Applications of molecular modeling and supramolecular chemistry: de novo design of MHC class II inhibitors and rational design of ligands for asymmetric catalysis

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Applications of Molecular Modeling and Supramolecular Chemistry:
*De Novo* Design of MHC Class II Inhibitors
and
Rational Design of Ligands for Asymmetric Catalysis

A dissertation submitted to the
SWISS FEDERAL INSTITUTE OF TECHNOLOGY ZÜRICH

for the degree of
Doctor of Natural Sciences

Presented by

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Prof. Dr. Hans-Jürg Borschberg, co-examiner
Dr. Gary L. Olson, co-examiner

Zürich 1998
À mes parents,
pour leurs encouragements, leur aide et leur amour
The most fundamental and lasting objective of synthesis is not production of new compounds, but production of properties.

George S. Hammond
Norris Award Lecture, 1968
Acknowledgements

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**Abbreviations**

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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Å</td>
<td>Angstrom (1 Å = 10⁻¹⁰ m)</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azobisobutyronitrile</td>
</tr>
<tr>
<td>Anal.</td>
<td>analytical</td>
</tr>
<tr>
<td>APC</td>
<td>antigen-presenting cell</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>butyllithium</td>
</tr>
<tr>
<td>°C</td>
<td>degree centigrade (0 °C = 273.15 K)</td>
</tr>
<tr>
<td>calc.</td>
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</tr>
<tr>
<td>Cbz</td>
<td>benzyloxycarbonyl</td>
</tr>
<tr>
<td>CD</td>
<td>circular dichroism</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated</td>
</tr>
<tr>
<td>COSY</td>
<td>correlated spectroscopy</td>
</tr>
<tr>
<td>CVFF</td>
<td>Consistent-Valence-Force-Field</td>
</tr>
<tr>
<td>DAST</td>
<td>diethylaminosulfur trifluoride</td>
</tr>
<tr>
<td>de</td>
<td>diastereoisomeric excess</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>decomp.</td>
<td>decomposition</td>
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<td>DEI</td>
<td>desorption electron impact</td>
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<td>DHC-CLB</td>
<td>dihydrocinchonine p-chlorobenzoate</td>
</tr>
<tr>
<td>DHQ-CLB</td>
<td>dihydroquinine p-chlorobenzoate</td>
</tr>
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<td>DHQD-CLB</td>
<td>dihydroquinidine p-chlorobenzoate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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</table>
DMF  dimethylformamide
DMPU  $N,N'$-dimethyl-$N,N'$-propylene urea
EDC  $N'$-(3-dimethylaminopropyl)-$N$-ethylcarbodiimide hydrochloride
ee  enantiomeric excess
EI  electron impact
ESI  electrospray ionization
Et  ethyl
Et$_2$O  diethyl ether
EtOAc  ethyl acetate
EtOH  ethanol
FAB  fast atom bombardment
g  gram
h  hour
HIV  human immunodeficiency virus
HLA  human leucocyte antigen
HMPT  hexamethylphosphorous triamide
HOBt  1-hydroxybenzotriazole
HOMO  highest occupied molecular orbital
HPLC  high performance liquid chromatography
HR  high resolution
Hz  Hertz, (s$^{-1}$)
IR  infrared (spectroscopy)
$J$  coupling constant
K  Kelvin
kcal  kilocalories
l  liter
LDA  lithium diisopropylamide
lit.  literature (reference)
LUMO  lowest unoccupied molecular orbital
M  molarity (moles·l$^{-1}$)
m  meta
MAb  monoclonal antibody
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>MAS</td>
<td>magic angle spinning</td>
</tr>
<tr>
<td>MCMM</td>
<td>Monte-Carlo Multiple Minimum</td>
</tr>
<tr>
<td>MHC</td>
<td>major histocompatibility complex</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
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<td>milligram</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>ml</td>
<td>milliliter</td>
</tr>
<tr>
<td>µl</td>
<td>microliter</td>
</tr>
<tr>
<td>MM</td>
<td>molecular mechanics</td>
</tr>
<tr>
<td>mM</td>
<td>millimolar (10^{-3} M)</td>
</tr>
<tr>
<td>µM</td>
<td>micromolar (10^{-6} M)</td>
</tr>
<tr>
<td>mmol</td>
<td>millimoles</td>
</tr>
<tr>
<td>mol</td>
<td>moles</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>M.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>nM</td>
<td>nanomolar (10^{-9} M)</td>
</tr>
<tr>
<td>NMM</td>
<td>4-methylmorpholine</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear <em>Overhauser</em> effect</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>Pec</td>
<td>pipecolic acid</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>pentamethylbenzene</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PTC</td>
<td>phase transfer catalysis</td>
</tr>
<tr>
<td>quant.</td>
<td>quantitative</td>
</tr>
</tbody>
</table>
quats  quaternary ammonium salt
QM    quantum mechanical
resp. respectively
r.t.   room temperature
SAR   structure-activity relationship
sat.  saturated
soln. solution
SOMO  singly occupied molecular orbital
SPA   scintillation proximity assay
'Bu  tert-butyl
TCR   T-cell receptor
TFA   trifluoroacetic acid
THF   tetrahydrofuran
TLC   thin layer chromatography
TMEDA $N,N,N',N'$-tetramethylenediamine
UV    ultraviolet
VIS   visible
Abstract

In the past few years, supramolecular chemistry has received much attention, resulting in a greater understanding of the weak, non-covalent forces governing intermolecular interactions (Chapter 1). The emergence of computer calculations has, moreover, allowed quantification of these interactions, opening the door to the design of new molecules with pre-defined supramolecular properties.

In medicinal chemistry, molecular modeling has changed the way new drugs are discovered and developed (Chapter 2.1). De novo drug design can be considered as an alternative to the traditional screening methods used for the discovery of lead structures. The HLA-DR molecules are a family of major histocompatibility complex (MHC) class II proteins which play a central role in the immune system. They have been shown to be linked to rheumatoid arthritis. The availability of an X-ray crystal structure of HLA-DR1 complexed with the HA 307-319 peptide makes them suitable for a de novo design approach to potential inhibitors (Chapter 2.2). First generation inhibitors were designed and synthesized with the aim of preserving the interactions present between the protein and a natural peptide in the three-dimensional structure (Chapter 2.3). The inhibitors consist of the cyclic sulfonylurea scaffold I, hydrogen-bonding to the MHC protein. This scaffold has two side-chains; the first (R1) is aromatic and was designed to complex a large hydrophobic pocket, while the second (R2) was intended to reach another region of the binding groove where important functionalities for hydrogen bonding are present. These compounds however exhibited only low potency (single digit millimolar inhibition for the HLA-DR4 protein).

Second generation inhibitors were designed by modifying the R2 side-chain (Chapter 2.4). A simplified compound, prepared as synthetic model, proved inactive. The synthesis of the second generation nonpeptide inhibitors was however not finished as priority was moved onto peptidomimetic inhibitors (Chapter 2.5). These compounds still incorporate the sulfonylurea scaffold, but in addition to the R1 aromatic side-chain,
a peptide residue was attached as second functionality (R2). Urea analogs (scaffold II) were also prepared to investigate the effect of structural modification of the cyclic template. None of these compounds showed improved binding affinity for HLA-DR molecules. A hypothesis for the decreased potency observed when using the peptidomimetic scaffolds I or II compared to fully peptidic compounds is presented (Chapter 2.6), and structural modifications for next generation inhibitors are proposed.

Computer calculations were next applied to asymmetric catalysis, a field where the rational design approach has not yet been exploited (Chapter 3.1). Ligands incorporating a 1,1'-binaphthyl unit substituted in the major groove by a Cinchona alkaloid moiety were designed for enantioselective phase transfer catalysis (Chapter 3.2). The unsymmetrical 1,1'-binaphthyl fragment was prepared via the oxidative cross-coupling of two differently substituted naphthalen-2-ols, and resolved using camphorsulfonyl chiral auxiliaries. Coupling with the alkaloid unit was achieved by nucleophilic addition of a 1,1'-binaphthyllithium to a Weinreb amide-type quinuclidine. Subsequent stereoselective reduction of the resulting carbonyl afforded the four precursors III with different configurations at C(8) and C(9). These compounds were quaternized and used as phase transfer agents for the PTC allylation of 6,7-dichloro-5-methoxy-2-phenylindanone, giving 6 to 32% ee's. Monte-Carlo computer calculations were in agreement with the experimental enantioselectivities and in each case correctly predicted the preferentially formed enantiomers. An attempt to immobilize phase transfer agents into organically modified aerogels was made to allow complete and easy recovery of such catalysts. Covalent incorporation of dihydrocinchonine quats resulted in a large decrease in enantioselectivity (from 73% to 7%) in the allylation of 6,7-dichloro-5-methoxy-2-phenylindanone, but represents, nevertheless, the first example of an enantioselective silicate sol-gel catalyst.

The p-chlorobenzoate esters of diastereoisomers III were used in the Sharpless asymmetric dihydroxylation (Chapter 3.3), and revealed in some cases useful catalytic activity for the enantioselective dihydroxylation of trans-stilbene (2 to 67% ee). Studies towards the synthesis of 1,1'-binaphthyl compounds substituted in the minor groove with a Cinchona alkaloid have also been made (Chapter 3.4).
Résumé

Ces dernières années, la chimie supramoléculaire a reçu une attention toute particulière. Il en a résulté une bien meilleure compréhension des interactions faibles gouvernant la formation d'édifices de ce type (Chapitre 1). De plus, l'apparition de la simulation assistée par ordinateur a ouvert la porte au design de nouvelles molécules ayant des propriétés supramoléculaires prédéfinies.

En chimie médicinale, la modélisation moléculaire a modifié la manière dont les médicaments sont découverts et développés (Chapitre 2.1). La conception de novo de médicaments peut être considérée comme une alternative aux méthodes d'échantillonnage traditionnellement utilisées pour la découverte de composés têtes de série. Les molécules HLA-DR sont une famille de protéines du complexe majeur d'histocompatibilité (CMH) de classe II, jouant un rôle central dans le système immunitaire et qui sont liées à l'arthrite rhumatoïde. L'existence d'une structure cristallographique de HLA-DR1 complexé par le peptide HA 307-319 a permis la conception de novo d'inhibiteurs potentiels (Chapitre 2.2). Une première génération a été modélisée et synthétisée avec le souci de préserver les interactions présentes entre la protéine et le peptide naturel dans la structure en trois dimensions (Chapitre 2.3). Ces inhibiteurs ont la structure I, une sulfonylurée formant des liaisons hydrogène avec le CMH. Ils possèdent en outre deux chaînes latérales; la première (R1), aromatique, a été modelisée pour complexer une grande cavité hydrophobe, alors que la seconde (R2) doit atteindre une autre partie du site actif où d'importants groupes fonctionnels pouvant former des liaisons hydrogène sont présents. Ces composés n'ont cependant qu'une faible activité (inhibition millimolaire de HLA-DR4).

Les inhibiteurs de la seconde génération ont été modélisés en modifiant R2 (Chapitre 2.4). Un composé simplifié, préparé comme modèle, s'est révélé inactif. La synthèse des inhibiteurs de la seconde génération n'a cependant pas été terminée, la priorité ayant été donnée aux inhibiteurs peptidomimétiques (Chapitre 2.5). Ces composés, en plus de la sulfonylurée cyclique et du substituant aromatique R1,
contiennent un peptide comme second groupe fonctionnel (R²). Des urées (structure II) ont également été préparées comme analogues. Aucune de ces molécules n'a cependant montré une meilleure affinité envers les protéines HLA-DR. Une hypothèse expliquant la faible affinité des structures de type I ou II est présentée (Chapitre 2.6), et des modifications sont proposées pour une future génération d'inhibiteurs.

Le calcul assisté par ordinateur a ensuite été appliqué à la catalyse asymétrique, un domaine où des méthodes de conception rationnelles n'ont pas encore été utilisées (Chapitre 3.1). Des ligands incorporant un groupe 1,1'-binaphthyl substitué dans le grand sillon par un Cinchona alcaloïde ont été conçus comme ligands pour la catalyse énantiométrique par transfert de phase (Chapitre 3.2). Le fragment 1,1'-binaphthyl non symétrique a été préparé par le couplage croisé oxidatif de deux naphthalen-2-ols différemment substitués et dédoublés à l'aide d'auxiliaires camphresulfonés chiraux. Le couplage avec la partie alcaloïde a été réalisé par addition nucléophile d'un 1,1'-binaphthyllithium sur une amide de Weinreb dérivée d'une quinuclidine. Le groupe carboxyl en résultant a ensuite été réduit stéréosélectivement pour fournir les quatre précurseurs III ayant différentes configurations en C(8) et C(9). Ces composés ont été quaternisés puis utilisés comme catalyseurs par transfert de phase pour l'alllylation du 6,7-dichloro-5-methoxy-2-phénylindanone avec 6 à 32% d'ee. Les calculs Monte-Carlo étaient en accord avec les énantiométries obtenues expérimentalement. D'autre part, ils ont correctement prédit quel serait l'énantiomère en excès, ceci dans chaque cas. Un essai d'immobilisation des catalyseurs sur des aérogels modifiés a été effectué afin de permettre un recyclage facile et complet de ceux-ci. Une forte diminution de l'énantiométrie pour l'alllylation du 6,7-dichloro-5-methoxy-2-phénylindanone (de 73 à 7%) a résulté de l'incorporation d'une dihydrocinchonine quaternisée. Il s'agit néanmoins du premier exemple de catalyseur sol-gel énantiométrique.

Les esters p-chlorobenzoate des diastéréoisomères III ont été utilisés dans la dihydroxylation asymétrique de Sharpless (Chapitre 3.3) et ont, dans certains cas, montré une énantiométrie lors de la dihydroxylation du trans-stilbène (de 2 à 67% ee). Des études en vue de la synthèse de dérivés 1,1'-binaphthyl substitués dans le petit sillon par un Cinchona alcaloïde ont également été effectuées (Chapitre 3.4).
1. Introduction

The 'lock-and-key' concept introduced by Emil Fischer [1] around 100 years ago can be seen as the beginning of supramolecular chemistry and certainly is a major keystone in today's chemistry. This metaphor, comparing enzyme and substrate to lock and key, points out that two molecules need good steric and electronic complementarity in order to fit together and have strong binding affinity. Much has been done to understand and quantify the weak non-covalent forces [2-5] which are governing intermolecular interactions:

- electrostatic interactions:

Electrostatic interactions are a result of different static charge distribution in molecules. Ionic interactions, where two charged groups are involved obey the Coulomb law which states that the energy is inversely proportional to the distance between the ions (1/r) and to the dielectric constant of the surrounding medium. Such salt bridges are very important in for example proteins. At physiological pH (ca 7.4), the guanidine side-chain of arginine and the amine side-chain of lysine are protonated, therefore positively charged, and the carboxylic acid side-chains of aspartate and glutamate are deprotonated and so negatively charged. Depending on the micro environment, energies of ionic interactions between proteins and ligands can vary from 0.2 to 5 kcal/mol [6]. Ion-dipole interactions between a charged group and a dipole (a group having an asymmetric electron distribution) are lower in energy and more strongly distance dependent (1/r^4). In particular, cations are strongly attracted by the \( \pi \) face of aromatic rings owing to interactions between a positive charge and the quadrupole moment of the aromatic \( \pi \) system [7]. Dipole-dipole interactions are weaker and their energy falls off as 1/r^6. However, they are ubiquitous, applying to almost any molecule, and are therefore also important in supramolecular chemistry.
Chapter 1

- hydrogen bonds:

The H-bond is an attractive electrostatic force between a proton donor group (hard acid) and an electronegative atom (hard base). The proton is generally at its normal covalent bond distance from the atom to which it is formally bonded, and at a longer distance (from 1.5 to 2.5 Å) from the second atom. This is however not the case for strong ionic H-bonds where the distance between the donor atom and the hydrogen is elongated. The optimal configuration is linear, although bending has been shown to cause only small energy losses [8]. To a first approximation, the strength of a hydrogen bond depends on the acidity of the X-H group and on the basicity of the Y atom [9,10]. With Gibbs free energy estimated between 3 and 9 kcal/mol in proteins [2,11], H-bonds are of particular importance in providing significant binding free energy. A statistical analysis of high resolution protein crystal structures showed that less than 2% of the potential hydrogen bond donors or acceptors are buried without forming a hydrogen bond [12]. The favorable contribution of hydrogen bonds to the enzyme-substrate binding free energy essentially arises from the entropic factors: the entropy of water involved in hydrogen-bonding to the enzyme or substrate is lower when compared to that of bulk water [13].

- non-polar interactions (van der Waals or dispersion forces):

Atoms in non polar molecules have temporary, non symmetrical distribution of electron density as a result of the movement of electrons around the nuclei. As atoms from different molecules approach one other, temporary, opposing dipoles are induced, resulting in an intermolecular attraction known as van der Waals or dispersion force. Such interactions have a potential energy curve given by:

\[ U = A/r^{12} - B/r^6 \]

with a most favorable distance of separation known as the van der Waals contact distance. Although the attractive forces are weak (0.01 to 0.5 kcal/mol for pairs of atoms at optimal separation [14]), they are additive and can make significant contributions to binding when summed over the whole molecule.

- hydrophobic interactions:

Hydrophobicity is a way of describing the tendency of non polar groups to come in close contact to each other in water [15,16]. The aggregation of lipophilic molecules is accompanied by the release of many structured water molecules
from the near vicinity of the apolar solute. As a consequence, the released water molecules from the organized solvation shells are no longer positionally confined and this orientational freedom results in a gain in entropy. There is also an enthalpic contribution to hydrophobic interactions since the released water molecules can form hydrogen bonds with other water molecules more efficiently than when occupying lipophilic binding sites [17]. The specific interactions between aromatics rings are of particular importance and have gained increasing attention. Aryl groups prefer to associate in either a face-to-face ($\pi-\pi$ stacking) or an edge-to-face (T-shaped) orientation. Calculations [18] as well as analysis of protein structures [19] tend to indicate that T-shaped conformations are more favorable although this can be substituent dependent.

These non covalent forces play a major role in determining the structures of biological macromolecules and in mediating processes such as receptor-ligand interactions, enzyme-agonist or -antagonist complexation and catalyst-substrate binding.

Having looked at the different forces involved in supramolecular chemistry, we will next discuss approaches to predict them by means of computer calculations. The rapid evolution of computers nowadays allows the chemist to examine compounds from the atomic to the supramolecular level. Computer calculations can be carried out at very different levels depending on the inevitable simplifying assumptions made. The extent of these assumptions is more or less dictated by the size of the molecules to be calculated. The computational methods can be roughly divided into two groups:

- quantum mechanical simulations:

  Quantum mechanical (QM) simulations [20,21] are based on the Schrödinger equation and, owing to their accuracy, are very demanding in terms of computational time. One can distinguish two further levels of approximation. \textit{Ab initio} methods [20,22] do not use any empirical parameters and are the most accurate kind of calculations since they have an exact physical basis. \textit{Semi}-empirical methods [23-25] neglect the more complicated integrals of the \textit{Hartree-Fock} matrix and use instead empirically derived parameters.

- molecular mechanics methods:

  Molecular mechanics (MM) methods [26,27] consider the atoms as points interacting with each other through completely empirical potential energy functions defined in the force field. The total energy of the system is defined as
the sum of several terms representing the energy of bond stretching ($E_s$), angle bending ($E_b$), torsional interactions ($E_{tor}$), *van der Waals* interactions ($E_{vdW}$) and electrostatic interactions ($E_{elec}$):

$$E_{total} = E_s + E_b + E_{tor} + E_{vdW} + E_{elec}$$

These potentials are only parameterized for the ground state, but allow simulations on larger systems such as proteins or solvated organic molecules. There exist two main techniques for generating the different possible conformations. In *Monte-Carlo* simulations [28], the atoms are displaced in a random way and the new configuration accepted or not, depending on the change in potential energy. *Molecular dynamics* [29-31] use the equations of motion to generate a trajectory, which describes the dynamics of the molecular system.

The subject of this work is to benefit from such computer calculation techniques in order to design new molecules with supramolecular properties. Based on the non-covalent forces previously described and using molecular modeling to calculate and evaluate them, our goal is to access organic molecules with pre-defined characteristics. This was carried out first on a medicinal chemistry project where the design and synthesis of antagonists was attempted. In a second project, design, synthesis, and evaluation of asymmetric ligands for enantioselective catalysis was undertaken. These two examples are the subject of this dissertation and will be presented separately in the following chapters.
2. De Novo Design of MHC Class II Inhibitors

2.1 Medicinal Chemistry: An Introduction

The discovery of new drugs remains one of the most challenging areas in chemical research. However, there is a constant evolution in the way new bioactive compounds are discovered. In the nineteenth century and the first part of the twentieth century, most of medicinal chemistry lay in the isolation and purification of active compounds principally from plants and other natural sources. The first drugs were therefore naturally occurring molecules, for example penicillin (1) discovered by Fleming from Staphylococcus aureus in 1928 [32]. Usually, the structural basis of the molecule's activity was discovered much later. By the mid twentieth century, it was realized that changes in chemical structure lead to an increase or decrease in potency and molecular modification of natural products for better drugs was initiated. The classical way of developing a new drug therefore was and still remains the random screening of massive libraries containing naturally occurring and synthetically obtained molecules, followed by modification of the lead compounds in conjunction with biological evaluation. Structure-activity relationships (SAR) and isosteric replacement [33] are used for lead modification. However, one has to recognize that chance plays a major role in such a drug discovery process.
Such was the discovery of the benzodiazepine tranquilizers by Sternbach leading to Valium (2), one of the most successful drugs in the history of medicinal chemistry [34]. Non-random screening is a slightly different approach where compounds which resemble weakly active molecules are tested in a bioassay. However, none of these traditional methods involves a major rational component and random synthesis of compounds for screening is not a cost-effective way of making new drugs (except maybe in the case of combinatorial chemistry [35,36] where a large number of compounds can be synthesized during the same experiment).

Nowadays, progress made in supramolecular chemistry and molecular modeling (see Chapter 1), as well as in molecular biology and X-ray crystallography has made more rational approaches to drug design a real possibility [37-46]. When a potential therapeutic target is identified, and structural information is available, then there is the possibility for a rational approach to drug discovery. NMR techniques are useful in elucidating the general 3D structure of small proteins [47,48], but X-ray crystallography is the method of choice for accessing accurate structural information of therapeutically relevant macromolecules [38]. A high resolution X-ray crystal structure can indeed provide crucial information on the active site in terms of size, shape, and electrostatic properties and therefore is usually the starting point of rational drug design. Furthermore, the advent of powerful computer graphics has made it possible to visualize and analyze proteins as well as to optimize ligands within their active sites. Docking is the term for computer-assisted molecular modeling of a molecule into its receptor. Such design using X-ray crystal-structure-based information can be divided into two types:

- analog-base or structure-based drug design:

Analog-based design is an iterative approach where the structure of a receptor-inhibitor co-crystal is generally utilized in order to optimize binding. Knowledge of the three-dimensional structure of a lead within the active site can greatly facilitate the optimization of its binding properties, based on receptor and ligand complementarity. Cycles of crystallographic analysis, design, synthesis, and evaluation can be repeated in order to find the best possible drug candidate. Many examples of such a rational drug design have already been published and rational lead optimization is now widely used in the pharmaceutical industry. For example, after a screening program to identify HIV protease inhibitors, an iterative structure-based design process was carried out and afforded sulfonamide 3 as an optimized non-peptidic drug candidate [49].
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- de novo drug design:

Molecular modeling of drug candidates within an active site is not limited to molecules which resemble the natural ligand of the receptor or a known lead compound whose structure has been determined. Once the binding site has been characterized, completely novel and specific structures can be created and docked to determine which shape fits best a particular receptor binding site. Such a purely rational drug design can be seen as the ultimate goal of medicinal chemists. New programs have emerged to automatically build up candidate ligands from atoms or fragments [50-55]. Most automated docking methods dock the ligand in a fixed conformation into a rigid binding site. Performing a search which would allow for conformational flexibility of both binding partners, would be very time consuming, but could have the advantage of not missing active compounds as a result of an unfortunate choice of ligand or receptor conformation. Having a good scoring function to estimate the free energy of binding is also a critical point to select the best ligands. The crucial problem however is to evaluate the synthetic accessibility of the suggested molecules. An interactive design approach is therefore a valuable alternative to automated database searching since only molecules that can be prepared will be considered. In addition, this method benefits from the chemist's experience, creativity, and intuition.
Hirschmann et al. have for example successfully replaced the cyclic hexapeptide structure of the somatostatine hormone analog 4 by a β-D-glucose scaffold (molecule 5), maintaining the side chains critical for the biological activity [56]. Even more impressive are cases where a cyclic scaffold, commonly used to rigidify the molecule, not only bears some important side chains but is directly involved in key interactions, as is the case with the cyclic urea 6, a HIV protease inhibitor [57], or the bicyclic molecule 7, a thrombin inhibitor that was developed within this group [58].

\[ \text{Chemical structures of molecules 6 and 7.} \]

The \textit{de novo} construction of potential bioactive molecules based solely on 3D structures of macromolecular receptors however remains a very difficult and challenging field. Nevertheless, it can be expected that this promising research area will dramatically expand over the next few years and that drug discovery will be accelerated by its judicious application.

\section*{2.2 Major Histocompatibility Complex Proteins}

\subsection*{2.2.1 General Considerations: The Immune System}

To protect the body against microorganisms and to fight infections and diseases, more advanced vertebrates have developed an elaborate immune system that can recognize pathogens and selectively respond to them. At the molecular level, this response is the search for foreign molecules called antigens that are the ultimate target to be identified and eliminated. The immune system adapts its response to the nature of the pathogen and the way in which it invades the body. Indeed, there are two aspects to
this defense, corresponding to the nature and, more particularly, to the location of the antigens. The humoral immune response acts against antigens present outside the host's cells while the cellular immune response targets the antigens established inside the cell [59-61].

In the humoral immune response, a class of lymphatic cells called B lymphocytes are responsible for detecting pathogens [60-62]. They have specific receptors located on their surface that can recognize antigens selectively. Although each B lymphocyte bears only one kind of receptor, a foreign antigen entering the body generally encounters a lymphocyte having the matching receptors. Thus there are large numbers of lymphocytes in each individual, ensuring the highest possible protection.

A B-type lymphocyte that recognizes and binds an antigen (Figure 1, a) becomes stimulated. It activates other similar B cells (those having the same receptor) which divide themselves several times (b), giving rise to large quantities of activated B lymphocytes (c). They then produce antibody proteins (d) that are soluble forms of their receptors. The antibodies directly bind the parasites (antigens) and neutralize them or mark them for the destructive action of other immunologic molecules such as macrophages or complement enzymes. The antibodies are, in summary, specific immunoglobulins that bind antigens and instigate their destruction.

![Figure 1](image-url)

**Figure 1:** *In the humoral immune response, B lymphocytes recognize antigens and produce antibodies to neutralize them.*

However, despite their enormous diversity and efficiency, antibodies alone cannot provide full protection from infectious attack. Some viruses, bacteria, and parasites
establish their infections inside the host's cells, where antibodies cannot reach them. In these cases, another part of the immune system comes into play.

Similar to the humoral immune response that largely relies on B lymphocytes to fight antigens, the cellular immune response involves cytotoxic T cells called T lymphocytes [60-62]. These cells carry receptor molecules on their surfaces that are similar to antibodies (that is to say similar to B lymphocytes receptors). However T lymphocytes, in contrast to B lymphocytes, cannot recognize free antigens. Before recognition, the antigens must be transported into the cell (Figure 2, a), where they are fragmented into small peptide fragments by the action of proteases of the cathepsin family (b), bound to the molecules of the major histocompatibility complex (MHC) (c) and presented on the cell surface (d) where they can then be recognized by the T cell receptors. Thus, the antigenic peptides have to be 'sandwiched' between the MHC and the T cell molecules in a termolecular complex to elicit a cellular immune response. For the discovery of this fundamental immunological recognition process known as major histocompatibility complex restriction, the 1996 Nobel prize in medicine was awarded to Zinkernagel and Doherty [63].

Figure 2: The cellular immune response requires the presentation of antigenic peptides by MHC molecules before T lymphocytes can recognize them.
There are two fundamental types of major histocompatibility complexes designated class I and class II molecules, that bind antigenic peptides derived from different intracellular compartments [60,61,64]. Peptides that are derived from endogenous proteins (synthesized within the cell) or proteins introduced directly into the cell cytoplasm are found in complexes with MHC class I molecules, while peptides derived from exogenous proteins (coming from outside the cell) that enter the cell by phagocytosis, endocytosis or internalization of the cell membrane are associated with MHC class II molecules. This allows the class II molecules to be elicited without direct interaction with infected cells. Thus, another difference between the two classes of MHC molecules is their location. Class I MHC molecules are found on the surface of most nucleated body cells, binding antigens that are infecting the cell on which they are located. Class II MHC molecules are found only on specialized cells of the immune system termed antigen-presenting cells (APC), recognizing antigens infecting any cell.

The specialization of the immune system does not end with its division into B and T cells. T cells themselves comprise two subpopulations, CD8 (T killer lymphocytes) and CD4 (T helper lymphocytes), each corresponding to one class of MHC molecules. So, peptides bound to class I or class II MHC molecules are the ligands for specific T-cell receptors (TCR) of CD8 and CD4 respectively [60,61,64]. When a T killer lymphocyte recognizes an MHC class I-peptide complex on the surface of an infected cell, it creates chemicals like perforins that kill the cell, thus limiting the spread of the virus. Because of their murderous nature, CD8 T cells are also referred to as cytotoxic T cells. On the other hand, when a T helper lymphocyte binds a MHC class II-peptide complex on the surface of an antigen-presenting cell (Figure 2), it becomes activated (e) and secretes large amounts of lymphokines (f) such as interleukin-1, inducing B cell proliferation (g) and activation (h) so that they start producing antibodies (i). They can actually stimulate a wide range of responses, from complete activation to total inhibition, thus controlling antibody production.

The two parts of the immune system (humoral and cellular immune responses) are therefore not completely separated. So far, B and T lymphocytes have been described as though they operate independently. In fact, they form an interconnected system through a feedback mechanism. T cells can stimulate B cells and promote antibody formation. Thus the recognition of an MHC-peptide complex on the surface of a cell is a critical event in the initiation of all immune responses because it is involved in both humoral and cellular immune response.
2.2.2 Autoimmunity and Selective Immunosuppression

Under normal circumstances, the immune system is self-tolerant, meaning that it can distinguish between self and non-self and that only antigenic peptides are eliminated. This discrimination is carried out primarily by T cells. T cell receptors lacking this ability may break the tolerance of the immune system for self peptides and cause autoimmune diseases. Five percent of adults in Europe and North America suffer from an autoimmune disease. The challenge of clinical immunosuppression is to reduce the destructive immune activity without incurring the complications of immunodeficiency, such as infections.

Many autoimmune diseases show associations with particular MHC alleles (alleles are alternative forms of a gene within a species, resulting in different phenotypes, in this case different MHC proteins), demonstrating that it is the ternary complex between MHC, peptide and TCR that is responsible for the self-tolerance, and not only the T cells themselves. In particular, a relatively large number has been linked to DR alleles [65]. Insulin-dependent diabetes mellitus, an autoimmune disease in which the beta cells of the pancreas are destroyed by the immune system, is associated with HLA-DR3 and HLA-DR4. Rheumatoid arthritis (RA) is characterized by an inflammation of the synovial lining joints and tendons owing to an overproduction of cytokine which stimulates the immune system. Although the mechanism remains so far undetermined, HLA (human MHC) genes contribute to the disease and RA was shown to be linked to HLA-DR1 and HLA-DR4 [66]. Rheumatoid arthritis affects one percent of the world population and is the principal autoimmune disorder in terms of mortality, disability, and economic impact. Current immunosuppressive treatments are inadequate because they are non-specific, meaning that they abolish the activity of the immune system regardless of the antigen. However, based on recent progress in understanding antigen presentation to T cell, new specific therapeutic strategies can be envisaged. In the context of rheumatoid arthritis, which is the concern of our project, new targets have been identified [67,68].

A first approach consists in the neutralization of the cytokines [67]. Natural interleukin-1 receptor (IL-1R) antagonists or tumor necrosis factor (TNF) inhibitors were tested but high doses were required to observe significant improvement. Soluble interleukin-1 receptor can bind IL-1 and prevent its binding to cell receptors, but no significant improvement was shown in clinical tests. Treatment with interferon-γ to inhibit cytokine production resulted in controversial reports. In some cases, the treatment showed improvements in combating the disease whereas other results suggested the converse to be the case.
With their central role in the immune system, T cells offer a second possible target for reducing the immune response. Use of immunosuppressive agents like cyclosporin was investigated but was accompanied by serious side effects. Humanized monoclonal antibodies (MAb) directed against certain cell surface markers expressed on T cells such as CD4, CD5, CD52, and CD7 failed to exert significant effects. Only MAb directed against interleukin-2 receptor (IL-2R), another cell surface marker of T cells, was reported to be beneficial in the preliminary study [69].

Other therapeutic targets are the disease-associated class II MHC alleles. Since peptides binding to the same class II molecule compete with each other [70], selective immunosuppression by blocking the binding site of the alleles linked to rheumatoid arthritis should be possible. One can speak of MHC blockade (Figure 3) when an antagonist occupies the MHC binding site, preventing any peptide, including autoantigens, to be bound and presented to the T cell receptors. As a consequence, selective inhibition of the T-cell response would be achieved, modifying the course of the autoimmune disease.

MAbs directed against appropriate MHC II alleles can inhibit T cell activation. They were tested in animal models with apparent therapeutic effectiveness [71,72], but toxicity might be a problem. Antigenic peptides were also used as class II antagonists [73]. For example, a synthetic MHC II-binding peptide corresponding to residues 53-61 of hen egg white lysozyme was shown to inhibit in vivo T cell activation when administrated in soluble form [74]. The human cartilage glycoprotein-39 (HC gp-39) was also recently reported to bind specifically to MHC class II proteins and, through inhalation, to lead to T cell toleration and suppression of HC gp-39-induced arthritis [75]. Moreover, by selectively binding to the alleles responsible for the disease, the treatment should not deactivate the rest of the immune system so that patients would not suffer from infections as side effects.
Since MHC molecules are of central importance in the immune system, binding studies toward the understanding of their complexation mechanism are of fundamental interest. Such an approach could improve our understanding of immunological recognition processes. Moreover, a molecule that binds to the major histocompatibility complex could, as discussed, lead to selective immunosuppression, reducing destructive immune activity and preventing graft rejection. This would have a tremendous biomedical impact. We were therefore interested in carrying out a drug design study in order to synthesize a molecule binding to HLA-DR, that is to say, an inhibitor specific for the DR alleles of MHC class II proteins.

2.2.3 Structure and Binding of MHC Molecules

The major histocompatibility complex molecules are highly polymorphic membrane glycoproteins. This diversity is consistent with their capacity to bind an extremely large number of structurally diverse peptides. In the human MHC, also known as human leukocyte antigens (HLA), the class I isotopes are subdivided into A, B, and C, while the class II isotopes consist of DR, DP, and DQ (for a review see [76]). In the mouse MHC, called H-2, there are K, D, and L as class I isotopes and I-A and I-E as class II isotopes. Both isotopes are highly polymorphic, comprising up to a hundred different forms or alleles each. Indeed, HPLC experiments that have been made with columns containing immunoaffinity-purified MHC class II molecules have shown that each allele has a characteristic profile of eluted peptides [77-80].

However, a given individual expresses only a small number of different MHC molecules. Thus, each histocompatibility protein must be able to bind a large number of different peptides to ensure an immune response against many possible pathogens. For this reason, only a low degree of specificity is expected in the interaction between peptides and major histocompatibility complex molecules. This raises the intriguing question of how can MHC molecules bind a wide variety of peptides with high affinity and selectivity.

Class I MHC molecules consist of a heavy subunit (45 kDa) non-covalently associated with a lighter β2m subunit (12 kDa). Class II MHC molecules comprise two subunits (called α and β) of similar size (34 kDa and 29 kDa respectively) [81]. They also have similar structures formed by two antiparallel α helices overlying a β-pleated sheet structure. A deep groove located on the top surface of the molecule runs between the two α helices forming the binding site for foreign antigens (Figure 4).
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Figure 4: The peptide is buried into a cleft running between the two antiparallel α helices of HLA-DR molecules.

Not all amino acids are involved in this recognition process. In fact, only a limited number of residues bind to the MHC molecule. Most of the peptidic residues can be widely varied, although in certain positions, one or only a few amino acids recur with considerably increased frequencies. Such residues, called anchor residues, are characteristic and almost invariant for each MHC allotype. They fit into well-separated pockets in the MHC binding cleft, providing most of the binding free energy. Moreover, MHC molecules do not fully use all their pockets for peptide binding. Rather, they preferentially favor one major pocket and one or two minor pockets in the peptide recognition process. Such a limited usage of pockets allows alternate choices of anchor residues and therefore binding of a huge number of different peptides. This could explain the broad but specific binding of peptides to major histocompatibility complex molecules.

MHC Class I Molecules

Within the last few years, considerable progress has been made in understanding the structure of MHC class I molecules. This is mainly the result of the several three-dimensional structures obtained for MHC class I molecules complexed with different peptides [82]. Owing to the success in identifying common structural motifs in class I-associated peptides, a general understanding of peptide binding by MHC class I molecules has been provided. Peptides binding to class I MHC molecules are usually
eight or nine amino acid residues long [82d,83]. That length seems to be optimal for allowing the two ends of a peptide to fit into pockets at the opposite ends of the MHC binding clefts (Figure 5). Conserved pockets at both ends of the peptide-binding groove actually accommodate the -NH$_2$ and -COOH termini of peptides through an extensive hydrogen bond network, providing a major part of the binding free energy and thus defining an optimum length for interaction. Other anchor residues are located at positions 2 and 9, fitting into pockets that determine the allele specificity. The rest of the peptide chain extends above the surface of the cleft and is not strongly constrained by interactions with MHC molecule. This observation that peptides bulge out of the cleft in the middle was well exploited by Schreiber and coworkers [84] who successfully replaced that part of the peptide by a rigid spacer.

**Figure 5:** MHC class I proteins binds peptides by complexing both ends of the peptide.

Recently, two crystal structures of termolecular complexes between MHC class I, peptide, and T cell receptor have been solved [85] and their interactions analyzed [86]. The peptide is bound in the MHC binding groove and the TCR is oriented diagonally on the top of it, interacting both with the MHC and the peptide (Figure 6).

**Figure 6:** The peptide (in white) is bound between the MHC molecule (in blue) and the T cell receptor (in yellow).
MHC Class II Molecules

Although there is little overall homology between class I and class II amino acid sequences, similarities in their tertiary structure as well as similarities in their biological function suggested they would have similar structural features as well as a similar binding groove [87]. So, the crystal structure of MHC class I was used to model the antigen binding site of MHC class II molecules [88].

However, peptides binding to MHC class II molecules are longer and more variable in size than those binding to class I molecules. Most of them have from 12 to more than 20 residues [77,79,80]. Resulting from this lack of a length constraint, it was proposed that peptide ends are not bound into defined pockets like in class I complexes, but that at least one end should extend out of the binding site [77]. In fact, class II-associated peptides are not only longer than class I peptides, but also have a higher degree of heterogeneity at both ends, differing at both the amino and carboxyl termini. Later, both N and C terminal extensions were observed and it was found that both peptide ends could extend out of the MHC binding site, the groove being open at both ends [78,79]. This explained why long peptides with different residues close to the -NH$_2$ and -COOH termini could be accommodated without loss of binding free energy. As a consequence, binding interactions between class II major histocompatibility complexes and peptides mainly involve the central part of the peptide rather than its ends, making comparison with the MHC class I crystal structures irrelevant for that region.

The development of assays for peptide binding to affinity purified class II MHC proteins has permitted the direct measurement of the MHC-peptide interaction, and many class II-associated peptides have been reported in the literature (Table 1). Screening such a large number of peptides should have allowed, as for class I, the identification of common features and thus determination of structural characteristics required for complexation. However, this approach is much more difficult to apply to MHC class II molecules, largely because of the significant size heterogeneity of the binding peptides. Since the critical residues are variably positioned in the different peptides, there is no more reference to align sequences of amino acids. Residues important for binding can actually be located at variable distances from the ends of class II-associated peptides, making comparison of sequences and identification of precise structural requirements for peptide binding very difficult. An original approach was done by calculating an average structural dissimilarity factor based on amino acid sequences in order to align peptides [89]. However, the great overall length of class II-associated peptides gives rise to multiple possibilities for alignment that may have little
biological relevance and so might not reveal the binding pattern as clearly as in the case of class I ligands.

Table 1: Binding Experiments between Peptides and MHC Class II Isotopes.

<table>
<thead>
<tr>
<th>Alleles</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-A</td>
<td>[77-79,89-98]</td>
</tr>
<tr>
<td>I-E</td>
<td>[77,93,96,97,99-103]</td>
</tr>
<tr>
<td>DR</td>
<td>[80,104-139]</td>
</tr>
<tr>
<td>DP</td>
<td>[108,109,139]</td>
</tr>
<tr>
<td>DQ</td>
<td>[108,139]</td>
</tr>
</tbody>
</table>

As a consequence of the peptide structure hardly providing direct information from the key residues involved in the recognition mechanism, various strategies were used to better characterize this complexation:

- Truncation analysis at N and/or C termini of several HLA binding peptides to define the minimal core region required for binding to MHC class II proteins. Alignment of these sequences allows the determination of overlapping residues [78,89,94,100,103,106,109,115,119,125,128,134].

- Single- or poly-amino acid substitution of HLA-associated peptides to elucidate the residues crucial for MHC binding [89,98,100,102,103,109,110,112,116,119,121-123,131,134-137].

- Experiments with biotinylated analogs or other large side chain substituted peptides to explore the steric requirements for class II complexation [103,118,132].

- Selection of peptides from a large, highly diverse library with binding assays to detect enrichment of common motifs taken as crucial for peptide binding [124,133,138,140].

- Binding analysis with modified MHC class II molecules to determine the effect of residue replacement in the MHC protein sequence [141,142].

These methods have allowed a clearer understanding of the association between peptides and MHC class II molecules. Some structural characteristics important for
peptide binding were determined. We will now focus on the HLA-DR alleles which are the target of this work. Since there is no pocket for specially binding the ends of the peptide, binding interactions occur in the middle part of the peptide where five pockets are present (Figure 7).

Figure 7: MHC II proteins bind peptides by complexing their central part.

The DR alleles share significant structural similarities (the α chain is invariant, all the allelic polymorphism being associated with the β subunit) [143], so that general requirements can be presented for those cavities (for reviews see [144-146]):

- The first pocket is highly conserved in all DR alleles and appears to be essential for high affinity interaction (this position is therefore referred as position 1 in the peptide sequence). The only polymorphic residue contributing to the p1 pocket is residue 86 [120,130,131]. If residue 86 is glycine, the pocket is spacious and bulky aromatic residues (F, Y, W) are favored, and if 86 is valine, the pocket is smaller which results in a preference for aliphatic residues (V, I, L) [110,115,117,121-124,128,133,135,136].

- A hydrophobic residue [122,124,133] or amino acids such as Q, N, or D [97,135,136] are accommodated at relative position 4.

- The position 6 pocket determines the allele specificity in peptide binding to HLA-DR molecules. HLA-DR1 binds small amino acids (A, V), whereas HLA-DR4 requires side chains with hydroxyl groups (S, T) and HLA-DR11 positively charged residues (R, K) [79,117,121,123].
• The shallow pocket at position 7 favors small hydrophobic residues. This pocket however does not appear to contribute greatly to the HLA-DR peptide specificity.

• Hydrophobic residues (A, V, I, L) are preferred at position 9 [80,117,121,123,135].

These features allowed the alignment of class II related peptides. For example, some good DR1 binders (Table 2) were compared to show that the various amino acid residues do not have the same importance in complexation. This is illustrated by the high degree of heterogeneity at certain positions, resulting from a lack of structural requirement, compared to very conserved positions corresponding to the p1, p4, p6, p7, and p9 pockets.

Table 2: Sequences and IC$_{50}$ values (concentration of inhibitor producing 50% inhibition) of some good DR1 Binders [114].

<table>
<thead>
<tr>
<th>Protein</th>
<th>Position</th>
<th>Peptide Sequence</th>
<th>IC$_{50}$ [µM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcal nuclease</td>
<td>101-120</td>
<td>L V R Q G L A K V</td>
<td>0.4</td>
</tr>
<tr>
<td>Influenza hemagglutinin</td>
<td>307-319</td>
<td>Y V K Q N T L K L</td>
<td>1.0</td>
</tr>
<tr>
<td>Influenza matrix protein</td>
<td>19-31</td>
<td>L K A E I A Q R L</td>
<td>1.0</td>
</tr>
<tr>
<td>Myelin basic protein</td>
<td>75-98</td>
<td>F K N I V T P R T</td>
<td>2.0</td>
</tr>
<tr>
<td>Tetanus toxin</td>
<td>830-843</td>
<td>Y I K A N S K F I</td>
<td>2.1</td>
</tr>
<tr>
<td>Circumsporozoite protein</td>
<td>378-398</td>
<td>I A K M E K A S S</td>
<td>3.4</td>
</tr>
<tr>
<td>Pigeon cytochrome c</td>
<td>88-104</td>
<td>Y L K Q A T A K</td>
<td>3.4</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>1-15</td>
<td>V K R G L T V A V</td>
<td>3.7</td>
</tr>
<tr>
<td>Ragweed</td>
<td>51-65</td>
<td>V W R E E A Y H A</td>
<td>5.5</td>
</tr>
</tbody>
</table>

More recently, two dimensional NMR analysis of a labeled peptide bound to a mouse class II MHC molecule was performed [147]. A crystal structure determination of a mouse MHC protein was also made [148]. A major improvement was achieved by the attainment of high-resolution crystal structures of human-derived MHC proteins complexed with peptides [149-151] or superantigens [152,153]. These results gave, as for class I, a great deal of information about peptide-MHC complexes [154], confirming largely the characteristics already discovered. In addition to the five cavities already
described, many hydrogen bonds between the peptides and the MHC were revealed. In the structure determined for a complex of HLA-DR1 with an influenza virus peptide [150] fifteen hydrogen bonds between the peptide main chain and the MHC protein are spaced all along the binding groove (Figure 8).

![Figure 8: Crystal structure of HLA-DR1 complexed by an influenza virus peptide [150]. The main interactions consist of hydrogen bonds as well as hydrophobic contacts within the cavities.]

From these structures, the principles of peptide interactions became well understood. Most of the binding forces are provided by the bonds between the peptide backbone and the MHC class II protein. These are non-allele specific interactions, the specificity being determined by the pockets in the MHC binding groove (for reviews see [155-157]). Based on this structural knowledge, pharmaceutical companies have started research programs to access small peptides and peptidomimetic molecules as lead compounds.

*Hoffmann-La Roche* has discovered a heptapeptide [133,138] (Figure 9) with improved potency (IC$_{50}$ = 0.033 µM) compared to the influenza virus peptide found in the crystal structure (IC$_{50}$ = 0.245 µM).
Figure 9: *The Ac-(Cha)RAMASL-NH₂ heptapeptide developed by Roche scientists has an improved potency as compared to the natural influenza virus peptide.*

To determine the minimum peptide length required for binding, the *Roche* group synthesized truncated derivatives of the heptapeptide with consecutive single amino acid deletions from the C-terminus (Table 3) [158]. Elimination of the amino acid at position 7 had little effect, but further truncation significantly reduced the binding affinity. The tetrapeptide was the shortest derivative retaining some activity.

**Table 3:** *Comparison of truncated derivatives showed the minimum peptide length required for maintaining binding affinity.*

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Relative Potency</th>
</tr>
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<tbody>
<tr>
<td>Ac-(CHₐ)RAMASL-NH₂</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>Ac-(CHₐ)RAMAS-NH₂</td>
<td>1.14 0.34</td>
</tr>
<tr>
<td>Ac-(CHₐ)RAMA-NH₂</td>
<td>0.07 0.25</td>
</tr>
<tr>
<td>Ac-(CHₐ)RAM-NH₂</td>
<td>0.005 0.046</td>
</tr>
<tr>
<td>Ac-(CHₐ)RA-NH₂</td>
<td>0.000 0.000</td>
</tr>
</tbody>
</table>

*N*-methylation studies were carried out in order to determine which amide hydrogen atoms in the peptide backbone are participating in binding to the MHC protein. All
seven possible N-methylated peptides have been synthesized and their potency determined. Comparison of their relative potency for DR molecules with Ac-(Cha)RAMASL-NH$_2$ clearly indicated that methylation of the amide nitrogen atoms at residues 1, 3, 5, 6 and 7 had minimal effect on the binding affinity, whereas methylation at position 2 and 4 resulted in anything from a 20-fold to 1000-fold decreased binding affinity (Table 4). These data are consistent with the crystal structure of the influenza virus peptide [150] where hydrogen bonds are formed at position 2 and 4 with Asn $\beta$82 and Gln $\alpha$9 respectively. Their importance can be understood by their buried location at the bottom of the binding groove. The two hydrogen bonds are therefore not exposed to bulk solvent, meaning that only the ligand can form H-bonds with the CO groups of Asn $\beta$82 and Gln $\alpha$9.

Table 4: The relative potency of N-methylated peptides relative to Ac-(Cha)RAMASL-NH$_2$ shows that the amide NH residues at positions 2 and 4 forms hydrogen bonds which are required for strong binding.

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Relative Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DR4</td>
</tr>
<tr>
<td>Ac-(MeCha)RAMASL-NH$_2$</td>
<td>0.67</td>
</tr>
<tr>
<td>Ac-(Cha)(MeR)AMASL-NH$_2$</td>
<td>0.001</td>
</tr>
<tr>
<td>Ac-(Cha)R(MeA)MASL-NH$_2$</td>
<td>0.56</td>
</tr>
<tr>
<td>Ac-(Cha)RA(MeM)ASL-NH$_2$</td>
<td>0.005</td>
</tr>
<tr>
<td>Ac-(Cha)RAM(MeA)SL-NH$_2$</td>
<td>0.60</td>
</tr>
<tr>
<td>Ac-(Cha)RAMA(MeS)L-NH$_2$</td>
<td>0.97</td>
</tr>
<tr>
<td>Ac-(Cha)RAMAS(MeL)-NH$_2$</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Peptides are generally poor drug targets since they are readily cleaved enzymatically in vivo. As a result, identification of peptide mimetics retaining the affinity for the DR alleles was also carried out. The dipeptide mimetics Odapdc 8 and Haic 9 were found to successfully replace the 4-5 site ($IC_{50} = 0.105$ and $0.033 \mu M$ respectively) [158].
It was also possible to combine the dipeptide mimetic modifications with \( N \)-methylated amino acids at position 3 and 6, resulting in analogs with good affinity for DR4 and high activity in T-cell assays. The 6-7 positions were replaced by the more simple serinol group resulting in enhanced affinity (IC\(_{50} = 0.021 \, \mu \text{M}\)). High resolution crystal structures were obtained for complexes between DR4 and some of these ligands. One important result was that the Arg side chain (position 2) is not involved in a salt-bridge interaction with Glu \( \alpha \)55, but is oriented towards the beta chain, stacking against the His \( \beta \)81 residue. Based on these data, the arginine was replaced by an alloisoleucine residue (H\(_2\)N-CH(CH(CH\(_3\))CH\(_2\)CH\(_3\))-COOH) leading to non-Arg peptides with good DR1 and DR4 affinity.

*Merck* scientists have performed SAR studies on tetrapeptide inhibitors [159] resulting in an optimized compound with a nanomolar IC\(_{50}\) value for DR1 (Figure 10).

![Figure 10: Tetrapeptide optimization by SAR has allowed the identification of very potent DR1 inhibitors.](image)

High potency ligands for MHC class II proteins were also reported by *Searle* [160]. Isosteric replacements and conformational restrictions with pipecolic acid (Pec) and proline were performed. In particular, (\( S \))-3-(phenylbutyric acid)V(Pec)DPT-NH-\( n \)-Pr (IC\(_{50} = 50 \, \text{nM}\)) proved to be a potent and stable DR4 ligand (Figure 11).
2.3 First Generation Inhibitors

2.3.1 Molecular Modeling

When this project was initiated, many natural or modified peptides were known to strongly bind to MHC class II molecules. However, the usefulness of peptides or peptide-like molecules as drug candidates has been shown to be limited. They generally have poor pharmacological properties such as oral bioavailability, metabolic stability, and pharmacokinetics. Since no non-peptidic molecules have been described to bind to MHC II proteins and no hit was found from a massive screening process, a de novo design approach appeared to be the method of choice for finding a non-peptidic lead having the required properties. With the structural information accumulated on the MHC binding groove, the knowledge of peptide binding motifs and with a crystal structure available, it should be possible to design a small non-peptidic ligand that could successfully compete with peptides for binding to MHC proteins. Such an inhibitor would probably overcome the problems specific to peptides, which suffer from poor oral bioavailability and low metabolic stability [161-164], and certainly represent a promising drug for the selective immunotherapy of MHC-associated disorders.
We learned from the peptide binding studies that the aromatic pocket at position 1 plays a key role in the recognition process. Four phenylalanines (Phe α24, Phe α32, Phe α54, and Phe β89) and one tryptophan residue (Trp α43) are lining the cavity. The aromatic interactions provided by these residues are required for binding, meaning that this area is a key binding site for HLA-DR ligands. As shown in crystal structures as well as by the N-methylation studies, the hydrogen bonds formed between the substrate and the Asn β82, Gln α9, and Asn α62 residues are also very important for obtaining high potency. These interactions were considered the essential forces governing HLA-DR binding and were used to define a pharmacophore hypothesis (Figure 12). Consequently, we decided to incorporate functional groups into our inhibitor that would preserve them.

![Figure 12: The pharmacophore model illustrates the key interactions for HLA-DR complexation. A designed inhibitor should bear appropriately positioned functional groups for preserving them.](image)

The *de novo* design work began by the removal of the influenza virus ligand from the 2.75 Å crystal structure of the receptor-ligand complex [150], thereby revealing the empty active site. It is preferable to use such a receptor-ligand co-structure rather than an apoprotein, since it will more likely reflect the binding conformation of the protein. Molecular mechanics calculations were performed on Silicon Graphics workstations using two different programs. Insight 2.3.1 together with Discover 2.9.5 was used with the Consistent-Valence-Force-Field (CVFF) which is parameterized for peptides and proteins [165,166]. In Moloc, a program developed by *Hoffmann-La Roche*, the
A generally applicable MAB force field was implemented [167]. This force field was especially parameterized for medicinal chemistry modeling, the electrostatic terms being replaced by geometrical hydrogen bonding terms. In both cases, a geometry optimization of the candidate inhibitor was first performed, and the lowest-energy conformation obtained was manually put into the empty active site. Energy minimization was then carried out, maintaining fixed coordinates for the heavy atoms of the MHC protein, until convergence was reached. Using Insight, a first minimization was performed according to the steepest-descent algorithm, followed by a second one using the conjugate-gradient algorithm.

We started our modeling work by complexing the p1 aromatic pocket and built up a suitable inhibitor from that position. A benzene ring was first docked into the aromatic cavity at position 1 and minimized alone in order to determine its most favorable position inside the cavity. The next step involved the design of a template\(^1\) linked to the benzene ring and bearing the required side chain functionality to hydrogen-bond to Asn \(\beta82\). In order to reduce the unfavorable entropy changes of a bimolecular association, we required a preorganized template, that is to say a rigid molecule having little conformational freedom. A cyclic molecule would serve this purpose since its restricted conformational mobility reduces the entropic costs of complex formation. However, the active site is narrow and cannot accommodate a cyclic scaffold bearing the additional side chain required for making the double hydrogen bond with Asn \(\beta82\). The functional group forming this necessary interaction therefore had to be incorporated within the ring structure. 5-Membered ring lactams and sultams have the appropriate geometry to donate a hydrogen bond to Asp \(\beta82\) while accepting one from the same amino acid residue (Figure 13). The main difference between these two structures is the position of the sp\(^2\) oxygen atoms. The lactam carbonyl group is in the ring plane, whereas the S=O groups of the sultam are above and below it.

![Lactam and Sultam Structures](Image)

**Figure 13:** \(\gamma\)-Lactam and \(\gamma\)-sultam structures were found to be suitable templates for complexing HLA-DR molecules.

\(^1\)In medicinal chemistry, 'template' is commonly used to describe a scaffold bearing functional groups and/or side chains in a defined geometry.
The modeling showed a higher hydrogen-bonding complementarity for the cyclic sulfonamide (the strength of H-bonds towards S=O groups will be discussed in Chapter 2.5.3). Moreover, the top S=O group, which is not involved in hydrogen-bonding to Asn β82, is directed outside the binding groove and was expected to shield the S=O--H-N hydrogen bond located in the cavity below from water molecules, thereby contributing to enhanced binding. It was also recognized that the desolvation energy of this second S=O group might provide a negative contribution to the binding free energy. However, since it is mostly solvent-exposed, this contribution was expected to be reasonably low. Consequently, the γ-sultam was preferred and selected as a template.

The next target was the hydrogen bond network formed by Gln α9 and Asn α62 at position 4. A rigid spacer was required to access the site departing from the template molecule. Because of possible aromatic interactions with Phe α54 and Tyr β78 lining the groove between the template (at position 2) and the Gln α9 and Asn α62 residues (at position 4), we were interested in using a phenyl ring spacer. Indeed, introducing a p-amidomethylphenyl substituent next to the S=O group allowed the formation of three hydrogen bonds between the para primary amide and the Asn α62 and Gln α9 residues. Compared with the influenza virus, a hydrogen bond toward the Gln α9 carbonyl group
is missing. Although burying the carbonyl group of Gln α9 was certainly not optimal (see Chapter 1), this was thought to be compensated for by the additional hydrogen bond formed with the carbonyl of Asn α62. Finally, a synthetically guided modification of the template was made. In order to limit the number of stereogenic centers and to reduce the synthetic complexity of the target molecule, a second nitrogen atom was built into the template, revealing a thiourea structure (Figure 14). This modification had no influence upon binding, and molecular modeling suggested the inhibitor would form five hydrogen bonds with HLA-DR molecules in addition to the aromatic interactions in the p1 pocket. Both the geometry and the length of the hydrogen bonds are almost optimal (Figure 15) and were expected to strongly contribute to the binding energy.

![Figure 15: The minimized ligand-MHC class II structure showed high structural complementarity between the ligand and receptor both in terms of hydrogen bonds and hydrophobic surface (H-atoms are omitted for clarity).](image)

The rigidity and high preorganization of the designed inhibitor was next checked by conformational analysis. A 5000-step pseudo-Monte-Carlo Multiple Minimum (MCMM) calculation in water using the Amber* force-field [168] showed that the low-energy conformations are all very similar to the conformation of the molecule bound to the MHC protein (Figure 16).
A certain degree of conformational flexibility is present in the two aromatic side chains, but this is desirable since movements in the target protein may occur upon ligand binding. A complete analysis of the energy of rotation around the N(2)-C(4') bond was also undertaken. Using the modeling program Insight 2.3.1, successive rotations of one degree were made. After each rotation, the molecule was minimized and the total energy plotted as function of the dihedral angle between the template and the aromatic ring (Figure 17). A rotational barrier of 14.7 kcal was obtained between the two low energy conformations.
In addition to the first designed molecule, modifications of the aromatic side-chain for complexing position 1 were also planned. In analogy to the influenza virus peptide found in the crystal structure [150], a p-hydroxyl substituent was incorporated (inhibitor 11, see Scheme 6). A water molecule located at the bottom of the p1 aromatic pocket would then hydrogen bond to it.

Figure 18: The comparison between the designed inhibitors (in gray) and the natural ligand (in black) showed that the aromatic side chain of 10 is not deep enough in the cavity. The aromatic pocket complexation could be improved with molecules 12 and 13.

Figure 18: The comparison between the designed inhibitors (in gray) and the natural ligand (in black) showed that the aromatic side chain of 10 is not deep enough in the cavity. The aromatic pocket complexation could be improved with molecules 12 and 13.
Another concern was the position of the aromatic ring in the cavity. Comparison of the minimized inhibitor 10 with the natural peptide found in the X-ray structure showed that the designed benzyl side chain does not enter the hydrophobic cavity as deeply as is the case for the natural ligand (Figure 18). In order to optimize this interaction, a longer spacer between the template and the aromatic ring was considered (molecule 12). Another target molecule designed to maximize the aromatic interactions was the naphthalene derivative 13. According to molecular modeling, both molecules 12 and 13 showed improved complexation of the aromatic pocket. Their side chain extends deeper into the cavity and should best mimic the influenza virus peptide (Figure 18). At this stage, the synthesis of the thiazolide inhibitors bearing various side chains for complexation of the p1 hydrophobic pocket was undertaken.

2.3.2 Synthesis

The challenging feature of the targeted inhibitors is the unusual thiazolide moiety. Although many sulfamide-containing heterocycles have been synthesized (for a review see [169]), 1,1-dioxo-1,2,5-thiadiazolidin-3-ones are rather unusual. Only a few examples have been reported, the first by Unterhalt and Hanewacker in 1988 [170], where sulfamide2 15 was cyclized in 1,4-dioxane in the presence of sodium hydroxide to afford the cyclic sulfonyleurea 16 (Scheme 1).

\[ \text{Scheme 1: Thiazolides were synthesized by the cyclization of sulfamides under basic conditions.} \]

2'Sulfamide' is not only used to describe H₂NSO₂NH₂ (14), but is also the general name for all compounds incorporating a sulfonyleurea functionality (for a review on sulfamides see [171]).
Montero and coworkers studied this cyclization with enantiomerically pure sulfamides (R$_2$ = H) and reported that it occurred without racemization at position 4 [172]. The same cyclization was also successfully accomplished using sodium methoxide [173-175] or sodium hydride [176] as base. None of these examples however involved a sulfamide bearing an aromatic substituent as is the case in our target molecules (R$_3$ = Ar). The only reported alternative to 16 is the reaction of α-amino amide 17 with sulfonyl chloride (Scheme 1), however this proceeds in low yield (23 %) [177]. We therefore decided to base our synthesis on the base mediated sulfamide cyclization.

The first method for the synthesis of N, N'-disubstituted sulfamides is the reaction of amines with sulfonyl chloride (Scheme 2) [178]. Even if this reaction was shown to be suitable for N-aryl sulfamide [179], only symmetrical sulfamides can be prepared in that way.

\[
2 \text{R}^1\text{-NH}_2 \xrightarrow{\text{SO}_2\text{Cl}_2} \text{R}^1\text{N} = \text{S} = \text{NH}\text{R}^1
\]

Scheme 2: Symmetrically substituted sulfamide 19 can be prepared by the reaction of sulfonyl chloride with amine 18.

Another route is the substitution of sulfamide 14 with an amine (Scheme 3) [180] to yield monosubstituted 20 with one equivalent, or the symmetrically disubstituted sulfamide 19 when two equivalents of amine are used. The same reaction was also carried out on the monosubstituted sulfamide 20 to afford the unsymmetrically disubstituted sulfamide 21. Other unsymmetrical disulfamides have been synthesized using modified versions of this procedure [181]. The major limitation of this method is the prolonged high temperature required.

\[
\begin{align*}
\text{H}_2\text{N} = \text{SO} = \text{NH}_2 & \quad \xrightarrow{\text{R}^1\text{-NH}_2, (1 \text{ eq.})} \quad \text{R}^1\text{N} = \text{S} = \text{NH}\text{R}^1 \\
\text{R}^1\text{N} = \text{S} = \text{NH}\text{R}^1 & \quad \xrightarrow{\text{R}^2\text{-NH}_2} \quad \text{R}^1\text{N} = \text{S} = \text{NH}\text{R}^2
\end{align*}
\]

Scheme 3: Another route to the synthesis of sulfamides is the condensation of unsubstituted or monosubstituted sulfamides with amines.
The third synthetic method involves the reaction of sulfamoyl chloride 22 with amine 18 (Scheme 4) [182]. It is the most general route to unsymmetrically disubstituted sulfanides and the one which has been most used for the synthesis of thiazolides described to date [170,172,174,176]. Moreover, mixed aliphatic-aromatic sulfanides have already been synthesized by this method [182].

\[
R^1\cdot-NH_2 + \text{Cl-SO}_2-NH\cdot R^2 \rightarrow \begin{array}{c}
\text{18} \\
\text{22}
\end{array} \rightarrow 21
\]

**Scheme 4:** *The most general route to unsymmetrically disubstituted sulfamide 21 is the nucleophilic addition/elimination of amine 18 to sulfamoyl chloride 22.*

This was the preferred route and the synthesis of the required sulfamoyl chloride was next addressed. An aliphatic or an aromatic sulfamide could be prepared and reacted with an aromatic or aliphatic amine respectively, in order to obtain the desired N-aryl or N'-alkyl sulfamide respectively. Since the formation of aromatic sulfamoyl chlorides has been reported to work efficiently [183], this approach was first attempted. Sulfamoyl chloride 24 was obtained in high yield by sequential treatment of methyl 4-aminobenzoate (23) with chlorosulfonic acid and phosphorus pentachloride (Scheme 5).

\[
\begin{array}{c}
\text{MeOOC} \\
\text{23}
\end{array} \xrightarrow{1. \text{ClSO}_3\text{H}, \text{CH}_2\text{Cl}_2, \ \text{0}^\circ\text{C, 1 h}} \begin{array}{c}
\text{MeOOC} \\
\text{24}
\end{array} \xrightarrow{2. \text{PCl}_5, \ \text{reflux, 3 h, 95%}} \begin{array}{c}
\text{MeOOC} \\
\text{23}
\end{array}
\]

**Scheme 5:** *Treatment of aromatic amine 23 with chlorosulfonic acid followed by phosphorus pentachloride afforded 24 in high yield.*

Amino acid building blocks were used as the required aliphatic amines. Since the expensive unnatural (R)-amino acids have the desired configuration, the inhibitor synthesis was first carried out on racemic starting material. Use of enantiomerically pure building blocks was delayed to a later stage when more potent inhibitors would be in hand. DL-Phenylalanine and DL-tyrosine provided the desired side chains for target molecules (±)-10 and (±)-11 respectively. The aromatic hydroxyl group of tyrosine ((±)-25) had first to be protected. A copper chelate was formed with the amino and carboxylic acid groups during this step allowing selective monobenzylation of the
phenol group (Scheme 6) [184]. Phenylalanine (±)-26, as well as protected tyrosine (±)-27 were esterified to the corresponding methyl ester hydrochlorides (±)-28 and (±)-29 which were then used in the reaction with sulfamoyl chloride 24 in the presence of triethylamine, yielding sulfamides (±)-30 and (±)-31 respectively. The subsequent cyclization was first attempted using sodium hydroxide as base under the conditions reported by Montero and coworkers [172]. No reaction however took place, presumably because of the poor solubility of the sulfamides in the ethanol-water mixture used as solvent.

Scheme 6: The synthesis of inhibitors (±)-10 and (±)-11 was accomplished by the formation of unsymmetrical sulfamides and subsequent cyclization.
Further attempts were made with sodium methoxide or potassium tert-butoxide in methanol, however without success. The use of tert-butyllithium at room temperature eventually afforded thiazolides (±)-32 and (±)-33. Syringe pump addition of the sulfamides to a dilute tert-BuLi solution gave the best results. A low sulfamide concentration was used to avoid polymerization. Sodium hydride in refluxing THF was later found to also afford the cyclized products in good yields but this method was not further investigated. Ester hydrolysis of (±)-32 and (±)-33, followed by treatment of the resulting acids with N’-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt) to form an activated ester, and subsequent addition of ammonium hydroxide [185] gave rise to amides (±)-10 and (±)-34. Deprotection of the O-benzyl thiazole (±)-34 was quantitatively achieved by treatment with trifluoroacetic acid in the presence of pentamethylbenzene [186]. Pentamethylbenzene has been reported to not only improve the yield of deprotection but also, by trapping the benzyl cation, to avoid an intramolecular O to C rearrangement of O-benzyltyrosine to 3-benzyltyrosine [186-187].

Scheme 7: The synthesis of inhibitors (±)-12 and (±)-13 containing unnatural amino acids proceeded similarly as for the first two inhibitors.
The next goal was to synthesize inhibitors (±)-12 and (±)-13 which bear longer aromatic side chains. In order to use the same synthetic pathway as for the phenylalanine and tyrosine derivatives (±)-10 and (±)-11, we prepared the unnatural homophenylalanine and 2-naphthylalanine amino acid methyl esters (±)-37 and (±)-38 respectively. This was achieved by first protecting glycine methyl ester 35 as a Schiff base by reaction of the amino acid with benzaldehyde (Scheme 7). Subsequent deprotonation with LDA in the presence of DMPU [188] followed by addition of the appropriate benzyl bromide and selective acidic deprotection of the N-benzyldiene group without hydrolysis of the methyl ester gave rise to amino acids (±)-37 and (±)-38 respectively [189]. The remaining steps were accomplished in a similar manner as for the previous inhibitors (±)-10 and (±)-11. Nucleophilic substitution of sulfamoyl chloride 24 afforded sulfamides (±)-39 and (±)-40. Cyclization and final conversion to the primary amide yielded thiazolides (±)-12 and (±)-13, respectively.

The moderate yield observed in the last step, namely the conversion of the methyl ester group into the primary amide was somewhat disappointing. This is the result of a side reaction in which nucleophilic substitution of the sulfamide moiety of (±)-42 by methoxy anions occurs under the base catalyzed hydrolysis conditions used for the ester hydrolysis (Scheme 8). This side reaction was established by the isolation of sulfamate ester (±)-43. The corresponding sulfamic acid was probably also formed but removed during the aqueous work-up. Improvement of this step would certainly be possible, however other conditions were not tried at this stage since the target molecules were obtained in sufficient amounts for performing the biological assays.

\[ \text{Scheme 8: The low yield observed in the last step resulted from the nucleophilic substitution of the sulfonamide group by methoxy anions as established by the isolation of sulfamate ester (±)-43.} \]
2.3.3 Biological Results

The four benzamide inhibitors (±)-10, (±)-11, (±)-12, and (±)-13 were tested in a competitive inhibition assay using the Scintillation Proximity Assay (SPA) method [137]. The assay involves incubating HLA-DR molecules, bound to streptavidin-SPA beads, with a $^{125}$I-labeled reference peptide (YAAFRAASAKAAA-NH$_2$) and the compound under test. Light is only emitted by the SPA beads when they are in close contact to the radiolabeled peptides, i.e. when the peptide is bound to the HLA-DR protein. Light emission is therefore inversely proportional to the binding affinity of the test compound which competes with the reference peptide for the HLA-DR binding site. None of these molecules however was found to have significant potency (IC$_{50}$ > 100 µM). Use of more concentrated conditions lowered the detection limit of the biological assay and the compounds were found to have single digit millimolar inhibition for HLA-DR4 molecules (Table 5).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibition at 5 mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-10</td>
<td>50%</td>
</tr>
<tr>
<td>(±)-11</td>
<td>50%</td>
</tr>
<tr>
<td>(±)-12</td>
<td>35%</td>
</tr>
<tr>
<td>(±)-13</td>
<td>50%</td>
</tr>
</tbody>
</table>

The low potency measured for these thiazolides derivatives might be a result of incomplete complexation of Gln α9 at position 4. Only the amide hydrogen atom is actually hydrogen bonded, whereas H-bonding requirement of the carboxylic oxygen atom is not satisfied. Further refinement of the modeling was therefore necessary to design second generation targets.

2.4 Second Generation Inhibitors

2.4.1 Molecular Modeling

In order to perform more accurate computer calculation, a force field specifically parameterized for the thiazolide inhibitors would be optimal. Most modeling packages
however lack specific parameters for $S,S$-dioxide groups. We therefore looked at computational studies carried out on structurally similar functionality to improve our modeling calculations. Nothing could be found for sulfamides [190], however there are reports of \textit{ab initio} as well as semi-empirical calculations [191], which provide specific force field parameters for sulfonamides. The force field parameters developed from \textit{ab initio} calculations [191c] were added to the Tripos force field [192] and new minimizations of first generation inhibitor 13 were performed using the Sybyl modeling program. A slightly different position of the thiazolidine ring in the binding groove resulted from these modeling studies, allowing better hydrogen bonding interactions between the sulfamide group and Asn $\beta 82$. This shift had only a slight effect on the aromatic side chain at position 1 which still fits into the hydrophobic cavity, probably because of the flexible character of the aliphatic linkage to the thiazolidine ring. However, the benzamide substituent was dramatically affected and was no longer capable of interacting with Gln $\alpha 9$ at position 4.

Consequently, a new side chain for complexing position 4 had to be designed. It was found that, as in the first generation targets, a phenyl group is suitable as linker from the ring template, but \textit{meta} and not \textit{para} substitution is now required to obtain the proper vector (Figure 19).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure19.png}
\caption{The second generation target 44 was designed to form one extra hydrogen bond with the carbonyl oxygen of Gln $\alpha 9$ (the distances between the heteroatoms are given). The additional propionamido side chain is filling the hydrophobic pocket at position 4.}
\end{figure}
A methylene group was also introduced between the phenyl linker and the terminal amide in order to reach the Asn α62 and Gln α9 residues. Furthermore, this one-carbon elongation allowed the introduction of an propionamido side chain to simultaneously hydrogen bond the carbonyl oxygen of Gln α9 and fill the narrow hydrophobic pocket at position 4. According to the modeling calculations, the second generation target can form six hydrogen bonds with HLA-DR molecules. The structure of the inhibitor is still fairly rigid. The most impressive feature is the large Van der Waals surface making multiple hydrophobic interactions with the protein and nicely fitting into the binding groove (Figure 20).

![Figure 20: As illustrated by the CPK model, the target inhibitor is nicely fitting inside the binding groove, having extended hydrophobic contacts with the protein.](image)

### 2.4.2 Synthesis

The synthesis of the new target 44 was logically based on the experience gained with the first generation inhibitors. We anticipated that the template ring structure
could be obtained by a similar cyclization and therefore disconnected the N(2)-C(3) thiazolide bond, revealing sulfamide precursor 45 (Scheme 9). Retrosynthetic analysis of 45 led to starting materials 38 and 46.

Scheme 9: The retrosynthetic analysis of 44 revealed sulfamide molecule 45, which was further disconnected into building blocks 38 and 46.

We however anticipated that sulfamide formation, which requires harsh reaction conditions, might prove more difficult with 46 than with the less labile methyl 4-aminobenzoate (23). This reaction was therefore first studied on a model system (Scheme 10). Reaction of chlorosulfonic acid with amine 49, followed by treatment with phosphorous pentachloride failed to generate the corresponding sulfamoyl chloride. This resulted from the instability of 49 under the reaction conditions. The reaction of 2-naphthylalanine methyl ester ((±)-38) with sulfuryl chloride, followed by addition of 49 in the presence of triethylamine as base was next attempted [193], again without success. For the next approach, sulfamide (±)-47 was synthesized in two steps from 2-naphthylalanine methyl ester ((±)-38) following a published procedure [174]. Sulfamide (±)-47 and amine 49 were then refluxed in diglyme in order to achieve a transamination [181,194], an alternative route to unsymmetrical sulfamides. This reaction was also unsuccessful.
Scheme 10: The three general methods for the synthesis of sulfamides (see Scheme 2, 3 and 4) were tried but none of them gave access to the desired unsymmetrically disubstituted sulfamide $\pm$-51.

Fortunately, a novel method for the versatile synthesis of unsymmetrically $N,N'$-disubstituted sulfamides was published by Montero and coworkers [195]. Reaction of chlorosulfonyl isocyanate with 2-chloroethanol followed by the addition of amine 52 to the in situ-prepared sulfamoyl chloride afforded sulfamide 53 (Scheme 11). Cyclization of 53 was reported to proceed quantitatively affording oxazolidinone 54 which, via a transsulfamoylation with nucleophiles, gave access to various unsymmetrically disubstituted sulfamides 55.

Scheme 11: Starting from chlorosulfonyl isocyanate, successive addition of 2-chloroethanol and amine 52 gave sulfamide 53. Cyclization to oxazolidinone 54 followed by transsulfamoylation afforded unsymmetrically disubstituted sulfamide 55.
Oxazolidinone (±)-56 was synthesized in one step from 2-naphthylalanine methyl ester (±)-38. Unlike in the literature procedure, the uncyclized precursor 53 was not isolated since partial cyclization had already occurred. Addition of an excess of triethylamine to the reaction mixture ensured complete cyclization to (±)-56. The substitution of the oxazolidinone by amine 49 however failed (Scheme 12). This was rationalized by the relatively poor nucleophilicity of aromatic amine 49 compared with the aliphatic amines described in the literature.

We therefore reversed the sequence of construction and next introduced the oxazolidinone moiety on the aromatic amine 49, in order to use the aliphatic amine functionality of 2-naphthylalanine methyl ester ((±)-38) to displace the oxazolidinone. Esterification of carboxylic acid 48 followed by oxazolidinone formation afforded 50 in high yield (Scheme 13). The oxazolidinone group of 50 was then substituted by 2-naphthylalanine methyl ester ((±)-38), giving access to (±)-51 in excellent yield. This nicely demonstrates that Montero's oxazolidinone strategy can be extended to the synthesis of $N$-alkyl-$N'$-arylsulfamides provided the oxazolidinone is introduced on the aromatic amine allowing displacement by an aliphatic amine. Cyclization with tert-BuLi to thiazolide (±)-57 under the same reaction conditions as for the first generation inhibitors worked smoothly. Subsequent methyl ester hydrolysis was achieved with potassium trimethylsilanolate [196] in order to avoid the presence of hydroxy and methoxy anions which previously caused partial cleavage of the thiazolide scaffold (Scheme 8). Final conversion of the carboxylic acid to a primary amide [185] yielded molecule (±)-58. The binding affinity of this model compounds was determined but was also found to be below the detection limit (IC$_{50} > 100$ µM).
Scheme 13: The synthesis of the model compound \((\pm)-58\) was achieved via the oxazolidinone strategy.

Having proved the feasibility of our synthetic strategy with a model compound, we next addressed the synthesis of target inhibitor 44. The first task towards this goal was the synthesis of the required aromatic amino building block 59. The most direct route would have been the nitration of commercially available phenylglycine. However, this reaction proved to be difficult and neither standard conditions [197] nor the use of nitronium tetrafluoroborate [198] were successful. An alternative is the Strecker amino acid synthesis, but we failed to convert 3-nitrobenzaldehyde into the corresponding amino cyanide. A similar route was explored by submitting 3-nitrobenzaldehyde to Bucherer-Berg conditions [199], but this also failed to yield the desired compound and only decomposition products were obtained.
In another approach, methyl ester 61, obtained from carboxylic acid 60, was converted into bromide (±)-62 (Scheme 14). This α-bromination was accomplished using N-bromosuccinimide with AIBN as radical initiator [200] to give racemic (±)-62 in reasonable yield. A Gabriel synthesis was used to introduce the required amine functionality. Substitution of bromide (±)-62 by the phthalimide anion yielded compound (±)-63. Subsequent hydrogenation furnished the desired protected 3-aminophenylglycine (±)-59.

Scheme 14: The synthesis of protected 3-aminophenylglycine (±)-59 was achieved by the bromination of the methyl 3-nitrophenylacetate (61), followed by a Gabriel synthesis and reduction of the nitro functionality.

The same sequence used in the model reaction was then carried out on amine (±)-59 (Scheme 15). Oxazolidinone (±)-64, obtained in high yield from (±)-59, was substituted by racemic 2-naphthylalanine methyl ester ((±)-38) to give sulfamide (±)-65/(±)-66 as a mixture of diastereoisomers. No separation was attempted since epimerization was expected to occur in the following step. The cyclization was therefore carried out directly and afforded thiazolide (±)-67/(±)-68 (as detected by mass spectrometry analysis). Preliminary investigations to separate the mixture of diastereoisomers failed. This was however not extensively examined, since several attempts to remove the phthalimide protecting group failed. Normal deprotection conditions such as the use of hydrazine, as well as acidic hydrolysis, preferentially cleaved the sulfonylurea moiety present in the thiazolide ring system. Consequently, another protecting group had to be introduced earlier in the synthesis.
We planned to directly introduce the desired propionamido side chain at the beginning of the synthesis so that, after cyclization, no further functional group manipulation would be required. The phthalimide protecting group of 3-nitrophenylglycine (±)-63 was therefore hydrolyzed, and the free amino group acylated with propionyl chloride (Scheme 16). Hydrogenation of the aromatic nitro group yielded (±)-71.

Scheme 15: Starting from (±)-59, the synthesis of thiazolide (±)-67/(±)-68 was achieved in a similar manner to the model compound. Removal of the phthalimide protecting group however failed.

Scheme 16: To avoid a problematic phthalimide deprotection at a later stage of the synthesis, it was replaced by the required propionamido side chain prior to sulfamide synthesis.
With the 3-aminophenylglycine (±)-71 bearing the final N-propionamido group in hand, the thiazolidine synthesis was again carried out. As previously, oxazolidinone (±)-72 was prepared, however only in moderate yield (Scheme 17). Substitution by 2-naphthylalanine methyl ester (±)-38 furnished sulfamides (±)-73/(±)-74 as a 1:1 mixture of diastereoisomers which were cyclized to (±)-75/(±)-76 in good yield. At this point, separation of the two diastereoisomers would be required, followed by the conversion of the ester group into a primary amide. This was however not undertaken since the priority was given to the synthesis of the peptidomimetic inhibitors (Chapter 2.5).

Scheme 17: The reaction sequence was repeated on compound (±)-71 already bearing the desired N-propionamido side chain to afford (±)-73/(±)-74. Separation of the diastereoisomers was not investigated.

### 2.5 Peptidomimetic Inhibitors

#### 2.5.1 Concept and Design

As discussed previously (see Chapter 2.3.3), the first generation compounds were not very potent MHC class II inhibitors. This result was attributed to the incomplete complexation of Gln α9 at position 4. This resulted in the design of a new binding
motif in that region (second generation of inhibitors, Chapter 2.4). However, even if the benzamide moiety present in the first generation of inhibitors was not optimal, there is nothing to suggest that the rest of the molecule, namely the cyclic template and the p1 aromatic anchor, did fit well into the binding groove. It was therefore important to determine the biological activity of the thiazolide bearing the naphthyl side chain independently from the rest of the molecule. Since a larger molecule than just the naphthyl-substituted thiazolide is required to have minimal detectable activity, this cannot be done directly. We therefore decided to couple our template to a peptide fragment, the MASL sequence, which had been shown to bind to MHC class II molecules (see Hoffmann-La Roche heptapeptide, Chapter 2.2.3). Using the thiazolide scaffold as a position 1 and 2 peptidomimetic (Figure 21) should allow, by comparison with a reference peptide, evaluation of the suitability of such fragments as a binding motif for position 1 and 2, thereby giving an answer regarding the relevance of the de novo design work.

Figure 21: The validity of the modeling can be checked by the use of the thiazolide template as a peptidomimetic molecule bound to a peptidic fragment and comparison with a fully peptidic molecule.

A linker was designed to allow attachment of the peptide fragment to the thiazolide template. The appropriate linker length to allow the peptidic fragment to be superimposed with the reference peptide was determined by molecular modeling (Figure 22). A propionate moiety was found to be optimal. The linker itself lies somewhat above the cavity. Introduction of hydrophobic groups into the linker was also planned to verify that the comparison between the peptidomimetic and fully peptidic molecules was valid.
2.5.2 Synthesis

We planned to couple the peptide fragment, prepared by solid-phase synthesis, to a template already functionalized with the designed linker. The latter should therefore bear a carboxylic acid functionality which would allow ready attachment of the peptide. Amide bond formation between this carboxylic acid and the peptide terminal amine should be effectively accomplished by standard coupling methods developed for peptide chemistry. We next elaborated a synthetic strategy towards the thiazolidine template bearing the linker. Unlike generation 1 and 2 inhibitors, an alkyl substituent needs to be present on the thiazolidine nitrogen. It should be possible to introduce it as an electrophile by the alkylation of the more acidic N(2) sulfamide nitrogen of (±)-77 (Scheme 18).

Scheme 18: A retrosynthetic analysis revealed unsubstituted thiazolidine 77 as building block which could be substituted by an electrophilic linker. The last step would be the attachment of the peptide through an amide linkage.
The synthesis of N(2)-unsubstituted thiazolides from α-amino acids has already been reported [174]. *In situ* reaction of chlorosulfonylisocyanate with benzyl alcohol, followed by substitution of the resulting sulfamoyl chloride with amino acids (±)-28 or (±)-78 afforded (±)-79 and (±)-80, respectively (Scheme 19). Quantitative removal of the benzyl group by hydrogenation followed by cyclization under basic conditions yielded thiazolides (±)-81 and (±)-77, respectively.

\[
\text{COOMe} \quad \text{(±)-28}\quad \text{R = phenyl} \\
\text{NH}_{2} \cdot \text{HCl} \quad \text{(±)-78}\quad \text{R = 2-naphthyl}
\]

1. CONSO\textsubscript{2}Cl, PhCH\textsubscript{2}OH, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 1.5 h

2. (±)-28 or (±)-78, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to r.t., 18 h

\[
\text{MeOOC} \quad \text{(±)-79}\quad \text{R = phenyl}\quad 92\%
\]

\[
\text{(±)-80}\quad \text{R = 2-naphthyl}\quad 76\%
\]

H\textsubscript{2} (4 bar), Pd/C, EtOH, 18 h

\[
\text{MeOOC} \quad \text{(±)-82}\quad \text{R = phenyl}\quad \text{quant.}
\]

\[
\text{(±)-47}\quad \text{R = 2-naphthyl}\quad 81\%
\]

Scheme 19: *The synthesis of the unsubstituted thiazolides (±)-81 and (±)-77 was achieved in analogy to a published procedure [174].*

The introduction of the linker moiety on the unsubstituted thiazolides was then addressed. Nucleophilic substitution of mesylate 83 by the deprotonated N(2) sulfamide nitrogen was tried but repeatedly failed, and starting material was recovered (Scheme 20). The alkylation of N-unsubstituted 3-oxo-β-sultams has actually already been reported to be problematic [201] and only the use of sodium hydride in DMF together with bromo compounds bearing electron-withdrawing substituents in the α-position was found to be effective in substitution reactions. We then anticipated that a *Mitsunobu* reaction, which has been shown to be applicable to N-acyl sulfonylamides [202], would be an alternative. Treatment of alcohol 84 with diethyl azodicarboxylate, triphenylphosphine, and thiazolide (±)-81 or (±)-77 did indeed afford the desired N-substituted compounds (±)-85 and (±)-86 as a mixture of diastereoisomers. However, the major products were (±)-87 and (±)-88 resulting from O-alkylation.
Scheme 20: The functionalization of thiazolides (±)-81 and (±)-77 could only be achieved using a Mitsuobu reaction, albeit in low yield; the major products were the O-alkylated compounds (±)-87 and (±)-88.

Consequently, we decided to change our synthetic strategy and planned to introduce the linker moiety earlier in the synthesis so that all the required functional groups would be present in the molecule before the cyclization step. Montero’s oxazolidinone procedure [195] turned out to be the method of choice for the synthesis of unsymmetrical sulfamides (Scheme 21). Starting from the amino acid methyl esters (±)-28 and (±)-78, it was possible to obtain the corresponding oxazolidinones (±)-89 and (±)-56 respectively, in high yields. Displacement of the oxazolidinone moiety by β-alanine benzyl ester (90), obtained by esterification of β-alanine [203], afforded the desired unsymmetrical sulfamides (±)-91 and (±)-92, respectively. For the subsequent cyclization, the presence of two ester groups, as well as two similarly acidic nitrogens, could lead to four different regioisomers. The three- and four-membered ring compounds are clearly disfavored because of their ring strain and were anticipated not to be formed. It was our hope that the kinetically-favored, five-membered ring would be selectively formed over the six-membered ring. This selectivity should be enhanced by the slightly higher reactivity of methyl esters compared with benzyl esters, which results from the stronger acidity of methanol (pKₐ = 15.09) over benzyl alcohol (pKₐ = 15.4) [204]. However, the cyclization step failed to afford either the five- or six-membered ring sulfamide, and presumably led to polymerization. In order to make the carboxylate group present on the β-amino acid linker moiety unreactive towards nucleophiles, the benzyl group of (±)-92 was removed by hydrogenation. However, carboxylic acid (±)-93 also failed to access the desired thiazolide (±)-94.
Scheme 21: The synthesis of the sulfamides (±)-91 and (±)-92, already bearing the required substituents, was achieved via the oxazolidinone method. However, the cyclization failed both in the presence of a benzyl ester and of a carboxylic acid.

A tert-butyl ester, sterically too hindered to undergo facile nucleophilic substitution, was next used. The same reaction cascade was repeated with β-alanine tert-butyl ester (97), affording the unsymmetrical sulfamides (±)-98 and (±)-99 respectively (Scheme 22). It was then possible to effect the cyclization to the corresponding thiazolides (±)-100 and (±)-101. The moderate yields observed for this reaction result from a facile β-elimination side-reaction which also takes place under the basic reaction conditions. Evidence for this side-reaction was the isolation of unsubstituted thiazolides. We however do not know whether β-elimination occurs before or after the cyclization. Finally, the cleavage of the tert-butyl ester was achieved by treatment of (±)-101 with trifluoroacetic acid, yielding thiazolide (±)-94.

The next goal was the synthesis of analogs in order to investigate the binding affinity of various peptidomimetic molecules towards MHC class II proteins. First, we decided to introduce alkyl substituents on the β-amino acid linker. According to molecular modeling, they should have favorable hydrophobic contacts with the HLA-DR proteins at position 3 by filling the empty space left between the linker and the protein (see Figure 22).

Compounds (±)-102 and (±)-103 were synthesized by Stefan Reinelt during his diploma work [205].
The synthesis of the substituted β-amino acid started from alcohol 104 (Scheme 23). Hydroxyl group conversion into an amine was efficiently achieved by a Gabriel synthesis. A Mitsunobu reaction afforded the phthalimide ester 105 which was hydrolyzed to the corresponding β-amino acid 106. Carbobenzyloxy-protection of the amino group [206], esterification with isobutylene and subsequent deprotection of the amino functionality afforded the desired β-amino acid tert-butyl ester 109.
With molecule 109 in hand, the targeted thiazolides were synthesized using the same strategy as for the preceding peptidomimetic compounds. Both homophenylalanine oxazolidinone (±)-110 and 2-naphthylalanine oxazolidinone (±)-56 were substituted with the 2,2-dimethyl-β-amino acid tert-butyl ester 109 in order to also investigate the affinity of a variety of side chains for the position 1 hydrophobic cavity (Scheme 24). Subsequent sulfamide cyclization followed by final deprotection of the ester group afforded thiazolides (±)-102 and (±)-103.

Scheme 24: The synthesis of the 2',2'-dimethyl-substituted thiazolides was achieved using the same reaction sequence as previously.

In addition to varying the aromatic substituent at position 1, as well as the linker at position 3, we were also interested in modifying the sulfonamide system present in the template for complexing position 2. The sulfamide functionality can, according to molecular modeling, provide a stronger hydrogen-bond to Asn β82 than a simple urea (see Chapter 2.3.1). Both systems have a different geometry since the carbonyl group of a urea is in the plane of the ring, as opposed to the sulfamide where the two S=O groups are pointing out of the plane. A remaining question, however, is what influence the upper S=O group of the thiazolide has on binding. Since it is directed outside the cavity, one would expect it to be solvent exposed and have a positive effect by shielding the hydrogen-bond formed by the second S=O group. However, if the upper S=O group has to be desolvated, it might be that just one carbonyl group would be energetically more favorable. Use of a hydantoin instead of a thiazolide as peptidomimetic template should answer this question.
Treatment of 3-carbomethoxypropionyl chloride 115 with sodium azide afforded isocyanate 116 via a Curtius rearrangement (Scheme 25) [207]. Addition of amino acids (±)-26 and (±)-117 to the isocyanate 116 followed by cyclization and ester hydrolysis yielded hydantoins (±)-118 and (±)-119 in one step [207, 208].

Scheme 25: The hydantoins (±)-118 and (±)-119 were obtained in one step from the reaction of the corresponding amino acids with isocyanate 116.

2.5.3 Structural and Physical Data

Some structural and physical data have been collected on these peptidomimetic compounds with the aim of providing a better understanding of their binding activity as well as to allow more accurate computer calculations. Of particular interest is the determination of the suitability of the thiazolidine ring system as a template for an MHC class II inhibitor, compared to the hydantoin analog. From the modeling studies, the sulfonylurea system was considered most suitable, its functional groups having a better complementary to those of the binding site. However, a critical point is the accuracy of the modeling calculations.

Figure 23: The X-ray crystal structure of (±)-100 (crystallized from hexane/EtOAc in the monoclinic space group P2₁/n) revealed a conformation similar to the one of the molecule when bound to the MHC protein. Vibrational ellipsoids are drawn at the 30% probability level.
One concern was the similarity of the bound conformation obtained from the minimizations compared with the energy-minimum conformation of the uncomplexed molecule. Conformational changes would otherwise cost a lot of binding free energy due to loss of entropy. The conformation of molecule (±)-100 as determined by X-ray crystallography (Figure 23) corresponds to the one calculated by molecular modeling using both Moloc and Sybyl for the peptidomimetic compound (±)-94 (Figure 24) as well as first generation inhibitor (±)-10, and should therefore be favorable in terms of both entropy and enthalpy (details for X-ray crystallography are provided in the Appendix, Chapter 5).

Figure 24: The template conformation in the X-ray crystal structure of (±)-100 (in dark) is almost identical to the minimized conformation of inhibitors derived from (±)-94 (in light).

The intermolecular interactions observed in the crystal structure are also important for understanding the supramolecular properties of such thiazolide ring systems. Besides the weak π–π stacking of the aromatic rings (interplanar distance of 3.96 Å between the centers of the rings), a 1.86 Å intermolecular hydrogen bond between the sulfonamide N-H and the ester carbonyl group is of particular interest (Figure 25). The conformation of the sulfamide was actually problematic since the MAB force field implemented in Moloc calculated the N(5) (numbered N14 in the X-ray labeling, Figure 23) hydrogen out of the ring plane, towards Asn β82. It was troublesome to have such a non-planar sulfamide group even if sulfamide and sulfonamide do not possess electron delocalization like amides (there is no S-N double bond character, unlike C-N bonds in amides). In the crystal packing, the hydrogen-bond is clearly out of the ring plane, nicely confirming the relevance of the calculated conformation of the hydrogen on N(5).
Besides the directionality of the hydrogen bonds formed by the template, we were also interested in studying their strength. From ab initio calculations [209], we learned that the S-O bond is particularly polarized, the oxygen retaining practically three lone pairs. This should be associated with good H-bond acceptor character, as illustrated by the ability of N,N'-disubstituted sulfamides to assemble in a two-dimensional hydrogen-bonded network [210]. Sulfoxide groups have been reported to be strong hydrogen bond acceptors [211]. Sulfonamide S=O groups were however calculated to be poorer H-bond acceptors than phosphonamide, although better than phosphonamidates [212]. In a separate study, sulfonamides were reported to be weaker hydrogen-bond acceptors than amide, carbamate, and even ester carbonyl groups in chloroform [213], although conformational effect and use of different H-bond donors might have influenced this result. Examples of both efficient [49,214] and unsuccessful [215] sulfonamide inhibitors have been published, so that the H-bond acceptor strength of sulfonamide and sulfamide SO₂ groups remain unclear.

Another consequence of the sulfur being so electron deficient is that the N(5) nitrogen atom, to satisfy its electronegativity, is withdrawing a considerable amount of charge from the attached proton. This explains the acidic character of the sulfamide. Moreover, Spillane and coworkers [216] have reported that five-membered ring sulfamides are ca. 4 pKₐ units more acidic than their open-chain counterparts. However, none of the molecules studied is similar to ours. We therefore decided to determine the pKₐ of the thiazolidine and hydantoin rings used in the peptidomimetic compounds in order to better quantify and compare the hydrogen-bond strength of such templates. Molecules (±)-100 and (±)-120 are not suitable for potentiometric pKₐ
determination since the expected values are too high for accurate measurement. Another possibility could be to use UV spectrophotometry, a method relying on the direct determination of the ratio of neutral to ionized species in a series of non-absorbing buffer solutions. However, (±)-100 and (±)-120 do not have a chromophore sufficiently close to the acidic nitrogen for a significant difference between the UV spectra of the neutral and ionized species to be observed. We therefore determined the pKₐ values by ¹H-NMR titration [217]. The compounds were not soluble in pure water, so that 0.03 M solutions of (±)-100 and (±)-120 in CD₃C(O)CD₃/D₂O 1:1 were prepared and titrated with sodium deuteroxide solutions (Table 6). A 0.1M sodium deuteroxide solution in D₂O (solution 1) was used up to pH 12.0. Thereafter, at higher pH, titrations were performed with a 1.0M solution (solution 2) so as to minimize the dilution. The deprotonation was monitored by measuring the chemical shift of non-exchanging protons (H-C(4'), H-C(6') and H-C(3), Figure 26) at different pH. More precisely, the chemical shift difference between one of these protons influenced by deprotonation and the signal of the tert-butyl group which remains practically unchanged was measured.

**Table 6**: The chemical shift differences (in [Hz]) between H-(4'), H-C(6') and H-C(3) and the protons of the tert-butyl group were measured at different pH values. The pH was adjusted by titration with sodium deuteroxide solutions.

<table>
<thead>
<tr>
<th>Titrant added [μl]</th>
<th>pH</th>
<th>Thiazolidine (±)-100</th>
<th>Hydantoin (±)-120</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>H-C(4')</td>
<td>H-C(6')</td>
</tr>
<tr>
<td>0.0 (soln. 1)</td>
<td>7.0</td>
<td>953</td>
<td>506</td>
</tr>
<tr>
<td>0.5 (soln. 1)</td>
<td>11.0</td>
<td>946</td>
<td>503</td>
</tr>
<tr>
<td>0.5 (soln. 1)</td>
<td>11.3</td>
<td>942</td>
<td>501</td>
</tr>
<tr>
<td>1.0 (soln. 1)</td>
<td>11.6</td>
<td>931</td>
<td>496</td>
</tr>
<tr>
<td>3.0 (soln. 1)</td>
<td>12.0</td>
<td>899</td>
<td>481</td>
</tr>
<tr>
<td>0.5 (soln. 2)</td>
<td>12.3</td>
<td>895</td>
<td>479</td>
</tr>
<tr>
<td>1.0 (soln. 2)</td>
<td>12.6</td>
<td>855</td>
<td>461</td>
</tr>
<tr>
<td>3.0 (soln. 2)</td>
<td>13.0</td>
<td>854</td>
<td>461</td>
</tr>
<tr>
<td>5.0 (soln. 2)</td>
<td>13.3</td>
<td>854</td>
<td>461</td>
</tr>
<tr>
<td>10.0 (soln. 2)</td>
<td>13.6</td>
<td>852</td>
<td>460</td>
</tr>
</tbody>
</table>

Titration curves were obtained by plotting the difference in chemical shift against the pH of the solutions (Figure 26).
Thiazolide (±)-100:

\[
pK_a = 11.9
\]

Hydantoin (±)-120:

\[
pK_a = 12.5
\]

Figure 26: The titration curves were obtained by plotting the chemical shift difference of the protons at position 6' and those of the tert-butyl group against the pH. The pH value taken at the inflection point gave the pK_a values of the thiazolide and hydantoin compounds.
It is notable and reassuring that almost identical results were obtained by following the protons H-C(4'), H-C(6'), and H-C(3) (H-C(4') could not be measured in the case of (±)-120 owing to the resonance overlapping with that produced by residual acetone). Proton H-C(6') was used for the titration curves of both compounds. The usual sigmoidal curve was obtained and the pH taken at the inflection point as a measure of the pKₐ value. pKₐ values of 11.9 and 12.5 were obtained for the thiazolide and hydantoin systems respectively, with an accuracy of at least ±0.3 [218]. This confirmed the assumption that, as in open-chain systems, cyclic sulfonylureas are slightly more acidic than ureas. Compound (±)-100 and similar derivatives should therefore be better hydrogen bond donors than (±)-120.

2.5.4 Biological Results

Despite the fact that the structural and physical data obtained for the peptidomimetic compounds are consistent with the minimized structures obtained from molecular modeling, the biological assays revealed that none of them had detectable binding affinity for HLA-DR molecules when bound to the MASL-NH₂ peptide fragment⁴ (IC₅₀ > 100 µM according to the test sensitivity). Any problem with the peptidic part of these compounds can be excluded, since it is identical to the one used in the Roche heptapeptide (Ac-(Cha)RAMASL-NH₂) (Figure 27) which has an IC₅₀ of 0.033 µM for HLA-DR4. The structural reason accounting for the binding difference between these two compounds must therefore come from the non-peptidic part of the molecule. One major difference in this region is the presence of a positively charged arginine residue at position 2 in the Roche lead peptide which has no equivalent in either the thiazolide or hydantoin templates. However, it was shown that no positive charge is required for binding to MHC class II proteins since replacement of arginine by isoleucine results in a similarly strong binding affinity for HLA-DR4 (IC₅₀ of 0.048 µM) [158]. Another difference is the nature of the hydrophobic group in the aromatic pocket at position 1. However, a naphthyl substituent has been shown to be suitable for binding to HLA-DR molecules [160], and substitution by an homophenyl group, as in molecule (±)-102, does not lead to any improvement. We therefore believe that the pi complexation cannot account for the large potency difference observed between these two molecules.

⁴The peptide synthesis and coupling work was performed by Dr. David R. Bolin at Hoffmann-La Roche in Nutley.
Figure 27: Based on the comparison of peptidomimetic compound (±)-94 (bound to the MASL-NH₂ peptide fragment) and Roche lead peptide (the hydrogen bonds are indicated by arrows), a possible reason for the binding affinity difference might be the lack of an N-acetyl side chain at position 1.

It is also notable that the pattern of the position 2 hydrogen bond network of the thiazolide (and hydantoin) templates is different from what is found in peptides. Whereas in the cis sulfamide present in our compounds, the N-H group is α to the S=O group (or carbonyl in the case of the hydantoins) the amide N-H present in peptides is in the β position from the hydrogen-bonded carbonyl group (Figure 28). There is however no reason why this should be problematic. On the contrary, it should be even better suited to the Asn β82 amide side chain which has the complementary H-bond pattern.
The cis sulfamide or amide structure present in the thiazolide template should have a more complementary pattern than peptides in order to hydrogen bond to a primary amide like that in the side chain of Asn β82.

One structural difference remains that might account for the results obtained. The N-acetyl terminus of the Roche lead peptide, which was actually used to protect the N-terminus of the peptide, was recently found in MHC-peptide co-crystal X-ray structures to form hydrogen bonds to Ser α53 and His β81. These interactions were initially not considered to be important until the recent discovery that other compounds, in which the N-acetyl side chain at position 1 is also absent are all inactive (Figure 29).

Figure 28: The cis sulfamide or amide structure present in the thiazolide template should have a more complementary pattern than peptides in order to hydrogen bond to a primary amide like that in the side chain of Asn β82.

Figure 29: Compounds where the amino acid residue at position 1 was replaced by a cyclic molecule lacking an N-acetyl side chain were inactive.
It is therefore very likely that these interactions, also present in the influenza virus peptide (see Chapter 2.2.3), are required to maintain high binding affinity. A hypothesis explaining their importance is that they hold the α- and β-chains together. We were therefore very interested to test this idea by incorporating an N-acetyl side chain into our compounds.

2.6 Conclusions and Perspectives

During the two-and-a-half year period in which we have been involved in the MHC class II project, we have been able to design and synthesize various compounds that were tested by Hoffmann-La Roche. A first generation of inhibitors was prepared and found to have high micromolar affinity for HLA-DR molecules. In order to improve the potency of such compounds, a second generation of targets with a new structure at position 4 was designed and synthesized. We felt however that complexation at position 4 was not the only region to be improved, and undertook a more fundamental investigation to determine the suitability of the cyclic sulfonylurea core used in our inhibitors. This was achieved by binding a reference peptidic residue to our template, and we established that indeed some additional modifications would be required to achieve high affinity ligands. In particular, we believe that the pharmacophore model (see Chapter 2.3.1) has to be extended in order to incorporate the previously underestimated importance of an N-acetyl side chain for complexation of Ser α53 and His β81. Based on this hypothesis, molecular modeling studies were again undertaken. Introduction of an N-acetyl side chain was investigated together with further modifications at positions 4 to 6. Even if these modifications should be introduced separately in order to measure their individual effect upon binding, molecule 121 can be proposed as a long-term target based on the experience gained from this project.
Maintaining the usual sulfamide template, modification of the p1 aromatic side chain would allow the introduction of the new N-acetyl functionality. The most reasonable approach would be to first carry out this modification on a peptidomimetic compound in order to test this new hypothesis. The next step would be to introduce the side chain designed for position 4 in the second generation targets. In this way, we would benefit from our synthetic effort already accomplished towards the second generation inhibitors. Introduction of a proline residue at position 5 is essentially guided by the need for rigidity and was already shown to be compatible with HLA-DR molecules (see Figure 11). Finally, we planned to introduce a (3S,4S)-pyrrolidin-3,4-diol group for complexing position 6. Molecular modeling showed it to undergo similar interactions with HLA-DR molecules as a serinol group which was shown by Hoffmann-La Roche to have high binding affinity (see Chapter 2.2.3). This dihydroxyproline group would have the added advantage of being much more rigid than the serinol moiety and it is also readily synthesized in enantiomerically pure form from L-(+)-tartaric acid [219]. The discontinuation of the MHC program at Roche would have made it necessary to find another collaborator or to set up the assay at the ETH. We however decided not to go into the synthesis of 121 and related analogs since the modeling had not been predictive as we had initially envisaged.
3. Rational Design of Ligands for Asymmetric Catalysis

3.1 Introduction

3.1.1 Cinchona Alkaloids

*Cinchona* alkaloids are found in the bark of *Cinchona*- and *Remija*-trees. The medicinal properties of these alkaloids were first recognized in the 17th century, and Europeans soon used powdered bark of these trees to treat fever. There are many other examples in which *Cinchona* alkaloids have found medical uses [220]. Quinine (122) for example, is the oldest drug used for prevention and treatment of malaria. Quinine or quinine salts have also been used to treat various conditions including varicose veins, hemorrhoids (in combination with other alkaloids), as well as night cramps. Quinidine (123) has been used in the treatment of certain heart conditions.

\[ R = \text{OMe} \quad (-)-\text{quinine (122)} \]
\[ R = \text{H} \quad (-)-\text{cinchonidine (124)} \]
\[ R = \text{OMe} \quad (+)-\text{quinidine (123)} \]
\[ R = \text{H} \quad (+)-\text{cinchonine (125)} \]
Cinchona alkaloids can be divided into two groups according to their structure. The major one (over 80%) consist of a 1-azabicyclo[2.2.2]octane bicyclic structure called quinuclidine, and of a quinoline ring system. The most common representatives are quinine (122), quinidine (123), cinchonidine (124) and cinchonine (125). A second smaller group, comprising for example cinchonamine (126), has an indole ring system instead of a quinoline bound to the quinuclidine moiety.

\[ (+)-\text{cinchonamine (126)} \]

The Cinchona alkaloids from the first group contain four stereogenic centers at C(3), C(4), C(8), and C(9). There are therefore \(2^4 = 16\) possible stereoisomers. However, all known examples have the same configuration at C(3) (R) and C(4) (S). It is therefore likely that they are all derived from the same biosynthetic pathway, starting from tryptophan and geraniol [221]. The difference between quinine (122) and quinidine (123), and between cinchonidine (124) and cinchonine (125), are the C(8) and C(9) configurations. Quinine has the (8S,9R) configuration, quinidine the (8R,9S). Their absolute configurations were determined by Prelog et al. in the forties through derivatization and comparison with compounds of known configuration [222]. The configurations at C(8) and C(9) usually dominate the stereochemical properties of these alkaloids. Thus quinine (122) and quinidine (123), and cinchonidine (124) and cinchonine (125), respectively, may be considered as pairs of 'pseudo-enantiomers'.

Conformational studies of Cinchona alkaloids and related analogs using a combination of NMR, X-ray, and molecular mechanics computations have been reported [223]. From these calculations, four possible conformations were obtained for the quinine- or quinidine-type molecules: two 'open' conformations where the quinuclidine nitrogen is away form the quinoline moiety, and two 'closed' in which the nitrogen is directed towards the aromatic ring system. The 'open' conformation was calculated to be 2 kcal/mol more stable than the 'closed' one. Consistently, 80-90% of the alkaloids in solution were found by NOE experiments to be in the 'open' conformation. However, in the case of modified Cinchona alkaloids, the preferred
conformation can vary. For example, esterification of the C(9) hydroxyl group produces compounds which preferentially adopt a 'close' conformation, whereas protonation of the quinuclidine nitrogen results in an 'open' conformation, regardless of the hydroxyl group substitution.

_Cinchona_ alkaloids are widely used as chiral auxiliaries in enantiomer separations (for examples see [224-229]): about 25% of all resolutions have been carried out using them [230]. In the molecular recognition area, analogs of _Cinchona_ alkaloids incorporating a 9,9'-spirobifluorene moiety have been synthesized by _Diederich_ and coworkers [231]. However, since these molecules presumably adopted a 'closed' conformation, preventing the formation of strong H-bonds with the basic quinuclidine nitrogen, these analogs formed less stable host-guest associations than quinine (122) or quinidine (123). Natural or modified _Cinchona_ alkaloids also have a great potential as chiral catalysts for asymmetric synthesis. For example, reduction of benzaldehyde by Et₂Zn in the presence of quinine (122) has been achieved in 68% ee [232]. The aldol addition of silyl enol ethers to aldehydes was reported to occur with up to 90% ee when cinchonine (125) is added [233]. Catalytic hydrogenation of ketones [234], ethyl pyruvate [235], as well as α,β-unsaturated acids [236] have also been accomplished stereoselectively with the aid of _Cinchona_ alkaloids. Many other examples could be cited; however an extensive description of all enantioselective reactions catalyzed by _Cinchona_ alkaloids is beyond the scope of this work (for a review see: [237]). We will rather focus on two very successful reaction types where _Cinchona_ alkaloids play a central role: the enantioselective phase transfer catalysis and the _Sharpless_ asymmetric dihydroxylation, which will both be presented and discussed in the following chapters.

### 3.1.2 1,1'-Binaphthyls

1,1'-Binaphthyls do not possess any asymmetric center, but are nonetheless chiral. Chirality originates from the high barrier of rotation around the 1,1'-bond of the molecule (axial chirality), which was experimentally determined to be 22.5 kcal/mol for the unsubstituted 1,1'-binaphthyl [238], but rises to values of the order of 40 kcal/mol for 2,2'-disubstituted molecules [239] for which stable atropisomers can be isolated [240]. The 1,1'-binaphthyl unit has two distinct clefts. The smaller is referred to as the minor groove and the larger as the major groove (Figure 30 (a)). At a dihedral angle about the chirality axis of around 90°, the minor groove is rather small, and does not provide a sufficiently large cavity for molecular recognition (Figure 30 (b)). To benefit
from its chiral properties, the 1,1'-binaphthyl unit has to be incorporated into macrocyclic structures or used as a ligand for metal chelation. The major groove is quite large and offers a large aromatic surface that can be involved in π-π stacking and edge-to-face interactions with aromatic guests.

![Figure 30: 1,1′-Binaphthyls possess a minor and a major groove (a). The dihedral angle between the two naphthalene subunits is around 90° as illustrated in the top view (b).](image)

Owing to its synthetic accessibility and possibility for further functionalization, the 1,1'-binaphthyl moiety has been extensively used in association with transition metals to form chiral catalysts in various reaction types [241,242]. A particularly successful example is the Rh(BINAP) (127) used in the Noyori asymmetric hydrogenation (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) [243]. It is notable that only the minor groove has so far been successfully used as a ligand for metal chelation in stereoselective catalysis. One 1,1'-binaphthyl ligand with phosphine substituents at the 7- and 7'-positions instead of the conventional 2- and 2'-positions has been synthesized [244] but no asymmetric catalysis application has been reported to date.

![Rh(BINAP) (127)](image)

1,1'-Binaphthyls are also versatile chiral molecular scaffolds in molecular recognition [242]. Again, use of the minor groove has been most explored. Cram and coworkers were the first to recognize the potential of the 1,1'-binaphthyl unit and incorporated it into crown ethers for the enantioselective complexation of chiral amino acid esters and ammonium ions [245]. Chiral 1,1'-binaphthyl-derived cyclophanes have been synthesized by Diederich and coworkers for carbohydrate recognition [246]. The
major groove, with its larger cleft, is more suited to accommodate organic molecules than the minor groove. Diederich and coworkers were the first to recognize the potential offered by the major groove for molecular recognition. Consequently, they synthesized enantiomerically pure 1,1′-binaphthalene-derived receptors like 128 with \(N\)-(pyridine-2,6-diyl)acetamide side chains in the 6,6′-positions, for enantioselective recognition of amino acid derivatives [247]. The 1,1′-binaphthyl-containing cyclophane 129 was shown to effect an enantioselective separation of naproxen derivatives by the formation of inclusion complexes [225a].

3.1.3 Concept

We were interested in combining the properties of Cinchona alkaloids and 1,1′-binaphthyls in the hope of gaining access to high levels of enantioselectivity in catalytic processes. To our knowledge, no molecule incorporating both 1,1′-binaphthyl and quinuclidine fragments has been synthesized to date. The intermolecular interactions between Cinchona alkaloids and 1,1′-binaphthyl receptors have been studied and reported [225b], but the properties of a compound based on both 1,1′-binaphthyl and Cinchona alkaloid moieties remain unexplored. We therefore decided to covalently bind 1,1′-binaphthyls to quinuclidine moieties in order to study the catalytic opportunities offered by such systems. We felt that, in order to benefit from the
chirality of both molecules, it would be preferable to have the quinuclidine unit either close to the minor or the major groove of the 1,1'-binaphthyl moiety. The positions 2 and 7 of the 1,1'-binaphthyl fragment should therefore be the most promising for attachment of the quinuclidine moiety. Consequently, molecules 130 and 131, which both have a direct linkage between the 1,1'-binaphthyl and alkaloid moieties, were considered as potential targets.

As previously discussed, complexation in the minor and the major groove has already been explored. Although enantioselective catalysis has so far only been reported to be successful when using the minor groove, the higher recognition potential of the major groove through its larger surface area and extended possible interactions seemed worthy of exploration. Therefore, encouraged by computer calculations which showed that a 1,1'-binaphthyl compound bearing a quaternized quinuclidine residue in its major groove would be suitable for enantioselective alkylation under phase transfer catalysis conditions (*vide infra*), we decided to synthesize major groove substituted 1,1'-binaphthyls like 131. An important goal was to study the ability of molecular modeling to create new enantioselective catalysts. Starting from the idea that the chiral properties of 1,1'-binaphthyls and quinuclidines can be combined, a new type of catalyst was designed and synthesized. Investigation of its catalytic properties in enantioselective phase transfer catalysis as well as in the asymmetric dihydroxylation reaction should allow an evaluation of the validity of computer-aided catalyst design.

### 3.2 Phase Transfer Catalysis

#### 3.2.1 Introduction

Generally, reactions between substances in different phases are slow, inefficient, or just do not take place at all. Phase transfer catalysis (PTC) facilitates reactions between
hydrophilic and lipophilic substances in biphasic systems. PTC has many advantages over conventional, homogeneous reaction procedures, and has become a very important method in synthetic organic chemistry [248]. Typically, a phase transfer catalyst (Q⁺, Scheme 26) is involved in a reaction where the anionic reactive species cannot enter the organic phase because its associated cation is too hydrophilic. When the catalyst, a lipophilic cation, is added, ion exchange produces more lipophilic ion-pairs which easily migrate into the organic phase where reaction can then take place.

\[
\begin{align*}
&\text{Organic phase:} \\
&\text{Aqueous phase:} \\
&\text{Scheme 26: The mechanism of phase transfer reactions is illustrated by the reaction of 1-chlorooctane (RX) and aqueous sodium cyanide.}
\end{align*}
\]

The displacement reaction of 1-chlorooctane and aqueous sodium cyanide in a biphasic system occurs, in the presence of the quaternary ammonium salt (C₆H₁₃)₄N⁺Cl⁻ (Q⁺Cl⁻), with high conversion within 2-3 h. In the absence of catalyst, no reaction is observed over the same period [249]. The ammonium chloride in the aqueous phase is in equilibrium with the ammonium cyanide by the equilibrium reaction with sodium chloride (aqueous phase reaction). The quaternary ammonium cation Q⁺, which forms a soluble ion-pair in lipophilic media, transfers the cyanide into the organic phase (transfer step), thereby allowing rapid substitution of the chloride, producing 1-cyanoctane and QCl (organic phase reaction). The displaced chloride anion, together with Q⁺, is then transferred back to the aqueous phase where a new cycle can be initiated.

Phase transfer catalysis can also be used for the preparation of enantiomerically enriched compounds. The phase transfer agent, which is a ligand for the reactive species, can impose enantioselectivity onto the reaction by selective binding to one face of an enantiotopic functional group. Typically, organic molecules, after being deprotonated at the interface (Scheme 27), can be stereoselectively complexed by chiral phase transfer catalysts which transport them into the organic phase where further reaction can then take place.
A number of different asymmetric phase transfer reactions have been reported (for reviews see: [250]). Most catalysts used for enantioselective PTC reactions can be divided into two general types:

- Chiral quaternary ammonium salts (quats), mostly derived from *Cinchona* and *Ephedra* alkaloids:

\[
\begin{align*}
\text{Quinidine and cinchonine quats} & \quad 132 \\
\text{Quinine and cinchonidine quats} & \quad 133 \\
\text{(-)-Ephedrine quats} & \quad 134 \\
\text{(-)-Ephedrine quats} & \quad 135
\end{align*}
\]

- Chiral crown ethers:

\[
136
\]
Chiral crown ethers and other chelating agents will not be discussed here, because these phase transfer agents act in a different way, not exchanging the counterion, but solubilizing it through complexation, and are thus not relevant for this project. A chiral phosphonium salt with multiple hydrogen-bonding sites was recently reported to give up to 50% ee in phase transfer alkylation [251]. Although promising, this class of PTC ligands is only emerging and will also not be presented in more detail. We will rather focus on some examples in which phase transfer agents derived from \textit{Cinchona} alkaloids have been successfully used in enantioselective reactions.

- Alkylations:

A very successful example was reported by a group at Merck, interested in the industrial synthesis of the diuretic indacrinone via chiral phase transfer catalysis. Alkylation of the phenylindanone 137 by Dolling et al. [252] demonstrates the high degree of enantioselectivity that can be obtained in phase transfer catalysis. Methylation of 137 using methyl chloride and cinchonine quats 132 (R\(^1\) = H, R\(^2\) = CF\(_3\), X = Br) as catalyst provided the methylated indanone 138 in ee's up to 92% (Scheme 28).

\[
\begin{align*}
\text{Cl} & & \text{MeO} \\
\text{MeO} & & \text{MeCl, 132, toluene, 50 % aq. NaOH} \\
\text{137} & \rightarrow & \text{Cl} \\
& & \text{MeO} \\
& & \text{Me, 95% yield, 92% ee}
\end{align*}
\]

\textbf{Scheme 28:} The asymmetric phase transfer-catalyzed methylation of indanone 137 was achieved in high yield and high enantioselectivity, demonstrating the usefulness of asymmetric PTC.

Electrostatic interactions hold the enolate and the cationic catalyst together, but alone cannot account for the stereoselectivity. A tight ion-pair with well-organized geometry is required. Based on molecular models and on an X-ray crystal structure of the cinchonium cation in which the N-benzyl, the quinoline, and the carbon-oxygen bond lie almost in a single plane, the authors proposed a three-points interaction model that accounts for the asymmetric induction. In this model, two of the interaction points are provided by \(\pi-\pi\) stacking interactions between the \(N\)-benzyl and quinoline groups of the catalyst, and the two aromatic rings of the enolate (Figure 31). The high selectivity between the two aromatic rings of the indanone enolate mostly arises from their different electron density. While the indanone aromatic ring bearing two chlorine atoms
is electron-deficient, the phenyl substituent is electron-rich as a consequence of the conjugated enolate functionality. It is therefore reasonable to predict that the electron-rich aromatic ring will selectively interact with the electron-poor N-benzyl group present on the positively charged ammonium center. Consistently, the enantioselectivity was shown to be dependent upon the substituent of the N-benzyl group [252c]. For example, the enantioselectivity drops from 94 to 70% ee when the $p$-CF$_3$ substituent is replaced by a para methoxy group. Electron-withdrawing substituents make the benzyl group more electron-deficient and increase its selectivity in binding to the electron-rich phenyl enolate. The hydroxyl group at the C(9) position of the catalyst provides the third interaction point by hydrogen bonding with the negatively charged enolate oxygen. Consequently a tight ion-pair in which the catalyst preferentially bind to one face of the indanone is formed. The alkylating agent will therefore selectively approach the less hindered face of the enolate, i.e. opposite to the catalyst.

![Figure 31: Electrostatic effects, hydrogen bonding, and π–π stacking interactions between the aromatic rings hold the enolate and the catalyst together and account for the observed enantioselectivity.](image)

Another useful example of asymmetric PTC is the stereoselective synthesis of $\alpha$-amino acids by the alkylation of Schiff base esters like 139 with alkyl halides [253]. In the presence of Cinchona quats 133 (R$^1 = $OMe, R$^2 = $H, X = Cl), this reaction typically proceeds with enantioselectivities of 40 to 66% (Scheme 29).

![Scheme 29: Enantiomerically enriched $\alpha$-amino acids were synthesized by asymmetric PTC alkylation of Schiff base esters.](image)
Corey et al. have recently achieved the alkylation of 139 in 92 to 99.5% ee with catalyst 141 [254]. They explained the enantioselectivity by the fact that three of the four faces of a tetrahedron taken around the ammonium center of the catalyst are well shielded by the bicyclic quinuclidine, the anthracenyl subunit, and the allylic side chain. Thus, only one face is accessible for the substrate to come into close contact with the ammonium center and form a tight ion-pair. This hypothesis is supported by X-ray crystal structures of the catalyst where the counterion is indeed located in the open face.

- Aldol reactions:

*Cinchona* alkaloid quats are also efficient catalysts for aldol reactions. Cinchonine quats (132, R1 = R2 = H, X = F) has been reported to catalyze the addition of silyl enol ether 142 to benzaldehyde with good enantioselectivity [255] (Scheme 30). Fluoride instead of bromide was used as the counterion for the catalyst, since the chemical affinity of the silyl group for the fluoride anion improved the efficacy of enolate formation.

**Scheme 30:** The asymmetric aldol reaction of silyl enol ether 142 and benzaldehyde was catalyzed by cinchonine quats (132).
Asymmetric PTC aldol condensation of protected glycinate 139 to give β-hydroxy-α-amino acid derivatives has also been reported, however only moderate enantio- and diastereoselectivities have been achieved so far [256].

- Michael additions:

The Merck catalyst 132 (R₁ = H, R₂ = CF₃, X = Br) also gave very good results (80% ee) in the phase transfer-catalyzed Michael addition of phenylindanone 137 with methyl vinyl ketone [257]. The 'pseudo-enantiomer' catalyst 133 (R₁ = H, R₂ = CF₃, X = Br) derived from cinchonidine afforded an excess of the opposite enantiomer, although with lower selectivity. Cinchona- and Ephedra-derived quats have also been employed in the Michael addition of acetylaminomalonate 146 to chalcone (147) [258] (Scheme 31).

\[
\begin{align*}
\text{AcHN} & \text{CH(COOEt)}_2 \\
146 & \\
\text{PhCH} & \text{CO} \\
147 & \\
\text{Ph} & \\
\text{132 or 135, KOH} & \\
\text{AcHN} & \text{CH(COOEt)}_2 \\
147 & \\
\text{Ph} & \text{CO} \\
148 & \\
\text{EtOOC} & \text{COOEt} \\
\end{align*}
\]

Scheme 31: Asymmetric induction in the Michael addition of acetylaminomalonate 146 to chalcone was achieved with Cinchona and Ephedra quats.

Wynberg and coworkers have studied the addition of nitromethane to chalcone (147) and other α,β-unsaturated ketones using Cinchona and Ephedra quats as chiral catalysts [259]. They reported that the hydroxyl group β to the ammonium function is essential for obtaining substantial asymmetric induction: when the C(9) hydroxyl group of quinine quats 133 was esterified, a much lower enantioselectivity was observed. They also were able to show that with Cinchona alkaloid salts, the absolute configuration at C(8) and C(9) determines the stereochemical course of the addition.

- Epoxidations:

Epoxidations of both cyclic and acyclic, electron-deficient alkenes have been well studied [260,261]. These reactions, for example the epoxidation of quinone 149 [260b] or chalcone (147) [261d] (Scheme 32), generally work best when catalyzed by quinine (132, R₁ = OMe, R₂ = H, X = Cl) rather than cinchonine quats.
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Scheme 32: Asymmetric epoxidations of enones under phase transfer conditions in the presence of Cinchona quats 132 have been reported to work with medium to high enantioselectivities.

- α-Hydroxylations:

Ketones have been converted to α-hydroxyketones with excellent asymmetric induction using molecular oxygen in the presence of catalyst 132 (R^1 = H, R^2 = CF_3, X = Cl). The highest enantioselectivity (79% ee) was obtained in the α-hydroxylation of tetralone 152 [262] (Scheme 33).

Scheme 33: Enantioselective PTC is a powerful method to convert ketones to α-hydroxyketones with good asymmetric induction.

A transition state model accounting for the enantioselectivity of the reaction has been proposed (Figure 32). Similarly to the alkylation of phenylindanone 137 (see Figure 31), π-π stacking, hydrogen bonding, ion-pair and hydrophobic interactions should account for the selective complexation of the enolate derived from ketone 152 and Cinchona quats 132 and consequent enantioselectivity. The stereoselectivity was shown to be highly dependent on the para substituent present on the benzylammonium (the best enantioselectivities were obtained with the electron-withdrawing substituents -CF_3 and -SO_2CF_3).
The catalyst configuration at C(8) and C(9) again played a dominant role in determining the absolute configuration of the product.

- Reductions:

Reduction of carbonyl groups with sodium borohydride in the presence of chiral ammonium salts has also been investigated, although the optical purity of the resulting products is generally low. Benzylquinium chloride 133 (R¹ = OMe, R² = H, X = Cl) was shown to give the best results. In the case of phenyl tert-butyl ketone (154), the corresponding carbinol 155 was obtained in 32% ee (Scheme 34) [263].

\[
\text{Scheme 34: The enantioselective borohydride reduction of phenyl tert-butyl ketone (154) and analogs was accomplished by phase transfer catalysis, albeit with moderate ee.}
\]

### 3.2.2 Design of a Phase Transfer Catalyst

Efficient methods for the enantioselective formation of C-C bonds are of primary importance in organic synthesis. This field has attracted much attention in the last two decades, resulting in numerous methods for the stereoselective creation of secondary...
and tertiary centers [264-269]. The synthesis of quaternary all-carbon-substituted stereocenters is however a much more challenging task, and despite considerable efforts, relatively few reactions are known which proceed in reasonable chemical and optical yields [270,271].

Many approaches may be used for the stereocontrolled synthesis of stereogenic centers [264-269]. With chiral starting materials, the formation of a new stereogenic center can occur diastereoselectively, under the control of existing centers (substrate-controlled method). An alternative approach is to use a chiral auxiliary, deliberately attached to the achiral substrate, in order to direct the reaction. The chiral auxiliary can be removed once it has served its purpose, and ideally be recovered. Chiral reagents can be used to intermolecularly induce a stereoselective reaction (reagent-controlled method). In each of these methods however, stoichiometric amounts of an enantiomerically pure compound are required. Use of a relatively small amount of an enantiopure catalyst to direct the conversion of an achiral substrate to a chiral product, using an achiral reagent, is therefore highly desirable owing to the high atom efficiency of this approach. Biological catalysts are highly efficient and selective. There are, however, many reactions for which nature has not developed an enzyme, as well as many substrates which do not resemble natural products. Synthetic stereoselective catalysts are therefore in increasing demand, and the development of new chiral catalysts remains a major research area.

Since high enantioselectivities are often difficult to obtain and generally rely on extensive optimization work, progress in this field can be rather slow. Many catalysts often have to be prepared and tested in order to obtain high enantioselectivities, and methods to accelerate this process are desirable. Combinatorial chemistry has been explored as a better way to improve the efficiency of asymmetric catalyst discovery and optimization [272,273]. Parallel synthesis and high-throughput screening of catalysts is likely to play an important role in the years to come. Another way to accelerate this process would be to use computer calculations to design new chiral catalysts. In a similar manner to rational drug design, molecular modeling could provide a new insight into transition states and efficiently generate new catalysts. Moreover, rationally designed catalysts might allow the prediction of the preferentially formed enantiomers, which is otherwise rarely the case.

The rational design of catalysts has, to our knowledge, never been undertaken, or at least not in a fully rational way, using only the reaction mechanism and the structure of the transition state. This approach is a challenging task since only small energy differences separate non-selective from highly selective catalysts (~1-2 kcal/mol
variance in the transition state energy [272a]). Nevertheless, we felt that, for some well-understood reactions, sufficient knowledge exists for the design of enantioselective catalysts. It is necessary for such a rational approach to understand as much as possible the factors governing the stereoselectivity of the reaction. We therefore decided to explore this new design approach using a well-known PTC reaction and proposed to re-investigate the asymmetric alkylation of phenylindanone 137 developed by the Merck group [252]. Our goal was to investigate the feasibility of such a rational design approach. We decided to create a chiral phase transfer agent based on the *Cinchona* alkaloid and 1,1'-binaphthyl moieties. By developing a new catalyst which would efficiently and stereoselectively form quaternary carbon stereocenters, we hope to demonstrate the utility of molecular modeling for the design of new asymmetric catalysts. In the long term, if the modeling is successful in calculating and predicting key ion-pair structures which procure high levels of enantioselectivity, completely new reactions may be discovered (*de novo* catalyst design).

1,1'-Binaphthyls substituted in the minor and the major groove (see compounds 130 and 131) and having various configurations at C(8) and C(9) were examined as potential PTC catalysts. Molecular dynamics as well as Monte-Carlo minimizations were performed with MacroModel 6.0 [274] using the MM2* force field [275]. Because of the large aromatic surface of the 1,1'-binaphthyl group, such compounds are good candidates for enantioselectively catalyzing alkylation reactions on molecules like *Dolling*’s indanone 137. The cleft of 1,1'-binaphthyls substituted in the minor groove was found however to be too small a space for accommodating the enolate of phenylindanone 137. 1,1'-Binaphthyls substituted in the major groove have a larger hydrophobic surface for substrate complexation (see Chapter 3.1.2), and the (8R,9S)-enantiomer 156 was found, according to computer modeling, to complex the enolate of 137 making all the necessary interactions. The (aS)-1,1'-binaphthyl$^5$ unit of 156 is substituted at positions 2 and 2' to prevent free rotation around the 1,1'-binaphthyl axis.

$^5$The (aR) and (aS) descriptors (for recent literature examples, see [276]) are used for the axial chirality.
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thereby fixing the axial chirality. The alkoxyethyl substituent at position 3' was
designed into the synthesis as a site for potential further functionalization in the sol-gel
project (vide infra). The second half of the molecule is a (8R,9S)-quinuclidine ring
quaternized by a p-trifluorobenzyl group.

(a)

![H-bond](image1)

(b)

![ion-pair interaction](image2)

Figure 33: The schematic (a) and computer-calculated (b) representations of the p-
trifluoromethylbenzyl-(aS)-1,1'-binaphthyl-(3R,4S,8R,9S)-quinuclidine quats
156 and indanone enolate ion-pair illustrate the key interactions responsible
for the selective complexation and subsequent enantioselectivity.

The ion-pair obtained from a 5000-step pseudo Monte-Carlo Multiple Minimum
(MCMM) calculation in chloroform using the MM2* force field was similar to the one
postulated by the Merck group. Hydrogen-bonding (1.62 Å) and ion-pair interactions (4.95 Å) were calculated to be almost identical (Figure 33). The π-π stacking interactions between the p-trifluorobenzyl side chain and the indanone phenyl ring are also very similar. The 1,1'-binaphthyl fragment also makes edge-to-face and hydrophobic interactions with the phenylindanone, in addition to comparable π-π stacking interactions. Comparison of the minimized ion-pair complexes formed between phenylindanone 137 and cinchonine quats 132, and between 137 and 1,1'-binaphthyl quats 156, allows a better evaluation of these hydrophobic interactions. Whereas 30 van der Waals contacts shorter than 4 Å were found between the quinoline ring of cinchonine quats 132 and phenylindanone 137, the ion-pair complex calculated with the 1,1'-binaphthyl quats 156 has 54 van der Waals contacts. The substrate is complexed within the 1,1'-binaphthyl groove, resulting in extended hydrophobic contacts.

3.2.3 Synthesis

In order to benefit from commercially available quinuclidines, we looked for a convergent synthetic approach that would allow the attachment of the alkaloid moiety to an already functionalized 1,1'-binaphthyl. Among the various total syntheses published by Uskokovic and coworkers [277], two complementary ways to synthesize Cinchona alkaloids by combining quinuclidine derivatives with suitable quinoline rings have been proposed [277]. Both methods used a lithiated quinoline, obtained by halogen-metal exchange from the corresponding bromide, as a key intermediate (Scheme 35). The first method involves the condensation of the lithiated quinoline with racemic aldehydes 157a and 157b, leading to alkaloids 158a to d as a mixture of four diastereoisomers (13% quinine, 15% quinidine, and 5% of each of the two 9-epi isomers in the case where R = CH=CH₂). In the second approach, quinuclidine esters 159a and 159b were used instead of aldehydes. Condensation of 159a and b with lithiated quinoline afforded a mixture of diastereoisomeric ketones 160a and 160b in 30 to 40% yield. Stereoselective reduction with diisobutylaluminium hydride in benzene stereoselectively led to the C(8)-C(9) erythro pair of diastereoisomers 158a and 158b ((8S,9R)-quinine and (8R,9S)-quinidine, respectively, when R = CH=CH₂). The diastereoselectivity of the reduction step is presumably a result of initial chelation of the DIBAL-H reducing agent to the quinuclidine nitrogen, followed by intramolecular delivery of hydride to the ketone (Figure 34).
Sodium borohydride reduction of quinidones 160a and 160b in ethanol also proceeded stereoselectively, affording the C(8)-C(9) threo pair 158c and 158d ((8S,9S)-9-epi-quinine and (8R,9R)-9-epi-quinidine, respectively, when R = CH=CH2) by attacking the presumably less hindered side [277f].

Scheme 35: Cinchona alkaloids have been prepared by direct condensation of aldehydes 157a and 157b with 6-methoxy-4-quinolyllithium, or via the ketone intermediates 160a and 160b obtained from the esters 159a and 159b.
This second method has been applied to the synthesis of analogs of *Cinchona* alkaloids incorporating a 9,9'-spirobifluorene moiety [231]. These compounds were prepared as a mixture of diastereoisomers by reacting lithiated 2-bromo-9,9'-spirobifluorene with ethyl esters 159a and 159b, providing ketones 161a and 161b (Scheme 36). Subsequent diastereoselective reduction with diisobutylaluminium hydride afforded the corresponding alcohols.

![Scheme 36](image)

**Scheme 36:** *Cinchona* alkaloid analogs incorporating a 9,9'-spirobifluorene fragment have been prepared by condensation of esters 159a and 159b with a lithiated spirobifluorene.

The stereoselectivity obtained in the DIBAL-H reduction step makes the second method, namely condensation with quinuclidine esters instead of aldehydes, very attractive. Since this route should allow the controlling of the stereochemistry at C(9), we decided to base our synthesis on it. Another electrophile than ethyl esters, which were used in the published examples, is, however, desirable in order to improve the yield in the condensation step (~ 35% in the total synthesis of *Cinchona* alkaloids, 5-35% for the spirobifluorene analogs). We therefore turned our attention to Weinreb amides which are known to couple in high yields with *Grignard* and organolithium reagents [278]. The stable lithium-chelate intermediate (Scheme 37) not only prevents over-addition, but should also reduce the possibility of epimerization of the alkaloid moiety.

![Scheme 37](image)

**Scheme 37:** *Electrophilic addition of organolithium to Weinreb amides occurs via a stable metal-chelated intermediate accounting for the lack of over-addition products.*
Retrosynthetic analysis of 156 first led to the disconnection of the quaternary benzyl group, revealing compound 162 as an advanced intermediate. Disconnection of the C(9)-C(7') bond according to the strategy discussed above, revealed the 7-bromo-1,1'-binaphthyl fragment 163 and the alkaloid moiety 164 as key building blocks (Scheme 38). It was planned to convert bromide 163 into an organometallic nucleophile which would then add to Weinreb amide 164. Subsequent reduction with diisobutylaluminium hydride was anticipated to proceed stereoselectively affording 162.

Scheme 38: The retrosynthetic analysis of 156 revealed bromide 163 and Weinreb amide 164 as building blocks.

The synthesis of the quinuclidine building block (3R,4S,8R)-(+)-164 was first addressed. Oxidation of the commercially available (3R,4S,8R)-8-hydroxymethyl-3-vinylquinuclidine ((+)-165) to the corresponding carboxylic acid and purification by ion-exchange chromatography on acidic Dowex gave access to (3R,4S,8R)-(+)-166 (Scheme 39). In situ formation of the acid chloride and subsequent reaction with N,O-dimethylhydroxylamine hydrochloride under basic conditions afforded Weinreb amide (3R,4S,8R)-(−)-167. Finally, the desired amide (3R,4S,8R)-(−)-164 was quantitatively obtained by reductive hydrogenation of the vinylic olefin.
The synthesis of the 1,1'-binaphthyl building block (aS)-163 was next addressed. This fragment proved quite challenging owing to its unsymmetrical structure. Symmetrical 1,1'-binaphthol synthesis by oxidative homo-coupling of 2-naphthols has been extensively studied, however, cross-coupling methods leading to unsymmetrical 1,1'-binaphthalen-2,2'-diols remain relatively unexplored [279]. This case is more complicated owing to the possible formation of three products (two homo-coupled and one cross-coupled products) (Scheme 40).

Scheme 39: The synthesis of Weinreb amide (+)-164 was accomplished in three steps starting from commercially available alcohol (+)-165.

Scheme 40: Three possible products can be formed by the oxidative cross-coupling reaction of two different 2-naphthols.
Hovorka et al. have reported Cu(II)-mediated cross-coupling reactions between differently substituted 2-naphthols [279,280]. They noted that the selectivity of the reaction depends on the substitution pattern of both partners. A synthetically useful degree of selectivity was achieved when the difference in electron density between the reacting partners was large. For example, cross-coupling of (a) and (b) (Scheme 41) was found to yield almost selectively the unsymmetrical 1,1'-binaphthyl, whereas coupling (b) and (c) afforded a nearly statistical mixture of the three possible products. Enantioselective syntheses of unsymmetrical 2-amino-2'-hydroxy-1,1'-binaphthyl and methyl 2,2'-dihydroxy-1,1'-binaphthalen-3-ylcarboxylate have also been reported using an in situ-generated complex of CuCl₂ and (-)-sparteine [281].

Mechanistic studies of the Cu(II)-mediated coupling were undertaken in order to understand the observed selectivity [282]. Three possible mechanisms were proposed. The first two are based on the widely-accepted generation of a phenoxy radical from the corresponding phenolate as the initial step. A third mechanism, which will not be further discussed, consists of an ionic reaction between an oxidized phenoxonium ion and an unreacted phenol.

In the first, commonly accepted mechanism, free phenoxy radicals formed by oxidation of the phenolate, recombine to give the 1,1'-binaphthol products in a radical recombination process (Scheme 42). In the presence of two different 2-naphthols, the oxidation potentials, which determine the ease of radical formation, are the main controlling factor determining product distribution. When the oxidation potentials of the two competing phenolic substrates are similar, a statistical mixture of homo- and cross-coupled products is expected. However, when the oxidation potentials of the two
2-naphthols differ significantly, the product of the homo-coupling of the substrate possessing the lower oxidation potential will prevail in the early stage of the reaction, followed later by a slower homo-coupling of the second substrate (less easily oxidizable). Such a mechanism can however not explain the selectivity for the cross-coupled product observed by Hovorka.

Scheme 42: The radical recombination mechanism can not explain the selectivity observed in some cross-coupling reactions.

The second, proposed mechanism involves the insertion of a radical into the C-H bond of a phenolate (Scheme 43). This situation is more complex. In addition to the oxidation potential which determines which substrate will preferentially form the phenoxy radical, the intrinsic insertion selectivity of the individual radicals may also participate in the product control. At one extreme, if the phenoxy radical behaves as an electrophile, the more easily oxidizable phenolate which is a stronger nucleophile would be attacked preferentially giving rise to the homo-coupled product. If however, at the other extreme, the phenoxy radical behaves as a nucleophile, the less easily oxidizable naphthol which is a better electrophile would be a more convenient partner and the cross-coupled product will be formed preferentially. Even if this mechanistic scheme represents an oversimplification, such a radical insertion could explain the
selectivity sometimes obtained. Moreover, \textit{ab initio} calculations [283] are in excellent agreement with the experiment. Electrochemical data clearly show that it is much easier to generate a radical from (b) compared to (a) (see Scheme 41). Then, with the energy difference between the SOMO of (b) and the HOMO of the anionic form of (a) being smaller than that between the SOMO of (b) and the HOMO of the anionic form of (b), stabilization will be greater for the cross-coupled product which can be anticipated to predominate.

\textbf{Scheme 43:} The radical insertion mechanism was proposed to explain the selective formation of unsymmetrical 1,1'-binaphthyl in the case where the oxidation potential and the intrinsic insertion selectivity of the two reacting partners are different.

In order to benefit from such a selective approach to unsymmetrical 1,1'-binaphthyls, we prepared two 2-naphthols with different electron densities. Methyl 3-hydroxy-2-naphthoate (169) was synthesized from the corresponding carboxylic acid 168 (Scheme 44). 7-Bromonaphthalen-2-ol (171) was obtained by bromination of the diol 170 using a similar method to that published for the preparation of 2-bromonaphthalene [284].
With compounds 169 and 171 in hand, the synthesis of the unsymmetrical 1,1'-binaphthyl was addressed. Some selectivity in the cross-coupling reaction was anticipated, for we are dealing with a very similar situation to that published by Hovorka et al. (case (a) + (b), Figure 34) [279,280]. Indeed, the unsymmetrical 1,1'-binaphthyl (±)-173 was obtained in very good yield and with high selectivity (Scheme 45).

\[
\begin{align*}
\text{Scheme 44:} & \quad \text{Compounds 169 and 171 were synthesized as building blocks for the unsymmetrical 1,1'-binaphthyl.} \\
& \quad \text{With compounds 169 and 171 in hand, the synthesis of the unsymmetrical 1,1'-binaphthyl was addressed. Some selectivity in the cross-coupling reaction was anticipated, for we are dealing with a very similar situation to that published by Hovorka et al. (case (a) + (b), Figure 34) [279,280]. Indeed, the unsymmetrical 1,1'-binaphthyl (±)-173 was obtained in very good yield and with high selectivity (Scheme 45).}
\end{align*}
\]
The next step was the resolution of the racemic 1,1'-binaphthyl (±)-173. An elegant approach would have been an enantioselective synthesis of the 1,1'-binaphthyl fragment by a CuCl₂-sparteine catalyzed reaction [281]. However, if enantiomerically pure homo-coupled 1,1'-binaphthalen-2-ol was obtained by this method, only 41% enantiomeric excess was obtained for the unsymmetrical cross-coupled product [281c]. In the absence of more enantioselective cross-coupling protocols, we used a recently published method for the resolution of substituted 1,1'-binaphthols [285].

Scheme 46: The resolution of 1,1'-binaphthyl (±)-173 was accomplished through bis-functionalization with camphorsulfonyl chloride followed by chromatographic separation of the two diastereoisomers.

1,1'-Binaphthyl (±)-173 was reacted with (1S)-(−)-camphor-10-sulfonyl chloride which acts as the chiral auxiliary (Scheme 46). The two diastereoisomers (+)-175 and (−)-176 were then separated by column chromatography on silica gel using CH₂Cl₂/EtOAc (99:1) as eluent. Analytical HPLC analysis on a silica gel column (gradient of CH₂Cl₂/EtOAc 100:0 to 80:20) showed that both compounds were isolated free from the other diastereoisomer (Figure 35).
After the chromatographic resolution, the chiral camphor auxiliary was removed by hydrolysis. Methylation of the two resulting hydroxyl groups and the carboxylic acid, yielded 1,1'-binaphthyls (+)- and (-)-177 (Scheme 47). Reduction of the methyl ester with diisobutylaluminium hydride afforded alcohols (+)- and (-)-178 which had to be protected prior to the coupling step with the quinuclidine derivative. A methoxymethyl (MOM) protecting group was first introduced, but as a result of the modest yield in the protection step as well as the lability of the MOM group in the subsequent coupling reaction, we chose to first synthesize the methoxy protected (+)- and (-)-179 for addressing the rest of the synthesis as well as the phase transfer catalysis experiments, and planned to use a different protecting group only for the sol-gel project (vide infra).
The absolute configuration of the 1,1'-binaphthyl fragment was determined through derivatization of (+)-175 to a product with known configuration. Treatment of (+)-175 with n-butyllithium followed by quenching with hydrochloric acid and methanol provided the reduction product (Scheme 48). Subsequent cleavage of the camphorsulfonfonyl auxiliaries and esterification of the resulting carboxylic acid afforded (-)-181 which has been reported to have the (aS)-configuration [281c]. In a separate study, the (aR)-configuration has been assigned to (+)-181 by comparison with the CD spectrum of optically pure (+)-dimethyl 2,2'-dihydroxy-1,1'-binaphthylene-3,3'-dicarboxylate [280b].
Scheme 48: The absolute configuration of the 1,1'-binaphthyl fragment was determined by derivatization of (±)-175 to (aS)-(−)-181.

With both enantiomerically pure 1,1'-binaphthyls (aR)-(+)- and (aS)-(−)-179, as well as Weinreb amide (3R,4S,8R)-(−)-164 in hand, we next addressed the key coupling step (first with racemic 1,1'-binaphthyl). This reaction however proved quite challenging. Sequential addition of n-butyllithium and Weinreb amide (±)-164 to bromide (±)-179 using various conditions repeatedly failed to furnish the desired ketone 182 (Scheme 49).

Scheme 49: Lithiation of 7-bromo-1,1'-binaphthyl (±)-179 followed by addition of the Weinreb amide (+)-164 repeatedly failed to afford the desired ketone 182. The reduced product (±)-183 was isolated instead.
We therefore first investigated the lithiation of bromide (±)-179 in order to gain a better understanding of the problem occurring during this reaction. Surprisingly, the starting material was completely recovered when one equivalent of n- or t-butyllithium was added (with or without TMEDA as co-solvent). The first equivalent of base is presumably complexed by the three methoxy groups, preventing the halogen-lithium exchange to take place. Lithiation was achieved by using an excess of n-BuLi (two or more equivalents), however the lithiated intermediate proved to be very labile in diethyl ether as well as in THF. This was shown by deuteration experiments in which the reaction mixture was quenched with deuterated methanol directly after the addition of BuLi (Scheme 50).

Scheme 50: The lability of lithiated (±)-179 was shown by the presence of a proton at C(7) after deuteration experiments. The lithiated molecule obtained from stannane (±)-185 was however stable and could be deuterated.
Bromide \( \pm\)-179 was completely reduced to \( \pm\)-183, demonstrating complete lithiation, but a proton and not a deuterium was present at position 7 (as indicated by \(^1\)H- and \(^2\)D-NMR spectra). The same experiment carried out in d\(^8\)-THF afforded the deuterated product \( \pm\)-184, establishing that the proton or deuterium comes from the solvent. In the next attempt, bromide \( \pm\)-179 was first converted into the corresponding tin derivative \( \pm\)-185 by treatment with tributylstannyllithium \([286]\). In that case, the lithium complex formed from \( \pm\)-185 was found to be stable at \(-78^\circ\)C for prolonged periods of time and could be trapped by deuterated methanol to afford \( \pm\)-184. Organolithium compounds are known to associate and form \((RLi)_n\) aggregates, and mixed complexes in the presence of salts \([287]\). It is therefore reasonable to think that the 1,1'-binaphthyllithium aggregate is not influenced by tetrabutylstannane, the second reaction product, whereas the bromide forms a much more reactive mixed aggregate with the organolithium species.

\[\text{Scheme 51: The key coupling reaction was achieved from bromide } \pm\text{- and } \pm\text{-179 as well as stannane } \pm\text{-185, however epimerization could not be prevented.}\]

Based on these results, the addition of lithiated 1,1'-binaphthyls to Weinreb amide \((3R,4S,8R)-(+)-164\) was re-investigated (Scheme 51). Since the lithium complex
formed from bromide (±)-179 was shown to be unstable, n-butyllithium was added to a pre-formed mixture of (aS)-(−)-179 and (3R,4S,8R)-(−)-164, giving access to (aS,3R,4S,8R)-182 and (aS,3R,4S,8S)-186 (40-46% yield) as an inseparable mixture of diastereoisomers (ca. 1:1) owing to rapid epimerization at C(8). A second approach was to first lithiate stannane (±)-185 and then add a solution of Weinreb amide (3R,4S,8R)-(−)-164 in THF. Epimerization could again not be prevented, even by using less than one equivalent of base, and a mixture of diastereoisomeric ketones (aS,3R,4S,8R)-182, (aS,3R,4S,8S)-186, (aR,3R,4S,8R)-187, and (aR,3R,4S,8S)-188 was obtained (35-42%). Consequently, as epimerization occurred with both methods, the direct route via the 7-bromo-1,1′-binaphthyl (−)-179 was preferred. The coupling step was also carried out with (aR)-(−)-179, affording a mixture of diastereoisomeric ketones (aR,3R,4S,8R)-187 and (aR,3R,4S,8S)-188. The time scale of this project however made further investigation with the (aR)-1,1′-binaphthyl derivatives impossible, and completion of the synthesis was only done for the designed (aS)-1,1′-binaphthyl compounds.

Alternatives were investigated in order to avoid epimerization at C(8). Use of less basic Grignard reagents was considered. However, conversion of bromide (±)-179 into the corresponding Grignard reagent repeatedly failed and starting material was recovered. Metal-catalyzed cross-coupling reactions between stannane (±)-185 and acid chloride derivatives were attempted. The cross-coupling of phenylacetyl chloride as model reagent proved successful (Scheme 52), but could not be achieved with the acid chloride hydrochloride derived from Cinchona alkaloid (+)-166.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{SnBu}_3 \\
(±)-185 & \quad \text{[Pd(Ph}_{3}]_4, \\
& \quad \text{PhCH}_2\text{COCl,} \\
& \quad \text{benzene,} \\
& \quad 40 \degree \text{C,} 8 \text{h,} \\
& \quad 62\% \\
\text{MeO} & \quad \text{MeO} \\
(±)-185 & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
(±)-189 & \quad \text{MeO}
\end{align*}
\]

Scheme 52: Phenylacetyl chloride was coupled to stannane (±)-185 via a Stille cross-coupling reaction, but the reaction could not be successfully applied to the Cinchona alkaloids.

The subsequent reduction step was carried out on the diastereoisomeric mixture of (aS,3R,4S,8R)-182 and (aS,3R,4S,8S)-186. As already discussed, the reduction of similar ketones with diisobutylaluminium hydride in benzene selectively leads to the C(8)-C(9) erythro diastereoisomers [277f]. The same conditions were therefore used...
for the reduction of ketones 182/186, affording diastereoisomeric alcohols
(aS,3R,4S,8S,9S)-(+)-190, (aS,3R,4S,8R,9R)-(−)-191, (aS,3R,4S,8S,9R)-(−)-192, and
(aS,3R,4S,8R,9S)-(−)-193 (Scheme 53), however not with complete selectivity (Table
7). In analogy to the literature examples, we attributed the erythro configuration to the
diastereoisomers (aS,3R,4S,8S,9S)-(−)-192 and (aS,3R,4S,8R,9R)-(−)-193 which were obtained in 18% de. Steric hindrance might account for this reduced selectivity since the 1,1'-binaphthyl unit is larger than the quinoline ring present in the naturally occurring Cinchona alkaloids.

Scheme 53: The reduction was carried out on the diastereoisomeric mixture of ketones 182 and 186.

Sodium borohydride reduction should stereoselectively afford the C(8)-C(9) threo pair of diastereoisomers. Again, on the 1,1'-binaphthyl system, reduced stereocontrol was observed (50% de for the threo pair of diastereoisomers). The favored formation of the two other diastereoisomers ((aS,3S,4S,8S,9S)-(+)-190 and (aS,3R,4S,8R,9R)-(−)-191) as compared to the DIBAL-H reduction further indicates that the stereoselectivity in the reduction step is similar to the one reported in the literature by Uskokovic et al. [277f] and that the relative configuration at C(8) and C(9) can be attributed on this basis.

Table 7: Some stereoselectivity was obtained in the reduction of ketones 182 and 186. The diastereoisomeric ratio were determined by analytical HPLC in the case of the DIBAL-H reduction, and by integration of the 1H-NMR signals for the NaBH4 reduction.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>(+)-190</th>
<th>(+)-191</th>
<th>(−)-192</th>
<th>(+)-193</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIBAL-H, benzene, 0 °C, 4 h</td>
<td>20 mol%</td>
<td>21 mol%</td>
<td>29 mol%</td>
<td>30 mol%</td>
</tr>
<tr>
<td>NaBH4, EtOH, 0 °C, 15 min</td>
<td>39 mol%</td>
<td>36 mol%</td>
<td>14 mol%</td>
<td>11 mol%</td>
</tr>
</tbody>
</table>
Separation of the four diastereoisomers was possible by column chromatography on silica gel. With enantiomerically pure (+)-190, (+)-191, (-)-192, and (+)-193 in hand, elucidation of the absolute configuration was next addressed using NMR methods. The 1,1'-binaphthyl hydrogens could be assigned on the basis of their chemical shift and coupling pattern. The assignment of the protons in the quinuclidine ring were however more challenging and COSY experiments were made in order to identify their ¹H-NMR signals (see Appendix in Chapter 5). NOE measurements were next performed to determine the absolute configuration of the diastereoisomers. The (85)-configuration was assigned to compounds (aS,3R,4S,8S,9S)-(+)-190 and (aS,3R,4S,8S,9R)-(-)-192 on the basis of NOE effects between H-C(2trans) and H-C(8) (Figure 36). For diastereoisomer (aS,3R,4S,8R,9R)-(+)-191, irradiation of H-C(9) yielded a strong NOE around δ 2.40 which corresponds to H-C(2trans). Irradiation of H-C(2trans) gave an NOE at δ 4.15-4.30 corresponding to H-C(9). Consequently, the H-C(8) hydrogen has to be in an axial position and the (8R)-configuration attributed to (aS,3R,4S,8R,9R)-(+)-191. In the case of (aS,3R,4S,8R,9S)-(+)-193, no NOE was detected between H-C(2trans) and H-C(8), but direct proof for assigning the absolute configuration could not be obtained owing to signal overlap. However, having proved the C(8) configuration for the three other diastereoisomers, the configuration of the last one must be represented as shown in Figure 36.

![Figure 36](image-url)
Owing to the rotational freedom around the C(8)-C(9) and C(9)-C(9') bonds, the absolute configuration of the aliphatic C(9) stereocenter could unfortunately not be established by the NOE experiments. However, the configuration of the C(9) stereocenter was deduced on the assumption that the reduction steps proceeded with similar stereoselectivity to the reported examples.

**Figure 37**: The CD spectra of the four diastereoisomers are dominated by the 1,1'-binaphthyl moiety and therefore very similar.
Circular dichroism (CD) spectra were next measured to confirm the configuration attributed to diastereoisomers \((\alpha S,3R,4S,8S,9S)-(+)\-190, (\alpha S,3R,4S,8R,9R)-(+)\-191, (\alpha S,3R,4S,8S,9R)-(--)\-192, and \((\alpha S,3R,4S,8R,9S)-(+)\-193\). However, the CD effect of the 1,1'-binaphthyl chromophore dominates and the four compounds, which all incorporate the same \((\alpha S)\-1,1'-binaphthyl moiety, have very similar CD spectra (Figure 37). The only significant difference between the CD spectra of the four diastereoisomers is the intensity of the Cotton effect at 290-295 nm. A possible interpretation is that this negative Cotton effect partially arises from the quinuclidine part of the molecules. Compounds \((-)\-192\) and \((+)\-193\) could have a Cotton effect almost exclusively influenced by the 1,1'-binaphthyl fragment, whereas for compounds \((+)\-190\) and \((+)\-191\), which are 'pseudo-enantiomers' and have, respectively, the smallest and largest Cotton effect, the \((8S,9S)\- and the \((8R,9R)\-quinuclidine-alcohol moiety could provide a positive and negative contribution, respectively, to the Cotton effect. This hypothesis would fit with the experimental \(\Delta \varepsilon\) values which, at 293 nm, are small \((-4.25)\) for \((\alpha S,3R,4S,8S,9S)-(+)\-190\), medium for \((\alpha S,3R,4S,8S,9R)-(--)\-192\) and \((\alpha S,3R,4S,8R,9S)-(+)\-193\) \((-5.60\) and \(-5.29,\) respectively), and large for \((\alpha S,3R,4S,8R,9R)-(+)\-191\) \((-6.00)\).

Completion of the synthesis was achieved through quaternization of the four diastereoisomers \((+)\-190, (+)\-191, (--)\-192, and (++)\-193\) (Scheme 54). The reaction worked in 50 to 57% yield for three diastereoisomers, which corresponds to standard yields for such a quaternization. The \((+)\-195\) diastereoisomer was, however, obtained in very low yield (0 to 12%).

![Scheme 54: The quaternization gave access to the targeted catalysts, albeit in poor yield in the case of \((+)\-191\).](image-url)
In order to understand the low yield obtained for compound (+)-195 in the quaternization step, a conformational analysis was performed using the MM2* force field implemented in MacroModel 6.0 [274]. A sterically hindered tertiary nitrogen could explain this low yield. The force field was selected in analogy to the most recent molecular mechanics computational study carried out on Cinchona alkaloids [223d]. The four diastereoisomers (+)-190, (+)-191, (-)-192, and (+)-193 were minimized with the conjugate gradient method and subsequently submitted to a 1000-step pseudo Monte-Carlo Multiple Minimum (MCMM) conformational search in chloroform using the GB/SA solvation model [288]. The particular case of (aS,3Ä,4S,8Ä,9Ä)-(+)-191 is described in some detail. Thereafter, only the main results for the other diastereoisomers will be given.

The C(8)-C(9) and C(9)-C(7') bonds link the rigid quinuclidine and 1,1'-binaphthyl fragments, and are therefore most important in determining the overall conformation. Four different conformations were obtained from the MCMM calculations (Figure 38 and 39): two 'closed' conformations, with a H-C(8)-C(9)-H dihedral angle of about 60° (gauche conformers), have the quinuclidine nitrogen pointing towards the adjacent naphthalene ring, while the two 'open' conformations have the quinuclidine nitrogen pointing away from the naphthalene ring, with H-C(8) and H-C(9) antiperiplanar.

\[ \text{Figure 38: Newman projections of the C(8)-C(9) bond for the four possible conformers of diastereoisomer (+)-191.} \]
(dihedral angle of 180°). By further rotation around the C(8)-C(9) bond, two additional gauche conformations are theoretically possible. They are however presumably not formed owing to unfavorable steric repulsions between the 1,1'-binaphthyl and quinuclidine moieties. These conformations can be further distinguished according to the rotation about the C(9)-C(7') bond. Conformation 'closed 1', with proton H-C(9) close to H-C(8'), has the quinuclidine nitrogen pointing inside the 1,1'-binaphthyl major groove. When H-C(9) is close to H-C(6') ('closed 2'), the quinuclidine nitrogen is directed towards the opposite face of the adjacent naphthalene ring (front face in Figure 39). According to the same criteria, 'open 1' and 'open 2' can be distinguished, with the quinuclidine nitrogen pointing on the side of the second naphthalene ring (H-C(9) close to H-C(6')) or not (H-C(9) close to H-C(8')), respectively. From the computer calculations, 'open 2' is the most stable conformation (relative energy of 0.0 kcal/mol). The 'open 1' conformation was calculated to have almost the same energy (0.1 kcal/mol), whereas 'closed 1' and 'closed 2' are disfavored (1.9 and 0.6 kcal/mol, respectively).

Figure 39: Four possible conformations, with different relative energies, were obtained from Monte-Carlo computations (shown for compound (+)-191).
Monte-Carlo conformational searches using the same parameters were carried out for the other diastereoisomers. Compound \((aS,3R,4S,8S,9S)-(+)-190\) was found to preferentially adopt an 'open 2' conformation. The 'open 1' (0.9 kcal/mol), 'closed 1' (1.0 kcal/mol), and 'closed 2' (2.5 kcal/mol) were all higher in energy. For \((aS,3R,4S,8S,9R)-(--)-192\), 'closed 1' and 'closed 2' are favored (0.0 and 0.1 kcal/mol) over 'open 2' (1.8 kcal/mol) and 'open 1' (3.3 kcal/mol). Similarly, compound \((aS,3R,4S,8R,9S)-(+)-193\) was calculated to preferentially adopt the 'closed 1' and 'closed 2' conformations (0.1 and 0.0 kcal/mol) over 'open 2' (1.2 kcal/mol) and 'open 1' (2.2 kcal/mol).

These calculated conformations do not however match the experimental data for three of the four diastereoisomers ((+)-190, (+)-191, and (-)-192). The \(^1H\)-NMR coupling constants are not in agreement with those predicted with the H-C(8)-C(9)-H dihedral angle obtained from the Monte-Carlo calculations using the Karplus rule. For all four compounds, the computer calculations predicted an anti conformation of the H-C(8)-C(9)-H fragment. Only (+)-193 has a large coupling constant between these vicinal protons \(3J(H-C(8)-H-C(9)) = 13.4 \text{ Hz}\) compatible with a 180° dihedral angle, whereas (+)-190, (+)-191, and (-)-192 have smaller coupling constants (9.7, 9.6, and 6.7 Hz, respectively). Conformational searches in vacuo, or using different force fields (AMBER* [168] and OPLS* [289]), were then performed. Various preferred conformations were obtained, however these were still not compatible when compared to the \(^1H\)-NMR data.

Since the accuracy of the computer calculations was not sufficient, in this case, to predict the preferred conformation, we ignored the calculated relative energies of the conformers. The molecular mechanics studies were however helpful for the interpretation of the NMR data. From the different calculated conformations, we searched for the one matching the \(^1H\)-NMR coupling constants and NOE signals. On this basis, we deduced that diastereoisomer (+)-191 adopts a 'closed 1' conformation, as indicated by a NOE signal between H-C(9) and H-C(8') and its \(3J(H-C(8)-H-C(9))\) coupling constant of 9.6 Hz (compatible with a dihedral angle of 60°). In the case of compound (+)-190, similar vicinal coupling constant and NOE effect correspond to the 'closed 2' conformation (some 'closed 1' is also present, as indicated by a weaker NOE effect between H-C(9) and H-C(6')). For compound (-)-192, the 'open 1' conformation, with a 90° H-C(8)-C(9)-H dihedral angle, matched the \(^1H\)-NMR coupling constant (6.7 Hz) and the NOE signal between H-C(9) and H-C(8'). A weak NOE effect between H-C(9) and H-C(6') indicated that 'open 2' is also present as a minor conformer. Finally, the 'closed 1' and 'closed 2' conformations, calculated for (+)-193 to have the lowest relative energies, are indeed the preferred conformations \(3J(H-C(8)-H-C(9)) = 13.4 \text{ Hz}\).
and NOE effects on H-C(6') and H-C(8') upon irradiation of H-C(9')). From these results, diastereoisomer (+)-191 is the only one adopting exclusively 'closed 1' as a preferred conformation. Since this conformation is the one in which the quinuclidine nitrogen is the most hindered, it possibly accounts for the lower yield obtained in the quaternization reaction. It is however important to note that the quaternization was carried out in THF at reflux, whereas the Monte-Carlo minimization and the NMR experiments were performed in chloroform.

3.2.4 Catalysis Experiments

The asymmetric methylation of phenylindanone 137 was extensively studied by Dolling et al. [252]. Mechanistic investigations and extended optimization work resulted in a reasonably good understanding of the reaction parameters. Nonpolar solvents such as toluene were found to give higher ee's than polar solvents. The enantioselectivity also improved with higher dilution, higher NaOH concentration, greater agitation, and lower temperature. The rate of reaction is controlled by the catalyst concentration. The enantiomeric excess dropped from 90% to 0% when the amount of catalyst (in mol%) was reduced from 10 to 2.5%, however, increasing the catalyst concentration above 10 mol% had little effect on the ee. Chloride and bromide produced similar results when used as the catalyst counterion, whereas iodide substantially decreased the stereoselectivity. Out of the various methylating agents tried, methyl chloride clearly gave the best selectivity relative to methyl bromide, methyl iodide, or dimethyl sulfate.

(+)-194, (+)-195, (-)-196, and (+)-197
In order to benefit from these investigations, the conditions reported to give high enantioselectivity with $N$-(p-trifluoromethylbenzyl)cinchonium bromide ($\pm$-132, $R^1 = H$, $R^2 = CF_3$, $X = Br$) as chiral phase transfer agent were used for the catalysis experiments with the 1,1'-binaphthyl quats (+)-194, (+)-195, (−)-196, and (+)-197. The alkylation agent was however changed owing to the problematic use of methyl chloride which is a toxic gas. Since the more reactive alkyl bromide or iodide resulted in a decrease of the enantioselectivity, an alkyl chloride reagent should be used. Allyl chloride was chosen since its reactivity should be similar to that of methyl chloride and handling of a liquid would be more convenient. In order to have reproducible results, all catalysis experiments were performed according to the same procedure.

Scheme 55: The phase transfer catalyzed alkylation of phenylindanone 137 was chosen to investigate the catalytic properties of the 1,1'-binaphthyl quats.

The PTC alkylation (Scheme 55) was first carried out using the achiral catalyst tetrabutylammonium bromide, affording racemic indanone ($\pm$)-198 in 43% yield (Table 8). A method for the determination of the enantiomeric excess was next developed. Analytical HPLC with chiral columns was investigated and separation of the two enantiomers was best achieved on a 'Pirkle Covalent D-Phenylglycine' chiral phase, using 0.1% ethanol in hexane as solvent and a 3.0 ml/min flow. Perfect baseline separation could not however be obtained. The reaction was next catalyzed by cinchonine quats (3$R$,4$S$,8$R$,9$S$)-(+)\textsuperscript{-}132 ($R^1 = H$, $R^2 = CF_3$, $X = Br$), affording indanone (5)-(+)-198 in 59% yield and 73% ee. Both the chemical and optical yields are somewhat lower than for the methylation reaction reported in the literature (95% yield, 92% ee) [252a]. The lower yield together with the recovery of some starting material indicated that the alkylation reaction is slower than the methylation and that a longer reaction time should be used to complete the reaction.
Table 8: Low to medium enantiomeric excess were obtained in the PTC allylation of phenylindanone 137 catalyzed by the 1,1'-binaphthyl quats (+)-194, (+)-195, (-)-196, and (+)-197.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>yield</th>
<th>(S)-(+)198</th>
<th>(R)-(−)-198</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu4NBr</td>
<td>43%</td>
<td>50%</td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td>(3R,4S,8R,9S)-(+)132</td>
<td>59%</td>
<td>87%</td>
<td>13%</td>
<td>73% (S)</td>
</tr>
<tr>
<td>(aS,3R,4S,8S,9S)-(+)194</td>
<td>13%</td>
<td>53%</td>
<td>47%</td>
<td>6% (S)</td>
</tr>
<tr>
<td>(aS,3R,4S,8R,9R)-(+)195</td>
<td>45%</td>
<td>39%</td>
<td>61%</td>
<td>22% (R)</td>
</tr>
<tr>
<td>(aS,3R,4S,8S,9R)(−)-196</td>
<td>38%</td>
<td>42%</td>
<td>58%</td>
<td>16% (R)</td>
</tr>
<tr>
<td>(aS,3R,4S,8R,9S)(−)-197</td>
<td>57%</td>
<td>66%</td>
<td>34%</td>
<td>32% (S)</td>
</tr>
</tbody>
</table>

The PTC allylation was finally carried out using the four 1,1'-binaphthyl quats (+)-194, (+)-195, (-)-196, and (+)-197 as catalysts without other changes in the reaction conditions in order to have comparable results. Diastereoisomer (aS,3R,4S,8S,9S)-(+)194 afforded indanone (S)-(+)198 in 13% yield and 6% ee (Table 8), indicating that (aS,3R,4S,8S,9S)-(+)194 is not an efficient catalyst for this reaction which proceeds slowly and, as often observed in such cases, with poor enantioselectivity. Fortunately, the PTC agents (aS,3R,4S,8R,9R)(+)195 and (aS,3R,4S,8S,9R)(−)-196 (Figure 40) were more successful and yielded indanone (R)-(−)198 in 22% and 16% ee, respectively. The most rewarding result was however the 32% ee (57% yield) obtained with the designed catalyst (aS,3R,4S,8R,9S)(−)-197 (Figure 40). In accordance with the designed ion-pair model, the enantiomer (S)-(+)198 was the predominant product.

(a)  
(b)  

Figure 40: The enantiomeric excess was determined by analytical HPLC on a chiral column. As illustrated by the HPLC spectra, the opposite enantiomers were preferentially formed when the PTC allylation of 137 was catalyzed by 1,1'-binaphthyl quats (−)-196 (a) or (+)-197 (b).
Chapter 3

The enantioselectivity obtained with catalyst (+)-197, despite being lower than that obtained with the cinchonine quats (+)-132, illustrates the ability of molecular modeling to predict which compound will be a stereoselective PTC ligand. It must also be noted that no optimizations of the reaction condition was attempted. This was necessary in the Dolling case to achieve the reported high ee and yield. Thus, the 32% ee obtained in a first attempt can be regarded as a very encouraging result and strongly supports the use of molecular modeling in developing enantioselective catalysts. Moreover, the preferentially formed enantiomer was correctly predicted, giving additional value to the modeling work.

The structure of the ion-pair complexes formed by the three other 1,1'-binaphthyl quats, using the same computational parameters as for catalyst (+)-197, were next calculated in order to rationalize the obtained enantioselectivities. The ion-pairing complexes formed by diastereoisomers (+)-194, (+)-195, and (-)-196 with the enolate of indanone 137 were submitted to a 5000-step pseudo MCMM calculation in chloroform using the MM2* force field (Figure 41). In order to reject the structures lacking a hydrogen-bond between the catalyst hydroxyl group and the indanone enolate, a maximal hydroxyl-enolate (O-H—O") distance of 2.0 Å was defined as constraint. Since the H-bond is largely responsible for stereoselective ion-pair formation, only the ion-pair complexes which might explain the enantioselectivity were thereby selected.

The most stable ion-pair complex calculated for diastereoisomer (aS,3Ä,4S,8/?,9S)-(+)-197 makes, as already discussed (see Chapter 3.2.2), efficient aromatic and hydrophobic interactions, in addition to a short, strong H-bond. The ion-pair complex calculated for catalyst (aS,3/?,4S,8S,9Ä)-(-)-196 also undergoes π–π stacking between the indanone and the 1,1'-binaphthyl moiety, some hydrophobic and edge-to-face interactions with the phenyl ring of indanone 137, and develops a reasonably good H-bond (Figure 41). The calculated ion-pair complex predicts, based on the selective approach of the alkylating agent from the face opposite to the catalyst, that the indanone (R)-(–)-198 will be preferentially formed, in agreement with the experimental data. It is therefore reasonable to postulate that the calculated ion-pair complex accounts for the observed enantioselectivity. In the case of catalyst (aS,3R,4S,8S,9Ä)-(+)194, no ion-pair complex forming an hydrogen bond was obtained, so that all the calculated structures were rejected by the constraint. Although one should be careful when interpreting negative results, it is perhaps noteworthy that the modeling result (absence of a ion-pair complex leading to the preferential formation of one enantiomer) matches the low ee (6%) obtained experimentally. The last 1,1'-binaphthyl quats, compound (aS,3R,4S,8R,9Ä)-(+)195, led to a complex in which the required hydrogen-bond and aromatic-aromatic interactions between the p-trifluoromethylbenzyl side chain of the
catalyst and the indanone phenyl ring are formed. However, the 1,1'-binaphthyl fragment remained essentially non-complexed. The calculated ion-pair structure however correctly predicts the preferential formation of the indanone (R)-(−)-198.

![Diagram](image)

**Figure 41:** The four 1,1'-binaphthyl quats (+)-194, (+)-195, (−)-196, and (+)-197, complexed with the enolate of 137, were submitted to a 5000-step Monte-Carlo conformational search in order to calculate the ion-pair complexes responsible for the enantioselectivity in the PTC allylation reactions.

The Monte-Carlo conformational searches correctly predicted which catalyst would afford significant enantioselectivity ((+)-195, (−)-196, and (+)-197 but not (+)-194), as well as which enantiomer would be favored. These results clearly indicate that molecular modeling can indeed be extremely useful for the design of new catalysts and that further investigation is warranted. However, the accuracy of such calculations are, so far, not sufficient to predict how good the enantioselectivity will be. The designed catalyst (+)-197 was expected, according to the computer calculations, to catalyze the asymmetric allylation of 137 with higher stereoselectivity than the cinchonine quats 132, yet it was found to give a lower enantioselectivity (32% instead of 73% ee). Similarly, the ion-pair complex calculated for catalyst (−)-196 was expected to provide a higher selectivity than the corresponding complex of (+)-195, which is not the case (16% and 22% ee, respectively). Improvement of the force field parameters as well as the solvation models should, in the future, allow more accurate calculations.
3.2.5 Sol-Gel Catalysts

One of the major limitations for the practical use of chiral catalysts is the large synthetic effort required to prepare them. This not only slows down the development of structurally innovative catalysts but also makes them too expensive for use on production scale. This is particularly true for the 1,1'-binaphthyl quats (+)-194, (+)-195, (-)-196, and (+)-197 which were prepared in 13 steps (2% overall yield calculated either from quinuclidine (+)-165 or naphthalen-2-ol 168). A promising way to extend the use of chiral catalysts outside the research laboratory would be to allow their complete and simple recovery after the reaction, which is rarely the case in homogeneous catalysis. We were therefore very interested in developing a method for the incorporation of 1,1'-binaphthyl quats onto a solid support, making separation from the product, recovery, and recycling efficient and easy.

Enantioselective heterogeneous catalysis has already attracted much attention, and its exhaustive coverage would exceed the scope of this chapter (for reviews see [290]). Synthesizing heterogeneous catalysts is however still a difficult task and, in most cases, the enantioselectivities are significantly lower than those of the corresponding homogeneous catalysts. Three general classes of heterogeneous catalysts can be distinguished:

- Modified 'classical' heterogeneous catalysts:

  This strategy consists of using classical achiral heterogeneous catalysts and modifying them with small chiral organic molecules. This can be done by modifying transition metal catalysts, as for example Cinchona-modified palladium catalysts [236] or platinum colloids [291], both of which have been used in enantioselective hydrogenations. Shape-selective microporous catalysts like zeolites [292], which are largely used as solid acids or bases, have also been studied by inserting chiral modifiers into the cavities, or by using chiral templating agents.

- Chiral polymers:

  In this case, the chiral organic molecules are directly used as building blocks for the polymerization. The monomeric catalyst is thereby introduced into a rigid polymer chain and not anchored to an irregular polymer. This technique was recently applied to minor and major grooves 1,1'-binaphthyls and used for the asymmetric reduction of various aldehydes with very high ee's [293].
Immobilization of homogeneous catalysts:

In many cases, homogeneous catalysts have enantioselectivities that cannot be obtained with classical heterogeneous catalysts. Immobilization of chiral catalysts on insoluble supports therefore has an impressive potential scope, owing to the numerous homogeneous catalysis examples described in the literature. Chiral catalysts have so far mainly been incorporated into polystyrene and silicate matrices. Some very successful alkaloid-derived catalysts for the Sharpless asymmetric dihydroxylation have been attached to solid supports [294-298]. High enantioselectivities (>99% ee) were obtained with, for example, catalyst 199, prepared by polymerization of 1,4-bis(9-O-quinyl)phthalazine with methyl methacrylate [295], or with the polyethylene glycol (PEG) ligand 200 [297].
Unfortunately, the attachment of homogeneous catalysts on a polymeric support often leads to a decrease in enantioselectivity.

The first class, namely the chiral modification of heterogeneous catalysts, is not relevant for our purpose. Use of the 1,1'-binaphthyl quats as building blocks for polymerization, although theoretically possible after some modifications, would however require large amounts of material. The third class of heterogeneous catalysts is the most suitable approach. The immobilization of chiral homogeneous catalysts in aerogels is especially promising. Indeed, aerogels, such as SiO₂ aerogels, offer interesting catalytic opportunities owing to their unique porous structure (for reviews see [299-301]). Their very high porosity and high specific surface area makes them ideally suited for serving as polymeric catalyst carriers. Silicate aerogels are readily formed through acid-catalyzed condensation of commercially available orthosilicates (Scheme 56). The orthosilicate monomer is first hydrolyzed leading to oligomerization and formation of a sol (colloidal dispersion of particles in a liquid). The continuation of the condensation results in the formation of a gel (continuous solid skeleton enclosing a liquid phase). Supercritical drying of the ‘wet’ gel replaces the pore liquid by air without altering the network structure, affording the ‘dry’ gel called aerogel. The formation of a highly porous, three-dimensional network is the key feature of the sol-gel process.

Scheme 56: The sol-gel process allows, through acid-catalyzed condensation of orthosilicate and supercritical drying, the formation of aerogels.

A potentially very important use of SiO₂ aerogels is their modification with organic groups, forming inorganic-organic hybrid polymers, which would further extend the applications of aerogels [302,303]. The incorporation of organic molecules in the aerogel structure was made possible by the very mild reaction conditions, particularly the low reaction temperatures, used in the sol-gel process. Various organic functionalities have already been introduced into silicate aerogels in order to modify their physical or chemical properties: nonlinear optical (NLO) chromophores [302], crown ethers [304], amphiphilic monolayers [305], flavin mononucleotides for specific
hydrogen bonding recognition [306], and even proteins [307-309]. However, the porous nature of aerogels, allowing good molecular diffusion rates, makes them particularly suited for the incorporation of organic catalysts. Oxidation catalysts and Lewis acids have been incorporated via an organic group into sol-gel matrices [310,311]. The entrapped molecules retained much of their catalytic properties and were accessible to external reagents through the pore network. However, no enantioselective reaction has, to our knowledge, been reported to be catalyzed by an organically-doped sol-gel material.

Preparation of insoluble polymer-supported phase transfer catalysts has also been investigated. The first triphase catalysts, a concept introduced by Regen [312], were based on polystyrene resins [312-316]. Incorporation of tetramethylammonium [317] or tetraphenylphosphonium [318-320] salts onto a silica support has been performed and shown to provide efficient catalysts with high rate enhancements. These studies, although carried out on achiral PTC agents, demonstrated that the principle of triphase catalysis is valid and encouraged us to incorporate chiral ligands into a silicate sol-gel.

The covalent incorporation of organic molecules to SiO₂ polymers can be achieved by performing the sol-gel process on a mixture of orthosilicates ([Si(OR)₄] and organically substituted alkoxysilanes ([R'Si(OR)₃]. Addition of organically modified alkoxides to tetraalkyl orthosilicate, followed by dilute acid, leads to the polycondensation-gelation process with immobilization of the organic compounds in a crosslinked solid in which most of the organic groups are located at the surface [321]. In order to covalently incorporate the 1,1'-binaphthyl quats (+)-197 into a sol-gel matrix, a trialkoxysilyl functionality had to be introduced into the catalyst.
A potential linkage would be to use the vinyl group originally present on the quinuclidine (Figure 42 A). Instead of reducing the vinyl functionality during the catalyst synthesis, we could react it with thiols to the corresponding thioethers, followed by treatment with (3-mercaptopropyl)trimethoxysilane to obtain the desired alkoxysilane. This strategy has, for example, already been used for binding Cinchona alkaloid derivatives to silica gel in the preparation of chiral stationary phases [229e-f] or silica gel-supported catalysts for the asymmetric dihydroxylation reaction [296]. Another possibility would be to use the alkyalted hydroxymethyl group at position 3′ (Figure 42 B). Instead of methylating the position, a suitable protecting group could be used (see Chapter 3.2.3 and Scheme 45). Selective deprotection of this benzylic alcohol would then provide a hydroxyl group suitable for further functionalization, for example by alkylation with 3-bromopropyltrimethoxysilane. In both cases however, completion of the synthesis, separation of the diastereoisomers, and assignment of the absolute configuration would have to be carried out again. A third alternative for the introduction of the trialkoxysilyl group was therefore considered. In order to benefit as much as possible from the synthetic route established for the 1,1′-binaphthyl quats (+)-197, introduction at as late a stage as possible was desirable. Introduction of this functional group on the benzylammonium side chain (Figure 42 C) would have the advantage that the synthesis of the unquaternized 1,1′-binaphthyl precursor (+)-193 would be preserved.

A newly substituted benzyl bromide for quaternization of compound (+)-193 was designed. In order to prevent steric hindrance, which could prove problematic in the catalytic process, we decided to modify the para substituent. The presence of an electron-withdrawing substituent was, however, necessary for maintaining the stereoselectivity [252a]. Consequently, compound 203, bearing an electron-withdrawing p-difluoroacetamido substituent, was selected as a target.
The synthesis of the desired $p$-substituted benzyl bromide 204 was first addressed. Friedel-Crafts acylation of toluene (205) with ethyl oxalyl chloride [322], followed by treatment with (diethylamido)sulfur trifluoride (DAST) afforded ethyl ester 207 [323] (Scheme 57). Hydrolysis of the ester, followed by treatment with oxalyl chloride gave the corresponding acid chloride which was directly converted to tert-butyl ester 208. Subsequent radical bromination afforded 209 in 79% yield. Finally, cleavage of the tert-butyl ester with trifluoroacetic acid, treatment with oxalyl chloride followed by addition of amine 210 gave access to the desired benzyl bromide 204. Amine 210 was prepared in one step by selective mono-Cbz-protection of ethylenediamine according to a published procedure [324].

Scheme 57: The desired $p$-substituted benzyl bromide 204 was prepared from ester 209 and amine 210, both synthesized according to known procedures.

With benzyl bromide 204 in hand, quaternization was next addressed. This step was, however, first carried out on an easily accessible Cinchona alkaloid rather than on 1,1'-binaphthyl-derived alkaloid (+)-211. This should allow the establishment of a synthetic...
route towards the required alkoxysilane, the experimentation of the sol-gel process with a mixed inorganic-organic hybrid, and the investigation of the asymmetric triphase catalysis. Dihydrocinchonine ((+)-212) was therefore quaternized with benzyl bromide 204, using the same reaction conditions as for the homogeneous catalysts, to afford (+)-213 (Scheme 58). Removal of the Cbz-protecting group of ammonium bromide (+)-213 by catalytic hydrogenation, and treatment of the resulting primary amine with 3-(triethoxysilyl)propylisocyanate yielded 203 which, owing to the labile triethoxysilyl group, was directly submitted to the sol-gel process without further purification.

![Scheme 58: The triethoxysilyl quats 203 was prepared by quaternizing dihydrocinchonine ((+)-212) and then introducing the triethoxysilyl functional group. This PTC catalyst was then directly submitted to the sol-gel process.](image)

Alkoxysilane 203 (160 mg) and tetramethyl orthosilicate (10 g) dissolved in methanol were treated with dilute acid. After a one week gelation period, the 'wet' gel was submitted to supercritical drying and afforded a very fine colorless powder, with a catalyst concentration, calculated from the sol-gel weight, of about 0.02 mmol/g. Both texture and structure of the heterogeneous catalyst have been studied by N2 adsorption, 29Si-, and 13C-MAS-NMR (see Appendix). The 29Si-MAS-NMR spectra showed a relative ratio for Q2:Q3:Q4 of 6:51:43, which is typical for aerogels (in Qn, n gives the number of siloxane bridges surrounding the Si atom). The surface area was shown to be 389 m2/g as determined by volumetric physisorption with the Brunauer-Emmett-Teller (BET) method [325]. The micropore area was found to be negligible, which is
consistent with the mesoporous-type isotherm measured (micropores: <2 nm, mesopores: 2-50 nm, macropores: >50 nm). The average pore diameter, calculated for cylindrical pores from the hysteresis in the adsorption/desorption curve, is 8 nm (maximum of the pore volume distribution at 26 nm).

The catalysis experiment was first carried out under the same reaction conditions as for the homogeneous catalysts (0.1 equivalent of catalyst, 5.0 eq. of allyl chloride in toluene/50% aqueous NaOH), affording alkylated indanone (S)-(−)-198 in 11% yield and 6% ee. The aerogel was, however, denatured during the reaction, forming an aqueous gel, which presumably made the catalyst inaccessible and accounts for the low yield obtained. Solid-solid-liquid triphasic catalysis was next performed using solid sodium hydroxide (10.0 eq.) as base instead of an aqueous solution. Use of non-aqueous reaction conditions preserved the sol-gel which could be recycled after use by simple filtration. The yield improved (27%) although the enantioselectivity remained about the same (7% ee). The moderate yield is not very surprising and likely reflects the lower accessibility of the polymeric catalyst compared to the homogeneous ones. The yield could probably be improved by extending the reaction time above the 20 h that were used for all the catalysis experiments. Even if low, the enantioselectivity obtained with this first heterogeneous catalyst, without optimization work, is nevertheless encouraging and is, to our knowledge, the first ever observed for a silicate aerogel.

Both chemical and optical yields could probably be slightly improved by increasing the catalyst concentration in the sol-gel. The low catalyst concentration can alone hardly explain the drop in enantioselectivity (73 to 7% ee) observed when incorporating the PTC catalyst into the sol-gel matrix. The low stereoselectivity possibly arises from the modification of the benzylammonium side chain. This hypothesis is supported by the insignificant enantioselectivity obtained when using (+)-213, the synthetic precursor of 203, as homogeneous catalyst (36% yield, 2% ee). The presence of an aromatic protecting group on the benzylammonium side chain can strongly affect the conformation of (+)-213, making that compound a poor reference for comparison with the sol-gel catalyst. Another possible reason explaining the decreased stereoselectivity of the sol-gel catalyst could be an unsuitable cavity surrounding the catalyst within the aerogel matrix. The pore size and shape is undefined and possibly constrains the substrate orientation. If this is the case, not only the chiral PTC agent but also the achiral polymer is influencing the ion-pair geometry, with the net result of a decrease in enantioselectivity. Variation of the sol-gel process could modify the pore size and possibly influence the enantioselectivity. Another approach to better control the geometry of the cavity surrounding the catalyst would be to introduce substituents on
the catalyst which might predefine it. Incorporation of bulky substituents into the catalysts in order to open a larger cavity and thereby decrease the influence of the polymeric matrix on the substrate orientation would be a possible alternative. The 1,1'-binaphthyl quats would therefore offer some possible linkages for further functionalization, for example for the introduction of bulky dendritic side chains (Figure 43) which could be useful for preorganizing the sol-gel matrix.

![Figure 43: Bulky substituents like dendritic side chains could be introduced into the 1,1'-binaphthyl quats in order to preorganize the sol-gel matrix by opening a cavity for the substrate.](image)

Such substituents should however be carefully designed to avoid steric hindrance at the active site which would then reduce the accessibility to the catalyst. The time scale of this work however did not allow the incorporation of catalyst (+)-197 or an analog bearing bulky substituents into a silicate sol-gel polymer.

### 3.3 Sharpless Asymmetric Dihydroxylation

#### 3.3.1 Introduction

The osmium tetroxide-mediated asymmetric cis dihydroxylation of olefins developed by Sharpless and coworkers is a major achievement in enantioselective synthesis (for a review see [326]). Its high specificity for double bonds and remarkable stereoselectivity makes it one of the most useful reaction in organic synthesis.
The reaction mechanism (Scheme 59), proposed by Criegee [327], involves a [3+2] cycloaddition of olefin 214 with OsO₄ to form osmium (VI) monoglycolate ester 215 which can then be reduced to the corresponding diol 216 with H₂S or Na₂SO₃. A different mechanism, initiated by a [2+2] addition of the olefin across an Os=O bond, followed by rearrangement of the resulting osmaoxetane to the glycolate product, has also been proposed [326]. More than one selectivity determining step is therefore possible. Criegee also observed that the dihydroxylation rate increased in the presence of amines such as pyridine (ligand accelerated catalysis), presumably by formation of an electron-rich coordination complex with the osmium atom. This observation led to the first attempt at making the dihydroxylation enantioselective by using as the ligand, the chiral, enantiomerically pure, pyridine 217 derived from menthol, giving access to moderate enantiomeric excess (3-18%) [328]. The higher affinity of osmium for tertiary amines [329] opened the door to the use of Cinchona alkaloid derivatives as chiral ligands, leading to medium to good enantioselectivities (25-83% ee) [328].
(NMO) was found to work best [330]. Extension of the Sharpless stoichiometric asymmetric dihydroxylation with the convenient Upjohn NMO process resulted in good yields (8-95%) and moderate to good enantiomeric excess (20-88% ee) with as little as 0.2% OsO₄ [331]. Dihydroquinidine p-chlorobenzoate (DHQD-CLB, 218) was found to be the most effective catalyst, together with its 'pseudo-enantiomer' dihydroquinine p-chlorobenzoate (DHQ-CLB, 219), and accomplished the dihydroxylation of trans-stilbene (220) in 80% yield and 88% ee of the (R,R)-dihydrobenzoin ((+)-221) (Scheme 60).

Scheme 60: The asymmetric dihydroxylation of trans-stilbene (220) was achieved in 88% ee with DHQD-CLB (218) as catalyst and using NMO as co-oxidant.

Improved insight into the stereoselectivity of the reaction was obtained with the X-ray crystal structure determination of the complex of dioxo[(3S,4S)-2,2,5,5-tetramethyl-3,4-hexanediolato]osmium (VI) with dihydroquinine p-chlorobenzoate, clearly showing the osmium(VI) monoglycolate intermediate complexed to the quinuclidine nitrogen (Figure 44) [332].

Figure 44: An X-ray crystal structure of the osmium(VI) monoglycolate complex gave some structural information in order to rationalize the enantioselectivity of the reaction.

A limitation for obtaining higher enantioselectivities was the presence of a second catalytic cycle in which the chiral ligand is not involved. Indeed, after the oxidation of
the initially formed osmium(VI) glycolate 222 to osmium(VIII) glycolate 223 with the loss of the chiral ligand (Scheme 61), this complex instead of reductively eliminating diol 216 can enter another catalytic cycle which is not enantioselective. This secondary dihydroxylation consists of the oxidative addition of a second olefin molecule to give diglycolate 224 which leads to racemic diol 216.

Scheme 61: Use of NMO as co-oxidant allowed to considerably decrease the necessary amount of osmium tetroxide, but introduced a second, non-enantioselective, catalytic cycle which slightly lowered the stereoselectivity.

A change of co-oxidant from NMO to K₃[Fe(CN)₆]-K₂CO₃ in tert-butanol/water reduced that problem by confining the oxidant to the aqueous phase [333]. The osmium(VI) glycolate 222 is thereby hydrolyzed in the organic phase before being re-oxidized, preventing the second catalytic cycle and improving the ee's a little. Further improvement was made with the emergence of bidentate ligands incorporating two Cinchona alkaloid units as catalysts. In particular, the 1,4-bis-(9-O-dihydroquinine)phthalazine ((PHQ)₂-PHAL 225) and 1,4-bis-(9-O-
dihydroquinidine)phthalazine ((PHQD)$_2$-PHAL 226) were found to give the best enantioselectivities and even allowed, through an empirical rule, the prediction of the absolute stereochemical outcome of the reaction [334].

### 3.3.2 Synthesis

In analogy to Sharpless' DHQD-CLB ligand (218), a $p$-chlorobenzoyl side chain was introduced into the four diastereoisomers (+)-190, (+)-191, (-)-192, and (+)-193. This was easily accomplished by treating the alcohols (aS,3R,4S,8S,9S)-(+)\(-190\), (aS,3R,4S,8R,9R)-(+)\(-191\), (aS,3R,4S,8S,9R)-(+)\(-192\), and (aS,3R,4S,8R,9S)-(+)\(-193\) with $p$-chlorobenzoyl chloride and dimethylaminopyridine (DMAP) providing the desired catalysts (aS,3R,4S,8S,9S)-(+)\(-227\), (aS,3R,4S,8R,9R)-(+)\(-228\), (aS,3R,4S,8S,9R)-(+)\(-229\), and (aS,3R,4S,8R,9S)-(+)\(-230\), respectively (Scheme 62).

![Scheme 62](image)

Scheme 62: Treatment of alcohols (+)-190, (+)-191, (-)-192, and (+)-193 with $p$-chlorobenzoyl chloride afforded the desired catalysts (+)-227, (+)-228, (+)-229, and (+)-230, respectively.
3.3.3 Catalysis Experiments

The catalytic addition of osmium tetroxide to trans-stilbene (220), using the same conditions as Sharpless and coworkers [331], was studied in order to evaluate catalysts (+)-227, (+)-228, (+)-229, and (+)-230. The dihydroxylation was first carried out with dihydrocinchonine p-chlorobenzoate (DHC-CLB, (3R,4S,8R,9S)-(-)-231) as reference catalyst. The enantiomeric excess was determined by analytical HPLC with a 'Pirkle Covalent (S,S)-Whelk-O1' chiral column, hexane/isopropanol (95:5) as eluent and 1.5 ml/min flow. Catalyst (-)-231 preferentially yielded (R,R)-(R)-dihydrobenzoin ((+)-221) in 88% ee (Table 9), the same enantioselectivity obtained by Sharpless and coworkers with dihydroquinidine p-chlorobenzoate (DHQ-CLB, 218) as catalyst [331].

Table 9: The Sharpless asymmetric dihydroxylation of trans-stilbene (220) was accomplished in 2 to 67% ee with the 1,1'-binaphthyl catalysts (+)-227, (+)-228, (-)-229, and (+)-230.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>yield</th>
<th>(S,S)-(−)-221</th>
<th>(R,R)-(+)−221</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3R,4S,8R,9S)-(−)-231</td>
<td>95%</td>
<td>6%</td>
<td>94%</td>
<td>88% (R,R)</td>
</tr>
<tr>
<td>(aS,3R,4S,8S,9S)-(+)−227</td>
<td>57%</td>
<td>51%</td>
<td>49%</td>
<td>2% (S,S)</td>
</tr>
<tr>
<td>(aS,3R,4S,8R,9R)-(+)−228</td>
<td>96%</td>
<td>46%</td>
<td>54%</td>
<td>8% (R,R)</td>
</tr>
<tr>
<td>(aS,3R,4S,8S,9R)-(−)-229</td>
<td>68%</td>
<td>84%</td>
<td>17%</td>
<td>67% (S,S)</td>
</tr>
<tr>
<td>(aS,3R,4S,8R,9S)-(+)−230</td>
<td>99%</td>
<td>29%</td>
<td>71%</td>
<td>42% (R,R)</td>
</tr>
</tbody>
</table>

The same dihydroxylation was next carried out with the 1,1'-binaphthyl catalysts (+)-227, (+)-228, (+)-229, and (+)-230 instead of DHC-CLB ((−)-231). Low enantioselectivities (2 and 8%) were obtained instead of DHC-CLB ((−)-231). Fortunately, catalysts (aS,3R,4S,8S,9R)-(+)−229 and (aS,3R,4S,8R,9S)-(+)−230 proved much better and afforded dihydrobenzoin (221) in 67% ee (major enantiomer (S,S)-(−)-221) and 42% ee (major enantiomer (R,R)-(−)-221), respectively. It is noteworthy that catalysts (aS,3R,4S,8S,9R)-(+)−229 and (aS,3R,4S,8R,9S)-(+)−230, having the same alkaloid configuration as DHQ-CLB and DHQD-CLB, respectively, are efficient, enantioselective catalysts, whereas (aS,3R,4S,8S,9S)-(+)−227 and (aS,3R,4S,8R,9R)-(+)−228, the 9-epi isomers of DHQ-CLB and DHQD-CLB, are poor stereoselective catalysts. A similar octahedral osmium glycolate-ligand transition state as postulated by Sharpless (Figure 44) [332] probably accounts for the enantioselectivity.
3.4 Conclusions and Outlook

The preparation of the four diastereoisomeric precursors (+)-190, (+)-191, (-)-192, and (+)-193, incorporating 1,1'-binaphthyl and Cinchona alkaloid moieties, was the major synthetic effort of this one year project. These compounds were quaternized with p-trifluoromethylbenzyl bromide and the resulting phase transfer agents used for the enantioselective allylation of phenylindanone 137. Enantiomeric excesses ranging from 6 to 32% (13 to 57% yield) were obtained without optimization of the reaction conditions. Although the yields and enantioselectivities remain to be improved, this research demonstrated the potential of combining 1,1'-binaphthyl moieties with Cinchona alkaloids for obtaining stereoselective catalysts. In addition, the computer calculations performed, in each case, rationalized the enantioselectivity and predicted which enantiomer would be preferentially formed. The potential of molecular modeling in asymmetric catalysis was demonstrated, and we expect that its use will be generalized over the next few years allowing a more systematic approach to the design of new catalysts. Overall, taken together with the results from the MHC project, it is clear that additional work needs to be done to perform quantitative estimates of, for example, binding energies and reactive conformations in the future.

An attempt was made to allow more convenient use and easy recycling of phase transfer catalysts by incorporating them into a sol-gel matrix. Early results showed that incorporating the best homogeneous catalyst 132 (73% ee) into the aerogel matrix resulted in a large decrease in stereoselectivity (7% ee). This study, however, established a synthetic route for preparing organofunctional alkoxysilanes that can be covalently attached to sol-gel materials. Moreover, compound 132 is to our knowledge the first enantioselective catalyst incorporated into a sol-gel. We believe that the stereoselectivity of such polymeric catalysts could be improved by preorganizing the catalyst environment. This promising result should encourage further incorporation of chiral organic compounds into a sol-gel matrix with the aim of improving our understanding of such functionalized polymers. We expect significant developments in this area in the years to come.

Compounds (+)-190, (+)-191, (-)-192, and (+)-193 were also used to esterify p-chlorobenzoyl chloride. The resulting compounds were tested as chiral catalysts in the Sharpless asymmetric dihydroxylation. Good ee's (42 and 67%) were obtained with (αS,3R,4S,8R,9S)-(−)-230 and (αS,3R,4S,8S,9R)-(−)-229, respectively, the 1,1'-
binaphthyl-derived equivalents of DHQD-CLB and DHQ-CLB. The 9-epi isomers (\(aS,3R,4S,8S,9S\))-(+)-227 and (\(aS,3R,4S,8R,9R\))-(+)-228, however, proved to be poor catalysts (2 and 8% ee, respectively). Structural optimizations of the catalysts have so far not been made. Variation of the benzoate side chain would be synthetically easy and might give access to more selective catalysts. Replacement of NMO by \(K_3[Fe(CN)_6]\)-\(K_2CO_3\) as co-oxidant is expected, as for DHQ- and DHQD-CLB [333], to improve the enantioselectivity by reducing the importance of the secondary catalytic cycle. Substrates more complex than trans-stilbene should also be dihydroxylated in order to better judge the potential of catalysts (-)-192 and (+)-193.

New 1,1'-binaphthyl and Cinchona alkaloid-based compounds should be prepared in order to further explore the potential of such catalysts. More precisely, minor groove substituted 1,1'-binaphthyls like 232 look very promising. The potential hydrophobic contacts in the minor groove are somewhat reduced compared to the major groove, but the chirality of the 1,1'-binaphthyl moiety can be expected to have a stronger influence upon catalysis. Studies towards the synthesis of such compounds have already been made, but the enantiomerically pure 1,1'-binaphthyl fragment 233 (Scheme 63), suitable for coupling with the alkaloid moiety (Weinreb amide (+)-164), could not be obtained. This work demonstrated that derivatization of enantiomerically enriched 1,1'-binaphthalen-2,2'-diol or 2'-amino-1,1'-binaphthalen-2-ol to 233 is problematical. Synthesis of 233 via a Suzuki cross-coupling reaction was also unsuccessful. A valuable alternative would be to take advantage of a 1,1'-binaphthyl synthesis reported by Miyano and coworkers [336] based on nucleophilic aromatic substitution of 1-menthoxy-2-naphthoates with a 1-naphthyl Grignard reagent.

![Scheme 63](image)

**Scheme 63:** Minorgroove-substituted 1,1'-binaphthyl 232 or related analogs offer promising catalytic opportunities. They should be obtained, similarly to the major groovesubstituted compounds, by the coupling of Weinreb amide (+)-164 with the appropriately substituted 1,1'-binaphthyl precursor 233.

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6 Progress towards the synthesis of minor groove-substituted 1,1'-binaphthyl compounds were made by Christiane Meyers in her diploma thesis [335].
The coupling between 1,1'-binaphthyl 233 and Weinreb amide (+)-164 is expected to work more smoothly than for the major groove-substituted 1,1'-binaphthyls owing to the stabilizing presence of a methoxy group in the minor groove. We believe that compound 232 and related analogs are exciting target molecules and that they represent the future of this project.
4. Experimental Part

4.1 Materials and Methods

Reagents and reaction solvents were of highest available quality obtainable from either Aldrich, Fluka, Merck, or Riedel-de Haën. THF and Et₂O were distilled from Na/benzophenone immediately before use. Hydrochloric acid was dried by passage through conc. sulfuric acid. Molecular sieves (4Å) were activated by heating at 300 °C in vacuo (10⁻² Torr) for 10 h. Evaporation and concentration in vacuo was done at water aspirator pressure; drying in vacuo at 10⁻² Torr. The IUPAC nomenclature and numbering system has been used for all compounds. However, for the purposes of describing the ¹H-NMR data, a different numbering system, shown in the structural representation, has sometimes been used. Compounds (±)-27 [184], (±)-79 [174], (±)-82 [174], (±)-81 [174], 90 [203], (±)-117 [337], 206 [322], 207 [323], 208 [323], 209 [323], and 210 [324] were prepared according to literature procedures or slight modifications of them.

Column chromatography and flash chromatography: silica gel 60 (230 - 400 mesh, 0.04 - 0.063 mm) from Fluka. Dowex ion-exchange resin (H⁺ form, 20 - 50 mesh, 50WX4) from Fluka.

Thin layer chromatography (TLC): Polygram SIL G/UV₂54 from Macherey-Nagel. The compounds were visualized by 254 or 366 nm light.

Preparative thin layer chromatography (PTLC): pre-coated plates silica gel 60 F₂54 from Merck. The compounds were visualized by 254 or 366 nm light.

High performance liquid chromatography (HPLC). Hewlett Packard HP 1090 Liquid Chromatograph, with UV-detector (detector wavelength fixed at λ = 230, 254, and 260 nm). All chromatograms have been taken at ambient temperature.
Melting points: Büchi 510 apparatus. All melting points were measured in open capillaries and are uncorrected. The solvent used for recrystallization is given in brackets.

IR spectra: Perkin-Elmer-FT1600 spectrometer. The spectra were measured as KBr pellets or as solutions in CHCl₃. The absorptions are given in wavenumbers (cm⁻¹). The intensity of the bands is described as vs (very strong), s (strong), m (medium), or w (weak).

Optical rotation: Perkin Elmer-241 polarimeter using a 10 cm cell (1 ml volume) and the solvent as indicated. Concentrations are in grams of solute per 100 ml of solvent.

NMR spectra: ¹H- and ¹³C-NMR spectra: Bruker AMX-500, Bruker AMX-400, Varian GEMINI-200 and -300 spectrometers. All spectra were measured at 293 K in the indicated solvents. The chemical shift values are given in ppm relative to the solvent resonances. The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Broad resonances are indicated (br.). Coupling constants J are given in Hz.

Mass spectra: EI, FAB and ESI mass spectra were performed by the MS service at ETH Zürich. EI-MS (m/z (%)): VG-TRIBRID spectrometer; spectra were measured at 70 eV. FAB-MS (m/z (%)): VG-ZAB2-SEQ spectrometer; spectra were determined in m-nitrobenzyl alcohol (3-NOBA) as the matrix. ESI-MS (m/z (%)): Finnigan TSQ 7000 spectrometer; spectra were measured at 2-3 kV in the negative mode; the capillary temperature was at 150 - 200 °C.

Kugelrohr distillations: Büchi GKR-50 apparatus. Quoted temperatures refer to the temperature of the air surrounding the distilling flask.

Hydrogenation experiments: Büchiglas Uster hydrogenator.

Elemental analyses: Mikrolabor für Organische Chemie at ETH-Zürich.

UV/VIS spectra: Varian-CARY-5 spectrophotometer.

CD spectra: Jasco J-710 spectropolarimeter.
4.2 Experimental Part for Chapter 2.1

Procedure A. Amino Acid Esterification.

To a stirred solution of the amino acid (40.00 mmol) in methanol (250 ml) cooled to 0 °C was added dry HCl gas until no more absorption could be observed. The solution was allowed to stand at r.t. for 12 h and evaporated in vacuo.

Procedure B. Sulfamide Formation.

To a solution of methyl 4-aminobenzoate (23) (16.50 mmol) in CH₂Cl₂ (100 ml) cooled to 0 °C was added dropwise chlorosulfonic acid (18.00 mmol). After stirring at r.t. for 1 h, phosphorus pentachloride (18.00 mmol) was added and the solution was heated to reflux for 3.5 h. The amino acid methyl ester hydrochloride (15.00 mmol) was added to the solution of sulfamoyl chloride (24) prepared in situ. The solution was made basic (pH 8-9) by the addition of triethylamine and stirred at r.t. for 2.5 h. The reaction was quenched with a sat. aq. NaCl solution (100 ml), the organic phase was separated, and the aqueous phase extracted with CH₂Cl₂ (2 x 100 ml). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo.

Procedure C. Cyclization of a Sulfamide to a Thiazolide.

To tert-BuLi (1.7M soln. in pentane, 5.00 mmol) in dry THF (100 ml) at r.t. under an argon atmosphere was added a solution of sulfamide (2.00 mmol) in THF (20 ml) over 4 h via syringe pump, and the solution was then stirred for 12 h. The reaction was quenched with a sat. aq. NaCl solution (100 ml) and with 1M aq. HCl (50 ml), the organic phase was separated and the aqueous phase extracted with CH₂Cl₂ (2 x 100 ml). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo.

Procedure D. Amide Formation.

A solution of thiazolide methyl ester (2.00 mmol) in methanol (50 ml) and a 1M aq. KOH solution (50 ml) was stirred at r.t. for 12 h. The methanol was evaporated in vacuo, the solution made acidic with 1M aq. HCl (60 ml), and extracted with EtOAc (4 x 100 ml). The combined organic extracts were dried (MgSO₄) and evaporated in
The residue was dissolved in THF (20 ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2 mmol) and 1-hydroxybenzotriazole (2 mmol) were added, and the solution was stirred at r.t. for 1 h. A 25% ammonium hydroxide solution (2 mmol) was then added and stirring was continued for 4 h. The reaction mixture was filtered and the filtrate evaporated in vacuo.

**DL-Phenylalanine methyl ester hydrochloride ((±)-28).**

\[
\overset{\text{COOMe}}{\text{NH}_2} \cdot \text{HCl}
\]

The ester (±)-28 was prepared from DL-phenylalanine ((±)-26) (10.00 g, 60.54 mmol) according to Procedure A. Colorless solid (quant.), M.p. 150-152 °C. $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): 8.78 (s, 2 H, NH$_2$); 7.36-7.22 (m, 5 H, ArH); 4.26 (m, 1 H, H-C(2)); 3.64 (s, 3 H, COOCH$_3$); 3.22, 3.09 (AB of ABX, $J_{AX}= 5.8$, $J_{BX} = 7.4$, $J_{AB} = 13.9$, 2 H, H$_2$C(3)).

**(2RS)-Methyl 2-[N-(4-methoxycarbonylphenyl)sulfonamido]-3-phenylpropanoate ((±)-30).**

The amino acid methyl ester hydrochloride (±)-28 (5.00 g, 23.18 mmol) was converted to the corresponding sulfamide (±)-30 according to Procedure B. Purification by flash chromatography (hexane/EtOAc 6:4) on silica gel gave (±)-30 as a colorless solid (6.34 g, 70%), M.p. 153-155 °C (hexane/EtOAc). IR (KBr): 3223m cm$^{-1}$ (NH); 1724s (C=O); 1700m (C=O); 1610m; 1350m (SO$_2$); 1281m (C-O); 1154s (SO$_2$). $^1$H-NMR (200 MHz, CDCl$_3$): 7.93, 7.04 (AA'BB', $J = 8.8$, 4 H, ArH); 7.22-7.16 (m, 3 H, ArH); 7.06-7.01 (m, 2 H, ArH); 5.31 (d, $J = 9.1$, 1 H, NH); 4.33 (m, 1 H, H-C(2)); 3.90 (s, 3 H, COOCH$_3$); 3.61 (s, 3 H, COOCH$_3$); 3.00 (m, 2 H, H$_2$C(3)). $^{13}$C-NMR (75 MHz, CDCl$_3$): 171.8; 166.5; 141.2; 134.8; 131.1; 129.2; 128.7; 127.5; 125.4; 117.8; 57.4;
52.8; 52.2; 38.8. DEI-MS: 392 (14, M⁺); 333 (9, [M - COOCH₃]⁺); 241 (46); 230 (12); 151 (32, [H₂NPhCOOCH₃]⁺); 120 (62); 91 (100, [C₇H₇]⁺). Anal. calc. for C₁₈H₂₀N₂O₆S (392.4): C 55.09, H 5.14, N 7.14, S 8.17; found: C 55.26, H 5.12, N 7.21, S 8.09.

(4RS)-Methyl 4-[4-benzyl-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]benzoate ((±)-32).

((4RS)-Methyl 4-[4-benzyl-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]benzoate ((±)-32).

The sulfamide (±)-30 (1.50 g, 3.82 mmol) was cyclized to the corresponding thiazolide (±)-32 according to Procedure C. Purification by flash chromatography (CH₂Cl₂/MeOH 9:1) on silica gel gave (±)-32 as a yellow solid (1.03 g, 75%), M.p. 169-171 °C (hexane/EtOAc). IR (KBr): 3267m cm⁻¹ (NH); 1725m (C=O); 1605m; 1333m (SO₂); 1289m (C-O); 1153s (SO₂); 1106m. ¹H-NMR (200 MHz, (CD₃)₂SO): 8.38 (d, J = 9.4, 1 H, NH); 7.75, 7.05 (AA'BB', J= 8.7, 4 H, ArH); 7.16-7.05 (m, 5 H, ArH); 3.90-3.84 (m, 1 H, H-C(4)); 3.81 (s, 3 H, COOCH₃); 2.89 (AB of ABX, Jₐₓ = 6.0, Jₜₙ = 13.7, 2 H, H₂C(6)). ¹³C-NMR (75 MHz, (CD₃)₂SO): 172.5; 165.9; 143.1; 136.6; 130.0; 128.9; 127.9; 126.3; 122.4; 116.5; 57.2; 51.7; 37.5. DEI-MS: 360 (1, M⁺); 332 (5); 151 (51, [H₂NPhCOOCH₃]⁺); 120 (100); 91 (43, [C₇H₇]⁺). HR-DEI-MS: 360.0779 (M⁺, C₁₇H₁₆N₂O₅S; calc. 360.0780).

(4-RS)-4-[4-Benzyl-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]benzamide ((±)-10).

((4-RS)-4-[4-Benzyl-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]benzamide ((±)-10).
Thiazolide methyl ester (±)-32 (500 mg, 1.39 mmol) was converted to the corresponding primary amide (±)-10 according to Procedure D. Purification by flash chromatography (CH2Cl2/MeOH/NH3 65:10:1) on silica gel gave (±)-10 as a colorless solid (172 mg, 36%), M.p. 174-176 °C (Et2O/MeOH). IR (KBr): 3456 m cm⁻¹ (NH); 3367 m (NH2); 1744 m (C=O); 1654 s (N=C=O); 1606 m; 1325 s (SO2); 1183 m (SO2); 1161 m (SO2). ¹H-NMR (200 MHz, (CD3)2SO): 9.08 (*, 1 H, NH); 8.11 (s, 1 H, NH); 8.03, 7.45 (AA'BB', J = 8.6, 4 H, ArH); 7.54 (s, 1 H, NH); 7.37-7.27 (m, 5 H, ArH); 4.76, 3.28, 3.04 (ABX, Jax = 3.9, Jbx = 10.1, Jab = 14.3, 3 H, H-C(4), H2C(6)). ¹³C-NMR (75 MHz, (CD3)2SO): 168.1; 166.8; 136.2; 135.2; 132.7; 129.5; 128.9; 128.2; 126.7 (two overlapping signals); 61.0; 36.3. DEI-MS: 345 (2, M⁺); 317 (11); 146 (19); 136 (13); 118 (28); 91 (100, [C7H7]+). Anal. calc. for C16H15N3O4S (345.4): C 55.64, H 4.38, N 12.17, S 9.28; found: C 55.78, H 4.46, N 12.05, S 9.16.

DL-O-Benzytyrosine ((±)-27) [184].

To a solution of DL-tyrosine ((±)-25) (20.00 g, 110.38 mmol) in a 2M aq. NaOH solution (100 ml) was added a solution of copper(II) sulfate pentahydrate (13.78 g, 55.19 mmol) in water (40 ml). After stirring for 10 min at r.t., methanol (200 ml) and benzyl bromide (15.73 ml, 132.46 mmol) were added sequentially and vigorous stirring was continued for 4 h. The blue copper complex was collected by filtration and washed with H2O and methanol. The solution was stirred for 15 min at 50 °C with 1M aq. HCl (200 ml). The solid was collected by filtration and stirred again for 15 min at 50 °C with 1M aq. HCl (200 ml). The white hydrochloride salt was collected by filtration, washed with 2M aq. HCl (100 ml), and then stirred for 15 min at 90 °C with sodium acetate (20 g) in H2O (200 ml). The product was collected by filtration, washed with H2O (100 ml), and dried to give (±)-27 as a colorless solid (18.61 g, 63%), M.p. 238-240 °C (90% aqueous acetic acid, lit. [184] 223 °C). IR (KBr): 3033 m cm⁻¹; 1606 s; 1511 s; 1250 m (PhOC). EI-MS: 271 (1, M⁺); 225 (1); 197 (23, [CH2PhOBn]+); 107 (7, [C7H7O]+); 91 (90, [C7H7]+). Anal. calc. for C16H17NO3 (271.4): C 70.83, H 5.16; found: C 70.55, H 6.60, N 5.33.
Experimental Part 133

DL-O-Benzyltyrosine methyl ester hydrochloride (±-29).

![Chemical Structure of DL-O-Benzyltyrosine methyl ester hydrochloride (±-29)]

The ester (±)-29 was prepared from O-benzyltyrosine ((±)-27) (10.00 g, 36.90 mmol) according to Procedure A. Colorless solid (11.18 g, 95%), M.p. 175-177 °C (MeOH, lit. [184] 181 °C). 1H-NMR (200 MHz, (CD3)2SO): 8.63 (s, 2 H, NH2); 7.47-7.33 (m, 5 H, ArH); 7.16, 6.98 (AA'BB', J = 8.6, 4 H, ArH); 5.09 (s, 2 H, OCH2Ph); 4.21 (m, 1 H, H-C(2)); 3.67 (s, 3 H, COOCH3); 3.09 (m, 2 H, H2C(3)).

(2RS)-Methyl 2-{A'-(4-methoxycarbonylphenyl)sulfonamido}-3-(4-phenylmethoxyphenyl)propanoate ((±)-31).

![Chemical Structure of (2RS)-Methyl 2-{A'-(4-methoxycarbonylphenyl)sulfonamido}-3-(4-phenylmethoxyphenyl)propanoate ((±)-31)]

The amino acid methyl ester hydrochloride (±)-29 (4.50 g, 13.98 mmol) was converted to the corresponding sulfamide (±)-31 according to Procedure B. Purification by flash chromatography (hexane/EtOAc 6:4) on silica gel gave (±)-31 as a colorless solid (2.48 g, 36%), M.p. 152-154 °C (hexane/EtOAc). IR (KBr): 3300m cm⁻¹ (NH); 3224m (NH); 1722r (C=O); 1612m; 1514m; 1351m (S02); 1278m (C-O); 1156m (SO2); 1117m. 1H-NMR (200 MHz, CDCl3): 7.95, 7.05 (AA'BB', J = 8.8, 4 H, ArH); 7.45-7.32 (m, 5 H, ArH); 6.96, 6.81 (AA'BB', J = 8.7, 4 H, ArH); 5.24 (d, J = 9.1, 1 H, NH); 4.99 (s, 2 H, OCH2Ph); 4.29 (m, 1 H, H-C(2)); 3.86 (s, 3 H, COOCH3); 3.63 (s, 3 H, COOCH3); 2.96 (m, 2 H, H2C(3)). 13C-NMR (75 MHz, CDCl3): 171.9; 166.5; 158.1; 141.1; 136.9; 131.0; 130.3; 128.6; 128.0; 127.5; 126.9; 125.4; 117.7; 115.0; 69.9; 57.5; 52.8; 52.1; 38.0. DEI-MS: 498 (3, M⁺); 226 (4); 197 (78, [CH2PhOBn]⁺); 178 (11); 151 (36, [H2NPhCOOCH3]⁺); 120 (57); 107 (10, [C7H7O]⁺); 91 (100, [C7H7]⁺). Anal. calc. for C25H26N2O7S (498.6): C 60.23, H 5.26, N 5.62, S 6.43; found: C 60.16, H 5.30, N 5.78, S 6.43.
(4RS)-Methyl 4-[4-(4-benzyloxybenzyl)-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]benzoate ((±)-33).

The sulfamide (±)-31 (1.13 g, 2.27 mmol) was cyclized to the corresponding thiazolide (±)-33 according to Procedure C. Purification by flash chromatography (CH₂Cl₂/MeOH 9:1) on silica gel gave (±)-33 as a yellow solid (0.87 g, 83%), M.p. 113-115 °C (hexane/EtOAc). IR (KBr): 3262m cm⁻¹ (NH); 1718m (C=O); 1609s; 1513m; 1282s (C-O); 1239m; 1152s (SO₂); 1106m. ¹H-NMR (200 MHz, (CD₃)₂SO): 7.81, 7.04 (AA'BB', J = 8.6, 4 H, ArH); 7.45-7.31 (m, 5 H, ArH); 7.04, 6.77 (AA'BB', J = 8.6, 4 H, ArH); 5.00 (s, 2 H, OCH₂Ph); 3.77 (s, 3 H, COOCH₃); 3.90-3.84 (m, 1 H, H-C(4)); 3.00, 2.77 (AB of ABX, Jₓᵧ = 4.3, JＢₓ ＝ 7.8, J_AB ＝ 13.7, 2 H, H-C(6)). ¹³C-NMR (75 MHz, (CD₃)₂SO): 172.8; 165.8; 156.7; 143.3; 137.1; 130.0 (two overlapping signals); 129.1; 128.3; 127.6; 127.4; 122.2; 116.4; 114.0; 68.8; 57.8; 51.6; 36.6. DEI-MS: 466 (3, M⁺); 435 (2, [M - OCH₃]⁺); 197 (17, [CH₂PhOBn]⁺); 178 (5); 151 (49, [H₂NPhCOOCH₃]⁺); 134 (3); 120 (100); 91 (42, [C₇H₇]⁺). HR-DEI-MS: 466.1226 (M⁺, C₂₄H₂₂N₂O₆S; calc. 466.1198).

(4RS)-4-[4-(4-Benzyloxybenzyl)-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]benzamide ((±)-34).
Experimental Part

Thiazolide methyl ester (±)-33 (600 mg, 1.29 mmol) was converted to the corresponding primary amide (±)-34 according to Procedure D. Purification by flash chromatography (CH$_2$Cl$_2$/MeOH/NH$_4$OH 65:10:1) on silica gel gave (±)-34 as a colorless solid (300 mg, 52%), M.p. 216-218 °C (Et$_2$O/MeOH). IR (KBr): 3222m cm$^{-1}$ (NH); 1724m (C=O); 1689m (N=C=O); 1672m (N=C=O); 1513m; 1395m; 1317s (SO$_2$); 1233m; 1178s (SO$_2$). $^1$H-NMR (200 MHz, CD$_3$)$_2$SO): 9.06 (s, 1 H, NH); 8.13 (s, 1 H, NH); 8.05 (d, J = 8.7, 2 H, ArH); 7.56 (s, 1 H, NH); 7.49-7.34 (m, 7 H, ArH); 7.28, 7.01 (AA'BB', J = 8.6, 4 H, ArH); 5.12 (s, 2 H, OCH$_2$Ph); 4.72, 3.22, 3.00 (ABX, J$_{AX}$ = 3.9, J$_{BX}$ = 9.9, J$_{AB}$ = 14.0, 3 H, H-C(4), H$_2$C(6)). $^{13}$C-NMR (75 MHz, (CD$_3$)$_2$SO): 168.2; 166.8; 157.2; 137.1; 135.1; 132.8; 130.7; 128.8; 128.3; 127.7; 127.5; 126.6; 114.5; 69.0; 61.2; 35.5. DEI-MS: 451 (1, M$^+$); 197 (3, [CH$_2$PhOBn]$^+$); 146 (3); 134 (2); 120 (4); 107 (6, [C$_7$H$_7$O]$^+$); 91 (65, [C$_7$H$_7$]$^+$). Anal. calc. for C$_{23}$H$_{21}$N$_3$O$_5$S (451.5): C 61.19, H 4.69, N 9.31, S 7.10; found: C 61.15, H 4.71, N 9.16, S 7.00.

(4RS)-4-[4-(4-hydroxybenzyl)-1,1,3-trioxo-(1,2,5-thiadiazola-2-yl)]benzamide (±)-11.

A solution of sulfonamide (±)-34 (330 mg, 0.73 mmol) and pentamethylbenzene (1.08 g, 7.29 mmol) in trifluoroacetic acid (20 ml) was allowed to stand at r.t. for 1 h. The solution was evaporated in vacuo, the residue washed with Et$_2$O (5 ml), and dried in vacuo to give (±)-11 as a colorless solid (240 mg, quant.), M.p. > 200 °C decomp. (hexane/EtOAc/MeOH). IR (KBr): 3433m cm$^{-1}$ (NH); 3189m (NH); 1728m (C=O); 1646s (N-C=O); 1611m; 1511m; 1339s (SO$_2$); 1189s (SO$_2$); 1167s (SO$_2$). $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): 9.22 (s, 1 H, OH); 9.03 (s, 1 H, OH); 9.03 (s, 1 H, NH); 8.12 (s, 1 H, NH); 8.05, 7.46 (AA'BB', J = 8.7, 4 H, ArH); 7.55 (s, 1 H, NH); 7.15, 6.75 (AA'BB', J = 8.7, 4 H, ArH); 4.67, 3.17, 2.95 (ABX, J$_{AX}$ = 3.7, J$_{BX}$ = 9.9, J$_{AB}$ = 14.1, 3 H, H-C(4), H$_2$C(6)). $^{13}$C-NMR (75 MHz, (CD$_3$)$_2$SO): 168.5; 167.2; 156.5; 135.4; 133.0; 130.7; 129.1; 126.9; 126.4; 115.2; 61.5; 35.7. DEI-MS: 361 (4, M$^+$); 238 (4); 191 (6); 146 (20); 136
(31); 120 (39); 107 (100, [C\textsubscript{7}H\textsubscript{7}O]\textsuperscript{+}). HR-DEI-MS: 361.0729 (M\textsuperscript{+}, C\textsubscript{16}H\textsubscript{15}N\textsubscript{3}O\textsubscript{5}S; calc. 361.0732).

**N-Phenylmethylene glycine (36).**

![Structure of N-phenylmethylene glycine (36)](image)

A solution of glycine methyl ester hydrochloride (35) (10.00 g, 79.64 mmol), freshly distilled benzaldehyde (8.05 ml, 79.64 mmol) and triethylamine (11.10 ml, 79.64 mmol) in ethanol (100 ml) was stirred at r.t. for 24 h. The ethanol was then evaporated *in vacuo*, the residue diluted with CH\textsubscript{2}Cl\textsubscript{2} (100 ml), and washed with H\textsubscript{2}O (100 ml). The organic phase was dried (MgSO\textsubscript{4}) and evaporated *in vacuo* to give 36 as a colorless oil (13.32 g, 95%). \textsuperscript{1}H-NMR (200 MHz, CDCl\textsubscript{3}): 8.33 (\textit{j}, 1 H, NCH\textsubscript{Ph}); 7.50-7.35 (m, 5 H, ArH); 4.45 (s, 2 H, H\textsubscript{2}C(2)); 3.81 (s, 3 H, COOCH\textsubscript{3}).

**(2RS)-2-Amino-4-phenylbutyric acid methyl ester ((±)-37).**

![Structure of (2RS)-2-Amino-4-phenylbutyric acid methyl ester ((±)-37)](image)

To a solution of N-phenylmethylene glycine (36) (3.00 g, 16.93 mmol) and DMPU (4.08 ml, 33.9 mmol) in dry THF (100 ml) at -78 °C under an argon atmosphere was added LDA (2M soin, in heptane/tetrahydrofuran/ethylbenzene, 9.31 ml, 18.62 mmol) followed by (2-bromoethyl)benzene (2.29 ml, 16.93 mmol). The solution was allowed to reach r.t. over 4 h and then stirred for 12 h. The THF was removed by distillation *in vacuo* and the residue dissolved in methanol (100 ml) and in 2M aq. HCl (100 ml) and stirred for 2 h. The methanol was removed by distillation *in vacuo*, the aqueous phase washed with CH\textsubscript{2}Cl\textsubscript{2} (100 ml), made basic with 1M aq. NaOH (190 ml) and a sat. aq. NaHCO\textsubscript{3} solution (60 ml) and extracted with EtOAc (3 x 200 ml). The combined organic phases were dried (MgSO\textsubscript{4}) and evaporated *in vacuo* to give (±)-37 as a yellow oil (1.47 g, 45%). \textsuperscript{1}H-NMR (200 MHz, CDCl\textsubscript{3}): 7.35-7.16 (m, 5 H, ArH); 3.72 (s, 3 H, COOCH\textsubscript{3}); 3.48 (\textit{dd}, J = 7.7, 5.2, 1 H, H-C(2)); 2.74 (m, 2 H, H\textsubscript{2}C(4)); 2.16-2.00 (m, 1 H, H-C(3)); 1.95-1.77 (m, 1 H, H-C(3)).
(2RS)-Methyl 2-[N-(4-methoxycarbonylphenyl)sulfonamido]-4-phenylbutanoate (±)-39).

The amino acid methyl ester (±)-37 (1.69 g, 8.75 mmol) was converted to the corresponding sulfamide (±)-39 according to Procedure B. Purification by flash chromatography (CH₂Cl₂) on silica gel gave (±)-39 as a colorless solid (762 mg, 22%), M.p. 143-145 °C (hexane/EtOAc). IR (KBr): 3263m cm⁻¹ (NH); 1722s (C=O); 1610m; 1437m; 1349m (SO₂); 1292s (C-O); 1147s (SO₂); 1106m. ¹H-NMR (200 MHz, CDCl₃): 8.01 (d, J = 8.3, 2 H, ArH); 7.29-7.14 (m, 5 H, ArH); 7.06-7.02 (m, 2 H, ArH); 4.09 (m, 1 H, H-C(2)); 3.91 (s, 3 H, COOCH₃); 3.58 (s, 3 H, COOCH₃); 2.60 (m, 2 H, H₂C(4)); 2.17-1.87 (m, 2 H, H₂C(3)). ¹³C-NMR (75 MHz, CDCl₃): 172.8; 166.8; 141.7; 140.2; 131.4; 128.8; 128.6; 126.6; 125.8; 118.0; 56.0; 52.9; 52.2; 34.4; 31.2. DEI-MS: 406 (20, M⁺); 347 (7, [M - COOCH₃]⁺); 182 (9); 151 (100, [H₂NPhCOOCH₃]⁺); 120 (40); 117 (74); 105 (29); 91 (97, [C₇H₇]⁺). Anal. calc. for C₁₉H₂₂N₂O₆S (406.5): C 56.15, H 5.46 N 6.89, S 7.89; found: C 56.27, H 5.53, N 7.07, S 7.92.

(4RS)-Methyl 4-[1,1,3-trioxo-4-phenethyl-(1,2,5-thiadiazolan-2-yl)]benzoate (±)-41).
The sulfamide (±)-39 (750 mg, 1.85 mmol) was cyclized to the corresponding thiazolide (±)-41 according to Procedure C. Purification by flash chromatography (CH₂Cl₂/MeOH 9:1) on silica gel gave (±)-41 as a yellow solid (592 mg, 86%), M.p. 105-107 °C (hexane/EtOAc). IR (KBr): 3265m cm⁻¹ (NH); 1718 (C=O); 1609; 1433m; 1322 (SO₂); 1283s (C-O); 1151 m (SO₂); 1106. ¹H-NMR (200 MHz, (CD₃)₂SO): 7.89, 7.21 (AA'BB', J = 8.7, 4 H, ArH); 7.24-7.13 (m, 3 H, ArH); 6.98-6.94 (m, 2 H, ArH); 3.83 (s, 3 H, COOCH₃); 3.63-3.58 (m, 1 H, H-C(4)); 2.50-2.41 (m, 2 H, H₂C(7)); 1.92-1.80 (m, 2 H, H₂C(6)). ¹³C-NMR (75 MHz, (CD₃)₂SO): 173.8; 166.2; 144.3; 142.1; 130.6; 128.3 (two overlapping signals); 125.7; 122.4; 116.6; 56.9; 51.8; 45.3; 34.1. DEI-MS: 374 (2, M⁺); 346 (3); 343 (2, [M - OCH₃]⁺); 270 (22, [M - PhCH₂CH⁺]); 191 (11); 151 (90, [H₂NPhCOOCH₃]⁺); 120 (100). HR-DEI-MS: 374.0939 (M⁺, C₁₈H₁₈N₂O₅S; calc. 374.0936).

(4RS)-4-[l,l^-Trioxo-4-phenethyl-(l^-thiadiazolan-2-yl)]benzamide ((±)-12).

Thiazolide methyl ester (±)-41 (500 mg, 1.34 mmol) was converted to the corresponding primary amide (±)-12 according to Procedure D. Purification by flash chromatography (CH₂Cl₂/MeOH/NH₃ 65:10:1) on silica gel gave (±)-12 as a colorless solid (270 mg, 57%), M.p. 168-170 °C (EtOAc). IR (KBr): 3445m cm⁻¹ (NH); 3378m (NH); 1739m (C=O); 1654s (N-C=O); 1606m; 1322m (SO₂); 1183m (SO₂); 1161m (SO₂). ¹H-NMR (200 MHz, (CD₃)₂SO): 7.87, 7.42 (AA'BB', J = 8.7, 4 H, ArH); 7.25-7.07 (m, 5 H, ArH); 4.09 (dd, J = 9.5, 4.6, 1 H, H-C(4)); 2.92-2.65 (m, 2 H, H₂C(7)); 2.33-2.05 (m, 2 H, H₂C(6)). ¹³C-NMR (75 MHz, (CD₃)₂SO): 169.5; 169.4; 139.9; 134.3; 133.9; 129.1; 128.8; 128.7; 126.9; 126.6; 59.5; 32.9; 31.5. DEI-MS: 360 (5, [M + H⁺]); 359 (4, M⁺); 331 (5); 255 (54, [M - PhCH₂CH⁺]); 191 (38); 147 (33); 134 (63); 117 (45); 105 (29, [C₈H₉⁺]); 91 (100, [C₇H₇⁺]). Anal. calc. for C₁₇H₁₇N₃O₄S (359.4): C 56.81 H 4.77, N 11.69, S 8.92; found: C 56.54, H 4.80, N 11.76, S 8.93.
**Experimental Part**

(2RS)-2-Amino-3-(naphthalen-2-yl)propionic acid methyl ester ((±)-38).

To a solution of N-phenylmethylene glycine (36) (4.40 g, 24.83 mmol) in dry THF (100 ml) at -78 °C under an argon atmosphere was added LDA (2M soln. in heptane/tetrahydrofuran/ethylbenzene, 14.90 ml, 29.80 mmol) followed by a solution of (2-bromomethyl)naphthalene (5.50 g, 24.83 mmol) in THF (20 ml). The solution was allowed to reach r.t. over 4 h and then stirred for 12 h. The THF was removed by distillation in vacuo, the residue dissolved in methanol (100 ml) and in 2M aq. HCl (100 ml), and stirred for 2 h. The methanol was removed by distillation in vacuo, the aqueous phase washed with CH₂Cl₂ (100 ml), made basic with 1M aq. NaOH (190 ml) and a sat. aq. NaHCO₃ solution (60 ml), and extracted with EtOAc (3 x 200 ml). The combined organic phases were dried (MgSO₄) and evaporated in vacuo to give (±)-38 as a yellow solid (2.56 g, 45%). \(^{1}H\)-NMR (200 MHz, CDCl₃): 7.85-7.79 (m, 3 H, ArH); 7.67 (s, 1 H, ArH); 7.49-7.41 (m, 2 H, ArH); 7.33 (dd, J = 8.5, 1.8, 1 H, ArH); 3.85, 3.28, 3.03 (ABX, Jₓₓ = 5.2, Jₓᵧ = 8.0, Jᵧᵧ = 13.4, 3 H, H-C(2), H₂C(3)); 3.74 (s, 3 H, COOCH₃).

(2RS)-Methyl 2-[N-(4-methoxycarbonylphenyl)sulfonamido]-3-(naphthalen-2-yl)propanoate ((±)-40).

The amino acid methyl ester (±)-38 (700 mg, 3.05 mmol) was converted to the corresponding sulfamide (±)-40 according to Procedure B. Purification by flash chromatography (CH₂Cl₂) on silica gel gave (±)-40 as a colorless solid (1.28 g, 95%), M.p. 180-182 °C (hexane/EtOAc). IR (KBr): 3278m cm⁻¹ (NH); 3230m (NH); 1717m
(C=O); 1697s (C=O); 1610m; 1339m (SO2); 1290s (C-O); 1239m; 1154s (SO2).

1H-NMR (200 MHz, CDCl3): 7.80-7.67 (m, 3 H, ArH); 7.70 (d, J = 8.7, 2 H, ArH); 7.56-7.44 (m, 3 H, ArH); 7.18 (d, J = 8.3, 1 H, ArH); 6.92 (d, J = 8.7, 2 H, ArH); 6.83 (s, 1 H, NH); 5.26 (d, J = 8.7, 1 H, NH); 4.48-4.38 (m, 1 H, H-C(2)); 3.91 (s, 3 H, COOCH3); 3.70 (s, 3 H, COOCH3); 3.28, 3.11 (AB of ABX, JAX = 4.8, JBX = 6.6, JAB = 14.0, 2 H, H2C(3)).

13C-NMR (75 MHz, CDCl3 + CD3OD ca. 99:1): 172.7; 167.2; 142.2; 133.3; 133.1; 132.5; 130.6; 128.2; 128.1; 127.6 (two overlapping signals); 126.8; 126.1; 125.7; 123.8; 116.5; 57.4; 52.4; 51.8; 38.6. DEI-MS: 442 (5, M+); 241 (8); 212 (14); 168 (7); 151 (14, [H2NPhCOOCH3]+); 141 (100, [C11H9]+); 120 (19). Anal. calc. for C22H22N2O6S (442.5): C 59.72, H 5.01 N6.33, S 7.25; found: C 59.92, H 5.16, N 6.52, S 7.16.

(4RS)-Methyl 4-{(naphthalen-2-yl)methyl}-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)benzoate ((±)-42).

The sulfamide (±)-40 (900 mg, 2.03 mmol) was cyclized to the corresponding thiazolide (±)-42 according to Procedure C. Purification by flash chromatography (CH2Cl2/MeOH 9:1) on silica gel gave (±)-42 as a yellow solid (425 mg, 56%). M.p. 172-175 °C (hexane/EtOAc). IR (KBr): 3251m cm⁻¹ (NH); 1722m (C=O); 1609s; 1434m; 1406m; 1322m (SO2); 1280s (C-O); 1148s (SO2); 1106m. 1H-NMR (200 MHz, (CD3)2SO): 7.78-7.62 (m, 3 H, ArH); 7.67 (d, J = 8.7, 2 H, ArH); 7.50 (s, 1 H, ArH); 7.40-7.30 (m, 3 H, ArH); 7.00 (d, J = 8.7, 2 H, ArH); 3.89-3.83 (m, 1 H, H-C(4)); 3.77 (s, 3 H, COOCH3); 3.19, 2.98 (AB of ABX, JAX = 4.6, JBX = 7.3, JAB = 14.0, 2 H, H2C(6)).

13C-NMR (75 MHz, (CD3)2SO): 173.5; 166.1; 136.4; 132.9; 131.8; 130.4; 128.3; 127.8; 127.4 (two overlapping signals); 127.1; 125.7; 125.2; 122.2; 116.4; 58.9; 51.7; 38.0. DEI-MS: 410 (1, M+); 169 (2); 151 (55, [H2NPhCOOCH3]+); 141 (9, [C11H9]+); 120 (100); 92 (19). HR-DEI-MS: 410.0936 (M+, C21H18N2O5S; calc. 410.0936).
Expérimentât Part 141

(4RS)-4-[(Naphthalen-2-yl)methyl]-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)-benzamide ((±)-13)

and

(2RS)-Methyl N-[1-(4-carbamoylphenylcarbamoyl)-2-(naphthalen-2-yl)ethyl]-sulfamoate ((±)-43).

Thiazolide methyl ester (±)-42 (400 mg, 0.97 mmol) was reacted according to Procedure D. The residue was separated by preparative thin layer chromatography on silica gel (acetone/hexane 50:50).

(±)-13 : colorless solid (104 mg, 27%), M.p. > 175 °C decomp. IR (KBr): 1754m cm⁻¹ (C=O); 1742m (C=O); 1729m (C=O); 1610m; 1322s (SO₂); 1186s (SO₂); 1165s (SO₂).

¹H-NMR (200 MHz, (CD₃)₂SO): 9.13 (br. s, 1 H, NH); 8.10 (s, 1 H, CONH₂); 8.02 (d, J = 7.8, 2 H, ArH); 7.91-7.85 (m, 4 H, ArH, CONH₂); 7.52-7.46 (m, 6 H, ArH); 4.87-4.84 (m, 1 H, H-C(4)); 3.47-3.41 (m, 1 H, H-C(6)); 3.26-3.21 (m, 1 H, H-C(6)). ¹³C-NMR (100 MHz, (CD₃)₂SO): 168.5; 167.0; 135.0; 134.2; 133.2; 132.9; 132.0; 128.8 (two overlapping signals); 127.9 (two overlapping signals); 127.7; 127.4; 126.5; 126.1; 125.6; 61.3; 36.8. FAB-MS: 396 (25, [M + H]+); 391 (41); 149 (100); 141 (19, [CHH₉]+). HR-FAB-MS: 296.1015 ([M+H]+, C_{20}H_{17}N_{3}O_{4}S; calc. 296.1018).

(±)-43 : colorless solid (54 mg, 13%), M.p. > 165 °C decomp. IR (KBr): 3489m cm⁻¹ (NH); 3378m (NH); 1733m (C=O); 1659s (N=C=O); 1606m; 1144m (SO₂).

¹H-NMR (200 MHz, (CD₃)₂SO): 10.08 (br. s, 1 H, NH); 8.62 (br. s, 1 H, NH); 7.86-7.62 (m, 7 H, ArH, CONH₂); 7.51-7.43 (m, 2 H, ArH); 7.30-7.26 (m, 1 H, ArH); 7.20 (s, 1 H, CONH₂); 7.06 (d, J = 8.7, 2 H, ArH); 4.18-4.04 (m, 1 H, H-C(2)); 3.40 (s, 3 H, COOCH₃); 3.09, 2.95 (AB of ABX, J_{AX} = 7.3, J_{BX} = 8.1, J_{AB} = 13.7, 2 H, H₂C(3)). ¹³C-NMR (100 MHz, (CD₃)₂SO): 171.8; 167.6; 141.4; 134.1; 133.0; 132.0; 128.4;
127.9; 127.8; 127.6; 127.5; 127.4; 126.1; 125.8; 116.6; 57.2; 51.7; 37.8. DEIMS: 427 (2, \(M^+\)); 409 (3); 229 (10); 212 (7); 141 (100, \([\text{C}_{11}\text{H}_9]^+\)). Anal. calc. for C\(_{21}\)H\(_{21}\)N\(_3\)O\(_5\)S (427.5): C 59.00, H 4.95, N 9.83, S 7.50; found: C 58.82, H 5.15, N 9.60, S 7.30.

4.3 Experimental Part for Chapter 2.2

**Procedure E. Carboxylic Acid Esterification.**

To a stirred solution of the amino acid (40.00 mmol) in methanol (250 ml) cooled to 0 °C was added dry HCl gas until no more absorption could be observed. The solution was allowed to stand at r.t. for 12 h and evaporated in vacuo.

**Procedure F. Oxazolidinone Formation.**

To a stirred solution of chlorosulfonylisocyanate (4.00 mmol) in CH\(_2\)Cl\(_2\) (50 ml) cooled to 0 °C was added 2-chloroethanol (4.00 mmol) at such a rate that the reaction temperature did not rise above 5 °C. After stirring at 0 °C for 1.5 h, a solution of amine hydrochloride (4.00 mmol) and triethylamine (12.00 mmol) in CH\(_2\)Cl\(_2\) (50 ml) was added at such a rate that the reaction temperature did not rise above 5 °C. When the addition was complete, the solution was allowed to warm to r.t. and stirred for 12 h. The reaction was quenched with 2M aq. HCl saturated with NaCl (100 ml), the organic phase was separated, and the aqueous phase extracted with CH\(_2\)Cl\(_2\) (2 x 100 ml). The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and filtered. Triethylamine (5 ml) was added and the solution was stirred at r.t. for 6 h. The reaction was quenched with 1M aq. HCl (200 ml), the organic phase was separated, and the aqueous phase extracted with CH\(_2\)Cl\(_2\) (2 x 100 ml). The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo.

**Procedure G. Sulfamide Formation.**

A solution of oxazolidinone (1.00 mmol), amine (1.00 mmol), and triethylamine (1 ml) in acetonitrile (25 ml) was heated to reflux for 12 h. The acetonitrile was removed in vacuo, 1M aq. HCl (50 ml) was added to the residue, and the product was extracted with CH\(_2\)Cl\(_2\) (3 x 50 ml). The combined organic extracts were dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo.
Procedure H. Cyclization of a Sulfamide to a Thiazolide.

To tert-BuLi (1.7M soln. in pentane, 5.00 mmol) in dry THF (100 ml) at r.t. under an argon atmosphere was added a solution of sulfamide (2.00 mmol) in THF (20 ml) over 4 h via syringe pump, and the solution was then stirred for 12 h. The reaction was quenched with 1M aq. HCl (100 ml) and the mixture extracted with EtOAc (3 x 100 ml). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo.

Methyl 4-aminophenylacetate (49).

![Structure of 49](image)

The ester 49 was prepared from 3-aminophenylacetic acid (48) (3.00 g, 19.85 mmol) according to Procedure E. Colorless solid (quant.), M.p. 169-170 °C (Et₂O/CH₂Cl₂/MeOH, lit. [338] 167-170 °C). ¹H-NMR (200 MHz, CDCl₃): 7.46-7.34 (m, 5 H, ArH); 3.68 (s, 3 H, COOCH₃); 3.65 (s, 2 H, H₂C(2)).

Methyl 2-{3-[(2-oxo-1,3-oxazolan-3-yl)sulfonamido]phenyl}acetate (50).

![Structure of 50](image)

The oxazolidinone 50 was prepared from amine 49 (1.00 g, 4.96 mmol) according to Procedure F. Colorless solid (1.39 g, 89%), M.p. 72-74 °C (hexane/EtOAc). IR (CHCl₃): 1773s cm⁻¹ (C=O); 1737s (C=O); 1418m; 1388m (SO₂); 1182s (C-O); 1156s (SO₂). ¹H-NMR (200 MHz, CDCl₃): 7.39-7.18 (m, 4 H, ArH); 4.33-4.25 (m, 2 H, H₂C(4)); 3.88-3.80 (m, 2 H, H₂C(3)); 3.70 (s, 3 H, COOCH₃); 3.63 (s, 2 H, H₂C(2)). ¹³C-NMR (50 MHz, CDCl₃): 172.1; 153.4; 136.0; 135.6; 130.1; 128.1; 124.0; 122.0; 63.0; 52.0; 46.5; 40.7. DEI-MS: 314 (100, M⁺), 255 (24, [M–COOCH₃]⁺); 165 (63, [M–PhCH₂COOCH₃]⁺); 163 (54, [NH₂PhCH₂COOCH₃]⁺); 106 (69). Anal. calc. for C₁₂H₁₄N₂O₆S (314.3): C 45.86, H 4.49, N 8.91, S 10.20; found: C 45.93, H 4.52, N 8.76, S 10.47.
(2RS)-Methyl 2-\{N-[3-(2-methoxycarbonyl)ethylphenyl]sulfonamido\}-3-(naphthalen-2-yl)propanoate ((±)-51).

Oxazolidinone 50 (2.06 g, 6.55 mmol) was reacted with 2-naphthylalanine methyl ester ((±)-38) (1.50 g, 6.54 mmol) according to Procedure G. Purification by chromatography (hexane/EtOAc 7:3) on silica gel gave (±)-51 as a colorless solid (2.69 g, 90%), M.p. 128-130 °C (EtOAC/Hexane). IR (KBr): 3278 m cm\(^{-1}\) (NH); 3222 m (NH); 1739 s (C=O); 1721 s (C=O); 1350 m (SO\(_2\)); 1289 s (C=O); 1149 s (SO\(_2\)). \(^1\)H-NMR (200 MHz, CDCl\(_3\)): 7.81-7.69 (m, 3 H, ArH); 7.51-7.44 (m, 3 H, ArH); 7.20-7.14 (m, 1 H, ArH); 7.08 (d, J = 7.9, 1 H, ArH); 6.97-6.88 (m, 3 H, ArH); 6.54 (s, 1 H, H-N(6)); 5.19 (d, J = 9.1, 1 H, H-N(4)); 4.49-4.38 (m, 1 H, H-C(2)); 3.66 (s, 3 H, COOCH\(_3\)); 3.64 (s, 3 H, COOCH\(_3\)); 3.50 (s, 2 H, H\(_2\)C(7)); 3.28-3.10 (m, 2 H, H\(_2\)C(3)). \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): 171.8; 171.6; 137.0; 135.2; 133.3; 132.5; 132.5; 129.3; 128.3; 128.3; 127.6; 127.6; 127.0; 126.2; 125.9; 125.4; 120.7; 118.5; 57.3; 52.6; 52.0; 40.8; 39.0. DEI-MS: 456 (11, M⁺); 255 (36); 212 (24); 165 (29); 141 (100, [C\(_{11}\)H\(_9\)]\(^+\)). Anal. calc. for C\(_{23}\)H\(_{24}\)N\(_2\)O\(_6\)S (456.5): C 60.51, H 5.30, N 6.14, S 7.02; found: C 60.65, H 5.52 N 6.02, S 7.09.

(4RS)-Methyl 2-\{3-[4-(naphthalen-2-yl)methyl]-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)phenyl\}acetate ((±)-57).
The sulfamide (±)-51 (1.32 g, 2.89 mmol) was cyclized to the corresponding thiazolide (±)-57 according to Procedure H. Purification by flash chromatography (CH$_2$Cl$_2$/MeOH 9:1) on silica gel gave (±)-57 as a yellow solid (1.05 g, 86%), M.p. 135-137 °C. IR (KBr): 3256 m cm$^{-1}$ (NH); 1733 m (C=O); 1594 m; 1561 m (SO$_2$); 1144 s (SO$_2$). $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): 7.81-7.76 (m, 1 H, ArH); 7.69-7.65 (m, 2 H, ArH); 7.51 (s, 1 H, NH); 7.45-7.29 (m, 3 H, ArH); 7.15-7.03 (m, 1 H, ArH); 6.96-6.93 (m, 2 H, ArH); 6.81 (d, J = 7.5, 2 H, ArH); 3.90-3.82 (m, 1 H, H-C(4')); 3.55 (s, 3 H, COOCH$_3$); 3.53 (s, 2 H, H$_2$C(2)); 3.16, 2.77 (AB of ABX, J$_{AX}$ = 5.4, J$_{BX}$ = 6.2, J$_{AB}$ = 14.1, 2 H, H$_2$C(6')). $^{13}$C-NMR (75 MHz, (CD$_3$)$_2$SO): 173.5; 171.6; 139.5; 126.6; 135.1; 133.0; 131.8; 129.0; 128.7; 127.9; 127.5 (two overlapping signals); 127.0; 125.7; 125.2; 123.1; 119.0; 116.6; 58.7; 51.6; 45.3; 37.9. DEI-MS: 424 (8, $M^+$); 165 (82); 141 (53, [C$_{11}$H$_9$]+); 106 (100). HR-DEI-MS: 424.1116 ($M^+$, C$_{22}$H$_{20}$N$_2$O$_5$S; calc. 424.1093).

(4RS)-2-{3-[4-(Naphthalen-2-yl)methyl]-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)-phenyl}acetamide ((±)-58).

A solution of thiazolide (±)-57 (500 mg, 1.18 mmol) and potassium trimethylsilanolate (452 mg, 3.54 mmol) in THF (25 ml) was stirred at r.t. for 24 h. The reaction was quenched with 1 M aq. HCl (50 ml) and the mixture extracted with EtOAc (3 x 50 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and evaporated in vacuo. The residue was dissolved in THF (25 ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (226 mg, 1.18 mmol), and 1-hydroxybenzotriazole (159 mg, 1.18 mmol) were added, and the solution was stirred at r.t. for 1 h. A 25% ammonium hydroxide solution (0.09 ml, 1.18 mmol) was added and stirring was continued for 4 h. The reaction mixture was filtered, evaporated in vacuo, and purified by chromatography (CH$_2$Cl$_2$/MeOH/NH$_4$OH 65:10:1) on silica gel to give (±)-58 as a colorless solid (180 mg, 38%), M.p. 160-163 °C (Et$_2$O/CH$_2$Cl$_2$). IR (KBr): 3378 m cm$^{-1}$ (NH); 1739 m (C=O); 1656 s (N-C=O); 1339 m (SO$_2$); 1322 m (SO$_2$); 1178 m (SO$_2$). $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): 7.95-7.88 (m, 4 H, ArH, NH); 7.59-7.42 (m, 6 H, ArH, NH); 7.30-
7.22 (m, 2 H, ArH); 6.99 (s, 1 H, ArH); 4.87 (dd, J = 9.9, 3.7, 1 H, H-C(4')); 3.50-3.42 (m, 1 H, H-C(6')); 3.48 (s, 2 H, H$_2$C(2)); 3.23 (dd, J = 14.3, 9.9, 1 H, H-C(6')). $^{13}$C-NMR (75 MHz, (CD$_3$)$_2$SO): 171.8; 168.6; 138.6; 134.3; 133.1; 132.2; 130.7; 130.4; 129.7; 128.1; 128.0 (two overlapping signals); 127.9; 127.7 (two overlapping signals); 126.3; 125.9; 125.6; 61.0; 41.2; 36.7. DEI-MS: 409 (9, M$^+$); 169 (18); 141 (100, [C$_{11}$H$_9$]$^+$). Anal. calc. for C$_{21}$H$_{19}$N$_3$O$_4$S (409.46): C 61.60, H 4.68, N 10.26, S 7.83; found: C 61.39, H 5.08 N 9.83, S 7.66.

Methyl 3-nitrophenylacetate (61).

The ester 61 was prepared from 3-nitrophenylacetic acid (60) (5.00 g, 27.60 mmol) according to Procedure A. Colorless solid (quant.), M.p. 25-30 °C. $^1$H-NMR (200 MHz, CDCl$_3$): 8.16-8.10 (m, 2 H, ArH); 7.62 (d, J = 8.1, 1 H, ArH); 7.54-7.46 (m, 1 H, ArH); 3.74 (s, 2 H, H$_2$C(2)); 3.72 (s, 3 H, COOCH$_3$).

(2RS)-Methyl 2-bromo-2-(3-nitrophenyl)acetate ((±)-62).

A solution of methyl 3-nitrophenylacetate (61) (5.85 g, 29.97 mmol), N-bromosuccinimide (8.00 g, 44.96 mmol), and azobisisobutyronitrile (493 mg, 3.00 mmol) in CCl$_4$ (200 ml) was heated to reflux for 48 h. The reaction mixture was allowed to cool to r.t., evaporated in vacuo, and purified by chromatography (hexane/CH$_2$Cl$_2$ 50:50) on silica gel to give (±)-62 as a yellow oil (6.85 g, 84%). IR (CHCl$_3$): 1748 m cm$^{-1}$ (C=O); 1535 s (NO$_2$); 1354 s (NO$_2$). $^1$H-NMR (200 MHz, CDCl$_3$): 8.42-8.39 (m, 1 H, ArH); 8.25-8.19 (m, 1 H, ArH); 7.93-7.88 (m, 1 H, ArH); 7.61-7.53 (m, 1 H, ArH); 5.40 (s, 1 H, H-C(2)); 3.82 (s, 3 H, COOCH$_3$). $^{13}$C-NMR (50 MHz, CDCl$_3$): 168.0; 148.2; 137.7; 134.7; 129.8; 124.1; 123.8; 53.7; 44.1. ESI-MS: 274/272 (8/10, M$^-$ (81Br/79Br)); 239 (100); 194 (52, [M - Br$^-$]). Anal. calc. for C$_9$H$_8$BrN$_2$O$_4$ (274.1): C 39.44, H 2.94, N 5.11, S 29.16; found: C 39.70, H 2.93, N 5.01, S 29.44.
A solution of bromide (±)-62 (1.58 g, 5.76 mmol) and potassium phthalimide (1.28 g, 6.92 mmol) in DMF (25 ml) was stirred at r.t. for 3 h. The reaction was quenched with a sat. aq. NaCl solution (50 ml) and the mixture extracted with EtOAc (3 × 50 ml). The combined organic extracts were dried (Na₂SO₄), filtered through silica gel, evaporated in vacuo, and the residue washed with EtOH (20 ml) to give (±)-63 as a colourless solid (1.85 g, 95%), M.p. 119-121 °C (hexane/EtOAc). IR (CHCl₃): 1700 m cm⁻¹ (C=O); 1672 m (C=O); 1601 s; 1530 s (NO₂); 1410 m; 1353 m (NO₂). ¹H-NMR (200 MHz, CDCl₃): 8.41 (s, 1 H, ArH); 8.23-8.18 (m, 1 H, ArH); 7.93-7.85 (m, 3 H, ArH); 7.80-7.74 (m, 2 H, ArH); 7.59-7.51 (m, 1 H, ArH); 6.09 (s, 1 H, H-C(2)); 3.83 (s, 3 H, COOCH₃). ¹³C-NMR (50 MHz, CDCl₃): 167.5; 167.0; 148.2; 136.2; 135.8; 134.6; 131.6; 129.6; 124.9; 123.7; 54.8; 53.5. EI-MS: 340 (2, M⁺); 308 (6); 281 (100, [M - COOCH₃]⁺); 235 (18, [M - COOCH₃-NH₂]⁺). Anal. calc. for C₁₇H₁₂N₂O₆ (340.3): C 60.00, H 3.55, N 8.23; found: C 59.78, H 3.49, N 8.25.

(2RS)-Methyl 2-phthalimido-2-(3-aminophenyl)acetate ((±)-59).

A solution of ester (±)-63 (500 mg, 1.47 mmol) in ethanol (50 ml) was treated with 5% Pd/C (200 mg) under a hydrogen atmosphere (1 bar) for 2 h. The reaction mixture was filtered through Celite, evaporated in vacuo and purified by chromatography (CH₂Cl₂/MeOH 98:2) on silica gel to give (±)-59 as a yellow solid (380 mg, 84%). IR (CHCl₃): 3379 w cm⁻¹ (NH₂); 1744 m (C=O); 1720 s (C=O); 1713 s (C=O); 1386 m. ¹H-NMR (200 MHz, CDCl₃): 7.86-7.80 (m, 2 H, ArH); 7.74-7.68 (m, 2 H, ArH); 7.16-7.09 (m, 1 H, ArH); 6.92-6.89 (m, 2 H, ArH); 6.67-6.62 (m, 1 H, ArH); 5.91 (s, 1 H, H-C(2)); 3.79 (s, 3 H, COOCH₃); 3.55 (br. s, 2 H, NH₂). ¹³C-NMR (50 MHz, CDCl₃): 168.6;
167.1; 146.7; 135.5; 134.2; 131.9; 129.5; 123.6; 119.8; 116.2; 115.4; 55.8; 53.0. EIMS: 310 (28, $M^+$); 278 (38); 251 (100, [$M - COOCH_3]^+$); 132 (50); 130 (34); 104 (21). HR-FAB-MS: 310.0959 ($M^+$, C$_{17}$H$_{14}$N$_2$O$_4$; calc. 310.0954).

(2RS)-Methyl 2-[(2-oxo-1,3-oxazolan-3-yl)-sulfonamido]phenyl}-2-phthalimidoacetate (±)-64.

![Diagram](image)

The oxazolidinone (±)-64 was prepared from amine (±)-59 (850 mg, 2.74 mmol) according to Procedure F. Yellow solid (1.13 g, 90%), M.p. 69-71°C. IR (KBr): 3267m cm$^{-1}$ (NH); 1772m (C=O); 1750m (C=O); 1711s (C=O); 1383* (SO$_2$); 1178m (SO$_2$); 1150m (SO$_2$). $^1$H-NMR (200 MHz, CDCl$_3$): 7.90-7.84 (m, 2 H, ArH); 7.39-7.36 (m, 2 H, ArH); 7.32-7.20 (m, 1 H, ArH); 7.00 (s, 1 H, H-C(2)); 4.34 (t, $J = 7.8$, 2 H, H$_2$C(3)); 3.93 (t, $J = 7.8$, 2 H, H$_2$C(4)); 3.82 (s, 3 H, COOCH$_3$). $^{13}$C-NMR (50 MHz, CDCl$_3$): 168.4; 167.4; 153.4; 136.2; 135.8; 134.7; 131.9; 130.2; 127.7; 124.0; 123.5; 123.4; 63.0; 55.3; 53.3; 46.3. DEI-MS: 459 (22, $M^+$), 427 (42); 400 (65, [$M - COOCH_3]^+$); 313 (100, [$M - Phthalimide]^+$); 251 (91); 132 (95); 104 (85). Anal. calc. for C$_{20}$H$_{17}$N$_3$O$_9$S (459.4): C 52.29, H 3.73, N 9.15, S 6.98; found: C 52.29, H 3.97, N 9.13, S 6.87.


Oxazolidinone (±)-64 (580 mg, 1.26 mmol) was reacted with 2-naphthylalanine methyl ester (±)-38 (319 mg, 1.39 mmol) according to Procedure G. Purification by chromatography (hexane/EtOAc 6:4) on silica gel gave (±)-65/(±)-66 as a 1:1 mixture.
of diastereoisomers. Colorless solid (350 mg, 48%). DEI-MS: 601 (6, M+); 400 (27); 310 (21); 278 (24); 251 (39); 141 (100, [C\textsubscript{11}H\textsubscript{9}]+).

(2RS,2'SS)-Methyl 2-\{3-\{4-\{naphthalen-2-yl\}methyl\}-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)phenyl\}-2-phthalimidoacetate ((\pm)-67/(\pm)-68).

The sulfamide ((\pm)-65/((\pm)-66 (700 mg, 1.16 mmol) was cyclized to the corresponding thiazolide ((\pm)-67/(\pm)-68 according to Procedure H. Purification by flash chromatography (CH\textsubscript{2}Cl\textsubscript{2}/MeOH 9:1) on silica gel gave ((\pm)-67/(\pm)-68 as a 1:1 mixture of diastereoisomers. Yellow solid (239 mg, 37%). DEI-MS: 569 (1, M+); 510 (1, [M-COOC\textsubscript{3}]+); 310 (27); 251 (100); 141 (44, [C\textsubscript{11}H\textsubscript{9}]+).

(2RS)-Methyl 2-amino-2-(3-nitrophenyl)acetate ((\pm)-69).

A solution of ester ((\pm)-63 (1.06 g, 3.11 mmol) in glacial acetic acid (15 ml), conc. hydrochloric acid (15 ml), and water (15 ml) was heated to reflux for 12 h. The reaction mixture was allowed to cool to r.t., washed with CH\textsubscript{2}Cl\textsubscript{2} (50 ml), and evaporated in vacuo. The residue was dissolved in methanol (50 ml) and treated with dry HCl gas at 0 °C for 10 min. The solution was allowed to stand at r.t. for 15 h and the methanol evaporated in vacuo. The residue was diluted with a sat. aq. NaHCO\textsubscript{3} solution (50 ml) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 50 ml). The combined organic extracts were dried (MgS\textsubscript{2}O\textsubscript{4}), evaporated in vacuo, and purified by chromatography (EtOAc/NH\textsubscript{4}OH 99:1) on silica gel to give ((\pm)-69 as a colorless oil (380 mg, 59%). IR (CHCl\textsubscript{3}): 1741 m cm\textsuperscript{-1} (C=O); 1534 s (NO\textsubscript{2}); 1352 * (N0\textsubscript{2}); 1136 m. \textsuperscript{1}H-NMR (200 MHz, CDCl\textsubscript{3}): 8.33-8.31 (m, 1 H, ArH); 8.21-8.15 (m, 1 H, ArH); 7.81-7.75 (m, 1 H, ArH); 7.59-7.51 (m, 1 H, ArH); 4.76 (s, 1 H, H-C(2)); 3.75 (s, 3 H, COOCH\textsubscript{3}); 1.82 (s,
2 H, NH₂). \(^{13}\text{C}\)-NMR (75 MHz, CDCl₃): 173.6; 148.8; 142.4; 133.3; 129.9; 123.2; 122.3; 58.0; 52.9. EI-MS: 211 (1, [M + H]⁺); 151 (100, [M - COOCH₃]⁺); 105 (33). Anal. calc. for C₉H₁₀N₂O₄ (210.2): C 51.43, H 4.80, N 13.33; found: C 51.37, H 4.69, N 13.08.

\((2RSJ-Methyl 2-acetamido-2-(3-nitrophenyl)acetate ((±)-70).\)

\[
\begin{align*}
&\begin{array}{c}
\text{O}_2\text{N} \\
2 \text{COOMe} \\
\text{N} \\
\end{array} \\
\text{H} \\
\end{align*}
\]

To a solution of amine (±)-69 (500 mg, 2.38 mmol) in THF (50 ml) was added propionyl chloride (0.21 ml, 2.38 mmol) followed by 1M aq. NaOH (10 ml), and the solution was stirred at r.t. for 4 h. The reaction was quenched with a sat. aq. NaCl solution (50 ml) and the mixture extracted with EtOAc (3 x 50 ml). The combined organic extracts were dried (Na₂SO₄), evaporated in vacuo, and purified by flash chromatography (hexane/EtOAc 1:1) on silica gel to give (±)-70 as a colorless solid (570 mg, 90%), M.p. 97-99 °C (hexane/EtOAc). IR (KBr): 3334\,\text{m} \,\text{cm}^{-1} \,\text{(NH)}; 1743\,\text{s} \,\text{cm}^{-1} \,\text{(C=O)}; 1646\,\text{s} \,\text{cm}^{-1} \,\text{(N-C=O)}; 1532\,\text{s} \,\text{cm}^{-1} \,\text{(NO₂)}; 1352\,\text{m} \,\text{cm}^{-1} \,\text{(NO₂)}; 1311\,\text{w} \,\text{cm}^{-1} \,\text{(NO₂)}; 1311\,\text{w} \,\text{cm}^{-1} \,\text{(NO₂)}. \,\text{H-NMR} (200 \,\text{MHz, CDCl₃}): 8.23-8.15 \,(\text{m}, 2 \,\text{H}, \text{ArH}); 7.77-7.73 \,(\text{m}, 1 \,\text{H}, \text{ArH}); 7.58-7.50 \,(\text{m}, 1 \,\text{H}, \text{ArH}); 6.73 \,(\text{d}, J = 6.4, 1 \,\text{H}, \text{NH}); 5.70 \,(\text{d}, J = 6.4, 1 \,\text{H}, \text{C}(2)); 3.77 \,(\text{s}, 3 \,\text{H}, \text{COOCH₃}); 2.33 \,(\text{q}, J = 7.5, 2 \,\text{H}, \text{H₂C}(4)); 1.17 \,(\text{t}, J = 7.5, 3 \,\text{H}, \text{H₃C}(5)). \,\text{C-NMR} (75 \,\text{MHz, CDCl₃}): 173.5; 170.8; 148.9; 139.4; 133.8; 130.1; 123.6; 122.2; 55.8; 53.4; 29.4; 9.4. \,\text{DEI-MS}: 266 (1, M⁺); 236 (3); 207 (30, [M - COOCH₃]⁺); 151 (100, [O₂NPhCHNH₂]⁺). \,\text{Anal. calc. for C₁₂H₁₄N₂O₅ (266.3): C 54.13, H 5.30, N 10.52; found: C 54.22, H 5.40, N 10.49.}

\((2RS)-Methyl 2-acetamido-2-(3-aminophenyl)acetate ((±)-71).\)

\[
\begin{align*}
&\begin{array}{c}
\text{H}_2\text{N} \\
2 \text{COOMe} \\
\text{N} \\
\end{array} \\
\end{align*}
\]

A solution of ester (±)-70 (570 mg, 2.14 mmol) in ethanol (50 ml) was treated with 10% Pd/C (55 mg) under a hydrogen atmosphere (1 bar) for 4 h. The reaction mixture was filtered through Celite and evaporated in vacuo to give (±)-71 as a yellow oil (510 mg,
quant.). IR (CHCl₃): 3007w cm⁻¹; 1742s (C=O); 1674s (N-C=O); 1621m; 1495s; 1167m (C-O); 1136m (C-O). ¹H-NMR (200 MHz, CDCl₃): 7.17-7.10 (m, 1 H, ArH); 6.73-6.60 (m, 3 H, ArH); 6.37-6.28 (m, 1 H, NH); 5.48 (d, J = 7.5, 1 H, H-C(2)); 3.73 (s, 3 H, COOCH₃); 2.27 (q, J = 7.7, 2 H, H₂C(4)); 1.16 (t, J = 7.7, 3 H, H₃C(5)). ¹³C-NMR (75 MHz, CDCl₃): 173.4; 172.0; 147.3; 137.9; 130.2; 117.4; 115.4; 114.1; 56.4; 52.8; 29.4; 9.5. DEI-MS: 236 (29, M⁺); 204 (31); 179 (57, [M - COCH₂CH₃]⁺); 121 (100). HR-DEI-MS: 236.1155 (M⁺, C₁₂H₁₆N₂O₃; calc. 236.1161).

(2RS)-Methyl 2-acetamido-2-{3-[(2-oxo-1,3-oxazolan-3-yl)-sulfonamidophenyl]acetate ((±)-72).

The oxazolidinone (±)-72 was prepared from amine (±)-71 (500 mg, 2.12 mmol) according to Procedure F. Purification by chromatography (CH₂Cl₂/MeOH 95:5) on silica gel gave (±)-72 as a yellow solid (140 mg, 18%). IR (KBₐr): 1742s cm⁻¹ (C=O); 1673m (N-C=O); 1497m; 1348m; 1160s (SO₂); 1133m. ¹H-NMR (200 MHz, CDCl₃): 7.38-7.14 (m, 4 H, ArH); 6.69 (d, J = 6.6, 1 H, H-N(3)); 5.59 (d, J = 6.6, 1 H, H-C(2)); 4.44-4.38 (m, 2 H, H₂C(8)); 3.75 (s, 3 H, COOCH₃); 3.70-3.64 (m, 2 H, H₂C(7)); 2.35-2.23 (m, 2 H, H₂C(5)); 1.19-1.11 (m, 3 H, H₃C(6)). ¹³C-NMR (75 MHz, CDCl₃): 173.9; 171.5; 151.2; 138.6; 136.6; 130.3; 124.9; 122.0; 120.9; 66.3; 56.1; 53.2; 41.4; 29.4; 9.5. DEI-MS: 385 (2, M⁺), 328 (16, [M - COCH₂CH₃]⁺); 326 (14, [M - COOCH₃]⁺); 270 (26); 236 (19); 204 (24); 179 (44); 167 (41); 121 (100). HR-DEI-MS: 385.0944 (M⁺, C₁₅H₁₉N₃O₇S; calc. 385.0943).

(2RS,2'RS)-Methyl 2-{N-[3-(2-acetamido-2-methoxycarbonyl)phenyl]-sulfonamido}-3-(naphthalen-2-yl)propanoate ((±)-73/(±)-74).
Oxazolidinone (±)-72 (130 mg, 0.34 mmol) was reacted with 2-naphthylalanine methyl ester ((±)-38) (92 mg, 0.40 mmol) according to Procedure G. Purification by chromatography (hexane/EtOAc 5:5) on silica gel gave (±)-73/(±)-74 as a 1:1 mixture of diastereoisomers. Colorless solid (75 mg, 42%). DEI-MS: 527 (2, M⁺); 495 (5); 470 (10, [M-COCH₂CH₃]⁺); 438 (11); 380 (26); 179 (29); 141 (100, [C₁₁H₉]⁺).

(2RS,2'SS)-Methyl 2-acetamido-2-[3-[4-[naphthalen-2-yl]methyl]-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)phenyl]acetate ((±)-75/(±)-76).

The sulfamide (±)-73/(±)-74 (75 mg, 0.14 mmol) were cyclized to the corresponding thiazolides (±)-75/(±)-76 according to Procedure H. Purification by flash chromatography (CH₂Cl₂/MeOH 9:1) on silica gel gave (±)-75/(±)-76 as a 1:1 mixture of diastereoisomers. Colorless solid (47 mg, 71%). DEI-MS: 495 (1, M⁺); 438 (2, [M-COCH₂CH₃]⁺); 380 (4); 236 (22); 204 (26); 179 (48); 141 (12, [C₁₁H₉]⁺); 121 (100).

4.4 Experimental Part for Chapter 2.3

Procedure I. Oxazolidinone Formation.

To a stirred solution of chlorosulfonylisocyanate (4.00 mmol) in CH₂Cl₂ (50 ml) cooled to 0 °C was added 2-chloroethanol (4.00 mmol) at such a rate that the reaction temperature did not rise above 5 °C. After stirring at 0 °C for 1.5 h, a solution of amine hydrochloride (4.00 mmol) and triethylamine (12.00 mmol) in CH₂Cl₂ (50 ml) was slowly added so that the reaction temperature remained under 5 °C. When the addition was complete, the solution was allowed to warm to r.t. and stirred for 12 h. The reaction was quenched with 2M aq. HCl saturated with NaCl (100 ml), the organic phase was separated, and the aqueous phase extracted with CH₂Cl₂ (2 x 100 ml). The
combined organic extracts were dried (Na$_2$SO$_4$) and filtered. Triethylamine (5 ml) was added to the filtrate, and the solution was stirred at r.t. for 6 h. The reaction was quenched with 1M aq. HCl (200 ml), the organic phase was separated, and the aqueous phase extracted with CH$_2$Cl$_2$ (2 x 100 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and evaporated in vacuo.

Procedure J. Sulfamide Formation.

A solution of oxazolidinone (1.00 mmol), amine (1.00 mmol), and triethylamine (1 ml) in acetonitrile (25 ml) was heated to reflux for 12 h. The acetonitrile was removed in vacuo, 1M aq. HCl (50 ml) was added to the residue, and the product was extracted with CH$_2$Cl$_2$ (3 x 50 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and evaporated in vacuo.

Procedure K. Cyclization of a Sulfamide to a Thiazolide.

A solution of sulfamide (1.00 mmol) and sodium hydride (2.50 mmol) in THF (50 ml) was heated to reflux for 7 h. The reaction mixture was allowed to cool to r.t., quenched with 1M aq. HCl (50 ml), and extracted with EtOAc (3 x 50 ml). The combined organic extracts were dried (MgSO$_4$) and evaporated in vacuo.

Procedure L. tert-Butyl Ester Hydrolysis.

A solution of thiazolide (1 mmol) in trifluoroacetic acid (50 ml) was stirred at r.t. for 3 h. The trifluoroacetic acid was evaporated in vacuo and the residue recrystallized (hexane/Et$_2$O).

(2RS)-Methyl 2-(N-carbobenzyloxysulfonamido)-3-phenylpropanoate ((±)-79) [174].
To a stirred solution of chlorosulfonyl isocyanate (4.76 ml, 54.79 mmol) in CH₂Cl₂ (150 ml) cooled to 0 °C was added benzyl alcohol (5.68 ml, 54.79 mmol) at such a rate that the reaction temperature did not rise above 5 °C. After stirring for 1.5 h at 0 °C, a solution of DL-phenylalanine methyl ester hydrochloride ((±)-28) (13.00 g, 60.27 mmol) and triethylamine (22.91 ml, 164.37 mmol) in CH₂Cl₂ (300 ml) was slowly added so that the reaction temperature remained under 5 °C. When the addition was complete, the solution was allowed to warm to r.t. and stirred for 12 h. The reaction mixture was then quenched with 2M aq. HCl sat. with NaCl (400 ml). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 x 200 ml). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo to give (±)-79 as a colorless solid (21.70 g, 92%), M.p. 101-102 °C (hexane/EtOAc, lit. [174] 101.5-102.5 °C). ¹H-NMR (200 MHz, CDCl₃): 7.81 (s, 1 H, NH); 7.37-7.07 (m, 10 H, ArH); 5.74 (d, J = 8.1, 1 H, NH); 5.11 (s, 2 H, OCH₂Ph); 4.56-4.45 (m, 1 H, H-C(2)); 3.63 (s, 3 H, COOCH₃); 3.20-3.00 (m, 2 H, H₂C(3)).

(2RS)-Methyl 3-phenyl-2-sulfonamidopropanoate (±)-82 [174].

A solution of sulfamide (±)-79 (21.70 g, 55.30 mmol) in ethanol (200 ml) was treated with 10% Pd/C (260 mg) under a hydrogen atmosphere (4 bar) for 18 h. The reaction mixture was filtered through Celite and evaporated in vacuo to afford (±)-82 as a colorless solid (13.62 g, quant.), M.p. 115-116 °C (hexane/EtOAc, lit. [174] 114.5-115.5 °C). ¹H-NMR (200 MHz, CDCl₃): 7.35-7.14 (m, 5 H, ArH); 5.20 (d, J = 9.2, 1 H, NH); 4.62 (s, 2 H, NH₂); 4.43-4.32 (m, 1 H, H-C(2)); 3.74 (s, 3 H, COOCH₃); 3.20-3.02 (m, 2 H, H₂C(3)).

(4RS)-4-Benzyl-1,1-dioxo-1,2,5-thiadiazolidin-3-one (±)-81 [174].
A solution of sulfamide (±)-82 (2.00 g, 7.74 mmol) and sodium methoxide (836 mg, 15.48 mmol) in methanol (25 ml) was heated to reflux for 24 h. The methanol was evaporated in vacuo, the residual oil diluted with 1M aq. HCl (50 ml) and extracted with CH$_2$Cl$_2$ (3 x 50 ml). The combined organic extracts were dried (MgSO$_4$) and evaporated in vacuo to afford (±)-81 as a colorless solid (1.32 g, 76%), M.p. 162-164 °C (hexane/EtOAc, lit. 174 163-164 °C). $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): 7.40-7.17 (m, 5 H, ArH); 4.41, 3.11, 2.83 (ABX, $J_{AX}$ = 3.7, $J_{BX}$ = 10.2, $J_{AB}$ = 14.0, 3 H, H-C(2), H$_2$C(3)).

(2R,4RS)-Methyl 3-[4-benzyl-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]-2-methylpropanoate ((±)-85) and

(2R,4RS)-Methyl 3-[3-benzyl-1,1-dioxo-4,5-dihydro-(1,2,5-thiadiazol-4-yl)oxy]-2-methylpropanoate ((±)-87).

To a solution of thiazolide (±)-81 (1.00 g, 4.42 mmol) in dry THF (100 ml) was added triphenylphosphine (2.32 g, 8.84 mmol), (R)-methyl 3-hydroxy-2-methylpropionate (0.49 ml, 4.42 mmol), and diethyl azodicarboxylate (1 ml, 6.63 mmol), and the solution was stirred at r.t. under an argon atmosphere for 1 h. The reaction was quenched with a sat. aq. NaCl solution (100 ml), the organic phase separated, and the aqueous phase extracted with EtOAc (2 x 200 ml). The combined organic phases were dried (Na$_2$SO$_4$), evaporated in vacuo, and subjected to silica gel chromatography (hexane/EtOAc 6:4).

(±)-85 : light yellow oil (285 mg, 20%). IR (CHCl$_3$): 1740 s cm$^{-1}$ (C=O); 1338w; 1319w; 1186m (SO$_2$). $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): 7.41-7.17 (m, 5 H, ArH); 4.61-4.56 (m, 1 H, NH); 4.43-3.32 (m, 1 H, H-C(4')); 3.97-3.81 (m, 1 H, H-C(3)); 3.74-3.57 (m, 1 H, H-C(3)); 3.69 (s, 1.5 H, COOCH$_3$); 3.67 (s, 1.5 H, COOCH$_3$); 3.32-3.14 (m, 2 H, H$_2$C(6')); 3.11-2.91 (m, 1 H, H-C(2)); 1.19-1.14 (m, 3 H, CH$_3$). $^{13}$C-NMR (50
MHz, (CD$_3$)$_2$SO): 173.7; 168.0; 134.2; 129.4; 129.2; 128.0; 61.4; 52.1; 43.4; 38.1; 36.4; 14.8. FAB-MS: 327 (99, [M + H]$^+$); 295 (72); 181 (56); 120 (100). HR-DEI-MS: 326.0922 (M$^+$, C$_{14}$H$_{18}$N$_2$O$_5$S; calc. 326.0936).

(±)-87: light yellow oil (835 mg, 58%). IR (CHCl$_3$): 1739 m cm$^{-1}$ (C=O); 1618 s (O–C=N); 1331 m (SO$_2$); 1172 s (SO$_2$). $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): 7.37-7.18 (m, 5 H, ArH); 4.87 (d, $J = 5.4$, 1 H, NH); 4.61-4.45 (m, 3 H, H$_2$C(3), H-C(3')); 3.73 (s, 3 H, COOCH$_3$); 3.16, 2.92 (AB of ABX, $J_{AX} = 4.2$, $J_{BX} = 9.6$, $J_{AB} = 14.2$, 2 H, H$_2$C(6')); 3.02-2.91 (m, 1 H, H-C(2)); 1.26 (d, $J = 7.0$, 3 H, CH$_3$). $^{13}$C-NMR (50 MHz, (CD$_3$)$_2$SO): 176.5; 173.3; 134.8; 129.2; 129.1; 127.8; 73.4; 62.8; 52.3; 38.7; 38.0; 13.7. FAB-MS: 327 (73, [M + H]$^+$); 295 (37); 120 (44); 101 (100). HR-DEI-MS: 326.0937 (M$^+$, C$_{14}$H$_{18}$N$_2$O$_5$S; calc. 326.0936).

(2S,R)-Methyl 2-(N-carbobenzyloxysulfonamido)-3-(naphthalen-2-yl)propanoate ((±)-80).

To a stirred solution of chlorosulfonyl isocyanate (0.45 ml, 5.13 mmol) in CH$_2$Cl$_2$ (30 ml) cooled to 0 °C was added benzyl alcohol (0.53 ml, 5.13 mmol) at such a rate that the reaction temperature did not rise above 5 °C. After stirring for 1.5 h at 0 °C, a solution of 2-naphthylalanine methyl ester hydrochloride ((±)-78) (1.50 g, 5.64 mmol) and triethylamine (2.15 ml, 15.39 mmol) in CH$_2$Cl$_2$ (100 ml) was slowly added so that the reaction temperature remained under 5 °C. When the addition was complete, the solution was allowed to warm to r.t. and stirred for 12 h. The reaction mixture was then quenched with 2 M aq. HCl sat. with NaCl (100 ml). The organic layer was separated and the aqueous layer extracted with CH$_2$Cl$_2$ (2 x 100 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and evaporated in vacuo to give (±)-80 as a colorless solid (1.89 g, 76%), M.p. 110-112 °C (hexane/EtOAc). IR (CHCl$_3$): 3314 m cm$^{-1}$ (NH); 1751 m (C=O); 1728 s (C=O); 1466 m; 1453 m; 1364 m (SO$_2$); 1224 m (C-O); 1167 m (SO$_2$). $^1$H-NMR (200 MHz, CDC$_3$): 7.82-7.75 (m, 3 H, ArH); 7.61 (s, 1 H, ArH); 7.49-7.22 (m, 8 H, ArH); 5.63 (d, $J = 8.7$, 1 H, NH); 5.10 (s, 2 H, OCH$_2$Ph); 4.64-4.54 (m, 1 H, H-C(2)); 3.64 (s, 3 H, COOCH$_3$); 3.36-3.16 (m, 2 H, H$_2$C(3)). $^{13}$C-NMR (50
MHz, CDCl₃): 171.2; 151.0; 134.6; 133.4; 132.5; 132.4; 128.6; 128.6; 128.5; 128.3; 128.3; 127.7; 127.6; 127.2; 126.2; 125.9; 68.3; 57.7; 52.6; 39.0. FAB-MS: 443 (4, \([M + H]^+)\), 382 (9), 141 (100, \([C_1H_9]^+)\). Anal. calc. for C₂₂H₂₂N₂O₆S (442.5): C 59.72, H 5.01, N 6.33, S 7.25; found: C 59.81, H 4.80, N 6.26, S 7.05.

(2RS)-Methyl 3-(naphthalen-2-yl)-2-sulfonamidopropanoate ((±)-47).

Asolution of sulfamide (±)-80 (1.89 g, 4.28 mmol) in ethanol (50 ml) was treated with 5% Pd/C (480 mg) under a hydrogen atmosphere (4 bar) for 4 h. The reaction mixture was filtered through Celite and evaporated in vacuo to afford (±)-47 as a colorless solid (1.06 g, 81%), M.p. 96-98 °C (hexane/EtOAc). IR (CHCl₃): 3373w cm⁻¹ (NH); 3279m (NH); 1735s (C=O); 1346i (SO₂); 1163s (SO₂). ¹H-NMR (200 MHz, CDCl₃): 7.78-7.68 (m, 3 H, ArH); 7.63 (s, 1 H, ArH); 7.53-7.42 (m, 2 H, ArH); 7.31-7.25 (m, 1 H, ArH); 5.52 (d, J = 9.1, 1 H, NH); 4.74 (s, 2 H, NH₂); 4.49-4.36 (m, 1 H, H-C(2)); 3.66 (s, 3 H, COOCH₃); 3.25, 3.15 (AB of ABX, Jₐₓ = 5.7, Jₜₓ = 6.4, Jₐ₋ₜ = 13.5, 2 H, H₂C(3)). ¹³C-NMR (50 MHz, CDCl₃): 173.0; 133.5; 132.2; 132.6; 128.4 (two overlapping signals); 127.8 (two overlapping signals); 127.5; 126.3; 126.0; 57.4; 52.8; 38.9. ESI-MS: 307 (100, \([M - H]^-)\). Anal. calc. for C₁₄H₁₆N₂O₄S (308.4): C 54.53, H 5.23, N 9.08, S 10.40; found: C 54.54, H 5.06, N 8.89, S 10.35.

(2RS)-4-(Naphthalen-2-yl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one ((±)-77).

A solution of sulfamide (±)-47 (1.05 g, 3.41 mmol) and sodium methoxide (277 mg, 5.12 mmol) in methanol (20 ml) was heated to reflux for 10 h. The reaction mixture
was allowed to cool to r.t., and the methanol was evaporated in vacuo. The residual oil was diluted with 1M aq. HCl (50 ml) and extracted with CH$_2$Cl$_2$ (4 x 50 ml). The combined organic extracts were dried (Na$_2$SO$_4$) and evaporated in vacuo to afford (±)-77 as a colorless solid (860 mg, 92%), M.p. > 200 °C decomp. (hexane/EtOAc). IR (CHCl$_3$): 3330w cm$^{-1}$ (NH); 1738w (C=O); 1666m; 1616m; 1331m (SO$_2$); 1262m; 1251m; 1144s (SO$_2$). $^1$H-NMR (200 MHz, (CD$_3$)$_2$SO): 7.89-7.77 (m, 3 H, ArH); 7.71 (s, 1 H, ArH); 7.49-7.38 (m, 3 H, ArH); 6.44 (br. s, 1 H, NH); 4.04-3.99 (m, 1 H, H-C(2)); 3.23, 2.79 (AB of ABX, $J_{AX} = 2.2$, $J_{BX} = 10.2$, $J_{AB} = 14.2$, 2 H, H$_2$C(3)). $^{13}$C-NMR (75 MHz, (CD$_3$)$_2$SO): 171.5; 134.6; 133.1; 132.1; 128.0; 127.9; 127.8; 127.6 (two overlapping signals); 126.2; 125.8; 62.3; 36.9. DEI-MS: 276 (12, M$^+$); 141 (100, [C$_{11}$H$_9$]$^+$). Anal. calc. for C$_{13}$H$_{12}$N$_2$O$_3$S (276.3): C 56.51, H 4.39, N 10.14, S 11.60; found: C 56.70, H 4.59, N 10.05, S 11.24.

β-Alanine benzyester (90) [203].

A solution of β-alanine (4.50 g, 50.51 mmol), p-toluenesulfonic acid monohydrate (11.53 g, 60.61 mmol), and benzyl alcohol (25 ml) in benzene (100 ml) was heated to reflux for 6 h. The benzene was removed by distillation in vacuo, the residue diluted with CH$_2$Cl$_2$ (100 ml) and 1M aq. HCl (100 ml). The organic phase was separated, and the aqueous phase was extracted with CH$_2$Cl$_2$ (1 x 100 ml). The combined organic extracts were washed with 1M aq. NaOH (100 ml), dried (Na$_2$SO$_4$), evaporated in vacuo, and purified by chromatography (CH$_2$Cl$_2$/MeOH 95:5) on silica gel to give 90 as a colorless, highly viscous oil (4.32 g, 48%). $^1$H-NMR (200 MHz, CDCl$_3$): 7.39-7.32 (m, 5 H, ArH); 5.15 (s, 2 H, OCH$_2$Ph); 3.01 (t, $J = 6.2$, 2 H, H$_2$C(3)); 2.52 (t, $J = 6.2$, 2 H, H$_2$C(2)).

(2RS)-Methyl 2-[(2-oxo-1,3-oxazolan-3-yl)sulfonamido]-3-phenylpropanoate ((±)-89).
The oxazolidinone (±)-89 was prepared from DL-phenylalanine methyl ester hydrochloride ((±)-28) (5.00 g, 23.18 mmol) according to Procedure I. Colorless solid (6.88 g, 91%), M.p. 132-133 °C (hexane/EtOAc). IR (CHCl3): 3196m cm⁻¹; 1754s (C=O); 1380m (SO₂); 1223m (C-O); 1175m (SO₂); 1149m (SO₂). ¹H-NMR (200 MHz, CDCl₃): 7.38-7.17 (m, 5 H, ArH); 4.66-4.60 (m, 1 H, H-C(2)); 4.30 (t, J = 7.7, 2 H, H₂C(5)); 3.86 (t, J = 7.7, 2 H, H₂C(4)); 3.77 (s, 3 H, COOCH₃); 3.18, 3.08 (AB of ABX, JAX = 6.0, JBX = 7.1, JAB = 14.2, 2 H, H₂C(3)). ¹³C-NMR (75 MHz, CDCl₃): 171.6; 153.3; 135.3; 129.7; 129.1; 127.7; 62.6; 58.2; 53.1; 45.2; 38.9. DEI-MS: 329 (5, [M+H]+); 269 (7, [M-COOCH₃]+); 237 (17); 182 (12); 177 (10); 162 (100); 150 (24); 118 (26); 91 (67, [C₇H₇]+). Anal. calc. for C₁₃H₁₆N₂O₆S (328.3): C 47.55, H 4.91, N 8.53, S 9.77; found: C 47.48, H 4.84, N 8.51, S 9.67.

(2RS)-Methyl 2-[N-(3-benzyloxycarbonylpropyl)sulfonamido]-3-phenylpropanoate ((±)-91).

Oxazolidinone (±)-89 (1.00 g, 3.05 mmol) was reacted with amine 90 (546 mg, 3.05 mmol) according to Procedure J. Purification by chromatography (hexane/EtOAc 7:3) on silica gel gave (±)-91 as a colorless oil (820 mg, 65%). IR (CHCl₃): 1739s cm⁻¹ (C=O); 1351m (SO₂); 1178m (C-O); 1154s (SO₂). ¹H-NMR (200 MHz, CDCl₃): 7.41-7.16 (m, 10 H, ArH); 5.12 (s, 2 H, OCH₂Ph); 4.92 (d, J = 9.6, 1 H, H-N(4)); 4.90-4.83 (m, 1 H, H-N(6)); 4.29-4.18 (m, 1 H, H-C(2)); 3.75 (s, 3 H, COOCH₃); 3.13, 2.98 (AB of ABX, JAX = 5.8, JBX = 7.5, JAB = 13.7, 2 H, H₂C(3)); 3.17-2.92 (m, 2 H, H-C(7)); 2.49 (t, J = 5.6, 2 H, H-C(8)). ¹³C-NMR (125 MHz, CDCl₃): 172.2; 171.9; 135.5; 135.4; 129.4; 128.7; 128.6; 128.4; 128.3; 127.3; 66.7; 57.1; 52.6; 39.0; 38.5; 33.8. DEI-MS: 421 (1, [M+H]+); 361 (4, [M-COOCH₃]+); 329 (18, [M-CH₂Ph]+); 178 (10, [M-SO₂NHCH₂CH₂COOBn]+); 162 (14); 120 (8); 91 (100, [C₇H₇]+). HR-DEI-MS: 421.1434 ([M+H]+, C₂₀H₂₅N₂O₆S; calc. 421.1433).
(2RS)-Methyl 2-[N-(3-tert-butyloxycarbonylpropyl)sulfonamido]-3-phenyl-propanoate ((±)-98).

Oxazolidinone (±)-89 (3.77 g, 11.48 mmol) was reacted with β-alanine tert-butyl ester hydrochloride (97) (2.09 g, 11.48 mmol) according to Procedure J. Purification by chromatography (hexane/EtOAc 7:3) on silica gel gave (±)-98 as a light yellow oil (2.61 g, 59%). IR (CHCl₃): 1739 m cm⁻¹ (C=O); 1721 m (C=O); 1153 s (SO₂). ¹H-NMR (200 MHz, CDCl₃): 7.38-7.13 (m, 5 H, ArH); 4.94-4.87 (m, 1 H, H-N(3)); 4.86 (d, J = 9.6, 1 H, H-N(4)); 4.36-4.21 (m, 1 H, H-C(2)); 3.78 (s, 3 H, COOCH₃); 3.15 (dd, J = 13.5, 5.6, 1 H, H-C(3)); 3.07-2.97 (m, 1 H, H-C(3)); 3.09-2.89 (m, 2 H, H₂C(7)); 2.38 (t, J = 5.8, 2 H, H₂C(8)); 1.46 (s, 9 H, C(CH₃)₃). ¹³C-NMR (75 MHz, CDCl₃): 172.6; 171.8; 135.8; 129.7; 128.9; 127.6; 81.6; 57.1; 52.7; 39.1; 38.8; 34.8; 28.1. DEI-MS: 387 (1, [M + H]+); 331 (12); 313 (9, [M - OC(CH₃)₃]+); 295 (12, [M - C₇H₇]+); 281 (11); 271 (40); 253 (28); 239 (100); 162 (9); 91 (5, [C₇H₇]+). HR-DEI-MS: 387.1595 ([M + H]+, C₁₇H₂₇N₂O₆S; calc. 387.1590).

(4RS)-tert-Butyl 3-[4-benzyl-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]propanoate ((±)-100).

The sulfamide (±)-98 (150 mg, 0.39 mmol) was cyclized to the corresponding thiazolidine (±)-100 according to Procedure K. Purification by chromatography (hexane/EtOAc 7:3) on silica gel gave (±)-100 as a colorless solid (70 mg, 51%), M.p. 86-88 °C. IR (KBr): 3222 m cm⁻¹ (NH); 1722 s (C=O); 1708 s (C=O); 1350 m (SO₂); 1327 m (SO₂); 1183 m (C-O); 1144 m (SO₂). ¹H-NMR (200 MHz, CDCl₃): 7.43-7.23 (m, 5 H, ArH); 4.75 (d, J = 6.6, 1 H, NH); 4.45-4.35 (m, 1 H, H-C(4′)); 3.88 (t, J = 7.6, 2 H, H₂C(3)); 3.31, 3.16 (AB of ABX, Jₓᵧ = 4.4, Jₓᵧ = 8.5, Jₓᵧ = 14.3, 2 H, H₂C(6′)); 2.67 (t, J = 7.6, 2 H, H₂C(2)); 1.47 (s, 9 H, C(CH₃)₃). ¹³C-NMR (75 MHz, CDCl₃): 169.5; 167.8;
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134.6; 129.6; 129.5; 128.2; 81.7; 61.7; 36.8; 36.6; 33.5; 28.1. DEI-MS: 355 (1, [M + H]+); 298 (60, [M - C(CH₃)₃]+); 281 (34); 270 (25); 253 (25); 120 (17); 91 (100, [C₇H₇]+). Anal. calc. for C₁₆H₂₂N₂O₅S (354.4): C 54.22, H 6.26, N 7.90, S 9.05; found: C 54.35, H 6.49, N 7.80, S 9.16.

(2RS)-2-Amino-3-naphthalen-2-yl-propionic acid ((±)-117) [338].

[Diagram of (±)-117]

To a solution of sodium (1.10 g, 47.85 mmol) in ethanol (35 ml) was added diethyl acetamidomalonate (10.00 g, 46.04 mmol) and 2-bromomethylnaphthalene (10.00 g, 45.23 mmol), and the solution was heated to reflux for 2 h. The ethanol was removed in vacuo, a 50% hydrobromic acid solution (100 ml) was added, and the solution heated to reflux for 12 h. The reaction mixture was filtered, the filtrate neutralized with ammonium hydroxide, and the precipitate was collected by filtration to give (±)-117 as a colorless solid (8.45 g, 87%). M.p. > 200 °C (lit. [337] 263-264 °C). Anal. calc. for C₁₃H₁₃NO₂ (215.3): C 72.54, H 6.09, N 6.51; found: C 72.01, H 6.45, N 6.46.

(2RS)-2-Amino-3-(naphthalen-2-yl)propionic acid methyl ester hydrochloride ((±)-78).

[Diagram of (±)-78]

To a stirred solution of the amino acid (±)-117 (8.45 g, 39.25 mmol) in methanol (100 ml) cooled to 0 °C was added dry HCl gas until no more absorption could be observed. The solution was allowed to stand for 12 h at r.t. and evaporated in vacuo to afford (±)-78 as a colorless solid (quant.), M.p. 174-176 °C. ¹H-NMR (200 MHz, CDCl₃): 7.85-7.79 (m, 3 H, ArH); 7.67 (s, 1 H, ArH); 7.52-7.42 (m, 2 H, ArH); 7.33 (dd, J = 8.3, 1.7,
1 H, ArH): 3.88-3.82 (m, 1 H, H-C(2)); 3.74 (s, 3 H, COOCH₃); 3.28, 3.03 (AB of ABX, 
Jₓₓ = 5.0, Jₓᵧ = 7.9, Jᵧᵧ = 13.5, 2 H, H₂C(3)).

(2RS)-Methyl 3-(naphthalen-2-yl)-2-[2-oxo-1,3-oxazolan-3-yl)sulfonamido]-
propanoate ((±)-56).

![Chemical structure of (±)-56](image)

The oxazolidinone (±)-56 was prepared from 2-naphthylalanine methyl ester hydrochloride ((±)-78) (2.50 g, 9.41 mmol) according to Procedure I. Colorless solid (3.48 g, 98%), M.p. 115-117 °C (hexane/EtOAc). IR (KBr): 3216m cm⁻¹ (NH); 1751s 
(C=O); 1380m (SO₂); 1205m (C-O); 1181m (SO₂). ¹H-NMR (200 MHz, CDCl₃): 7.83-
7.78 (m, 3 H, ArH); 7.64 (s, 1 H, ArH); 7.50-7.42 (m, 2 H, ArH); 7.33-7.27 (m, 1 H, 
ArH); 5.71 (br. s, 1 H, NH); 4.78-4.63 (m, 1 H, H-C(2)); 4.17-3.97 (m, 2 H, H₂C(5));
3.82-3.66 (m, 2 H, H₂C(4)); 3.77 (s, 3 H, COOCH₃); 3.33, 3.20 (AB of ABX, Jₓₓ = 5.4, 
Jₓᵧ = 7.2, Jᵧᵧ = 14.2, 2 H, H₂C(3)). ¹³C-NMR (50 MHz, CDCl₃): 171.4; 153.0; 133.4;
132.7; 132.6; 128.6 (two overlapping signals); 127.8; 127.6; 127.3; 126.5; 126.1; 62.4;
58.2; 53.0; 45.0; 39.1. ESI-MS: 442 (100, [M+Na]+ CH₃CN); 401 (49, [M+Na]+);
8.47; found: C 54.17, H 4.82 N 7.34, S 8.22.

(2RS)-Methyl 2-[N-(3-benzyloxycarbonylpropyl)sulfonamido]-3-(naphthalen-2-
yl)propanoate ((±)-92).

![Chemical structure of (±)-92](image)
Oxazolidinone (±)-56 (470 mg, 1.24 mmol) was reacted with amine 90 (223 mg, 1.25 mmol) according to Procedure J. Purification by chromatography (hexane/EtOAc 7:3) on silica gel gave (±)-92 as a colorless oil (200 mg, 35%). IR (CHCl₃): 1739m cm⁻¹ (C=O); 1350m (SO₂); 1178m (C-O); 1152s (SO₂), 1139s (SO₂). ¹H-NMR (200 MHz, CDCl₃): 7.83-7.81 (m, 3 H, ArH); 7.79 (s, 1 H, ArH); 7.78-7.27 (m, 8 H, ArH); 5.08 (s, 2 H, OCH₂Ph); 4.96 (d, J = 9.1, 1 H, H-N(4)); 4.86 (t, J = 6.6, 1 H, H-N(6)); 4.40-4.29 (m, 1 H, H-C(2)); 3.75 (s, 3 H, COOCH₃); 3.29, 3.16 (AB of ABX, Jₓₓ = 5.4, Jₓᵧ = 7.1, Jᵧᵧ = 13.9, 2 H, C(3)); 3.08-2.88 (m, 2 H, H-C(7)); 2.38 (t, J = 6.0, 2 H, H-C(8)). ¹³C-NMR (75 MHz, CDCl₃): 172.6; 172.2; 135.7; 133.6; 133.2; 132.8; 128.9; 128.7; 128.6; 127.9; 127.9; 127.5; 126.6; 126.2; 66.8; 57.2; 52.8; 39.3; 38.6; 33.7. DEI-MS: 470 (1, M⁺); 438 (4); 411 (2, [M - COOCH₃]⁺); 329 (5, [M - C₇H₇]⁺); 212 (55); 141 (100, [C₁₁H₉]⁺); 91 (61, [C₇H₇]⁺). Anal. calc. for C₂₄H₂₆N₂O₆S (470.5): C 61.26, H 5.57, N 5.95, S 6.81; found: C 61.10, H 5.54 N 5.92, S 6.63.

(2RS)-Methyl 2-[N-(3-carboxypropyl)sulfonamido]-3-(naphthalen-2-yl)propanoate ((±)-93).

A solution of benzyl ester (±)-92 (145 mg, 0.31 mmol) in ethanol (10 ml) and CH₂Cl₂ (2 ml) was treated with 10% Pd/C (14 mg) under a hydrogen atmosphere (4 bar) for 5 h. The reaction mixture was filtered through Celite and evaporated in vacuo to afford (±)-93 as a colorless, highly viscous oil (117 mg, quant.). IR (CHCl₃): 1742m cm⁻¹ (C=O); 1344w (SO₂); 1152s (C-O); 1136s (SO₂). ¹H-NMR (200 MHz, (CD₃)₂SO): 7.88-7.84 (m, 3 H, ArH); 7.76 (s, 1 H, ArH); 7.55-7.37 (m, 3 H, ArH); 4.15-4.05 (m, 1 H, H-C(2)); 3.58 (s, 3 H, COOCH₃); 3.19-3.00 (m, 2 H, H₂C(3)); 2.90-2.64 (m, 2 H, H₂C(7)); 2.21 (t, J = 6.9, 2 H, H₂C(8)). ¹³C-NMR (75 MHz, (CD₃)₂SO): 173.0; 172.6; 134.6; 133.1; 132.1; 127.8; 127.7 (two overlapping signals); 127.6; 127.6; 126.2; 125.7; 57.0; 51.8; 38.2; 37.9; 33.9. DEI-MS: 380 (1, M⁺); 348 (6); 229 (5); 212 (14); 170 (10); 141 (100, [C₁₁H₉]⁺). HR-DEI-MS: 380.1034 (M⁺, C₁₇H₂₆N₂O₆S; calc. 380.1042).
Oxazolidinone \((±)-56\) (500 mg, 1.32 mmol) was reacted with \(β\)-alanine \(t\)-butyl ester hydrochloride \((97)\) (241 mg, 1.32 mmol) according to Procedure J. Purification by chromatography (hexane/EtOAc 7:3) on silica gel gave \((±)-99\) as a colorless oil (350 mg, 61%). IR \((\text{CHCl}_3)\): 1740\(m\) \(\text{cm}^{-1}\) (C=O); 1722\(m\) (C=O); 1150\(s\) (SO2); 1136\(s\) (SO2).

\(1^H\)-NMR (200 MHz, CDCl3): 7.85-7.78 (m, 3 H, ArH); 7.66 (s, 1 H, ArH); 7.53-7.43 (m, 2 H, ArH); 7.33-7.28 (m, 1 H, ArH); 4.92-4.88 (m, 2 H, 2 x NH); 4.41-4.30 (m, 1 H, H-C(2)); 3.76 (s, 3 H, COOCH3); 3.30, 3.19 (AB of ABX, \(J_{AX} = 5.8\), \(J_{BX} = 6.9\), \(J_{AB} = 13.8\), 2 H, H2C(3)); 3.11-2.82 (m, 2 H, H2C(7)); 2.28 (t, \(J = 5.8\), 2 H, H2C(8)). 13C-NMR (75 MHz, CDCl3): 172.6; 171.8; 133.6; 133.2; 128.6 (two overlapping signals); 127.9 (two overlapping signals); 127.5; 126.5; 126.2; 81.6; 57.1; 52.7; 39.3; 38.8; 34.6; 28.1. DEI-MS: 436 (1, \(M^+\)); 239 (16); 212 (70); 168 (16); 141 (100, \([C_11H_9]^+\)). Anal. calc. for \(C_{21}H_{28}N_2O_6S\) (436.5): C 57.78, H 6.46, N 6.42, S 7.35; found: C 57.70, H 6.28 N 6.16, S 7.41.

The sulfamide \((±)-99\) (300 mg, 0.69 mmol) was cyclized to the corresponding thiazolide \((±)-101\) according to Procedure K. Purification by chromatography (hexane/EtOAc 7:3) on silica gel gave \((±)-101\) as a yellow, highly viscous oil (100 mg, 36%). IR (KBr): 1729\(m\) \(\text{cm}^{-1}\) (C=O); 1333\(w\) (SO2); 1150\(s\) (SO2); 1137\(s\) (SO2). \(1^H\)-NMR (200
Experimental Part

165

MHz, CDCl₃): 7.88-7.81 (m, 3 H, ArH); 7.71 (m, 1 H, ArH); 7.56-7.49 (m, 2 H, ArH); 7.38-7.32 (m, 1 H, ArH); 4.67 (d, J = 6.2, 1 H, NH); 4.52-4.45 (m, 1 H, H-C(4')); 3.89 (t, J = 7.6, 2 H, H₂C(3)); 3.47, 3.31 (AB of ABX, Jₓ = 3.9, Jₓ = 8.5, Jₓ = 14.3, 2 H, H₂C(6')); 2.67 (t, J = 7.6, 2 H, H₂C(2)); 1.45 (s, 9 H, C(CH₃)₃). ¹³C-NMR (75 MHz, CDCl₃): 169.5; 167.9; 133.7; 132.1; 129.4; 128.7; 128.0; 127.9; 127.0; 126.0; 11.3; 81.7; 61.7; 36.9; 36.8; 33.5; 28.1. DEI-MS: 404 (5, M⁺); 348 (10); 331 (5, [M - COO'Bu⁺]); 303 (4, [M - COO'Bu⁺]); 168 (6); 141 (100, [C₁₁H₉⁺]). HR-DEI-MS: 404.1398 (M⁺, C₂₀H₂₄N₂O₅S; calc. 404.1406).

(4RS)-3-{{[Naphthalen-2-yl]methyl}-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)}-propionic acid ((±)-94).

Hydrolysis of thiazolidine (±)-101 (100 mg, 0.25 mmol) according to Procedure L afforded (±)-94 as a colorless solid (60 mg, 70%), M.p. 128-131 °C. IR (KBr): 1717s (C=O); 1344m (SO₂); 1167m (SO₂). ¹H-NMR (200 MHz, (CD₃)₂SO): 7.91-7.87 (m, 3 H, ArH); 7.81 (s, 1 H, ArH); 7.54-7.46 (m, 3 H, ArH); 4.68 (dd, J = 9.8, 3.9, 1 H, H-C(4')); 3.75 (t, J = 7.5, 2 H, H₂C(3)); 3.10-2.98 (m, 2 H, H₂C(6')); 2.61 (t, J = 7.5, 2 H, H₂C(2)). ¹³C-NMR (125 MHz, (CD₃)₂SO): 171.3; 168.4; 134.0; 132.9; 127.8; 127.7; 127.6; 127.4 (two overlapping signals); 126.0; 125.6; 60.9; 36.8; 36.0; 32.1. DEI-MS: 348 (4, M⁺); 168 (6); 141 (100, [C₁₁H₉⁺]). HR-DEI-MS: 348.0775 (M⁺, C₁₆H₁₆N₂O₅S; calc. 348.0780).

Methyl 2,2-dimethyl-3-phthalimidopropanoate (105).

To a solution of phthalimide (2.52 g, 17.16 mmol), triphenylphosphine (4.50 g, 17.16 mmol), and methyl 2,2-dimethyl-3-hydroxy-propanoate (104) (1.99 ml, 15.60 mmol)
in dry THF (180 ml) was added diethylazodicarboxylate (2.91 ml, 18.72 mmol), and the solution was stirred at r.t. for 20 h. The reaction was quenched with a sat. aq. NaCl solution (100 ml) and the mixture extracted with EtOAc (3 x 100 ml). The combined organic phases were dried (MgSO₄), evaporated in vacuo and purified by flash chromatography (hexane/EtOAc 6:4) on silica gel to give 105 as a colorless solid (3.60 g, 77%), M.p. 92-94 °C. IR (KBr) : 1767 m cm⁻¹ (C=O); 1719 s (C=O); 1428 m; 1388 m; 1344 m; 1267 m; 1156 m (C-O). 'H-NMR (200 MHz, CDCl₃): 7.88-7.82 (m, 2 H, ArH); 7.77-7.70 (m, 2 H, ArH); 3.85 (s, 2 H, H₂C(3)); 3.73 (s, 3 H, COOCH₃); 1.26 (s, 6 H, C(CH₃)₂). ¹³C-NMR (75 MHz, CDCl₃): 176.5; 168.8; 134.3; 132.1; 123.6; 52.4; 46.2; 43.7; 23.4. DEI-MS: 261 (3, M⁺); 202 (7, [M - COOCH₃]⁺); 160 (100, [M - C(CH₃)₂COOCH₃]⁺). Anal. calc. for C₁₄H₁₅N₀₄ (261.3): C 64.36, H 5.79, N 5.36; found C 64.41, H 5.84, N 5.31.

3-Amino-2,2-diethylpropionic acid (106).

A solution of methyl ester 105 (800 mg, 3.06 mmol) in glacial acetic acid (10 ml), conc. HCl (10 ml), and water (10 ml) was heated to reflux for 16 h. The solution was evaporated in vacuo, the residue diluted with water (50 ml), washed with Et₂O (2 x 50 ml), and purified by ion-exchange chromatography (Dowex WX8) to afford 106 as a colorless solid (243 mg, 67%), M.p. >200 °C (lit. [339] 239 °C). 'H-NMR (200 MHz, D₂O): 3.04 (s, 2 H, CH₂); 1.22 (s, 6 H, (CH₃)₂).

3-(Benzylcarbamato)-2,2-dimethylpropionic acid (107).

To a solution of β- amino acid 106 (573 mg, 4.89 mmol) in 1 M aq. NaOH (20 ml) at 0 °C was added dropwise a solution of benzylchloroformate (0.90 ml, 6.36 mmol) in dioxane (3 ml) over 30 min, and the solution was stirred at r.t. for 5 h. The dioxane was removed in vacuo, the solution made acidic with 1 M aq. HCl (50 ml), and extracted with EtOAc (3 x 50 ml). The combined organic extracts were dried (MgSO₄) and evaporated in vacuo to give 107 as a colorless oil (830 mg, 68%). 'H-NMR (200 MHz,
Experimental Part

CDCl₃: 7.39-7.30 (m, 5 H, ArH); 5.35-5.25 (m, 1 H, NH); 5.16 (s, 2 H, OCH₂Ph); 3.33 (d, J = 6.6, 2 H, H₂C(3)); 1.25 (s, 6 H, (CH₃)₂).

**tert-Butyl 3-(benzylcarbamato)-2,2-dimethylpropanoate (108).**

![Diagram of 108](image)

To a suspension of carboxylic acid 107 (2.02 g, 8.04 mmol) in CH₂Cl₂ (16 ml) in a sealed tube was added conc. H₂SO₄ (0.08 ml). Isobutene (16 ml) was then added at -78 °C, and the solution was shaken at r.t. for 65 h. The reaction mixture was poured in 1M aq. NaOH (50 ml) and extracted with CH₂Cl₂ (3 x 50 ml). The combined organic extracts were dried (Na₂SO₄), evaporated in vacuo, and purified by flash chromatography (hexane/EtOAc 9:1) on silica gel to give 108 as a colorless oil (2.10 g, 85%). IR (CHCl₃): 2981 m cm⁻¹ (CH); 1719 s (C=O); 1514 s; 1369 m; 1314 m; 1144 s (C-O). \(^1\)H-NMR (200 MHz, CDCl₃): 7.38-7.36 (m, 5 H, ArH); 5.32-5.30 (br. s, 1 H, NH); 5.11 (s, 2 H, OCH₂Ph); 3.27 (d, J = 6.2, 2 H, H₂C(3)); 1.44 (s, 9 H, C(CH₃)₃); 1.15 (s, 6 H, C(CH₃)₂). \(^13\)C-NMR (75 MHz, CDCl₃): 176.7; 157.0; 136.9; 128.7; 128.3 (two overlapping signals); 80.9; 66.8; 48.9; 44.0; 28.0; 23.1. FAB-MS: 308 (39, [M+H]+); 252 (100); 234 (26, [M-O′Bu]+); 208 (26); 91 (52, [C₇H₇]⁺). Anal. calc. for C₁₇H₂₅N⁰₄ (307.4): C 66.43, H 8.20, N 4.56, O 20.82; found C 66.62, H 8.11 N 4.74, O 20.96.

**tert-Butyl 3-amino-2,2-dimethylpropanoate (109).**

A solution of β-amino acid 108 (600 mg, 1.95 mmol) in methanol (50 ml) was treated with 10% Pd/C (60 mg) under a hydrogen atmosphere (1 bar) for 3 h. The reaction mixture was filtered and evaporated in vacuo to give 109 as a colorless oil (2.10 g, 85%). IR (CHCl₃): 2979 m cm⁻¹ (CH); 1714 s (C=O); 1474 m; 1392 m; 1380 m; 1151 s (C-O). \(^1\)H-NMR (200 MHz, CDCl₃): 2.68 (s, 2 H, H₂C(3)); 1.44 (s, 9 H, C(CH₃)₃); 1.11 (s, 6 H, C(CH₃)₂). \(^13\)C-NMR (75 MHz, CDCl₃): 176.9; 80.3; 51.6; 45.0; 28.1; 22.9. EI-MS: 173 (2, M⁺); 144 (28); 100 (21, [M-O′Bu]+); 88 (100).
(2RS)-Methyl 2-[(3-tert-butyloxycarbonyl-2,2-dimethylpropyl)sulfonamido]-3-(naphthalen-2-yl)propanoate ((±)-112).

\[
\text{MeOOC} \quad \text{O} \quad \text{O} \\
\text{S} \quad \text{N} \quad \text{O} \\
(\pm)-112
\]

Oxazolidinone (±)-56 (574 mg, 1.52 mmol) was reacted with amine 109 (239 mg, 1.38 mmol) according to Procedure J. Purification by chromatography (hexane/EtOAc 7:3) on silica gel gave (±)-112 as a colorless solid (400 mg, 65%), M.p. 121-122 °C (hexane/EtOAc). IR (KBr): 3263 m cm\(^{-1}\) (NH); 1740 s (C=O); 1705 s (C=O); 1162 s (SO\(_2\)). \(\text{H-NMR (200 MHz, CDCl}_3\)): 7.82-7.78 (m, 3 H, ArH); 7.66 (s, 1 H, ArH); 7.51-7.44 (m, 2 H, ArH); 7.34-7.29 (m, 1 H, ArH); 4.93-4.79 (m, 2 H, 2 x NH); 4.37-4.26 (m, 1 H, H-C(2)); 3.76 (s, 3 H, COOCH\(_3\)); 3.31, 3.16 (AB of ABX, \(J_{ax} = 5.4, J_{bx} = 7.1, J_{ab} = 13.7, 2 \text{H, H}_2\text{C(3)}\)) ; 2.71 (dd, \(J = 12.5, 7.1, 1 \text{H, H-C(7)}\)); 2.51 (dd, \(J = 12.5, 6.6, 1 \text{H, H-C(7)}\)); 1.41 (s, 9 H, C(CH\(_3\))\(_3\)); 1.01 (s, 3 H, CH\(_3\)); 0.91 (s, 3 H, CH\(_3\)). \(\text{C-NMR (75 MHz, CDCl}_3\)): 176.3; 172.8; 133.7; 133.5; 132.8; 128.7; 128.6; 127.9; 127.7; 126.5; 126.1; 81.2; 57.4; 52.7; 50.7; 42.8; 39.3; 27.9; 23.1. DEI-MS : 464 (1, \(M^+\)); 267 (15); 249 (8); 232 (6); 212 (97); 187 (23); 168 (15); 141 (100, \([\text{C}_1\text{H}_9]^+\)). Anal. calc. for \(\text{C}_{23}\text{H}_{32}\text{N}_2\text{O}_6\text{S}\) (464.6): C 59.46, H 6.94, N 6.03, S 6.90; found C 59.69, H 6.86, N 6.03, S 7.10.

(4RS)-tert-Butyl 2,2-dimethyl-3-[[4-[(naphthalen-2-yl)methyl]-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]propanoate ((±)-114).

\[
\text{MeOOC} \quad \text{O} \quad \text{O} \\
\text{S} \quad \text{N} \quad \text{O} \\
(\pm)-114
\]
The sulfamide (±)-112 (340 mg, 0.73 mmol) was cyclized to the corresponding thiazolide (±)-114 according to Procedure K. Purification by chromatography (hexane/EtOAc 8:2) on silica gel gave (±)-114 as a yellow, highly viscous oil (160 mg, 51%). IR (CHCl₃): 1726 s cm⁻¹ (C=O); 1348 m (SO₂); 1294 m (C=O); 1183 s (SO₂); 1144 s (SO₂). H-NMR (200 MHz, CDCl₃): 7.87-7.79 (m, 3 H, ArH); 7.70 (s, 1 H, ArH); 7.55-7.46 (m, 2 H, ArH); 7.36-7.31 (d, J = 8.3, 1.7, 1 H, ArH); 4.66 (d, J = 6.7, 1 H, NH); 4.51-4.42 (m, 1 H, H-C(4')); 3.82 (s, 2 H, H₂C(3)); 3.45, 3.34 (AB of ABX, Jₓ = 4.8, Jᵧ = 7.9, Jₓᵧ = 13.9, 2 H, H₂C(6')); 1.45 (s, 9 H, C(CH₃)₃); 1.19 (s, 3 H, CH₃); 1.14 (s, 3 H, CH₃). C-NMR (75 MHz, CDCl₃): 174.9; 169.4; 133.7; 133.0; 132.4; 129.2; 128.7; 128.0; 127.9; 127.2; 126.8; 126.5; 81.6; 61.6; 48.9; 43.5; 36.9; 27.8; 23.7; 23.4. DEI-MS: 432 (31, M⁺); 376 (15); 359 (17, [M - COO'Bu]⁺); 331 (15, [M - COO'Bu++]); 279 (17); 168 (20); 141 (100, [C₁₁H₉]⁺). HR-DEI-MS: 432.1732 (M⁺, C₂₂₂₈N₂O₅S; calc. 432.1719).

Hydrolysis of thiazolide (±)-114 (100 mg, 0.23 mmol) according to Procedure L afforded (±)-103 as a colorless solid (60 mg, 69%). M.p. 188-189 °C. IR (KBr): 3344 m cm⁻¹ (NH); 3189 m; 1750 s (C=O); 1730 m (C=O); 1333 m (SO₂); 1256 m (C=O); 1190 m (SO₂); 1154 m (SO₂). H-NMR (200 MHz, CD₃OD): 7.84-7.76 (m, 4 H, ArH); 7.47-7.41 (m, 3 H, ArH); 4.53, 3.40, 3.09 (ABX, Jₓ = 3.9, Jᵧ = 10.0, Jₓᵧ = 14.1, 3 H, H-C(4'), H₂C(6')); 3.76 (s, 1 H, H-C(3)); 3.74 (s, 1 H, H-C(3)); 1.19 (s, 3 H, CH₃); 1.17 (s, 3 H, CH₃). C-NMR (75 MHz, CD₃OD): 179.8; 171.9; 135.6; 135.3; 134.3; 129.6; 129.4; 129.0; 128.9 (two overlapping signals); 127.4; 127.1; 63.0; 44.0; 38.7; 24.1. DEI-MS: 376 (7, M⁺); 169 (23); 167 (23); 141 (100, [C₁₁H₉]⁺). HR-DEI-MS: 376.1098 (M⁺, C₁₈H₂₀N₂O₅S; calc. 376.1093).

One signal is under the solvent signal
(2RS)-2-Amino-4-phenylbutyric acid ((±)-234).

![Chemical structure of (±)-234](image)

To a solution of sodium (556 mg, 24.17 mmol) in ethanol (35 ml) was added diethyl acetamidomalonate (5.00 g, 23.02 mmol) and (2-bromoethyl)benzene (4.25 g, 22.96 mmol) and the solution was heated to reflux for 2 h. The ethanol was removed in vacuo, a 50% hydrobromic acid solution (100 ml) was added, and the solution was heated to reflux for 12 h. The reaction mixture was filtered, the filtrate neutralized with ammonium hydroxide, and the precipitate was collected by filtration to give (±)-234 as a colorless solid (643 mg, 16%). M.p. > 200 °C (lit. [340] 290-293 °C).

(2RS)-2-Amino-4-phenylbutyric acid methyl ester hydrochloride ((±)-235).

![Chemical structure of (±)-235](image)

To a stirred solution of the amino acid (±)-234 (643 mg, 3.59 mmol) in methanol (25 ml) cooled to 0 °C was added dry HCl gas until no more absorption could be observed. The solution was allowed to stand for 12 h at r.t. and evaporated in vacuo to afford (±)-235 as a colorless solid (quant.), M.p. 145-147 °C. 1H-NMR (200 MHz, CDCl3): 9.03 (s, 2 H, NH2); 7.31-7.14 (m, 5 H, ArH); 4.20-4.17 (m, 1 H, H-C(2)); 3.70 (s, 3 H, COOCH3); 2.98-2.87 (m, 2 H, H2C(3)); 2.48-2.42 (m, 2 H, H2C(4)).

(2RS)-Methyl 2-[(2-oxo-1,3-oxazolan-3-yl)sulphonamido]-4-phenylbutanoate ((±)-110).

![Chemical structure of (±)-110](image)
The oxazolidinone (±)-110 was prepared from homophenylalanine methyl ester hydrochloride (±)-235 (637 mg, 2.77 mmol) according to Procedure I. Colorless solid (540 mg, 57%), M.p. 87-89 °C (hexane/EtOAc). IR (KBr): 3208 m cm⁻¹ (NH); 1746 s (C=O); 1385 m (SO₂); 1178 m (SO₂). ¹H-NMR (200 MHz, CDCl₃): 7.35-7.21 (m, 5 H, ArH); 5.94 (s, 1 H, NH); 4.46-4.38 (m, 2 H, H₂C(5)); 4.38-4.31 (m, 1 H, H-C(2)); 4.12-3.92 (m, 2 H, H₂C(6)); 3.77 (s, 3 H, COOCH₃), 2.82-2.74 (m, 2 H, H₂C(4)); 2.32-1.98 (m, 2 H, H₂C(3)). ¹³C-NMR (75 MHz, CDCl₃): 172.2; 153.5; 140.3; 128.8; 128.7; 126.6; 62.8; 56.9; 53.1; 45.5; 34.5; 31.3. DEI-MS: 343 (5, [M + H]⁺); 342 (4, M⁺); 283 (2, [M - COOCH₃]⁺); 132 (52); 117 (100); 91 (82, [C₇H₇]⁺). Anal. calc. for C₉H₁₈N₂O₆S (342.4): C 49.11, H 5.30, N 8.18, S 9.37; found C 49.23, H 5.35, N 8.01, S 9.35.

(2RS)-Methyl 2-[N-(3-tert-butyloxycarbonyl-2,2-dimethylpropyl)sulfonamido]-4-phenylbutanoate ((±)-111).

Oxazolidinone (±)-110 (747 mg, 2.18 mmol) was reacted with amine 109 (340 mg, 1.96 mmol) according to Procedure J. Purification by chromatography (hexane/EtOAc 7:3) on silica gel gave (±)-111 as a colorless solid (58%, M.p. 79-81 °C (hexane/EtOAc). IR (CHCl₃): 1739 s cm⁻¹ (C=O); 1711 m (C=O); 1369 m (SO₂); 1348 m (SO₂); 1309 m; 1145 vs (SO₂). ¹H-NMR (200 MHz, CDCl₃): 7.34-7.12 (m, 5 H, ArH); 5.02-4.97 (m, 2 H, 2 x NH); 4.15-3.99 (m, 1 H, H-C(2)); 3.75 (s, 3 H, COOCH₃); 3.02 (d, J = 6.6, 2 H, H₂C(8)); 2.78-2.70 (m, 2 H, H₂C(4)); 2.24-1.93 (m, 2 H, H₂C(3)); 1.44 (s, 9 H, C(CH₃)₃); 1.19 (s, 3 H, CH₃); 1.17 (s, 3 H, CH₃). ¹³C-NMR (75 MHz, CDCl₃): 176.5; 173.4; 140.6; 128.8; 128.7; 126.5; 81.4; 55.7; 52.8; 51.1; 43.1; 34.8; 31.4; 28.0; 23.4. DEI-MS: 429 (1, [M + H]⁺); 372 (26); 313 (46); 285 (68, [M - C(CH₃)₂COO'Bu]⁺); 256 (14); 196 (32); 117 (100); 91 (43, [C₇H₇]⁺). Anal. calc. for C₂₀H₃₂N₂O₆S (428.6): C 56.05, H 7.53, N 6.54, S 7.48; found C 56.27, H 7.78, N 6.49, S 7.47.
(4RS)-*tert*-Butyl 2,2-dimethyl-3-[4-phenethyl-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]propanoate ((±)-113).

The sulfamide (±)-111 (450 mg, 1.05 mmol) was cyclized to the corresponding thiazolide (±)-113 according to Procedure K. Purification by chromatography (hexane/EtOAc 8:2) on silica gel gave (±)-113 as a colorless solid (270 mg, 65%), M.p. 98-99 °C (hexane/EtOAc). IR (KBr): 3165m cm⁻¹ (NH); 1743* (C=O); 1702j (C=O); 1351m (S02); 1277m (C-O); 1180s (SO2); 1151m (SO2). 1H-NMR (200 MHz, CDCl3): 7.38-7.17 (m, 5 H, ArH); 5.05 (d, J = 7.5, 1 H, NH); 4.20-4.09 (m, 1 H, H-C(4')); 3.81 (s, 2 H, H2C(3)); 2.95-2.72 (m, 2 H, H2C(7')); 2.42-2.03 (m, 2 H, H2C(6')); 1.48 (s, 9 H, C(CH3)3); 1.22 (s, 6 H, CH3). 13C-NMR (75 MHz, CDCl3): 175.0; 170.0; 139.7; 129.0; 128.8; 126.9; 81.6; 60.0; 48.8; 43.5; 33.0; 31.6; 27.9; 23.6. NH4-DCl-MS: 414 (1, [M + NH4]+); 397 (1, [M + H]+); 341 (29); 323 (42, [M - O'Bu]+); 295 (17, [M - COO'Bu]+); 236 (100). Anal. calc. for C19H28N2O5S (396.5): C 57.55, H 7.12, N 7.07, S 8.09; found C57.54, H7.32, N7.08, S 8.07.

(4RS)-2,2-Dimethyl-3-[4-phenethyl-1,1,3-trioxo-(1,2,5-thiadiazolan-2-yl)]propionic acid ((±)-102).

Hydrolysis of thiazolide (±)-113 (190 mg, 0.48 mmol) according to Procedure L afforded (±)-102 as a colorless solid (140 mg, 86%), M.p. 105.5-106 °C (hexane/EtOAc). IR (KBr): 3199m cm⁻¹ (NH); 1735s (C=O); 1325m (SO2); 1264m (C-O); 1180m (SO2); 1146m (SO2). 1H-NMR (200 MHz, CD3OD): 7.33-7.15 (m, 5 H, ArH); 4.12-4.06 (m, 1 H, H-C(4')); 3.74 (s, 2 H, H2C(3)); 2.87-2.67 (m, 2 H, H2C(7'));
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2.26-1.90 (m, 2 H, H2C(6')); 1.22 (s, 6 H, CH3). 13C-NMR (75 MHz, CD3OD): 179.4; 172.7; 142.0; 129.9; 127.6; 60.8; 44.0; 34.5; 32.7; 24.1. NH4-DCl-MS: 341 (9, [M + H]+); 323 (12, [M - OH]+); 295 (4, [M - COOH]+); 236 (12); 218 (12); 134 (43); 104 (74), 91 (100, [C7H7]+). Anal. cale. for C15H2oN205S (340.4): C 52.93, H 5.92, N 8.23, S 9.42; found C 52.99, H 5.78, N 8.09, S 9.33.

Methyl 3-isocyanatopropanoate (116).

\[
\begin{align*}
\text{MeOOC} & \quad 2 \\
\text{N} & \quad \text{C} \\
\end{align*}
\]

To a solution of sodium azide (10.60 g, 0.16 mol) in toluene (50 ml) was added a solution of 3-carbomethoxypropionyl chloride (115) (12.26 g, 0.10 mol) over 20 min. The solution was then heated to 70 °C for 30 min and at reflux for 1.5 h. The toluene was removed by distillation under reduced pressure and the product distilled in vacuo (60 °C/20 mmHg) to give 116 as a colorless oil (7.01 g, 57%). 1H-NMR (200 MHz, CDCl3): 3.76 (s, 3 H, COOCH3); 3.62 (t, J = 6.4, 2 H, H2C(3)); 2.64 (t, J = 6.4, 2 H, H2C(2)).

(4RS)-3-(4-Benzyl-1,3-dioxo-2,5-imidazolan-2-yl)propionic acid ((±)-118).

\[
\begin{align*}
\text{N} & \quad \text{C} \\
\end{align*}
\]

To a solution of DL-phenylalanine ((±)-26) (268 mg, 1.63 mmol) and sodium hydroxide (100 mg, 2.5 mmol) in water (20 ml) was added isocyanate 116 (210 mg, 1.63 mmol) in water (10 ml). The solution was stirred at r.t. for 30 min and then at 50 °C for 1 h. The reaction mixture was then made acidic by the addition of 6M aq. HCl (10 ml) and heated to 100 °C for 1 h. The reaction mixture was allowed to cool to r.t. and extracted with EtOAc (3 x 50 ml). The combined organic extracts were dried (MgSO4) and evaporated in vacuo to give (±)-118 as a colorless solid (340 mg, 80%), M.p. 128-131 °C (hexane/EtOAc). IR (KBr): 3228m cm⁻¹ (COOH); 3100m (COOH); 1767m (C=O); 1724s (C=O); 1458m; 1422m; 1224m (C-O). 1H-NMR (200 MHz, (CD3)2SO): 12.29

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*One signal is under the solvent signal.*
(s, 1 H, COOH); 8.24 (s, 1 H, NH); 7.34-7.15 (m, 5 H, ArH); 4.39-4.34 (m, 1 H, H-C(4')); 3.43-3.30 (m, 2 H, H₂C(3)); 3.05-2.87 (m, 2 H, H₂C(6')); 2.19-2.10 (m, 2 H, H₂C(2)). ¹³C-NMR (75 MHz, (CD₃)₂SO): 173.5; 172.0; 156.3; 135.4; 129.8; 128.2; 126.9; 56.9; 36.5; 33.3; 31.7. DEI-MS: 262 (10, M⁺); 91 (100, [C₇H₇]⁺). Anal. calc. for C₁₃H₁₄N₂O₄ (262.3): C 59.54, H 5.38, N 10.68; found: C 59.49, H 5.21 N 10.66.

(4RS)-tert-Butyl-3-(4-benzyl-1,3-dioxo-2,5-imidazolan-2-yl)propionate ((±)-120).

To a suspension of carboxylic acid (±)-118 (1.44 g, 5.49 mmol) in CH₂Cl₂ (25 ml) in a sealed tube was added conc. H₂SO₄ (0.1 ml). Isobutene (25 ml) was then added at -78 °C, and the solution was shaken at r.t. for 72 h. The reaction mixture was poured in 1M aq. NaOH (50 ml) and extracted with EtOAc (3 x 50 ml). The combined organic extracts were dried (Na₂SO₄) and evaporated in vacuo to give (±)-120 as a colorless oil (1.62 g, 93%), M.p. 125-127 °C (hexane/EtOAc). IR (KBr): 3322 m cm⁻¹ (NH); 1778 m (C=O); 1722 m (C=O); 1702 s (C=O); 1456 m. ¹H-NMR (200 MHz, CDCl₃): 7.38-7.17 (m, 5 H, ArH); 5.53 (s, 1 H, NH); 4.25-4.19 (m, 1 H, H-C(4')); 3.71 (t, J = 7.5, 2 H, H₂C(3')); 3.28, 2.83 (AB of ABX, Jₐₓ = 3.5, J₉x = 8.9, J₉ₐ = 13.9, 2 H, H₂C(6')); 2.46 (t, J = 7.5; 2 H, H₂C(2)); 1.44 (s, 9 H, C(CH₃)₃). ¹³C-NMR (75 MHz, CDCl₃): 173.2; 170.1; 157.4; 135.3; 129.6; 129.1; 127.7; 81.3; 58.4; 37.9; 34.5; 33.4; 28.1. FAB-MS: 319 (41, [M + H]⁺); 263 (100); 245 (54, [M - OC(CH₃)₃]⁺). Anal. calc. for C₁₇H₂₂N₂O₄ (318.4): C 64.13, H 6.96, N 8.80; found: C 63.91, H 6.77 N 8.80.

(4RS)-3-{4-[(Naphthalen-2-yl)methyl]-1,3-dioxo-2,5-imidazolan-2-yl}propionic acid ((±)-119).
To a solution of DL-napthylalanine ((±)-117) (1.00 g, 4.65 mmol) and sodium hydroxide (200 mg, 3.0 mmol) in water (50 ml) was added isocyanate 116 (600 mg, 4.65 mmol) in water (10 ml). The solution was stirred at r.t. for 30 min and then at 50 °C for 1 h. The reaction mixture was then made acidic by the addition of 6M aq. HCl (20 ml) and heated to 100 °C for 1 h. The reaction mixture was allowed to cool to r.t. and the product collected by filtration and dried in vacuo to give (±)-119 as a colorless solid (717 mg, 49%), M.p. 144-146 °C (hexane/EtOAc). IR (KBr): 3289m cm⁻¹ (COOH); 1756m (C=O); 1698s (C=O); 1456m; 1424m. ¹H-NMR (200 MHz, (CD₃)₂SO): 12.24 (s, 1 H, COOH); 8.30 (s, 1 H, NH); 7.92-7.83 (m, 3 H, ArH); 7.70 (s, 1 H, ArH); 7.55-7.45 (m, 2 H, ArH); 7.36 (dd, J = 8.3, 1.7, 1 H, ArH); 4.48-4.43 (m, 1 H, H-C(4')); 3.45-3.37 (m, 2 H, H₂C(3)); 3.20, 3.08 (AB of ABX, J₆,J₇ = 4.8, J₈,J₉ = 6.0, J₉,J₁₀ = 13.9, 2 H, H₂C(6')); 2.32-2.09 (m, 2 H, H₂C(2)). ¹³C-NMR (75 MHz, (CD₃)₂SO): 173.6; 172.0; 156.4; 133.4; 133.0; 132.1; 128.2; 128.0; 127.7; 127.6 (two overlapping signals); 126.2; 125.8; 57.1; 36.9; 33.5; 31.8. DEI-MS: 312 (6, M⁺); 141 (100, [C₇H₁₆N₂O₄]⁺). Anal. calc. for C₁₇H₁₆N₂O₄ (312.3): C 65.38, H 5.16, N 8.97; found: C 65.10, H 5.19 N 8.95.

4.5 Experimental Part for Chapter 3

Procedure M. Coupling of a Bromo-1,1'-binaphthyl with a Weinreb Amide.

To a solution of bromo-1,1'-binaphthyl (0.50 mmol) and Weinreb amide (1.00 mmol) in dry THF (25 ml) at -78 °C under an argon atmosphere was added dropwise n-BuLi (1.6M soln. in hexanes, 2.00 mmol) and the solution stirred at this temperature for 10 min. The reaction was quenched with a sat. aq. NaHCO₃ solution (50 ml) and the mixture extracted with CH₂Cl₂ (3 x 50 ml). The combined organic extracts were dried (Na₂SO₄), evaporated in vacuo, and purified by chromatography (EtOAc) on silica gel.

Procedure N. Quaternization of an Alkaloid.

A solution of alkaloid (0.50 mmol) and p-trifluoromethylbenzylbromide (0.50 mmol) in THF (10 ml) was heated to reflux for 72 h. The reaction mixture was then evaporated in vacuo and purified by chromatography (CH₂Cl₂/MeOH 95:5) on silica gel.

Procedure O. Acylation of an Alkaloid.

To a solution of alkaloid (0.10 mmol) and 4-dimethylaminopyridine (0.25 mmol) in CH₂Cl₂ (25 ml) was added 4-chlorobenzoyl chloride (0.25 mmol), and the solution was
stirred at r.t. for 4 h. The reaction was quenched with a sat. aq. NaHCO₃ solution (25 ml) and the mixture extracted with CH₂Cl₂ (3 x 25 ml). The combined organic extracts were dried (Na₂SO₄), evaporated in vacuo, and purified by chromatography (CH₂Cl₂/MeOH/NH₄OH 97:2:1) on silica gel.

(3R,4S,8R)-N-Methoxy-N-methyl-3-vinyl-1-azabicyclo[2.2.2]octane-8-carboxamide ((+)-167).

To a solution of quinuclidine (+)-165 (130 mg, 0.78 mmol) in acetone (10 ml) cooled to 0 °C was added chromium(VI) oxide (94 mg, 0.94 mmol) and conc. sulfuric acid (0.42 ml, 7.78 mmol), and the solution was stirred at r.t. for 5 h. The reaction mixture was then neutralized with 1M aq. NaOH (ca. 8 ml), washed with CH₂Cl₂ (50 ml), filtered, and purified by ion-exchange chromatography. To the residue was added CH₂Cl₂ (100 ml) and phosphorous pentachloride (145 mg, 0.72 mmol), and the solution was heated to reflux for 4 h. The solution was then cooled to 0 °C, N,O-dimethylhydroxylamine hydrochloride (68 mg, 0.72 mmol) was added followed by triethylamine (dropwise up to pH 9), and the solution was stirred at r.t. for 3 h. The reaction was quenched with a sat. aq. NaHCO₃ solution (100 ml), the organic phase separated and the aqueous phase extracted with CH₂Cl₂ (2 x 100 ml). The combined organic extracts were dried (Na₂SO₄), evaporated in vacuo, and purified by chromatography (CH₂Cl₂/MeOH/NH₄OH 90:9:1) on silica gel to give (+)-167 as a yellow oil (76 mg, 44%). [α]D° +121.1 (c = 1.00, CHCl₃). IR (CHCl₃): 2939m cm⁻¹; 1658s (C=O); 1456w; 1178w; 1136w; 909m (CH=CH₂). ¹H-NMR (200 MHz, CDCl₃): 6.11-5.94 (m, 1 H, H-C(10)); 5.10-5.04 (m, 1 H, H-C(11)); 5.00 (d, J = 0.8, 1 H, H-C(11)); 3.83-3.71 (m, 1 H, H-C(8)); 3.75 (s, 3 H, OCH₃); 3.22 (s, 3 H, NCH₃); 3.02-2.77 (m, 4 H); 2.32-2.16 (m, 2 H); 1.84-1.77 (m, 1 H); 1.68-1.58 (m, 2 H); 1.53-1.38 (m, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 140.7; 114.9; 61.4; 55.3; 49.0; 48.7; 40.2; 27.7; 26.5; 22.6. EI-MS: 224 (10, M⁺); 193 (34, [M - OMe]⁺); 164 (21, [M - N(Me)OMe]⁺); 136 (100, [M - CON(Me)OMe]⁺). EI-HRMS: 224.1531 (M⁺, C₁₂H₂₀N₂O₂, calc. 224.1525).

₉Two signals are missing.
(3R,4S,8R)-N-Methoxy-N-methyl-3-ethyl-1-azabicyclo[2.2.2]octane-8-carboxamide ((+)-164).

A solution of olefin (+)-167 (90 mg, 0.40 mmol) in ethanol (10 ml) was treated with 10% Pd/C (10 mg) under a hydrogen atmosphere (2 bar) for 3 h. The reaction mixture was filtered through Celite and evaporated in vacuo to give (+)-164 as a colorless oil (quant.). \([\alpha]_D^20 = +111.5\) (c = 1.00, CHCl3). IR (CHCl3): 2937* cm\(^{-1}\); 2873 m; 1657* (C=O); 1456 m; 983 m (N-O). \(^1\)H-NMR (200 MHz, CDCl3): 3.75 (s, 3 H, OCH3); 3.75-3.65 (m, 1 H, H-C(8)); 3.22 (s, 3 H, NCH3); 2.98-2.40 (m, 4 H); 2.28-2.10 (m, 1 H); 1.74-1.26 (m, 7 H); 0.86 (t, J = 7.1, 3 H, H3C(11)). \(^13\)C-NMR (75 MHz, CDCl3): 61.4; 55.3; 50.7; 48.9; 37.5; 27.5; 25.8; 25.3; 22.4. EI-MS: 226 (2, M\(^+\)); 195 (41, [M - OMe]\(^+\)); 166 (51, [M - N(Me)OMe]\(^+\)); 138 (100, [M - CON(Me)OMe]\(^+\)). EI-HRMS: 226.1681 (M\(^+\), C\(_{12}\)H\(_{22}\)N\(_2\)O\(_2\); calc. 226.1682).

Methyl 3-hydroxy-2-naphthoate (169).

To a stirred solution of 3-hydroxy-2-naphthoic acid (168) (20.00 g, 106.28 mmol) in methanol (100 ml) cooled to 0 °C was added dry HCl gas until no more absorption could be observed. The solution was then heated to reflux for 2 h, left to stand at r.t. for 12 h, and evaporated in vacuo to give 169 as a light brown solid (quant.), M.p. 74-75 °C (lit. [341] 72 °C). \(^1\)H-NMR (200 MHz, CDCl3): 10.43 (s, 1 H, OH); 8.50 (s, 1 H, ArH); 7.83-7.79 (m, 1 H, ArH); 7.72-7.67 (m, 1 H, ArH); 7.55-7.47 (m, 1 H, ArH); 7.37-7.29 (m, 1 H, ArH); 7.32 (s, 1 H, ArH); 4.04 (s, 3 H, COOCH3).

7-Bromonaphthalen-2-ol (171).
To a mechanically stirred solution of triphenylphosphine (14.41 g, 54.94 mmol) in acetonitrile (12.5 ml) was added dropwise bromine (2.82 ml, 54.94 mmol) at 0 °C. The solution was allowed to reach r.t., and a solution of 2,7-dihydroxynaphthalene (170) (8.00 g, 45.95 mmol) in acetonitrile (10 ml) was added in one portion. The reaction mixture was heated to 60-70 °C for 30 min, and the acetonitrile was distilled off under reduced pressure. The reaction mixture was then heated to 250 °C for 1 h, cooled down to r.t., and dissolved in CH$_2$Cl$_2$ (200 ml). The solution was washed with 1M aq. NaOH (200 ml), acidified with 1M aq. HCl (250 ml), and extracted with CH$_2$Cl$_2$ (3 x 200 ml). The combined organic extracts were dried (MgSO$_4$), evaporated in vacuo, and purified by chromatography (CH$_2$Cl$_2$) on silica gel to give 171 as a colorless solid (7.11 g; 64%), M.p. 128-130 °C. $^1$H-NMR (200 MHz, CDCl$_3$): 7.84 (d, $J = 1.9$, 1 H, ArH); 7.72 (d, $J = 8.7$, 1 H, ArH); 7.63 (d, $J = 8.7$, 1 H, ArH); 7.40 (dd, $J = 8.7$, 1.9, 1 H, ArH); 7.11 (dd, $J = 8.7$, 2.3, 1 H, ArH); 7.06 (d, $J = 2.3$, 1 H, ArH); 5.14 (br. s, 1 H, OH).

(aRS)-Methyl 7'-bromo-2,2'-dihydroxy-1,1'-binaphthalen-3-ylcarboxylate ((±)-173).

To a degassed solution of methyl 3-hydroxynaphthoate (169) (4.53 g, 22.41 mmol), 7-bromonaphthalen-2-ol (171) (5.00 g, 22.41 mmol), and copper(II) chloride (12.05 g, 89.64 mmol) in methanol (800 ml) was slowly added tert-butylamine (37.84 ml, 358.56 mmol), and the solution was heated to 50 °C for 2 h. The reaction mixture was then allowed to cool to r.t., 1M aq. HCl (400 ml) was added, and the methanol was evaporated in vacuo. Water (100 ml) was added and the solution extracted with CH$_2$Cl$_2$ (500 ml). The organic phase was washed with water (300 ml) and a sat. aq. NaHCO$_3$ solution (300 ml), dried (MgSO$_4$), evaporated in vacuo, and purified by chromatography (CH$_2$Cl$_2$) on silica gel to give (±)-173 as a light yellow solid (7.46 g, 79%), M.p. 229-232 °C. IR (CHCl$_3$): 1684$^m$ cm$^{-1}$ (C=O); 1616$^w$; 1503$^m$; 1445$^w$; 1433$^w$; 1340$m$; 1322$m$; 1279$^w$; 1183$m$; 1156$s$; 1136$s$. $^1$H-NMR (200 MHz, CDCl$_3$): 10.88 (s, 1 H, OH); 8.76 (s, 1 H, ArH); 7.99-7.94 (m, 1 H, ArH); 7.89 (d, $J = 8.7$, 1 H, ArH); 7.74 (d, $J = 8.7$, 1 H, ArH); 7.44-7.35 (m, 4 H, ArH); 7.22-7.13 (m, 2 H, ArH);
Experimental Part

To a solution of binaphthol (±)-173 (100 mg, 0.23 mmol) in CH$_2$Cl$_2$ (10 ml) was added at 0 °C triethylamine (0.08 ml, 0.58 mmol) followed by (+)-camphor-10-sulfonyl chloride (128 mg, 0.51 mmol). The solution was stirred at 0 °C for 3 h and then at r.t. for 2 h. The reaction was quenched with water (50 ml) and the mixture extracted with CH$_2$Cl$_2$ (3 x 50 ml). The combined organic extracts were dried (MgSO$_4$), evaporated in vacuo, and purified by chromatography (CH$_2$Cl$_2$/EtOAc 99:1) on silica gel.

(aS)-(+-)-175: colorless solid (80 mg, 40%), M.p = 105-107 °C. [α]$_D^{+}$ = +29.1 (c = 1.00, CHCl$_3$). IR (CHCl$_3$): 2961s cm$^{-1}$; 1746s (C=O); 1496m; 1453m; 1378s (SO$_2$); 1365s (SO$_2$); 1290m; 1189m; 1167s (SO$_2$). $^1$H-NMR (200 MHz, CDCl$_3$): 8.66 (s, 1 H, ArH); 8.07-8.01 (m, 2 H, ArH); 7.86-7.80 (m, 2 H, ArH); 4.01 (s, 3 H, COOCH$_3$); 3.05, 2.58 (AB, $J_{AB}$ = 15.0, 2 H, CH$_2$SO$_2$); 3.02, 2.87 (AB, $J_{AB}$ = 14.7, 2 H, CH$_2$SO$_2$); 2.31-1.72 (m, 10 H); 1.53-1.14 (m, 4 H); 0.88 (s, 3 H, CH$_3$); 0.77 (s, 3 H, CH$_3$); 0.66 (s, 3 H, CH$_3$); 0.59 (s, 3 H, CH$_3$). $^{13}$C-NMR (75 MHz, CDCl$_3$)$^{10}$: 213.8; 213.7; 166.1; 147.2; 143.0; 134.9; 134.6; 131.2; 130.1; 130.3; 130.1 (two overlapping signals); 129.9; 129.5; 128.5; 127.8; 126.9; 126.2; 125.2; 122.6; 122.2; 121.5; 58.0; 57.8; 52.8; 49.3; 49.2; 47.8; 47.7; 42.8; 42.8; 42.3; 42.3; 26.8; 26.7; 24.9; 24.8; 19.6; 19.4; 19.3 (two overlapping signals).

10 One signal is missing in the aromatic region.
DEI-MS: 852/850 (1/1, $M^+$ ($^{81}$Br/$^{79}$Br)); 821/819 (1/1, [M - OCH$_3$]$^+$); 638/636 (80/75); 424/422 (100/99). Anal. calc. for C$_{42}$H$_{43}$BrO$_{10}$S$_2$ (851.8): C 59.22, H 5.09, S 7.53, Br 9.38; found: C 59.08, H 5.11, S 7.28, Br 9.10.

(aR)-(--)-176: colorless solid (80 mg, 40%), M.p = 101-104 °C. [α]$_D^{25}$ = -36.6 (c = 1.00, CHCl$_3$). IR (CHCl$_3$): 2962 w cm$^{-1}$; 1747 s (C=O); 1496 w; 1454 w; 1367 m (SO$_2$); 1367 m (SO$_2$); 1290 w; 1189 m; 1167 s (SO$_2$). $^1$H-NMR (200 MHz, CDCl$_3$): 8.66 (s, 1 H, ArH); 8.08-8.03 (m, 2 H, ArH); 7.89-7.81 (m, 2 H, ArH); 7.63-7.42 (m, 3 H, ArH); 7.34-7.33 (m, 1 H, ArH); 7.22-7.18 (m, 1 H, ArH); 4.02 (s, 3 H, COOCH$_3$); 3.32, 2.46 (AB, $J_{AB}$ = 14.9, 2 H, CH$_2$SO$_2$); 3.19, 2.36 (AB, $J_{AB}$ = 14.5, 2 H, CH$_2$SO$_2$); 2.28-1.73 (m, 10 H); 1.42-1.19 (m, 4 H); 0.80 (s, 3 H, CH$_3$); 0.74 (s, 3 H, CH$_3$); 0.54 (s, 3 H, CH$_3$); 0.48 (s, 3 H, CH$_3$). 13C-NMR (75 MHz, CDCl$_3$): 213.8; 213.6; 166.2; 147.0; 143.1; 134.9; 134.5; 131.2 (two overlapping signals); 130.4; 130.3; 130.2; 129.8; 129.5; 128.5; 127.7; 126.9; 126.0; 125.5; 122.6; 122.5; 121.7; 58.0; 57.8; 52.8; 49.5; 49.3; 47.7; 47.5; 42.8 (two overlapping signals); 42.3 (two overlapping signals); 26.7 (two overlapping signals); 24.8; 24.6; 19.5; 19.4; 19.2; 19.2. DEI-MS: 852/850 (1/1, $M^+$ ($^{81}$Br/$^{79}$Br)); 821/819 (1/1, [M - OCH$_3$]$^+$); 638/636 (97/87); 424/422 (96/100). Anal. calc. for C$_{42}$H$_{43}$BrO$_{10}$S$_2$ (851.8): C 59.22, H 5.09, S 7.53, Br 9.38; found: C 58.94, H 5.27, S 7.28, Br 9.11.

(aS)- resp. (aR)-Methyl 7'-bromo-2,2'-dimethoxy-1,1'-binaphthalen-3-ylcarboxylate ([−]- resp. (+)-177).

(A solution of binaphthyl (+)-175 (respectively (−)-176) (760 mg, 0.89 mmol) in methanol (50 ml) and 1M aq. NaOH (25 ml) was heated to reflux for 20 h. The methanol was evaporated in vacuo, 1M aq. HCl (60 ml) added and the solution extracted with CH$_2$Cl$_2$ (3 x 60 ml). The combined organic extracts were dried (MgSO$_4$) and evaporated in vacuo. The residue was dissolved in acetone (100 ml), and potassium hydroxide (400 mg, 7.12 mmol) was added. After stirring for 30 min, dimethyl sulfate

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11One signal is missing in the aromatic region.
(0.51 ml, 5.34 mmol) was added and the solution heated to reflux for 3 h. The reaction was quenched with 1M aq. HCl (50 ml), the acetone was evaporated in vacuo, and the solution extracted with CH₂Cl₂ (3 x 50 ml). The combined organic extracts were dried (Na₂SO₄), evaporated in vacuo, and purified by chromatography (hexane/EtOAc 8:2) on silica gel to afford (aS)-(-)-177 (respectively (aR)-(+)177) as a colorless, amorphous solid (389 mg, 97%). IR (CHCl₃): 1705.$ cm⁻¹ (C=O); 1257m (C-O); 1175m (C-O); 1150m (C-O); 1139m (C-O). ¹H-NMR (200 MHz, CDCl₃): 8.55 (s, 1 H, ArH); 8.00-7.96 (m, 2 H, ArH); 7.74 (d, J = 8.7, 1 H, ArH); 7.50-7.30 (m, 4 H, ArH); 7.23 (d, J = 1.7, 1 H, ArH); 7.12-7.07 (m, 1 H, ArH); 6.01 (s, 3 H, OCH₃); 3.79 (s, 3 H, OCH₃). ¹³C-NMR (75 MHz, CDCl₃): 167.3; 155.9; 154.7; 135.9; 135.5; 133.6; 130.2; 129.9; 129.4; 128.7; 127.6; 127.4; 127.2; 126.6; 125.8; 125.5; 125.0; 121.7; 118.1; 113.8; 61.9; 56.5; 52.5. DEI-MS: 452/450 (100/100, M⁺ (81Br/79Br)). Anal. calc. for C₂₄H₁₉BrO₄ (451.3): C 63.87, H 4.24, Br 17.70; found: C63.93, H4.22, Br 17.59.

(aS)-(-)-177: [α]D⁻² = -43.5 (c = 1.00, CHCl₃).

(aR)-(+)177: [α]D⁺² = +44.0 (c = 1.00, CHCl₃).

To a solution of binaphthyl (-)-177 (respectively (+)-177) (360 mg, 0.80 mmol) in CH₂Cl₂ (30 ml) at -78 °C under an argon atmosphere was added diisobutylaluminium hydride (1M soin. in hexane, 3.19 ml, 3.19 mmol) and the solution was stirred at r.t. for 2.5 h. The reaction was quenched with a sat. aq. NaCl solution (50 ml), the organic phase separated, and the aqueous phase extracted with CH₂Cl₂ (2 x 50 ml). The combined organic extracts were dried (MgSO₄), evaporated in vacuo, and purified by chromatography (CH₂Cl₂/MeOH 99:1) on silica gel to give (aS)-(+)178 (respectively (aR)-(−)-178) as a colorless, amorphous solid (243 mg, 72%). IR (CHCl₃): 3422m cm⁻¹ (OH); 1611m; 1500m; 1255s (C-O). ¹H-NMR (200 MHz, CDCl₃): 8.76-7.88 (m, 3 H, ArH); 7.75 (d, J = 8.7, 1 H, ArH); 7.51-7.37 (m, 3 H, ArH); 7.30-7.21 (m, 2 H, ArH);
7.11-7.07 (m, 1 H, ArH); 5.04-4.88 (m, 2 H, ArCH2OH); 3.80 (s, 3 H, OCH3); 3.41 (s, 3 H, OCH3). 13C-NMR (75 MHz, CDCl3): 156.0; 155.0; 135.5; 134.0; 133.8; 131.0; 130.2; 129.9; 128.5; 128.3; 127.7; 127.5; 127.4; 126.5; 125.3; 125.3; 124.0; 121.7; 118.6; 113.9; 62.5; 60.8; 56.6. DEI-MS: 424/422 (97/100, M+ (81Br/79Br)). DEI-HRMS: 422.0516 (M+, C23H19BrO3, calc. 422.0518).

(aS)-(+)-178: $[\alpha]_D^{+} = +63.2$ (c = 1.00, CHCl3).

(aR)-(−)-178: $[\alpha]_D^{+} = -68.7$ (c = 1.00, CHCl3).

(aS)- resp. (aR)-7'-Bromo-2,2'-dimethoxy-3-methoxymethyl-1,1'-binaphthalene ((−)- resp. (+)-179).

To a solution of binaphthyl (+)-178 (respectively (−)-178) (180 mg, 0.43 mmol) in acetone (20 ml) was added dimethyl sulfate (0.12 ml, 1.29 mmol) followed by sodium hydride (41 mg, 1.72 mmol), and the solution was stirred at r.t. for 1 h. The reaction was quenched with 1M aq. HCl (50 ml) and the mixture extracted with CH2Cl2 (3 x 50 ml). The combined organic extracts were dried (Na2SO4), evaporated in vacuo, and purified by chromatography (hexane/EtOAc 90:10) on silica gel to give (aS)-(−)-179 (respectively (aR)-(+)-179) as a colorless, amorphous solid (180 mg, 97%). IR (CHCl3): 1499m cm−1; 1257.5 (ArC−O−C); 1150s (C−O−C); 1136s (C−O−C); 1111s (C−O−C). 1H-NMR (200 MHz, CDCl3): 8.05 (s, 1 H, ArH); 7.99 (d, J = 8.7, 1 H, ArH); 7.93 (d, J = 8.3, 1 H, ArH); 7.76 (d, J = 8.7, 1 H, ArH); 7.51-7.39 (m, 3 H, ArH); 7.29-7.23 (m, 2 H, ArH); 7.12-7.07 (m, 1 H, ArH); 4.78 (s, 2 H, ArCH2O); 3.80 (s, 3 H, OCH3); 3.59 (s, 3 H, OCH3); 3.41 (s, 3 H, OCH3). 13C-NMR (75 MHz, CDCl3): 156.0; 155.0; 135.7; 133.8; 131.7; 131.0; 130.1; 129.9; 129.1; 128.4; 127.7; 127.4 (two overlapping signals); 126.4; 125.3; 125.1; 124.2; 121.6; 118.9; 114.0; 70.6; 61.1; 58.7; 56.6. DEI-MS: 438/436 (100/100, M+ (81Br/79Br)); 407/405 (16/16, [M−OCH3]+). Anal. calc. for C24H21BrO3 (437.3): C 65.91, H 4.84, Br 18.27; found: C 65.97, H 4.87, Br 18.35.

(aS)-(−)-179: $[\alpha]_D^{+} = -14.6$ (c = 1.00, CHCl3).

(aR)-(−)-179: $[\alpha]_D^{+} = +14.2$ (c = 1.00, CHCl3).
(aRS)-7'-Bromo-2,2'-dimethoxy-3-methoxymethoxymethyl-1,1'-binaphthalene ((±)-180).

To a solution of binaphthyl (±)-178 (425 mg, 1.00 mmol) and potassium carbonate (1.39 g, 10.04 mmol) in acetonitrile (25 ml) was added chloromethylmethylether (0.38 ml, 5.02 mmol), and the solution was stirred at r.t. for 2 h. The reaction mixture was filtered through Celite, evaporated in vacuo, and purified by chromatography (hexane/ EtOAc/ Et₃N 80:19:1) on silica gel to give (±)-180 as a colorless, amorphous solid (208 mg, 45%). IR (CHCl₃): 1265 s cm⁻¹ (ArC=O-C); 1148 s (C-O-C); 909 s. ¹H-NMR (200 MHz, CDCl₃): 8.07 (s, 1 H, ArH); 7.98 (d, J = 8.7, 1 H, ArH); 7.91 (d, J = 7.9, 1 H, ArH); 7.74 (d, J = 8.7, 1 H, ArH); 7.49-7.37 (m, 3 H, ArH); 7.28-7.21 (m, 2 H, ArH); 7.08 (dd, J = 7.9, 0.8, 1 H, ArH); 4.91 (s, 2 H, OCH₂); 4.89 (s, 2 H, ArCH₂O); 3.79 (s, 3 H, OCH₃); 3.51 (s, 3 H, OCH₃); 3.39 (s, 3 H, OCH₃). ¹³C-NMR (75 MHz, CDCl₃): 156.0; 154.9; 135.6; 133.8; 131.5; 130.9; 129.9; 129.8; 129.2; 128.3; 127.7; 127.4 (two overlapping signals); 126.5; 125.3; 125.1; 124.1; 121.6; 118.8; 113.9; 96.5; 65.5; 61.0; 56.6; 55.6. DEI-MS: 468/466 (1/1, M⁺ (8¹Br/7⁹Br)); 388 (100, [M - Br]⁺); 328 (38); 282 (29).

(aS)-Methyl 2,2'-dihydroxy-1,1'-binaphthalen-3-ylcarboxylate (−)-181.

To a solution of (+)-175 (165 mg, 0.19 mmol) in dry THF (10 ml) at -78 °C under an argon atmosphere was added n-BuLi (1.6M soln. in hexanes, 0.36 ml, 0.58 mmol), and the solution was stirred at r.t. for 2 h. The reaction was quenched with methanol (0.5 ml) and 1M aq. HCl (50 ml), and the mixture extracted with CH₂Cl₂ (3 x 50 ml). The combined organic extracts were dried (Na₂SO₄) and evaporated in vacuo. The residue was dissolved in methanol (25 ml) and 1M aq. NaOH (25 ml) and the solution heated to
reflux for 12 h. The methanol was evaporated in vacuo, 1M aq. HCl (50 ml) added, and
the solution extracted with CH₂Cl₂ (3 x 50 ml). The combined organic extracts were
dried (Na₂SO₄) and evaporated in vacuo. The residue was diluted with methanol (50
ml), treated with dry HCl gas at 0 °C for 15 min, and left to stand at r.t. for 12 h. The
methanol was evaporated in vacuo and the product purified by chromatography
(CH₂Cl₂) on silica gel to give (-)-181 as a yellow solid (40 mg, 60%). [α]ᵣ' = -48.0 (c
= 1.00, CHCl₃), -126.0 (c = 1.00, THF). ¹H-NMR (200 MHz, CDCl₃): 10.88 (s, 1 H, OH); 8.76 (s, 1 H, ArH); 7.99-7.87 (m, 2 H, ArH); 7.74 (d, J = 8.7, 1 H, ArH); 7.44-
7.13 (m, 7 H, ArH); 4.99 (s, 1 H, OH), 4.10 (s, 3 H, COOCH₃).

(aRS)-2,2'-Dimethoxy-3-methoxymethyl-1,1'-binaphthalene ((±)-183).

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(±)-183
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Colorless solid, M.p. 132-134 °C (EtOAc). IR (CHCl₃): 3007m cm⁻¹ (C-H); 1359m;
1266s (ArC-O-C); 1248s (ArC-O-C); 1148m (C-O-C); 1112s (C-O-C); 1089m (C-O-C).
¹H-NMR (200 MHz, CDCl₃): 8.04-8.00 (m, 2 H, ArH); 7.92-7.86 (m, 2 H, ArH); 7.47
(d, J = 9.1, 1 H, ArH); 7.43-7.10 (m, 6 H, ArH); 4.77 (s, 2 H, ArCH₂O); 3.80 (s, 3 H,
OCH₃); 3.57 (s, 3 H, OCH₃); 3.38 (s, 3 H, OCH₃). ¹³C-NMR (75 MHz, CDCl₃): 155.3;
154.9; 134.3; 134.0; 131.7; 130.9; 130.0; 129.3; 128.6; 128.2; 128.1; 126.9;
126.2; 125.6; 125.5; 125.0; 123.9; 119.4; 113.8; 70.6; 61.0; 58.7; 56.7. DEI-MS: 358

(aRS)-Tributyl-(2,2'-dimethoxy-3'-methoxymethyl-1,1'-binaphthalen-7-yl)-
stannane ((±)-185).

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(±)-185
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¹²One signal is missing in the aromatic region.
To a solution of hexabutyldistannane (1.35 ml, 2.70 mmol) in dry THF (10 ml) at 0 °C under an argon atmosphere was added n-BuLi (1.6M soln. in hexanes, 1.56 ml, 2.50 mmol), and the solution was stirred at 0 °C for 15 min to afford a 0.17M solution of Bu3SnLi [286]. A portion of the resulting solution (5.56 ml, 0.95 mmol) was added at 0 °C under an argon atmosphere to a solution of bromide (±)-179 (277 mg, 0.63 mmol) in dry THF (20 ml), and the solution was stirred at 0 °C for 30 min. The reaction was quenched with a sat. aq. NH4Cl solution (50 ml) and the mixture extracted with EtOAc (2 x 50 ml). The combined organic extracts were dried (Na2SO4), evaporated in vacuo, and purified by chromatography (hexane/ EtOAc 90:10) on silica gel to give (±)-185 as a colorless oil (209 mg, 51%). IR (CHCl3): 2973s cm⁻¹ (C-H); 2928s (C-H); 1247s (ArC-O-C); 1139m (C-O-C); 1111m (C-O-C); 1047s (C-O-C). ¹H-NMR (200 MHz, CDCl3): 8.00 (s, 1 H, ArH); 7.97 (d, J = 9.1, 1 H, ArH); 7.88 (d, J = 8.3, 1 H, ArH); 7.81 (d, J = 7.9, 1 H, ArH); 7.46-7.32 (m, 3 H, ArH); 7.23-7.09 (m, 3 H, ArH); 4.77 (s, 2 H, ArCH2O); 3.79 (s, 3 H, OCH3); 3.55 (s, 3 H, OCH3); 3.35 (s, 3 H, OCH3); 1.37-1.01 (m, 12 H, Bu); 0.84-0.69 (m, 15 H, Bu). ¹³C-NMR (75 MHz, CDCl3)¹³: 155.2; 154.9; 140.7; 134.4; 134.0; 133.8; 131.4; 131.1; 130.9; 129.8; 129.2; 128.4; 128.2; 126.9; 126.1; 125.7; 124.8; 119.1; 114.0; 70.6; 60.9; 58.5; 56.9; 28.9; 27.2; 13.6; 9.5. DEI-MS: 648/646 (4/3, M⁺ [120Sn/118Sn]); 561/559 (100/73, [M - OCH3 - Bu + H⁺]); 447/445 (49/39, [M - OCH3 - 3 x Bu + H⁺]); 282 (36). Anal. calc. for C₃₆H₄₈C₃Sn (647.5): C 66.78, H 7.47; found: C 66.51, H 7.47.

(aRS)-(2,2'-Dimethoxy-3'-methoxymethyl-1,1'-binaphthalen-7-yl)-2-phenylethanone ((±)-189).

A degassed solution of stannane (±)-185 (20 mg, 0.03 mmol), phenylacetylchloride (0.01 ml, 0.06 mmol) and [Pd(PPh₃)₄] (1 mg, 3 mol%) was heated to 40 °C under an argon atmosphere in a sealed tube for 8 h. The reaction mixture was allowed to cool to r.t., water (20 ml) was added, and the mixture extracted with CH₂Cl₂ (3 x 20 ml). The

¹³One signal is missing in the aromatic region.
combined organic extracts were dried (Na$_2$SO$_4$), evaporated in vacuo, and purified by chromatography (hexane/EtOAc 8:2) on silica gel to give (±)-189 as a yellow, highly viscous oil (8 mg, 54%). $^1$H-NMR (200 MHz, CDCl$_3$): 8.13 (s, 1 H, ArH); 8.03 (d, $J$ = 9.1, 1 H, ArH); 8.01-7.55 (m, 4 H, ArH); 7.58 (d, $J$ = 9.1, 1 H, ArH); 7.50-7.43 (m, 1 H, ArH); 7.32-7.22 (m, 2 H, ArH); 7.10-7.01 (m, 3 H, ArH); 6.78-6.74 (m, 2 H, ArH); 4.79 (s, 2 H, ArCH$_2$O); 3.98-3.80 (m, 2 H, COCH$_2$Ph); 3.83 (s, 3 H, OCH$_3$); 3.61 (s, 3 H, OCH$_3$); 3.28 (s, 3 H, OCH$_3$). DEI-MS: 476 (51, M$^+$); 385 (100, [M - CH$_2$Ph]$^+$).

(aS,3R,4S,8RS)-(2',Dimethoxy-3'-methoxymethyl-1,1'-binaphthalen-7-yl)-(3-ethyl-1-azabicyclo[2.2.2]oct-8-yl)methanone (182/186).

Bromide (−)-179 (250 mg, 0.57 mmol) and Weinreb amide (+)-164 (258 mg, 1.14 mmol) were coupled according to Procedure M to afford 182/186 as a 1:1 mixture of two diastereoisomers which could not be separated. Colorless oil (137 mg, 46%). IR (CHCl$_3$): 2956s cm$^{-1}$; 2935s; 1459m; 1136vs (C-O-C). $^1$H-NMR (200 MHz, CDCl$_3$): 8.05-7.85 (m, 6 H, ArH); 7.56 (dd, $J$ = 9.1, 1.7, 1 H, ArH); 7.43-7.36 (m, 1 H, ArH); 7.23-7.04 (m, 2 H, ArH); 4.78 (s, 1 H, ArCH$_2$O); 4.77 (s, 1 H, ArCH$_2$O); 3.83 (s, 1.5 H, OCH$_3$); 3.82 (s, 1.5 H, OCH$_3$); 3.82-3.69 (m, 1 H, H-C(8)); 3.58 (s, 1.5 H, OCH$_3$); 3.57 (s, 1.5 H, OCH$_3$); 3.38 (s, 1.5 H, OCH$_3$); 3.35 (s, 1.5 H, OCH$_3$); 2.95-2.04 (m, 4 H); 1.68-0.91 (m, 8 H); 0.82 (t, $J$ = 6.9, 1.5 H, H$_3$C(11)); 0.76 (t, $J$ = 6.9, 1.5 H, H$_3$C(11)). $^{13}$C-NMR (75 MHz, CDCl$_3$)$^{14}$: [199.4; 199.3]; [155.8; 155.7]; [155.1; 155.0]; 134.3; 134.1; 133.9; 133.6; 133.5; 131.8; 131.5; 131.3; 130.9; 129.8; 129.7; 128.9; 128.9; 128.8; 128.8; 128.4 (two overlapping signals); 128.2; [126.4; 126.3]; 125.7; 125.5; [125.1; 125.0]; [124.3; 124.3]; 122.6; 122.5; 121.2; 116.1; 116.0; [70.7; 70.6]; [61.2; 61.1]; 60.5; [58.7; 58.7]; [56.8; 56.7]; 50.8; 48.2; 42.8; [37.5; 37.5]; 28.1; 27.7; 27.5; 25.9; 25.4; 25.3; 22.6; 22.5; 21.8. DEI-MS: 523 (14, M$^+$); 508 (20, [M - CH$_3$]$^+$); 357 (13, [M - COC$_9$H$_{16}$N]$^+$); 138 (100, [C$_9$H$_{16}$N]$^+$). DEI-HRMS: 523.2713 (M$^+$, C$_{34}$H$_{37}$NO$_4$, calc. 523.2722).

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$^{14}$Three aliphatic and three aromatic signals are missing.
Experimental Part

(bR,3R,4S,8R)-(2,2'-Dimethoxy-3'-methoxymethyl-1,1'-binaphthalen-7-yl)-(3-ethyl-1-azabicyclo[2.2.2]oct-8-yl)methanone (187/188).

Bromide (+)-179 (85 mg, 0.19 mmol) and Weinreb amide (+)-164 (86 mg, 0.38 mmol) were coupled according to Procedure M to afford 187/188 as a 1:1 mixture of two diastereoisomers which could not be separated. Colorless oil (40 mg, 40%). IR (CHCl₃): 2936m cm⁻¹; 1682m (C=O); 1459m; 1137w (C-O-C). ¹H-NMR (200 MHz, CDCl₃): 8.05-7.89 (m, 6 H, ArH); 7.56 (dd, J = 9.1, 2.1, 1 H, ArH); 7.44-7.37 (m, 1 H, ArH); 7.28-7.07 (m, 2 H, ArH); 4.78-4.76 (m, 2 H, ArCH₂O); 3.83 (s, 1.5 H, OCH₃); 3.82 (s, 1.5 H, OCH₃); 3.83-3.67 (m, 1 H, H-C(8)); 3.58 (s, 1.5 H, OCH₃); 3.57 (s, 1.5 H, OCH₃); 3.37 (s, 1.5 H, OCH₃); 3.36 (s, 1.5 H, OCH₃); 2.70-2.28 (m, 3 H); 2.18-0.91 (m, 9 H); 0.86 (t, J = 7.1, 1.5 H, H₃C(11)); 0.76 (t, J = 7.1, 1.5 H, H₃C(11)). ¹³C-NMR (75 MHz, CDCl₃): 199.4; 155.7; [155.1; 155.0]; [134.2; 134.2]; 133.9; [133.6; 133.6]; 131.8; 131.5; [131.3; 131.2]; 131.0; [129.7; 129.7]; [129.0; 129.0]; 128.8; 128.3; 128.2; [126.4; 126.3]; [125.6; 125.5]; [125.1; 125.0]; [124.4; 124.4]; 122.6; [121.2; 121.2]; [116.0; 116.0]; [70.7; 70.6]; [61.1; 61.1]; 60.7; 60.4; [58.7; 58.7]; 56.8; 56.7; 56.5; 51.0; 48.4; 42.7; [37.6; 37.5]; 28.1; [27.7; 27.6]; 25.8; 25.4 (two overlapping signals); 22.2; 21.7; [12.1; 11.9]. DEI-MS: 523 (28, M⁺); 508 (31, [M - CH₃]⁺); 493 (18, [M - OCH₃]⁺); 138 (100, [C₉H₁₆N]⁺). DEI-HRMS: 523.2713 (M⁺, C₃₄H₃₇NO₄, calc. 523.2722).

(bS,3R,4S)-(2,2'-Dimethoxy-3'-methoxymethyl-1,1'-binaphthalen-7-yl)-(3-ethyl-1-azabicyclo[2.2.2]oct-8-yl)methanol ((+)-190, (+)-191, (-)-192, and (+)-193).

¹⁵One carbonyl and six aromatic signals are missing.
To a solution of ketones 182/186 1:1 (120 mg, 0.23 mmol) in benzene (50 ml) at 0 °C was added diisobutylaluminium hydride (1 M soln. in hexane, 0.69 ml, 0.69 mmol), and the solution was stirred at r.t. for 4 h. The reaction was quenched with a sat. aq. NaHCO₃ solution (50 ml) and the mixture extracted with CH₂Cl₂ (3 x 50 ml). The combined organic extracts were dried (Na₂SO₄), evaporated in vacuo, and purified by chromatography on silica gel (CH₂Cl₂/MeOH/NH₄OH 90:9:1) to give the pure four diastereoisomers.

(aS,3R,4S,8S,9S)-(+)-190: yellow, highly viscous oil (12 mg, 10%). [α]D° = +36.7 (c = 0.50, CHCl₃). IR (CHCl₃): 2925 w cm⁻¹; 1133 vs (C-O). ¹H-NMR (300 MHz, CDCl₃): 8.02 (s, 1 H, H-C(4')); 7.98 (d, J = 9.0, 1 H, H-C(4')); 7.90 (d, J = 7.4, 1 H, H-C(5')); 7.88 (d, J = 8.7, 1 H, H-C(5')); 7.47-7.45 (m, 1 H, H-C(6')); 7.44 (d, J = 9.0, 1 H, H-C(3')); 7.40-7.35 (m, 1 H, H-C(6')); 7.22-7.17 (m, 1 H, H-C(7')); 7.08 (d, J = 8.4, 1 H, H-C(8')); 7.04 (s, 1 H, H-C(8')); 4.79 (d, J = 12.5, 1 H, H-C(12)); 4.73 (d, J = 12.5, 1 H, H-C(12)); 4.13 (d, J = 9.7, 1 H, H-C(9)); 3.77 (s, 3 H, OCH₃); 3.55 (s, 3 H, OCH₃); 3.33 (s, 3 H, OCH₃); 3.08 (dd, J = 13.5, 10.1, 1 H, H-C(2)); 2.96-2.84 (m, 1 H, H-C(6)); 2.64-2.52 (m, 2 H, H-C(8), H-C(6)); 2.38-2.31 (m, 1 H, H-C(2)); 1.57-1.53 (m, 1 H, H-C(4')); 1.48-1.30 (m, 3 H, H-C(3), H2C(5)); 1.21-1.10 (m, 3 H, H-C(7), H2C(10)); 0.78 (t, J = 7.3, 3 H, H3C(11)); 0.73-0.66 (m, 1 H, H-C(7)). ¹³C-NMR (75 MHz, CDCl₃): 155.5; 155.1; 139.3; 134.1; 134.0; 131.5; 130.9; 129.8; 129.1; 128.7; 128.6; 128.2; 126.3; 125.7; 125.0; 124.7; 124.6; 123.1; 119.6; 113.9; 74.9; 70.6; 63.8; 61.0; 58.6; 57.2; 56.8; 40.7; 37.7; 28.3; 27.6; 25.0; 24.2; 12.1. DEI-MS: 525 (39, M⁺); 510 (30, [M - CH₃]+); 495 (31, [M - 2 X CH₃]+); 386 (49, [M - C9H16N - H]+); 356 (38, [M - CH(OH)C9H16N - H]+); 302 (76); 139 (100, [C9H16N + H]+). DEI-HRMS: 525.2875 (M⁺, C34H39NO4, calc. 525.2879).  

(aS,3R,4S,8R,9R)-(−)-191: yellow, highly viscous oil (12 mg, 10%). [α]D° = +33.2 (c = 0.50, CHCl₃). IR (CHCl₃): 2935w cm⁻¹; 1261w (C-O-C); 1111s (C-O). ¹H-NMR (300 MHz, CDCl₃): 8.03 (s, 1 H, H-C(4')); 7.98 (d, J = 9.2, 1 H, H-C(4')); 7.90 (d, J = 8.4, 1 H, H-C(5')); 7.87 (d, J = 9.3, 1 H, H-C(5')); 7.50 (dd, J = 8.4, 1.6, 1 H, H-C(6')); 7.46 (d, J = 9.2, 1 H, H-C(3')); 7.33-7.28 (m, 1 H, H-C(6')); 7.00 (d, J = 8.4, 1 H, H-C(8')); 6.88 (s, 1 H, H-C(8')); 4.80 (d, J = 12.5, 1 H, H-C(12)); 4.75 (d, J = 12.5, 1 H, H-C(12)); 4.28 (d, J = 9.6, 1 H, H-C(9)); 3.77 (s, 3 H, OCH₃); 3.59 (s, 3 H, OCH₃); 3.10-2.89 (m, 4 H, H-C(2), H2C(6), H-C(8)); 2.51-2.44 (m, 1 H, H-C(2)); 1.64-1.56 (m, 1 H, H-C(5)); 1.54-1.50 (m, 1 H, H-C(4)); 1.47-1.37 (m, 1 H, H-C(3)); 0.90-0.68 (m, 5 H, H-C(5), H2C(7), H₂C(10)); 0.71 (t, J = 7.1, 3 H, H3C(11)). ¹³C-NMR (75 MHz, CDCl₃): 155.8; 155.2; 138.1; 133.8; 133.8; 132.0; 131.0; 129.8; 129.2; 129.1; 128.6; 128.3; 125.8; 125.7; 124.9; 124.6; 124.5; 121.8; 119.4; 114.4; 73.2; 70.6; 63.8; 61.1; 58.9; 57.0; 48.4; 48.0;
Experimental Part

36.1; 25.5; 25.2; 24.7; 23.2; 11.7. DEI-MS: 525 (5, M⁺); 510 (5, [M - CH₃⁺); 495 (5, [M - 2 x CH₃⁺); 386 (9, [M - C₉H₁₆N - H⁺); 139 (100, [C₉H₁₆N + H⁺). DEI-HRMS: 525.2881 (M⁺, C₃₄H₄₀NO₄, calc. 525.2879).

(aS,3R,4S,8S,9R)-(−)-192: yellow, highly viscous oil (12 mg, 10%). [α]₀^D = −3.2 (c = 0.50, CHCl₃). IR (CHCl₃): 2964w cm⁻¹; 1265s (C-O-C); 1136vs (C-O). ¹H-NMR (300 MHz, CDCl₃): 8.01 (s, 1 H, H-C(4")); 7.96 (d, J = 9.0, 1 H, H-C(4')); 7.87 (d, J = 9.0, 1 H, H-C(5")); 7.84 (d, J = 8.7, 1 H, H-C(5')); 7.41 (d, J = 9.0, 1 H, H-C(3')); 7.40-7.36 (m, 1 H, H-C(6')); 7.37-7.32 (m, 1 H, H-C(6")); 7.19-7.14 (m, 1 H, H-C(7")); 7.09 (d, J = 8.4, 1 H, H-C(8")); 6.99 (s, 1 H, H-C(8')); 4.77 (d, J = 12.5, 1 H, H-C(12)); 4.72 (d, J = 12.5, 1 H, H-C(12)); 4.57 (d, J = 6.7, 1 H, H-C(9)); 3.76 (s, 3 H, OCH₃); 3.56 (s, 3 H, OCH₃); 3.34 (s, 3 H, OCH₃); 2.93-2.72 (m, 3 H, H-C(2), H-C(6), H-C(8)); 2.31-2.17 (m, 2 H, H-C(2), H-C(6)); 1.66-1.55 (m, 2 H, H-C(4), H-C(7)); 1.47-1.16 (m, 6 H, H-C(3), H₂C(5), H₂C(7), H₂C(10)); 0.80 (t, J = 7.2, 3 H, H₃C(11)). ¹³C-NMR (75 MHz, CDCl₃): 155.5; 154.9; 141.7; 134.1; 134.0; 131.5; 130.9; 129.8; 129.0; 128.8; 128.7; 128.2; 126.7; 125.7; 124.9; 123.2; 119.5; 113.8; 111.2; 70.7; 61.0 (two overlapping signals); 58.7; 58.0; 56.7; 42.3; 37.4; 28.1; 27.5; 25.5; 23.8; 12.1. DEI-MS: 525 (20, M⁺); 510 (33, [M - CH₃⁺); 495 (35, [M - 2 x CH₃⁺); 138 (100, [C₉H₁₆N⁺). DEI-HRMS: 525.2874 (M⁺, C₃₄H₄₀NO₄, calc. 525.2879).

(aS,3R,4S,8S,9S)-(−)-193: yellow, highly viscous oil (15 mg, 12%). [α]₀^D = +38.0 (c = 0.50, CHCl₃). IR (CHCl₃): 2922w cm⁻¹; 1139vs (C-O). ¹H-NMR (300 MHz, CDCl₃): 8.01 (s, 1 H, H-C(4")); 7.97 (d, J = 9.0, 1 H, H-C(4')); 7.89 (d, J = 8.1, 1 H, H-C(5")); 7.84 (d, J = 8.4, 1 H, H-C(5')); 7.42 (d, J = 9.0, 1 H, H-C(3')); 7.39-7.32 (m, 2 H, H-C(6'), H-C(6")); 7.20-7.15 (m, 1 H, H-C(7')); 7.08 (d, J = 9.0, 1 H, H-C(8")); 7.04 (s, 1 H, H-C(8')); 5.28 (i, 2 H, H₂C(12)); 4.72 (d, J = 13.4, 1 H, H-C(9)); 3.77 (s, 3 H, OCH₃); 3.55 (s, 3 H, OCH₃); 3.35 (s, 3 H, OCH₃); 2.84-2.76 (m, 1 H, H-C(8)); 2.69-2.26 (m, 4 H, H₂C(2), H₂C(6)); 1.63-1.06 (m, 8 H, H-C(3), H-C(4), H₂C(5), H₂C(7), H₂C(10)); 0.74 (t, J = 7.3, 3 H, H₃C(11)). ¹³C-NMR (75 MHz, CDCl₃): 155.5; 154.9; 141.1; 134.1; 134.0; 131.6; 131.0; 129.8; 128.9; 128.7; 128.3; 128.2; 126.1; 125.7; 124.8; 123.2; 122.7; 119.5; 113.8; 75.2; 70.6; 61.3; 61.0; 58.6; 56.7; 50.4; 49.6; 37.1; 26.7; 26.0; 24.9; 22.7; 11.8. DEI-MS: 525 (12, M⁺); 510 (17, [M - CH₃⁺); 495 (17, [M - 2 x CH₃⁺); 168 (25, [CH(OH)C₉H₁₆N⁺); 138 (100, [C₉H₁₆N⁺). DEI-HRMS: 525.2875 (M⁺, C₃₄H₄₀NO₄, calc. 525.2879).

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¹⁶One signal is missing in the aromatic region.
(aS,3R,4S,8S,9S)-N-(4-Trifluoromethylbenzyl)-8-[(2',2'-dimethoxy-3'-methoxy-methyl-1,1'-binaphthalen-7-yl)hydroxymethyl]-3-ethylazoniabicyclo[2.2.2]octane bromide (+(+)194).

Quaternization of binaphthyl (+(+)190 (11 mg, 0.02 mmol) according to Procedure N afforded (+(+)194 as a colorless solid (9 mg, 56%). \[\alpha\]D\textsuperscript{+} = +4.1 (c = 0.25, CHCl\textsubscript{3}). IR (CHCl\textsubscript{3}): 3456\textsuperscript{s} cm\textsuperscript{-1}; 1461\textsuperscript{w}; 1322\textsuperscript{s} (C-O); 1250\textsuperscript{w}; 1167\textsuperscript{m} (C-O); 1067\textsuperscript{m} (C-O). \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): 8.03 (s, 1 H, H-\textsuperscript{C(4\textquoteright)}); 7.99 (d, J = 9.0, 1 H, H-\textsuperscript{C(4\textquoteright)}); 7.87 (d, J = 8.4, 1 H, ArH); 7.84 (d, J = 8.0, 1 H, ArH); 7.78, 7.51 (AA\textsuperscript{'1}'BB\textsuperscript{'1}', J = 7.9, 4 H, 2 x H-\textsuperscript{C(15)}, 2 x H-\textsuperscript{C(16)}); 7.48 (d, J = 9.0, 1 H, H-\textsuperscript{C(3\textquoteright)}); 7.47-7.45 (m, 1 H, H-C(6\textquoteright)); 7.34-7.29 (m, 1 H, H-C(6\textquoteright)); 7.17-7.13 (m, 1 H, H-C(7\textquoteright)); 7.08-7.05 (m, 2 H, H-C(8\textquoteright), H-C(8\textquoteright)); 5.52 (d, J = 12.8, 1 H, H-C(13)); 5.28 (d, J = 10.0, 1 H); 5.09 (d, J = 12.8, 1 H, H-C(13)); 4.75 (d, J = 12.3, 1 H, H-C(12)); 4.69 (d, J = 12.3, 1 H, H-C(12)); 4.45-4.39 (m, 1 H); 3.95-3.89 (m, 1 H); 3.80 (s, 3 H, OCH\textsubscript{3}); 3.56-3.51 (m, 1 H); 3.53 (s, 3 H, OCH\textsubscript{3}); 3.33 (s, 3 H, OCH\textsubscript{3}); 2.32-2.26 (m, 1 H); 2.02-1.95 (m, 1 H); 1.92-1.80 (m, 2 H); 1.80-1.75 (m, 1 H, H-C(4)); 1.32-0.80 (m, 5 H); 0.76 (t, J = 7.4, 3 H, H\textsubscript{3}C(11)). \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{3}): 155.5; 154.8; 138.1; 134.0; 133.7; 133.6; 132.1 ([q, J = 31.5], C(17)); 131.9; 131.5; 130.7; 129.8; 129.1; 128.9; 128.2; 125.9; 125.8; 125.8; 125.3; 124.6; 124.0; 123.9; 123.7 ([q, J = 273.0], CF\textsubscript{3}); 119.1; 114.2; 70.6; 66.6; 65.3; 63.2; 61.0; 58.7; 56.5; 51.2; 35.3; 29.7; 25.6; 24.7; 24.6; 24.3; 11.1. FAB-MS: 684 (100, [M - Br\textsuperscript{+}]). FAB-MS: 684.3304 ([M - Br\textsuperscript{+}], C\textsubscript{42}H\textsubscript{45}F\textsubscript{3}NO\textsubscript{4}, calc. 684.3300).
Quaternization of binaphthyl (+)-191 (11 mg, 0.02 mmol) according to Procedure N afforded (+)-195 as a colorless solid (2 mg, 12%). $[\alpha]_D^1 = +3.9$ (c = 0.25, CHCl$_3$). IR (CHCl$_3$): 3422s cm$^{-1}$; 1461w; 1322s (C-O); 1250w; 1167w; 1122m (C-O); 1067m (C-O). $^1$H-NMR (300 MHz, CDCl$_3$): 8.03 (s, 1 H, H-C(4")); 7.92 (d, $J = 8.9$, 1 H, H-C(4")); 7.90 (d, $J = 6.5$, 1 H, H-C(5")); 7.76 (d, $J = 8.1$, 1 H, H-C(5")); 7.74, 7.56 (AA'BB', $J = 7.9$, 4 H, 2 x H-C(15), 2 x H-C(16)); 7.67-7.63 (m, 1 H, H-C(6")); 7.44 (d, $J = 8.9$, 1 H, H-C(3")); 7.39-7.26 (m, 2 H, H-C(6"), H-C(7")); 7.10 (d, $J = 8.4$, 1 H, H-C(8")); 6.99 (s, 1 H, H-C(8")); 6.00-5.96 (m, 1 H); 5.72 (d, $J = 12.1$, 1 H, H-C(13)); 4.80-4.65 (m, 3 H, H$_2$C(12), H-C(13)); 4.28-4.16 (m, 1 H); 3.80 (s, 3 H, OCH$_3$); 3.62-3.57 (m, 1 H); 3.55 (s, 3 H, OCH$_3$); 3.31 (s, 3 H, OCH$_3$); 3.24-3.14 (m, 1 H); 3.06-2.94 (m, 1 H); 2.74-2.66 (m, 1 H); 2.18-0.83 (m, 8 H); 0.77 (t, $J = 7.3$, 3 H, H$_3$C(11)). FAB-MS: 684 (100, [M - Br]$^+$. FAB-HRMS: 684.3302 ([M - Br]$^+$, C$_{42}$H$_{45}$F$_3$NO$_4$, calc. 684.3300).

Quaternization of binaphthyl (-)-196 according to Procedure N afforded (-)-196 as a colorless solid (2 mg, 12%). $[\alpha]_D^1 = -3.9$ (c = 0.25, CHCl$_3$). IR (CHCl$_3$): 3422s cm$^{-1}$; 1461w; 1322s (C-O); 1250w; 1167w; 1122m (C-O); 1067m (C-O). $^1$H-NMR (300 MHz, CDCl$_3$): 8.03 (s, 1 H, H-C(4")); 7.92 (d, $J = 8.9$, 1 H, H-C(4")); 7.90 (d, $J = 6.5$, 1 H, H-C(5")); 7.76 (d, $J = 8.1$, 1 H, H-C(5")); 7.74, 7.56 (AA'BB', $J = 7.9$, 4 H, 2 x H-C(15), 2 x H-C(16)); 7.67-7.63 (m, 1 H, H-C(6")); 7.44 (d, $J = 8.9$, 1 H, H-C(3")); 7.39-7.26 (m, 2 H, H-C(6"), H-C(7")); 7.10 (d, $J = 8.4$, 1 H, H-C(8")); 6.99 (s, 1 H, H-C(8")); 6.00-5.96 (m, 1 H); 5.72 (d, $J = 12.1$, 1 H, H-C(13)); 4.80-4.65 (m, 3 H, H$_2$C(12), H-C(13)); 4.28-4.16 (m, 1 H); 3.80 (s, 3 H, OCH$_3$); 3.62-3.57 (m, 1 H); 3.55 (s, 3 H, OCH$_3$); 3.31 (s, 3 H, OCH$_3$); 3.24-3.14 (m, 1 H); 3.06-2.94 (m, 1 H); 2.74-2.66 (m, 1 H); 2.18-0.83 (m, 8 H); 0.77 (t, $J = 7.3$, 3 H, H$_3$C(11)). FAB-MS: 684 (100, [M - Br]$^+$. FAB-HRMS: 684.3302 ([M - Br]$^+$, C$_{42}$H$_{45}$F$_3$NO$_4$, calc. 684.3300).
Quaternization of binaphthyl (-)-192 (14 mg, 0.03 mmol) according to Procedure N afforded (-)-196 as a colorless solid (11 mg, 54%). \([\alpha]_D^{25} = -1.4 (c = 0.25, \text{CHCl}_3)\). IR (CHCl₃): 3444s cm⁻¹; 1461w; 1328s (C-O); 1250w; 1172w; 1117m (C-O); 1067m (C-O). ¹H-NMR (300 MHz, CDCl₃): 8.02 (s, 1 H, H-C(4'')); 7.88 (d, \(J = 7.8\), 1 H, H-C(5'')); 7.86 (d, \(J = 8.9\), 1 H, H-C(4'')); 7.66, 7.46 (AA'BB', \(J = 7.9\), 4 H, 2 x H-C(15), 2 x H-C(16)); 7.64 (d, \(J = 6.7\), 1 H, H-C(5'')); 7.56-7.52 (m, 1 H, H-C(6'')); 7.42 (d, \(J = 8.9\), 1 H, H-C(3'')); 7.39-7.34 (m, 1 H, H-C(6'')); 7.24-7.19 (m, 1 H, H-C(7'')); 7.11 (d, \(J = 8.4\), 1 H, H-C(8'')); 7.03 (s, 1 H, H-C(8'')); 5.95-5.92 (m, 1 H); 5.56 (d, \(J = 12.9\), 1 H, H-C(13)); 4.99 (d, \(J = 12.9\), 1 H, H-C(13)); 4.76 (d, \(J = 12.5\), 1 H, H-C(12)); 4.70 (d, \(J = 12.5\), 1 H, H-C(12)); 4.63-4.52 (m, 1 H); 3.79 (s, 3 H, OCH₃); 3.52 (s, 3 H, OCH₃); 3.29 (s, 3 H, OCH₃); 3.22-2.96 (m, 3 H); 2.82-2.74 (m, 1 H); 1.88-0.80 (m, 8 H); 0.75 (t, \(J = 7.3\), 3 H, H₃C(11)). ¹³C-NMR (75 MHz, CDCl₃): 155.5; 155.2; 138.1; 134.2; 133.9; 133.7; 132.4 ([q, \(J = 33.0\), C(17)]; 131.9; 131.5; 130.9; 129.9; 128.9; 128.7; 128.4; 126.0; 125.9; 125.6; 124.8; 124.5; 123.8 ([q, \(J = 272.0\), CF₃]); 122.4; 122.1; 119.2; 114.0; 70.7; 69.9; 67.2; 63.0; 62.2; 61.0; 58.7; 56.8; 36.3; 29.7; 26.3; 25.5; 24.1; 20.7; 11.4. FAB-MS: 684 (100, [M - Br]+). FAB-HRMS: 684.3300 ([M - Br]+, C₄₂H₄₅F₃NO₄, calc. 684.3300).

(aS,3R,4S,8R,9S)-N-(4-Trifluoromethylbenzyl)-8-[(2,2'-dimethoxy-3'-methoxy-methyl-1,1'-binaphthalen-7-yl)hydroxymethyl]-3-ethylazoniabicyclo[2.2.2]octane bromide ((+-)197).

Quaternization of binaphthyl (+)-193 (11 mg, 0.02 mmol) according to Procedure N afforded (+)-197 as a colorless solid (8 mg, 50%). \([\alpha]_D^{25} = +15.2 (c = 0.25, \text{CHCl}_3)\). IR (CHCl₃): 3433s cm⁻¹; 1461w; 1322s (C-O); 1250w; 1167w; 1117m (C-O); 1067m (C-O). ¹H-NMR (300 MHz, CDCl₃): 8.06 (s, 1 H, H-C(4'')); 7.88 (d, \(J = 7.8\), 1 H, H-C(5'')); 7.60, 7.35 (AA'BB', \(J = 8.3\), 4 H, 2 x H-C(15), 2 x H-C(16)); 7.49 (d, \(J = 9.0\), 1 H, H-C(4'')); 7.38 (d, \(J = 9.0\), 1 H, H-C(3'')); 7.29-7.24 (m, 2 H, H-C(5''), H-C(6'')); 7.20-7.16 (m, 1 H, H-C(6'')); 7.04-6.99 (m, 1 H, H-C(7'')); 6.91-6.87 (m, 2 H, H-C(8''), H-
Experimental Part

C(8") (J = 11.7, 1 H, H-C(13)); 5.87-5.83 (m, 1 H); 5.03 (d, J = 11.7, 1 H, H-C(13)); 4.87 (s, 2 H, H2C(12)); 4.26-4.17 (m, 1 H); 4.13-4.01 (m, 1 H); 3.83-3.73 (m, 1 H); 3.81 (s, 3 H, OCH3); 3.63 (s, 3 H, OCH3); 3.62 (s, 3 H, OCH3); 3.01-2.94 (m, 1 H); 2.48-2.36 (m, 1 H); 1.80-1.22 (m, 5 H); 0.98-0.83 (m, 3 H); 0.65 (t, J = 7.2, 3 H, H3C(11)). 13C-NMR (75 MHz, CDCl3): 155.5; 155.3; 137.4; 134.2; 134.0; 132.2 ([q, J = 33.0], C(17)); 132.0; 132.0; 131.1; 129.7; 128.7; 128.3; 128.1; 125.9; 125.6; 125.3; 124.8; 124.4; 123.6 ([q, J = 271.5], CF3); 123.0; 121.9; 119.5; 114.1; 70.7; 68.4; 68.2; 61.5; 60.2; 58.8; 57.1; 55.8; 36.0; 29.7; 24.5; 24.5; 23.6; 20.8; 11.4. FAB-MS: 684 (100, [M - Br]+). FAB-HRMS: 684.3324 ([M - Br]+, C42H45F3NO4, calc. 684.3300).

(3R,4S,8R,9S)-A'-(4-Trifluoromethylbenzyl)cinchoninium bromide ((+)-132).

Quaternization of cinchonine (+)-125 (1.00 g, 3.40 mmol) according to Procedure N afforded (+)-132 as a colorless solid (1.39 g, 77%), M.p. > 180 °C (decomp.). [α]D25 = +146.3 (c = 1.00, MeOH). IR (KBr): 3188s (OH); 1327s; 1150m (C-O); 1130* (C-O); 1068m (C-O). 1H-NMR (200 MHz, CDCl3): 8.82 (d, J = 4.6, 1 H, H-C(14)); 8.25 (d, J = 7.9, 1 H, H-C(16)); 7.85-7.83 (m, 3 H, 2 x H-(23), H-C(13)); 7.51 (dd, J = 8.1, 1.5, 1 H, H-C(19)); 7.39 (d, J = 7.9, 2 H, 2 x H-(24)); 7.02-6.87 (m, 2 H, H-C(17), H-C(18)); 5.40 (d, J = 12.0, 1 H, H-C(21)); 5.24 (d, J = 10.2, 1 H, H-C(11)); 5.17 (d, J = 16.9, 1 H, H-C(11)); 4.35-4.24 (m, 1 H); 4.26-4.08 (m, 2 H); 3.22-3.11 (m, 1 H); 2.71-2.56 (m, 1 H); 2.35-2.22 (m, 1 H); 2.15-2.02 (m, 1 H); 1.82-1.64 (m, 3 H); 0.85-0.72 (m, 1 H). 13C-NMR (50 MHz, CDCl3): 147.1; 144.7; 141.6; 132.5; 132.1; 129.9 ([q, J = 31.9], C(25)); 128.7; 127.3; 125.9; 124.8; [123.1 + 123.0]; 121.0 ([q, J = 273.0], CF3); 121.0; 120.7; 117.3; 116.0; 64.7; 63.2; 57.8; 54.0; 51.6; 35.5; 24.5; 21.2; 19.3. FAB-MS: 454 (100, [M - Br + H]+). Anal. calc. for C27H28F3N2OBr (533.4): C 60.79, H 5.29, N 5.25, F 10.68; found: C 60.66, H 5.35, N 5.39, F 10.43.
2-Allyl-6,7-dichloro-5-methoxy-2-phenyl-1-indanone (198).

Procedure A: A suspension of indanone 137 (50 mg, 0.16 mmol), phase transfer catalyst (0.02 mmol, 10 mol%), and allyl chloride (0.07 ml, 0.80 mmol) in toluene (2.5 ml) and 50% aq. NaOH (0.5 ml) was shaken at r.t. for 20 h. After the addition of water (10 ml) and EtOAc (10 ml), the organic phase was separated, washed with 1M aq. HCl (2 x 10 ml) and water (10 ml), dried (Na2SO4), evaporated in vacuo, and purified by chromatography (hexane/Et2O 8:2) on silica gel to give 198.

Procedure B: A suspension of indanone 137 (100 mg, 0.32 mmol), sol-gel catalyst 203 (800 mg, 0.03 mmol, 10 mol%), powdered NaOH (128 mg, 3.20 mmol), and allyl chloride (0.14 ml, 1.60 mmol) in toluene (50 ml) was stirred at r.t. for 20 h. The reaction mixture was filtered and purified by chromatography (hexane/Et2O 8:2) on silica gel to give 198.

Colorless solid, M.p. 118-121 °C. IR (KBr): 1700 s cm⁻¹ (C=O); 1578 s; 1300 m; 1267 w (C-O); 1156 m (C-O); 1067 m. ¹H-NMR (200 MHz, CDCl3): 7.42-7.18 (m, 5 H, ArH); 6.91 (s, 1 H, ArH); 5.70-5.50 (m, 1 H, H-C(5)); 5.18-5.08 (m, 1 H, H-C(6,trans)); 5.07-5.01 (m, 1 H, H-C(6cis)); 4.01 (s, 3 H, OCH3); 3.49 (dd, J = 17.7, 0.8, 1 H, H-C(3)); 3.36 (dd, J = 17.7, 1.0, 1 H, H-C(3)); 2.86-2.82 (m, 2 H, H-C(4)). ¹³C-NMR (75 MHz, CDCl3): 202.6; 161.4; 154.7; 142.0; 133.8; 132.4; 128.9; 127.2; 126.7; 126.1; 123.3; 119.3; 106.7; 57.7; 57.0; 42.7; 39.2. EI-MS: 348/346 (21/32, M⁺) (CI⁻/Cl⁻); 307/305 (66/100, [M - CH₂CH=CH₂⁺]). Anal. calc. for C₁₉H₁₆Cl₂O₂ (347.2): C 65.72, H 4.64, Cl 20.42; found: C 65.65, H 4.87, Cl 20.33.

Catalysis experiments:

with Bu₄NBr

| (3R,4S,8R,9S)-(+) | Procedure A | 43% yield | 0% ee |
| (aS,3R,4S,8S,9S)-(+) | Procedure A | 59% yield | 73% ee (S) |
| (aS,3R,4S,8R,9R)-(+) | Procedure A | 13% yield | 6% ee (S) |
| (aS,3R,4S,8S,9R)-(+) | Procedure A | 45% yield | 22% ee (R) |
| (aS,3R,4S,8R,9S)-(+) | Procedure A | 38% yield | 16% ee (R) |
| (aS,3R,4S,8R,9S)-(+) | Procedure A | 57% yield | 32% ee (S) |
| (aS,3R,4S,8R,9S)-(+) | Procedure B | 27% yield | 7% ee (S) |
The enantiomeric excess was determined by analytical HPLC on a 'Pirkle Covalent D-Phenylglycine' chiral phase (0.1% EtOH in hexane).

**Ethyl (4-methylphenyl)oxoacetate (206) [322].**

![image of ethyl (4-methylphenyl)oxoacetate](image)

To a solution of toluene (205) (4.70 ml, 44.45 mmol) and ethyl oxalyl chloride (4.95 ml, 44.45 mmol) in chloroform (80 ml) cooled to 0 °C was added aluminium trichloride (11.85 g, 88.90 mmol), and the solution was stirred at 0 °C for 2 h. The reaction was quenched with ice (50 ml) and the mixture extracted with CH$_2$Cl$_2$ (2 x 50 ml). The combined organic extracts were dried (Na$_2$SO$_4$), the chloroform was removed by distillation, and the residual oil distilled in vacuo (70-80 °C, 0.5 Torr) to give 206 as a colorless oil (3.05 g, 36%). 1H-NMR (300 MHz, CDC$_3$): 7.91, 7.31 (AA'BB', J= 8.2, 4 H, ArH); 4.44 (q, J= 7.2, 2 H, COOEt); 2.44 (s, 3 H, CH$_3$); 1.42 (t, J = 7.2, 3 H, COOEt).

**Ethyl difluoro-(4-methylphenyl)acetate (207) [323].**

![image of ethyl difluoro-(4-methylphenyl)acetate](image)

A solution of ester 206 (2.0 g, 10.42 mmol) and diethylaminosulfur trifluoride (DAST) (2.75 ml, 20.84 mmol) was stirred at 0 °C for 1 h, allowed to warm to r.t., and stirred for 12 h. The reaction mixture was carefully quenched with ice (50 ml) and extracted with hexane (3 x 50 ml). The combined organic extracts were dried (Na$_2$SO$_4$), evaporated in vacuo, and purified by chromatography (hexane/EtOAc 95:5) on silica gel to give 207 as a colorless oil (1.96 g, 88%). 1H-NMR (300 MHz, CDCl$_3$): 7.49, 7.25 (AA'BB', J = 7.8, 4 H, ArH); 4.29 (q, J = 7.2, 2 H, COOEt); 2.39 (s, 3 H, CH$_3$); 1.30 (t, J = 7.2, 3 H, COOEt).
**tert-Butyl difluoro-(4-methylphenyl)acetate (208) [323]**.

![Diagram of 208]

A solution of ethyl ester 207 (1.0 g, 4.67 mmol) in acetonitrile (8 ml) and 5M aq. NaOH (2 ml) was stirred at r.t. for 1 h. The acetonitrile was evaporated *in vacuo*, and water (20 ml) was added. The solution was washed with Et₂O (20 ml), acidified with 1M aq. HCl (20 ml), and extracted with Et₂O (3 x 20 ml). The combined organic extracts were dried (Na₂SO₄) and evaporated *in vacuo*. The colorless residue was dissolved in toluene (20 ml) containing one drop of DMF, oxalyl chloride (0.44 ml, 5.14 mmol) was added, and the solution was stirred at r.t. for 20 h. *tert*-Butanol (3.5 ml) was then added and stirring continued for 24 h. The reaction was quenched with a sat. aq. NaHCO₃ solution (50 ml) and the mixture extracted with CH₂Cl₂ (3 x 50 ml). The combined organic extracts were dried (Na₂SO₄), evaporated *in vacuo*, and purified by chromatography (hexane/EtOAc 9:1) on silica gel to give 208 as a colorless oil (260 mg, 23%). ¹H-NMR (200 MHz, CDCl₃): 7.49, 7.25 (AA'BB', J = 8.5, 4 H, ArH); 2.40 (s, 3 H, CH₃); 1.49 (s, 9 H, COO'Bu).

**tert-Butyl (4-bromobenzyl)difluoroacetate (209) [323]**.

![Diagram of 209]

To a solution of ester 208 (260 mg, 1.07 mmol) and benzoylperoxide (11 mg, 0.05 mmol) in tetrachlorocarbon (20 ml) heated to reflux was added N-bromosuccinimide (190 mg, 1.07 mmol), and the solution was further heated for 2.5 h. The reaction mixture was allowed to cool to r.t., and water (30 ml) was added. The organic phase was separated and the aqueous phase extracted with CH₂Cl₂ (2 x 30 ml). The combined organic extracts were dried (Na₂SO₄), evaporated *in vacuo*, and purified by chromatography (hexane/EtOAc 95:5) on silica gel to give 209 as a colorless oil (270 mg, 79%). ¹H-NMR (200 MHz, CDCl₃): 7.60, 7.49 (AA'BB', J = 8.3, 4 H, ArH); 4.52 (s, 2 H, CH₂Br); 1.49 (s, 9 H, COO'Bu).
Benzyl (2-aminoethyl)carbamate (210) [324].

To a solution of ethylenediamine (239) (2.00 ml, 29.83 mmol) in 1 M aq. HCl (60 ml, 60 mmol) was added a solution of benzyl chloroformate (4.21 ml, 29.83 mmol) in dioxane (20 ml). A 1 M potassium acetate solution (50 ml) was then added dropwise over 3 h. The reaction was quenched with 1 M aq. HCl (50 ml), the mixture washed with CH₂Cl₂ (100 ml), made basic with 1 M aq. NaOH (100 ml), and extracted with CH₂Cl₂ (2 x 100 ml). The combined organic extracts were dried (Na₂SO₄) and evaporated in vacuo to give 210 as a colorless oil (2.68 g, 46%). ¹H-NMR (200 MHz, CDCl₃): 7.40-7.31 (m, 5 H, ArH); 5.12 (s, 2 H, OCH₂Ph); 3.30-3.21 (m, 2 H, H₂C(1)); 2.83 (d, J = 5.8, 2 H, H₂C(2)).

Benzyl {2-[(2-(4-bromoethylphenyl)-2,2-difluoroacetylamino)ethyl]carbamate (204).

A solution of ester 209 (726 mg, 2.26 mmol) in trifluoroacetic acid (30 ml) was stirred at r.t. for 3 h and evaporated in vacuo. The residue was dissolved in toluene (30 ml) containing two drops of dimethylformamide. Oxalyl chloride (0.29 ml, 3.39 mmol) was added and the solution stirred at r.t. for 20 h. The amine 210 (438 mg, 2.26 mmol) was added and stirring continued for 24 h. The reaction was quenched with a sat. aq. NaHCO₃ solution (50 ml) and the mixture extracted with CH₂Cl₂ (3 x 50 ml). The combined organic extracts were dried (Na₂SO₄), evaporated in vacuo, and purified by chromatography (CH₂Cl₂/MeOH 98:2) on silica gel to give 204 as a colorless solid (790 mg, 79%), M.p. 133-136 °C (CHCl₃/hexane). IR (CHCl₃): 1705* cm⁻¹ (O=O); 1257m (C-O); 1175m (C-O); 1150m (C-O); 1139m (C-O). ¹H-NMR (200 MHz, CDCl₃): 7.65 (s, 1 H, NH); 7.61, 7.46 (AA'BB', J = 7.9, 4 H, ArH); 7.37-7.39 (m, 5 H, ArH); 5.14 (s, 2 H, OCH₂Ph); 5.14-5.05 (m, 1 H, NH); 4.49 (s, 2 H, CH₂Br); 3.50-3.40 (m, 4 H, H₂C(8), H₂C(9)). ¹³C-NMR (75 MHz, CDCl₃): 165.1 ([t, J = 31.7], C(1));
157.7; 156.7; 142.3; 136.4; 129.1; 128.8; 128.5; 128.3; 125.8 ([J, J = 5.6], C(3)); 114.9 ([J, J = 252.7], C(2)); 67.2; 58.3; 40.8; 40.3. EI-MS: 442/440 (1/1, M⁺ (81Br/79Br)); 355/353 (1/1); 335/333 (3/3, [M - OCH₂Ph]⁺); 221/219 (8/7, [M - NHCH₂CH₂NHCbz]⁺); 177/175 (4/6); 140 (35, [M - NHCH₂CH₂NHCbz - Br]⁺); 91 (100, [C₇H₇]⁺). Anal. calc for C₁₉H₁₉BrF₂N₂O₃ (441.3): C 51.72, H 4.34, N 6.35; found: C 51.31, H 4.34, N 6.28.

**(3R,4S,8R,9S)-10,11-Dihydrocinchonan-9-ol ((+)-212).**

A solution of cinchonine (+)-125 (1.00 g, 3.40 mmol) in ethanol (50 ml) was treated with 10% Pd/C (50 mg) under a hydrogen atmosphere (4 bar) for 5 h. The reaction mixture was filtered through Celite and evaporated in vacuo to give (+)-212 as a colorless solid (quant.), M.p. > 200 °C (lit. [342] 268-269 °C). [α]⁰⁺ = +67.7 (c = 0.50, THF). ¹H-NMR (200 MHz, CDCl₃): 8.90 (d, J = 4.6, 1 H, H-C(14)); 8.16-8.11 (m, 1 H, ArH); 8.04-8.00 (m, 1 H, ArH); 7.74-7.66 (m, 1 H, ArH); 7.61 (d, J = 4.6, 1 H, H-C(13)); 7.55-7.47 (m, 1 H, ArH); 5.64 (d, J = 4.6, 1 H, H-C(9)); 3.18-3.04 (m, 1 H); 2.96-2.66 (m, 4 H); 1.99-1.76 (m, 1 H); 1.74-1.66 (m, 1 H, H-C(4)); 1.64-1.13 (m, 6 H); 0.87 (t, J = 7.2, 3 H, H₃C(11)).

**(3R,4S,8R,9S)-N-{4-[(2-Benzoylcarbonylaminoethyl)carbamoyldifluoromethyl]-phenyl}methyl-3-ethyl-8-(hydroxyquinolin-4-ylmethyl)azoniabicyclo[2.2.2]octane bromide ((+)-213).**
A solution of (+)-10,11-dihydrocinchonine ((+)-212) (268 mg, 0.91 mmol) and benzyl bromide 204 (401 mg, 0.91 mmol) in THF (30 ml) was heated to reflux for 72 h. The reaction mixture was allowed to cool to r.t., evaporated in vacuo, and purified by chromatography (EtOAc/MeOH 9:1) on silica gel to give (+)-213 as a colorless, highly viscous oil (210 mg, 31%). $[\alpha]_D^{19} = +58.3$ (c = 1.00, CHCl$_3$). IR (CHCl$_3$): 1704 (C=O) cm$^{-1}$; 1510 m; 1259 s (C-O); 1136 s (C-O); 909 s. $^1$H-NMR (300 MHz, CDCl$_3$): 8.84 (d, $J$ = 4.5, 1 H, H-C(14)); 8.25-8.20 (m, 1 H, H-C(16)); 8.05-8.00 (m, 1 H, OH); 7.84 (d, $J$ = 4.5, 1 H, H-C(13)); 7.71, 7.42 (AA'BB', $J = 7.5$, 4 H, 2 x H-(23), 2 x H-(24)); 7.62-7.59 (m, 1 H, H-C(19)); 7.34-7.30 (m, 5 H, ArH); 7.12-7.04 (m, 2 H, H-C(17), H-C(18)); 6.48-6.41 (m, 2 H, 2 x NH); 6.04 (d, $J$ = 11.7, 1 H, H-C(21)); 5.82-5.76 (m, 1 H, H-C(9)); 5.22 (d, $J$ = 11.7, 1 H, H-C(21)); 5.10 (s, 2 H, OCH$_2$Ph); 4.14-3.98 (m, 3 H); 3.53-3.35 (m, 4 H, H$_2$C(28), H$_2$C(29)); 3.20-3.13 (m, 1 H); 2.65-2.55 (m, 1 H); 2.10-1.90 (m, 2 H); 1.75-1.38 (m, 6 H); 0.81 (t, $J$ = 6.8, 3 H, H$_3$C(11)). $^{13}$C-NMR (75 MHz, CDCl$_3$): 164.7 ([t, $J$ = 31.1], C(27)); 157.7; 149.8; 147.4; 144.5; 136.5; 134.3; 130.4; 129.8; 128.8 (two overlapping signals); 128.7; 128.5; 127.5; 126.3 ([t, $J$ = 5.2], C(25)); 123.8; 123.4; 119.9; 114.6 ([t, $J$ = 254.5], C(26)); 67.5; 67.1; 65.6; 60.6; 56.7; 56.1; 40.7; 40.3; 35.9; 24.6; 24.2; 24.1; 21.6; 11.4. FAB-MS: 657 (100, [M - Br$^+$]). FAB-HRMS: 657.3241 ([M - Br$^+$, C$_{38}$H$_{43}$F$_2$N$_4$O$_4$, calc. 657.3252).

(3R,4S,8R,9S)-N-[4-(Difluoro-(2-(3-triethoxysilyl)propylureido)ethyl)carbamoylmethyl]phenyl)methyl-3-ethyl-8-(hydroxyquinolin-4-ylmethyl)azoniabicyclo[2.2.2]octane bromide (203).

A solution of cinchonium bromide (+)-213 (190 mg, 0.26 mmol) in ethanol (20 ml) was treated with 10% Pd/C (20 mg) under a hydrogen atmosphere (1 bar) for 4 h. The mixture was filtered through Celite, evaporated in vacuo, and the residue washed with Et$_2$O. The solid was dissolved in THF (25 ml), cooled to 0 °C, and 3-(triethoxysilyl)propylisocyanate (0.06 ml, 0.26 mmol) and pyridine (0.10 ml, 1.30
mmol) were added, and the solution was stirred at r.t. for 2 h. The reaction mixture was evaporated in vacuo to afford 203 as a yellow solid which was directly submitted to the sol-gel process without further purification.

\[(aS,3R,4S,8S,9S)-(2',3'-Dimethoxy-3'-methoxymethyl-1,1'-binaphthalen-7-yl)-(3-ethyl-1-azabicyclo[2.2.2]oct-8-yl)4-chlorobenzoate \((+)-227\).\]

Acetylation of alcohol \((+)-190\) (15 mg, 0.03 mmol) according to Procedure O afforded \((+)-227\) as a colorless solid (11 mg, 58%). \([\alpha]_D^\circ = +28.5 \ (c = 0.50, \text{CHCl}_3)\). IR (CHCl₃): 2935w cm⁻¹; 1715w (C=O); 1267w; 1167m (C-O); 1133vs (C-O); 1117vs (C-O). \(^1\)H-NMR (300 MHz, CDCl₃): 8.07 (s, 1 H, H-C(4')); 7.98 (d, \(J = 9.0, 1 \text{ H}, \text{H-C(4')}\); 7.93 (d, \(J = 8.1, 1 \text{ H}, \text{H-C(5')}\)); 7.86 (d, \(J = 8.4, 1 \text{ H}, \text{H-C(5')}\)); 7.75, 7.29 (AA′BB′, \(J = 8.6, 4 \text{ H}, 2 \times \text{H-(15)}, 2 \times \text{H-(16)}\)); 7.45 (d, \(J = 9.0, 1 \text{ H}, \text{H-C(3')}\)); 7.43 (dd, \(J = 8.4, 1.6, 1 \text{ H}, \text{H-C(6')}\)); 7.41-7.36 (m, 1 H, H-C(6')); 7.22-7.16 (m, 2 H, H-C(7'), H-C(8')); 7.09-7.06 (m, 1 H, H-C(8')); 5.84 (d, \(J = 10.0, 1 \text{ H}, \text{H-C(9)}\)); 4.70 (s, 2 H, H₂C(12)); 3.77 (s, 3 H, OCH₃); 3.58 (s, 3 H, OCH₃); 3.16 (s, 3 H, OCH₃); 3.10-2.86 (m, 3 H); 2.60-2.49 (m, 1 H); 2.28-2.21 (m, 1 H); 1.54-1.22 (m, 4 H); 1.14-0.99 (m, 3 H); 0.88-0.71 (m, 1 H); 0.77 (s, \(J = 3.2, 3 \text{ H}, \text{H}_{3}\text{C(11)}\)). \(^1\)C-NMR (75 MHz, CDCl₃): 165.4; 155.7; 155.0; 139.2; 136.6; 134.2; 133.9; 131.7; 131.4; 131.0; 129.8; 129.4; 129.1; 128.8; 128.7; 128.4; 128.3; 126.2; 125.6; 125.0; 124.5 (two overlapping signals); 124.3; 119.6; 114.5; 70.6; 60.4; 59.4; 58.7; 57.4; 56.8; 41.4; 37.4; 28.6; 27.6; 25.3; 25.2; 12.1. DEI-MS: 663 (13, \(M^+\); 648 (9, [\(M - \text{CH}_3\)]^+); 524 (9, [\(M - \text{COPhCl}\)]^+); 508 (100, [\(M - \text{COPhCl} - \text{CH}_3\)]^+); 492 (24, [\(M - \text{COPhCl} - \text{OCH}_3\)]^+); 138 (96, [\(\text{C}_9\text{H}_{16}\text{N}\)]^+). DEI-MS: 663.2763 (\(M^+\), C₄₁H₄₂ClNO₅, calc. 663.2751).

\(^{17}\)One signal is under the solvent signal.
(aS,3R,4S,8R,9R)-(2,2'-Dimethoxy-3',methoxymethyl-1,1'-binaphthalen-7-yl)-(3-ethyl-1-azabicyclo[2.2.2]oct-8-yl) 4-chlorobenzoate ((+)-228).

Acylation of alcohol (+)-191 (10 mg, 0.02 mmol) according to Procedure O afforded (+)-228 as a colorless solid (6 mg, 47%). \([\alpha]_D^2 = +30.2 \ (c = 0.50, \text{CHCl}_3)\). IR (CHCl3): 2933w cm\(^{-1}\); 1717w (C=O); 1267w; 1136vs (C-O). \(^1\)H-NMR (300 MHz, CDCl3): 8.06 (s, 1 H, H-C(4')); 7.97 (d, \(J = 9.0, 1 \text{ H, H-C(4')})\); 7.90-7.86 (m, 2 H, H-C(5'), H-C(5'')); 7.73, 7.26 (AA'BB', \(J = 8.2, 4 \text{ H, 2 x H-(15), 2 x H-(16)})\); 7.46 (d, \(J = 9.0, 1 \text{ H, H-C(3')}\)); 7.44-7.41 (m, 1 H, H-C(6')); 7.31-7.23 (m, 1 H, H-C(6'')); 7.13 (s, 1 H, H-C(8')); 7.03-6.92 (m, 2 H, H-C(7'), H-C(8')); 5.75 (d, \(J = 10.0, 1 \text{ H, H-C(9)})\); 4.80 (s, 2 H, H2C(12)); 3.77 (s, 3 H, OCH3); 3.60 (s, 3 H, OCH3); 3.35 (s, 3 H, OCH3); 3.07-2.96 (m, 1 H); 2.86-2.73 (m, 3 H); 2.46-2.37 (m, 1 H); 1.50-1.20 (m, 4 H); 0.96-0.79 (m, 4 H); 0.73 (s, \(J = 7.0, 3 \text{ H, H3C(11)})\). \(^{13}\)C-NMR (75 MHz, CDCl3): 165.3; 155.9; 155.2; 139.2; 138.8; 134.1; 133.7; 131.8; 131.0; 129.8; 129.1; 129.0; 128.9; 128.8; 128.7; 128.2; 126.0; 125.5 (two overlapping signals); 125.2; 124.8; 122.7; 119.7; 114.7; 77.4; 70.6; 61.1; 60.2; 58.8; 56.9; 49.2; 37.1; 31.0; 29.8; 25.9; 25.1; 24.1; 12.0. DEI-MS: 663 (9, \(M^+\)); 648 (7, \([M - \text{CH}_3]^+)\); 524 (12, \([M - \text{COPhCl}]^+)\); 508 (62, \([M - \text{COPhCl} - \text{CH}_3]^+)\); 492 (21, \([M - \text{COPhCl} - \text{OCH}_3]^+)\); 138 (100, \([\text{C}_9\text{H}_{16}\text{N}]^+)\). DEI-HRMS: 663.2770 (\(M^+, \text{C}_{41}\text{H}_{42}\text{ClNO}_5\), calc. 663.2751).
Acylation of alcohol \((-\text{192})\) (15 mg, 0.03 mmol) according to Procedure \(O\) afforded \((+)-\text{229}\) as a colorless solid (14 mg, 74%). \([\alpha]_D^{\text{I}} = +54.0\ (c = 0.50, \text{CHCl}_3)\). IR (CHCl\(_3\)): 2933\(w\) cm\(^{-1}\); 1717\(w\) (C=O); 1267\(w\); 1136\(vs\) (C-O); 1117\(vs\) (C-O). \(^1\)H-NMR (300 MHz, CDCl\(_3\)): 8.01 (s, 1 H, H-C(4\(\text{"}\))); 7.94 (d, \(J= 9.0, 1\) H, H-C(4')); 7.84 (d, \(J= 8.6, 1\) H, H-C(5')); 7.81 (d, \(J= 8.4, 1\) H, H-C(5'')); 7.60, 7.26 (AA'BB', \(J= 8.6, 4\) H, 2 \(\times\) H-(15), 2 \(\times\) H-(16)); 7.41 (d, \(J= 9.0, 1\) H, H-C(3')); 7.37 (dd, \(J= 8.6, 1.9, 1\) H, H-C(6')); 7.29-7.23 (\(m\), 1 H, H-C(6'')); 7.21-7.15 (\(m\), 1 H, H-C(7')); 7.14-7.12 (\(m\), 1 H, H-C(8')); 6.93 (d, \(J= 3.4, 1\) H, H-C(8'')); 5.87 (d, \(J= 8.7, 1\) H, H-C(9)); 4.82 (d, \(J= 12.5, 1\) H, H-C(12)); 4.75 (d, \(J= 12.5, 1\) H, H-C(12)); 3.74 (s, 3 H, OCH\(_3\)); 3.60 (s, 3 H, OCH\(_3\)); 3.34 (s, 3 H, OCH\(_3\)); 3.07-2.89 (\(m\), 2 H); 2.84-2.72 (\(m\), 1 H); 2.42-2.31 (\(m\), 1 H); 2.18-2.09 (\(m\), 1 H); 1.79-1.13 (\(m\), 7 H); 0.81 (t, \(J= 7.2, 3\) H, H\(_3\)C(11)); 0.80-0.70 (\(m\), 1 H). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): 165.0; 155.6; 155.1; 139.4; 138.4; 134.2; 133.8; 131.6; 130.9; 130.8; 129.8; 129.1; 128.9; 128.8; 128.6; 128.4; 128.0; 126.0; 125.5; 124.8; 124.6; 123.3; 122.9; 119.6; 114.4; 79.2; 70.7; 61.1; 60.5; 58.8; 58.3; 56.9; 42.1; 37.4; 28.5; 27.6; 25.3; 25.2; 12.1. DEI-MS: 663 (11, \(M^+\)); 648 (15, \([M - \text{CH}_3]^+\)); 524 (10, \([M - \text{COPhCl}]^+\)); 508 (100, \([M - \text{COPhCl} - \text{CH}_3]^+\)); 492 (33, \([M - \text{COPhCl} - \text{OCH}_3]^+\)); 138 (91, \([\text{C}_9\text{H}_{16}\text{N}]^+\)). DEI-HRMS: 663.2758 (\(M^+, \text{C}_{41}\text{H}_{42}\text{ClNO}_5\), calc. 663.2751).
Experimental Part 203

(aS,3R,4S,8R,9S)-(2',2'-Dimethoxy-3'-methoxymethyl-1,1'-binaphthalen-7-yl)-(3-ethyl-1-azabicyclo[2.2.2]oct-8-yl) 4-chlorobenzoate ((+)-230).

Acylation of alcohol (+)-193 (10 mg, 0.02 mmol) according to Procedure O afforded (+)-230 as a colorless solid (7 mg, 55%). \( \alpha \)\(^{2} \) = +14.0 (c = 0.50, CHCl\(_{3}\)). IR (CHCl\(_{3}\)): 2933w cm\(^{-1}\); 1716w (C=O); 1272w; 1136vs (C-O). \(^{1}\)H-NMR (300 MHz, CDCl\(_{3}\)): 8.02 (j, 1 H, H-C(4'')); 7.99-7.91 (m, 2 H); 7.83 (d, J = 8.4, 1 H, H-C(5'')); 7.69, 7.34 (AA'BB', J = 8.6, 4 H, 2 x H-(15), 2 x H-(16))); 7.42-7.34 (m, 3 H, H-C(3'), H-C(6'), H-C(6'')); 7.24-7.15 (m, 1 H, H-C(7'')); 7.12-7.08 (m, 2 H, H-C(8'), H-C(8'')); 5.97 (d, J = 8.1, 1 H, H-C(9)); 4.60 (d, J = 12.6, 1 H, H-C(12)); 4.51 (d, J = 12.6, 1 H, H-C(12)); 3.75 (s, 3 H, OCH\(_{3}\)); 3.52 (s, 3 H, OCH\(_{3}\)); 3.08 (s, 3 H, OCH\(_{3}\)); 2.91-2.72 (m, 2 H); 2.65-2.41 (m, 2 H); 1.65-1.20 (m, 5 H); 0.94-0.83 (m, 1 H); 0.86 (q, J = 7.2, 2 H, H\(_{2}\)C(10)); 0.74 (t, J = 7.2, 3 H, H\(_{3}\)C(11)). \(^{13}\)C-NMR (75 MHz, CDCl\(_{3}\)): 165.0; 155.5; 154.7; 139.6; 134.1; 133.9; 131.7; 131.5; 131.0; 130.9; 129.8; 129.0; 128.9; 128.8; 128.3; 128.2; 128.1; 126.1; 125.9; 124.9; 124.8; 123.4; 122.7; 119.5; 114.2; 78.1; 70.4; 60.7; 60.3; 58.7; 56.8; 50.4; 49.7; 37.4; 27.2; 25.9; 25.3; 24.2; 11.9. DEI-MS: 663 (15, \( M^{+} \)); 648 (8, [\( M \) - CH\(_{3}\)]\(^{+} \)); 524 (14, [\( M \) - COPhCl\(^{+} \))]; 508 (58, [\( M \) - COPhCl - CH\(_{3}\)]\(^{+} \)); 492 (16, [\( M \) - COPhCl - OCH\(_{3}\)]\(^{+} \)); 138 (100, [C\(_{9}\)H\(_{16}\)N\(^{+} \))]. DEI-HRMS: 663.2768 (\( M^{+} \), C\(_{41}\)H\(_{42}\)ClNO\(_{5}\), calc. 663.2751).

(3R,4S,8R,9S)-(5-Ethyl-1-azabicyclo[2.2.2]oct-2-yl)quinolin-4-yl 4-chlorobenzoate ((-)-231).
Acylation of 10,11-dihydrocinchonine (+)-212 (100 mg, 0.34 mmol) according to Procedure O afforded (-)-231 as a colorless solid (70 mg, 47%), M.p. 126-128 °C. \([\alpha]_D^\circ = -41.8\ (c = 1.00, \text{CHCl}_3)\). IR (KBr): 2933w cm\(^{-1}\); 1717m (C=O); 1589w; 1267m; 1106m (C-O); 1083m (C-O). \(^1\)H-NMR (200 MHz, CDCl\(_3\)): 8.89 (d, \(J = 3.9, 1 \text{ H}, \text{H-C}(14)\)); 8.33-8.28 (m, 1 H); 8.17-8.11 (m, 1 H); 8.03, 7.45 (AA'BB', \(J = 8.5, 4 \text{ H}, 2 \times \text{H-(23)}, 2 \times \text{H-(24)}\)); 7.79-7.59 (m, 2 H); 7.47 (d, \(J = 3.9, 1 \text{ H}, \text{H-C}(13)\)); 6.77 (d, \(J = 7.5, 1 \text{ H}, \text{H-C}(19)\)); 3.51-3.39 (m, 1 H); 2.93-2.67 (m, 4 H); 1.94-1.44 (m, 8 H); 0.92 (t, \(J = 7.1, 3 \text{ H}, \text{H}_3\text{C}(11)\)). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): 150.3; 148.9; 145.7; 140.2; 131.3; 130.8; 129.5; 129.2; 129.0; 128.5; 127.1; 126.4; 123.6; 118.9; 74.8; 60.1; 50.8; 50.0; 37.5; 27.2; 26.2; 25.5; 24.0; 12.0. DEI-MS: 434 (13, \(M^+\)); 295 (18, \([M - \text{COPhCl}]^+\)); 279 (77, \([M - \text{OCOPhCl}]^+\)); 138 (100, \([\text{C}_9\text{H}_16\text{N}]^+\)). Anal. calc. for C\(_{26}\)H\(_{27}\)ClN\(_2\)O\(_2\) (434.97): C 71.80, H 6.26, N 6.44, found: C 70.30, H 6.18, N 6.41.

Dihydrobenzoin (221).

\[
\text{HO} \quad \text{Ph} \quad \text{221} \quad \text{OH} \quad \text{Ph}
\]

To a solution of trans-stilbene (220) (15 mg, 0.08 mmol), catalyst (5 mg, 0.01 mmol, 10 mol%), and \(N\)-methylmorpholine-\(N\)-oxide (12 mg, 0.10 mmol) in acetone (0.50 ml) and water (0.10 ml) was added a 0.5M solution of osmium tetroxide in toluene (0.4 \(\mu\)l, 0.2 \(\mu\)mol). The solution was shaken (30 s) and placed in a refrigerator at 4 °C with occasional shaking for 10 h. Solid Na\(_2\)S\(_2\)O\(_5\) (10 mg) was added to the cold solution and the mixture shaken and left at r.t. for 1 h. The mixture was then diluted with CH\(_2\)Cl\(_2\) (20 ml) and washed with 1M HCl (2 \(\times\) 20 ml). The organic phase was dried (Na\(_2\)SO\(_4\)), evaporated \textit{in vacuo}, and purified by chromatography (hexane/EtOAc 80:20) on silica gel to give 221 as a colorless solid, M.p. 110-112 °C (lit. [343] 122.5 °C). \(^1\)H-NMR (200 MHz, CDCl\(_3\)): 7.27-7.12 (m, 10 H, ArH); 4.74 (5, 2 H).

**Catalysis experiments:**

with (3R,4S,8R,9S)-(−)-231 95% yield 88% (\(R,R\))

(aS,3R,4S,8S,9S)-(−)-227 57% yield 2% (\(S,S\))

(aS,3R,4S,8R,9R)-(−)-228 96% yield 8% (\(R,R\))

(aS,3R,4S,8S,9R)-(−)-229 68% yield 67% (\(S,S\))

(aS,3R,4S,8R,9S)-(−)-230 99% yield 42% (\(R,R\))

The enantiomeric excess was determined by analytical HPLC on a 'Pirkle Covalent (S,S)-Whelk-O1' chiral phase (hexane/isopropanol 95:5).
5. Appendix

Crystal Structure Data of Compound (±)-100:

Table 1. Crystal data and structure refinement for C16 H22 N2 O5 S

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<td>alpha = 90.0 deg., beta = 93.90(2) deg., gamma = 90.0 deg.</td>
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<td>Approximate crystal size</td>
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Data collection

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<td>Theta range for data collection</td>
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<td>Index ranges</td>
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<td>Reflections collected</td>
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<td>Independent reflections</td>
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Solution (SHELXS-86), Refinement (SHELXL-93)

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<th>Refinement method</th>
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<td>Exponentially mod. weight factor</td>
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<td>Goodness-of-fit on $F^2$</td>
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<td>Final R indices ($I &gt; 2\sigma(I)$)</td>
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<tr>
<td>Largest diff. peak and hole</td>
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Table 2. Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters ($A^2 x 10^3$) for 1. $U(eq)$ is defined as one third of the trace of the orthogonalized Uij tensor.

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<th>x</th>
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<th>U(eq)</th>
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Table 3. Bond lengths [Å] and angles [deg] for 1.

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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å^2 x 10^{-3}) for 1.
The anisotropic displacement factor exponent takes the form:
-2 \pi^2 \left[ h^2 a^* a^* U_{11} + \ldots + 2 h k a^* b^* U_{12} \right]

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Table 5. Hydrogen coordinates (Å x 10^{-4}) and isotropic
displacement parameters (Å^2 x 10^{-3}) for 1.

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Appendix 209

\[ {^1H,^1H}-\text{COSY Spectra (500 MHz, CDCl}_3 \text{)} \text{ of Compound (+)-190:} \]
\{^1\text{H},^1\text{H}\}\text{-COSY Spectra (500 MHz, CDCl}_3\}\text{ of Compound (+)-191:}
Appendix

$^{1\text{H},1\text{H}}$-COSY Spectra (500 MHz, CDCl$_3$) of Compound (−)-192:
\{^{1}\text{H},^{1}\text{H}\}\text{-COSY Spectra (500 MHz, CDCl}_{3}\text{ of Compound (\pm)-193:}
$^{1}H(^{1}H)$-NOE Spectra (300 MHz, CDCl$_3$) of Compound (+)-190:
$^1$H$_{(1H)}$-NOE Spectra (300 MHz, CDCl$_3$) of Compound (+)-191:
$^1$H-$^1$H-NOE Spectra (300 MHz, CDCl$_3$) of Compound (−)-192:
$^1$H-$^1$H-NOE Spectra (300 MHz, CDCl$_3$) of Compound (+)-193:
$^{29}$Si-MAS-NMR Spectra (80 MHz) of the Sol-Gel:

$^{13}$C-MAS-NMR Spectra (100 MHz) of the Sol-Gel:
Sol-Gel Isotherm (N\textsubscript{2} adsorption/desorption at 77K):

![Isotherm Plot](image)

Sol-Gel Pore Distribution:

![Pore Distribution](image)
6. References


Computer Simulations of the Solvent Dependence of Apolar Association Strength: Gibbs Free Energy Calculations on a Cyclophane-Pyrene Complex in Water and Chloroform.


References


References 227


References


References 231


Conformation (Inversion and Rotational Barriers) and Electronic Properties of Sulfamide.


T. Horiiuchi, T. Ohta, M. Stephan, H. Takaya, Tetrahedron Asymmetry 1994, 5, 325-328. Synthesis of (R) - and (S)-7,7'-Bis(diphenylphosphino)-2,2'-dimethoxy-1,1'-binaphthyl, a New Axially Dissymmetric Bis(triarylphosphine).


Chapter 6

piperidineacetic Acids, Synthetic Precursors of Cinchona and Indole Alkaloids.
Reinvestigation of Classical Synthesis of Cinchona Alkaloids. 
Reinvestigation of the Classical Synthesis of Cinchona Alkaloids. II. The Synthesis of Quinine and its Naturally Occurring Diastereomers from Quinotoxine. 
Total Synthesis of Cinchona Alkaloids. 2. Stereoselective Total Synthesis of Quinine and Quinidine. 
Total Synthesis of Cinchona Alkaloids. 3. Syntheses of Quinuclidine Intermediates. 
Total Synthesis of Cinchona Alkaloids. 4. Syntheses via Quinuclidine Precursors. 

N-Methoxy-N-Methylamides as Effective Acylating Agents. 
An Efficient Synthesis of Optically Active α-(β-Butoxy carbonyl amino)-aldehydes from α-Amino Acids.

Highly Selective Oxidative Cross-Coupling of Substituted 2-Naphthols: A Convenient Approach to Unsymmetrical 1,1'-Binaphthalene-2,2'-diols.

An Optimized Synthesis of Dimethyl 2,2'-Dihydroxy-1,1'-Binaphthalene-3,3'-dicarboxylate and of Methyl 2,2'-Dihydroxy-1,1'-Binaphthalene-3-Carboxylate. 
The Oxidative Cross-Coupling of Substituted 2-Naphthols, Part I: The Scope and Limitations.

A Facile Synthesis of 2-Amino-2'-Hydroxy-1,1'-Binaphthyl and 2,2'-Diamino-1,1'-binaphthyl by Oxidative Coupling Using Copper(II) Chloride. 
Synthesis of Enantiomerically Pure 2,2'-Dihydroxy-1,1'-binaphthyl, 2,2'-Diamino-1,1'-binaphthyl, and 2-Amino-2'-hydroxy-1,1'-binaphthyl. 
Comparison of Processes Operating as Diastereoselective Crystallization and as Second-Order Asymmetric Transformation. 

The Oxidative Cross-Coupling of Substituted 2-Naphthols, Part 2. Selectivity as a Mechanistic Probe.

Selective Cross-Coupling of 2-Naphthol and 2-Naphthylamine Derivatives. A Facile Synthesis of 2,2',3-Trisubstituted and 2,2',3,3'-Tetrasubstituted 1,1'-Binaphthyls.

2-Bromonaphthalene.

A Versatile Method for the Resolution and Absolute Configuration Assignment of Substituted 1,1'-Bi-2-naphthols.


1125-1136. Carboxylic Acids and Tetrazoles as Isosteric Replacements for Sulfate in Cholecystokinin Analogues.


Curriculum Vitae

1971 Born on February 14, in Martigny, Switzerland.


1990-1994 Undergraduate chemistry studies at the Université de Lausanne; Final year research project with Dr. Y. Landais: 'Dimethylthienylsilane as a New Masked Hydroxyl Group'. Diploma October 1994.

1994 Diploma thesis with Prof. Dr. T. Gallagher at the University of Bristol, UK: 'Synthetic Studies Directed Towards Understanding the Biological Function of Anatoxin-A'.

1995-1998 Ph. D. thesis in organic chemistry at the Swiss Federal Institute of Technology (ETH) Zürich, under the direction of Prof. Dr. F. Diederich: 'Applications of Molecular Modeling and Supramolecular Chemistry: De Novo Design of MHC Class II Inhibitors and Rational Design of Ligands for Asymmetric Catalysis'.

1996 Research experience with Dr. G. Olson at Hoffmann-La Roche Inc., Nutley (New Jersey) on the MHC class II project in collaboration with Roche scientists (Inflammation/Autoimmune Disease Department).

1997, 1998 Teaching assistant in the organic chemistry practica and supervisor of the diploma thesis of two final year students.

from 1999 Post-doctoral position with Prof. Dr. A. B. Smith, III at the University of Pennsylvania, Philadelphia.

Zürich, December 1998

Laurent Ducry