 468 with crystalline 9-BBN dimer\textsuperscript{248} resulted in clean conversion to a single intermediate as indicated by TLC analysis of the reaction.\textsuperscript{249} Subsequent oxidative workup using H\textsubscript{2}O\textsubscript{2} and 3M NaOH resulted in exclusive formation of primary alcohol 481 as a single diastereomer in 69\% yield. Analysis of 481 by steady state NOE experiments suggested that the newly formed stereocenter at C(5) exhibited the

\begin{center}
\begin{tikzpicture}

\node at (-5.2,0) {468}; \node at (-2,0) {469}; \node at (0,0) {481}; \node at (2,0) {482}; \node at (4,0) {483}; \node at (6,0) {484}; \node at (8,0) {485}; \node at (10,0) {486};
\node at (-1.8,-1.5) {Scheme 92. Hydroboration of enecarbamate 468.}
\end{tikzpicture}
\end{center}

\textsuperscript{248}Good quality of 9-BBN proved essential to achieve full consumption of the starting material. Therefore, only crystalline reagent was used and not the commercially available THF solution.
\textsuperscript{249}Attempted isolation of this intermediate by column chromatography over SiO\textsubscript{2} resulted in decomposition of the compound.
desired configuration as shown in Scheme 92.\textsuperscript{250} This outcome can be explained by exclusive attack of the hydroborating agent from the \textit{exo} face of the enecarbamate double bond as shown for transition state \textit{482}.

In order to exploit this selective hydroboration reaction for the direct introduction of an indole or oxindole substituent at C(6), we attempted to intercept the alkylborane intermediate in an alternative fashion. Alkylboranes are well known to undergo Suzuki–Miyaura cross coupling reactions with arylhalide derivatives.\textsuperscript{251} Accordingly, we subjected enecarbamate \textit{468} to the previously established hydroboration conditions, followed by treatment of the crude alkylborane intermediate with Pd(II) in the presence of 3-iodoindole \textit{483}. Unfortunately, none of the desired product \textit{484} could be isolated. Control experiments revealed that arylhalide \textit{483} is a very poor coupling partner in Suzuki cross coupling reactions.\textsuperscript{252} Alternatively, we decided to investigate addition of a radical species derived from an alkylborane intermediate to isatin \textit{485}.\textsuperscript{253} When a solution of alkylborane derived from \textit{468} was irradiated with UV light in the presence of isatin \textit{483}, no formation of product \textit{486} was observed and the alkyl borane intermediate slowly decomposed.

Investigations towards introduction of an oxindole substituent at C(6) in primary alcohol \textit{481} were undertaken next (Scheme 93). Conversion of the hydroxyl group into a leaving group might allow for an \textit{S}_2\textit{2}-type substitution reaction with an oxindole nucleophile.\textsuperscript{254} To this end, alcohol \textit{481} was readily converted into mesylate \textit{487} using MsCl and triethylamine. Attempted substitution reactions under

\begin{center}
\includegraphics[width=\textwidth]{Scheme93.png}

\textbf{Scheme 93. Attempted substitution of alcohol 481.}
\end{center}

\textsuperscript{250} At a later stage of the synthesis, detailed NOE analysis of derivative \textit{498} confirmed this assignment (\textit{vide infra}).
\textsuperscript{252} Coupling of aryliodide \textit{483} with phenylboronic acid delivered only 25\% of the desired product.
\textsuperscript{253} Radical additions of organoboranes to isatine derivatives were reported previously: Miyabe, H. \textit{Synthesis}, \textbf{2012}, 1709-1724.
\textsuperscript{254} Oxindole enolates are commonly alkylated by a variety of electrophiles including alkylbromides or alkylmesylates.
various conditions with either oxindole 358 or iodide as nucleophile failed to produce any of the desired products 488 or 489, respectively. The starting material was reisolated unchanged in all cases. Application of Appel conditions (PPh₃, I₂) to alcohol 481 did not provide any of the desired iodide 489. The pronounced lack of reactivity of C(6) leaving groups towards substitution is most likely due to the conformational preferences of the system. As shown for 490 (box), attack of any nucleophile to C(6) has to occur from the concave face of the ring system as the bulky C(6) substituent is forced to point outwards. However, this angle of attack is blocked by the nearby pyran ring.

We next set out to oxidize alcohol 481 to the corresponding aldehyde 491, as shown in Scheme 94. A carbonyl functionality would allow for attack from the two faces of the C=O double bond. Moreover, the Bürgi–Dunitz trajectory for attack on a carbonyl group (107°) is tilted with respect to an S_N2 angle of attack (180°) (Scheme 94, box). Thus, aldehyde 491 was prepared in 89% by Dess–Martin periodinane oxidation of alcohol 481.

![Scheme 94. Synthesis of aldehyde 491.](image)

Detailed 1D NMR spectroscopic analysis of aldehyde 491 revealed a 1:1 splitting of most peaks in the ¹³C and ¹H NMR spectra, which could not be explained by dipolar coupling (Figure 18 for the ¹H NMR spectrum). Two possible explanations could be given to account for this phenomenon. α-Amino

![Figure 18. ¹H NMR spectrum of 491 with splitting of several proton signals (J₁,₃ coupling indicated).](image)

aldehydes are often configurationally unstable. Thus, aldehyde 491 could undergo epimerization at the C(5) stereocenter during the oxidation reaction, resulting in a 1:1 mixture of product diastereomers. Alternatively, the Boc protecting group on the nitrogen could induce the formation of rotamers in the NMR spectrum of 491. To clearly distinguish between these two options, high temperature NMR experiments were conducted with aldehyde 491 as shown in Figure 19.

When a solution of aldehyde 491 in d_6-DMSO was slowly heated, broadening of all proton signals was observed (Figure 19, 50 °C). After heating to 100 °C sharp peaks appeared, which did not show the initial splitting anymore. After cooling the NMR solution back to ambient temperature, the original spectrum was obtained again. This clearly indicates the presence of rotameric species at ambient temperature. Notably, formation of rotamers was observed throughout the synthesis, as long as a Boc protecting group was present on the azetidine nitrogen.\(^{258}\)

We next turned our attention to the addition of oxindole nucleophiles to aldehyde 491. A variety of oxindole derivatives were tested for this purpose as shown in Scheme 95. Treatment of 491 with boron enolate 492\(^{158c}\) or lithium enolate 493, respectively, resulted in the formation of complex product mixtures. None of the desired secondary alcohol 494 could be isolated. Attempted Horner–Wadsworth–Emmons olefination using phosphonate 495 did not provide the desired product either.

Next, aryllithium species 496 was prepared through halogen-lithium exchange on the corresponding 3-iodoindole. Addition of a solution of 496 to aldehyde 491 at -78 °C resulted in the formation of two isomeric products. Closer spectroscopic analysis revealed that aryllithium reagent 496 had indeed

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\(^{258}\) As discussed later, removal of the Boc group resulted in products which did not exhibit rotamers in their NMR spectra anymore.
added to the aldehyde but with scrambling of the lithiation site to produce C(3) as well as C(2) indole linked products.\textsuperscript{259} Lithium migration can be explained by a directing effect of the \textit{N}-methoxy substituent, which favors C(2)-lithiated isomer \textit{497} (Scheme 95, box).\textsuperscript{255b}

**Scheme 95.** Oxindole nucleophiles tested for addition to aldehyde \textit{491}.

We reasoned that the harsh conditions (strong bases) used for the previously described addition reactions might be incompatible with a secondary alcohol product like \textit{494}. We were thus looking for milder protocols to effect an aldol type condensation of oxindole \textit{358} with our aldehyde substrate. Evans and co-workers recently reported a magnesium halide catalyzed \textit{anti}-aldol reaction between chiral acyloxazolidinones and a variety of different aldehydes.\textsuperscript{260} The mild reaction conditions of this transformation motivated us to apply this reaction to our system. Accordingly, aldehyde \textit{491} was treated with a premixed suspension of MgBr\textsubscript{2}, TMSCl, triethylamine and oxindole \textit{358} (Scheme 96). Within a few minutes, a 5:1 mixture of alkene products \textit{498} and \textit{499} was cleanly formed in an excellent yield of 83%. Only a small amount (<5%) of TMS ether \textit{500} was isolated. We speculate that the reaction proceeds \textit{via} initial activation of the aldehyde functionality by MgBr\textsubscript{2}.

**Scheme 96.** Successful condensation of oxindole \textit{487} with aldehyde \textit{491}.

\textsuperscript{259} Both regioisomeric products were obtained as single diastereomers at C(6).
\textsuperscript{261} Using MgCl\textsubscript{2} as catalyst gave the product in significantly lower yield.
This activated carbonyl compound is then attacked by the TMS enol ether 501, or N-methoxyoxindole, to form 500. Rapid elimination of TMSOH released alkene 498. We also observed that upon removal of the TMS group in 500, unstable secondary alcohol product 502 results, which cannot be chromatographed. This observation accounts for the failure of the addition reaction described in Scheme 95, as the products formed might equally suffer from instability upon isolation and analysis.

Detailed spectroscopic analysis of the major product 498 by steady state NOE experiments led to the assignment of an E-olefin geometry as shown in Figure 20. Moreover, the configuration at the C(5) stereocenter could again be confirmed based on correlations of the terminal CH2 of the olefin in the side chain with the C(5)-proton, as well as the C(6) hydrogen with H(3a).

Figure 20. Steady state NOE analysis of 498 (only diagnostic correlations shown).

9.3. Attempts towards C(3)-Oxidation

Oxidation reactions of unactivated C–H bonds have a long history in organic chemistry. In recent years the increasing interest of synthetic chemists for these transformations has led to the development of a myriad of novel methodologies targeted towards the functionalization of seemingly inert hydrocarbon bonds. Incorporation of such strategies into the toolkit of synthetic chemists offers new opportunities for synthesis design orthogonal to traditional approaches. However, application of C–H oxidation strategies to complex natural product synthesis is still poorly investigated. In this context, we decided to evaluate the feasibility of such an approach in the total synthesis of gelsemoxonine for the functionalization of the C(3) carbon.

A number of general reactivity rules have to be considered for the oxidation of highly functionalized substrates. The ease of C–H bond oxidation is directly related to the strength of the C–H bond in question. Hence, bond dissociation energies are a good measure for the propensity of a particular C–H bond towards oxidation. Table 12 summarizes the most relevant bond dissociation

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262 After premixing oxindole 358 with TMSCl, NEt3 and MgBr2, immediate formation of a white precipitate is observed, indicating initial formation of TMS enol ether 501 and triethylammonium hydrochloride, which precipitates.

263 For further details, see experimental part.


energies. The numbers indicate a general trend with tertiary, allylic and benzylic hydrogens as well as α-heteroatom methylenes being most prone to homolytic bond cleavage. Electron-donating substituents can further lower these values. In addition to electronic influences, steric factors and directing effects can guide C–H oxidations.

Table 12. Bond dissociation energies (BDE) for common types of C–H bonds.266

<table>
<thead>
<tr>
<th>C–H</th>
<th>BDE (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>92-93</td>
</tr>
</tbody>
</table>

The C(3) oxidation envisioned in hydropyran derivative 503 would entail selective functionalization of an ether methylene in the presence of a number of potentially reactive C–H groups to furnish product 504 (Scheme 97, box). In particular, allylic and benzylic positions at C(19), C(5) and C(7) could interfere with the desired site of reactivity. Moreover, the tertiary C(16)–H and the

Scheme 97. Preparation of C–H oxidation substrates and sites prone to C–H oxidation in 503.

C(17) methylene in the ether bridge are potentially prone to homolytic C–H cleavage based on the above analysis. We reasoned that steric factors, as well as the adjustment of the substitution pattern and the degree of unsaturation of a putative C–H oxidation substrate, might enable us to control its reactivity profile. These considerations prompted us to prepare various precursors for the evaluation of oxidizing conditions. As outlined in Scheme 97, selective oxidation of the electron rich double bond in 498 was achieved under Lemieux–Johnson conditions through OsO4 promoted dihydroxylation, followed by periodate cleavage to obtain ketone 505. Alternatively, the trisubstituted C(6)–C(7) olefin was easily reduced by treatment of 498 with NaBH4 to produce oxindole 506 as an inconsequential mixture of diastereomers at C(7). Conversion into ketone 507 was carried out by ozonolysis, followed by reductive quenching using Me2S.

With these four substrates 498 and 505-507 in hand, we set out to test conditions for hydropyran oxidation (Table 13). First introduced by Djerassi in 1953, RuO4 has found wide application for the oxidation of C–H bonds adjacent to ether oxygens. In the past decades, various improvements of the original protocol have enabled the functionalization of complex substrates. Generally, RuO4 can either be used as stoichiometric oxidant, or catalytically when in the presence of an oxidizing agent such as NaIO4 to regenerate the active ruthenium species. The mildness of this protocol has prompted its applications in various total syntheses. As outlined in Table 13, different variations of this protocol were tested on hydropyran substrates 505 and 507 (entries 1 and 2). Subjection of alkene 505 to the catalytic conditions led to dihydroxylation of the electron deficient double bond to produce diol 508, accompanied by isatin 509, resulting from oxidative cleavage of this diol. Subjecting oxindole 507 to the same reaction conditions led to complete decomposition of the starting material. However, using a stoichiometric amount of RuO4 for the oxidation of 507 generated alcohol 510 by activation of the benzylic C–H bond (entry 2). Oxidation of alkanes using catalytic amounts of a Pt(II) species under an atmosphere of oxygen gas has emerged as an alternative method to ruthenium

268 Attempted ozonolysis of 498 resulted in oxidation of the unsaturated oxindole system.
270 The reduction had to be carefully controlled to avoid reduction of the oxindole carbonyl to give the corresponding aromatic indole product.
273 For an overview on RuO4 chemistry, see: Plietker, B. Synthesis, 2005, 2453-2472.
276 Substrates 498 and 506 were not tested under these conditions as the electron rich terminal double bond was expected to be dihydroxylated under these conditions.
Table 13. C–H oxidation attempts on various hydropyran derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Substrate</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RuO$_2$/NaIO$_4$, 60 °C</td>
<td><img src="image1" alt="Structure" /></td>
<td><img src="image2" alt="Structure" /> + <img src="image3" alt="Structure" /></td>
</tr>
<tr>
<td>1</td>
<td>or RuCl$_3$/NaIO$_4$</td>
<td><img src="image4" alt="Structure" /></td>
<td><img src="image5" alt="Structure" /></td>
</tr>
<tr>
<td>2</td>
<td>RuO$_4$ (stoichiometric)</td>
<td><img src="image6" alt="Structure" /></td>
<td><img src="image7" alt="Structure" /></td>
</tr>
<tr>
<td>3</td>
<td>Pt/C, O$_2$ (1 atm)</td>
<td><img src="image8" alt="Structure" /></td>
<td><img src="image9" alt="Structure" /></td>
</tr>
<tr>
<td>4</td>
<td>Ce(NH$_4$)$_2$(NO$_3$)$_6$, NaBrO$_3$</td>
<td><img src="image10" alt="Structure" /></td>
<td>formation of dimeric products</td>
</tr>
<tr>
<td>5</td>
<td>CrO$_3$</td>
<td><img src="image11" alt="Structure" /></td>
<td><img src="image12" alt="Structure" /></td>
</tr>
<tr>
<td>6</td>
<td>(t-BuO)$_2$, 160 °C</td>
<td><img src="image13" alt="Structure" /></td>
<td>formation of dimeric products</td>
</tr>
<tr>
<td>7</td>
<td>Sc(OTf)$_3$, 50 °C</td>
<td><img src="image14" alt="Structure" /></td>
<td><img src="image15" alt="Structure" /></td>
</tr>
</tbody>
</table>

Catalyzed C–H oxidations. Accordingly, hydropyran 507 was treated with PtO$_2$ in the presence of O$_2$, resulting in the generation of a mixture of products (entry 3). Benzylic alcohol 510 could again be identified, along with an alcohol product 511 that most likely results from oxidation at C(16). Cerium salts have also been reported to effect ether oxidation under various conditions. We thus subjected substrate 507 to cerium ammonium nitrate in the presence of sodium borate as

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278 Although $^1$H NMR analysis proved difficult, disappearance of the C(16) proton and the shift of neighboring hydrogen peaks along with the high resolution mass of this product led to the assignment of structure 511.

Surprisingly, analysis of the reaction mixture by LC-MS indicated the formation of various dimeric products. This outcome could be explained by formation of radical intermediates (or caged radical pairs), which can undergo intermolecular recombination reactions to provide dimers. Next, we investigated the use of chromium salts to effect the desired C(3) oxidation. CrO$_3$ and related oxidants have previously been employed for the functionalization of sensitive substrates. However, application of this strategy to hydropyran 507 again produced benzylic alcohol 510 (entry 5).

We next envisioned C(3) functionalization by abstraction of a hydrogen radical by an appropriate radical species. To this end, 507 was treated with di-tert-butylperoxide at 160 °C (entry 6). Again, the exclusive formation of dimers was observed, as seen for the cerium oxidation (entry 4). Recently, Lambert and co-workers reported the use of stable carbocation salts such as tropylium tetrafluoroborate as electron deficient hydride abstracting reagents for the oxidation of amines to imines. We were hoping that the same conditions might enable hydride abstraction at C(3) in α-position to the ether oxygen. Accordingly, 498 was treated with commercially available tropylium tetrafluoroborate at elevated temperature (entry 7). To our surprise, rearranged tetrahydropyridine derivative 512 was isolated as the sole product. A mechanistic explanation for this transformation is given in Scheme 98. Lewis acid activation of the Boc carbamate might trigger ionization of 498 through C(15)–N bond cleavage to generate an allylic carbocation intermediate 513. Trapping of the carbocation at C(21) by the carbamate nitrogen could provide tetrahydropyridine 512, incorporating a fully substituted double bond.

Scheme 98. Mechanistic explanation for the formation of tetrahydropyridine 512.

Very recently, Sames and Akiyama independently reported a very different approach to the selective oxidation of etheral C–H groups. Their strategy relied on the proximity of unsaturated

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280 Sodium bromate has been reported to effect ether oxidation also in the absence of Ce(IV) salts: Metsger, L.; Bittner, S. *Tetrahedron* **2000**, 56, 1905-1910.
282 Treatment of diene 498 with CrO$_3$ produced a complex mixture of compounds including oxindole products resulting from cleavage of the C(6)–C(7) olefin.
285 Stable carbocations such as tropylium or trityl can serve as Lewis acids: *Encyclopedia of Reagents in Organic Synthesis; Trityl tetrakis(pentafluorophenyl)borate*; Wiley: Chichester.
carbonyl functionalities to the ethereal C–H bond. In the event, treatment of substrates such as unsaturated ester 514 with Sc(OTf)$_3$, or other Lewis acids, triggered the formation of a carbocation 515 (Scheme 99, top). Proper positioning of this carbocation allowed for a [1,5]-hydrogen shift of the ethereal C–H, thus producing carbocation 516. A ring closure was then effected by attack of the enolate nucleophile onto this oxonium intermediate, providing product 517. Such a strategy could also be applicable to oxindole system 498 (Scheme 99, bottom). In particular, activation of the oxindole carbonyl group could generate the carbocation intermediate 518. A subsequent hydrogen-shift would produce oxonium 519. Finally, ring closure could deliver gelsemoxonine core 520. According to this plan, 498 was treated with Sc(OTf)$_3$ and heated to 50 °C (Table 13, entry 7). Unfortunately, the only two products detected again included the rearranged hydropyran 512, presumably formed by a mechanism analogous to the one proposed in Scheme 98. Moreover, partial loss of the Boc protecting group was observed, generating azetidine 521.

Scheme 99. C–H abstraction by an unsaturated carbonyl functionality and potential application to the synthesis of oxindole 520.

Interestingly, attempted protection of azetidine 521 for recovery of this material, again led to an unexpected outcome. As outlined in Scheme 100, treatment of 521 with ethylchloroformate produced spirolactone 522 as the major product, along with some of the expected protected azetidine. A rationale for the formation of 522 is given in Scheme 100 (bottom). Acylation of the benzylic carbon might occur by sequential addition of chloride to the double bond of ethylcarbamate 523 followed by trapping of the enolate intermediate 524 by excess chloroformate. Elimination of hydrochloric acid from 525 would produce enamine 526. Hydrolytic cleavage of the strained heterocycle would provide ketone 527, which could cyclize to 522 via its enol form.
We further tested a radical abstraction strategy involving the photolytic cleavage of a thiophosphate derivative (Scheme 101). Thiophosphate 528, derived from hydroxyester 529, was reported to undergo homolytic C–O bond cleavage upon irradiation with UV light to generate a caged radical pair 530. In the presence of ether substrates, such as THF, the phosphate radical can abstract a hydrogen atom from the ether methylene. Subsequent recombination of the two radical species produces α-functionalized ether product 531. Such a strategy could be applied to our system in an intramolecular setting. Accordingly, thiophosphate starting material 532 was prepared by oxidation of oxindole 507 using Davis’ oxaziridine, followed by treatment of benzylic alcohol 510 with CIP(OEt)_2 and elemental sulfur. However, irradiation of 532 led to clean formation of rearranged thiophosphate 533. It can be assumed that the putative radical pair intermediate is not able to abstract the remote C(3)-hydrogen due to either steric or energetic reasons.

Scheme 101. Thiophosphate mediated radical abstraction approach.

Finally, a series of other oxidation conditions were tested on the four substrates prepared (Figure 21). However, all of these protocols produced complex product mixtures or led to complete decomposition of the starting material. As shown in Figure 21, the conditions tested include metal-oxo complexes\(^{289,290}\) and radical generating reagents.\(^{291}\)

![Figure 21. Unsuccessful oxidation conditions.](image)

### 9.4. Conclusion

In summary, we have successfully constructed the azetidine motif of gelsemoxonine employing an unusual ring contraction of a spirocyclopropane isoxazolidine (Scheme 102). The precursor for this key step was prepared starting from known vinyl tosylate 434. Tsuji–Trost allylation with sodium alkoxide 446 delivered alkylidenecyclopropane 442. This intermediate was further elaborated into

![Scheme 102. Synthetic route to C-H oxidation precursor 498.](image)


isoxazolidine 447 in a sequence of only three steps. Ring contraction of 447 proceeded smoothly without the need of a nitrogen protecting group, providing β-lactam 456 in excellent yield. Installation of the C(5) stereocenter was achieved through Petasis olefination followed by a face selective hydroboration to generate primary alcohol 481. Aldol condensation of oxindole with the aldehyde derived from 481 delivered diene 498 in two further steps.

Attempts for the selective oxidation of the C(3) position via C–H bond activation remained elusive. As outlined in Figure 22, oxidizing agents preferentially reacted with a number of C–H bonds more prone to oxidation than the C(3) methylene. This issue reflects the dense functionalization pattern of azetidine 534, which complicates the application of C–H oxidation strategies.

![Figure 22](image.png)

**Figure 22.** Comparison of desired and observed sites of C–H oxidation in hydropyran 534.

In order to avoid interference of undesired side reactions with the projected oxidation state adjustment at C(3), a strategy involving a directed C–H functionalization (535 → 536) would offer an attractive alternative (Scheme 103). The subsequent chapter will discuss the implementation of this strategy towards construction of the gelsemoxonine core.

![Scheme 103](image.png)

**Scheme 103.** Revised synthetic strategy involving the directed oxidation at C(3).
Directed C–H Functionalization at C(3)

As our initial attempts for innate C–H functionalization at C(3) of gelsemoxonine were hampered by the dense substitution pattern of the system under investigation, we set out to explore directed C–H oxidation approaches to achieve this transformation.\(^\text{292}\) A guided C–H oxidation approach would entail installation of a suitable reactive tether that could reach only a defined area in space. In this instance, only C–H bonds within the reach of the reactive site would be susceptible to oxidation, thus avoiding side reactions with remote functionalities. Implementation of such a strategy in the synthesis of gelsemoxonine could conveniently rely on the C(14) hydroxyl group of the natural product, which offers a versatile site for tether attachment in close proximity to the C(3) methylene. Moreover, such a strategy would allow for a late stage C(3) oxidation state adjustment, circumventing the need of carrying a sensitive C(3) acetal or lactone functionality through the synthesis.

As outlined in Scheme 104, our revised strategy required the preparation of oxazoline 537 incorporating a hydroxyl group at C(14). Application of the chemistry developed previously should provide azetidine 535 containing the full gelsemoxonine carbon skeleton. Attachment of a suitable tether to the C(14)-OH would then enable the late stage adjustment of the C(3) oxidation state, thus allowing efficient access to oxonium precursor 536.

Scheme 104. Revised synthetic strategy based on the directed oxidation of the C(3) methylene.

10.1. Introduction of the C(14) Hydroxyl Group

We first investigated installation of the C(14) hydroxyl group in a putative precursor for the key spirocyclopropane isoxazolidine ring contraction. To this end, initial construction of a nitrile oxide cycloaddition substrate was required. Scheme 105 summarizes the successful synthesis of oxime 537. Starting from glycidaldehyde (oxiranecarboxaldehyde) (538), prepared by oxidation of acrolein\(^{293}\), diethylacetal 539 was generated by treatment of 538 with triethylorthoformate. Subsequent regioselective epoxide opening with sodium alkoxide 540 delivered secondary alcohol 541 in 52% yield.\(^{295}\) The alcohol was protected as a benzyl ether using BnBr. The diethylacetal was converted into oxime 542, followed by nitrile oxide cycloaddition using bistrichyline oxide and tert-butyl hypochlorite, as established before (chapter 9). Surprisingly, isoxazoline 543 was formed with an excellent diastereomeric ratio of 10:1 and in good yield (88%). Steady state NOE analysis of the major isomer\(^{296}\) strongly suggested a cis-relationship of the OBn substituent and the C(16) hydrogen as shown for 543. This corresponds to the configuration found in the natural product. The stereochemical outcome of this cycloaddition can be explained by electronic and steric factors (Scheme 105, box). In the transition state 544 en route to 543, the local dipole induced by the nitrile oxide functionaility is partially opposed to the benzyl ether dipole. In contrast, the arrangement of the substituents in transition state 545 produces a less favorable dipolar interaction. Additionally, 1,2 allylic strain between the pseudoequatorial benzyl ether and the nitrile oxide might further disfavor transition state 545 over diastereomeric structure 544, given that the diaxial interaction in 544 is less severe.

Scheme 105. Synthesis of isoxazoline 537.

Initial attempts to cleave the benzyl ether in 543 under hydrogenolytic conditions resulted in reductive cleavage of the N–O bond. Hydrolysis of the intermediate imine produced the corresponding ketoalcohol (not shown). Screening various conditions to effect benzyl group cleavage led to the


\(^{294}\) For the preparation of the corresponding alcohol, see section 9.1.


\(^{296}\) NOE analysis of the minor diastereomer of alcohol 537 confirmed the conformational assignment.
identification of FeCl$_3$ as the optimal reagent.\textsuperscript{297} Treatment of 543 with FeCl$_3$ cleanly provided secondary alcohol 537 in 87\% yield.

Although the presented route to 537 provided the desired intermediate, limited scalability of this approach severely hampered the preparation of substantial amounts of 537. To address this problem, a shorter and more scalable route to alcohol 537 was developed. As outlined in Scheme 106, we initially synthesized known aldehyde 546 \textit{via} a slightly modified protocol.\textsuperscript{298,299} Starting from cyclopropyl tosylate 434,\textsuperscript{300} a palladium catalyzed Tsuji–Trost reaction with the sodium alkoxide of ethyl glycolate afforded ethylester 547 in 83\% yield on a 14 g scale. Subsequent DIBAL-H reduction cleanly produced aldehyde 546. The complete selectivity for reduction to the aldehyde intermediate can be explained by the neighboring ether oxygen. Coordination of the ether group to aluminum might stabilize the tetrahedral hemiacetal intermediate of this reaction, thus preventing over-reduction to the alcohol. Aldehyde 546 was next subjected to a Henry (nitro aldol) reaction with lithiated nitromethane. Careful quenching of this reaction with pH 7 buffer allowed for the isolation of the secondary alcohol product.\textsuperscript{301} In order to circumvent an additional protection step, it proved beneficial to quench the reaction by addition of TMSCl. Accordingly, silyl ether 548 was isolated in good yield (78\% from 547). Treatment of 548 with phenylisocyanate\textsuperscript{302} in the presence of base, followed by acidic workup using hydrochloric acid in MeOH provided alcohol 537 in 75\% yield and in a diastereomeric ratio of 4:1. The decreased stereoselectivity for this reaction compared to the cycloaddition of benzyl ether 543.

\textbf{Scheme 106.} Second generation route for the preparation of secondary alcohol 537.
can be explained by an enhanced diaxial interaction in transition state 544 (Scheme 105, box), whereas the increased size of a TMS group disfavors formation of product 543.303

![Scheme 105. Synthesis of enol ether 550 from nitroalcohol 549.](image)

Upon screening different cycloaddition procedures for the synthesis of alcohol 537, an interesting side reaction was observed (Scheme 107). Treatment of unprotected alcohol 549 with Boc₂O in the presence of 10 mol% of DMAP exclusively afforded enol ether 550.304 TLC analysis of this reaction indicated fast formation of an intermediate product, which then slowly converted to product 550.305 This intermediate could be isolated and was identified as nitroolefin 551. Subjecting 551 to the same reaction conditions again produced the expected product. Accordingly, our mechanistic proposal involves initial elimination of the alcohol followed by formation of nitrile oxide intermediate 552. The double bond undergoes migration thus allowing for functionalization of the C(3) carbon. Although E-isomer 552 is most likely preferred over 553, cycloaddition can only occur from the Z-isomer 553. We suspect the two isomers to exist in equilibrium, which could be established by the DMAP additive via nucleophilic addition to the electron deficient double bond followed by elimination.

These results led us to consider an alternative strategy involving an intramolecular nitronate cycloaddition of nitroalkene 554 (PG = protecting group).306 Nitronates are typically generated by alkylation, acylation or silylation of one oxygen atom of a nitro group in a nitroalkane and subsequent loss of a proton α to the nitro functionality. The reactive dipole readily participates in a cycloaddition reaction with olefins. The resulting N-hydroxy species finally undergoes dehydration to form an isoxazoline product. Nitronates can thus be considered as synthetic equivalents of nitrile oxides. We hoped that a nitronate reaction pathway towards the formation of 555 might result in an enhanced diastereoselectivity with regard to the newly formed stereocenter at C(16), due to the bulky substituent

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303 Different protecting groups were evaluated for this cycloaddition. See also section 15.3.
305 When the reaction was conducted in an NMR tube in d₆-benzene, NMR analysis also indicated fast formation of nitroolefin 551 and subsequent slow conversion to product 550 without any further detectable intermediates.
on the nitrogen. In particular, we envisioned formation of a nitronate species 556 from protected alcohol 554 (Scheme 108, top). Dipolar cycloaddition would provide 557, which upon dehydration could convert into isoxazoline 555. To explore this strategy, alcohol 549 was treated with $N,N$-dimethyltrimethylsilylamine\(^{307}\) in the presence of triethylamine.\(^{308,309}\) The reaction was directly followed by $^1H$ NMR analysis as presented in Figure 23.

Scheme 108. Attempted nitronate cycloaddition of nitroalkene 549. PG = protecting group.

After addition of the silylating agent, rapid appearance of two doublet peaks at 6.16 ppm and 6.33 pm were observed (Figure 23, 1 min). In analogy to observations reported by Seebach and Dunitz, who investigated the spectroscopic and structural properties of silyl nitronates,\(^{310}\) we propose the initial formation of two isomeric silyl nitronate intermediates *cis*-558 (at low field) and *trans*-558 (at higher field) (Scheme 108, bottom). Upon recording another NMR spectrum of the reaction after 3 min, we observed a pronounced change in the ratio of these two species. In particular, *trans*-558 was now clearly predominant over *cis*-558. The *cis* and *trans* forms of nitronate esters have been postulated to exist in rapid equilibrium with each other, with the *trans* isomer being preferred for steric reasons.\(^{311,312}\) We thus hypothesize that after initial formation of an isomeric mixture of silyl nitronates, *cis*-558 converts into its more stable isomer to avoid steric interaction with the adjacent

\(^{307}\) Other silylating agents such as TMSCl or $N,O$-bistrimethylsilylacetamide were found to be less effective than Me$_2$NSiMe$_3$.
\(^{309}\) NEt$_3$ was reported to have a stabilizing effect on silyl nitronates: Torssell, K.B.G.; Zenthen, O. *Acta. Chem. Scand. B* 1978, 32, 118.
\(^{312}\) An intramolecular silyl exchange mechanism has been postulated: see ref. 310 and 311.
hydroxyl group. Silylation of this alcohol might further drive the equilibrium towards the trans form. The observed conversion of cis-558 into trans-558 continued over the course of the reaction, leading to the complete disappearance of the olefinic proton signal at lower field (Figure 23, 5 min and 60 min). Moreover, integration of the nitronate signal indicated slow decomposition of trans-560 over time, possibly forming silyl ether 559 (60 min). However, addition of an excess of TMSCl to the reaction mixture led to the restoration of the signal at 6.15 ppm (Figure 23, +TMSCl). This intermediate proved completely inert towards cycloaddition with the olefin to furnish 560. Even after 24 h no change of the NMR spectrum of the reaction mixture was observed. This again supports the hypothesis of exclusive formation of the trans nitronate 559, which is not able to undergo cycloaddition for stereoelectronic reasons. Further attempts to effect nitronate cycloaddition of alcohol 549 under various conditions remained without success.

Figure 23. $^1$H NMR spectroscopic analysis of the reaction of alcohol 549 with Me$_2$NSiMe$_3$ in CDCl$_3$.

$^313$ The integral over the alkylidene cyclopropane signals was used as internal standard.

$^314$ We found the alkylidene cyclopropane motif to be unreactive in various attempted dipolar cycloaddition reactions.

10.2. Construction of the C(15) Stereocenter

We next attempted the construction of the C(15) stereocenter by addition of isoprenyl lithium to benzyl protected alcohol 543, as done for the C(14) unfunctionalized substrate (chapter 9). However, no expected product 561 was isolated when using the previously established protocol (Figure 24). We therefore set out to identify conditions for the introduction of a C(15) substituent as outlined in Figure 24.

![Figure 24](image)

**Figure 24.** Unsuccessful attempts for addition of nucleophiles to isoxazoline 543.

A possible issue associated with addition of organolithium reagents to oxime ethers like 543 is competing deprotonation of the acidic proton in α-position to the imino group. Side reactions of this type are commonly observed for reactions of Grignard reagents with hindered or easily enolizable ketones due to the strong basicity of these reagents. Several strategies to suppress undesired reactive pathways have been developed and include solvent change or conducting the reaction in the presence of additives such as MgBr₂, Bu₄NBr, LiClO₄, or (iPrO)₃TiCl. More recently, Imamoto and Knochel have reported the use of lanthanum salts in the reaction of both

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316 Although the recovered starting material was in all cases obtained as a single diastereomer, intermediate enolate formation cannot be excluded, as such an enolate could be diastereoselectively protonated upon aqueous workup, thus providing the starting material with retention of configuration at the enolizable carbon.


organolithium\textsuperscript{321} and Grignard reagents\textsuperscript{322,323} with sterically demanding ketones. In the latter case, formation of an organolanthanum species was postulated, which exhibits reduced basicity compared to the parent lithium and magnesium derivatives.\textsuperscript{322b} Following these reports, we added anhydrous CeCl\textsubscript{3}\textsuperscript{324} to the reaction with substrate 543. However, under these conditions only unreacted starting material was recovered as well. Various other conditions, including sterically less demanding nucleophiles, were evaluated but remained without success. We speculate that the axial benzyl ether shields the oxime carbonyl from attack by nucleophiles as shown for 562 in Figure 24.

Based on the above considerations, we expected that removal of the alcohol protecting group might reduce the steric shielding of the imine group. Furthermore, a free alcohol could serve as a handle for the guided delivery of a nucleophile. We first decided to explore hydrocyanation of oxime ether 537. As outlined in Scheme 109, a selection of commonly used conditions for the hydrocyanation of ketones including TMSCN/ZnI\textsubscript{2},\textsuperscript{325} acetone cyanohydrin/AlCl\textsubscript{3} and Mander’s reagent/AlCl\textsubscript{3} were tested without success. Pleasingly, treatment of alcohol 537 with an excess of Et\textsubscript{2}AlCN at 60 °C efficiently produced nitrile 563 as a single diastereomer.\textsuperscript{326} We surmised that coordination of the aluminum reagent to the free alcohol brings the cyanide nucleophile into close proximity to the reactive site as shown for intermediate 564 (Scheme 109, box). A second equivalent of the Lewis acid is likely activating the isoxazoline by coordination to the nitrogen (or oxygen) of the oxime ether.

\begin{center}
\begin{tikzpicture}
% TikZ code for the diagram
\end{tikzpicture}
\end{center}

\textbf{Scheme 109.} Conditions examined for hydrocyanation of oxime ether 537.

\textsuperscript{324} CeCl\textsubscript{3} was prepared by careful drying of CeCl\textsubscript{3}7H\textsubscript{2}O following a literature procedure: Dimitrov, V.; Kostova, K.; Genov, M. \textit{Tetrahedron Lett.} 1996, 37, 6787-6790.
Nitrile 563 was then subjected to the conditions established for the key ring contraction (Scheme 110). To our surprise, no reaction to β-lactam 565 occurred and only starting material was recovered. Various proton sources were tested including CF₃CO₂H, MsOH, HCl and TfOH but no product was detected. Notably, this observation might shine light on some mechanistic aspects of the spirocyclopropane isoxazolidine ring contraction as the electronic properties of the reactive system are directly affected by an electron withdrawing substituent at C(15).

Scheme 110. Failed ring contraction of nitrile 563.

Realizing that an electron poor C(15) appendage is not tolerated in the subsequent transformation, an alternative substituent at this stereocenter was required. Based on the hypothesis that the success of the previously described hydrocyanation reaction relied on the presence of an unprotected hydroxyl group next to the oxime ether, we reinvestigated organometal addition to alcohol 537 as outlined in Figure 25. Again, the use of isoprenyl lithium or vinyl magnesium bromide was met with failure, even when ZnCl₂ was added as an activator. Gratifyingly, employing 2-propenyl lithium as a smaller nucleophile produced the desired product 566, albeit in low yield (19%) due to low conversion of the substrate (Figure 25, box).

Figure 25. Initial attempts for addition of organometallic reagents to alcohol 537.

We reasoned that a sterically less demanding propynyl metal species might act as a more potent nucleophile in this reaction. Accordingly, a detailed screen to find optimal reaction conditions was undertaken as presented in Table 14.

327 For a more detailed discussion of possible consequences of this observation on the mechanistic rationale of the ring contraction, see chapter 16.
Table 14. Optimization of the propynyl lithium addition to isoxazoline 537.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal (M)</th>
<th>Additive</th>
<th>Solvent</th>
<th>Conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>-</td>
<td>THF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Li</td>
<td>-</td>
<td>Et₂O/NEt₃ 1:1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Li</td>
<td>-</td>
<td>THF/TMEDA 1:1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Li</td>
<td>BF₃OEt₂</td>
<td>THF</td>
<td>35%</td>
<td>22%</td>
</tr>
<tr>
<td>5</td>
<td>Li</td>
<td>TiCl₄</td>
<td>THF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Ti(Oi-Pr)₃</td>
<td>TiCl₄</td>
<td>THF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Li</td>
<td>TiCl₄/Ti(Oi-Pr)₄</td>
<td>THF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8[4]</td>
<td>Li</td>
<td>BF₃OEt₂</td>
<td>THF</td>
<td>60%</td>
<td>45%</td>
</tr>
<tr>
<td>9[5]</td>
<td>Li</td>
<td>BF₃OEt₂/CeCl₃</td>
<td>THF</td>
<td>82%</td>
<td>68%</td>
</tr>
</tbody>
</table>

[a] 4 equiv. of organometal reagent were used; [b] 1 equiv. of additive was used; [c] yield of isolated product; [d] 8 equiv. of propynyl lithium used; [e] 5 equiv. of BF₃ OEt₂ used; [f] yield given for a 50 mg scale, on a 4 g scale a yield of 49% (65% brsm) and 75% convn. was obtained; [g] 4 equiv. of propynyl lithium, mixed with anhydrous CeCl₃ prior to addition of the substrate.

Reaction of freshly prepared propynyl lithium with 537 in THF did not result in product formation (entry 1). Solution studies of lithium acetylides have indicated that addition of tertiary amines can alter the aggregation behavior of these compounds. Accordingly, solvent mixtures with triethylamine (entry 2) and TMEDA (entry 3) as additives were tested, albeit without success. Addition of BF₃OEt₂ to the original reaction conditions resulted in formation of the desired product 567, again as a single diastereomer (entry 4). The low yield (22%) obtained for this procedure can again be attributed to poor conversion of the substrate (35% convn.). In order to further enhance activation of the oxime ether, we substituted the Lewis acid BF₃OEt₂ with TiCl₄, a reagent that was reported to promote additions of nucleophiles to β-hydroxyketones. However, no addition product was isolated under these conditions (entry 5). Other titanium based conditions screened, including the use of a preformed titanium acetylide reagent, as reported by Seebach, were unsuccessful (entry 6, 7). In order to improve the successful protocol described in entry 4, we found that employing a large excess of reagent (8 equiv.) and Lewis acid (4 equiv.) resulted in significantly increased yield of 45%.

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329 Propynyl lithium was prepared from 1-bromo-1-propene by treatment with 2 equiv. of n-BuLi: Toussaint, D.; Suffert, J. Org. Synth. 1999, 76, 214-220.
Further improvement was achieved by addition of CeCl₃ following the concept of lowering the basicity of the organometal reagent, as described above (entry 9).³³³ This optimized protocol allowed the efficient access to isoxazolidine 567 in good yield (68%, 83% brsm) and complete diastereoselectivity.

We hypothesize that this reaction relies on the initial coordination of the organometal nucleophile, possibly a propynyl cerium species,³³⁴,³²² to the alcohol or alkoxide at C(14) as shown for 568 (Scheme 111, box). This coordination enables delivery of the propynyl residue to the reactive site. Moreover, the Lewis acid additive serves to activate the oxime ether functionality towards nucleophilic addition. This hypothesis was supported by the observation outlined in Scheme 111. Subjecting diastereomeric alcohol 569 to the established reaction conditions did not result in formation of expected product 570 and the starting material was recovered unchanged. This outcome is surprising as substrate 569 is devoid of unfavorable steric effects which might block attack from the convex face of the bicycle, as is the case for benzyl ether 543 (see Figure 24). However, the alcohol stereochemistry in 569 makes direct delivery of the propynyl residue by the coordinating metal species impossible, as shown for intermediate 571 (Scheme 111, box).

Scheme 111. Failed attempt for addition of propinyl lithium to alcohol 569.

10.3. Directed Oxidation at C(3)

Ring contraction of isoxazolidine 567 was effected by treatment with CF₃CO₂H (Scheme 112) and the desired product was obtained in good yield (67%). This gives further evidence to our hypothesis that the interness of nitrile substituted substrate 563 is indeed a consequence of the electron-withdrawing substituent at C(15), and not a result of electronic effects induced by the C(14) hydroxyl group. Application of the chemistry developed for the first generation synthesis proceeded smoothly. Boc protection of β-lactam 572 generated carbamate 573 along with a minor amount of bisprotected

³³³ The amount of propynyl lithium reagent could again be reduced to 4 equiv.
product (not shown). X-ray crystallographic analysis of this intermediate unambiguously confirmed the assigned structure (Scheme 112, box). Subsequent Petasis olefination produced enecarbamate 574 in excellent yield. It is noteworthy that a free secondary alcohol, as well as an alkyne, are tolerated under the reaction conditions, as alkynes have been reported to react with Cp₂TiMe₂.³³⁵ Hydroboration of alkene 574 provided diol 575, again as a single diastereomer. Selective oxidation of the primary alcohol in 575 was achieved using TEMPO/PhI(OAc)₂ generating aldehyde 576 in 80% yield.³³⁶ Condensation of aldehyde 576 with N-methoxy oxindole 358 using the conditions developed previously (MgCl₂, TMSCl, NEt₃ in EtOAc) gave product 577 in 39% yield. Changing the Lewis acid catalyst to more reactive MgBr₂ and switching the solvent to THF resulted in an improved yield of 82%. The product was thereby obtained as an inconsequential mixture of double bond isomers (2:1).

With the full carbon skeleton of gelsemoxonine established, we set out to implement the directed C–H oxidation strategy described above. Three overall approaches were evaluated as outlined in the following sections.

Scheme 112. Synthesis of oxindole derivative 577.

### 10.3.1. Alcohol Dehydration

A straightforward means to adjust the oxidation state at C(3) of an intermediate such as 578 would be elimination of the C(14) hydroxyl group to produce enol ether 579 as shown in Scheme 113 (top). Enol ethers are well investigated intermediates en route to the generation of reactive oxonium species. In particular, sugar glycols have found wide application in O- and C-glycosylation reactions.³³⁸ Intermediate 579 would then necessitate oxidation of the enol ether double bond to arrive at an α-

³³⁷ Other Lewis acids including Yb(OTf)₃ (*J. Am. Chem. Soc.* **2004**, *126*, 12897) and TMSOTf were tested but resulted in lower yield of the product.
hydroxy oxonium species 580. Such an oxidation reaction could involve epoxidation or dihydroxylation of the electron rich olefin.

According to this plan, we investigated elimination of the secondary alcohol in oxindole 581 (Scheme 113, bottom).339 Numerous protocols to effect transformation to alkene 582 were evaluated, including Martin sulfurane,340 Burgess reagent,341 Tf₂O/base, MsCl/base and Mitsunobu dehydration.342 Unfortunately, all protocols tested resulted in decomposition of the starting material, even at low temperature.343 We therefore investigated enolization of ketone 583, synthesized by Dess–Martin oxidation of alcohol 581, to provide product 584. Treatment of 583 with a variety of bases only effected decomposition of the ketone. Attempted vinyl triflate formation (Tf₂O, i-Pr₂NEt) followed the same fate. We speculate that the reason for our inability to access a C(14)–C(3) double bond lies in the elimination reaction detailed in Scheme 113 (box). Upon dehydoration, the desired enol ether 579 might be generated. Most likely, the allylic C(15)–N bond can then be cleaved to generated oxonium 585. This elimination is a result of the inherent ring strain of the azetidine moiety. Resulting product 585 is likely to follow numerous decomposition pathways.

Scheme 113. Failed attempts for dehydration of alcohol 581 and enolization of ketone 583.

339 581 was prepared by reduction of the olefin in 577 using NaBH₄, as discussed in chapter 9.
343 In some cases (e.g. MsCl, Tf₂O) activated alcohol intermediates could be isolated or observed. However, treatment of these intermediates with bases again resulted in decomposition of the material.
10.3.2. Nitrrene Insertion

A highly efficient strategy for directed C–H oxidation has been developed by Du Bois and co-workers.\textsuperscript{344} As outlined in Scheme 114, this approach is based on the generation of a rhodium nitrrene species tethered to a hydroxyl substituent. The nitrrene intermediate can undergo insertion into an adjacent C–H bond to provide a cyclic product.\textsuperscript{345,346} The authors have developed protocols that allow for differential activation of the C–H bonds α or β to the tether attachment site, respectively. In particular, the use of sulfamate starting materials (X = SO\textsubscript{2}) leads to the formation of six membered ring products of β-C–H functionalization, whereas carbamate substrates (X = CO) produce five membered ring oxazolidinones under essentially identical conditions. The mildness of the reaction conditions and the high functional group tolerance of the reaction has enabled its application in the total synthesis of various highly challenging target compounds.\textsuperscript{347}

\begin{center}
\begin{align*}
\text{Scheme 114. Differential C–H amination by formation of rhodium nitrrene intermediates.}
\end{align*}
\end{center}

We decided to test this protocol on alcohol as shown in Scheme 115. Reduction of the electron poor double bond using NaBH\textsubscript{4} was followed by installation of a primary carbamate on the secondary alcohol using standard conditions.\textsuperscript{348} Treatment of hydropyran with Rh\textsubscript{2}(esp)\textsubscript{2} in the presence of PhI(OAc)\textsubscript{2} and MgO as a heterogeneous base indeed produced the desired oxazolidinone in an excellent yield of 81%. Notably, the rhodium nitrrene intermediate reacts exclusively with the ether C–H bond without undergoing any side reaction with the proximal alkyne.\textsuperscript{351}

\textsuperscript{350} Ether C–H oxidation by rhodium nitrrene insertion has been previously documented: Fiori, K.W.; Fleming, J.J.; Du Bois, J. J. Am. Chem. Soc. 2006, 128, 3926-3927.
Scheme 115. Rhodium nitrene insertion strategy to access oxazolidinone 591.

The synthesis of oxazolidinone 591 represents the first transformation enabling late stage functionalization at C(3) of the gelsemoxonine skeleton. However, elaboration to the projected oxonium intermediate necessitates opening of the cyclic carbamate. As outlined in Table 15, a variety of strategies towards this goal were investigated. Initially, we attempted opening of the oxazolidinone ring by attack of different nucleophiles on the carbamate carbonyl group to access alcohol 593 (entry 1). The nucleophilic reagents we screened include Ba(OH)$_2$, acids such as AcOH or HCl and, 1,2-diaminoothane. None of these conditions led to opening of the five membered ring but resulted in the decomposition of 591 instead. In 2003, Kunz and Pleuss reported the activation of glycosyl amides using a combination of PPh$_3$ and CBr$_4$ to generate glycosyl bromide products, which were subsequently activated by AgOTf. According to this procedure, oxazolidinone 591 was treated with this reagent combination. In the event, only the loss of the Boc group was observed. In an alternative approach, we tried to exploit the nucleophilicity of the amide carbonyl. Unfortunately, neither reaction with Tf$_2$O to effect formation of a triflimide product, nor treatment with Lawesson’s reagent to convert 593 into the corresponding thiocarbonyl compound, proved successful. We reasoned that the oxindole carbonyl group might interfere with the desired reactivity. Accordingly, the oxindole was protected by bromination at C(6) to provide 594. Attempts to react the oxazolidinone carbonyl in 594 with Meerwein’s salt (entry 2) or Tf$_2$O (entry 3) did not furnish the desired products 595 or 596, respectively. Conversion of carbamate 591 into imide 597 was thought to facilitate nucleophilic opening of the oxazolidinone by turning the nitrogen substituent into a better leaving group. Unfortunately, treatment of 597 with LiOH, Cs$_2$CO$_3$ or AcOH did not effect ring opening either (entry 4). Finally, oxazolidinone cleavage was successfully achieved on brominated derivative 598 using primary carbamate substrates: d) Deng, Q.-H.; Wang, J.-C.; Xu, Z.-J.; Zhou, C.-Z.; Che, C.-M. Synthesis 2011, 2959-2967.

Table 15. Attempts to open oxazolidinone 591.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Attempted Transformation</th>
<th>Conditions tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Diagram" /></td>
<td>Ba(OH)$_2$, AcOH, aq. HCl, diaminoethane, PPh$_3$, CBr$_4$, then AgOTf, Tf$_2$O, then MeOH, Lawesson’s reagent</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Diagram" /></td>
<td>Me$_3$OBF$_4$</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Diagram" /></td>
<td>Tf$_2$O</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Diagram" /></td>
<td>Cs$_2$CO$_3$/MeOH, AcOH, LiOH</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Diagram" /></td>
<td>LiOH, 16% yield</td>
</tr>
</tbody>
</table>

(entry 5). Treatment of 598 with LiOH provided Boc carbamate 599 in 16% yield. Attempts for further elaboration of the $N,O$-acetal into an oxonium precursor were met with failure.

Although we had successfully achieved functionalization of the C(3) methylene in a late stage intermediate for the first time, the sensitive nature of the system studied did not allow us to exploit this strategy to access gelsemoxonine. We therefore opted for an alternative C(3) functionalization strategy to produce an intermediate that would be amenable to further manipulations.
10.3.3. Hydrogen Atom Abstraction

Besides C–H insertion reactions including carbone-, nitrene- or metaloxo intermediates, approaches based on hydrogen abstraction by radical species have found wide application in the area of C–H functionalization.\(^\text{355}\) One of the earliest reports in this field is the Hofmann–Löffler–Freytag reaction (Scheme 116, top).\(^\text{356}\) In this transformation, an \(N\)-haloamine 600 is irradiated with UV light in the presence of strong acid leading to the homolytic cleavage of the \(N\–X\) bond, thus generating a highly reactive \(N\)-centered radical 601.\(^\text{357}\) This free radical species can then abstract a hydrogen atom from a remote C–H bond to provide 602, and upon oxidation and cyclization, form pyrrolidine product 603. Barton and Petterson have reported a modification of the original protocol in which a \(N\)-haloamide 604 serves as the substrate (Scheme 116, bottom).\(^\text{358}\) Generation of an amidyl radical 605,\(^\text{359}\) followed by hydrogen abstraction to form the carbon-centered radical 606 and subsequent oxidation, produces alkylhalide 607. Cyclization of the amide carbonyl group provides imidoester 608, and, upon hydrolysis, lactone 609. More recently, Suárez has developed a modified protocol for the generation of amidyl radicals starting directly from primary amides and using PhI(OAc)\(_2\)/I\(_2\) as the oxidant.\(^\text{360}\) The mild conditions employed in this modification allow its application to highly sensitive compounds.

The use of such as strategy in our system could allow for C(3) functionalization as outlined in Scheme 117.\(^\text{361}\) Generation of carbamoyl radical intermediate 610 from carbamate 611 might trigger a

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\(^{355}\) For a review on remote free radical functionalization, see: Majetich, G.; Wheless, K. Tetrahedron 1995, 51, 7095-7129.


\(^{361}\) Functionalization of C–H bonds next to ether oxygens has been reported: Martín, A.; Pérez-Martín, I.; Suárez, E. Org. Lett. 2005, 7, 2027-2030.
[1,5]-hydrogen shift to produce 612. This carbon-centered radical could undergo further oxidation, followed by cyclization, to give carbonate 613 or alternatively, through trapping by a nucleophile (Y) afford compound 614.

Scheme 117. Hydrogen abstraction at C(3) by amidyl radical 610.

Implementation of this strategy was first evaluated on a model system as shown in Scheme 118. Reduction of the triple bond in β-lactam 573, followed by introduction of a primary carbamate provided 615. Subjecting carbamate 615 to Suárez conditions produced carbonate 616 in 35% along with minor amounts of the corresponding lactam product resulting from cyclization of the carbamate nitrogen. However, extrapolation of this result to a relevant system was not possible. In particular, the C(15) alkynyl substituent was not tolerated. Moreover, numerous azetidine starting materials tested decomposed under the reaction conditions.

Scheme 118. Synthesis of carbonate 616 by a Hofmann–Löffler–Freytag reaction.

We anticipated that milder protocols for the generation of the reactive carbamoyl radical might help to circumvent problems associated with functional group incompatibility. Figure 26 summarizes conditions we have tested on different model systems towards this end.362

362 A number of these protocols have also been applied to derivatives of alcohol 577. However, none of these attempts proved successful.
In particular, we first addressed carbamoyl radical formation starting from N-chloro derivatives 617 and 618. Irradiation of these intermediates with UV light only led to recovery of dechlorinated starting materials. Baran and co-workers have recently documented an improved procedure for the generation of carbamoyl radicals in complex systems starting from N-trifluoroethyl carbamates. Following this report, N-chloro and N-bromo carbamates 619 and 620, were subjected to the reported conditions. However, the desired hydrogen abstraction was not observed, but again dehalogenated starting material was reisolated. Nicolaou has reported the generation of N-centered radicals by treatment of amides with IBX. For our system 621, no reaction could be observed and the substrate was recovered unchanged. Following a report by Bach, we also investigated the use of acylazide 622 as a precursor for a carbamoyl radical under iron catalysis. This attempt was also without success. The use of N-hydroxy derivatives as radical precursors has been reported. In the

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63 N-chloro carbamates 617 and 618 were prepared using Ca(OCl)₂/Al₂O₃; Larionov, O.V.; Kozhushov, S.I.; de Meijere, A. *Synthesis* 2003, 1916-1919. These compounds proved stable to silica gel chromatography.

64 When photochemical reaction of 617 was performed in benzene, some of the N-aryl product was isolated.


66 N-bromination was carried out according to: Demko, Z.P.; Bartsch, M.; Sharpless, K.B. *Org. Lett.* 2000, 2, 2221-2223.


event, subjecting hydroxamic acid 623 to t-BuSOCl produced a mixture of various products.\cite{Lin, X.; Stien, D.; Weinreb, S.M. Tetrahedron Lett. 2000, 41, 2333-2337.} In this instance, oxidation of the N-methyl group was observed as a side reaction. Attempts to convert benzyolated derivate 624 to a C(3) functionalized product were also met with failure.\cite{a) Sekar, G.; DattaGupta, A.; Singh, V.K. Tetrahedron Lett. 1996, 37, 8435-8436; b) Clark, A.; Filik, R.P.; Peacock, J.L.; Thomas, G.H. Synlett 1999, 441-443; c) Sharp, L.A.; Zard, S.Z. Org. Lett. 2006, 8, 831-834.} Either unreacted starting material was recovered (lauroyl peroxide) or reduction of the N–O bond was observed (Cu(OTf)2). Finally, generation of a carbon centered radical from silane derivative 625 was tested. This parallels with the generation of reactive alkyl radical species in the Ueno–Stork reaction or related radical processes.\cite{a) Ollivier, C.; Renaud, P. In Radicals in Organic Synthesis, Renaud, P.; Sibi, M.P., Eds.; Wiley-VCH: Weihnheim, 2001; pp. 93-112; for a review about the Ueno-Stork reaction, see: b) Salom-Roig, X.J.; Dénès, F.; Renaud, P. Synthesis 2004, 1903-1928.} In the event, only dehalogenated starting material was recovered under the conditions tested.

Scheme 119. Unexpected side reaction of carbamate 626 upon treatment with NIS under UV irradiation.

As outlined in Scheme 119, an attempt to generate an N-iodo carbamate from oxindole 626 by treatment with NIS under UV light irradiation unexpectedly produced vinyl iodide 627 in 70% yield.\cite{A vinyl bromide analogue of 627 was obtained when carbamate 626 was treated with AcOBr.} Our mechanistic explanation to account for this outcome involves iodonium intermediate 628. This highly reactive species could be intercepted by the nucleophilic carbonyl group of the Boc carbamate. Selective attack at C(19)\cite{Molecular modeling studies indicated that C(19) is much better aligned for nucleophilic attack by the Boc carbonyl then C(20). Moreover, MM2 calculations suggest that the six-membered ring product formed is less strained than the alternative five-membered cyclic carbamate.} would provide oxonium 629. Upon loss of a tert-butyl carbocation, product 627 could be formed. Interestingly, although the substrate of this reaction was employed as a single double bond isomer, the olefin of the product had isomerized to a 1:1 E/Z mixture. This is most likely a result of a photochemically mediated isomerization process.\cite{For reviews covering alkene isomerization processes, see: a) Wyman, G.M. Chem. Rev. 1955, 55, 625-657; b) Sonnet, P.E. Tetrahedron 1980, 36, 557-604.}
Alternatively, an inversion process involving addition and subsequent elimination of a nucleophile, possibly succinimide, could account for this observation.

It is not clear to us why the hydrogen abstraction attempts described remained fruitless. On the one hand, some of the systems investigated appear to be sensitive to many of the conditions examined. This was not surprising as the alkyne substituent is in close proximity to the putative N-centered radical and could therefore participate in various side reactions. Moreover, the azetidine and β-lactam motifs in the model substrates employed are likely to react with nucleophiles (e.g. halide anions) and radical intermediates. The complete lack of reactivity of other substrates towards C(3) hydrogen abstraction might reflect the inability of a tethered carbamoyl radical to overlap with the σ* orbital of the C(3)–H bond. Steric clash around this methylene might force the carbamate substituent to point away from the ring, thus making proper orbital overlap impossible.  

### 10.4. Conclusion

In summary, we have developed a modified route to the gelsemoxonine carbon skeleton that allows for the stereoselective introduction of the C(14) hydroxyl group (Scheme 120). The revised strategy starts with known aldehyde 546. A nitro aldon reaction, followed by a diastereoselective nitrile oxide cycloaddition, delivered alcohol 537 in excellent yield. Installation of a surrogate for the ethyl ketone moiety in the natural product was achieved by addition of propynyl lithium to oxime ether 537 in the presence of CeCl₃. Notably, this reaction required an unprotected hydroxyl group in α-position to the isoxazoline. Moreover, the stereochemical configuration of this alcohol proved decisive for the reaction to proceed. Isoxazolidine 567 then underwent smooth ring contraction to provide β-lactam 572. Application of the chemistry developed for the previous route delivered oxindole 577 in five steps.

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375 The orbital alignment requirements for reactions or amidyl radicals have been studied: Chow, Y.L.; Mojelsky, T.W.; Magdzinski, L.J.; Tichý, M. Can. J. Chem. 1985, 63, 2197-2202.
As outlined in Scheme 121, we further attempted C–H functionalization at C(3) by a guided C–H oxidation strategy. As a result of these studies, we were able to access oxazolidinone 591 by a directed rhodium nitrene insertion starting from carbamate 590. Moreover, application of the Suárez modification of the Hofmann–Löffler–Freytag reaction on model system 615 successfully produced cyclic carbonate 616. However, both of these valuable intermediates could not be elaborated into the projected key oxonium intermediate 630. The failure to manipulate these intermediates reflects the complex substitution pattern and the associated high sensitivity of the system investigated.

Scheme 121. Successful C(3) functionalization in intermediates 590 and 615.

Based on these considerations, we decided to explore C(3) functionalization at an early stage of the synthesis. A potential drawback of such a strategy was the necessity of carrying a potentially sensitive acetal derivative through the synthesis. For instance, introduction of a heteroatom substituent in alcohol 537 would provide acetal derivative 631 (Scheme 122). It was not clear if such a species would survive the various reaction conditions en route to oxonium precursor 632.

Scheme 122. Revised synthetic strategy including early C(3) functionalization.
11. Oxonium Addition Strategy

As outlined in chapter 8, our tactic for the late stage construction of the seven membered carbocycle 633 in gelseomoxonine relies on two alternative strategies. As shown in Scheme 123, we envisioned either the attack of an enolate nucleophile on a preactivated C(6) carbon in 405 (path a) or, alternatively, trapping of an oxonium ion 404 by a C(7) nucleophile (path b). Both of these strategies entail the need to functionalize the C(3) carbon. As our initial attempts to elaborate an electrophilic reactive site at C(3) using a C–H functionalization approach remained without success, we turned to a strategy involving early functionalization of the ether methylene to produce intermediate 631. This approach would require us to carry a potentially sensitive functional group through a large part of the synthesis.

Scheme 123. Revised synthetic strategy based on early functionalization of C(3).

11.1. Introduction of the C(3) Substituent

We started our efforts towards the synthesis of intermediate 631 by evaluating the previously successful C–H oxidation protocols on an early intermediate. As outlined in Scheme 124, carbamate 634 was chosen as a test substrate. To our surprise, none of the previously established strategies for
the late stage functionalization of the C(3) methylene were successful with substrate 634. Reaction of 634 with Rh₂(esp)₂, PhI(OAc)₂ and MgO did not produce any product 635 and the starting material was recovered unchanged. Attempted Suárez-type Hofmann–Löffler–Freytag reaction resulted in complete decomposition of 634. We next focused our efforts on dehydration of alcohol 537 in order to establish enol ether 550 as a convenient precursor for installation of a substituent at C(3). Subjecting either diastereomer of alcohol 537 to dehydration conditions such as MsCl/base, TFAA/DBU or Martin sulfurane did not provide any of the desired alkene. Activation of the secondary alcohol with Tf₂O in the presence of pyridine produced the desired enol ether 550 only in low yield (30-40%).³⁷⁶ Dehydration of derivatives 636 incorporating either a β-lactam (X = O) or the fully constructed azetidine (X = H, R) resulted in complete decomposition of the starting material without any formation of product 637. This was consistent with earlier observations, which suggested that enol ethers, such as 636, likely undergo four membered ring opening triggered by the allylic oxygen substituent as discussed in section 10.3.1.

![Scheme 124](image)

**Scheme 124.** Attempts for C(3) functionalization early in the synthesis.

Remembering an initially undesired side reaction we had observed previously, whereby treatment of nitroalcohol 549 under dehydrative conditions provided enol ether 550 in a moderate yield of 54% (section 10.1.; Table 16, entry 1), we set out to study this reaction more closely. As outlined in Table 16, performing the reaction in CH₂Cl₂ in the presence of NEt₃ resulted in a lower yield then observed under the original conditions (entry 2). A possible cause of the low yield in this transformation could be competing side reactions such as intermolecular cycloadditions or the dimerization of two nitrile oxide species.³⁷⁷ Such bimolecular side reactions could be avoided by conducting the cycloaddition at higher dilution. Indeed, lowering the starting material concentration led to a marked increase in product yield (entry 3). As discussed earlier, the reaction most probably proceeds *via* unsaturated nitrile oxide intermediate 552 (Scheme 125; section 10.1.). In order to enable cycloaddition, the *trans*

³⁷⁶ Dehydration of alcohol 537 was later investigated in more detail. See section 15.3.
³⁷⁷ Nitrile oxides are prone to dimerization to produce furoxanes: Torssell, K.B.G. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis; Organic Nitro Chemistry Series*; VCH Publisher Inc.: Deerfield Beach; Vol. 2, 1988, pp. 55-60.
double bond in 552 needs to be isomerized to the reactive cis isomer 553. We reasoned that addition of a nucleophile to the reaction could promote such an isomerization through a mechanism outlined in Scheme 125. Addition of the nucleophilic species to the electron poor double bond in 552 would provide intermediate 638. After bond rotation to form 639, an elimination event would produce the required cis isomer 553. Accordingly, we decided to add an excess amount of DMAP to the reaction (entry 4), which led to a further increase of the yield. Finally, we found that a substrate concentration of 0.015 M along with the use of 2 equivalents of DMAP produced enol ether 550 in 79% yield on a 5 g scale (entry 5).

Table 16. Optimization of dehydrative formation of enol ether 549.

<table>
<thead>
<tr>
<th>Entry[^a]</th>
<th>equiv. DMAP</th>
<th>Solvent</th>
<th>Concentration[^b]</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>toluene</td>
<td>0.12 M</td>
<td>54</td>
</tr>
<tr>
<td>2[^c]</td>
<td>0.05</td>
<td>CH₂Cl₂</td>
<td>0.18 M</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>toluene</td>
<td>0.07 M</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>toluene</td>
<td>0.02 M</td>
<td>77</td>
</tr>
<tr>
<td>5[^d]</td>
<td>2.0</td>
<td>toluene</td>
<td>0.015 M</td>
<td>79</td>
</tr>
</tbody>
</table>

[^a] Conditions: Boc₂O (3.0 equiv.), DMAP, solvent, rt, 12 h;[^b] concentration in respect to substrate 549;[^c] NEt₃ (3.0 equiv.) was added to the reaction;[^d] 5 g scale.

Scheme 125. Double bond isomerization in nitrile oxide 552 through the action of a nucleophile.

The projected use of enol ether 550 to access intermediate 640 would now necessitate the introduction of the C(14) alcohol, along with a C(3) substituent across the double bond. As depicted in Scheme 126, this tactic would entail initial oxidation of the olefin, either through dihydroxylation or epoxidation, to arrive at intermediates like 641 or 642, respectively. Acetal chemistry would then enable installation of the C(3) substituent.
Scheme 126. Strategy for functionalization of enol ether 550.

Initial attempts to effect oxidation of 550 by dihydroxylation conditions (OsO₄/NMO, AD-mix α or β) did not result in any product formation. Instead, the substrate was recovered unchanged. We next turned to protocols directed towards epoxidation of the double bond in 550. For this purpose, we particularly relied on previous work directed towards the synthesis of anhydrosugar epoxides. Attempted epoxidation of 550 using m-CPBA under biphasic conditions resulted in decomposition of the starting material. Application of a protocol involving m-CPBA in the presence of KF to sequester the benzoic acid generated, led to recovery of the starting material. However, treatment of 550 with anhydrous m-CPBA at 50 °C provided a mixture of oxidized products 643 and 644, formed by opening of an intermediate enol epoxide by 3-chlorobenzoic acid, albeit in low yield (28%) (Scheme 127).

Scheme 127. Oxidation of enol ether 550.

This outcome indicated that no face selectivity in the oxidation of the olefin in 550 was achieved using these conditions, thus providing an equimolar mixture of the two diastereomeric products 643 and 644. More recently, Gin and co-workers reported a very mild protocol for the conversion of glycals into their corresponding epoxides. Following this report, 550 was treated with Ph₂SO, Tf₂O and base. Again, only decomposition of the starting material was observed. Danishefsky has established the use of dimethylidioxirane (DMDO) to access 1,2-anhydrosugars. Althought DMDO

---

380 Commercial m-CPBA (ca. 30% water content) was dried as described in the experimental.
is a relatively strong oxidizing agent, careful control of the reaction parameters (quantity of DMDO, temperature, solvent) allow for the efficient preparation of highly functionalized enol epoxides. As outlined in Scheme 127, DMDO oxidation of substrate 550 in the presence of 4Å molecular sieves produced the desired epoxide 645 in quantitative yield and as a 2:1 mixture of diastereomers. This highly sensitive intermediate could be isolated by filtration and concentration of the reaction mixture. Furthermore, 645 could be stored at -20 °C for several days without any detectable decomposition. Interestingly, this reaction provides 645 in good diastereoselectivity in favor of the desired isomer. This is insofar very surprising, as enol ether 550 exists in an almost flat conformation as suggested by molecular modeling studies (Scheme 127, box). A drawback of the described strategy is that water-free DMDO can only be obtained as a dilute solution (approximately 0.07 M) in acetone, which limits the scalability of reactions involving DMDO. A number of procedures were developed for the in situ generation of DMDO in biphasic systems. The use of trifluoromethyl(methyl)dioxirane (TFDO) was also documented in this context. Attempted application of several of these protocols resulted in complete decomposition of our starting material. This likely reflects the unusual sensitivity of epoxide 645 towards even weak nucleophiles like water.

We next set out to investigate opening of epoxide 645 by a range of different nucleophiles to furnish alcohol 646. A summary of these studies is given in Table 17. The choice of the nucleophiles we envisioned to employ was strongly influenced by considerations regarding product stability. As discussed in the introduction to this chapter, we were worried about the potential sensitivity of acetal derivatives towards various reaction conditions in later steps of the synthesis. Moreover, the projected tactic would require elaboration of this acetal functionality into an oxonium ion at a late stage of the synthesis. This also prompted us to consider the possibility of an easy acetal cleavage in the presence of sensitive functional groups. To this end, we first investigated hydrolysis of epoxide 645 by simple addition of water. The resulting lactol could then be oxidized to a stable lactone ring. In the event, this transformation proved not successful (entry 1). Various conditions, including the use of weak acids such as PPTS, resulted in decomposition of the starting material. Thioacetals have been extensively investigated in sugar chemistry as glycosyl donors. The major advantage associated with this

385 Residual water in the DMDO stock solution resulted in complete decomposition of the product. To circumvent this problem, addition of molecular sieves or Na2SO4 was necessary.
386 Assignment of the relative configuration is based on the analysis of downstream intermediates (see later in the text).
functional group is a pronounced stability towards acidic conditions that normally affect \(O,O\)-acetals. Moreover, thiaacetals can be easily activated under oxidative conditions (e.g. NBS, \(m\)-CPBA, MeOTf). We therefore investigated introduction of a sulfide substituent at C(3) (entries 2-6). Generally, the desired products were obtained in superior yields when basic conditions were employed (EtSLi or PhSLi). Interestingly, upon activation under acidic conditions, the product was obtained as a mixture of diastereomers reflecting the isomeric distribution of the starting material. In the case of lithium sulfide addition however, only one product isomer was obtained, suggesting decomposition of the undesired epoxide.

Table 17. Opening of epoxide 645 by different nucleophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Additive</th>
<th>Yield(^{[a]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H(_2)O</td>
<td>PPTS</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>PhSH</td>
<td>-</td>
<td>27%</td>
</tr>
<tr>
<td>3</td>
<td>PhSH</td>
<td>K(_2)CO(_3)</td>
<td>25%</td>
</tr>
<tr>
<td>4</td>
<td>PhSLi</td>
<td>-</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>EtSH</td>
<td>TFAA</td>
<td>40%</td>
</tr>
<tr>
<td>6</td>
<td>EtSLi</td>
<td>-</td>
<td>73%</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>TFAA</td>
<td>42%</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>CF(_3)CO(_2)H</td>
<td>66%</td>
</tr>
<tr>
<td>9</td>
<td>MeOLi</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>(i)-PrOH</td>
<td>CF(_3)CO(_2)H</td>
<td>42%</td>
</tr>
<tr>
<td>11</td>
<td>BnOH</td>
<td>CF(_3)CO(_2)H</td>
<td>52%</td>
</tr>
<tr>
<td>12</td>
<td>BnOH</td>
<td>-</td>
<td>73%</td>
</tr>
<tr>
<td>13</td>
<td>Ph(_2)CHOH</td>
<td>CF(_3)CO(_2)H</td>
<td>20%</td>
</tr>
<tr>
<td>14</td>
<td>Ph(_2)CHOH</td>
<td>(Ph(_3)P)AuOTf</td>
<td>34%</td>
</tr>
<tr>
<td>15</td>
<td>2-NO(_2)C(_6)H(_4)CH(_2)OH</td>
<td>CF(_3)CO(_2)H</td>
<td>55%</td>
</tr>
<tr>
<td>16</td>
<td>PhCO(_2)H</td>
<td>-</td>
<td>63%</td>
</tr>
<tr>
<td>17</td>
<td>NaOBz</td>
<td>-</td>
<td>&lt; 20%</td>
</tr>
</tbody>
</table>

\(^{[a]}\) refers to total yield including the undesired diastereomer, if isolated (see text).

We further investigated the use of various alcohol derived nucleophiles (entries 7-15). In this case, acidic epoxide activation provided the acetal products in good yield, whereas attempted epoxide opening using lithium methoxide resulted in complete decomposition of 645 (entry 9). Alcohols with different steric requirement were employed (\(i\)-PrOH) along with benzyl derived nucleophiles (BnOH, Ph\(_2\)CHOH, 2-nitrobenzyl alcohol), which would allow for easy cleavage of the corresponding acetals.
In particular, 2-nitrobenzyl acetal can be cleaved under very mild photochemical conditions (entry 15).\textsuperscript{390} Besides epoxide activation by protic acids, (Ph₃P)AuOTf was tested as Lewis acid activator, but provided the product in inferior yield (entry 14).\textsuperscript{391} Finally, we introduced a benzoate substituent by treatment of 645 with benzoic acid (entries 16-17).

**Table 18.** Propynyl lithium addition to isoxazoline 647.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield of 648</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SPh</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>SEt</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>OCH₂Ar\textsuperscript{[d]}</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>O-i-Pr</td>
<td>18%</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>45%</td>
</tr>
<tr>
<td>6</td>
<td>OBz</td>
<td>34%</td>
</tr>
<tr>
<td>7</td>
<td>OBn</td>
<td>35%\textsuperscript{[c]}</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Conditions: propynyl lithium (4.0 equiv.), CeCl₃ (4.0 equiv.), BF₃·OEt₂ (2.0 equiv.), -78 °C to rt, 2h; \textsuperscript{[b]} low yields can always be attributed to poor conversion of the substrate; \textsuperscript{[c]} the reaction was performed on a 800 mg scale, 77% brsm; \textsuperscript{[d]} Ar = 2-nitrophenyl.

We next set out to test the previously established propynyl lithium addition to various isoxazoline derivatives 647 (Table 18). To our surprise, the nature of the C(3) substituent (R in Table 18) played a crucial role in this reaction. In particular, sulfur substituents prevented the reaction altogether (entries 1 and 2). Other bulky substituents including i-Pr and 2-nitrobenzyl resulted in very low conversion of the starting material (entries 3 and 4). The use of substrates with smaller substituents at C(3) produced the desired acetal 648 in markedly better yield (entries 5-7). A possible explanation for this substituent effect is given in Scheme 128. As hypothesized before (section 10.2.), the reactive conformation responsible for product formation might be best described as 649. In this conformation, the C(14) alcohol delivers the organocerium species to the oxime ether. Changing substituent R to a larger residue in this system will possibly induce a conformational change, whereby R can accommodate a more favorable pseudo-equatorial position. Molecular modeling studies suggest that in the resulting boat-like conformation, the hydroxyl substituent at C(14) is forced to point away from the isoxazoline ring as drawn for 650. In such a conformation, delivery of the reagent could no longer be insured, thus accounting for the low product yield or the complete shutdown of the reaction. An alternative


11. Oxonium Addition Strategy

Explanation might involve coordination of the propynyl cerium nucleophile to the sulfur atom in the thioacetal substrates. This coordination effect could sequester some of the organometallic reagent.

Scheme 128. Proposed conformational changes in intermediates en route to 648.

As indicated in Table 18, we again observed that diastereoisomeric derivatives 651 were completely unreactive, irrespective of the substituent R. This parallels with the observation made previously (section 10.2.).

It is particularly noteworthy that we have never observed reaction of the acetal moiety in 647. The presence of a strong Lewis acid (BF$_3$·OEt$_2$) in this transformation might suggest activation of the acetal functionality and subsequent addition of the organometallic nucleophile to either the resulting aldehyde or oxonium species. However, the above described reaction always proceeded very cleanly to provide only the desired product resulting from exclusive addition to the oxime ether group, along with reisolated starting material. Low yields were always due to poor conversion of the starting material.

Scheme 129. Observed side reaction during the conversion of 652 to 654.

During attempts to further optimize the conversion of the aforementioned propynyl lithium addition to isoxazoline 652, we discovered the side reaction described in Scheme 129 (top). When we
employed more than the usual 2 equivalents of the Lewis additive BF$_3$·OEt$_2$, we were able to isolate hydropyridine 653 as a minor side product in 20-30% yield along with desired alkyne 634. This compound seems to be the result of a ring expansion involving the isoxazoline ring. Interestingly, this exact transformation has been previously reported by De Sarlo and Salaün but under markedly different conditions.\textsuperscript{392} In the original report, spirocyclopropane isoxazoline\textsuperscript{392a,b} and isoxazolidine\textsuperscript{392c,d} starting materials were heated to 130-200 °C. Moreover, the addition of protic acid was reported to have no beneficial effect on this reaction.\textsuperscript{200} The authors speculated that a radical mechanism was operating, as depicted in Scheme 129 (middle). Thermal homolytic cleavage of the N–O bond in 655 was proposed to result in the formation of diradical 656. Fragmentation of the cyclopropane ring would provide intermediate 657, which could produce piperdone 658 upon radical recombination. In contrast, we propose a different mechanism for the generation of hydropyridine 653. A radical mechanism seems unlikely for our reaction considering the low temperature used (-78 °C).\textsuperscript{393} We therefore propose an ionic mechanism as outlined in Scheme 129 (bottom). Coordination of BF$_3$·OEt$_2$ to the nitrogen atom in 659 would weaken the N–O bond, thus making it susceptible to heterolytic cleavage producing carbocation 660.\textsuperscript{394} Subsequent extrusion of a proton might provide unsaturated ketone 661. Conjugate addition of the nitrogen nucleophile would then produce product 662. Alternatively, Lewis acid coordination to 659 might induce a rearrangement event to arrive at spirooxetane intermediate 663, \textit{via} carbocation 664.\textsuperscript{395} Subsequent acetal opening accompanied by proton loss would also provide unsaturated ketone 662.

Having a diverse set of isoxazoline derivatives 648 in hand, we explored the acid mediated ring contraction of these systems to give β-lactam 665 (Table 19). The use of a benzoyl acetal substrate, not quite unexpectedly, resulted in complete decomposition of the starting material (entry 1). When its methyl ether analogue was subjected to the established conditions, the desired product was isolated but in very low yield (entry 2). These two results can be explained by the sensitivity of these acetal derivatives to the harsh acidic conditions needed for the ring contraction (CF$_3$CO$_2$H, 80 °C). To our delight, the more stable isopropyl acetal was well suited for ring contraction and enabled isolation of the β-lactam product in an excellent 89% yield (entry 3). A similarly good result was obtained when using the benzyl ether derivative as substrate (entry 4). When turning to bulkier C(3) substituents, we observed a marked decrease in product yield (entries 5 and 6). This is most likely an effect of the


\textsuperscript{393} Although the N–O bond strength is relatively weak (approx. 50 kcal/mol), a homolytic cleavage at cryogenic temperature is unlikely.


\textsuperscript{395} Although a ring expansion of a hydroxycyclopropane to from an oxetane product has to our knowledge never been reported, ring expansions of cyclopropanes to produce cyclobutane derivatives are well known: Salaün, J. \textit{In The Chemistry of the Cyclopropyl Group}; Rappaport, Z., Ed.; John Wiley & Sons, Ltd.: Chichester, \textbf{1987}; pp. 809-878.
longer reaction times required for these substrates. However, it is not clear to us why these substrates require more time to achieve full conversion.

Table 19. Ring contraction of Isoxazolidine 647.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>reaction time[b]</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OBz</td>
<td>3.5 h</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
<td>1.5 h</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>3</td>
<td>O-i-Pr</td>
<td>1.5 h</td>
<td>89%</td>
</tr>
<tr>
<td>4</td>
<td>OBn</td>
<td>2 h</td>
<td>78%</td>
</tr>
<tr>
<td>5</td>
<td>OCHPh2</td>
<td>6 h</td>
<td>55%</td>
</tr>
<tr>
<td>6</td>
<td>OCH2Ar[c]</td>
<td>6 h</td>
<td>50%</td>
</tr>
</tbody>
</table>

[a] Conditions: CF3CO2H (1.1 equiv.), MeCN, 80 °C; [b] reaction time for full consumption of the starting material; [c] Ar = 2-nitrophenyl.

Having successfully established an access route to β-lactam 665, we introduced the C(6) methylene group employing the chemistry developed previously (Scheme 130). We chose to use the benzyl acetal 666 to carry on in the synthesis, as a benzyl ether could later be easily cleaved under reductive conditions (e.g. H2/Pd or Li/NH3). As shown in Scheme 130, Boc protection of 666 delivered carbamate 667. The structure of 667 was confirmed by X-ray crystallographic analysis (box). It is noteworthy that the hydroxyran ring adopts a boat conformation in the crystal structure while the benzyl ether substituent, as well as the C(14) alcohol, are forced into a pseudo-axial position. Petasis olefination of 667 proceeded smoothly to produce enecarbamate 668. Again, the acetal functionality was not affected by the Lewis acidic reaction conditions. We then set out to hydroborate this intermediate using the conditions established previously. Most interestingly, we isolated primary alcohol 669 as a 3:1 mixture of diastereomers at C(5), favoring the configuration shown in Scheme 130.396

396 The stereochemical assignment was confirmed after derivatization through NOE analysis of both diastereomers.
A possible explanation for this observation might involve coordination of the hydroborating agent to the benzyl ether oxygen and thus delivery of the reagent from the concave face of bicycle 668. However, considering the crystal structure of 667, the respective face of the olefin seems highly hindered due to the boat conformation of the hydroxyran ring and the axial benzylether substituent. In solution, this structure might be more dynamic, thus allowing for opening of the concave space and possible coordinative delivery of 9-BBN.

Having alcohol 669 in hand, we now envisioned the preparation of various activated precursors to test our key oxonium addition strategy.

### 11.2. Oxonium Addition Attempts

As outlined at the beginning of this chapter, two alternative approaches for a late stage ring closure of the gelsemoxonine core were considered (Scheme 123). Primary alcohol 669 could serve as a intermediate to access suitable precursors for both of these strategies. We initially opted for the introduction of an oxindole substituent at C(3) to investigate the alkylation strategy represented by intermediate 405 in Scheme 123.

#### 11.2.1. Intermolecular Addition Reactions

Introduction of a carbon substituent at C(3) of primary alcohol 669 would formally correspond to a C-glycosylation reaction. C-glycosylations have been extensively studied in the past for the synthesis of...
of synthetic sugar derivatives and natural products.\textsuperscript{398} Glycosylation reactions usually rely on the activation of the sugar hemiacetal (anomeric center) to generate a reactive oxonium species. Various activation modes have been established towards this end. These strategies generally involve the installation of a potent leaving group at the anomeric carbon. Following this tactic, we prepared a number of differently activated acetal derivatives as shown in Scheme 131.

Scheme 131. Preparation of various oxonium precursors for intermolecular addition reactions.

We decided to focus on the installation of stable entities thereby allowing for isolation and purification of the oxonium precursors. One of the most popular acetal activating functionalities is the trichloroacetimidate group developed by Schmidt.\textsuperscript{399} It can be easily installed by treatment of the free hemiacetal with trichloroacetoneitrile. According to this procedure, we prepared trichloroacetimidate 670 after protection of the primary alcohol in 669 as an acetate followed hydrogenolytic cleavage of the benzyl ether.\textsuperscript{400,401} Starting from hemiacetal 671, we further prepared carbonate 672 by cyclization of the Boc carbonate on the C(14) hydroxyl group (see also Scheme 132). Recently, glycosyl fluorides have emerged as convenient glycosyl donors in sugar chemistry due to their high stability and the ease of activation.\textsuperscript{402} Introduction of the fluoride leaving group was easily achieved by treatment of the


\textsuperscript{400} Reductive cleavage of the benzyl ether in 669 was sometimes difficult to reproduce, which manifested in low conversion of the substrate. Even conducting the reaction at 10 bar in a hydrogen bomb did not significantly improve the conversion of the reaction.

\textsuperscript{401} Hemiacetal 671 was obtained as a single diastereomer. Moreover, the stereochemistry at C(3) proved stable. We have never observed opening of the six membered ring to form an aldehyde product.

hemiacetal starting material with DAST or other fluorinating agents.\textsuperscript{403} We could easily prepare different fluorinated oxonium precursors with varying protecting groups on the C(14) secondary alcohol (673-676).\textsuperscript{404}

As outlined in Scheme 132, we investigated the intermolecular addition of oxindole 358 to these substrates. To this end, trichloroacetimidate 670 was subjected to various conditions known to induce oxonium formation (TMSOTf, BF\textsubscript{3} \cdot OEt\textsubscript{2} or ZnCl\textsubscript{2}) in the presence of 358 or its silyl enol ether derivative.\textsuperscript{405} However, none of these conditions led to the formation of product 677. Treatment of carbonate 672 under similar conditions also did not provide any products. In contrast, subjecting glycosyl fluoride 673 to standard reaction conditions involving Lewis acid mediated activation of the fluoride, produced carbonate 672 as the sole product. This reaction likely proceeds \textit{via} oxonium intermediate 678 followed by loss of a tert-butyl carbocation.

Scheme 132. Initial attempts for intermolecular addition of oxindole 358 to various oxonium precursors.

Although reaction of the fluoride substrate did not provide the desired product, formation of 672 indicated the successful activation of the hemiacetal functionality. We therefore continued to investigate glycosyl fluorides as oxonium precursors. As shown in Scheme 133, we decided to change the protecting group on the adjacent secondary alcohol to avoid the reaction observed for 673. Acetate protecting groups adjacent to anomeric positions are well known to participate in glycosylation reactions, stabilizing the oxonium intermediate and controlling the face selectivity of the glycosidic bond formation (so called anomeric assistance). We hoped that the acetate group in 674 might help to

\textsuperscript{404} Fluorination of the free hemiacetal 671 always resulted in the production of only one diastereomer at C(3). We did not assign the configuration at this stereocenter.
\textsuperscript{405} The TMS and TBS silyl enol ether of 358 was either prepared \textit{in situ} by treatment of 358 with the respective silyl triflate or alternatively, the TBS enol ether could be prepared (LDA, TBSCI) prior to use and purified by passage over Al\textsubscript{2}O\textsubscript{3}. 
ensure delivery of the oxindole nucleophile from the concave face of the bicyclic system. According to this plan, we subjected 674 to the previously disclosed glycosylation conditions (Scheme 133).

Scheme 133. Reaction of acetate protected fluoride 674.

To our delight, we isolated a product resulting from addition of oxindole 358 to our substrate. Unfortunately, closer spectroscopic analysis revealed that undesired compound 679 was formed as the only product of this reaction. This observation indicated that projected intermediate 680 was indeed formed through participation of the acetate group. However, addition of the nucleophile occurred exclusively to the acetate derived carbonyl group in intermediate 680. Similar reactivity patterns have been observed for highly hindered glycosylation substrates.406

To circumvent this undesired reactivity, we next employed substrate 675 having an unprotected hydroxyl group at C(14) (Scheme 134). Indeed, when 675 was treated with BF₃·OEt₂ in the presence of TMS enol ether of 358, generated in situ, we isolated C(3) coupled product 681 in moderate yield. Spectroscopic analysis suggested that 681 exhibited the undesired configuration at C(3).407 This result is not surprising, as the upper face of a putative oxonium intermediate is much less hindered than the concave side of the bicyclic system.

Scheme 134. Reaction alcohol 675 under C-glycosylation conditions.

We finally turned to a substrate having a TBS silyl ether at C(14). This bulky group was expected to shield the upper face of the oxonium ion, thus forcing the oxindole nucleophile to approach from the

desired side. To our surprise, treatment of 676 under the previously used conditions cleanly produced a product, which did not incorporate an oxindole ring system (Scheme 135). Spectroscopic analysis of the product suggested that the primary alcohol at C(6) had cyclized to the oxonium intermediate to form tricyclic acetal 682.

Scheme 135. Cyclization of bis-TBS silyl ether 676.

We surmise that our putative oxonium intermediate is intercepted by the TBS silyl ether at C(6) to produce an intermediate such as 683. Subsequent loss of the TBS group by attack of a nucleophile (e.g. OTf) would then lead to product formation. Although we did not obtain the envisioned product, this result showed that an intramolecular addition of a nucleophilic species is indeed a feasible strategy to effect closure of the tricyclic gelsemoxonine core. We therefore set out to explore this approach further.

11.2.2. Intramolecular Addition Reactions

Introduction of an oxindole substituent in aldehyde 684 was again tested using the aldol condensation approach developed earlier. Treatment of 684 with oxindole 685, TMSCl, NEt3 and MgBr2 did not produce the desired condensation product (Scheme 136). Instead, a TMS-protected secondary alcohol aldol product was obtained as the only compound.408 Pleasingly, when we changed the Lewis acid to MgI2, we were able to obtain alkene 686 as desired. Again, a number of oxonium precursors were synthesized starting from 686 including a glycosyl acetate 687, carbonate 688, free hemiacetal 689, glycosyl chloride 690 and various glycosyl fluorides (e.g. 691 and 692), along with other substrates not shown here.

408 See experimental for further details.
With these substrates in hand, we tested a wide variety of different activating conditions. Unfortunately, in none of these cases was an intramolecular cyclization observed. In many instances, especially while using glycosyl fluoride substrates, we observed formation of dimeric products. In most cases, hydrolysis of the activated acetal functionality was the only reaction detected. We attribute the unreactivity of all these substrates to the steric situation of the system, as depicted in Figure 27.

In particular, the azetidine ring in oxonium intermediate 693 forces the hydropyran ring and the C(6) methylene together, thus creating a highly sterically crowded environment around the lower face of the oxonium ion. This situation is also exemplified by molecular model 694. As apparent, attack of a nucleophile from the concave face of the bicycle is blocked by the C(6) substituent and the Boc protecting group on the azetidine. The cavity between C(3) and C(6) is too narrow for the approach of a nucleophile from the concave face of the C(3)-oxonium, even if the nucleophile is tethered to C(6).

Based on the analysis above, we reasoned that installation of a smaller carbon nucleophile at C(6) might enable ring closure. Accordingly, we prepared ester 695 and amide 696 from aldehyde 684 (not shown). Various reaction conditions were evaluated to effect closure of an enolate nucleophile, derived from the ethylester in 695, to an oxonium ion generated by extraction of the fluoride.
substituent (Scheme 137). Unfortunately, no formation of product 697 was observed under any of the conditions investigated. However, when amide 696 was treated with LiHMDS in the presence of TMSCl, followed by the addition of BF₃·OEt₂, we were able to detect the formation of a minor product by LC-MS, which had the correct mass of tricycle 698. Although we were able to isolate minute quantities of this compound, spectroscopic analysis proved difficult due to broad peaks in the ¹H NMR spectrum possibly attributed to the formation of rotamers, as well as the presence of several isomeric compounds. We were therefore not able to confirm the formation of product 698 in this reaction.

Scheme 137. Attempts for cyclization of ester 695 and amide 696.

11.3. Conclusion

In conclusion, we were able to introduce an ether substituent at C(3) of the hydropyran ring in gelsemoxonine by DMDO mediated epoxidation of enol ether 550 followed by opening of epoxide 645 by benzyl alcohol (Scheme 138). Subsequent addition of propynyl lithium to isoxazoline 652 provided 654, which underwent ring contraction to form β-lactam 666. Notably, the acetal functional group remained intact during all of these transformations. Conversion of 666 into primary alcohol 669.
11. Oxonium Addition Strategy

proceeded by application of the chemistry developed previously. Interestingly, the benzyl ether substituent in 669 seemed to inflict a weak directing effect in the hydroboration reaction, thus providing alcohol product 669 with reduced diastereoselectivity. Starting from 669, we were able to access various oxonium precursors 699 to test in the key ring closure.

The efficient access to oxonium precursor 699 now allowed us to evaluate our originally proposed strategies for the construction of the gelsemoxonine core structure. Both, inter- and intramolecular addition of oxindole nucleophiles to oxonium intermediates 700 and 404 were attempted (Scheme 139).

Scheme 139. Failed attempts for oxonium addition.

Although in some cases we observed the successful union of the oxindole ring with our hydropyran substrate, the desired chemo- and diastereoselectivity could not be achieved. In fact, intermolecular additions to oxonium species 700 always proceeded from the wrong face, providing the undesired product isomer instead of oxindole 701. In addition, intramolecular addition was only observed for small nucleophiles (oxygen). An oxindole substituent at C(6) was unable to reach the electrophilic site at the other end of the pyran ring. We believe that these observations exemplify the highly congested nature of the system investigated and the natural product gelsemoxonine. Any synthesis route towards gelsemoxonine would have to account for these exceptional challenges.
12. Construction of the Gelsemoxonine Core

Construction of the Gelsemoxonine Core

As outlined in the preceding chapters, our previous attempts for the introduction of the C(7) carbon substituent at a late stage of the synthesis were met with failure. The difficulties associated with stereoselective functionalization of advanced intermediates were largely attributed to the steric crowding and the compact nature of the gelsemoxonine core. These issues severely limited any modification of the carbon skeleton in the natural product. We therefore reasoned that introduction of the C(7) moiety would have to be addressed in an early stage of the synthesis. According to this notion, we proposed a strategic revision of our route towards gelsemoxonine as outlined in Scheme 140. Relying on the previously developed strategy for C(3) oxidation, the revised route commences with enol epoxide 645. Regioselective opening by a carbon nucleophile would provide alcohol 702 incorporating both the designated C(7) carbon and a suitable electron-withdrawing substituent (EWG) thus allowing for further modification of this appendage. Elaboration of the azetidine moiety would then produce intermediate 703 following our previously developed chemistry. The revised tactic would further entail closure of the seven membered carbocycle in gelsemoxonine by exploiting the nucleophilic character of C(7), thus allowing access to the gelsemoxonine core 704 through nucleophilic displacement, as indicated in Scheme 140.

Scheme 140. Revised synthetic strategy including the early introduction of C(7). EWG = electron-withdrawing group.

Implementation of this strategy would address one of the major issues in the synthesis of the natural product gelsemoxonine, namely the construction of its compact tricyclic core. Moreover, additional challenges including formation of the spiro-fused oxindole ring system would still have to be addressed later in the synthesis.
12. Construction of the Gelsemoxonine Core

12.1. Introduction of the C(7) Substituent

Following this plan, we first set out to explore various carbon nucleophiles for their ability to open enol epoxide 645. Table 20 summarizes our attempts undertaken towards this end. Installation of the natural product’s oxindole motif early in the synthesis would represent a major tactical advantage. However, we were skeptical about potential side reactivity of the oxindole carbonyl group under various conditions used for the construction of the azetidine. For example, the oxindole amide is likely to participate in a Petasis olefination reaction. Moreover, the carbonyl group is prone to reduction, resulting in the formation of an aromatic indole product, as observed previously (section 9.3.). This reactivity could potentially interfere with the hydroboration step. However, we were more optimistic that an indole moiety could be carried through subsequent steps and later be oxidized to the corresponding oxindole.409

Table 20. Opening of epoxide 645 by carbon nucleophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Catalyst</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Image of nucleophile]</td>
<td>Bi(OTf)₃</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CF₃CO₂H</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>InCl₃</td>
<td>43%</td>
</tr>
<tr>
<td>2</td>
<td>![Image of nucleophile]</td>
<td>InCl₃</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>![Image of nucleophile]</td>
<td>InCl₃</td>
<td>45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BF₃∙OEt₂</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>![Image of nucleophile]</td>
<td>Bi(OTf)₃</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>InBr₃</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TMSOTf</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>![Image of nucleophile]</td>
<td>InCl₃</td>
<td>38%</td>
</tr>
</tbody>
</table>

[a] Conditions: nucleophile (10 equiv.), catalyst (5-10 mol%), CH₂Cl₂, 0 °C; [b] conducted in THF; [c] this reaction was difficult to reproduce (see text); Nu = nucleophile.

Accordingly, epoxide \textbf{645} \textsuperscript{410} was treated with \textit{N}-methoxy indole \textbf{705} \textsuperscript{411} in the presence of different Lewis acids to effect activation of the oxirane (entry 1). \textsuperscript{412,413} In this case, InCl\textsubscript{3} \textsuperscript{412a,b} proved most effective providing the desired product \textbf{646} in 43\% yield. Next, addition of other nucleophiles was investigated. Allyltrimethylsilane \textbf{706} did not add to epoxide \textbf{645} (entry 2), but instead the starting material underwent decomposition under the employed conditions. Treatment of \textbf{645} with allyl magnesium bromide \textbf{707} also led to destruction of the starting material (entry 3). Next, the use of silyl enol ethers as the nucleophilic species was investigated. Silyl enol ethers have previously been reported to react with various glycosyl donors in \textit{C}-glycosylation reactions. \textsuperscript{414} Again, several Lewis and Brønsted acids were examined as activator for the opening of epoxide \textbf{645} with ethylacetate derived silyl ketene acetal \textbf{708} \textsuperscript{415} (entry 4). Although InCl\textsubscript{3} again induced product formation in moderate yield (45\%), the reaction proved difficult to reproduce. After extensive studies we found that the batch of InCl\textsubscript{3} used greatly influences the reaction outcome. In particular we found that an old batch of the reagent in powder form stored in a glove box promotes the reaction with excellent yield (up to 60\%), whereas the use of newly purchased InCl\textsubscript{3} in crystalline form does not deliver any product. It is not clear to us, if the crystal form of the reagent or other effects are responsible for this outcome. The issue could be circumvented by substituting InCl\textsubscript{3} with InBr\textsubscript{3}. Under these conditions the product was obtained in a yield of 56\% on large scale (2 g). As indicated in Table 20, the use of methyl acetate derived silyl ketene acetal \textbf{709} generated the product in inferior yield (entry 5). It is noteworthy that ethyl acetate derivative \textbf{710} was obtained as a single diastereomer, although the starting epoxide was employed as an isomeric mixture as indicated (Scheme 141). We assume that only one oxirane isomer is reactive under these conditions. Indeed, when the reaction was quenched with MeOH and a few drops of HCl in MeOH, acetal \textbf{711} was obtained along with the desired product. This observation confirms that the minor epoxide isomer remains untouched by InBr\textsubscript{3}. Moreover, when the reaction was performed on large scale, we observed formation of trace amounts of unsaturated ester \textbf{712} resulting from opening of the hydropyran ring after epoxide opening (Scheme 141, box).

\textsuperscript{410} As reported before, \textbf{645} was obtained as a 2:1 mixture of diastereomers in favor of the one shown. This mixture was used for all reactions.

\textsuperscript{411} Prepared according to: Somei, M.; Kawasaki, T. \textit{Heterocycles} \textbf{1989}, 29, 1251-1254.


Scheme 141. Side products obtained in the opening of epoxide 645 with silyl enol ether 708.

As outlined in Scheme 142, the obtained products were now subjected to the propynyl lithium addition protocol. Interestingly, when indole 713 was treated under the previously established conditions, only ring expanded product 714 was obtained along with reisolated starting material. This again supports the aforementioned notion that bulky C(3) substituents are not tolerated in this reaction (section 11.1.). To exclude the possibility of competitive metalation of the indole C(2) position by the organolithium species, the reaction was quenched by addition of TMSCl. The only compound isolated under these conditions was substrate 715, in which C(16) stereocenter had epimerized, indicating deprotonation at this position in the course of the reaction. In contrast, when ester 710 was subjected to the established propynyl addition protocol, the desired isoxazolidine 716 was obtained in excellent yield and with full conversion of the starting material.\footnote{An N-methoxy substituent on the indole nitrogen is known to facilitate C(2) metalation (ref. 255b).} Notably, the ester carbonyl was not affected and remained intact. This was surprising, as ester carbonyl groups are generally known to be more electrophilic than oxime ether derivatives.\footnote{Careful optimization of solvent ratio (hexanes/THF) and substrate concentration proved essential to achieve full conversion.}

Scheme 142. Attempts for propynyl lithium addition to isoxazolines 713 and 710.

\footnote{An N-methoxy substituent on the indole nitrogen is known to facilitate C(2) metalation (ref. 255b).}
\footnote{Careful optimization of solvent ratio (hexanes/THF) and substrate concentration proved essential to achieve full conversion.}
\footnote{For an example, see: Gravestock, M.B.; Carcanague, D.R. WO 2005116024.}
Having C(3) functionalized isoxazolidine 716 in hand, we again turned our attention to the key ring contraction for the formation of the corresponding β-lactam product 717 (Table 21). Treatment of 716 with CF₃CO₂H at 80 °C produced the desired product albeit in moderate yield compared to previous substrates (entry 1). In order to allow for efficient scale up of the current route, we were therefore interested in improving the efficiency of this transformation. To this end, we initially set out to screen different protic acids with a pKₐ value similar to CF₃CO₂H (entries 2-10). The use of ion exchange resin Amberlyst 15 thereby produced the product in equal yield and conversion (entry 6). Moreover, side product formation was reduced under these conditions allowing for easy purification of the product. However, none of the other acids screened led to an improvement of the reaction outcome.

**Table 21. Optimization of ring contraction of isoxazolidine 716.**

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Acid</th>
<th>Conversion</th>
<th>Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CF₃CO₂H</td>
<td>89%</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>p-TsOH</td>
<td>decomp.</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>MsOH</td>
<td>78%</td>
<td>27%</td>
</tr>
<tr>
<td>4</td>
<td>K10 clay</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Dowex 50WX8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Amberlyst 15</td>
<td>90%</td>
<td>41%</td>
</tr>
<tr>
<td>7</td>
<td>PPTS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Ph₃P·HBr</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>HBF₄·OMe₂</td>
<td>decomp.</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>HCl[c]</td>
<td>decomp.</td>
<td>-</td>
</tr>
<tr>
<td>11[d]</td>
<td>CF₃CO₂H</td>
<td>100%</td>
<td>68%</td>
</tr>
<tr>
<td>12[d,e]</td>
<td>CF₃CO₂H</td>
<td>50%</td>
<td>35%</td>
</tr>
<tr>
<td>13[d,e]</td>
<td>CF₃CO₂H</td>
<td>100%</td>
<td>45%</td>
</tr>
</tbody>
</table>

[a] Conditions: substrate (20 mg), acid (2 equiv.), MeCN, 80 °C; [b] yield of isolated product; [c] HCl was tested as a solution in EtOAc, dioxane and water, respectively; [d] the reaction was quenched by addition of NEt₃; [e] carried out on a 1 g scale.

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419 Different solvents were tested as well including toluene, DCE, THF. However, under all of these conditions the starting material decomposed completely.

Closer investigation of the reaction mixture revealed that acid \( 718 \) was formed as a byproduct in varying amounts, accounting for the low yield of \( 717 \).\(^{421}\) The formation of \( 718 \) can be easily explained by attack of \( \text{CF}_3\text{CO}_2\text{H} \) on \( \beta \)-lactam product \( 717 \), generating a mixed anhydride intermediate \( 719 \) (Scheme 143). \( N \)-acylation of the free amine in \( 719 \) then produces acid \( 718 \). Based on TLC analysis of the reaction, we suspected that formation of this side product most likely occurred during column chromatography on \( \text{SiO}_2 \). We thus decided to quench the reaction by addition of triethylamine thereby sequestering the remaining \( \text{CF}_3\text{CO}_2\text{H} \) in the reaction mixture. Application of this tactic led to a significant increase in the yield of \( 717 \) (68%, Table 21, entry 11). Increasing the scale of the reaction to 1g of substrate however required interruption of the reaction after 50% conversion to obtain an optimal yield of 70% brsm (entry 12). When the reaction was run until all the substrate had been consumed, the product was obtained in only 45% yield (entry 13).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{Et} \\
\hline
\text{CF}_3 & \quad \text{CO}_2\text{H} \\
\hline
\text{N} & \quad \text{NH}_2 \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{Et} \\
\hline
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{Et} \\
\hline
\text{CF}_3 & \quad \text{CO}_2\text{H} \\
\hline
\text{N} & \quad \text{NH}_2 \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{Et} \\
\hline
\end{align*}
\]

Scheme 143. Proposed rationale for the formation of acid \( 718 \) in the ring contraction of \( 716 \) to \( 717 \).

We further proceeded to elaborate the azetidine as shown in Scheme 144. Application of the previously successful strategy proved uneventful. Boc protection of \( 717 \) delivered carbonate \( 720 \) in 85% yield. X-ray crystallographic analysis once again confirmed the structure of \( 720 \) (Scheme 144, box). As observed before, the hydropyran ring adopted a boat-like conformation, where the C(3) substituent is located in a pseudo-axial position. Subsequent Petasis olefination produced enecarbamate \( 721 \) in 77% yield. Hydroboration of \( 721 \) generated primary alcohol \( 722 \) as a single

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{Et} \\
\hline
\text{Boc} & \quad \text{O} \\
\text{NEt}_3, \text{DMAP} \\
\text{CH}_2\text{Cl}_2 & \quad 85\% \\
\hline
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{Et} \\
\hline
\text{Boc} & \quad \text{O} \\
\text{NEt}_3, \text{DMAP} \\
\text{CH}_2\text{Cl}_2 & \quad 85\% \\
\hline
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{Et} \\
\hline
\text{Boc} & \quad \text{O} \\
\text{NEt}_3, \text{DMAP} \\
\text{CH}_2\text{Cl}_2 & \quad 85\% \\
\hline
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{Et} \\
\hline
\end{align*}
\]

Scheme 144. Synthesis of primary alcohol \( 722 \).

diastereomer. In order to avoid potential hydrolysis of the ethyl ester under the usually highly basic conditions employed for oxidative cleavage of organoboranes, we switched to sodium perborate (NaBO$_3$) as the oxidizing agent. Under these optimized conditions, alcohol 722 was obtained in an excellent yield of 92%.

12.2. C(6)-C(7) Ring Closure

With the azetidine ring established, we could now address the closure of the carbocyclic ring of the gelsemoxonine core fragment. Formally, this would entail displacement of the primary alcohol in 722 by the nucleophilic α-carbon of the ester on the opposite side of the hydropyran ring. As depicted in Scheme 145, a number of attempts were undertaken to achieve such a transformation. Treatment of mesylate 723 with various bases did not effect the desired ring closure but instead led to decomposition of the starting material. Subjecting the more stable tosylate 724 to KHMDS or KOt-Bu produced tetrahydrofuran derivative 725 as the sole product. Formation of 725 can be explained by initial deprotonation of the ester followed by hydropyran opening. The intermediate alcoholate can then undergo intramolecular alkylation to close the hydrofuran ring. We further tested the intramolecular nucleophilic displacement of a C(6) mesylate by an enamine generated by treatment of aldehyde 726 with an amine. Unfortunately, none of the amines tested (Et$_2$NTMS, piperidine, 

Scheme 145. Unsuccessful attempts to close the seven membered carbocycle of the gelsemoxonine core.

---

423 The use of LDA in this reaction did not produce any product.
proline) effected the desired ring closure to 727. We next explored the use of esteraldehyde 728. Various bases (LDA, LiHMDS, NaHMDS) in the absence or presence of Lewis acid additives (MgBr₂, BF₃·OEt₂, TMSOTf) were evaluated to this end. Unfortunately, we never observed the formation of a ring closed product 729. Also attempted conversion of the aldehyde functionality into a nitrone (HONH₂/DBU) did not produce any product.⁴²⁵

We finally envisioned an intramolecular aldol condensation of a dialdehyde 730 (Scheme 146). Although the aldol reaction belongs to the most basic repertoire of synthetic organic chemistry,⁴²⁶ intramolecular aldol condensations of dialdehydes have been met with various difficulties. In particular, the issue of potential formation of different regioisomeric products has only scarcely been addressed.⁴²⁷ However, we strongly suspected that dialdehyde 730 will be biased for the formation of the desired regioisomer based on steric grounds. We expected the C(7) aldehyde to act as a nucleophile attacking the C(6) carbonyl group. Accordingly, the projected substrate was prepared by reduction of ester 722 with DIBAL-H to give diol 731 (Scheme 146, top). Subsequent oxidation of both alcohols under Swern conditions⁴²⁸ provided dialdehyde 730 in good yield. We now explored conditions for aldol ring closure. Treatment of 730 with Bn₂NH·TFA led to decomposition of the starting material.⁴²⁹ However, treatment of dialdehyde 730 with catalytic amounts of piperidine for

![Scheme 146. Synthesis of dialdehyde 730 and ring closure by an aldol condensation.](image)

---


⁴²⁸ Oxidation with Dess–Martin periodinane, PDC or TEMPO/PhI(OAc)₂ was very sluggish and provided the product in inferior yield.

the first time effected the desired ring closure to provide a 1:2 mixture of condensed aldehyde 732 and alcohol 733\textsuperscript{430}, albeit in low yield. Switching to the more hindered 2,2,6,6-tetramethylpiperidine (TMP) abolished the reaction completely. To our delight, when a catalytic amount of pyrrolidine was used, unsaturated aldehyde 732 was cleanly generated as the only compound. Careful optimization of the reaction conditions revealed that lowering the temperature to -40 °C allowed for the synthesis of 732 in 73% yield.

In the course of optimization studies targeted towards increasing the reaction yield of this reaction, we decided to follow the cyclization by NMR. To our surprise, we observed instantaneous and clean formation of an intermediate species when aldehyde 730 was mixed with pyrrolidine in an NMR tube. Based on 2D NMR analysis of the reaction mixture we assigned structure 734 to this intermediate (Scheme 147). Interestingly, slow decomposition of 734 was observed, when the reaction was left standing. Only upon attempted chromatographic purification on SiO\textsubscript{2} did the cyclization event occur. The exceptional stability of hemiaminal 734 is not entirely clear to us. On one hand, formation of an enamine at C(6) seems unfavorable as a highly strained enecarbamate would thereby be generated. On the other hand, the steric environment around the C(6) aldehyde might favor a tetrahedral geometry of this stereocenter or otherwise stabilize the hemiacetal intermediate. Moreover, the great difficulty for cyclization of 734 might be a manifestation of the compact nature of the bicyclic system. It is very likely that the proximity of C(6) and C(7) lead to steric repulsion between these two residues. Such an interaction might cause a conformational change of the hydropyran ring bringing the two substituents further away from each other. On the other hand, unfavorable conformational preferences of the two side chains might hamper proper orbital overlap. Such an explanation would also account for the lack of reactivity towards ring closure of the previously investigated system (Scheme 145).

Scheme 147. NMR analysis of the aldol condensation of dialdehyde 730 with pyrrolidine.

\textsuperscript{430} The relative stereochemistry of 733 was not determined at this point, but could later be assigned based on NOE analysis of the product of the reaction described in Scheme 148.
Upon screening of different secondary amine catalysts for the aldol reaction of dialdehyde 730, we discovered that the use of racemic proline in this reaction selectively delivers only the secondary alcohol product 733 in excellent yield (Scheme 148). Interestingly, only a single diastereomer was isolated from the reaction mixture. NOE and J-coupling analysis suggested the relative stereochemistry shown for 733 (Scheme 148, box). This secondary alcohol could also be converted into unsaturated aldehyde 732 by treatment with TFAA in the presence of DBU.431

Scheme 148. Aldol cyclization of dialdehyde 730 with DL-proline.

In order to adjust the oxidation state at C(6), we explored reduction of the double bond in unsaturated aldehyde 732 (Scheme 149). Interestingly, hydrogenation of 732 (H2, Pd/C) effected rapid decomposition of the starting material. Treatment of 732 with Hantzsch ester produced the same result.432 Finally, we turned our attention to protocols involving metalhydride reagents. In particular, copper hydride species have found wide application in the reduction of unsaturated carbonyl compounds.433 One of the most commonly used reagents of that type is the hexameric copper complex [{(PPh3)CuH}6] developed by Stryker.434 The reductions of various unsaturated carbonyl compounds can be achieved by using this reagent. When we treated aldehyde 732 with a slight excess of freshly prepared [{(PPh3)CuH}6]435 in toluene, the immediate reduction of the endocyclic olefin was observed providing the desired product in moderate yield (ca. 40%). We found that lowering the reaction temperature to -78 °C leads to a significant increase of the yield, generating an epimeric mixture of aldehydes 727a and 727b in 68% (Scheme 149). This is quite remarkable, as unsaturated aldehydes generally require several hours to undergo complete reduction at ambient temperature, whereas our substrate undergoes complete reduction within a few minutes at cryogenic temperature.434 The unusual reactivity of our system might reflect the strained nature of the double bond in 732, which is a consequence of the polycyclic framework of the gelsemoxonine core. Also later in the synthesis, we have observed an unusually high reactivity of this olefin towards various conditions (vide infra).

During further attempts to optimize the conjugate reduction of 732, we explored the addition of

431 See later in the text for a more detailed discussion of this elimination.
TMSCl to the reaction mixture.\textsuperscript{436} Interestingly, under these conditions a mixture of TMS enol ether 734 and diastereomerically pure aldehyde 727a was obtained. When silyl enol ether 734 was then treated with TBAF, only the isomeric aldehyde 727b was generated. We surmise that diastereomer 727a is produced upon kinetic protonation of a copper enolate intermediate, while thermodynamic protonation generates only aldehyde 727b.\textsuperscript{437} Furthermore, this result indicates that stereoselective introduction of an aryl moiety at C(7) as required later in the synthesis, might be achieved under kinetic control.

Scheme 149. Conjugate reduction of unsaturated aldehyde 732 using Stryker’s reagent.

As outlined in Scheme 150, we were also able to oxidize aldehyde 727 to acid 735 under Pinnick conditions.\textsuperscript{438} Subsequent esterification was achieved by treatment of 735 with trimethylsilyl diazomethane generating methyl ester 736 in good yield (65%).

Scheme 150. Oxidation of aldehyde 727 under Pinnick conditions.

\textsuperscript{436} TMSCl was reported to have a beneficial effect in reductions of unsaturated carbonyl compounds by Stryker’s reagent: see ref. 434.
\textsuperscript{437} A pseudo-equatorial position of the aldehyde substituent is likely to be thermodynamically favored. This notion is also confirmed by the exclusive formation of diastereomer 733 in the intramolecular aldol reaction of diaddehyde 730 (Scheme 148).
**12.3. Conclusion**

In summary, we have synthesized the tricyclic core fragment of gelsemoxonine relying on an intramolecular aldol reaction. As outlined in Scheme 151, the revised strategy starts with addition of ethylacetate derived ketene silyl acetal 708 to enol epoxide 645. Careful tuning of the reaction conditions thereby allowed for controlled reaction of only the major diastereomer of the epoxide starting material. Therefore, only diastereomeric product 710 was obtained under the reaction conditions. Elaboration of azetidine 722 was carried out following the previously developed tactic. Finally, the seven membered carbocycle of gelsemoxonine was established by an aldol reaction of dialdehyde 730, available through a sequence of reduction/oxidation starting from primary alcohol 722. In the event, treatment of dialdehyde 730 with pyrrolidine effected an intramolecular condensation to obtain unsaturated carbonyl compound 732 as the only product. Alternatively, the use of DL-proline in this reaction allowed for the production of secondary alcohol 733 in excellent yield.

![Scheme 151](image.png)

**Scheme 151.** Synthesis of the gelsemoxonine core fragment relying on an intramolecular aldol cyclization.

With the full carbon skeleton of the gelsemoxonine core in hand, we next addressed the construction of the oxindole motif of the natural product. This would entail stereoselective formation of a quaternary stereocenter at C(7). Our studies undertaken towards this end are outlined in the following chapter.
Construction of the C(7) Quaternary Stereocenter

After the successful construction of the tricyclic core fragment of gelsemoxonine, complete elaboration of the carbon skeleton of the natural product demanded installation of the spiro-fused oxindole ring system including the quaternary stereocenter at C(7) (Scheme 152). As a consequence of our synthetic tactic which relied on the early construction of the tricyclic core, the C(7) carbon was already in a highly congested environment. In particular, the hydropyran ether bridge at C(3) would likely hamper functionalization from the top face of C(7). This situation is in stark contrast with most previously reported syntheses of gelsemium alkaloids, in which this ether bridge is generally constructed after oxindole formation (see section 7.5.).

Scheme 152. Tactical options for the construction or the oxindole ring system in gelsemoxonine.

In general terms, we envisioned two differential tactics for the introduction of an aryl group at C(7). As indicated in Scheme 152, a saturated carbonyl compound 737 could serve as a substrate for arylation of its corresponding enolate, or related derivatives. Alternatively, the double bond of unsaturated system 738 might serve as a handle for C(7) functionalization by formal hydroarylation. This approach seemed particularly attractive due to the high reactivity of the endocyclic olefin we have observed previously.
13.1. Intermolecular Arylation Attempts

Following the first tactic described above, we envisioned to explore intermolecular enolate arylation chemistry to allow for installation of the C(7) quaternary stereocenter. The α-arylation of carbonyl compounds has traditionally gained great attention in both organic and organometallic chemistry due to the wide abundance of this motif in many biologically relevant compounds. The first strategies developed to achieve α-arylation of carbonyl substrates generally involved the stoichiometric use of highly toxic metal species such as aryl bismuth or lead compounds.\(^{439}\) In addition, the substrate scope of these reactions was usually limited due to the harsh conditions required for product formation. In recent years however, highly efficient catalytic enolate arylation protocols were developed.\(^{440}\) In particular the pioneering work of Miura, Buchwald, and Hartwig has established the use of palladium catalysts to effect this transformation.\(^{441,442}\)

![Scheme 153](image)

**Scheme 153.** General pathway for the palladium catalyzed α-arylation of enolates (box) and projected application to aldehyde 727.

As outlined in Scheme 153 (box), the general reaction path for palladium catalyzed enolate arylation proceeds *via* the initial generation of a metal enolate 739 (M = Na, Li, etc.) or an equivalent species (e.g. silyl enol ethers) from carbonyl compound 740. Aryl palladium complex 741, generated by oxidative insertion of Pd(0) into an aryl halide bond, reacts with this enolate derivative to form intermediate 742. Subsequent reductive elimination of palladium regenerates the active catalyst and delivers the product 743. The application of such a strategy for construction of the quaternary C(7) center of gelsemoxonine would preferentially start from aldehyde precursor 727 (Scheme 153,

bottom). This substrate class would later allow for facile formation of the oxindole amide functionality by oxidative cyclization \((744\rightarrow 745)\). Moreover, arylation reactions with aldehydes are commonly performed under very mild conditions favorable for sensitive substrates (\textit{vide infra}).

As depicted in Scheme 154, we first set out to test this approach on cyclohexanecarboxaldehyde 746 as a simple model system. Several protocols for the palladium catalyzed arylation of \(\alpha\)-branched aldehydes with a wide range of substituted arylhalides to generate quaternary stereocenters have been reported by Buchwald and Hartwig.\(^{443}\) The coupling of \textit{ortho} substituted bromoarenes with \(\alpha\)-disubstituted aldehydes has not been documented to date. In order to finally construct the oxindole system in gelsemoxonine, the use of a 1,2-disubstituted aryl precursor would be desired. We thus investigated the coupling of various aryl substrates (747-749) with aldehyde 746 under conditions reported by Hartwig (Scheme 154).\(^{444}\) However, none of the tested substrates delivered the desired product. Instead, biphenyl derivatives such as 750 were obtained as the sole products. It is most likely that \textit{ortho} substituents on the arene ring are not tolerated due to steric clash with the aldehyde substrates.

\[\text{Scheme 154. Attempted arylation of model system 746 with various \textit{ortho}-substituted bromoarenes.}\]

Besides the aryl bromides depicted in Scheme 154, we also tested the use of \(N\)-alkylated aniline derivatives as coupling partners. To our great surprise, treatment of cyclohexanecarboxaldehyde 746 with \(N\)-benzyl-2-bromoaniline 751\(^{445}\) under standard arylation conditions afforded oxindole 752 as the only observable product (Scheme 155).\(^{446}\)

\[\text{Scheme 155. Formation of oxindole 752 upon palladium catalyzed arylation of aldehyde 746.}\]


\(^{444}\) Also the Buchwald protocols were tested, but without success.

\(^{445}\) Unprotected 2-haloanilines cannot be used in this transformation.

\(^{446}\) \(N\)-methyl-2-bromoaniline can also be used as coupling partner to provide the corresponding product in similar yield.
Table 22. Optimization of the oxidative oxindole formation from aldehyde 746.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd-source</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent (b)</th>
<th>Convn. in % (c)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>S-Phos</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>HIPr-HBF$_4$</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>IPr-HCl</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>[(t-Bu$_3$P)PdBr]$_2$</td>
<td>-</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>Pd$_2$(dba)$_3$</td>
<td>t-Bu$_3$P</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>Pd$_2$(dba)$_3$</td>
<td>Cy$_3$P</td>
<td>Cs$_2$CO$_3$</td>
<td>dioxane</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Pd$_2$(dba)$_3$</td>
<td>t-Bu$_2$MeP</td>
<td>Cs$_2$CO$_3$</td>
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<td>-</td>
</tr>
<tr>
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<td>BINAP</td>
<td>Cs$_2$CO$_3$</td>
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<td>14</td>
<td>Pd(MeCN)$_2$(BF$_4$)$_2$</td>
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<td>Cs$_2$CO$_3$</td>
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<td>NaHCO$_3$</td>
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<td>BINAP</td>
<td>K$_3$PO$_4$</td>
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<td>-</td>
</tr>
<tr>
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<td>BINAP</td>
<td>Cs$_2$CO$_3$</td>
<td>toluene</td>
<td>21</td>
</tr>
<tr>
<td>21</td>
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<td>BINAP</td>
<td>Cs$_2$CO$_3$</td>
<td>THF</td>
<td>56</td>
</tr>
<tr>
<td>22</td>
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<td>BINAP</td>
<td>Cs$_2$CO$_3$</td>
<td>DMF</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>23</td>
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<td>BINAP</td>
<td>Cs$_2$CO$_3$</td>
<td>DCE</td>
<td>-</td>
</tr>
<tr>
<td>24</td>
<td>Pd(TFA)$_2$</td>
<td>BINAP</td>
<td>Cs$_2$CO$_3$</td>
<td>DME</td>
<td>22</td>
</tr>
</tbody>
</table>

[a] conditions: aldehyde (1 equiv.), N-benzyl-2-bromoaniline 751 (2 equiv.), Pd-source (4 mol%), ligand (4 mol%), base (2 equiv.), solvent, 80 °C, overnight; b) The solvent was degassed prior to use. However no difference in conversion was observed when the degassing step was omitted; c) Conversion based on 751, determined by crude NMR analysis.

We were intrigued by this unprecedented transformation for numerous reasons. On one hand, this reaction harbors a synthetic potential for the preparation of fully substituted oxindole rings starting from simple aldehyde precursors. Moreover, the reaction seems mechanistically intriguing. To account for the formation of the amide functionality in 752, an oxidation event has to occur in the course of the
reaction. The origin of this oxidation is still unclear as no designated oxidant is present in the reaction and the reaction works with equal efficiency under argon\(^{447}\), air, or an oxygen atmosphere. Moreover, protodebrominated arene substrate was observed as the only side product.\(^{448,449}\) In order to improve the reaction outcome, we started a detailed screen of reaction conditions as outlined in Table 22. The addition of various additives like \(\text{Bu}_4\text{NBr}, \text{Bu}_4\text{NCl}, \text{LiCl}, \text{H}_2\text{O},\) pyrroldine, or diphenylmethanamine, as well as addition of oxidants such as benzoquinone, \(\text{AgNO}_3, \text{Ag}_2\text{CO}_3, \text{Cu(OAc)}_2, \text{Cu(OTf)}_2,\) or diacetoxy iodobenzene did not improve the reaction outcome (not shown in the table). Next, we tested various palladium sources and ligands including phosphate and \(N\)-heterocyclic carbene ligands (entries 1-14). We found inexpensive BINAP to be one of the most efficient ligands (entry 10). Moreover, \(\text{Pd(TFA)}_2\) was identified as the optimal palladium source (entry 13). Interestingly, when different bases were tested, we discovered that only \(\text{Cs}_2\text{CO}_3\) could promote the reaction (entries 15-19).\(^{450}\) Finally, a solvent screen revealed THF to be clearly superior over other solvents (entries 20-24). However, after all these optimization attempts, we were not able to achieve more than 56% conversion of the aldehyde substrate (entry 21).

![Scheme 156](image)

**Scheme 156.** Mechanistic options for the formation of oxindole 752.

A mechanistic rationale of this unprecedented transformation would have to account for two peculiarities of the reaction. First, the successful aldehyde arylation would have to be explained with regards to the inability of other \textit{ortho}-substituted bromoarene substrates to undergo a coupling reaction with aldehyde 746 (Scheme 154). Second, the cause of the aforementioned cryptic oxidation step needs to be included. A possible mechanistic pathway is given in Scheme 156. Two possible options for the arylation step can be imagined (path a and b). Either the aniline could first condense with the aldehyde substrate to form enamine 753 (path a). Oxidative insertion of \(\text{Pd(0)}\) would produce intermediate 754. From this intermediate, two possibilities for further reaction are depicted (c and d). An enamine arylation reaction would proceed \textit{via} iminium 755, whereby the enamine functionality

\(^{447}\) The solvent was thoroughly degassed by freeze/pump/thaw before use.

\(^{448}\) One might expect the aldehyde substrate to serve as an electron acceptor producing a corresponding alcohol product. Such a side product was never observed.

\(^{449}\) Protodehalogenation is a common side reaction in palladium catalyzed coupling reactions.

\(^{450}\) The use of \(\text{NaO}t\text{-Bu}\) and \(\text{KO}t\text{-Bu}\) led to rapid decomposition of the starting materials.
serves as a nucleophile displacing a bromide ligand on the palladium (path c). After reductive elimination, iminium ion 756 would be produced. Alternatively, an intramolecular carbo-palladation of 754 would provide alkyl-palladium intermediate 757 (path d).451,452 Subsequent elimination of Pd(0) would then also produce iminium ion 756. The same intermediate could also be accessed by path b involving a traditional aldehyde arylation. This pathway would not readily explain the ease of the coupling compared to the previously unsuccessful reactions. Possibly, intramolecular coordination of the amino group in 758 might influence the reactivity of the putative aryl palladium intermediate, thus allowing for coupling with enolate 759. After successful union of these two components, aldehyde 760 would be produced, which upon dehydrative iminium ion formation would also furnish intermediate 756. Finally, oxidation of this iminium ion produces the observed oxindole product 752. The nature of this oxidation remains unclear.453

Application of this newly discovered transformation was tested on substrate 727b as shown in Scheme 157. Unfortunately, treatment of 727b with N-benzyl-2-bromoaniline 751 and dimeric palladium(I) catalyst [(t-Bu3P)PdBr]2454,455 led to complete decomposition of aldehyde 727b. Further attempts to effect oxindole formation remained without success.

Scheme 157. Attempted application of the oxidative oxindole formation with aldehyde 727b.

The inability to install a pre-functionalized aryl ring in tricyclic aldehyde 727 prompted us to investigate an alternative strategy as depicted in Scheme 158. The use of C–H oxidation approaches for the direct functionalization of aryl C–H bonds has recently attracted immense interest.456 In

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452 When treating aldehyde 746 and aniline 751 under previously reported Heck-type conditions (Pd(OAc)2, DABCO), no product formation was observed.

453 The oxidation of the aldehyde carbon could in principle occur before the arylation event. However, this seems unlikely, as amide arylations are more challenging than aldehyde arylations.

454 This catalyst has been reported to be exceptionally active for difficult coupling reactions including ester enolate arylations: Hama, T.; Hartwig, J.F. Org. Lett. 2008, 10, 1545-1548; and references therein.

455 This experiment was performed on an early stage of the optimization studies outlined in Table 22. Palladium catalyst [(t-Bu3P)PdBr]2 had previously proved beneficial to prevent substrate decomposition, while other palladium sources were inferior in this regard. However, for this transformation, decomposition of the starting material was observed.

particular, intramolecular amination reactions have been documented, which allow for the formation of ring systems, including oxindoles.\textsuperscript{457,458} As depicted in Scheme 158, such a transformation could be exploited to enable access to spiro-fused oxindole 761 from aldehyde precursor 746. Arylation of 746 with bromobenzene (762) would then produce aldehyde 763. After conversion into hydroxamic ester 764, this compound would be subjected to a C–H oxidation protocol producing oxindole 761. As shown in Scheme 158 (top), arylation of cyclohexanecarboxaldehyde 746 was indeed successful using bromobenzene as coupling partner. We next set out to test this protocol on the gelsemoxonine core fragment 727a (Scheme 158, bottom). Unfortunately, no product formation was observed with this substrate. Instead, the starting material epimerized to produce a mixture of C(7) epimers 727.

Scheme 158. Aldehyde arylation using bromobenzene and projected C–H oxidation to produce an oxindole product (top) and attempted application to gelsemoxonine system 727a (bottom).

Besides aldehyde substrates, ester derivatives have also been reported to undergo α-arylation under palladium coupling conditions.\textsuperscript{459} However, stronger bases such as NaHMDS or LiNCy\textsubscript{2} are required to generate the respective ester enolate nucleophile. More recently, milder protocols starting from zinc enolate precursors\textsuperscript{460} or silyl ketene acetals\textsuperscript{461} have been documented. In all of the reported reactions, 1,2-disubstituted haloarenes were never used as coupling partners with α-branched esters to generate quaternary stereocenters. Nevertheless, we set out to test 2-bromo-nitrobenzene as a potential substrate for the coupling with model silyl ketene acetal 765 (Scheme 159, top).\textsuperscript{462} The mild conditions for this transformation reported by Hartwig and coworkers rely on the addition of ZnF\textsubscript{2} as an activating


\textsuperscript{462} 765 was prepared from the corresponding cyclohexane carbocyclic acid by esterification and silyl ketene acetal formation.
agent.\textsuperscript{463} When silyl ketene acetal 765 was subjected to this protocol, no formation of expected product 766 could be observed. We next focused on arylation of unactivated methyl ester 767. Several bases were tested, whereby LiNCy\textsubscript{2} was found to give superior results, producing 768 in 75% yield when palladium(I) catalyst [(t-Bu\textsubscript{3}P)PdBr\textsubscript{2}] was used (\textit{vide supra}).

\begin{equation}
\begin{array}{c}
\text{OTMS} \quad \text{O} \quad \text{OH} \\
\text{765} \quad \text{766}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{OMe} \quad \text{767} \quad \text{768}
\end{array}
\end{equation}

\textbf{Scheme 159.} Attempts for intermolecular ester arylation.

Unfortunately, application of this protocol to substrate 736a did not provide any of the desired product 769 (Scheme 159, box). A number of different bases were tested (NaHMDS, LiHMDS, LiNCy\textsubscript{2}) without success. Interestingly, no epimerization of the ester α-carbon was observed in any of these reactions and the substrate was reisolated unaffected. In order to test if deprotonation at C(7) in fact occurred upon treatment of 736a with these strong bases, we tested a variety of different electrophiles as trapping agents for the putative enolate intermediate, as shown in Scheme 160. We first investigated different alkylating reagents including allylbromide, nitroolefin 770\textsuperscript{464} and methyl iodide for reaction with 736a. In particular, a successful coupling of 736a to nitroolefin 770 would offer the opportunity to access a corresponding nitroarene by oxidation of the resulting product. However, in none of these reactions could any product 771 be observed and again, the starting material was recovered unchanged.\textsuperscript{465} Finally, to unambiguously determine if the enolate could be formed in this system, we subjected ester 736a to NaHMDS at ambient temperature and quenched the reaction with D\textsubscript{2}O. In this case, substrate 736a was recovered without any incorporation of deuterium, as determined by \textsuperscript{1}H NMR analysis. This result strongly suggests that ester 736a cannot be enolized,  

\textsuperscript{463} Several observations suggest that this reaction does not proceed \textit{via} a zinc enolate. The mode of activation of the ZnF\textsubscript{2} additive is not clear (see ref. 22).

\textsuperscript{464} Prepared in two steps from cyclohexene according to: Efremova, I.E.; Vakulenko, M.I.; Lysenko, K.A.; Bushmarinov, I.S.; Lapshina, L.V.; Berkova, G.A.; Berestovitskaya, V.M. Russ. J. Gen. Chem. 2010, 80, 2298-2305.

\textsuperscript{465} The reaction was tested on both epimers of 736 and different bases were employed.
even with strong bases. We suspect that steric clash between the ester group in 736a and the tricyclic gelsemoxonine core forces the ester to adopt a conformation whereby the plane of the C=O double bond stands perpendicular to the ring system. This renders efficient overlap of the carbonyl π* with the C(7)-H σ orbital impossible, thus blocking enolate formation.

Scheme 160. Experiments for the addition of various electrophiles to ester 736a.

As enolization at C(7) seemed a major challenge, we opted for a strategy employing an enolate precursor as arylation substrate. In this context, the use of vinyl acetate derivatives such as 772 for the construction of quaternary stereocenteres has recently been reported (Scheme 161).466 This approach relies on the treatment of a vinyl acetate with Bu₃SnOMe to generate an intermediate tin enolate 773. This reactive species would then undergo a Stille-type arylation reaction from its isomer 774 to provide product 775. Treatment of vinyl acetate 772 under the reported conditions allowed for the successful incorporation of bromobenzene, giving 775 in 50% yield. We thus set out to prepare an appropriate vinyl acetate derivative of our gelsemoxonine core structure. To this end, unsaturated aldehyde 732 was treated with Stryker’s reagent in the presence of Ac₂O to trap the intermediate copper enolate (Scheme 161, bottom). Vinyl acetate 776 was isolated in moderate yield. Subjecting this compound to the previously successful Stille coupling protocol did not produce any arylated product, but led exclusively to hydrolysis of the vinyl acetate moiety furnishing 727a.

Scheme 161. Attempted arylation of vinyl acetate 776.

Analysis of the results from the attempted intermolecular enolate arylation reactions strongly suggested that the steric hindrance around the C(7) carbon was too pronounced to allow any functionalization of this position by intermolecular approaches. Prior attachment of the aryl moiety to the C(2) carbonyl appendage, followed by an intramolecular cyclization might circumvent these problems through favorable entropic effects and conformational restraints. We thus set out to implement such a strategy as detailed in the following section.

13.2. Intramolecular Arylation Attempts

13.2.1. Fischer Indole Synthesis

Oxindole rings, such as the one found in gelsemoxonine, can be derived from indole substrates by oxidation of the electron rich pyrrole moiety. In fact, the construction of indoles and their derivatives represents an extensively investigated problem in organic chemistry. One of the first procedures for indole synthesis that is still used today, was reported by Fischer in 1883. Fischer observed that the treatment of carbonyl compounds with arylhydrazines under acidic conditions effects a cyclization reaction to produce indole products with concomitant extrusion of ammonia. This strategy could potentially serve our goal of constructing the C(7) quaternary stereocenter of gelsemoxonine from an α-disubstituted aldehyde substrate. As outlined in Scheme 162 (top), this plan was tested by treatment of our model substrate with phenylhydrazine in the presence of CF₃CO₂H (2 equivalents). Indeed, indolenine was produced in 66% yield, possibly via intermediates and Elaboration of the N-hydroxy oxindole ring system was further tested as outlined in Scheme 162 (bottom). In the event, reduction of using NaBH₃CN produced indoline. Subsequent oxidation with sodium tungstate delivered a mixture of N-hydroxy oxindole and nitrone. Alternatively, m-CPBA mediated oxidation of to indoxyl proceeded with low

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yield.\textsuperscript{475} If needed, this intermediate could be further oxidized to install the hydroxamic acid functionality of 781 (\textit{vide infra}).

**Scheme 162.** Indolenine formation and oxidation with model substrate 746.

Application of this Fischer indolization protocol to aldehyde 727\textit{a} is described in Scheme 163. Treatment of 727\textit{a} with phenyl hydrazine in the presence of CF\textsubscript{3}CO\textsubscript{2}H indeed produced hydrazone 784. Although this intermediate was unstable, we succeeded in isolating and purifying the compound.

**Scheme 163.** Attempted application of the Fischer indole synthesis to aldehyde 727\textit{a}.

The use of other acids such as AcOH or diphenylphosphoric acid\textsuperscript{476} also produced 784 without any detectable cyclization to the desired indolenine. Moreover, treatment of isolated hydrazone 784 with AcOH or other acids resulted only in complete decomposition of the starting material.

### 13.2.2. Alkene Arylation Strategies

As detailed at the beginning of this chapter, the tricyclic gelsemoxonine core we have synthesized, offers two general possibilities for C(7) functionalization. We have so far only investigated one of these two tactics, namely functionalization of saturated carbonyl derivatives such as aldehyde 727 or its ester counterpart 736. The alternative strategy we initially envisioned involved reaction of the highly strained double bond in an unsaturated derivative of the gelsemoxonine core, such as aldehyde


We now decided to divert our effort towards such an approach hoping for a less crowded steric environment in the vicinity of C(7) of an unsaturated system 732, as suggested by molecular modeling (MM2 energy minimized) (Figure 28).

![Figure 28. Molecular models of unsaturated aldehyde 732 and saturated derivative 727a.](image)

Various strategies for the synthesis of oxindoles starting from an unsaturated carbonyl compound have been reported. Some of this work has been key to several total syntheses of gelsemine as outlined in section 7.5. One approach focused on the generation of a reactive aryl radical species. As shown in Scheme 164 (top), aryl radical 785 is generated from haloarene 786. Subsequent 5-exo-trig cyclization of the carbon centered radical to the double bond produces alkyl radical 787. Upon reductive quenching, oxindole 788 is obtained. A number of conditions and reagents have been reported for this transformation including Bu3SnH/AIBN,477 Co(I)(salen),478 or SmI2.479 We set out to synthesize model system 789480 in order to explore this possibility for the construction of the gelsemoxonine oxindole fragment. Treatment of amide 789 with Bu3SnH/AIBN produced protodeiodinated starting material as

![Scheme 164. SmI2 mediated radical cyclization of amide 789. TMG = tetramethylguanidine.](image)

480 Prepared by coupling of 2-iodoaniline with cyclohexene carboxylic acid.
the only compound. The use of freshly prepared SmI$_2$ in the presence of tetramethylguanidine (TMG) in a THF/H$_2$O solvent mixture successfully delivered oxindole 790. The reaction likely proceeds via aryl samarium intermediate 791.

Besides the radical based strategy for oxindole synthesis, Overman developed a protocol for the preparation of spiro-fused oxindole ring systems based on an intramolecular Heck reaction of easily available N-aryl amides 785 (Scheme 165, box). The putative aryl palladium intermediate 792 selectively cyclizes in a 5-exo-trig fashion, much alike the radical cyclization detailed above. As a consequence, only oxindole 793 is formed via β-hydride elimination from alkyl palladium intermediate 794. This contrasts with the generally observed reactivity of unsaturated carbonyl systems in inter- and intramolecular Heck reactions, which would suggest the formation of product 795 by a 6-endo-trig addition. In this case, such a reactivity has not been observed.

Scheme 165. Intramolecular Heck cyclization for the synthesis of oxindoles developed by Overman.

Application of this palladium catalyzed alkene arylation to the total synthesis of gelsemoxonine would raise questions about the fate of alkyl palladium intermediate 794 generated upon cyclization. It was thought that β-hydride elimination from intermediate 794 to produce a new alkene would not occur, as a highly strained polycyclic ring system would result (Scheme 165, bottom). The expected high reactivity of such an olefin 796 would likely cause problems such as side reactions, hydrolysis of the enamine or complete decomposition of the product. These issues might be addressed by application of a reductive Heck protocol. Under such conditions, addition of a reductant, serves to

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intercept the alkyl-palladium intermediate by reduction of the Pd–C bond. Application of this strategy to gelsemoxonine would produce a product such as oxindole 797 from precursor 798.

**Scheme 166.** Attempted reductive Heck cyclization on model system 789.

As outlined in Scheme 166 (bottom), aryl iodide 789 was subjected to conditions reported for reductive Heck reactions. Several protocols screened delivered oxindole 799 in good yield. Notably, only formation of olefin 799 was observed and no reduced product 800 could be detected. This indicates that β-hydride elimination from alkyl palladium species 801 is much faster than the desired reductive cleavage of the Pd–C bond, even when a large excess of reductant was employed. Nevertheless, we were optimistic that β-hydride elimination could be suppressed in the gelsemoxonine system, as generation of an alkene product would lead to the buildup of severe ring-strain. Moreover, molecular modeling suggested that the orbital overlap required for β-hydride elimination would not be very good in the gelsemoxonine system.

In order to test the two strategies described, preparation of a suitable precursor was required. This proved more challenging than initially anticipated.

### 13.2.3. Oxidation of the C(2) Aldehyde

We first set out for the oxidation of the aldehyde functionality in 732 to a carboxylic acid derivative (Scheme 167, top). Application of a Pinnick protocol delivered an acid product, which was then directly subjected to amide coupling conditions with N-methyl-2-iodoaniline 802 and DCC. To our surprise, tetracycle 803 was obtained as the only product. Closer analysis of the reaction revealed that the initial oxidation step produced epoxide 804, instead of the desired unsaturated acid. Subsequent reaction of the acid moiety in 804 with DCC leads to epoxide opening to give 803. This observation suggested that the high strain energy of the double bond in 732 rendered this olefin highly reactive under oxidative conditions. Indeed, when other protocols for the oxidation of allylic aldehydes such as Ag₂O⁴⁸⁵, MnO₂/NaCN,⁴⁸⁶ AgO/NaCN,⁴⁸⁷ KMnO₄,⁴⁸⁸ TPAP/NMO,⁴⁸⁹ or an NHC

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based strategy were tested, only decomposition of aldehyde 732 was observed. We attributed this outcome again to the high reactivity of the olefin in 732.

Scheme 167. Attempted modification of unsaturated aldehyde 732 under oxidative (top) or reductive (bottom) conditions.

Alternatively, we investigated reductive amination of 732 using 2-iodoaniline as the coupling partner (Scheme 167, bottom). Again various conditions were employed including InCl₃/Et₃SiH, NaBH(OAc)₃, and NaBH₃CN. The products obtained from this reaction (e.g. 727 or 805) always arose from reduction of the double bond, again indicating that the olefin is more reactive than the aldehyde functionality.

As outlined in Scheme 168, C(2) aldehyde oxidation was successful on secondary alcohol 733. Treatment of 733 under Pinnick conditions cleanly delivered acid 806 in quantitative yield (not isolated). Notably, the alcohol functionality in 733 was not touched with this protocol and only the aldehyde was oxidized. However, this strategy required elimination of the alcohol to produce the requisite unsaturated acid derivative 807. Elimination directly from acid 806 was unsuccessful under various conditions. Fortunately, acid 806 could be esterified by treatment of the crude product from the oxidation reaction with trimethylsilyl diazomethane to provide methyl ester 808. This ester was again subjected to various conditions for alcohol elimination. This transformation proved surprisingly difficult. Various protocols involving MsCl/NEt₃, Tf₂O/pyridine, TFAA/pyridine or DCC/CuCl.

492 The tolerance for unprotected alcohols is a known feature of the Pinnick oxidation.
failed to produce the desired unsaturated ester 809. Gratifyingly, treatment of 808 with TFAA in the presence of DBU cleanly delivered 809 in excellent yield. The structure of ester 809 could be unambiguously confirmed by X-ray crystallographic analysis (Scheme 168, box). The difficulty associated with elimination of the secondary alcohol in 808 is probably twofold. First, the strain of the alkene product renders dehydration more challenging. Secondly, molecular models suggest that the hydroxy group is in a cis-relationship with the C–H bond at C(7). Cis-elimination reactions are inherently more difficult than the respective trans-eliminations. Finally, we subjected ester 809 to hydrolysis conditions to access the unsaturated acid 807 amenable to amide coupling reactions. Again, the unusually high propensity of the double bond in 809 to react with nucleophiles posed us with challenges. Treatment of 809 with LiOH in a THF/H2O solvent mixture resulted in 1,4-addition of hydroxide to the olefin. Other protocols known to effect mild hydrolysis of methyl esters including TMSOK494 or (Bu3Sn)2O495 led to decomposition of the starting material. To our delight, treatment of ester 809 with trimethyltin hydroxide delivered acid 807 cleanly and in quantitative yield.496

![Scheme 168. Successful oxidation of the C(2) aldehyde.](image)

We next envisioned introduction of an ortho-halogen-substituted aniline derivative in the tricyclic gelsemonoxine core. As outlined in Scheme 169, we first explored amide bond formation by oxidation of an imine intermediate.497 Condensation of aniline 810 with aldehyde 733 was carried out in refluxing toluene. Subsequent oxidation of imine 811 under Pinnick conditions498 delivered the desired amide 812, albeit in low yield (15-20%). Attempted dehydration of the secondary alcohol to produce

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under various conditions, including TFAA/DBU, was met with failure. This can either be attributed to the reduced acidity of amides compared to esters, or to the altered conformational preference of bulky amide 812, which might hamper deprotonation at C(7).

We next turned to amide coupling protocols using unsaturated acid 807. A number of standard coupling reagents such as DCC, EDC, BOP or HATU/HOAt were tested to effect the union of 807 with N-methyl-2-iodoaniline 802. Surprisingly, under none of these conditions was product formation observed. As outlined in Scheme 169 (bottom), successful amide bond formation was achieved using a sequential protocol involving acid chloride formation and in situ treatment of 814 with N-methyl-2-iodoaniline 802 in the presence of NEt3. Pleasingly, amide 815 was obtained in 70% yield.

13.2.4. Construction of the Oxindole by a Reductive Heck Cyclization

With amide 815 in hand, we set out to test the oxindole ring closure. As outlined in Scheme 170, we first investigated radical cyclization using the previously established SmI2 conditions. Treatment of iodoarene 815 with SmI2 in the presence of TMG led to the formation of numerous products. Unfortunately, none of these compounds corresponded to the desired ring closed product.499

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813

Scheme 169. Coupling of 2-iodoaniline with the tricyclic gelsemoxonine core.

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Scheme 170. Attempted radical cyclization of amide 815. TMG = tetramethylguanidine.

499 Determined by comparison with successfully prepared cyclized oxindole 819 (vide infra).
We next explored application of the reductive Heck reaction. The use of this transformation for cyclization of 815 posed a few special challenges as outlined in Scheme 171 (top). First, addition of putative aryl-palladium intermediate 816 would have to occur stereoselectively only from the top face of the alkene. However, as apparent from the crystal structure of unsaturated ester 809 (Scheme 168), the two faces of the olefin are essentially equivalent based on steric considerations. Moreover, attack at the sterically more hindered C(7) end of the double bond was required. Furthermore, the cyclization event was likely to compete with reduction of the aryl-palladium bond in 816 by the reductant present under reductive Heck conditions. Even if alkene arylation were successful, the resulting alkyl-palladium intermediate 817 would likely be prone to various side reactions including reverse reaction to regenerate amide 816, β-hydride elimination involving the C(5)–H bond, or side reactions with the strained azetidine adjacent to the reactive center. Reductive quenching of the C–Pd bond would need to outcompete these undesired reactivity patterns in order to produce 818.

Scheme 171. Successful construction of oxindole 819 by a reductive Heck cyclization.

In the event, when amide 815 was treated under reductive Heck conditions using catalytic Pd(OAc)$_2$, Bu$_4$NBr, and potassium formate as the stoichiometric reductant, formation of two products was observed in a ratio of approximately 10:1. Detailed spectroscopic analysis of the two products revealed that cyclization was indeed successful, providing the two diastereomeric oxindoles 819 and 820. NOE analysis further confirmed that the desired isomer 819 was in fact the major component isolated from this reaction (Figure 29). This outcome was intriguing, as no preference for the formation of this diastereomer was apparent (vide supra). We speculate that coordination of putative aryl palladium intermediate 816 to the ether oxygen adjacent to the reactive C(7) center might

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guide the approach of the nucleophile from the top face of the alkene.\textsuperscript{501} Moreover, none of the aforementioned side reactions were observed and the product was obtained cleanly and in good yield.

![Figure 29. NOE analysis of oxindoles 819 and 820.](image)

### 13.3. Introduction of the N-Hydroxy Substituent on the Oxindole

Having successfully constructed the spiro-fused oxindole of gelsemoxonine, including the selective formation of the C(7) quaternary stereocenter, we next focused on the introduction of the N-hydroxy substituent on the oxindole nitrogen to complement the substitution pattern of the natural product. As outlined in Scheme 172, our initial efforts centered around oxidation of the nitrogen after the Heck cyclization. Accordingly, unprotected amide 813 was prepared \textit{via} a similar protocol as employed for the synthesis of 815. Application of the originally successful Heck protocol using Pd(OAc)$_2$, Bu$_4$NBr and KHCO$_2$ did not produce the desired oxindole 821. Screening of alternative reaction conditions led to the finding that the use of PdCl$_2$(MeCN)$_2$ in the presence of 1,2,2,6,6-pentamethylpiperidine and formic acid\textsuperscript{484} delivered the desired product 821 in moderate yield (45%). In this reaction, protodeiodinated starting material was the major side product, accounting for the low yield of 821. We surmise that an additional substituent on the amide nitrogen of the cyclization precursor, as in N-methylated compound 815, forces the amide bond into an \textit{s-cis} configuration.\textsuperscript{502} Such an arrangement is likely to have a beneficial effect on the cyclization event due to preorganization of the substrate. In the absence of a nitrogen substituent, this cyclization is more difficult, thus leading to side reactions such as reduction of the iodoarene as observed.

![Scheme 172. Reductive Heck reaction of unprotected amide 813 and attempted N-hydroxylation.](image)


\textsuperscript{502} Similar effects of N-protecting groups have been previously observed for oxindole cyclizations: see ref. 482 and ref. 477a.
Oxidation of amides to N-hydroxy amides (hydroxamic acids) through initial silylation of the amide using \( N,O \)-(bistrimethylsilyl)acetamide (BSA) following oxidation by Vedej’s reagent (MoOPH)\(^{503} \) has been reported by Sammes.\(^{504} \) Treatment of \( \text{821} \) under these conditions did not produce any product \( \text{822} \) and the starting material was recovered unchanged. NMR analysis of the reaction mixture indicated successful formation of the silylated intermediate but this compound proved inert towards the oxidation conditions.

We thus envisioned introduction of the hydroxy substituent before the Heck cyclization event. As outlined in Scheme 173 (top), we prepared \( N \)-methoxyaniline \( \text{823} \) for this purpose. 2-Nitroiodobenzene \( \text{824} \) was reduced by zinc powder and the intermediate arylhydroxylamine was protected with ethylchloroformate to give \( \text{825} \). Selective cleavage of the carbonate, followed by \( O \)-methylation, delivered carbamate \( \text{826} \). Reductive cleavage of the protecting group finally provided iodoaniline \( \text{823} \).

To our surprise, when the coupling of iodoarene \( \text{823} \) with model acid \( \text{827} \) was attempted under the conditions used previously, no formation of the desired product \( \text{828} \) was observed (Scheme 173, bottom).\(^{505} \)

**Scheme 173.** Preparation of \( N \)-methoxyaniline \( \text{823} \) and attempted coupling to unsaturated acid \( \text{827} \).

As outlined in Table 23, we next turned to a strategy involving \( N \)-selective acylation of an unprotected arylhydroxylamine derivate.\(^{506} \) According to the reported procedure, we first subjected model acid chloride \( \text{829} \)\(^{507} \) to bromoarene \( \text{830} \)\(^{508} \) in a biphasic system using \( \text{NaHCO}_3 \) as base (entry 1). The desired product \( \text{831} \) was obtained in 15% yield, along with some \( O \)-acylated compound (not quantified). Interestingly, the use of amine bases such as pyridine or \( \text{NEt}_3 \) did not provide any amide.

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\(^{505}\) Attempted acetylation of \( \text{823} \) with AcCl was equally met with failure.


\(^{507}\) Employing the corresponding acid fluoride did not provide any product.

\(^{508}\) As aryl hydroxylamines are light sensitive, \( \text{830} \) was always prepared freshly prepared according to *Aust. J. Chem.* 1983, 36, 1455-1467.
product (entries 3 and 4). Moreover, the use of Et₂O as the solvent proved crucial (data not shown). Various other bases were tested in different solvent mixtures and NaHCO₃ in Et₂O gave the best result, producing 831 in 44% yield (entry 5).

**Table 23. Optimization of the amide coupling between acid chloride 829 and N-arylhydroxylamine 830.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaHCO₃</td>
<td>Et₂O/H₂O</td>
<td>15%</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>Et₂O/pH 7 buffer</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>pyridine</td>
<td>CH₂Cl₂</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>NEt₃</td>
<td>Et₂O</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>NaHCO₃</td>
<td>Et₂O</td>
<td>44%</td>
</tr>
<tr>
<td>6</td>
<td>Na₂CO₃</td>
<td>Et₂O</td>
<td>39%</td>
</tr>
<tr>
<td>7</td>
<td>K₂CO₃</td>
<td>Et₂O</td>
<td>40%</td>
</tr>
</tbody>
</table>

We next applied the optimized conditions to tricyclic acid 807 (Scheme 174). After formation of the corresponding acid chloride as before, treatment with 830 in the presence of NaHCO₃ delivered hydroxamic acid 832 in good yield (58%) along with reisolated starting material.⁵⁰⁹ Notably, no side products resulting from O-acylation were observed under these conditions. We then subjected hydroxamic acid 832 to the previously established Heck conditions. To our delight, oxindole 822 was formed as a single diastereomer in an excellent yield of 72%. NOE analysis of the product again confirmed that 822 had the desired configuration at C(7) (see experimental part). Moreover, no side product resulting from protodebromination of the starting material was observed.

**Scheme 174. Synthesis of N-hydroxyoxindole 822.**

⁵⁰⁹ Minor amounts of CH₂Cl₂ had to be added to the reaction to dissolve the substrate completely.
13.4. Conclusion

In conclusion, we achieved the stereoselective construction of the oxindole spirocycle in gelsemoxonine. As shown in Scheme 175, the developed strategy relies on the synthesis of unsaturated carboxylic acid 807 as a key intermediate. Oxidation of the C(2) aldehyde is only possible starting from secondary alcohol 733. Therefore, the ability to control the outcome of the aldol cyclization described in the previous chapter was crucial for our synthetic strategy. In fact, Pinnick oxidation/esterification of aldehyde 733 followed by dehydration and ester hydrolysis delivered acid 807 in an excellent overall yield of 86%. Oxindole construction then relied on an intramolecular reductive Heck reaction of hydroxamic acid 832, prepared by N-selective acylation of arylhydroxylamine 830. In the event, treatment of 832 under reductive Heck conditions delivered oxindole 822 in excellent yield. Remarkably, 822 was formed as a single diastereomer, which contrasts the difficulties encountered for stereoselective formation of the spiro-oxindole stereocenter in previous syntheses of gelsemium alkaloids (see section 7.5.).

Scheme 175. Preparation of oxindole 822 through a reductive Heck cyclization.
Completion of the Total Synthesis of (±)-Gelsemoxonine

14.5. Introduction of the C(20) Ketone Functionality

For the completion of the total synthesis of gelsemoxonine, elaboration of the ethyl ketone appendage at C(15) was the last task to be solved. As outlined in Scheme 176, conversion of the alkyne at C(15) into a ketone functionality could be carried out through two principal tactics. Formal hydration of the triple bond in intermediate 833, if regionselective, would give C(20) ketone 834. Alternatively, the Boc protecting groups in close proximity of the alkyne could be exploited for a similar purpose. Triple bond activation might trigger nucleophilic attack of one of the adjacent Boc carbonyl groups onto the C(20) carbon to provide intermediates 835 or 836, respectively. Subsequent hydrolysis would furnish the corresponding ketone product.

Scheme 176. Alternative pathways for the introduction of a ketone functionality at C(20).

We first set out to explore the alkyne hydration strategy. Formal addition of water to a triple bond is commonly promoted by carbophilic metal ions such as Pd(II), Pt(II), Hg(II) or Au(I).510 It has been observed that activation of sterically hindered alkynes generally proceeds in a regioselective fashion to give the ketone at the sterically more hindered end of the triple bond.511 We were therefore optimistic that treatment of a substrate like 833 under such conditions would produce the desired ketone at the

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510 For a comprehensive review covering alkyne hydration, see: Hintermann, L.; Labonne, A. *Synthesis* 2007, 1121-1150.
more hindered C(20) carbon. As shown in Scheme 177, we initially tested hydration conditions on model systems. Unfortunately, treatment of alkyne 837 with various Lewis acids such as PtI$_2$, HgSO$_4$/H$_2$SO$_4$ or NaAuCl$_4$ in the presence of water did not produce any product. Recently, Hg(OTf)$_2$ has been reported as a particularly reactive promoter for the activation of alkenes and alkynes. When freshly prepared Hg(OTf)$_2$ (10 mol%) was added to a solution of 837 in a MeCN/CH$_2$Cl$_2$ solvent mixture, ketone product 838 was isolated, albeit in low yield. NMR spectroscopic analysis revealed that the undesired regioisomer was formed as the exclusive product, thus contradicting the generally observed regioselectivity rules. Addition of tetramethylurea (TMU) has been reported to modify the chemical properties of Hg(OTf)$_2$. Experiments involving addition of TMU to a solution of alkyne 837 in the presence of a catalytic amount of Hg(OTf)$_2$ inhibited the reaction completely. We speculated that the carbamate substituent on the C(14) alcohol might be responsible for production of the undesired regioisomer, possibly by a coordinating effect. We therefore subjected unprotected alcohol 839 to identical reaction conditions. Indeed, formation of a new product was observed, but full characterization suggested the production of furan derivative 840 in 71% yield. This outcome can be explained by initial activation of the triple bond by Hg(II), which renders the alkyne susceptible to attack of the adjacent alcohol, producing intermediate 841. β-Lactam ring opening can then lead to aromatization of the five-membered heterocycle providing furan 840.

![Scheme 177. Attempted Hg(OTf)$_2$ promoted alkyne hydration in model systems.](image)

It was hoped that this reactivity would no longer be possible on the fully elaborated gelsemoxonine core, which is lacking the sensitive β-lactam moiety of model system 839. As outlined in Scheme 178,
we applied the Hg(OTf)$_2$ protocol to secondary alcohol 842. Unfortunately, this sensitive intermediate decomposed under the strongly Lewis acidic conditions. Moreover, application of the aforementioned triple bond hydration strategies (PtI$_2$, HgSO$_4$/H$_2$SO$_4$) did not effect any reaction of substrate 842. Interestingly, when bis-Boc protected derivative 821 was treated with either Zeise’s dimer ([Cl$_2$Pt(C$_2$H$_4$)$_2$], not shown) or freshly prepared (Ph$_3$P)AuNTf$_2$, clean formation of cyclic carbamate 843 was observed. 2D NMR spectroscopic analysis clearly suggested the formation of six-membered ring product 843, with the C(19) carbon bearing an oxygen substituent. Interestingly, reaction of the C(14) carbonate was never observed under the conditions tested. Attempts of hydrolyzing enol 843 under acidic (AcOH, aq. HCl, HgSO$_4$/H$_2$SO$_4$) or basic (LiOH, LiOOH, K$_2$CO$_3$/MeOH) conditions failed to give any ring opened product.

![Figure 178. Attempted triple bond hydration with alkynes 842 and 821.](image)

The complete failure of the alkyne hydration attempts led us to consider an alternative strategy. As shown in Scheme 179, we envisioned to employ an alkyne hydrosilylation approach for the regioselective functionalization of the triple bond. It has been documented that intramolecular hydrosilylation of homopropargylic alcohols such as 844 can proceed via two alternative reactions paths (a and b in Scheme 179). The reaction generally relies on the oxidative insertion of a metal species into the Si–H bond of silane 845, followed by hydrometallation of the alkyne. Depending on the metal catalyst employed, either exo- or endo-cyclization can occur to produce vinylsiloxanes

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520 For a comprehensive review of alkyne hydrosilylation, see: Trost, B.M.; Ball, Z.T. *Synthesis* 2005, 853-887.
846 or 847, respectively. Finally, oxidation of the carbon-silicon bond in these intermediates delivers the respective hydroxyketones 848 or 849.

Scheme 179. Hydrosilylation of homopropargylic alcohols 844 to give hydroxyketone 848 or 849.

As outlined in Scheme 180, we explored this tactic for model compound 573. Installation of the hydrosilane moiety proceeded well upon treatment of alcohol 573 with dimethylchlorosilane. However, these reaction conditions required purification of unstable product 850, resulting in partial loss of the newly installed silyl group. Treatment of 850 with H$_2$PtCl$_6$ afforded undesired furan product 851, probably via a similar mechanism to that suggested for the formation of furan 840 (Scheme 177). Gratifyingly, the use of dimeric ruthenium catalyst 852 produced vinylsiloxane 853 as the sole product in good yield. Notably, only the desired $\alpha$-exo-cyclization product was obtained under these conditions. Unfortunately, attempted Tamao–Fleming oxidation$^{524}$ of 853 led to decomposition of the starting material, which was attributed to the sensitive $\beta$-lactam ring in this model system.

Scheme 180. Intramolecular hydrosilylation of model system 573.

With a successful alkyne functionalization protocol in hand, we turned to its application to the gelsemoxonine system. As depicted in Scheme 181, we first methylated hydroxamic acid 822 using NaH and MeI in DMF to give 7-methoxyoxindole 745 in excellent yield. Subsequent cleavage of the carbonate protecting group on the C(14) alcohol was achieved by the action of K$_2$CO$_3$ in MeOH at

$^{525}$ The use of K$_2$CO$_3$ as base mostly led to decomposition of the starting material.
The hydrosilane was then installed employing tetramethyldisilazane,\textsuperscript{524a,527} which allowed for convenient isolation of the siloxane intermediate by simple evaporation of the reagent under vacuum. To our delight, treatment of this crude intermediate with dichloro(benzene)ruthenium dimer \textsuperscript{852} afforded vinylsiloxane \textsuperscript{854} in 58\% yield. Again, no product resulting from \textit{endo}-cyclization was observed.

Scheme 181. Synthesis of ethyl ketone \textsuperscript{861}.

Interestingly, \textsuperscript{854} was obtained as an inconsequential mixture of double bond isomers.\textsuperscript{528} Formation of isomeric olefin products in this reaction has been documented previously.\textsuperscript{523} It has been speculated that double bond isomerization can occur \textit{via} two different intermediates as shown in Scheme 182.\textsuperscript{520,529} After initial \textit{cis}-addition of ruthenium silane species \textsuperscript{855} to alkyne \textsuperscript{856}, vinylsilane \textsuperscript{857} is obtained. Formation of ruthenium carbenoid \textsuperscript{858}, or alternatively metallocyclopropene \textsuperscript{859}, would account for the production of isomeric species \textsuperscript{860}.

Scheme 182. Mechanistic explanation for the double bond isomerization during the hydrosilylation reaction.

\textsuperscript{526} The use of excess base and conducting the reaction at 50 °C proved crucial to achieve fast conversion. Prolonged reaction times led to decomposition of the product.

\textsuperscript{527} Tamao, K. \textit{e-EROS Encycl. Org. Synth. „1,1,3,3-Tetramethyldisilazane“}.

\textsuperscript{528} The double bond isomers could be separated by silica gel chromatography and were independently subjected to Tamao–Flemming oxidation. In either case, ethyl ketone \textsuperscript{861} was obtained.

\textsuperscript{529} For rhodium catalyzed hydrosilylations, a similar mechanism has been proposed: a) Jun, C.H.; Crabtree, R.H. \textit{J. Organomet. Chem.} 1993, 447, 177-187; b) Ojima, I.; Clos, N.; Donovan, R.J.; Ingallina, P. \textit{Organometallics} 1990, 9, 3127-3133.
Finally, Tamao–Flemming oxidation of 854 under mild conditions (KHF$_2$, H$_2$O$_2$, Ac$_2$O)$^{522,524}$ afforded ethylketone 861 in 65% yield. To elaborate the natural product gelsemoxonine, deprotection of the azetidine nitrogen was the final transformation required.

14.6. Completion of the Total Synthesis and Chemistry of Gelsemoxonine

In the course of our synthetic studies towards the completion of the gelsemoxonine synthesis, we had prepared N-methyl oxindole 862. Various protocols for final deprotection of the Boc group were evaluated using this compound, including the use of protic acids (CF$_3$CO$_2$H, AcOH, aq. HCl) and Lewis acids (Sc(OTf)$_3$). We found that treatment of 862 with anhydrous HCl in EtOAc$^{530}$ cleanly afforded azetidine 863 (Scheme 183).

Scheme 183. Deprotection of azetidine 862 and subsequent follow up reaction to compound 864.

Short column chromatography of this compound allowed for the isolation of gelsemoxonine analogue 863. Comparison of the $^1$H NMR spectrum of this compound with the spectral data of natural gelsemoxonine$^{530,531}$ corroborated with our notion that we had synthesized the N-methyl oxindole analogue of the natural product (Figure 30).

Figure 30. Comparison of the $^1$H NMR spectra in CDCl$_3$ (5.0-1.0 ppm range) of a) synthetic gelsemoxonine (278) and; b) gelsemoxonine analogue 863.

---

$^{530}$ Freshly prepared by addition of AcCl to EtOH.
$^{531}$ In Figure 30, the $^1$H spectrum of the later obtained synthetic gelsemoxonine is shown.
To our surprise, when we concentrated a solution of 863 from CHCl₃ a new compound 864 was produced⁵³² which showed significant differences in its ^1H NMR spectrum compared to gelsemoxonine analogue 863. As depicted in Figure 31, numerous protons on the bottom face of the polycyclic structure had shifted downfield considerably (0.4-0.6 ppm).

Unfortunately, closer NMR spectroscopic analysis of compound 864 did not allow for the unambiguous assignment of its structure. We realized however, that all peaks with significant shifts in the ^1H and ^13C NMR spectra were centered around the ketone and the azetidine motives, as outlined in Figure 32. As mentioned previously, only the protons pointing into the direction of the azetidine had shifted, whereas the hydrogens pointing away from the bottom face seemed largely unaffected. This observation strongly suggested reaction of the azetidine ring as well as the ketone, possibly by an intermolecular condensation reaction.

---

⁵³² This product could again be purified by column chromatography on SiO₂.
Intrigued by these observations, we next set out to test the Boc deprotection protocol on N-methoxy oxindole 861 (Scheme 184). Again, treatment of 861 with anhydrous HCl in EtOAc led to clean and fast conversion to a new compound, as observed by TLC. Aqueous workup with NaHCO$_3$ was conducted to neutralize the excess hydrochloric acid. Several attempts were undertaken to concentrate the resulting solution of the crude product under vacuum. During these attempts, we generally observed that the crude product converted into a complex mixture of compounds. Only upon very careful evaporation at low temperature could we obtain synthetic (±)-gelsemoxonine (278) in good purity and in excellent yield (97%).

![Scheme 184](image)

Scheme 184. Deprotection of 861 to give synthetic (±)-gelsemoxonine (278).

As outlined in Table 24, the NMR spectroscopic data of synthetic gelsemoxonine (278) matched the reported data very well. The same was true for the IR and MS characterization data.

Table 24. Comparison of the NMR spectroscopic data in CDCl$_3$ for natural vs. synthetic gelsemoxonine.

<table>
<thead>
<tr>
<th>Carbon</th>
<th>$^1$H natural[a]</th>
<th>$^1$H synthetic[b]</th>
<th>$^{13}$C natural[c]</th>
<th>$^{13}$C synthetic[d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>173.4 173.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.80 (1H, d, $J$ = 2.4 Hz)</td>
<td>3.82 (1H, d, $J$ = 2.6 Hz)</td>
<td>78.6 78.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3.89 (1H, br-ddd, $J$ = 8.2, 4.6, 1.5 Hz)</td>
<td>3.98-3.95 (1H, br-m)</td>
<td>55.6 55.6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2.39 (1H, dd, $J$ = 16.2, 1.5 Hz)</td>
<td>2.41 (1H, dd, $J$ = 16.1, 1.5 Hz)</td>
<td>34.7 34.4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>53.9 53.9</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>7.47 (1H, dd, $J$ = 7.6, 0.6 Hz)</td>
<td>7.48 (1H, dd, $J$ = 7.5, 0.6 Hz)</td>
<td>125.2 125.2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>7.18 (1H, ddd, $J$ = 7.6, 7.6, 0.9 Hz)</td>
<td>7.18 (1H, td, $J$ = 7.6, 1.1 Hz)</td>
<td>124.1 124.2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>7.36 (1H, ddd, $J$ = 7.6, 7.6, 0.9 Hz)</td>
<td>7.36 (1H, td, $J$ = 7.7, 1.2 Hz)</td>
<td>128.8 128.9</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>7.02 (1H, dd, $J$ = 7.6, 0.6 Hz)</td>
<td>7.03 (1H, ddd, $J$ = 7.8, 1.0, 0.5 Hz)</td>
<td>107.5 107.6</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>-</td>
<td>138.0 138.0</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>4.51 (1H, br-d, $J$ = 6.1 Hz)</td>
<td>4.53 (1H, d, $J$ = 2.3 Hz)</td>
<td>68.7 68.5</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>-</td>
<td>-</td>
<td>67.2 67.2</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>3.34 (1H, br-ddd, $J$ = 8.2, 4.0 Hz)</td>
<td>3.39 (1H, br-ddd, $J$ = 8.5, 3.7 Hz)</td>
<td>33.6 33.7</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>4.26 (1H, dd, $J$ = 12.0, 4.1 Hz)</td>
<td>4.27 (1H, dd, $J$ = 12.1, 4.0 Hz)</td>
<td>61.8 61.7</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>1.11 (3H, t, $J$ = 7.3 Hz)</td>
<td>1.12 (3H, t, $J$ = 7.2 Hz)</td>
<td>7.0 7.0</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>2.82 (1H, dq, $J$ = 18.3, 7.3 Hz)</td>
<td>2.83 (1H, dq, $J$ = 18.2, 7.2 Hz)</td>
<td>28.9 29.2</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>-</td>
<td>-</td>
<td>211.8 211.2</td>
<td></td>
</tr>
<tr>
<td>N$_2$-OMe</td>
<td>4.05 (3H, s)</td>
<td>4.05 (3H, s)</td>
<td>63.7 63.8</td>
<td></td>
</tr>
</tbody>
</table>

[a] according to ref. 150, 500 MHz; [b] 600 MHz; [c] according to ref. 150, 125 MHz; [d] 150 MHz.
Further purification of gelsemoxonine was attempted by column chromatography on SiO₂ using a variety of eluent systems (hexanes/EtOAc, CH₂Cl₂/MeOH, CHCl₃/MeOH, acetone/toluene). However, in all these cases the natural product converted to a similar mixture of compounds to that observed upon fast evaporation of the crude material. Interestingly, the product mixture obtained differed from batch to batch. In one instance, a single product was obtained, which was spectroscopically very similar to compound 864 obtained from N-methyl gelsemoxonine (Scheme 183). All these results led us to suspect that a dynamic mixture of compounds is generated upon concentration, or chromatographic purification, of the natural product. Based on this hypothesis, we decided to subject this compound mixture to acetylating conditions (Ac₂O, pyridine). To our delight, a single product 865 was isolated from this reaction, which proved to be bisacetylated gelsemoxonine, a compound previously prepared by the isolation group upon acetylation of natural gelsemoxonine (Scheme 184). As outlined in Figure 33, the reaction sequence was followed by NMR analysis of the respective products. Interestingly, similar peak shift compared to the ones observed for N-methylgelsemoxonine (Figure 31) were observed again.

Figure 33: Comparison of ¹H NMR spectra CDCl₃ (5.5-3.0 ppm range) of a) crude Gelsemoxonine (278); b) compound mixture obtained after column chromatography (CH₂Cl₂/MeOH) or concentration of 278 from solution (CHCl₃ or EtOAc); c) product of acetylation of the mixture shown in b) corresponding to diacetoxy gelsemoxonine 865 (after chromatography). Hypothesized peak shifts indicated by dashed arrows (in analogy to the transformation of 863 to 864, see Figure 31).* peaks from rotamers (see also 2D NMR spectra of 865).

533 This solvent mixture was used in the first total synthesis of gelsemoxonine by Fukuyama and co-workers (ref. 175).
534 Minor amounts of monoacetylated gelsemoxonine (N-Ac) were also isolated.
535 As indicated in Figure 33, bisacetylated gelsemoxonine 865 showed rotamers in the NMR as confirmed by 2D NMR analysis (see experimental part).
These combined results clearly confirmed our suggestion that gelsemoxonine, when concentrated, exists in a dynamic equilibrium of different species. As shown in Scheme 185, 278 likely forms dimeric or oligomeric species, as indicated for structure 866. Treatment of this mixture with Ac₂O traps the monomeric form selectively, thus providing bisacetoxy gelsemoxonine 865.

Scheme 185. Proposed equilibrium of gelsemoxonine (278) with different oligomeric derivatives 866.

14.7. Evaluation of the Antitumor Activity of Gelsemoxonine and Synthetic Intermediates

Based on the strong antitumor activity of some gelsemine alkaloids, in particular gelsedine (see section 7.3.), we set out to evaluate the cytotoxicity of several gelsemoxonine^536 analogs and synthetic intermediates prepared in the course of our project. As outlined in Figure 34, we tested six different compounds for their ability to inhibit tumor cells growth.\(^537\) Gelsemoxonine derivatives 867, 865, 863, 842 and 820 did not show any cytotoxic effect towards A549, Hepa or HT-29 cell lines. Unsaturated aldehyde 732 on the other hand, exhibited moderate activity against all three cancer cell types (Figure 34, box). For A549 cells (lung cancer) an IC₅₀ of 29 μM was measured. A similar value of 36 μM was obtained for Hepa cells (liver cancer). The cytotoxic activity against HT-29 cells (colon cancer) was considerably reduced (IC₅₀: 63 μM).

Figure 34. Compounds tested for cytotoxicity against A549, Hepa and HT-29 cells.

^536 Gelsemoxonine itself was not tested due to its chemistry described above.
^537 All bioactivity assays were carried out by Dr. Susanne Wolfrum.
In light of the complete inactivity of most gelsemoxonine analogs, the moderate cytotoxicity of 732 can likely be attributed to the highly reactive unsaturated aldehyde functionality, and not to the characteristic structural elements of the natural product.

14.8. Conclusion

We have completed the total synthesis of (±)-gelsemoxonine (278) by the late stage elaboration of the alkyne to an ethyl ketone motif, as outlined in Scheme 186.

Scheme 186. Completion of the total synthesis of gelsemoxonine.

After methylation of hydroxamic acid 822, carbonate hydrolysis delivered secondary alcohol 842 in excellent yield. Introduction of the ketone functionality of the natural product was then achieved through an intramolecular hydrosilylation protocol. In this transformation, the C(14) alcohol in 842 served as a directing group. In the event, silylation of alcohol 842, followed by treatment with dichloro(benzene)ruthenium dimer, delivered vinylsiloxane 854 with complete regioselectivity and as a mixture of double bond isomers. Subsequent Tamao–Fleming reaction produced the desired ethyl ketone 861. Finally, removal of the remaining Boc protecting group on the azetidine afforded synthetic (±)-gelsemoxonine (278) in excellent yield. Although the natural product was found to be unstable, acetylation of 278 provided stable bisacetoxy gelsemoxonine 865.

Scheme 187. Total synthesis of (±)-gelsemoxonine (278) in 21 steps from aldehyde 546.
In summary, we have achieved a total synthesis of racemic (±)-gelsemoxonine (278) in 21 steps starting from known aldehyde 546 (Scheme 187). This compares favorably to the previously reported synthesis by Fukuyama, which accesses enantiopure (−)-gelsemoxonine in 28 linear steps (see section 7.5.5.).
Enantioselective Approach to (−)-Gelsemoxonine

With a concise total synthesis of racemic (±)-gelsemoxonine (278) established, we decided to explore strategies to access a key intermediate en route to the natural product in enantioenriched form. Given that a minimal modification of the synthesis route was desired, such an objective would necessarily have to account for the asymmetric preparation of isoxazoline 550 or a derivative thereof. The preparation of enantiomerically pure isoxazolines by asymmetric [3+2] dipolar cycloaddition has only been scarcely investigated to date. In particular, the substrate scope of the reported protocols is essentially limited to aryl nitrile oxide starting materials. We therefore reasoned that enantioselective preparation of isoxazoline 550 would require the installation of stereochemical elements in the starting material to control the diastereoselectivity of the dipolar cycloaddition. As outlined in Scheme 187, we considered two general approaches to achieve this goal.


Substitution of the cyclopropane ring in a putative nitrile oxide intermediate 868 could serve to block one face of the reacting olefin leading to the production of enol ether 869 (equation 1). Alternatively, a substituent at C(14) was assumed to exert a controlling effect in the cycloaddition of nitrile oxide 870 to selectively deliver isoxazoline 871. This notion was supported by earlier results as documented in section 10.1.

538 For a review covering asymmetric dipolar cycloadditions, see: Pellissier, H. Tetrahedron 2007, 63, 3235-3285.
15.1. Allene Cyclopropanation

Our initial efforts towards the asymmetric preparation of a derivative of enol ether relied on the substitution of the cyclopropane ring in alkylidenecyclopropane, as outlined in Scheme 188. Proper enantioselective functionalization of the three membered carbocycle could control the dipolar cycloaddition event by blocking one side of the reacting olefin. As shown for intermediate, intramolecular attack of a nitrile oxide could only occur from the alkene face opposite the cyclopropane substituents (R₁ and R₂), leading to enol ether in a diastereoselective fashion.

Scheme 188. Stereochemical effect of cyclopropane substitution on the dipolar cycloaddition.

We realized that functionalization of an alkylidenecyclopropane moiety would not be trivial. Although, some examples of substituted alkylidenecyclopropanes have been documented in the literature, none of these reports could serve our purpose to construct allylic ether. We therefore thought of novel strategies relying on the intramolecular cyclopropanation of an allene. As outlined in Scheme 189, such an approach could involve application of an asymmetric cyclopropanation strategy to diazoacetate. Based on geometric and energetic considerations, we were hoping that the exo-double bond in would react preferentially. However, it was not clear, if a chiral catalyst could control the newly formed stereocenter in. Subsequent lactone opening of product would provide allylic alcohol, which incorporates a monosubstituted alkylidene cyclopropane motif.

Scheme 189. Projected asymmetric allene cyclopropanation for the synthesis of allylic alcohol.

Scheme 190 describes the synthesis of diazoacetate. Known allenic alcohol was prepared according to a literature procedure by deprotonation of propargyl chloride with n-BuLi followed by addition of formaldehyde. The resulting propargylic alcohol was then treated with LiAlH₄ to produce alcohol in 92% yield. Introduction of the diazoacetate was carried out in two steps using a procedure developed by Fukuyama.

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540 See section 9.1, and in particular ref. 221.
Enantioselective Approach to (−)-Gelsemoxonine

Scheme 190. Preparation of diazoacetate 874.

Following previous reports for the enantioselective intramolecular cyclopropanation of allylic and homoallylic diazoacetates, we screened various Rh(I)-complexes for their ability to promote the conversion of 874 into lactone 875 (Table 25). Unfortunately, instead of the desired six-membered lactone 875 we exclusively obtained methylenecyclopropane 880 in all cases. Moreover, the product yield was very low. We suspect that this is due to the high strain energy of this product, rendering it prone to decomposition. Alternatively, dimerization of the intermediate rhodium carbenoid species is likely to compete with the cyclopropanation reaction.

Table 25. Intramolecular cyclopropanation of allene 874.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Convn.</th>
<th>Yield of 808</th>
<th>Yield of 875</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh₂(4S-MEPY)₄</td>
<td>20%</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Rh₂(4S-MPPIM)₄</td>
<td>30%</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Rh₂(R-TBSP)₄</td>
<td>100%</td>
<td>&lt; 10%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Rh₂(S-DOSP)₄</td>
<td>100%</td>
<td>&lt; 10%</td>
<td>-</td>
</tr>
</tbody>
</table>

[a] conditions: 1 mol% catalyst, slow addition of substrate (30 mg) over 8 h, CH₂Cl₂, reflux, 12 h.

The failure of this cyclopropanation approach prompted us to revise our strategy to access a substituted alkylidene cyclopropane intermediate. As outlined in Scheme 191, we envisioned an alternative strategy starting from a chiral allene precursor 881. Two possible cyclopropanation pathways were thought to deliver the projected alkylidene cyclopropane. A Simmons–Smith reaction of allene 881 could rely on the directing effect of an unprotected alcohol substituent. Regioselective reaction of the alkene closer to the alcohol would provide product 882. Alternatively, based on our previous observations we proposed that intramolecular cyclopropanation of diazoacetate 881 (R = COCHN₂) would provide five-membered lactone 883 in a stereoselective fashion.

Scheme 191. Projected cyclopropanation of chiral allene 881.

As outlined in Scheme 192, we first set to synthesize the requisite of enantioenriched chiral allenic alcohol 884. Chiral allenes can be easily prepared starting from propargylic alcohol building blocks. Accordingly, propargylic alcohol 885 was first alkylated with bromide 886 to give ether 887 in 55% yield. Subsequent asymmetric addition of this alkyne to aldehyde 888 using stoichiometric Zn(OTf)₂ and (−)-N-methylephedrine as the chiral ligand delivered propargylic alcohol 889 in excellent enantiomeric excess of 90%. The use of ligand 890 was also tested but did not provide the product with a significantly higher enantiomeric purity.

Scheme 192. Synthesis of allenic alcohol 884.

Myers has reported the direct conversion of chiral propargylic alcohols into allenes by treatment of the substrates with sulfonated hydrazines under Mitsunobu conditions. In particular, ortho-nitrobenzene sulfonyl hydrazine proved most effective for this reaction. The hazardous preparation of this compound prompted us to use the more stable tosylhydrazine for this purpose. In the event,
treatment of alcohol 889 with tosylhydrazine, followed by quenching of the reaction with MeOH produced primary alcohol 884. The reaction is believed to proceed via tosylhydrazine 891, which undergoes elimination to diazene 892. Subsequent extrusion of nitrogen delivers the product.

**Scheme 193.** SmI$_2$ promoted directed cyclopropanation of 884.

As outlined in Scheme 193, we next explored Simmons–Smith cyclopropanation of allenic alcohol 884. If there are multiple olefins present in the cyclopropanation substrate, standard Simmons–Smith conditions have been reported to react with several double bonds in the molecule. Molander has developed an alternative cyclopropanation protocol relying on the use of SmI$_2$ to generate a reactive species. These conditions were found to selectively react with allylic alcohols in the presence of other electron rich double bonds. Treatment of allenic alcohol 884 with SmI$_2$, HgCl$_2$ and CH$_2$I$_2$ at -78 °C provided alkylidenecyclopropane 893 in low yield and with a dr of 3:1. This reactivity can be explained by preferential attack of the alkyl-Sm species from the top face of allene 884, as indicated in Scheme 193. Coordination of the metal complex to the alcohol, as drawn for intermediate 894, has been proposed. In addition to the desired product 893, we also obtained bis-spirocyclopropane 895 in small amounts.

**Scheme 194.** Cyclization of alkylidenecyclopropane 893.

Hydrolysis of the diethylacetal in 893 followed by a nitro aldol reaction delivered nitroalcohol 896 as shown in Scheme 194. Treatment of this intermediate under the established cycloaddition protocol indeed produced enol ether 897 in good diastereoselectivity, thus confirming our hypothesis that a substituent on the cyclopropane ring can block one side of the olefin during the cycloaddition reaction.

The low yield of the cyclopropanation reaction detailed in Scheme 193 prevented the preparation of significant quantities of chiral enol ether 897, therefore an alternative strategy was required. To this

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552 The TBS group was lost during the quenching procedure.
554 The addition of mercury salts to this reagent combination was found to be beneficial (ref. 553).
555 The configuration of the major isomer was assigned based on steric considerations. No experimental evidence was collected to support this hypothesis.
end, diazoacetate 898 was synthesized as outlined in Scheme 195. Treatment of alcohol 8884 with acid chloride 899 in the presence of dimethylaniline followed by addition of triethylamine afforded diazoacetate 898 in one step and in 83% yield.\textsuperscript{556} Subjecting this compound to cyclopropanation protocols involving Rh(I) complexes effected decomposition of the starting material. Gratifyingly, the use of Cu(II) catalyst 900 successfully delivered lactone 901 in 74% yield.\textsuperscript{557} Unfortunately, this reaction was completely unselective regarding the side of olefin attack. Consequently, a 1:1 mixture of diastereomers at C(5) was produced.

Scheme 195. Intramolecular cyclopropanation for the synthesis of alkylidene cyclopropane 901.

This unfavorable outcome prompted us to search for a completely different strategy for the introduction of chirality into our key intermediate towards gelsemoxonine.\textsuperscript{558}

15.2. Asymmetric Nitro Aldol Reaction

An alternative strategy towards the construction of enantioenriched enol ether intermediate 550 en route to (–)-gelsemoxonine centered around the application of an asymmetric Henry reaction as outlined in Scheme 196. Chiral nitroalcohol 549 was planned to be obtained in enantioenriched form by treatment of aldehyde 546 with nitromethane in the presence of a chiral catalyst (cat.*). Subsequent elimination of the hydroxy group in 902 would provide enol ether 550 as a single enantiomer.

Scheme 196. Projected asymmetric synthesis of enol ether 550 through an enantioselective Henry reaction.

\textsuperscript{558} Although the use of chiral copper-catalysts would have offered an option to circumvent this problem, this route was no longer pursued due to the number of steps required. Furthermore, acetal 901 was carried on to the respective substrate for the ring contraction step using the chemistry developed previously. Subjecting this substrate to the standard contraction conditions didn’t produce any of the desired product (data not shown).
Table 26. Catalyst screening for the asymmetric Henry reaction of aldehyde 546 with nitromethane.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield</th>
<th>% ee[^c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>903</td>
<td>THF</td>
<td>-50 °C</td>
<td>63%</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>904</td>
<td>THF</td>
<td>-50 °C</td>
<td>63%</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>905</td>
<td>MeNO₂</td>
<td>-20 °C</td>
<td>50%</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>906</td>
<td>THF</td>
<td>-20 °C</td>
<td>8%</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>907</td>
<td>THF</td>
<td>-20 °C</td>
<td>9%</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>908</td>
<td>EtOH</td>
<td>rt</td>
<td>26%</td>
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</tr>
<tr>
<td>7</td>
<td>909</td>
<td>EtOH</td>
<td>rt</td>
<td>-</td>
<td>nd</td>
</tr>
<tr>
<td>8</td>
<td>910</td>
<td>EtOH</td>
<td>rt</td>
<td>nd</td>
<td>19[^d]</td>
</tr>
<tr>
<td>9</td>
<td>911</td>
<td>EtOH</td>
<td>rt</td>
<td>nd</td>
<td>62</td>
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<td>60</td>
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<tr>
<td>11</td>
<td>913</td>
<td>EtOH</td>
<td>rt</td>
<td>nd</td>
<td>61</td>
</tr>
<tr>
<td>12[^e]</td>
<td>908</td>
<td>EtOH</td>
<td>rt</td>
<td>50%</td>
<td>40</td>
</tr>
</tbody>
</table>

[^a]: conditions: see text; 50 mg scale; [^b]: 5-10 mol% of catalyst were used; [^c]: determined by SFC analysis; [^d]: the opposite enantiomer is formed preferentially; [^e]: 100 mg scale, 5 days.

In recent years, the development of the catalytic enantioselective version of the Henry reaction has become a popular subject of study. In particular, numerous catalyst systems were developed for the asymmetric addition of nitromethane to aldehyde substrates. As summarized in Table 26, we applied several of these methodologies to aldehyde 546. The first catalyst system promoting an

15. Enantioselective Approach to (−)-Gelsemonoxonine

Enantioselective nitro aldol reaction was reported by Shibasaki.\textsuperscript{560} His group has pioneered the field of heterobimetallic catalysis, relying on a dual activation mode of a Lewis acidic and Brønsted basic component in the catalyst scaffold.\textsuperscript{561} In this context, trimeric LaLi-BINOL complex 903 was reported to promote the addition of nitromethane to a variety of aliphatic aldehydes in excellent enantioselectivity. In particular, α-ether substituted aldehydes such as 546 were found to be superior substrates. This observation was attributed to coordination of the oxygen atom to the Lewis acidic site of the catalyst.\textsuperscript{562} When aldehyde 546 was subjected to the reported conditions, nitroalcohol 549 was isolated in 63\% yield, but with low ee of only 44\% after three days\textsuperscript{563} of reaction time at -50 °C (entry 1). Notably, the reaction was somewhat difficult to reproduce, which we attribute to difficulties with the catalyst preparation protocol. In this reaction sequence 903 is prepared as a heterogeneous solution, of which only the supernatant is used.\textsuperscript{564} Moreover, the exact concentration of this solution could not be determined. Despite these difficulties, we set out to test related BINOL-substituted catalyst 904, which was reported to give superior enantioselectivity.\textsuperscript{565} To our great surprise, product 549 was obtained in the same yield as before, but in completely racemic form (entry 2). We suspect that proper preparation of the catalyst had failed in this instance. Trost and co-workers have reported an alternative strategy for the asymmetric Henry reaction\textsuperscript{566} employing dinuclear zinc complex 905, which has been previously reported to promote various aldol reactions.\textsuperscript{567} Application of this strategy to aldehyde 546 afforded the desired product, but again with low enantioselectivity (entry 3). The use of improved catalyst system 906 led to a significant increase in asymmetric induction. In this case however, the yield was unexpectedly low (entry 4).\textsuperscript{568} We next turned to an approach based on the use of catalytic Zn(II) salts in the presence of a chiral ligand.\textsuperscript{569} In the event, treatment of aldehyde 546 with freshly dried Zn(OTf)_2 in the presence of (+)-N-methyl ephedrine 907 and Hüning’s base provided nitroalcohol 549 in 52\% ee but only 9\% yield (entry 5). Finally, we investigated a methodology developed by Evans which uses chiral copper-bis(oxazoline) (Box) complexes as catalysts for this


\textsuperscript{563} A long reaction time is a commonly observed problem in asymmetric Henry reactions. Although Shibasaki has reported an improved procedure, which allows for shorter reaction times, this protocol was not tested: Araí, T.; Yamada, Y.M.A.; Yamamoto, N.; Sasai, N.; Shibasaki, M. \textit{Chem. Eur. J.} 1996, 2, 1368-131372.


transformation. To our delight, treatment of 546 with catalyst 908 in the presence of nitromethane as nucleophile produced the desired product in a good enantiomeric excess of 84% (entry 6). Motivated by this result, we set out to screen various bis(oxazoline) ligands (909-913) as outlined in Table 26 (entries 7-11). However, none of the tested complexes were able to promote this reaction in a higher enantioselectivity. Moreover, when the original reaction was performed on a larger scale and for a prolonged period of time to drive the reaction to completion, the enantiomeric purity of the product dropped to 40% ee (entry 12). Considering these results, it can be inferred that aldehyde 546 is not a suitable substrate for the asymmetric Henry protocols so far developed. In general, all these methodologies suffer from long reaction times and poor reproducibility.

15.3. Incorporation of a Chiral Building Block

To circumvent the unsuccessful nitro aldol reaction, we envisioned the early introduction of the C(14) stereocenter through the incorporation of a chiral precursor. This could most easily be achieved by choosing an appropriate alcoholate nucleophile, such as compound 914, for the Tsuji–Trost reaction with allylic tosylate 434 (Scheme 197). The resulting adduct 915 could be readily transformed into nitrile oxide 916. Elimination of the hydroxy group would then provide enantioenriched enol ether 550.

![Scheme 197. Strategy relying on the early incorporation of chiral alcohol 914. PG = protecting group.](image)

In order to ensure optimal chirality transfer from C(14) to the newly formed C(5) stereocenter, we screened a number of alcohol protecting groups (PG) on the C(14) hydroxyl as summarized in Table 27. As observed before, a benzyl protecting group affords the product 902 in a dr of 10:1 (entry 1). Interestingly, the use of the easily removable PMB group resulted in a slightly reduced diastereomeric ratio (entry 2). Moreover, acetal protecting groups such as MOM or MEM did not give a superior result either (entries 3 and 4). Subjecting an acetate protected substrate to cyclization conditions afforded 902 with 10:1 diastereomeric ratio. The use of bulky silyl groups such as TMS or TBS again

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led to a reduced selectivity.\textsuperscript{571} Based on the ease of introduction and the stability of the putative intermediates under various conditions, we decided to use the benzyl group for our purpose.

**Table 27.** Screening of alcohol protecting groups of the diastereoselective cyclization of 916.

<table>
<thead>
<tr>
<th>Entry\textsuperscript{[a]}</th>
<th>Protecting Group (PG)</th>
<th>dr of 902\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bn</td>
<td>10:1</td>
</tr>
<tr>
<td>2</td>
<td>PMB</td>
<td>7:1</td>
</tr>
<tr>
<td>3</td>
<td>MOM</td>
<td>6:1</td>
</tr>
<tr>
<td>4</td>
<td>MEM</td>
<td>7:1</td>
</tr>
<tr>
<td>5</td>
<td>Ac</td>
<td>10:1</td>
</tr>
<tr>
<td>6</td>
<td>TMS</td>
<td>4:1</td>
</tr>
<tr>
<td>7</td>
<td>TBS</td>
<td>2.5:1</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} conditions: nitrile oxide 916 was generated from the corresponding oxime by treatment with (Bu\textsubscript{3}Sn)\textsubscript{2}O and t-BuOCl, CH\textsubscript{2}Cl\textsubscript{2}, -30 °C to rt; \textsuperscript{[b]} determined by \textsuperscript{1}H NMR.

We set out to prepare enantiopure benzyl protected alcohol 917 as shown in Scheme 198. Literature known alcohol 918 was synthesized starting from (+)-diethyl tartrate 919 by a slightly modified procedure.\textsuperscript{572} Acetal formation under Dean–Stark conditions produced diester 920.\textsuperscript{573} Subsequent reduction with AlH\textsubscript{3}, generated from LiAlH\textsubscript{4} and AlCl\textsubscript{3}, delivered triol 918 in moderate yield.\textsuperscript{574} Diol cleavage with periodic acid in refluxing methanol directly afforded dimethyl acetal 917 in 79% yield.\textsuperscript{575}

**Scheme 198.** Synthesis of alcohol 917 from (+)-diethyl tartrate (919).

Tsuji–Trost allylation of tosylate 434 with sodium alkoxide 921, prepared by deprotonation of 917 with NaH, proceeded smoothly under the previously used conditions affording alkylidinecyclopropane

\textsuperscript{571} The bulky TBS group probably leads to a reduced selectivity due to increased diaxial interactions (see section 10.1. for more details about the putative transition state).

\textsuperscript{572} 918 has been previously prepared: Suami, T.; Tadano, K.-i.; Suga, A.; Ueno, Y. *J. Carbohydr. Chem.* 1984, 3, 429.


\textsuperscript{574} Extraction of the product from the aluminum residue proved challenging. Only continuous extraction using a Soxhlet extractor afforded the product in acceptable yield.

922 in 52% yield (Scheme 199). Oxime formation was achieved by treatment of dimethyl acetal 922 with hydroxylamine hydrochloride in a MeCN/H$_2$O solvent mixture to provide 542 in 82% yield. As described earlier (section 10.1.), dipolar cycloaddition using (Bu$_3$Sn)$_2$O/t-BuOCl delivered isoxazoline 843 in excellent yield and with a dr of 10:1.

Scheme 199. Enantioselective synthesis of enol ether 550.

As we were worried about possible epimerization of the C(14) stereocenter during oxime formation under acidic conditions, we tested the enantiomeric purity of alcohol 537, obtained after benzyl deprotection using FeCl$_3$ (87% yield). Gratifyingly, SFC analysis confirmed that 537 was obtained without loss of stereoinformation in 98% ee.

Finally, we explored dehydration of 537 to arrive at the projected key intermediate 550. A number of protocols were tested to effect elimination of the hydroxyl group in 537. As detailed before, employing common dehydration conditions such as MsCl/base, Martin’s sulfurane, or TFAA/base did not afford the desired product. Moreover, treatment of 537 with thionyl chloride effected decomposition of the starting material. We had previously observed that subjecting 537 to Tf$_2$O in the presence of pyridine delivered enol ether 550, albeit in low yield (30-40%). A number of alternative bases such as DBU, Hüning’s base, or NaH were tested in order to increase the yield, but none of these conditions led to a significant improvement of the reaction outcome. Transformation of 537 into the corresponding bromide under Appel conditions (PPh$_3$, CBr$_4$) was successful. Unfortunately, the bromide could not be eliminated to the desired enol ether 550. To our delight, after conversion of 537 into the corresponding iodide by the use of PPh$_3$/I$_2$, we were able to access enol ether 550 in 82% yield through elimination of the halide with DBU. Alternatively, the addition of DBU to the Appel reaction delivered 550 in one step from alcohol 537, albeit in slightly reduced yield of 62% (see experimental part).
15.4. Conclusion

In conclusion, we have developed a concise route to enantioenriched enol ether 550 en route to the natural product gelsemoxonine (Scheme 200). We have prepared 550 in 5 linear steps from known tosylate 434, which compares to 4 steps for the racemic route. From intermediate 550, the natural enantiomer of gelsemoxonine (278) could be accessed in 19 linear steps following the chemistry previously developed.

Mechanistic Studies on the Isoxazolidine Ring Contraction

Our total synthesis of gelsemoxonine documented in the previous chapters relies on the ring contraction of spirocyclopropane isoxazolidines to form a β-lactam product. The mechanism of this intriguing transformation is not understood until to date. Although numerous mechanistic schemes have been proposed by the groups of Cordero, Salanü and Brandi (vide supra), only scarce experimental evidence has been collected to support any of these suggestions. We were curious to find out more about the nature of this transformation by conducting experimental studies.

Scheme 201. Spirocyclopropane isoxazolidine ring contraction accompanied by the extrusion of ethylene.

As indicated in Scheme 201, Cordero and Brandi, who reported the ring contraction for the first time, hypothesized that ethylene gas is extruded during the reaction, thus accounting for the loss of the two carbon atoms in the cyclopropane ring. Notably, the extrusion of ethylene from a cyclopropane precursor parallels the biosynthetic generation of ethylene as observed in plants. Ethylene is a plant hormone controlling various processes including fruit ripening and plant development. Accordingly, the biosynthesis of ethylene has been extensively studied.

16.1. Biosynthesis of the Plant Hormone Ethylene

As outlined in Scheme 202 (top), the biosynthesis of ethylene in plants proceeds in two steps, starting from S-adenosyl methionine (SAM) (923). The enzyme ACC synthase induces the formation of a cyclopropane ring through nucleophilic displacement of the sulfonium leaving group by the amino acid α-carbon, resulting in the formation of amino cyclopropane carboxylic acid ACC (924). This intermediate is then further processed by the enzyme ACC oxidase (ACCO), a non-heme iron

Mechanistic Studies on the Isoxazolidine Ring Contraction

oxygenase, which is ultimately responsible for the synthesis of ethylene from ACC. Carbon dioxide and hydrogen cyanide\(^{578}\) are produced as side products in this reaction.

\[
\begin{align*}
\text{H}_2\text{C}_3\text{N}_2\text{H}_2\text{COO}^- & \xrightarrow{\text{Adenine synthase}} \text{NH}_3\text{CO}_2^- \xrightarrow{\text{ACC oxidase}} \text{CO}_2 + \text{HCN}
\end{align*}
\]

**Scheme 202.** Proposed biosynthetic generation of ethylene in plants.

Baldwin and Pirrung have proposed a stepwise reaction path for the oxidation of ACC as depicted in Scheme 202 (bottom) based on experimental and computational evidence.\(^{579}\) In particular, the stereochemical analysis of the reaction with deuterium-substituted ACC analogs suggested the intermediacy of a radical intermediate, which triggers cyclopropane opening. It was hypothesized that ACC (924) is oxidized to nitrogen-centered radical 925. This reactive species could undergo C–C bond cleavage of the cyclopropane ring to provide radical 926. A second oxidation event would produce carbocation 927, which would further fragment to produce ethylene and cyanoformic acid 928. Decarboxylation of 928 would result in the production of \(\text{CO}_2\) and HCN.

\[
\begin{align*}
\text{CO}_2^- & \xrightarrow{[\text{O}]} \text{CO}_2^- \xrightarrow{\text{H}^+} \text{NH}_2\text{CO}_2^- \xrightarrow{[\text{O}]} \text{NH} \xrightarrow{[\text{O}]} \text{CO}_2\text{H}^- \xrightarrow{\text{CO}_2^-} \text{H}^+ + \text{HCN} \downarrow \text{CO}_2 + \text{HCN}
\end{align*}
\]

**Figure 35.** A) Crystal structure of the ACC oxidase (adapted from ref. 581) and; B) Mechanism of ACC oxidase according to ref. 580 and 581.

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\(^{578}\) HCN is immediately detoxified by conversion into \(\alpha\)-cyanoalanine.

More recently, EPR studies and kinetic experiments, along with an X-ray crystal structure of ACC oxidase, allowed for a more detailed characterization of this process. As depicted in Figure 35 (A), the iron cofactor of ACCO is positioned by coordination to two histidines and an aspartate residue in a relatively open active site. A carbonate anion is present in the close vicinity of the iron center. This carbonate has been suggested to play a crucial role in catalysis. The proposed catalytic cycle of ACCO is outlined in Figure 35 (B). ACC binds to Fe(II) by displacing two water ligands on complex 929. Oxygen can now coordinate to the iron center thereby generating Fe(III) superoxo species 930. The carbonate anion stabilizes this complex by hydrogen bonding. Reduction of 930 by ascorbate then produces peroxo intermediate 931. After electron transfer from ACC to iron and extrusion of water by O–O bond cleavage, Fe(IV) intermediate 932 results. Fragmentation of ACC will produce ethylene, along with Fe(III) species 933. A final reduction step completes the catalytic cycle.

The overall mechanistic schemes for the spirocyclopropane isoxazolidine ring contraction and the ethylene biosynthesis seem quite different upon initial inspection, but the two transformations share certain key characteristics. Both reactions rely on an α-heteroatom substituted cyclopropane ring as the ethylene precursor. Furthermore, the oxygen atom α to the cyclopropane ring in the contraction precursor is isoelectronic to the nitrogen centered radical of ACC intermediate 925. This suggests that the spirocyclopropane isoxazolidine ring contraction might also proceed in a stepwise fashion, in analogy with the cyclopropane opening step during the ACC biosynthesis (925 → 926 in Scheme 202, bottom).

16.2. Mechanistic Hypotheses

As mentioned previously, mechanistic speculations have been made by the groups originally reporting on the spirocyclopropane isoxazolidine ring contraction. As outlined in Scheme 203 (A), two distinct pathways have been discussed, both involving a stepwise opening of the cyclopropane ring. The authors assumed that initial nitrogen protonation of substrate 934 initiates the reaction. One rationale involves the ring expansion of the three membered carbocycle in 935, displacing the protonated nitrogen at the oxygen atom to provide oxetane intermediate 936. It has been suggested that nitrogen protonation weakens one or two of the C–C bonds of the cyclopropane ring. This hypothesis is supported by the observation that the pKa value of the ether protons in 5-unsubstituted isoxazolidines is dramatically reduced upon quaternization of the nitrogen. Although cyclopropane

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582. Although ascorbate was reported not to be absolutely essential for catalytic turnover, it serves as a potent reductant and an effector of the whole transformation; see ref. 580 and 581.
rings are well known to undergo ring expansion to cyclobutane adducts, an analogous oxo-variant of this reaction to produce oxetane products has never been reported. Next, trapping of the carbocation in by the nitrogen would provide spirocycle. The authors then suggested a retro-Paterno–Büchi reaction to take place accounting for the formation of product and ethylene. Although retro-Paterno–Büchi reactions are well known, these transformations generally proceed under very harsh pyrolytic conditions, illustrating the fact that thermal retro-[2+2] cycloadditions are Woodward–Hoffmann disallowed.

Scheme 203. A) Alternative mechanistic explanations for the spirocyclopropane isoxazolidine ring contraction according to ref. 200; B) Mechanistic rationale for the ring expansion leading to piperidones (ref. 392c,d).

The authors also proposed an alternative mechanistic pathway relying on the homolytic cleavage of the N–O bond in to produce biradical. A similar initial rupture of the N–O bond has been suggested for the conversion of spirocyclopropane isoxazolidines to piperidones (Scheme 203, B). However, this transformation generally requires pyrolytic temperatures to generate radical. In the case of the protic acid mediated ring contraction, it has been suggested that nitrogen protonation weakens the N–O bond, thus facilitating homolytic N–O bond breaking. Biradical intermediate can then cyclopropane cleavage to give ketone. In order to account for the formation of β-lactam from this intermediate, Brandi and co-workers suggest initial attack of the nitrogen in to form hemiacetal-type intermediate followed by radical fragmentation leading to product formation.

In addition to the mechanistic proposals reported by Brandi and co-workers, alternative pathways can also be imagined. As outlined in Scheme 204, protonated isoxazolidine would also offer the possibility of heterolytic N–O bond cleavage, possibly assisted by a trifluoroacetate anion (if CF₃CO₂H is employed as the acid promoter). Accordingly, cyclopropane opening would produce

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trifluoroacetate species 945. Hemiacetal formation would generate 946, which would be susceptible to fragmentation by extrusion of ethylene and trifluoroacetate. Alternatively, heterolytic N–O cleavage might produce carbocation 947 (path b). Loss of ethylene could produce oxonium intermediate 948, which would rapidly cyclize to form β-lactam product 938.

Scheme 204. Possible mechanistic scheme based on heterolytic cleavage of the N–O bond.

A contrasting mechanistic alternative, which has so far not been considered, involves protonation of the cyclopropane ring (Scheme 205). In this instance, oxonium 949 would be in equilibrium with ketal 950, thus stabilizing this intermediate. Again, several options are possible for the conversion of 949/950 to the product. Direct extrusion of ethylene would produce oxonium species 948, which would cyclize to β-lactam 938. Alternatively, intermediate 949/950 would be amenable to oxaziridine formation by attack of the nitrogen onto the electrophilic carbon center. Concerted loss of ethylene from 951 might again produce 938. Finally, homolytic N–O cleavage of the highly strained oxaziridine 951 would deliver biradical 944, which could undergo fragmentation to give 938.

Scheme 205. Mechanistic options based on initial protonation of the cyclopropane ring.

588 Direct conversion of 951 to 938 seems unlikely based on orbital considerations.
16.3. Previous Experimental and Computational Studies

In order to shed light on the contraction mechanism Cordero and Brandi synthesized mono-substituted cyclopropane derivative 952. Treatment of 952 with p-TsOH at ambient temperature produced the expected β-lactam product 953 along with styrene 954 (yields not given). This outcome supported the hypothesis of ethylene extrusion during the reaction sequence. Furthermore, byproducts 955 and 956 were isolated. The authors speculated that formation of these side products might favor a stepwise radical mechanism as outlined in Scheme 206 (path b) as recombination of biradical 957, resulting by fragmentation of 958, would produce piperidone 955. However, the phenyl group on the cyclopropane ring seems to deter the usual reactivity and thus no definite conclusions about the mechanism can be drawn.

![Scheme 206.](image_url)

Scheme 206. Ring contraction of phenyl substituted isoxazolidine 952 (box) and mechanistic explanation for the formation of piperidone 955.

In a second experiment, Cordero and Brandi subjected cis- and trans-fused bicycles 959 and 960 to the standard reaction conditions (Scheme 207, equations 1 and 2). As expected, treatment of 959 with CF₃CO₂H produced β-lactam 961 in good yield. Subjecting isoxazolidine 960 to the same conditions delivered ring expanded product 962. Interestingly, the N-methyl group seems to have been incorporated into the piperidone ring. This hypothesis was confirmed by subjecting tri-deuterated derivative d₃-960 to the CF₃CO₂H conditions, which delivered adduct d₂-962 with deuterium incorporation at the methylene adjacent to the amino group (equation 3). The authors suggested that this outcome would again support a stepwise radical mechanism. In the case of the trans-fused starting material, biradical 963 would be generated (Scheme 207, box). A 1,7-deuterium shift followed by a Mannich reaction could account for the formation of 962. However, deuterium incorporation into the methyl group in 962 would be expected. Such a deuteration was not observed and the authors did not comment on this discrepancy.

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589 The phenyl group also allows the reaction to occur at ambient temperature instead of 80-110 °C needed for unsubstituted substrates.
16. Mechanistic Studies on the Isoxazolidine Ring Contraction

Scheme 207. Ring contraction of cis- vs. trans-fused ring systems and mechanistic explanation for the formation of 962 according to ref. 200b.

More recently, Gandolfi and Brandi carried out computational studies on the spirocyclopropane isoxazolidine ring contraction. As outlined in Scheme 208, the transition state free energies were calculated by DFT methods for a homolytic (path a) and a concerted (path b) mechanism. Heterolytic N–O cleavage was not considered in this work. The very close values calculated for the two transition states 964 and 965 did not allow to clearly favor one pathway over the other.

Scheme 208. Calculated transition states 964 and 965 for a stepwise (path a) and concerted (path b) mechanism.

In order to clarify the situation, we envisioned to collect experimental evidence to distinguish between a concerted and a stepwise mechanism for this unusual reaction.

16.4. Studies on the Stereochemical Course of the Ring Contraction

In the course of their studies directed towards the elucidation of the biosynthetic mechanism for ethylene generation, Baldwin et al. analyzed the stereochemical course of the reaction using various deuterium-substituted ACC analogs. The observation that cis- as well as trans-2,3-dideuterated ACC precursors both result in the generation of a mixture of cis- and trans-1,2-dideuterioethylene, led the authors to propose a stepwise mechanism allowing for the isomerization by bond rotation in an intermediate. We planned to conduct similar studies on the spirocyclopropane isoxazolidine ring contraction to distinguish between a stepwise and a concerted mechanism. As outlined in Scheme 209, stepwise ring-opening of a substituted starting material 966 would proceed via biradical intermediate 967 in the case of a homolytic N–O cleavage (path a). In this intermediate, rapid rotation around the free C–C bond would result in scrambling of the stereoinformation initially encoded in the cyclopropane ring. A mixture of cis- and trans-olefins, 968 and 969, were expected to be produced from this pathway. Alternatively, a concerted mechanism proceeding via a transition state similar to 970 would result in retention of the stereochemistry, producing a single isomer of olefin 968.

Scheme 209. Stereochemical outcome of homolytic (path a) vs. concerted (path b) ring contraction.

In order to implement the strategy detailed above, we embarked on the synthesis of cis- and trans-substituted spirocyclopropane isoxazolidine derivatives. The incorporation of deuterium atoms seemed cumbersome from a preparative point of view. Moreover, analysis of the ethylene product would demand technical expertise in the analysis of gaseous compounds. We thus opted for the introduction of carbon substituents on the cyclopropane ring. The synthesis of carbon substituted methylenecyclopropanes as precursors for a dipolar cycloaddition was therefore required. Feist’s acid 971 represents an easily accessible member of this compound class. We prepared 971 according to literature procedures as outlined in Scheme 210. Condensation of ethyl acetoacetate 972 produced pyranone 973. Bromination delivered compound 974, which was then subjected to ring contraction under basic conditions. Hydrolytic cleavage of the ester bond produced enolate 975. After

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591 The same arguments hold for a heterolytic rupture of the N-O bond.
isomerization of the tetrasubstituted double bond to form 976, nucleophilic ring closure delivered methylenecyclopropane 977. Finally, KOH mediated extrusion of acetic acid from 977 generated Feist’s acid 971 with a trans-configuration of the cyclopropane substituents. The acid was esterified under Fischer conditions to yield ethyl ester 978.593

\[ 
\begin{align*}
\text{Methylenecyclopropane } & 978 \\
\text{Then used as dipolarophile in a nitrile oxide cycloaddition with} & \\
\text{nitroethane as the nitrile oxide precursor furnishing 979 (Scheme 211, top). The resulting oxazoline} & \\
\text{was reduced under alkylative conditions using a combination of Meerwein’s salt and sodium} & \\
\text{borohydride to yield spirocyclopropane isoxazolidine 980.594} \text{Unfortunately, treatment of 980 with} & \\
\text{CF}_3\text{CO}_2\text{H in refluxing acetonitrile did not provide the desired products 981 and 982 but led to} & \\
\text{decomposition of the starting material (Scheme 211, box).595} 
\end{align*}
\]

\[ 
\begin{align*}
\text{We reasoned that the electron-withdrawing ester substituents on the cyclopropane ring might be} & \\
\text{responsible for the unfavorable reaction outcome. We therefore turned our attention to the synthesis of} & \\
\text{alkyl substituted cyclopropane derivatives.} 
\end{align*}
\]

595 TLC co-spotting of the reaction mixture with ethylfumarate 982 clearly indicated that no ethylfumarate was produced in this reaction.
As outlined in Scheme 212, we subjected Feist’s acid ethyl ester 978 to LiAlH₄ reduction giving diol 983 in good yield. Subsequent acetylation of the hydroxyl groups delivered 984 in 99% yield. Dipolar cycloaddition with nitroethane using the conditions employed previously gave isoxazoline 985 in 58% yield. Finally, alkylationative reduction of the oxime ether functionality produced trans-substituted cyclopropane 986.

Scheme 212. Preparation of trans-substituted cyclopropane 986.

The synthesis of a corresponding cis-substituted cyclopropane derivative could start form cis-Feist’s acid. However, we were not able to prepare significant quantities of this compound. As we had a well-established route to a cis-substituted methylenecyclopropane derivative in hand from our studies directed towards the enantioselective synthesis of gelsemoxonine (see section 15.2.), we envisioned using this strategy to access a suitable cyclization precursor for our mechanistic investigations.

As outlined in Scheme 213, the synthesis of cis-substituted cyclopropane derivative 987 started with alkylation of propargyl alcohol 885 with bromide 988. Subsequent alkyne addition of 989 to aldehyde 888 produced secondary alcohol 990 in 83% yield. Treatment of this intermediate under the previously employed Myers conditions delivered allenic alcohol 991. A sequence involving diazoacetate installation and treatment of intermediate 992 with copper catalyst 900 gave cis-substituted methylenecyclopropane derivate 993 in good yield and as an inconsequential 1:1 mixture of double bond isomers. Reductive cleavage of the strained lactone ring, followed by acetylation of the resulting diol produced bisacetate 994. Nitrile oxide cycloaddition was carried out using the protocol previously employed. Treatment of dioxolane 994 with hydroxylamine hydrochloride delivered the corresponding oxime, which was then converted into the nitrile oxide using bis-tributyltin oxide and t-BuOCl. Reduction of the resulting oxime ether was again undertaken by treatment of 995 with Meerwein’s salt followed by addition of sodium borohydride to give isoxazolidine 987 in 63% yield.

596 Reduction of the methyl ester of Feist’s acid under the same conditions has been reported: ref. 592c.


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Scheme 213. Preparation of cis-substituted cyclopropane 987.

In order to effect ring contraction of the cis- and trans-substituted spirocyclopropane isoxazolidine derivatives 986 and 987, the compounds were dissolved in CD$_3$CN (Scheme 214). The reactions were monitored by $^1$H NMR spectroscopy. After addition of d-TFA, rapid conversion of the starting materials was observed. Analysis of the crude reaction mixture and isolation of the products revealed that the alkene products generated were isomerically pure (Figure 36 and 37). Ring contraction of trans-substituted cyclopropane 986 exclusively delivered E-configured alkene 996, along with volatile and unstable β-lactam 981, whereas cis-substrate 987 produced Z-olefin 997 as the only product besides bicycle 998.

Scheme 214. Ring contraction of substituted cyclopropanes 986 and 987.

Closer inspection of the $^1$H NMR spectra of the crude reaction mixture confirmed exclusive formation of only one olefinic product by retention of the cyclopropane stereochemistry (Figure 36 and 37). Moreover, no deuterium incorporation into the olefinic product was observed, allowing to exclude a mechanism involving initial cyclopropane protonation (Scheme 205).
Mechanistic Studies on theIsoxazolidine Ring Contraction

Figure 36. $^1$H NMR experiment (300 MHz) in CDCl$_3$ for the ring contraction of trans-cyclopropane 986 (6.5-4.0 ppm range). a) $^1$H NMR spectrum of the independently synthesized E-alkene 996; b) $^1$H NMR spectrum of independently synthesized Z-alkene 997; c) $^1$H NMR spectrum of the crude reaction mixture of the ring contraction of isoxazolidine 986.

Figure 37. $^1$H NMR experiment (300 MHz) in CDCl$_3$ for the ring contraction of cis-cyclopropane 987 (6.5-4.0 ppm range). a) $^1$H NMR spectrum of the independently synthesized E-alkene 996; b) $^1$H NMR spectrum of independently synthesized Z-alkene 997; c) $^1$H NMR spectrum of the crude reaction mixture of the ring contraction of isoxazolidine 987.
Control experiments confirmed that the individual alkene products were configurationally stable under the reaction conditions (Scheme 215).

\[
\begin{align*}
\text{AcO} & \xrightarrow{\text{TFA}} \text{AcO} \\
\text{MeCN} & \text{80 °C} \\
\text{no isomerization}
\end{align*}
\]

Scheme 215. Control experiments to rule out olefin isomerization under the contraction conditions.

Based on these findings of a completely stereoretentive cleavage of the cyclopropane ring, we propose a revised mechanistic scheme for the spirocyclopropane isoxazolidine ring contraction as described below.

### 16.5. Revised Mechanistic Rationale for the Isoxazolidine Ring Contraction

The stereoretentive nature of the ring contraction observed above strongly suggests a concerted mechanism for cyclopropane cleavage. Based on this observation, we propose an alternative mechanism for this reaction as outlined in Scheme 216.

\[
\begin{align*}
\text{cheletropic} \\
\text{via:}
\end{align*}
\]

Scheme 216. Revised mechanistic explanation of the spirocyclopropane isoxazolidine ring contraction.

After initial protonation of the isoxazolidine nitrogen, the protonated species 935 undergoes a cheletropic cleavage of the cyclopropane ring,\(^{599}\) possibly assisted by the electron-withdrawing effect of the positively charged quaternary amine. The cleavage of three membered rings by stereoretentive

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Mechanistic Studies on the Isoxazolidine Ring Contraction

cheletropic reactions has been documented for several transformations (Scheme 217).\textsuperscript{600} Rearrangement of 999 via transition state 1000 will thereby produce putative oxonium intermediate 948. It is not clear, to what extent the individual bonds are broken in the transition state. For example, in an extreme case of a semi-concerted mechanism, initial extrusion of ethylene from compound 1001 by a concerted “retro-cyclopropanation” would give an oxacarbene intermediate 1002.\textsuperscript{601,602} In a second step, rearrangement of this carbene might deliver product 938. It seems unlikely, that N–O bond cleavage occurs first in the reaction pathway as this would result in a transition state with strong biradical character. Such a putative biradical intermediate is expected to preferentially undergo radical fragmentation of the cyclopropane ring in a non-concerted fashion. This mechanistic scenario would not be consistent with the observed stereoretention during ethylene extrusion.

\[
\begin{align*}
\text{SO}_2 & \rightarrow \quad \parallel + \quad \text{SO}_2, \quad (1) \\
\text{N} & : \text{CR}_x \rightarrow \quad \text{N} + \quad : \text{CR}_x, \quad (2) \\
\text{N} & = \text{N} \rightarrow \quad \parallel + \quad \text{N}_2, \quad (3)
\end{align*}
\]

Scheme 217. Related cheletropic reactions of three-membered rings.


\textsuperscript{602} Carbenes with π-donating oxygen substituents have been found to be particularly stable. For an example, see: Moss, R.A.; Xue, S.; Liu, W. J. Am. Chem. Soc. 1994, 116, 1583-1584; and references therein.
16.6. Conclusion

In summary, we have investigated the stereochemistry of the spirocyclopropane isoxazolidine ring contraction. We observed that substituted cyclopropane precursors lead to the stereoretentive production of ethylene equivalents. Based on this data, we propose a concerted mechanism for this ring contraction in contrast to the stepwise pathways proposed to date. As outlined in Scheme 218, we suggest that nitrogen protonation in 934 weakens the cyclopropane C–C bonds, as well as the N–O bond, thus allowing for the concerted cleavage of the cyclopropane ring. The resulting oxonium intermediate 948 then cyclizes to the β-lactam product.

Scheme 218. Proposed mechanism for the spirocyclopropane isoxazolidine ring contraction.
Conclusion and Outlook

Gelsemoxonine (278) is an oxindole alkaloid isolated from the toxic plant *Gelsemium elegans* bentham. Its structure incorporates an unusual azetidine, which is completely embedded in the polycyclic scaffold of the natural product. Furthermore, gelsemoxonine harbors six densely packed contiguous stereocenters including a quaternary spiro-fused carbon at the oxindole moiety. These structural features along with the medicinal relevance of the gelsemium alkaloids prompted us to embark on a total synthesis of gelsemoxonine (278).

As outlined in Scheme 219, the central feature of our synthetic strategy towards gelsemoxonine is the ring contraction of a spirocyclopropane isoxazolidine 716 to form β-lactam 717. The substrate for this intriguing transformation was accessed in four steps starting from known aldehyde 546. The β-lactam moiety in 717 was then further elaborated into the azetidine motif of the natural product. Construction of the spiro-fused oxindole system was achieved employing a reductive Heck reaction. Hydroxamic acid 832, available from ester 717 in 10 steps, was treated with a palladium catalyst in the presence of formic acid to provide oxindole 822 as a single diastereomer in good yield. Finally, introduction of the ethyl ketone through a directed hydrosilylation delivered racemic gelsemoxonine (278) in five steps from alkyne 822.

![Scheme 219](image-url)

Scheme 219. Total synthesis of (±)-gelsemoxonine (278) relying on the acid mediated ring contraction of spirocyclopropane isoxazolidine 716.
In the course of our efforts directed towards the total synthesis of gelsemoxonine (278), we have conducted experimental studies on the mechanism of the isoxazolidine ring contraction. Our results suggest that this reaction proceeds via a concerted mechanism as presented in Scheme 220. We propose two possible pathways starting from $N$-protonated isoxazolidine 935. $\beta$-lactam 938 could either be accessed through a cheletropic mechanism producing oxonium intermediate 948 through the extrusion of ethylene from 1000 (path a), or alternatively, via carbene 1002, which then rearranges to the product (path b).

**Scheme 220.** Proposed mechanism for the acid mediated ring contraction of spirocyclopropane isoxazolidines.

We have established the spirocyclopropane isoxazolidine ring contraction as an efficient method to generate highly substituted $\beta$-lactam and azetidine products. This transformation could prove useful in the total synthesis of numerous natural products incorporating azacyclobutane rings. As exemplified in Figure 38, our approach could in particular serve to access various $\beta$-lactam antibiotics or azetidine containing alkaloids.

**Figure 38.** Selected azacyclobutane containing alkaloids.
Furthermore, the combination of a nitrile oxide cycloaddition followed by the acid mediated isoxazolidine ring contraction, offers the possibility of accessing fully substituted β-lactams, which are otherwise difficult to prepare by standard methods. We propose a reaction sequence starting from readily available isoxazoline 1005 (Scheme 221). Stereoselective functionalization of C(4) could be guided by the substituents on the cyclopropane ring. Subsequent organolithium addition to 1006 would produce isoxazolidine 1007, and upon ring contraction the fully substituted β-lactam 1008.

Scheme 221. Novel approach for the synthesis of fully substituted β-lactams.

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603 For a summary of the methods available for β-lactam synthesis, see section 7.7.
604 The isoxazoline C(4) position can be selectively deprotonated when R₁ is an alkyl chain: Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. Tetrahedron 1986, 42, 2129-2134.
Part III

Diazonium Salts as Novel Reagents for Amine Selective Bioconjugation to Proteins and Peptides
18

Introduction

In the past decades, the study of biomolecules has gained tremendous importance in biology and biological chemistry. Numerous techniques have been developed to investigate properties such as function, localization or regulation of these entities in living cells or \textit{in vitro}. In this context, researchers have been interested early on in modifying biopolymers by chemical means, allowing for the attachment of functional units to these molecules. Out of this interest, the field of bioconjugative chemistry\textsuperscript{605} emerged, aimed at finding chemical agents that can be coupled to biomolecules under physiological conditions.\textsuperscript{606}

18.1. Bioconjugative Chemistry

Bioconjugation involves the union of two (or more) distinct components, generally at least one of them being derived from a biological source (Figure 39). The components can include antibodies, enzymes, receptor ligands, short peptides, oligosaccharides, DNA or RNA strands, small dye molecules, bioactive secondary metabolites such as toxins, synthetic polymers and many more. The coupling of the individual partners is achieved by reaction with a linker molecule carrying reactive groups designed to interact with designated functional groups on each component. The resulting bioconjugate unites the functional properties of both components. This strategy therefore allows for the creation of molecules with functional properties, which are otherwise not found in biological systems. For instance, fluorescent dyes for radioactive probes\textsuperscript{607} can be attached to proteins or polynucleotides.

\begin{figure}[h]
\centering
\includegraphics[width=0.6\textwidth]{bioconjugate_principle.png}
\caption{The principle of biocjugative chemistry.}
\end{figure}

\textsuperscript{605}For a definition of bioconjugate chemistry, see: Meares, C.F. \textit{Bioconjugate Chemistry} 1990, 1, 1.
In contrast to the direct linkage of components A and B by a single linker as depicted in Figure 39, a more often encountered situation involves the sequential functionalization of each of the components, followed by a linkage step (Figure 40). Each component is first reacted with a linker molecule carrying a distinct functional group, which is inert towards the biomolecule (indicated in yellow in Figure 40). In a second step, the two conjugates are combined. The union of the components is achieved through the reaction of the functional groups attached to each linker. This strategy has several advantages. First, formation of homodimeric and oligomeric products can be avoided. Second, a large excess of the linker molecule can be employed in the first step, thus ensuring full conversion of the precious biomolecule.

![Figure 40. Sequential bioconjugation of two components.](image)

The biophysical properties of the linker molecule play a crucial role in bioconjugative chemistry as they exert a significant influence on the nature of the resulting conjugate. Hydrophobic linker chains for instance, lead to enhanced membrane permeability. However, side effects, such as unspecific interaction with biomolecules and aggregation of the conjugates, are observed with this linker type. In contrast, hydrophilic spacers often lead to better solubility and less unspecific interactions of the conjugate. Furthermore, functional linkers, such as polymers, can be employed. Through the use of a multivalent linker system, multiple attachments of the bioactive components to a linker scaffold can be achieved, thus leading to an enhanced activity of the conjugate.

Bioconjugates are used for a wide variety of different purposes. They can be employed for quantification assays or for imaging and detection purposes. Furthermore, bioconjugates can be used to capture receptor molecules or for other purification procedures. Attachment of a linker to an enzyme can lead to an interesting new catalyst system. Bioconjugative chemistry also finds wide application for the modification of therapeutic agents or for in vivo diagnostics.609,610

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610 As an example, see the use of antibody-drug conjugates: Alley, S.C.; Okeley, N.M.; Senter, P.D. Chem. Biol. 2010, 14, 529-537.
18.2. Chemical Ligation to Native Proteins

The chemical strategies available for the formation of a bioconjugate can be subdivided into two major categories. One approach relies on the use of the functional groups inherent to native biomolecules for chemical modification of the component. Alternatively, bioorthogonal functional groups can be introduced, creating an artificial biomolecule, which can then participate in chemical transformations otherwise not applicable to the native biomolecule. In general, the chosen ligation strategy must fulfill a few key requirements: The chemical reaction employed must be selective for the functional group targeted, avoiding any side reactivity. Furthermore, the reaction has to occur in aqueous solution under mild pH conditions and preferentially at ambient temperature in order not to harm the sensitive coupling partners involved.

18.2.1. General Considerations

The most extensively investigated biomolecules amenable to bioconjugation are proteins and oligopeptides. The commonly targeted native reactive groups in proteins are the amino group of the N-terminus, the carboxylate moiety at the C-terminus, and the amino acid side chains. Figure 41 summarizes the 20 proteinogenic amino acids according to their side chain functionality. The hydrophobic amino acid side chains are generally inert towards most transformations used in

![Figure 41. The 20 proteogenic amino acids according to their side chain functionality.](image-url)
bioconjugative chemistry. Nucleophilic functionalities such as alcohols (Ser, Thr), thiols (Cys) and amines (Lys) are very popular sites of modification by reaction with an appropriate electrophile. Carboxylic acid derivatives (Gln, Glu, Asn, Asp) are less used for bioconjugation. Finally, electron rich aromatic side chains (Tyr, Trp, His) are amenable to oxidative manipulation as detailed below or can also participate in reactions with electrophiles.

For most reactions employed in biocojugative chemistry in aqueous solution, the pKₐ values of the reactive groups are of prime importance when considering selectivity and reactivity issues. Table 28 summarizes the most relevant pKₐ values of amino acid side chains, as well as the N- and C-termini.

Table 28. Important pKₐ values for amino acid side chain functionalities.

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Residue</th>
<th>pKₐ Range[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-terminus</td>
<td><img src="image" alt="C-term" /></td>
<td>2.1-2.4</td>
</tr>
<tr>
<td>Aspartate/Glutamate carboxyl group</td>
<td><img src="image" alt="Asp/Glu" /></td>
<td>3.7-4.5</td>
</tr>
<tr>
<td>Histidine NH</td>
<td><img src="image" alt="Histidine" /></td>
<td>6.7-7.1</td>
</tr>
<tr>
<td>N-terminus</td>
<td><img src="image" alt="N-term" /></td>
<td>7.6-8.0</td>
</tr>
<tr>
<td>Cystein thiol</td>
<td><img src="image" alt="Cystein" /></td>
<td>8.8-9.1</td>
</tr>
<tr>
<td>Lysine NH₂</td>
<td><img src="image" alt="Lysine" /></td>
<td>9.3-9.5</td>
</tr>
<tr>
<td>Tyrosine phenol</td>
<td><img src="image" alt="Tyrosine" /></td>
<td>9.7-10.1</td>
</tr>
<tr>
<td>Arginine guanidinyl group</td>
<td><img src="image" alt="Arginine" /></td>
<td>&gt;12</td>
</tr>
</tbody>
</table>

[^a]: adapted from ref. 606.
For instance, the amino group at the N-terminus of proteins has generally a lower pKₐ than the NH₂ of lysine side chains. This can allow for the selective modification of the N-terminus, while leaving the lysine residues untouched. However, the microenvironment around a specific residue can greatly influence the pKₐ value of functional groups. In particular, certain lysine amines can have pKₐ values that allow efficient reaction already at neutral pH.

In additions to the general considerations detailed above, the choice of a proper bioconjugative strategy also has to take into account the abundance of the targeted reactive group on the surface of the biomolecule. In the case of proteins, the amino acid distribution on the solvent exposed proteins surface can differ significantly from the amino acid content of the overall polypeptide. Figure 42 shows a general trend for the abundance of each of the 20 proteogenic amino acids on protein surfaces compared to its total number in the protein sequence. It is apparent that highly polar and charged amino acids such as glutamate, lysine or arginine are preferentially located at solvent exposed sites and are thus better accessible for chemical modification.

Figure 42. Solvent exposure of the 20 proteogenic amino acids. (calculated from data of ref. 613).

The following section presents a brief overview of the most commonly used methods for bioconjugation to proteins.

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611 For an example, see: Rana, T.M.; Mears, C.F. Bioconj. Chem. 1990, 1, 357-362.
613 The data for Figure 42 was taken from: Bordo, D.; Argos, P. J. Mol. Biol. 1991, 217, 721-729, according to a discussion in ref 606.
18.2.2. Ligation Chemistry for Amino Groups

Lysine side chains are some of the most abundant residues on protein surfaces. For this reason, numerous approaches have been designed for the selective modification of the lysine amino group on polypeptides.

One of the traditional methods to couple linker molecules to amines involves the use of isocyanate (1009) or isothiocyanate (1010) reagents (Scheme 222). Both these functional groups react preferentially at alkaline pH. Besides the formation of urea (1011) or thiourea (1012) products by reaction with an amine, isocyanate reagents also react with nucleophilic phenolic groups or thiols.\textsuperscript{615} However, the products from these coupling reactions are less stable than the urea derivatives. Another disadvantage of isocyanate based linker molecules is their instability in water. Their moisture-sensitivity also renders storage of the reagents problematic.

\begin{equation}
\text{linker} + \text{H}_2\text{N} \rightarrow \text{linker} \text{H}_2\text{N}
\end{equation}

\textbf{Scheme 222.} Isocyanate and isothiocyanate protein conjugation.

Sulfonyl chlorides (1013) have also been employed for the bioconjugation with amines (Scheme 223). Due to their steric bulk, sulfonyl chlorides react only slowly with proteins to form the corresponding sulfamide products 1014.

\begin{equation}
\text{linker} + \text{H}_2\text{N} \rightarrow \text{linker} \text{H}_2\text{N}
\end{equation}

\textbf{Scheme 223.} Sulfonyl chlorides for protein bioconjugation.

The most widely used strategy for the functionalization of side chain amines in proteins relies on the use of N-hydroxysuccinimide esters (NHS-ester, 1015) as shown in Scheme 224. These reagents can be easily prepared from the corresponding carboxylate precursors by an esterification protocol. However, NHS-esters are relatively unstable in aqueous solution due to hydrolysis.\textsuperscript{616} This problem generally requires the use of high protein concentrations to achieve good conversion of the substrates to the corresponding products 1016.


Aldehyde carbonyl groups attached to linker molecules $\textit{1017}$ readily react with amines to form imine products $\textit{1018}$ (Scheme 225). Due to their instability in aqueous solution, these imine intermediates are generally reduced to form secondary amines such as $\textit{1019}$. Traditionally, borohydride-based reductants such as $\text{NaCNBH}_3$ are employed for this transformation. More recently, the use of transition metal catalysis in bioconjugate chemistry has attracted the interest of biological chemists. $^{617}$ For instance, iridium catalyst $\textit{1020}$ (Scheme 225, box) was employed by Francis and co-workers for the transfer hydrogenation of imine $\textit{1018}$ to form secondary amine bioconjugates under mild conditions (neutral pH). $^{618}$ Remarkably, catalyst $\textit{1020}$ only reduces imine intermediate $\textit{1018}$, while leaving the aldehyde starting material untouched.

Scheme 225. Protein bioconjugation by reductive amination.

The selective targeting of the N-terminal amine of a protein is a particular challenge in bioconjugate chemistry. Traditional approaches generally rely on the difference of $pK_a$ values for N-terminal amines and lysine residues. $^{619}$ Francis and co-workers have recently developed an alternative strategy as outlined in Scheme 226. $^{620}$ Treatment of a protein with pyridoxal-5-phosphate (PLP, $\textit{1021}$) leads to the formation of imine intermediate $\textit{1022}$, which is in equilibrium with $\alpha$-carbonylimine $\textit{1023}$, if an N-terminal amino group participated in the reaction. Hydrolysis of this intermediate produces primary amine $\textit{1024}$ along with dicarbonyl compound $\textit{1025}$. With this transformation, a bioorthogonal functional group was introduced into the native protein. The newly formed dicarbonyl species can subsequently be reacted with a hydroxylamine derivative $\textit{1026}$ attached to an appropriate linker, producing bioconjugate $\textit{1027}$. A disadvantage of this strategy is that only a limited set of N-terminal residues (Ala, Gly, Asp, Glu or Asn) react efficiently, while others are completely incompatible with this methodology (Ser, Thr, Cys, Trp). Moreover, the final hydroxylamine coupling generally proceeds very slowly, taking several days for complete conversion.

$^{619}$ See table 28 and ref. 611.
18. Introduction

Scheme 226. Pyridoxal-5-phosphate (PLP, 1021) mediated selective functionalization of protein N-termini.

Fakuse and co-workers have reported a highly efficient linkage strategy relying on an electrocyclization step (Scheme 227). Treatment of a protein exhibiting exposed amino groups with unsaturated aldehyde 1028 generates intermediate imine 1029. This triene rapidly undergoes a 6π-electrocyclization at ambient temperature to give dihydropyridine derivative 1030. Most remarkably, this transformation proceeds in only 10 min reaction time, which allowed the attachment of rapidly decaying radioactive PET tracers to various protein targets.

Scheme 227. Conjugation of amines with aldehydes through a 6π-electrocyclization.

18.2.3. Ligation Chemistry of Thiol Groups

Another commonly targeted functionality for protein bioconjugation is the sulfhydryl group. The high nucleophilicity of thiols render them highly susceptible to the reaction with electrophilic partners. However, a major disadvantage of thiol-based bioconjugative chemistry is the low abundance of cysteine residue in protein structures. This problem can be avoided by introduction of a thiol residue by chemical modification of other protein side chains, such as amino groups of lysines.622


622 Various protocols have been developed to this end. For selected examples, see: a) Perham, R.N.; Thomas, J.O. J. Mol. Biol. 1971, 62, 415-418; b) Traut, R.R.; Bollen, A.; Sun, R.R.; Hershey, J.W.B.; Sundberg, J.; Pierce, L.R. Biochemistry 1973, 12, 3266-3273; c) Duncan, R.J.S.; Weston, P.D.; Wrigglesworth, R. Anal. Biochem. 1983, 132, 68-73; for more details, see also ref. 606.
As outlined in Scheme 228 (equation 1), thiol groups readily undergo alkylation with alkyliodides to give thioether products $^{1031}$. Commonly used reagents for this purpose include $\alpha$-iodoketones ($^{1032}$). However, also histidine, methionine and lysine residues react with this reagent class.

A more specific bioconjugation of thiols is achieved by the use of maleimide derivatives $^{1033}$ at pH values between 6.5 and 7.5 (equation 2). $^{624}$ Sulfhydryl groups undergo 1,4-addition to the electron-poor double bond of $^{1033}$ producing stable thioether $^{1034}$.

![Scheme 228. Common strategies for the reaction of thiol groups for bioconjugation.](image)

Only recently, Davis and co-workers have reported a novel strategy for the manipulation of cysteine residues (Scheme 229). $^{625}$ Their approach relies on the initial oxidative elimination of the thiol group in $^{1035}$ using $O$-mesitylsulfonylhydroxylamine (MSH, $^{1036}$) as the oxidant. The resulting dehydroalanine intermediate $^{1037}$ is then amenable to nucleophilic addition of an external thiol reagents producing thioether $^{1038}$. This sequence of events leads to a loss of the stereochemistry at the cysteine stereocenter. Moreover, methionine residues in the native protein are also oxidized by MSH to form iminosulfonium salts.

![Scheme 229. Two-step functionalization of cysteine residues through oxidative elimination/1,4-addition.](image)

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18.2.4. Ligation Chemistry with Electron-Rich Aromatic Rings

A more recent trend in bioconjugate chemistry is the development of reactions designed to modify electron-rich aromatic residues on the protein surface. In 1995, Kodadek and co-workers reported the nickel catalyzed oxidation of tyrosine side chains as outlined in Scheme 230. Upon treatment of an exposed phenol group with nickel catalyst \textbf{1039} in the presence of the peracid MMPP, radical intermediate \textbf{1040} is formed. A linker molecule with an attached second phenol group can then react with this intermediate to form bioconjugate \textbf{1041}. Interestingly, no cross-linking of the protein substrates was observed with this protocol even at high concentrations.

Scheme 230. Oxidative tyrosine ligation using nickel(II) catalyst \textbf{1039}.

An alternative oxidative modification of tyrosines was reported by the group of Francis (Scheme 231). Treatment of native proteins with ceriumammonium nitrate (CAM) leads to the selective oxidation of solvent exposed phenols. Subsequent reaction with electron-rich arenes, such as aniline \textbf{1042}, generate a product mixture of C- and O-linked conjugates \textbf{1043} and \textbf{1044}.

Scheme 231. CAM mediated tyrosine oxidation.

The electron-rich aromatic ring of the amino acid tyrosine has also been used as a nucleophilic reaction partner. As outlined in Scheme 232, Francis and co-workers have developed a protocol allowing for the allylation of the phenol hydroxyl group. In this reaction, an allyl acetate derivative reacts with tyrosines in the presence of Pd(OAc)$_2$ to form allylic ether \textbf{1045} (equation 1). The same

\begin{thebibliography}{99}
\end{thebibliography}
group has reported a three component Mannich protocol involving the condensation of aniline substrates with formaldehyde (equation 2). The resulting imine intermediate is then trapped by a tyrosine residue of a protein coupling partner to furnish amine 1046. The group of Barbas and coworkers developed a bioconjugation protocol relying on the reaction of diazocarboxylate 1047 with tyrosine side chain resulting in the formation of products such as 1048.

\[
\text{HO-} \text{protein} \xrightarrow{\text{Pd(OAc)}_2} \text{R} \xrightarrow{\text{H}_2\text{N} \text{R}} \text{R} \xrightarrow{\text{H}_2\text{O}} \text{R} \xrightarrow{\text{pH 6.5 18 h}} \text{R} \xrightarrow{\text{1046}} \text{R} \xrightarrow{\text{O}_2\text{N-N-N}} \text{R} \xrightarrow{\text{pH 7.4}} \text{R} \xrightarrow{\text{1048}}
\]

Scheme 232. Tyrosine residues as nucleophiles in bioconjugation.

Also tryptophan residues can be selectively modified as depicted in Scheme 233. It was found that indole moieties readily react with donor-acceptor substituted rhodium carbenes generated through the reaction of diazo compound 1049 with \(\text{Rh}_2(\text{OAc})_4\) in the presence of hydroxylamine hydrochloride. Again, a mixture of regioisomeric products 1050 is generated.

\[
\text{HN} \text{protein} \xrightarrow{\text{1049}} \text{Ph} \xrightarrow{\text{R}_2\text{(OAc)}_4} \text{HN} \xrightarrow{\text{Ph}} \text{CO}_2\text{R} \xrightarrow{\text{pH 1.5-2 17 h}} \text{Ph} \xrightarrow{\text{1050}} \text{CO}_2\text{R}
\]

Scheme 233. Reaction of tryptophan residues with rhodium carbenes.

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632 Addition of hydroxylamine was found to enhance catalyst reactivity.
18.3. Bioorthogonal Chemical Ligation

As an alternative to bioconjugation to native biomolecules, bioorthogonal chemical ligation has emerged as a versatile tool for the highly selective coupling of two partners. This approach relies on the initial installation of a functional group not found in native biopolymers that can react with a specific partner functionality on a linker component. This cross-reaction must be selective for this functional group pair, avoiding any interaction with reactive groups on the native biopolymer. This scenario can either be achieved through manipulation of the natural biopolymer by chemical reactions. Alternatively, incorporation of synthetic building blocks (e.g. synthetic amino acid analogs) into the polymer chain itself can serve the introduction of such bioorthogonal functionality. This section briefly summarizes the most important concepts developed to date.

Introduction of aldehydes or ketones into proteins have been reported by several research groups. These carbonyl groups on modified proteins such as 1051 can be brought to react with hydroxylamines (1052) or hydrazines to form the corresponding condensed products 1053 (Scheme 234).

Scheme 234. Bioconjugation to aldehydes.

Bertozzi and co-workers have pioneered the use of the classical Staudinger ligation for the coupling of azide functionalized proteins (1054) and sugars with arylphosphines (Scheme 235). The original protocol developed involves the use of ester functionalized arylphosphines 1055, reacting with azides to give phosphorous azaylids 1056 (equation 1). Subsequent intramolecular trapping of the nitrogen leads to the formation of a new amide bond in product 1057. Soon after the first report of this novel bioconjugation strategy, the research groups of Raines and Bertozzi documented a traceless variant of this transformation. For instance, the use of thioester 1058 can lead to the formation of amide 1059 via intermediate 1060 (equation 2). In this case, the product does not contain the phosphine oxide byproduct anymore.

---


A more widely used reaction of azides in bioorthogonal chemistry is the [3+2] cycloaddition between alkynes and azides (Huisgen cycloaddition). This transformation was introduced for bioconjugation by Sharpless and co-workers under the name of “click-chemistry”.\(^\text{637}\) The original reaction conditions involved the use of copper(I) salts to promote the cycloaddition of alkynes\(^\text{1061}\) with azide functionalized coupling partners such as\(^\text{1054}\) furnishing triazole\(^\text{1062}\) (Scheme 236). Alternatively, the functional groups can be switched using starting materials\(^\text{1063}\) and\(^\text{1064}\) resulting in regioisomeric product\(^\text{1065}\). Recently, Bertozzi and co-workers have introduced a copper-free protocol for “click-chemistry” relying on the employment of strained alkyne coupling partners (Scheme 236, box for selected examples).\(^\text{638,639}\) These reagents are reactive enough to couple with azides at ambient temperature without any additives.

Scheme 235. Staudinger ligation for the coupling of alkynes and azides.

Scheme 236. Bioconjugation through alkyne/azide cycloaddition.


More recently, other cycloaddition reactions have been employed in bioconjugate chemistry (Scheme 237). Fox and co-workers have reported an inverse-electron-demand Diels–Alder reaction between strained \textit{trans}-cyclooctyne 1067 and tetrazine 1068 (equation 1). Upon nitrogen extrusion, product 1069 is formed. Another Diels–Alder-based strategy uses strained cyclopropene derivatives 1070 as dienophiles (equation 2). Reaction of these reactive entities with tetrazines 1071 lead to the rapid formation of product 1072.

\begin{equation}
\begin{align*}
\text{1068} + \text{1067} & \rightarrow \text{1069} \\
\text{1071} + \text{1070} & \rightarrow \text{1072}
\end{align*}
\end{equation}

\textbf{Scheme 237.} Bioconjugation through Diels–Alder cycloaddition.

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Aim of the Project

Diazonium salts have first been prepared and characterized more than 150 years ago. Only recently, they have regained the attention of many synthetic chemists proving useful in a variety of transformations as highly electrophilic components. However, in spite of their high water solubility and mild reactive behaviour, they have not found wide application in biological chemistry to date. We herein present a novel approach for the use of diazonium salts as bioconjugation reagents.

19.1. Diazonium Salts as Novel Reagents for Bioconjugation

Diazonium salts have previously found limited application for the modification of tyrosine and histidine residues in the bioconjugation to proteins and peptides. Their reaction with DNA purine bases has also been documented. As outlined in Scheme 238, diazonium salts, such as 1073, react with the electron-rich aromatic ring of tyrosines to form diazo products 1074. This reactivity parallels

Scheme 238. Coupling of diazonium salts to tyrosine residues of proteins.

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642 Diazonio compounds were first synthesized and characterized by Peter Griess in 1858. For a biographical sketch, see: Cliffe, W.H. Chem. Ind. 1958, 616-621.
the commonly used chemistry for the synthesis of azo dyes, such as methyl orange. However, a number of problems have been encountered with this bioconjugation protocol. In particular, most diazonium salts show poor reactivity towards proteins. Only reagents with strongly electron-withdrawing substituents on the arene ring lead to efficient conversion to the bioconjugate. This circumstance limits the substrate scope to para-nitrobenzene diazonium salts, which are most reactive, or ortho-carboxy substituted derivatives. As a consequence, the initially formed conjugate will need further chemical modification for the attachment of a second functional component. Moreover, the diazonium coupling reactions presented in Scheme 238 are generally performed at a very high pH of 9 or more. This requirement further limits the scope of substrates available.

Besides the reaction with aromatic rings, diazonium salts are well known to couple with primary amines forming triazene products. Based on this reactivity, we propose an alternative bioconjugative strategy as outlined in Scheme 239. We reasoned that a functionalized aryl diazonium salt could be brought to react with a protein component generating triazene. Possibly, a system could be developed, which allows selective targeting of free amines on the protein surface without touching tyrosine and histidine residues. The advantages of such a strategy would include mild reaction conditions, preferentially at neutral pH, as well as the high functional group tolerance generally associated with diazonium compounds. This might possibly enable the direct coupling of highly complex functional units such as natural products, peptides and DNA strands with proteins, a task which has been met with difficulties using previously developed bioconjugation strategies.

Scheme 239. Projected bioconjugation of aryl diazonium salts with amino groups of proteins.

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19.2. Chemistry of Diazonium Salts

The preparation and reactivity of organic diazonium compounds has been extensively studied during the last decades.\(^\text{650}\) Diazonium salts are often highly unstable and in many cases explosive. Their stability depends on the organic framework of the compound and, to a lesser extent, on the counterion associated with the cationic diazonium species. Alkyl diazonium derivatives are the least stable representative of this compound class. The stability then increases form alkenyl to aryl diazoniums, which are most stable.

The structure of a diazonium species can be represented by three different resonance forms (1077-1079) as outlined in Scheme 240. It is commonly assumed that structure 1077 contributes most to the characteristics of diazoniums. This is further supported by X-ray crystallographic analysis and theoretical studies.\(^\text{651,652}\)

\[
\begin{array}{c}
\text{1077} \quad \equiv \quad \text{N=N} \\
\text{1078} \quad \equiv \quad \text{N=N} \\
\text{1079} \quad \equiv \quad \text{N=N} \\
\end{array}
\]

Scheme 240. Resonance forms of the diazonium cation.

Numerous protocols have been developed for the preparation of aryl\(^\text{653}\) and alkenyl\(^\text{654}\) diazonium compounds. The most common methods for the preparation of aromatic diazonium salts 1080 rely on the oxidation of anilines 1081 as outlined in Scheme 241. This transformation can be achieved by treatment of the amine substrate with sodium nitrite or alternatively, with an organic nitrite, in the presence of strong acid. In the event, \(N\)-nitroso intermediate 1082 is formed, which in a second step undergoes dehydration triggered by protonation of the oxygen, forming product 1080. The traditional protocol involves hydrochloric acid as the proton source.\(^\text{655}\) However, the generated diazonium chlorides (\(X^-=\text{Cl}\)) are highly explosive. Generally, tosylate or tetrafluoroborate salts are more stable. These compounds can be synthesized either through anion exchange from the corresponding diazonium chlorides or directly by using of the respective acid in the diazotisation step. As a particularly useful protocol, the use of organic nitrates as oxidants in the presence of \(\text{BF}_3\) etherate has been documented to produce diazonium tetrafluoroborates.\(^\text{656}\)

\(^{650}\) For an overview on diazonium compounds, see: The Chemistry of Diazonium and Diazo Groups; Patai, S., Ed.; John Wiley & Sons Ltd.: Chichester, 1978.


Less commonly used strategies for the preparation of diazonium salts involve elimination reactions from various precursors. For example, \(N\)-nitroso amides 1083 decompose already at room temperature through an acyl migration via intermediate 1084 to form diazonium carboxylates 1085 (Scheme 242, equation 1).\(^{657}\) Furthermore, triazenes 1086 are known to convert into diazonium products 1080 upon treatment with strong acids (equation 2).\(^{658}\) This transformation corresponds to the reverse reaction of the aforementioned coupling of diazonium salts with amines to form triazene products (Scheme 239).

Besides the transformations already described above, aryl diazonium salts show a rich chemistry as exemplified in Scheme 243.\(^{659}\) The diazonium group at the aryl ring can be displaced through a number of reactions. The Sandmeyer reaction for example, converts diazonium cations 1087 into aryl halides or nitriles (1088) (equation 1).\(^{660}\) This transformation proceeds via a radical intermediate 1089, generated by single electron transfer (SET) oxidation of the diazionium group by a copper(I) salt. The

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\(^{659}\) For a comprehensive overview covering the chemistry of diazonium salts, see: Wulfman, D.S. In The Chemistry of Diazonium and Diazo Groups; Patai, S., Ed.; John Wiley & Sons Ltd.: Chichester, 1978; pp. 247-339.

Balz–Schiemann reaction is somewhat related to this transformation allowing for the production of aryl fluorides.\textsuperscript{661} Diazonium salts can also be used for C–C bond forming reactions. A classic example is the Pschorr reaction as shown in Scheme 243 (1090→1091, equation 2).\textsuperscript{662} This transformation was proposed to proceed via radical intermediates 1092 and 1093. More recently, diazonium salts have found application in palladium catalyzed cross coupling reactions (equation 3).\textsuperscript{663} A palladium(0) catalyst thereby readily inserts into the C–N bond of the starting material 1087 forming aryl palladium species 1094. This intermediate is now amenable to a plethora of coupling reactions with electrophiles such as aryl or alkenyl halides to form product 1095.

\textbf{Scheme 243}. Selected reactions of aryl diazonium salts.

Preliminary Studies

20.1. Prospecting Experiments with Simple Aryl Diazonium Salts

As discussed in the preceding chapter, aryl diazonium salts have been used for the functionalization of electron-rich aromatic rings of tyrosine and histidine residues on protein surfaces. Our objective to devise an amine selective bioconjugation method based on diazonium salts would require us to address the problem of cross-reactivity with these functionalities. In order to identify a general selectivity trend between \(N\)- and \(C\)-coupling, we set out our studies by reacting tyrosine methyl ester hydrochloride \(1096\) with commercially available \(para\)-nitrobenzenediazonium tetrafluoroborate \(1097\) (Scheme 244). The reaction was performed in a pH 9 buffer (0.5M NaH\(_2\)PO\(_4\)) as generally described for diazonium based bioconjugation protocols. Immediately upon mixing the two components, an orange precipitate formed in the reaction mixture. Purification of this adduct led to the isolation of diazoarene \(1098\) as the sole product in this reaction in a yield of only 32%. Notably, no triazene product \(1099\) resulting from reaction of the free amine was observed under these conditions (Scheme 244, box).

\[
\begin{align*}
\text{Scheme 244. Reaction of tyrosine methyl ester with commercial diazonium salt 1097.}
\end{align*}
\]

\(^{664}\) Prepared by esterification of L-tyrosine in SOCl\(_2\)/MeOH.

\(^{665}\) This reagent is commonly used for bioconjugation with tyrosines. See ref. 648; see also: Gavrilyuk, J.; Ban, H.; Nagano, M.; Hakamata, W.; Barbas III., C.F. \textit{Bioconj. Chem.} \textbf{2012}, \textit{23}, 2321-2328.
As the reaction of non-aromatic amino acids with diazonium salts to form triazene products had been previously described in the literature,\(^{666}\) we set out to test the coupling of glycine ethyl ester \(1100\) with commercial diazonium reagent \(1097\) (Scheme 245, box). When the reaction was performed in a pH 7 phosphate buffer, triazene \(1101\) could indeed be obtained, albeit in very low yield of approximately 5%. Along with this desired adduct, we were able to isolate substantial amounts of 4-nitroaniline \(1102\) from the reaction mixture. Moreover, when adduct \(1101\) was left standing open to air for several days, complete decomposition to aniline \(1102\) was observed. We therefore reasoned that the low yield observed in the reaction of \(1097\) with glycine ethyl ester is a consequence of rapid \textit{in situ} decomposition of the product formed. The decomposition of alkyl triazenes in aqueous solution has been noted before.\(^{667,668}\) As outlined in Scheme 245 (bottom), triazenes exist in two tautomeric forms \(1103\) and \(1104\). In aqueous solution, and in particular in the presence of acid, protonation of a nitrogen occurs readily to form ammonium ion \(1105\). This protonation event turns the aniline nitrogen into a potent leaving group, resulting in the decomposition of the triazene \textit{via} two alternative pathways (a and b in Scheme 245). Nucleophilic attack of water at the \(\alpha\)-carbon (intermediate \(1106\)) leads to the extrusion of nitrogen and the formation of aniline \(1107\) along with primary alcohol \(1108\) (path a). Alternatively, a unimolecular fragmentation of intermediate \(1109\) can also result in the extrusion of aniline \(1107\) along with alkyl diazonium ion \(1110\). This highly reactive species either undergoes rapid reaction with a nucleophile or follows other decomposition pathways triggered by the loss of nitrogen from \(1110\). The general reactivity of triazenes as electrophiles can include various types of nucleophilic reaction partners. For this reason, triazenes can serve as reagents for alkylation reactions.


which has been exploited for the design of DNA alkylating agents and other pharmaceutically active
substances.\textsuperscript{669,670}

\section*{20.2. Intramolecular Trapping of the Triazene Product}

In order to circumvent decomposition of the triazene products, we envisioned a revised strategy
relying on the intramolecular trapping of the initial coupling product (Scheme 246, box). In particular,
we surmised that a suitably positioned electrophile in the close proximity of the diazonium
functionality in 1111 might allow for an intramolecular ring closure \textit{via} triazene 1112, furnishing
heterocycle 1113. Such a product was expected to be more stable than triazene intermediate 1112 as
no tautomerization (1103$\rightarrow$1104), initiating a decomposition pathway, would be possible anymore.

\begin{center}
\textbf{Scheme 246.} Intramolecular trapping of the diazonium adduct to form lactam 1116.
\end{center}

The intramolecular cyclization of aryl triazenes to electrophiles such as ketone, nitriles and esters has
been documented previously.\textsuperscript{671,672,673} According to these reports, we subjected methyl anthranilate

to diazotization conditions (NaNO₂, p-TsOH) to form the corresponding diazonium tosylate (Scheme 246, equation 1). Subsequent addition of glycine ethyl ester did not result in any product formation. However, adjustment of the pH value by addition of an excess of sodium acetate (approx. pH 5) prior to addition of glycine ethyl ester led to formation of desired amide in 36% yield. Notably, cyclized adduct was the only compound isolated from the reaction mixture. In order to improve the yield of this reaction, we set out to examine alternative electrophilic groups on the aryl ring. It was thought that the different steric and electronic properties of a thioester electrophile might be beneficial for the reaction outcome. Accordingly, thioester derivative was prepared and subjected to the previously employed reaction conditions generating diazonium salt (equation 2). Unfortunately, product was obtained in only 12% yield. Also reaction of ortho-diazonium nitrile, prepared in situ from commercial aniline, did not couple efficiently with our test substrate glycine ethyl ester and product was obtained in less than 5% yield (equation 3).

20.3. Installation of a Linker Component

In order to further increase the efficiency of the coupling of diazonium ester with the amino group of amino acids, we set out to alter the substitution pattern on the aryl ring of the diazonium precursor. The influence of aryl substitution in the reaction of diazonium salts has been studied for the Sandmeyer reaction. We reasoned that substitution of aryl diazonium ion with an electron-withdrawing substituent might enhance the electrophilicity of both, the diazonium functionality, as well as the ester moiety. At the same time, substitution of might serve for the introduction of an appropriate linker molecule as ultimately envisioned. Following this hypothesis, we prepared two distinct aniline substrates differing in the site of substitution.

As outlined in Scheme 247, aniline was prepared starting from nitro arene. According to a literature procedure, was converted into carboxylic acid by oxidation with potassium permanganate, followed by esterification of resulting diacid. Saponification of delivered acid in 15% yield. A linker mimic was attached to by initial conversion into the

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673 An alternative approach exploiting the triazene decomposition pathway described in Scheme 245 was evaluated (data not shown). Following a report on diazonium transfer reactions (Saeki, T.; Son, E.-C.; Tamao, K. Bull. Chem. Soc. Jpn. 2005, 78, 1654-1658), nucleophilic substitution of ortho-methoxy stabilized species by a carboxylic acid nucleophile was tested but remained without success.
674 Thioesters are generally more electrophilic than oxoesters. Moreover, the bulky sulfur substituent might influence the conformational preferences of the carbonyl group, possibly bringing it into a more reactive conformation in regard to the triazene nucleophile.
675 was prepared from the corresponding carboxylic acid by reaction with SOCl₂, followed by thioesterification of the resulting acid chloride with EtSH.
corresponding acid chloride, followed by treatment with 2-methoxyethylamine. Finally, the nitro group in 1127 was reduced with tin powder providing aniline 1122.

Scheme 247. Synthesis of para-substituted aniline 1122.

In addition to 1122 harboring an electron-withdrawing carboxy-substituent in para-position to the aniline amine, we prepared compound 1128 with an alternative substitution pattern (Scheme 248). Commercially available dimethylnitroterephthalate 1129 was saponified according to a known protocol to generate acid 1130 in 46% yield. Installation of the 2-methoxyethylamine linker mimic was carried out using the same procedure employed for the synthesis of 1122.

Scheme 248. Synthesis of meta-substituted aniline 1128.

With the two trisubstituted aryl diazonium precursors 1122 and 1128 in hand, we tested these substrates for the reaction with glycine ethyl ester (Scheme 249). Initial generation of diazonium salts 1131 and 1132 was again carried out using the NaNO₂/p-TsOH system. Alternatively, we tested the use of n-butyl nitrite in the presence of aqueous tetrafluoroboric acid for diazotization. We observed comparable results using either of the two conditions. Treatment of the in situ formed diazonium species 1131 and 1132 with glycine ethyl ester 1100, after adjustment of the pH to 5 (0.5M NaOAc buffer), delivered in both cases the desired cyclized products 1133 and 1134, respectively. In particular, reaction of 1122 delivered product 1133 in varying yield between 60% and 90% (equation 1). In contrast, employing aniline 1128 produced adduct 1134 more reliably with 75-80% yield along with minor amounts of uncyclized triazene product (equation 2).

678 Hydrogenation of 1127 over Pd/C was not reproducible.
680 The uncyclized byproduct could not be separated from cyclized product 1134 by column chromatography.
preparation of isomer 1128 compared to 1122 and the more reliable reaction outcome, we decided to proceed with this substitution pattern for further optimization studies. Furthermore, we believed that the problem of incomplete cyclization observed in the reaction of 1128 might be easily solved by proper adjustment of the reaction conditions.

Scheme 249. Reaction of anilines 1122 and 1128 with glycine ethyl ester.

20.4. Studies on the pH Dependency of the Reaction

As discussed previously, the reaction of tyrosine aromatic rings with diazonium salts is generally conducted at high pH (> 9). Moreover, we had observed that the coupling of amines with our reaction systems does only work well at pH 5 or above (vide supra). We thus hypothesized that both reactions might exhibit a pronounced pH dependency. Eventually, it might be possible to suppress tyrosine cross-reactivity in the amine coupling reaction by proper adjustment of the pH in the buffer solution. Accordingly, we set out to conduct a pH screen for both, the tyrosine, as well as the amine coupling to diazonium salts. In order to be able to optimally compare the two reaction systems, we opted for the preparation of similarly substituted aniline precursors. As outlined in Scheme 250, we synthesized aniline 1135 as the coupling partner for a tyrosine derivative. Starting with 4-nitrobenzoic acid 1136, amide 1137 was prepared in 73% yield following the protocol employed previously. Hydrogenolytic reduction of the nitro group in 1137 delivered aniline 1135 in excellent yield (87%).

Scheme 250. Synthesis of mono-substituted aniline 1135.

As outlined in Scheme 251, Cbz-protected tyrosine methyl ester 1138 was used as the coupling partner for diazonium tosylate 1139 (equation 1). The reaction was performed in various pH buffers (pH 3, 5, 5.5, 6, 6.5, 7, 9; 100mM NaH₂PO₄) and the conversion of the reaction was determined by NMR analysis of the crude reaction mixture after extraction of the product from the aqueous phase. As
shown in Figure 43 (black circles), a strong pH dependency for this transformation was indeed observed. Interestingly, the pH profile of the reaction of diazonium \textbf{1139} with tyrosine to form diazo adduct \textbf{1140} exhibits a relatively sharp on/off switch between pH 6 and 7. Only above pH 7 can efficient coupling be observed.

\[ \text{Scheme 251. Reactions carried out to determine the pH dependency of the tyrosine (1) and the amine (2) coupling to diazonium salts.} \]

\[ \text{Figure 43. Dependency of the coupling of diazonium } \textbf{1132} \text{ with glycine ethyl ester on the pH (red triangles) compared to the reaction of } \textbf{1139} \text{ with tyrosine derivative } \textbf{1138} \text{ (black circles). For the reaction with glycine the yield of the product is shown. For the reaction with tyrosine the conversion was determined by NMR analysis of the crude reaction mixture.} \]

We next examined the pH dependency of the reaction between \textit{ortho}-ester substituted diazonium species \textbf{1132} and glycine ethyl ester. In this case, we isolated and purified the product allowing for the determination of an exact yield. To our surprise, a similarly sharp transition was observed for this transformation as depicted in Figure 43 (red triangles). However, the curve for the amine coupling is significantly shifted towards lower pH values compared to the tyrosine coupling curve. This outcome
suggested that careful control of the pH value in the reaction mixture could allow for the selective reactivity of amino groups in the presence of tyrosine residues. An interesting detail in Figure 43 is the observation that the amine coupling is completely inhibited when using a phosphate pH 5 buffer (100 mM), whereas with the pH 5 acetate buffer (0.5M) used for the experiments described in Scheme 249, the desired product was obtained in excellent yield. The effects responsible for this difference are not entirely clear to us.\[^{681}\]

We next examined the coupling of free amino acids to diazonium reagent 1131 (Scheme 252). Unprotected amino acids exist as zwitterionic species at neutral pH and might therefore show a different behavior than substrates lacking a free carboxylic acid (such as the ethyl ester of glycine used before). Treatment of diazonium tosylate 1131 with L-phenylalanine 1141 in various pH buffers (100 mM NaH$_2$PO$_4$) produced amide 1142 with varying yields. Interestingly, only with buffers with a pH 7 or higher was product formation observed. The reaction did not proceed in phosphate buffers with lower pH. Moreover, when using pH 9 buffer, substantial decomposition of the product was observed.

![Scheme 252. Coupling of diazonium salt 1131 with unprotected phenylalanine 1141.](image)

**20.5. Amine-Selective Diazonium Coupling**

As described before, we ultimately opted for the development of a bioconjugation methodology allowing for the selective functionalization of amino groups on protein surfaces while leaving the aromatic rings of tyrosines and histidines untouched. In order to test the feasibility of the developed reactive system for this purpose, we synthesized tyrosine containing dipeptide 1143 as test substrate.

![Scheme 253. Synthesis of dipeptide 1143.](image)

\[^{681}\] The ionic strength of the solvent might influence the reactive behavior of the charged diazonium component. Alternatively, the counterion of the diazonium species might play a role in the reactivity of this reagent as observed before for other reactions of diazonium salts: Jackson, A.H.; Lynch, P.P. J. Chem. Soc., Perkin Trans. 2 1987, 1483-1488.
20. Preliminary Studies

(Scheme 253). Starting with L-tyrosine methyl ester 1096, amide coupling to Cbz-glycine 1144 using HATU as the coupling reagent delivered dipeptide 1145 in 54% yield. Hydrogenolytic cleavage of the Cbz-carbamate furnished primary amine 1143 in quantitative yield.

Treatment of diazonium tosylate 1131 with dipeptide 1143 at pH 5 (0.5M NaOAc buffer) produced a single product as indicated by LC-MS analysis (Scheme 254). Isolation of this compound confirmed the exclusive formation of amide 1146.

Notably, we were not able to observe any of the tyrosine-coupled diazoadduct 1147 by LC-MS analysis of the reaction mixture. This outcome suggested that the diazonium based linkage system we have developed is indeed selective for bioconjugation to amino groups, leaving tyrosine untouched.

Scheme 254. Reaction of diazonium salt 1131 with dipeptide 1143.

\[^{682} \text{The yield was not determined.}\]
With a successful amine-selective diazonium bioconjugation strategy established, we next turned to the development of a suitable linker system allowing for the coupling of functional units with proteins and peptides. As depicted in Figure 44, our plan focused on a novel bioconjugation agents, which should include an ortho-methyl ester substituted aniline fragment as the key diazonium precursor (drawn in red). Moreover, a hydrophilic spacer component was planned to be introduced enhancing the water solubility of the linker molecule. Finally, a second functional residue should be installed at the opposite end of the spacer, allowing of the attachment of various bioactive components. We were particularly interested in the coupling of highly functionalized natural products to our linker.

Figure 44. General linker design.

19.1. Preparation of the Linker System

As outlined in Scheme 255, we implemented this plan by synthesizing amine 1148 and various derivatives thereof. The route started with benzoic acid 1130, available in one step from commercial dimethyl nitroterephthalate (see section 20.3.). Conversion of 1130 into the corresponding acid chloride was followed by reaction with primary amine 1149 furnishing amide 1150 in 78% yield. Removal of the Boc-carbamate was carried out by treatment of 1150 with trifluoroacetic acid producing primary amine 1148 in 98% yield. Subjecting 1148 to succinic anhydride delivered carboxylic acid 1151. Subsequent hydrogenolytic reduction of the nitro group in 1151 gave aniline 1154 in 87% yield. Finally, we envisioned the construction of a bifunctional linker allowing for the sequential attachment of two amine containing components in a single reaction sequence. In particular, a functionalization pattern was required, which would enable initial coupling of an amine to one end

\[^{683}\text{1149 was prepared by mono-Boc protection of commercially available diethylene glycol bis(3-aminopropyl) ether according to: Noblin, D.J.; Page, C.M.; Tae, H.S.; Gareiss, P.C.; Schneekloth, J.S.; Crews, C.M. ACS Chem. Biol. 2012, 7, 2055-2063.}\]
of a linker molecule. Direct in situ generation of the diazonium salt would then free the second reactive site for merger with another amino group. According to this plan, we prepared NHS-ester 1153 by reaction of acid 1152 with N-hydroxysuccinimide 1154 under standard peptide coupling conditions. Ester 1153 was thereby obtained in 52% yield as the sole product.\textsuperscript{684}

\begin{equation}
\text{HOOC} \quad \begin{array}{c}
\text{H}_{2}\text{N} \quad \text{O} \\
\text{CO}_{2}\text{Me} \\
\text{NO}_{2}
\end{array} \quad \text{1150} \\
\text{1) (COCl)} \quad \text{2) 1149, NEt}_{3} \\
\text{CH}_{2}\text{C}_{2}, 78\% \\
\text{NH} \quad \text{O} \\
\text{N} \quad \text{O} \\
\text{H} \\
\text{Boc} \\
\text{1149}
\end{equation}

\begin{equation}
\text{HOOC} \quad \begin{array}{c}
\text{H}_{2}\text{N} \quad \text{O} \\
\text{CO}_{2}\text{Me} \\
\text{NO}_{2}
\end{array} \quad \text{CF}_{2}\text{CO}_{2}\text{H} \quad 98\% \\
\text{1150: } R = \text{Boc} \\
\text{1148: } R = \text{H}
\end{equation}

\begin{equation}
\text{HOOC} \quad \begin{array}{c}
\text{H}_{2}\text{N} \quad \text{O} \\
\text{CO}_{2}\text{Me} \\
\text{NO}_{2}
\end{array} \quad \text{1151: } R = \text{NO}_{2} \\
\text{1152: } R = \text{NH}_{2}
\end{equation}

\begin{equation}
\text{HOOC} \quad \begin{array}{c}
\text{H}_{2}\text{N} \quad \text{O} \\
\text{CO}_{2}\text{Me} \\
\text{NO}_{2}
\end{array} \quad \text{1153}
\end{equation}

Scheme 255. Preparation of bifunctional linker 1154.

Alternatively, a shorter route towards acid 1153 was developed later during our studies as outlined in Scheme 256. The synthesis commenced with commercial aniline 1155. Peptide coupling to amine 1156\textsuperscript{685} delivered Cbz-carbamate 1157 in 47% yield. Subsequent deprotection of the amino group in 1157 produced 1158. As described above, treatment of this intermediate with succinic anhydride gave acid 1152 in 75% yield.

\begin{equation}
\text{HOOC} \quad \begin{array}{c}
\text{H}_{2}\text{N} \quad \text{O} \\
\text{CO}_{2}\text{Me} \\
\text{NH}_{2}
\end{array} \quad \text{1155} \\
\text{EDC, HOBt, NEt}_{3} \\
\text{CH}_{2}\text{C}_{2}, 47\% \\
\text{H}_{2}, \text{Pd/C} \\
\text{quant}\%
\end{equation}

\begin{equation}
\text{HOOC} \quad \begin{array}{c}
\text{H}_{2}\text{N} \quad \text{O} \\
\text{CO}_{2}\text{Me} \\
\text{NH}_{2}
\end{array} \quad \text{1156} \\
\text{1156} \\
\text{1156}
\end{equation}

\begin{equation}
\text{HOOC} \quad \begin{array}{c}
\text{H}_{2}\text{N} \quad \text{O} \\
\text{CO}_{2}\text{Me} \\
\text{NH}_{2}
\end{array} \quad \text{1152} \\
\text{NEt}_{3} \\
\text{CH}_{2}\text{C}_{2}, 75\%
\end{equation}

\begin{equation}
\text{HOOC} \quad \begin{array}{c}
\text{H}_{2}\text{N} \quad \text{O} \\
\text{CO}_{2}\text{Me} \\
\text{NH}_{2}
\end{array} \quad \text{1151: } R = \text{Cbz} \\
\text{1158: } R = \text{H}
\end{equation}

\begin{equation}
\text{HOOC} \quad \begin{array}{c}
\text{H}_{2}\text{N} \quad \text{O} \\
\text{CO}_{2}\text{Me} \\
\text{NH}_{2}
\end{array} \quad \text{1157: } R = \text{Cbz} \\
\text{1158: } R = \text{H}
\end{equation}

Scheme 256. Alternative preparation of acid 1152.

In order to test the compatibility of this linker system with the diazonium coupling conditions, we decided to prepare a test substrate as outlined in Scheme 257. Acid 1151 was subjected to standard

\textsuperscript{684} No reaction of the aniline nitrogen could be observed.

peptide coupling conditions for the attachment of benzyl amine as a model substrate. The resulting nitroarene was then reduced to aniline 1159 under hydrogenolytic conditions.

![Scheme 257. Synthesis of test substrate 1159.](image)

### 19.2. Synthesis and Bioconjugation of Tripeptide Substrates

In order to assess the functional group compatibility of the diazonium bioconjugation, and in particular the behavior of our linker towards electron rich aromatic rings, we prepared a number of short peptide substrates containing various functional groups. Tripeptide 1160 incorporating a serine residue at the C-terminus as well as a sterically hindered N-terminal valine was synthesized as shown in Scheme 258. Union of glycine ethyl ester 1100 with Cbz-valine 1161 furnished dipeptide 1162 in 90% yield. Saponification, followed by a second amide coupling to intermediate acid 1163 with serine benzyl ester 1164 provided protected tripeptide 1165. Overall reductive deprotection allowed for the isolation of amine 1160 by simple filtration. 686

![Scheme 258. Synthesis of serine containing tripeptide 1160.](image)

Next, tyrosine containing peptide 1166 was prepared (Scheme 259). Peptide coupling between Cbz-alanine 1167 and tyrosine methyl ester 1096 using HATU as coupling reagent delivered amide 1168 in 68% yield. Hydrolysis of the ester in 1168 provided acid 1169 in 99% yield. Subsequent amide bond formation with phenylalanine benzyl ester 1170 as the coupling partner furnished 1171. Finally, hydrogenolysis of the protecting groups again delivered desired tripeptide 1166 in quantitative yield.

686 Some of the final peptide products synthesized in this subchapter were not well soluble in MeOH and precipitated from solution upon final deprotection. The addition of water to this mixture was therefore necessary prior to filtration.
In order to study the competition between the N-terminus and lysine ε-amino groups in the reaction with the diazonium linker, we decided to prepare lysine containing tripeptide 1172 as outlined in Scheme 260. Following the strategy used before, alanine derivative 1167 was reacted with ε-N-Cbz lysine methyl ester 1173 to provide dipeptide 1174. Saponification to give 1175, followed by attachment of phenylalanine benzyl ester 1170 produced tripeptide 1176. Finally, overall deprotection gave 1172.

In addition to tyrosines, tryptophan residues can also react with diazonium salts. We therefore prepared tripeptide 1177 incorporating a tryptophan residue in order to test a possible cross reactivity. **Scheme 260.** Synthesis of lysine containing tripeptide 1172.

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with our diazonium linker system. As outlined in Scheme 261, valine derivative 1161 was coupled to tryptophan methyl ester 1178 providing 1179 in 92% yield. Subsequent ester hydrolysis and amide bond formation with acid 1180 and phenylalanine benzyl ester 1170 furnished 1181. As before, removal of the protecting groups was achieved by hydrogenolysis to give 1177.

Scheme 261. Synthesis of tryptophan containing tripeptide 1177.

As outlined in Scheme 262, serine containing peptide 1160 was first tested as coupling partner. To this end, model substrate 1159 was subjected to the previously employed diazotization conditions (NaNO₂, p-TsOH) to form diazonium tosylate 1182. The diazonium solution was then transferred into a flask containing tripeptide 1160 dissolved in pH 7 phosphate buffer (100 mM). Following the reaction by LC-MS analysis suggested the formation of a sole product as a result of the desired coupling at the N-terminus of 1160 with the diazonium agent. Isolation of this product after a total reaction time of 2 hours indeed cleanly provided amide 1183. The hindered primary amine had efficiently reacted with our reagent systems. Moreover, a free C-terminus as well as a serine residue were tolerated under the reaction conditions.

Scheme 262. Reaction of tripeptide 1160 with diazonium salt 1182.
We next tested the compatibility of tyrosine residues within a peptide substrate. To this end, tripeptide 1166 was reacted with diazonium salt 1182 under the reaction conditions described above (Scheme 263). The reaction was again monitored by LC-MS analysis. As outlined in Figure 45, after 2 hours of reaction time, the LC-chromatogram indicated formation of a major product 1184 corresponding to the desired amine coupling adduct ([M+H]⁺ = 965 Da). As a minor byproduct, bis-coupled compound 1185 was formed (< 5%), probably resulting from reaction of product 1184 with excess reagent. Again, extraction of the reaction mixture, followed by purification and characterization of the product by 2D NMR confirmed this analysis.

Scheme 263. Reaction of diazonium salt 1182 with tripeptide 1166.

Figure 45. LC-MS trace of the reaction of 1182 with tripeptide 1166 after 2 h.

This outcome confirmed our previously established notion that ortho-ester substituted diazonium reagents selectively react with amino groups in the presence of electron-rich aromatic rings. We therefore turned to a more challenging substrate as shown in Scheme 264. Reaction of the pentapeptide Leu-enkephalin (1186), incorporating an N-terminal tyrosine residue, with diazonium salt 1182 was tested under the established conditions. Again, monitoring of the reaction by LC-MS
suggested the formation of amide 1187 as the major product (Figure 46). In this case however, a significant amount of bis-coupled diazo compound 1188 was also observed (approx. 30%). Repeating the reaction with less diazonium reagent did not lead to an enhancement of this ratio in favor of the mono-coupled product. Interestingly, also in this case we were not able to observe any of the mono-tyrosine coupled product.

Scheme 264. Reaction of diazonium salt 1182 with Leu-enkephalin (1186).

Figure 46. LC-MS trace of the reaction of 1182 with Leu-enkephaline (1186) after 2 h.

In order to evaluate the reactivity of lysine residues towards diazonium salt 1182, we subjected tripeptide 1172 to the standard reaction conditions (Scheme 265). After 2 hours of reaction, only bis-coupled product 1189 was observed by LC-MS analysis. Again, lowering the reagent concentration to sub-equimolar amounts did not effect formation of a mono-coupled product.
22. Conclusion and Outlook

Finally, tryptophan containing peptide 1177 was examined as coupling partner (Scheme 266). Surprisingly, only diazo adduct 1190 was formed when the reaction was performed in a pH 7 buffer. Lowering the pH of the buffer solution gave the same result. We were not able to observe the desired amine-coupled product with tripeptide 1177. This outcome indicates that tryptophan residues successfully compete with amino groups for the reaction with diazonium salt 1182. We were however confident, that the low abundance of tryptophan residues on protein surfaces would render this cross-reactivity inconsequential for protein bioconjugation.

Scheme 266. Reaction of diazonium salt 1182 with tripeptide 1177.

19.3. Diazonium Bioconjugation to Proteins

We next set out to apply the newly developed bioconjugation strategy to proteins, whereby lysozyme was chosen as a test substrate. As outlined in Table 29, our initial attempts for protein bioconjugation involved the reaction of model substrate 1182 (10 equiv. of reagents compared to lysozyme has been previously employed as test substrate for bioconjugation. The protein was purchased from Aldrich (Lysozyme from chicken egg white, dialyzed powder, No. 62970).

Prepared as previously described by reaction of aniline 1159 with NaNO₂/p-TsOH in water/MeOH.
21. Diazonium Bioconjugation to Proteins and Peptides

Table 29. Reaction of diazonium salt 1182 with lysozyme in different buffer solutions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Buffer</th>
<th>Unmod. (%)</th>
<th>+1 (%)</th>
<th>+2 (%)</th>
<th>+3 (%)</th>
<th>+4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pH 5.0 NaOAc</td>
<td>50</td>
<td>38</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>pH 6.0 NaOAc</td>
<td>30</td>
<td>40</td>
<td>22</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>pH 6.5 NaOAc</td>
<td>27</td>
<td>43</td>
<td>26</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>pH 7.0 NaOAc</td>
<td>24</td>
<td>39</td>
<td>26</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>pH 5.0 NaH₂PO₄</td>
<td>71</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>pH 6.0 NaH₂PO₄</td>
<td>28</td>
<td>45</td>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>pH 6.5 NaH₂PO₄</td>
<td>4</td>
<td>32</td>
<td>43</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>pH 7.0 NaH₂PO₄</td>
<td>5</td>
<td>26</td>
<td>47</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Conditions: 500 μM lysozyme, 10 equiv. diazonium salt 1182, 2 h; [b] 100 mM salt; [c] determined by ESI-MS analysis through the ratio of the corresponding peak intensities; unmod. = unmodified; +1 = singly modified protein; +2 = doubly modified protein.

Interestingly, at low pH the reaction proceeded more efficiently in a NaOAc buffer solution compared to a NaH₂PO₄ buffer (entries 1 and 5). The conversion of protein was best in a pH 6.5 or 7.0 phosphate buffer (entries 7 and 8). Based on these results, we employed a 100 mM NaH₂PO₄ for all of the subsequent reactions. Most importantly, in all of these transformations we only observed products resulting from the reaction of amino groups on the protein surface to form the desired heterocyclic amide bioconjugates 1191 (Figure 47). We have never observed any side products 1192 from the reaction of tyrosine or tryptophan aromatic rings with the diazonium reagent as judged by ESI-MS analysis. The two products would thereby be clearly distinguishable by their mass difference of 32 Da.

![Figure 47](image_url)
Generally, protein bioconjugation is optimally performed at low protein concentrations. We therefore tested the efficiency of our diazonium coupling strategy at varying concentrations of the lysozyme substrate (Table 30). Protein concentrations from 10 to 100 μM were examined for the reaction with different amounts for diazonium reagents (5-100 equiv.). At a lysozyme concentration of 100 μM, the use of only 5 equiv. of coupling partner already lead to efficient modification of the protein (entry 1). When 10 equiv. of reagent were used, no unmodified lysozyme substrate could be observed after 2 hours of reaction time (entry 2). As indicated, the protein concentration can easily be lowered to 10 μM, still achieving full conversion to modified products (entry 8). In this case however, 100 equiv. of the reagent needed to be employed. But also with lower diazonium concentrations, lysozyme was efficiently modified in dilute solution (entries 6-7).

### Table 30. Concentration dependency of the diazonium coupling to lysozyme.

<table>
<thead>
<tr>
<th>Entry[^a]</th>
<th>Lysozyme Concentration</th>
<th>equiv. Reagent</th>
<th>unmod. (%)[^b]</th>
<th>+1 (%)</th>
<th>+2 (%)</th>
<th>+3 (%)</th>
<th>+4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100 μM</td>
<td>5</td>
<td>17</td>
<td>40</td>
<td>32</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>100 μM</td>
<td>10</td>
<td>0</td>
<td>21</td>
<td>41</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>50 μM</td>
<td>5</td>
<td>43</td>
<td>42</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>50 μM</td>
<td>10</td>
<td>21</td>
<td>41</td>
<td>28</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>10 μM</td>
<td>5</td>
<td>81</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>10 μM</td>
<td>10</td>
<td>66</td>
<td>31</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>10 μM</td>
<td>50</td>
<td>15</td>
<td>37</td>
<td>34</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>10 μM</td>
<td>100</td>
<td>0</td>
<td>20</td>
<td>37</td>
<td>30</td>
<td>13</td>
</tr>
</tbody>
</table>

[^a]: conditions: 100 mM pH 7.0 NaH₂PO₄ buffer, 2 h;[^b]: determined by ESI-MS analysis through the ratio of the corresponding peak intensities; unmod. = unmodified; +1 = singly modified protein; +2 = doubly modified protein.

As depicted in Table 31, we also examined the reaction time required to achieve optimal conversion. Interestingly, already after 30 min the substrate had converted to modified products to a considerably extent (entry 3). After 2 hours, the best conversion was observed.^[693^] Longer reaction times did not lead to any improvement of the conversion.
Table 31. Diazonium bioconjugation to lysozyme with different reaction times.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Time</th>
<th>unmod (%)</th>
<th>+1 (%)</th>
<th>+2 (%)</th>
<th>+3 (%)</th>
<th>+4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 min</td>
<td>69</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>10 min</td>
<td>68</td>
<td>29</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>30 min</td>
<td>42</td>
<td>42</td>
<td>11</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1 h</td>
<td>42</td>
<td>39</td>
<td>17</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2 h</td>
<td>17</td>
<td>40</td>
<td>32</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] conditions: 100 μM lysozyme, 5 equiv. diazonium salt 1182, 100 mM pH 7 NaH₂PO₄ buffer; [b] determined by ESI-MS analysis through the ratio of the corresponding peak intensities; unmod. = unmodified; +1 = singly modified protein; +2 = doubly modified protein.

With optimized reaction conditions established, we next turned to the evaluation of the scope of our bioconjugation system. First, different protein substrates were tested in the reaction with diazonium tosylate 1182 (Table 32). Treatment of the individual substrates at 100 μM protein concentration in pH 7.0 phosphate buffer with 10 equiv. of 1182 in all cases led to complete conversion to modified products after 2 hours of reaction time. Only trace amounts of unmodified protein could be observed by ESI-MS analysis. In contrast to the lysozyme test substrate employed previously, multiple modifications with up to 9 linker molecules attached to the native protein could be observed (entry 3). This can most likely be attributed to a higher number of accessible amino groups on the surface of these protein substrates.

Table 32. Evaluation of different protein substrates in the reaction with diazonium salt 1182.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protein</th>
<th>unmod. (%)</th>
<th>+1 (%)</th>
<th>+2 (%)</th>
<th>+3 (%)</th>
<th>+4 (%)</th>
<th>+5 (%)</th>
<th>+6 (%)</th>
<th>+7 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>myoglobin[c]</td>
<td>1</td>
<td>5</td>
<td>12</td>
<td>19</td>
<td>22</td>
<td>20</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>α-chymotrypsinogen</td>
<td>0</td>
<td>6</td>
<td>13</td>
<td>22</td>
<td>26</td>
<td>20</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>cytochrome C[d]</td>
<td>4</td>
<td>10</td>
<td>12</td>
<td>22</td>
<td>21</td>
<td>13</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>albumin (BSA)[e]</td>
<td>0</td>
<td>13</td>
<td>16</td>
<td>22</td>
<td>22</td>
<td>15</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>ribonuclease A</td>
<td>0</td>
<td>12</td>
<td>21</td>
<td>27</td>
<td>21</td>
<td>13</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] conditions: 100 μM protein, 10 equiv. diazonium salt 1182, 100 mM pH 7 NaH₂PO₄ buffer, 2 h; [b] determined by ESI-MS analysis through the ratio of the corresponding peak intensities; [c] 3% of +8 conjugates were also obtained; [d] minor amounts of +8 (3%) and +9 (1%) conjugates were also obtained; [e] characterization of the product proved difficult by ESI-MS (see experimental part for further details).

As shown in Figure 48, the ESI-MS spectra of the conjugated products exhibited an almost Gaussian distribution. Again, only products resulting from amine-selective coupling were observed as exemplified by the clean spectra shown in Figure 48.⁶⁹⁴

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⁶⁹⁴ For further details and more spectra, see chapter 24.3.
19.4. Direct Coupling of Natural Products to Proteins

The amine based bioconjugation protocols that have been previously developed generally suffer from a low functional group tolerance for the linker component (see chapter 18.2.2.). Moreover, long reaction times are often required to achieve acceptable conversion of protein substrates. In contrast, the amine-selective diazonium bioconjugation strategy we have developed, proceeds relatively fast even at very low protein concentration. Furthermore, only a small excess of reagent in respect to protein is required for full modification of the substrate. The high selectivity of our diazonium linker to react only with primary amines, renders this protocol interesting for direct attachment of sensitive and highly functionalized components to proteins. Based on this assumption we set out to examine the direct modification of proteins with various natural products and derivatives thereof.

As shown in Figure 49, a number of linkers were prepared incorporating members of different natural product classes. Carboxylic acid derivatives were first examined based on the straightforward way for linker attachment by amide bond formation. We initially prepared linkers incorporating small natural products such as pantothenic acid (vitamin B5) (1193), biotin (vitamin H) (1194) or the plant hormone abscisic acid (1195). In particular, the biotin conjugate might later offer a versatile handle for further modification by reaction with (strept)avidin. Similarly, the incorporation of hexynoic acid into linker 1196 would present a platform for a subsequent Huisgen dipolar cycloaddition. More complex secondary metabolites including the antibiotic lincomycin (1197), the terpenoid plant hormone gibberellic acid (1198), cholic acid (1199) or the toxic alkaloid colchicine (1200) could be attached to a linker component via amide or ester bond formation.

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695 See experimental part for details on the preparation of these linkers.
Figure 49. Natural product conjugates for attachment to proteins.

As outlined in Table 33, the linker molecules presented in Figure 49 were subjected to the standard diazotization conditions followed by reaction with the protein lysozyme in pH 7.0 buffer. In all cases, only formation of the desired amine conjugates was observed. As apparent from Table 33, a large number of functional groups were well tolerated including electron-rich and electron-deficient olefins (entries 2 and 4), thioethers (entries 1 and 3), free hydroxyl groups (entries 2-5), tertiary amines (entry 3), ureas (entry 1), esters (entries 3 and 4) and even electron rich aromatic rings (entry 6). In all cases, good to excellent conversion of the protein to modified products was observed.

Table 33. Coupling of natural products to lysozyme.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>unmod. (%)</th>
<th>+1 (%)</th>
<th>+2 (%)</th>
<th>+3 (%)</th>
<th>+4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1194</td>
<td>6</td>
<td>28</td>
<td>37</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>1195</td>
<td>11</td>
<td>27</td>
<td>39</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1197[c]</td>
<td>10</td>
<td>38</td>
<td>32</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1198</td>
<td>0</td>
<td>18</td>
<td>42</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>1199</td>
<td>21</td>
<td>45</td>
<td>31</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1200</td>
<td>12</td>
<td>35</td>
<td>37</td>
<td>15</td>
<td>1</td>
</tr>
</tbody>
</table>

[a] conditions: 100 μM lysozyme, 10 equiv. reagent, 100 mM pH 7 NaH₂PO₄ buffer, 2 h; [b] determined by ESI-MS analysis through the ratio of the corresponding peak intensities; [c] 50 equiv. of reagent used.

As shown in Table 34, we tested the same set of substrates on the protein myoglobin. Similar results were obtained as for lysozyme. Again, products with up to 8 attached linkers were detected by ESI-MS analysis (entries 4 and 6).
Table 34. Coupling of natural products to myoglobin.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>unmod. (%)&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>+1 (%)</th>
<th>+2 (%)</th>
<th>+3 (%)</th>
<th>+4 (%)</th>
<th>+5 (%)</th>
<th>+6 (%)</th>
<th>+7 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1193</td>
<td>5</td>
<td>11</td>
<td>20</td>
<td>22</td>
<td>19</td>
<td>12</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>1194</td>
<td>7</td>
<td>18</td>
<td>23</td>
<td>22</td>
<td>16</td>
<td>9</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1196</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td>19</td>
<td>21</td>
<td>19</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>1195&lt;sup&gt;[c]&lt;/sup&gt;</td>
<td>2</td>
<td>9</td>
<td>16</td>
<td>21</td>
<td>22</td>
<td>14</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>1197&lt;sup&gt;[d]&lt;/sup&gt;</td>
<td>55</td>
<td>33</td>
<td>10</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>1198&lt;sup&gt;[c]&lt;/sup&gt;</td>
<td>2</td>
<td>8</td>
<td>16</td>
<td>20</td>
<td>20</td>
<td>13</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>1199&lt;sup&gt;[e]&lt;/sup&gt;</td>
<td>20</td>
<td>28</td>
<td>27</td>
<td>18</td>
<td>5</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>1200</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>15</td>
<td>12</td>
<td>7</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

[a] conditions: 100 μM myoglobin, 10 equiv. reagent, 100 mM pH 7 NaH₂PO₄ buffer, 2 h; [b] determined by ESI-MS analysis through the ratio of the corresponding peak intensities; [c] trace amounts of +8 conjugate were also observed; [d] 50 equiv. of reagent used; [e] 20 equiv. of reagent used.

Figure 50 shows a few natural product conjugates, which were employed with only limited success. Linker 1201, incorporating the antimalarial agent artemesunate, underwent partial hydrolysis of the ester bond to produce a mixture of conjugates. As presented in Figure 51, the major set of products resulted from reaction of acid 1202, generated upon ester cleavage in 1201. Penicillin G based linker 1203 underwent cleavage of the strained β-lactam ring, presumably during the diazotization step (data not shown). Verbenol conjugate 1204 followed the same fate as the artemesunate incorporating linker. Only products resulting from ester hydrolysis were obtained with this starting material. Similarly, farnesol substrate 1205 coupled very inefficiently to either lysozyme or myoglobin, producing only traces of conjugated products (approx. 5% conversion). We hypothesize that the strongly acidic conditions need in the diazotization step are responsible for the observed hydrolysis of these functional...
groups. Employing aniline 1206 incorporating the peptidic neurotransmitter Leu-enkephaline again resulted only on minimal product formation (approx. 10%). We suspect that the electron rich tyrosine ring in 1206 might interfere with the desired reactivity towards the protein’s amino groups.

Figure 51. ESI-MS spectrum (deconvoluted) of the product mixture obtained from reaction of artesunate incorporating linker 1201 with myoglobin. unmod. = unmodified.

Finally, a few substrates proved completely resistant to the diazonium bioconjugation protocol. As depicted in Figure 52, this includes conjugated electron rich polyenes as found in amphotericin B based linker 1207. The highly functionalized conjugate 1208 with the antibiotic rifampicin attached, completely decomposed in the diazotization step. Moreover, electron-rich aromatic rings as found in

Figure 52. Natural product derivatives incompatible with diazonium bioconjugation.
fluorescein or dopamine derivatives 1209 and 1210 were also not tolerated under the diazonium generating protocol. Surprisingly, although diosgenin incorporating linker 1211 was successfully transformed into the corresponding diazonium salt as indicated by LC-MS, no reaction with the protein substrates was observed.

We speculate that the incompatibility of the natural product derivatives depicted above with our diazonium bioconjugation strategy is due the harsh conditions so far employed for the generation of the diazonium salt. We believe that the diazonium functionality itself is not responsible for the limited substrate scope. This opens the opportunity of developing an alternative method for the generation of the reactive diazonium species under milder conditions tolerating a wider array of functional groups.
Conclusion and Outlook

Aryl diazonium salts have previously found application as bioconjugation agents based on their reactivity with the electron rich aromatic rings of tyrosine residues in proteins. However, the inefficiency of this method, along with the harsh pH conditions required, have largely hampered the use of diazonium salts as reagents in bioconjugative chemistry. We have developed an alternative system enabling the selective targeting of amino groups with aryl diazonium salts. Amino groups are much more abundant on protein surfaces then tyrosine side chains, rendering an amine-selective coupling strategy generally more efficient for statistical reasons. As outlined in Scheme 267, our protocol relies on the use of ortho-methyl ester substituted aniline derivatives as diazonium precursors. The easily generated reactive species 1213 initially forms triazenes intermediates such as 1214, when a protein substrate is added. Although this species is unstable under aqueous conditions suffering from hydrolytic cleavage of the triazene functionality, rapid cyclization involving the ortho-ester substituent leads to the formation of stable amide product 1215. Notably, the reaction proceeds under physiological conditions (pH 7.0) in only 2 hours of reaction time. Only a small excess of the coupling reagent is needed to achieve full conversion of the protein substrate to modified products. Moreover, protein concentrations as low as 10 μM are well tolerated for this reaction. Most importantly, we have never observed any reactivity of tyrosine residues or other electron rich aromatic amino acid side chains with our reagent. Amide product 1215 resulting from reaction with free amino groups was the exclusive product detected with this protocol.

Scheme 267. Amine-selective bioconjugation of ortho-methyl ester substituted diazonium salts.

A number of highly functionalized natural products could be coupled to different proteins using the described method. These results compare favorably to previously developed amine-selective
bioconjugation strategies, which often have a very limited substrate scope and require much larger excess of reagent along with longer reaction times.

A significant drawback or our protocol represents the synthesis of the diazonium reagents. The harsh conditions required for this step (strong acid, strong oxidant) are not compatible with certain functionalities including polyenes or easily cleavable ester linkages. An alternative methodology for the generation of diazonium salts is therefore highly desirable. Raines and co-workers have recently documented a strategy for the synthesis of acyl diazo compounds starting from alkyl azide precursors (Scheme 268). This reaction relies on the use of phosphine 1216 as a mild stoichiometric reductant. In the event, reaction of azide 1217 with this reagent generates Staudinger intermediate 1218. In contrast to the conventional Staudinger reduction of azides, this intermediate next undergoes hydrolysis to produce acyl triazene 1219. Subsequent elimination furnishes product 1220.

![Scheme 268. Synthesis of acyl diazonium compounds from alkyl azides according to ref. 697.](image)

The generation of aryl diazonium salts might be achieved using a similar strategy. As outlined in Scheme 269, treatment of aryl azide 1221 with a phosphine reagent related to 1216 would produce acyl triazene 1222. As outlined in chapter 19, acyl triazenes represent versatile precursors for the mild generation of diazonium derivatives. Accordingly, cleavage of the triazene by extrusion of a primary amide byproduct could furnish aryl diazonium salt 1223. If such a strategy could be applied for the generation of a diazonium bioconjugation agent, an even wider array of substrates might be accessible for this bioconjugation strategy.

![Scheme 269. Possible application of a Staudinger reduction strategy for the synthesis of aryl diazonium salts.](image)

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Experimental Part
**Experimental Part**

18.1. General Methods

**Chemicals and Solvents:** All chemicals were purchased from Acros, Aldrich, Strem, Fluka, Merck, ABCR or Alfa Aesar and used as such unless stated otherwise. For flash chromatography technical grade solvents were used without further purification. For reactions diethyl ether, tetrahydrofuran, acetonitrile, toluene and dichloromethane were purified by passage over activated alumina under argon atmosphere ($\text{H}_2\text{O}$ content $< 30\text{ppm}$, *Karl Fischer* titration). Methanol was distilled from magnesium turnings under an atmosphere of nitrogen. Benzene was distilled over sodium/benzophenone under an atmosphere of nitrogen. Pyridine was distilled from KOH under an atmosphere of nitrogen. Triethylamine was distilled under nitrogen from CaH$_2$. pH 7 buffer was prepared with NaH$_2$PO$_4$·2H$_2$O (8g), Na$_2$HPO$_4$·12H$_2$O (18g) in water (1000 mL). Deuterated solvents were obtained from ARMAR chemicals (Switzerland).

**Reactions:** All non-aqueous reactions were carried out using oven dried glassware under an atmosphere of argon unless otherwise stated. Reactions were magnetically stirred and monitored by TLC unless otherwise stated. Chromatographic purification was performed as flash chromatography (Fluka silica gel, 60 Å pore size) using the solvents indicated as eluent with 0.3-0.5 bar pressure. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F$_{254}$ TLC glass plates and visualized with UV light or stained in ceric ammonium molybdate or potassium permanganate solutions. The yields given refer to chromatographically purified and spectroscopically pure compounds unless otherwise stated.

**Analysis:** $^1\text{H}$- and $^{13}\text{C}$-NMR spectra were recorded on VARIAN Mercury (300 MHz), BRUKER DRX (400 MHz, 500MHz, 600 MHz), BRUKER Avance (400 MHz, 600 MHz) spectrometers in the solvents indicated. All signals are reported in ppm with the internal chloroform signal at 7.26 ppm or 77.0 ppm, the internal DMSO signal at 2.50 ppm or 39.5 ppm or the internal acetonitrile signal at 1.94 ppm or 1.3 ppm as standard. The data is being reported as ($s$=singlet, $d$=doublet, $t$=triplet, $q$=quadruplet, $m$=multiplet or unresolved, $b$=broad signal, coupling constant(s) in Hz, integration).

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Service measurements were performed by the NMR service team of the Laboratorium für Organische Chemie at ETH Zürich by Mr. Philipp Zumbrunnen, Mr. Rainer Frankenstein and Mr. René Arnold under the direction of Dr. Marc-Olivier Ebert. Infrared spectra were recorded on a Perkin Elmer RXI FT-IR Spectrophotometer as thin films. Absorptions are given in wavenumbers (cm⁻¹). Mass spectrometric measurements were performed as high resolution ESI measurements on a Bruker maXis ESI-Q-TOF by the mass spectrometry service of the LOC at the ETHZ. Melting points are uncorrected and were measured on a Büchi B-540 melting point apparatus using open glass capillaries.

18.2. Experimental Part to Chapter 3

To a stirred solution of L-tosyltryptophan⁶⁹⁸ (2.8 g, 7.8 mmol) in CH₂Cl₂ (30 mL) was added n-butylidichloroborane⁶⁹⁹ (6.4 mL, 1.0M in hexane) and the mixture was stirred at room temperature for 1 h after which all volatile materials were removed under high vacuum. The residue was dissolved in CH₂Cl₂ (65 mL) and cooled to -78 °C. Furan (65 mL) was added with stirring over 10 minutes. Bromoacrolein⁷⁰⁰ was added (7.0 g, 52 mmol) and the reaction was stirred at -78 °C for 12 hours. In a second flask diisopropylamine (11 mL, 76 mmol) was dissolved in THF (80 mL) and cooled to 0 °C. n-BuLi (49 mL, 79 mmol) was added to the solution and the reaction was stirred for 10 minutes. The mixture was then cooled to -78 °C and treated with EtOAc (7.0 mL, 72 mmol). After 30 minutes at -78 °C, the aldehyde solution was transferred to the enolate solution via cannula. Stirring at -78 °C was continued for 2 h and then slowly warmed to ambient temperature. The mixture was quenched with sat. NH₄Cl and extracted three times with EtOAc. The combined organic phases were dried over MgSO₄ and the solvent was evaporated. The residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to give alcohol 108 (9.5 g, 32.6 mmol, 63%) as a 1.6:1 mixture of diastereomers. **Major diastereomer:** Rp 0.34 (2:1, hexanes/EtOAc); [α]b²²⁴ 25.1 (c 0.93, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): δ 6.54-6.43 (m, 2H), 5.28 (s, 1H), 5.02 (d, J = 4.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.97-3.91 (m, 1H), 3.15 (d, J = 6.1 Hz, 1H), 2.77-2.49 (m, 2H), 1.98 (dd, J = 4.7, 12.6 Hz, 1H), 1.70 (d, J = 12.6 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); ¹³C-NMR (75 MHz, CDCl₃): δ 172.1, 136.0, 135.3, 128.4, 127.3, 125.1, 123.7, 118.1, 114.5, 113.3, 112.3, 69.1, 53.4, 40.3, 37.9, 31.6, 21.9, 14.2, 13.9.

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81.6, 79.4, 73.0, 70.2, 61.0, 60.3, 39.7, 39.2, 14.1; \textbf{IR} \nu_{\text{max}} (\text{film})/cm^{-1}: 3474, 2982, 1731, 1374, 1279, 1181, 1029, 794, 702, 554, 438; \textbf{HRMS} (ESI) m/z calculated for C_{11}H_{15}BrO_{4}Na ([M+Na]^+) 313.0051, found 313.0042.

To a solution of alcohol 108 (2.6 g, 9.1 mmol) at -65 °C in THF (0.18 L) was added KO\text{-}t\text{-}Bu (0.92 g, 8.2 mmol) and the mixture was slowly warmed to -40 °C over 1 hour. The mixture was stirred at -40 °C for 30 minutes and quenched with sat. NH_{4}Cl. The organic phase was separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over MgSO_{4} and the solvent was removed. The crude product was purified by flash column chromatography (hexanes/EtOAc 2:1) to yield allylic alcohol 100 (0.70 g, 3.3 mmol, 37%, 81% brsm) along with re-isolated starting material 108 (1.4 g, 4.8 mmol, 61%).

\( R_f \) 0.29 (1:1, hexanes/EtOAc); \([\alpha]_D^{22.4} \) 34.3 (c 2.27, CHCl_{3}); \( ^1H\text{-NMR} \) (300 MHz, CDCl_{3}): \( \delta \) 6.60-6.52 (m, 2H), 6.38 (d, \( J = 4.3 \) Hz, 1H), 6.23 (d, \( J = 15.5 \) Hz, 1H), 5.12 (d, \( J = 4.4 \) Hz, 1H), 4.56 (s, 1H), 4.20 (q, \( J = 7.1 \) Hz, 1H), 2.36 (s, 1H), 1.93 (dd, \( J = 4.5, 12.5 \) Hz, 1H), 1.77 (d, \( J = 12.5 \) Hz, 1H), 1.29 (t, \( J = 7.1 \) Hz, 2H); \( ^{13}C\text{-NMR} \) (75 MHz, CDCl_{3}): \( \delta \) 166.4, 149.0, 138.7, 132.5, 120.9, 88.0, 79.1, 78.6, 60.4, 43.5, 14.3; \textbf{IR} \nu_{\text{max}} (\text{film})/cm^{-1}: 3455, 2984, 1715, 1656, 1306, 1094, 910, 1177, 1094, 910, 726, 608; \textbf{HRMS} (ESI) m/z calculated for C_{11}H_{14}O_{4}Na ([M+Na]^+) 233.0790, found 233.0787.

An oven-dried flask was charged with 1,3-bis(2,6-di-iso-proplyphenyl)imidazolium chloride\textsuperscript{701} 110 (121 mg, 0.3 mmol), CuCl_{2}2H_{2}O (49 mg, 0.3 mmol) and KO\text{-}t\text{-}Bu (320 mg, 2.9 mmol). THF (40 mL) was added to the solids and the mixture was stirred at ambient temperature for 30 min. Poly(methylhydrosiloxane) (PMHS) (1.8 mL, 28.5 mmol) was added and the mixture was stirred for additional 15 min. The solution was cooled to 0 °C and a solution of ester 100 (2 g, 9.5 mmol) in THF (10 mL) and t\text{-}BuOH (0.4 mL, 4.8 mmol) was added. The reaction was quenched after 10 min by addition of pH 7 buffer (50 mL). The phases were separated and the aqueous phase was extracted three

\textsuperscript{701} Prepared according to \textit{Tetrahedron 1999}, 55, 14523.
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times with CH₂Cl₂. The combined organic phases were dried over MgSO₄ and the solvents were evaporated. The residue was purified by flash column chromatography (hexanes/EtOAc 5:1→1:1) to yield lactone 102 and the open ethyl ester. The ethyl ester was taken up in CH₂Cl₂ (10 mL) and HCl in MeOH (10 drops, 1.25M in MeOH) was added. The mixture was stirred overnight at ambient temperature. The reaction was then quenched by addition of pH 7 buffer (10 mL). The phases were separated and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were dried over MgSO₄ and the solvent was evaporated. The residue was purified by flash column chromatography (hexane/EtOAc 2:1→1:1) to yield lactone 102 (combined yield: 985 mg, 5.9 mmol, 62%).

Rf 0.46 (EtOAc); [α]D<sup>20.7</sup> 14.5 (c 0.86, CHCl₃); <sup>1</sup>H-NMR (300 MHz, CDCl₃): δ 6.60 (dd, J = 5.9, 1.5 Hz, 1H), 6.38 (dd, J = 5.8, 1.6 Hz, 1H), 5.09 (d, J = 4.6 Hz, 1H), 4.78 (s, 1H), 2.57 (t, J = 8.2 Hz, 2H), 2.22 (dd, J = 12.0, 4.7 Hz, 1H), 2.09-2.03 (m, 2H), 1.63 (d, J = 12.0 Hz, 1H); <sup>13</sup>C-NMR (75 MHz, CDCl₃): δ 176.0, 141.0, 131.8, 90.6, 84.4, 78.5, 41.3, 30.5, 29.2; IR v<sub>max</sub> (film)/cm⁻¹: 2952, 1771, 1317, 1264, 1156, 1072, 1050, 1013; HRMS (ESI) m/z calculated for C₉H₁₀O₃Na ([M+Na]<sup>+</sup>) 189.0522, 189.0521 found.

Rf 0.62 (1:1, hexane/EtOAc); [α]D<sup>21.9</sup> 6.4 (c 2.4, CHCl₃); <sup>1</sup>H-NMR (400 MHz, CDCl₃): δ 6.14 (ddd, J = 20.0, 5.8, 1.3 Hz, 2H), 4.75 (d, J = 2.5 Hz, 1H), 4.51 (dd, J = 18.6, 0.9 Hz, 1H), 3.89 (q, J = 7.1 Hz, 2H), 2.36-2.17 (m, 2H), 1.99-1.88 (m, 1H), 1.71-1.48 (m, 2H), 1.13 (d, J = 11.9 Hz, 1H), 1.02 (t, J = 7.1 Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl₃): δ 173.8, 173.7, 138.6, 138.5, 133.3, 133.2, 85.8, 82.7, 82.6, 78.3, 78.2, 60.3, 40.5, 40.4, 35.3, 29.9, 14.2; IR v<sub>max</sub> (film)/cm⁻¹: 3450 (bs), 2978, 1734, 1446, 1377, 1312, 1264, 1176, 1091, 1021; HRMS (ESI) not obtained.

General procedure for the synthesis of sulfonyl azides

Sulfonyl chloride (4 mmol) was dissolved in acetone (3 mL). The solution was cooled to 0 °C and sodium azide (6 mmol) in H₂O (1.5 mL) was added slowly. The mixture was allowed to warm to ambient temperature and stirred overnight. Acetone was removed under reduced pressure at 25 °C and the remaining aqueous phase was extracted twice with EtOAc. The combined organic phases were

<sup>702</sup> Using more expensive triphenylsilane instead of PMHS provided the same product in slightly higher yield.
washed with H₂O, 5% Na₂CO₃ aqueous solution and again with H₂O. The organic phase was dried over MgSO₄ and the solvent was removed. The sulfonyl azide was dried at high vacumm.

Although these compounds proved stable in our hands, organoazides should be handled carefully as there are potentially explosive.

\[ \text{1H-NMR} \ (300 \text{ MHz, CDCl}_3): \delta \ 7.25 \ (s, 2H), \ 4.08 \ (\text{hept}, \ J = 6.7 \text{ Hz}, \ 2H), \ 2.95 \ (\text{hept}, \ J = 6.9 \text{ Hz}, \ 1H), \ 1.34-1.27 \ (m, \ 18H); \text{13C-NMR} \ (75 \text{ MHz, CDCl}_3): \delta \ 154.5, \ 150.5 \ (2C), \ 131.7, \ 123.9, \ 123.8, \ 34.5, \ 34.4, \ 30.1, \ 29.9, \ 24.9, \ 24.8 \ (2C), \ 23.6, \ 23.5; \text{IR} \ \nu_{\text{max}} \ (\text{film})/\text{cm}^{-1}: \ 2963, \ 2932, \ 2872, \ 2121, \ 1599, \ 1567, \ 1463, \ 1426, \ 1380, \ 1364, \ 1353, \ 1258, \ 1196, \ 1168, \ 1106, \ 1073, \ 1060, \ 1035; \text{HRMS} \ (\text{EI}) m/z \ \text{calculated for} \ C_{15}H_{23}N_3O_2S \ ([M]^+): 309.1511, \ \text{found} \ 309.1504. \]

\[ \text{1H-NMR} \ (300 \text{ MHz, CDCl}_3): \delta \ 7.91-7.87 \ (m, \ 2H), \ 7.08-7.03 \ (m, \ 2H), \ 3.90 \ (s, \ 3H); \text{13C-NMR} \ (75 \text{ MHz, CDCl}_3): \delta \ 164.7, \ 129.9, \ 129.8, \ 114.9, \ 55.9; \text{IR} \ \nu_{\text{max}} \ (\text{film})/\text{cm}^{-1}: \ 2950, \ 2850, \ 2131, \ 1593, \ 1577, \ 1497, \ 1462, \ 1444, \ 1418, \ 1369, \ 1351, \ 1319, \ 1296, \ 1272, \ 1188, \ 1176, \ 1127, \ 1110, \ 1088, \ 1021; \text{HRMS} \ (\text{EI}) m/z \ \text{calculated for} \ C_7H_7N_3O_3S \ ([M]^+): 213.0203, \ \text{found} \ 213.0201. \]

\[ \text{1H-NMR} \ (300 \text{ MHz, CDCl}_3): \delta \ 8.48-8.44 \ (m, \ 2H), \ 8.19-8.14 \ (m, \ 2H); \text{13C-NMR} \ (75 \text{ MHz, CDCl}_3): \delta \ 151.2, \ 143.7, \ 128.9, \ 125.0; \text{IR} \ \nu_{\text{max}} \ (\text{film})/\text{cm}^{-1}: \ 3108, \ 2144, \ 1606, \ 1536, \ 1478, \ 1405, \ 1378, \ 1351, \ 1312, \ 1178, \ 1160, \ 1110, \ 1086, \ 1014; \text{HRMS} \ (\text{EI}) m/z \ \text{calculated for} \ C_6H_4N_4O_4S \ ([M]^+): 227.9948, \ \text{found} \ 227.9949. \]
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$^{1}$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.47 (s, 5H), 4.55 (s, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 131.0, 129.9, 129.3, 126.7, 62.0; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2137, 1584, 1496, 1457, 1406, 1365, 1265, 1191, 1158, 1075; HRMS (EI) $m/z$ calculated for C$_7$H$_7$N$_3$O$_2$S ([M]$^+$) 197.0254, found 197.0250.

For 116: $[\alpha]_D^{22.4^\circ}$ -47.2 (c 1.31, CHCl$_3$); $^{1}$H-NMR (300 MHz, CDCl$_3$): $\delta$ 3.79 (d, $J$ = 14.9 Hz, 1H), 3.21 (d, $J$ = 14.9 Hz, 1H), 2.45-2.27 (m, 2H), 2.18-1.99 (m, 2H), 1.96 (d, $J$ = 18.5 Hz, 1H), 1.77 (ddd, $J$ = 13.8, 9.3, 4.6 Hz, 1H), 1.47 (ddd, $J$ = 12.9, 9.2, 3.8 Hz, 1H), 1.06 (s, 3H), 0.87 (s, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$, all peaks reported): $\delta$ 213.5, 58.4, 53.5, 53.4, 48.5, 42.6, 42.5, 27.0, 25.0, 19.8, 19.7, 19.6; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2965, 2892, 2139, 1748, 1484, 1472, 1456, 1417, 1395, 1366, 1326, 1280, 1199, 1162, 1107, 1069, 1053; HRMS (EI) $m/z$ calculated for C$_{10}$H$_{15}$N$_3$O$_3$S ([M]$^+$) 257.0829, found 257.0827.

$[\alpha]_D^{22.4^\circ}$ 43.2 (c 1.13, CHCl$_3$).

$^{1}$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.88 (d, $J$ = 8.5 Hz, 2H), 7.62 (d, $J$ = 8.5 Hz, 2H), 1.36 (s, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 159.1, 135.5, 127.4, 126.8, 35.5, 31.0; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2967, 2908, 2873, 2126, 1593, 1429, 1464, 1404, 1373, 1297, 1269, 1171, 1112, 1084, 1014; HRMS (EI) $m/z$ calculated for C$_{10}$H$_{13}$N$_3$O$_2$S ([M]$^+$) 239.0723, found 239.0724.

$^{1}$H-NMR (300 MHz, CDCl$_3$): $\delta$ 8.55 (d, $J$ = 1.4 Hz, 1H), 8.07-7.88 (m, 4H), 7.76-7.65 (m, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 135.7, 135.2, 131.9, 130.2, 130.0, 129.7, 129.5, 128.2, 128.1, 121.8; IR
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$\nu_{\text{max}}$ (film)/cm$^{-1}$: 3060, 2129, 1627, 1590, 1505, 1456, 1371, 1270, 1242, 1166, 1133, 1073, 1021; HRMS (EI) $m/z$ calculated for $C_{10}H_7N_3O_2S ([M]^+) 233.0254$, found 233.0256.

**General procedure for the screening of azidation reagents**

To a stirred solution of lithium hexamethyldisilazane (30 mg, 0.18 mmol) in CH$_2$Cl$_2$ (1.5 mL) at -78 °C was slowly added a solution of lactone 102 (20 mg, 0.12 mmol) in CH$_2$Cl$_2$ (1 mL). The mixture was stirred at -78 °C for 30 min and subsequently warmed to -45 °C. After 5 min a solution of sulfonyl azide (0.16 mmol) in CH$_2$Cl$_2$ (0.3 mL) was added and the mixture was stirred for 2 min at -45 °C. The reaction was quenched by addition of AcOH/KOAc (29 $\mu$L, 0.55 mmol) and the mixture was allowed to warm up to ambient temperature. After 1 h dilute brine (2 mL) was added and the phases were separated. The aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were dried over MgSO$_4$ and the solvent was removed. The residue was subjected to flash column chromatography (EtOAc/hexanes 2:1).

**Optimized Conditions:**

To a stirred solution of lithium hexamethyldisilazane (755 mg, 4.5 mmol) in CH$_2$Cl$_2$ (30 mL) at -78 °C was slowly added a solution of lactone 102 (500 mg, 3.0 mmol) in CH$_2$Cl$_2$ (10 mL). The mixture was stirred at -78 °C for 30 min and then warmed to -45 °C. After 5 min a solution of 2,4,6-trisopropylsulfonyl azide 112 (1.21 g, 3.9 mmol) in CH$_2$Cl$_2$ (5 mL) was added and the mixture was stirred for 2 min at -45 °C. The reaction was quenched by addition of AcOH/KOAc (0.8 mL, 13.8 mmol) and the mixture was allowed to warm up to ambient temperature. After stirring for 1 h dilute brine (20 mL) was added and the phases were separated. The aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were dried over MgSO$_4$ and the solvent was removed. The residue was subjected to flash column chromatography (EtOAc/hexanes 3:1 → 1:1) to give azide 104 (460 mg, 2.2 mmol, 73%, 81% brsm) as a white 1:2:1 mixture of diastereomers along with reisolated lactone 102 (45 mg, 0.3 mmol, 9%).

**1:1 Mixture of diastereomers at C(2):** $R_f$ 0.53 (EtOAc); $[\alpha]_D^{20, 7} 9.0$ (c 0.66, CHCl$_3$); $^1$H-NMR (400 MHz, CDCl$_3$), 1:2:1 mixture of diastereomers, all peaks reported): $\delta$ 6.63 (ddd, $J = 7.4, 5.9, 1.6$ Hz,

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703 The two isomers could not be separated by chromatography. For the subsequent reactions this diastereomeric mixture was used.
1H), 6.37 (dt, J = 5.4, 2.4 Hz, 1H), 5.12-5.08 (m, 1H), 4.86-4.74 (m, 1H), 4.36 (td, J = 8.1, 5.9 Hz, 1H), 2.35-2.17 (m, 2H), 2.13-1.96 (m, 1H), 1.67 (dd, J = 12.3, 8.1 Hz, 1H); 13C-NMR (100 MHz, CDCl3, 1.2:1 mixture of diastereomers, all peaks reported): δ 172.2, 172.1, 141.7, 141.3, 131.6, 131.4, 89.1, 88.6, 84.8, 84.2, 78.5, 78.4, 57.9, 57.5, 41.5, 40.8, 36.9, 36.8; IR νmax (film)/cm⁻¹: 2955, 2116, 1773, 1320, 1250, 1163, 1047, 1013; HRMS (ESI) m/z calculated for C₉H₉N₃O₃Na ([M+Na⁺]⁺) 230.0536, 230.0527 found.

To a stirred solution of lactone 104 (300 mg, 1.4 mmol) in CH₂Cl₂ (4 mL) was added benzylamine (0.47 mL, 4.3 mmol) and HCl in MeOH (0.2 mL, 0.3 mmol, 1.25 M in MeOH). The mixture was stirred at ambient temperature for 2 h. The solvent was evaporated and the residue was purified by flash column chromatography (hexane/EtOAc 2:1 → 1:1) to yield 118 (360 mg, 1.1 mmol, 79%).

To a stirred solution of azide 118 (360 mg, 1.1 mmol) in acetonitril (10 mL) was added trimethylphosphine (2.3 mL, 2.3 mmol, 1M in THF). The mixture was stirred for 30 min at ambient temperature. H₂O (1 mL) was added and the reaction was stirred for additional 45 min. Na₂SO₄ (2.5 g) was added to the mixture and the suspension was stirred for 10 min. The mixture was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (CH₂Cl₂/MeOH 20:1) to yield amine 119 as a yellow oil (240 mg, 0.83 mmol, 73%).

Rf 0.13 (9:1, CH₂Cl₂/MeOH ); [α]D²⁰ 8.0 (c 0.40, CHCl₃, mixture of diastereomers, all peaks reported); ¹H-NMR (300 MHz, CDCl₃): δ 7.66 (bs-s, 1H, NH), 7.33-7.18 (m, 5H), 6.44-6.26 (m, 2H), 4.98-4.91 (m, 1H), 4.60-4.47 (m, 1H), 4.40-4.34 (m, 2H), 3.60-3.50 (m, 1H), 2.50 (bs-s, 3H, NH₂, OH), 1.89-1.69 (m, 3H), 1.48-1.40 (m, 1H); ¹³C-NMR (75 MHz, CDCl₃, mixture of diastereomers, all peaks reported): δ 174.8, 174.6, 137.9, 137.8, 137.7, 132.8, 132.7, 132.7, 128.4, 128.3, 127.4, 127.3, 127.1, 87.2, 87.0, 86.3, 86.2, 79.9, 79.8, 78.2, 78.0, 53.8, 53.8, 43.2, 43.0, 42.2, 42.1, 41.6; IR νmax (film)/cm⁻¹: 3277 (br), 3068, 2989, 1658, 1548, 1533, 1450, 1425, 1307, 1292, 1224, 1152, 1082, 998; HRMS (ESI) m/z calculated for C₁₆H₂₀N₂O₃Na ([M+Na⁺]⁺) 311.1366, 311.1363 found.
To a stirred solution of the amine 119 (185 mg, 0.64 mmol) in CH$_2$Cl$_2$ (4 mL) was added benzoic anhydride (160 mg, 0.71 mmol). The mixture was stirred at ambient temperature for 1 h. The reaction was quenched by addition of saturated NaHCO$_3$ solution. The phases were separated and the aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were dried over MgSO$_4$ and the solvent was removed. The residue was purified by flash column chromatography (hexane/EtOAc 1:1) to yield 120 (192 mg, 0.49 mmol, 76%).

$R_f$ 0.29 (EtOAc); [α]$_D^{20.7}$ 7.9 (c 0.29, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$, mixture of diastereomers, all peaks reported): δ 8.00-7.73 (m, 5H), 7.52-7.23 (m, 7H), 6.41-6.23 (m, 2H), 5.05-4.85 (m, 2H), 4.67-4.47 (m, 1H), 4.44-4.38 (m, 2H), 4.28-3.92 (m, 1H), 2.24-1.96 (m, 2H), 1.93-1.68 (m, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$, mixture of diastereomers, all peaks reported): δ 171.4, 171.3, 167.1, 167.0, 138.3, 137.5, 133.1, 132.2, 131.5, 128.3, 127.2, 126.9, 126.8, 86.6, 86.4, 78.7, 78.5, 78.3, 77.8, 51.3, 43.5, 42.3, 41.8, 40.6; IR $\nu_{max}$ (film)/cm$^{-1}$: 3303, 3068, 2999, 1640, 1536, 1484, 1450, 1430, 1312, 1249, 1165, 1082, 1028; HRMS (ESI) $m/z$ calculated for C$_{23}$H$_{24}$N$_2$O$_4$Na ([M+Na]$^+$) 415.1628, 415.1620 found.

To a stirred solution of amide 120 (15 mg, 0.04 mmol) in CH$_2$Cl$_2$ (1 mL) was added 4Å molecular sieve (powdered, ca. 5 mg) and tert-butyldimethylsilyl triflate (80 μL, 0.38 mmol). After stirring the mixture for 3 h at ambient temperature the reaction was quenched by addition of MeOH (3 mL). The solvents were evaporated and the residue was taken up in EtOAc (10 mL). The organic phase was extracted with pH 6.8 buffer. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over MgSO$_4$ and the solvent was removed. The residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 40:1 → 20:1) to yield 121 as a yellow oil (6 mg, 0.02 mmol, 50%) along with some unreacted starting material 120 (not optimized).

Major diastereomer: $R_f$ 0.16 (20:1, CH$_2$Cl$_2$/MeOH); $^1$H-NMR (600 MHz, CD$_2$OD): δ 7.85-7.81 (m, 2H), 7.56 (dt, $J = 7.4, 1.2$ Hz, 1H), 7.48-7.40 (m, 6H), 7.33-7.26 (m, 1H), 5.74 (ddd, $J = 10.2, 4.0, 2.1$ Hz, 1H), 5.59 (dt, $J = 10.0, 2.0$ Hz, 1H), 4.88 (t, $J = 10.1$ Hz, 1H), 4.39 (dd, $J = 4.8, 2.4$ Hz, 1H), 4.36-4.32.
Experimental Part

(m, 1H), 4.10 (s, 2H), 2.70 (dd, J = 12.4, 10.0 Hz, 1H), 2.44-2.41 (m, 1H), 2.21 (dd, J = 12.7, 9.6 Hz, 1H), 1.98 (dd, J = 20.4, 10.3 Hz, 1H); 13C-NMR (150 MHz, CD3OD): δ 176.9, 169.8, 134.8, 133.2 (2C), 131.0, 130.2, 130.0, 129.6, 128.5, 128.4, 87.3, 73.3, 67.0, 52.4, 44.4, 43.9, 34.1; IR νmax (film)/cm⁻¹: 3470 (br), 2950, 1703, 1651, 1532, 1259, 1172, 1030; HRMS (ESI) m/z calculated for C23H25N2O4 ([M+H]+) 393.1809, 393.1806 found.

To a stirred solution of lactone 102 (100 mg, 0.48 mmol) in MeOH (10 mL) at -10 °C was added sodium borohydrid (40 mg, 1.06 mmol). The mixture was stirred at 0 °C for 30 min. The reaction was quenched by addition of saturated aqueous NH4Cl. The phases were separated and the aqueous phase was extracted three times with EtOAc and CH2Cl2 respectively. The combined organic phases were dried and the solvents were removed. The residue was purified by flash column chromatography (hexane/EtOAc 1:1 → 0:1) to yield the primary alcohol S2704 (68 mg, 0.32 mmol, 67%).

Rf 0.29 (EtOAc); [α]D22.4° 0.7 (c 1.07, CHCl3); 1H-NMR (300 MHz, CDCl3, mixture of diastereomers, all peaks reported): δ 6.48-6.30 (m, 2H), 5.00 (dd, J = 10.9, 4.5 Hz, 1H), 4.72-4.53 (m, 1H), 3.87-3.57 (m, 3H), 3.20-2.99 (m, 2H), 1.92-1.78 (m, 2H), 1.71-1.39 (m, 2H); 13C-NMR (75 MHz, CDCl3, mixture of diastereomers, all peaks reported): δ 138.3, 137.6, 133.0, 132.3, 87.3, 87.1, 86.6, 86.5, 78.2, 77.8, 77.8, 65.5, 65.3, 61.2, 61.0, 60.6, 60.4, 43.3, 41.6, 38.7, 38.0; IR νmax (film)/cm⁻¹: 3400, 2950, 2117, 1632, 1348, 1314, 1280, 1167, 1089, 1034, 1003.

To a stirred solution of primary alcohol S2 (9 mg, 0.04 mmol) in CH2Cl2 (0.5 mL) at 0 °C was added triethylamine (9 µL, 0.06 mmol) and tert-butyldiphenylsilyl chloride (12 µL, 0.06 mmol). The mixture was stirred for 5 min and then warmed to ambient temperature. DMAP (cat.) was added and the mixture was stirred for 1 h at ambient temperature. The reaction was quenched by addition of saturated NH4Cl solution. The phases were separated and the aqueous phase was extracted three times with CH2Cl2. The combined organic phases were dried over MgSO4 and the solvent was evaporated. The

704 Alcohol S2 proved highly unstable and was directly subjected to TBDPS protection.
residue was purified by flash column chromatography (hexane/EtOAc 3:1 → 1:1) to yield 124 (18 mg, 0.04 mmol, 94%).

**R**<sub>f</sub> 0.75 (EtOAc); [**α**]<sub>D</sub><sup>22</sup> 2.9 (c 0.23, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>, mixture of diastereomers, all peaks reported): δ 7.75-7.68 (m, 4H), 7.49-7.37 (m, 6H), 6.47-6.19 (m, 2H), 4.99 (dd, <em>J</em> = 13.8, 4.4 Hz, 1H), 4.77-4.45 (m, 1H), 4.01-3.83 (m, 1H), 3.80-3.63 (m, 2H), 1.87-1.61 (m, 3H), 1.42-1.27 (m, 2H), 1.12 (s, 9H); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>, mixture of diastereomers, all peaks reported): δ 138.4, 137.2, 135.4, 133.5, 132.8, 132.2, 129.7, 129.3, 127.6, 127.5, 87.1, 86.7, 78.2, 77.5, 67.6, 67.5, 60.7, 60.0, 43.1, 41.5, 38.2, 37.5, 26.6, 26.4; IR <em>ν</em><sub>max</sub> (film)/cm<sup>-1</sup>: 3450, 2931, 2858, 2118, 1464, 1428, 1390, 1357, 1306, 1282, 1112, 1007, 937, 909; HRMS (ESI) <em>m/z</em> calculated for C<sub>25</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>SiNa ([M+Na]<sup>+</sup>) 472.2027, 472.2028 found.

To a stirred solution of azide 124 (78 mg, 0.17 mmol) in acetonitrile (2 mL) was added trimethylphosphine (0.35 mL, 0.35 mmol, 1M in THF). The mixture was stirred for 30 min at ambient temperature. <em>H</em><sub>2</sub>O (0.2 mL) was added and the reaction was stirred for additional 45 min. Na<sub>2</sub>SO<sub>4</sub> (400 mg) was added to the mixture and the suspension was stirred for 10 min. The mixture was filtered and the filtrate was concentrated by removal of the solvent. The residue was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 20:1) to yield amine S3 (52 mg, 0.12 mmol, 71%).

**R**<sub>f</sub> 0.11 (9:1, CH<sub>2</sub>Cl<sub>2</sub>/MeOH); [**α**]<sub>D</sub><sup>22</sup> 0.5 (c 0.26, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>, mixture of diastereomers, all peaks reported): δ 7.69-7.60 (m, 4H), 7.47-7.32 (m, 6H), 6.40-6.16 (m, 2H), 5.00 (dd, <em>J</em> = 11.8, 4.5 Hz, 1H), 4.65-4.52 (m, 1H), 3.55-3.34 (m, 2H), 3.09 (bs-s, 3H), 2.98-2.89 (m, 1H), 1.91 (ddd, <em>J</em> = 16.6, 11.6, 4.8 Hz, 1H), 1.75-1.39 (m, 2H), 1.37-1.31 (m, 1H), 1.10-1.04 (m, 9H); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>, mixture of diastereomers, all peaks reported): δ 138.1, 137.6, 135.3, 135.2, 133.0, 132.9, 129.6, 127.6, 127.5, 87.4, 87.3, 86.4, 86.3, 80.1, 79.7, 78.2, 78.1, 69.8, 69.6, 52.2, 42.3, 41.3, 40.3, 39.7, 29.8, 27.2, 27.1, 27.0, 26.8, 19.4; IR <em>ν</em><sub>max</sub> (film)/cm<sup>-1</sup>: 2929, 2856, 1645, 1425, 1112, 999, 909; HRMS (ESI) <em>m/z</em> calculated for C<sub>23</sub>H<sub>34</sub>NO<sub>3</sub>Si ([M+H]<sup>+</sup>) 424.2307, 424.2300 found.
To a stirred solution of amine S3 (360 mg, 0.85 mmol) in CH$_2$Cl$_2$ (14 mL) was added benzoic anhydride (212 mg, 0.93 mmol) and DMAP (10 mg, 0.08 mmol). The mixture was stirred at ambient temperature for 2 h. The solvent was removed and the residue was purified by flash column chromatography (hexane/EtOAc 2:1 → 1:1) to yield 125 (440 mg, 0.83 mmol, 98%).

**R$_f$ 0.68 (EtOAc); [α]$_D^{22}$ $^{22}$ 8.0 (c 0.20, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$, mixture of diastereomers, all peaks reported): δ 7.79-7.63 (m, 6H), 7.51-7.32 (m, 9H), 7.10 (dd, $J$ = 31.3, 7.5 Hz, 1H, NH), 6.41-6.30 (m, 2H), 4.94 (bs-s, 1H), 4.60 (d, $J$ = 15.8 Hz, 1H), 4.48-4.37 (bs-m, 1H), 3.96-3.80 (m, 2H), 1.97-1.79 (m, 3H), 1.54 (dd, $J$ = 37.6, 12.0 Hz, 1H), 1.12 (s, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$, mixture of diastereomers, all peaks reported): δ 167.0, 166.8, 137.9, 137.5, 135.0, 133.8, 132.7, 132.5, 132.3, 131.1, 129.5, 128.1, 127.3, 126.4, 86.6, 86.4, 78.6, 78.4, 78.2, 77.7, 65.9, 65.7, 49.4, 49.2, 42.4, 41.9, 39.5, 39.2, 27.0, 26.8, 19.3; IR $\nu$$_{max}$ (film)/cm$^{-1}$: 3347, 2930, 2851, 1639, 1534, 1488, 1428, 1312, 1112; HRMS (ESI) $m/z$ calculated for C$_{32}$H$_{37}$NO$_4$SiNa ([M+Na]$^+$) 550.2384, 550.2381 found.

To a stirred solution of amide 125 (50 mg, 0.09 mmol) in CH$_2$Cl$_2$ (2 mL) was added triethylamine (80 µL, 0.57 mmol) and trimethylsilyltriflate (31 µL, 0.19 mmol). After stirring the mixture for 30 min additional trimethylsilyltriflate (31 µL, 0.19 mmol) was added. After 30 min the solvent was evaporated and the residue was purified by flash column chromatography (hexane/EtOAc 3:1 → 0:1) to yield 126 as a mixture of separable diasteromers along with mono and di-TMS protected products (~1:1). The protected products (10 mg, ~0.02 mmol) were taken up in CH$_2$Cl$_2$ (0.5 mL) and (+)-camphorsulfonic acid (0.4 mg, 0.002 mmol) was added. The mixture was stirred over night at ambient temperature. The solvent was evaporated and the residue was purified by flash column chromatography (hexane/EtOAc 1:1 → 0:1) to yield 126 (38 mg, 0.06 mmol, 66%, combined yield).

**Major Diastereomer:**

R$_f$ 0.56 (EtOAc); [α]$_D^{22}$ $^{22}$ 62.2 (c 0.17, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$): δ 7.70-7.60 (m, 5H), 7.47-7.28 (m, 10H), 5.86 (s, 1H), 5.59 (d, $J$ = 10.1 Hz, 1H), 5.17 (dt, $J$ = 2.2, 9.2 Hz, 1H), 4.54-4.51 (m, 2H), 4.39 (dd, $J$ = 1.7, 10.7 Hz, 1H), 4.30-4.25 (m, 1H), 3.50 (dd, $J$ = 1.8, 10.9 Hz, 1H), 2.42 (dd, $J$ = 5.7, 12.7 Hz, 1H), 2.30 (dd, $J$ = 11.1, 13.7 Hz, 1H), 1.96 (d, $J$ = 13.9 Hz, 1H), 1.78 (dd, $J$ = 9.4,
Experimental Part

To a stirred solution of alkene 100 (2.00 g, 9.51 mmol) in CH₂Cl₂ (100 mL) was added 3-chloroperoxy-benzoic acid (4.69 g, 19.03 mmol). The mixture was stirred at ambient temperature for 6 h. The reaction was quenched at 0 °C by slow addition of a saturated sodium thiosulfate solution. The phases were separated and the organic phase was washed twice with saturated NaHCO₃. The organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (EtOAc/hexanes 5:1 → 1:2) to give epoxide 145 (2.00 g, 8.84 mmol, 93%).

Rᵣ 0.56 (EtOAc); [α]D₂¹⁺⁺⁵⁺ 4.26 (c 1.35, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): δ 6.81 (dd, J = 15.4, 1.2 Hz, 1H), 6.30 (d, J = 15.4 Hz, 1H), 4.62 (dd, J = 3.8, 1.7 Hz, 1H), 4.24-4.17 (m, 3H), 3.43 (dd, J = 11.2, 3.3 Hz, 2H), 2.88 (s, 1H), 1.95-1.89 (m, 2H), 1.30 (t, J = 7.1 Hz, 2H); ¹³C-NMR (75 MHz, CDCl₃): δ 165.8, 144.4, 122.4, 83.3, 82.0, 74.6, 60.7, 50.1, 47.6, 45.5, 14.4; IR νmax (film)/cm⁻¹: 3454, 2984, 1713, 1657, 1445, 1370, 1308, 1267, 1219, 1181, 1120, 1070; HRMS (ESI) m/z calculated for C₁₃H₂₅O₃Na ([M+Na]⁺) 249.0733, found 249.0731.

A flask containing epoxide 145 (3.80 g, 16.80 mmol) was evacuated and purged with argon. MeOH (20 mL) was added followed by palladium on activated carbon (200 mg, 10% wt Pd). The reaction flask was evacuated and purged with H₂ (1 atm, balloon). The reaction was stirred for 1 h. The mixture was filtered through a plug of Celite and the solvent was removed under reduced pressure. The residue was resuspended in MeOH (20 mL) and K₂CO₃ (116 mg, 0.84 mmol) was added. The mixture was...
coevaporated with MeOH several times until full conversion to the product was observed (crude NMR analysis). MeOH was removed completely and the residue was suspended in CH₂Cl₂. The mixture was filtered through a plug of Celite and the filtrate was collected. The solvent was removed under reduced pressure to give lactone 144 (2.40 g, 13.17 mmol, 78%). No further purification was necessary.

Rf 0.29 (EtOAc); [α]D 24.1° - 10.78 (c 0.50, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): δ 4.62 (d, J = 5.3 Hz, 1H), 4.42 (s, 1H), 3.39 (dd, J = 10.1, 3.2 Hz, 2H), 2.64-2.57 (m, 2H), 2.39-2.17 (m, 3H), 1.77 (d, J = 13.1 Hz, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 174.7, 91.4, 79.5, 74.2, 49.9, 46.5, 42.6, 29.0, 28.0; IR νmax (film)/cm⁻¹: 1771, 1422, 1376, 1293, 1264, 1213, 1186, 1157, 1113, 1050, 1020; HRMS (ESI) m/z calculated for C₉H₁₀O₄Na ([M+Na]+) 205.0471, found 205.0471.

To a stirred solution of lithium hexamethyldisilazane (1.24 g, 7.41 mmol) in CH₂Cl₂ (300 mL) at -78 °C was slowly added a solution of lactone 144 (900 mg, 4.94 mmol) in CH₂Cl₂ (100 mL). The mixture was stirred at -78 °C for 30 min and subsequently warmed to -50 °C. After 5 min a solution of 2,4,6-triisopropylsulfonyl azide 112 (1.99 g, 6.42 mmol) in CH₂Cl₂ (5 mL) was added and the mixture was stirred for 2 min at -50 °C. The reaction was quenched by addition of AcOH/KOAc (1.30 mL, 22.73 mmol) and the mixture was allowed to warm up to ambient temperature. After 1h dilute brine (100 mL) was added and the phases were separated. The aqueous phase was extracted three times with CH₂Cl₂ (300 mL). The combined organic phases were dried over MgSO₄ and the solvent was removed. The residue was subjected to flash column chromatography (EtOAc/hexanes 5:1 → 1:2) to give azide 148 (640 mg, 2.87 mmol, 58%, 92% brsm) as a 1.2:1 mixture of chromatographically separable diastereomers along with reisolated lactone 144 (333 mg, 1.99 mmol, 37%).

Desired Diastereomer 148a: Rf 0.61 (EtOAc); [α]D 24.1° - 10.78 (c 0.40, MeOH); ¹H-NMR (300 MHz, CDCl₃): δ 4.63 (d, J = 5.2 Hz, 1H), 4.38 (s, 1H), 4.34 (dd, J = 7.9, 6.0 Hz, 1H), 3.43 (d, J = 3.2 Hz, 1H), 3.35 (d, J = 3.2 Hz, 1H), 2.54 (dd, J = 13.8, 7.9 Hz, 1H), 2.32 (dd, J = 13.6, 5.2 Hz, 1H), 2.17 (dd, J = 13.8, 6.0 Hz, 1H), 1.85 (d, J = 13.6 Hz, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 170.7, 90.2, 79.3, 74.0, 57.6, 50.1, 46.4, 42.8, 34.0; IR νmax (film)/cm⁻¹: 2996, 2879, 2116, 1778, 1454, 1372, 1249, 1207, 1162, 1125, 1106, 1042, 1018; HRMS (ESI) m/z calculated for C₉H₁₀O₃N₃Na ([M+Na]+) 246.0485, found 246.0478.

148b: Rf 0.56 (EtOAc); [α]D 24.1° - 10.78 (c 0.40, MeOH); ¹H-NMR (300 MHz, CDCl₃): δ 4.65 (d, J = 5.2 Hz, 1H), 4.49 (s, 1H), 4.37 (t, J = 8.3 Hz, 1H), 3.42 (d, J = 3.2 Hz, 1H), 3.36 (d, J = 3.2 Hz, 1H), 2.48 (dd, J = 13.2, 8.0 Hz, 1H), 2.28-2.18 (m, 2H), 1.78 (d, J = 13.1 Hz, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 171.0, 89.3, 79.9, 74.2, 57.2, 49.8, 46.2, 42.3, 34.6; IR νmax (film)/cm⁻¹: 2116, 1782, 1249,
1163, 1108, 1045, 1020; HRMS (ESI) m/z calculated for C₉H₉O₄N₃Na ([M+Na]+) 246.0485, found 246.0485.

151 was prepared in analogy to amide 155 using phenethylamine instead of 4-(tert-butyl-diphenylsilyloxy)butan-1-amine as nucleophile. An X-ray structure of 151 could be obtained (see chapter 24) and was deposited at the Cambridge Crystallographic Data Centre under CCDC 785240. To a stirred solution of lactone 148a (78 mg, 0.35 mmol) in CH₂Cl₂ (2 mL) was added phenethylamine (63 μL, 0.53 mmol) and 1 drop of HCl in MeOH (1.25M). The reaction mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1 → EtOAc) to give azide 151 (81 mg, 0.24 mmol, 67%).

R₇ 0.29 (EtOAc); [α]D²³⁰ -22.96 (c 0.65, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): δ 7.36-7.15 (m, 5H), 6.51 (t, J = 5.5 Hz, 1H, NH), 4.46 (d, J = 5.3 Hz, 1H), 4.23-4.14 (m, 2H), 3.58-3.50 (m, 2H), 3.36 (dd, J = 23.1, 3.3 Hz, 2H), 3.04 (bs-s, 1H, OH), 2.84 (t, J = 7.0 Hz, 2H), 2.30 (dd, J = 14.7, 3.6 Hz, 1H), 1.88-1.71 (m, 2H), 1.60 (d, J = 13.2 Hz, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 169.3, 138.2, 128.6 (2C), 128.5 (2C), 126.6, 81.4, 80.6, 73.3, 61.2, 49.9, 47.6, 45.0, 40.7, 37.6, 35.5; IR νmax (film)/cm⁻¹: 3319, 2115, 1660, 1536, 1368, 1235, 1116, 1067; HRMS (ESI) m/z calculated for C₁₇H₂₀O₄N₄Na ([M+Na]+) 367.1377, found 367.1371.

To a stirred solution of lactone 148a (53 mg, 0.24 mmol) in CH₂Cl₂ (2 mL) was added tert-butyl(4-aminobutyl)carbamate 152₇⁰⁵ (68 μL, 0.36 mmol) and 1 drop of HCl in MeOH (1.25M). The reaction mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1 → EtOAc) to give azide 154 (94 mg, 0.23 mmol, 96%).

Experimental Part

R<sub>t</sub> 0.31 (EtOAc); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 6.72 (bs-s, 1H, NH), 4.63 (bs-s, 1H, NH), 4.52 (d, J = 5.2 Hz, 1H), 4.23 (dd, J = 7.8, 4.6 Hz, 1H), 4.19 (s, 1H), 3.50 (d, J = 3.3 Hz, 1H), 3.34 (d, J = 3.3 Hz, 1H), 3.29 (q, J = 6.0 Hz, 2H), 3.12 (q, J = 6.4 Hz, 2H), 2.39 (dd, J = 14.5, 4.5 Hz, 1H), 1.97-1.87 (m, 2H), 1.76 (d, J = 13.2 Hz, 1H), 1.57-1.48 (m, 4H), 1.48 (s, 9H).

A flask containing azide 154 (276 mg, 0.67 mmol) was evacuated and purged with argon. MeOH (5 mL) was added followed by palladium on activated carbon (28 mg, 10% wt Pd). The reaction flask was evacuated and purged with H<sub>2</sub> (1 atm, balloon). The reaction was stirred for 2 h. The mixture was filtered over Celite and the solvent was removed under reduced pressure. The residue was taken up in EtOAc (3 mL) and water (3 mL) was added. To the vigorously stirred suspension was added sodium bicarbonate (282 mg, 3.35 mmol) and benzyl chloroformate (0.12 mL, 0.81 mmol). The reaction mixture was stirred overnight at ambient temperature. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give amide 156 (309 mg, 0.60 mmol, 89%).

Amine 153 was prepared according to a literature procedure.\(^{706}\)

To a solution of 4-aminobutanol (2.1 g, 23.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added triethylamine (2.0 mL, 14.1 mmol) and TBDPSCI (2.6 g, 9.4 mmol). The mixture was stirred for 1 h. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> and the organic phase was washed with 10% sodium bisulfate and sat. NaHCO<sub>3</sub>. The solvent was evaporated and the residue was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 20:1) to give amine 153 (2.5 g, 7.6 mmol, 81%).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.65-7.60 (m, 4H), 7.43-7.33 (m, 6H), 3.64 (t, J = 6.1 Hz, 2H), 2.98-2.91 (m, 2H), 1.90-1.78 (m, 2H), 1.68-1.58 (m, 2H), 1.03 (s, 9H).

Experimental Part

To a stirred solution of lactone 148a (1.84 g, 8.24 mmol) in CH$_2$Cl$_2$ (20 mL) was added 4-(tert-butyl-diphenylsilyloxy)butan-1-amine 153 (2.97 g, 9.07 mmol). The reaction mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 40:1) to give azide 155 as a colorless foam (4.25 g, 7.72 mmol, 94%).

R$_f$ 0.46 (EtOAc); [α]$_D^{26.0}$ -5.63 (c 1.00, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$): δ 7.68-7.63 (m, 4H), 7.46-7.35 (m, 6H), 6.55 (t, $J = 5.7$ Hz, 1H, NH), 4.48 (d, $J = 5.3$ Hz, 1H), 4.25-4.20 (m, 2H), 3.71-3.67 (m, 2H), 3.43 (d, $J = 3.3$ Hz, 1H), 3.32 (d, $J = 3.3$ Hz, 1H), 3.31-3.25 (m, 2H), 3.21 (s, 1H, OH), 2.35 (dd, $J = 14.7$, 3.7 Hz, 1H), 1.91-1.79 (m, 2H), 1.66-1.56 (m, 5H), 1.05 (s, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 169.0, 135.1 (4C), 133.4 (2C), 129.3 (2C), 127.3 (4C), 81.3, 80.5, 73.3, 63.31, 61.0, 49.9, 47.7, 44.9, 39.5, 37.7, 29.8, 27.0 (3C), 26.1, 19.3; IR $\nu_{max}$ (film)/cm$^{-1}$: 3325, 2932, 2858, 2115, 1660, 1533, 1469, 1428, 1238, 1112; HRMS (ESI) m/z calculated for C$_{29}$H$_{39}$O$_3$N$_4$Si ([M+H]$^+$) 551.2684, found 551.2677.

A flask containing azide 155 (2.05 g, 3.72 mmol) was evacuated and purged with argon. MeOH (40 mL) was added followed by palladium on activated carbon (100 mg, 10% wt Pd). The reaction flask was evacuated and purged with H$_2$ (1 atm, balloon). The reaction was stirred for 1 h. The mixture was filtered over Celite and the solvent was removed under reduced pressure. The residue was taken up in EtOAc (40 mL) and water (40 mL) was added. To the vigorously stirred suspension was added sodium bicarbonate (1.56 g, 18.61 mmol) and benzyl chloroformate (0.64 mL, 4.47 mmol). The reaction mixture was stirred overnight at ambient temperature. The phases were separated and the aqueous phase was extracted three times with EtOAc (200 mL). The combined organic phases were dried over MgSO$_4$ and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 40:1) to give amide 157 (2.16 g, 3.28 mmol, 88%).

R$_f$ 0.60 (9:1, CH$_2$Cl$_2$/MeOH); [α]$_D^{21.8}$ 0.47 (c 1.00, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$): δ 7.67-7.63 (m, 4H), 7.46-7.32 (m, 11H), 6.52 (bs, 1H, NH), 6.14 (d, $J = 7.5$ Hz, 1H, NH), 5.11 (s, 2H), 4.47-4.37

$^{707}$ Prepared according to QSAR Comb. Sci. 2007, 2, 215.
Experimental Part

(m, 2H), 4.14 (bs, 1H), 3.70-3.62 (m, 2H), 3.55 (d, J = 2.9 Hz, 1H), 3.44-3.38 (m, 1H), 3.29-3.17 (m, 3H), 2.19-2.00 (m, 2H), 1.80 (dd, J = 13.1, 5.3 Hz, 1H), 1.63-1.49 (m, 5H), 1.05 (s, 9H); ¹³C-NMR (75 MHz, CDCl₃): δ 171.3, 156.3, 135.9, 135.4 (4C), 133.8 (2C), 129.5 (2C), 128.5 (2C), 128.2, 128.0 (2C), 127.6 (4C), 81.9, 81.2, 73.2, 67.2, 63.3, 52.3, 49.8, 47.6, 44.8, 39.44, 37.4, 29.7, 26.8 (3C), 25.8, 19.1; IR νmax (film)/cm⁻¹: 3305, 2932, 2847, 1716, 1652, 1538, 1477, 1428, 1244, 1112; HRMS (ESI) m/z calculated for C₃₇H₄₇O₇N₂Si ([M+H]+) 659.3147, found 659.3157.

An oven dried flask was evacuated and purged with argon. Bis(cyclopentadienyl)titanium dichloride (1.07g, 4.30 mmol) and activated zinc powder (380 mg, 5.81 mmol) were added and the flask was evacuated again. After 5 min the flask was purged with argon. Freshly distilled THF (20 mL) was added. The mixture was stirred for 1h to give a dark green solution of bis(cyclopentadienyl)titanium chloride (approx. 0.2M).

A flask containing epoxide 157 (200 mg, 0.30 mmol) was evacuated and purged with argon. The substrate was dissolved in freshly distilled THF (20 mL) and 1,4-cyclohexadiene (2.8 mL, 30.4 mmol) was added to the solution. The solution was cooled to 0 °C and a freshly prepared solution of bis(cyclopentadienyl) titanium chloride (2 mL, 0.61 mmol, 0.2 M) was slowly added over 6 h. The solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 20:1) to give alcohol 158 (109 mg, 0.20 mmol, 75% brsm) with partial epimerization at C(2) along with reisolated compound 157 (56 mg, 0.05 mmol, 28%).

R₉ 0.51 (9:1, CH₂Cl₂/MeOH); [α]D²⁵ = -5.37 (c 0.80, MeOH); ¹H-NMR (600 MHz, CD₃OD, 3:1 mixture of diastereomers, major diastereomer reported): δ 7.70-7.67 (m, 4H), 7.47-7.40 (m, 4H), 7.37-7.27 (m, 5H), 5.15-5.06 (m, 2H), 4.38-4.35 (m, 1H), 4.27 (d, J = 6.4 Hz, 1H), 4.15 (d, J = 6.0 Hz, 1H), 3.80 (dd, J = 6.7, 1.6 Hz, 2H), 3.72-3.68 (m, 2H), 3.23-3.17 (m, 2H), 2.14 (dd, J = 14.1, 6.8 Hz, 1H), 2.10 (dd, J = 14.8, 4.5 Hz, 1H), 1.87 (dd, J = 14.6, 7.9 Hz, 1H), 1.72 (dd, J = 1.0, 6.4, 13.3 Hz, 1H), 1.61-1.54 (m, 4H), 1.42-1.38 (m, 1H), 1.36 (d, J = 13.4 Hz, 1H), 1.06 (s, 9H); ¹³C-NMR (150 MHz, CD₃OD, 3:1 mixture of diastereomers, major diastereomer reported): δ 174.7, 158.0, 136.6, 135.0 (4C), 130.8, 129.5 (2C), 129.1 (2C), 128.9 (2C), 128.8 (4C), 84.8, 83.2, 80.0, 73.9, 67.8, 64.7, 53.8, 43.2, 40.4, 39.1, 36.5, 31.0, 27.4 (3C), 26.9, 20.0; IR νmax (film)/cm⁻¹: 3311, 3061, 2927.

A 3:1 mixture of not separable diastereomers was obtained. The diastereomeric mixture was carried on for the subsequent steps. Separation was possible after coupling to the peptide side chain.
2888, 2850, 1705, 1652, 1532, 1421, 1244, 1105; **HRMS** (ESI) m/z calculated for C$_{37}$H$_{49}$O$_7$N$_2$Si ([M+H]$^+$) 661.3304, found 661.3299.

R$_f$ 0.56 (9:1, CH$_2$Cl$_2$/MeOH); [α]$_D^{22.9}$ 0.82 (c 0.94, CH$_2$Cl$_2$).

**1H-NMR** (400 MHz, CD$_3$OD): δ 7.69-7.63 (m, 4H), 7.47-7.22 (m, 11H), 5.08 (t, $J = 5.4$ Hz, 1H), 4.35 (t, $J = 6.4$ Hz, 1H), 4.17 (d, $J = 5.1$ Hz, 1H), 4.01 (s, 1H), 3.70-3.62 (m, 2H), 3.22-3.12 (m, 2H), 2.06 (dd, $J = 14.3$, 6.1 Hz, 1H), 1.93-1.83 (m, 2H), 1.70 (ddd, $J = 12.7$, 5.6, 2.1 Hz, 1H), 1.64-1.53 (m, 4H), 1.52-1.47 (m, 1H), 1.43 (d, $J = 12.8$ Hz, 1H), 1.03 (s, 9H); **13C-NMR** (100 MHz, CD$_3$OD): δ 174.7, 158.1, 138.1, 136.7 (4C), 135.0 (2C), 130.8 (2C), 129.5 (2C), 129.0, 128.9 (2C), 128.8 (4C), 92.7, 78.4, 76.8, 70.0, 67.8, 64.6, 54.0, 47.3, 42.4, 40.4, 39.4, 31.0, 27.4 (3C), 26.8, 20.0; **IR** $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3334, 2934, 2857, 1712, 1659, 1536, 1453, 1428, 1392, 1243, 1112; **HRMS** (ESI) m/z calculated for C$_{37}$H$_{49}$O$_7$N$_2$Si ([M+H]$^+$) 661.3304, found 661.3302.

166 was synthesized analogous to its diastereomer 158 starting from azide 148b.

R$_f$ 0.60 (9:1, CH$_2$Cl$_2$/MeOH); [α]$_D^{21.3}$ -3.14 (c 0.90, CHCl$_3$); **1H-NMR** (300 MHz, CDC$_3$): δ 7.69-7.62 (m, 4H), 7.46-7.29 (m, 11H), 6.75 (bs-s, 1H, NH), 6.11 (d, $J = 7.0$ Hz, 1H, NH), 5.10 (s, 2H), 4.43 (d, $J = 5.2$ Hz, 1H), 4.39-4.33 (m, 1H), 4.08 (s, 1H), 3.68-3.64 (m, 2H), 3.34-3.18 (m, 5H), 2.12 (dd, $J = 14.4$, 5.4 Hz, 1H), 1.99-1.86 (m, 2H), 1.69 (dd, $J = 13.2$, 5.3 Hz, 1H), 1.60-1.52 (m, 4H), 1.05 (s, 9H); **13C-NMR** (75 MHz, CDC$_3$): δ 170.8, 156.0, 135.9, 135.4 (4C), 133.6 (2C), 129.5 (2C), 128.4 (2C), 128.2, 128.0 (2C), 127.5 (4C), 81.7 (2C), 74.0, 67.2, 63.3, 52.4, 49.8, 47.4, 43.5, 39.5, 37.4, 29.9, 26.9 (3C), 25.9, 19.3; **IR** $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3308, 2933, 2847, 1705, 1652, 1538, 1467, 1428, 1244, 1112; **HRMS** (ESI) m/z calculated for C$_{37}$H$_{49}$O$_7$N$_2$Si ([M+H]$^+$) 659.3147, found 659.3134.
Experimental Part

$R_f$ 0.51 (9:1, CH$_2$Cl$_2$/MeOH); $[\alpha]_D^{24.3}$ -4.71 (c 1.25, CHCl$_3$); $^1$H-NMR (300 MHz, CD$_2$OD): $\delta$ 7.70-7.64 (m, 4H), 7.47-7.26 (m, 11H), 5.15-5.05 (m, 2H), 4.32 (dd, $J = 8.5$, 4.3 Hz, 1H), 4.42 (d, $J = 6.2$ Hz, 1H), 4.13 (d, $J = 5.8$ Hz, 1H), 3.79 (dd, $J = 6.8$, 2.0 Hz, 1H), 3.71-3.65 (m, 2H), 3.22-3.14 (m, 2H), 2.09 (dd, $J = 13.9$, 6.8 Hz, 2H), 2.01 (dd, $J = 14.7$, 4.5 Hz, 1H), 1.87 (dd, $J = 14.5$, 8.7 Hz, 1H), 1.67-1.52 (m, 5H), 1.47 (d, $J = 13.4$ Hz, 1H), 1.44-1.37 (m, 1H), 1.05 (s, 9H); $^{13}$C-NMR (75 MHz, CD$_2$OD): $\delta$ 174.2, 157.7, 137.8, 136.3 (4C), 134.6, 130.5 (2C), 129.1 (2C), 128.7 (2C), 128.6 (2C), 128.5 (4C), 84.9, 83.5, 79.6, 73.8, 67.7, 64.6, 54.0, 42.9, 40.3, 38.7, 36.4, 31.0, 27.5 (3C), 27.0, 20.1; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3324, 2932, 2862, 1709, 1692, 1657, 1548, 1536, 1465, 1427, 1258, 1111; HRMS (ESI) $m/z$ calculated for C$_{37}$H$_{49}$O$_7$N$_2$Si ([M+H]$^+$) 661.3304, found 661.3298.

$R_f$ 0.52 (9:1, CH$_2$Cl$_2$/MeOH); $[\alpha]_D^{22.8}$ -2.31 (c 0.50, CH$_2$Cl$_2$); $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.69-7.62 (m, 4H), 7.46-7.28 (m, 11H), 6.61 (bs, 1H, NH), 6.15 (d, $J = 6.9$ Hz, 1H, NH), 5.10 (s, 2H), 4.60 (t, $J = 5.2$ Hz, 1H), 4.39-4.30 (m, 1H), 4.16-4.09 (m, 1H), 4.05 (s, 1H), 3.69-3.62 (m, 2H), 3.27-3.18 (m, 2H), 3.06 (bs-s, 1H, OH), 2.12 (dd, $J = 14.3$, 5.0 Hz, 1H), 1.96-1.86 (m, 3H), 1.76-1.70 (m, 1H), 1.59-1.48 (m, 5H), 1.05 (s, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 170.8, 155.9, 135.8, 135.3 (4C), 133.6, 129.4 (2C), 128.3 (2C), 128.1 (2C), 128.0 (2C), 127.4 (4C), 91.7, 78.3, 76.1, 69.3, 67.2, 63.4, 52.8, 46.7, 42.2, 39.6, 38.3, 30.0, 27.1 (3C), 26.1, 19.4; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3321, 2932, 2851, 1709, 1658, 1536, 1503, 1428, 1246, 1112; HRMS (ESI) $m/z$ calculated for C$_{37}$H$_{49}$O$_7$N$_2$Si ([M+H]$^+$) 661.3304, found 661.3307.
Azide S4 was synthesized as described above.

A flask containing azide S4 (500 mg, 0.91 mmol) was evacuated and purged with argon. MeOH (10 mL) was added followed by palladium on activated carbon (50 mg, 10% wt Pd). The reaction flask was evacuated and purged with H₂ (1 atm, balloon). The reaction was stirred for 1 h. The mixture was filtered over Celite and the solvent was removed under reduced pressure. The residue was taken up in MeOH (3 mL). Freshly distilled benzaldehyde (0.10 mL, 0.99 mmol) was added followed and sodium cyanoborohydride (54 mg, 0.82 mmol). The mixture was cooled to 0 °C and acetic acid (26 μL, 0.45 mmol) was added. The mixture was warmed to ambient temperature and stirred overnight. The reaction was quenched by addition of saturated NH₄Cl (20 mL) and EtOAc (50 mL) was added. The phases were separated and the aqueous phase was extracted three times with EtOAc (50 mL). The combined organic phases were dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 40:1) to give amine 172 (420 mg, 0.68 mmol, 75%).

Rf 0.37 (EtOAc); [α]D²⁹⁻⁸⁻⁵.18 (c 1.00, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): δ 7.70-7.66 (m, 4H), 7.46-7.20 (m, 11H), 4.41 (d, J = 5.0 Hz, 1H), 4.08 (s, 1H), 3.79-3.66 (m, 3H), 3.59 (d, J = 13.1 Hz, 1H), 3.32-3.21 (m, 5H), 197-1.74 (m, 2H), 1.72-1.55 (m, 6H), 1.07 (s, 9H); ¹³C-NMR (75 MHz, CDCl₃): δ 173.1, 138.6, 135.1 (4C), 133.4, 129.3 (2C), 128.3 (2C), 128.0 (2C), 127.3 (2C), 127.2 (4C), 82.9, 80.7, 73.7, 63.4, 60.7, 52.5, 49.9, 47.7, 45.2, 39.0, 38.2, 30.0, 27.0 (3C), 26.3, 19.3; IR νmax (film)/cm⁻¹: 3325, 2932, 2855, 1652, 1534, 1468, 1428, 1387, 1302, 1239, 1112; HRMS (ESI) m/z calculated for C₃₆H₄₇O₅N₂Si ([M+H]+) 615.3249, found 615.3255.

Amine 170 was synthesized analogous to its C(2) epimer 172.

Rf 0.23 (EtOAc); [α]D²⁹⁻³⁻².86 (c 1.00, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): δ 7.70-7.64 (m, 4H), 7.46-7.25 (m, 11H), 4.8 (d, J = 5.3 Hz, 1H), 3.89 (s, 1H), 3.79 (d, J = 13.2 Hz, 1H), 3.72-3.68 (m, 2H), 3.60 (d, J = 13.2 Hz, 1H), 3.49 (dd, J = 3.3, 1.3 Hz, 1H), 3.44 (bs-s, 2H), 3.33-3.3 (m, 3H), 3.19 (dd, J = 9.4, 3.1 Hz, 1H), 1.89 (dd, J = 15.0, 9.6 Hz, 1H), 1.89 (dd, J = 14.8, 2.9 Hz, 1H), 1.78 (dd, J = 13.1, 5.4 Hz, 1H), 1.66-1.59 (m, 4H), 1.50 (d, J = 13.1 Hz, 1H), 1.08 (s, 9H); ¹³C-NMR (75 MHz, CDCl₃): δ 173.1, 138.6, 135.1 (4C), 133.4, 129.3 (2C), 128.3 (2C), 128.0 (2C), 127.3 (2C), 127.2 (4C), 82.9, 80.7, 73.7, 63.4, 60.7, 52.5, 49.9, 47.7, 45.2, 39.0, 38.2, 30.0, 27.0 (3C), 26.3, 19.3; IR νmax (film)/cm⁻¹: 3325, 2932, 2855, 1652, 1534, 1468, 1428, 1387, 1302, 1239, 1112; HRMS (ESI) m/z calculated for C₃₆H₄₇O₅N₂Si ([M+H]+) 615.3249, found 615.3255.
CDCl$_3$): δ 173.8, 139.1, 135.3 (4C), 133.6, 129.5 (2C), 128.3 (2C), 128.1 (2C), 127.5 (2C), 127.1 (4C), 82.5, 81.7, 73.5, 63.2, 60.2, 52.4, 49.7, 47.5, 43.2, 38.8, 37.4, 29.8, 26.7 (3C), 26.1, 19.0; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3326, 2931, 2855, 1652, 1532, 1472, 1428, 1387, 1234, 1112; HRMS (ESI) $m/z$ calculated for C$_{36}$H$_{47}$N$_2$O$_5$Si ([M+H]$^+$) 615.3249, found 615.3231.

R$_f$ 0.45 (9:1, CH$_2$Cl$_2$/MeOH); [$\alpha$]$_D^{21.0^\circ}$ -1.97 (c 1.00, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$): δ 7.68-7.63 (m, 4H), 7.46-7.27 (m, 11H), 4.32 (d, $J = 6.3$ Hz, 1H), 3.87 (d, $J = 5.8$ Hz, 1H), 3.80 (dd, $J = 6.7$, 1.7 Hz, 1H), 3.75 (d, $J = 13.3$ Hz, 1H), 3.71-3.65 (m, 2H), 3.55 (d, $J = 13.3$ Hz, 1H), 3.29-3.21 (m, 2H), 3.10 (dd, $J = 9.9$, 3.1 Hz, 1H), 3.02 (bs-s, 3H), 2.16 (dd, $J = 14.3$, 6.7 Hz, 1H), 1.92 (dd, $J = 15.0$, 9.9 Hz, 1H), 1.82 (dd, $J = 15.0$, 3.1 Hz, 1H), 1.71 (dd, $J = 13.7$, 6.5 Hz, 1H), 1.65-1.56 (m, 4H), 1.43 (dd, $J = 14.4$, 6.1 Hz, 1H), 1.28 (d, $J = 13.7$ Hz, 1H), 1.05 (s, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 173.8, 139.1, 135.5 (4C), 133.8, 129.6 (2C), 128.5 (2C), 128.3 (2C), 127.6 (2C), 127.4 (4C), 82.8, 82.3, 80.8, 73.2, 63.4, 60.4, 52.6, 43.6, 38.8, 38.2, 36.2, 29.9, 26.8 (3C), 26.2, 19.2; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3324, 2931, 2858, 1652, 1532, 1472, 1428, 1387, 1362, 1112; HRMS (ESI) $m/z$ calculated for C$_{36}$H$_{49}$N$_2$O$_5$Si ([M+H]$^+$) 617.3405, found 617.3412.

R$_f$ 0.45 (9:1, CH$_2$Cl$_2$/MeOH); [$\alpha$]$_D^{22.5^\circ}$ -9.71 (c 0.40, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$): δ 7.67-7.63 (m, 4H), 7.45-7.21 (m, 11H), 4.34 (d, $J = 6.3$ Hz, 1H), 4.13 (d, $J = 5.9$ Hz, 1H), 3.81 (dd, $J = 6.1$ Hz, 1H), 3.73 (d, $J = 13.1$ Hz, 1H), 3.69-3.65 (m, 2H), 3.58 (d, $J = 13.1$ Hz, 1H), 3.29-3.23 (m, 2H), 3.19 (dd, $J = 8.5$, 4.3 Hz, 1H), 2.20 (dd, $J = 14.4$, 6.7 Hz, 1H), 1.69-1.74 (m, 2H), 1.63-1.57 (m, 5H), 1.43 (dd, $J = 14.5$, 5.9 Hz, 1H), 1.36 (d, $J = 13.7$ Hz, 1H), 1.05 (s, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 173.8, 139.1, 135.3 (4C), 133.6, 129.4 (2C), 128.3 (2C), 128.0 (2C), 127.4 (2C), 127.1 (4C), 84.1, 82.1, 80.6, 73.4, 63.5, 60.8, 52.8, 41.1, 39.1, 37.9, 36.1, 30.1, 27.1 (3C), 26.4, 19.5; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3324, 2932, 2858, 1651, 1531, 1473, 1450, 1428, 1385, 1112; HRMS (ESI) $m/z$ calculated for C$_{36}$H$_{49}$N$_2$O$_5$Si ([M+H]$^+$) 617.3405, found 617.3399.
174 was synthesized by photochemical deoxygenation of alcohol 157 analogous as described in the subsequent chapter.

\[ R_f \text{ 0.58 (9:1, CHCl}_2/\text{MeOH); } [\alpha]_D^{26.8^\circ} -0.07 (c \text{ 0.55, CHCl}_3); \text{ } ^1H\text{-NMR (300 MHz, CDCl}_3): \delta 7.67-7.62 (m, 4H), 7.46-7.30 (m, 11H), 6.07 (bs-s, 1H, NH), 5.29 (d, } J = 7.3 \text{ Hz, 1H, NH), 5.09 (s, 2H), 4.45 (d, } J = 5.2 \text{ Hz, 1H), 4.30 (d, } J = 4.6 \text{ Hz, 1H), 4.06 (q, } J = 8.0, 7.5 \text{ Hz, 1H), 3.69-3.64 (m, 2H), 3.44-3.40 (m, 1H), 3.29 (d, } J = 3.3 \text{ Hz, 1H), 3.27-3.18 (m, 2H), 2.20 (dt, } J = 9.8, 5.0 \text{ Hz, 1H), 2.04-1.84 (m, 1H), 1.80-1.72 (m, 1H), 1.62-1.50 (m, 5H), 1.05 (s, 9H), 1.00 (dd, } J = 12.3, 4.7 \text{ Hz, 1H); } ^{13}\text{C-NMR (75 MHz, CDCl}_3): \delta 170.9, 156.1, 135.9, 135.5 (4C), 133.7, 129.6 (2C), 128.5 (2C), 128.3 (2C), 128.0 (2C), 127.6 (4C), 75.4, 74.5, 67.2, 63.3, 54.8, 49.9, 48.0, 39.5, 39.2, 33.1, 32.5, 29.7, 26.8 (3C), 25.9, 19.2; \text{ IR } \nu_{\text{max}}(\text{film})/\text{cm}^{-1}: 3308, 2932, 2858, 1712, 1652, 1537, 1454, 1245, 1112, 1028; \text{ HRMS (ESI) } m/z \text{ calculated for C}_{37}H_{47}O_6N_2Si ([M+H]^+) 643.3198, \text{ found } 643.3176. \]

To a suspension of sodium hydride (0.54 g, 22.7 mmol, 60% dispersion in mineral oil) in THF (150 mL) was slowly added diethyl malonate (15.1 g, 94 mmol). The mixture was stirred at ambient temperature for 15 min before cooling the solution to 0 °C. 1-Bromo-2-butene (3.0 g, 18.9 mmol, 7:3 trans/cis mixture) was added and the mixture was stirred for another 30 min. The reaction was quenched by addition of sat. NaHCO₃ and diluted with EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 80:1 → 40:1) to give the malonate product (2.1 g, 9.6 mmol, 51%).

\[ R_f \text{ 0.66 (4:1 hexane/EtOAc); } ^1H\text{-NMR (300 MHz, CDCl}_3): \delta 5.58-5.48 (m, 1H), 5.42-5.29 (m, 1H), 4.20 (q, } J = 7.1 \text{ Hz, 4H), 3.36 (dd, } J = 8.3, 7.0 \text{ Hz, 1H), 2.65 (t, } J = 7.5 \text{ Hz, 1H), 2.57 (t, } J = 7.2 \text{ Hz, 1H), 1.63 (d, } J = 6.3 \text{ Hz, 1H), 1.26 (t, } J = 7.0 \text{ Hz, 1H); } ^{13}\text{C-NMR (75 MHz, CDCl}_3): \delta 168.7, 128.0, 126.8, 126.3, 125.4, 61.1, 52.1, 51.8, 31.8, 26.3, 17.8, 14.1, 12.8; \text{ IR } \nu_{\text{max}}(\text{film})/\text{cm}^{-1}: 2983, 2360, 1752, 1734, 1466, 1369, 1228, 1776, 1035; \text{ HRMS (ESI) } m/z \text{ calculated for C}_{11}H_{19}O_4 ([M+H]^+) 215.1278, 215.1278 \text{ found.} \]

Paraformaldehyde (3.3 g, 110 mmol) and tosylamide (22.6 g, 132 mmol) were dissolved in CH₂Cl₂ (120 mL) and mixture was stirred for 10 min. In a separate flask the malonate form the first step (4.7
Experimental Part

**g, 22.0 mmol** and **DBU (16.6 ml, 110 mmol)** were dissolved in **CH₂Cl₂ (120 mL)**. The sulfonimine solution was added to the malonate and the mixture was stirred over night. The reaction was quenched by addition of sat. **NaHCO₃** and diluted with **CH₂Cl₂**. The phases were separated and the aqueous phase was extracted three times with **CH₂Cl₂**. The combined organic phases were washed with brine and dried over **MgSO₄**. The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 10:1 → 0:1) to give sulfonamide **S5 (2.3 g, 13.4 mmo, 61%)**.

**Rf 0.61 (3:2 hexane/EtOAc); **

**¹H NMR (300 MHz, CDCl₃) δ 7.74-7.69 (m, 2H), 7.33-7.28 (m, 2H), 5.61-5.46 (m, 1H), 5.10-4.99 (m, 1H, NH), 4.16 (q, J = 7.1 Hz, 4H), 3.29 (d, J = 6.9 Hz, 2H), 2.61 (d, J = 7.4 Hz, 2H), 2.43 (s, 3H), 1.61-1.57 (m, 3H), 1.27-1.22 (m, 3H); **

**¹³C NMR (75 MHz, CDCl₃) δ 169.1 (2C), 142.9, 136.4, 130.2, 129.2 (2C), 126.6 (2C), 123.3, 61.4 (2C), 57.7, 44.7, 34.6, 21.2, 17.7, 13.7 (2C); **

**IR νmax (film)/cm⁻¹: 3282, 2983, 2938, 2360, 1732, 1599, 1446, 1369, 1334, 1304, 1221, 1164, 1093, 1041; HRMS (ESI) m/z calculated for C₁₉H₂₈NO₆S ([M⁺]) 398.1632, 398.1620 found.**

To a suspension of sodium hydride (0.32 g, 13.4 mmol, 60% dispersion in mineral oil) in **THF (20 mL)** was slowly added a solution of sulfonamide **S5 (2.1 g, 5.4 mmol)** in **THF (30 mL)**. The mixture was stirred for 30 min before benzylchloroformate (2.3 g, 13.4 mmol) was added. The suspension was stirred over night and then quenched by addition of sat. **NH₄Cl**. After dilution with **EtOAc**, the phases were separated and the aqueous phase was extracted three times with **EtOAc**. The combined organic phases were washed with brine and dried over **MgSO₄**. The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 10:1 → 2:1) to give the product (1.9 g, 3.5 mmo, 65%).

**Rf 0.69 (3:2 hexane/EtOAc); **

**¹H NMR (300 MHz, CDCl₃) δ 7.61 (d, J = 8.4 Hz, 2H), 7.27-7.20 (m, 3H), 7.10-7.05 (m, 4H), 5.50-5.45 (m, 2H), 4.96 (s, 2H), 4.53 (s, 2H), 4.17-4.01 (m, 4H), 2.66 (d, J = 5.2 Hz, 2H), 2.31 (s, 3H), 1.56-1.55 (m, 3H), 1.18 (t, J = 7.1 Hz, 3H); **

**¹³C NMR (75 MHz, CDCl₃) δ 169.6, 152.5, 144.3, 136.3, 134.1, 129.6, 129.1, 128.3, 128.3, 128.1, 124.7, 69.2, 61.4, 58.0, 48.6, 35.0, 21.6, 18.1, 14.0, 13.9; **

**IR νmax (film)/cm⁻¹: 2982, 2983, 2938, 2360, 1732, 1597, 1446, 1359, 1275, 1173, 1088, 1031; HRMS (ESI) m/z calculated for C₂₇H₃₄NO₈S ([M+H]^+) 532.2000, 532.1997 found.**

To a solution of this compound (1 g, 1.9 mmol) in **MeOH (80 mL)** were added magnesium turnings (460 mg, 18.9 mmol). The mixture was sonicated in an ultrasound bath for 16 h. The solvent was evaporated and the crude product was subjected to flash column chromatography (hexanes/EtOAc 20:1) to give the benzyl carbamate product **S6 (210 mg, 0.6 mmol, 32%)**.

**¹H NMR (300 MHz, CDCl₃) δ 7.38-7.30 (m, 5H), 5.58-5.51 (m, 1H), 5.29-5.24 (m, 2H), 3.69-3.63 (m, 8H), 2.69 (d, J = 7.1 Hz, 2H), 1.64 (d, J = 6.1 Hz, 3H).**
To a solution of the benzyl carbamate S6 (360 mg, 1.0 mmol) in CH₂Cl₂ (10 mL) was added m-CPBA (693 mg, 3.1 mmol, 77% purity). After 5.5 h, the reaction was quenched by the addition of sat. Na₂S₂O₅ followed by sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 10:1) to give epoxide 181 (327 mg, 0.9 mmol, 87%).

Rₚ 0.29 (2:1, hexane/EtOAc); ᵃ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.28 (m, 5H), 5.40 (bs, 1H), 5.08 (s, 2H), 3.96-3.91 (m, 1H), 3.75-3.69 (m, 7H), 2.77-2.70 (m, 2H), 2.33 (dd, J = 14.8, 3.6 Hz, 1H), 1.98-1.92 (m, 1H), 1.28 (d, J = 5.2 Hz, 3H); ᵃ¹³C NMR (100 MHz, CDCl₃) δ 170.8 (2C), 156.6, 136.3, 128.5 (2C), 128.2 (3C), 67.7, 67.0, 58.3, 52.7 (2C), 43.1, 33.4, 27.8, 23.5; IR νmax (film)/cm⁻¹: 3390, 3066, 2957, 2360, 1771, 1738, 1538, 1520, 1456, 1436, 1254, 1150, 1013; HRMS (ESI) m/z calculated for C₁₈H₂₄NO₇ ([M+H⁺]⁺) 366.1547, 366.1548 found.

A flask containing 181 (100 mg, 0.27 mmol) was evacuated and purged with argon. The substrate was dissolved in freshly distilled THF (35 mL) and Cp₂TiCl (1.4 mL, 0.28 mmol, ca. 0.2M) was slowly added over 6 h. The reaction was allowed to stir overnight before the solvent was removed. The residue was directly subjected to flash column chromatography (hexane/EtOAc 10:1 → 0:1) to provide a mixture of 182 (14 mg, 0.04 mmol, 15 %) and 183 (7 mg, 0.02 mmol, 7%).

182: ᵃ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.32 (m, 13H), 5.40 (bs, 1H), 5.29 (b, 1H), 5.16-5.09 (m, 6H), 4.53 (b, 1H), 4.12 (b, 1H), 3.83-3.71 (m, 20H), 2.52-2.47 (m, 2H), 2.36 (b, 1H), 2.14-2.06 (m, 2H), 2.00-1.92 (m, 2H), 1.68-1.64 (m, 3H), 1.48-1.40 (m, 3H), 1.30-1.19 (m, 9H); ᵃ¹³C NMR (100 MHz, CDCl₃) δ 170.8 (2C), 156.6, 136.3, 128.5 (2C), 128.2 (3C), 67.7, 67.0, 58.3, 52.7 (2C), 43.1, 33.4, 27.8, 23.5; IR νmax (film)/cm⁻¹: 3390, 3066, 2957, 2360, 1771, 1738, 1538, 1520, 1456, 1436, 1254, 1150, 1013; HRMS (ESI) m/z calculated for C₁₈H₂₆NO₇ ([M+H⁺]⁺) 368.1704, 368,1705 found.

DBU (4.9 ml, 32.2 mmol) and paraformaldehyde (1.0 g, 32.3 mmol) were added to a solution of alkylated malonate from above (1.4 g, 6.5 mmol) in THF (40 ml) and the mixture was stirred for 30
The solvent was removed and the crude product was purified by flash column chromatography (hexane/EtOAc 10:1 → 3:2) to give alcohol S7 (1.0 g, 3.9 mmol, 61%).

R_f 0.26 (4:1, hexane/EtOAc); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.64-5.51 (m, 1H), 5.38-5.27 (m, 1H), 4.23 (q, \(J = 7.1\) Hz, 1H), 3.94-3.90 (m, 2H), 2.71-2.56 (m, 3H), 1.65 (d, \(J = 6.3\) Hz, 1H), 1.27 (t, \(J = 7.1\) Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.2 (2C), 129.6, 124.2, 63.9, 61.1 (2C), 59.4, 34.4, 17.8, 13.8 (2C); \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1}\): 3522, 2983, 2940, 1732, 1465, 1446, 1368, 1300, 1300, 1215, 1095, 1036; HRMS (ESI) \(m/z\) calculated for C\(_{12}\)H\(_{20}\)NaO\(_5\) ([M+Na\(^{+}\)]\(^+\)) 267.1203, 267.1204 found.

To a solution of alcohol S7 (1.0 g, 3.9 mmol) in CH\(_2\)Cl\(_2\) (30 mL) was added \(m\)-CPBA (1.3 g, 5.9 mmol, 77% purity). After 3 h, the reaction was quenched by the addition of sat. Na\(_2\)S\(_2\)O\(_3\) followed by sat. NaHCO\(_3\). The phases were separated and the aqueous phase was extracted three times with CH\(_2\)Cl\(_2\). The combined organic phases were washed with brine and dried over MgSO\(_4\). The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 5:1 → 0:1) to give epoxide 184 (223 mg, 0.9 mmol, 22%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.26-4.19 (m, 4H), 4.13-4.05 (m, 2H), 3.09-2.78 (m, 3H), 2.38-2.32 (m, 1H), 2.05-1.95 (m, 1H), 1.30-1.22 (m, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 170.1 (2C), 64.3, 61.6 (2C), 58.5, 55.7, 55.0, 34.2, 17.2, 13.9 (2C); \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1}\): 3516, 2986, 1732, 1467, 1447, 1368, 1300, 1221, 1097, 1034; HRMS (ESI) \(m/z\) calculated for C\(_{12}\)H\(_{21}\)O\(_6\) ([M+H\(^{+}\)]\(^+\)) 261.1333, 261.1327 found.

A flask containing 184 (100 mg, 0.38 mmol) was evacuated and purged with argon. The substrate was dissolved in freshly distilled THF (35 mL) and Cp\(_2\)TiCl (3.5 mL, 0.7 mmol, ca. 0.2M) was slowly added over 6 h. The mixture was stirred overnight and the solvent was removed. The residue was directly subjected to flash column chromatography (hexane/EtOAc 10:1 → 0:1) to provide 185 (12 mg, 0.05 mmol, 12%).

R_f 0.18 (2:3 hexane/EtOAc); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.25 (q, \(J = 7.1\) Hz, 4H), 3.97 (s, 2H), 3.83-3.79 (m, 1H), 2.95 (bs, 1H), 2.15-2.07 (m, 1H), 2.02-1.94 (m, 1H), 1.82 (bs, 1H) 1.51-1.44 (m, 2H), 1.29 (t, \(J = 7.1\) Hz, 2H), 1.22 (d, \(J = 6.2\) Hz, 1H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 171.0, 116.7, 68.0, 64.3, 61.6, 61.5, 59.3, 33.6, 27.3, 23.4, 14.0; \(\nu_{\text{max}}(\text{film})/\text{cm}^{-1}\): 3392, 2978, 1728, 1448, 1369, 1218, 1096, 1033; HRMS (ESI) \(m/z\) calculated for C\(_{12}\)H\(_{23}\)O\(_6\) ([M+H\(^{+}\)]\(^+\)) 263.1489, 263.1475 found.
To a degassed suspension of potassium tert-butoxide (458 mg, 4.1 mmol) in cyclohexene (10 mL) was added n-BuLi (2.7 mL, 4.3 mmol, 1.6M in hexanes). The reaction was stirred at ambient temperature over night and then cooled to 0 °C. Paraformaldehyde (135 mg, 4.5 mmol) was added carefully and the mixture was heated to 60 °C for 3 h. After cooling back to 0 °C, the reaction was quenched by addition of sat. NaHCO₃. The mixture was diluted with CH₂Cl₂ and the phases were separated. The aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 10:1 → 0:1) to give alcohol S8 (483 mg, 3.79 mmol, 83%).

$^1$H NMR (300 MHz, CDCl₃) δ 5.86-5.79 (m, 1H), 5.62-5.56 (m, 1H), 3.55 (t, J = 4.9, 2H), 2.34-2.28 (m, 1H), 2.01-1.97 (m, 2H), 1.83-1.71 (m, 2H), 1.63-1.49 (m, 2H), 1.46-1.34 (m, 2H).

To a solution of S8 (2.7 g, 24.1 mmol) in CH₂Cl₂ (30 mL) was added TBDPSCI (7.4 mL, 28.9 mmol), triethylamine (5.1 mL, 36.1 mmol) and DMAP (cat.). The mixture was stirred over night. The solvent was evaporated and the crude product was subjected to flash column chromatography (hexanes/CH₂Cl₂ 20:1 → 10:1) to give the silyl ether product (7.9 g, 22.6 mmol, 94%).

$^1$H NMR (300 MHz, CDCl₃) δ 7.77-7.66 (m, 6H), 7.48-7.26 (m, 9H), 5.76-5.71 (m, 1H), 5.65-5.61 (m, 1H), 3.58-3.47 (m, 2H), 2.37 (m, 1H), 1.99-1.95 (m, 2H), 1.81-1.65 (m, 2H), 1.59-1.26 (m, 5H), 1.06 (s, 9H).

To a solution of this silyl ether (3.8 g, 10.8 mmol) in CH₂Cl₂ (70 mL) was added m-CPBA (4.8 g, 21 mmol, 77% purity). After 3 h, the reaction was quenched by the addition of sat. Na₂S₂O₃ followed by sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 2:1 → 0:1) to give epoxide diastereomer S9 (830 mg, 2.3 mmol, 21%).

$^{13}$C NMR (100 MHz, CDCl₃) δ 135.7, 135.6, 133.7, 129.8, 129.7, 127.8, 66.2, 54.4, 52.7, 37.3, 26.9, 25.0, 23.9, 19.4, 17.1; HRMS (EI+) m/z calculated for C₁₉H₂₁O₂Si ([M-C₄H₉]+) 309.1306, 309.1309 found.
To a solution of S9 (830 mg, 2.3 mmol) in THF (15 mL) was added TBAF (2.7 mL, 2.7 mmol, 1M in THF). The mixture was stirred over night. The solvent was removed and the crude product was purified by flash column chromatography (hexane/EtOAc 2:1) to give 186 (239 mg, 1.87 mmol, 82%).

**Rf 0.41 (1:3 hexane/EtOAc)**; **1H NMR** (300 MHz, CDCl₃) δ 3.77-3.60 (m, 2H), 3.25-3.17 (m, 1H), 3.10 (d, J = 3.9 Hz, 1H), 2.13-1.99 (m, 2H), 1.88-1.50 (m, 4H), 1.44-1.23 (m, 2H), 1.02-0.89 (m, 1H); **13C NMR** (75 MHz, CDCl₃) δ 64.7, 54.1, 52.7, 37.2, 24.6, 23.6, 16.9; **IR νmax(film)/cm⁻¹: 3409, 2937, 1652, 1445, 1353, 1269, 1126, 1087, 1069, 1049, 1022, 995; HRMS (EI+) m/z calculated for C₇H₁₁O₂ ([M-H]⁺) 127.0754, 127.0754 found.

A flask containing 186 (239 mg, 1.9 mmol) was evacuated and purged with argon. The substrate was dissolved in freshly distilled THF (35 mL) and Cp₂TiCl (9 mL, 1.8 mmol, ca. 0.2M) was slowly added over 6 h. The mixture was stirred over night and the solvent was removed. The residue was directly subjected to flash column chromatography (CH₂Cl₂/MeOH 1:0 → 10:1) to provide 187 (176 mg, 1.4 mmol, 73 %) along with regioisomer 188 (18 mg, 0.1 mmol, 7%).

**187**: **Rf 0.40 (10:1 DCM/MeOH)**; **1H NMR** (400 MHz, CD₃OD) δ 4.04-4.01 (m, 1H), 3.41-3.35 (m, 2H), 1.94-1.87 (m, 1H), 1.77-1.64 (m, 4H), 1.55-1.47 (m, 2H), 1.29 (ddd, J = 13.7, 11.0, 2.8 Hz, 1H), 1.11-1.05 (m, 1H); **13C NMR** (100 MHz, CD₃OD) δ 68.0, 67.0, 36.6, 35.4, 33.8, 29.6, 20.6; **IR νmax(film)/cm⁻¹: 3448, 2934, 2360, 1630, 1450, 1400, 1257, 1126, 1086, 1015, 981; HRMS (EI+) m/z calculated for C₇H₁₂O₂ ([M-H₂O]⁺) 112.0883, 112.0882 found.

**188**: **1H NMR** (400 MHz, CD₃OD) δ 3.76-3.72 (m, 1H), 3.58-3.54 (m, 1H), 3.39-3.36 (m, 2H), 1.96-1.92 (m, 1H), 1.84-1.68 (m, 4H), 1.49-1.37 (m, 2H), 1.32-1.18 (m, 2H), 1.11-1.01 (m, 3H); **13C NMR** (101 MHz, CD₃OD) δ 73.7, 66.2, 48.1, 36.4, 28.9, 26.4, 25.8; **IR νmax(film)/cm⁻¹: 3340, 2937, 2864, 1448, 1347, 1296, 1262, 1144, 1088, 1026, 991; HRMS (EI+) m/z calculated for C₇H₁₄O₂ ([M-H₂O]⁺) 112.0883, 112.0883 found.
To a suspension of sodium hydride (824 mg, 2.6 mmol, 60% dispersion in mineral oil) in THF (75 mL) was slowly added diethyl malonate (4.7 mL, 31.2 mmol). After 10 min, 3-bromocyclohexene (3.6 mL, 31.2 mmol) was added to this solution and the mixture was stirred overnight. The reaction was quenched by the addition of sat. NH₄Cl and the mixture was diluted with Et₂O. The phases were separated and the aqueous phase was extracted three times with Et₂O. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 20:1) to give the malonate intermediate (5.0 g, 20.7 mmol, 42%).

**¹H NMR** (300 MHz, CDCl₃) δ 5.80-5.73 (m, 1H), 5.54 (dd, J = 10.2, 2.4 Hz, 1H), 3.24 (d, J = 9.4 Hz, 1H), 2.94-2.85 (m, 1H), 2.02-1.95 (m, 2H), 1.84-1.67 (m, 2H), 1.62-1.50 (m, 1H), 1.44-1.33 (m, 1H).

To a solution of this intermediate (5.0 g, 20.7 mmol) in DMSO (150 mL) was added water (1.5 mL, 83 mmol) and lithium chloride (1.9 g, 45.4 mmol). The mixture was heated to 160°C for 2 days. The reaction was cooled to ambient temperature and diluted with water and EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with water and brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 10:1) to give S10 (1.8 g, 10.6 mmol, 51%).

**R₉** 0.44 (10:1 hexane/EtOAc); **¹H NMR** (300 MHz, CDCl₃) δ 5.75-5.68 (m, 1H), 5.56-5.52 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.66-2.54 (m, 1H), 2.35-2.20 (m, 2H), 2.01-1.94 (m, 2H), 1.87-1.65 (m, 2H), 1.62-1.49 (m, 2H), 1.26 (t, J = 7.1 Hz, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 172.8, 130.1, 128.0, 60.2, 40.8, 32.2, 28.8, 25.0, 21.0, 14.3; **IR** ν_max (film)/cm⁻¹: 3020, 2982, 2931, 2863, 1738, 1448, 1371, 1336, 1279, 1255, 1209, 1161, 1134, 1096; **HRMS** (ESI) ml/z calculated for C₁₀H₁₆O₂Na ([M+Na]^⁺) 191.1043, 191,1042 found.

To a solution of S10 (1.8 g, 10.6 mmol) in THF (20 mL) was added a solution of LiAlH₄ (5.3 mL, 21.2 mmol, 4M in Et₂O) in THF (40 mL). The reaction was allowed to stir at ambient temperature for 20 min before water was added followed by 1M HCl. The mixture was diluted with Et₂O and the phases were separated. The aqueous phase was extracted three times with Et₂O. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 5:1 → 3:1) to give the corresponding alcohol (1.3 g, 10.5 mmol, 99%).
**Experimental Part**

**R**f 0.31 (3:1 hexane/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 5.71-5.66 (m, 1H), 5.60-5.56 (m, 1H), 3.73, (t, J = 5.9 Hz, 1H), 2.27-2.21 (m, 1H), 2.01-1.94 (m, 2H), 1.83-1.49 (m, 6H), 1.31-1.21 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 131.4, 126.9, 60.3, 39.0, 31.8, 29.0, 25.3, 21.4; **IR** νmax(film)/cm⁻¹: 3326, 3017, 2928, 2859, 2360, 1648, 1447, 1139, 1067, 1050, 1010; **HRMS** (EI⁺) m/z calculated for C₈H₁₄O ([M⁺]⁺) 126.1039, 126.1038 found.

To a solution of this alcohol (1.4 g, 11.4 mmol) in CH₂Cl₂ (30 mL) was added m-CPBA (5.1 g, 22.8 mmol, 77% purity). After 3 h, the reaction was quenched by the addition of sat. Na₂S₂O₃ followed by sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexane/EtOAc 4:1 → 2:1) to give epoxide **192** (116 mg, 0.8 mmol, 7%) along with diastereomer **189** (803 mg, 5.7 mmol, 50%).

**192**: Rf 0.18 (1:1 DCM/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 4.02-3.83 (m, 2H), 3.69-3.62 (m, 2H), 2.40 (m, 1H), 1.92-1.32 (m, 9H); **¹³C NMR** (75 MHz, CDCl₃) δ 83.2, 69.3, 66.2, 37.2, 30.2, 29.8, 25.7, 19.0; **IR** νmax(film)/cm⁻¹: 3418, 2933, 2876, 1721, 1455, 1260, 1144, 1084, 1034; **HRMS** (EI⁺) m/z calculated for C₈H₁₄O₂ ([M⁺]⁺) 142.0989, 142.0988 found.

**189**: Rf 0.25 (1:1 DCM/EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 3.86-3.72 (m, 2H), 3.22 (t, J = 4.1 Hz, 1H), 3.14-3.11 (m, 1H), 2.15 (m, 1H), 1.95-1.13 (m, 9H); **HRMS** (EI⁺) m/z calculated for C₈H₁₄O₂ ([M⁺]⁺) 142.0989, 142.0991 found.

A flask containing **189** (205 mg, 1.4 mmol) was evacuated and purged with argon. The substrate was dissolved in freshly distilled THF (35 mL) and Cp₂TiCl (7.2 mL, 1.4 mmol, ca. 0.2M) was slowly added over 6 h. The mixture was stirred over night and the solvent was removed. The residue was directly subjected to flash column chromatography (hexane/EtOAc 4:1 → 0:1) to provide **190** (124 mg, 0.9 mmol, 60 %) along with regioisomer **191** (70 mg, 0.5 mmol, 34%).

**190**: Rf 0.21 (EtOAc); ¹H NMR (400 MHz, CD₂OD) δ 3.62 (t, J = 6.5 Hz, 2H), 3.55-3.48 (m, 1H), 3.34-3.32 (m, 1H), 2.18-2.10 (m, 2H), 2.01-1.92 (m, 1H), 1.80-1.67 (m, 2H), 1.56-1.42 (m, 3H), 1.31 (qt, J = 13.2, 3.6 Hz, 1H), 0.93-0.77 (m, 2H); **¹³C NMR** (100 MHz, CD₂OD) δ 71.3, 60.6, 43.2, 40.7, 36.3, 34.1, 33.2, 25.1; **IR** νmax(film)/cm⁻¹: 3515, 2935, 2856, 1626, 1464, 1451, 1403, 1367, 1099, 1042, 1008.
An oven dried flask was evacuated and purged with argon. Bis(cyclopentadienyl)titanium dichloride (310 mg, 1.25 mmol) and activated zinc powder (111 mg, 1.70 mmol) were added and the flask was evacuated again. After 5 min the flask was purged with argon. Freshly distilled THF (20 mL) was added. The mixture was stirred for 1 h to give a dark green solution of bis(cyclopentadienyl)titanium chloride.

A flask containing epoxide 156 (98 mg, 0.19 mmol) was evacuated and purged with argon. The substrate was dissolved in freshly distilled THF (4 mL) and the freshly prepared solution of bis(cyclopentadienyl) titanium chloride (8 mL, 0.50 mmol) was added slowly over a period of 10 min. After 2 h more bis(cyclopentadienyl) titanium chloride (5 mL) was added. After another 2 h the solvent was evaporated under reduced pressure and the residue was subjected to flash column chromatography (CH$_2$Cl$_2$ → CH$_2$Cl$_2$/MeOH 20:1) to give alcohol 203 (85 mg, 0.16 mmol, 86% brsm) with complete epimerization at C(2).

To a stirred solution of alcohol 203 (100 mg, 0.19 mmol) in CH$_2$Cl$_2$ (4 mL) was added triethylamine (0.22 mL, 1.53 mmol), acetic anhydride (90 µL, 0.96 mmol) and DMAP (cat.). The mixture was
stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure and the
residue was coevaporated three times with toluene (3 mL). The residue was subjected to flash column
chromatography (CH$_2$Cl$_2$/MeOH 40:1) to give acetate 204 (106 mg, 0.19 mmol, 98%).

R$_f$ 0.36 (9:1, CH$_2$Cl$_2$/MeOH); [α]$_b$$_{21}^{21}$ -6.45 (c 0.93, CHCl$_3$); $^1$H-NMR (300 MHz, d$_6$-DMSO, 100 °C,
mixture of diastereomers at C(2), all peaks reported): δ 7.41 (bs-s, 1H, NH), 7.37-7.27 (m, 5H), 6.87
(bs-d, J = 7.2 Hz, 1H, NH), 6.28 (bs-s, 1H, NH), 5.10-5.00 (m, 2H), 4.61 (ddd, J = 13.8, 7.0, 2.6 Hz,
1H), 4.43 (d, J = 13.9 Hz, 1H), 4.33 (d, J = 5.9 Hz, 1H), 4.27-4.18 (m, 1H), 4.10 (d, J = 5.6 Hz, 1H),
3.11-3.03 (m, 2H), 2.97-2.91 (m, 2H), 2.23-2.19 (m, 2H), 1.92 (dd, J = 14.4, 4.4 Hz, 1H), 1.84-1.65
(m, 2H), 1.61-1.57 (m, 1H), 1.43-1.37 (m, 13H); $^{13}$C-NMR (75 MHz, d$_6$-DMSO, 100 °C, mixture of
diastereomers at C(2), all peaks reported): δ 171.1, 171.0, 169.2, 154.9, 136.5, 127.5 (2C), 127.0,
126.9, 126.8, 126.8, 82.9, 78.7, 77.6, 77.2, 76.9, 74.9, 65.0, 51.9, 32.9, 32.7, 27.9 (3C), 26.5, 25.9,
20.2; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3330, 2976, 2934, 1713, 1657, 1526, 1456, 1392, 1366, 1248, 1170,
1107, 1043; HRMS (ESI) m/z calculated for C$_{28}$H$_{41}$O$_9$N$_3$Na ([M+Na]$^+$) 586.2735, found 586.2735.

To a stirred solution of alcohol 158a (260 mg, 0.39 mmol) in CH$_2$Cl$_2$ (3 mL) was added triethylamine
(0.22 mL, 1.57 mmol), acetic anhydride (56 μL, 0.59 mmol) and DMAP (cat.). The mixture was
stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure and the
residue was coevaporated three times with toluene (3 mL). The residue was subjected to flash column
chromatography (CH$_2$Cl$_2$/MeOH 40:1) to give acetate 210 (275 mg, 0.39 mmol, 99%).

R$_f$ 0.61 (9:1, CH$_2$Cl$_2$/MeOH); [α]$_b$$_{22}^{22}$ -2.90 (c 0.75, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$, 3:1 mixture
of diastereomers at C(2), major diastereomer reported): δ 7.68-7.62 (m, 4H), 7.46-7.29 (m, 11H), 6.51
(bs-s, 1H, NH), 6.05 (d, J = 7.4 Hz, 1H, NH), 5.10 (s, 2H), 4.65 (dd, J = 7.0, 2.1 Hz, 1H), 4.48 (d, J =
6.3 Hz, 1H), 4.39-4.25 (m, 2H), 3.68-3.63 (m, 2H), 3.26-3.15 (m, 2H), 2.92 (bs, 1H, OH), 2.23-2.03
(m, 6H), 1.80 (dd, J = 14.5, 7.1 Hz, 1H), 1.64-1.52 (m, 5H), 1.43 (d, J = 13.9 Hz, 1H), 1.05 (s, 9H);
$^{13}$C-NMR (100 MHz, CDCl$_3$, 3:1 mixture of diastereomers at C(2), major diastereomer reported): δ
171.4, 170.8, 156.1, 136.0, 135.4 (4C), 133.7, 129.5 (2C), 128.4 (2C), 128.2 (2C), 128.0 (2C), 127.6
(4C), 83.4, 79.8, 79.3, 75.2, 67.0, 63.3, 52.2, 42.8, 39.4, 37.7, 32.7, 29.7, 26.8 (3C), 25.8, 21.0, 19.1;
IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3314, 2972, 2959, 1731, 1657, 1538, 1428, 1360, 1244, 1111; HRMS (ESI) m/z
calculated for C$_{36}$H$_{51}$O$_9$N$_3$Si ([M+H]$^+$) 703.3409, found 703.3433.
To a stirred solution of alcohol 210 (290 mg, 0.43 mmol) in CH$_2$Cl$_2$ (3 mL) was added triethylamine (0.17 mL, 1.24 mmol), 3-(trifluoromethyl)benzoyl chloride 211 (92 µL, 0.62 mmol) and DMAP (cat.). The mixture was stirred at ambient temperature for 2 h. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 40:1) to give benzoate 209 (330 mg, 0.38 mmol, 91%).

R$_f$ 0.35 (20:1, CH$_2$Cl$_2$/MeOH); [α]$_D$$^{22.0}$ -7.74 (c 0.75, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$, 3:1 mixture of diastereomers at C(2), major diastereomer reported): δ 8.28-8.23 (m, 1H), 8.16 (d, $J$ = 7.9 Hz, 1H), 7.77 (d, $J$ = 7.7 Hz, 1H), 7.66-7.61 (m, 4H), 7.54-7.48 (m, 1H), 7.45-7.33 (m, 6H), 7.30-7.25 (m, 3H), 7.17-7.11 (m, 2H), 5.93 (t, $J$ = 5.8 Hz, 1H, NH), 5.18 (d, $J$ = 8.4 Hz, 1H, NH), 5.02-4.92 (m, 2H), 4.77-4.65 (m, 2H), 4.56 (d, $J$ = 6.5 Hz, 1H), 4.20-4.11 (m, 1H), 3.66-3.58 (m, 2H), 3.20-3.14 (m, 2H), 1.80-1.70 (m, 2H), 1.56-1.44 (m, 4H), 1.04 (s, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$, 3:1 mixture of diastereomers at C(2), major diastereomer reported): δ 170.6, 170.3, 164.8, 155.6, 135.3 (4C), 133.6 (2C), 132.8 (2C), 131.2, 129.5 (3C), 128.9 (2C), 128.3 (2C), 128.1 (2C), 127.8 (2C), 127.5 (4C), 126.4, 89.1, 81.1, 79.7, 75.0, 67.1, 63.2, 52.3, 40.9, 39.6, 35.3, 33.6, 29.7, 26.9 (3C), 25.9, 21.1, 19.2; $^{19}$F-NMR (280 MHz, CDCl$_3$): δ -62.7 (3F); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3306, 2937, 2859, 1722, 1660, 1537, 1428, 1363, 1339, 1259, 1245, 1170, 1131, 1112, 1072; HRMS (ESI) m/z calculated for C$_{47}$H$_{54}$F$_3$O$_9$N$_2$Si ([M+H]$^+$) 875.3545, found 875.3562.

To a solution of benzoate 209 (300 mg, 0.34 mmol) in THF/H$_2$O (80 mL, 1:1) was added N-methylcarbazole (52 mg, 0.51 mmol) and 1,4-cyclohexadiene (3.21 mL, 34.3 mmol). The solution was partitioned into ten Pyrex test tubes (10 mL). The reaction mixture was degassed by bubbling argon through the solution for 15 min. The test tubes were capped with a septum and arranged around a UV lamp. After 12 h of UV irradiation the solvent was removed under reduced pressure and the residue
Experimental Part

was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 50:1) to give acetate 212 (160 mg, 0.23 mmol, 68%, 96% brsm) along with reisolated starting material 209 (87 mg, 0.10 mmol, 29%).

$R_f$ 0.29 (20:1, CH$_2$Cl$_2$/MeOH); $[\alpha]_{D}^{22.9\circ}$ -6.38 (c 0.65, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$, 3:1 mixture of diastereomers at C(2), major diastereomer reported): $\delta$ 7.68-7.69 (m, 4H), 7.46-7.35 (m, 6H), 4.69 (dd, $J = 7.2$, 2.7 Hz, 1H), 4.47(t, $J = 5.1$ Hz, 1H), 4.37 (d, $J = 6.1$ Hz, 1H), 3.71-3.66 (m, 2H), 3.22-3.13 (m, 3H), 2.29 (dd, $J = 7.3$, 13.8 Hz, 1H), 2.09-1.87 (m, 5H), 1.68-1.49 (m, 7H), 1.03 (s, 9H), 0.93 (dd, $J = 5.2$, 12.2 Hz, 1H); $^{13}$C-NMR (75 MHz, CDCl$_3$, 3:1 mixture of diastereomers at C(2), major diastereomer reported): $\delta$ 176.9, 172.2, 136.5 (4C), 134.8 (2C), 130.7 (2C), 128.6 (4C), 82.0, 79.5, 77.9, 64.6, 55.7, 40.3, 38.4, 38.0, 34.7, 33.1, 31.1, 27.4 (3C), 27.1, 21.1, 20.1; IR $\nu_{max}$ (film)/cm$^{-1}$: 3322, 2932, 2858, 1732, 1652, 1526, 1472, 1428, 1358, 1244, 1110, 1056; HRMS (ESI) m/z calculated for C$_{31}$H$_{45}$O$_7$N$_2$Si ([M+H]$^+$) 553.3092, found 553.3093.

A flask containing carbamate 212 (500 mg, 0.73 mmol) was evacuated and purged with argon. MeOH (10 mL) was added followed by palladium on activated carbon (50 mg, 10% wt Pd). The reaction flask was evacuated and purged with H$_2$ (1 atm, balloon). The reaction was stirred for 1 h. The mixture was filtered over Celite and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to give amine 215 (376 mg, 0.68 mmol, 93%).

$R_f$ 0.41 (9:1, CH$_2$Cl$_2$/MeOH); $[\alpha]_{D}^{23.9\circ}$ -11.52 (c 0.50, CHCl$_3$); $^1$H-NMR (300 MHz, CD$_2$OD, 3:1 mixture of diastereomers at C(2), major diastereomer reported): $\delta$ 7.68-7.69 (m, 4H), 7.46-7.35 (m, 6H), 4.69 (dd, $J = 7.2$, 2.7 Hz, 1H), 4.47(t, $J = 5.1$ Hz, 1H), 4.37 (d, $J = 6.1$ Hz, 1H), 3.71-3.66 (m, 2H), 3.22-3.13 (m, 3H), 2.29 (dd, $J = 7.3$, 13.8 Hz, 1H), 2.09-1.87 (m, 5H), 1.68-1.49 (m, 7H), 1.03 (s, 9H), 0.93 (dd, $J = 5.2$, 12.2 Hz, 1H); $^{13}$C-NMR (75 MHz, CD$_2$OD, 3:1 mixture of diastereomers at C(2), major diastereomer reported): $\delta$ 176.9, 172.2, 136.5 (4C), 134.8 (2C), 130.7 (2C), 128.6 (4C), 82.0, 79.5, 77.9, 64.6, 55.7, 40.3, 38.4, 38.0, 34.7, 33.1, 31.1, 27.4 (3C), 27.1, 21.1, 20.1; IR $\nu_{max}$ (film)/cm$^{-1}$: 3322, 2932, 2858, 1732, 1652, 1526, 1472, 1428, 1358, 1244, 1110, 1056; HRMS (ESI) m/z calculated for C$_{31}$H$_{45}$O$_7$N$_2$Si ([M+H]$^+$) 553.3092, found 553.3093.
To a stirred solution of amine 215 (100 mg, 0.18 mmol) in CH₂Cl₂ (10 mL) was added triethylamine (0.20 mL, 1.45 mmol) and freshly distilled TMSOTf (0.20 mL, 1.09 mmol). The reaction was stirred for 1h at ambient temperature and the solvent was removed under reduced pressure. The residue was purified by short flash column chromatography (hexanes/EtOAc /MeOH 40:20:1) to give the doubly TMS protected Choi core 216 (102 mg, 0.15 mmol, 81%).

A number of conditions were screened for removal of the TMS protecting groups (see Table 8 for details). Optimal conditions:

A solution of this bisTMS protected intermediate 216 (450 mg, 0.65 mmol) in acetonitril (18 mL) was divided into 18 eppendorf tubes (1.5 mL volume). A premixed solution of hexafluorosilic acid (293 µL, 0.65 mmol, 25% aqueous solution) and triethylamine (136 µL, 0.97 mmol) in acetonitril (1.8 mL) was divided into the eppendorf tubes. The mixture was stirred at ambient temperature for 30 min and then warmed to 65 °C for 12 h. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 20:1) to give amine 217 (62 mg, 0.11 mmol, 89% brsm) along with reisolated singly TMS protected starting material (325 mg, 0.52 mmol, 81%), which was resubjected to the reaction conditions.

Rᵣ 0.41 (9:1, CH₂Cl₂/MeOH); [α]ᵣ₂20ˌ -3.21 (c 0.70, CHCl₃); ¹H-NMR (400 MHz, CD₃OD): δ 7.69-7.66 (m, 4H), 7.48-7.39 (m, 6H), 5.09 (ddd, J = 10.6, 4.3, 2.4 Hz, 1H), 3.95-3.91 (m, 1H), 3.74-3.70 (m, 2H), 3.67 (dd, J = 10.8, 4.3 Hz, 1H), 3.47 (dd, J = 9.0, 4.7 Hz, 1H), 3.24-3.12 (m, 2H), 2.40-2.32 (m, 1H), 2.31-2.23 (m, 1H), 2.14-2.05 (m, 4H), 1.84-1.71 (m, 2H), 1.66-1.59 (m, 5H), 1.58-1.51 (m, 1H), 1.04 (s, 9H); ¹³C-NMR (100 MHz, CD₃OD): δ 178.2, 172.6, 136.6 (4C), 135.0 (2C), 130.8 (2C), 128.8 (4C), 73.0, 67.8, 64.6, 59.9, 58.6, 39.9, 36.7, 34.0, 33.9, 31.0, 29.1, 27.4 (3C), 27.2, 21.2, 20.0; IR νₘₐₓ (film)/cm⁻¹: 3334, 2932, 2858, 1738, 1657, 1652, 1525, 1472, 1428, 1371, 1246, 1112; HRMS (ESI) m/z calculated for C₃₁H₄₅O₅N₂Si ([M+H]⁺) 553.3092, found 553.3096.

After subjecting mono-TMS protected starting material to the reaction conditions again, 217 was obtained in a total yield of 81% after 3 rounds of deprotection.
Experimental Part

To a stirred solution of (S)-3-(p-benzzyloxyphenyl)lactic acid \( \text{219}^{710} \) (2.90 g, 10.65 mmol) in \( \text{CH}_2\text{Cl}_2/\text{MeOH} 3:1 \) (50 mL) at 0 °C was added (trimethylsilyl)diazomethane (8 mL, 15.98 mmol, 2.0M in \( \text{Et}_2\text{O} \)). The mixture was warmed to ambient temperature and stirred for 15 min. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/\( \text{EtOAc} 4:1 \)) to give \( \text{222} \) as a colorless crystalline solid (2.97 g, 10.37 mmol, 97%).

**R\(_f\)** 0.37 (2:1, hexanes/\( \text{EtOAc} \)); \([\alpha]_D^{23.6°} = -12.16 \) (c 2.00, \( \text{CHCl}_3 \)); \(^1\text{H-NMR}\) (300 MHz, \( \text{CDCl}_3 \)): \( \delta \) 7.45-7.32 (m, 5H), 7.13 (d, \( J = 9.0 \) Hz, 2H), 6.91 (d, \( J = 9.0 \) Hz, 2H), 5.04 (s, 2H), 4.43 (dt, \( J = 4.5, 6.4 \) Hz, 1H), 3.77 (s, 3H), 3.08 (dd, \( J = 4.4, 14.0 \) Hz, 1H), 2.92 (dd, \( J = 6.6, 14.0 \) Hz, 1H), 2.71 (d, \( J = 6.2 \) Hz, 1H); \(^{13}\text{C-NMR}\) (75 MHz, \( \text{CDCl}_3 \)): \( \delta \) 174.4, 157.7, 136.9, 130.4 (2C), 128.5 (3C), 127.8, 127.4 (2C), 114.7 (2C), 71.4, 70.0, 52.5, 39.8; \( \text{IR} \) \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 3035, 2905, 2865, 1732, 1612, 1583, 1514, 1454, 1380, 1217, 1112, 1092, 973; \text{HRMS} (ESI) \text{m/z} \text{calculated for } \text{C}_{17}\text{H}_{18}\text{O}_4\text{Na} ([\text{M+Na}]^+) 309.1097, \text{found } 309.1088.

To a stirred suspension of sodium hydride (30 mg, 1.26 mmol) in \( \text{THF} \) (5 mL) at 0 °C was added a solution of \( \text{222} \) (300 mg, 1.05 mmol) in \( \text{THF} \) (2 mL). The mixture was stirred at 0 °C for 15 min. Benzyl bromide (0.14 mL, 1.15 mmol) and tetrabutylammonium iodide (39 mg, 0.11 mmol) were added and the mixture was stirred at ambient temperature for 1.5 h. The reaction was quenched by addition of pH 6.8 buffer. The aqueous phase was extracted three times with \( \text{EtOAc} \). The combined organic phases were dried over \( \text{MgSO}_4 \) and concentrated under reduced pressure. The residue was subjected to flash column chromatography (hexanes/\( \text{EtOAc} 20:1 \) → 5:1) to give \( \text{223} \) as a colorless oil (165 mg, 0.44 mmol, 42%).

**R\(_f\)** 0.60 (2:1, hexanes/\( \text{EtOAc} \)); \([\alpha]_D^{21.2°} = -24.91 \) (c 1.50, \( \text{CHCl}_3 \)); \(^1\text{H-NMR}\) (300 MHz, \( \text{CDCl}_3 \)): \( \delta \) 7.50-7.17 (m, 12H), 6.98-6.93 (m, 2H), 5.09 (s, 2H), 4.72 (d, \( J = 11.9 \) Hz, 1H), 4.42 (d, \( J = 11.9 \) Hz, 1H), 4.16 (dd, \( J = 5.3, 7.8 \) Hz, 1H), 3.75 (s, 3H), 3.12-2.99 (m, 2H); \(^{13}\text{C-NMR}\) (75 MHz, \( \text{CDCl}_3 \)): \( \delta \) 172.3, 157.4, 137.1, 136.9, 130.3 (2C), 129.2, 128.4 (2C), 128.1 (2C), 127.8, 127.7 (2C), 127.6, 127.3 (2C), 114.6 (2C), 79.4, 72.5, 70.0, 52.0, 38.7; \( \text{IR} \) \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 3031, 2949, 1748, 1610, 1580, 1511, 1454, 1380, 1241, 1175, 1113, 1023; \text{HRMS} (ESI) \text{m/z} \text{calculated for } \text{C}_{24}\text{H}_{24}\text{O}_4\text{Na} ([\text{M+Na}]^+) 399.1572, \text{found } 399.1571.

To a stirred solution of 223 (530 mg, 1.41 mmol) in THF (10 mL) was added lithium hydroxide monohydrate (135 mg, 5.63 mmol) in water (2 mL). MeOH was added dropwise until the solution turned clear. The mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of pH 6.8 buffer (50 mL). The mixture was adjusted to pH 5 with 1N HCl. The aqueous phase was extracted three times with Et₂O. The combined organic phases were dried over MgSO₄ and the solvent was removed. The residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 20:1) to give 224 as a colorless oil (458 mg, 1.26 mmol, 90%).

Rf 0.25 (9:1, CH₂Cl₂/MeOH); [α]D²₃.6° -19.43 (c 0.50, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): δ 10.20 (bs, 1H), 7.47-7.26 (m, 8H), 7.21-7.15 (m, 4H), 6.94-6.89 (m, 2H), 5.06 (s, 2H), 4.66 (d, J = 11.7 Hz, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.16 (dd, J = 4.2, 8.1 Hz, 1H), 3.07 (ddd, J = 6.1, 14.2, 22.3 Hz, 2H);
¹³C-NMR (75 MHz, CDCl₃): δ 177.5, 157.8, 137.1, 136.9, 130.7 (2C), 129.1, 128.7 (2C), 128.5 (2C), 128.0 (4C), 127.6 (2C), 114.8 (2C), 78.8, 72.8, 70.1, 38.2; IR νₘₐₓ (film)/cm⁻¹: 3032, 2864, 1721, 1611, 1512, 1454, 1377, 1295, 1241, 1177, 1114, 1026; HRMS (ESI) m/z calculated for C₂₃H₂₁O₄ ([M-H]⁻) 361.1445, found 361.1447.

To a stirred solution of 224 (1.60 g, 4.41 mmol) in CH₂Cl₂ (70 mL) were added L-phenylalanine methylester (1.14 g, 5.30 mmol), EDC (1.02 g, 5.30 mmol), HOBT (0.72 g, 5.30 mmol), triethylamine (1.55 mL, 11.04 mmol) and DMAP (cat.). The mixture was stirred at ambient temperature over night. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give 225 as a white solid (1.26 g, 2.41 mmol, 55%).

An X-ray crystal structure of 225 could be obtained (see chapter 24).

Rf 0.48 (1:1, hexanes/EtOAc); [α]D²⁰.₇° 0.86 (c 0.75, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): δ 7.45-7.22 (m, 11H), 7.19-7.11 (m, 4H), 7.02 (d, J = 8.7 Hz, 1H, NH), 6.95-6.89 (m, 4H), 5.06 (s, 2H), 4.93 (dt, J = 5.8, 8.8 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.38 (d, J = 11.4 Hz, 1H), 4.04 (dd, J = 3.6, 7.4 Hz, 1H), 3.72 (s, 3H), 3.11-3.02 (m, 2H), 2.96 (dd, J = 5.6, 13.8 Hz, 1H), 2.84 (dd, J = 7.5, 14.2 Hz, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 171.4, 171.2, 157.5, 137.0, 136.8, 135.4, 130.8 (2C), 129.4, 129.1 (2C), 128.5 (4C), 128.3 (2C), 127.8 (2C), 127.3 (2C), 127.0, 114.5 (2C), 80.7, 72.8, 70.0,
52.3, 52.2, 38.1, 38.1; \textbf{IR} \nu_{\text{max}} \text{(film)/cm}^{-1}: 3030, 2937, 1743, 1677, 1610, 1510, 1454, 1241, 1177, 1079, 1025; \textbf{HRMS \ (ESI)} \ m/z \text{ calculated for } C_{13}H_{14}O_{5}N \ ([M+H]^+) 524.2431, \text{ found 524.2435.}

\begin{center}
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\end{center}

To a stirred solution of dipeptide 225 (1.08 g, 2.06 mmol) in THF (30 mL) was added lithium hydroxide monohydrate (0.36 g, 8.25 mmol) in water (15 mL). MeOH was added dropwise until the solution turned clear. The mixture was stirred at ambient temperature for 30 min. The reaction was quenched by addition of pH 6.8 buffer (50 mL). The pH of the solution was adjusted to pH 5 with 1N HCl. The aqueous phase was extracted three times with Et₂O. The combined organic layers were dried over MgSO₄ and the solvent was removed. The crude product 218 was obtained as a colorless foam and did not require further purification (1.01 g, 1.98 mmol, 96%).

\textbf{R}_{f} 0.39 (9:1, CH₂Cl₂/MeOH); \ [\alpha]_D^{22.2} -4.63 \ (c \ 0.35, \ CHCl₃); \ ^1\text{H-NMR} (300 MHz, CDCl₃): \ \delta \ 11.36 \ (bs, 1H), 7.43-7.30 \ (m, 5H), 7.25-7.20 \ (m, 6H), 7.13-7.04 \ (m, 5H), 6.99-6.93 \ (m, 2H), 6.90-6.87 \ (m, 2H), 5.03 \ (s, 2H), 4.86 \ (dt, \ J = 8.4, 6.0 \ Hz, 1H), 4.43 \ (d, \ J = 11.4 \ Hz, 1H), 4.33 \ (d, \ J = 11.4 \ Hz, 1H), 4.02 \ (dd, \ J = 7.4, 3.6 \ Hz, 1H), 3.12-2.96 \ (m, 3H), 2.79 \ (dd, \ J = 14.2, 7.3 \ Hz, 1H); \ ^{13}\text{C-NMR} (75 MHz, CDCl₃): \ \delta \ 174.0, 172.5, 157.6, 136.9, 136.6, 135.3, 130.7 \ (2C), 129.2 \ (2C), 129.1, 128.4 \ (4C), 128.2 \ (2C), 127.9 \ (2C), 127.8 \ (2C), 127.3 \ (2C), 127.0, 114.5 \ (2C), 80.4, 72.7, 69.8, 52.1, 37.9, 37.4; \ \textbf{IR} \ \nu_{\text{max}} \text{(film)/cm}^{-1}: 3031, 2926, 1773, 1738, 1674, 1633, 1511, 1454, 1383, 1351, 1241, 1217, 1174, 1113, 1087, 1026; \textbf{HRMS \ (ESI)} \ m/z \text{ calculated for } C_{32}H_{32}O_{5}N \ ([M+H]^+) 510.2280, \text{ found 510.2284.}

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To a stirred solution of amine 217 (290 mg, 0.53 mmol) and acid 218 (294 mg, 0.58 mmol) in CH₂Cl₂ (3 mL) was added diisopropylethylamine (0.11 mL, 0.63 mmol) and HATU (239 mg, 0.63 mmol). The mixture was stirred at ambient temperature for 12 h. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 100:1) to give compound 228 (420 mg, 0.40 mmol, 77%).
**R**f 0.44 (9:1, CH$_2$Cl$_2$/MeOH); [**α**]$_D^{24.8}$ -34.20 (c 0.20, CHCl$_3$); **^1H-NMR** (600 MHz, CDCl$_3$, mixture of rotamers): δ 7.66-7.63 (m, 4H), 7.43-7.33 (m, 6H), 7.32-7.21 (m, 12H), 7.20-7.12 (m, 3H), 7.10-7.08 (m, 1H), 7.06-7.04 (m, 1H), 7.01-6.99 (m, 1H), 6.89-6.86 (m, 1H), 6.77-6.74 (m, 1H, NH), 5.09-5.02 (m, 2H), 4.99-4.97 (m, 1H), 4.75-4.71 (m, 1H), 4.50-4.44 (m, 2H), 4.38-4.33 (m, 2H), 3.98-3.92 (2H), 3.70-3.66 (m, 2H), 3.32-3.27 (m, 1H), 3.18-3.13 (m, 1H), 3.00 (dd, $J = 14.0$, 3.5 Hz, 1H), 2.97 (dd, $J = 12.7$, 7.6 Hz, 1H), 2.78 (dd, $J = 7.8$, 14.2 Hz, 1H), 2.66 (dd, $J = 6.0$, 13.2 Hz, 1H), 2.42-2.38 (m, 2H), 2.20-2.18 (m, 2H), 2.13-2.11 (m, 1H), 2.04-2.00 (m, 1H), 1.95-1.90 (m, 2H), 1.62-1.52 (m, 4H), 1.41-1.36 (m, 1H), 1.30-1.24 (m, 1H), 1.04 (m, 9H); **^13C-NMR** (150 MHz, CDCl$_3$, mixture rotamers, major peaks reported): δ 171.5, 171.4, 171.0, 170.0, 157.7, 137.0, 136.7, 136.5 (4C), 135.9 (2C), 130.6 (2C), 129.6 (3C), 129.2 (2C), 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.1 (2C), 128.0, 127.9, 127.6 (4C), 127.4 (2C), 127.3, 114.6 (2C), 80.7, 72.9, 72.5, 70.0, 65.9, 63.5, 59.4, 54.9, 51.5, 39.6, 39.3, 38.2, 37.4, 30.0, 29.7, 28.8, 28.6, 26.9 (3C), 26.0, 21.2, 19.2; **IR** $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2927, 2852, 1732, 1664, 1652, 1641, 1638, 1510, 1453, 1427, 1374, 1239, 1112; **HRMS** (ESI) $m/z$ calculated for C$_{63}$H$_{73}$O$_9$N$_3$SiNa ([M+Na$^+$]+) 1066.5008, found 1066.5000.

To a stirred solution of alcohol 228 (420 mg, 0.40 mmol) in CH$_2$Cl$_2$ (10 mL) was added triethylamine (0.17 mL, 1.21 mmol), 3-(trifluoromethyl)benzoyl chloride 211 (89 $\mu$L, 0.60 mmol) and DMAP (cat.). The mixture was stirred at ambient temperature for 30 min. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 100:1) to give benzoate 229 (290 mg, 0.24 mmol, 59%; 45% over 2 steps).

**R**f 0.65 (20:1, CH$_2$Cl$_2$/MeOH); [**α**]$_D^{23.1}$ -23.29 (c 0.42, CHCl$_3$); **^1H-NMR** (500 MHz, CDCl$_3$): δ 8.19-8.18 (m, 1H), 8.14-8.12 (m, 1H), 7.82-7.79 (m, 1H), 7.67-7.64 (m, 4H), 7.59-7.55 (m, 1H), 7.43-7.34 (m, 10H), 7.32-7.27 (m, 4H), 7.23-7.16 (m, 4H), 7.11-7.09 (m, 2H), 7.08-7.06 (m, 1H), 7.01-6.99 (m, 2H), 6.90-6.87 (m, 2H), 6.75-6.72 (m, 1H, NH), 5.29-5.27 (m, 1H), 5.24 (ddd, $J = 12.2$, 5.1, 2.7 Hz, 1H), 5.04 (s, 2H), 4.76-4.71 (m, 1H), 4.52-4.44 (m, 3H), 4.35 (d, $J = 11.5$ Hz, 1H), 3.99 (dd, $J = 7.8$, 3.6 Hz, 1H), 3.72-3.67 (m, 2H), 3.36-3.30 (m, 1H, 3.21-3.15 (m, 1H), 3.02 (dd, $J = 14.2$, 3.6 Hz, 1H), 2.98 (dd, $J = 11.5$, 6.5 Hz, 1H), 2.80 (dd, $J = 14.2$, 7.8 Hz, 1H), 2.68 (dd, $J = 13.3$, 6.0 Hz, 1H), 2.59-2.46 (m, 2H), 2.25 (dt, $J = 5.3$, 13.1 Hz, 1H), 2.19 (s, 3H), 2.12-2.07 (m, 1H), 2.05 (dd, $J = 13.4$, 5.4 Hz, 1H), 1.68 (ddd, $J = 14.1$, 12.0, 1.9 Hz, 1H), 1.64-1.59 (m, 4H), 1.35 (dt, $J = 14.5$, 4.9 Hz, 1H),
1.05-1.04 (m, 9H); ^{13}\text{C}-\text{NMR} (125 MHz, CDCl\textsubscript{3}, mixture of rotamers, major peaks reported): \(\delta\) 171.6, 171.1, 170.0, 169.9, 164.2, 157.7, 136.8, 135.6, 135.5 (4C), 133.9 (2C), 132.8 (2C), 130.8, 130.6 (2C), 129.6 (3C), 129.4, 129.2 (2C), 129.1, 128.8 (2C), 128.6 (2C), 128.5 (2C), 128.1 (2C), 128.0, 127.9, 127.6 (4C), 127.4 (2C), 127.3, 126.5, 126.5, 114.7 (2C), 80.7, 72.9, 70.0, 69.0, 69.0, 63.5, 59.6, 54.7, 54.7, 39.7, 39.4, 38.2, 37.2, 30.3, 30.0, 28.8, 26.9 (3C), 26.1, 25.4, 21.0, 19.2; ^{19}\text{F}-\text{NMR} (280 MHz, CDCl\textsubscript{3}): \(\delta\) -62.7 (3F); IR \(\nu\max\) (film)/cm\(^{-1}\): 2932, 2850, 1742, 1728, 1678, 1645, 1512, 1448, 1428, 1336, 1258, 1170, 1126, 1113, 1087, 1073; HRMS (ESI) \(m/z\) calculated for C\textsubscript{71}H\textsubscript{77}N\textsubscript{10}O\textsubscript{10}F\textsubscript{3}Si ([M+H]\textsuperscript{+}) 1216.5325, found 1216.5321.

To a solution of benzoate 229 (250 mg, 0.21 mmol) in THF/H\textsubscript{2}O (70 mL, 1:1) was added \(N\)-methylcarbazole (37 mg, 0.21 mmol) and 1,4-cyclohexadiene (3.85 mL, 41.1 mmol). The solution was partitioned into ten Pyrex test tubes (10 mL). The reaction mixture was degassed by bubbling argon through the solution for 15 min. The test tubes were arranged around a UV lamp. After 18 h of UV irradiation THF was removed under reduced pressure and the remaining aqueous phase was extracted three times with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic phase was dried over MgSO\textsubscript{4} and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 50:1) to give peptide 230 (80 mg, 0.078 mmol, 37%, 75% brsm) along with reisolated alcohol 228\textsuperscript{711} (106 mg, 0.101 mmol, 49%).

\(R_s\) 0.59 (9:1, CH\textsubscript{2}Cl\textsubscript{2}/MeOH); [\(\alpha\)]\textsubscript{D}\textsuperscript{24,3} -42.93 (c 0.08, CHCl\textsubscript{3}); ^{1}\text{H}-\text{NMR} (600 MHz, CDCl\textsubscript{3}): \(\delta\) 7.67-7.62 (m, 4H), 7.44-7.13 (m, 21H), 7.10-7.07 (m, 2H), 7.01-6.98 (m, 1H), 6.89-6.85 (m, 2H), 6.80-6.77 (m, 1H, NH), 5.06-5.01 (m, 2H), 4.96-4.94 (m, 1H), 4.81 (dd, \(J = 14.8, 7.7\) Hz, 1H), 4.51-4.48 (m, 2H), 4.37 (dd, \(J = 12.1, 5.9\) Hz, 1H), 4.33 (d, \(J = 11.5\) Hz, 1H), 3.96 (dd, \(J = 7.9, 3.6\) Hz, 1H), 3.70-3.64 (m, 2H), 3.32-3.27 (m, 1H), 3.17-3.12 (m, 1H), 3.01-2.96 (m, 1H), 2.78 (dd, \(J = 14.3, 7.9\) Hz, 1H), 3.70 (dd, \(J = 13.4, 6.2\) 1H), 2.50-2.44 (m, 1H), 2.32-2.27 (m, 1H), 2.13-2.11 (m, 3H), 1.99-1.91 (m, 2H), 1.74-1.69 (m, 1H), 1.64-1.50 (m, 6H), 1.45-1.39 (m, 2H), 1.05-1.03 (m, 9H); ^{13}\text{C}-\text{NMR} (150 MHz, CDCl\textsubscript{3}, mixture of rotamers, major peaks reported): \(\delta\) 171.5, 170.9, 170.4 (2C), 157.7, 137.1, 136.9, 135.7, 135.5 (4C), 133.9 (2C), 130.6 (2C), 129.6 (2C), 129.5, 129.2 (2C), 128.6 (2C), 128.6 (2C), 128.6

\textsuperscript{711} The benzoate group of starting material 229 partially hydrolized during the reaction furnishing alcohol 228. This compound could again be subjected to the benzylation/deoxygenation sequence.
Experimental Part

To a stirred solution of alcohol 228 (21 mg, 0.02 mmol) in CH$_2$Cl$_2$ (1 mL) was added N-methyl morpholine oxide (7 mg, 0.06 mmol) and TPAP (0.7 mg, 2 μmol). The reaction was stirred for 20 min until TLC analysis indicated full consumption of the starting material. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 100:1) to give ketone 231 (19 mg, 0.018 mmol, 91%).

$R_f$ 0.51 (1:2, hexanes/EtOAc); $[\alpha]_D^{245}$ -39.16 (c 0.85, CHCl$_3$); $^1$H-NMR (400 MHz, CDCl$_3$, mixture of rotamers): δ 8.17 (bs-t, J = 5.6 Hz, 0.5H, NH), 7.68-7.62 (m, 4H), 7.46-7.01 (m, 24H), 6.92-6.85 (m, 2H), 6.61 (bs-t, $J = 5.7$ Hz, 0.5 H, NH), 5.11-5.03 (m, 2.5H), 4.82-4.68 (m, 1.5H), 4.62-4.25 (m, 3H), 4.04-3.98 (m, 1H), 3.72-3.63 (m, 2H), 3.45-3.13 (m, 3H), 3.06-2.98 (m, 2H), 2.93-2.65 (m, 4H), 2.63-2.35 (m, 2H), 2.28-1.85 (m, 6H), 1.66-1.55 (m, 4H), 1.06-1.00 (m, 9H); $^{13}$C-NMR (100 MHz, CDCl$_3$, mixture rotamers, all peaks reported): δ 204.5, 203.9, 172.6, 171.7, 171.5, 171.2, 170.6, 169.6, 169.5, 157.7, 157.6, 137.0, 137.0, 136.8, 135.6, 135.5, 134.9, 133.9, 133.9, 133.8, 130.6, 130.5, 129.6, 129.5, 129.3, 129.2, 129.1, 128.8, 128.6, 128.5, 128.5, 128.1, 128.1, 128.0, 127.9, 127.8, 127.6, 127.6, 127.4, 127.4, 114.6, 114.6, 80.6, 73.9, 73.1, 73.0, 72.4, 70.0, 70.0, 63.5, 63.4, 60.5, 59.8, 56.1, 54.4, 53.2, 51.8, 40.3, 40.0, 39.6, 39.1, 39.0, 38.6, 38.2, 38.1, 37.2, 34.6, 32.8, 32.7, 31.0, 30.1, 30.0, 26.9, 26.0, 25.6, 20.8, 20.7, 19.2; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3300 (bs), 2930, 2858, 1748, 1652, 1511, 1454, 1428, 1373, 1227, 1111, 1027; HRMS (ESI) $m/z$ calculated for C$_{63}$H$_{72}$O$_8$N$_4$Si ([M+Na]$^+$) 1059.5303, found 1059.5287.
A stirred solution of ketone 231 (19 mg, 0.018 mmol) in THF (1 mL) was cooled to 0 °C and sodium borohydride (1.4 mg, 0.036 mmol) was added. After 20 min the solution was diluted with EtOAc and sat. NaHCO₃. The aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 50:1) to give alcohol 232 (12 mg, 0.011 mmol, 63%).

Rf 0.68 (EtOAc); [α]D 23.6° -35.89 (c 0.40, CHCl₃); ¹H-NMR (600 MHz, CDCl₃, mixture of rotamers): δ 7.67–7.62 (m, 4H), 7.44–7.14 (m, 20H), 7.12–7.04 (m, 4H), 6.89–6.85 (m, 2H), 6.42 (t, J = 5.8 Hz, 1H, NH), 5.06–5.01 (m, 2H), 4.85–4.71 (m, 2H), 4.61–4.28 (m, 4H), 4.03–3.94 (m, 1H), 3.85 (q, J = 3.9 Hz, 1H), 3.70–3.64 (m, 2H), 3.40–3.08 (m, 3H), 3.05–2.95 (m, 2H), 2.83–2.65 (m, 3H), 2.31–2.21 (m, 1H), 2.19–2.04 (m, 4H), 2.03–1.90 (m, 2H), 1.79 (dt, J = 14.8, 3.2 Hz, 1H), 1.62–1.54 (m, 4H), 1.30 (dt, J = 14.4, 4.2 Hz, 1H), 1.06–1.00 (m, 9H); ¹³C-NMR (150 MHz, CDCl₃, mixture rotamers, all peaks reported): δ 172.2, 171.5, 171.0, 170.6, 170.6, 157.6, 157.6, 137.1, 137.1, 137.0, 136.8, 135.9, 135.5, 133.9, 130.6, 129.6, 129.5, 129.3, 129.2, 129.0, 128.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.6, 127.6, 127.4, 127.2, 114.6, 114.6, 80.7, 74.5, 73.3, 73.0, 72.9, 70.0, 69.4, 66.5, 63.6, 63.5, 60.5, 60.0, 55.6, 55.1, 51.4, 39.7, 39.5, 39.3, 38.2, 38.2, 35.2, 35.0, 31.6, 30.9, 30.0, 30.0, 28.2, 27.6, 26.9, 26.8, 26.1, 25.7, 21.2, 19.2; IR νmax (film)/cm⁻¹: 3406 (bs), 2930, 2858, 1733, 1635, 1510, 1454, 1428, 1373, 1240, 1110, 1029; HRMS (ESI) m/z calculated for C₆₃H₇₄O₉N₃Si ([M+H]⁺) 1044.5189, found 1044.5177.

To a stirred solution of acid S11 (550 mg, 2.4 mmol) in CH₂Cl₂ (10 mL) was added amine 153 (786 mg, 2.4 mmol), EDC (506 mg, 2.6 mmol), HOBt (357 mg, 2.6 mmol), and triethylamine (0.68 mL, 4.8 mmol). The mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give amide S12 (1.03 g, 1.9 mmol, 80%).
Experimental Part

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.67-7.62 (m, 4H), 7.44-7.34 (m, 6H), 6.07 (bs-s, 1H, NH), 4.70 (bs-s, 1H), 4.04 (bs-s, 1H), 3.70-3.62 (m, 2H), 3.35-3.16 (m, 2H), 2.72 (d, \(J = 12.9\) Hz, 1H), 2.31 (bs-s, 1H), 1.69-1.33 (m, 19H), 1.04 (s, 9H).

To a stirred solution of silylether S12 (50 mg, 0.09 mmol) in THF (2 mL) was added a solution of TBAF (30 μL, 0.1 mmol, 1M in THF). After 1 h the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (CH\(_2\)Cl\(_2\)/MeOH 40:1) to give alcohol 233 (23 mg, 0.08 mmol, 83%).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.48 (bs-s, 1H, NH), 4.70 (bs-s, 1H), 4.02 (bs-s, 1H), 3.69-3.60 (m, 2H), 3.34-3.24 (m, 2H), 2.76 (t, \(J = 11.8\) Hz, 1H), 2.36-1.87 (m, 2H), 1.69-1.33 (m, 18H).

To a solution of triphenylphosphine (87 mg, 0.33 mmol) and imidazole (23 mg, 0.33 mmol) in CH\(_2\)Cl\(_2\) (3 mL) was added iodine (101 mg, 0.40 mmol). The mixture was stirred for 5min before a solution of alcohol 233 (100 mg, 0.33 mmol) was added. The mixture was stirred for 3h and then diluted with water and CH\(_2\)Cl\(_2\). The phases were separated and the aqueous phase was extracted three times with CH\(_2\)Cl\(_2\). The combined organic phases were washed with brine and dried over MgSO\(_4\). The solvent was evaporated and the residue was purified by flash column chromatography (CH\(_2\)Cl\(_2\)/MeOH 40:1) to give iodide 234 (99 mg, 0.24 mmol, 73%).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.12 (bs-s, 1H, NH), 4.71 (bs-s, 1H), 4.11-3.95 (m, 1H), 3.40-3.24 (m, 2H), 3.20 (t, \(J = 6.8\) Hz, 2H), 2.75 (t, \(J = 12.2\) Hz, 1H), 2.37-2.24 (m, 1H), 1.89-1.77 (m, 2H), 1.69-1.40 (m, 16H).

To a stirred solution of alcohol 233 (50 mg, 0.17 mmol) in CH\(_2\)Cl\(_2\) (3 mL) was added carbon tetrabromide (110 mg, 0.33 mmol) and 2,6-lutidine (19 μL, 0.17 mmol). The mixture was cooled to 0 °C and triphenylphosphine (87 mg, 0.33 mmol) was added. The solution was stirred overnight. The
solvent was evaporated and the residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 40:1) to give bromide S13 (47 mg, 0.13 mmol, 78%).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 6.15 (bs-s, 1H, NH), 4.69 (bs-s, 1H), 4.15-3.93 (m, 1H), 3.41 (t, $J = 6.6$ Hz, 2H), 3.37-3.19 (m, 2H), 2.73 (t, $J = 12.5$ Hz, 1H), 2.35-2.20 (m, 1H), 1.91-1.80 (m, 2H), 1.70-1.36 (m, 16H).

Triflate 239 was prepared according to a literature procedure.$^{712}$

To a solution of NaOH (2.1 g, 52.3 mmol) in water (10 mL) was added guanidine hydrochloride (1 g, 10.5 mmol). CH$_2$Cl$_2$ (20 mL) was added and the mixture was cooled to 0 ºC. Benzyl chloroformate (4.5 mL, 31.4 mmol) was added slowly over 45 min while vigorously stirring the guanidine solution. The mixture was then allowed to warm to ambient temperature and stirred overnight. The phases were separated and the aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with water and dried over MgSO$_4$. The solvent was evaporated and the resulting solid was recrystallized form methanol to give guanidine 235 (2.2 g, 6.7 mmol, 64%).

$^1$H-NMR (300 MHz, d$_6$-DMSO): $\delta$ 10.89 (bs-s, 1H, NH), 8.68 (bs-s, 2H, NH), 7.41-7.29 (m, 10H), 5.11 (s, 4H).

To a solution of guanidine 235 (500 mg, 1.5 mmol) in chlorobenzene (15 mL) at 0 ºC was added sodium hydride (122 mg, 3.1 mmol, 60% dispersion in mineral oil). After 1 h the mixture was cooled to -45 ºC and triflic anhydride (0.26 mL, 1.5 mmol) was added. The solution was allowed to warm to ambient temperature and stirred overnight. The solvent was removed and the residue was taken up in EtOAc. 2M sodium bisulfate was added and the phases were separated. The organic layer was washed with water and brine and dried over MgSO$_4$. The solvent was removed and the residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 95:5) to give triflate 239 (370 mg, 0.81 mmol, 53%).

$^1$H-NMR (300 MHz, d$_6$-DMSO): $\delta$ 7.43-7.34 (m, 10H), 5.20 (s, 4H). $^{19}$F-NMR (280 MHz, d$_6$-DMSO): $\delta$ -78.2.

**Experimental Part**

RF 0.50 (20:1, CH₂Cl₂/MeOH); \(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ 3.89 (d, J = 12.1 Hz, 1H), 3.56-3.25 (m, 6H), 1.98-1.78 (m, 6H), 1.72-1.54 (m, 4H), 1.43 (s, 9H).

\[\text{To a stirred solution of alcohol 233 (50 mg, 0.17 mmol) in CH}_2\text{Cl}_2 (2 \text{ mL}) was added triethylamine (35 μL, 0.25 mmol) followed by MsCl (16 μL, 0.20 mmol). The solution was stirred for 1 h and the solvent was evaporated. The residue was subjected to flash column chromatography (CH}_2\text{Cl}_2/\text{MeOH 40:1) to give mesylate 237 (58 mg, 0.15 mmol, 92%).} \]

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ 6.19 (bs-s, 1H, NH), 4.69 (bs-s, 1H), 4.23 (t, J = 6.2 Hz, 2H), 4.10-3.94 (m, 1H), 3.36-3.23 (m, 2H), 3.00 (s, 3H), 2.74 (t, J = 12.6 Hz, 1H), 2.33-2.21 (m, 1H), 1.81-1.69 (m, 2H), 1.68-1.30 (m, 16).

\[\text{To a stirred solution of mesylate 237 (58 mg, 0.15 mmol) in DMF (2 mL) was added NaN}_3 (20 mg, 0.31 mmol). The solution was stirred overnight and was then diluted with water and Et}_2\text{O. The phases were separated and the aqueous phase was extracted three times with Et}_2\text{O. The combined organic phases were washed with water and brine and dried over MgSO}_4. The solvent was evaporated and the residue was subjected to flash column chromatography (CH}_2\text{Cl}_2/\text{MeOH 40:1) to give azide 238 (29 mg, 0.09 mmol, 58%) along with reisolated starting material (10 mg, 0.02 mmol).} \]

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ 6.16 (bs-s, 1H, NH), 4.70 (bs-s, 1H), 4.15-3.94 (m, 1H), 3.34-3.19 (m, 4H), 2.73 (t, J = 12.0 Hz, 1H), 2.36-2.23 (m, 1H), 1.70-1.32 (m, 18H).
Experimental Part

To a stirred solution of azide 238 (29 mg, 0.089 mol) in MeOH (3 mL) was added Pd/C (3 mg, 10 wt% Pd). The mixture was set under vacuum and the flask was backfilled with argon. After another round of evacuation the mixture was put under a hydrogen atmosphere (balloon). The mixture was stirred for 1 h and then filtered over celite. The solvent was removed and the crude amine was taken up in CH₂Cl₂ (2 mL). Triethylamine (13 µL, 0.089 mmol) and N,N’-di-Cbz-N’'-trifluoromethanesulfonyl guanidine 239 (41 mg, 0.089 mmol) were added to the stirred solution. The mixture was stirred at ambient temperature for 2 h. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 50:1) to give guanidine 240 (21 mg, 0.034 mmol, 39%).

¹H-NMR (300 MHz, CDCl₃): δ 11.73 (s, 1H, NH), 8.32 (t, J = 5.0 Hz, 1H, NH), 7.42-7.27 (m, 10H), 6.16 (bs-s, 1H, NH), 5.17 (s, 2H), 5.12 (s, 2H), 4.70 (bs-s, 1H), 4.11-3.92 (m, 1H), 3.49-3.39 (m, 2H), 3.36-3.23 (m, 2H), 2.75 (t, J = 11.8 Hz, 1H), 2.35-2.23 (m, 1H), 1.68-1.37 (m, 19H); IR ν_max (film)/cm⁻¹: 3339, 2939, 2866, 1729, 1686, 1637, 1573, 1525, 1423, 1321, 1255, 1203, 1140, 1048; HRMS (ESI) m/z calculated for C₃₂H₄₄O₇N₅ ([M+H]⁺) 610.3235, found 610.3219.

To a solution of alcohol 233 (50 mg, 0.16 mmol) in THF (3 mL) was added guanidine 235 (163 mg, 0.50 mmol) and triphenylphosphine (66 mg, 0.25 mg). The mixture was cooled to 0 °C and a solution of DEAD (40, 0.25 mmol) in THF (1 mL) was added slowly. The mixture was allowed to warm to ambient temperature and stirred overnight. The solvent was evaporated and the residue was taken up in Et₂O. After filtration and removal of the solvent the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give 241 (74 mg, 0.12 mmol, 73%).

R̂₁ 0.50 (9:1, CH₂Cl₂/MeOH); ¹H-NMR (300 MHz, CDCl₃): δ 9.44 (bs-s, 1H, NH), 9.25 (bs-s, 1H NH), 7.42-7.28 (m, 10H), 6.23 (bs-s, 1H, NH), 5.26-5.11 (m, 4H), 4.74-4.62 (m, 1H), 4.03-3.91 (m, 2H), 3.29-3.19 (m, 2H), 2.80-2.65 (m, 1H), 2.33-2.18 (m, 1H), 1.66-1.29 (m, 19H); IR ν_max (film)/cm⁻¹: 3388, 2937, 2860, 1718, 1686, 1609, 1513, 1455, 1408, 1378, 1251, 1196, 1162, 1099; HRMS (ESI) m/z calculated for C₃₂H₄₄O₇N₅ ([M+H]⁺) 610.3235, found 610.3221.
To a stirred solution of silyl ether 230 (80 mg, 0.078 mmol) in acetonitrile (2 mL) was added TAS-F (43 mg, 0.156 mmol). The solution was stirred for 2 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 50:1) to give alcohol 242 (54 mg, 0.068 mmol, 88%).

R$_f$ 0.45 (9:1, CH$_2$Cl$_2$/MeOH); $[\alpha]_{D}^{22.5}$ -48.71 (c 1.10, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.44-7.20 (m, 12H), 7.18-7.14 (m, 2H), 7.11-7.07 (m, 2H), 7.04-7.00 (m, 1H), 6.90-6.85 (m, 2H), 5.05-5.00 (m, 2H), 4.98-4.94 (m, 1H), 4.81 (dd, $J = 15.0$, 7.5 Hz, 1H), 4.49 (d, $J = 11.2$ Hz, 1H), 4.47-4.34 (m, 2H), 4.33 (d, $J = 11.5$ Hz, 1H), 4.03-3.94 (m, 1H), 3.68-3.59 (m, 2H), 3.32-3.18 (m, 2H), 3.10-2.95 (m, 2H), 2.77 (dd, $J = 14.4$, 7.8 Hz, 1H), 2.72 (dd, $J = 13.5$, 6.4 Hz, 1H), 2.40 (dd, $J = 11.8$, 8.7 Hz, 1H), 2.34-2.20 (m, 1H), 2.14-2.04 (m, 3H), 2.02-1.89 (m, 3H), 1.77-1.45 (m, 8H),; $^{13}$C-NMR (75 MHz, CDCl$_3$, mixture of rotamers, major peaks reported): $\delta$ 171.3, 170.7, 170.4, 170.2, 157.4, 136.8, 136.7, 135.5, 130.5 (2C), 129.3, 129.1 (2C), 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.0 (2C), 127.9, 127.8, 127.2 (2C), 114.5 (2C), 80.7, 72.8, 69.9, 69.3, 62.3, 59.7, 55.6, 51.4, 39.3, 38.2, 36.4, 30.7, 28.9, 28.3, 26.1, 23.1, 21.4, 19.8; IR $\nu$$_{max}$ (film)/cm$^{-1}$: 3407, 3321, 2935, 2868, 1732, 1668, 1652, 1644, 1634, 1512, 1455, 1378, 1237, 1177, 1076, 1020; HRMS (ESI) m/z calculated for C$_{47}$H$_{56}$O$_8$N$_3$ ([M+H]$^+$) 790.4062, found 790.4059.

To a stirred solution of alcohol 242 (29 mg, 0.037 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C was added triethylamine (7.7 µL, 0.055 mmol) and methanesulfonyl chloride (3.4 µL, 0.044 mmol). The solution was stirred at that temperature for 1 h. The mixture was concentrated under reduced pressure to a volume of 0.5 mL. The residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 50:1) to give mesylate S14 (30.5 mg, 0.035 mmol, 96%).

R$_f$ 0.50 (9:1, CH$_2$Cl$_2$/MeOH); $[\alpha]_b^{23.1}$ -51.70 (c 1.50, CHCl$_3$); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.47-7.24 (m, 12H), 7.18-7.15 (m, 2H), 7.11-7.09 (m, 1H), 7.03-7.00 (m, 2H), 6.90-6.86 (m, 2H), 6.83 (t, $J = 5.7$ Hz, 1H, NH), 5.07-5.00 (m, 2H), 4.99-4.94 (m, 1H), 4.82 (q, $J = 7.5$ Hz, 1H), 4.53-4.47 (m, 2H),
4.43-4.33 (m, 2H), 4.27-4.22 (m, 2H), 4.04-3.96 (m, 1H), 3.39-3.30 (m, 1H), 3.24-3.14 (m, 1H), 3.05-3.00 (m, 4H), 2.83-2.69 (m, 2H), 2.50-2.40 (m, 1H), 2.36-2.26 (m, 1H), 2.16-2.09 (m, 3H), 2.02-1.92 (m, 2H), 1.83-1.68 (m, 4H), 1.67-1.55 (m, 4H), 1.50-1.41 (m, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$, mixture of rotamers, major peaks reported): $\delta$ 171.4, 171.0, 170.7, 170.3, 157.6, 137.0, 136.9, 135.7, 130.6 (2C), 129.4, 129.2 (2C), 128.6 (2C), 128.5 (2C), 128.0 (2C), 128.0, 127.9, 127.4 (2C), 127.2, 114.6 (2C), 80.7, 72.9, 70.0, 69.4, 69.3, 59.5, 55.6, 51.4, 39.3, 38.8, 38.2, 37.3, 36.4, 30.7, 27.9, 26.5, 25.6, 23.0, 21.3, 19.7; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3405, 3330, 2934, 1732, 1675, 1644, 1512, 1454, 1352, 1237, 1174; HRMS (ESI) $m/z$ calculated for C$_{48}$H$_{58}$O$_7$N$_3$S ([M+H]$^+$) 868.3837, found 868.3836.

To a stirred solution of mesylate S14 (30 mg, 0.035 mmol) in DMF (1 mL) was added sodium azide (4.5 mg, 0.069 mmol). The mixture was warmed to 50 °C and stirred over night. The reaction was quenched by addition of pH 7 buffer (5 mL). The aqueous phase was extracted three times with Et$_2$O. The combined organic phase was washed with water and dried over MgSO$_4$. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 50:1) to give azide S15 (24 mg, 0.029 mmol, 85%).

R$_f$ 0.50 (9:1, CH$_2$Cl$_2$/MeOH); [\(\alpha\)]$_{D}^{21.5\varepsilon}$ -54.00 (c 1.20, CHCl$_3$); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.47-7.24 (m, 12H), 7.21-7.17 (m, 2H), 7.15-7.10 (m, 3H), 7.06-7.02 (m, 1H), 6.93-6.85 (m, 3H), 5.09-5.03 (m, 2H), 5.00-4.97 (m, 1H), 4.85 (q, $J$ = 7.5 Hz, 1H), 4.65-4.50 (m, 2H), 4.48-4.34 (m, 2H), 4.07-3.98 (m, 1H), 3.39-3.29 (m, 3H), 3.25-3.16 (m, 1H), 3.06-2.98 (m, 2H), 2.85-2.71 (m, 2H), 2.55-2.44 (m, 1H), 2.38-2.28 (m, 1H), 2.16-2.08 (m, 3H), 2.03-1.95 (m, 2H), 1.79-1.71 (m, 1H), 1.69-1.56 (m, 7H), 1.49-1.44 (m, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$, mixture of rotamers, major peaks reported): $\delta$ 171.5, 171.0, 170.6, 170.4, 157.6, 137.0, 136.9, 135.7, 130.6 (2C), 129.4, 129.2 (2C), 128.6 (2C), 128.5 (2C), 128.4 (2C), 128.1 (2C), 128.0, 127.9, 127.4 (2C), 127.2, 114.6 (2C), 80.7, 72.9, 70.0, 69.3, 59.4, 55.7, 51.4, 39.3, 39.0, 38.2, 36.4, 30.7, 27.8, 26.8, 26.2, 23.0, 21.3, 19.7; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3405, 3326, 2934, 2096, 1734, 1675, 1652, 1512, 1455, 1435, 1237, 1086, 1020; HRMS (ESI) $m/z$ calculated for C$_{47}$H$_{58}$O$_7$N$_3$Na ([M+Na]$^+$) 837.3946, found 837.3945.
To a stirred solution of acetate S15 (24 mg, 0.029 mmol) in THF (1 mL) at 0 °C was added a solution of lithium hydroxide monohydrate (2.6 mg, 0.059 mmol) in H₂O (0.2 mL). A few drops of MeOH were added to the solution. The mixture was stirred at 0 °C for 4 h. The reaction was quenched by addition of pH 7 buffer. The aqueous phase was extracted twice with CH₂Cl₂ (40 mL). The combined organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 50:1) to give the unprotected alcohol 244 (15 mg, 0.019 mmol, 70% brsm) along with reisolated starting material S15 (1.5 mg, 0.01 mmol, 6%).

To a stirred solution of this intermediate 244 (15 mg, 0.019 mol) in acetonitrile (1 mL) was added trimethylphosphine (39 µL, 0.039 mol, 1M in THF). The solution was stirred for 30 min and H₂O (50 µL) was added. After 45 min Na₂SO₄ (100 mg) was added. The reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (1 mL). Triethylamine (5.5 µL, 0.039 mmol) and N,N'-di-Cbz-N''-trifluoromethanesulfonyl guanidine 239 (18 mg, 0.039 mmol) were added to the stirred solution. The mixture was stirred at ambient temperature for 2 h. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 50:1) to give guanidine 245 (17.5 mg, 0.017 mmol, 85%).

Rᵣ 0.46 (9:1, CH₂Cl₂/MeOH); [α]D⁰⁺⁴₈.₄ —48.47 (c 0.70, CHCl₃); ¹H-NMR (400 MHz, CDCl₃): δ 11.71 (bs-s, 1H, NH), 8.35 (t, J = 5.1 Hz, 1H, NH), 7.45-7.21 (m, 21H), 7.18-7.07 (m, 7H), 6.91-6.87 (m, 3H), 5.15-5.12 (m, 4H), 5.06-5.05 (m, 2H), 4.91 (q, J = 7.1 Hz, 1H), 4.54-4.47 (m, 3H), 4.34 (d, J = 11.5 Hz, 1H), 4.04 (bs-s, 1H), 3.97 (dd, J = 7.9, 3.6 Hz, 1H), 3.51-3.44 (m, 2H), 3.36-3.17 (m, 2H), 3.08-2.95 (m, 2H), 2.80-2.70 (m, 2H), 2.47-2.37 (m, 1H), 2.30-2.20 (m, 1H), 2.17-2.06 (m, 1H), 2.00-1.86 (m, 2H), 1.69-1.42 (m, 8H); ¹³C-NMR (100 MHz, CDCl₃, mixture of rotamers, major peaks reported): δ 171.5, 170.9 (2C), 163.6, 157.6, 156.0, 153.8, 137.1, 136.9, 136.8, 136.0, 134.5, 130.6 (2C), 129.5, 129.4 (2C), 128.7, 128.7 (2C), 128.5 (2C), 128.5 (2C), 128.4 (2C), 128.4 (4C), 128.1 (2C), 128.1 (2C), 127.9, 127.9 (2C), 127.4 (2C), 127.1, 114.6 (2C), 80.8, 72.9, 70.0, 68.1, 67.1, 66.0, 59.6, 55.4, 51.2, 40.7, 39.2, 39.1, 38.2, 36.6, 33.5, 28.0, 26.6, 26.4, 26.0, 19.1; IR νmax (film)/cm⁻¹: 3326, 3166, 3024, 2934, 1732, 1633, 1574, 1512, 1456, 1386, 1324, 1258, 1230, 1195, 1152; HRMS (ESI) m/z calculated for C₆₂H₆₉O₁₀N₆ ([M+H]⁺) 1057.5070, found 1057.5056.
A flask containing peptide 245 (15 mg, 0.013 mmol) was evacuated and purged with argon. MeOH (2 mL) was added followed by palladium on activated carbon (20 mg, 10% wt Pd). The reaction flask was evacuated and purged with H\(_2\) (1 atm, balloon). The reaction was stirred for 6 h. The mixture was filtered over Celite and the solvent was removed under reduced pressure to give microcin SF 608 (19) (7 mg, 0.011 mmol, 87%).

R\(_f\) 0.00 (9:1, CH\(_2\)Cl\(_2\)/MeOH); [\(\alpha\)]\(_D\)\(^{245}\) -30.69 (c 0.25, MeOH); \(^1\)H-NMR (600 MHz, d\(_6\)-DMSO, mixture of rotamers, major peaks reported): \(\delta\) 7.24 (t, \(J = 2.0\) Hz, 2H), 7.20 (t, \(J = 2.3\) Hz, 1H), 7.17 (d, \(J = 7.0\) Hz, 2H), 6.90 (d, \(J = 8.5\) Hz, 2H), 6.61 (d, \(J = 8.5\) Hz, 2H), 4.69 (dd, \(J = 8.2, 5.2\) Hz, 1H), 4.42 (dt, \(J = 9.2, 7.5\) Hz, 1H), 4.25 (dd, \(J = 9.8, 8.1\) Hz, 1H), 3.92 (dd, \(J = 8.3, 3.8\) Hz, 1H), 3.22-3.03 (d, 4H), 2.89 (dd, \(J = 14.0, 5.0\) Hz, 1H), 2.83-2.76 (m, 2H), 2.43 (dd, \(J = 13.9, 8.3\) Hz, 1H), 2.23-2.17 (m, 1H), 1.87-1.80 (m, 1H), 1.69 (bs-d, \(J = 8.0\) Hz, 2H), 1.51-1.34 (m, 7H); \(^{13}\)C-NMR (150 MHz, d\(_6\)-DMSO, mixture of rotamers, major peaks reported): \(\delta\) 172.8, 171.2, 169.5, 157.0, 156.0, 137.0, 130.2 (2C), 129.5 (2C), 128.1 (3C), 126.4, 114.8 (2C), 72.2, 64.0, 59.8, 54.4, 50.5, 40.5, 39.6, 38.1, 38.0, 36.4, 34.2, 30.3, 26.3, 25.8, 19.0; IR \(\nu\)\(_{\text{max}}\) (film)/cm\(^{-1}\): 3322, 2927, 1672, 1657, 1631, 1613, 1444, 1262, 1238, 1078; HRMS (ESI) \(m/z\) calculated for C\(_{32}\)H\(_{45}\)O\(_6\)N\(_6\) ([M+H]\(^+\)) 609.3395, found 609.3394.

The C(2) epimer of the natural product microcin SF608 (19) was synthesized starting from azide 148b. R\(_f\) 0.00 (9:1, CH\(_2\)Cl\(_2\)/MeOH); [\(\alpha\)]\(_D\)\(^{245}\) -90.97 (c 0.30, MeOH); \(^1\)H-NMR (600 MHz, d\(_6\)-DMSO, 1:1 mixture of rotamers, all peaks reported): \(\delta\) 9.16 (d, \(J = 13.0\) Hz, 1H, PhO\(\cdot\)H), 7.31-7.09 (m, 5H), 6.95 (d, \(J = 8.5\) Hz, 0.5H), 6.86 (d, \(J = 8.5\) Hz, 0.5H), 6.65 (d, \(J = 8.5\) Hz, 0.5H), 6.60 (d, \(J = 8.5\) Hz, 0.5H), 5.65 (d, \(J = 6.1\) Hz, 0.5H, Hpla-OH), 5.28 (d, \(J = 6.4\) Hz, 0.5H, Hpla-OH), 4.78 (d, \(J = 9.1\) Hz, 0.5H), 4.60-4.56 (m, 0.5H), 4.55 (d, \(J = 2.8\) Hz, 0.5H, C(6)-OH), 4.42-4.38 (m, 1H), 4.29-4.25 (m, 0.5H), 4.24-4.20 (m, 0.5H), 4.16-4.12 (m, 0.5H), 3.99-3.95 (m, 0.5H), 3.89-3.85 (m, 0.5H), 3.82-3.79 (m, 0.5H), 3.76-3.72 (m, 0.5H), 3.22-2.92 (m, 5H), 2.85-2.74 (m, 2H), 2.63-2.59 (m, 0.5H), 2.45-2.26 (m,
A solution of ethylacrylate (300 g, 3.0 mol) in EtOAc (300 mL) and ethanol (260 mL, 4.5 mol) was cooled to 0 °C. Acetyl chloride (320 mL, 4.5 mol) was slowly added over a period of 15 min. The resulting solution was allowed to warm to ambient temperature overnight. The reaction was cooled to 0 °C and carefully quenched by addition saturated NaHCO₃. The phases were separated and the aqueous phase was washed with EtOAc. The combined organic phases were dried over MgSO₄ and the solvent was evaporated to give 3-chloropropionate 436 as a colorless liquid, which was sufficiently pure for further use.

Tosylate 434 was prepared according to a slightly modified literature procedure.\textsuperscript{713,714}

A 2L three neck round bottom flask was charged with toluene (300 mL) a magnetic stirring bar and fine cut sodium metal (52 g). The mixture was carefully heated to refluxed and stirred vigorously until the sodium was finely dispersed. Stirring was stopped and the mixture was allowed to cool to ambient temperature. Toluene was decanted off and the remaining sodium metal was carefully washed twice with dry Et₂O (200 mL). Dry Et₂O (300 mL) was added followed by chlorotrimethylsilane (126 mL). The mixture is heated to gentle reflux (ca. 50 °C) and 436 (136 g) is slowly added \textit{via} dropping funnel


\textsuperscript{714} The reported procedure for tosylation of 434 gave low yields. The tosylation was therefore performed in CH₂Cl₂ using triethylamine as base.
over a period of 3-4 h. The reaction is stirred at reflux for another 30 min and then filtrated. The filter cake is washed with dry ether. The combined organic phases are concentrated to yield 438 as a yellow liquid.

To a solution of 438 in MeOH were added a few drops of HCl in MeOH (ca. 1.25 M). The reaction was monitored by $^1$H NMR analysis of small fractions. Upon completion (ca. 10 min) the solvent is removed. Flash column chromatography (pentane/Et$_2$O 10:1) yields 435 as a brown liquid.

A three neck 2L flask was charged with vinyl magnesium chloride$^{715}$ (1 L, 1.6 mol, 1.6M in THF). To the vigorously stirred solution was slowly added a solution of hemiacetal 435 (82 g, 0.8 mol) in THF (50 mL) to maintain the reaction at a gentle reflux. After the addition is complete, the reaction was heated to 80 °C and stirred for another 30 min at reflux. The mixture was poured into sat. NH$_4$Cl and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO$_4$. The organic phases were concentrated to give allylic alcohol 441 (ca. 50 g, 0.6 mol, ca. 75%) as a brown oil which was used without further purification.

To a solution of crude allylic alcohol 441 (ca. 50 g, 0.6 mmol) in CH$_2$Cl$_2$ (300 mL) was added triethylamine (83 mL, 0.6 mol) and p-toluenesulfonyl chloride (114 g, 0.6 mol) followed by DMAP (ca. 2 g). The mixture was stirred overnight and then poured into water. The phases were separated and the aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with brine and dried over MgSO$_4$. The organic phases were concentrated and the residue was purified by flash column chromatography (first column: hexanes/CH$_2$Cl$_2$ 20:1; second column: hexanes/EtOAc 10:1) to give tosylate 434 (95 g, 0.4 mmol, 67%) as a colorless solid.$^{716}$

R$_f$ 0.36 (1:2, hexanes/CH$_2$Cl$_2$); m.p. 35 °C; $^1$H-NMR (300 MHz, CDCl$_3$): δ 7.77 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 5.89 (dd, J = 17.1, 10.9 Hz, 1H), 5.13-4.98 (m, 2H), 2.44 (s, 3H), 1.38-1.32 (m, 2H), 0.95-0.89 (m, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 144.8, 136.5, 135.0, 129.7 (2C), 127.8 (2C), 113.4, 65.3, 21.6, 13.9 (2C); IR $\nu_{max}$ (film)/cm$^{-1}$: 3027, 2359, 1651, 1597, 1574, 1495, 1448, 1421, 1360, 1307, 1292, 1238, 1197, 1188, 1166, 1094, 1027; HRMS (EI) $m/z$ calculated for C$_{12}$H$_{14}$O$_3$Na ([M+Na]$^+$) 261.0556, found 261.0552.

$^{715}$ Vinyl magnesium chloride was used instead of vinyl magnesium bromide due to the lower cost of the former reagent. Both reagents produced to product in comparable yield.

$^{716}$ A high purity of this intermediate is crucial for the success of the following reaction.
Alcohol 433 was prepared according to the literature procedure.\textsuperscript{717, 718}

To a solution of hemiacetal 435 (2 g, 19.6 mmol) in benzene (35 mL) was added benzoic acid (478 mg, 3.9 mmol). The solution was brought to reflux and a solution of ylid 437 (7.16 g, 20.6 mmol) in benzene (35 mL) was added slowly by dropping funnel over a period of 30 min. After complete addition the reaction was allowed to stir for another 2 h. The solvent was evaporated and the residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to give ester 440 (920 mg, 7.3 mmol, 37%).

To a solution of AlCl\textsubscript{3} (3.14 g, 23.6 mmol) in Et\textsubscript{2}O (30 mL) at 0 °C was added a solution of LiAlH\textsubscript{4} (8.8 mL, 35.4 mmol, 4M in Et\textsubscript{2}O) in Et\textsubscript{2}O (30 mL). The mixture was stirred for 15 min. A solution of ester 440 (4.5 g, 35.4 mmol) in Et\textsubscript{2}O (30 mL) was added. The mixture was stirred for another 2 h at 0 °C. The reaction was quenched by slow addition of MeOH. An aqueous solution of Rochelle’s salt was added and the phases were separated. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over MgSO\textsubscript{4} and the solvent was removed to obtain alcohol 433 (1.5 g, 17.8 mmol, 76%). The product proved sufficiently clean for further use.

\textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}): δ 6.04-6.97 (m, 1H), 4.31-4.24 (m, 2H), 1.57 (bs-s, 1H, OH), 1.17-1.01 (m, 4H).

To a solution of 1,3-propanediol (10 g, 131 mmol) in DMF (200 mL) at 0 °C was slowly added a suspension of sodium hydride (5.26 g, 131 mmol, 60% dispersion in mineral oil, washed three times with hexanes) in DMF (30 mL) over a period of 1 h. The solution was stirred for another 30 min at 0 °C before benzyl bromide (14.1 mL, 118 mmol) was added. The reaction was allowed to stir at ambient temperature overnight. The mixture was carefully quenched by addition of water and diluted with Et\textsubscript{2}O. The aqueous phase was extracted three times with Et\textsubscript{2}O. The combined organic phases were washed with water and brine and dried over MgSO\textsubscript{4}. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 1:1) to afford the corresponding monobenzylether (14.5 g, 87 mmol, 66%).


\textsuperscript{718} For the reduction of ester 440, LiAlH\textsubscript{4}/AlCl\textsubscript{3} proved superior to the reported DIBAL-H procedure.
To a solution of oxalyl chloride (24.5 mL, 280 mmol) in CH$_2$Cl$_2$ (150 mL) at -78 °C was slowly added a solution of DMSO (41 mL, 578 mmol) in CH$_2$Cl$_2$ (150 mL). After 15 min a solution of the above alcohol (31 g, 187 mmol) in CH$_2$Cl$_2$ (150 mL) was added to this mixture. After another 15 min at -78 °C triethylamine (157 mL, 1.12 mol) was added and the reaction was allowed to warm to ambient temperature over 30 min. Water was added and the phases were separated. The aqueous phase was extracted three times with CH$_2$Cl$_2$ and the combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1→4:1) to afford aldehyde S17 (25.9 g, 158 mmol, 85%).

To a solution of aldehyde S17 (8.5 g, 51.8 mmol) in benzene (50 mL) was added ethylene glycol (14.4 mL, 259 mmol) and p-toluenesulfonic acid (200 mg, 1 mmol). The mixture was heated to reflux for 4 h and the water was collected in a Dean-Stark trap. After cooling the mixture to ambient temperature the solution was poured into sat. NaHCO$_3$ and diluted with Et$_2$O. The phases were separated and the aqueous phase was extracted three times with Et$_2$O. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to afford the corresponding dioxolane (9 g, 43 mmol, 83%).

To a solution of the above dioxolane (2.5 g, 12 mmol) in THF (50 mL) was added tert-butanol (2.3 mL, 24 mmol). The solution was cooled to -78 °C and ammonia was condensed into the flask (ca. 50 mL). Small pieces of sodium metal (414 mg, 18 mmol) were added to the solution. After 1 h the reaction had turned dark blue. After stirring for another 30 min the cooling bath was removed and the ammonia was allowed to slowly evaporate over a period of 6 h. The reaction was quenched by addition of sat. NH$_4$Cl and diluted with EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to afford alcohol S18 (1.12 g, 9.5 mmol, 79%).


Rf 0.20 (1:1, hexanes/EtOAc); $^1$H-NMR (300 MHz, CDCl$_3$): δ 5.02 (t, J = 4.4 Hz, 1H), 4.04-3.98 (m, 2H), 3.90-3.84 (m, 2H), 3.79 (q, J = 5.6 Hz, 2H), 2.51-2.43 (m, 1H, OH), 1.99-1.93 (m, 2H).
An oven dried flask was charged with bis(dibenzylideneacetone)palladium(0) (555 mg, 0.97 mmol) and 1,2-bis(diphenylphosphino)ethane (477 mg, 1.18 mmol). The flask was evacuated for 1h while stirring the solids and then flushed with argon. A solution of tosylate 434 (4.6 g, 19.3 mmol) in dry THF (75 mL) was added. After 10 min the reaction turned green. Meanwhile, a separate flask was charged with sodium hydride (1.16 g, 29.0 mmol, 60% dispersion in mineral oil, washed three times with hexanes) and a solution of alcohol S18 (2.74 g, 23.2 mmol) in THF (75 mL) was added. After 10 min the palladium-allyl solution was transferred into the flask containing the sodium alkoxide solution. After 20 min full consumption of the starting material was observed. The mixture was poured into pH 7 buffer. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over MgSO₄ and the solvent was removed. The residue was purified by flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to afford ether 442 (2.9 g, 15.7 mmol, 82%).

Rf 0.35 (4:1, hexanes/EtOAc); ^1H-NMR (300 MHz, CDCl₃): δ 5.94-5.87 (m, 1H), 4.86 (t, J = 5.0 Hz, 1H), 4.11-4.07 (m, 2H), 3.96-3.88 (m, 2H), 3.88-3.80 (m, 2H), 3.55 (t, J = 6.6 Hz, 2H), 1.94 (dt, J = 6.6, 5.0 Hz, 2H), 1.07 (bs, 4H); ^13C-NMR (75 MHz, CDCl₃): δ 126.5, 114.7, 102.4, 71.1, 65.59, 64.8 (2C), 34.4, 2.3, 1.82; IR νmax (film)/cm⁻¹: 2983, 2879, 1477, 1409, 1366, 1138, 1110, 1034; HRMS (EI) m/z calculated for C₁₀H₁₅O₃ ([M-H]⁻) 183.1016, found 183.1011.

To a solution of dioxolane 442 (7.2 g, 39.1 mmol) in MeCN/H₂O 1:1 (100 mL) was added hydroxylamine hydrochloride (5.4 g, 78.0 mmol). The solution was heated to 60 °C for 1 h. The mixture was poured into pH 7 buffer. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over MgSO₄ and the solvent was removed. The residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to afford oxime 448 (5.2 g, 33.5 mmol, 86%).

To a solution of oxime 448 (2.6 g, 16.8 mmol) in CH₂Cl₂ (50 mL) was added bis(tributyltin)oxide (4.7 mL, 9.2 mmol). The mixture was stirred for 1 h and then cooled to -30 °C. tert-Butylhypochlorite (2.1 mL, 18.4 mmol, freshly prepared) was added and the mixture was warmed to ambient temperature.
Experimental Part

The solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to afford oxazoline 450 (1.64 g, 10.7 mmol, 64%).

\[ R_f 0.43 \ (1:1, \text{hexanes/EtOAc}); ^1H-NMR (600 MHz, CDCl}_3): \delta 4.25 (ddt, J = 11.2, 6.5, 0.9 Hz, 1H), 4.04-3.99 (m, 1H), 3.41-3.33 (m, 3H), 2.72-2.69 (m, 1H), 2.58-2.52 (m, 1H), 1.22 (ddd, J = 11.5, 7.1, 6.2 Hz, 1H), 0.94 (ddd, J = 11.6, 7.3, 6.2 Hz, 1H), 0.72 (ddd, J = 10.9, 7.3, 6.2 Hz, 1H), 0.63 (ddd, J = 10.9, 7.1, 6.2 Hz, 1H); ^13C-NMR (150 MHz, CDCl}_3): \delta 157.4, 70.6, 67.7, 65.9, 48.4, 27.1, 9.5, 8.6; IR \nu_{\text{max}} (film)/\text{cm}^{-1}: 2928, 2862, 1631, 1474, 1434, 1414, 1383, 1324, 1286, 1228, 1211, 1166, 1088, 1026; HRMS (EI) m/z calculated for C8H11NO2 ([M]+) 153.0790, found 153.0787.

To a solution of 450 (500 mg, 3.26 mmol) in toluene (20 mL) at -78 °C was added BF3·OEt2 (0.48 mL, 3.92 mmol) followed by isoprenyl lithium 451 (6.2 mL, 3.59 mmol, 0.5M in Et2O). After 1.5 h the reaction was quenched by addition of water and extracted three times with EtOAc. The combined organic phases were dried over MgSO4 and concentrated. The residue was purified by flash column chromatography to give 447 (212 mg, 1.01 mmol, 31%) along with reisolated starting material 450 (252 mg).

\[ R_f 0.36 \ (4:1, \text{hexanes/EtOAc}); ^1H-NMR (300 MHz, d_6-acetone): \delta 6.06 (bs, 1H, NH), 5.28 (s, 1H), 5.09 (s, 1H), 3.75-3.66 (m, 2H), 3.48 (dd, J = 12.4, 4.5 Hz, 1H), 3.41 (bs, 1H), 2.55 (t, J = 4.4 Hz, 1H), 2.18 (q, J = 7.4 Hz, 2H), 2.04 (dt, J = 4.4, 2.2 Hz, 1H), 1.99-1.76 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H), 0.82-0.67 (m, 3H), 0.53-0.45 (m, 1H); HRMS (ESI) m/z calculated for C12H20NO2 ([M+H]+) 210.1489, found 210.1487.

To a solution of 454 (33 mg, 0.17 mmol) in DMF (1 mL) was added K2CO3 (23 mg, 0.17 mmol) and benzyl bromide (24 μL, 0.20 mmol). The mixture was heated to 50 °C and stirred for 12 h (TLC monitoring). The reaction was diluted with water and the aqueous phase was extracted three times.

\textsuperscript{720} Preparation of isoprenyl lithium stock solution (0.5M): To Et2O (5 mL) at -78 °C was added n-BuLi (3.26 mL, 5.22 mmol, 1.6M in hexanes) followed by 2-bromo-1-butene (661 mg, 4.9 mmol). After 30 min the mixture was allowed to warm to ambient temperature and the solution was used as a 0.5M stock solution.

\textsuperscript{721} Oxazolidine 545 was prepared analogous to 447 but using 2-propenyl lithium as nucleophile.
with Et₂O. The combined organic phases were washed with water and brine and dried over MgSO₄. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to give 453 benzylamine (34 mg, 0.12 mmol, 71%).

**Rf** 0.48 (4:1; hexanes/EtOAc); ¹H-NMR (600 MHz, CDCl₃): δ 7.36-7.33 (m, 2H), 7.32-7.28 (m, 2H), 7.24-7.21 (m, 1H), 5.30-5.29 (m, 1H), 5.14 (s, 1H), 3.90 (bs-s, 1H), 3.85 (d, J = 14.1 Hz, 1H), 3.71 (d, J = 14.1 Hz, 1H), 3.64 (bs-s, 1H), 3.50 (d, J = 12.5 Hz, 1H), 3.44-3.36 (bs-m, 1H), 2.88 (s, 1H), 2.36 (t, J = 11.5 Hz, 1H), 1.93 (s, 3H), 1.89 (dd, J = 14.1, 1.8 Hz, 1H), 1.06 (dd, J = 11.5, 7.1, 5.7 Hz, 1H), 0.91-0.83 (m, 2H), 0.57-0.51 (bs-m, 1H); ¹³C-NMR (150 MHz, CDCl₃): δ 142.5, 138.6, 128.7 (2C), 128.2 (2C), 126.9, 116.9, 71.8, 64.6, 63.9 (2C), 54.0, 44.4, 29.7, 19.6, 11.3 (2C); HRMS (ESI) m/z calculated for C₁₈H₂₄NO₂ ([M+H]+) 286.1802, found 286.1804.

To a solution of 453 (26 mg, 0.091 mmol, previously dried by coevaporation with benzene and MeCN) in MeCN (2 mL) was added p-TsOH (17 mg, 0.091 mmol, dried by coevaporation with benzene). The mixture was heated to 80 °C and stirred for 2 h. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1 → EtOAc) to give 455 (19 mg, 0.074 mmol, 81%).

**Rf** 0.33 (1:1; hexanes/EtOAc); ¹H-NMR (500 MHz, CDCl₃): δ 7.35-7.25 (m, 5H), 5.08-5.07 (m, 1H), 5.00 (t, J = 0.9 Hz, 1H), 4.59 (d, J = 15.0 Hz, 1H), 4.09 (dd, J = 12.4, 2.2 Hz, 1H), 3.98 (d, J = 15.0 Hz, 1H), 3.76 (dd, J = 12.3, 4.0 Hz, 1H), 3.57 (dd, J = 11.0, 6.3, 3.6 Hz, 1H), 3.41 (dd, J = 10.8, 10.5, 4.8 Hz, 1H), 3.09 (dd, J = 4.0, 2.1 Hz, 1H), 2.17 (dd, J = 14.9, 10.5, 6.3 Hz, 1H), 1.73-1.68 (m, 4H); ¹³C-NMR (125 MHz, CDCl₃): δ 168.2, 144.2, 136.3, 128.9 (2C), 128.6 (2C), 127.7, 114.4, 61.0, 60.9, 60.4, 54.3, 44.6, 26.7, 18.1; IR vₖₘₚₐₓ (film)/cm⁻¹: 2950, 2858, 1748, 1496, 1456, 1387, 1349, 1246, 1182, 1102, 1030; HRMS (ESI) m/z calculated for C₁₆H₂₃NO₂ ([M+H]+) 258.1489, found 258.1489.

To a solution of oxazolidine 447 (830 mg, 3.97 mmol) in MeCN (16 mL) was added TFA (0.37 mL, 4.76 mmol). The mixture was heated to 80 °C for 6 h. After this period TFA (0.15 mL) was added
again. After another 1.5 h the solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 1:1) to afford lactam 546 (503 mg, 2.78 mmol, 70%).

**R**<sub>t</sub> 0.41 (EtOAc); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 6.46 (bs, 1H, NH), 5.02 (s, 1H), 4.95 (s, 1H), 4.18 (d, J = 12.4 Hz, 1H), 4.01-3.93 (m, 1H), 3.87 (dd, J = 12.3, 4.9 Hz, 1H), 3.70 (dt, J = 11.2, 5.5 Hz, 1H), 2.98 (d, J = 3.5 Hz, 1H), 2.29-2.20 (m, 1H), 2.17-2.03 (m, 2H), 1.96-1.88 (m, 1H), 1.12 (t, J = 7.3, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ 169.1, 152.2, 108.5, 62.1, 62.0, 57.6, 53.8, 31.9, 24.0, 12.3; IR v<sub>max</sub> (film)/cm<sup>-1</sup>: 3244, 2966, 1756, 1644, 1462, 1376, 1244, 1144, 1101; HRMS (ESI) m/z calculated for C<sub>10</sub>H<sub>16</sub>NO<sub>2</sub> ([M+H]+) 182.1176, found 182.1177.

To a solution of oxazolidine 447 (20 mg, 0.10 mmol) in MeCN (2 mL) was added TfOH (8.5 μL, 0.10 mmol). The mixture was stirred at 80 °C for 5 h. The solvent was evaporated and the residue was subjected to flash column chromatography to afford lactam 457 (20-30% yield).

**R**<sub>t</sub> 0.36 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH; 9:1); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ 5.38 (bs, 1H, NH), 4.48-4.40 (m, 2H), 3.86 (t, J = 5.4 Hz, 2H), 2.34-2.28 (m, 1H), 2.27-2.21 (m, 1H), 1.93-1.86 (m, 1H), 1.71-1.65 (m, 1H), 1.44 (s, 3H), 0.83-0.77 (m, 3H); <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): δ 169.7, 159.8, 126.3, 93.8, 63.0, 61.9, 30.4, 23.3, 23.1, 7.5; IR v<sub>max</sub> (film)/cm<sup>-1</sup>: 3278, 2974, 2929, 1658, 1652, 1454, 1416, 1478, 1247, 1224, 1158, 1104, 1074, 1031; HRMS (ESI) m/z calculated for C<sub>10</sub>H<sub>16</sub>NO<sub>2</sub> ([M+H]+) 182.1176, found 182.1166.

To a solution of lactam 456 (500 mg, 2.76 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added triethylamine (0.58 mL, 4.14 mmol), DMAP (cat.) and di-tert-butyldicarbonate (903 mg, 4.14 mmol). The solution was stirred for 1 h. The solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to afford carbamate 467 (550 mg, 1.96 mmol, 71%).

**R**<sub>t</sub> 0.73 (1:1, hexanes/EtOAc); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 5.06 (s, 1H), 5.01 (s, 1H), 4.12 (dd, J = 12.5, 1.7 Hz, 1H), 3.91 (ddd, J = 11.1, 9.0, 5.5 Hz, 1H), 3.83-3.73 (m, 2H), 2.95-2.91 (m, 1H), 2.47-2.27 (m, 2H), 2.18-2.97 (m, 2H), 1.49 (s, 9H), 1.10 (t, J = 7.3 Hz, 3H); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 165.8, 149.1, 147.5, 109.6, 83.3, 62.0, 61.6, 60.9, 55.2, 28.2 (3C), 27.5, 23.8, 12.6; IR v<sub>max</sub> (film)/cm<sup>-1</sup>: 
Experimental Part

HRMS (ESI) \( m/z \) calculated for \( \text{C}_{16}\text{H}_{25}\text{NO}_{3}\text{Na} \) ([M+Na]⁺) 302.1727, found 302.1723.

To a solution of freshly prepared Petasis reagent \( \text{Cp}_2\text{TiMe}_2 \)\(^{722} \) in toluene (10 mL, ca. 0.3M) was added lactam 467 (400 mg, 1.42 mmol) and pyridine (0.46 mL, 5.69 mmol). The mixture was heated to 70 °C in the dark and stirred over night. The solvent was removed under reduced pressure and the residue was filtrated through a pad of silica gel (hexanes/EtOAc 4:1 as eluent). The filtrate was concentrated and the residue was purified by flash column chromatography (hexanes/EtOAc 20:1 → 4:1) to give enamine 468 (340 mg, 1.22 mmol, 86%).

\[ R_f \] 0.34 (4:1, hexanes/EtOAc); \(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ 5.11-5.01 (m, 1.5H), 4.96-4.94 (m, 1H), 4.78 (bs, 0.5H), 4.23 (bs, 1H), 4.00-3.90 (m, 1H), 3.89-3.82 (m, 2H), 3.80-3.70 (m, 1H), 2.75 (bs, 1H), 2.40-2.31 (m, 1H), 2.22-2.02 (m, 3H), 1.54-1.40 (m, 9H), 1.11 (t, \( J = 7.3 \) Hz, 3H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): δ 151.8, 150.5, 146.7, 108.5, 86.5, 81.3 (0.5C), 80.5 (0.5C), 68.0 (0.5C), 67.1 (0.5C), 63.3, 62.0, 44.5, 28.4 (3C), 27.7, 23.3, 12.4; IR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 2972, 1709, 1385, 1366, 1250, 1172, 1136, 1109, 1099; HRMS (ESI) \( m/z \) calculated for \( \text{C}_{14}\text{H}_{23}\text{NO}_{3}\text{Na} \) ([M+Na]⁺) 304.1515, found 304.1515.

Enamine 468 slowly hydrolyzed upon standing at room temperature in CDCl\(_3\) to give ketone 469.

\[ R_f \] 0.28 (4:1, hexanes/EtOAc); \(^1\)H-NMR (500 MHz, CDCl\(_3\)): δ 6.22 (bs, 1H, NH), 5.02 (s, 1H), 4.96 (s, 1H), 3.82 (ddd, \( J = 11.6, 4.5, 2.0 \) Hz, 1H), 3.76-3.71 (m, 3H), 3.17 (dd, \( J = 9.6, 5.7 \) Hz, 1H), 2.78 (bd, \( J = 13.7 \) Hz, 1H), 2.13-2.08 (m, 5H), 1.89 (ddd, \( J = 13.7, 12.1, 4.6, 1.3 \) Hz, 1H), 1.43 (s, 9H), 1.12 (t, \( J = 7.3 \) Hz, 3H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): δ 211.3, 154.7, 151.6, 109.4, 79.1, 64.3, 63.9.

\(^{722}\) Freshly prepared according to \textit{J. Org. Chem.} 1999, 64, 7074-7080:
A suspension of Bis(cyclopentadienyl)titanium dichloride (10g, 40.2 mmol) in toluene (100 mL) was cooled to -20 °C. Methylthium (29.5 mL, 88 mmol, 3M in diethoxyethane) was slowly added over a period of 15 min. THF (1 mL) was added to the mixture and the solution was then stirred at 0 °C for 1h. After completion of the reaction (monitored by crude NMR analysis) the mixture was transferred \textit{via} cannula into a 6% aqueous solution of NH\(_4\)Cl. The phases were separated and the organic phase was washed twice with ice cold water and once with brine. The organic phase was dried over MgSO\(_4\), filtered and concentrated to a volume of ca. 100 mL to obtain an orange solution of Petasis’ reagent (ca. 0.3 M). Additional THF (1 mL) was added for stabilization of the reagent.
Experimental Part

59.3, 54.9, 33.5, 30.5, 28.4 (3C), 24.4, 12.5; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3382, 2969, 2866, 1726, 1698, 1694, 1641, 1502, 1469, 1366, 1247, 1171, 1127, 1108, 1074; HRMS (ESI) $m/z$ calculated for C$_{16}$H$_{27}$NO$_4$Na ([M+Na]$^+$) 320.1832, found 320.1835.

To a solution of enamine 468 (820 mg, 2.94 mmol) in dry THF (8 mL) was added a solution of 9-BBN dimer (639 mg, 2.64 mmol) in THF (3.5 mL). After 1 h TLC analysis indicated full consumption of the starting material. The reaction was diluted with 20 mL of THF and hydrogen peroxide (15 mL, 150 mmol, 30% aq. Solution) and aq. NaOH (15 mL, 44 mmol, 3M) were added. The mixture was stirred vigorously for 4h. The layers were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over MgSO$_4$, filtrated and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc 4:1 $\rightarrow$ 1:1) to give alcohol 481 (600 mg, 2.02 mmol, 69%).

R$_f$ 0.35 (1:1, hexanes/EtOAc); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 5.01 (s, 1H), 4.94 (s, 1H), 4.72 (d, $J = 10.8$ Hz, 1H, OMe), 4.53 (dt, $J = 8.7$, 2.0 Hz, 1H), 4.34 (dd, $J = 11.9$, 8.7 Hz, 1H), 4.05-3.95 (m, 2H), 3.81-3.75 (m, 3H), 2.36-2.31 (m, 1H), 2.30-2.24 (m, 1H), 2.21-2.04 (m, 3H), 1.42 (s, 9H), 1.15 (t, $J = 7.3$ Hz, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 156.2, 151.3, 107.7, 80.4, 68.1, 63.5, 63.4, 62.0, 60.9, 37.9, 28.5 (3C), 28.4, 23.2, 12.4; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3418 (bs), 2969, 1694, 1666, 1412, 1319, 1254, 1161, 1128, 1092, 1041; HRMS (ESI) $m/z$ calculated for C$_{16}$H$_{27}$NO$_4$Na ([M+Na]$^+$) 320.1832, found 320.1830.

To a solution of alcohol 481 (600 mg, 2.02 mmol) in CH$_2$Cl$_2$ (40 mL) was added Dess-Martin reagent (1.7 g, 4.04 mmol) and pyridine (0.33 mL, 4.04 mmol). The solution was stirred until full consumption of the starting material was observed by TLC analysis (15 min). The mixture was concentrated and directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to afford aldehyde 491 (530 mg, 1.79 mmol, 89%).

R$_f$ 0.68 (1:1, hexanes/EtOAc); $^1$H-NMR (300 MHz, d$_6$-DMSO, 100 °C): $\delta$ 9.83 (d, $J = 2.3$ Hz, 1H), 5.05 (s, 1H), 4.94 (s, 1H), 4.47 (dd, $J = 9.2$, 2.3 Hz, 1H), 4.00-3.92 (m, 1H), 3.80-3.70 (m, 2H), 3.52 (d, $J = 13.3$ Hz, 1H), 2.75-2.70 (m, 1H), 2.37-2.03 (m, 4H), 1.40 (s, 9H), 1.09 (t, $J = 7.3$ Hz, 3H); $^{13}$C-NMR...
NMR (75 MHz, CDCl₃, mixture of rotamers, all peaks reported): δ 201.9, 201.6, 154.8, 153.2, 150.8, 150.8, 108.7, 80.6, 80.5, 68.1, 67.9, 65.0, 63.7, 62.3, 62.0, 59.9, 59.4, 42.4, 42.1, 28.4, 28.4, 26.8, 23.1, 22.9, 12.2; IR ν_max (film)/cm⁻¹: 2972, 2880, 1723, 1704, 1478, 1456, 1398, 1367, 1311, 1257, 1216, 1161, 1128, 1091; HRMS (ESI) m/z calculated for C₁₆H₂₆NO₄ ([M+H]+) 296.1856, found 296.1856.

To a solution of indoline (1 g, 8.39 mmol) in MeOH (100 mL) was added sodium tungstate (554 mg, 1.68 mmol) and hydrogen peroxide (8.57 mL, 84 mmol, 30% solution). The mixture was stirred until full consumption of the starting material was observed by TLC (ca. 20 min). Potassium carbonate (5.8 g, 42 mmol) and dimethylsulfate (1.04 mL, 10.91 mmol) were added and the reaction was stirred for another 45 min. The reaction was quenched by slow addition of sat. sodium thiosulfate and water was added. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over MgSO₄ and the solvent was evaporated. Flash column chromatography gave 705 (480 mg, 3.26 mmol, 39%).

To a solution of 705 (480 mg, 3.26 mmol) in t-BuOH (35 mL) was added N-bromosuccinimide (1.74 g, 9.78 mmol). The solution was stirred for 30 min. After removal of the solvent the residue was taken up in toluene and water was added. The phases were separated and the aqueous phase was extracted three times with toluene. The combined organic phases were dried over MgSO₄ and the solvent was evaporated. Flash column chromatography gave the corresponding dibromo oxindole (650 mg, 2.03 mmol, 62%).

To a solution of this dibromo oxindole (650 mg, 2.03 mmol) in acetic acid (50 mL) was added activated zinc dust (1.32 g, 20.3 mmol). The reaction was stirred for 1.5 h and then filtrated to remove the remaining zinc dust. The solution was diluted with CH₂Cl₂ and washed with water and brine. The organic phase was dried over MgSO₄ and the solvent was evaporated. Flash column chromatography gave 358 (278 mg, 1.70 mmol, 84%).

¹H-NMR (300 MHz, CDCl₃): δ 7.31 (td, J = 7.7, 1.0 Hz, 1H), 7.26-7.21 (m, 1H), 7.07 (td, J = 7.6, 1.0 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 4.03 (s, 3H), 3.51 (s, 2H).
To a solution of *N*-methoxyoxindole\textsuperscript{23} (199 mg, 1.22 mmol) in EtOAc (15 mL) was added MgCl\textsubscript{2} (19 mg, 0.20 mmol) and triethylamine (0.29 mL, 2.03 mmol). The solution was stirred for 10 min before chlorotrimethylsilane (0.20 mL, 1.52 mmol) was added. After another 5 min a solution of aldehyde 491 (300 mg, 1.02 mmol) in EtOAc (2 mL) was added. After full consumption of the starting material (2 h) the reaction was quenched by addition of sat. NaHCO\textsubscript{3}. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over MgSO\textsubscript{4} and the solvent was removed. The residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to afford 498 (370 mg, 0.84 mmol, 83%). The NMR spectra showed a 1:1 mixture of rotamers.

\[ R_{f} 0.48 \text{(1:1, hexanes/EtOAc)}; \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \delta 7.52 (dd, \textit{J} = 12.8, 7.1 Hz, 1H), 7.35-7.30 (m, 1H), 7.15 (t, \textit{J} = 8.0 Hz, 1H), 7.07-6.98 (m, 2H), 5.58-5.51 (m, 1H), 5.12 (d, \textit{J} = 13.3 Hz, 1H), 5.03 (d, \textit{J} = 10.6 Hz, 1H), 4.18-4.11 (m, 1H), 4.06 (d, \textit{J} = 12.0 Hz, 3H), 3.87-3.79 (m, 1H), 3.77-3.71 (m, 1H), 3.50 (d, \textit{J} = 12.9 Hz, 1H), 2.80-2.76 (m, 1H), 2.43-2.11 (m, 4H), 1.43 (d, \textit{J} = 14 Hz, 9H), 1.21 (t, \textit{J} = 7.3 Hz, 3H); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}, mixture of rotamers, all peaks reported): \delta 162.2, 154.4, 153.5, 151.3, 141.5, 139.7, 139.6, 129.5, 129.3, 124.8, 124.4, 123.0, 122.6, 122.5, 118.4, 118.3, 108.2, 108.2, 107.5, 107.3, 80.4, 80.2, 67.7, 67.5, 63.9, 63.8, 62.2, 62.0, 60.9, 60.6, 59.1, 57.9, 41.8, 41.6, 26.5, 28.4, 28.3, 28.0, 23.5, 23.3, 12.3; IR \textit{\nu}_{\text{max}} \text{(film)} / \text{cm}^{-1} \text{:} 2971, 1722, 1694, 1614, 1461, 1392, 1366, 1320, 1213, 1160, 1130, 1075; HRMS (ESI) \textit{m/z} calculated for C\textsubscript{25}H\textsubscript{36}N\textsubscript{3}O\textsubscript{5} ([M+NH\textsubscript{4}\textsuperscript{+}]\textsuperscript{+}) 458.2649, found 459.2650.

A solution of 498 (370 mg, 0.84 mmol) in THF/MeOH 1:1 (20 mL) was cooled to 0 °C and sodium borohydride (38 mg, 1.01 mmol) was slowly added. The mixture was stirred at 0 °C for 1.5 h. The reaction was quenched by addition of sat. sat. NaHCO\textsubscript{3}. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over MgSO\textsubscript{4}.

and the solvent was removed. The residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to afford 506 (300 mg, 0.68 mmol, 81%) as a 1:1 mixture of diastereomers.

Due to multiple rotamers and diastereomers at C(7) NMR spectra were difficult to analyze. $^1$H and $^{13}$C NMR spectra are given in chapter 25.

R$_f$ 0.59/0.53 (1:1, hexanes/EtOAc); IR $\nu_{max}$ (film)/cm$^{-1}$: 2970, 2939, 1728, 1694, 1619, 1480, 1465, 1393, 1366, 1323, 1247, 1157, 1124, 1090; HRMS (ESI) $m/z$ calculated for C$_{25}$H$_{35}$N$_2$O$_5$ ([M+H]$^+$) 443.2540, found 443.2543.

A two neck round bottom flask was charged with a solution of 506 (150 mg, 0.34 mmol) in CH$_2$Cl$_2$ (15 mL). Through a gas inlet oxygen was carefully bubbled through the solution. The mixture was cooled to -78 °C and ozone was bubbled through the solution for 10 min (full consumption of starting material based on TLC analysis). Again, oxygen and then nitrogen was bubbled through the reaction mixture. Dimethylsulfide (1.25 mL, 17 mmol) was added and the mixture was allowed to warm to ambient temperature. After 2 h the solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to afford 507 (116 mg, 0.26 mmol, 77%).

R$_f$ 0.35 (1:1, hexanes/EtOAc); $^1$H-NMR (400 MHz, CDCl$_3$, mixture of rotamers and diastereomers, all peaks reported): $\delta$ 7.53-7.50 (m, 0.5H), 7.36-7.24 (m, 1.5H), 7.13-7.05 (m, 1H), 7.01-6.94 (m, 1H), 5.10-4.92 (m, 0.5H), 4.84-4.76 (m, 0.5H), 4.12-3.48 (m, 8H), 2.92 (dt, $J$ = 13.9, 6.8 Hz, 0.5H), 2.83-2.30 (m, 5.5H), 2.19-1.92 (m, 1H), 1.51-1.36 (m, 9H), 1.17-1.09 (m, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$, mixture of rotamers and diastereomers, all peaks reported): $\delta$ 209.8, 209.5, 209.3, 209.3, 172.8, 172.5, 172.0, 171.9, 155.0, 154.9, 154.9, 154.8, 140.3, 140.1, 140.0, 128.5, 128.5, 128.2, 128.1, 125.4, 125.4, 125.3, 125.2, 125.0, 124.5, 124.3, 123.9, 123.2, 123.1, 123.1, 123.0, 107.4, 107.1, 80.9, 80.8, 80.4, 70.0, 69.7, 69.4, 69.1, 63.5, 62.5, 62.3, 62.2, 62.0, 61.9, 61.0, 60.7, 59.4, 58.6, 42.5, 42.3, 41.8, 41.4, 35.6, 35.0, 34.6, 34.5, 31.6, 31.2, 31.0, 30.8, 30.1, 30.0, 29.4, 29.3, 28.5, 28.5, 28.4, 28.4, 27.8, 27.2, 27.0, 26.9, 7.8, 7.8, 7.7, 7.6; IR $\nu_{max}$ (film)/cm$^{-1}$: 2976, 2340, 1716, 1695, 1619, 1467, 1393, 1368, 1324, 1248, 1162, 1125, 1093; HRMS (ESI) $m/z$ calculated for C$_{26}$H$_{33}$N$_2$O$_6$ ([M+H]$^+$) 445.2333, found 445.2333.
Experimental Part

512: $R_f$ 0.67 (1:1, hexanes/EtOAc); $^1H$-NMR (600 MHz, CDCl$_3$): $\delta$ 8.01-7.69 (bs-m, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.11-7.05 (bs-m, 1H), 6.92 (d, $J = 10.7$ Hz, 1H), 5.76-5.55 (bs-m, 1H), 4.32-4.11 (bs-m, 1H), 4.04 (s, 3H), 3.98 (dd, $J = 11.0$, 6.0 Hz, 1H), 3.88 (dd, $J = 10.9$, 5.5 Hz, 1H), 3.65 (bs-d, $J = 18.2$ Hz, 1H), 3.31 (ddd, $J = 13.6$, 11.4, 2.6 Hz, 1H), 3.03 (t, $J = 11.6$ Hz, 1H), 2.97-2.91 (bs-m, 1H), 2.56 (d, $J = 14.9$ Hz, 1H), 2.25-2.16 (m, 2H), 1.98-1.90 (bs-m, 1H), 1.42 (bs-s, 9H), 1.04 (t, $J = 7.6$ Hz, 3H); $^{13}C$-NMR (150 MHz, CDCl$_3$, broad signals and splitted peaks, all peaks reported): $\delta$ 162.7, 154.2, 139.9, 134.4, 129.9, 129.2, 124.8, 124.2, 123.9, 123.3, 123.0, 122.7, 117.9, 107.4, 80.6, 68.4, 67.9, 63.8, 48.4, 46.9, 43.3, 42.5, 38.5, 28.4, 27.4, 23.1, 12.9; HRMS (ESI) m/z calculated for C$_{25}$H$_{33}$N$_2$O$_5$ ([M+H]$^+$) 441.2384, found 441.2378.

521: $R_f$ 0.46 (9:1, CH$_2$Cl$_2$/MeOH); $^1H$-NMR (600 MHz, CDCl$_3$): $\delta$ 7.38 (td, $J = 7.8$, 1.0 Hz, 1H), 7.19 (d, $J = 7.6$ Hz, 1H), 7.06 (td, $J = 7.7$, 1.1 Hz, 1H), 7.02 (ddd, $J = 7.8$, 1.0, 0.6 Hz, 1H), 6.69 (d, $J = 9.1$ Hz, 1H), 5.33-5.31 (m, 1H, NH), 5.31 (d, $J = 8.1$ Hz, 1H), 5.26 (t, $J = 1.7$ Hz, 1H), 5.01 (dd, $J = 9.1$, 4.6 Hz, 1H), 4.05 (s, 3H), 3.93 (dd, $J = 11.7$, 5.0 Hz, 1H), 3.84 (dd, $J = 11.7$, 4.8 Hz, 1H), 3.79 (td, $J = 11.9$, 2.2 Hz, 1H), 3.74 (t, $J = 11.6$ Hz, 1H), 2.61 (dd, $J = 11.1$, 5.1, 1.3 Hz, 1H), 2.30-2.16 (m, 2H), 2.05 (ddd, $J = 14.4$, 12.1, 5.6 Hz, 1H), 1.83 (d, $J = 14.3$ Hz, 1H), 1.25 (t, $J = 7.3$ Hz, 3H); $^{13}C$-NMR (150 MHz, CDCl$_3$): $\delta$ 161.8, 151.2, 140.5, 134.8, 130.9, 128.2, 123.8, 123.0, 117.0, 110.8, 108.1, 83.2, 63.9, 63.5, 63.0, 48.5, 36.5, 36.5, 24.0, 12.7; HRMS (ESI) m/z calculated for C$_{20}$H$_{25}$N$_2$O$_3$ ([M+H]$^+$) 341.1860, found 341.1858.

To a solution of azetidine 521 (8 mg, 0.024 mmol) in CH$_2$Cl$_2$ (1 mL) was added triethylamine (9.9 μL, 0.071 mmol), ethylchloroformate (4.5 μL, 0.071 mmol) and DMAP (cat.). The reaction was allowed to stir at ambient temperature for 1.5 h. The solvent was removed and the residue was directly subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 40:1) to obtain some of the expected azetidine ethylcarbamate along with product 522 as a 2:1 mixture of diastereomers.

**Major diastereomer:** $R_f$ 0.78 (9:1, CH$_2$Cl$_2$/MeOH); $^1H$-NMR (600 MHz, CDCl$_3$): 2:1 mixture of diastereomers, major peaks reported): $\delta$ 8.86 (s, 1H, NH), 7.40 (td, $J = 7.7$, 1.1 Hz, 1H), 7.32 (d, $J = 7.0$ Hz, 1H), 7.16 (td, $J = 7.6$, 1.1 Hz, 1H), 7.03 (d, $J = 7.8$ Hz, 1H), 5.17 (t, $J = 1.0$ Hz, 4.94 (t, $J = 1.7$ Hz, 1H), 4.48 (s, 1H), 4.22-4.13 (m, 2H), 4.04 (s, 3H), 3.92 (dd, $J = 11.8$, 5.7 Hz, 1H), 3.87-3.76
(m, 2H), 3.64 (t, J = 11.6 Hz, 1H), 2.95 (dd, J = 11.4, 5.7 Hz, 1H), 2.06-2.00 (m, 2H), 1.86-1.83 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H), 1.03 (d, J = 7.3 Hz, 3H); ^13_C-NMR (150 MHz, CDCl₃, 2:1 mixture of diastereomers, major peaks reported): δ 167.9, 167.3, 150.0, 149.8, 139.2, 136.7, 129.8, 125.2, 124.3, 123.7, 110.5, 108.0, 98.4, 81.4, 67.6, 63.6, 63.5, 63.0, 57.5, 40.3, 35.1, 23.0, 13.9, 12.4; HRMS (ESI) m/z calculated for C₂₃H₂₉N₂O₇ ([M+H]⁺) 457.1969, found 457.1974.

18.6. Experimental Part to Chapter 10

A suspension of sodium hydride (566 mg, 14.16 mmol, 60% dispersion in mineral oil, washed twice with hexanes) in DMF (5 mL) was cooled to 0 °C. A solution of alcohol 433 (1.19 g, 14.16 mmol) in DMF (5 mL) was added slowly and the mixture was allowed to warm to ambient temperature. After 15 min a solution of epoxide 539^224 (1.38 g, 9.44 mmol) in DMF (5 mL) was added and the reaction was stirred for 20 h. The reaction was quenched by addition of pH 7 buffer. Et₂O was added and the phases were separated. The aqueous phase was extracted three times with Et₂O and the combined organic phases were washed with water and brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 1:1) to yield secondary alcohol 541 (1.14 g, 4.95 mmol, 52%).

Rf 0.47 (4:1, hexanes/EtOAc); ^1H-NMR (300 MHz, CDCl₃): δ 5.91-5.84 (m, 1H), 4.43 (d, J = 6.0 Hz, 1H), 4.10 (d, J = 6.7 Hz, 2H), 3.77-3.63 (m, 3H), 3.60-3.42 (m, 4H), 2.50 (d, J = 3.7 Hz, 1H, OH), 1.17 (dd, J = 15.3, 7.1 Hz, 6H), 1.06-1.01 (m, 4H); ^13_C-NMR (75 MHz, CDCl₃): δ 126.7, 114.5, 102.4, 71.4, 71.2, 69.8, 63.7, 63.3, 15.4 (2C), 2.3, 1.8; IR v max (film)/cm⁻¹: 3468 (bs), 2973, 2878, 1444, 1373, 1315, 1244, 1115, 1068; HRMS (ESI) m/z calculated for C₁₂H₃₂O₄Na ([M+Na]⁺) 253.1410, found 253.1409.

A suspension of sodium hydride (782 mg, 19.54 mmol, 60% dispersion in mineral oil, washed twice with hexanes) in DMF (20 mL) was cooled to 0 °C. A solution of alcohol 541 (3 g, 1303 mmol) in

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^224 Known epoxide 539 was prepared by epoxidation of acrolein (Wellman, G.R.; Lam, B.; Anderson, E.L.; White, E., V Synthesis 1976, 547) followed by diethylacetal formation using triethylorthoforamte.
DMF (5 mL) was added slowly and the mixture was allowed to warm to ambient temperature. After 20 min a benzyl bromide (2.32 mL, 19.54 mmol) was added and the reaction was stirred for 12 h. The reaction was quenched by addition of pH 7 buffer. Et₂O was added and the phases were separated. The aqueous phase was extracted three times with Et₂O and the combined organic phases were washed with water and brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 20:1) to yield benzyl ether S19 (3.25 g, 10.16 mmol, 78%).

\[ \text{Rf} \ 0.67 \ (4:1, \ \text{hexanes/EtOAc}); \ H^1\text{-NMR} \ (300 \text{ MHz, CDCl}_3): \ \delta \ 7.40-7.25 \ (m, \ 5H), \ 5.97-5.90 \ (m, \ 1H), \ 4.76 \ (s, \ 2H), \ 4.55-4.50 \ (m, \ 1H), \ 4.16-4.16 \ (m, \ 2H), \ 3.76-3.51 \ (m, \ 7H), \ 1.22 \ (q, \ J = 7.1 \text{ Hz, } 6H), \ 1.11-1.06 \ (m, \ 4H); \ C^13\text{-NMR} \ (75 \text{ MHz, CDCl}_3): \ \delta \ 138.8, \ 128.1, \ 127.8, \ 127.5, \ 127.3, \ 126.3, \ 114.9, \ 102.9, \ 79.3, \ 73.2, \ 71.5, \ 69.8, \ 64.1, \ 63.7, \ 15.6, \ 15.4, \ 2.4, \ 1.9; \ \text{IR} \ \nu_{\text{max}} \ (\text{film})/\text{cm}^{-1}: \ 2977, \ 2871, \ 1740, \ 1450, \ 1368, \ 1314, \ 1261; \ \text{HRMS} \ (\text{ESI}) \ m/z \ \text{calculated for C}_{19}H_{28}O_4Na (\lbrack \text{M+Na}^+ \rbrack) 343.1880, \ \text{found} \ 343.1883. \]

To a solution of acetal S19 (551 mg, 1.72 mmol) in MeCN/H₂O (6 mL, 1:1) was added hydroxylamine hydrochloride (239 mg, 3.44 mmol) and the mixture was heated to 60 °C. After 5 h the solvent was evaporated and the residue was directly subjected to flash column chromatography (hexanes/EtOAc 10:1) to give oxime 542 (368 mg, 1.41 mmol, 82%) as a mixture of double bond isomers.

\[ \text{Rf} \ 0.35 \ (4:1, \ \text{hexanes/EtOAc}); \ H^1\text{-NMR} \ (300 \text{ MHz, CDCl}_3, \ \text{mixture of double bond isomers}): \ \delta \ 8.64 \ (bs, \ 1H, \ \text{OH}), \ 7.43 \ (d, \ J = 7.5 \text{ Hz, } 0.8H), \ 7.38-2.27 \ (m, \ 5H), \ 6.85 \ (d, \ J = 6.2 \text{ Hz, } 0.2H), \ 5.96-5.88 \ (m, \ 1H), \ 4.67 \ (d, \ J = 11.9 \text{ Hz, } 1H), \ 4.50 \ (d, \ J = 12.0 \text{ Hz, } 1H), \ 4.19-4.13 \ (m, \ 3H), \ 3.67-3.63 \ (m, \ 2H), \ 3.76-3.51 \ (m, \ 7H), \ 1.11-1.02 \ (m, \ 4H); \ C^13\text{-NMR} \ (75 \text{ MHz, CDCl}_3, \ \text{mixture of double bond isomers, all peaks reported}): \ \delta \ 151.22, \ 149.7, \ 137.6, \ 137.5, \ 128.3, \ 127.9, \ 127.7, \ 127.2, \ 127.0, \ 114.5, \ 114.3, \ 77.6, \ 77.4, \ 77.2, \ 76.7, \ 75.2, \ 72.1, \ 69.7, \ 2.5, \ 1.9; \ \text{IR} \ \nu_{\text{max}} \ (\text{film})/\text{cm}^{-1}: \ 3336 \ (bs), \ 2858, \ 1489, \ 1441, \ 1364, \ 1256, \ 1205, \ 1111, \ 1073; \ \text{HRMS} \ (\text{ESI}) \ m/z \ \text{calculated for C}_{15}H_{20}NO_3 (\lbrack \text{M+H}^+ \rbrack) 262.1438, \ \text{found} \ 262.1439. \]

To a solution of oxime 542 (206 mg, 0.79 mmol) in CH₂Cl₂ (2 mL) was added bis(tributyltin)oxide (0.22 mL, 0.434 mmol). The mixture was stirred at ambient temperature for 1 h and then cooled to -30 °C.
°C. tert-Butyl hypochlorite (0.12 mL, 1.03 mmol) was added carefully and the mixture was allowed to warm to ambient temperature. After 30 min the starting material was consumed. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give isoxazoline 543 (180 mg, 0.69 mmol, 88%, dr = 10:1).

Rf 0.36 (2:1, hexanes/EtOAc); [α]D 25.4˚ -28.2 (c 4.3, CHCl3); 1H-NMR (400 MHz, CDCl3, 10:1 mixture of diastereomers, major isomer reported): δ 7.44-7.29 (m, 5H), 4.69 (d, J = 12.1 Hz, 1H), 4.53 (d, J = 12.1 Hz, 1H), 4.33-4.29 (m, 2H), 4.03 (dd, J = 10.4, 6.5 Hz, 1H), 3.62 (dd, J = 11.1, 6.5 Hz, 1H), 3.51 (dd, J = 12.6, 2.2 Hz, 1H), 3.41 (t, J = 11.0 Hz, 1H), 1.26-1.20 (m, 1H), 1.02-0.96 (m, 1H), 0.78-0.65 (m, 2H); 13C-NMR (100 MHz, CDCl3, 10:1 mixture of diastereomers, major isomer reported): δ 156.4, 137.0, 128.3 (2C), 128.0 (2C), 127.7, 72.3, 70.6, 70.4, 69.6, 66.6, 45.7, 10.0, 8.1; IR νmax (film)/cm⁻¹: 2945, 2857, 1624, 1601, 1499, 1450, 1413, 1371, 1321, 1279, 1210, 1105; HRMS (ESI) m/z calculated for C15H18NO3 ([M+H]+) 260.1281, found 260.1282.

A flame dried flask was charged with bis(dibenzylideneacetone)palladium(0) (345 mg, 0.60 mmol, 1 mol%) and 1,2-bis(diphenylphosphino)ethane (478 mg, 1.20 mmol, 2 mol%) and high vacuum was applied during 1 h. The flask was flushed with argon and a solution of 1-vinylcyclopropyl 4-methylbenzenesulfonate 434 (14.3 g, 60.0 mmol) in THF (20 mL) was added. After 10 min the reaction had turned green.

A separate flask was charged with sodium hydride (3.12 g, 78 mmol, 60% dispersion in mineral oil, washed twice with hexanes) and THF (100 mL) was added. The mixture was cooled to 0 °C and ethyl glycolate 725 (6.94 mL, 72 mmol) was slowly added. The suspension was warmed to ambient temperature and stirred for 30 min. To this suspension was added the allyl-palladium solution previously prepared. The reaction was stirred until full consumption of the starting material was observed (12 h). The reaction was quenched by addition of pH 7 buffer. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO4. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give ester 547 (8.49 g, 49.9 mmol, 83%).

Rf 0.63 (4:1, hexanes/EtOAc); 1H-NMR (300 MHz, CDCl3): δ 5.98-5.90 (m, 1H), 4.25-4.18 (m, 4H), 4.05 (s, 2H), 1.28 (dt, J = 7.1, 1.3 Hz, 3H), 1.16-1.04 (m, 4H); 13C-NMR (75 MHz, CDCl3): δ 170.3,

725 Ethyl glycolate is commercially available but can also be prepared easily by Fischer esterification of glycolic acid: Zhou, Z.; Meyerhoff, M.E. Biomacromolecules 2005, 6, 780-789.
128.2, 113.7, 71.3, 66.9, 60.8, 14.3, 2.5, 1.8; IR ν<sub>max</sub> (film)/cm<sup>-1</sup>: 2977, 1753, 1738, 1374, 1273, 1200, 1127, 1090, 1031; HRMS (ESI) m/z calculated for C₉H₁₅O₃ ([M+H]<sup>+</sup>) 171.1016, found 171.1018.

A solution of ester 547 (7.7 g, 45.2 mmol) in CH₂Cl₂ (150 mL) was cooled to -78 °C. A solution of DIBAL (68 mL, 68 mmol, 1M in hexanes) was slowly added over 30 min. The reaction was stirred for another 2 h and then quenched by addition of a saturated solution of Rochelle’s salt. The aqueous layer was diluted with pH 7 buffer and the phases were separated. The aqueous phase was extracted three times with CH₂Cl₂ and the combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed to obtain crude aldehyde 546, which was sufficiently pure to use in the next step.

H-NMR (300 MHz, CDCl₃): δ 9.74 (t, J = 1.0 Hz, 1H), 5.99-5.91 (m, 1H), 4.23 (dt, J = 6.8, 1.1 Hz, 2H), 4.06 (d, J = 0.9 Hz, 2H), 1.16-1.06 (m, 4H).

A solution of diisopropylamine (2.0 mL, 13.8 mmol) in THF (10 mL) was cooled to -78 °C and n-BuLi (8.0 mL, 12.75 mmol, 1.6 M in hexanes) was added. The reaction was allowed to warm to ambient temperature and stirred for 10 min. After cooling back to -78 °C nitromethane (0.75 mL, 13.81 mmol) was added. After 30 min at -78 °C a solution of aldehyde 546 (1.34 g, 10.62 mmol) in THF (5 mL) was added. After another 30 min the reaction was warmed to ambient temperature and stirred for 1 h. Chlorotrimethylsilane (2.0 mL, 15.93 mmol) was added and the resulting suspension was stirred for 1 h before quenching the reaction with pH 7 buffer. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 40:1) to give silyl ether 548 (2.15 g, 8.28 mmol, 78%) as a colorless oil.

R<sub>f</sub> 0.50 (9:1, hexanes/EtOAc); H-NMR (300 MHz, CDCl₃): δ 5.92-5.84 (m, 1H), 4.59-4.49 (m, 2H), 4.44-4.35 (m, 1H), 4.12 (dt, J = 6.7, 1.1 Hz, 2H), 3.47 (dd, J = 9.8, 4.8 Hz, 1H), 3.35 (dd, J = 9.8, 7.1 Hz, 1H), 1.17-1.03 (m, 4H), 0.11 (s, 9H); C-NMR (75 MHz, CDCl₃): δ 127.4, 114.0, 79.5, 71.6, 71.0, 69.1, 2.6, 2.1, 0.1 (3C); IR ν<sub>max</sub> (film)/cm<sup>-1</sup>: 2951, 2856, 1554, 1420, 1251, 113, 1078, 1005; HRMS (ESI) m/z calculated for C₁₁H₂₄N₂O₄Si ([M+NH₄]<sup>+</sup>) 277.1578, found 277.1580.

Aldehyde 546 was prepared according to a literature procedure: Eur. J. Org. Chem. 1999, 2725.
A solution of diisopropylamine (22.9 mL, 161 mmol) in THF (300 mL) was cooled to -78 °C and n-BuLi (94 mL, 150 mmol, 1.6 M in hexanes) was added. The reaction was warmed to ambient temperature and stirred for 10 min. The mixture was then cooled to -78 °C and nitromethane (8.7 mL, 161 mmol) was added. The solution was stirred for 15 min at -78 °C and then for 15 min at ambient temperature. After cooling back to -78 °C a solution of aldehyde 246 (13.5 g, 107 mmol) in THF (20 mL) was added and the reaction was allowed to stir at -78 °C for 1 h. The mixture was then warmed to ambient temperature and stirred for another 1 h. The reaction was quenched by addition of pH 7 buffer and diluted with EtOAc. The phases were separated and the aqueous phase was extracted twice with EtOAc. The aqueous phase was acidified with 1M HCl and extracted again twice with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give nitroalcohol 549 (14 g, 75 mmol, 70%) as a colorless oil.

\( R_f \) 0.23 (4:1, hexanes/EtOAc); \(^1\)H-NMR (300 MHz, CDCl₃): \( \delta \) 5.93-5.86 (m, 1H), 4.55-4.44 (m, 3H), 4.18-4.13 (m, 2H), 3.57-3.49 (m, 2H), 2.77-2.73 (m, 1H, OH), 1.19-1.04 (m, 4H); \(^{13}\)C-NMR (75 MHz, CDCl₃): \( \delta \) 127.9, 113.7, 78.1, 71.4, 70.0, 67.7, 2.4, 1.8; IR \( \nu_{max} \) (film)/cm\(^{-1}\): 3415 (bs), 2924, 2865, 1554, 1421, 1382, 1303, 1200, 1117, 1068; HRMS (ESI) m/z calculated for C₈H₁₃NO₄Na ([M+Na]⁺) 210.0737, found 210.0739.

From 543: To a solution of benzylether 543 (1.6 g, 6.17 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added FeCl₃ (2.0 g, 12.3 mmol). The reaction was stirred at 0 °C for 15 min and was then allowed to warm to ambient temperature. After 45 min water was added to the reaction the mixture was vigorously stirred for 1 min. The mixture was diluted with CH₂Cl₂ and the phases were separated. The aqueous phase was first extracted three times with CH₂Cl₂ and then three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give alcohol 537 (904 mg, 5.34 mmol, 87%).
From 548: To a solution of nitroalkene 548 (8.6 g, 33.2 mmol) in benzene (250 mL) was added triethylamine (23 mL, 166 mmol) and phenyl isocyanate (7.25 mL, 66.3 mmol). The reaction was stirred overnight. The solvent was evaporated and the residue was subjected to flash column chromatography to obtain the TMS protected alcohol S20. The product was taken up in CH₂Cl₂ (20 mL) and a few drops of HCl in MeOH (1.25 M) were added. After full consumption of the TMS ether the solvent was evaporated and the residue was purified by flash column chromatography (hexanes/EtOAc 2:1) to give alcohol 537 (4.2 g, 24.8 mmol, 75%) as a 4:1 mixture of diastereomers.

**Major diastereomer:** Rₚ 0.24 (1:1, hexanes/EtOAc); [α]₀^25° +98.6 (c 0.8, CHCl₃); ¹H-NMR (300 MHz, CDCl₃): δ 4.63 (d, J = 5.2 Hz, 1H), 4.22 (dt, J = 12.5, 1.1 Hz, 1H), 4.04 (dd, J = 10.5, 6.6 Hz, 1H), 3.72 (dd, J = 11.2, 6.6 Hz, 1H), 3.52 (dd, J = 12.4, 1.7, 0.9 Hz, 1H), 3.40 (t, J = 10.8 Hz, 1H), 2.88-2.78 (m, 1H, OH), 1.25-1.17 (m, 1H), 1.00-0.92 (m, 1H), 0.79-0.61 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃): δ 157.5, 73.8, 70.9, 66.8, 64.0, 45.5, 10.4, 8.6; IR νₘₐₓ (film)/cm⁻¹: 3404 (bs), 2915, 2859, 1639, 1455, 1409, 1376, 1224, 1091, 1071, 1030; HRMS (ESI) m/z calculated for C₈H₁₂NO₃ ([M+H]⁺) 170.0812, found 170.0807.

**Minor diastereomer (S21):** Rₚ 0.24 (1:1, hexanes/EtOAc); ¹H-NMR (400 MHz, CDCl₃): δ 4.63 (dt, J = 10.2, 6.2 Hz, 1H), 4.34 (dd, J = 10.6, 6.6 Hz, 1H), 4.00 (dd, J = 10.0, 6.2 Hz, 1H), 3.57 (d, J = 5.9 Hz, 1H, OH), 3.48-3.35 (m, 2H), 3.18 (t, J = 10.4 Hz, 1H), 1.27-1.21 (m, 1H), 1.05-0.99 (m, 1H), 0.79-0.66 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 160.7, 73.1, 70.4, 67.1, 65.7, 49.3, 10.0, 8.6; IR νₘₐₓ (film)/cm⁻¹: 3382 (bs), 2970, 2865, 1633, 1456, 1413, 1375, 1346, 1318, 1284, 1207, 1097, 1083, 1021; HRMS (ESI) m/z calculated for C₈H₁₂NO₃ ([M+H]⁺) 170.0812, found 170.0811.

Intermediate silyl ether S20 could also be isalted:

**Major diastereomer:** ¹H-NMR (300 MHz, CDCl₃): δ 4.57 (s, 1H), 4.12 (d, J = 11.8 Hz, 1H), 4.02 (dd, J = 10.4, 6.5 Hz, 1H), 3.63 (dd, J = 11.2, 6.5 Hz, 1H), 3.46 (dd, J = 12.1, 1.7 Hz, 1H), 3.38 (t, J = 10.8 Hz, 1H), 1.26-1.15 (m, 1H), 1.00-0.92 (m, 1H), 0.76-0.61 (m, 2H), 0.18 (s, 3H).

To a solution of alcohol S21 (20 mg, 0.12 mmol) in benzene was added triphenylphosphine (62 mg, 0.24 mmol) and p-nitrobenzoic acid (30 mg, 0.18 mmol). The solution was cooled to 0 °C and DEAD
(37 µL, 0.24 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and stirred for 5 h. The solvent was evaporated and the residue was purified by flash column chromatography (hexanes/EtOAc 2:1) to give p-nitrobenzoate S22 (28 mg, 0.09 mmol, 74%).

R<sub>f</sub> 0.70 (1:1, hexanes/EtOAc); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.26-8.13 (m, 4H), 5.85 (s, 1H), 4.40 (d, J = 13.2 Hz, 1H), 4.07 (dd, J = 10.4, 6.5 Hz, 1H), 3.73-3.61 (m, 2H), 3.45 (t, J = 10.8 Hz, 1H), 1.22-1.13 (m, 1H), 1.01-0.92 (m, 1H), 0.80-0.64 (m, 2H); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 163.3, 154.0, 150.6, 134.6, 130.9 (2C), 123.5 (2C), 71.3, 70.6, 67.5, 67.2, 45.9, 10.5, 8.4; HRMS (ESI) m/z calculated for C<sub>15</sub>H<sub>15</sub>N<sub>2</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 319.0925, found 319.0928.

**Optimized conditions:**

To a solution of nitroalcohol 549 (5 g, 26.7 mmol) in toluene (1.5 L) was added DMAP (6.5 g, 53.4 mmol) followed by di-tert-butyl dicarbonate (17.5 g, 80 mmol). The reaction was stirred over night and the solvent was evaporated. The residue was purified by flash column chromatography (hexanes/EtOAc 10:1) to give enol ether 550 (3.2 g, 21.2 mmol, 79%) as a white solid.

R<sub>f</sub> 0.37 (4:1, hexanes/EtOAc); m.p. 97 °C; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 6.79 (d, J = 5.9 Hz, 1H), 5.79 (d, J = 6.0 Hz, 1H), 4.24 (dd, J = 9.8, 5.2 Hz, 1H), 3.92 (dd, J = 13.1, 9.8 Hz, 1H), 3.80 (dd, J = 13.0, 5.3 Hz, 1H), 1.39-1.31 (m, 1H), 0.96-0.80 (m, 2H), 0.51-0.43 (m, 1H); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 152.2, 95.1, 68.0, 66.2, 44.7, 27.7, 10.7, 6.7; IR <i>v</i><sub>max</sub> (film)/cm<sup>-1</sup>: 3007, 2881, 1747, 1617, 1573, 1458, 1405, 1337, 1289, 1247, 1212, 1101, 1048, 1019; HRMS (EI) m/z calculated for C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub> ([M+H]<sup>+</sup>) 151.0628, found 151.0629.

The cycloaddition (549 → 550) proceeds via an intermediate nitroalkene 551, which can be isolated. When this nitroalkene is subjected to the same reaction conditions<sup>728</sup>, formation of enol ether 550 is observed as before:

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<sup>727</sup> For a discussion of the optimization of this reaction see section 11.1.

<sup>728</sup> The cycloaddition of nitroalkene 551 to enol ether 550 can also be achieved using phenylisocyanate as dehydrating reagent (45% yield).
A solution of nitroalcohol 549 (100 mg, 0.53 mmol) in toluene (3 mL) was cooled to 0 °C and di-tert-butyl dicarbonate (128 mg, 0.59 mmol) was added. The reaction was stirred for 2 h at 0 °C. The solution was poured into a separatory funnel containing pH 7 buffer. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over MgSO₄ and the solvent was evaporated. The residue was purified by flash column chromatography (hexanes/EtOAc 10:1) to give nitroalkene 551 (90 mg, 0.532 mmol, 100%) as a mixture of double bond isomers.

**Major isomer:** Rₐ 0.62 (4:1, hexanes/EtOAc); ¹H-NMR (400 MHz, CDCl₃): δ 7.27 (dt, J = 13.3, 3.5 Hz, 1H), 7.20 (dt, J = 13.3, 2.0 Hz, 1H), 5.92 (tp, J = 6.2, 2.1 Hz, 1H), 4.23 (dd, J = 3.4, 2.0 Hz, 2H), 4.19 (dp, J = 6.6, 1.1 Hz, 2H), 1.18-1.07 (m, 4H); ¹³C-NMR (100 MHz, CDCl₃): δ 139.7, 138.7, 128.3, 113.7, 71.3, 65.3, 2.4, 1.8; IR νmax (film)/cm⁻¹: 2984, 2837, 1526, 1355, 1339, 1275, 1219, 1128, 1091, 1026; HRMS (ESI) m/z calculated for C₈H₁₅N₂O₃ ([M+NH₄⁺]⁺) 187.1077, found 187.1074.

To a solution of nitroalkene 551 (90 mg, 0.532 mmol) in toluene (2 mL) was added DMAP followed by di-tert-butyl dicarbonate (232 mg, 1.06 mmol). The reaction was stirred overnight and the solvent was evaporated. The residue was purified by flash column chromatography (hexanes/EtOAc 10:1) to give enol ether 550 (48 mg, 0.318 mmol, 60%) as a white solid.

A solution of oxime ether 537 (30 mg, 0.18 mmol) in THF (1 mL) was cooled to 0 °C and diethylaluminum cyanide (0.36 mL, 0.36 mmol, 1M in toluene) was added. The mixture was heated to reflux and after 2.5 h more diethylaluminum cyanide (0.36 mL, 0.36 mmol, 1M in toluene) was added. After another 2 hours the reaction was cooled to 0 °C and quenched by addition of sat. NH₄Cl. The mixture was filtrated over celite and the solvent was removed. The residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 40:1) to give nitrile 563 (22 mg, 0.11 mmol, 63%, 82% brsm) along with some reisolated starting material 537 (7 mg, 77% convn.).

Rₐ 0.34 (20:1, CH₂Cl₂/MeOH); ¹H-NMR (300 MHz, CDCl₃): δ 5.06 (bs, 1H, NH), 4.58-4.55 (m, 1H), 3.97-3.93 (m, 2H), 3.77-3.75 (m, 2H), 2.69-2.62 (m, 2H), 0.93-0.86 (m, 2H), 0.73-0.68 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃/CD₃OD ca. 9:1, splitting of some peaks²²⁹, all peaks reported): δ 118.7, 118.7.

²²⁹ Peak splitting might be due to partial deuterium of exchangeable protons by CD₃OD.
To a solution of isoxazoline 537 (63 mg, 0.37 mmol) in THF (3 mL) at -78 °C was added borontrifluoride etherate (46 μL, 0.372 mmol). A freshly prepared solution of 2-propenyl lithium (1.3 mL, 0.75 mmol, 0.58 M in Et₂O) was added slowly. The reaction was stirred for 1h before the same amount of organolithium solution was added again. After another 1.5 h the reaction was quenched by addition of pH 7 buffer and diluted with EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give isoxazolidine S23 (15 mg, 0.07 mmol, 19%, 36% brsm) along with reisolated starting material 537 (30 mg, 0.18 mmol, 52% convn.).

R_f 0.48 (EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 5.66 (bs-s, 1H, NH), 5.21 (s, 1H), 5.10 (s, 1H), 4.16-4.00 (m, 1H), 3.95-3.79 (m, 2H), 3.63-3.46 (m, 2H), 2.82-2.48 (bs-m, 2H, OH), 2.00 (s, 3H), 1.06-0.76 (m, 3H), 0.51-0.40 (m, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 142.9, 115.5, 72.6, 68.8, 67.7, 66.8, 65.4, 48.5, 22.3, 11.8, 7.4; HRMS (ESI) m/z calculated for C₁₁H₁₈NO₃ ([M+H]+) 212.1281, found 212.1279.

Isoxazolidine S23 (10 mg, 47 μmol) was carefully dried by coevaporation with benzene (3 x 2 mL) and MeCN (2 mL). The compound was taken up in MeCN (1 mL) and TFA (4.4 μL, 57 μmol) was added. The mixture was heated to 80 °C. After 6 h TLC analysis indicated full consumption of the starting material. The solvent was evaporated and the residue was directly subjected to flash column chromatography (hexanes/EtOAc 4:1 → 0:1) to give β-lactam S24 (5 mg, 27 μmol, 58%).

R_f 0.19 (EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 5.12 (s, 1H), 4.93 (s, 1H), 4.14-3.92 (m, 4H), 3.58 (dd, J = 11.8, 4.9 Hz, 1H), 3.18 (d, J = 3.9 Hz, 1H), 1.84 (s, 3H); HRMS (ESI) m/z calculated for C₉H₈NO₃Na ([M+H]+) 184.0968, found 184.0961.
A solution of 1-bromopropene (8.1 mL, 95 mmol) in THF (150 mL) was cooled to -78 °C and n-BuLi (120 mL, 194 mmol, 1.6M in hexanes) was added. The mixture was stirred for 1.5 h at -78 °C. Anhydrous cerium chloride\(^{730}\) (23.3 g, 95 mmol) was added and the mixture was stirred for another 30 min. To this mixture was added a premixed solution of oxime ether 537 (4 g, 23.6 mmol) and borontrifluoride etherate (5.8 mL, 47.3 mmol) in THF (10 mL). The reaction was stirred for 2.5 h and then quenched by addition of pH 7 buffer. The phases were separated and the aqueous phase was extracted three times with EtOAc and twice with CH\(_2\)Cl\(_2\). The aqueous phase was then acidified by 1M HCl until it turned clear and was then extracted again twice with CH\(_2\)Cl\(_2\). The combined organic layers were washed with brine and dried over MgSO\(_4\). The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give alkyne 567 (2.4 g, 11.5 mmol, 49%, 65% brsm) along with reisolated starting material 537 (970 mg, 5.7 mmol, 75% convn.).

R\(_f\) 0.43 (EtOAc); \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.70 (bs, 1H, NH), 3.98-3.87 (m, 2H), 3.75 (dd, \(J = 12.7, 3.5\) Hz, 1H), 3.45 (d, \(J = 12.6\) Hz, 1H), 3.31 (t, \(J = 10.4\) Hz, 1H), 2.83 (bs, 1H, OH), 2.71 (s, 1H), 1.91 (s, 3H), 1.10-1.02 (m, 1H), 0.97-0.78 (m, 2H), 0.55-0.46 (m, 1H); \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta\) 85.2, 72.7, 68.1, 66.9, 66.1, 63.3 (2C), 52.7, 10.0, 9.7, 4.1; IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3413 (bs), 3195 (bs), 2914, 2860, 2361, 2244, 1640, 1456, 1410, 1352, 1311, 1279, 1234, 1207, 1107, 1066, 1021; HRMS (ESI) \(m/z\) calculated for C\(_{11}\)H\(_{16}\)NO\(_3\) ([M+H\(^+\)]\(^\text{+}\)) 210.1125, found 210.1120.

To a suspension of anhydrous CeCl\(_3\) (241 mg, 0.98 mmol) in THF (1mL) at -78 °C was slowly added propynyllithium (2.57 mL, 0.95 mmol, 0.37M in THF). The mixture was stirred for 30 min at -78 °C. A solution of isoxazoline 550 (36 mg, 0.24 mmol) and BF\(_3\)OEt\(_2\) (56 mL, 0.48 mmol) in THF (1 mL) was then added. After 1 h the reaction was quenched by addition of pH 7 buffer. The aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over Mg\(_2\)SO\(_4\) and concentrated. The residue was purified by flash column chromatography to give two diastereomeric products S25.

\(^{730}\) CeCl\(_3\) heptahydrate was dried according to a literature procedure: Dimitrov, V.; Kostova, K.; Genov, M. Tetrahedron Lett. 1996, 37, 6787-6790.
**Diastereomer 1:** $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 6.79 (d, $J = 6.1$ Hz, 1H), 5.91 (d, $J = 6.1$ Hz, 1H), 4.57 (d, $J = 11.0$ Hz, 1H), 4.11 (dd, $J = 10.3$, 6.6 Hz, 1H), 4.00 (d, $J = 11.0$ Hz, 1H), 3.80 (dd, $J = 11.9$, 2.5 Hz, 1H), 3.50 (t, $J = 11.0$ Hz, 1H), 3.39 (dd, $J = 11.0$, 6.4 Hz, 1H), 2.89 (dd, $J = 13.6$, 2.5 Hz, 1H), 2.58 (ddd, $J = 13.4$, 11.9, 1.1 Hz, 1H), 1.30-1.20 (m, 3H), 1.01-0.90 (m, 2H), 0.78-0.72 (m, 1H), 0.69-0.62 (m, 1H), 0.41 (ddd, $J = 10.8$, 8.4, 6.4 Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 157.3, 152.4, 151.9, 96.3, 78.8, 72.1, 70.2, 69.3, 66.1, 51.3, 48.0, 28.4, 10.9, 9.6, 8.6, 4.5; HRMS (ESI) m/z calculated for C$_{16}$H$_{19}$N$_2$O$_4$ ([M+H]$^+$) 303.1339, found 303.1340.

**Diastereomer 2:** $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 6.81 (d, $J = 6.0$ Hz, 1H), 5.90 (d, $J = 6.0$ Hz, 1H), 4.46 (d, $J = 11.1$ Hz, 1H), 4.24 (dd, $J = 8.7$, 6.5 Hz, 1H), 4.02-3.94 (m, 3H), 3.61 (t, $J = 7.9$ Hz, 1H), 3.03 (ddd, $J = 16.4$, 8.8, 1.1 Hz, 1H), 2.73 (ddd, $J = 16.4$, 6.4, 2.0 Hz, 1H), 1.34-1.22 (m, 3H), 1.03-0.89 (m, 2H), 0.86-0.80 (m, 1H), 0.76-0.70 (m, 1H), 0.40 (ddd, $J = 11.2$, 7.8, 6.4 Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 156.2, 152.7, 151.8, 96.0, 73.0, 70.9, 69.2, 68.8, 67.0, 52.0, 45.9, 26.5, 11.1, 10.0, 8.4, 5.3; HRMS (ESI) m/z calculated for C$_{16}$H$_{19}$N$_2$O$_4$ ([M+H]$^+$) 303.1339, found 303.1346.

Isoxazolidine 567 (1 g, 4.78 mmol) was carefully dried by coevaporation with benzene (3 x 10 mL) and MeCN (10 mL). The compound was taken up in MeCN (20 mL) and freshly distilled TFA (0.44 mL, 5.73 mmol) was added. The mixture was heated to 80 °C. After 6 h TLC analysis indicated full consumption of the starting material. The solvent was evaporated and the residue was directly subjected to flash column chromatography (hexanes/EtOAc 4:1 → 0:1) to give β-lactam 572 (580 mg, 3.20 mmol, 67%).

**R$_f$**: 0.30 (EtOAc); $^1$H-NMR (400 MHz, CD$_2$CN): $\delta$ 6.85 (bs, 1H, NH), 4.01 (dd, $J = 11.9$, 4.1 Hz, 1H), 3.98 (dd, $J = 12.1$, 3.5 Hz, 1H), 3.90 (q, $J = 4.0$ Hz, 1H), 3.83 (dd, $J = 12.1$, 1.9 Hz, 1H), 3.61 (dd, $J = 12.0$, 2.8 Hz, 1H), 3.54 (d, $J = 4.3$ Hz, 1H, OH), 3.25 (dt, $J = 3.5$, 1.8 Hz, 1H), 1.87 (s, 3H); $^{13}$C-NMR (100 MHz, CD$_2$CN): $\delta$ 169.0, 83.5, 78.4, 69.6, 67.3, 61.1, 58.8, 51.3, 3.7; IR $\nu_{max}$ (film)/cm$^{-1}$: 3423 (bs), 3197 (bs), 2927, 2240, 1733, 1368, 1263, 1112, 1089; HRMS (ESI) m/z calculated for C$_9$H$_{12}$NO$_3$ ([M+H]$^+$) 182.0812, found 182.0810.
To a solution of β-lactam 572 (452 mg, 2.5 mmol) in MeCN (5 mL) was added triethylamine (0.70 mL, 5.0 mmol) and DMAP (cat.). A solution of di-tert-butyl dicarbonate (544 mg, 2.5 mmol) was slowly added over 5 min. After complete consumption of the starting material as judged by TLC, the solvent was evaporated and the residue was purified by flash column chromatography to give carbamate 573 (406 mg, 1.4 mmol, 58%) along with bis-Boc protected compound S26.

The structure of 573 was unambiguously confirmed by X-ray crystallographic analysis (see chapter 24).

Rf 0.42 (1:1, hexanes/EtOAc); H-NMR (300 MHz, CDCl3): δ 4.24-4.20 (m, 1H), 4.10 (dd, J = 12.4, 1.7 Hz, 1H), 3.99 (td, J = 11.9, 4.5 Hz, 2H), 3.61 (dd, J = 12.1, 4.8 Hz, 1H), 3.40-3.37 (m, 1H), 2.62 (d, J = 2.9 Hz, 1H, OH), 1.94 (s, 3H), 1.54 (s, 9H); C-NMR (75 MHz, CDCl3): δ 164.5, 146.7, 84.0, 84.0, 74.2, 67.4, 66.2, 60.5, 56.7, 55.0, 28.0 (3C); IR νmax (film)/cm⁻¹: 3496 (bs), 2977, 2934, 2873, 2251, 1806, 1732, 1456, 1369, 1330, 1261, 1153, 1080; HRMS (ESI) m/z calculated for C14H20NO5 ([M+H]+) 282.1336, found 282.1339.

To a solution of β-lactam 572 (61 mg, 0.34 mmol) in CH₂Cl₂ (1 mL) was added triethylamine (0.07 mL, 0.51 mmol), di-tert-butyl dicarbonate (81 mg, 0.37 mmol) and DMAP. The reaction was stirred overnight. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give carbonate S26 (126 mg, 0.33 mmol, 98%).

Rf 0.26 (4:1, hexanes/EtOAc); H-NMR (300 MHz, CDCl3): δ 5.49 (dd, J = 4.6, 1.5 Hz, 1H), 4.12 (dd, J = 13.2, 4.6 Hz, 1H), 4.06-4.03 (m, 2H), 3.90 (dd, J = 13.2, 1.6 Hz, 1H), 3.35 (t, J = 2.4 Hz, 1H), 1.84 (s, 3H), 1.53 (s, 9H), 1.50 (s, 9H); C-NMR (75 MHz, CDCl3): δ 164.4, 152.0, 146.3, 84.0, 82.9, 82.8, 74.3, 69.2, 65.1, 60.1, 57.5, 52.7, 28.1 (3C), 27.7 (3C), 3.7; IR νmax (film)/cm⁻¹: 2982, 2933, 2250, 1818, 1749, 1728, 1477, 1456, 1369, 1323, 1278, 1250, 1156, 1100; HRMS (ESI) m/z calculated for C19H31N2O7 ([M+NH₄]+) 399.2126, found 399.2139.
An oven dried flask was charged with carbamate 573 (730 mg, 2.60 mmol) and Petasis’ reagent \( \text{Cp}_2\text{TiMe}_2 \)\(^{731} \) (43 mL, 13.0 mmol, 0.3 M) and pyridine (0.84 mL, 10.4 mmol) were added. The mixture was heated to 70 °C in the dark for 5 h. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to give encarbamate 574 (535 mg, 1.92 mmol, 74%).\(^{732} \)

Due to slow hydrolysis of 574 in solution, we were not able to obtain a clean \(^{13}\)C NMR spectrum. A clean \(^1\)H NMR spectrum was obtained but shows broad peaks.

\[ R_f 0.53 \text{ (1:1, hexanes/EtOAc); } \text{\textit{\textsuperscript{1}H-NMR}} \text{ (300 MHz, CDCl}_3\text{): } \delta 5.07-4.67 \text{ (bs-m, 1H), 4.25 (bs-s, 1H), 4.16-4.05 (bs-m, 1H), 4.01-3.83 (m, 3H), 3.61-3.36 (bs-m, 1H), 3.21 (bs-s, 1H), 3.02 (s, 9H); HRMS (ESI) m/z calculated for C}_{15}H_{22}NO_4 ([M+H]^+) 280.1543, found 280.1539. \]

An oven dried flask was charged with 9-BBN dimer (175 mg, 0.73 mmol) and a solution of encarbamate 574 (135 mg, 0.48 mmol) in THF (3 mL) was added. After full consumption of the starting material (ca. 1 h) the reaction was diluted with THF (6 mL) and aqueous H\(_2\)O\(_2\) (2.5 mL, 24 mmol, 30% in H\(_2\)O) and 3M NaOH (2.5 mL) were added. After vigorous stirring for 4 h the phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO\(_4\). The solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 2:1) to give diol 575 (113 mg, 0.38 mmol, 79%).

Due to rotamers and broad peaks in the NMR spectra, alcohol 575 was first oxidized to its corresponding aldehyde 576 for easier characterization. A \(^1\)H NMR spectrum is reported.

\[ R_f 0.25 \text{ (1:1, hexanes/EtOAc); } \text{\textit{\textsuperscript{1}H-NMR}} \text{ (300 MHz, CDCl}_3\text{): } \delta 4.57-4.37 \text{ (m, 1H), 4.28-3.87 (m, 5H), 3.78-3.67 (m, 2H), 2.93-2.74 (m, 1H, OH), 2.68-2.59 (m, 1H), 2.42 (bs-s, 1H, OH), 1.92 (s, 3H), 1.46 (s, 9H); HRMS (ESI) m/z calculated for C}_{15}H_{23}NO_5Na ([M+Na]^+) 320.1468, found 320.1467. \]

\(^{731}\) Freshly prepared, see ref. 723.

\(^{732}\) The product slowly hydrolyzes to the corresponding methylketone but can be stored at -20 °C for several days.
To a solution of diol 575 (343 mg, 1.15 mmol) in CH$_2$Cl$_2$ (5 mL) was added iodobenzene diacetate (557 mg, 1.73 mmol) and TEMPO (54 mg, 0.35 mmol). The reaction was stirred for 2 h and the solvent was removed. The residue was purified by flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give aldehyde 576 (274 mg, 0.93 mmol, 80%).

R$_f$ 0.45 (1:1, hexanes/EtOAc); $^1$H-NMR (300 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): $\delta$ 9.77 (d, $J = 1.4$ Hz, 1H, CHO), 4.55 (t, $J = 8.1$ Hz, 1H), 4.24-4.05 (m, 2H), 4.01-3.94 (m, 1H), 3.92-3.76 (m, 1H), 3.60 (d, $J = 12.7$ Hz, 1H), 2.92 (dd, $J = 17.0$, 9.2 Hz, 1H), 2.63-2.30 (m, 1H), 1.94 (s, 3H), 1.50-1.44 (m, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): $\delta$ 201.0, 200.4, 154.7, 152.7, 84.7, 83.9, 80.9, 80.7, 76.4, 75.5, 66.9, 66.8, 63.7, 62.1, 60.3, 60.1, 59.2, 58.7, 42.5, 42.0, 28.1, 27.9, 3.7, 3.5; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3473 (bs), 2968, 2925, 2359, 1719, 1701, 1453, 1367, 1301, 1153, 1119; HRMS (ESI) m/z calculated for C$_{15}$H$_{21}$NO$_5$Na ([M+Na]$^+$) 318.1312, found 318.1313.

To a solution of N-methoxy oxindole 358 (41 mg, 0.25 mmol) in THF (2 mL) was added triethylamine (94 µL, 0.68 mmol) and magnesium bromide (7.8 mg, 0.04 mmol). The mixture was stirred for 15 min and chlorotrimethylsilane (65 µL, 0.51 mmol) was added. After another 5 min a solution of aldehyde 576 (50 mg, 0.17 mmol) in THF (0.5 mL) was added. The reaction was quenched after 15 min (full consumption of aldehyde) by addition of pH 7 buffer. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give alkene 577 (61 mg, 0.14 mmol, 82%) as a 2:1 mixture of double bond isomers.

Major isomer: R$_f$ 0.44 (1:1, hexanes/EtOAc); $^1$H-NMR (400 MHz, CD$_3$CN, mixture of rotamers, all peaks reported): $\delta$ 7.56-7.48 (m, 1H), 7.36-7.30 (m, 1H), 7.25-7.14 (m, 1H), 7.11-7.04 (m, 1H), 7.03-6.98 (m, 1H), 5.94-5.79 (m, 1H), 4.20-4.02 (m, 2H), 3.97 (s, 3H), 3.92-3.85 (m, 1H), 3.76-3.61 (m, 1H), 3.49-3.33 (m, 2H), 3.00-2.91 (m, 1H), 1.97-1.91 (m, 3H), 1.50-1.35 (m, 9H); $^{13}$C-NMR (100
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MHz, CD$_3$CN, mixture of rotamers, all peaks reported): δ 162.5, 156.9, 155.1, 142.2, 141.7, 139.9, 130.3, 125.4, 123.6, 121.0, 119.8, 108.1, 84.3, 83.8, 81.0, 79.0, 78.5, 68.3, 68.0, 64.4, 61.3, 61.1, 60.7, 59.3, 58.2, 43.8, 43.6, 39.0, 28.7, 28.5, 3.8, 3.7; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3442 (bs), 2969, 2934, 2242, 1705, 1612, 1460, 1368, 1236, 1153, 1131, 1096, 1048; HRMS (ESI) $m/z$ calculated for C$_{24}$H$_{29}$N$_2$O$_6$ ([M+H$^+$]) 441.2020, found 441.2011.

Minor isomer: $R_f$ 0.28 (1:1, hexanes/EtOAc); $^1$H-NMR (400 MHz, CD$_3$CN, mixture of rotamers, all peaks reported): δ 7.37-7.33 (m, 2H), 7.17-7.01 (m, 3H), 5.59-5.46 (m, 1H), 4.21-4.03 (m, 2H), 3.97 (s, 3H), 3.91-3.84 (m, 1H), 3.74-3.59 (m, 1H), 3.53-3.45 (m, 1H), 3.36-3.27 (m, 1H), 3.13-3.05 (m, 1H), 1.96 (s, 3H), 1.49-1.33 (m, 9H); $^{13}$C-NMR (100 MHz, CD$_3$CN, mixture of rotamers, all peaks reported): δ 162.9, 156.5, 154.8, 141.2, 140.7, 130.8, 125.9, 124.7, 123.8, 118.9, 118.2, 84.5, 84.0, 81.3, 78.7, 78.3, 68.4, 68.2, 68.1, 68.0, 64.4, 61.4, 61.0, 60.6, 59.5, 43.2, 42.9, 28.6, 28.5, 3.9, 3.8; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3443 (bs), 2971, 2928, 2353, 2241, 1708, 1690, 1455, 1365, 1318, 1253, 1223, 1155, 1127, 1099, 1075; HRMS (ESI) $m/z$ calculated for C$_{24}$H$_{29}$N$_2$O$_6$ ([M+H$^+$]) 441.2020, found 441.2011.

A solution of alkene 577 (87 mg, 0.198 mmol) in THF/MeOH (4 mL, 1:1) was cooled to 0 °C and sodium borohydride (14.9 mg, 0.395 mmol) was added in one portion. After 20 min the solution was quenched by addition of sat. NaHCO$_3$. The aqueous phase was extracted three times with EtOAc, the combined organic phases were washed with brined and dried over MgSO$_4$. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give the intermediate alcohol (55 mg, 0.124 mmol, 63%) as a 1:1 mixture of diastereomers at C(7).

To a solution of this alcohol (85 mg, 0.192 mmol) in CH$_2$Cl$_2$ (4 mL) was added trichloroacetyl isocyanate (25 μL, 0.211 mol). After 15 min the solvent was evaporated and the residue was taken up in MeOH (4 mL). NaHCO$_3$ (24 mg, 0.288 mmol) was added and the mixture was stirred for 1 h. The solvent was evaporated and the residue was taken up in CH$_2$Cl$_2$/MeOH (9:1) and filtered through a pad of celite. The solvent was evaporated and the residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 40:1) to give carbamate 590 (80 mg, 0.165 mmol, 80%).

$R_f$ 0.67 (EtOAc); $^1$H-NMR (400 MHz, CD$_3$CN, mixture of rotamers and diastereomers, all peaks reported): δ 7.48-7.28 (m, 2H), 7.12-7.06 (m, 1H), 7.00 (dd, $J = 7.6$, 4.8 Hz, 1H), 5.27 (bs-s, 2H, NH$_2$), 5.10 (d, $J = 4.0$ Hz, 1H), 4.83-4.53 (m, 1H), 4.18-4.06 (m, 1H), 3.99-3.80 (m, 5H), 3.76-3.58 (m, 2H), 2.60-2.20 (m, 3H), 1.87-1.81 (m, 3H), 1.46-1.39 (m, 9H); $^{13}$C-NMR (100 MHz, CD$_3$CN,
mixture of rotamers and diastereomers, all peaks reported): \( \delta 173.1, 172.7, 156.6, 156.6, 141.6, 141.3, 129.1, 129.1, 126.9, 125.2, 123.8, 123.7, 108.0, 82.6, 81.1, 78.5, 69.4, 69.2, 66.4, 66.3, 64.1, 61.4, 61.3, 60.1, 59.6, 58.5, 55.3, 42.5, 42.4, 40.2, 40.0, 32.1, 31.7, 28.6, 3.6; \) \textit{IR} \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 3356 (bs), 3012, 2932, 1705, 1616, 1464, 1368, 1322, 1218, 1148, 1075, 1033, 1012; \textit{HRMS} (ESI) \( m/z \) calculated for \( \text{C}_{25}\text{H}_{31}\text{N}_{3}\text{O}_{7}\text{Na} \) ([M+Na\(^{+}\)]\(^{+}\)) 508.2054, found 508.2055.

A flame dried sealed tube was charged with MgO (11 mg, 0.28 mmol), iodobenzene diacetate (58 mg, 0.18 mmol) and \( \text{Rh}_{2}\)(esp)\(_{2} \) (1 mg, 1.2 \( \mu \)mol). A solution of carbamate 490 (58 mg, 0.12 mmol) in \( \text{CH}_{2}\text{Cl}_{2} \) (1 mL) was added. The sealed tube was tightly closed and the reaction was heated to 60 \(^\circ\)C for 4 h. The solution was filtered through a pad of celite and the solvent was removed. The residue was purified by flash column chromatography (\( \text{CH}_{2}\text{Cl}_{2}/\text{MeOH} \) 40:1) to give oxazolidinone 491 (47 mg, 0.10 mmol, 81%).

For easier characterization the Boc group in 491 was removed by treatment with silver triflate (2 equiv.) in MeCN to give azetidine S27:

\( R_{f} \) 0.48 (9:1, \( \text{CH}_{2}\text{Cl}_{2}/\text{MeOH} \)); \(^{1}\text{H}-\text{NMR} \) (600 MHz, CD\(_{3}\)CN, 1:1 mixture of diastereomers at C(7), all peaks reported): \( \delta 7.34-7.29 \) (m, 2H), 7.08 (dd, \( J = 7.5, 4.1 \), 1.0 Hz, 1H), 7.01-6.98 (m, 1H), 6.43 (bs-s, 1H, C(O)NH), 5.44 (td, \( J = 7.3, 6.7 \), 1.1 Hz, 1H), 4.54-4.33 (m, 1H), 4.27 (dd, \( J = 12.1, 6.7 \) Hz, 1H), 3.94 (s, 3H), 3.81-3.70 (m, 2H), 3.39-3.36 (m, 1H), 2.48 (ddddd, \( J = 15.0, 8.1, 2.9, 1.1 \) Hz, 1H), 2.27 (dddd, \( J = 23.2, 13.9, 8.3, 5.8 \) Hz, 1H), 2.11-2.01 (m, 1H), 1.89 (d, \( J = 6.0 \) Hz, 3H); \(^{13}\text{C}-\text{NMR} \) (150 MHz, CD\(_{3}\)CN, 1:1 mixture of diastereomers at C(7), all peaks reported): \( \delta 173.0, 172.9, 158.1, 158.1, 141.4, 129.1, 129.0, 127.0, 126.6, 125.7, 125.4, 123.7, 123.7, 108.0, 107.9, 82.1, 82.1, 81.8, 81.7, 79.2, 79.2, 75.8, 75.7, 64.1, 64.0, 56.8, 56.7, 53.9, 51.8, 51.7, 42.1, 41.7, 39.8, 39.7, 33.8, 33.4, 3.7; \) \textit{IR} \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 3308 (bs), 2923, 2852, 1771, 1705, 1616, 1521, 1463, 1367, 1339, 1219, 1149, 1081, 1063; \textit{HRMS} (ESI) \( m/z \) calculated for \( \text{C}_{20}\text{H}_{32}\text{N}_{3}\text{O}_{5} \) ([M+H\(^{+}\)]\(^{+}\)) 384.1554, found 384.1551.
To a solution of alkyne 537 (30 mg, 0.11 mmol) in EtOAc (1 mL) was added Pd/C (3 mg, 10 wt%, 10% palladium). The flask was evacuated and purged with Ar. After evacuating a second time, the suspension was set under an atmosphere of H\textsubscript{2} (balloon). After 1 h the mixture was filtered through a pad of celite and the solvent was removed. The crude alcohol was taken up in CH\textsubscript{2}Cl\textsubscript{2} (1 mL) and trichloroacetyl isocyanate (14 μL, 0.12 mmol) was added. After stirring for 15 min the solvent was removed under vacuum and the residue was dissolved in MeOH (1 mL). NaHCO\textsubscript{3} (14 mg, 0.16 mmol) was added and the mixture was allowed to stir for 1.5 h. After this time the solution was diluted with CH\textsubscript{2}Cl\textsubscript{2} (5 mL) and filtered through a pad of celite. After removal of the solvent the resulting residue was subjected to flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give carbamate 615 (19 mg, 0.06 mmol, 53%).

R\textsubscript{f} 0.29 (1:1, hexanes/EtOAc); \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}, mixture of rotamers, all peaks reported): δ 5.66-5.43 (m, 1H), 4.82 (bs-s, 2H, NH\textsubscript{2}), 4.15-4.06 (m, 2H), 3.96-3.81 (m, 2H), 3.16-3.02 (m, 1H), 2.04-1.81 (m, 2H), 1.52 (s, 9H), 1.44-1.30 (m, 2H), 1.02-0.94 (m, 3H); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}, mixture of rotamers, major rotamer reported): δ 165.6, 155.1, 147.3, 83.8, 69.9, 66.0, 60.7, 60.1, 52.9, 34.1, 28.0 (3C), 15.9, 14.2; IR ν\textsubscript{max} (film)/cm\textsuperscript{-1}: 3447 (bs), 3364 (bs), 2964, 2934, 2874, 1798, 1715, 1600, 1506, 1457, 1369, 1337, 1310, 1254, 1154, 1093, 1073; HRMS (ESI) m/z calculated for C\textsubscript{15}H\textsubscript{28}N\textsubscript{3}O\textsubscript{6} ([M+NH\textsubscript{4}]\textsuperscript{+}) 346.1973, found 346.1968.

A solution of carbamate 615 (10 mg, 0.030 mmol) in MeCN (1 mL) was degassed by bubbling N\textsubscript{2} through the solution for 15 min. Then iodobenzene diacetate (25 mg, 0.076 mmol) and iodine (8 mg, 0.030 mmol) were added. The mixture was irradiated with a UV lamp for 45 min. The reaction was quenched by addition of sat. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over Mg\textsubscript{2}SO\textsubscript{4} and the solvent was evaporated. The residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give carbonate 616 (3.5 mg, 35%) along with some carbamate product resulting from cyclization of the nitrogen.

R\textsubscript{f} 0.65 (1:1, hexanes/EtOAc); \textsuperscript{1}H-NMR (600 MHz, CDCl\textsubscript{3}): δ 6.04 (d, J = 6.2 Hz, 1H), 5.23 (d, J = 6.2 Hz, 1H), 4.20 (dd, J = 13.0, 1.2 Hz, 1H), 3.92 (dd, J = 13.0, 2.5 Hz, 1H), 3.13-3.12 (m, 1H), 2.19 (ddd, J = 14.6, 12.4, 4.7 Hz, 1H), 1.99 (ddd, J = 14.8, 12.1, 4.5 Hz, 1H), 1.54 (s, 9H), 1.50-1.33 (m,
To a solution of carbamate 626 (5 mg, 10 μmol) in CH₂Cl₂ (1 mL) was added NIS (2.6 mg, 11 μmol, single double bond isomer). After 12 h (light was left on) the reaction was quenched by addition of sat. Na₂S₂O₅. The aqueous phase was extracted three times with CH₂Cl₂, the combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography to give vinyl iodide 627 (4 mg, 7.2 μmol, 70%) as a mixture of double bond isomers.

Rᵣ 0.64 (EtOAc); ¹H-NMR (600 MHz, CD₃CN, mixture of double bond isomers, all peaks reported): δ 7.63 (dt, J = 7.5, 1.0 Hz, 0.5H), 7.41 (d, J = 7.6 Hz, 0.5H), 7.40-7.35 (m, 1H), 7.34-7.33 (m, 0.5H), 7.26 (d, J = 8.4 Hz, 0.5H), 7.09 (ddt, J = 13.5, 7.6, 1.0 Hz, 1H), 7.03 (dddd, J = 14.1, 7.8, 0.6 Hz, 1H), 6.06 (dd, J = 10.0, 7.6 Hz, 0.5H), 5.66 (t, J = 8.7 Hz, 0.5H), 5.30 (dd, J = 11.0, 6.4 Hz, 0.5H), 5.30 (bs-s, 2H, NH₂), 5.24 (dd, J = 10.9, 6.3 Hz, 0.5H), 4.07 (dddd, J = 30.4, 11.5, 6.4 Hz, 1H), 3.99-3.97 (m, 3H), 3.70-3.66 (m, 1H), 3.58-3.51 (m, 2H), 3.45-3.41 (m, 1H), 2.16-2.12 (m, 3H); ¹³C-NMR (150 MHz, CD₃CN, mixture of double bond isomers, all peaks reported): δ 162.6, 165.3, 156.3, 156.3, 152.2, 152.2, 151.2, 151.1, 141.2, 140.3, 138.8, 136.8, 131.4, 130.9, 128.5, 127.3, 125.0, 123.9, 123.7, 121.6, 119.7, 108.4, 108.2, 75.4, 75.4, 71.8, 71.7, 71.1, 70.1, 70.0, 67.6, 67.5, 65.7, 65.7, 64.5, 64.5, 64.5, 63.3, 63.1, 48.8, 47.9, 21.5; IR νmax (film)/cm⁻¹: 3423 (bs), 3300 (bs), 2926, 2832, 1715, 1705, 1669, 1521, 1386, 1361, 1325, 1268, 1217, 1169, 1147, 1085, 1014; HRMS (ESI) m/z calculated for C₂₁H₂₀I₃O₇Na ([M+Na⁺]⁺) 576.0238, found 576.0235.
18.7. Experimental Part to Chapter 11

A stock solution of dry m-CPBA was prepared by dissolving commercial m-CPBA (181 mg, 0.73 mmol, 70%) in CDCl₃ (3 mL) followed by addition of Na₂SO₄. The mixture was stirred for 30 min before use.

An NMR tube was charged with enol ether 550 (37 mg, 0.25 mmol) and 0.7 mL of the m-CPBA stock solution was added. The solution was heated to 50 °C and the conversion was monitored by ¹H-NMR. After 2 h the mixture was poured into sat. NaHCO₃ and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography (CH₂Cl₂/MeOH 100:1) to give 643 (10 mg) and 644 (12 mg) (total yield: 22 mg, 0.07 mmol, 28%).

643: R₁ 0.42 (20:1, CH₂Cl₂/MeOH); ¹H-NMR (400 MHz, CDCl₃): δ 8.13 (s, 1H), 8.04 (dt, J = 7.8, 1.3 Hz, 1H), 7.62 (ddd, J = 8.0, 2.1, 1.0 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 5.74 (d, J = 7.7 Hz, 1H), 4.72 (d, J = 7.5 Hz, 1H), 4.07 (dd, J = 10.7, 6.6 Hz, 1H), 3.75 (t, J = 10.9 Hz, 1H), 3.65 (dd, J = 11.1, 6.5 Hz, 1H), 2.99 (bs, 1H, OH), 1.35-1.26 (m, 1H), 1.11 (dt, J = 12.2, 6.4 Hz, 1H), 0.88-0.73 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 163.9, 134.7, 133.9, 130.6, 130.1, 129.9, 128.3, 98.0, 69.1, 68.0, 66.9, 48.9, 10.2, 8.6.

644: R₁ 0.36 (20:1, CH₂Cl₂/MeOH); ¹H-NMR (400 MHz, CDCl₃): δ 8.02 (t, J = 1.7 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.61 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 6.46 (s, 1H), 4.74 (s, 1H), 4.02-3.91 (m, 2H), 3.83 (dd, J = 11.5, 6.7 Hz, 1H), 2.89 (bs, 1H, OH), 1.32-1.26 (m, 1H), 1.11 (dt, J = 12.6, 6.1 Hz, 1H), 0.85-0.72 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 163.2, 155.3, 134.9, 133.9, 130.6, 130.0, 128.1, 94.4, 67.4, 64.8, 64.3, 44.2, 10.7, 8.0.

The relative configuration of 643 and 644 was determined by NOE analysis. See chapter 24.
Experimental Part

To a solution of 550 (2.4 g, 15.9 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (150 mL) was added 4Å molecular sieves (ca. 2 g). The solution was cooled to 0 °C and a freshly prepared solution of DMDO\textsuperscript{734} (ca. 150 mL, ~0.07 M in acetone) was added. After 2 h the solution was filtered and the solvent was removed under reduced pressure at ambient temperature to give epoxide 645 (2.7 g, 15.9 mmol, 100%) as a 2:1 mixture of diastereomers.

A \textsuperscript{1}H NMR spectrum of crude 645 is given in chapter 25.

To a solution of crude epoxide 645 (20 mg, 0.13 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (0.5 mL) and thiophenol (0.5 mL) was added 4Å molecular sieves (ca. 50 mg). The reaction was stirred overnight and the mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2}. The solution was washed with 1M NaOH, dried over MgSO\textsubscript{4} and concentrated. The residue was purified by flash column chromatography to give S28 (10 mg, 0.04 mmol, 27%) as a single diastereomer. \n
\textit{R}\textsubscript{f} 0.57 (1:1, hexanes/EtOAc); \textit{\textsuperscript{1}H-NMR} (400 MHz, CDCl\textsubscript{3}): \textit{\delta} 7.51-7.48 (m, 2H), 7.37-7.30 (m, 3H), 5.70 (s, 1H), 4.83 (dd, \textit{J} = 5.5, 0.8 Hz, 1H), 4.43-4.36 (m, 1H), 3.82-3.75 (m, 2H), 2.65 (d, \textit{J} = 5.5 Hz, 1H, OH), 1.31-1.25 (m, 1H), 1.12-1.07 (m, 1H), 0.82-0.75 (m, 2H); \textit{\textsuperscript{13}C-NMR} (100 MHz, CDCl\textsubscript{3}): \textit{\delta} 155.4, 133.1, 131.3, 129.2, 127.6, 88.9, 67.4, 66.9, 62.5, 44.6, 10.4, 8.4.

To a solution of enol ether 550 (2.4 g, 15.9 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (150 mL) was added 4Å molecular sieves (ca. 2 g). The solution was cooled to 0 °C and a freshly prepared solution of DMDO (ca. 150 mL, ~0.07 M in acetone) was added. After 2 h the solution was filtered and the solvent was removed under reduced pressure at ambient temperature. The resulting crystalline solid was taken up in CHCl\textsubscript{3} (5 mL) and benzyl alcohol (6.6 mL, 63.5 mmol) was added. The solution was stirred over night while

a precipitate formed. The suspension was then heated to 60 °C for 2 h whereupon the precipitate dissolved again. The remaining CHCl₃ was removed under reduced pressure and the residue was purified by flash column chromatography (hexanes/EtOAc 10:1 → 1:1) to give benzyl ether 652 (3.17 g, 11.5 mmol, 73%) as a 2:1 mixture of diastereomers.

Rₐ 0.49 (1:1, hexanes/EtOAc); ¹H-NMR (300 MHz, CDCl₃, major diastereomer): δ 7.41-7.28 (m, 5H), 4.98 (bs-s, 1H), 4.75 (d, J = 12.3 Hz, 1H), 4.55 (d, J = 12.2 Hz, 1H), 4.52-4.50 (m, 1H), 3.87 (d, J = 12.8 Hz, 1H), 3.74-3.66 (m, 2H), 2.50 (bs-s, 1H, OH), 1.27-1.18 (m, 1H), 1.03-0.94 (m, 1H), 0.78-0.63 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃, major diastereomer): δ 156.1, 136.6, 128.5 (2C), 128.0, 127.9 (2C), 98.6, 68.8, 67.0, 65.5, 61.7, 44.1, 10.0, 8.3; IR (film)/cm⁻¹: 3354 (bs), 2920, 1448, 1376, 1323, 1241, 1212, 1058, 1005; HRMS (ESI) m/z calculated for C₁₅H₁₇NO₄Na ([M+Na]⁺) 298.1050, found 298.1054.

A solution of 1-bromopropene (0.96 mL, 11.2 mmol) in THF (15 mL) was cooled to -78 °C and n-BuLi (14.3 mL, 22.9 mmol, 1.6M in hexanes) was added. The mixture was stirred for 1.5 h at -78 °C. Anhydrous cerium chloride (2.76 g, 11.2 mmol) was added and the mixture was stirred for another 30 min. To this mixture was added a premixed solution of isoxazoline 652 (770 mg, 2.8 mmol, 4:1 mixture of diastereomer) and borontrifluoride etherate (0.69 mL, 5.6 mmol) in THF (5 mL). The reaction was stirred for 2.5 h and then quenched by addition of pH 7 buffer. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give isoxazolidine 654 (305 mg, 0.97 mmol, 35%, 77% brsm) along with reisolated starting material 652 (420 mg, 1.53 mmol, enriched in the minor diastereomer).

Rₐ 0.27 (1:1, hexanes/EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 7.37-7.21 (m, 5H), 5.57 (bs-s, 1H, NH), 4.82 (d, J = 11.9 Hz, 1H), 4.75 (d, J = 7.1 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 3.97 (d, J = 6.3 Hz, 1H), 3.77-3.63 (m, 3H), 2.82 (t, J = 7.3 Hz, 1H), 1.83 (s, 3H), 1.01-0.86 (m, 2H), 0.74-0.67 (m, 1H), 0.53-0.43 (m, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 137.4, 127.9 (2C), 127.3 (2C), 127.1, 100.2, 83.6, 74.3, 69.9, 69.6, 68.4, 66.4, 59.6, 54.0, 11.5, 6.1, 3.7; IR (film)/cm⁻¹: 3440 (bs), 3209, 2970, 2920, 1491, 1448, 1409, 1352, 1222, 1106, 1082, 1043, 1014; HRMS (ESI) m/z calculated for C₁₈H₂₁NO₄Na ([M+Na]⁺) 338.1363, found 338.1363.
653 was isolated as a side product (10-20% yield) from the alkyne addition (652→654) when more than 2 equiv. of boron trifluoride etherate were employed.

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\text{R}_f 0.64 \text{ (EtOAc); } ^1\text{H-NMR (400 MHz, CD}_3\text{CN): } \delta 9.71 \text{ (s, 1H, OH), 7.37-7.30 (m, 5H), 5.98 (d, } J = 2.3 \text{ Hz, 1H), 4.80 (d, } J = 11.8 \text{ Hz, 1H), 4.75-4.66 (m, 2H), 4.63 (d, } J = 11.8 \text{ Hz, 1H), 4.56 (dd, } J = 6.4, 2.3 \text{ Hz, 1H), 4.16 (t, } J = 6.1 \text{ Hz, 2H), 3.85 (d, } J = 6.5 \text{ Hz, 1H, OH), 3.06 (t, } J = 6.0 \text{ Hz, 2H); } ^{13}\text{C-NMR (100 MHz, CD}_3\text{CN): } \delta 163.5, 159.9, 138.5, 129.4 \text{ (2C), 129.0 (2C), 128.8, 109.5, 100.6, 73.7, 70.9, 63.6, 56.3, 25.8; IR } \nu_{\text{max}} \text{ (film)/cm}^{-1}: 3345 \text{ (bs), 2929, 1641, 1464, 1123, 1069, 1010; HRMS (ESI) could not be obtained.}
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654 (1.16 g, 3.68 mmol) was carefully dried by coevaporation with benzene (3 x 10 mL) and MeCN (10 mL). The compound was taken up in MeCN (20 mL) and freshly distilled TFA (0.31 mL, 4.05 mmol) was added. The mixture was heated to 80 °C. After 2 h TLC analysis indicated full consumption of the starting material. The solvent was evaporated and the residue was directly subjected to flash column chromatography (CH\(_2\)Cl\(_2\)/MeOH 40:1) to give β-lactam 666 (820 mg, 2.85 mmol, 78%).

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\text{R}_f 0.48 \text{ (9:1, CH}_2\text{Cl}_2/\text{MeOH); } ^1\text{H-NMR (300 MHz, CD}_3\text{CN): } \delta 7.39-7.28 \text{ (m, 5H), 7.01 (bs-s, 1H, NH), 4.77 (d, } J = 12.1 \text{ Hz, 1H), 4.64 (d, } J = 5.1 \text{ Hz, 1H), 4.53 (d, } J = 12.0 \text{ Hz, 1H), 3.93 (qd, } J = 12.2, 6.3 \text{ Hz, 2H), 3.77 (dd, } J = 5.7, 5.1 \text{ Hz, 1H), 3.61 (d, } J = 5.8 \text{ Hz, 1H), 3.49 (td, } J = 6.0, 0.9 \text{ Hz, 1H), 1.85 (s, 3H); } ^{13}\text{C-NMR (100 MHz, CD}_3\text{CN): } \delta 167.2, 139.2, 129.3 \text{ (2C), 128.8 (2C), 128.6, 102.0, 84.1, 77.3, 74.7, 70.8, 58.8, 58.5, 51.7, 3.7; IR } \nu_{\text{max}} \text{ (film)/cm}^{-1}: 3286 \text{ (bs), 2881, 1742, 1727, 1385, 1356, 1289, 1246, 1217, 1140, 1063, 1043; HRMS (ESI) m/z calculated for C\(_{16}\)H\(_{21}\)NO\(_2\)Na ([M+Na]\(^+\)) 310.1050, found 310.1049.}
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**S29** was prepared from 645 following the procedure detailed above for the preparation of 654.

$R_f$ 0.20 (1:3, hexanes/EtOAc); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 6.34 (bs-s, 1H, NH), 4.54 (d, $J = 5.1$ Hz, 1H), 4.06 (dd, $J = 12.2, 6.2$ Hz, 1H), 3.96 (dd, $J = 12.2, 6.8$ Hz, 1H), 3.80 (d, $J = 5.1$ Hz, 1H), 3.63 (ddd, $J = 6.9, 6.3, 1.0$ Hz, 1H), 3.46 (s, 3H), 2.10 (bs-s, 1H, O$_{\text{H}}$), 1.92 (s, 3H); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 166.4, 101.8, 85.3, 74.9, 73.8, 57.7, 57.5, 56.3, 51.1, 3.8; HRMS (ESI) m/z calculated for C$_{10}$H$_{17}$NO$_4$Na ([M+Na]$^+$) 234.0737, found 234.0735.

**S31** was prepared from 645 following the procedure detailed above for the preparation of 554.

$R_f$ 0.24 (20:1, CH$_2$Cl$_2$/MeOH); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 6.35 (bs-s, 1H, NH), 4.71 (d, $J = 5.2$ Hz, 1H), 4.08 (dd, $J = 12.2, 6.1$ Hz, 1H), 3.95 (td, $J = 12.2, 6.5$ Hz, 2H), 3.77 (t, $J = 4.7$ Hz, 1H), 3.60 (t, $J = 6.6$ Hz, 1H), 2.45 (d, $J = 4.6$ Hz, 1H, OH), 1.92 (s, 3H), 1.22 (d, $J = 6.2$ Hz, 3H), 1.17 (d, $J = 6.1$ Hz, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 166.5, 98.5, 85.0, 75.2, 74.1, 70.3, 57.6, 57.4, 51.1, 3.4, 21.5, 3.8.; HRMS (ESI) m/z calculated for C$_{12}$H$_{17}$NO$_4$Na ([M+Na]$^+$) 262.1050, found 262.1051.

To a solution of β-lactam 666 (1.20 g, 4.18 mmol) in MeCN (20 mL) was added triethylamine (1.75 mL, 12.5 mmol), di-tert-butyl dicarbonate (2.28 g, 10.4 mmol) and DMAP (cat.). The solution was stirred for 30 min. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to give carbonate 667 (1.25 g, 3.23 mmol, 77%) as a colorless foam.

The structure of 667 was confirmed by X-ray crystallographic analysis (see chapter 24).

$R_f$ 0.33 (4:1, hexanes/EtOAc); $^1$H-NMR (300 MHz, CD$_3$CN): $\delta$ 7.37-7.27 (m, 5H), 5.34 (d, $J = 2.4$ Hz, 1H), 4.95 (d, $J = 2.4$ Hz, 1H), 4.73 (d, $J = 11.8$ Hz, 1H), 4.48 (d, $J = 11.8$ Hz, 1H), 4.08 (dd, $J = 12.5, 2.9$ Hz, 1H), 4.00 (dd, $J = 12.5, 4.9$ Hz, 1H), 3.50 (dd, $J = 4.9, 2.9$ Hz, 1H), 1.84 (s, 3H), 1.48 (s, 9H), 1.38 (s, 9H); $^{13}$C-NMR (100 MHz, CD$_3$CN): $\delta$ 164.8, 153.0, 147.3, 138.3, 129.3 (2C), 128.9
Experimental Part

(2C), 128.7, 98.9, 84.4, 84.3, 84.0, 75.1, 71.4, 71.0, 58.0, 56.2, 53.2, 28.2 (3C), 27.9 (3C), 3.6; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2978, 2929, 1814, 1756, 1728, 1496, 1472, 1452, 1390, 1371, 1328, 1279, 1250, 1154, 1106, 1019; HRMS (ESI) m/z calculated for C$_{26}$H$_{33}$NO$_8$Na ([M+Na]$^+$) 510.2098, found 510.2096.

An oven dried flask was charged with carbamate 667 (445 mg, 0.91 mmol) and Petasis reagent Cp$_2$TiMe$_2$ $^{735}$ (15.2 mL, 4.56 mmol, 0.3 M) and pyridine (0.30 mL, 3.65 mmol) were added. The mixture was heated to 70 °C in the dark for 6 h. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to give encarbamate 668 (356 mg, 0.73 mmol, 80%).

R$_f$ 0.56 (4:1, hexanes/EtOAc); $^1$H-NMR (300 MHz, CD$_3$CN): $\delta$ 7.39-7.25 (m, 5H), 5.25-5.18 (bs, 1H), 4.88 (bs-s, 0.5H), 4.80 (d, $J$ = 4.3 Hz, 1H), 4.75 (d, $J$ = 12.1 Hz, 1H), 4.65 (bs-s, 1H), 4.52 (d, $J$ = 12.1 Hz, 1H), 4.24 (bs-s, 1H), 3.93 (d, $J$ = 5.3 Hz, 2H), 3.29 (bs-s, 1H), 1.85 (s, 3H), 1.47 (s, 9H), 1.41 (s, 9H); $^{13}$C-NMR (100 MHz, CD$_3$CN) (splitting of some carbon signals, all peaks reported): $\delta$ 153.3, 151.2, 146.8, 146.2, 138.8, 129.2, 128.7, 128.6, 99.8, 99.1, 87.7, 84.4, 83.6, 82.5, 81.9, 76.0, 74.1, 70.8, 61.7, 61.2, 47.2, 28.5, 28.0, 3.7; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2978, 2929, 1752, 1713, 1472, 1452, 1366, 1279, 1250, 1164, 1125, 1111, 1072; HRMS (ESI) m/z calculated for C$_{27}$H$_{36}$NO$_7$ ([M+H]$^+$) 486.2486, found 486.2491.

To a flask containing 9-BBN dimer (482 mg, 1.98 mmol) was added a solution of encarbamate 668 (800 mg, 1.65 mmol) in THF (2 mL). After 3 h TLC control showed complete conversion of the starting material. The reaction was diluted with THF (6 mL) and aq. H$_2$O$_2$ (8.4 mL, 82 mmol, 30% in water) was added followed by 4M NaOH (8 mL). After 1 h the reaction was diluted with EtOAc. The aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography to give primary alcohol 669 (730 mg, 1.45 mmol, 88%) as a mixture of diastereomers at C(5) (dr 3:1).

$^{735}$ Freshly prepared. See ref. 723.
**Mixture of diastereomers:** $R_f$ 0.71 (1:1, hexanes/EtOAc); $^1$H-NMR (300 MHz, d$_6$-DMSO, 100 °C, all peaks reported): $\delta$ 7.35-7.25 (m, 5H), 5.21-5.17 (m, 1H), 4.78-4.73 (m, 1.3H), 4.69-4.67 (m, 0.7H), 4.59-4.54 (m, 1H), 4.44-4.39 (m, 1H), 4.29-4.19 (m, 1.7H), 4.09-4.03 (m, 0.3H), 3.88-3.72 (m, 2.7H), 3.64-3.55 (m, 0.3H), 2.90-2.83 (m, 0.7H), 2.72-2.65 (m, 0.3H), 1.87-1.83 (m, 3H), 1.46-1.44 (m, 9H), 1.41-1.34 (m, 9H); due to multiple rotamers no clean $^{13}$C-NMR could be obtained for this compound, a $^{13}$C spectrum at 100 °C is given in chapter 25; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3415 (bs), 2972, 2925, 1751, 1699, 1671, 1449, 1388, 1364, 1275 1251, 1157 1105, 1035; HRMS (ESI) $m/z$ calculated for C$_{27}$H$_{37}$NO$_8$Na ([M+Na]$^+$) 526.2411, found 526.2405.

The two diastereomers of 669 could not be separated at this stage. However, after reduction of the triple bond and acetylation of the primary alcohol the isomers were separated and characterized individually:

To a solution of alcohol 669 (100 mg, 0.20 mmol) in CH$_2$Cl$_2$ (2 mL) was added triethylamine (55 μL, 0.40 mmol), acetic anhydride (28 μL, 0.30 mmol) and DMAP (cat.). After 30 min, the reaction was quenched by the addition of sat. NaHCO$_3$ and diluted with CH$_2$Cl$_2$. The phases were separated and the aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with brine, dried over MgSO$_4$ and the solvent was evaporated. The residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give intermediate acetate (96 mg, 0.18 mmol, 89%).

This acetate was taken up in MeOH (2 mL) and palladium on carbon (10 mg, 10 wt%) were added. The flask was evacuated and refilled with hydrogen gas (balloon). After 30 min the reaction mixture was filtered through celite and the solvent was evaporated. The residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to give 671 and S33 (in total 58 mg, 0.13 mmol, 72%) as two separable diastereomers (3:1). The two diastereomers were characterized individually. The relative configuration at C(5) was elucidated by 1D NOE experiments (see chapter 24).

$R_f$ 0.64 (1:1, hexanes/EtOAc); $^1$H-NMR (400 MHz, CD$_3$CN, mixture of rotamers, all peaks reported): $\delta$ 7.36-7.27 (m, 5H), 5.8-5.17 (m, 1H), 4.76 (d, $J$ = 12.2 Hz, 1H), 4.59 (dd, $J$ = 19.9, 5.8 Hz, 1H), 4.53 (d, $J$ = 12.2 Hz, 1H), 4.35-4.11 (m, 3H), 3.88-3.72 (m, 2H), 2.68-2.60 (m, 1H), 2.03 (s, 3H), 1.86 (ddt,
J = 15.6, 11.6, 4.5 Hz, 2H), 1.62 (ddd, J = 14.0, 12.1, 4.7 Hz, 1H), 1.53-1.31 (m, 20H), 0.99-0.92 (m, 3H); ^{13}\text{C-NMR} (100 MHz, CD$_3$CN, mixture of rotamers, all peaks reported) δ 171.4, 153.6, 153.4, 139.0, 138.7, 129.3, 129.2, 128.9, 128.7, 128.6, 99.6, 99.4, 83.4, 82.8, 80.3, 80.2, 77.4, 76.9, 70.8, 70.6, 68.4, 67.5, 64.1, 63.8, 62.6, 62.1, 60.5, 58.8, 37.7, 37.3, 36.1, 36.0, 28.5, 28.1, 28.0, 21.0, 17.6, 17.6, 14.8. IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3020, 2969, 1743, 1695, 1394, 1369, 1254, 1216, 1165, 1111, 1048; HRMS (ESI) $m/z$ calculated for C$_{29}$H$_{44}$NO$_9$ ([M+H$^+$]) 550.3011, found 550.3003.

R$_f$ 0.58 (1:1, hexanes/EtOAc); ^{1}H-NMR (400 MHz, CD$_3$CN, mixture of rotamers, all peaks reported): δ 7.37-7.27 (m, 5H), 5.49-5.35 (m, 1H), 4.76 (d, J = 12.2 Hz, 1H), 4.62-4.56 (m, 1H), 4.52 (d, J = 12.3 Hz, 1H), 4.48-4.15 (m, 4H), 3.77-3.71 (m, 1H), 2.95-2.86 (m, 1H), 2.09-1.99 (m, 4H), 1.54-1.19 (m, 21H), 0.99-0.93 (m, 3H); ^{13}\text{C-NMR} (100 MHz, CD$_3$CN, mixture of rotamers, all peaks reported) δ 171.2, 171.2, 155.3, 154.2, 153.7, 153.5, 139.3, 139.0, 129.3, 128.5, 128.4, 100.1, 99.6, 83.2, 82.7, 80.4, 80.1, 79.3, 78.9, 70.3, 70.1, 68.9, 67.9, 62.4, 59.8, 59.5, 58.8, 58.2, 36.1, 36.0, 34.5, 33.5, 28.6, 28.5, 28.1, 28.0, 21.1, 21.1, 16.6, 14.6, 14.5. IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2976, 1749, 1700, 1394, 1254, 1057; HRMS (ESI) $m/z$ calculated for C$_{29}$H$_{43}$NO$_9$Na ([M+Na$^+$]) 572.2830, found 572.2830.

To a solution of benzyl ether $S_{34}$ (96 mg, 0.18 mmol) in MeOH (2 mL) was added Pd/C (10 mg, 10% wt Pd). The mixture was put into a hydrogen bomb and a hydrogen pressure of 10 bar was applied. After 12 h the reaction was filtered through a pad of celite. The solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 1:1 → EtOAc) to give intermediate hemiacetal $S_{35}$ (58 mg, 0.13 mmol, 72%).

This hemiacetal $S_{35}$ (10 mg, 0.02 mmol) was dissolved in CH$_2$Cl$_2$ (1 mL) and trichloroacetonitrile (22 μL, 0.22 mmol, freshly distilled) was added followed by Cs$_2$CO$_3$ (3.6 mg, 11 μmol). After 30 min TLC analysis indicated full consumption of the starting material. The solvent was removed and the residue was directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to give trichloroacetimidate $670$ (10 mg, 0.017 mmol, 76%).

R$_f$ 0.80 (1:1, hexanes/EtOAc); HRMS (ESI) $m/z$ calculated for C$_{29}$H$_{37}$N$_2$O$_9$Cl$_3$Na ([M+Na$^+$]) 625.1457, found 625.1457.
A solution of hemiacetal \textbf{S35} (10 mg, 22 μmol) in THF (1 mL) was cooled to -30 °C and DAST (3.5 μL, 26 μmol) was added. After 15 min MeOH was added to the reaction and the mixture was allowed to warm to ambient temperature. The solvent was removed and the residue was directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to give alkylfluoride \textbf{673} (8 mg, 17 μmol, 80%).

R\textsubscript{f} 0.42 (3:1, hexanes/EtOAc); HRMS (ESI) m/z calculated for C\textsubscript{22}H\textsubscript{36}NO\textsubscript{8}FNa ([M+Na]\textsuperscript{+}) 484.2317, found 484.2306.

To a solution of glycosyl fluoride \textbf{673} (8 mg, 0.017 mmol) and TBS enol ether \textbf{S36} (14 mg, 0.052 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1 mL) at 0 °C was added 4Å molecular sieves and BF\textsubscript{3}\cdot OEt\textsubscript{2} (1 μL, 8.7 μmol). After 15 min the starting material had completely disappeared (TLC analysis). The mixture was filtered through a pad of celite, the solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give carbonate \textbf{672} (4 mg, 10 μmol, 60%).

Due to the instability of this compound, purification and characterization proved difficult.

R\textsubscript{f} 0.31 (3:1, hexanes/EtOAc); \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}, mixture of rotamers, all peaks reported): δ 6.08-5.90 (m, 1H), 4.91-4.69 (m, 1H), 4.51 (dd, J = 11.2, 4.3 Hz, 1H), 4.43-4.30 (m, 2H), 4.10 (dd, J = 13.2, 7.8 Hz, 1H), 3.90-3.86 (m, 1H), 2.47-2.42 (m, 1H), 2.11-2.03 (m, 3H), 2.03-1.88 (m, 2H), 1.63-1.54 (m, 1H), 1.47-1.42 (m, 9H), 1.35-1.26 (m, 1H), 1.03-0.94 (m, 3H); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}, mixture of rotamers, all peaks) δ 170.6, 170.4, 155.5, 155.0, 153.2, 153.1, 96.2, 96.1, 81.4, 81.2, 73.7, 73.4, 63.1, 62.7, 62.0, 58.9, 58.0, 57.6, 36.0, 34.6, 32.4, 28.3, 28.2, 28.2, 20.8, 20.8, 16.8, 14.4, 14.0; HRMS (ESI) m/z calculated for C\textsubscript{18}H\textsubscript{27}NO\textsubscript{8}Na ([M+Na]\textsuperscript{+}) 408.1629, found 408.1632.

\textsuperscript{736} Enol ether \textbf{S35} was prepared from N-methoxy oxdinole \textbf{358} by treatment with LiHMDS and TMSCl. Filtration over Al\textsubscript{2}O\textsubscript{3} delivered pure \textbf{S35}.
To a solution of carbonate $669$ (20 mg, 0.04 mmol) in MeOH (1 mL) was added potassium carbonate (11 mg, 0.08 mmol). The mixture was heated to 50°C over night. The solution was diluted with brine and EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give intermediate diol (9 mg, 22 μmol, 56%).

To a solution of this diol (80 mg, 0.20 mmol) in CH$_2$Cl$_2$ (1 mL) was added triethylamine (83 μL, 0.60 mmol), acetic anhydride (47 μL, 0.50 mmol) and DMAP (cat.). After 30 min the solvent was removed and the residue was directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to give bisacetate $S37$ (89 mg, 0.18 mmol, 92%).

To a solution of $S37$ (90 mg, 0.18 mmol) in MeOH (2 mL) was added Pd/C (10 mg, 10%wt Pd). The mixture was set under a hydrogen atmosphere (balloon). After 30 min the suspension was filtered over a pad of celite and the solvent was removed. The residue was directly subjected to flash column chromatography (hexanes/EtOAc 1:1) to give the corresponding hemiacetal (59 mg, 0.15 mmol, 80%).

A solution of this hemiacetal (48 mg, 0.12 mmol) in THF (1 mL) was cooled to -30 °C and DAST (19 μL, 0.14 mmol) was added. After 15 min MeOH was added to the reaction and the mixture was allowed to warm to ambient temperature. The solvent was removed and the residue was directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to give alkylfluoride $674$ (39 mg, 97 μmol, 81%).

To a solution of oxindole $358$ (12 mg, 0.074 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 0 °C was added 4Å molecular sieves, triethylamine (12 μL, 0.087 mmol) and TBSOTf$^{737}$ (20 μL, 0.087 mmol). After 10 min, the suspension was cooled to -78 °C. A solution of glycosyl fluoride $674$ (10 mg, 0.025 mmol) in CH$_2$Cl$_2$ (0.5 mL) was slowly added. After 45 min at -78 °C the reaction was allowed to warm to 0 °C and BF$_3$·OEt$_2$ (1.5 μL, 12 μmol) was added. TLC analysis indicated complete consumption of the

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$^{737}$ TBSOTf was freshly distilled under vacuum prior to use.
starting material after 15 min. The reaction mixture was directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to give acetal 679 (10 mg, 18 μmol, 74%).

For better characterization (less rotamers) acetate 679 was converted into the corresponding aldehyde S38.

Rf 0.72 (1:1, hexanes/EtOAc); 1H-NMR (600 MHz, CD3CN, mixture of rotamers and diastereomers, all peaks reported): δ 9.72-9.60 (m, 1H), 7.51-7.43 (m, 1H), 7.42-7.33 (m, 1H), 7.12-7.05 (m, 1H), 7.02-6.98 (m, 1H), 5.79-5.59 (m, 1H), 4.52-4.16 (m, 1H), 3.97-3.93 (m, 1H), 3.89-3.80 (m, 1H), 3.77-3.73 (m, 1H), 3.53-3.48 (m, 2H), 7.26-2.48 (m, 1H), 1.77-1.61 (m, 5H), 1.52-1.26 (m, 10H), 1.16-1.03 (m, 1H), 1.06-0.93 (m, 3H); 13C-NMR (150 MHz, CD3CN, mixture of rotamers and diastereomers, for clarity only major peaks reported) δ 203.1, 168.9, 156.0, 142.0, 130.3, 127.5, 124.1, 123.1, 112.0, 108.1, 99.0, 81.6, 76.7, 75.7, 74.1, 74.0, 65.2, 64.1, 63.9, 57.3, 53.7, 37.4, 37.1, 36.9, 36.9, 28.6, 24.7, 16.1, 14.4; IR νmax (film)/cm⁻¹: 3017, 2973, 2938, 1724, 1699, 1466, 1385, 1369, 1318, 1234, 1216, 1159, 1104, 1074, 1056; HRMS (ESI) could not be obtained. For acetate 679: HRMS was obtained: HRMS (ESI) m/z calculated for C28H38N2O9Na ([M+Na]+) 569.2470, found 569.2466.

To a solution of hemiacetal S35 (27 mg, 59 μmol) in THF (1 mL) at 0 °C was added a solution of lithium hydroxide monohydrate (3 mg, 71 μmol) in water (0.3 mL). A drop of MeOH was added to have a clear solution. After 30 min the reaction was diluted with EtOAc and brine and the phases were separated. The aqueous phase was extracted three times with EtOAc and the combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1 → EtOAc) to give diol S39 (ca. 50-60% yield).

To a solution of S39 (28 mg, 78 μmol) in THF (1 mL) at 0 °C was added DAST (12 μL, 93 μmol). After 15 min the solvent was removed and the residue was directly subjected to flash column chromatography (hexane/EtOAc 1:1) to give alkylfluoride 675 (16 mg, 44 μmol, 57%).
To a solution of oxindole 358 (14 mg, 0.083 mmol) in CH$_2$Cl$_2$ (1 mL) at 0 °C was added 4Å molecular sieves, triethylamine (7.7 μL, 0.055 mmol) and TBSOTf$^{738}$ (13 μL, 0.055 mmol). After 10 min, the suspension was cooled to -78 °C. A solution of glycosyl fluoride 675 (10 mg, 0.028 mmol) in CH$_2$Cl$_2$ (1 mL) was slowly added followed by BF$_3$·OEt$_2$ (3.4 μL, 28 μmol). The reaction was allowed to warm to 0 °C. After 2 h, the reaction was quenched by addition of sat. NaHCO$_3$ and diluted with EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over MgSO$_4$ and the solvent was removed. The residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give acetal 681 (6 mg, 12 μmol, 43%).

The stereochemistry at C(3) could not be clearly assigned by a NOESY experiment. However, based on follow-up experiments (attempted ring closure) and based on steric reasons, the configuration is believed to be the one depicted.

R$_f$ 0.18 (3:1, hexanes/EtOAc);$^1$H-NMR (600 MHz, CD$_3$CN, mixture of rotamers and diastereomers, all peaks reported): δ 7.49-7.35 (m, 1H), 7.35-7.31 (m, 1H), 7.09-7.05 (m, 1H), 7.01-6.98 (m, 1H), 4.56-4.29 (m, 3H), 4.23-4.13 (m, 1H), 4.08-3.84 (m, 4H), 3.82-3.77 (m, 1H), 3.76-3.67 (m, 1H), 3.64-3.55 (m, 1H), 3.36-3.03 (m, 1H, OH), 2.80-2.63 (m, 1H), 2.02-1.97 (m, 4H), 1.87-1.84 (m, 1H), 1.59-1.51 (m, 1H), 1.45-1.34 (m, 10H), 1.03-0.96 (m, 3H); $^{13}$C-NMR (150 MHz, CD$_3$CN, mixture of rotamers and diastereomers, all peaks reported) δ 171.2, 169.8, 155.7, 154.9, 142.3, 129.3, 129.3, 129.2, 129.2, 126.8, 126.5, 125.5, 125.4, 124.6, 123.6, 123.5, 123.5, 118.3, 108.0, 107.9, 107.8, 107.7, 80.9, 80.8, 80.7, 80.4, 80.1, 79.6, 78.4, 78.3, 74.8, 74.5, 74.1, 73.3, 71.5, 70.9, 70.8, 70.6, 65.6, 65.1, 65.0, 64.9, 64.1, 63.8, 63.8, 62.8, 62.7, 62.4, 62.1, 60.2, 59.9, 58.3, 58.0, 47.3, 47.0, 46.8, 46.6, 36.7, 36.3, 36.2, 35.7, 35.6, 35.2, 34.5, 34.4, 28.7, 28.6, 21.1, 21.0, 20.9, 20.8, 17.6, 17.4, 17.2, 14.9, 14.8, 14.8; HRMS (ESI) m/z calculated for C$_{26}$H$_{36}$N$_2$O$_8$Na ([M+Na]$^+$) 527.2364, found 527.2364.

$^{738}$ TBSOTf was freshly distilled under vacuum prior to use.
To a solution of diol S40 (50 mg, 0.12 mmol) (obtained as described in the synthesis of 674) in DMF (1 mL) was added imidazole (34 mg, 0.50 mmol) and TBSCI (56 mg, 0.37 mmol). The mixture was allowed to stir at ambient temperature over night. The reaction was then diluted with water and Et₂O. The phases were separated and the aqueous phase was extracted three times with Et₂O. The combined organic phases were washed with water and brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give silyl ether S41 (62 mg, 98 μmol, 79%).

To a solution of benzyl ether S41 (12 mg, 19 μmol) in THF (1 mL) was added Pd/C (5 mg, 10%wt Pd) and the mixture was set under a hydrogen atmosphere (balloon). After stirring the suspension for 12 h, the mixture was filtered over a pad of celite and the solvent was removed. The residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give intermediate hemiacetal (9 mg, 16 μmol, 87%).

To a solution of this hemiacetal (9 mg, 16 μmol) in THF (1 mL) at -78 °C was added DAST (3 μL, 20 μmol). After 5 min the reaction was warmed to ambient temperature and stirred for another 5 min. After cooling back to -78 °C MeOH was added. The solvent was removed and the residue was directly subjected to flash column chromatography (hexane/EtOAc 10:1) to give alkylfluoride 676 (7 mg, 13 μmol, 77%).

To a solution of oxindole 358 (6 mg, 38 μmol) in CH₂Cl₂ (1 mL) at 0 °C was added 4Å molecular sieves, triethylamine (4.5 μL, 32 μmol) and TMSOTf₇³⁹ (13 μL, 0.055 mmol). After 10 min, the suspension was cooled to -78 °C. A solution of glycosyl fluoride 676 (7 mg, 13 μmol) in CH₂Cl₂ (0.5 mL) was slowly added followed by BF₃·OEt₂ (1.6 μL, 13 μmol). The reaction was allowed to warm to 0 °C. After 1 h, the reaction directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to give acetal 682 (3 mg, 7 μmol, 57%).

₇³⁹ TMSOTf was freshly distilled under vacuum prior to use.
Rt 0.48 (4:1, hexanes/EtOAc); $^1$H-NMR (600 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): $\delta$ 5.14 (dd, $J = 5.8$, 3.2 Hz, 1H), 4.29 (dd, $J = 12.1$, 3.4 Hz, 0.5H), 4.20 (dd, $J = 3.2$, 1.1 Hz, 0.5H), 4.17 (dd, $J = 8.4$, 3.4 Hz, 0.5H), 4.10-4.04 (m, 2H), 3.96 (dd, $J = 3.2$, 1.1 Hz, 0.5H), 3.89-3.85 (m, 1H), 3.83-3.78 (m, 1H), 2.74-2.70 (m, 1H), 1.82 (ddd, $J = 14.4$, 12.2, 4.9 Hz, 0.5H), 1.65-1.58 (m, 1.5H), 1.50-1.33 (m, 11H), 0.99-0.95 (m, 3H), 0.92-0.89 (m, 9H), 0.12-0.10 (m, 6H);

$^{13}$C-NMR (150 MHz, CDCl$_3$, mixture of rotamers, all peaks reported) $\delta$ 154.3, 97.6, 97.4, 79.7, 79.6, 70.2, 68.7, 67.1, 66.8, 60.6, 60.5, 59.9, 59.4, 58.9, 35.7, 35.4, 34.2, 33.9, 28.6, 28.5, 25.7, 18.0, 16.2, 15.8, 14.4, 14.4, -4.5, -4.6, -4.8, -4.8; IR $\nu_{max}$ (film)/cm$^{-1}$: 3018, 2958, 1689, 1464, 1391, 1256, 1215, 1165, 1137, 1114; HRMS (ESI) $m/z$ calculated for C$_{21}$H$_{39}$NO$_5$SiNa ([M+Na]$^+$) 436.2490, found 436.2485.

To a solution of N-methoxy oxindole 685 (671 mg, 0.46 mmol) in THF (3 mL) was added triethylamine (210 µL, 1.51 mmol) and magnesium bromide (3.5 mg, 0.02 mmol). The mixture was stirred for 15 min and chlorotrimethylsilane (97 µL, 0.76 mmol) was added. After another 5 min a solution of aldehyde 684 (190 mg, 0.17 mmol) in THF (0.5 mL) was added. The reaction was quenched after 30 min by addition of sat. NaHCO$_3$. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was purified by flash column chromatography (CH$_2$Cl$_2$/EtOAc 4:1) to give silyl ether S42.

R$_f$ 0.54 (3:1, hexanes/EtOAc); $^1$H-NMR (400 MHz, CD$_3$CN, mixture of diastereomers): $\delta$ 7.39-7.26 (m, 7H), 7.04 (q, $J = 7.1$ Hz, 1H), 6.88 (dd, $J = 7.7$, 4.2 Hz, 1H), 5.39 (dd, $J = 25.4$, 6.7 Hz, 1H), 4.88-4.47 (m, 4.5H), 4.40-4.25 (bs-m, 0.5H), 3.91-3.72 (bs-m, 1H), 3.43 (d, $J = 5.3$ Hz, 0.5H), 3.24-2.78 (m, 4.5H), 1.90-1.80 (m, 3H), 1.49-1.37 (m, 18H), 0.03-(-0.17) (m, 9H); $^{13}$C-NMR (100 MHz, CD$_3$CN, mixture of diastereomers, all peaks reported): $\delta$ 175.0, 153.5, 153.5, 146.4, 146.1, 139.3, 129.5, 129.3, 129.3, 128.5, 128.5, 128.5, 128.5, 128.4, 127.3, 126.4, 126.1, 122.7, 122.7, 109.2, 109.1, 99.2, 98.8, 83.1, 80.9, 78.3, 77.4, 70.1, 69.9, 60.7, 58.9, 58.7, 50.1, 43.2, 28.7, 28.1, 26.7, 26.4, 3.8, 3.7, 1.9, 1.7, 1.5, 1.3, 1.1, 0.9, 0.7, -0.0; HRMS (ESI) $m/z$ calculated for C$_{38}$H$_{52}$NO$_9$SiNa ([M+Na]$^+$) 743.3334, found 743.3300.
To a solution of N-methoxy oxindole 685 (123 mg, 0.84 mmol) in THF (1.5 mL) was added triethylamine (0.34 mL, 2.8 mmol) and magnesium iodide (155 mg, 0.56 mmol). The mixture was stirred for 15 min and chlorotrimethylsilane (0.29 mL, 2.2 mmol) was added. After another 5 min the solution was cooled to -40 °C and a solution of aldehyde 684 (280 mg, 0.56 mmol) in THF (0.5 mL) was added. After 30 min the reaction was allowed to warm to ambient temperature and stirred for another 2 h. The reaction was quenched by addition of sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to give oxindole 686 (ca. 50% yield) as a mixture of double bond isomers.

Compound 686 was carried on for the synthesis of alkyl fluorides 687-692 using the chemistry developed for the substrates described above.

18.8. Experimental Part to Chapter 12

Optimized conditions for the synthesis of 710:

To a solution of enol ether 550 (1.81 g, 12.0 mmol) in CH₂Cl₂ (250 mL) was added 4Å molecular sieves (ca. 2 g). The solution was cooled to 0 °C and a freshly prepared solution of DMDO₇⁴⁰ (ca. 260 mL, 18.0 mmol, ~0.07 M in acetone) was added. After 2 h at 0 °C the solution was filtered and the solvent was removed under reduced pressure at ambient temperature. The resulting crude epoxide 645 (2.0 g, 12.0 mmol, dr 2:1) was taken up in CH₂Cl₂ (200 mL) and ketene silyl acetal 708₇⁴¹ (28 g, 180 mmol) was added. The solution was cooled to -60 °C and InBr₃ (212 mg, 0.60 mmol) was added. The reaction was allowed to slowly warm to 0 °C over 1 h and stirred for another hour at 0 °C (ice bath).

The mixture was then poured into sat. NaHCO$_3$. The aqueous phase was extracted three times with EtOAc and the combined organic layers were washed with 1M HCl and brine and then dried over MgSO$_4$. The solvent was evaporated and the mixture was subjected to flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give alcohol 710 (1.78 g, 7.0 mmol, 58%, single diastereomer) as a white solid. 

\[ R_f: 0.45 \ (2:3, \text{hexanes/EtOAc}); \text{m.p.}: 85^\circ C; \text{^1H-NMR} \ (400 \text{ MHz, CDCl}_3): \delta \ 4.56 - 4.52 \ (m, 1H), \ 4.50 \ (s, 1H), \ 4.17 \ (q, J = 7.1 \text{ Hz, } 2H), \ 3.85 - 3.78 \ (m, 1H), \ 3.73 - 3.66 \ (m, 2H), \ 2.81 \ (bs, 1H, OH), \ 2.67 \ (dd, J = 15.6, 7.9 \text{ Hz, } 1H), \ 2.55 \ (dd, J = 15.6, 7.1 \text{ Hz, } 1H), \ 1.27 \ (t, J = 7.1 \text{ Hz, } 3H), \ 1.23 - 1.15 \ (m, 1H), \ 1.06 - 0.98 \ (m, 1H), \ 0.76 - 0.68 \ (m, 2H); \text{^13C-NMR} \ (101 \text{ MHz, CDCl}_3): \delta \ 169.9, \ 156.5, \ 67.4, \ 66.5, \ 64.0, \ 61.1, \ 55.1, \ 44.8, \ 34.2, \ 14.1, \ 10.8, \ 7.8; \text{IR } \nu_{\text{max}} \ (\text{film/cm}^{-1}): \ 3409 \ (bs), \ 2981, \ 1731, \ 1630, \ 1375, \ 1248, \ 1088, \ 1021; \text{HRMS (ESI) m/z calculated for C}_{12}H_{18}NO_5 ([M+H]^+) 256.1179, found 256.1173.}

To a solution of 1-bromo-1-propene (27 μL, 0.318 mmol) in THF (1 mL) at -78 °C was slowly added n-BuLi (0.41 mL, 0.652 mmol, 1.6 M in hexanes). The mixture was stirred at -78 °C for 1.5 h and anhydrous CeCl$_3$ (78 mg, 0.318 mmol) was added. After 30 min a solution of alcohol 713 (25 mg, 0.080 mmol) in THF (1 mL) was added followed immediately by addition of BF$_3$-OEt$_2$ (20 μL, 0.159 mmol). The reaction was stirred for 2 h and then quenched by addition of pH 7 buffer. The aqueous phase was extracted twice with EtOAc. The aqueous phase was then acidified with 1M HCl and extracted with EtOAc and CH$_2$Cl$_2$. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give dihydropyridine 714 (10 mg, 32 μmol, 40%) along with major amounts of reisolated starting material.

\[ \text{^1H-NMR} \ (600 \text{ MHz, CDCl}_3): \delta \ 8.20 \ (bs, 1H, OH), \ 7.75 \ (d, J = 8.0 \text{ Hz, } 1H), \ 7.45 \ (d, J = 8.2 \text{ Hz, } 1H), \ 7.31 - 7.25 \ (m, 2H), \ 7.16 \ (td, J = 7.5, 7.1, 0.9 \text{ Hz, } 1H), \ 5.15 \ (d, J = 6.8 \text{ Hz, } 1H), \ 4.87 \ (d, J = 7.3 \text{ Hz, } 1H), \ 4.80 - 4.73 \ (m, 2H), \ 4.27 \ (td, J = 6.1, 2.1 \text{ Hz, } 2H), \ 4.09 \ (s, 3H), \ 3.11 \ (t, J = 6.0 \text{ Hz, } 2H), \ 2.61 \ (bs, 1H, OH); \text{^13C-NMR} \ (150 \text{ MHz, CDCl}_3): \delta \ 162.1, \ 161.5, \ 132.4, \ 123.1, \ 122.7, \ 121.7, \ 120.5, \ 120.0, \ 110.9, \ 108.5, \ 107.4, \ 75.6, \ 73.3, \ 66.1, \ 65.6, \ 60.5, \ 25.1. \]
Experimental Part

To a solution of 1-bromo-1-propene (1.34 mL, 15.7 mmol) in THF (20 mL) at -78 °C was slowly added n-BuLi (20 mL, 32 mmol, 1.6 M in hexanes). The mixture was stirred at -78 °C for 1.5 h and anhydrous CeCl₃ (3.86 g, 15.7 mmol) was added. After 30 min a solution of alcohol 710 (1 g, 3.92 mmol) in THF (3 mL) was added followed immediately by addition of BF₃·OEt₂ (0.96 mL, 7.83 mmol). The reaction was stirred for 2 h and then quenched by addition of pH 7 buffer. The aqueous phase was then extracted with EtOAc. The aqueous phase was then acidified with 1M HCl and extracted with EtOAc and CH₂Cl₂. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give isoxazolidine 716 (902 mg, 3.05 mmol, 78%, single diastereomer) as a colorless foam.

**R**f 0.63 (EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 6.33 (bs, 2H), 4.17 (qd, J = 7.1, 2.2 Hz, 2H), 3.91-3.83 (m, 2H), 3.76 (d, J = 9.9 Hz, 1H), 3.47 (d, J = 13.0 Hz, 1H), 2.97 (dd, J = 16.0, 2.9 Hz, 1H), 2.90 (d, J = 2.6 Hz, 1H), 2.46 (dd, J = 16.0, 8.9 Hz, 1H), 1.94 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.19-1.10 (m, 1H), 1.01-0.87 (m, 2H), 0.64-0.55 (m, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 171.6, 85.3, 74.7, 72.5, 69.3, 67.0 (2C), 62.4, 60.4, 53.1, 37.3, 14.1, 9.6, 9.5, 3.7; IR νmax (film)/cm⁻¹: 3442 (bs), 2980, 2360, 2341, 1730, 1457, 1379, 1310, 1254, 1186, 1113, 1077, 1041, 1014; HRMS (ESI) m/z calculated for C₁₅H₂₁NO₅Na ([M+Na]⁺) 318.1312, found 318.1314.

**Optimized conditions for the ring contraction:**

To a solution of isoxazolidine 716 (890 mg, 3.01 mmol, previously dried by coevaporation with benzene and MeCN) in MeCN (18 mL) was added freshly distilled TFA (0.35 mL, 4.52 mmol). The mixture was heated to 80 °C and stirred for 2 h. The reaction was quenched by addition of NEt₃ (0.84 mL, 6.03 mmol) and diluted with toluene (20 mL). The solvent was removed and the residue was coevaporated once more with toluene. The remaining oil was subjected to flash column chromatography (CH₂Cl₂/MeOH 100:1 → 30:1) to give β-lactam 717 (279 mg, 1.04 mmol, 35%, 70% brsm) as a colorless foam along with reisolated starting material 716 (443 mg, 1.50 mmol, 50% conversion).
Experimental Part

**Rf** 0.60 (EtOAc); **^1H-NMR** (300 MHz, CD$_3$CN): δ 6.99 (bs, 1H, NH), 4.10 (qd, J = 7.1, 0.7 Hz, 2H), 3.96 (dd, J = 12.5, 1.8 Hz, 1H), 3.78 (dd, J = 12.6, 4.5 Hz, 1H), 3.72 (ddd, J = 9.0, 6.5, 3.9 Hz, 1H), 3.61 (t, J = 6.3 Hz, 1H), 3.53 (d, J = 6.2 Hz, 1H), 3.36 (ddd, J = 4.4, 1.8, 1.1 Hz, 1H), 2.71 (ddd, J = 15.7, 3.9 Hz, 1H), 2.44 (dd, J = 15.7, 9.0 Hz, 1H), 1.87 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H); **^13C-NMR** (101 MHz, CD$_3$CN): δ 171.8, 168.4, 84.8, 77.4, 77.3, 73.7, 62.8, 61.3, 58.9, 53.3, 39.9, 14.5, 3.7; **IR** ν$_{max}$ (film)/cm$^{-1}$: 3291 (bs), 2982, 2360, 1731, 1373, 1301, 1248, 1179, 1134, 1096, 1067, 1036; **HRMS** (ESI) m/z calculated for C$_{13}$H$_{17}$NO$_5$Na ([M+Na]$^+$) 290.0999, found 290.0992.

To a solution of β-lactam 171 (1.10 g, 4.1 mmol) in CH$_2$Cl$_2$ (20 mL) was added triethylamine (1.7 mL, 12.4 mmol), di-tert-butyl dicarbonate (2.2 g, 10.3 mmol) and DMAP (50 mg, 0.41 mmol). The solution was stirred for 30 min. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to give carbamate 720 (1.63 g, 3.5 mmol, 85%) as a colorless foam. The structure of 720 was confirmed by X-ray crystallographic analysis (see chapter 24).

**Rf** 0.34 (3:1, hexanes/EtOAc); **^1H-NMR** (300 MHz, CDCl$_3$): δ 5.25 (d, J = 2.8 Hz, 1H), 4.24 (td, J = 6.9, 2.8 Hz, 1H), 4.17-4.10 (m, 3H), 3.94 (dd, J = 12.5, 3.0 Hz, 1H), 3.34 (dd, J = 2.8, 1.3 Hz 1H), 2.56 (d, J = 7.0 Hz, 2H), 1.84 (s, 3H), 1.55 (s, 9H), 1.49 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H); **^13C-NMR** (101 MHz, CDCl$_3$): δ 169.8, 164.4, 152.1, 146.3, 84.2, 83.1, 83.0, 75.3, 74.3, 70.9, 61.3, 60.9, 56.9, 54.1, 39.7, 28.0 (3C), 27.7 (3C), 14.1, 3.7; **IR** ν$_{max}$ (film)/cm$^{-1}$: 2981, 2359, 1819, 1731, 1458, 1395, 1370, 1327, 1276, 1253, 1154, 1088, 1051; **HRMS** (ESI) m/z calculated for C$_{23}$H$_{33}$NO$_9$Na ([M+Na]$^+$) 490.2048, found 490.2053.

A flask was charged with carbamate 720 (1 g, 2.1 mmol) and a solution of Petasis’ reagent Cp$_2$TiMe$_2$ 723 (37 mL, 11 mmol, 0.3M in toluene) was added followed by pyridine (0.7 mL, 8.6 mmol). The reaction was stirred in the dark for 8 h (TLC control). The solvent was evaporated and the residue was directly subjected to flash column chromatography (first column: hexanes/EtOAc 10:1 → 4:1;
second column: hexanes/CH_{2}Cl_{2} 1:1 → CH_{2}Cl_{2} → hexanes/EtOAc 4:1) to give encarbamate 721 \(^\text{742}\) (770 mg, 1.65 mmol, 77%, 85% brsm) as a colorless foam along with reisolated starting material 720 (96 mg, 0.2 mmol, 10%).

Due to slow hydrolysis of 721 in solution, we were not able to obtain a clean \(^{13}\)C NMR spectrum. A clean \(^{1}\)H NMR spectrum was obtained and is reported.

\(R_f\) 0.58 (3:1, hexanes/EtOAc); \(^{1}\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.13 (s, 1H), 5.03 (bs, 0.5H), 4.74 (bs, 0.5H), 4.30-4.08 (m, 4H), 3.96-3.85 (m, 2H), 3.09 (bs, 1H), 2.60 (bs, 2H), 1.85 (s, 3H), 1.53 (s, 9H), 1.50 (s, 9H), 1.25 (t, \(J = 7.1\) Hz, 3H); HRMS (ESI) \(m/z\) calculated for C_{24}H_{35}NO_{8}Na ([M+Na\(^+\)]\(^\text{+}\)) 488.2255, found 488.2275.

To a solution of 9-BBN dimer \(^\text{743}\) (692 mg, 2.8 mmol) in THF (1 mL) was added a solution of encarbamate 721 (1.1 g, 2.4 mmol) in THF (1 mL). After 45 min TLC analysis indicated full consumption of the starting material. The reaction was diluted with THF (8 mL) and water (5 mL). Sodium perborate tetrahydrate (5.3 g, 23.6 mmol) was added and the mixture was vigorously stirred for 1 h. The suspension was diluted with sat. NaHCO\(_3\) and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO\(_4\). The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give alcohol 722 (1.05 g, 2.2 mmol, 92%) as a colorless foam.

\(R_f\) 0.55 (1:1, hexanes/EtOAc); \(^{1}\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) 4.95 (d, \(J = 1.4\) Hz, 1H), 4.52 (td, \(J = 8.1, 2.4\) Hz, 1H), 4.21-4.08 (m, 4H), 3.88-3.63 (m, 4H), 2.69 (dd, \(J = 15.6, 8.3\) Hz, 1H), 2.60 (dd, \(J = 15.6, 5.8\) Hz, 1H), 2.48 (dd, \(J = 8.0, 2.3\) Hz, 1H), 1.82 (s, 3H), 1.48 (s, 9H), 1.47 (s, 9H), 1.24 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): \(\delta\) 170.2, 157.0, 152.2, 82.5, 82.0, 81.6, 76.3, 75.3, 71.3, 62.7, 62.3, 61.2, 60.7, 59.9, 40.5, 37.5, 28.3 (3C), 27.7 (3C), 14.1, 3.5; IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3443 (bs), 2979, 2360, 1740, 1710, 1678, 1458, 1368, 1276, 1255, 1156, 1095, 1037; HRMS (ESI) \(m/z\) calculated for C_{24}H_{37}NO_{9}Na ([M+Na\(^+\)]\(^\text{+}\)) 506.2361, found 506.2349.

\(^{742}\) The product slowly hydrolyzes to the corresponding methylketone but can be stored at -20 °C for several days.

\(^{743}\) Good quality of the reagent is crucial to achieve full conversion of the hydroboration reaction.
To a solution of alcohol 722 (60 mg, 0.124 mmol) in CH$_2$Cl$_2$ (1 mL) was added triethylamine (52 μL, 0.372 mmol) and p-toluenesulfonyl chloride (47 mg, 0.248 mmol). The reaction was stirred overnight. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give tosylate 724 (55 mg, 0.086 mmol, 70%).

R$_f$ 0.29 (4:1, hexanes/EtOAc); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 7.78 (d, $J$ = 8.3 Hz, 2H), 7.33 (d, $J$ = 7.9 Hz, 2H), 4.88 (bs-s, 1H), 4.58-4.53 (m, 1H), 4.50-4.45 (m, 1H), 4.35-4.32 (m, 1H), 4.16-4.12 (m, 3H), 3.99-3.94 (m, 1H), 3.84 (dd, $J$ = 13.1, 3.0 Hz, 1H), 2.63-2.49 (m, 3H), 2.44 (s, 3H), 1.82 (s, 3H), 1.48 (s, 9H), 1.44 (s, 9H), 1.24 (t, $J$ = 7.1 Hz, 3H); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 170.2, 155.8, 152.2, 144.9, 132.6, 129.9 (2C), 128.0 (2C), 82.6, 82.4, 81.2, 76.3, 75.0, 71.4, 67.1, 61.2, 60.7, 59.9, 56.8, 40.6, 37.0, 28.3 (3C), 27.7 (3C), 21.6, 14.1, 3.5.

To a solution of alcohol 722 (1.05 g, 2.2 mmol) in THF (20 mL) at -40 °C was added a diisobutylaluminum hydride (8.7 mL, 8.7 mmol, 1M in CH$_2$Cl$_2$). The reaction was stirred at -40 °C for 30 min and then warmed to ambient temperature. After another 45 min the reaction was quenched by addition of MeOH followed by sat. Rochelle’s salt. The aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give diol 731 (780 mg, 1.8 mmol, 81%) as a colorless foam.

R$_f$ 0.29 (1:2, hexanes/EtOAc); $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 4.99-4.93 (m, 1H), 4.55 (td, $J$ = 8.1, 2.5 Hz, 1H), 4.13 (dd, $J$ = 11.5, 8.2 Hz, 1H), 3.96-3.87 (m, 2H), 3.85-3.66 (m, 5H), 2.51 (d, $J$ = 7.9 Hz, 1H), 2.32-2.20 (m, 1H), 2.06-1.86 (m, 2H), 1.84 (s, 3H), 1.48 (s, 18H); $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$ 157.0, 152.7, 82.8, 82.0, 81.6, 78.0, 76.5, 72.2, 62.8, 62.4, 61.3, 60.3, 60.0, 37.7, 37.6, 28.4 (3C), 27.8 (3C), 3.6; IR $\nu_{max}$ (film)/cm$^{-1}$: 3421 (bs), 2977, 2360, 1746, 1676, 1368, 1275, 1256, 1156, 1090, 1036; HRMS (ESI) m/z calculated for C$_{22}$H$_{35}$NO$_6$Na ([M+Na$^+$]) 464.2255, found 464.2257.
To a solution of DMSO (0.48 mL, 6.8 mmol) in CH$_2$Cl$_2$ (10 mL) at -78 °C was slowly added oxalyl chloride (0.40 mL, 4.5 mmol). The mixture was stirred at -78 °C for 15 min before a solution of diol 731 (500 mg, 1.1 mmol) in CH$_2$Cl$_2$ (3 mL) was added. The reaction was stirred for 45 min and then triethylamine (1.3 mL, 9.1 mmol) was added. After 30 min at -78 °C the mixture was allowed to warm to ambient temperature during another 30 min. The reaction was quenched by addition of brine. The phases were separated and the aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to give dialdehyde 730 (360 mg, 0.82 mmol, 73%) as a colorless foam.

$\textbf{Rf}$ 0.43 (3:1, hexanes/EtOAc); $^1\text{H}$-NMR (300 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): $\delta$ 9.74 (s, 1H), 9.72 (s, 1H), 5.01-4.88 (m, 1H), 4.56 (d, $J = 8.7$ Hz, 1H), 4.38 (dd, $J = 8.8, 4.7$ Hz, 1H), 3.85-3.68 (m, 2H), 2.99-2.68 (m, 3H), 1.85 (s, 3H), 1.54-1.40 (m, 18H); $^{13}\text{C}$-NMR (101 MHz, CDCl$_3$, mixture of rotamers, major rotamer reported): $\delta$ 201.8, 199.1, 155.4, 152.3, 83.3, 83.0, 81.8, 77.2, 74.8, 71.8, 62.4, 60.5, 49.1, 41.0, 28.4 (3C), 28.2, 27.7 (3C), 3.6; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2978, 2360, 1724, 1477, 1457 1368, 1272, 1254, 1153, 1086, 1039; HRMS (ESI) could not be obtained.

A solution of dialdehyde 730 (10 mg, 23 μmol) in toluene (1 mL) was cooled to -40 °C and pyrrolidine (0.4 μL, 4.6 μmol) was added. After 1 h the same amount of pyrrolidine (0.4 μL, 4.6 μmol) was added again. After a total reaction time of 2 h the solvent was evaporated and the residue was directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to give unsaturated aldehyde 732 (7 mg, 17 μmol, 73%).

$\textbf{Rf}$ 0.49 (1:1, hexanes/EtOAc); $^1\text{H}$-NMR (300 MHz, CDCl$_3$): $\delta$ 9.56 (s, 1H), 7.50-7.27 (m, 1H), 5.34-5.02 (m, 2H), 4.59 (dd, $J = 7.8, 5.6$ Hz, 1H), 4.18 (dd, $J = 12.2, 6.4$ Hz, 1H), 3.75 (d, $J = 12.3$ Hz, 1H), 3.19-3.14 (m, 1H), 1.89 (s, 3H), 1.51 (s, 9H), 1.46 (s, 9H); $^{13}\text{C}$-NMR (100 MHz, CDCl$_3$): $\delta$ 190.8, 154.1, 152.3, 140.0, 83.8, 82.3, 81.9, 75.6, 71.4, 65.8, 62.4, 59.0, 57.7, 38.2, 28.1 (3C), 27.8 (3C), 3.8; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2977, 2359, 1747, 1691, 1457, 1368, 1336, 1300, 1273, 1255, 1147, 1125, 1105, 1090; HRMS (ESI) $m/z$ calculated for C$_{22}$H$_{29}$NO$_7$Na ([M+Na]$^+$) 442.1836, found 442.1830.
An NMR tube was charged with a solution of dialdehyde 730 (5 mg, 11 μmol) in $d_6$-benzene (0.7 mL). To this solution was added pyrrolidine (2 μL, 22 μmol). The reaction was followed by $^1$H NMR spectroscopy and the intermediate formed was characterized by 2D NMR analysis directly in the NMR tube. Over time, this intermediate started to decompose to a complex mixture of compounds.

$^1$H-NMR (600 MHz, CDCl$_3$): δ 6.38 (d, J = 13.3 Hz, 1H), 5.73 (d, J = 8.8 Hz, 1H), 5.65-5.64 (m, 1H), 4.68 (t, J = 8.4 Hz, 1H), 4.58-4.53 (m, 2H), 4.47 (dd, J = 8.7, 2.1 Hz, 1H), 4.01 (dd, J = 12.2, 3.3 Hz, 1H), 3.03-2.98 (m, 2H), 2.83-2.67 (m, 6H), 2.67-2.56 (m, 8H), 2.54-2.51 (m, 1H), 1.59 (s, 3H), 1.40-1.29 (m, 18H);

$^{13}$C-NMR (150 MHz, CDCl$_3$): δ 158.5, 153.4, 138.9, 96.7, 83.3, 81.4, 81.3, 81.1, 80.4, 75.9, 64.1, 61.2, 60.7, 48.6, 47.2, 46.3, 39.1, 28.5, 27.8, 25.7, 25.2, 25.0, 24.8, 3.4.

A solution of Stryker’s reagent 744 (82 mg, 42 μmol) in toluene (1 mL) was cooled to -78 °C and a solution of unsaturated aldehyde 732 (35 mg, 83 μmol) in toluene (0.5 mL) was added. After 20 min TLC analysis indicated full consumption of the starting material. The reaction was quenched by addition of sat. NH$_4$Cl and diluted with EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was evaporated and the residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to give a 2:1 mixture of aldehydes 727a and 727b (combined yield: 24 mg, 57 μmol, 68%).

Minor diastereomer 727b: R$_f$ 0.46 (1:1, hexanes/EtOAc); $^1$H-NMR (600 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): δ 9.71 (s, 1H), 5.32-5.12 (m, 1H), 4.73 (bs-s, 1H), 4.57-4.46 (m, 1H), 4.15-4.08 (m, 1H), 3.83 (dd, J = 12.2, 1.5 Hz, 1H), 2.97 (d, J = 8.4 Hz, 1H), 2.75-2.49 (m, 2H), 2.01-1.95 (m, 1H), 1.90-1.85 (m, 3H), 1.52-1.44 (m, 18H); $^{13}$C-NMR (150 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): δ 200.7, 200.5, 152.5, 83.6, 83.3, 82.8, 82.6, 80.8, 75.5, 73.0, 71.7, 69.9, 69.8, 59.8, 59.3, 58.5, 58.4, 50.9, 40.5, 28.4, 27.8, 27.7, 24.3, 23.6, 4.1, 3.7; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3019, 2978, 1749, 1686, 1256, 1215, 1153, 1086, 1047.

744 Stryker’s reagent was prepared according to: Lee, D.-w.; Yun, J. Tetrahedron Lett. 2005, 46, 2037.
Major diastereomer 727a: $R_f$ 0.37 (1:1, hexanes/EtOAc); $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 9.59 (s, 1H), 5.33 (bs-s, 1H), 4.74-4.67 (m, 1H), 4.57-4.47 (m, 1H), 4.18-4.12 (m, 1H), 3.91-3.87 (m, 1H), 3.17-3.14 (m, 1H), 2.98-2.87 (m, 2H), 2.25-2.15 (m, 1H), 1.90-1.82 (m, 3H), 1.58-1.41 (m, 18H); $^{13}$C-NMR (150 MHz, CDCl$_3$): $\delta$ 201.8, 152.8, 152.2, 83.0, 82.3, 80.8, 75.3, 70.9, 70.4, 59.2, 58.4, 52.8, 50.9, 40.8, 28.3 (3C), 27.8 (3C), 24.7, 3.7; IR $\nu_{max}$ (film)/cm$^{-1}$: 3019, 2978, 1749, 1686, 1256, 1215, 1153, 1086, 1047.

To a solution of 727b (13 mg, 31 $\mu$mol) in $t$-BuOH/H$_2$O (1 mL, 5:1) was added 2-methyl-2-butene (23 $\mu$L, 0.21 mmol), NaH$_2$PO$_4$·2H$_2$O (7 mg, 46 $\mu$mol) and NaOCl$_2$ (8 mg, 93 $\mu$mol). After 1 h the reaction was diluted with water and EtOAc. The phases were separated and the aqueous phase was extracted twice with EtOAc. The aqueous phase was then acidified with 1M HCl and again extracted twice with EtOAc. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was evaporated and the crude acid was taken up in CH$_2$Cl$_2$/MeOH (2 mL, 9:1). A solution of TMSCHN$_2$ (46 $\mu$L, 93 $\mu$mol, 2M in Et$_2$O) was added and the mixture was stirred for 15 min. The solvent was evaporated and the residue was purified by flash column chromatography (hexanes/EtOAc 4:1) to give 736b (9 mg, 20 $\mu$mol, 65%).

$R_f$ 0.37 (1:1, hexanes/EtOAc); $^1$H-NMR (600 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): $\delta$ 5.32-5.13 (m, 1H), 4.70 (bs-s, 1H), 4.50-4.40 (m, 1H), 4.15-4.08 (m, 1H), 3.88-3.85 (m, 1H), 3.74-3.70 (m, 3H), 2.94 (d, $J$ = 8.6 Hz, 1H), 2.74-2.53 (m, 2H), 2.13-2.06 (m, 1H), 1.89-1.83 (m, 3H), 1.53-1.43 (m, 18H); $^{13}$C-NMR (150 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): $\delta$ 173.2, 153.2, 152.8, 152.4, 83.1, 82.6, 82.4, 80.7, 75.6, 72.9, 72.5, 72.2, 71.6, 59.9, 59.3, 58.7, 52.3, 44.2, 43.8, 40.5, 28.4, 27.8, 26.4, 25.5, 4.1, 3.6; IR $\nu_{max}$ (film)/cm$^{-1}$: 3019, 1741, 1698, 1394, 1255, 1214, 1145; HRMS (ESI) $m/z$ calculated for C$_{23}$H$_{33}$NO$_8$Na ([M+Na$^+$]) 474.2098, found 474.2095.

To a solution of dialdehyde 730 (225 mg, 0.51 mmol) in dry DMSO (5 mL) was added DL-proline (12 mg, 0.10 mmol). The mixture was stirred overnight. Water was added to the reaction and the aqueous phase was extracted three times with Et$_2$O. The combined organic phases were washed with water and brine and dried over MgSO$_4$. The solvent was evaporated and the residue was subjected to flash
column chromatography (hexanes/EtOAc 4:1 → 1:1) to give aldehyde 733 (185 mg, 0.42 mmol, 82%, single diastereomer)\(^{745}\) as a colorless foam.

\(R_f\) 0.55 (1:1, hexanes/EtOAc); \(^1^H\)-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.00 (s, 1H), 5.05 (d, \(J = 2.0\) Hz, 1H), 4.69 (d, \(J = 9.0\) Hz, 1H), 4.64 (d, \(J = 2.8\) Hz, 1H), 4.60 (d, \(J = 11.5\) Hz, 1H, OH), 4.36 (t, \(J = 10.4\) Hz, 1H), 4.06 (dd, \(J = 12.3,\ 2.4\) Hz, 1H), 3.76 (dd, \(J = 12.3,\ 1.8\) Hz, 1H), 2.99 (d, \(J = 9.0\) Hz, 1H), 2.35 (d, \(J = 9.5\) Hz, 1H), 1.86 (s, 3H), 1.51 (s, 9H), 1.50 (s, 9H); \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): \(\delta\) 201.0, 156.1, 152.3, 83.6, 82.7, 82.4, 74.7, 72.5, 70.0, 67.5, 65.8, 59.7, 58.9, 58.3, 38.8, 28.2 (3C), 27.7 (3C), 3.6; IR \(\nu_{\text{max}}\) (film)/\(\text{cm}^{-1}\): 3419 (bs), 2979, 2934, 2359, 1746, 1727, 1666, 1475, 1395, 1368, 1349, 1307, 1274, 1252, 1147, 1096, 1042; HRMS (ESI) could not be obtained.

18.9. Experimental Part to Chapter 13

Oxindole 752 was prepared through many different pathways (see main text).

\(R_f\) 0.42 (9:1, hexanes/EtOAc); \(^1^H\)-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.47-7.45 (m, 1H), 7.32-7.22 (m, 5H), 7.15 (td, \(J = 7.7,\ 1.2\) Hz, 1H), 7.01 (td, \(J = 7.6,\ 1.1\) Hz, 1H), 6.72 (d, \(J = 7.7\) Hz, 1H), 4.91 (s, 2H), 2.04-1.89 (m, 4H), 1.83-1.61 (m, 6H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 180.7, 141.8, 136.2, 135.4, 128.7 (2C), 127.4, 127.3, 127.1 (2C), 123.9, 121.9, 108.9, 47.4, 43.4, 33.2 (2C), 25.2, 21.2 (2C); IR \(\nu_{\text{max}}\) (film)/\(\text{cm}^{-1}\): 3032, 2927, 2849, 1811, 1697, 1610, 1521, 1486, 1465, 1361, 1273, 1210, 1179, 1076, 1029; HRMS (ESI) \(m/z\) calculated for C\(_{20}\)H\(_{22}\)NO ([M+H\(^{+}\)]\(^{\ddagger}\)) 292.1696, found 292.1701.

To a solution of cyclohexane carboxaldehyde (13 \(\mu\)L, 0.107 mmol, freshly distilled) in CH\(_2\)Cl\(_2\) (1 mL) was added phenylhydrazine (13 \(\mu\)L, 0.128 mmol) and TFA (21 \(\mu\)L, 0.267 mmol). The reaction was stirred overnight and then quenched by addition of sat. NaHCO\(_3\). The phases were separated and the aqueous phase was extracted three times with CH\(_2\)Cl\(_2\). The combined organic layers were washed with brine and dried over MgSO\(_4\). The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to give idoline 777 (13 mg, 0.070 mmo, 66%).

\(^{745}\) The relative stereochemistry of 733 was assigned by NOE analysis. See main text and chapter 25 for a NOESY spectrum.
**Experimental Part**

**Rf** 0.35 (4:1, hexanes/EtOAc); **1H-NMR** (400 MHz, CDCl₃): δ 8.38 (s, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.37 (td, J = 7.6, 1.2 Hz, 1H), 7.30-7.25 (m, 1H), 2.00-1.57 (m, 10 H); **13C-NMR** (100 MHz, CDCl₃): δ 178.3, 154.6, 144.6, 127.7, 125.8, 122.2, 121.2, 57.8, 31.7 (2C), 25.6, 23.9 (2C).

To a solution of imine 777 (100 mg, 0.54 mmol) in CH₂Cl₂ (1 mL) at 0 °C was added m-CPBA (145 mg, 0.648 mmol, 77%). The mixture was allowed to warm to ambient temperature. After 10 min TLC analysis indicated full consumption of the starting material. The reaction was directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to give oxindole 783 (30 mg, 0.149 mmol, 28%).

**Rf** 0.19 (4:1, hexanes/EtOAc); **1H-NMR** (400 MHz, CDCl₃): δ 9.00 (bs-s, 1H, NH), 7.45 (d, J = 7.4 Hz, 1H), 7.21 (t, J = 7.3 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 7.7 Hz, 1H), 2.00-1.57 (m, 10H); **13C-NMR** (100 MHz, CDCl₃): δ 183.6, 140.0, 135.8, 127.4, 124.2, 121.8, 109.8, 48.0, 32.9 (2C), 29.7, 25.1, 21.1 (2C).

To a solution of aldehyde 733 (339 mg, 0.78 mmol) in tert-butanol (6 mL) was added 2-methyl-2-butene (4.1 mL, 38.7 mmol) followed by water (1.5 mL), solid sodium chlorite (350 mg, 3.87 mmol) and NaH₂PO₄ dihydrate (484 mg, 3.10 mmol). The reaction was stirred for 20 min and then diluted with brine and EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The aqueous phase was then acidified with 1M HCl and again extracted twice with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was evaporated and the crude acid 806 was taken up in CH₂Cl₂/MeOH 9:1 (6 mL). Trimethylsilyldiazomethane (0.78 mL, 1.55 mmol, 2M in Et₂O) was added and the reaction was stirred for 10 min. The reaction was quenched by addition of AcOH (67 μL, 1.16 mmol). The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give ester 808 (329 mg, 0.70 mmol, 91%) as a colorless foam.

**Rf** 0.40 (1:1, hexanes/EtOAc); **1H-NMR** (400 MHz, CDCl₃): δ 5.08 (s, 1H), 4.58 (d, J = 9.2 Hz, 1H), 4.46 (t, J = 9.7 Hz, 1H), 4.35-4.27 (m, 2H), 4.01 (dd, J = 12.2, 2.2 Hz, 1H), 3.80 (dd, J = 12.2, 1.6 Hz,
1H), 3.72 (s, 3H), 2.94 (d, J = 9.0 Hz, 1H), 2.58 (d, J = 8.8 Hz, 1H), 1.81 (s, 3H), 1.47 (s, 9H), 1.45 (s, 9H); 13C-NMR (101 MHz, CDCl3): δ 172.0, 155.7, 152.2, 83.4, 82.5, 82.0, 74.6, 72.6, 70.9, 70.5, 65.4, 59.4, 58.8, 53.4, 52.3, 38.6, 28.1 (3C), 27.6 (3C), 3.5; IR v_max (film)/cm⁻¹: 3429 (bs), 2980, 2363, 1745, 1668, 1395, 1369, 1348, 1275, 1253, 1156, 1095, 1043; HRMS (ESI) m/z calculated for C23H33NO9Na ([M+Na]⁺) 490.2048, found 490.2051.

To a solution of ester 808 (329 mg, 0.70 mmol) in THF (8 mL) was added DBU (1.0 mL, 7.0 mmol) and TFAA (0.3 mL, 2.1 mmol). After 30 min at ambient temperature TLC analysis indicated full conversion and the reaction was quenched by addition of sat. NaHCO₃. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give ester 809 (298 mg, 0.66 mmol, 94%) as a colorless foam.

The structure of 809 was confirmed by X-ray crystallographic analysis (see chapter 24).

Rf 0.66 (1:1, hexanes/EtOAc); 1H-NMR (400 MHz, CDCl3, mixture of rotamers, all peaks reported): δ 7.66-7.49 (m, 1H), 5.35 (s, 0.5H), 5.08 (s, 1.5H), 4.42 (dd, J = 7.8, 6.0 Hz, 1H), 4.20-4.08 (m, 1H), 3.79-3.70 (m, 4H), 3.10-3.02 (m, 1H), 1.84 (s, 3H), 1.51-1.33 (m, 18H); 13C-NMR (101 MHz, CDCl3, mixture of rotamers, all peaks reported): δ 165.6, 153.2, 152.6, 152.3, 145.0, 131.4, 83.8, 83.4, 82.4, 82.1, 81.4, 81.1, 75.7, 71.7, 69.5, 69.3, 69.0, 62.1, 61.4, 58.8, 57.3, 52.5, 37.8, 28.1, 27.7, 4.0, 3.7; IR v_max (film)/cm⁻¹: 2977, 2360, 1746, 1703, 1437, 1368, 1338, 1304, 1273, 1248, 1157, 1130, 1114, 1091, 1064; HRMS (ESI) m/z calculated for C23H31NO8Na ([M+Na]⁺) 472.1942, found 472.1947.

To a solution of ester 809 (298 mg, 0.66 mmol) in 1,2-dichloroethane (15 mL) was added trimethyltinhydroxide (1.2 g, 6.6 mmol). The suspension was heated to 80 °C. After 24 h the solvent was evaporated and the residue was taken up in EtOAc. The solution was washed three times with 0.01 M aqueous KHSO₄ and then dried over MgSO₄. The solvent was removed to give crude acid 807 (ca. 300 mg), which was sufficiently pure for use in the next step.
Experimental Part

Rf 0.19 (9:1, CH₂Cl₂/MeOH); ¹H-NMR (300 MHz, CDCl₃, mixture of rotamers, all peaks reported): δ 7.85-7.54 (bs, 1H), 5.43 (bs, 0.5H), 5.13 (bs, 1.5H), 4.46 (t, J = 6.7 Hz, 1H), 4.26-4.11 (bs, 1H), 3.79 (d, J = 12.2 Hz, 1H), 3.13-3.06 (m, 1H), 1.88 (s, 3H), 1.53-1.38 (m, 18H); ¹³C-NMR (101 MHz, CDCl₃, mixture of rotamers, all peaks reported): δ 169.8, 169.3, 153.2, 152.7, 152.2, 145.6, 131.7, 83.6, 83.3, 82.3, 82.0, 81.5, 81.5, 75.7, 75.5, 71.6, 69.4, 68.9, 62.1, 61.4, 58.8, 58.6, 57.3, 37.8, 28.0, 27.6, 3.9, 3.6; IR νmax (film)/cm⁻¹: 2978, 2360, 2341, 1747, 1702, 1476, 1457, 1368, 1339, 1274, 1254, 1155, 1130, 1092, 1057; HRMS (ESI) m/z calculated for C₂₂H₂₉NO₈Na ([M+Na]+) 458.1785, found 458.1792.

To a solution of acid 807 (30 mg, 70 μmol) in CH₂Cl₂ (1 mL) at 0 °C was added oxalyl chloride (30 μL, 0.34 mmol) and a drop of DMF. After 1.5 h the solvent was removed at high vaccum. A solution of N-methyl-2-iodoaniline (80 mg, 0.34 mmol) in CH₂Cl₂ (1 mL) was added to the crude acid chloride followed by triethylamine (50 μL, 0.34 mmol). After 45 min the reaction was quenched by addition of sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 3:1 → 1:1) to give amide 815 (32 mg, 49 μmol, 70%).

To a flask containing amide 815 (22 mg, 34 μmol) was added a stock solution (previsouly degassed) of Pd(OAc)₂ (0.8 mg, 3.4 μmol) in DMF (0.2 mL). To this mixture was added tetrabutylammonium bromide (13 mg, 41 μmol) and potassium formate (14 mg, 0.17 mmol). The reaction was stirred at ambient temperature overnight. Water and Et₂O were added to the reaction mixture and the phases were separated. The aqueous phase was extracted three times with Et₂O. The combined organic layers were washed with water and brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 3:1 → 1:1) to give oxindole 819 (12 mg, 23 μmol, 68%) along with 1.5 mg of isomer 820 (ca. 7%).

The relative configurations of both isomers were determined by NOE analysis.

819 (major): Rf 0.52 (1:1, hexanes/EtOAc); ¹H-NMR (600 MHz, CDCl₃): δ 7.39 (dd, J = 7.4, 0.8 Hz, 1H), 7.24 (dd, J = 7.7, 1.2 Hz, 1H), 7.04 (td, J = 7.6, 1.0 Hz, 1H), 6.74 (d, J = 7.4 Hz, 1H), 5.78 (d, J = 2.2 Hz, 1H), 4.54 (ddd, J = 8.6, 4.1, 1.7 Hz, 1H), 4.33 (dd, J = 12.1, 3.8 Hz, 1H), 4.10 (d, J = 11.4 Hz, 1H), 3.77 (d, J = 2.4 Hz, 1H), 3.16 (s, 3H), 3.09 (dd, J = 8.5, 3.6 Hz, 1H), 2.67 (dd, J = 15.9, 4.1 Hz, 1H), 2.10 (dd, J = 15.9, 1.7 Hz, 1H), 1.89 (s, 3H), 1.58 (s, 9H), 1.48-1.43 (m, 9H); ¹³C-NMR (150
MHz, CDCl₃): δ 175.1, 153.2, 152.4, 142.5, 134.0, 128.3, 125.3, 122.4, 107.5, 82.3, 82.0, 79.7, 76.1, 75.9, 70.0, 59.6, 59.1, 59.0, 54.4, 39.9, 33.2, 28.6 (3C), 27.8 (3C), 26.6, 3.7; HRMS (ESI) m/z calculated for C₂₉H₃₈N₂O₇Na ([M+Na⁺]⁺) 547.2415, found 547.2417.

820 (minor): ¹H-NMR (600 MHz, CDCl₃): δ 7.34-7.31 (m, 1H), 7.29 (td, J = 7.7, 1.2 Hz, 1H), 7.03 (td, J = 7.6, 1.1 Hz, 1H), 6.84 (d, J = 7.3 Hz, 1H), 5.31-5.30 (m, 1H), 4.64-4.57 (m, 1H), 4.21 (dd, J₁ = 12.0, J₂ = 4.3 Hz, 1H), 4.18 (d, J = 11.6 Hz, 1H), 3.75-3.72 (m, 1H), 3.22 (s, 3H), 3.20-3.16 (m, 1H), 2.60 (dd, J₁ = 15.5, J₂ = 1.9 Hz, 1H), 2.35-2.28 (m, 1H), 1.90 (s, 3H), 1.61-1.48 (m, 1H); ¹³C-NMR (150 MHz, CDCl₃): δ 178.5, 153.2, 152.1, 143.5, 130.1, 128.6, 126.3, 122.7, 108.2, 82.3, 80.6, 79.8, 76.1, 75.9, 71.5, 60.4, 59.6, 58.8, 55.0, 40.2, 33.5, 28.5 (3C), 27.8 (3C), 26.6, 3.9. HRMS (ESI) m/z calculated for C₂₉H₃₇N₂O₇ ([M+H⁺]⁺) 525.2595, found 525.2587.

To a solution of crude acid 807 (200 mg, 0.46 mmol) in CH₂Cl₂ (6 mL) was added DMF (7 μL, 0.09 mmol) followed by oxalyl chloride (0.2 mL, 2.30 mmol). After 1 h at ambient temperature the solvent was removed carefully at high vacuum. The crude acid chloride was taken up in Et₂O (6 mL) and cooled to 0 °C. CH₂Cl₂ (2 mL) was added to help dissolve the solid material. To this solution was added NaHCO₃ (77 mg, 0.92 mmol) quickly followed by a solution of N-(2-bromophenyl)hydroxylamine 746 (345 mg, 1.84 mmol) in Et₂O (6 mL). The reaction was allowed to stir in the dark at 0 °C for 45 min. The mixture was diluted with EtOAc and poured into brine. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was evaporated and the residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 50:1 → 3:1) to give hydroxamic acid 832 (161 mg, 0.46 mmol, 58% over 2 steps, 85% brsm) along with reisolated acid 807 (64 mg, 0.15 mmol).

Rf 0.61 (9:1,CH₂Cl₂/MeOH); ¹H-NMR (400 MHz, CDCl₃, mixture of rotamers, all peaks reported): δ 8.39 (bs, 1H, NOH), 7.65 (d, J = 7.7 Hz, 1H), 7.46 (bs, 1H), 7.39 (t, J = 7.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H).

Fresly prepared according to Aust. J. Chem. 1983, 36, 1455:
To a solution of 1-bromo-2-nitrobenzene (2g, 9.9 mmol) and ammonium chloride (609 mg, 11.4 mmol) in EtOH/H₂O (100 mL, 1:1) was added zinc dust (1.5 g, 22.8 mmol) in small portions. After complete addition of zinc the reaction was stirred for 20 min and then filtered. The filter cake was washed with EtOH, the filtrate was concentrated under reduced pressure and the remaining aqueous phase was saturated with NaCl. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was evaporated and the residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 50:1 → 3:1) to give hydroxamic acid 832 (161 mg, 0.46 mmol, 58% over 2 steps, 85% brsm) along with reisolated acid 807 (64 mg, 0.15 mmol).

¹H-NMR (300 MHz, CDCl₃): δ 7.45-7.42 (m, 1H), 7.31-7.28 (m, 2H), 6.84 (dt, J = 8.8, 4.2 Hz, 1H), 5.46 (bs, 1H, NH), 1.62 (bs, 1H, OH).

Arylhydroxylamines are light sensitive.
Hz, 1H), 6.77 (bs, 1H), 5.28-5.01 (m, 1H), 4.81 (bs, 1H), 4.21 (bs, 1H), 4.12-3.99 (m, 1H), 3.49 (bs, 1H), 2.97 (bs, 1H), 1.86 (s, 3H), 1.51 (s, 9H), 1.45 (s, 9H); $^{13}$C-NMR: Characterization by $^{13}$C NMR proved difficult due to multiple rotamers and broad peaks. $^{13}$C and HSQC spectra are given in chapter 25; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3210 (bs), 2977, 2929, 2360, 1749, 1270, 1661, 1474, 1393, 1368, 1340, 1273, 1254, 1157, 1132, 1092, 1060, 1031; HRMS (ESI) $m/z$ calculated for C$_{28}$H$_{33}$BrN$_2$O$_8$Na ([M+Na]$^+$) 627.1312, found 627.1318.

To a solution of hydroxamic acid 832 (48 mg, 0.079 mmol) in DMF (1 mL) was added bis(acetonitrile) dichloropalladium(II) (2.1 mg, 7.9 μmol). The mixture was degassed using freeze/pump/thaw. To the degassed solution was added 1,2,2,6,6-pentamethylpiperidine (87 μL, 0.476 mmol) and formic acid (12 μL, 0.317 mmol). The mixture was heated to 60 °C for 1.5 h. The reaction was then quenched by addition of water and diluted with Et$_2$O. The phases were separated and the aqueous phase was extracted three times with Et$_2$O. The combined organic phases were washed with water and brine and dried over MgSO$_4$. The solvent was evaporated and the residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 50:1 → 10:1) to give oxindole 822 (30 mg, 0.057 mmol, 72%) as a single diastereomer.

R$_f$ 0.45 (9:1, CH$_2$Cl$_2$/MeOH); $^1$H-NMR (300 MHz, CDCl$_3$/CD$_3$OD 10:1, mixture of rotamers, all peaks reported): $\delta$ 7.30-7.23 (m, 1H), 7.21-7.13 (m, 1H), 6.98-6.84 (m, 2H), 5.65-5.48 (m, 1H), 4.41 (dd, $J$ = 8.3, 3.0 Hz, 1H), 4.21 (dd, $J$ = 12.2, 3.7 Hz, 1H), 4.04-3.94 (m, 1H), 3.72-3.66 (m, 1H), 3.06-2.97 (m, 1H), 2.46 (dd, $J$ = 15.8, 3.9 Hz, 1H), 2.06 (d, $J$ = 15.7 Hz, 1H), 1.77 (s, 3H), 1.49-1.29 (m, 18H); $^{13}$C-NMR (101 MHz, CDCl$_3$/CD$_3$OD 10:1, mixture of rotamers, major rotamer reported): $\delta$ 170.7, 153.8, 152.0, 140.4, 129.9, 128.4, 124.7, 122.7, 107.0, 82.7, 82.2, 80.4, 75.7, 75.1, 69.9, 60.3, 59.3, 58.9, 52.8, 39.8, 32.9, 28.2 (3C), 27.4 (3C), 3.3; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2977, 2360, 1748, 1731, 1674, 1617, 1435, 1367, 1309, 1279, 1257, 1216, 1164, 1145, 1086, 1007; HRMS (ESI) $m/z$ calculated for C$_{28}$H$_{34}$N$_2$O$_8$Na ([M+Na]$^+$) 549.2207, found 549.2204.
18.10. **Experimental Part to Chapter 14**

To a solution of alkyne 837 (5 mg, 17 μmol) in MeCN/CH₂Cl₂ (1 mL, 3:1) was added water (1 μL, 50 μmol) and a solution of Hg(OTf)₂ ⁷⁴⁸ (17 μL, 1.7 μmol, 0.1M in MeCN). The mixture was stirred for 20 h at ambient temperature. The solvent was removed and the residue was directly subjected to flash column chromatography (CH₂Cl₂/MeOH 20:1) to give ketone 838 (2 mg, 6 μmol, 38%) as the sole regioisomer.

R₉ 0.30 (EtOAc); ¹H-NMR (600 MHz, CDCl₃):  δ 7.40-7.32 (m, 4H), 7.12 (t, J = 7.0 Hz, 1H), 6.81 (bs-s, 1H, NH), 6.49 (bs-s, 1H, NH), 5.24 (t, J = 4.4 Hz, 1H), 4.22-4.15 (m, 2H), 4.07-4.02 (m, 1H), 3.82 (dd, J = 12.4, 4.3 Hz, 1H), 3.13 (d, J = 18.4 Hz, 1H), 3.00 (bs-s, 1H), 2.78 (d, J = 18.4 Hz, 1H), 2.20-2.13 (bs-m, 3H); ¹³C-NMR (150 MHz, CDCl₃): δ 205.8, 167.6, 152.3, 152.1, 137.0, 129.3 (2C), 124.2, 118.7 (2C), 71.2, 65.4, 61.9, 55.4, 53.4, 48.1, 30.5.

To a solution of alcohol 572 (7 mg, 39 μmol) in MeCN/CH₂Cl₂ 3:1 (1 mL) was added water (2 μL, 0.12 mmol) and a freshly prepared solution of Hg(OTf)₂ ⁷⁴⁹ (40 μL, 4 μmol). The reaction was stirred overnight and the residue was directly subjected to flash column chromatography (CH₂Cl₂/MeOH 20:1) to give furan 840 (5 mg, 28 μmol, 71%).

R₉ 0.31 (9:1; CH₂Cl₂/MeOH); ¹H-NMR (300 MHz, CDCl₃): δ 6.02 (bs-s, 2H, NH), 5.59 (bs-s, 1H, NH), 4.73-4.60 (m, 2H), 4.32 (dd, J = 11.6, 2.1 Hz, 1H), 3.83 (dd, J = 11.6, 4.1 Hz, 1H), 3.36 (s, 1H), 2.32 (2, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 174.9, 152.1, 146.8, 114.1, 105.4, 67.7, 63.8, 42.2, 13.5; HRMS (ESI) m/z calculated for C₉H₁₁NO₃Na ([M+Na⁺]⁺) 204.0631, found 204.0629.

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To a suspension of yellow HgO (22 mg, 0.10 mmol) in MeCN (1 mL) was added Tf₂O (17 μL, 0.10 mmol). The initial orange color disappear to give a colorless solution of Hg(OTf)₂ (0.1 M), which was used instantaneously.
To a solution of alkyne 821 (4 mg, 7.8 μmol) in CH₂Cl₂ (0.5 mL) was added triphenylphosphine gold(I) bistriflimide (cat.). After 30 min the solvent was removed and the residue was directly subjected to flash column chromatography (CH₂Cl₂/MeOH 40:1) to give carbamate 843 (2 mg, 4.4 μmol, 56%).

Rᶠ 0.59 (9:1, CH₂Cl₂/MeOH); ¹H-NMR (600 MHz, CDCl₃): δ 7.62 (bs-s, 1H, NH), 7.45-7.43 (m, 1H), 7.23 (td, J = 7.7, 1.2 Hz, 1H), 7.05 (td, J = 7.6, 1.1 Hz, 1H), 6.85-6.83 (m, 1H), 5.58 (dd, J = 2.6, 0.7 Hz, 1H), 5.12 (d, J = 1.1 Hz, 1H), 4.84 (ddd, J = 8.6, 4.6, 1.5 Hz, 1H), 4.28 (dd, J = 12.2, 3.2 Hz, 1H) 4.13 (d, J = 2.6 Hz, 1H), 4.05 (dd, J = 12.2, 1.4 Hz, 1H), 3.33-3.31 (m, 1H), 2.65 (dd, J = 15.8, 4.7 Hz, 1H), 2.32 (dd, J = 15.8, 1.5 Hz, 1H), 1.93 (s, 3H), 1.44 (s, 9H); ¹³C-NMR (151 MHz, CDCl₃): δ 176.5, 152.2, 151.8, 150.4, 139.2, 134.3, 128.6, 125.3, 122.7, 109.2, 97.8, 83.0, 75.6, 74.5, 65.0, 64.4, 60.9, 54.8, 45.0, 34.8, 27.7 (3C), 19.2; IR ν_max (film)/cm⁻¹: 3256 (bs), 2924, 1732, 1619, 1474, 1369, 1352, 1282, 1255, 1175, 1158, 1090; HRMS (ESI) m/z calculated for C₂₄H₂₇N₂O₇ ([M+H]⁺) 455.1813, found 455.1818.

To a solution of silane 850 (10 mg, 29 μmol) in CH₂Cl₂ (1 mL) was added dichloro(benzene)ruthenium dimer 852 (cat.). After 45 min TLC analysis indicated good conversion of the starting material. The solvent was evaporated and the residue was directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to give silane 853 (6.5 mg, 19 μmol, 65%) along with some desilated secondary alcohol.

Rᶠ 0.66 (1:1, hexanes/EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 6.16 (q, J = 7.2 Hz, 1H), 4.51 (dd, J = 6.5, 5.6 Hz, 1H), 4.19 (dd, J = 12.2, 1.8 Hz, 2H), 4.10 (dd, J = 12.4, 5.5 Hz, 1H), 3.77 (dd, J = 12.2, 6.1 Hz, 1H), 3.37 (dd, J = 12.3, 6.6 Hz, 1H), 3.27 (dd, J = 6.1, 1.9 Hz, 1H), 1.87 (d, J = 7.2 Hz, 3H), 1.51 (s, 9H), 0.34 (s, 3H), 0.26 (s, 3H); HRMS (ESI) m/z calculated for C₁₆H₂₅N₂O₅SiNa ([M+Na]⁺) 362.1394, found 362.1397.

749 The reaction can also be carried out using Ziese’s dimer ([Cl₂Pt(C₅H₄)]₂) as catalyst.
750 Prepared by treatment of the corresponding secondary alcohol with dimethylchlorosilane, triethylamine and DMAP. The silane 850 proved unstable to SiO₂.
To a solution of oxindole 822 (52 mg, 0.099 mmol) in DMF (2 mL) at 0 °C was added sodium hydride (6 mg, 0.148 mmol, 60% suspension in mineral oil). After 15 min iodomethane (19 μL, 0.296 mmol) was added and the mixture was allowed to warm to ambient temperature. After 30 min water was added to the reaction. The aqueous phase was extracted three times with Et₂O. The combined organic phases were washed with water and brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give N-methoxy oxindole 745 (49 mg, 0.091 mmol, 92%).

The relative stereochemistry of 745 was again confirmed by NOE analysis (see chapter 24).

\( R_f \) 0.49 (1:1, hexanes/EtOAc); \(^1\)H-NMR (400 MHz, CDCl₃, mixture of rotamers, major rotamer reported): \( \delta \) 7.41 (d, \( J = 7.2 \) Hz, 1H), 7.31-7.24 (m, 1H), 7.06 (td, \( J = 7.6, 1.0 \) Hz, 1H), 6.91 (d, \( J = 7.4 \) Hz, 1H), 5.75 (d, \( J = 2.3 \) Hz, 1H), 4.54 (ddd, \( J = 8.5, 4.1, 1.5 \) Hz, 1H), 4.33 (dd, \( J = 12.1, 3.7 \) Hz, 1H), 4.07 (d, \( J = 12.1 \) Hz, 1H), 3.98 (s, 3H), 3.84 (d, \( J = 2.5 \) Hz, 1H), 3.09 (dd, \( J = 8.5, 3.6 \) Hz, 1H), 2.68 (dd, \( J = 15.8, 4.1 \) Hz, 1H), 2.12 (dd, \( J = 15.8, 1.4 \) Hz, 1H), 1.88 (s, 3H), 1.58 (s, 9H), 1.50-1.44 (m, 9H); \(^{13}\)C-NMR (101 MHz, CDCl₃, mixture of rotamers, major rotamer reported): \( \delta \) 170.5, 152.9, 152.1, 138.8, 130.3, 128.5, 125.5, 123.1, 106.9, 82.5, 82.0, 79.9, 75.9, 75.7, 70.2, 63.3, 59.6, 59.0, 58.9, 53.1, 40.1, 33.4, 28.6 (3C), 27.8 (3C), 3.7; IR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 2978, 2931, 2361, 1731, 1697, 1617, 1477, 1466, 1409, 1367, 1308, 1279, 1279, 1254, 1159, 1144, 1088; HRMS (ESI) \( m/z \) calculated for C\(_{29}\)H\(_{37}\)N\(_2\)O\(_8\) ([M+H]\(^+\)) 541.2544, found 541.2545.

To a solution of carbonate 745 (48 mg, 0.089 mmol) in MeOH (1.5 mL) was added K\(_2\)CO\(_3\) (123 mg, 0.888 mmol). The reaction was heated to 50 °C for 1 h and then quenched by addition of water. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was evaporated and the residue was purified by flash column chromatography (CH\(_2\)Cl\(_2\)/MeOH 100:1 → 30:1) to give alcohol 842 (34 mg, 0.077 mmol, 87%).

\( R_f \) 0.56 (EtOAc); \(^1\)H-NMR (300 MHz, CDCl₃, mixture of rotamers, all peaks reported): \( \delta \) 7.43 (dd, \( J = 7.3, 2.3 \) Hz, 1H), 7.31-7.26 (m, 1H), 7.08 (t, \( J = 7.3 \) Hz, 1H), 6.92 (d, \( J = 7.8 \) Hz, 1H), 4.68-4.58 (m, 1H), 4.55-4.40 (m, 1H), 4.36-4.27 (m, 1H), 4.06 (dd, \( J = 11.9, 7.7 \) Hz, 1H), 3.99-3.96 (m, 3H), 3.86
Experimental Part

(dd, $J = 12.4, 2.5$ Hz, 1H), 3.08 (dd, $J = 8.6, 3.3$ Hz, 1H), 2.70-2.52 (m, 1H), 2.50 (dd, $J = 15.0, 3.4$ Hz, 1H, OH), 2.16-2.08 (m, 1H), 1.98-1.94 (m, 3H), 1.56-1.48 (m, 9H); $^{13}$C-NMR (75 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): $\delta$ 170.8, 170.7, 152.8, 151.6, 138.5, 138.4, 130.5, 128.3, 125.4, 125.4, 123.0, 106.7, 106.6, 85.0, 83.9, 79.5, 79.4, 77.14, 77.0, 76.0, 75.3, 66.8, 66.3, 63.3, 63.1, 60.3, 59.4, 59.3, 59.2, 58.7, 52.9, 39.9, 39.6, 33.4, 33.0, 28.6, 28.5, 4.0, 3.6; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3440 (bs), 976, 2930, 1728, 1684, 1617, 1477, 1466, 1414, 1366, 1322, 1280, 1240, 1160, 1140, 1098, 1070, 1032, 1008; HRMS (ESI) $m/z$ calculated for C$_{24}$H$_{28}$N$_2$O$_6$Na ([M+Na]$^+$) 463.1840, found 463.1344.

To a flask containing alcohol 842 (70 mg, 0.16 mmol) was added 1,1,3,3-tetramethyldisilazane (4 mL). The mixture was heated to 50 °C for 2.5 h. The solvent was evaporated and the residue was dissolved in CH$_2$Cl$_2$ (3 mL). Dichloro(benzene)ruthenium dimer 852 (8 mg, 0.016 mmol) was added to the solution. After 1.5 h the same amount of ruthenium catalyst was added again and the mixture was allowed to stir for 15 h. The mixture was filtered over silica gel using EtOAc as eluent. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give vinyl silane 854 (46 mg, 0.092 mmol, 58%) as a mixture of double bond isomers (ca. 2:1).$^{751}$

R$_f$ 0.48 (1:1, hexanes/EtOAc, major isomer); $^1$H-NMR (400 MHz, CDCl$_3$, mixture of rotamers and double bond isomers, all peaks reported): $\delta$ 7.46-7.39 (m, 1H), 7.30-7.23 (m, 1H), 7.06 (t, $J = 7.5$ Hz, 1H), 6.91 (dd, $J = 7.3, 4.6$ Hz, 1H), 6.21-6.07 (m, 1H), 5.00-4.80 (m, 1H), 4.61-4.31 (m, 1H), 4.20-4.04 (m, 2H), 4.01-3.93 (m, 3H), 3.85 (dd, $J = 9.9, 2.2$ Hz, 1H), 3.00-2.90 (m, 1H), 2.83-2.51 (m, 1H), 2.17-2.07 (m, 1H), 2.05-1.95 (m, 3H), 1.54-1.42 (m, 9H), 0.28-0.08 (m, 6H); $^{13}$C-NMR (101 MHz, CDCl$_3$, mixture of rotamers and double bond isomers, all peaks reported): $\delta$ 171.5, 171.3, 153.3, 152.0, 139.4, 138.7, 138.6, 138.5, 138.1, 130.9, 128.2, 128.2, 125.5, 123.1, 123.0, 106.7, 106.7, 79.4, 78.8, 77.3, 73.3, 73.1, 68.0, 67.2, 63.5, 63.2, 59.6, 59.5, 59.4, 58.2, 53.1, 40.2, 40.2, 33.3, 32.7, 28.7, 28.6, 15.1, 14.4, 0.3, 0.2, 0.0, 0.0, -0.1; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2930, 1731, 1696, 1617, 1466, 1411, 1365, 1320, 1254, 1172, 1127, 1052; HRMS (ESI) $m/z$ could not be obtained.

$^{751}$ The isomers could not be cleanly separated for individual characterization. However, subjecting the enriched isomers to Tamao–Flemming conditions gave in both cases the expected ethylketone product.
To a solution of vinyl silane 854 (5.0 mg, 10.0 μmol) in DMF (0.5 mL) was added KHF$_2$ (2.3 mg, 30.0 μmol) followed by Ac$_2$O (24 μL, 0.25 mmol) and hydrogen peroxide (26 μL, 0.25 mmol, 30% in water). The reaction was stirred for 3.5 h. The mixture was poured into water and the aqueous phase was extracted three times with Et$_2$O. The combined organic phases were washed with water and brine and dried over MgSO$_4$. The solvent was removed and the residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 50:1 → 20:1) to give ketone 861 (3.0 mg, 6.5 μmol, 65%).

$R_f$ 0.38 (1:1, hexanes/EtOAc); $^1$H-NMR (400 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): $\delta$ 7.44 (dd, $J = 12.5$, 7.5 Hz, 1H), 7.33-7.27 (m, 1H), 7.13-7.07 (m, 1H), 6.94 (t, $J = 7.6$ Hz, 1H), 5.11-5.03 (m, 1H), 4.68-4.41 (m, 1H), 4.32 (d, $J = 3.4$ Hz, 0.5H, OH), 4.25 (dt, $J = 12.1$, 3.9 Hz, 1H), 4.15-4.09 (m, 1H), 4.00-3.96 (m, 3H), 3.81 (dd, $J = 21.4$, 2.5 Hz, 1H), 3.73 (d, $J = 6.1$ Hz, 0.5H, OMe), 3.32-3.24 (m, 1H), 3.14-2.76 (m, 2H), 2.70 (ddd, $J = 47.8$, 15.8, 4.0 Hz, 1H), 2.23-2.14 (m, 1H), 1.53-1.45 (m, 9H), 1.14 (dt, $J = 11.4$, 7.2 Hz, 3H); $^{13}$C-NMR (151 MHz, CDCl$_3$, mixture of rotamers, all peaks reported): $\delta$ 210.8, 210.5, 170.8, 170.8, 152.7, 152.4, 138.7, 138.6, 130.4, 130.2, 128.6, 128.5, 125.5, 125.4, 123.3, 123.3, 107.0, 106.9, 81.2, 80.2, 78.5, 78.2, 69.1, 68.5, 66.9, 66.4, 63.5, 63.3, 60.7, 60.2, 60.0, 59.9, 53.0, 52.9, 35.2, 33.6, 33.3, 33.0, 32.1, 30.4, 28.6, 28.5, 7.7, 7.6; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3420 (bs), 3013, 2979, 2938, 1729, 1700, 1617, 1477, 1466, 1417, 1368, 1235, 1236, 1216, 1165, 1140, 1043; HRMS (ESI) m/z calculated for C$_{24}$H$_{30}$N$_2$O$_7$Na ([M+Na]$^+$) 481.1945, found 481.1950.

A solution of ketone 861 (4.5 mg, 9.8 μmol) in EtOAc (0.1 mL) was cooled to 0 °C and 3M HCl in EtOAc$^{752}$ (1.5 mL, precooled to 0 °C) was added. The mixture was stirred for 10 min (TLC monitoring) and then diluted with EtOAc to a total volume of 4 mL. This solution was transferred into a separatory funnel containing sat. NaHCO$_3$ and EtOAc. After extraction of the organic phase, the aqueous phase was washed once with EtOAc. The combined organic phases were dried over Na$_2$SO$_4$

$^{752}$ To a mixture of EtOAc (2.4 mL) and MeOH (0.72 mL) at 0 °C was slowly added AcCl (0.85 mL). The solution was allowed to warm to ambient temperature and stirred for 15 min before use.
and the solvent was evaporated at approx. 10 °C to give synthetic gelsemoxonine (278) (3.4 mg, 9.5 μmol, 97%), which was used for characterization without further purification.\textsuperscript{753}

\( R_f \) 0.48 (9:1, CH\(_2\)Cl\(_2\)/MeOH); \( ^1H\)-NMR (600 MHz, CDCl\(_3\)): \( \delta \) 7.48 (dd, \( J = 7.5, 0.6 \) Hz, 1H), 7.36 (td, \( J = 7.7, 1.2 \) Hz, 1H), 7.18 (td, \( J = 7.6, 1.1 \) Hz, 1H), 7.03 (ddd, \( J = 7.8, 1.0, 0.5 \) Hz, 1H), 4.53 (d, \( J = 2.3 \) Hz, 1H), 4.27 (dd, \( J = 12.1, 4.0 \) Hz, 1H), 4.17 (d, \( J = 11.8 \) Hz, 1H), 4.05 (s, 3H), 3.98-3.59 (br-m, 1H), 3.82 (d, \( J = 2.6 \) Hz, 1H), 3.65 (d, \( J = 2.2 \) Hz, 1H, OH), 3.39 (br-dd, \( J = 8.5, 3.7 \) Hz, 1H), 2.83 (dq, \( J = 18.2, 7.2 \) Hz, 1H), 2.54 (dq, \( J = 18.2, 7.2 \) Hz, 1H), 2.41 (dd, \( J = 16.1, 1.5 \) Hz, 1H), 2.30 (dd, \( J = 16.0, 4.5 \) Hz, 1H), 1.12 (t, \( J = 7.2 \) Hz, 3H); \( ^13C\)-NMR (151 MHz, CDCl\(_3\)): \( \delta \) 211.2, 173.4, 138.0, 130.2, 128.9, 125.2, 124.2, 107.6, 78.5, 68.5, 67.2, 63.8, 61.7, 53.9, 34.4, 33.7, 29.2, 7.0; IR \( \nu_{max} \) (film)/cm\(^{-1}\): 3250 (bs), 2921, 1688, 1616, 1465, 1319, 1245, 1150, 1039; HRMS (ESI) \( m/z \) calculated for C\(_{19}\)H\(_{23}\)N\(_2\)O\(_5\) ([M+H]+) 359.1601, found 359.1607.

Crude gelsemoxonine (278) was acetylated employing the reported procedure to provide diacetate 865.\textsuperscript{754}

\( R_f \) 0.33 (EtOAc); \( ^1H\)-NMR (600 MHz, CDCl\(_3\), mixture of rotamer, major rotamer reported): \( \delta \) 7.39 (d, \( J = 7.5 \) Hz, 1H), 7.33 (td, \( J = 7.7, 1.2 \) Hz, 1H), 7.11 (td, \( J = 7.6, 1.1 \) Hz, 1H), 6.98 (d, \( J = 7.7 \) Hz, 1H), 6.08 (dd, \( J = 2.7, 0.8 \) Hz, 1H), 4.58 (ddd, \( J = 8.7, 4.3, 1.5 \) Hz, 1H), 4.14 (dd, \( J = 3.5, 2.5 \) Hz, 1H), 4.05 (s, 3H), 3.95 (d, \( J = 2.7 \) Hz, 1H), 3.74 (br-d, \( J = 8.6 \) Hz, 1H), 3.18 (dq, \( J = 17.5, 7.2 \) Hz, 1H), 2.50 (dd, \( J = 16.0, 4.3 \) Hz, 1H), 2.45 (dq, \( J = 17.5, 7.1 \) Hz, 1H), 2.35 (dd, \( J = 16.0, 1.5 \) Hz, 1H), 2.02 (s, 3H), 1.91 (s, 3H), 1.13 (t, \( J = 7.2 \) Hz, 2H); \( ^13C\)-NMR (151 MHz, CDCl\(_3\), mixture of rotamers, major rotamer reported): \( \delta \) 205.8, 171.5, 169.4, 169.2, 138.8, 129.5, 128.9, 125.1, 123.4, 107.4, 75.2, 69.1, 68.1, 64.0, 61.1, 60.7, 53.4, 34.3, 32.7, 32.6, 21.0, 20.5, 8.5; IR \( \nu_{max} \) (film)/cm\(^{-1}\): 2933, 1719, 1653, 1617, 1465, 1436, 1373, 1325, 1229, 1179, 1139, 1070, 1033; HRMS (ESI) \( m/z \) calculated for C\(_{23}\)H\(_{36}\)N\(_2\)O\(_7\)Na ([M+Na]+) 465.1632, found 465.1627.

\textsuperscript{753} Attempted chromatographic purification on silica gel using either CH\(_2\)Cl\(_2\)/MeOH or acetone/toluene (see J. Am. Chem. Soc. 2011, 133, 17634.) as eluent systems did not provide us with pure Gelsemoxonine, but lead to the formation of a complex mixture of unidentified compounds.

\textsuperscript{754} Org. Lett. 2003, 5, 2075-2078.
Gelsemoxonine analogue 863 was prepared from oxindole 819 using the chemistry detailed above.

Rf 0.49 (9:1; CH$_2$Cl$_2$/MeOH); $^1$H-NMR (400 MHz, CDCl$_3$): δ 7.47 (d, $J = 7.5$ Hz, 1H), 7.33 (td, $J = 7.7$, 1.2 Hz, 1H), 7.15 (td, $J = 7.6$, 0.9 Hz, 1H) 6.87 (d, $J = 7.7$ Hz, 1H), 4.54 (bs-s, 1H), 4.38 (bs-s, 1H, NH or OH), 4.26 (dd, $J = 12.0$, 4.1 Hz, 1H), 4.18 (d, $J = 12.0$ Hz, 1H), 3.88 (dq, $J = 6.1$, 2.3, 1.5 Hz, 1H), 3.76 (d, $J = 2.6$ Hz, 1H), 3.35 (dd, $J = 8.2$, 3.9 Hz, 1H), 3.26 (s, 3H), 2.83 (dq, $J = 18.2$, 7.3 Hz, 1H), 2.52 (dq, $J = 18.3$, 7.2 Hz, 1H), 2.46 (bs-s, 1H, NH or OH), 2.38 (dd, $J = 16.0$, 1.6 Hz, 1H), 2.26 (dd, $J = 16.0$, 4.5 Hz, 1H), 1.11 (t, $J = 7.2$ Hz, 3H); $^{13}C$-NMR (100 MHz, CDCl$_3$): δ 211.8, 178.2, 141.7, 134.1, 128.6, 124.9, 123.5, 108.2, 78.8, 68.4, 67.3, 61.8, 55.7, 55.2, 34.8, 33.5, 28.8, 26.7, 7.1; HRMS (ESI) m/z calculated for C$_{23}$H$_{26}$N$_2$O$_7$Na ([M+Na]$^+$) 465.1632, found 465.1627.

864: $^1$H-NMR (600 MHz, CDCl$_3$): δ 7.40 (dd, $J = 7.5$, 0.8 Hz, 1H), 7.33 (td, $J = 7.7$, 1.2 Hz, 1H), 7.12 (td, $J = 7.6$, 1.0 Hz, 1H), 6.84 (d, $J = 7.4$ Hz, 1H), 5.13 (bs-s, 1H), 4.66 (dd, $J = 8.8$, 4.0, 1.7 Hz, 1H), 4.27 (dd, $J = 12.4$, 4.2 Hz, 1H), 4.21 (d, $J = 11.9$ Hz, 1H), 3.76 (d, $J = 2.6$ Hz, 1H), 3.50 (dd, $J = 8.7$, 4.0 Hz, 1H), 3.24 (s, 3H), 3.11 (bs-s, 1H, OH or NH), 3.04 (dq, $J = 18.7$, 7.1 Hz, 1H), 2.96 (dq, $J = 18.9$, 7.1 Hz, 1H), 2.86 (dd, $J = 16.1$, 4.1 Hz, 1H), 2.28 (dd, $J = 16.1$, 1.8 Hz, 1H), 1.13 (t, $J = 7.1$ Hz, 3H); $^{13}C$-NMR (150 MHz, CDCl$_3$): δ 206.9, 175.5, 142.3, 133.1, 128.8, 125.0, 123.0, 108.1, 78.4, 72.3, 64.9, 64.0, 59.8, 54.1, 33.2, 32.3, 32.1, 26.7, 7.5.
Table 35: Comparison of $^{13}$C and $^1$H NMR shifts in CDCl$_3$ (given in ppm) of gelsemoxonine analogue 863 and product 864 obtained upon concentration of 863 from a CHCl$_3$ solution. Differences in carbon shift $> 4$ ppm and in hydrogen shift $> 0.4$ ppm are highlighted in red.

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Allenic alcohol 877 was prepared according to a literature procedure.\(^{755}\)

To a solution of propargyl chloride (3.1 mL, 40 mmol) in Et\(_2\)O (30 mL) at -78 °C was added \(n\)-BuLi (38 mL, 60 mmol, 1.6M in hexanes). The mixture was stirred at that temperature for 15 min before paraformaldehyde (3.6 g, 121 mmol) was added. The mixture was warmed to -40 °C and stirred for 2 h and then for 12 h at ambient temperature. The reaction was quenched by the addition of water and diluted with EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over MgSO\(_4\) and the solvent was removed. The residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give alcohol 879 (1.3 g, 12.4 mmol, 31%).

To a suspension of LiAlH\(_4\) (1.4 g, 37 mmol) in Et\(_2\)O (40 mL) at 0 °C was slowly added a solution of alcohol 879 (1.3 g, 12.4 mmol) in Et\(_2\)O (10 mL). The mixture was warmed to ambient temperature and stirred for 1 h. The reaction was quenched at 0 °C by the addition of water and 2M NaOH. After stirring this suspension vigorously for 45 min, Et\(_2\)O was added and the phases were separated. The aqueous phase was extracted three times with Et\(_2\)O. The combined organic phases were dried over MgSO\(_4\) and the solvent was removed to give allenic alcohol 877 (800 mg, 11.4 mmol, 92%).

To a solution of allene 877 (800 mg, 11.4 mmol) in MeCN (20 mL) was added NaHCO\(_3\) (4.8 g, 57 mmol) and 2-bromoacetyl bromide (3 mL, 34 mmol). After 10 min the reaction was quenched by addition of water and the aqueous phase was extracted three times with CH\(_2\)Cl\(_2\). The combined organic phases were washed with brine and dried over MgSO\(_4\). The solvent was removed to obtain crude bromoacetate.

The crude product was taken up in THF (20 mL) and ditosylhydrazine (3.9 g, 11.4 mmol) was added. The mixture was then cooled to 0 °C and DBU (5.2 mL, 34 mmol) was slowly added. The solution thereby turned dark red. After 10 min the reaction was quenched by addition of sat. NaHCO\(_3\). The aqueous phase was extracted three times with Et\(_2\)O. The combined organic phases were washed with brine and dried over MgSO\(_4\). The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give diazoacetate 874 (840 mg, 6.1 mmol, 53%).

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Experimental Part

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 5.22 (p, $J = 6.8$ Hz, 1H), 4.78 (dt, $J = 6.6$, 2.4 Hz, 2H), 4.73 (bs-s, 1H), 4.57 (dt, $J = 6.9$, 2.4 Hz, 2H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 209.4, 166.2, 86.2, 76.4, 62.1, 45.9.

This compound has been prepared previously from propargyl bromide and glycolaldehyde diethylacetal: Arch. Pharm. 1985, 318, 548.

A suspension of sodium hydride (6.3 g, 157 mmol, 60% suspension in mineral oil) in DMF (40 mL) was cooled to 0 °C and propargyl alcohol (8.3 mL, 143 mmol) was added slowly. The mixture was allowed to warm to ambient temperature and stirred for 30 min. Then bromoacetaldehyde diethylacetal 886 (22 mL, 143 mmol) was added and the reaction was stirred for 12 h. The mixture was diluted with Et$_2$O and the organic phase was extracted with water. The aqueous phase was extracted three times with Et$_2$O and the combined organic phases were washed with water and brine, dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give ether 887 (13.5 g, 78 mmol, 55%).

$R_f$ 0.61 (4:1, hexanes/EtOAc); $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 4.65 (t, $J = 5.2$ Hz, 1H), 4.21 (d, $J = 2.4$ Hz, 2H), 3.76-3.52 (m, 6H), 2.43 (t, $J = 2.4$ Hz, 1H), 1.22 (t, $J = 7.1$ Hz, 6H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 100.7, 79.4, 74.6, 69.9, 62.0 (2C), 58.4, 15.2 (2C); IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3261, 2976, 2876, 2116, 1444, 1374 1266, 1106, 1060, 1011; HRMS (EI) m/z calculated for C$_7$H$_{11}$O$_2$ ([M-C$_5$H$_5$O]$^+$) 127.0754, found 127.0753.

Racemic preparation:

To a solution of alkyne 887 (2.1 g, 12.2 mmol) in THF (30 mL) at -78 °C was added n-BuLi (9.2 mL, 14.6 mmol, 1.6 M in hexanes). The mixture was stirred at -78 °C for 1 h before a solution of aldehyde
Experimental Part

888 (2.1 g, 12.2 mmol) in THF (5 mL) was added slowly. The reaction was allowed to stir for 1 h. The mixture was then warmed to -40 °C and stirred for another hour. The reaction was quenched by addition of sat. NH₄Cl. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give propargylic alcohol 889 (2.9 g, 8.5 mmol, 70%).

Asymmetric protocol:

To a flask containing Zn(OTf)₂ (292 mg, 0.80 mmol) was added (–)-N-methyl ephedrine (154 mg, 0.86 mmol). The solids were stirred under vacuum for 20 min. The flask was flushed with N₂ and toluene (3.5 mL) was added. To this suspension was slowly added triethylamine (0.12 mL, 0.86 mmol). The resulting mixture was stirred for 2 h before a solution of alkyne 887 (148 mg, 0.86 mmol) in toluene (1 mL) was added over a period of 20 min (syringe pump). After stirring for another 30 min a solution of aldehyde 888 (100 mg, 0.57 mmol) in toluene (1 mL) was added. The reaction was allowed to stir for 15 h before quenching with sat. NH₄Cl. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give propargylic alcohol 889 (99 mg, 0.29 mmol, 50%, 90% ee).

Rₚ 0.30 (4:1, hexanes/EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 4.55 (t, J = 5.2 Hz, 1H), 4.38-4.31 (m, 1H), 3.70-3.42 (m, 8H), 2.49 (d, J = 4.7 Hz, 1H, OH), 1.13 (t, J = 7.0 Hz, 6H), 0.82 (s, 9H), 0.00 (s, 6H); ¹³C-NMR (100 MHz, CDCl₃): δ 100.8, 84.5, 81.2, 70.0, 66.9, 63.1, 62.1 (2C), 58.7, 25.8 (3C), 18.3, 15.3 (2C), -5.4, -5.4; IR νₘₚ (film)/cm⁻¹: 2973, 2360, 2341, 1558, 1540, 1507, 1394, 1252, 1066; HRMS (EI) m/z calculated for C₁₁H₂₄O₃SiNa ([M+Na]⁺) 369.2068, found 369.2069.

The ee of 889 was determined by SFC analysis of its benzoate derivative S42, prepared by treatment of 889 with benzoyl chloride:

SFC: Diacel Chiralpak IA, 100% CO₂, 2 mL/min, 25 °C, 225 nm, 90% ee, (tₚ(major) = 16.2 min; tₚ(minor) = 15.4 min).

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757 Zn(OTf)₂ was dried before use by heating to 130 °C under vacuum for 12 h.
To a solution of triphenylphosphine (1.1 g, 4.3 mmol) in THF (12 mL) at 0 °C was slowly added DIAD (0.84 mL, 4.3 mmol). After 10 min at 0 °C a solution of alcohol 889 (750 mg, 2.2 mmol) in THF (10 mL) was added slowly. The mixture was stirred for 10 min before a solution of tosylhydrazine (605 mg, 3.3 mmol) in THF (12 mL) was added. The mixture was allowed to stir at 0 °C 2 h and was then warmed to ambient temperature overnight. The reaction was quenched by addition of MeOH and stirred for 20 h. The mixture was diluted with NH₄Cl and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give allene 884 (305 mg, 1.4 mmol, 65%).

Rₚ 0.43 (1:1, hexanes/EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 5.48-5.32 (m, 2H), 4.63 (t, J = 5.2 Hz, 1H), 4.14 (dd, J = 5.9, 2.9 Hz, 2H), 4.08 (ddd, J = 9.9, 6.4, 2.5 Hz, 2H), 3.75-3.47 (m, 6H), 1.86 (bs, 1H, OH), 1.22 (td, J = 7.1, 1.3 Hz, 6H); ¹³C-NMR (75 MHz, CDCl₃): δ 204.1, 101.0, 93.0, 90.5, 70.2, 68.8, 62.3, 62.2, 60.2, 15.3 (2C); IR ν max (film)/cm⁻¹: 3420 (bs), 2975, 2901, 2360, 2340, 1967, 1374, 1250, 1104, 1065; HRMS (EI) m/z calculated for C₁₁H₂₀O₄Na ([M+Na]+) 239.1254, found 239.1260.

TBS protected derivative S43 can be isolated from the reaction of 889 with tosylhydrazine/PPh₃/DEAD upon careful workup of the reaction mixture.

Rₚ 0.57 (4:1, hexanes/EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 5.29-5.20 (m, 2H), 4.56 (t, J = 5.2 Hz, 1H), 4.15-4.10 (m, 2H), 4.02-3.97 (m, 2H), 3.68-3.41 (m, 6H), 1.15 (t, J = 7.1 Hz, 6H), 0.82 (s, 9H), 0.00 (s, 6H); ¹³C-NMR (75 MHz, CDCl₃): δ 209.3, 106.2, 97.8, 94.9, 75.3, 74.4, 67.3, 67.2, 66.5, 31.0 (3C), 23.4, 20.5 (2C), -0.0 (2C); IR ν max (film)/cm⁻¹: 2929, 2360, 2340, 1253, 1085; HRMS (EI) m/z calculated for C₁₇H₃₄O₣SiNa ([M+Na]+) 353.2119, found 353.2119.
To a flask containing samarium powder (904 mg, 6.0 mmol) was added HgCl₂ (163 mg, 0.60 mmol) followed by THF (10 mL). The suspension was stirred for 10 min at ambient temperature before a solution of alcohol 884 (260 mg, 1.2 mmol) in THF (10 mL) was added. The mixture was cooled to -78 °C and diiodomethane (0.49 mL, 6.0 mmol) was added slowly. After 2 h the reaction was allowed to warm to ambient temperature. After another 4 h the reaction was quenched by addition of sat. K₂CO₃. The aqueous phase was extracted three times with Et₂O. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give alkylidenecyclopropane 893 (45 mg, 0.20 mmol, 16%) along with some bis-spirocyclopropane 895 (10 mg).

1H-NMR (400 MHz, CDCl₃): δ 5.98-5.92 (m, 1H), 4.67 (t, J = 5.3 Hz, 1H), 4.19 (dt, J = 4.9, 1.5 Hz, 2H), 3.91-3.83 (m, 1H), 3.71 (dq, J = 9.3, 7.1 Hz, 2H), 3.62-3.50 (m, 4H), 3.25-3.20 (m, 1H, O-H), 3.15 (t, J = 9.8 Hz, 1H), 1.87 (tdq, J = 8.7, 7.1, 5.3 Hz, 1H), 1.30 (ddd, J = 10.6, 7.3, 1.7 Hz, 1H), 1.23 (t, J = 7.1 Hz, 6H), 0.91 (ddt, J = 8.7, 4.9, 1.8 Hz, 1H); 13C-NMR (100 MHz, CDCl₃): δ 128.5, 115.2, 101.0, 70.9, 70.7, 65.5, 62.5, 62.4, 17.8, 15.3, 15.3, 6.6.

To a solution of acetal 893 (45 mg, 0.20 mmol) in acetone (2 mL) was added 0.5 M HCl (2 mL). The mixture was stirred at ambient temperature for 4 h and then quenched by addition of sat. NaHCO₃. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 40:1) to give the corresponding aldehyde (10 mg, 0.06 mmol, 33%).

To a solution of diisopropylamine (27 μL, 0.19 mmol) in THF (1 mL) at -78 °C was added n-BuLi (120 μL, 0.19 mmol). The mixture was allowed to warm to ambient temperature and stirred for 10 min. After cooling back to -78 °C nitromethane (10.4 μL, 0.19 mmol) was added. After 30 min at -78 °C a solution of aldehyde (10 mg, 0.06 mmol) in THF was added. After 30 min the reaction was allowed to warm to ambient temperature and stirred for another hour. The reaction was quenched by addition of pH 7 buffer. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 100:1) to give the corresponding nitroalcohol (8 mg, 37 μmol, 58%).
To a solution of nitroalcohol (8 mg, 37 μmol) in toluene (1 mL) was added Boc₂O (32 mg, 0.15 mmol) and DMAP (9 mg, 74 μmol). After 7 h the solvent was evaporated and the residue was subjected to column chromatography (hexanes/EtOAc 4:1) to give enol ether 897 (7 mg, 25 μmol, 68%).

\[ ^1H-NMR \text{(600 MHz, CDCl}_3\text{)}: \delta 6.78 \text{ (dd, } J = 6.0, 0.5 \text{ Hz, 1H}), 5.76 \text{ (dd, } J = 6.0, 0.7 \text{ Hz, 1H}), 4.50 \text{ (dd, } J = 10.1, 5.3 \text{ Hz, 1H}), 4.13-4.07 \text{ (m, 2H)}, 3.97 \text{ (dd, } J = 13.3, 5.3 \text{ Hz, 1H}), 3.69 \text{ (dd, } J = 11.8, 8.4 \text{ Hz, 1H}), 1.73 \text{ (dtd, } J = 10.7, 8.3, 7.3 \text{ Hz, 1H}), 1.56-1.47 \text{ (m, 10H)}, 0.82 \text{ (t, } J = 7.2 \text{ Hz, 1H}); \]

\[ ^{13}C-NMR \text{(150 MHz, CDCl}_3\text{): } \delta 153.2, 152.2, 152.1, 95.2, 82.7, 69.2, 67.8, 65.7, 46.0, 27.8 \text{ (3C), 23.6, 12.9}. \]

To a solution of alcohol 884 (3.3 g, 15.3 mmol) in CH₂Cl₂ (20 mL) at 0 °C was added acid chloride 899\(^\text{758}\) (4 g, 15.3 mmol) followed by dimethylaniline (2.9 mL, 22.9 mmol). After 15 min at 0 °C triethylamine (10.6 mL, 76 mmol) was added. The reaction was allowed to warm to ambient temperature and stirred for another 15 min. The solvent was removed and the residue was directly subjected to flash column chromatography (hexanes/EtOAc 4:1) to give diazoacetate 898 (3.53 g, 12.4 mmol, 83%).

\[ R_f \text{ 0.26 (4:1, hexanes/EtOAc); } ^1H-NMR \text{(300 MHz, CDCl}_3\text{): } \delta 5.42-5.33 \text{ (m, 2H)}, 4.78 \text{ (bs-s, 1H), 4.76-4.61 \text{ (m, 3H), 4.11-4.06 \text{ (m, 2H), 3.75-3.63 \text{ (m, 2H), 3.63-3.53 \text{ (m, 2H), 3.50 (d, } J = 5.3 \text{ Hz, 3H), 1.22 \text{ (t, } J = 7.0 \text{ Hz, 6H); } \text{IR } v_{\text{max}} \text{ (film)}/cm^{-1}: 2976, 2925, 2110, 1692, 1630, 1590, 1488, 1461, 1442, 1383, 1341, 1290, 1268, 1236, 1178, 1102, 1059, 1015; HRMS (EI) } m/z \text{ calculated for C}_{13}H_{20}O_5N_2Na ([M+Na]^+) 307.1264, found 307.1259.} \]

To a solution of copper catalyst 900\(^{759}\) (512 mg, 1.2 mmol) in toluene (820 mL) at refluxing temperature was added a solution of diazoacetate 898 (3.5 g, 12.3 mmol) in toluene (820 mL) over a period of 10 h (syringe pump). After complete addition the solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give lactone 901 (2.3 g, 9.0 mmol, 73\%) as a 1:1 mixture of diastereomers.

1:1 Mixture of diastereomers: R\(_f\) 0.26 (1:1, hexanes/EtOAc); \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.16-6.10 (m, 1H), 4.65 (td, \(J = 5.2, 3.0\) Hz, 1H), 4.45-4.40 (m, 1H), 4.37-4.31 (m, 1H), 4.27-4.22 (m, 2H), 3.76-3.67 (m, 2H), 3.63-3.54 (m, 2H), 3.53-3.47 (m, 2H), 2.82-2.65 (m, 2H), 1.27-1.21 (m, 6H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 173.5 (0.5C), 173.1 (0.5C), 121.9 (0.5C), 121.5 (0.5C), 117.6 (0.5C), 117.3 (0.5C), 101.1 (0.5C), 101.0 (0.5C), 71.0 (0.5C), 70.0 (0.5C), 70.0 (0.5C), 68.9 (0.5C), 68.8 (0.5C), 62.4, 62.3, 21.7 (0.5C), 21.4 (0.5C), 21.2 (0.5C), 20.9 (0.5C), 15.4 (2C); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3520, 2975, 2908, 1778, 1771, 1480, 1450, 1372, 1239; HRMS (EI) \(m/z\) calculated for C\(_{13}\)H\(_{20}\)O\(_5\)Na ([M+Na]\(^+\)) 279.1203, found 279.1203.

Alcohol 918 was prepared according to Org. Synth. 1997, 74, 1.

R\(_f\) 0.23 (9:1, CH\(_2\)Cl\(_2\)/MeOH); [\(\alpha\)]\(_D\)\(^{19.7}\) 24.4 (c 1.0, CHCl\(_3\)); \(^1\)H-NMR (300 MHz, CD\(_2\)CN): \(\delta\) 7.39-7.24 (m, 5H), 4.67 (d, \(J = 11.6\) Hz, 1H), 4.55 (d, \(J = 11.6\) Hz, 1H), 3.75-3.42 (m, 6H), 3.35-3.29 (m, 6H), 3.18-3.07 (m, 2H, OH); \(^{13}\)C-NMR (100 MHz, CD\(_2\)CN): \(\delta\) 139.8, 129.2 (2C), 128.8 (2C), 128.5, 80.6, 73.0, 73.0, 63.7, 61.5; IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3254 (bs), 2969, 2941, 2360, 2341, 1494, 1481, 1451, 1404, 1364, 1329, 1257, 1215, 1202, 1124, 1081, 1037; HRMS (ESI) \(m/z\) calculated for C\(_{11}\)H\(_{16}\)O\(_4\)Na ([M+Na]\(^+\)) 235.0941, found 235.0943.

Dimethylacetal 917 has been prepared previously.\footnote{Suami, T.; Tadano, K.-i.; Suga, A.; Ueno, Y. J. Carbohydr. Chem. 1984, 3, 429.}

To a solution of triol 918 (7.5 g, 35.3 mmol) in MeOH (250 mL) was added periodic acid (9.7 g, 42.4 mmol) and conc. sulfuric acid (0.1 mL). The mixture was heated to reflux for 45 min and then cooled to 0 °C. Solid potassium hydroxide (3.4 g, 60.1 mmol) was slowly added whereupon a precipitate formed. The suspension was filtered and the filtrate was concentrated. The residue was diluted with Et₂O and extracted with water. The organic phase was dried over MgSO₄, the solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give dimethylacetal 917 (6.34 g, 28.0 mmol, 79%).

\[ R_f \text{ 0.43 (1:1, hexanes/EtOAc); } [\alpha]_D^{19.7} \text{ -21.9 (c 1.0, CHCl}_3) ; {^1H-NMR} (300 MHz, CDCl}_3) ; \delta 7.38-7.27 \text{ (m, 5H), 4.76 (d, } J = 11.6 \text{ Hz, 1H), 4.65 (d, } J = 11.6 \text{ Hz, 1H), 4.39 (d, } J = 5.9 \text{ Hz, 1H), 3.80-3.63 \text{ (m, 2H), 3.52 (dt, } J = 5.8, 4.9 \text{ Hz, 1H), 3.45 (s, 3H), 3.45 (s, 3H), 2.20 (t, } J = 6.3 \text{ Hz, 1H, OH); } {^{13}}C-NMR \text{ (75 MHz, CDCl}_3) ; \delta 138.1, 128.2 (2C), 127.7 (2C), 127.6, 105.6, 78.9, 72.8, 61.2, 55.5, 55.2; {IR} \nu_{max} \text{ (film)/cm}^{-1} : 3444 (bs), 2935, 1651, 1575, 1496, 1453, 1337, 1195, 1075; {HRMS} \text{ (ESI) } m/z \text{ calculated for } C_{12}H_{18}O_4Na ([M+Na]^+) 249.1097, \text{ found } 249.1101. \]

A flame dried flask was charged with bis(dibenzylideneacetone)palladium(0) (483 mg, 0.84 mmol, 5 mol%) and 1,2-bis(diphenylphosphino)ethane (468 mg, 1.18 mmol, 7 mol%) and high vacuum was applied during 1 h. The flask was flushed with argon and a solution of 434 (4 g, 16.8 mmol) in THF (5 mL) was added. After 10 min the reaction had turned green.

A separate flask was charged with sodium hydride (873 mg, 21.8 mmol, 60% dispersion in mineral oil, washed twice with hexanes) and THF (100 mL) was added. The mixture was cooled to 0 °C and a solution of 917 (4.93 g, 21.8 mmol) in THF (20 mL) was slowly added. The suspension was warmed to ambient temperature and stirred for 30 min. To this suspension was added the palladium allyl solution previously prepared. The reaction was stirred until full consumption of the starting material was observed (12 h). The reaction was quenched by addition of pH 7 buffer. The phases were
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The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give 922 (2.55 g, 8.7 mmol, 52%, 62% brsm) as a yellow oil along with reisolated 434 (660 mg, 2.8 mmol).

**R$_f$ 0.44 (4:1, hexanes/EtOAc); [$\alpha$]$_D^{24.3}$ -7.2 (c 3.0, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.41-7.23 (m, 5H), 5.97-5.89 (m, 1H), 4.74 (d, $J = 1.8$ Hz, 2H), 4.38 (d, $J = 5.1$ Hz, 1H), 4.14 (d, $J = 6.6$ Hz, 2H), 3.69-3.53 (m, 3H), 3.44 (s, 3H), 3.42 (s, 3H), 1.14-1.02 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 138.4, 127.7 (2C), 127.3 (2C), 126.9, 125.8, 114.6, 104.7, 78.4, 72.6, 71.0, 69.3, 55.0, 54.9, 1.7, 1.3; IR $\nu_{max}$ (film)/cm$^{-1}$: 2939, 1739, 1454, 1366, 1217, 1111, 1076; HRMS (ESI) $m/z$ calculated for C$_{17}$H$_{24}$O$_4$Na ([M+Na]$^+$) 315.1567, found 315.1571.

To a solution of 922 (2.55 g, 8.72 mmol) in MeCN/H$_2$O (30 mL, 1:1) was added hydroxylamine hydrochloride (1.21 g, 17.44 mmol) and the mixture was heated to 80 °C. After 12 h mixture was diluted with EtOAc and extracted with water. The aqueous phase was washed twice with EtOAc. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give 542 (1.96 g, 7.50 mmol, 86%) as a mixture of oxime $E$/Z isomers.

**Minor isomer: R$_f$ 0.60 (3:1, hexanes/EtOAc); [$\alpha$]$_D^{24.8}$ -49.9 (c 3.1, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.44-7.27 (m, 7H), 5.94-5.87 (m, 1H), 4.66 (d, $J = 12.0$ Hz, 1H), 4.50 (d, $J = 11.9$ Hz, 1H), 4.18-4.12 (m, 3H), 3.63 (d, $J = 5.4$ Hz, 2H), 1.14-1.01 (m, 4H); $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 149.7, 137.5, 128.2 (2C), 127.8 (2C), 127.6, 127.1, 114.3, 75.1, 71.4, 71.0, 70.6, 2.2, 1.6; IR $\nu_{max}$ (film)/cm$^{-1}$: 3320 (bs), 2987, 2928, 2875, 1454, 1369, 1326, 1208, 1117, 1058; HRMS (ESI) $m/z$ calculated for C$_{15}$H$_{20}$NO$_3$ ([M+H]$^+$) 262.1438, found 262.1438.

**Major isomer: R$_f$ 0.51 (3:1, hexanes/EtOAc); [$\alpha$]$_D^{25.1}$ -305.3 (c 0.5, CHCl$_3$); $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.95 (bs, 1H, OH), 7.38-7.27 (m, 5H), 6.84 (d, $J = 6.2$ Hz, 1H), 5.95-5.90 (m, 1H), 4.93-4.88 (m, 1H), 4.66 (d, $J = 12.0$ Hz, 1H), 4.57 (d, $J = 12.0$ Hz, 1H), 4.19-4.15 (m, 2H), 3.67-3.64 (m, 2H), 1.14-1.02 (m, 4H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 151.9, 137.7, 128.4 (2C), 127.9 (2C), 127.8, 127.0, 114.6, 72.1, 71.6, 71.45, 69.8, 2.3, 1.8; IR $\nu_{max}$ (film)/cm$^{-1}$: 3187 (bs), 3088, 2864, 1739, 1452, 1360, 1252, 1208, 1138, 1073, 1044; HRMS (ESI) $m/z$ calculated for C$_{15}$H$_{20}$NO$_3$ ([M+H]$^+$) 262.1438, found 262.1442.
Experimental Part

To a solution of 542 (206 mg, 0.79 mmol) in CH₂Cl₂ (2 mL) was added bis(tributyltin)oxide (0.22 mL, 0.434 mmol). The mixture was stirred at ambient temperature for 1h and then cooled to -30 °C. tert-Butyl hypochlorite (0.12 mL, 1.03 mmol) was added carefully and the mixture was allowed to warm to ambient temperature. After 30 min the starting material was consumed. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give 543 (180 mg, 0.69 mmol, 88%, dr = 10:1).

\[ R_f \text{ 0.36 (2:1, hexanes/EtOAc); } [\alpha]_{25.4}^D \text{ -28.2 (c 4.3, CHCl}_3) ] \]

\[^1^H\text{-NMR} \text{ (400 MHz, CDCl}_3, \text{ 10:1 mixture of diastereomers, major isomer reported): } \delta 7.44-7.29 \text{ (m, 5H), 4.69 (d, } J = 12.1 \text{ Hz, 1H), 4.53 (d, } J = 12.1 \text{ Hz, 1H), 4.33-4.29 \text{ (m, 2H), 4.03 (dd, } J = 10.4 \text{, 6.5 Hz, 1H), 3.62 (dd, } J = 11.1 \text{, 6.5 Hz, 1H), 3.51 (dd, } J = 12.6 \text{, 2.2 Hz, 1H), 3.41 (t, } J = 11.0 \text{ Hz, 1H), 1.26-1.20 \text{ (m, 1H), 1.02-0.96 (m, 1H), 0.78-0.65 (m, 2H); ]}^{13^C\text{-NMR} \text{ (100 MHz, CDCl}_3, \text{ 10:1 mixture of diastereomers, major isomer reported): } \delta 156.4, 137.0, 128.3 (2C), 128.0 (2C), 127.7, 72.3, 70.6, 70.4, 69.6, 66.6, 45.7, 10.0, 8.1; ]\]

\[^1^H\text{-NMR} \text{ (300 MHz, CDCl}_3)): \delta 4.63 (d, } J = 5.2 \text{ Hz, 1H), 4.22 (dt, } J = 12.5 \text{, 1.1 Hz, 1H), 4.04 (dd, } J = 10.5 \text{, 6.6 Hz, 1H), 3.72 (dd, } J = 11.2 \text{, 6.6 Hz, 1H), 3.52 (ddd, } J = 12.4 \text{, 1.7, 0.9 Hz, 1H), 3.40 (t, } J = 10.8 \text{ Hz, 1H), 2.88-2.78 (m, 1H, OH), 1.25-1.17 (m, 1H), 1.00-0.92 (m, 1H), 0.79-0.61 (m, 2H); ]^{13^C\text{-NMR} \text{ (75 MHz, CDCl}_3)): \delta 157.5, 73.8, 70.9,
Stepwise procedure:

To a solution of triphenylphosphine (930 mg, 3.55 mmol) in toluene (15 mL) was added iodine (750 mg, 2.96 mmol). The mixture was stirred for 5 min and then imidazole (483 mg, 7.09 mmol) was added. After another 5 min a solution of **537** (200 mg, 1.18 mmol) in MeCN (3 mL) was added and the reaction was allowed to stir for 12 h. The solvent was evaporated and the residue was taken up in CH₂Cl₂, filtered through celite and concentrated again. The resulting residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to give a mixture of alkyl iodide and enol ether **550** (ca. 5:1). The mixture was taken up in toluene (4 mL) and MeCN (1 mL) was added. DBU (0.27 mL, 1.77 mmol) was added and the solution was heated to 100 °C for 6 h. After evaporation of the solvent the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to give **550** (147 mg, 0.97 mmol, 82% over 2 steps).

One pot procedure:

To a solution of triphenylphosphine (930 mg, 3.55 mmol) in toluene (15 mL) was added iodine (750 mg, 2.96 mmol). The mixture was stirred for 5 min and then imidazole (483 mg, 7.09 mmol) was added. After another 5 min a solution of **537** (200 mg, 1.18 mmol) in MeCN (3 mL) was added and the reaction was allowed to stir for 12 h. To this solution was added DBU (0.27 mL, 1.77 mmol) and the mixture was heated to 100 °C for 12 h. The solvent was evaporated and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1 → 4:1) to give **550** (110 mg, 0.73 mmol, 62%).
18.12. Experimental Part to Chapter 16

Feist’s acid ethyl ester was prepared according to a literature procedure.\textsuperscript{761}

To a flask containing concentrated H$_2$SO$_4$ (450 mL) at 0 °C was added dropwise ethyl acetoacetate (325 g, 2.5 mol). After complete addition the mixture was allowed to warm to ambient temperature and stirred for 5 days. The solution was carefully poured onto ice and diluted with Et$_2$O. The phases were separated and the organic phase was dried over MgSO$_4$. The solvent was removed and the residue was used without further purification (365 g, 1.9 mol, 75%).

To a solution of 973 (80 g, 0.41 mol) in CHCl$_3$ (200 mL) at 0 °C was added a solution of bromine (32 mL, 0.61 mol) in CHCl$_3$ (50 mL). The mixture was allowed to warm to ambient temperature and stirred for 24 h. The solution was poured onto ice and diluted with Et$_2$O. The phases were separated and the organic phase was dried over MgSO$_4$. The solvent was removed and the residue was recrystallized from MeOH to give bromide 974 (95 g, 0.35 mol, 85%).

To a solution of KOH (104 gm 1.9 mol) in water (100 mL) at reflux was added a solution of bromide 974 (51 g, 0.19 mol) in dioxane (40 mL) over a period of 20 min. After 1 h at reflux, the mixture was cooled to 0 °C and carefully acidified with conc. H$_2$SO$_4$. The precipitated solid was filtered off and the resulting aqueous solution was extracted three times with Et$_2$O. The combined organic phases were dried over MgSO$_4$ and the solvent was removed. The residue was recrystallized from Et$_2$O to give Feist’s acid 971 (18 g, 0.13 mol, 68%).

To a solution of 971 (2 g, 14 mmol) in EtOH (15 mL) was added conc. H$_2$SO$_4$ (0.15 mL). The mixture was heated to reflux for 24 h. The solution was diluted with sat. NaHCO$_3$ and Et$_2$O and the phases were separated. The aqueous phase was extracted three times with Et$_2$O. The combined organic phases were dried over MgSO$_4$ and the solvent was removed. The resulting residue was subjected to flash column chromatography (hexanes/Et$_2$O 4:1) to give ester 978 (2.55 g, 12.9 mmol, 91%).

Experimental Part

To a suspension of LiAlH₄ (2.15 g, 56.5 mmol) in THF (10 mL) at -10 °C was slowly added a solution of Feist’s acid ethyl ester 978 (5.6 g, 28.3 mmol) in THF (5 mL). The mixture was allowed to warm to ambient temperature. After 5 h the reaction was quenched by careful addition of 1M HCl. The mixture was diluted with Et₂O, the phases were separated and the aqueous phase was extracted three times with Et₂O. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1 → EtOAc) to give diol 983 (2.2 g, 19.3 mmol, 68%).

Rₛ 0.28 (EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 5.44 (t, J = 2.1 Hz, 1H), 4.02-3.84 (m, 4H), 3.18 (dd, J = 11.4, 9.1 Hz, 2H), 1.69-1.60 (m, 2H).

To a solution of diol 983 (600 mg, 5.26 mmol) in CH₂Cl₂ (10 mL) was added triethylamine (2.6 mL, 18.4 mmol), acetic anhydride (1.5 mL, 15.8 mmol) and DMAP (cat.). The mixture was stirred for 1 h and then quenched by addition of sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give bisacetate 984 (1.03 g, 5.2 mmol, 99%).

Rₛ 0.84 (1:1; hexanes/EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 5.52 (t, J = 2.1 Hz, 2H), 4.08 (dd, J = 11.5, 5.9 Hz, 2H), 3.92 (dd, J = 11.5, 8.0 Hz, 2H), 2.06 (s, 6H), 1.80-1.70 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 170.6 (2C), 133.2 (2C), 106.3 (2C), 65.3 (2C), 20.7 (2C), 20.4 (2C); IR νmax (film)/cm⁻¹: 2953, 1735, 1605, 1448, 1385, 1365, 1223, 1139, 1110, 1028; HRMS (EI) m/z calculated for C₈H₁₁O₂ ([M-OAc]+) 139.0754, found 139.0754.

To a solution of alkene 984 (1.0 g, 5.05 mmol) and nitroethane (0.36 mL, 5.05 mmol) in Et₂O (2 mL) at 0 °C was added triethylamine (0.21 mL, 1.51 mmol) and phenyl isocyanate (1.1 mL, 10.1 mmol). The reaction was stirred at 0 °C for 6 h and then allowed to warm to ambient temperature overnight. The reaction was quenched by the addition of sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with Et₂O. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1 → EtOAc) to give diol 983 (2.2 g, 19.3 mmol, 68%).

chromatography (hexanes/EtOAc 4:1) to give diol 985 (750 mg, 2.94 mmol, 58%) as the only regioisomer.

Rf 0.41 (1:1; hexanes/EtOAc); \(^1\)H-NMR (300 MHz, CDCl\(_3\)): δ 4.18 (d, J = 7.6 Hz, 2H), 4.16 (dd, J = 11.5, 6.6 Hz, 1H), 3.85 (dd, J = 11.9, 8.2 Hz, 1H), 3.17 (d, J = 17.4 Hz, 1H), 2.85 (d, J = 17.3 Hz, 1H), 2.06-2.03 (m, 9H), 1.67 (dt, J = 8.2, 6.4 Hz, 1H), 1.24-1.16 (m, 1H); \(^13\)C-NMR (100 MHz, CDCl\(_3\)): δ 170.7, 170.5, 155.8, 70.1, 63.1, 61.8, 40.7, 27.0, 23.8, 20.7, 20.6, 13.3; IR \(\nu_{max}\) (film)/cm\(^{-1}\): 2957, 1733, 1433, 1380, 1366, 1329, 1227, 1105, 1030; HRMS (EI) m/z calculated for C\(_{10}\)H\(_{14}\)NO\(_3\) ([M-OAc]\(^+\)] \(\text{EI}\) m/z calculated for C\(_{13}\)H\(_{21}\)NO\(_5\) Na ([M+Na]\(^+\)] 196.0969, found 196.0973.

To a solution of isoxaoline 985 (330 mg, 1.3 mmol) in MeNO\(_2\) (5 mL) was added trimethyloxonium tetrafluoroborate (382 mg, 2.6 mmol). The mixture was stirred at ambient temperature for 24 h. The solvent was evaporated and the residue was taken up in EtOH (5 mL). Sodium borohydride (98 mg, 2.6 mmol) was added and the mixture was stirred for 1 h. The reaction was quenched by addition of water and diluted with EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO\(_4\). The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give isoxazolidine 986 (225 mg, 0.84 mmol, 65%).

Rf 0.41 (EtOAc); \(^1\)H-NMR (300 MHz, CDCl\(_3\), 1:1 mixture of diastereomers, all peaks reported): δ 4.25-4.19 (m, 0.5 H), 4.07-3.93 (m, 2.5H), 3.76 (dd, J = 11.5, 8.3 Hz, 1H), 2.91 (q, J = 6.1 Hz, 0.5H), 2.82-2.74 (m, 0.5H), 2.57 (s, 3H), 2.28 (dd, J = 12.1, 7.0 Hz, 0.5H), 2.05-1.92 (m, 7H), 1.77 (dd, J = 11.1, 6.1 Hz, 0.5H), 1.40-1.31 (m, 1H), 1.14-1.10 (m, 4H); \(^13\)C-NMR (75 MHz, CDCl\(_3\), 1:1 mixture of diastereomers, all peaks reported): δ 170.8, 170.7, 170.6, 170.6, 67.1, 66.8, 63.8, 63.7, 63.5, 62.6, 62.3, 44.2, 43.7, 39.5, 39.0, 26.5, 25.8, 23.5, 23.4, 20.8, 20.7, 20.7, 20.6, 18.6, 18.2; IR \(\nu_{max}\) (film)/cm\(^{-1}\): 2950, 1739, 1458, 1366, 1235, 1031; HRMS (ESI) m/z calculated for C\(_{13}\)H\(_{21}\)NO\(_5\)Na ([M+Na]\(^+\)] 294.1312, found 294.1317.
Experimental Part

To a suspension of sodium hydride (3.5 g, 88 mmol, 60% dispersion in mineral oil; washed three times with hexanes) in DMF (40 mL) at 0 °C was slowly added propargyl alcohol (4.7 mL, 80 mmol). After 30 min the mixture was allowed to warm to ambient temperature and dioxalane 988 (9.4 mL, 80 mmol) was added. The mixture was allowed to stir overnight. The reaction was quenched by careful addition of water followed by Et₂O. The phases were separated and the aqueous phase was extracted three times with Et₂O. The combined organic phases were washed with water and brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give alkyne 989 (1.57 g, 10.1 mmol, 13%).

Rf 0.41 (EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 4.98 (t, J = 4.9 Hz, 1H), 4.14 (d, J = 2.3 Hz, 2H), 4.00-3.91 (m, 2H), 3.90-3.82 (m, 2H), 3.67 (t, J = 6.5 Hz, 2H), 2.42 (t, J = 2.4 Hz, 1H), 1.97 (td, J = 6.6, 4.8 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 102.3, 79.7, 74.4, 65.7, 64.8 (2C), 58.1, 34.1; IR ν_max (film)/cm⁻¹: 2962, 2115, 1477, 1442, 1413, 1360, 1277, 1212, 1139, 1092, 1029; HRMS (El) m/z calculated for C₅H₇O₂ ([M-CH₃OH]⁺) 99.0441, found 99.0440; and calculated for C₃H₅O ([C₃H₅O⁻]) 57.0334, found 57.0334.

To a solution of alkyne 989 (1.6 g, 10.2 mmol) in THF (30 mL) at -78 °C was added n-BuLi (7.7 mL, 12.3 mmol, 1.6 M in hexanes). The mixture was stirred for 1h before a solution of aldehyde 888 (2.1 g, 12.3 mmol) in THF (5 mL) was added. After another hour the reaction was allowed to warm to ambient temperature and stirred for 1 h. The reaction was quenched by addition of sat. NH₄Cl followed by addition of EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give alcohol 990 (2.8 g, 8.5 mmol, 83%).
Rf 0.63 (1:1; hexanes/EtOAc); ¹H-NMR (400 MHz, CDCl₃): δ 4.92 (t, J = 4.9 Hz, 1H), 4.40-4.34 (m, 1H), 4.11 (d, J = 1.7 Hz, 2H), 3.92-3.86 (m, 2H), 3.70 (dd, J = 10.1, 4.0 Hz, 1H), 3.62-3.57 (m, 3H), 2.82 (d, J = 4.9 Hz, 1H), 1.90 (td, J = 6.5, 4.9 Hz, 2H), 0.85 (s, 9H), 0.04 (d, J = 0.9 Hz, 6H); ¹³C-NMR (100 MHz, CDCl₃): δ 102.2, 84.3, 81.2, 66.8, 65.5, 64.7 (2C), 63.0, 58.2, 33.9, 25.7 (3C), 18.2, -5.5, -5.5; IR ν_max (film)/cm⁻¹: 3450, 2930, 2858, 1738, 1472, 1364, 1409, 1391, 1361, 1320, 1252, 1120, 1094, 1029; HRMS (ESI) m/z calculated for C₁₆H₃₀O₅SiNa ([M+Na⁺]⁺) 353.1755, found 353.1756.

To a solution of triphenylphosphine (4.4 g, 16.9 mmol) in THF (35 mL) at 0 °C was slowly added DIAD (3.5 mL, 16.9 mmol). After 10 min a solution of alcohol 990 (2.8 g, 8.5 mmol) in THF (30 mL) was added slowly. The mixture was stirred for another 10 min before a solution of p-toluenesulfonyl hydrazine (2.4 g, 12.7 mmol) in THF (35 mL) was added. The mixture was stirred for another 2 h at 0 °C and was then allowed to warm to ambient temperature overnight. The reaction was quenched by addition of sat. NH₄Cl and diluted with Et₂O. The phases were separated and the aqueous phase was extracted three times with Et₂O. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1). The resulting residue was taken up in MeOH and the solution was stirred for 48 h. The solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 1:1) to give allenic alcohol 991 (800 mg, 4.0 mmol, 47%).

Rf 0.19 (1:1; hexanes/EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 5.39 (dqt, J = 18.4, 6.2, 3.2 Hz, 2H), 4.98 (t, J = 4.9 Hz, 1H), 4.13 (dd, J = 5.7, 2.6 Hz, 2H), 4.03-3.98 (m, 2H), 3.97-3.90 (m, 2H), 3.90-3.82 (m, 2H), 3.61 (tt, J = 6.5, 3.0 Hz, 2H), 2.10 (bs-s, 1H, OH), 1.94 (td, J = 6.6, 4.9 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 203.8, 102.3, 92.9, 90.7, 68.3, 65.4, 64.7 (2C), 60.2, 34.1; IR ν_max (film)/cm⁻¹: 3429, 2877, 1965, 1734, 1357, 1244, 1139, 1091, 1020; HRMS (EI) m/z calculated for C₁₀H₁₅O₃ ([M-OH⁻]⁻) 183.1016, found 183.1010.

To a solution of alcohol 991 (800 mg, 4.0 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added acid chloride 899 (1.25 g, 4.8 mmol) followed by dimethylaniline (0.76 mL, 6.0 mmol). After 15 min at 0 °C triethylamine (2.8 mL, 20.0 mmol) was added. After another 10 min the mixture was allowed to warm to ambient temperature and stirred for 15 min. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give diazoacetate 992 (650 mg, 2.4 mmol, 61%).

Rf 0.53 (1:1; hexanes/EtOAc); ¹H-NMR (300 MHz, CDCl₃): δ 5.42-5.34 (m, 2H), 4.97 (t, J = 4.9 Hz, 1H), 4.77 (bs-s, 1H), 4.67-4.64 (m, 2H), 4.05-4.01 (m, 2H), 3.98-3.94 (m, 2H), 3.88-3.82 (m, 2H), 3.59 (t, J = 6.6 Hz, 2H), 1.95 (td, J = 6.6, 4.9 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 205.5, 166.1, 102.1, 90.5, 87.9, 68.1, 65.4, 64.6 (2C), 62.0, 46.0, 34.0; IR ν_max (film)/cm⁻¹: 2880, 2108, 1968, 1690, 1382, 1351, 1231, 1174, 1142, 1093, 1016; HRMS (ESI) m/z calculated for C₁₂H₁₅O₃Na ([M+Na⁺]⁺) 291.0951, found 291.0953.
To a solution of copper catalyst 900 (53 mg, 0.13 mmol) in toluene (130 mL) at reflux was added a solution of diazoacetate 992 (345 mg, 1.29 mmol) in toluene (130 mL) via syringe pump over a period of 10 h. After complete addition the solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1 → 1:1) to give methylenecyclopropane 993 (202 mg, 0.84 mmol, 65%) as a 1:1 mixture of double bond isomers.

Rf 0.61 (EtOAc); 1H-NMR (300 MHz, CDCl3, 1:1 mixture of double bond isomers, all peaks reported): δ 6.16-6.06 (m, 1H), 4.98 (q, J = 4.9 Hz, 1H), 4.37-4.37 (m, 1H), 4.35-4.29 (m, 1H), 4.19-4.13 (m, 2H), 4.00-3.91 (m, 2H), 3.91-3.83 (m, 2H), 3.63-3.54 (m, 2H), 2.82-2.62 (m, 2H), 1.99-1.93 (m, 2H); 13C-NMR (100 MHz, CDCl3, 1:1 mixture of double bond isomers, all peaks reported): δ 173.2, 172.9, 121.6, 121.1, 117.4, 116.9, 102.0, 69.6, 69.3, 68.7, 68.6, 65.9, 65.8, 64.5, 64.5, 34.0, 34.0, 21.4, 21.1, 20.9, 20.5; IR νmax (film)/cm⁻¹: 2881, 1761, 1477, 1377, 1326, 1216, 1170, 1137, 1105, 1075, 1037; HRMS (ESI) m/z calculated for C12H16O5Na ([M+Na]+) 263.0890, found 263.0889.

To a solution of lactone 993 (202 mg, 0.84 mmol) in THF/MeOH (6 mL, 5:1) was added sodium borohydride (64 mg, 1.7 mmol). After 45 min the reaction was quenched by addition of sat. NaHCO3 and diluted with EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO4. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give the corresponding diol (140 mg, 0.57 mmol, 68%).

Rf 0.26 (EtOAc); 1H-NMR (300 MHz, CDCl3): δ 5.92 (tt, J = 5.8, 1.9 Hz, 1H), 4.97 (t, J = 4.9 Hz, 1H), 4.06-3.91 (m, 6H), 3.91-3.83 (m, 2H), 3.57 (td, J = 6.6, 1.7 Hz, 2H), 3.53-3.35 (m, 2H), 2.93 (bs, 1H, OH), 2.47 (bs-s, 1H, OH), 2.14-2.02 (m, 2H), 1.96 (td, J = 6.6, 5.0 Hz, 2H); 13C-NMR (100 MHz, CDCl3): δ 129.7, 116.5, 102.2, 70.5, 65.8, 64.7 (2C), 60.5, 60.4, 34.0, 21.5, 21.3; IR νmax (film)/cm⁻¹: 3371, 1412, 1223, 1104, 1019; HRMS (ESI) m/z calculated for C12H20O5Na ([M+Na]+) 267.1203, found 267.1209.

To a solution of this diol (140 mg, 0.57 mmol) in CH2Cl2 (5 mL) was added acetic anhydride (0.14 mL, 1.4 mmol), triethylamine (0.24 mL, 1.7 mmol) and DMAP (cat.). After 1 h the reaction was quenched by addition of sat. NaHCO3 and diluted with CH2Cl2. The phases were separated and the aqueous phase was extracted three times with CH2Cl2. The combined organic phases were washed with brine and dried over MgSO4. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give bisacetate 994 (160 mg, 0.49 mmol, 85%).

Rf 0.35 (1:1; hexanes/EtOAc); 1H-NMR (300 MHz, CDCl3): δ 6.02 (tt, J = 6.1, 2.0 Hz, 1H), 4.97 (t, J = 4.9 Hz, 1H), 4.30-4.22 (m, 2H), 4.06-3.92 (m, 6H), 3.90-3.82 (m, 2H), 3.56 (t, J = 6.6 Hz, 2H), 2.14-2.05 (m, 8H), 1.96 (td, J = 6.6, 5.0 Hz, 2H); 13C-NMR (100 MHz, CDCl3): δ 170.6, 170.5, 127.6, 118.3, 102.2, 70.3, 65.8, 64.6 (2C), 62.2, 62.1, 34.1, 20.7, 20.7, 18.2, 18.0; IR νmax (film)/cm⁻¹: 2882,
1734, 1365, 1224, 1105, 1027; **HRMS** (ESI) *m/z* calculated for C_{16}H_{24}O_{7}Na ([M+Na]^+) 351.1414, found 351.1412.

To a solution of dioxolane 994 (180 mg, 0.55 mmol) in MeCN/H_{2}O (10 mL, 1:1) was added hydroxylamine hydrochloride (76 mg, 1.1 mmol). The mixture was heated to 60 °C for 1.5 h. The reaction was diluted with pH 7 buffer and EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO_{4}. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give corresponding oxime (123 mg, 0.41 mmol, 75%) as a mixture of cis/trans isomers.

**R**<sub>f</sub> 0.21 (1:1; hexanes/EtOAc); **^1^H-NMR** (300 MHz, CDCl<sub>3</sub>, mixture of oxime isomers, all peaks reported): δ 7.63 (bs-s, 0.5H), 7.57 (bs-s, 0.5H), 7.47 (t, *J* = 5.9 Hz, 0.5H), 6.84 (t, *J* = 5.0 Hz, 0.5H), 6.13-5.99 (m, 1H), 4.39-4.19 (m, 2H), 4.11-4.05 (m, 2H), 4.04-3.87 (m, 2H), 3.59 (td, *J* = 6.3, 3.3 Hz, 2H), 2.67 (q, *J* = 6.2 Hz, 1H), 2.49 (qd, *J* = 6.2, 3.1 Hz, 1H), 2.13-5.99 (m, 1H), 4.39-4.19 (m, 2H), 4.11-4.05 (m, 2H), 4.04-3.87 (m, 2H), 3.59 (td, *J* = 6.3, 3.3 Hz, 2H), 2.67 (q, *J* = 6.2 Hz, 1H), 2.49 (qd, *J* = 6.2, 3.1 Hz, 1H), 2.13-5.99 (m, 1H); **^13^C-NMR** (100 MHz, CDCl<sub>3</sub>, mixture of oxime isomers, all peaks reported): δ 170.8, 149.1, 127.9, 127.9, 125.7, 120.8, 118.1, 118.0, 70.3, 70.2, 67.1, 66.5, 62.6, 62.4, 62.3, 62.3, 62.2, 30.0, 25.8, 20.9, 20.8, 20.8, 18.3, 18.2, 18.1, 18.0, 17.4; **IR** *v*<sub>max</sub> (film)/cm<sup>-1</sup>: 3384, 2865, 1733, 1433, 1365, 1225, 1101, 1027; **HRMS** (ESI) *m/z* calculated for C_{16}H_{24}O_{7}Na ([M+Na]^+) 351.1412, found 351.1412.

To a solution of this oxime (100 mg, 0.33 mmol) in CH_{2}Cl_{2} (2 mL) was added bis-tributyltin oxide (0.17 mL, 0.33 mmol). After 1 h the mixture was cooled to -50 °C and t-BuOCl (36 μL, 0.33 mmol) was added. The reaction was allowed to warm to ambient temperature and stirred for another 30 min. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give oxazoline 995 (50 mg, 0.17 mmol, 50%).

**R**<sub>f</sub> 0.21 (1:1; hexanes/EtOAc); **^1^H-NMR** (300 MHz, CDCl<sub>3</sub>): δ 4.34-4.21 (m, 2H), 4.17-4.02 (m, 4H), 3.94 (dt, *J* = 11.9, 8.5 Hz, 1H), 3.47-3.41 (m, 2H), 2.73 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.66-2.57 (m, 1H), 2.10-2.06 (m, 6H), 1.98 (dt, *J* = 11.0, 8.2 Hz, 1H), 1.81 (ddd, *J* = 11.0, 8.4, 7.5 Hz, 1H); **^13^C-NMR** (100 MHz, CDCl<sub>3</sub>): δ 170.8, 170.5, 157.2, 70.8, 70.6, 68.7, 60.0, 59.6, 47.5, 27.7, 23.9, 23.2, 20.9, 20.9; **IR** *v*<sub>max</sub> (film)/cm<sup>-1</sup>: 2966, 2861, 1732, 1433, 1367, 1224, 1085, 1028; **HRMS** (ESI) *m/z* calculated for C_{14}H_{20}O_{6}N ([M+H]^+) 298.1286, found 298.1286.

To a solution of oxazoline 995 (50 mg, 0.17 mmol) in MeNO_{2} (2 mL) was added trimethylxonium tetrafluoroborate (50 mg, 0.34 mmol). The mixture was stirred at ambient temperature for 15 h. The solvent was evaporated and the residue was taken up in EtOH (2 mL). Sodium borohydride (13 mg, 0.34 mmol) was added and the mixture was stirred for 1 h. The reaction was quenched by addition of water and diluted with EtOAc. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed with brine and dried over MgSO_{4}. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give isoxazolidine 987 (33 mg, 0.11 mmol, 63%).
**Experimental Part**

RF 0.35 (EtOAc); $^1$H-NMR (400 MHz, CD$_3$CN): $\delta$ 4.18 (dd, $J = 12.2$, 7.5 Hz, 1H), 4.12 (dd, $J = 11.9$, 7.2 Hz, 1H), 3.99 (ddd, $J = 12.0$, 9.0, 5.5 Hz, 2H), 3.74 (dd, $J = 11.3$, 6.5 Hz, 1H), 3.69-3.65 (m, 1H), 3.58-3.51 (m, 2H), 3.23-3.20 (m, 1H), 2.71 (s, 3H), 2.58 (ddd, $J = 11.3$, 6.4, 5.0 Hz, 1H), 2.01 (s, 3H), 1.99 (s, 3H), 1.92-1.83 (m, 1H), 1.67 (ddd, $J = 10.6$, 9.1, 7.3 Hz, 1H), 1.59-1.53 (m, 1H), 1.53-1.48 (m, 1H); $^{13}$C-NMR (100 MHz, CD$_3$CN): $\delta$ 171.6, 171.4, 69.0, 66.2, 66.1, 63.5, 61.5 (2C), 46.3, 41.5, 27.1, 26.1, 21.1, 21.1, 20.5; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 2948, 1735, 1458, 1435, 1367, 1228, 1099, 1031; HRMS (ESI) m/z calculated for C$_{15}$H$_{23}$NO$_6$Na ([M+Na]$^+$) 336.1418, found 336.1421.

An NMR tube was charged with isoxazolidine 986 (50 mg, 0.184 mmol) in CD$_3$CN (0.6 mL). To this solution was added d-TFA (28 μL, 0.37 mmol). The reaction was heated to 80 °C and monitored by $^1$H-NMR. After 30 min the starting material was consumed and the reaction was quenched by addition of triethylamine (77 μL, 0.553 mmol). The solvent was evaporated and the residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 40:1) to give β-lactam 981 (14 mg, 0.141 mmol, 77%) along with alkene 996 (25 mg, 0.145 μmol, 79%, only E isomer).

Exclusive formation of the E-alkene isomer was confirmed by $^1$H NMR of the crude reaction mixture and comparison with independently synthesized E- and Z-alkene.

981 proved to be volatile and unstable in CDCl$_3$ and other solvents. Only a $^1$H NMR could be obtained therefore.

981: RF 0.43 (9:1, CH$_2$Cl$_2$/MeOH); $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 3.59 (ddd, $J = 6.1$, 4.8, 2.2 Hz, 1H), 3.06 (dd, $J = 14.8$, 4.5 Hz, 1H), 2.76 (s, 3H), 2.53-2.47 (m, 1H), 1.31 (d, $J = 6.1$ Hz, 3H).

An NMR tube was charged with isoxazolidine 987 (7 mg, 22 μmol) in CD$_3$CN (0.6 mL). To this solution was added d-TFA (3.4 μL, 45 μmol). The reaction was heated to 80 °C and monitored by $^1$H-NMR. After 1.5 h the starting material was consumed and the reaction was quenched by addition of triethylamine (9.3 μL, 67 μmol). The solvent was evaporated and the residue was purified by flash
column chromatography (CH$_2$Cl$_2$/MeOH 40:1) to give β-lactam 998 (3 mg, 21 μmol, 95%) along with alkene 997 (3.5 mg, 20 μmol, 91%, only Z isomer).

Exclusive formation of the Z-alkene isomer was confirmed by $^1$H NMR of the crude reaction mixture and comparison with independently synthesized E- and Z-alkene.

998: R$_f$ 0.45 (9:1, CH$_2$Cl$_2$/MeOH); $^1$H-NMR (400 MHz, CD$_3$CN): δ 3.85 (dd, $J = 12.2$, 2.3 Hz, 1H), 3.81-3.71 (m, 3H), 3.65-3.60 (m, 1H), 3.13 (td, $J = 5.2$, 2.3 Hz, 1H), 2.73 (s, 3H), 2.02-1.88 (m, 2H); $^{13}$C-NMR (100 MHz, CD$_3$CN): δ 169.2, 62.3, 62.1, 49.2, 48.9, 26.5, 23.5; IR $\nu_{\max}$ (film)/cm$^{-1}$: 2933, 1731, 1427, 1398, 1388, 1246, 1159, 1060; HRMS (ESI) $m/z$ calculated for C$_7$H$_{11}$NO$_2$Na ([M+Na]$^+$) 164.0682, found 164.0682.

18.13. Experimental Part to Chapter 20

To a solution of 4-nitrobenzenediazonium tetrafluoroborate (27 mg, 0.11 mmol) in EtOH/H$_2$O (2 mL, 1:1) was added L-tyrosine methylester hydrochloride (20 mg, 0.11 mmol). After 30 min the mixture was diluted with CH$_2$Cl$_2$ and the phases were separated. The aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography (EtOAc) to give diazoarene 1098 (12 mg, 0.035 mmol, 32%).

R$_f$ 0.50 (EtOAc); $^1$H-NMR (500 MHz, CDCl$_3$): δ 12.47 (bs-s, 1H, OH), 8.41-8.38 (m, 2H), 8.02-7.98 (m, 2H), 7.85 (d, $J = 2.3$ Hz, 1H), 7.28 (dd, $J = 8.5$, 2.3 Hz, 1H), 7.02 (d, $J = 8.5$ Hz, 1H), 3.78 (dd, $J = 7.6$, 5.4 Hz, 1H), 3.75 (s, 3H), 3.13 (dd, $J = 13.8$, 5.3 Hz, 1H), 2.94 (dd, $J = 13.8$, 7.7 Hz, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 175.3, 154.0, 151.8, 148.7, 137.5, 136.2, 134.3, 129.5, 125.0 (2C), 122.8 (2C), 118.7, 55.7, 52.1, 39.9; IR $\nu_{\max}$ (film)/cm$^{-1}$: 3377, 2927, 1735, 1608, 1587, 1573, 1521, 1498, 1429, 1401, 1343, 1280, 1244, 1201, 1144, 1108; HRMS (ESI) $m/z$ calculated for C$_{16}$H$_{17}$N$_4$O$_5$ ([M+H]$^+$) 345.1193, found 345.1197.
To a solution of 4-nitrobenzenediazonium tetrafluoroborate (50 mg, 0.21 mmol) in pH 7 buffer (5 mL, 100 mM NaH$_2$PO$_4$) was added glycine ethylester hydrochloride (50 mg, 0.36 mmol). After 30 min the mixture was diluted with CH$_2$Cl$_2$ and the phases were separated. The aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give triazene 1101 (approx. 5%) along with 4-nitroaniline as the major product.

$R_f$ 0.31 (4:1, hexanes/EtOAc); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 9.51 (bs, 0.5H), 8.63 (bs, 0.5H), 8.25-8.19 (m, 2H), 7.58-7.28 (bs, 2H), 4.61-4.36 (bs, 2H), 4.28 (q, $J$ = 7.1 Hz, 2H), 1.32 (t, $J$ = 7.1 Hz, 3H); IR $\nu$max (film)/cm$^{-1}$: 3267, 2986, 1734, 1599, 1513, 1426, 1375, 1335, 1250, 1192, 1161, 1110, 1022; HRMS (ESI) $m/z$ calculated for C$_{10}$H$_{12}$N$_4$O$_4$Na ([M+H]$^+$) 275.0751, found 275.0751.

To a solution of methyl anthranilate 1114 (20 mg, 0.132 mmol) in water (1 mL) was added $p$-toluenesulfonic acid (151 mg, 0.79 mmol) and sodium nitrite (37 mg, 0.53 mmol). After 30 min the mixture was transferred into a flask containing glycine ethylester hydrochloride (28 mg, 0.20 mmol) in pH 7 buffer (6 mL, 100 mM NaH$_2$PO$_4$). After 3 h the mixture was diluted with CH$_2$Cl$_2$ and the phases were separated. The aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 4:1) to give acyltriazene 116 (11 mg, 0.047 mmol, 36%).

$R_f$ 0.67 (1:1, hexanes/EtOAc); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.37 (dd, $J$ = 7.9, 1.1 Hz, 1H), 8.19 (d, $J$ = 7.7 Hz, 1H), 8.00-7.95 (m, 1H), 7.85-7.80 (m, 1H), 5.19 (s, 2H), 4.28 (q, $J$ = 7.1 Hz, 2H), 1.31 (t, $J$ = 7.1 Hz, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 167.1, 155.5, 144.4, 135.1, 132.6, 128.6, 125.2, 119.8, 62.0, 50.9, 14.1; IR $\nu$max (film)/cm$^{-1}$: 3008, 1740, 1681, 1458, 1403, 1376, 1354, 1337, 1313, 1232, 1085, 1030; HRMS (ESI) $m/z$ calculated for C$_{11}$H$_{12}$N$_3$O$_3$ ([M+H]$^+$) 234.0873, found 234.0879.
Experimental Part

To a solution of 2-nitrobenzoic acid (450 mg, 2.7 mmol) in CH₂Cl₂ (2 mL) was added oxalyl chloride (0.47 mL, 5.4 mmol) and 1 drop of DMF. The reaction was stirred for 1 h and the solvent was removed. The crude acid chloride was taken up in CH₂Cl₂ (2 mL) and ethanethiol (0.40 mL, 5.4 mmol) followed by triethylamine (0.75 mL, 5.4 mmol) was added. After another 1.5 h the mixture was diluted with sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give thioester S44 (520 mg, 2.5 mmol, 91%).

Rf 0.67 (4:1, hexanes/EtOAc); ¹H-NMR (400 MHz, CDCl₃): δ 8.02-7.98 (m, 1H), 7.71-7.59 (m, 3H), 3.11 (q, J = 7.4 Hz, 2H), 1.39 (t, J = 7.4 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 191.4, 146.2, 134.9, 133.2, 131.5, 128.5, 124.5, 24.5, 14.3; IR νmax (film)/cm⁻¹: 2972, 2933, 1665, 1576, 1530, 1475, 1452, 1346, 1309, 1265, 1205.

To a solution of nitroarene S44 (520 mg, 2.5 mmol) in CH₂Cl₂ (5 mL) was added SnCl₂ (1.4 g, 7.4 mmol). The mixture was allowed to stir over night. The mixture was filtered and the organic phase was extracted with sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 10:1) to give aniline 1117 (380 mg, 2.1 mmol, 85%).

Rf 0.76 (4:1, hexanes/EtOAc); ¹H-NMR (400 MHz, CDCl₃): δ 7.91 (d, J = 8.1 Hz, 1H), 7.31-7.26 (m, 1H), 6.71-6.66 (m, 2H), 5.85 (bs-s, 2H, NH₂), 3.04 (q, J = 7.4 Hz, 2H), 1.36 (t, J = 7.4 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 193.3, 148.0, 134.1, 130.1, 118.6, 117.0, 116.3, 23.2, 14.9; IR νmax (film)/cm⁻¹: 3479, 3365, 2969, 2929, 1613, 1579, 1551, 1482, 1451, 1201, 1158, 1027; HRMS (EI) m/z calculated for C₉H₁₁NOS ([M⁺]⁺) 181.0556, found 181.0559.
Benzoic acid derivative 1130 was synthesized according to a literature procedure.\(^{763}\)

To a solution of 1129 (12 g, 50.2 mmol) in dioxane (100 mL) was added 1M NaOH (50 mL) over a period of 30 min (dropping funnel). The reaction was allowed to stir at ambient temperature overnight. The mixture was extracted once with Et\(_2\)O and the resulting organic phase was discarded. The aqueous phase was acidified using 1M HCl and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over MgSO\(_4\). The solvent was evaporated and the resulting oily residue was recrystallized from water (500 mL) to give benzoic acid 1130 (5.2 g, 23.1 mmol, 46%).

\( R_f \) 0.11 (9:1, CH\(_2\)Cl\(_2\)/MeOH); \(^1\)H-NMR (300 MHz, d\(_6\)-DMSO): \( \delta \) 13.97 (bs-s, 1H, OH), 8.45 (d, \( J = 1.5 \) Hz, 1H), 8.33 (dd, \( J = 7.9, 1.6 \) Hz, 1H), 7.98 (d, \( J = 8.1 \) Hz, 1H), 3.88 (s, 3H); \(^13\)C-NMR (100 MHz, d\(_6\)-DMSO): \( \delta \) 164.78 (2C), 147.53, 134.65, 134.06, 130.43, 129.80, 124.64, 53.47; IR \( \nu_{max} \) (film)/cm\(^{-1} \): 1725, 1695, 1643, 1499, 1431, 1373, 1284, 1250, 1191, 1133, 1064; HRMS (EI) \( m/z \) calculated for C\(_9\)H\(_7\)NO\(_6\) ([M]+) 225.0268, found 225.0264.

To a solution of acid 1130 (1 g, 4.44 mmol) in CH\(_2\)Cl\(_2\) was added oxalyl chloride (0.78 mL, 8.88 mmol) and 2 drops of DMF. After 1 h the solvent was removed and the residue was taken up in CH\(_2\)Cl\(_2\) (5 mL). 2-Methoxyethaneamine (0.57 mL, 6.66 mmol) and triethylamine (1.9 mL, 13.3 mmol) were added and the mixture was stirred overnight. The mixture was diluted with sat. NaHCO\(_3\) and the phases were separated. The aqueous phase was extracted three times with CH\(_2\)Cl\(_2\). The combined organic phases were washed with brine and dried over MgSO\(_4\). The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give an intermediate nitroarene (1 g, 3.54 mmol, 80%).

To a solution of this nitroarene (1 g, 3.54 mmol) in MeOH (40 mL) was added tin powder (1.68 g, 14.2 mmol) and conc. HCl (4 mL). The mixture was heated to reflux for 30 min. After filtration the solvent was removed and the residue was taken up in EtOAc and extracted with water. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic

phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give intermediated aniline 1128 (755 mg, 2.99 mmol, 84%).

Rf 0.56 (EtOAc); ¹H-NMR (400 MHz, CDCl₃): δ 7.88 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 1.7 Hz, 1H), 6.90 (dd, J = 8.3, 1.7 Hz, 1H), 6.53 (bs-s, 1H, NH), 5.85 (bs-s, 2H, NH₂), 3.88 (s, 3H), 3.65-3.60 (m, 2H), 3.56-3.55 (m, 2H), 3.38 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 168.0, 166.9, 150.4, 139.5, 131.7, 115.7, 113.7, 112.7, 71.1, 58.8, 51.7, 39.7; IR νmax (film)/cm⁻¹: 3461, 3372, 3348, 2931, 1697, 1648, 1620, 1594, 1533, 1497, 1440, 1315, 1247, 1192, 1115, 1083; HRMS (ESI) m/z calculated for C₁₂H₁₆N₂O₄Na ([M+Na]+) 275.1002, found 275.1001.

To a flask containing 4-nitrobenzoic acid (2.0 g, 12.0 mmol) was added thionyl chloride (10 mL). The mixture was heated to reflux overnight. After removal of the solvent the residue was taken up in CH₂Cl₂ (20 mL) and 2-methoxyethaneamine (1.65 mL, 12.0 mmol) and triethylamine (1.55 mL, 17.8 mmol) were added. The mixture was stirred for 12 h and then poured into a separatory funnel containing sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic phases were washed with brine and dried over MgSO₄. The solvent was removed and the residue was subjected to flash column chromatography (hexanes/EtOAc 1:1) to give amide 1137 (1.93 g, 8.6 mmol, 73%).

Rf 0.59 (EtOAc); ¹H-NMR (400 MHz, CDCl₃): δ 8.29-8.23 (m, 1H), 7.98-7.92 (m, 1H), 6.67 (bs-s, 1H, NH), 3.69-3.64 (m, 2H), 3.59-3.55 (m, 2H), 3.39 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 165.4, 149.5, 140.0, 128.2 (2C), 123.7 (2C), 70.8, 58.9, 40.0; IR νmax (film)/cm⁻¹: 3318, 2926, 2873, 2826, 1635, 1600, 1549, 1523, 1493, 1476, 1455, 1359, 1334, 1303, 1194, 1116, 1096, 1016; HRMS (ESI) m/z calculated for C₁₀H₁₂N₂O₄Na ([M+Na]+) 247.0689, found 247.0695.

To a solution of nitroarene 1137 (1.3 g, 5.8 mmol) in EtOH (15 mL) was added Pd/C (50 mg, 10wt% Pd). The flask was evacuated and backfilled with nitrogen. After evacuating a second time a hydrogen atmosphere (balloon) was applied. The mixture was stirred for 6 h and then filtered over celite. The
solvent was removed and the residue was purified by flash column chromatography (EtOAc) to give aniline **1135** (980 mg, 5.1 mmol, 87%).

**R**<sub>f</sub> 0.36 (EtOAc); **<sup>1</sup>H-NMR** (300 MHz, CDCl<sub>3</sub>): δ 7.61-7.55 (m, 2H), 6.63-6.56 (m, 2H), 6.51 (bs-s, 1H, NH), 4.02 (bs-s, 2H, NH<sub>2</sub>), 3.61-3.54 (m, 2H), 3.53-3.47 (m, 2H), 3.34 (s, 3H); **<sup>13</sup>C-NMR** (75 MHz, CDCl<sub>3</sub>): δ 167.2, 149.6, 128.6 (2C), 123.6, 113.9 (2C), 71.3, 58.6, 39.4; **IR** ν<sub>max</sub> (film)/cm<sup>-1</sup>: 3342, 2931, 1602, 1540, 1504, 1459, 1288, 1186, 1115, 1092; **HRMS** (ESI) m/z calculated for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>Na ([M+Na]<sup>+</sup>) 217.0947, found 217.0948.

This reaction was performed in different pH buffers (see main text).

**R**<sub>f</sub> 0.71 (EtOAc); **<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>): δ 12.65 (s, 1H, OH), 7.96-7.91 (m, 2H), 7.91-7.86 (m, 2H), 7.72 (d, J = 2.1 Hz, 1H), 7.34-7.27 (m, 5H), 7.11 (dd, J = 8.5, 2.2 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 6.66 (bs-t, J = 5.2 Hz, 1H, NH), 5.39 (d, J = 8.0 Hz, 1H, NH), 5.15-5.05 (m, 2H), 4.70 (q, J = 6.0 Hz, 1H), 3.75-3.68 (m, 2H), 3.61-3.57 (m, 2H), 3.41 (s, 3H), 3.20 (dd, J = 14.3, 5.8 Hz, 1H), 3.11 (dd, J = 14.1, 6.1 Hz, 1H); **<sup>13</sup>C-NMR** (100 MHz, CDCl<sub>3</sub>): δ 171.8, 166.5, 155.6, 152.2, 151.8, 137.2, 136.4, 134.9, 133.9, 128.5 (2C), 128.2 (2C), 128.1 (2C), 127.5, 126.9, 122.3 (2C), 118.5, 71.1, 67.0, 58.8, 54.9, 52.5, 39.8, 37.3; **IR** ν<sub>max</sub> (film)/cm<sup>-1</sup>: 3315, 2933, 1720, 1644, 1535, 1499, 1438, 1400, 1280, 1214, 1120, 1059, 1023; **HRMS** (ESI) m/z calculated for C<sub>28</sub>H<sub>31</sub>N<sub>4</sub>O<sub>7</sub> ([M+H]<sup>+</sup>) 535.2187, found 535.2190.

This reaction was performed in different pH buffers (see main text).

**R**<sub>f</sub> 0.53 (EtOAc); **<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>): δ 8.51 (d, J = 1.3 Hz, 1H), 8.39 (d, J = 8.2 Hz, 1H), 8.22 (dd, J = 8.2, 1.7 Hz, 1H), 6.89 (bs-s, 1H, NH), 5.18 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.73-3.68 (m, 2H), 3.62-3.58 (m, 2H), 3.40 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); **<sup>13</sup>C-NMR** (100 MHz, CDCl<sub>3</sub>): δ 166.9, 165.1, 154.9, 144.1, 140.9, 131.1, 126.9, 125.9, 121.4, 70.8, 62.1, 58.9, 50.9, 40.1, 14.1; **IR**
\( \nu_{\text{max}} \text{(film)/cm}^{-1} \): 3291, 2884, 1743, 1681, 1639, 1551, 1409, 1378, 1345, 1315, 1286, 1210, 1195, 1078, 1022; \text{HRMS (ESI) } m/z \) calculated for C\(_{15}\)H\(_{19}\)N\(_4\)O\(_5\) ([M+H]\(^+\)) 335.1350, found 335.1356.

**18.14. Experimental Part to Chapter 21**

Carbamate 1149 was synthesized according to a literature procedure.\(^{764}\)

To a solution of 1,13-diamino-4,7,10-trioxatridecane (5 g, 22.7 mmol) in CHCl\(_3\) (200 mL) at 0°C was slowly added a solution of Boc\(_2\)O (1.2 g, 5.7 mmol) in CHCl\(_3\) (50 mL) (dropping funnel). The mixture was allowed to warm to ambient temperature and stirred overnight. The organic phase was washed with water and brine and dried over MgSO\(_4\). The solvent was removed and the residue was subjected to flash column chromatography (CH\(_2\)Cl\(_2\)/MeOH 9:1) to give amine 1149 (3.9 g, 12.2 mmol, 54%).

R\(_f\) 0.15 (9:1, CH\(_2\)Cl\(_2\)/MeOH); \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta \) 5.10 (bs-s, 1H, NH), 3.65-3.49 (m, 12H), 3.21 (q, \( J = 5.7 \) Hz, 2H), 2.79 (t, \( J = 6.7 \) Hz, 2H, NH\(_2\)), 1.78-1.68 (m, 6H), 1.42 (s, 9H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 156.05, 78.83, 70.55, 70.19, 70.15, 69.47, 39.61, 38.47, 33.09, 29.60, 28.42 (3C); \(^\text{IR } \nu_{\text{max}} \text{(film)/cm}^{-1} \): 2871, 1700, 1523, 1456, 1365, 1251, 1173, 1119; \text{HRMS (ESI) } m/z \) calculated for C\(_{15}\)H\(_{32}\)N\(_2\)O\(_5\) ([M+H]\(^+\)) 321.2384, found 321.2387.

To a solution of acid 1130 (2.81 g, 12.5 mmol) in CH\(_2\)Cl\(_2\) (20 mL) was added oxalyl chloride (2.73 mL, 31.2 mmol) and 2 drops of DMF. After 1h the solvent was removed and the residue was taken up in CH\(_2\)Cl\(_2\) (20 mL). To this solution was added amine 1149 (2 g, 6.2 mmol) followed by triethylamine (2.61 mL, 18.7 mmol). The mixture was stirred overnight. The reaction was quenched by addition of sat. NaHCO\(_3\). The phases were separated and the aqueous phase was extracted three times with CH\(_2\)Cl\(_2\). The combined organic solvents were dried over MgSO\(_4\) and the solvent was evaporated. The residue was purified by flash column chromatography (hexanes/EtOAc 1:1) to give amide 1150 (2.56 g, 4.9 mmol, 78%).

Rf 0.41 (EtOAc); 1H-NMR (300 MHz, CDCl3): δ 8.37 (s, 1H), 8.17 (dd, J = 8.0, 1.3 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.72 (bs-s, 1H, NH), 4.88 (bs-s, 1H, NH), 3.94 (s, 3H), 3.71-3.55 (m, 10H), 3.48-3.39 (m, 4H), 3.16 (q, J = 6.4 Hz, 2H), 1.91 (p, J = 5.5 Hz, 2H), 1.70-1.62 (m, 2H), 1.14 (s, 9H); 13C-NMR (100 MHz, CDCl3): δ 165.3, 163.6, 156.0, 148.2, 138.4, 131.5, 130.1, 129.2, 122.7, 79.0, 70.9, 70.2, 70.1, 70.0, 69.3, 53.4, 39.7, 38.3, 29.6, 28.4 (4C);

IR νmax (film)/cm⁻¹: 2954, 2874, 1739, 1699, 1661, 1536, 1436, 1352, 1291, 1249, 1169, 1124; HRMS (ESI) m/z calculated for C24H38N3O10 ([M+H]+) 528.2552, found 528.2550.

To a solution of carbamate 1150 (1.46 g, 2.8 mmol) in CH2Cl2 (10 mL) was added TFA (5 mL). The mixture was stirred for 15 min (TLC control). The solvent was evaporated and the residue was coevaporated with toluene three times. The resulting amine (1.16 g, 2.7 mmol, 98%) was sufficiently pure and was used as such for the next step.

Rf 0.05 (9:1, CH2Cl2/MeOH); 1H-NMR (300 MHz, CDCl3): δ 8.84 (bs-t, J = 5.6 Hz, 1H, NH), 8.62 (d, J = 1.5 Hz, 1H), 8.40 (dd, J = 8.0, 1.7 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H), 3.69-3.49 (m, 14H), 3.22-3.15 (m, 2H), 2.02-1.86 (m, 4H); 13C-NMR (100 MHz, CDCl3): δ 165.2, 164.1, 147.9, 137.8, 131.9, 128.9, 123.2, 70.0, 69.9, 69.4, 69.3, 69.0, 53.2, 39.9, 37.7, 28.8, 26.2; IR νmax (film)/cm⁻¹: 2921, 1737, 1650, 1635, 1436, 1352, 1294, 1128; HRMS (ESI) m/z calculated for C19H30N3O8 ([M+H]+) 428.2027, found 428.2032.

To a solution of amine 1148 (1.16 g, 2.71 mmol) in CH2Cl2 (10 mL) was added triethylamine (1.9 mL, 13.6 mmol) and succinic anhydride (407 mg, 4.1 mmol). The reaction was stirred overnight. The solvent was removed and the residue was subjected to flash column chromatography (CH2Cl2/MeOH 20:1 CH2Cl2/MeOH/NEt3 9:1:0.01) to give acid 1151 (1.25 g, 2.37 mmol, 87%).

Rf 0.40 (5:1, CH2Cl2/MeOH); 1H-NMR (300 MHz, CDCl3): δ 8.41 (s, 1H), 8.21 (d, J = 7.9 Hz, 1H), 8.10 (bs-s, 1H, NH), 7.76 (d, J = 8.0 Hz, 1H), 7.06 (bs-s, 1H, NH), 3.89 (s, 3H), 3.67-3.33 (m, 14H), 3.29-3.14 (m, 2H), 2.65-2.40 (m, 4H), 1.92-1.80 (m, 2H), 1.70-1.58 (m, 2H); 13C-NMR (100 MHz,
CDCl$_3$): 8 173.2, 172.9, 165.3, 164.1, 148.0, 138.0, 131.8, 130.0, 129.2, 122.9, 70.1, 70.1, 70.0, 69.8, 69.8, 69.5, 53.4, 45.9, 39.0, 37.8, 30.9, 28.6, 28.6; IR $\nu_{max}$ (film)/cm$^{-1}$: 1737, 1647, 1543, 1437, 1352, 1293, 1127, 1030; HRMS (ESI) $m/z$ calculated for C$_{23}$H$_{34}$N$_3$O$_1$ ([M+H]$^+$) 528.2188, found 528.2189.

To a solution of acid 1151 (850 mg, 1.61 mmol) in CH$_2$Cl$_2$ (5 mL) was added benzylamine (0.26 mL, 2.42 mmol), HATU (919 mg, 2.42 mmol) and Hünig’s base (0.56 mL, 3.2 mmol). The reaction was allowed to stir overnight. The mixture was then diluted with sat. NaHCO$_3$ and CH$_2$Cl$_2$. The phases were separated and the aqueous phase was washed three times with CH$_2$Cl$_2$. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to give amide S45 (705 mg, 1.14 mmol, 71%).

R$_f$ 0.55 (9:1, CH$_2$Cl$_2$/MeOH); $^1$H-NMR (300 MHz, CDCl$_3$): 8 8.42 (d, $J = 1.3$ Hz, 1H), 8.19 (ddd, $J = 8.0$, 1.5, 0.7 Hz, 1H), 8.05 (bs-t, $J = 5.0$ Hz, 1H, NH), 7.74 (d, $J = 8.1$ Hz, 1H), 7.38-7.19 (m, 5H), 6.72 (bs-t, $J = 5.0$ Hz, 1H, NH), 6.64 (bs-t, $J = 5.3$ Hz, 1H, NH), 4.37 (d, $J = 5.8$ Hz, 2H), 3.93 (s, 3H), 3.66-3.43 (m, 14H), 3.29 (q, $J = 6.0$ Hz, 2H), 2.54 (s, 4H), 1.89 (dt, $J = 11.9$, 6.0 Hz, 2H), 1.68 (p, $J = 5.9$ Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$): 8 172.4, 172.2, 165.2, 163.9, 147.9, 138.1, 138.1, 131.4, 129.9, 129.0, 128.3 (2C), 127.2 (2C), 127.0, 122.8, 70.0 (2C), 69.8 (2C), 69.7, 69.3, 53.2, 43.2, 38.6, 37.5, 31.5, 31.4, 28.6, 28.6; IR $\nu_{max}$ (film)/cm$^{-1}$: 3301, 2924, 2870, 1736, 1644, 1536, 1436, 1352, 1248, 1124; HRMS (ESI) $m/z$ calculated for C$_{30}$H$_{41}$N$_4$O$_{10}$ ([M+H]$^+$) 617.2817, found 617.2812.

To a solution of nitroarene S45 (705 mg, 1.14 mmol) in MeOH (10 mL) was added Pd/C (50 mg, 10wt% Pd). The mixture was set under vacuum and the flask was purged with nitrogen gas. After applying vacuum again, the flask was backfilled with hydrogen (balloon). After 3 h the mixture was filtered over celite and the solvent was evaporated. The residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1 → 10:1) to give aniline 1159 (517 mg, 0.88 mmol, 77%).

R$_f$ 0.50 (9:1, CH$_2$Cl$_2$/MeOH); $^1$H-NMR (400 MHz, CDCl$_3$): 8 7.78 (d, $J = 8.3$ Hz, 1H), 7.48 (bs-t, $J = 5.4$ Hz, 1H, NH), 7.31-7.13 (m, 7H), 6.90 (dd, $J = 8.3$, 1.6 Hz, 1H), 6.90-6.86 (bs-m, 1H, NH), 6.07 (bs-s, 2H, NH$_2$), 4.28 (d, $J = 5.8$ Hz, 2H), 3.80 (s, 3H), 3.61-3.51 (m, 8H), 3.46-3.35 (m, 6H), 3.18 (q, $J = 6.4$ Hz, 2H), 2.46 (qt, $J = 9.2$, 4.6 Hz, 4H), 1.79 (p, $J = 5.9$ Hz, 2H), 1.62 (p, $J = 6.2$ Hz, 2H); $^{13}$C-
NMR (100 MHz, CDCl₃): δ 172.3, 172.3, 167.9, 166.9, 150.6, 139.3, 138.3, 131.3, 128.3 (2C), 127.3 (2C), 127.0, 115.5, 113.6, 111.9, 70.1, 70.1, 70.0, 69.7, 69.7, 69.2, 51.5, 43.2, 38.4, 37.3, 31.4 (2C), 28.8, 28.7; IR νₑₓₘₐₓ (film)/cm⁻¹: 3298, 2866, 1630, 1540, 1492, 1474, 1436, 1340, 1310, 1247, 1194, 1137, 1106; HRMS (ESI) m/z calculated for C₃₀H₃₁N₄O₈ ([M+H⁺]⁺) 587.3075, found 587.3066.

To a solution of nitroarene 1151 (200 mg, 0.38 mmol) in MeOH (3 mL) was added Pd/C (20 mg, 10wt% Pd). The mixture was set under vacuum and the flask was purged with nitrogen gas. After applying vacuum again, the flask was backfilled with hydrogen (balloon). After 1 h the mixture was filtered over celite and the solvent was evaporated. The residue was purified by flash column chromatography (CH₂Cl₂/MeOH/NEt₃ 10:1:0.01) to give the corresponding aniline 1152 adduct (165 mg, 0.33 mmol, 87%).

To a solution of this aniline intermediate (45 mg, 0.09 mmol) in THF (3 mL) was added N-hydroxysuccinimide (10 mg, 0.09 mmol) and DCC (19 mg, 0.09 mmol). After 3 h the mixture was filtered through a pad of celite. The solvent was removed and the residue was subjected to flash column chromatography (CH₂Cl₂/MeOH 20:1) to give aniline 1153 (28 mg, 0.05 mmol, 52%).

Rᶠ 0.49 (9:1, CH₂Cl₂/MeOH); ¹H-NMR (400 MHz, CDCl₃): δ 7.85 (d, J = 8.3 Hz, 1H), 7.23 (bs-s, 1H, NH), 7.14 (s, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.49 (bs-s, 1H, NH), 5.98 (bs-s, 2H, NH₂), 3.86 (s, 3H), 3.68-3.45 (m, 14H), 3.31 (q, J = 6.0 Hz, 2H), 2.95 (t, J = 7.3 Hz, 2H), 2.79 (s, 4H), 2.55 (t, J = 7.3 Hz, 2H), 1.86 (p, J = 5.6 Hz, 2H), 1.71 (p, J = 6.0 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 169.8, 169.0 (2C), 168.3, 168.1, 166.6, 150.6, 139.7, 131.5, 115.4, 113.9, 112.2, 70.7, 70.3, 70.1, 69.9, 69.9, 69.8, 51.7, 39.0, 37.9, 30.6, 28.8, 28.7, 26.8, 25.5 (2C); IR νₑₓₘₐₓ (film)/cm⁻¹: 3347, 2870, 1814, 1784, 1735, 1694, 1647, 1619, 1593, 1535, 1436, 1310, 1244, 1205, 1070; HRMS (ESI) m/z calculated for C₂₇H₃₉N₇O₁₁ ([M+H⁺⁺]⁺) 595.2610, found 595.2602.
To a solution of 1-methyl-2-aminoterephthalate (2.75 g, 14.11 mmol) in CH$_2$Cl$_2$ (20 mL) was added amine 1156$^{765}$ (5.0 g, 14.11 mmol), EDC (4.06 g, 21.2 mmol), HOBt (3.24 g, 21.2 mmol) and diisopropyl ethylamine (7.4 mL, 42.3 mmol). The mixture was stirred over night and then diluted with sat. NaHCO$_3$. The phases were separated and the aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic phases were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was purified by flash column chromatography (hexanes/EtOAc 1:1 → EtOAc) to give aniline 1157 (3.5 g, 6.6 mmol, 47%).

R$_f$ 0.35 (EtOAc); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.81 (d, $J = 8.3$ Hz, 1H), 7.34-7.24 (m, 6H), 7.14 (s, 1H), 6.94 (d, $J = 8.3$ Hz, 1H), 5.96 (bs-s, 2H, NH$_2$), 5.46-5.40 (bs-m, 1H, NH), 5.09-5.02 (m, 2H), 3.82 (s, 3H), 3.63-3.42 (m, 14H), 3.24 (q, $J = 6.2$ Hz, 2H), 1.81 (p, $J = 5.5$ Hz, 2H), 1.70 (p, $J = 6.0$ Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 167.9, 166.4, 156.3, 150.5, 139.6, 136.6, 131.3, 128.3 (2C), 127.9 (2C), 127.8, 115.4, 113.7, 112.0, 70.7, 70.2, 70.0, 69.9, 69.9, 69.4, 66.3, 51.5, 39.0, 39.0, 28.5; IR $\nu_{max}$ (film)/cm$^{-1}$: 3460, 3347, 2949, 2870, 1696, 1619, 1532, 1437, 1310, 1243, 1103; HRMS (ESI) m/z calculated for C$_{27}$H$_{38}$N$_3$O$_8$ ([M+H]$^+$) 532.2653, found 532.2651.

To a solution of carbamate 1157 (3.50 g, 6.6 mmol) in MeOH (20 mL) was added Pd/C (100 mg, 10wt% Pd). The mixture was set under vacuum and the flask was purged with nitrogen gas. After applying vacuum again, the flask was backfilled with hydrogen (balloon). After 1 h the mixture was filtered over celite and the solvent was evaporated. Amine 1158 was obtained in sufficient purity for use in subsequent reactions.

R$_f$ 0.05 (9:1, CH$_2$Cl$_2$/MeOH); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.98 (bs-s, 2H, NH$_2$), 7.77 (d, $J = 8.3$ Hz, 1H), 7.72-7.64 (m, 1H, NH), 7.21 (s, 1H), 6.92 (d, $J = 8.3$ Hz, 1H), 5.45 (bs-s, 2H, NH$_2$), 3.82 (s, 3H), 3.60-3.39 (m, 14H), 3.08 (bs-s, 2H), 1.93-1.83 (m, 2H), 1.83-1.74 (m, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 168.0, 167.4, 150.7, 138.9, 131.4, 115.8, 113.7, 112.2, 70.1, 69.8, 69.6 (2C), 69.5, 69.4,

51.6, 39.5, 38.0, 28.9, 26.3; **IR** $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3460, 3356, 2875, 1678, 1618, 1594, 1542, 1438, 1312, 1245, 1200, 1180, 1127; **HRMS** (ESI) $m/z$ calculated for $C_{19}H_{32}N_3O_6$ ([M+H]$^+$) 398.2286, found 398.2287.

To a solution of amine **1158** (1.8 g, 4.53 mmol) in CH$_2$Cl$_2$ (20 mL) was added succinic anhydride (453 mg, 4.53 mmol) and triethylamine (1.26 mL, 9.06 mmol). The mixture was allowed to stir over night. The solvent was removed and the residue was directly subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH/NEt$_3$ 10:1:0.01) to give acid **1152** (1.69 g, 3.40 mmol, 75%).

R$_f$ 0.21 (9:1, CH$_2$Cl$_2$/MeOH); **$^1$H-NMR** (400 MHz, CDCl$_3$): $\delta$ 11.62 (bs-s, 1H, CO$_2$H), 7.76 (d, $J = 8.3$ Hz, 1H), 7.54 (t, $J = 5.0$ Hz, 1H, NH), 7.13 (d, $J = 1.4$ Hz, 1H), 6.98 (bs-s, 1H, NH), 6.91 (dd, $J = 8.4$, 1.6 Hz, 1H), 3.78 (s, 3H), 3.60-3.48 (m, 8H), 3.48-3.41 (m, 4H), 3.38 (t, $J = 6.0$ Hz, 2H), 3.19 (q, $J = 6.3$ Hz, 2H), 2.53-2.45 (m, 2H), 2.38 (t, $J = 6.6$ Hz, 2H), 1.80 (p, $J = 5.8$ Hz, 2H), 1.63 (p, $J = 6.3$ Hz, 2H); **$^{13}$C-NMR** (100 MHz, CDCl$_3$): $\delta$ 177.2, 172.9, 167.9, 166.7, 150.6, 139.5, 131.2, 115.4, 113.7, 111.7, 70.2, 70.1, 70.0, 69.8, 69.7, 69.2, 51.4, 38.5, 37.1, 31.8, 31.5, 28.9, 28.7; **IR** $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3454, 3317, 2949, 2869, 1693, 1645, 1620, 1593, 1538, 1437, 1310, 1243, 1191, 1102; **HRMS** (ESI) $m/z$ calculated for $C_{23}H_{36}N_3O_9$ ([M+H]$^+$) 498.2446, found 498.2454.

To a solution of aniline **1159** (22 mg, 38 μmol) in MeOH/water (1 mL, 1:3) was added p-toluenesulfonic acid (44 mg, 230 μmol) followed by sodium nitrite (11 mg, 153 μmol). The solution was stirred for 30 min. In a separate flask tripeptide **1160** (5 mg, 19 μmol) was dissolved in pH 7 buffer (5 mL, 100 mM NaH$_2$PO$_4$). The diazonium solution was transferred to this flask and the reaction was allowed to stir at ambient temperature for 2 h. EtOAc was added to this mixture and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over MgSO$_4$ and the solvent was removed. The crude product was dissolved in CH$_2$Cl$_2$/MeOH (1 mL, 10:1) and trimethylsilyl diazomethane (excess) was added. After 15 min AcOH was added until the mixture
23. Experimental Part

turned form yellow to colorless. The solvent was removed and the residue was purified by flash column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 9:1) to give ester 1183 (9 mg, 11 μmol, 56%).

R\textsubscript{f} 0.22 (9:1, CH\textsubscript{2}Cl\textsubscript{2}/MeOH); \textsuperscript{1}H-NMR (600 MHz, CD\textsubscript{3}OD): δ 8.60 (dd, J = 1.7, 0.6 Hz, 1H), 8.39 (dd, J = 8.3, 0.5 Hz, 1H), 8.28 (dd, J = 8.3, 1.7 Hz, 1H), 7.30-7.24 (m, 4H), 7.23-7.20 (m, 1H), 5.31 (d, J = 9.7 Hz, 1H), 4.50 (t, J = 4.4 Hz, 1H), 3.34 (s, 2H), 3.99 (d, J = 16.8 Hz, 1H), 3.92 (d, J = 16.8 Hz, 1H), 3.86 (dd, J = 11.4, 4.7 Hz, 1H), 3.77 (dd, J = 11.3, 4.1 Hz, 1H), 3.70 (s, 3H), 3.67-3.65 (m, 2H), 3.64-3.61 (m, 6H), 3.57-3.53 (m, 4H), 3.47 (t, J = 6.2 Hz, 2H), 3.22 (t, J = 6.8 Hz, 2H), 3.03-2.94 (m, 1H), 2.54-2.50 (m, 2H), 2.50-2.47 (m, 2H), 1.95-1.90 (m, 2H), 1.73-1.68 (m, 2H), 1.21 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.6 Hz, 2H); \textsuperscript{13}C-NMR (150 MHz, CD\textsubscript{3}OD): δ 174.5, 174.5, 172.0, 171.3, 171.1, 167.6, 157.2, 144.9, 142.6, 140.0, 132.2, 129.5 (2C), 128.5 (2C), 128.2, 128.1, 126.8, 122.2, 71.6, 71.5, 71.3, 71.2, 70.2, 69.9, 68.2, 62.8, 56.2, 52.8, 44.1, 43.6, 39.1, 37.9, 32.3, 32.3, 30.4, 30.3, 30.0, 20.1, 19.8; IR ν\textsubscript{max} (film)/cm\textsuperscript{-1}: 3313, 2926, 1743, 1651, 1548, 1454, 1087; HRMS (ESI) m/z calculated for C\textsubscript{40}H\textsubscript{57}N\textsubscript{8}O\textsubscript{12} (\([\text{M+H}]^+) 841.4090, found 841.4088.

To a solution of aniline 1159 (10 mg, 17 μmol) in MeOH/water (1 mL, 1:3) was added p-toluenesulfonic acid (20 mg, 102 μmol) followed by sodium nitrite (5 mg, 68 μmol). The solution was stirred for 30 min. In a separate flask tripeptide 1166 (7.5 mg, 19 μmol) was dissolved in pH 6 buffer (5 mL, 100 mM NaH\textsubscript{2}PO\textsubscript{4}). The diazonium solution was transferred to this flask and the reaction was allowed to stir at ambient temperature for 2 h while the reaction was monitored by LC-MS (see main text). EtOAc was added to this mixture and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over MgSO\textsubscript{4} and the solvent was removed. The crude product by prep-HPLC to give acid 1184 (6.1 mg, 6.3 μmol, 37%).

R\textsubscript{f} 0.00 (9:1, CH\textsubscript{2}Cl\textsubscript{2}/MeOH); \textsuperscript{1}H-NMR (600 MHz, CD\textsubscript{3}OD): δ 8.58 (dd, J = 1.7, 0.6 Hz, 1H), 8.34 (dd, J = 8.3, 0.5 Hz, 1H), 8.26 (dd, J = 8.3, 1.7 Hz, 1H), 7.30-7.17 (m, 10H), 6.95-6.92 (m, 2H), 6.52-6.49 (m, 2H), 5.57 (q, J = 7.2 Hz, 1H), 4.64 (dd, J = 8.3, 5.3 Hz, 1H), 4.56 (dd, J = 8.8, 5.5 Hz, 1H), 4.34 (s, 2H), 3.67-3.65 (m, 2H), 3.64-3.61 (m, 6H), 3.57-3.53 (m, 4H), 3.46 (t, J = 6.2 Hz, 2H), 3.23-3.18 (m, 3H), 3.03-2.97 (m, 2H), 2.78 (dd, J = 14.1, 8.8 Hz, 1H), 2.53-2.50 (m, 2H), 2.49-2.46 (m, 2H), 1.96-1.91 (m, 2H), 1.74 (d, J = 7.2 Hz, 3H), 1.70 (t, J = 6.3 Hz, 2H); \textsuperscript{13}C-NMR (150 MHz, CD\textsubscript{3}OD): δ 174.5, 174.5, 174.2, 173.1, 171.6, 167.7, 157.1, 156.4, 145.1, 142.4, 140.0, 138.3, 132.1, 131.20 (2C), 130.4 (2C), 129.5 (2C), 128.7, 128.5 (2C), 128.2, 128.2, 127.8, 126.6, 122.3,
116.1 (2C), 71.5, 71.5, 71.3, 71.2, 70.2, 69.9, 58.5, 56.2, 55.1, 44.1, 39.1, 38.4, 37.9, 37.6, 32.3, 32.3, 30.4, 30.3, 16.3; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3300, 2927, 1640, 1553, 1517, 1455, 1204, 1137; HRMS (ESI) m/z calculated for C$_{50}$H$_{61}$N$_8$O$_{12}$ ([M+H]$^+$) 965.4403, found 965.4402.

**General Procedure for the Bioconjugation of Diazonium Salts to Proteins:**

A 25 $\mu$M solution of the diazonium salt was prepared by mixing the aniline substrate (12.5 $\mu$mol) with a solution of p-TsOH monohydrate (14 mg, 75 $\mu$mol) in MeOH (125 $\mu$L). Water (250 $\mu$L) was added followed by a solution of NaNO$_2$ (3.35 mg, 50 $\mu$mol) in water (125 $\mu$L). The mixture was allowed to stir for 15 min at ambient temperature before use. The conversion of the reaction could be easily checked by LC-MS analysis.

An Eppendorf tube was charged with a solution of protein (0.05 $\mu$mol) in pH 7.0 buffer (500 $\mu$L, 100 mM NaH$_2$PO$_4$) and the freshly prepared solution of diazonium salt (20 $\mu$L, 0.5 $\mu$mol) was added. The reaction was left standing for 2 h at ambient temperature. The reaction mixture was then filtered through a Nap-5 column (illustra Nap-5, GE-Healthcare) and the resulting protein solution was analyzed by ESI-MS. ESI samples were prepared by mixing 50 $\mu$L of the protein solution with 50 $\mu$L of a 0.1 % formic acid stock solution (75% MeCN, 25% H$_2$O, 0.1 % HCO$_2$H).

**ESI-MS conditions:**

The mass spectrometry was performed on an ESI-Q-TOF system (maXis, Bruker Daltonics, Germany) coupled with an Agilent 1200 system (Agilent Ltd., Germany). The MS instrument was operated in wide pass quadrupole mode, for MS experiments, with the TOF data being collected between m/z 100-5000 with low-collision energy of 10 eV. The optimized source conditions were drying gas 8.0 l/h (nitrogen 99.99 % purity) at a temperature of 200°C, nebulizer pressure 1.6 bar, capillary and endplate voltages 500 and 4500 V, respectively, TOF flight tube voltage 9870 V, reflection voltage 1999 V, pusher voltage 1642 V and MCP detector voltage 1554 V. The resolving power of the instrument was around 35’000 with 2.5 Hz spectra rate. The ESI-TOF mass spectrometer was calibrated routinely for flow injection analysis (FIA) in the positive electrospray ionization mode using Agilent-ESI-TOF tuning mix on the quadratic algorithmic mode.

Further data processing was carried out using Data Analysis 4.0 software (Bruker Daltonics, Germany) in combination with the deconvolution algorithm MaxEnt (Maximum Entropy, Spectrum Square Associates Inc.).
To a solution of calcium pantothenate (50 mg, 0.23 mmol) in CH$_2$Cl$_2$ (2 mL) was added amine 1158 (118 mg, 0.30 mmol), EDC (53 mg, 0.27 mmol), HOBT (42 mg, 0.27 mmol) and diisopropyl ethylamine (60 μL, 0.34 mmol). The reaction was stirred overnight. The solution was directly subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 10:1 → 5:1) and preparative TLC (CH$_2$Cl$_2$/MeOH 7:1) to give amide 1193 (27 mg, 0.05 mmol, 20%).

R$_f$ 0.50 (5:1, CH$_2$Cl$_2$/MeOH); [α]$_D$$_{22.4}^+$ +15.08 (c 1.35, CHCl$_3$); $^1$H-NMR (400 MHz, CDCl$_3$): δ 7.85 (d, J = 8.3 Hz, 1H), 7.46-7.39 (m, 2H, N$_H$), 7.17 (d, J = 1.5 Hz, 1H), 6.96 (dd, J = 8.3, 1.6 Hz, 1H), 6.61 (t, J = 5.3 Hz, 1H, N$_H$), 6.08 (bs-s, 2H, NH$_2$), 4.41 (bs-s, 1H, O$_H$), 3.98 (s, 1H), 3.87 (s, 3H), 3.67-3.56 (m, 9H), 3.56-3.42 (m, 10H), 3.27 (p, J = 6.3 Hz, 2H), 2.36 (t, J = 6.0 Hz, 2H), 1.87 (t, J = 5.7 Hz, 2H), 1.68 (p, J = 6.3 Hz, 2H), 0.98 (s, 3H), 0.90 (s, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 173.7, 171.4, 168.1, 166.9, 150.7, 139.5, 131.6, 115.6, 113.9, 112.3, 77.6, 70.9, 70.7, 70.2, 70.1, 69.9, 69.9, 69.8, 51.7, 39.3, 39.0, 37.7, 35.8, 35.3, 28.9, 28.8, 21.6, 20.4; IR ν$_{max}$ (film)/cm$^{-1}$: 3343, 2873, 1696, 1647, 1542, 1439, 1312, 1247, 1192, 1104; HRMS (ESI) m/z calculated for C$_{28}$H$_{47}$N$_4$O$_{10}$ ([M+H]$^+$) 599.3287, found 599.3286.

To a solution of D-biotin (50 mg, 0.21 mmol) in CH$_2$Cl$_2$ (2 mL) was added amine 1158 (106 mg, 0.27 mmol), EDC (47 mg, 0.25 mmol), HOBT (38 mg, 0.25 mmol) and diisopropyl ethylamine (54 μL, 0.31 mmol). The reaction was stirred overnight. The solution was directly subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to give amide 1194 (106 mg, 0.17 mmol, 83%).

R$_f$ 0.14 (9:1, CH$_2$Cl$_2$/MeOH); [α]$_D$$_{22.3}^+$ +22.76 (c 1.00, CH$_3$OH); $^1$H-NMR (400 MHz, CD$_3$OD): δ 7.80 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 1.6 Hz, 1H), 6.89 (dd, J = 8.4, 1.7 Hz, 1H), 4.45 (dd, J = 7.7, 4.6 Hz, 1H), 4.25 (dd, J = 7.8, 4.4 Hz, 1H), 3.82 (s, 3H), 3.61-3.48 (m, 10H), 3.46-3.39 (m, 4H), 3.22-3.12 (m, 5H), 2.87 (dd, J = 12.7, 4.9 Hz, 1H), 2.66 (d, J = 12.7 Hz, 1H), 2.15 (t, J = 7.4 Hz, 2H), 1.83 (p, J = 6.4 Hz, 2H), 1.74-1.47 (m, 6H); $^{13}$C-NMR (100 MHz, CD$_3$OD): δ 175.8, 169.5, 169.3, 165.9, 152.5, 140.9, 132.5, 116.7, 114.4, 112.8, 71.4, 71.4, 71.2, 71.1, 70.3, 69.9, 63.3, 61.5, 57.0, 52.2, 43.8, 41.1, 38.7, 36.8, 30.4, 30.3, 29.8, 29.5, 26.9; IR ν$_{max}$ (film)/cm$^{-1}$: 3298, 2941, 1695, 1644, 1543, 1438, 1312, 1246, 1109; HRMS (ESI) m/z calculated for C$_{28}$H$_{46}$N$_5$O$_8$S ([M+H]$^+$) 624.3062, found 624.3059.
To a solution of hexynoic acid (20 μL, 0.18 mmol) in CH₂Cl₂ (2 mL) was added amine 1158 (92 mg, 0.23 mmol), EDC (41 mg, 0.21 mmol), HOBt (33 mg, 0.21 mmol) and diisopropyl ethylamine (47 μL, 0.27 mmol). The reaction was stirred over night. The solution was directly subjected to flash column chromatography (CH₂Cl₂/MeOH 20:1) to give amide 1196 (76 mg, 0.16 mmol, 87%).

R<sub>f</sub> 0.45 (9:1, CH₂Cl₂/MeOH); <sup>1</sup>H-NMR (400 MHz, CDCl₃): δ 7.83 (d, J = 8.3 Hz, 1H), 7.28 (bs-s, 1H, NH), 7.15 (d, J = 1.6 Hz, 1H), 6.95 (dd, J = 8.3, 1.7 Hz, 1H), 6.25 (bs-s, 1H, NH), 5.98 (bs-s, 2H, NH₂), 3.84 (s, 3H), 3.67-3.57 (m, 8H), 3.54-3.48 (m, 4H), 3.45 (t, J = 5.9 Hz, 2H), 2.24 (t, J = 7.4 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.88-1.76 (m, 4H), 1.69 (p, J = 6.2 Hz, 2H); <sup>13</sup>C-NMR (100 MHz, CDCl₃): δ 172.1, 168.0, 166.5, 150.5, 139.6, 131.4, 115.4, 113.9, 112.1, 83.6, 70.8, 70.2, 70.1, 69.9 (2C), 69.7, 69.0, 51.6, 39.1, 37.5, 35.0, 29.0, 28.7, 24.2, 17.8; IR ν<sub>max</sub> (film)/cm⁻¹: 3458, 3302, 2948, 2869, 1695, 1644, 1619, 1536, 1437, 1310, 1243, 1191, 1100; HRMS (ESI) m/z calculated for C₂₅H₃₈N₃O₇ ([M+H]⁺) 492.2704, found 492.2703.

To a solution of abscisic acid (50 mg, 0.19 mmol) in CH₂Cl₂ (2 mL) was added amine 1158 (98 mg, 0.25 mmol), EDC (44 mg, 0.23 mmol), HOBt (35 mg, 0.23 mmol) and diisopropyl ethylamine (50 μL, 0.28 mmol). The reaction was stirred over night. The solution was directly subjected to flash column chromatography (CH₂Cl₂/MeOH 20:1) to give amide 1195 (115 mg, 0.18 mmol, 94%).

R<sub>f</sub> 0.45 (9:1, CH₂Cl₂/MeOH); <sup>1</sup>H-NMR (400 MHz, CDCl₃): δ 7.86 (d, J = 16.1 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H) 7.31 (t, J = 5.1 Hz, 1H, NH), 7.14 (d, J = 1.5 Hz, 1H), 6.92 (dd, J = 8.3, 1.6 Hz, 1H), 6.47 (t, J = 5.5 Hz, 1H, NH), 6.03 (bs-s, 2H, NH₂), 5.99 (d, J = 16.1 Hz, 1H), 5.83 (s, 1H), 5.59 (s, 1H), 3.81 (s, 3H), 3.63-3.54 (m, 8H), 3.51-3.40 (m, 6H), 3.28 (q, J = 6.3 Hz, 2H), 3.20 (bs-s, 1H, OH), 2.40 (d, J = 17.0 Hz, 1H), 2.20 (d, J = 17.0 Hz, 1H), 1.89-1.78 (m, 8H), 1.68 (p, J = 6.1 Hz, 2H), 1.02 (s, 3H), 0.93 (s, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl₃): δ 198.0, 167.9, 166.6, 166.1, 163.5, 150.5, 144.0, 139.5, 134.6, 131.3, 128.2, 126.4, 121.7, 115.4, 113.8, 112.0, 79.3, 70.6, 70.1, 69.9, 69.8, 69.7, 69.6, 51.5, 49.7, 41.4, 38.9, 37.3, 28.9, 28.6, 24.2, 23.0, 20.8, 18.9; IR ν<sub>max</sub> (film)/cm⁻¹: 3458, 3344, 2949, 2870, 1694,
1243, 1620, 1597, 1534, 1310, 1243, 1101; **HRMS (ESI) m/z** calculated for C\textsubscript{34}H\textsubscript{50}N\textsubscript{3}O\textsubscript{9} ([M+H]+) 644.3542, found 644.3536.

![Chemical Structure](image)

To a solution of acid 1151 (100 mg, 0.19 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (2 mL) was added lincomycin (92 mg, 0.23 mmol), DCC (43 mg, 0.21 mmol) and triethylamine (53 μL, 0.38 mmol). The mixture was stirred overnight before the solvent was removed. The residue was purified by flash column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 20:1) to give a mixture of regioisomeric inseparable nitroarene products (50 mg, 55 μmol, 29%).

To a solution of this nitroarene (50 mg, 55 μmol) in MeOH (2 mL) was added Pd/C (5 mg, 10wt% Pd). The reaction was set under a hydrogen atmosphere (balloon) and the mixture was stirred for 1 h. The suspension was filtered over a pad of celite and the solvent was removed. The crude aniline (48 mg, 55 μmol, 99%) was used without further purification.

R<sub>f</sub> 0.29 (9:1, CH\textsubscript{2}Cl\textsubscript{2}/MeOH); **1H-NMR**; as the product was obtained as a mixture of isomers (see main text), characterization by NMR proved difficult. 1D and 2D NMR spectra are given in section 25. **13C-NMR** (100 MHz, CD\textsubscript{3}OD): δ 174.4, 169.3, 163.4, 163.0, 152.6, 140.9, 132.5, 119.5, 116.7, 114.4, 113.0, 89.9, 72.0, 71.5, 71.2, 71.1, 70.6, 70.4, 70.3, 70.0, 69.8, 69.5, 67.7, 63.5, 55.8, 52.1, 47.8, 41.6, 38.8, 38.6, 38.1, 36.8, 30.3, 22.5, 22.4, 18.6, 14.5, 13.9, 13.6, 9.2; **IR ν\textsubscript{max}** (film)/cm\textsuperscript{-1}: 3356, 2930, 2877, 1671, 1554, 1440, 1248, 1200, 1184, 1131; **HRMS** (ESI) m/z calculated for C\textsubscript{41}H\textsubscript{68}N\textsubscript{5}O\textsubscript{12}S ([M+H]+) 886.4478, found 886.4471.

![Chemical Structure](image)

To a solution of gibberellic acid (50 mg, 0.14 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (2 mL) was added amine 1158 (75 mg, 0.19 mmol), EDC (33 mg, 0.17 mmol), HOBt (27 mg, 0.17 mmol) and diisopropyl ethylamine (38 μL, 0.22 mmol). The reaction was stirred overnight. The solution was directly subjected to flash column chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 20:1) to give amide 1198 (102 mg, 0.14 mmol, 97%).
Experimental Part

Rf 0.20 (9:1, CH₂Cl₂/MeOH); [α]D²² +41.24 (c 1.00, CH₃OH); ¹H-NMR (400 MHz, CD₃OD): δ 7.88 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 1.6 Hz, 1H), 6.95 (dd, J = 8.4, 1.7 Hz, 1H), 6.39 (d, J = 9.4 Hz, 1H), 5.90 (dd, J = 9.3, 3.6 Hz, 1H), 5.22 (s, 1H), 4.95 (s, 1H), 4.03 (d, J = 3.5 Hz, 1H), 3.90 (s, 3H), 3.70-3.60 (m, 8H), 3.59-3.47 (m, 6H), 3.37-3.27 (m, 3H), 2.65 (d, J = 10.2 Hz, 1H), 2.30-2.18 (m, 2H), 2.06-1.86 (m, 6H), 1.85-1.68 (m, 5H), 1.25 (s, 3H); ¹³C-NMR (100 MHz, CD₃OD): δ 181.3, 173.4, 169.6, 169.3, 158.2, 152.5, 140.9, 134.1, 133.2, 132.5, 116.7, 114.3, 112.9, 107.3, 92.8, 79.4, 78.7, 71.5, 71.4, 71.2, 70.6, 70.3, 69.7, 55.0, 54.2, 53.5, 52.1, 52.0, 51.6, 46.0, 44.5, 39.7, 38.8, 37.8, 30.5, 30.3, 18.0, 15.0; IR νmax (film)/cm⁻¹: 3356, 2936, 2874, 1756, 1641, 1621, 1542, 1439, 1312, 1246, 1101, 1046; HRMS (ESI) m/z calculated for C₃₂H₅₂N₃O₁₁ ([M+H]+) 726.3596, found 726.3592.

To a solution of cholic acid (50 mg, 0.12 mmol) in CH₂Cl₂ (2 mL) was added amine 1158 (63 mg, 0.16 mmol), EDC (28 mg, 0.15 mmol), HOBt (23 mg, 0.15 mg) and diisopropyl ethylamine (32 μL, 0.18 mmol). The reaction was stirred over night. The reaction was quenched by addition of sat. NaHCO₃. The phases were separated and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed and the residue was purified by flash column chromatography (CH₂Cl₂/MeOH 20:1) to give aniline 1199 (92 mg, 0.12 mmol, 95%).

Rf 0.29 (9:1, CH₂Cl₂/MeOH); [α]D²² +9.24 (c 2.40, CHCl₃); ¹H-NMR (400 MHz, d₆-DMSO): δ 8.40 (bs-t, J = 5.5 Hz, 1H, NH), 7.75-7.70 (m, 2H), 7.21 (d, J = 1.6 Hz, 1H), 6.90 (dd, J = 8.4, 1.6 Hz, 1H), 6.75 (bs-s, 2H, NH₂), 4.15-4.05 (bs-m, 2H, OH), 3.99 (bs-d, J = 2.7 Hz, 1H, OH), 3.80 (s, 3H), 3.77 (bs-s, 1H), 3.60 (bs-s, 1H), 3.54-3.43 (m, 8H), 3.39-3.24 (m, 6H), 3.21-3.17 (m, 2H), 3.05 (q, J = 6.3 Hz, 2H), 2.26-1.91 (m, 4H), 1.82-1.56 (m, 11H), 1.48-1.11 (m, 10H), 0.99-0.89 (m, 4H), 0.88-0.78 (m, 4H), 0.57 (s, 3H); ¹³C-NMR (100 MHz, d₆-DMSO): δ 172.5, 167.4, 165.9, 151.0, 139.8, 130.7, 115.8, 112.8, 110.2, 71.0, 70.4, 69.8, 69.7, 69.6, 69.5, 68.3, 68.1, 66.2, 51.6, 48.6, 46.2, 45.7, 41.5, 41.4, 39.5, 36.7, 35.7, 35.3, 35.1, 34.9, 34.4, 32.6, 31.8, 30.4, 29.4, 29.3, 28.6, 27.3, 26.2, 22.8, 22.6, 17.1, 12.3; IR νmax (film)/cm⁻¹: 3364, 2936, 2870, 1686, 1621, 1553, 1440, 1247, 1203, 1138; HRMS (MALDI) m/z calculated for C₃₈H₇₀N₃O₁₀ ([M+H]+) 788.5056, found 788.5055.
To a solution of deacetoxy colchicine\(^\text{766}\) (6 mg, 17 μmol) in THF (1 mL) was added NHS-ester 1153 (10 mg, 17 μmol). The mixture was allowed to stir for 24 h. The solvent was removed and the residue as subjected to flash column chromatography (CH\(_2\)Cl\(_2\)/MeOH 20:1) to give amide 1200 (12 mg, 14 μmol, 85%).

R\(_f\) 0.32 (9:1, CH\(_2\)Cl\(_2\)/MeOH); [α]\(_D\)\(^{24.1°}\) -9.12 (c 1.20, CHCl\(_3\) ); \(^1\)H-NMR (400 MHz, CDCl\(_3\)): δ 7.82 (d, \(J = 8.3\) Hz, 1H), 7.65 (d, \(J = 6.7\) Hz, 1H, NH), 7.43 (t, \(J = 5.1\) Hz, 1H, NH), 7.38 (s, 1H), 7.27 - 7.22 (m, 1H), 7.17 (d, \(J = 1.5\) Hz, 1H), 6.94 (dd, \(J = 8.3, 1.6\) Hz, 1H), 6.78 (d, \(J = 10.9\) Hz, 1H), 6.62 (t, \(J = 5.4\) Hz, 1H, NH), 6.50 (s, 1H), 6.05 (bs-s, 2H, NH\(_2\)), 4.54 (dt, \(J = 12.7, 6.6\) Hz, 1H), 3.94 (s, 3H, 3.88 (s, 3H), 3.85 - 3.55 (m, 11H), 3.54 - 3.42 (m, 6H), 3.33 - 3.27 (m, 2H), 2.55 - 2.32 (m, 6H), 2.20 (tt, \(J = 12.8, 6.5\) Hz, 1H), 1.89 - 1.78 (m, 3H), 1.69 (p, \(J = 6.1\) Hz, 2H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): δ 179.4, 172.1, 171.9, 168.0, 166.8, 163.9, 153.4, 151.2, 151.1, 150.7, 141.5, 139.6, 136.3, 134.9, 134.2, 131.4, 130.8, 125.6, 115.6, 113.8, 112.1, 112.0, 107.3, 70.6, 70.3, 70.1, 69.9, 69.9, 69.6, 61.4, 61.3, 56.2, 56.1, 52.2, 51.6, 38.8, 37.8, 36.5, 31.6, 31.4, 29.8, 28.8 (2C); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\): 3457, 3303, 2936, 2868, 1648, 1617, 1589, 1095, 1018; HRMS (ESI) \(m/z\) calculated for C\(_{43}\)H\(_{57}\)N\(_4\)O\(_{13}\) ([M+H]\(^+\)) 837.3917, found 837.3911.

To a solution of artesunate (100 mg, 0.26 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was added amine 1158 (134 mg, 0.34 mmol), EDC (60 mg, 0.31 mmol), HOBt (48 mg, 0.31 mmol) and diisopropyl ethylamine (68 μL, 0.39 mmol). The reaction was stirred over night. The solution was directly subjected to flash column chromatography (CH\(_2\)Cl\(_2\)/MeOH 20:1) to give amide 1201 (172 mg, 0.23 mmol, 87%).

R\(_f\) 0.25 (9:1, CH\(_2\)Cl\(_2\)/MeOH); [α]\(_D\)\(^{23.8°}\) -3.69 (c 1.00, CHCl\(_3\) ); \(^1\)H-NMR (400 MHz, CDCl\(_3\)): δ 7.80 (d, \(J = 8.3\) Hz, 1H), 7.28 (t, \(J = 5.2\) Hz, 1H, NH), 7.14 (d, \(J = 1.5\) Hz, 1H), 6.94 (dd, \(J = 8.3, 1.6\) Hz, 1H), 6.50 (t, \(J = 5.3\) Hz, 1H, NH), 6.02 (bs-s, 2H, NH\(_2\)), 5.66 (d, \(J = 9.9\) Hz, 1H), 5.30 (s, 1H), 3.81 (s, 3H), 3.64 - 3.54 (m, 8H), 3.51 - 3.41 (m, 6H), 3.26 (q, \(J = 5.7\) Hz, 2H), 2.72 (dt, \(J = 17.4, 7.4\) Hz, 1H), 2.59 (dt, \(J = 17.5, 6.6\) Hz, 1H), 2.51 - 2.25 (m, 4H), 1.96 (dt, \(J = 14.5, 4.3\) Hz, 1H), 1.86 - 1.78 (m, 3H), 1.70 - 1.59 (m, 4H), 1.53 (dt, \(J = 13.8, 4.3\) Hz, 1H), 1.44 - 1.31 (m, 4H), 1.28 - 1.15 (m, 3H), 0.97 - 0.86 (m,

4H), 0.77 (d, J = 7.1 Hz, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 171.8, 171.0, 167.9, 166.6, 150.5, 139.6, 131.3, 115.4, 113.8, 111.9, 104.3, 92.0, 91.3, 80.0, 70.3, 70.2, 70.0, 69.8, 69.8, 69.6, 51.5, 51.3, 45.0, 38.6, 37.6, 37.0, 36.1, 33.9, 31.6, 30.4, 29.4, 28.7 (2C), 25.7, 24.4, 21.8, 20.0, 11.8; IR ν$_{max}$ (film)/cm$^{-1}$: 3465, 3347, 2926, 2872, 1750, 1695, 1537, 1311, 1245, 1130, 1100, 1035, 1017; HRMS (ESI) m/z calculated for C$_{38}$H$_{58}$N$_3$O$_{13}$ ([M+H]$^+$) 764.3964, found 764.3947.

To a solution of penicillin G potassium salt (100 mg, 0.27 mmol) in CH$_2$Cl$_2$ (2 mL) was added amine 1158 (139 mg, 0.35 mmol), HATU (133 mg, 0.35 mmol), and diisopropyl ethylamine (140 μL, 0.81 mmol). The reaction was stirred overnight. The solution was directly subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to give amide 1203 (152 mg, 0.21 mmol, 79%).

R$_f$ 0.51 (9:1, CH$_2$Cl$_2$/MeOH); [α]$_D$$^{23.7}$ +98.6 (c 1.00, CHCl$_3$); $^1$H-NMR (400 MHz, CDCl$_3$, mixture of diastereomers, major peaks reported): δ 7.83 (d, J = 8.3 Hz, 1H), 7.36-7.10 (m, 9H), 6.93 (dd, J = 8.3, 1.6 Hz, 1H), 6.38 (d, J = 9.2 Hz, 1H), 5.98 (bs-s, 2H, NH$_2$), 5.69 (dd, J = 9.2, 4.4 Hz, 1H), 5.36 (d, J = 4.4 Hz, 1H), 3.84 (s, 3H), 3.65-3.39 (m, 18H), 1.86-1.79 (2H), 1.72-1.65 (m, 2H), 1.57 (s, 3H), 1.43 (s, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$, mixture of diastereomers, all peaks reported): δ 175.8, 171.0, 170.5, 170.4, 168.0, 167.9, 167.05, 166.7, 150.6, 150.5, 139.6, 139.5, 134.8, 133.7, 131.4, 129.4, 129.3, 128.9, 128.8, 127.5, 127.0, 115.5, 115.5, 113.8, 112.1, 73.4, 72.1, 70.5, 70.4, 70.1, 70.0, 69.9, 69.8, 69.8, 69.7, 69.6, 66.3, 65.6, 64.6, 58.4, 57.3, 57.1, 55.2, 52.5, 51.6, 43.2, 43.1, 38.8, 37.6, 37.5, 29.1, 29.0, 28.8, 28.6, 26.5, 26.4; IR ν$_{max}$ (film)/cm$^{-1}$: 3342, 2871, 1783, 1652, 1619, 1537, 1439, 1311, 1246, 1107; HRMS (ESI) m/z calculated for C$_{35}$H$_{48}$N$_5$O$_9$S ([M+H]$^+$) 714.3167, found 714.3162.

To a solution of verbenol (100 mg, 0.66 mmol) in THF (2 mL) was added succinic anhydride (66 mg, 0.66 mmol) and triethylamine (0.14 mL, 0.99 mmol). The solution was warmed to 60 °C and stirred for 24 h. The solvent was removed and the residue was directly subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to the corresponding acid (40 mg, 0.16 mmol, 24%).

To a solution of this acid (40 mg, 0.16 mmol) in CH$_2$Cl$_2$ (2 mL) was added amine 1158 (82 mg, 0.21 mmol), EDC (37 mg, 0.19 mmol), HOBt (29 mg, 0.19 mmol) and diisopropyl ethylamine (42 μL, 0.24
mmol). The reaction was stirred over night. The solution was directly subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to give amide 1204 (98 mg, 0.16 mmol, 98%).

$R_f$ 0.38 (9:1, CH$_2$Cl$_2$/MeOH); $[a]_b^{225}$ +21.15 (c 1.00, CHCl$_3$); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.82 (d, $J = 8.3$ Hz, 1H), 7.31 (t, $J = 5.1$ Hz, 1H, NH), 7.14 (dd, $J = 8.3$, 1.6 Hz, 1H), 6.94 (d, $J = 8.3$, 1.6 Hz, 1H), 6.42 (t, $J = 5.1$ Hz, 1H, NH), 6.02 (bs-s, 2H, NH$_2$), 5.45-5.40 (m, 1H), 5.27-5.22 (m, 1H), 3.84 (s, 3H), 3.66-3.56 (m, 8H), 3.55-3.43 (m, 6H), 3.28 (q, $J = 6.3$ Hz, 2H), 2.59 (t, $J = 7.1$ Hz, 2H), 2.45-2.39 (m, 3H), 2.27-2.22 (m, 1H), 1.94 (t, $J = 5.9$ Hz, 1H), 1.85 (p, $J = 5.7$ Hz, 2H), 1.72-1.65 (m, 5H), 1.32 (d, $J = 9.2$ Hz, 1H), 1.28 (s, 3H), 0.95 (s, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 172.7, 171.4, 168.0, 166.6, 149.6, 139.6, 131.4, 115.5, 115.4, 113.8, 112.0, 75.6, 70.6, 70.2, 70.1, 69.9, 69.8, 69.6, 51.6, 47.5, 45.4, 39.5, 38.9, 37.6, 35.3, 30.9, 29.9, 28.7, 26.7, 22.6, 22.5; IR $\nu_{\text{max}}$ (film)/cm$^{-1}$: 3342, 2927, 1697, 1651, 1438, 1311, 1246, 1106; HRMS (ESI) $m/z$ calculated for C$_{33}$H$_{50}$N$_3$O$_9$ ([M+H]$^+$) 632.3542, found 632.3536.

To a solution of farnesol (222 mg, 1 mmol) in CH$_2$Cl$_2$ (2 mL) was added succinic anhydride (100 mg, 1 mmol) and triethylamine (0.28 mL, 2 mmol). The reaction was stirred over night. The solvent was removed and the residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to give the intermediate acid (206 mg, 0.64 mmol, 64%).

To a solution of this acid (206 mg, 0.64 mmol) in CH$_2$Cl$_2$ (2 mL) was added amine 1158 (305 mg, 0.77 mmol), EDC (147 mg, 0.77 mmol), HOBt (117 mg, 0.77 mg) and diisopropyl ethylamine (0.22 mL, 1.28 mmol). The reaction was stirred over night. The reaction was quenched by addition of sat. NaHCO$_3$. The phases were separated and the aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with brine and dried over MgSO$_4$. The solvent was removed and the residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to give amide 1205 (320 mg, 0.46 mmol, 71%).

$R_f$ 0.50 (9:1, CH$_2$Cl$_2$/MeOH); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.88 (d, $J = 8.3$ Hz, 1H), 7.31 (t, $J = 5.0$ Hz, 1H, NH), 7.19 (d, $J = 1.6$ Hz, 1H), 7.00 (dd, $J = 8.3$, 1.7 Hz, 1H), 6.39 (t, $J = 5.0$ Hz, 1H, NH), 6.04 (bs-s, 2H, NH$_2$), 5.36-5.30 (m, 1H), 5.14-5.07 (m, 2H), 4.63-4.55 (m, 2H), 3.89 (s, 3H), 3.72-3.61 (m, 8H), 3.60-3.48 (m, 6H), 3.33 (q, $J = 6.3$ Hz, 2H), 2.70-2.64 (m, 2H), 2.50-2.45 (m, 2H), 2.15-1.96
(m, 8H), 1.90 (p, J = 5.7 Hz, 2H), 1.76-1.71 (m, 2H), 1.71-1.67 (m, 6H), 1.63-1.59 (m, 6H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 173.1, 171.3, 168.1, 166.6, 150.6, 142.3, 139.7, 135.4, 131.5, 124.4, 124.3, 123.6, 118.1, 115.5, 113.9, 112.2, 70.8, 70.3, 70.1, 69.9, 69.7, 61.6, 51.7, 39.6, 39.0, 37.7, 30.9, 29.5, 29.0, 28.7, 26.7, 26.2, 25.7, 23.3, 17.7, 16.4, 16.0; IR $\nu_{max}$ (film)/cm$^{-1}$: 3461, 3336, 2921, 2867, 1733, 1697, 1648, 1620, 1539, 1311, 1245, 1108; HRMS (ESI) m/z calculated for C$_{50}$H$_{76}$N$_3$O$_{11}$ ([M+H]$^+$) 894.5474, found 894.5466.

To a solution of diosgenin (100 mg, 0.24 mmol) in THF (2 mL) was added succinic anhydride (24 mg, 0.24 mmol) and triethylamine (50 μL, 0.36 mmol). The solution was warmed to 60 °C and stirred for 24 h. The solvent was removed and the residue was directly subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to the corresponding acid (61 mg, 0.12 mmol, 49%).

To a solution of this acid (61 mg, 0.12 mmol) in CH$_2$Cl$_2$ (2 mL) was added amine 1158 (61 mg, 0.15 mmol), EDC (27 mg, 0.14 mmol), HOBt (22 mg, 0.14 mmol) and diisopropyl ethylamine (31 μL, 0.18 mmol). The reaction was stirred overnight. The solution was directly subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to give amide 1211 (88 mg, 0.10 mmol, 83%).

R$_f$ 0.34 (9:1, CH$_2$Cl$_2$/MeOH); $[\alpha]_{D}^{23,\nu}$ -45.74 (c 1.00, CH$_3$OH); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.83 (d, J = 8.3 Hz, 1H), 7.30 (t, J = 5.2 Hz, 1H, NH), 7.14 (d, J = 1.6 Hz, 1H), 6.95 (dd, J = 8.3, 1.7 Hz, 1H), 6.43 (t, J = 5.5 Hz, 1H, NH), 6.02 (bs-s, 2H, NH$_2$), 5.29 (d, J = 3.8 Hz, 1H), 4.52 (ddt, J = 11.6, 8.7, 4.1 Hz, 1H), 4.37 (q, J = 7.5 Hz, 1H), 3.84 (s, 3H), 3.67-3.56 (m, 8H), 3.55-3.41 (m, 7H), 3.34 (t, J = 10.9 Hz, 1H), 3.28 (q, J = 6.3 Hz, 2H), 2.59 (t, J = 6.9 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H), 2.29-2.22 (m, 2H), 1.99-1.90 (m, 2H), 1.88-1.35 (m, 19H), 1.29-1.21 (m, 1H), 1.18-1.02 (m, 3H), 0.98 (s, 3H), 0.96-0.88 (m, 4H), 0.78-0.72 (m, 6H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 172.4, 171.3, 168.0, 166.0, 150.6, 139.6, 139.5, 131.4, 122.2, 115.5, 113.8, 112.0, 109.2, 80.7, 74.1, 70.6, 70.2, 70.1, 69.9, 69.8, 69.6, 66.7, 62.0, 56.3, 51.6, 49.8, 41.5, 40.1, 39.6, 38.9, 37.9, 37.6, 36.8, 36.6, 31.9, 31.7, 31.3 (2C), 30.9, 30.2, 29.8, 28.9, 28.7 (2C), 27.6, 20.7, 19.2, 17.1, 16.2, 14.4; IR $\nu_{max}$ (film)/cm$^{-1}$: 3460, 3338, 2948, 1733, 1697, 1647, 1621, 1544, 1245, 1175, 1109, 1080, 1052; HRMS (ESI) m/z calculated for C$_{50}$H$_{76}$N$_3$O$_{11}$ ([M+H]$^+$) 894.5474, found 894.5466.
To a solution of tosylate S46 (250 mg, 0.26 mmol) in MeCN (10 mL) was added amine 1158 (102 mg, 0.26 mmol). The reaction was stirred over night. The solution was directly subjected to flash column chromatography (CH$_2$Cl$_2$/MeOH 20:1) to give aniline 1208 (77 mg, 0.06 mmol, 25%) along with reisolated starting material.

R$_f$ 0.42 (9:1, CH$_2$Cl$_2$/MeOH); $^1$H-NMR (400 MHz, CDCl$_3$): δ 10.74 (bs-s, 1H), 8.99 (bs-s, 1H), 7.83 (d, $J = 8.3$ Hz, 1H), 7.75 (s, 1H), 7.32 (t, $J = 5.3$ Hz, 1H), 7.15 (s, 1H), 6.97 (d, $J = 8.1$ Hz, 1H), 6.81 (dd, $J = 15.4$, 11.1 Hz, 1H), 6.31 (d, $J = 10.7$ Hz, 1H), 6.08 (d, $J = 12.5$ Hz, 1H), 5.99 (bs-s, 2H), 5.86 (dd, $J = 15.8$, 4.7 Hz, 1H), 5.14 (d, $J = 9.9$ Hz, 1H), 5.03 (dd, $J = 12.4$, 5.7 Hz, 1H), 4.04 (d, $J = 4.6$ Hz, 1H), 3.92 (d, $J = 8.3$ Hz, 1H), 3.84 (s, 3H), 3.66-3.49 (m, 14H), 3.38 (d, $J = 5.1$ Hz, 1H), 3.22-3.16 (m, 4H), 3.05 (s, 3H), 2.97 (dd, $J = 8.8$, 4.0 Hz, 1H), 2.58-2.51 (m, 4H), 2.43 (dd, $J = 12.7$, 6.9 Hz, 1H), 2.08-1.97 (m, 9H), 1.90-1.82 (m, 4H), 1.78-1.67 (m, 5H), 1.41-1.32 (m, 1H), 1.01 (d, $J = 6.8$ Hz, 1H), 0.88 (d, $J = 6.9$ Hz, 3H), 0.49 (d, $J = 6.6$ Hz, 3H), 0.18 (d, $J = 6.9$ Hz, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 191.6, 182.1, 181.0, 172.4, 171.4, 168.0, 167.5, 166.5, 156.9, 150.6, 142.6, 141.8, 140.5, 139.7, 137.3, 133.1, 131.4, 129.3, 128.9, 124.9, 120.6, 117.7, 115.4, 114.0, 113.8, 112.1, 109.1, 107.2, 107.1, 77.8, 74.4, 71.1, 70.9, 70.2, 70.2, 70.0, 70.0, 68.4, 57.2, 53.9 (2C), 51.6, 50.5 (2C), 45.9, 44.8, 39.3, 39.1, 38.6, 37.1, 32.9, 30.6, 28.6, 22.6, 21.4, 20.8, 20.8, 17.2, 12.0, 11.9, 8.7, 8.5; HRMS (ESI) m/z calculated for C$_{62}$H$_{86}$N$_7$O$_{17}$ ([M+H]$^+$) 1200.6075, found 1200.6057.

Appendix

24.1. NOE Correlation Analyses

24.1.1. NOE Analysis for 498 (500 MHz steady-state)

a) Irradiation of C(6)-H

![Chemical shifts diagram with annotations C(6)-H and C(3)-Hα]
b) Irradiation of C(5)-H

NOE correlations for 498

NOE correlations (only diagnostic correlations shown)
24.1.2. NOE Analysis for 543 (500 MHz steady-state)

a) Irradiation of OCH$_2$Ph
b) Irradiation of C(14)-H
c) Irradiation of C(16)-H

NOE correlations for 543

NOE correlations (only diagnostic correlations shown)
24.1.3. NOE Analysis for S21 (500 MHz steady-state)

a) Irradiation of C(14)-H
b) Irradiation of C(16)-H

NOE correlations for S21

NOE correlations (only diagnostic correlations shown)
24.1.4. NOE Analysis for 644 (500 MHz steady-state)

a) Irradiation of C(3)-H

![Diagram showing NOE analysis for 644 (500 MHz steady-state)]
b) Irradiation of C(14)-H

C(14)-H

C(16)-H

ppm
c) Irradiation of C(16)-H

NOE correlations for 644
24.1.5. NOE Analysis for S33 (500 MHz steady-state)

a) Irradiation of C(5)-H

NOE correlations for S33:

NOE correlations (only diagnostic correlations shown)
24.1.6. NOE Analysis for 671 (500 MHz steady-state)

a) Irradiation of C(6)-H₂

NOE correlations for 671:

NOE correlations (only diagnostic correlations shown)
24.1.7. NOE Analysis for 727a (500 MHz steady-state)

a) Irradiation of C(2)-H
b) Irradiation of C(14)-H
c) Irradiation of C(7)-H

NOE analysis for 727a

NOE correlations (only diagnostic correlations shown)
24.1.8. NOE Analysis for 727b (500 MHz steady-state)

a) Irradiation of C(14)-H
b) Irradiation of C(7)-H

NOE analysis for 727b

NOE correlations (only diagnostic correlations shown)
24.1.9. NOE Analysis for 733 (500 MHz NOESY)

NOE correlations for 733 (only diagnostic correlations shown)
24.1.10. NOE Analysis for 819 (600 MHz NOESY)

NOE correlations for 819 (only diagnostic correlations shown)
24.1.11. NOE Analysis for 820 (600 MHz NOESY)

NOE correlations for 820 (only diagnostic correlations shown)
24.1.12. NOE Analysis for 745 (600 MHz NOESY)

NOE correlations for 745 (only diagnostic correlations shown)
24.2. X-ray Crystallographic Data

24.2.1. Crystal Structure for 151

CCDC deposition number  CCDC 785240
Chemical formula  C_{17}H_{20}N_{4}O_{4}
Formula weight  344.371
Temperature  223
Wavelength  0.71073 Å
Crystal size  0.22 x 0.18 x 0.14 mm
Crystal habit  clear colourless cube
Crystal system  Orthorhombic
Space group  P2_12_12_1
Unit cell dimensions
\[ a = 5.68260 (10) \text{ Å} \quad \alpha = 90^\circ \]
\[ b = 14.5420 (4) \text{ Å} \quad \beta = 90^\circ \]
\[ c = 20.1468 (7) \text{ Å} \quad \gamma = 90^\circ \]
Volume  1664.86 (8) Å³
\( Z = 4 \)
Density (calculated)  1.374 g/cm³
Absorption coefficient  0.100 mm⁻¹
F(000)  728

Table 1. Fractional atomic coordinates and equivalent isotropic thermal parameters (Å²) of 151

\[ U_{eq} = 1/3 \sum_{ij} U_{ij} a_i a_j \cdot \]

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<th>x</th>
<th>y</th>
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<td>-0.37564 (13)</td>
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Table 2. Anisotropic displacement parameters (Å$^2$) for 151
Table 3. Geometric parameters (Å, °) for 151

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C1—O7—C4 96.83 (17) C21—C20—C25 118.4 (2)
C5—O8—C6 60.76 (15) C21—C20—C19 120.5 (2)
N13—N12—C11 114.6 (2) C25—C20—C19 121.2 (2)
N14—N13—N12 173.8 (3) C22—C21—C20 121.7 (3)
C15—N17—C18 123.3 (2) C23—C22—C21 120.3 (3)
O7—C1—C6 102.03 (18) C22—C23—C24 119.5 (3)
O7—C1—C2 102.04 (18) C23—C24—C25 120.0 (3)
C6—C1—C2 107.68 (19) C20—C25—C24 120.1 (3)
O9—C2—C10 109.83 (19) C2—O9—H9 109 (2)
O9—C2—C1 105.96 (19) C15—N17—H17 117 (2)
C10—C2—C1 116.84 (19) C18—N17—H17 119 (2)
O9—C2—C3 113.06 (19) O7—C1—H1 114.1 (17)
C10—C2—C3 111.04 (19) C6—C1—H1 117.1 (17)
C1—C2—C3 99.83 (19) C2—C1—H1 112.4 (17)
C4—C3—C2 102.5 (2) C4—C3—H3A 109.9 (18)
C4—C3—C4 102.50 (19) C2—C3—H3A 110.2 (19)
O7—C4—C5 102.75 (19) C4—C3—H3B 110.8 (16)
O7—C4—C3 105.28 (19) C2—C3—H3B 110.7 (15)
O8—C5—C6 59.67 (15) H3A—C3—H3B 112 (2)
O8—C5—C4 113.4 (2) O7—C4—H4 106.8 (18)
C6—C5—C4 102.9 (2) C5—C4—H4 120.1 (18)
O8—C6—C5 59.57 (16) C3—C4—H4 117.1 (18)
O8—C6—C1 113.53 (19) O8—C5—H5 111.4 (18)
C5—C6—C1 103.40 (19) C6—C5—H5 122.0 (18)
C11—C10—C2 114.2 (2) C4—C5—H5 128.0 (18)
N12—C11—C15 110.7 (2) O8—C6—H6 121.4 (15)
N12—C11—C10 111.0 (2) C5—C6—H6 129.3 (16)
C15—C11—C10 110.1 (2) C1—C6—H6 117.0 (15)
O16—C15—N17 122.9 (2) C11—C10—H10A 108.5 (14)
O16—C15—C11 119.0 (2) C2—C10—H10A 113.5 (14)
N17—C15—C11 118.1 (2) C11—C10—H10B 107.6 (16)
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C20—C19—C18 112.2 (2) H10A—C10—H10B 107 (2)
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<td>C18—C19—H19B</td>
<td>111.5 (17)</td>
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24.2.2. Crystal Structure for 225

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<td>Wavelength</td>
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<tr>
<td>Crystal size</td>
<td>0.135 x 0.03 x 0.003 mm</td>
</tr>
<tr>
<td>Crystal habit</td>
<td>clear colourless needle</td>
</tr>
<tr>
<td>Crystal system</td>
<td>triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>$a = 5.1153 (2)$ Å, $a = 97.565 (2)^\circ$</td>
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<tr>
<td></td>
<td>$b = 9.5704 (4)$ Å, $\beta = 94.525 (2)^\circ$</td>
</tr>
<tr>
<td></td>
<td>$c = 14.3843 (6)$ Å, $\gamma = 93.097 (2)^\circ$</td>
</tr>
<tr>
<td>Volume</td>
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<td>Density (calculated)</td>
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<tr>
<td>Absorption coefficient</td>
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<td>F(000)</td>
<td>278</td>
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Table 1. Fractional atomic coordinates and equivalent isotropic thermal parameters (Å$^2$) for 225

$$U_{eq} = \frac{1}{3\sum_i\sum_j} U_{ij} a_i^* a_j^* a_i a_j .$$

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<th>z</th>
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<td>0.36459 (19)</td>
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<tr>
<td>O17</td>
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<td>0.11819 (17)</td>
<td>-0.07722 (11)</td>
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<tr>
<td>O26</td>
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<td>0.04728 (14)</td>
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<tr>
<td>O37</td>
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<td>-0.4712 (2)</td>
<td>-0.04572 (15)</td>
<td>0.0486 (6)</td>
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<td>O39</td>
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<td>-0.2873 (2)</td>
<td>-0.11055 (14)</td>
<td>0.0450 (5)</td>
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<tr>
<td>N27</td>
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<td>-0.0991 (2)</td>
<td>0.03923 (14)</td>
<td>0.0234 (4)</td>
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Table 2. Anisotropic displacement parameters (Å²) for 225

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<td>-0.0024 (7)</td>
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<td>0.0000 (6)</td>
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<td>0.0038 (6)</td>
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<td>0.0054 (7)</td>
<td>0.0024 (7)</td>
<td>0.0370 (10)</td>
<td>0.0105 (8)</td>
<td>0.0469 (11)</td>
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<td>0.0010 (8)</td>
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### Table 3. Geometric parameters (Å, °) for 225

|     | O39   | N27   | C1    | C2    | C3    | C4    | C5    | C6    | C7    | C8    | C9    | C10   | C11   | C12   | C13   | C14   | C15   | C16   | C17   | C18   | C19   | C20   | C21   | C22   | C23   | C24   | C25   | C26   | C27   | C28   | C29   | C30   | C31   | C32   | C33   | C34   | C35   | C36   | C37   | C38   |
|-----|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|     | 0.0721 (14) | 0.0065 (10) | -0.0128 (10) | 0.0298 (10) | 0.0042 (8) | 0.0306 (10) | 0.0199 (9) | 0.0032 (7) | 0.0006 (7) | 0.0215 (9) | 0.0068 (8) | 0.0296 (10) | 0.0256 (10) | 0.0003 (9) | -0.0010 (9) | 0.0242 (12) | 0.0229 (9) | 0.0235 (11) | 0.0299 (12) | 0.0048 (10) | -0.0015 (10) | 0.0259 (12) | 0.0017 (10) | 0.0278 (12) | 0.0317 (11) | 0.0026 (9) | 0.0010 (9) | 0.0222 (11) | 0.0002 (9) | 0.0228 (11) | 0.0457 (14) | -0.0081 (11) | 0.0008 (11) | 0.0276 (13) | 0.0011 (10) | 0.0290 (13) | 0.0493 (15) | -0.0054 (11) | -0.0007 (11) | 0.0280 (13) | 0.0058 (10) | 0.0220 (12) | 0.0309 (11) | 0.0031 (10) | 0.0000 (9) | 0.0279 (12) | 0.0013 (9) | 0.0224 (11) | 0.0352 (13) | -0.0070 (11) | -0.0026 (10) | 0.0316 (14) | 0.0082 (11) | 0.0300 (13) | 0.0396 (14) | -0.0006 (11) | -0.0006 (10) | 0.0314 (14) | 0.0108 (11) | 0.0274 (13) | 0.0339 (13) | -0.0074 (11) | -0.0011 (11) | 0.0346 (14) | 0.0064 (11) | 0.0318 (13) | 0.0292 (12) | -0.0061 (10) | 0.0002 (10) | 0.0289 (13) | 0.0070 (10) | 0.0301 (13) | 0.0348 (13) | 0.0012 (12) | 0.0030 (11) | 0.0416 (16) | 0.0014 (12) | 0.0315 (14) | 0.0329 (13) | 0.0019 (12) | -0.0028 (11) | 0.0483 (17) | 0.0079 (13) | 0.0371 (15) | 0.0475 (15) | -0.0083 (12) | -0.0047 (12) | 0.0379 (16) | 0.0032 (11) | 0.0298 (14) | 0.0621 (19) | 0.0076 (14) | -0.0041 (14) | 0.0335 (15) | -0.0038 (12) | 0.0358 (15) | 0.0441 (14) | 0.0054 (12) | -0.0029 (12) | 0.0347 (14) | 0.0073 (12) | 0.0387 (15) | 0.0338 (13) | 0.0101 (11) | 0.0002 (10) | 0.0393 (15) | 0.0016 (11) | 0.0217 (12) | 0.0298 (11) | 0.0075 (10) | 0.0035 (9) | 0.0305 (12) | 0.0017 (9) | 0.0226 (11) | 0.0368 (13) | 0.0038 (11) | 0.0064 (10) | 0.0337 (14) | 0.0080 (11) | 0.0297 (13) | 0.0340 (13) | 0.0018 (12) | 0.0009 (11) | 0.0432 (15) | 0.0054 (12) | 0.0344 (14) | 0.0374 (13) | 0.0074 (12) | 0.0006 (11) | 0.0523 (17) | 0.0085 (12) | 0.0260 (13) | 0.0428 (14) | 0.0059 (12) | 0.0065 (11) | 0.0387 (15) | 0.0137 (12) | 0.0325 (13) | 0.0372 (13) | 0.0023 (11) | 0.0045 (11) | 0.0524 (14) | 0.0058 (10) | 0.0281 (13) | 0.0235 (10) | 0.0006 (9) | 0.0013 (8) | 0.0225 (11) | 0.0021 (8) | 0.0191 (10) | 0.0251 (11) | 0.0016 (10) | 0.0002 (9) | 0.0235 (11) | 0.0068 (9) | 0.0250 (11) | 0.0316 (12) | -0.0076 (10) | -0.0016 (10) | 0.0304 (13) | 0.0090 (10) | 0.0277 (12) | 0.0264 (11) | -0.0099 (10) | 0.0012 (10) | 0.0324 (13) | 0.0092 (10) | 0.0292 (12) | 0.0364 (13) | -0.0023 (12) | -0.0061 (11) | 0.0413 (16) | 0.0150 (12) | 0.0381 (15) | 0.0457 (16) | -0.0167 (15) | -0.0116 (14) | 0.061 (2) | 0.0197 (15) | 0.0418 (17) | 0.0572 (18) | -0.0274 (17) | 0.0021 (14) | 0.061 (2) | 0.0046 (15) | 0.0326 (15) | 0.0509 (17) | -0.0077 (16) | 0.0117 (14) | 0.062 (2) | -0.0012 (15) | 0.0370 (16) | 0.0347 (14) | -0.0020 (13) | 0.0112 (11) | 0.0530 (18) | 0.0069 (13) | 0.0361 (14) | 0.0426 (13) | 0.0038 (10) | 0.0008 (10) | 0.0237 (12) | 0.0059 (9) | 0.0257 (12) | 0.107 (3) | 0.0036 (17) | -0.0140 (18) | 0.0266 (15) | -0.0005 (13) | 0.0358 (17) |

Note: The table lists geometric parameters for 225, with entries indicating bond lengths and angles in Å and °, respectively. The values are given with uncertainties in parentheses.
<table>
<thead>
<tr>
<th>Bond</th>
<th>Distance (Å)</th>
</tr>
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<tr>
<td>C2—H2A</td>
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</tr>
<tr>
<td>C2—H2B</td>
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</tr>
<tr>
<td>C4—H4</td>
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</tr>
<tr>
<td>C5—H5</td>
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</tr>
<tr>
<td>C7—H7</td>
<td>0.99 (3)</td>
</tr>
<tr>
<td>C8—H8</td>
<td>0.94 (4)</td>
</tr>
<tr>
<td>C10—H10A</td>
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</tr>
<tr>
<td>C10—H10B</td>
<td>1.01 (4)</td>
</tr>
<tr>
<td>C12—H12</td>
<td>0.99 (4)</td>
</tr>
<tr>
<td>C13—H13</td>
<td>1.07 (4)</td>
</tr>
<tr>
<td>C14—H14</td>
<td>1.01 (4)</td>
</tr>
<tr>
<td>C15—H15</td>
<td>0.97 (5)</td>
</tr>
<tr>
<td>C16—H16</td>
<td>1.00 (4)</td>
</tr>
<tr>
<td>C18—H18A</td>
<td>1.01 (3)</td>
</tr>
<tr>
<td>C18—H18B</td>
<td>1.07 (4)</td>
</tr>
<tr>
<td>C20—H20</td>
<td>0.93 (3)</td>
</tr>
<tr>
<td>C6—O9—C10</td>
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<tr>
<td>C1—O17—C18</td>
<td>111.94 (17)</td>
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<tr>
<td>C36—O37—C38</td>
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<tr>
<td>C25—N27—C28</td>
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</tr>
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<td>O17—C1—C2</td>
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<tr>
<td>O17—C1—C25</td>
<td>110.90 (18)</td>
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<tr>
<td>C2—C1—C25</td>
<td>113.0 (2)</td>
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<tr>
<td>C3—C2—C1</td>
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<td>C8—C3—C4</td>
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<tr>
<td>C8—C3—C2</td>
<td>120.9 (2)</td>
</tr>
<tr>
<td>C4—C3—C2</td>
<td>121.3 (2)</td>
</tr>
<tr>
<td>C3—C4—C5</td>
<td>121.1 (2)</td>
</tr>
<tr>
<td>C6—C5—C4</td>
<td>120.6 (3)</td>
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<tr>
<td>O9—C6—C5</td>
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<tr>
<td>O9—C6—C7</td>
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<td>C5—C6—C7</td>
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<td>C6—C7—C8</td>
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<tr>
<td>C3—C8—C7</td>
<td>121.7 (3)</td>
</tr>
<tr>
<td>O9—C10—C11</td>
<td>109.0 (2)</td>
</tr>
<tr>
<td>C16—C11—C12</td>
<td>119.3 (2)</td>
</tr>
<tr>
<td>C16—C11—C10</td>
<td>120.1 (2)</td>
</tr>
<tr>
<td>C12—C11—C10</td>
<td>120.7 (2)</td>
</tr>
<tr>
<td>C13—C12—C11</td>
<td>120.5 (3)</td>
</tr>
<tr>
<td>C14—C13—C12</td>
<td>119.9 (3)</td>
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<tr>
<td>C15—C14—C13</td>
<td>119.8 (3)</td>
</tr>
<tr>
<td>C14—C15—C16</td>
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<td>C11—C16—C15</td>
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</tr>
<tr>
<td>O17—C18—C19</td>
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<tr>
<td>C20—C19—C18</td>
<td>120.4 (2)</td>
</tr>
<tr>
<td>C24—C19—C18</td>
<td>120.6 (2)</td>
</tr>
<tr>
<td>C19—C20—C21</td>
<td>120.3 (3)</td>
</tr>
<tr>
<td>C22—C21—C20</td>
<td>119.9 (3)</td>
</tr>
<tr>
<td>C23—C22—C21</td>
<td>120.5 (3)</td>
</tr>
<tr>
<td>C22—C23—C24</td>
<td>119.6 (3)</td>
</tr>
<tr>
<td>C23—C24—C19</td>
<td>120.7 (3)</td>
</tr>
<tr>
<td>O26—C25—N27</td>
<td>123.2 (2)</td>
</tr>
<tr>
<td>O26—C25—C1</td>
<td>122.1 (2)</td>
</tr>
<tr>
<td>N27—C25—C1</td>
<td>114.76 (19)</td>
</tr>
<tr>
<td>N27—C28—C36</td>
<td>109.61 (19)</td>
</tr>
<tr>
<td>N27—C28—C29</td>
<td>112.79 (19)</td>
</tr>
<tr>
<td>C36—C28—C29</td>
<td>108.38 (19)</td>
</tr>
<tr>
<td>C30—C29—C28</td>
<td>114.74 (18)</td>
</tr>
</tbody>
</table>
24.2.3. Crystal Structure of 573

A rod-like specimen of C_{14}H_{19}NO_{5}, approximate dimensions 0.160 mm x 0.200 mm x 0.240 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Bruker Nonius APEX-II system equipped with a graphite monochromator.

Sample and Crystal Data for 573

<table>
<thead>
<tr>
<th>Chemical formula</th>
<th>C_{14}H_{19}NO_{5}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula weight</td>
<td>281.30</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
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<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.160 x 0.200 x 0.240 mm</td>
</tr>
<tr>
<td>Crystal system</td>
<td>triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P - 1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>(a = 9.1457(7) \text{ Å}, \quad \alpha = 99.622(3)^\circ)</td>
</tr>
<tr>
<td></td>
<td>(b = 9.4389(9) \text{ Å}, \quad \beta = 116.183(3)^\circ)</td>
</tr>
<tr>
<td></td>
<td>(c = 9.6930(8) \text{ Å}, \quad \gamma = 97.613(3)^\circ)</td>
</tr>
<tr>
<td>Volume</td>
<td>719.94(11) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.298 Mg/cm³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.099 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>300</td>
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</table>

Data Collection and Structure Refinement for 573

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<tr>
<th>Diffractometer</th>
<th>Bruker Nonius APEX-II</th>
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<tbody>
<tr>
<td>Theta range for data collection</td>
<td>2.25 to 27.62°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-11&lt;=h&lt;=11, -12&lt;=k&lt;=12, -12&lt;=l&lt;=12</td>
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<tr>
<td>Reflections collected</td>
<td>6637</td>
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<tr>
<td>Independent reflections</td>
<td>3311 [R(int) = 0.0221]</td>
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<tr>
<td>Absorption correction</td>
<td>multi-scan</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9844 and 0.9767</td>
</tr>
<tr>
<td>Structure solution technique</td>
<td>direct methods</td>
</tr>
<tr>
<td>Structure solution program</td>
<td>SHELXS-97 (Sheldrick, 2008)</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Refinement program</td>
<td>SHELXL-97 (Sheldrick, 2008)</td>
</tr>
<tr>
<td>Function minimized</td>
<td>(\Sigma w(F_o^2 - F_c^2))^2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3311 / 0 / 257</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>0.967</td>
</tr>
</tbody>
</table>
\( \Delta/\sigma_{\text{max}} \) 0.015

Final R indices

\( R_1 = 0.0430, wR_2 = 0.1134 \)

2704 data; I>2\( \sigma(I) \)

all data

\( R_1 = 0.0531, wR_2 = 0.1259 \)

Weighting scheme

\[ w = 1/\left[ \sigma^2(F_o^2) + (0.0740P)^2 + 0.2728P \right] \]

where \( P = (F_o^2 + 2F_c^2)/3 \)

Largest diff. peak and hole

0.753 and -0.253 eÅ

R.M.S. deviation from mean

0.063 eÅ

Table 1. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å\(^2\)) for 573

\( U(\text{eq}) \) is defined as one third of the trace of the orthogonalized \( U_{ij} \) tensor.

<table>
<thead>
<tr>
<th>x/a</th>
<th>y/b</th>
<th>z/c</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.04738(12)</td>
<td>0.24377(12)</td>
<td>0.36133(12)</td>
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<tr>
<td>O2</td>
<td>0.78638(13)</td>
<td>0.97905(11)</td>
<td>0.82437(13)</td>
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<tr>
<td>O3</td>
<td>0.77790(13)</td>
<td>0.27068(12)</td>
<td>0.70747(12)</td>
</tr>
<tr>
<td>O4</td>
<td>0.72227(13)</td>
<td>0.02940(12)</td>
<td>0.14976(13)</td>
</tr>
<tr>
<td>O5</td>
<td>0.09864(13)</td>
<td>0.42382(12)</td>
<td>0.24889(12)</td>
</tr>
<tr>
<td>N1</td>
<td>0.86486(14)</td>
<td>0.23821(13)</td>
<td>0.11496(14)</td>
</tr>
<tr>
<td>C1</td>
<td>0.3563(2)</td>
<td>0.3152(2)</td>
<td>0.4965(2)</td>
</tr>
<tr>
<td>C2</td>
<td>0.20172(18)</td>
<td>0.29966(18)</td>
<td>0.51770(18)</td>
</tr>
<tr>
<td>C3</td>
<td>0.01640(17)</td>
<td>0.31309(15)</td>
<td>0.24810(16)</td>
</tr>
<tr>
<td>C4</td>
<td>0.78204(16)</td>
<td>0.27219(15)</td>
<td>0.95773(16)</td>
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<tr>
<td>C5</td>
<td>0.73331(17)</td>
<td>0.41325(15)</td>
<td>0.96134(16)</td>
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<td>C6</td>
<td>0.68926(17)</td>
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<td>0.6410(2)</td>
<td>0.66643(18)</td>
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<td>C8</td>
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<td>0.01078(16)</td>
<td>0.77950(18)</td>
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<tr>
<td>C9</td>
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<td>C10</td>
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<td>C11</td>
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<td>C12</td>
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<tr>
<td>C14</td>
<td>0.1903(3)</td>
<td>0.1761(4)</td>
<td>0.5964(3)</td>
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Table 2. Bond lengths (Å) for 573

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<tr>
<td>O3-C10</td>
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<td>O4-C12</td>
<td>1.1948(17)</td>
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<td>N1-C3</td>
<td>1.3939(18)</td>
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<td>N1-C4</td>
<td>1.4860(17)</td>
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<td>C1-H1A</td>
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</tr>
<tr>
<td>C1-H1C</td>
<td>0.90(3)</td>
</tr>
<tr>
<td>C2-C14</td>
<td>1.513(3)</td>
</tr>
<tr>
<td>C4-C9</td>
<td>1.539(2)</td>
</tr>
<tr>
<td>C5-C6</td>
<td>1.194(2)</td>
</tr>
<tr>
<td>C7-H7A</td>
<td>0.96(2)</td>
</tr>
<tr>
<td>C7-H7C</td>
<td>0.94(3)</td>
</tr>
<tr>
<td>C8-H8A</td>
<td>0.974(18)</td>
</tr>
<tr>
<td>C9-C12</td>
<td>1.5307(19)</td>
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<tr>
<td>C10-C11</td>
<td>1.524(2)</td>
</tr>
<tr>
<td>C11-H11A</td>
<td>0.97(2)</td>
</tr>
<tr>
<td>C13-H13A</td>
<td>0.98(3)</td>
</tr>
<tr>
<td>C13-H13C</td>
<td>0.98(3)</td>
</tr>
<tr>
<td>C14-H14B</td>
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Table 3. Bond angles (°) for 573

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<th>Angle</th>
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<td>H1A-C1-H1B</td>
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</tr>
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<td>C6-C5-C7</td>
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<td>C4-C9-H9</td>
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<td>O3-C10-H10</td>
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<td>O2-C11-H11B</td>
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<td>H11A-C11-H11B</td>
<td>109.8(15)</td>
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Table 6. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å$^2$) for 573

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<th></th>
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<th>z/c</th>
<th>U(eq)</th>
</tr>
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<tr>
<td>H8A</td>
<td>0.584(2)</td>
<td>0.0383(19)</td>
<td>-0.321(2)</td>
<td>0.018(4)</td>
</tr>
<tr>
<td>H8B</td>
<td>0.550(2)</td>
<td>-0.0813(19)</td>
<td>-0.229(2)</td>
<td>0.016(4)</td>
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<tr>
<td>H9</td>
<td>0.9854(19)</td>
<td>0.3280(17)</td>
<td>-0.0827(18)</td>
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<tr>
<td>H10</td>
<td>0.531(2)</td>
<td>0.1525(19)</td>
<td>-0.112(2)</td>
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<tr>
<td>H11A</td>
<td>0.932(2)</td>
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<td>H11B</td>
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<td>0.0964(19)</td>
<td>-0.057(2)</td>
<td>0.020(4)</td>
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<tr>
<td>H1A</td>
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<td>0.334(2)</td>
<td>0.603(3)</td>
<td>0.042(6)</td>
</tr>
<tr>
<td>H1B</td>
<td>1.369(3)</td>
<td>0.401(3)</td>
<td>0.450(3)</td>
<td>0.046(6)</td>
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<tr>
<td>H3</td>
<td>0.797(3)</td>
<td>0.365(3)</td>
<td>-0.287(3)</td>
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<tr>
<td>H7A</td>
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<tr>
<td>H13A</td>
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<td>0.426(3)</td>
<td>0.609(3)</td>
<td>0.069(8)</td>
</tr>
<tr>
<td>H13B</td>
<td>1.200(3)</td>
<td>0.523(3)</td>
<td>0.547(3)</td>
<td>0.060(8)</td>
</tr>
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<td>H14A</td>
<td>1.082(4)</td>
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<td>0.599(4)</td>
<td>0.086(10)</td>
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<td>H7B</td>
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<td>0.712(3)</td>
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<tr>
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<td>H7C</td>
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<td>0.693(3)</td>
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<td>0.086(5)</td>
<td>0.539(5)</td>
<td>0.119(15)</td>
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</tbody>
</table>
24.2.4. Crystal Structure of 667

A clear colourless rod-like specimen of C_{26}H_{33}NO_8, approximate dimensions 0.030 mm x 0.080 mm x 0.210 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Bruker Kappa Apex-II Duo system equipped with a graphite monochromator.

Sample and Crystal Data for 667

<table>
<thead>
<tr>
<th>Chemical formula</th>
<th>C_{26}H_{33}NO_8</th>
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<tbody>
<tr>
<td>Formula weight</td>
<td>487.53</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
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<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.030 x 0.080 x 0.210 mm</td>
</tr>
<tr>
<td>Crystal habit</td>
<td>clear colourless rod</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P 1 c 1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 16.116(3) Å</td>
</tr>
<tr>
<td></td>
<td>b = 26.333(5) Å</td>
</tr>
<tr>
<td></td>
<td>c = 12.366(3) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>5160.7(18) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.255 Mg/cm³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
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<tr>
<td>F(000)</td>
<td>2080</td>
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<tr>
<td>F(000)</td>
<td>500</td>
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Data Collection and Structure Refinement for 667

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<tr>
<th>Diffractometer</th>
<th>Bruker Kappa Apex-II Duo</th>
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<tr>
<td>Theta range for data</td>
<td>1.84 to 26.40°</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>10791</td>
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<tr>
<td>Coverage of independent reflections</td>
<td>95.7%</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>multi-scan</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9972 and 0.9808</td>
</tr>
<tr>
<td>Structure solution technique</td>
<td>direct methods</td>
</tr>
<tr>
<td>Structure solution program</td>
<td>SHELXS-97 (Sheldrick, 2008)</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Refinement program</td>
<td>SHELXL-97 (Sheldrick, 2008)</td>
</tr>
<tr>
<td>Function minimized</td>
<td>Σ w(Fo² - Fc²)²</td>
</tr>
</tbody>
</table>
Data / restraints / parameters 10794 / 2 / 800
Goodness-of-fit on $F^2$ 1.481
$\Delta/\sigma_{\text{max}}$ 0.015
Final R indices 7357 data; I>2$\sigma$(I) R1 = 0.1106, wR2 = 0.2444
all data R1 = 0.1583, wR2 = 0.2632
Weighting scheme $w=1/\left[\sigma^2(F_o^2)+(0.1000P)^2+0.0000P\right]$
where $P=(F_o^2+2F_c^2)/3$
Absolute structure parameter -1.0(20)
Largest diff. peak and hole 0.688 and -0.559 eÅ$^{-3}$
R.M.S. deviation from mean 0.106 eÅ$^{-3}$

Table 1. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å$^2$) for 667

<table>
<thead>
<tr>
<th>x/a</th>
<th>y/b</th>
<th>z/c</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
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<td>0.0516(6)</td>
<td>0.6345(3)</td>
<td>0.7999(6)</td>
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<tr>
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<td>0.1945(6)</td>
<td>0.5568(3)</td>
<td>0.7982(7)</td>
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<tr>
<td>O8</td>
<td>0.2142(5)</td>
<td>0.5484(3)</td>
<td>0.6210(6)</td>
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<td>O18</td>
<td>0.1190(5)</td>
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<td>O22</td>
<td>0.1679(5)</td>
<td>0.6135(3)</td>
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<tr>
<td>O23</td>
<td>0.0463(5)</td>
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<td>O28</td>
<td>0.2376(5)</td>
<td>0.6682(3)</td>
<td>0.6437(6)</td>
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</tbody>
</table>

$U(eq)$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.
24. Appendix

C3A
C4A
C6A
C9A
C10A
C11A
C12A
C13A
C14A
C15A
C16A
C17A
C19A
C21A
C24A
C25A
C26A
C27A
C29A
C30A
C31A
C32A
C33A
C34A
C35A
O5B
O7B
O8B
O18B
O20B
O22B
O23B
O28B
N2B
C1B
C3B
C4B
C6B
C9B
C10B
C11B
C12B
C13B
C14B
C15B
C16B
C17B
C19B
C21B
C24B
C25B
C26B
C27B
C29B
C30B
C31B
C32B
C33B
C34B
C35B
O5C

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493

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Table 2. Bond lengths (Å) for 667

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<th>O8-C6</th>
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<td>C1</td>
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<td>1.346(14)</td>
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<td>1.458(15)</td>
<td>1.494(15)</td>
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24. Appendix
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| O5-C1-N2 | 133.6(11) | O5-C1-C4 | 133.5(10) |
| N2-C1-C4 | 92.9(8) | C13-C3-C16 | 108.1(10) |
| C13-C3-N2 | 111.9(9) | C16-C3-N2 | 117.1(10) |
| C13-C3-C4 | 121.6(10) | C16-C3-C4 | 110.8(9) |
| N2-C3-C4 | 86.6(8) | C19-C4-C1 | 115.5(11) |
| C19-C4-C3 | 114.2(10) | C1-C4-C3 | 85.6(9) |
| C19-C4-H4 | 112.9 | C1-C4-H4 | 112.9 |
| C3-C4-H4 | 112.9 | O7-C6-O8 | 129.1(11) |
| O7-C6-N2 | 118.7(10) | O8-C6-N2 | 112.0(9) |
| C12-C9-O8 | 110.7(9) | C12-C9-C11 | 112.6(12) |
| O8-C9-C11 | 106.6(9) | C12-C9-C10 | 112.7(11) |
| O8-C9-C10 | 103.4(10) | C11-C9-C10 | 110.2(10) |
| H10A-C10-H10C | 109.5 | H10B-C10-H10C | 109.5 |
| H11A-C11-H11C | 109.5 | H11B-C11-H11C | 109.5 |
| H12A-C12-H12C | 109.5 | H12B-C12-H12C | 109.5 |
| C14-C13-C3 | 170.6(12) | C13-C14-C15 | 177.6(13) |
| O20-C16-C3 | 105.8(9) | O20-C16-C17 | 107.5(9) |
| C3-C16-C17 | 113.7(10) | O20-C16-H16 | 109.9 |
| C3-C16-H16 | 109.9 | C17-C16-H16 | 109.9 |
| O18-C17-O28 | 108.7(9) | O18-C17-C16 | 114.2(9) |
| O28-C17-C16 | 108.1(9) | O18-C17-H17 | 108.6 |
| O28-C17-H17 | 108.6 | C16-C17-H17 | 108.6 |
| O18-C19-C4 | 114.4(10) | O18-C19-H19A | 109.3 |
| C4-C19-H19A | 109.3 | O18-C19-H19B | 109.3 |
| C4-C19-H19B | 109.3 | H19A-C19-H19B | 108.0 |
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| O23-C21-O20 | 105.9(9) | C25-C24-C26 | 112.1(9) |
| C25-C24-O23 | 102.4(8) | C26-C24-O23 | 111.7(9) |
| C25-C24-C27 | 110.1(9) | C26-C24-C27 | 112.0(9) |
| C24-C26-H26C | 109.5 | H26A-C26-H26C | 109.5 |
| H26B-C26-H26C | 109.5 | C24-C27-H27A | 109.5 |
| H27B-C27-H27C | 109.5 | O28-C29-C30 | 106.0(9) |
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| O28-C29-H29B | 110.5 | C30-C29-H29B | 110.5 |
| H29A-C29-H29B | 108.7 | C35-C30-C31 | 115.7(12) |
| C35-C30-C29 | 121.9(10) | C31-C30-C29 | 122.4(10) |
| C32-C31-C30 | 125.4(13) | C32-C31-H31 | 117.3 |
| C30-C31-H31 | 117.3 | C31-C32-C33 | 116.0(15) |
| C31-C32-H32 | 122.0 | C33-C32-H32 | 122.0 |
| C32-C33-C34 | 119.9(16) | C32-C33-H33 | 120.1 |
| C34-C33-H33 | 120.1 | C35-C34-C33 | 120.5(14) |
| C35-C34-H34 | 119.8 | C33-C34-H34 | 119.8 |
| C34-C35-C30 | 122.5(12) | C34-C35-H35 | 118.8 |
| 24. Appendix |
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| C30-C35-H35 118.8    | C6A-O8A-C9A 121.7(7) |
| C21A-O23A-C24A 117.6(8) | C17A-O28A-C29A 113.5(7) |
| C1A-N2A-C6A 134.3(8) | C1A-N2A-C3A 98.4(7) |
| C6A-N2A-C3A 126.4(9) | O5A-C1A-N2A 134.5(10) |
| O5A-C1A-C4A 133.5(10) | N2A-C1A-C4A 92.0(8) |
| C13A-C3A-N2A 113.5(8) | C13A-C3A-C16A 113.0(9) |
| N2A-C3A-C4A 83.5(7) | C16A-C3A-C4A 113.2(8) |
| C19A-C4A-C1A 110.9(8) | C19A-C4A-C3A 111.7(9) |
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| C1A-C4A-H4A 115.0 | C3A-C4A-H4A 115.0 |
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| O8A-C6A-N2A 109.6(8) | O8A-C9A-C10A 103.0(6) |
| O8A-C9A-C11A 110.0(7) | C10A-C9A-C11A 112.0(7) |
| H12E-C12A-H12F 109.5 | C14A-C13A-C3A 168.5(12) |
| H15E-C15A-H15F 109.5 | O20A-C16A-C3A 106.9(7) |
| O20A-C16A-C3A 103.9(7) | C17A-C16A-C3A 114.3(8) |
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| H19C-C19A-H19D 107.9 | O22A-C21A-O23A 130.1(10) |
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| C30A-C29A-H29D 110.5 | H29C-C29A-H29D 108.7 |
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The anisotropic atomic displacement factor exponent takes the form: \(-2\pi^2 h^2 a^2 b^2 c^2 \sum U_{ij} a_i a_j + \ldots + 2 h k a^* b^* c^* U_{12} \)

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Table 4. Anisotropic atomic displacement parameters (Å²) for 667

The anisotropic atomic displacement factor exponent takes the form: \(-2\pi^2 h^2 a^2 b^2 c^2 \sum U_{ij} a_i a_j + \ldots + 2 h k a^* b^* c^* U_{12} \)
Table 5. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å²) for 667

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24.2.5. Crystal Structure of 720

A clear colourless prism-like specimen of C\textsubscript{23}H\textsubscript{33}NO\textsubscript{9}, approximate dimensions 0.150 mm x 0.200 mm x 0.260 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Bruker Nonius APEX-II system equipped with a graphite monochromator.

Sample and Crystal Data for 720

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<td>Crystal system</td>
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Data Collection and Structure Refinement for 720

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<td>SHELXS-97 (Sheldrick, 2008)</td>
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<td>Refinement method</td>
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</table>
Refinement program

SHELXL-97 (Sheldrick, 2008)

Function minimized

\[ \Sigma w(F_o^2 - F_c^2)^2 \]

Data / restraints / parameters

5610 / 0 / 430

Goodness-of-fit on F^2

1.156

Final R indices

4260 data; I>2σ(I)  
R1 = 0.0427, wR2 = 0.0992  
all data  
R1 = 0.0623, wR2 = 0.1095

Weighting scheme

\[ w=1/\left[\sigma(F_o^2)+(0.0500P)\right]^2+0.0000P] \]

where \( P=(F_o^2+2F_c^2)/3 \)

Largest diff. peak and hole

0.590 and -0.366 eÅ^3

R.M.S. deviation from mean

0.050 eÅ^-3

Table 1. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å^2) for 720

| O5   | 0.93385(10) | 0.65074(9) | 0.81143(9) | 0.0172(2)  |
| O10  | 0.45027(11) | 0.57891(10) | 0.78133(9) | 0.0226(3)  |
| O11  | 0.50015(10) | 0.37095(9)  | 0.73168(9) | 0.0177(2)  |
| O16  | 0.69082(11) | 0.77362(10) | 0.97285(10)| 0.0254(3)  |
| O19  | 0.94252(11) | 0.34734(10) | 0.51306(9) | 0.0240(3)  |
| O20  | 0.71892(11) | 0.33616(11) | 0.45983(10)| 0.0278(3)  |
| O23  | 0.91230(10) | 0.33324(9)  | 0.80704(8) | 0.0150(2)  |
| O25  | 0.78087(11) | 0.14057(9)  | 0.67690(10)| 0.0237(3)  |
| O26  | 0.96336(10) | 0.14617(9)  | 0.79999(8) | 0.0160(2)  |
| N1   | 0.64784(12) | 0.54263(11) | 0.85921(10)| 0.0154(3)  |
| C2   | 0.71788(15) | 0.66529(14) | 0.94134(13)| 0.0175(3)  |
| C3   | 0.83787(15) | 0.60439(14) | 0.96835(13)| 0.0162(3)  |
| C4   | 0.96845(16) | 0.65883(15) | 0.92635(13)| 0.0181(3)  |
| C6   | 0.90742(15) | 0.54263(11) | 0.85921(10)| 0.0154(3)  |
| C7   | 0.82131(14) | 0.40936(13) | 0.77601(12)| 0.0143(3)  |
| C8   | 0.75118(14) | 0.46703(13) | 0.88101(12)| 0.0144(3)  |
| C9   | 0.52168(15) | 0.50275(13) | 0.78802(12)| 0.0156(3)  |
| C12  | 0.37567(15) | 0.29814(14) | 0.64596(13)| 0.0189(3)  |
| C13  | 0.39717(19) | 0.15543(16) | 0.60774(16)| 0.0265(4)  |
| C14  | 0.24545(18) | 0.30647(19) | 0.70217(18)| 0.0305(4)  |
| C15  | 0.37843(19) | 0.35529(17) | 0.54979(15)| 0.0261(4)  |
| C17  | 0.83542(16) | 0.51681(14) | 0.62360(13)| 0.0169(3)  |
| C18  | 0.84072(15) | 0.39238(14) | 0.52699(13)| 0.0176(3)  |
| C21  | 0.7165(2)   | 0.21587(19) | 0.36207(17)| 0.0351(4)  |
| C22  | 0.5696(2)   | 0.15396(18) | 0.30970(16)| 0.0306(4)  |
| C24  | 0.87479(15) | 0.19768(13) | 0.75272(14)| 0.0153(3)  |
| C27  | 0.95088(15) | 0.99719(13) | 0.75872(13)| 0.0171(3)  |
| C28  | 0.06999(17) | 0.98296(15) | 0.83230(15)| 0.0224(3)  |
| C29  | 0.97018(19) | 0.95096(16) | 0.63448(14)| 0.0231(4)  |
| C30  | 0.81203(18) | 0.29755(16) | 0.78014(18)| 0.0286(4)  |
| C31  | 0.69817(15) | 0.36262(14) | 0.92951(12)| 0.0167(3)  |
| C32  | 0.66348(15) | 0.27534(14) | 0.96815(13)| 0.0186(3)  |
| C33  | 0.6224(2)   | 0.16872(17) | 0.01658(17)| 0.0271(4)  |

U(eq) is defined as one third of the trace of the orthogonalized \( U_{ij} \) tensor.
Table 2. Bond lengths (Å) for 720

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Table 3. Bond angles (°) for 720

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Table 4. Torsion angles (°) for 720

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<td>C27-O26-C24-O25</td>
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<tr>
<td>C27-O26-C24-O23</td>
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<td>C7-O23-C24-O25</td>
<td>6.26(19)</td>
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<td>C24-O26-C27-C30</td>
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<td>C24-O26-C27-C29</td>
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<tr>
<td>N1-C8-C31-C32</td>
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<tr>
<td>C3-C8-C31-C32</td>
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<td>C8-C31-C32-C33</td>
<td>52.16(16)</td>
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Table 5. Anisotropic atomic displacement parameters (Å²) for 720

The anisotropic atomic displacement factor exponent takes the form: \(-2\pi^2 \left[ \hbar^2 a^2 U_{11} + \ldots + 2 h k a^2 b^2 U_{12} \right]

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<tr>
<th></th>
<th>(U_{11})</th>
<th>(U_{22})</th>
<th>(U_{33})</th>
<th>(U_{23})</th>
<th>(U_{13})</th>
<th>(U_{12})</th>
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<tr>
<td>O5</td>
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<tr>
<td>O10</td>
<td>0.0211(6)</td>
<td>0.0193(5)</td>
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<td>-0.0008(5)</td>
<td>0.0090(4)</td>
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<td>O11</td>
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<td>0.0141(5)</td>
<td>0.0207(6)</td>
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<td>-0.0027(4)</td>
<td>0.0031(4)</td>
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<tr>
<td>O16</td>
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<td>0.0005(5)</td>
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<tr>
<td>O19</td>
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<td>0.0236(5)</td>
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<td>0.0095(4)</td>
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<tr>
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<td>0.0051(5)</td>
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<td>y/b</td>
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<tr>
<td>H14A</td>
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<td>0.2504(18)</td>
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<tr>
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<tr>
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<td>0.9313(13)</td>
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<td>H28A</td>
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<td>0.0328(18)</td>
<td>0.8201(16)</td>
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<td>0.5889(16)</td>
<td>0.034(5)</td>
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Table 6. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å²) for 720
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<th>X</th>
<th>Y</th>
<th>Z</th>
<th>U</th>
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</thead>
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<td>-0.1465(17)</td>
<td>0.6101(15)</td>
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<td>1.0599(19)</td>
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<td>0.030(5)</td>
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<tr>
<td>H30A</td>
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<td>-0.0590(17)</td>
<td>0.7325(16)</td>
<td>0.032(5)</td>
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<td>H30B</td>
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<td>0.8627(18)</td>
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<tr>
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<td>0.963(2)</td>
<td>0.067(7)</td>
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<tr>
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<td>0.704(3)</td>
<td>0.179(3)</td>
<td>1.077(3)</td>
<td>0.095(9)</td>
</tr>
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</table>
24.2.6. Crystal Structure of 809

A colorless rod-like specimen of C_{23}H_{31}NO_{8}, approximate dimensions 0.020 mm x 0.040 mm x 0.140 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured on a Bruker Kappa Apex-II Duo system equipped with a mirror optics monochromator and a Cu Incoatec IμS microfocus X-ray tube (λ = 1.54178 Å).

Sample and Crystal Data for 809

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<td>CCDC 932549</td>
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<tr>
<td>Chemical formula</td>
<td>C_{23}H_{31}NO_{8}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>449.49</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.020 x 0.040 x 0.140 mm</td>
</tr>
<tr>
<td>Crystal habit</td>
<td>colorless rod</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P 1 21/c 1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 15.4759(10) Å, α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 12.6368(8) Å, β =</td>
</tr>
<tr>
<td></td>
<td>c = 12.4760(8) Å, γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>2396.4(3) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
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<tr>
<td>Density (calculated)</td>
<td>1.246 g/cm³</td>
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<tr>
<td>Absorption coefficient</td>
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<td>F(000)</td>
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Data Collection and Structure Refinement for 809

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</tr>
<tr>
<td>Radiation source</td>
<td>Incoatec IμS microfocus X-ray tube, Cu</td>
</tr>
<tr>
<td>Theta range for data</td>
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</tr>
<tr>
<td>Index ranges</td>
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<tr>
<td>Reflections collected</td>
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<tr>
<td>Independent reflections</td>
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<tr>
<td>Coverage of independent reflections</td>
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<tr>
<td>Absorption correction</td>
<td>multi-scan</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9883 and 0.8982</td>
</tr>
<tr>
<td>Structure solution technique</td>
<td>direct methods</td>
</tr>
<tr>
<td>Structure solution program</td>
<td>SHELXS-97 (Sheldrick, 2008)</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
</tbody>
</table>
Refinement program  SHELXL-97 (Sheldrick, 2008)
Function minimized  \( \Sigma w(F_o^2 - F_c^2)^2 \)
Data / restraints / parameters  3383 / 0 / 391
Goodness-of-fit on \( F^2 \)  1.657
Final R indices  
all data:  \( R_1 = 0.0410, \ wR_2 = 0.1082 \) 
Data:  \( R_1 = 0.0356, \ wR_2 = 0.1048 \)
Weighting scheme  
\[ w = \frac{1}{[\sigma^2(F_o^2) + (0.0450P)]^{1/2} + 0.0000P} \]
where \( P = (F_o^2 + 2F_c^2)/3 \)
Largest diff. peak and hole  0.253 and -0.162 e\( \cdot \)Å\(^{-3} \)
R.M.S. deviation from mean  0.035 e\( \cdot \)Å\(^{-3} \)

Table 1. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å\(^2\)) for 809

<table>
<thead>
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<th>( x/a )</th>
<th>( y/b )</th>
<th>( z/c )</th>
<th>( U(eq) )</th>
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<td>0.88460(9)</td>
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<td>0.35324(9)</td>
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<td>O22</td>
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<td>0.53874(9)</td>
<td>0.46597(10)</td>
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Table 2. Bond lengths (Å) for 809
Table 3. Bond angles (°) for 809

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Note: Distances in Ångström (Å).
Table 5. Anisotropic atomic displacement parameters (Å^2) for 809

The anisotropic atomic displacement factor exponent takes the form: -2π^2 h^2 a^2 U_{11} + ... + 2 h k a^2 b^2 U_{12}

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Table 6. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å²) for 809
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<td>0.9911(16)</td>
<td>0.7101(16)</td>
<td>0.053(6)</td>
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<tr>
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<td>0.045(5)</td>
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<tr>
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<td>0.9200(19)</td>
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24.3. SFC Spectra

24.3.1. SFC Spectra for S42

Racemate
24.3.2. SFC Spectra for 537

**Racemate**

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<th>Height [μV]</th>
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24.4. Mass Spectroscopic Data for Protein Bioconjugates

unmodified protein:

+MS, 0.86-1.35min, Deconvoluted (MaxEnt, 1016.48-2149.92, 0.1, 35000)

+MS, 1.02-1.47min, Deconvoluted (MaxEnt, 1069.45-2128.73, 0.1, 35000)

unmodified
unmodified protein:
unmodified protein:
unmodified protein:
unmodified protein:
unmod.

unmod.

unmod.
+MS, 0.81-1.27min, Deconvoluted (MaxEnt, 1248.24-2178.05, 0.1, 35000)

unmod.

+2
+3
+4

+MS, 0.84-1.34min, Deconvoluted (MaxEnt, 1368.63-2121.48, 0.1, 35000)
Appendix

unmod. +1

unmod. +2

unmod. +3

unmod. +4

unmod. +5

unmod. +6

unmod. +7

unmod. +8
byproducts
unmod.

+MS, 0.04-1.43 min, Deconvoluted (MaxEnt, 850.66-1437.30, 0.1, 35000)
25. NMR Spectral Data

NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

![NMR Spectra Diagrams]

- 600 MHz DQF-COSY in CD$_3$OD
- 600 MHz HSQC in CD$_3$OD

Diagram 1: DQF-COSY spectrum with resonances marked at specific ppm values.

Diagram 2: HSQC spectrum with additional connectivity information.
25. NMR Spectral Data
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

**300 MHz $^1$H NMR**

in CDCl$_3$

**75 MHz $^{13}$C NMR**

in CDCl$_3$
25. NMR Spectral Data

500 MHz $^1$H NMR in CDCl$_3$

125 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

148b
300 MHz $^1$H NMR in CDCl$_3$

148b
75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

**300 MHz $^1$H NMR in CDCl$_3$**

**75 MHz $^{13}$C NMR in CDCl$_3$**
25. NMR Spectral Data

600 MHz $^1$H NMR in CD$_3$OD

150 MHz $^{13}$C NMR in CD$_3$OD
25. NMR Spectral Data
25. NMR Spectral Data

600 MHz HMBC in CD$_3$OD

158a
25. NMR Spectral Data
25. NMR Spectral Data

400 MHz HMBC in CD$_3$OD
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR
in CDCl$_3$

75 MHz $^{13}$C NMR
in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

S5
300 MHz $^1$H NMR
in CDCl$_3$

S5
75 MHz $^{13}$C NMR
in CDCl$_3$
300 MHz $^1$H NMR in CDCl$_3$
25. NMR Spectral Data

181
400 MHz $^1$H NMR in CDCl$_3$

181
100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

**300 MHz $^1$H NMR in CDCl$_3$**

**75 MHz $^{13}$C NMR in CDCl$_3$**

(Chemical structures and spectra shown with peak assignments)
NMR Spectral Data

400 MHz \(^1\)H NMR in CDCl\(_3\)

100 MHz \(^{13}\)C NMR in CDCl\(_3\)
25. NMR Spectral Data

300 MHz $^1H$ NMR in CDCl$_3$

150 MHz $^{13}$C NMR in CDCl$_3$
300 MHz $^1$H NMR in CDCl₃
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$
25. NMR Spectral Data

400 MHz $^1H$ NMR in CD$_3$OD

100 MHz $^{13}C$ NMR in CD$_3$OD
25. NMR Spectral Data

400 MHz $^1$H NMR in CD$_3$OD

100 MHz $^{13}$C NMR in CD$_3$OD
25. NMR Spectral Data

300 MHz $^1$H NMR in $CDCl_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
280 MHz $^{19}$F NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz ¹H NMR
in CD₃OD

75 MHz ¹³C NMR
in CD₃OD
25. NMR Spectral Data
25. NMR Spectral Data
25. NMR Spectral Data

224

300 MHz $^1$H NMR
In CDCl$_3$

75 MHz $^{13}$C NMR
In CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

216
300 MHz ¹H NMR in CDCl₃

216
75 MHz ¹³C NMR in CDCl₃
25. NMR Spectral Data

**600 MHz $^1$H NMR**

in CDCl$_3$

**150 MHz $^{13}$C NMR**

in CDCl$_3$
25. NMR Spectral Data

228
600 MHz HSQC in CDCl₃
25. NMR Spectral Data

500 MHz $^1$H NMR in CDCl$_3$

125 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

500 MHz HSQC in CDCl₃

280 MHz $^{19}$F NMR in CDCl₃
25. NMR Spectral Data

600 MHz $^1$H NMR
in CDCl$_3$

150 MHz $^{13}$C NMR
in CDCl$_3$
25. NMR Spectral Data

600 MHz HSQC in CDCl$_3$
NMR Spectral Data

231
400 MHz $^1$H NMR
in CDCl$_3$

231
100 MHz $^{13}$C NMR
in CDCl$_3$
231
400 MHz HSQC in CDCl₃
25. NMR Spectral Data

![NMR Spectra](image)

**232**
600 MHz DQF-COSY in CDCl₃

![NMR Spectra](image)

**232**
600 MHz HSQC in CDCl₃
232
600 MHz HMBC in CDCl₃

S12
300 MHz ¹H NMR in CDCl₃
25. NMR Spectral Data

**233**

300 MHz $^1$H NMR in CDCl$_3$

![NMR Spectrum 233](image1)

**234**

300 MHz $^1$H NMR in CDCl$_3$

![NMR Spectrum 234](image2)
25. NMR Spectral Data
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

280 MHz $^{19}$F NMR in CDCl$_3$
236
300 MHz $^1$H NMR in CDCl$_3$

237
300 MHz $^1$H NMR in CDCl$_3$
25. NMR Spectral Data

238
300 MHz $^1$H NMR in CDCl$_3$

240
300 MHz $^1$H NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

$^1$C NMR in CDCl$_3$
25. NMR Spectral Data

microcin SF608 (19)
600 MHz $^1$H NMR
in $d_6$-DMSO

microcin SF608 (19)
150 MHz $^{13}$C NMR
in $d_6$-DMSO
microcin SF608 (19)
600 MHz DQF-COSY
in $d_6$-DMSO

microcin SF608 (19)
600 MHz HMQC
in $d_6$-DMSO
microcin SF608 (19)
600 MHz HMQC
in d$_{6}$-DMSO
25. NMR Spectral Data

2-epi-microcin SF608 (S16)
600 MHz $^1$H NMR in $d_6$-DMSO

150 MHz $^{13}$C NMR in $d_6$-DMSO
25. NMR Spectral Data

2-epi-microcin SF608 (S16)
600 MHz DQF-COSY
in d$_6$-DMSO

2-epi-microcin SF608 (S16)
600 MHz HSQC
in d$_6$-DMSO
2-epi-microcin SF608 (816)
600 MHz HMBC
in d$_2$-DMSO
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data
600 MHz $^1$H NMR in CDCl$_3$

150 MHz $^{13}$C NMR in CDCl$_3$
600 MHz HMBC in CDCl₃
500 MHz HMBC in CDCl₃
25. NMR Spectral Data

600 MHz DQF-COSY in CDCl₃

600 MHz HSQC in CDCl₃
600 MHz HMBC in CDCl₃
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

500 MHz DQF-COSY in CDCl₃

500 MHz HSQC in CDCl₃
500 MHz HMBC
in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data
25. NMR Spectral Data

400 MHz DQF-COSY in CDCl₃

400 MHz HSQC in CDCl₃
25. NMR Spectral Data

400 MHz HMBC in CDCl₃
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
664
25. NMR Spectral Data

600 MHz HMBC in CDCl$_3$
25. NMR Spectral Data

600 MHz DQF-COSY in CDCl₃

600 MHz HSQC in CDCl₃
25. NMR Spectral Data

600 MHz HMBC in DClO$_3$
25. NMR Spectral Data

522
600 MHz 'H NMR in CDCl₃

522
150 MHz ¹³C NMR in CDCl₃
NMR Spectral Data
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

543

400 MHz HMBC
in CDCl3
300 MHz $^1$H NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

400 MHz $^1$H NMR
in CDCl$_3$

100 MHz $^{13}$C NMR
in CDCl$_3$
25. NMR Spectral Data

400 MHz DQF-COSY
in CDCl₃

400 MHz HSQC
in CDCl₃
25. NMR Spectral Data

300 MHz $^1$H NMR
in CDCl$_3$

75 MHz $^{13}$C NMR
in CDCl$_3$/CD$_3$OD 9:1
300 MHz $^1$H NMR in CDCl$_3$
S25 (diastereomer 1)
400 MHz $^1$H NMR
in CDCl$_3$
S25 (diastereomer 1)
400 MHz DQF-COSY
in CDCl₃

S25 (diastereomer 1)
400 MHz HSQC
in CDCl₃
$S_{25}$ (diastereomer 1)
400 MHz HMBC
in CDCl$_3$
S25 (diastereomer 2)
400 MHz $^1H$ NMR
in CDCl$_3$

S25 (diastereomer 2)
100 MHz $^{13}C$ NMR
in CDCl$_3$
25. NMR Spectral Data

**S25 (diasteromer 2)**
400 MHz DQF-COSY in CDCl₃

**S25 (diasteromer 2)**
400 MHz HSQC in CDCl₃
S25 (diastereomer 2)
400 MHz HMBC
In CDCl₃
25. NMR Spectral Data
25. NMR Spectral Data
25. NMR Spectral Data

**577 (major isomer)**

400 MHz $^1$H NMR in CD$_3$CN

---

**577 (major isomer)**

100 MHz $^{13}$C NMR in CD$_3$CN
NMR Spectral Data

577 (major isomer)
400 MHz HMBC in CD$_3$CN
25. NMR Spectral Data

577 (minor isomer)
400 MHz $^1$H NMR in CD$_3$CN

577 (minor isomer)
100 MHz $^{13}$C NMR in CD$_3$CN
25. NMR Spectral Data

**NMR Spectral Data for Compound 577**

- **400 MHz DQF-COSY** in CD$_3$CN

- **Chemical Shifts:**
  - $f_1$ in ppm range from 0 to 170
  - $f_2$ in ppm range from 7.5 to 7.0

**Structural Formula:**

![NMR Spectral Data Diagram](image-url)
577 (minor isomer)
400 MHz HMBC
in CD$_3$CN
25. NMR Spectral Data

400 MHz DQF-COSY in CD$_3$CN

400 MHz HSQC in CD$_3$CN
25. NMR Spectral Data

600 MHz $^1$H NMR in CD$_3$CN

150 MHz $^{13}$C NMR in CD$_3$CN
25. NMR Spectral Data

600 MHz DQF-COSY in CD$_3$CN

600 MHz HSQC in CD$_3$CN
25. NMR Spectral Data

600 MHz HMBC in CD$_3$CN
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

600 MHz DQF-COSY in CD$_3$CN

600 MHz HSQC in CD$_3$CN
25. NMR Spectral Data

600 MHz HMBC in CD$_3$CN
25. NMR Spectral Data

400 MHz DQF-COSY in CDCl₃

400 MHz HSQC in CDCl₃
25. NMR Spectral Data

400 MHz HMBC in CDCl₃
25. NMR Spectral Data

644
400 MHz DQF-COSY in CDCl₃

644
400 MHz HSQC in CDCl₃
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

S28
400 MHz DQF-COSY in CDCl₃

S28
400 MHz HSQC in CDCl₃
25. NMR Spectral Data
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

600 MHz $^1$H NMR in CDCl$_3$

150 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

S32
400 MHz DQF-COSY
in CDCl₃

S32
400 MHz HSQC
in CDCl₃
400 MHz HMBC in CDCl₃
25. NMR Spectral Data

300 MHz $^1$H NMR in CD$_3$CN

100 MHz $^{13}$C NMR in CD$_3$CN
25. NMR Spectral Data

300 MHz $^1$H NMR in CD$_3$CN

100 MHz $^{13}$C NMR in CD$_3$CN
25. NMR Spectral Data

669 (3:1 dr)

300 MHz $^1$H NMR
in $d_6$-DMSO at 100°C

75 MHz $^{13}$C NMR
in $d_6$-DMSO at 100°C
NMR Spectral Data

S33
400 MHz $^1$H NMR
in CD$_3$CN

S33
100 MHz $^{13}$C NMR
in CD$_3$CN
25. NMR Spectral Data

**S33**

400 MHz DQF-COSY in CD$_3$CN

**S33**

400 MHz HSQC in CD$_3$CN
S33
400 MHz HMBC
in CD$_2$CN

25. NMR Spectral Data
25. NMR Spectral Data

400 MHz $^1$H NMR
in CD$_3$CN

100 MHz $^{13}$C NMR
in CD$_3$CN
25. NMR Spectral Data
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

S38
600 MHz DQF-COSY
in CD$_3$CN

S38
600 MHz HSQC
in CD$_3$CN
25. NMR Spectral Data
681
600 MHz HMBC
in CD$_3$CN
25. NMR Spectral Data

600 MHz $^1$H NMR in CDCl$_3$

150 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

600 MHz DQF-COSY in CDCl₃

600 MHz HSQC in CDCl₃
25. NMR Spectral Data

600 MHz HMBC in CDCl₃
25. NMR Spectral Data

400 MHz $^1$H NMR in CD$_3$CN

100 MHz $^{13}$C NMR in CD$_3$CN
25. NMR Spectral Data

400 MHz HMBC in CD$_2$CN

S42
25. NMR Spectral Data

---

**400 MHz $^1$H NMR**

in CDCl$_3$

---

**100 MHz $^{13}$C NMR**

in CDCl$_3$
NMR Spectral Data

600 MHz HMBC in CDCl₃
25. NMR Spectral Data

716
300 MHz $^1$H NMR in CDCl$_3$

716
75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CD$_3$CN

100 MHz $^{13}$C NMR in CD$_3$CN
25. NMR Spectral Data

720
300 MHz $^1$H NMR in CDCl$_3$

720
100 MHz $^{13}$C NMR in CDCl$_3$
300 MHz $^1$H NMR in CDCl$_3$
25. NMR Spectral Data

724
600 MHz ¹H NMR in CDCl₃

724
150 MHz ¹³C NMR in CDCl₃
25. NMR Spectral Data

724
600 MHz DQF-COSY in CDCl₃

724
600 MHz HSQC in CDCl₃
25. NMR Spectral Data

724
600 MHz HMBC in CDCl₃
NMR Spectral Data

**300 MHz $^1$H NMR**
in CDCl$_3$

**100 MHz $^{13}$C NMR**
in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

732
500 MHz DQF-COSY in CDCl₃

732
500 MHz HSQC in CDCl₃
25. NMR Spectral Data
25. NMR Spectral Data
25. NMR Spectral Data

727b
600 MHz $^1$H NMR in CDCl$_3$

727b
150 MHz $^{13}$C NMR in CDCl$_3$
727b
600 MHz HMBC
in CDCl₃
NMR Spectral Data

**727a**

600 MHz $^1$H NMR in CDCl$_3$

**727a**

150 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data
25. NMR Spectral Data

736b
600 MHz $^1$H NMR
in CDCl$_3$

736b
150 MHz $^{13}$C NMR
in CDCl$_3$
25. NMR Spectral Data

736b
600 MHz DQF-COSY in CDCl₃

736b
600 MHz HSQC in CDCl₃
NMR Spectral Data
25. NMR Spectral Data

733
600 MHz DQF-COSY
in CDCl₃

733
600 MHz HSQC
in CDCl₃
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

![NMR Spectra](image)

752 400 MHz DQF-COSY in CDCl₃

752 400 MHz HSQC in CDCl₃
400 MHz HMBD in CDCl₃
25. NMR Spectral Data

783
400 MHz DQF-COSY in CDCl₃

783
400 MHz HSQC in CDCl₃
25. NMR Spectral Data

808

400 MHz $^1$H NMR in CDCl$_3$

808

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

809

400 MHz $^1$H NMR in CDCl$_3$

809

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

400 MHz DQF-COSY in CDCl₃

400 MHz HSQC in CDCl₃
809
400 MHz 1H NMR in CDCl₃
25. NMR Spectral Data

600 MHz $^1$H NMR in CDCl$_3$

150 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

600 MHz DQF-COSY in CDCl₃

819

600 MHz HSQC in CDCl₃

819
25. NMR Spectral Data

600 MHz HMBC in CDCl₃

600 MHz NOESY in CDCl₃
25. NMR Spectral Data

600 MHz DQF-COSY in CDCl₃

600 MHz HSQC in CDCl₃
25. NMR Spectral Data
25. NMR Spectral Data

300 MHz $^1$H NMR
in CDCl$_3$/CD$_3$OD 10:1

100 MHz $^{13}$C NMR
in CDCl$_3$/CD$_3$OD 10:1
25. NMR Spectral Data

838
600 MHz HMBC
in CDCl₃
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
NMR Spectral Data

400 MHz DQF-COSY in CDCl₃

400 MHz HSQC in CDCl₃
25. NMR Spectral Data

400 MHz HMBC in CDCl₃
25. NMR Spectral Data

843
600 MHz $^1$H NMR in CDCl$_3$

843
150 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

600 MHz DQF-COSY in CDCl₃

600 MHz HSQC in CDCl₃
25. NMR Spectral Data

**843**
600 MHz HMBC in CDCl₃

**853**
300 MHz ¹H NMR in CDCl₃
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

400 MHz $^1$H NMR in CD$_2$Cl$_2$

100 MHz $^{13}$C NMR in CD$_2$Cl$_2$
25. NMR Spectral Data

400 MHz DQF-COSY in CD$_2$Cl$_2$

745

400 MHz HSQC in CD$_2$Cl$_2$
25. NMR Spectral Data

745
400 MHz HMBC
in CD$_2$Cl$_2$

745
600 MHz NOESY
in CD$_2$Cl$_2$
25. NMR Spectral Data
25. NMR Spectral Data

600 MHz $^1$H NMR in CDCl$_3$

150 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

Gelsemoxamine (278)
600 MHz $^1$H NMR in CDCl$_3$

Gelsemoxamine (278)
150 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

600 MHz $^1$H NMR in CDCl$_3$

150 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

600 MHz HMBC in CDCl₃
N-methyl gelsemoxonine (863)
400 MHz DQF-COSY
in CDCl₃
25. NMR Spectral Data

600 MHz HMBC
in CDCl₃
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

400 MHz DQF-COSY in CDCl₃

400 MHz HSQC in CDCl₃
25. NMR Spectral Data

400 MHz HMBC
in CDCl3
25. NMR Spectral Data

897
600 MHz DQF-COSY in CDCl₃

897
600 MHz HSQC in CDCl₃
25. NMR Spectral Data

897
600 MHz HMBC
in CDCl₃
25. NMR Spectral Data

901
400 MHz DQF-COSY in CDCl₃

901
400 MHz HSQC in CDCl₃
25. NMR Spectral Data

300 MHz $^1$H NMR in CD$_3$CN

100 MHz $^{13}$C NMR in CD$_3$CN
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

**542 (minor isomer)**

*300 MHz $^1$H NMR in CDCl$_3$*

**542 (minor isomer)**

*75 MHz $^{13}$C NMR in CDCl$_3$*
25. NMR Spectral Data

300 MHz $^1$H NMR
In CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

300 MHz $^1$H NMR in CDC$_3$

100 MHz $^{13}$C NMR in CDC$_3$
25. NMR Spectral Data

994
300 MHz $^1H$ NMR in CDCl$_3$

994
100 MHz $^{13}C$ NMR in CDCl$_3$
25. NMR Spectral Data
300 MHz $^1$H NMR in CDCl$_3$
25. NMR Spectral Data

400 MHz $^1$H NMR in CD$_3$CN

100 MHz $^{13}$C NMR in CD$_3$CN
25. NMR Spectral Data

500 MHz $^1$H NMR in CDCl$_3$

125 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

400 MHz DQF-COSY in CDCl$_3$
25. NMR Spectral Data

- 400 MHz DQF-COSY in CDCl₃
- 400 MHz HSQC in CDCl₃
NMR Spectral Data
300 MHz $^1$H NMR in $d_6$ DMSO

100 MHz $^{13}$C NMR in $d_6$ DMSO
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

400 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
NMR Spectral Data

1135
300 MHz $^1$H NMR in CDCl$_3$

1135
75 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

300 MHz $^1$H NMR in CDCl$_3$

1150

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

**1148**

300 MHz $^1$H NMR in CDCl$_3$

**1148**

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

1157
400 MHz $^1$H NMR
in CDCl$_3$

1157
100 MHz $^{13}$C NMR
in CDCl$_3$
25. NMR Spectral Data

1158
400 MHz $^1$H NMR in CDCl$_3$

1158
100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

1152

400 MHz \(^1\text{H}\) NMR
In CDCl\(_3\)

1152

100 MHz \(^{13}\text{C}\) NMR
In CDCl\(_3\)
25. NMR Spectral Data

1183
600 MHz $^1$H NMR in CD$_3$OD

1183
150 MHz $^{13}$C NMR in CD$_3$OD
25. NMR Spectral Data
25. NMR Spectral Data

600 MHz HMBC in CD3OD

1183
25. NMR Spectral Data

1184
600 MHz $^1$H NMR in CD$_2$OD

1184
150 MHz $^{13}$C NMR in CD$_2$OD
25. NMR Spectral Data

1184
600 MHz DQF-COSY in CD$_3$OD

1184
600 MHz HSQC in CD$_3$OD
25. NMR Spectral Data

1184
600 MHz HMBC in CD$_2$OD
25. NMR Spectral Data
25. NMR Spectral Data

400 MHz $^1$H NMR in CD$_3$OD

100 MHz $^{13}$C NMR in CD$_3$OD
25. NMR Spectral Data
25. NMR Spectral Data

1197 (mixture of isomers)
400 MHz $^1$H NMR
In CD$_3$OD

1197 (mixture of isomers)
100 MHz $^{13}$C NMR
In CD$_3$OD
25. NMR Spectral Data

1198

400 MHz $^1$H NMR in CD$_3$OD

1198

100 MHz $^{13}$C NMR in CD$_3$OD
25. NMR Spectral Data

1199
400 MHz $^1$H NMR
in d$_6$-DMSO

1199
100 MHz $^{13}$C NMR
in d$_6$-DMSO
25. NMR Spectral Data

400 MHz HMBC in d$_6$-DMSO
25. NMR Spectral Data

1200
400 MHz $^1$H NMR in CDCl$_3$

1200
100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

**1201**

400 MHz $^1$H NMR in CDCl$_3$

**1201**

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data

**1204**

400 MHz $^1$H NMR in CDCl$_3$

100 MHz $^{13}$C NMR in CDCl$_3$
25. NMR Spectral Data
25. NMR Spectral Data

1211
400 MHz $^1$H NMR in CDCl$_3$

1211
100 MHz $^{13}$C NMR in CDCl$_3$
DATE OF BIRTH
January, 9th, 1986

CITIZENSHIP
Swiss

EDUCATION
Kantonsschule Frauenfeld (High School), Thurgau, Switzerland
08/2000 to 07/2004, Matura in 2004

Eidgenössische Technische Hochschule Zürich, Zürich, Switzerland;
Bachelor Studies in Biochemistry; 08/2004 to 07/2007
Master Studies in Biological Chemistry, with special focus on Organic Synthesis; 08/2008 to 02/2009
Advisor: Professor Erick M. Carreira
Master thesis: Towards the Total Synthesis of Dysinosin D and Aeruginosin 298B
Master Diploma in Biology; 09/2009, „with distinction”

Undergraduate Research Project, Eidgenössische Technische Hochschule Zürich, Zürich, Switzerland
Advisor: Professor Peter H. Seeberger
08/2007 to 01/2008
Towards the Total Synthesis of 3-Deoxy-D-manno-octulosonic acid (KDO) Using Enzyme Catalyzed Aldol Reactions

Undergraduate Research Project, Eidgenössische Technische Hochschule Zürich, Zürich, Switzerland
Advisor: Professor René Peters
02/2008 to 07/2008
Ferrocene Bisimidazoline Palladium Complexes as Potential Catalysts for Enantioselective Michael and Caroll Reactions

Graduate Studies in Organic Chemistry
Eidgenössische Technische Hochschule Zürich, Zürich, Switzerland;
09/2009 to present
Advisor: Professor Erick M. Carreira
Total Synthesis of Alkaloid Natural Products

INTERNSHIPS
Student Research Biologist, Institut für Nutztierwissenschaften, Eidgenössische Technische Hochschule Zürich, Zürich, Switzerland
Advisor: Professor Peter Vögeli
09/2001 to 10/2001
Genetic studies of inheritable diseases in pigs

Schweizer Jugend Forscht, Syngenta Crop Protection AG, Stein, Switzerland;
10/2002
Studies towards the early detection of Septoria tritici infection in wheat

Research Chemist, Department of Chemistry, Boston University, Boston MA, USA
Advisor: Professor Corey R.J. Stephenson
05/2009 to 08/2009
New Avenues in Photoredox Catalysis
TEACHING

Undergraduate Teaching Assistant, 09/2008 to present
Eidgenössische Technische Hochschule Zürich, Zürich, Switzerland
Teaching Assistant for “Organic Chemistry I” and “Organic Synthesis: Methods and Strategies”

Supervision of two Undergraduate Research Project, 09/2010 to 12/2010 and 05/2012 to 08/2012
Eidgenössische Technische Hochschule Zürich, Zürich, Switzerland
“Directed Regioselective Reductive Opening of Epoxides by Ti(III)” and “Mechanistic Investigations of the Cyclopropaneisoxazolidine ring contraction”

Teaching Assistant for practical course, 02/2012 to 05/2012
Eidgenössische Technische Hochschule Zürich, Zürich, Switzerland
Teaching Assistant for “Praktikum Organische Chemie I”

AWARDS AND FELLOWSHIPS

Willi Studer Award 2009, Zürich, Switzerland; 2009
Award for the best Master Diploma in the Department of Biology
Novartis Master Fellowship 2007, Zürich, Switzerland; 2008
Novartis Predoctoral Fellowship 2010, Zürich, Switzerland; 2010
SSCI Fellowship 2011 (Stipendienfonds Schweizerische Chemische Industrie), Zürich, Switzerland; 2011 to present
First Prize Syngenta PhD workshop 2012, Syngenta Crop Protection AG, Stein, Switzerland; 2012
First Prize Roche Symposium Leading Chemists 2012, F. Hofmann-La Roche AG, Basel, Switzerland; 2012
Member of the „Schweizerische Studienstiftung“; Zürich, Switzerland
Foundation promoting and supporting academically gifted individuals 2008 to present

LANGUAGE SKILLS

German (native language); English (fluently); French (advanced level); Spanish (intermediate level)