Synthesis and evaluation as glycosidase inhibitors of aminocarbasugars, spiro-diaziridines, spiro-aziridines, and 7-azanorbornanes. Neighbouring group participation in the bromination of N-acylated cyclohex-3-en-1-amines

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“We are all agreed that your theory is crazy. The question, which divides us, is whether it is crazy enough to have a chance of being correct. My own feeling is that it is not crazy enough.”

Niels Bohr
For my parents

For Petra
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Abbreviations

DMAP 4-dimethylaminopyridine
DME 1,2-dimethoxy ethane
DMF dimethylformamide
DMSO dimethylsulfoxide
eq. equivalents
FC flash chromatography
FPT freeze-pump-thaw
$\tau_{1/2}$ half the width of an NMR signal at 50% of its height.
IC$_{50}$ inhibitor concentration at 50% inhibition
mCPBA 3-chloroperbenzoic acid
MS molecular sieves
NBS N-bromosuccinimide
NMO N-methyl morpholine N oxide
TLC thin layer chromatography

For analytical methods, substituents, and protecting groups I use the common abbreviations (see text books of general and organic chemistry and of protecting groups).
Summary

(+)-Valienamine (22) was prepared in seven steps and in an overall yield of 27% from 2,3,4,6-tetra-O-benzyl-D-glucopyranose (39). Key steps of the synthesis were a ring-closing metathesis of the diene 441 to the cyclohexenol 40 in the presence of Grubbs’s ruthenium complexes 312 (58% yield of 40) or 315 (91% yield of 40), and a [3.3]-sigmatropic rearrangement of the cyanate 457 derived from 40 to the isocyanate 458. Similarly, the cyclohexenol 42 was prepared in four steps and 64% yield from 2,3,4,6-tetra-O-benzyl-D-mannopyranose and transformed into the derivatives 43 (88%) and 479 (84%) of the manno-isomer of (+)-valienamine. The cyclopentenol 424 was prepared in four steps and 47% yield from 2,3,5-tri-O-benzyl-D-arabinofuranose.

The carbasugar-derived spiro-diaziridines 45 and 615, potential inhibitors of α- and β-glucosidases, were prepared from the validoxylamine A-derived cyclohexanone 606 using the Schmitz method. The trimethylsilyl protecting groups of 606 are crucial for the formation of 45 in good yields. Oxidation of 45 gave the spiro-diazirine 613. The diaziridine 45 (pKHA = 2.6) and the diazirine 613 did not inhibit the β-glucosidases from sweet almonds, the β-glucosidase from Caldocellum saccharolyticum, and the α-glucosidase from yeast. The N-benzyl diaziridine 615 proved a very weak inhibitor of the α-glucosidase, but did not inhibit the β-glucosidases.

To determine if the weak inhibition by the diaziridines is due to the low basicity or to geometric factors, I prepared the spiro-aziridines 46 and 47 and 1-epi-validamine (48) and evaluated their inhibitory activity. I also included the known inhibition data for validamine (12) in the comparison. The aziridines 46 and 47 were prepared from the alkene 53 which was obtained in a yield of 77% by Wittig methylenation of the known cyclohexanone 52. Aziridination of the alkene 53 was not successful, while epoxidation furnished the spiro-epoxides 619 (61%) and 618 (25%). Azide opening of the epoxides, mesylation, LiAlH4 reduction, and deprotection gave the aziridines 46 (29%) and 47 (ca. 35%). 1-Epi-validamine (48) was prepared from the known carbaglucose 54 by mesylation, substitution with azide, and deprotection. The aziridine 46 (pKHA = 6.8) is a weak irreversible inhibitor of the β-glucosidase from Caldocellum saccharolyticum (Kᵢ = 3 mM) and a weak reversible inhibitor of the α-glucosidase from yeast, but did not inhibit the β-glucosidases from sweet almonds.
The poorly stable aziridine 47 weakly inhibited the three enzymes. Also, 1-epi-validamine (48, pK_HA = 8.4) proved only a weak inhibitor, similarly as validamine (12). These results suggest that structural factors rather than basicity are at the root of the weak inhibition by the diaziridines, the aziridines, and 1-epi-validamine. This is highlighted by the strong inhibition by the known cyclopentylamines 35 (pK_HA = 7.9) and 36 which are micromolar inhibitors of these glycosidases. The small difference in the pK_HA of the cyclohexylamine 48 and the cyclopentylamine 35 cannot account for the observed difference in the affinity to the enzymes. To further elucidate the strong inhibition by the cyclopentylamine 36 I prepared the related cyclohexylamines 632 and 635. These are only weak inhibitors of the β-glucosidases from sweet almonds and the α-glucosidase from yeast, suggesting that the strong inhibition by the cyclopentylamines depends on the cyclopentane skeleton.

In view of the synthesis of bicyclic amines that are of interest as building blocks and potential glycosidase inhibitors I studied the intramolecular bromoamidation and the dibromination-cyclisation of the N-acylcyclohex-3-en-1-amines 712, 71, 714, 716, 72, 718, and 655. The trifluoroacetamides 71, 72, and 655 reacted with NBS in AcOH to give the dihydro-1,3-oxazines 720 (31%), 724 (79%), and 725 (81%). The trifluoroacetamide 71 led also to the bromo-acetate 721 (24%). The stereoselectivity of the dibromination of the alkenes 712 and 71 depends on the nature of the protecting group, the reagent, and the reaction conditions. Br₂ in CH₂Cl₂ transformed the alkenes 712 and 71 predominantly into the expected diaxial trans-
trans-dibromides 728 and 730. The reaction of 71 in CH2Cl2 with PhMe3NBr3 or with Br2 in the presence of Et4NBr gave predominantly the diequatorial trans-cis 729 besides some 730, denoting a neighbouring group participation of NHCOCF3. Bromination of the C(5) substituted N-acyl-4-aminocyclohexenes 714, 716, 72, and 718 in CH2Cl2 was accompanied by intramolecular side-reactions that were suppressed by the addition of excess Et4NBr to PhMe3NBr3. Under these conditions, 714 reacted to the dibromides 737 (84%) and 738 (6%), while the reaction with Br2 afforded 737 (28%) and 738 (30%) along with the dihydrooxazinone 739 (36%). Similarly, 716 reacted with PhMe3NBr3/Et4NBr to the dibromide 731 (82%), while bromination with Br2 led to the dibromides 731 (18%) and 732 (6%), the dihydrooxazinone 733 (43%), and the bicyclic ether 734 (32%). The N-trifluoroacetamide 72 reacted with PhMe3NBr3/Et4NBr to the dibromide 735 (89%), and with Br2 to the dibromides 735 (42%) and 736 (32%) and the dihydro-1,3-oxazine 724 (19%). The N-benzyl-N-Boc derivative 718 did not yield any dibromide; it reacted with PhMe3NBr3/Et4NBr to the dihydrooxazinone 740, and with Br2 to the dihydrooxazinone 740 (32%) and the bicyclic ether 741 (26%). The high stereoselectivity of the bromination with PhMe3NBr3/Et4NBr was rationalised by postulating a neighbouring group participation of the NHR substituent, leading to a preferred diaxial dibromination of the pseudoaxial N-acylcyclohex-3-enyl-1-amines.

Deprotection, cyclisation, and carbamoylation transformed the dibromides 729, 737, and 731 into the 7-azanorbornanes 744 (93%), 761 (62%), and 754 (84%). A corresponding transformation of the dibromides 728 and 738 into bicyclic azetidines (6-azabicyclo[3.1.1]heptanes) could not be achieved. Prolonged heating of the free amines 747 and 759 in 1,3-dichlorobenzene at temperatures above 120°C, followed by carbamoylation led to the 7-azanorbornanes 744 and 761. This suggests that at these temperatures the dibromides 747 and 759 epimerised. Further attempts to prepare 6-azabicyclo[3.1.1]heptanes were also not successful. A Pd(0)-catalysed decarboxylative rearrangement of the N-tosyl-2-oxa-4-azabicyclo[3.3.1]nona-2,7-dienes failed to undergo such a rearrangement.

The 7-azanorbornanes 744 and 754 were transformed via HBr-elimination and stereoselective dihydroxylation into the diols 58 (30% overall yield (8 steps) from cyclohex-3-enecarboxylic acid) and 59 (18% overall yield (13 steps) from butadiene and maleic anhydride). These hydroxylated 7-azanorbornanes, mimicking a manno-pyranoside in a 1,4B conformation, are
only weak inhibitors of the \( \beta \)-mannosidase from snail, the \( \alpha \)-mannosidase from jack bean, the \( \beta \)-glucosidases from sweet almonds, the \( \beta \)-glucosidase from *Caldocellum saccharolyticum*, and the \( \alpha \)-glucosidase from brewer’s yeast. The weak inhibition by 58 and 59 suggests that these enzymes do not stabilise \( 1,4_B \) reactive conformers.
Zusammenfassung

(+)-Valienamin (22) wurde in sieben Schritten und in einer Gesamtausbeute von 27% aus 2,3,4,6-Tetra-\(\text{O}\)-benzyl-D-glucopyranose (39) hergestellt. Die Schlüsselschritte dieser Synthese waren eine ringschliessende Alkenmetathese des Diens 441 zum Cyclohexenol 40 in Gegenwart der Grubbs’-schen Ruthenium-Komplexe 312 (58% Ausbeute an 40) oder 315 (91% Ausbeute an 40) und eine [3,3]-sigmatrope Umlagerung des von 40 abgeleiteten Cyanats 457 in das Isocyanat 458. Auf ähnliche Weise wurde das Cyclohexenol 42 in vier Schritten und 64% Ausbeute aus 2,3,4,6-Tetra-\(\text{O}\)-benzyl-D-mannopyranose hergestellt und in die Derivate 43 (88%) und 479 (84%) des Manno-Isomers von (+)-Valienamin umgewandelt. Das Cyclopentenol 424 wurde in vier Schritten und 47% Ausbeute aus 2,3,5-Tri-\(\text{O}\)-benzyl-D-arabinofuranose hergestellt.

Die spiro-Diaziridine 45 und 615 sind Carbazucker-Derivate und potentielle Hemmer von \(\alpha\)-und \(\beta\)-Glucosidasen. Sie wurden aus dem von Validoxylamin A abgeleiteten Cyclohexanon 606 mit der Schmitz-Methode hergestellt. Um hohe Ausbeuten an 45 zu erzielen, waren die Trimethylsilyl-Schutzgruppen von 606 essenziell. Die Oxidation von 45 führte zum spiro-Diazirin 613. Die Diaziridine 45 (p\(\text{KHA}\) = 2.6) und das Diazirin 613 hemmten weder die \(\beta\)-Glucosidasen aus Süßmandeln, noch die \(\beta\)-Glucosidase aus Caldocellum saccharolyticum, noch die \(\alpha\)-Glucosidase aus Bierhefe. Das \(N\)-Benzyldiaziridin 615 erwies sich als ein sehr schwacher Hemmer der \(\alpha\)-Glucosidase, war jedoch inaktiv gegen die \(\beta\)-Glucosidasen.

Um zu ergründen, ob die schwache Hemmwirkung der Diaziridine von ihrer geringen Basizität oder von geometrischen Faktoren herrührt, habe ich die spiro-Aziridine 46 und 47 und 1-epi-Validamin (48) hergestellt und ihre Hemmwirkung untersucht. Die bekannten Hemmwerte für Validamin (12) habe ich ebenso in den Vergleich mit aufgenommen. Die Aziridine 46 und 47 wurden aus dem Alken 53 hergestellt, welches man in 77% Ausbeute durch Wittig-Methylenierung des bekannten Cyclohexanons 52 erhielt. Eine Aziridinierung des Alkens 52 war nicht erfolgreich. Hingegen führte eine Epoxidierung zu den Spiro-Epoxiden 619 (61%) und 618 (25%). Ringöffnung der Epoxide mit Azid, Mesylierung, LiAlH\(_4\) Reduktion und Entfernung der Schutzgruppen ergab die Aziridine 46 (29%) und 47 (ca. 35%). 1-epi-Validamin (48) wurde aus der bekannten Carbaglucose 54 durch
Mesylierung, Substitution mit Azid und Entfernung der Schutzgruppen erhalten. Das Aziridin 46 (pK\textsubscript{HA} = 6.8) ist ein schwacher irreversibler Hemmer der $\beta$-Glucosidase aus *Caldocellum saccharolyticum* ($K_i = 3$ mM) und ein schwacher reversibler Hemmer der $\alpha$-Glucosidase aus Bierhefe. Es hemmte aber nicht die $\beta$-Glucosidasen aus Süßmandeln. Das wenig stabile Aziridin 47 hemmte diese drei Glucosidasen schwach. Ebenso erwies sich das 1-epti-Validamin (48, pK\textsubscript{HA} = 8.4) als schwacher Hemmer, ähnlich wie Validamin (12). Diese Ergebnisse weisen darauf hin, dass die schwache Hemmwirkung der Diaziridine, der Aziridine und des 1-epti-Validamins eher auf strukturellen Faktoren als auf der Basizität beruht. Dies wird untermauert durch die starke Hemmwirkung der Cyclopentylamine 35 (pK\textsubscript{HA} = 7.9) und 36, welche mikromolare Hemmer der untersuchten Glucosidasen sind. Der geringe pK\textsubscript{HA}-Unterschied zwischen dem Cyclohexylamin 48 und dem Cyclopentylamin 35 kann nicht für den beobachteten Unterschied der Hemmwirkung Ausschlag gebend sein. Um die starke Hemmwirkung des Cyclopentylamins 36 weiter zu ergründen, habe ich die verwandten Cyclohexylamine 632 und 635 hergestellt. Diese sind nur schwache Hemmer der $\beta$-Glucosidase aus Mandeln und der $\alpha$-Glucosidase aus Bierhefe, was darauf hindeutet, dass die starke Hemmwirkung der Cyclopentylamine auf dem Cyclopentangerüst basiert.

Im Hinblick auf die Synthese von bicyclischen Aminen, welche als Synthese-Bausteine und als potentielle Glycosidase-Hemmer von Interesse sind, habe ich die intramolekulare Bromoamidierung und die Dibromierung-Zyklisierung der *N*-[Acyl]cyclohex-3-en-1-amine
Die Reaktion der Trifluoracetamide 71, 72, und 655 mit NBS in AcOH führte zu den Dihydro-1,3-oxazinen 720 (31%), 724 (79%) und 725 (81%). Aus 71 wurde zudem das Bromacetat 721 (24%) gebildet. Die Stereoselektivität der Bromierung der Alkene 712 und 71 hängt von der Art der Schutzgruppen, dem Reagens und den Reaktionsbedingungen ab. Mit Br₂ in CH₂Cl₂ wurden die Alkene 712 und 71 vorwiegend in die erwarteten dialxialen trans-trans-Dibromide 728 und 730 umgewandelt. Die Reaktion von in CH₂Cl₂ gelöstem 71 mit PhMe₃NBr₃ oder mit Br₂ in Gegenwart von Et₄NBr führte überwiegend zum diequatorialen trans-cis 729 neben etwas 730, was auf eine Nachbargruppenbeteiligung von NHCOCF₃ hinweist. Die Bromierung der C(5)-substituierten N-Acyl-4-aminocyclohexene 714, 716, 72 und 718 in CH₂Cl₂ wurde von intramolekularen Nebenreaktionen begleitet. Diese Nebenreaktionen wurden bei der Bromierung mit PhMe₃NBr₃ durch einen Überschuss Et₄NBr unterdrückt. Unter diesen Bedingungen reagierte 714 zu den Dibromiden 737 (84%) und 738 (6%), während die Reaktion mit Br₂ neben 737 (28%) und 738 (30%) auch das Dihydrooxazinon 739 (36%) lieferte. Ähnlich reagierte 716 mit PhMe₃NBr₃/Et₄NBr zum Dibromid 731 (82%) und mit Br₂ zu den Dibromiden 731 (18%) und 732 (6%), dem Dihydrooxazinon 733 (43%) und dem bicyclischen Ether 734 (32%). Das N-trifluoracetamid 72 reagierte mit PhMe₃NBr₃/Et₄NBr zum Dibromid 735 (89%) und mit Br₂ zu den Dibromiden 735 (42%) und 736 (32%) und dem Dihydro-1,3-oxazin 724 (19%). Die Bromierung des N-Benzyl-N-Boc-Derivats 718 lieferte keine Dibromide; es reagierte mit PhMe₃NBr₃/Et₄NBr zum Dihydrooxazinon 740 und mit Br₂ zum Dihydrooxazinon 740 (32%) und dem bicyclischen Ether 741 (26%). Als Erklärung für die hohe Stereoselektivität der Bromierung mit PhMe₃NBr₃/Et₄NBr wurde eine Nachbargruppenbeteiligung durch den NHR Substituenten postuliert, welche zu einer bevorzugten dialxialen Bromierung der pseudoaxialen N-Acylcyclohex-3-enyl-1-amine führt.

[3.3.1]hept-2-enen. Aber die versuchte Umlagerung einiger 2-Oxa-4-aza-bicyclo[3.3.1]nona-2,7-diene misslang.

Die 7-Azanorbornane 744 und 754 wurden über HBr-Eliminierung und stereoselektive Dihydroxylierung in die Diole 58 (30% Gesamtausbeute (8 Schritte) aus Cyclohex-3-encarbonsäure) und 59 (18% Gesamtausbeute (13 Schritte) aus Butadien und Maleinsäureanhydrid) umgewandelt. Diese hydroxylierten 7-Azanorbornane ahmen ein manno-Pyranosid in einer 1,4\(B\) Konformation nach. Sie sind nur schwache Hemmer der \(\beta\)-Mannosidase aus Schnecken, der \(\alpha\)-Mannosidase aus der Jackbohne, der \(\beta\)-Glucosidasen aus Süßmandeln, der \(\beta\)-Glucosidase aus Caldocellum saccharolyticum und der \(\alpha\)-Glucosidase aus Bierhefe. Die schwache Hemmwirkung von 58 und 59 bedeutet, dass diese Enzyme allfällige reaktive 1,4\(B\) Konformere nicht stabilisieren.
Non-covalent intermolecular interactions are of decisive importance in supramolecular chemistry (molecular recognition, organic materials, nano architecture), in catalysis (binding of the substrate to the catalyst), in biochemistry (enzymatic catalysis, signal transduction, transcription and translation), and in medicinal chemistry (interaction of agonists, antagonists, and inhibitors with receptors, interaction of inhibitors with enzymes, induced fit: modification of the host in contact with the guest).

Although the molecular forces involved in non-covalent intermolecular interactions are fairly well understood, and several packages of modelling programs are available, predictions of the strength of these interactions are subject to most frequent failure, and even interpretations of experimental data are often ambiguous or wrong (see [1] [2] for a prominent example of a complete misinterpretation of experimental data by docking studies). Therefore, experimental studies of non-covalent complexes are still required in order to improve our understanding of these interactions. A complete knowledge of the underlying forces and their interrelations is a prerequisite for precise predictions of ligand-host complexes which would allow a truly rational design of catalysts, enzyme inhibitors, and drugs. The state of the art of current rational drug design is that 1 – 10% of the predicted ligands actually bind the target vs. 0.1 – 1% of randomly chosen compounds (H. J. Böhm, oral presentation at the University of Freiburg, Germany, 1998).

The subject of this thesis is the synthesis of 5a-carbapyranosides and their evaluation as glycosidase inhibitors.

Glycosidases are involved in important biological processes (vide infra) and therefore are potential pharmaceutical targets. In fact, several drugs in clinical use are glycosidase inhibitors. However, glycosidases have not (yet) received as much attention in medicinal chemistry as one might expect. This is in part due to the high hydrophilicity of saccharides and their analogues which may impair their translocation through membranes. Also, the complexity of the structure of glycosides and their analogues renders them rather challenging for large scale production. Glycosidases are, however, applied in large-scale technical processes such as the processing of municipal waste and the conversion of starch to glucose. Glycosidases are also used as fabric softeners in detergents.

Glycosidase inhibition studies provide information on the interaction between the enzyme's active site and the ligand and thus allow insight into the mechanism of enzymatic glycolysis which appears at first glance as a simple nucleophilic displacement reaction, but turns out to be highly complex upon close inspection. Understanding the mechanism at a molecular level
is not only interesting as such, but also relevant to the design of glycosidase inhibitors as potential therapeutic agents and of tuned glycosidases for biotechnological applications.
1. Introduction

1.1. Glycosides and Glycosidases

Glycosides and saccharides are ubiquitous. They are important as short- and long-term energy-storage compounds in plants (starch) and animals (glycogen, lactose), as major structural elements in plant and bacterial cell walls (cellulose), in the extracellular matrix of multicellular organisms (hyaluronic acid, heparin), and in the shells of crustaceans and insects and in the cell walls of fungi (chitin) [3] [4]. Nucleic acids (RNA and DNA) are glycosides linked as phosphoric acid diesters. (Complex) glycoconjugates at the cell surface (glycoproteins, glycolipids) are involved in signal transduction, cell-cell adhesion, parasitic infection, viral replication, fertilisation, immune defense, malignant transformation, and metastasis [5 – 9]. The conjugation of lipophilic molecules (e.g. steroid hormones) to glucuronic acid renders them hydrophilic and allows for their excretion with the urine [3].

In contrast to nucleic acids and proteins, which are almost exclusively linear and whose units are linked exclusively via phosphodiester bonds and almost exclusively via amide bonds, respectively¹), oligo- and polysaccharides may be highly branched, and their units may be linked by α- or β-glycosidic bonds via any of the hydroxyl groups, allowing for a huge variety of structure [5] (for a reducing tetrasaccharide composed of 9 common monosaccharides there are over 10⁷ possible isomers [6], whereas for a tetrapeptide composed of 20 amino acids there are only 160000 possible isomers). An army of enzymes catalysing the ligation and cleavage of glycosidic bonds manages the extensive variety of natural glycosides. Glycosyl transferases catalyse the transfer of glycosyl units to alcohols (including carbohydrates); glycosyl phosphorylases catalyse the transfer to phosphate.

Glycosyl hydrolases (glycosidases) catalyse the transfer of glycosyl units to water, i.e. the hydrolysis of glycosides. Glycosidases have been classified according to

- the nature of the glycosidic atom as O-, N-, and S-glycosidases (EC 3.2.1.x, EC 3.2.2.x, and EC 3.2.3.x)
- the ring size of the glycosyl donor as pyranosidases or furanosidases

¹) Exceptions: The "lariats" formed as intermediates in the splicing of mRNA contain an adenosine branchpoint linked to two guanosines via a 3'–5' and a 2'–5' phosphodiester [3]. Peptides and proteins may be branched via Cys–Cys disulfide bridges. Peptidoglycans contain Arg branchpoints, where both the α- and ε-NH₂ group are acylated by amino acids [3]. Crosslinking of collagen strands and of elastin strands occurs by branching [10].
• the anomic configuration of the glycosyl donor as $\alpha$- and $\beta$-glycosidases
• the relative configuration of the product with respect to the glycosyl donor as retaining and inverting glycosidases [11]
• the "regioselectivity" in the processing of oligosaccharides as exo-glycosidases, acting at a terminus of an oligosaccharide, and endo-glycosidases, acting within an oligosaccharide chain
• the trajectory of protonation by the catalytic acid as syn- or anti-protonators [12]
• the amino acid sequence (vide infra).

Sinnott introduced a new scheme to describe the stereoselectivity of glycosidases, designating retaining pyranosidases as e$\rightarrow$e (cleaving equatorial glycosides) and a$\rightarrow$a (cleaving axial glycosides) and inverting pyranosidases as e$\rightarrow$a (cleaving equatorial glycosides) and a$\rightarrow$e (cleaving axial glycosides) [13]. Retaining and inverting furanosidases are designated as f(r) and f(i), respectively. Sinnott’s scheme avoids the use of the $\alpha$/$\beta$-nomenclature of glycosides [4] (which may be confusing [14], as $\alpha$-D-pyranosides are axial and $\alpha$-L-pyranosides equatorial [4]), but it relies on the preferred conformation of the more or less flexible substrate and product and may in some cases (e.g. $\alpha$-D-altropyranosides, $\alpha$-D-idopyranosides) introduce some ambiguity, or even be misleading in cases where the reactive conformation of the substrate differs from its ground state conformation (vide infra).

According to the IUB nomenclature, glycosidases are classified according to their substrate specificity (e.g. $\beta$-O-glucosidases as EC 3.2.1.21, $\alpha$-O-glucosidases as EC 3.2.1.20, $\beta$-O-galactosidases as EC 3.2.1.23). This classification does not (and is not intended to) reflect structural features and evolutionary relations of the enzymes, and it is not appropriate for enzymes acting on several substrates (several family 1 $\beta$-O-glycosidases cleave both glucosides and galactosides). Based on amino acid sequence similarities Henrissat has classified glycosidases into currently 94 families [15 – 17]$.^2$ The tertiary structure (folding) is more highly conserved within a family than the amino acid sequence [15], allowing homology modelling if the structure of a member of the family is known. The general catalytic mechanism appears to be conserved within a given family [17]. A given family may contain glycosidases with different substrate specificities, reflecting divergent evolution (i.e. evolution from a common genetic ancestor to enzymes with different specificities). Thus, family 1 contains $\beta$-O-glucosidases, $\beta$-glucuronidases, $\beta$-mannosidases, $\beta$-O-galactosidases,

$^2$ A permanently updated database of the known glycosidases is available on the Carbohydrate Active Enzymes internet page at <http://afmb.cnrs-mrs.fr/CAZY/index.html>.
and $\beta$-fucosidases. On the other hand, enzymes hydrolysing the same substrate are found in different families, reflecting convergent evolution (i.e. evolution from different genetic ancestors to enzymes with the same substrate specificity).

Improved sequence comparison tools and crystal structure analyses revealed the relations between some glycosidase families, which were grouped into clans [17]. The members of a clan are thought to have evolved from a common evolutionary ancestor and are characterised by a similar tertiary structure and conserved catalytic residues and mechanism.

Although many protein folds are found in the glycosidase families for which the 3D structure is known, the overall active site topologies fall into only three general classes [18]. Monosaccharidases and exo-polysaccharidases like glucoamylase and $\beta$-amylase, adapted to substrates having a large number of available non-reducing chain ends, display a pocket or crater topology of the active site. Endo-glycosidases commonly possess a groove or cleft topology of the active site, allowing random binding of several sugar units of polymeric substrates. A tunnel topology, formally derived from the cleft topology by covering the cleft by long loops, is found in processive cellobiohydrolases. The substrate chain is thought to be threaded through the tunnel, and the small molecular weight product is released from the enzyme, while the polysaccharide chain moves forward, but remains firmly bound.

1.2. Medical Implications of Glycosidases

Glycosidases are indispensable in the normal functioning of most organisms. They are involved in the breakdown of food carbohydrates [4], in malignant transformation and metastasis [19] [20], viral and bacterial infection [5] [6], the processing of eukaryotic glycoproteins [8] [9], and the catabolism of polysaccharides and glycoconjugates [4]. The importance of glycosidases in biological processes is reflected by a number of diseases, which result from the lack or dysfunction of a glycosidase, as well as by the use of glycosidase inhibitors in the treatment of metabolic disorders or viral infections [21].

Lactose intolerance is one of the most common genetically based diseases in man (see [13] and references cited there). It results from a decline in the expression of lactase, a $\beta$-galactosidase. The only remedy for this condition is an essentially lactose-free diet.

Sphingolipidoses are rare, severe (and often fatal) hereditary diseases, caused by a deficiency in the activity of one of the lysosomal enzymes involved in the catabolism of glycosphingolipids (GSL), leading to an accumulation of one of these glycosphingolipids in the lysosomes (glycosphingolipid storage disease, lysosomal storage disease) [3] [21]. Type I Gaucher disease results from a mutation in the glucocerebrosidase (a $\beta$-glucosidase) gene
(e.g. N370S), which leads to the storage of glucosylceramide in the macrophages, resulting in an enlargement of the liver and spleen, anaemia, reduced number of platelets, bone pain, bone infarction and demineralisation of the bones\(^3\). To date the only treatment of Gaucher disease is enzyme replacement, \textit{i.e.} the administration of human (isolated from placenta) or recombinant glucocerebrosidase. There are two new approaches for the treatment of GSL storage diseases \([21]\). Substrate deprivation by attenuating the biosynthesis of GSL leads to decreased levels of GSL in the lysosomes. \textit{N}-butyldexnojirimycin (NB-DNJ, \(1a\), Scheme 1.2.1) is an inhibitor of the glucosyltransferase-catalysed biosynthesis of glucosylceramide and has been recommended for approval in the European Union for use in patients with mild to moderate type I Gaucher disease. Chemical chaperone therapy may be beneficial in patients expressing mutant lysosomal glycosidases, which are catalytically competent, but whose tertiary structure is unstable, leading to misfolding and thus abortive exit from the ER. Inhibitors of these glycosidases may serve as chemical chaperones, stabilising the wild type conformation and allowing for a correct transport through the ER. Indeed, at subinhibitory concentrations, \textit{N}-nonyldexnojirimycin (\(1b\)) leads to a twofold increase of mutant (N370S) \(\beta\)-glucocerebrosidase activity in cultured fibroblasts.

\[
\text{Scheme 1.2.1}
\]

\[
\begin{align*}
\text{1a} & \quad R = (\text{CH}_2)_3\text{CH}_3 \\
\text{1b} & \quad R = (\text{CH}_2)_8\text{CH}_3
\end{align*}
\]

Influenza is a serious respiratory viral infection causing substantial morbidity and mortality. Influenza virus replication and infectivity is dependent on neuraminidase (sialidase), a retaining \(\alpha\)-glycosidase, which cleaves terminal sialic acid residues from glycoproteins, glycolipids, and oligosaccharides. This enzyme is required for the release of newly synthesised virions from infected cells \([22]\). The nanomolar sialidase inhibitors zanamivir (\(2\), Scheme 1.2.2) \([23]\) \([24]\) and oseltamivir carboxylate (\(3a\), a carbasugar) \([25]\) are efficient drugs in the treatment of influenza \([21]\). Zanamivir must be administered intranasally or by inhalation due to its low oral bioavailability, resulting from the positive charge of the guanidino group. The prodrug oseltamivir \(3b\) \([26]\) (marketed by Roche as Tamiflu) is

\(^3\) See the website of the National Gaucher Foundation of the USA at www.gaucherdisease.org and the website of Genzyme Co. at www.genzyme.com for comprehensive information about Gaucher disease and its treatment.
administered orally and is hydrolysed by liver esterases to the active drug oseltamivir carboxylate.

\[
\text{Scheme 1.2.2}
\]

The blood glucose level in healthy humans is maintained at a concentration of \( \text{ca. 5 mmol/l} \) by the action of two antagonistic pancreatic hormones, insulin and glucagon [3]. The postprandial increase in serum glucose leads to the secretion of insulin, which stimulates the uptake of glucose into insulin-responsive cells (target cells). In patients with diabetes mellitus type II (insulin independent diabetes) a deficiency of insulin receptors on the target cells (or their insensitivity to insulin) leads to chronically increased blood glucose levels which may eventually result in heart disease and stroke, renal failure, eye problems up to blindness, neuropathy and nerve damage, foot problems, and skin complications\(^4\). Diabetes type II is treated by a strict diet, exercise, and by oral administration of strong inhibitors of intestinal \( \alpha \)-glucosidases, which inhibit the intestinal breakdown of starch, thus efficiently lowering the release of glucose and the postprandial increase in blood glucose levels [21] [27]. The carbocyclic \( \alpha \)-glucosidase inhibitors acarbose (4, \textit{Glucobay}, Scheme 1.2.3) [28] [29], voglibose (5, \textit{Basen}) [30] (a derivative of valiolamine [31]), and miglitol (6, \textit{Glyset}) [32] are currently used in the treatment of diabetes type II. Such inhibitors of the intestinal glycosidases may also be applied in the treatment of obesity [33] [34].

\(^4\) For comprehensive information on diabetes, see the website of the American Diabetes Association at www.diabetes.org.
Glycosidase inhibitors may be potential remedies in the treatment of cancer \(^5\) and HIV infection \(^6\) \([5] [21] [27] [36]\). Inhibitors of microbial glycosidases may be applied in the prophylaxis of dental caries \([33]\).

### 1.3. Reaction Mechanism of Glycosidases \(^7\)

*Koshland* proposed that retaining glycosidases work by a double-displacement involving an enzyme or substrate nucleophile (two inversions resulting in net retention of the anomeric configuration), whereas inverting glycosidases work by a single displacement of the aglycon by a nucleophilic water molecule \([40]\). The first insight into the mechanism of retaining \(\beta\)-glycosidases at a molecular resolution was provided by the X-ray crystal structure determination of lysozyme and its complexes with inhibitors (among them \(N\)-acetylglucosamine, tri-\(N\)-acetylchitotriose) \([41]\). Based on the structure of the complex with

---

\(^5\) The indolizidine swainsonine, an inhibitor of the glycoprotein processing \(\alpha\)-mannosidase II reduced organ colonization and solid tumor growth rate in tumor-bearing mice *in vivo* \([20]\).

\(^6\) *N*-butyldeoxyojirimycin (1a) inhibits HIV replication *in vitro* \([35]\), and it is claimed that this is due to inhibition of trimming glycosidases involved in the biosynthesis of the viral glycoprotein gp120.

\(^7\) For a comprehensive review on the elucidation of the mechanism of glycosidases, see the PhD thesis of *Heightman* \([14]\) and also of *Hoos* \([37]\), *Ermert* \([38]\), and *Panday* \([39]\).
tri-N-acetylchitotriose, which appeared not to be a productive enzyme/substrate complex, 
*Phillips* modelled a hexasaccharide into the active site. He reasoned that this hexasaccharide
be cleaved between the second and third residue (from the reducing end)\(^8\) and identified
residues glu 32 and asp 52 which are disposed on either side of the glycosidic bond in
question as the potential catalytic residues. *Phillips* speculated that in the hydrolysis of the
glycosidic bond "glu 35 donates a proton to the glycosidic oxygen, while the negatively
charged asp 52 stabilizes an intermediate carbonium ion at C(1)" of the glycon [41].

The general mechanism of a retaining \(\beta\)-glucosidase is shown in Scheme 1.3.1 [18] [42 – 46].
This mechanism was corroborated by structural analyses (e.g. [47 – 53]), kinetic studies (e.g. [54] [55]), inhibition studies (e.g. [12] [56 – 58]), active site labelling (e.g. [59] [60]), studies of the effects of site-directed mutations of the catalytic residues (e.g. [61]), trapping of the
glycosyl enzyme intermediate with suicide substrates (e.g. [62 – 65]), and combinations of
these\(^7\).

In the active site of retaining \(\beta\)-glycosidases there are, as a rule, at least two catalytic carboxyl
groups at a distance of ca. 5.5 Å, one acting as a general acid/base catalyst and the other as a
nucleophile [18] [42 – 46]. The first step of hydrolysis is characterised by glycosylation of the
catalytic nucleophile. In this step, the catalytic acid activates the aglycon, while the
nucleophile attacks the anomic centre forming a glycosyl-enzyme intermediate *via* a
pentacoordinated trigonal-bipyramidal transition state with substantial oxycarbenium ion
character in which the aglycon and the nucleophile adopt the apical positions (in some
publications – e.g. [39] [58] [66] – the aglycon or the nucleophile is incorrectly drawn in an
equatorial position). The aglycon leaves the active site, providing space for a water molecule
to be positioned above the anomic carbon. The second step is characterised by hydrolysis of
the glycosylenzyme ester. In this step the free carboxylate group acts as general base catalyst,
averting the water molecule that attacks the anomic carbon and displaces the catalytic
nucleophile *via* a similar transition state as in the first step.

\(^8\) This proposal was supported by the experimental finding that hexa-N-acetylchitohexaose is
hydrolyzed by lysozyme to a tetramer and a dimer, the cleavage separating two residues from
the reducing end.
In the hydrolysis of N-acetyl-hexosamines by glycosidases of families 18, 20, and 56 the 2-acetamido group of the substrate rather than an enzyme carboxylate group acts as the intramolecular nucleophile forming a (protonated?) oxazoline intermediate [18] [45] [46].

The active site of inverting glycosidases also contains at least two carboxyl groups, one acting as a general acid catalyst, the other as a general base catalyst. These carboxylates are ca. 9.5 Å apart, providing space for a water molecule to be positioned between the catalytic base and the anomeric carbon. Hydrolysis proceeds in a single step, in which the catalytic acid activates the aglycon while the catalytic base activates the nucleophilic water molecule which displaces the aglycon via a pentacoordinated trigonal-bipyramidal transition state with substantial oxycarbenium ion character [18] [42 – 46].

The principles of the glycosidase mechanism as outlined above are generally accepted, but
questions concerning the precise nature of the glyoxyl enzyme intermediate (covalent or ionic), the involvement of oxycarbenium ions as real, short-lived high-energy intermediates of the catalytic pathway, the relative positioning of the substrate and the catalytic groups, and the conformational itinerary of enzymatic glycolysis have been the subject of debate.

1.4. Oxycarbenium Ions

The non-enzymatic hydrolysis under specific acid catalysis of methyl α- and β-glucopyranosides is unimolecular and has been claimed to proceed via a (solvated?) glucosyl cation intermediate [67]. The estimated lifetime of glycosyl cations in water is between $10^{-10}$ s [67] to $10^{-12}$ s [68], thus these species are considered to be just on the borderline of a real existence [13] [43] (a low frequency skeletal vibration of 600 cm$^{-1}$ has a period of $\approx 5 \times 10^{-14}$ s). The reaction of α-glucopyranosyl fluoride with anionic nucleophiles in aqueous solution [69], the general acid and general base catalysed hydrolysis of α-glucopyranosyl fluoride [70], and the hydrolysis of α-glucopyranosyl fluoride at near-neutral pH [71] proceed according to an SN2-like mechanism with an "exploded" transition state characterised by a highly cationic character (i.e. according to a mechanism that is between the paradigmatic SN1 and SN2 processes). These studies revealed that glycosyl cations have no meaningful existence in the presence of an anionic nucleophile or leaving group. This means that glucosyl enzyme esters, which commonly have lifetimes of 1 - 10 ms, cannot be ionic, but must be covalent [13] [43]. This is corroborated by α-deuterium kinetic isotope effects of $> 1.05$ for the deglycosylation, showing a decrease in coordination number on going from the glycosyl enzyme intermediate to the transition state [13]. The crystal structures of several trapped glycosyl enzyme esters clearly show a covalent link between the catalytic nucleophile and the anomeric centre [48] [50] [53] [72 – 77].

Although it is most likely that a covalent glycosyl enzyme ester is formed in an SN2-type reaction via a pentacoordinated transition state (as shown in Scheme 1.3.1), one cannot preclude that this reaction proceeds via a short-lived high-energy oxycarbenium ion. In fact Davies, Sinnott, and Withers came to the conclusion that this question remains elusive, as it is difficult to be answered experimentally [43]. A study of the kinetic isotope effect showed that the cleavage of α-glucosyl pyridinium salts by yeast α-glucosidase is assisted by an enzyme active site nucleophile, but these results cannot be extrapolated to the cleavage of the natural substrates [78]. If a short-lived oxycarbenium ion is an intermediate in the glycosylation step, the transition state structure must be somewhere between the substrate and the oxycarbenium ion [46].
1.5. Geometrical Considerations

Maximum stabilisation of the oxycarbenium ion-like transition state requires delocalisation of non-bonded electrons of O–C(5) into the unoccupied p-orbital at C(1), and for this C(5)–O–C(1)–C(2) must be coplanar [13] [43]. Pyranose ring conformations in agreement with this stereochemical requirement are $4H_3$, $3H_4$, $2.5B$, $B_{2.5}$, $4E$, $E_4$, $3E$, and $E_3$. In conformations not allowing overlap of a C(5)–O lone pair and the "empty" orbital at C(1), O–C(5) can only act as a $\sigma$-acceptor, strongly destabilising the electron-deficient transition state.

Based on the principle of stereoelectronic control, Deslongchamps concluded that the hydrolysis of a pyranoside in its ground state chair conformation "can take place with the help of an electron pair in the case of $\alpha$-glycosides only" [79]$^9$ and proposed that such an assistance by non-bonded electrons of the ring oxygen is a stereoelectronic requirement of glycoside cleavage. Deslongchamps apparently assumed that an antiperiplanar orientation between the scissile glycosidic bond and a lone pair of C(5)–O is necessary to meet this stereoelectronic requirement$^{10}$ and hypothesised that "it seems quite clear that $\alpha$-glycosides must hydrolyse via their ground state conformation whereas $\beta$-glycosides must first assume a boat conformation in order to fulfil the stereoelectronic requirement"$^{11}$ [79]. As it was deduced from fundamental stereoelectronic principles, Deslongchamps’s hypothesis that $\beta$-glycosides must hydrolyse via a boat(like) reactive conformation with pseudoaxial orientation of the scissile bond received much currency and was also thought to apply to enzymatic glycoside cleavage.

Some experimental results appear to corroborate Deslongchamps’s hypothesis, such as the much slower HCl-catalysed hydrolysis of the tricyclic $\beta$-pyranoside 7, which cannot adopt a $1.4B$ conformation, than that of the $\alpha$-pyranoside 8 (Scheme 1.5.1) [80]. However, the trans-fused rings of the $\beta$-pyranoside 7 will not only preclude a boat(like) conformation, but also impede the formation of an oxycarbenium ion-like transition state (requiring planarity of C(5)–O–C(1)–C(2) and an elongation of the C(1)–OC(1) bond), therefore these results do not prove that hydrolysis of the $\beta$-anomer requires a reactive conformation with a pseudoaxial

$^9$ The “helping electron pair” corresponds to the axial non-binding, doubly occupied sp$^3$-orbital of the ring oxygen.

$^{10}$ This is evident from some figures (e.g. Fig. 17) and also from a text passage (p. 36, lines 8 – 10) in [79].

$^{11}$ This hypothesis is often referred to as the “antiperiplanar lone pair hypothesis” [14] [39] [67].
orientation of the scissile bond\textsuperscript{12}). Hydrolysis of the conformationally restrained \(n\)-pentenyl \(\beta\)-glucoside \(9a\) with electrophilic reagents (\textit{e.g.} NBS) "was not dramatically slower" than that of the \(\alpha\)-anomer \(9b\) \textsuperscript{81} [82], "raising doubts that \(\beta\)-anomers react via boat conformations" \textsuperscript{83}\textsuperscript{13}).

\textbf{Scheme 1.5.1}

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

An ab initio study of 2-oxanol (a simple pyranose) by \textit{Smith} showed that protonation of the chair conformer with an equatorial OH group yields an oxonium ion (\textit{i.e.} 2-oxanol protonated at the exocyclic oxygen) in the chair conformation \((2C5)\) which reacts \textit{via} a transition state with a slightly flattened chair conformation to an oxycarbenium ion-water complex with a \(5H4\) conformation. Protonation of chair and boat conformers with an axial OH group does not yield oxonium ions but results in a collapse to an oxycarbenium ion-water complex with a \(5H4\) conformation [84]. These calculations support \textit{Deslongchamps}'s hypothesis that an antiperiplanar electron lone pair of the ring oxygen assists the hydrolysis of axial pyranosides. However, protonated species originating from axial glycosides are observed by mass spectrometry [85 – 88]\textsuperscript{14}) which may restrict the validity to \textit{Smith's} conclusion that protonation of axial pyranosides leads directly to cleavage of the glycosidic bond to processes in the condensed phase.

\textsuperscript{12}) It was assumed that cleavage of the glycosidic bond is the rate-limiting step of the hydrolysis of \(7\) and \(8\), but this was not established [80]. Therefore, it cannot be excluded that the rate-limiting step might differ between the two anomers, or might be protonation of the glycosidic oxygen.

\textsuperscript{13}) It was assumed that cleavage of the glycosidic bond is the rate-limiting step. Although "valuable evidence" was claimed for this assumption, it was not proven.

\textsuperscript{14}) These protonated species fragment to \([M – (aglycon–OH)]^+\) ions, evidencing that the glycosidic oxygen is protonated. The conformation of the protonated species observed in MS remains obscure, therefore my argument that these results contradict those of \textit{Smith's} calculations may not hold water.
Sinnott determined kinetic isotope effects of the non-enzymatic and the enzymatic hydrolysis of glycosides and deduced transition state conformations for the non-enzymatic hydrolysis [67] [71] [89]. Determining transition state conformations from kinetic isotope effects may look far-fetched and consequently has been met with skepticism (see [14]), but the dependence of these effects on the structure is established. The value of "the dihedral angle between the empty orbital on C(1) and the p-type lone pair on the ring oxygen" ($\omega$) was derived from the observed kinetic isotope effect (KIE$_{\text{obs}}$) by solving the equation

$$\text{KIE}_{\text{obs}} = \cos^2(\omega) \times \text{KIE}_{\text{max}}$$

for $\omega$, setting an empirical upper limit KIE$_{\text{max}}$ for the kinetic isotope effect for $\omega = 0^\circ$ [67] [71].

From kinetic isotope effects on the specific acid catalysed hydrolysis of methyl $\alpha$- and $\beta$-glucosides, Bennett and Sinnott deduced that the transition state for the glycoside cleavage of the $\alpha$ anomer adopts a flattened $1S_3$ conformation ($\omega \approx 54 - 66^\circ$) and that for the glycoside cleavage of the $\beta$ anomer a $4C_1$ conformation flattened somewhat towards a $4H_3$ half chair ($\omega \approx 52^\circ$) [67]. Bennett and Sinnott concluded that these transition state conformations contradict the "antiperiplanar lone pair hypothesis", but that they are in accord with the expected ground state conformations of protonated glycosides ($4C_1$ for the $\beta$ anomer and $1S_3$ for the $\alpha$ anomer$^{15}$). From kinetic isotope effects on the hydrolysis of $\alpha$- and $\beta$-glucopyranosyl fluorides (not subject to the "inverse anomeric effect") at near neutral pH, Zhang et al. deduced that the transition state of the $\alpha$-anomer adopts a $4C_1$ conformation flattened towards $4H_3$ ($\omega \approx 32^\circ$) and that of the $\beta$-anomer a flattened $4C_1$ conformation ($\omega \approx 41^\circ$) [71]. A $4S$ transition state conformation ($\omega \approx 12^\circ$) was deduced for the hydrolysis of $\alpha$-glucosyl fluoride by comparing KIE$_{\text{obs}}$ with calculated (ab initio) kinetic isotope effects [71].

The rather large discrepancy between this value and that derived "empirically " ($\omega \approx 32^\circ$) shows that the error of the estimated $\omega$ values (and thus of the transition state conformations) is quite large. Another weakness of Sinnott's work is that $\omega$ is defined as "the dihedral angle between the empty orbital on C(1) and the p-type lone pair on the ring oxygen", but it is not evident what hybridisation of the ring oxygen and of C(1) was assumed in modelling the transition state conformation. For a given ring conformation the $\omega$ value will depend on these hybridisations. Apart from this, kinetic isotope effects reveal differences between the transition state conformation and the ground state conformation, but they will not account for

$^{15}$) Bennett and Sinnott say that the $1S_3$ ground state conformation of protonated $\alpha$-glucosides is due to the inverse anomeric effect. Others have established that this conformation is due to solvation [90] [91] that may be the dominant if not the only origin of the "inverse anomeric effect".
intermediate reactive conformers. Therefore, in the case of the methyl \( \beta \)-glucoside and the \( \beta \)-glucosyl fluoride Sinnott’s conclusion that the transition state conformation is derived directly from the ground state \( 4C_1 \) conformation may not be correct.

Hosie and Sinnott measured the kinetic isotope effects on the baker’s yeast \( \alpha \)-glucosidase catalysed cleavage of aryl \( \alpha \)-glucosides and \( \alpha \)-glucosyl pyridinium ions [89]. There was no \( ^{18}O \) (glycosidic oxygen) kinetic isotope effect on \( V_{\text{max}} \) for the hydrolysis of \( \alpha \)-\( p \)-nitrophenyl glucoside, indicating that the C–O bond is not being broken in the rate-determining step. Hosie and Sinnott concluded that the rate-determining step was a non-covalent event preceding bond cleavage. Kinetic isotope effects on \( V_{\text{max}} \) for the hydrolysis of the \( \alpha \)-glucosyl pyridinium pyrimidine salts evidenced that for these substrates cleavage of the glycosidic bond is the rate-limiting step, that the C–N bond is about half-broken and the anomeric carbon about half-rehybridised (from sp\(^3\) to sp\(^2\)) in the transition state, and that the C(2)–H bond is coperiplanar to the scissile bond. Hosie and Sinnott speculated that the oxycarbenium ion like transition state for the cleavage of the glycosidic bond adopts a \( 2.5B \) conformation and that the non-covalent event preceding cleavage of \( p \)-nitrophenyl \( \alpha \)-D-glucoside is a conjoint change in the conformation of the substrate (from \( 4C_1 \) to \( 2.5B \)). As \( \alpha \)-glucosyl pyridinium ions adopt a \( 1S_3 \) conformation (vide supra), a conformational change to the similar \( 2.5B \) conformation should be faster than for \( p \)-nitrophenyl \( \alpha \)-D-glucoside (\( 4C_1 \)). The \( 2.5B \) transition state conformation proposed by Hosie and Sinnott fulfils the stereoelectronic requirement of coplanarity of C(5)–O–C(1)–C(2) (vide supra) and may explain the relatively weak inhibition of baker’s yeast \( \alpha \)-glucosidase by castanospermine which cannot adopt a \( 2.5B \) conformation [89] and also the strong binding of \( \alpha \)-glucosyl pyridinium ions (which adopt a \( 1S_3 \) conformation similar to the \( 2.5B \) conformation – vide supra) to this enzyme [89] [92]. However, it seems rather improbable that a conformational change is rate-limiting in a process that leads to cleavage of a C–O bond (cf. [79] [84]). Protonation of the glycosidic oxygen might be the rate-limiting step. This was not explicitly considered by Hosie and Sinnott, but should lead to an \( ^{18}O \) kinetic isotope effect. It is also risky to assume that the substrate conformation of \( \alpha \)-glucosyl pyridinium ions in the enzyme’s active site (no solvation) is the same as that observed in water (\( 1S_3 \) due to solvation). Finally, it is hard to believe that the \( p \)-nitrophenyl \( \alpha \)-D-glucoside, bearing an axial leaving group, should change its conformation prior to cleavage.

Based on experimental results (e.g. the rate of hydrolysis of the \( n \)-pentenyl \( \beta \)-glucosides 9a and 9b [81] [82], vide supra) and ab initio calculations of glycoside cleavage (e.g. [93]) Fraser-Reid et al. concluded that \( \alpha \)-pyranosides are cleaved from the \( 4C_1 \) conformation via a transition state with a flattened \( 4H_3 \) conformation and a coplanar arrangement of C(5)–O–C(1)–C(2) and that \( \beta \)-pyranosides are cleaved from the ground state \( 4C_1 \) conformation via a transition state with \( 4E \) (or flattened \( 4C_1 \)) conformation and a coplanar
arrangement of C(5)–O–C(1)–C(2) [83]. This conformational itinerary contradicts Deslongchamps's hypothesis that the hydrolysis of β-glucosides proceeds via a boat(like) reactive conformation with antiperiplanar orientation between an O–C(5) lone pair and the scissile bond. Fraser-Reid proposes that upon distortion to the flattened 4C1 conformation, the scissile glycosidic bond is synperiplanar to the pseudoaxial lone pair at O–C(5), allowing significant overlap between this orbital and the σ* orbital of the glycosidic bond. Fraser-Reid postulated as a general rule for stereoelectronic control, that a "periplanar lone pair is needed for [glycoside] cleavage, whether it be anti or syn" [83].

Even the conformational itinerary proposed by Sinnott for the cleavage of α-glucosides by yeast α-glucosidase (vide supra) can be reconciled with stereoelectronic principles. Concomitantly with bond breaking at C(1), the C(5)–O–C(1) angle may increase with a rehybridisation of O–C(5) from sp3 to sp2, placing a p orbital in a syn-periplanar arrangement with the scissile glycosidic bond. Even in the proposed reactive 2,5B conformation of the substrate, considerable electron density is present in (or nearly in) the π plane of the planar C(5)–O–C(1)–C(2) moiety, if one not only considers sp3 hybridisation at O (which is one possible set of orbitals resulting from the linear combination of one s and 3 p orbitals) but also other hybridisations with two non-equivalent lone pairs of σ and π symmetry [83]. Bicyclic α- and β-glucopyranosides constrained in a B2,5 configuration hydrolyse at similar rates as non-constrained glucopyranosides [9416].

Deslongchamps's hypothesis – requiring an antiperiplanar arrangement of the scissile glycosidic bond and an sp3 lone pair of the ring oxygen in the reactive substrate conformation – is a restricted formulation of the principle of stereoelectronic control, considering only sp3 hybridisation at the ring oxygen and over-emphasising reactive substrate conformation vs. transition state conformation. It is a restricted formulation also in that it overemphasizes the probably (slightly?) preferred anti-periplanar arrangement, while the principle of stereoelectronic control postulates a coplanarity, irrespectively of a syn or anti orientation of lone pair and polar bond. The transition state for glycoside cleavage is late [95] and stabilising orbital overlap required at the transition state probably is not yet required at the level of the reactive substrate. If the transition state were early (and thus the geometry of the transition state were similar to the reactive conformation of the substrate) stabilising orbital overlap would be required in a conformation similar to the reactive conformation of the substrate; for a 4C1 or 1,4B conformer this requires an anti-periplanar orientation of the scissile bond and a lone pair of O–C(5).

16) No details of the kinetics of hydrolysis are given in this reference, so it is unclear whether it was established that cleavage of the glycosidic bond is the rate-limiting step in these hydrolyses.
1.6. High-Energy Reactive Substrate Conformations in Enzymatic Glycoside Hydrolysis – Crystal Structure Analysis of Glycosidases in Complex with Ligands

Deslongchamps's postulate "that α-glycosides must hydrolyse via their ground state conformation whereas β-glycosides must first assume a boat conformation in order to fulfil the stereoelectronic requirement" was thought to apply also to enzymatic glycoside hydrolysis. Spectacular evidence for the hypothesis that the enzymatic hydrolysis of β-glycosides proceeds via a boat(like) reactive conformation of the substrate came from the disclosure of a couple of crystal structures of endo-glycosidases in complex with a substrate or substrate analogue, clearly showing distortion of the ligand towards a skew boat conformation [96] [97].

An important question with regard to enzymatic glycoside hydrolysis proceeding via high-energy reactive substrate conformations is whether and, if so, how a glycosidase stabilises such high-energy conformations (the energy required for distorting the substrate to a boat conformation is estimated at 8 kcal/mol [98] [99]).

- It is conceivable that the enzyme does not stabilise a high-energy reactive conformation, but that the substrate spontaneously adopts this conformation within the active site of the enzyme before it is cleaved. This mechanism is in accord with that assumed for the non-enzymatic hydrolysis of β-glycosides, but the activation energy for enzymatic hydrolysis would have to be greater than the energy (8 kcal/mol, vide supra) required to distort the substrate from its ground state to the reactive conformation.

- If the enzyme stabilises a high energy reactive conformation of the substrate, the energy required must be provided by the binding energy of the ligand to the enzyme.

- The energy might be provided by binding interactions in the –1 subsite, that is the active site itself might stabilise the high-energy reactive conformation of the substrate. However, for efficient catalysis the –1 subsite must be optimised for maximum binding to the transition state [100], therefore the reactive substrate conformation might only be stabilised in the –1 subsite, if it is similar to the transition state conformation.

- The energy might be provided by interactions in other subsites, especially those involved in binding the aglycon, i.e. +1, +2, etc. This would allow the –1 subsite to be optimised for stabilising the transition state. However, if Deslongchamps’s stereoelectronic requirement does apply, deglycosylation should lead to a β-pyranose in a boat(like) conformation. One may argue that the β-pyranose product is formed in this high-energy
conformation without stabilisation by the enzyme and then relaxes to the more stable \( ^4C_1 \) conformation. It is also reasonable to ask whether the principle of microscopic reversibility applies to the enzymatic hydrolysis of \( \beta \)-glycosides in the sense that deglycosylation (in a sense the reverse process of glycosylation but with OH as the "aglycon") follows the same reaction coordinate as the reverse process of glycosylation. There are some hints that the deglycosylation step has a different transition state (more charge developed at the anomeric carbon, \textit{i.e.} more \( S_N1 \)-like) than the glycosylation step \cite{101} \cite{102}, indicating that the principle of microscopic reversibility does \textit{not} apply in the above mentioned sense.

- It is also conceivable that distortion of the substrate and glycosylation are concerted. In that case, the reactive conformation would not be a discrete species that requires particular stabilisation by the enzyme. Rather, the reactive conformation would probably be similar to the transition state and therefore benefit partially of the enzyme's maximum stabilisation of the transition state conformation.

In the remainder of this chapter I will report about structural studies that evidenced high-energy conformers along the reaction coordinate of enzymatic glycoside hydrolysis. These structural studies were performed by X-ray crystallography. As a \textit{caveat} it should be mentioned that structures observed by X-ray crystallography are stable, representing local energy minima, and consequently might not represent the structures involved in the dynamic process of enzymatic catalysis. Also, crystal packing may impose conformational changes (see \cite{103} for an illustrative example). Some of the structures of the enzyme-substrate complex reported below were obtained with inactive mutant enzymes, or under conditions where the enzyme is inactive \textit{(e.g. low pH)} and therefore might not represent the structures involved in catalysis.

\textit{Davies et al.} gained insight into the conformational itinerary of the retaining \textit{endo}-glucosidase Cel5A (family 5) from \textit{Bacillus agaradhaerens} by determining the crystal structure of the free enzyme, of an enzyme-substrate complex, a glycosyl enzyme ester, and an enzyme-product complex, representing all stable states along the reaction coordinate \cite{72}. In a complex with 2,4-dinitrophenyl 2-deoxy-2-fluoro-\( \beta \)-D-cellobioside, which was obtained at low pH where the enzyme is inactive, this substrate was bound to the -2, -1, and +1 subsites and displayed a \( ^1S_3 \) conformation of the sugar residue in the -1 subsite. Crystals of a glycosyl enzyme ester were obtained by incubating the enzyme with 2,4-dinitrophenyl 2-deoxy-2-fluoro-\( \beta \)-D-cellobioside (a suicide substrate) at pH 7.5 (where the enzyme is active) for 3 h, followed by acidification to pH 5.5 (where the enzyme is inactive) and crystallisation. The covalently bound sugar in subsite -1 of the trapped glycosyl enzyme ester was found in an undistorted \( ^4C_1 \) conformation. A product complex was obtained by soaking "the native crystals" in an
excess of the free product ($\beta$-D-cellotriose). In this complex, the trisaccharide was bound to subsites -3, -2, and -1, and the -1 subsite sugar exhibited a great deal of disorder (indicative of binding of this sugar unit in multiple orientations), but showed no evidence of ring distortion. These results suggested that the ring distortion observed in the enzyme-substrate complex must be driven by interactions in the +1 subsite. Interestingly, crystal structure analysis of complexes of Cel5A with a tetrathio-cellopentaose [104] and a "mixed-linkage cellotetrasaccharide" (possessing an $\alpha$-glycosidic bond between residues 2 and 3) [105] revealed an alternative substrate binding mode. In these complexes the sugar residue corresponding to the one to be bound at subsite -1 is undistorted and bypasses this subsite. This bypass binding may perhaps represent an early stage of substrate binding. Thus, the substrate may first be bound in an undistorted conformation, bypassing the active site. Conceivably, the substrate is then pulled into the active site and distorted to the $1S_3$ reactive conformation. In agreement with Deslongchamps's hypothesis [79], this places the glycosidic bond in an axial orientation antiperiplanar to an O–C(5) lone pair. This reactive conformation also allows for an in line attack of the catalytic nucleophile at the anomeric centre, yielding the covalent intermediate in a $4C_1$ conformation. This conformational change allows the displacement to occur with minimum heavy atom movement of the glycoside ring atoms - only the C(1) atom moves towards the nucleophile, while the other ring atoms remain virtually fixed. Nucleophilic attack of water at the anomeric carbon of the glycosyl enzyme ester probably yields the product in a skew or boat conformation, which relaxes to a loosely bound chair.

Castanospermine normally adopts a $4C_1$ conformation. However, in a complex with the retaining exo-$\beta$-(1,3)-glucanase from Candida albicans (another family 5 glucosidase) this inhibitor was found in a twisted $1,4B$ conformation [106]. Binding of the inhibitor was accompanied by relatively minor changes of the protein conformation, with the exception of the position of N146. It was concluded that this complex represents that of the substrate in a reactive $1,4B$ conformation (as proposed by Deslongchamps). Here, the high-energy conformation of castanospermine must be stabilised by interactions in the –1 subsite. Tight interactions of the inhibitor with several residues in the active site are evident in the crystal structure.

A crystal structure analysis of the endoglucanase I from Fusarium oxysporum (family 7) in complex with a thio-tetrasaccharide bound to the -2 to +2 subsites also displayed a distortion of the sugar residue in subsite -1 towards a distorted $1,4B$ conformation with C(1) located much closer to the ring plane than C(4) [96]. This substrate distortion is again in agreement with the reactive conformation of a $\beta$-glycoside proposed by Deslongchamps [79]. The boat appears to be flattened around C(1), and the C(1)–S bond is longer than the corresponding C(1)–O bond in an $O$-glycoside (1.8 Å vs. 1.5 Å). The flattening of the ring may be required
to put the glycosidic S near the catalytic acid. Alternatively, one may speculate that the flattened ring (towards coplanarity of C(5)–O–C(1)–C(2)) and the long glycosidic bond more closely resemble the transition state conformation of hydrolysis rather than a reactive substrate conformation. The truth may well be somewhere in-between: this complex might represent a point on the reaction coordinate between the reactive substrate conformation and the transition state conformation. However, the charge redistribution towards the transition state is probably not mimicked well.

No distortion of the sugar residue at subsite -1 was found by Divne et al. for the E212Q mutant of the retaining cellobiohydrolase I from *Trichoderma reesei*, another family 7 glycosidase, in complex with cellotetraose (spanning the –2 to +2 subsites [107]. However, the anomeric carbon of the sugar in subsite –1 was 7.1 Å away from the catalytic nucleophile and the glycosidic oxygen was 6.7 Å away from the catalytic acid. Therefore it was assumed that this complex represents an early stage of substrate binding, bypassing the active site (*vide supra*). A distorted sugar residue (1,4B) could be readily modelled into the active site. Divne et al. proposed the stepwise binding of the substrate (bypass binding of the undistorted substrate, then binding of the reactive conformer in the active site) which was already described above [107]. Binding of the cellotetraose resulted in only a few minor changes of the protein conformation.

The hydrolysis of *N*-acetyl-hexosaminides by glycosidases of families 18, 20, and 56 proceeds *via* a (protonated?) oxazoline intermediate rather than a glycosyl enzyme ester (*vide supra*). The complex of the *exo*-chitobiase of *Serratia marcescens* (family 20) with chitobiose (bound to subsites -1 and +1) displayed a 4S (or flattened 1,4B) conformation of the sugar ring at subsite -1, placing the scissile glycosidic bond in a nearly axial orientation [97], in agreement with the reactive conformation proposed by Deslongchamps [79]. The acetamido group is oriented below the ring plane, so that the carbonyl oxygen is positioned for in line attack at the anomeric centre. A similar distortion (1,4B) was found in enzyme-substrate complexes of an inactive mutant of the *exo*-chitinase B (ChiB; binding of the substrate resulted in a number of conformational changes of the protein) [108] and of an inactive mutant of the *exo*-chitobiosidase A from *Serratia marcescens* [99] (family 18) and in a product complex of bee venom hyaluronidase (family 56) [109]. The observation of a boat conformation in an enzyme-product complex evidences that this high energy conformation is stabilised by interactions in the -1 site, probably by tight contacts of the axial acetamido group. The oxazoline intermediate probably adopts a 4S or flattened 4C1 conformation and the transition state conformation must lie between one of these conformations and 1,4B. Therefore it is conceivable that the active site stabilises both the high-energy reactive substrate conformation and the conformationally related transition state, with maximum stabilisation provided for the transition state.
Hen egg-white lysozyme (family 22) was the first glycosidase for which substrate distortion towards a flattened half-chair conformation was proposed by a combination of X-ray crystallography and modelling [41]. Indeed, a more recent X-ray crystal structure analysis of an enzyme-product complex at high resolution showed an $S_3$ conformation of the sugar in subsite -1, which closely resembles the geometry required for an oxycarbenium ion-like transition state [110]. This distortion of the pyranoside ring appears to be directed towards a transition state ring conformation with $\Phi(C(5)-O-C(1)-C(2)) \approx 0^\circ$ rather than towards a boat-like reactive conformation with an antiperiplanar orientation of the scissile bond and an O–C(5) lone pair.

For family 11 glycosidases crystal structures of free enzymes, glycosyl enzyme esters, and product complexes are available, providing insight into the conformational itinerary of these enzymes. In a trapped glycosyl enzyme ester of the retaining $\beta$-1,4-xylanase from Bacillus circulans, the 2-fluoro-xylose residue covalently bound in subsite -1 was found in a $2,5B$ conformation [73]. A product complex of the same enzyme displayed an undistorted $4C_1$ conformation of the sugar residue in subsite -1 [111]. For the Bacillus agaradhaerens retaining $\beta$-1,4-xylanase both the $\alpha$-configured covalent glycosyl-enzyme intermediate and an enzyme-product complex displayed a $2,5B$ conformation of the sugar residue in subsite -1 (the conformation of the protein in the covalent complex was very similar to the native conformation) [74] [76]. This is not in accord with Deslongchamps's hypothesis "that $\alpha$-glycosides must hydrolyse via their ground state conformation" [79], which should also apply to $\alpha$-configured glycosyl enzyme esters of $\beta$-d-glycosidases. However, the $2,5B$ conformation fulfils the stereoelectronic requirements for an oxycarbenium ion-like transition state suggesting that the transition states leading to and from the covalent intermediate may also display a $2,5B$ conformation (a $2,5B$ transition state conformation was proposed by Sinnott for the hydrolysis of $\alpha$-glucosides [95] (vide supra)). Withers et al. suggested that the conformational itinerary from the $4C_1$ ground state conformation to the $2,5B$ conformation is $4C_1 \rightarrow 2H_3 \rightarrow 2SO \rightarrow 2,5B$ [73], but it remains elusive whether this distortion precedes bond cleavage or occurs concomitantly with it.

The retaining endo-$\beta$-(1,4)-mannanase from Pseudomonas cellulosa (family 26) binds the substrate in a $1S_5$ conformation and the covalent intermediate in a $OS_2$ conformer, suggesting a $B_{2,5}$ conformation for the transition state [77]. In the $1S_5$ conformation, the scissile bond is pseudoaxial and a O–C(5) lone pair is periplanar to it, so this conformation is in agreement with the reactive conformation proposed by Deslongchamps [79] (the $1S_5$ conformation is closely related to $1,4B$). The proposed $B_{2,5}$ transition state conformation fulfils the stereoelectronic requirements for an oxycarbenium ion-like transition state.

Substrate distortion was also found in complexes of inverting glycosidases. A non-
hydrolysable thiosaccharide bound to the subsites -2 to +1 of the cellulbiohydrolase Cel6A from *Trichoderma reesei* (family 6) displayed a $^{2}S_{0}$ conformation of the sugar in subsite -1 (only small changes in some side chains of the protein are observed upon binding of the substrate analogue) [112]. A cellulbio-derived isofagomine bound to the subsites -2 and -1 of Cel6A from *Humicola insolens* (family 6) displayed a $^{2.5}B$ conformation of the piperidine ring [113]. Cellopentaose bound to the subsites -3 to +2 of the endoglucanase CelA from *Clostridium thermocellum* (family 8) also displayed a $^{2.5}B$ conformation of the sugar in subsite −1 [114]. Thus, catalysis by these inverting enzymes likely proceeds *via* a transition state with $^{2.5}B$ conformation, in agreement with stereoelectronic requirements (*vide supra*).

Deslongchamps's hypothesis that β-D-glycosides are hydrolysed *via* a boat(like) reactive conformation [79] should also apply to the deglycosylation of the covalent β-glycosyl enzyme esters of retaining α-glucosidases and -transferases. The covalent intermediates of the retaining cyclodextrin glycosyltransferase from *Bacillus circulans* [115] and of the retaining amylosucrase from *Neisseria polysaccharea* [116] were found in an undistorted $^{4}C_{1}$ conformation. This does not confirm Deslongchamps's hypothesis, nor does it preclude that deglycosylation of these glycosyl enzyme esters proceeds *via* a boat-like reactive conformation. A maltononaose substrate bound to the subsites -7 to +2 of the amylosucrase displayed a flattening of the C(5)–O–C(1)–C(2) torsional angle (from $-63^\circ$ to $-44^\circ$) of the sugar in subsite -1 [115].

Similarly, the observation of undistorted substrate complexes, *e.g.* for glycosidases from families 3 [52] and 23 [47], does not preclude that glycoside hydrolysis catalysed by these enzymes proceeds *via* boat(like) reactive conformations.

In summary, crystal structure analysis of enzyme-substrate (analogue) complexes, covalent intermediates, and enzyme-product complexes of retaining β-D-glycosidases from families 5, 7, 18, 20, 26, and 56 provided evidence that glycoside hydrolysis by these enzymes proceeds *via* reactive conformations with an *anti*-periplanar arrangement of the scissile bond and an O–C(5) lone pair. On the other hand, crystal structure analysis of complexes of retaining β-glycosidases from families 11 and 22 and of inverting β-glycosidases from families 6 and 8 provided evidence that enzymatic glycoside hydrolysis may not require an *anti*-periplanar arrangement of the scissile bond and an O–C(5) lone pair. The distortions seen in these

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17) Both enzymes are glycosyl transferases belonging to family 13. The cyclodextrin glycosyltransferase catalyses the formation of cyclodextrin from starch by an intramolecular transfer of an α-D-oligopyranosyl donor onto the 4-OH group of its own reducing end. The amylosucrase catalyses the transfer of an α-D-glucopyranosyl moiety from sucrose onto an amylose acceptor.
complexes were towards the ring conformation of an oxycarbenium ion-like transition state ($\Phi(C(5)–O–C(1)–C(2)) \approx 0$) (and towards a syn-periplanar orientation of the scissile bond and an O–C(5) lone pair) rather than towards a ring conformation with an anti-periplanar orientation of the scissile bond and an O–C(5) lone pair (cf. [95]). Consequently, one must conclude that Deslongchamps’s hypothesis "that $\alpha$-glycosides must hydrolyse via their ground state conformation whereas $\beta$-glycosides must first assume a boat conformation in order to fulfil the stereoelectronic requirement" [79] is not generally applicable to enzymatic glycoside hydrolysis and glycosyl transfer.

The conformational itineraries harnessed by all glycosidases appear to fulfil the stereoelectronic requirement of electron delocalisation from an O–C(5) lone pair into the “empty p-orbital” at C(1) in an oxycarbenium ion-like transition state (which in turn requires a periplanar orientation of an O–C(5) lone pair and the scissile bond and thus $\Phi(C(5)–O–C(1)–C(2)) \approx 0$) [113]. Substrate distortion towards a conformation with a periplanar orientation of an O–C(5) lone pair and the scissile bond favours attainment of the transition state. It is intriguing, that the $2.5B$ and $B_{2.5}$ and closely related conformations observed in several glycosidase families allow nucleophilic displacement at the anomeric carbon to proceed without major changes of the ring conformation [73].
1.7. Glycosidase Inhibitors

Glycosidase inhibitors [12] [27] [36] [56 – 58] [117 – 125] are of interest because of their therapeutic potential (Chapter 1.2), and because of their application in biochemical studies of glycosidases.

Glycosidase inhibitors are classified as irreversible and reversible inhibitors, and the reversible inhibitors may be further classified as analogues of the substrate (in the ground state or in a reactive conformation), as analogues of the transition state, or as product analogues.

Irreversible glycosidase inhibitors are characterised by their irreversible binding to the enzyme by formation of a covalent bond. They have been used extensively for labelling and identifying active site residues [51] [57] [59] [60] [126]. 2-Deoxy-2-fluoro-β-pyranosides and 5-fluoro-α-pyranosides with good leaving groups (fluoride or dinitrophenolate) are "suicide substrates" used for trapping glycosyl enzyme esters which were characterised by peptic digestion and LC-MS ([62 – 65]) or by crystal structure analysis ([48] [53] [72 – 74] [77]) [44]. However, these trapped glycosyl enzyme esters are slowly turned over to the corresponding pyranose and the free enzyme, so that these inhibitors – in spite of binding covalently to the enzyme – are not truly irreversible.

Reversible inhibitors are used extensively as mechanistic probes for glycosidases. Structure activity relations of glycosidase inhibitors may provide detailed information about the active site and the mechanism of action. According to transition state theory, the essence of (enzymatic) catalysis is a lowering of the equilibrium constant $K^\ddagger$ between the ground state and the transition state [100]. In order to achieve this, an enzyme must stabilise (bind) the transition state more strongly than the ground state (Figure 1.7.1) [127]. The hypothetical dissociation constant for the transition state-enzyme complex $K_{tx}$ can be calculated according to equation (1) [100]. The catalytic efficiency of a β-glucosidase, expressed by the acceleration factor $k_{cat}/k_{non}$, is typically around $10^{12}$ to $>10^{14}$ [57] (for the 1,4-α-D-glucan maltohydrolase from sweet potato $k_{cat}/k_{non}$ is larger than $10^{17}$ [128]), and $K_M$ values are typically around $10^{-4}$ to $10^{-2}$ M, thus a range of $10^{-14}$ to $10^{-18}$ M is estimated for $K_{tx}$. Tight binding of the substrate is counter-productive to efficient catalysis, because an enzyme can enhance the rate of reaction only to the extent that it binds the transition state more strongly than the substrate [100] [127]. Therefore, weak binding is expected for analogues of the substrate (as well as analogues of the product), whereas tight binding is expected for transition state analogues. The lower limit for $K_i$ of an ideal transition state analogue is set by
the value of $K_{tx}$ (for the 1,4-$\alpha$-D-glucan maltohydrolase from sweet potato ($k_{\text{cat}}/k_{\text{non}} > 10^{17}$), Wolfenden et al. estimated an upper limit of $K_i$ of an ideal transition state analogue at $10^{-22}\text{M}$ [128]).

**Figure 1.7.1:** Reaction Coordinate for Non-Enzymatic and Enzymatic Glycoside Hydrolysis (Adapted from [100]).

Kinetic studies with deoxy-pyranosides provided insight into the contribution of the individual hydroxyl groups of glycopyranosides to the binding of substrate and transition state to glycosidases. While 2-deoxypyranosides are more than 2000 fold more sensitive to non-enzymatic acid hydrolysis (correlated with the absence of the destabilising effect of the electron withdrawing C(2)–OH on the oxycarbenium ion like transition state), Legler found that they are only poor substrates for glycosidases [57]. Thus, 4-methylumbelliferyl 2-deoxy-$\beta$-D-arabinopyranoside ($K_m = 0.7 \text{mM}$) binds more strongly to the $\beta$-glucosidase A from bitter almonds than the corresponding $\beta$-D-glucopyranoside ($K_m = 1.7 \text{mM}$), but is hydrolysed by this enzyme much more slowly ($k_{\text{cat}} = 12 \text{min}^{-1}$ vs. $26400 \text{min}^{-1}$) [57]. Legler concluded that the interaction energy of the enzyme with C(2)–OH not only shows up as binding energy as expressed by $K_m$, but is used to a large extent to lower the free energy of activation. According to transition state theory, this means that for the pyranoside the transition state is bound much more strongly to the enzyme than for the deoxypyranoside, while the ground state deoxypyranoside is bound slightly more strongly than the ground state pyranoside. It may be concluded that the "interaction energy" of C(2)–OH with the enzyme is much larger for the transition state than for the ground state. However, this is an approximation, because the differences in binding energy may not only be due to direct binding interactions with C(2)–OH, but also to indirect effects of C(2)–OH (e.g. conformational changes, changes of the electron donor/acceptor properties of the other hydroxyl groups, earlier or later transition
state).

By kinetic studies with deoxypyranosides Namchuk and Withers dissected the contributions of all the individual hydroxyl groups of gluco-pyranosides to the binding of the ground state and the transition state to the β-glucosidase from Agrobacterium faecalis [101]. At the ground state, the "interaction energies" (vide supra) of the hydroxyl groups with the enzyme were weak (0.8 kcal/mol or smaller). Except for C(6)–OH, the interaction energies of each hydroxyl group were much larger at the transition state (0.7 – 5.4 kcal/mol), the largest interaction contributed by C(2)–OH. This strong interaction of C(2)–OH is a common phenomenon with β-glycosidases (and also with some α-glycosidases [92] [115] 18), with the interaction energy exceeding 10 kcal/mol for some β-glycosidases [42] [44] [45]. C(2)–OH is claimed to donate a hydrogen bond to the catalytic nucleophile of β-glycosidases [48] [52] [73] [74] [96] [106] [129] [130] and to participate in (weaker) interactions with other residues in the active site, e.g. to accept a H-bond from NH2 of a conserved Asn residue in families 5 [106] [129] and 10 [48] [130], or from a conserved Arg residue in glycosidase families 3 [52] and 11 [73] [74], or from a conserved Gln residue in family 7 [96], or to accept a H-bond from conserved His and Arg residues and to donate a H-bond to a conserved Asp residue in glycosidase family 13 [115]. The strength of these H-bonds is maximised at the transition state, and this was suggested to lead to an increase of the negative charge on O–C(2), lowering the electronegativity of this oxygen, which would otherwise strongly disfavour formation of a positively charged transition state (vide supra), and to favour distortion of the glycon towards the transition state conformation [115] 19. The H-bond between C(2)–OH and the catalytic nucleophile becomes particularly strong in the transition state and this leads to a partial stabilisation of the negative charge on CO2– and thus to a weakening of the coulomb interaction with the developing positive charge at the anomeric centre. This reduces the activation energy, because the contribution of the coulomb interaction between CO2– and C(1) to the energy of the transition state is positive.

One wonders about the role of the interactions of C(2)–OH with retaining β-mannosidases [46] where C(2)–OH is on the opposite face of the pyranose ring than the catalytic nucleophile. For a family 26 mannanase, crystal structure analysis of a substrate complex and of a trapped glycosyl enzyme ester revealed boat-like conformations with a pseudoequatorial

18) There are exceptions where the interaction with C(2)–OH is not (or less) important, A. Planas, personal communication to A. Vasella.

19) A complementary aspect is that the positive charge developing at the anomeric carbon increases the acidity of C(2)–OH, leading to a stronger hydrogen bond, while distortion of the substrate towards the transition state leads to an optimum geometry for this hydrogen bond [44].
C(2)–OH [77] (see page 29). C(2)–OH interacted with His211, and Ducros et al. speculated that the equatorial orientation of C(2)–OH may permit an interaction with the carbonyl oxygen of the nucleophile on the other face of the ring plane [77]!

Another important contribution to the stabilisation of the transition state is an interaction between O–C(5) and a conserved Tyr residue. This Tyr residue is highly conserved in glycosidases, and its mutation to Phe reduces [75] or even abolishes [73] their catalytic efficiency. For the substrate complex of family 5 and 11 glycosidases, it was suggested that this tyrosine donates a bifurcated H-bond to O–C(5) of the glycon and to Oε2 of the catalytic nucleophile [73 – 75]. For a family 11 glycosidase, it was proposed that at the transition state this hydrogen bond becomes asymmetric, favouring donation to the catalytic nucleophile, while the interaction with O–C(5) becomes a direct oxygen-oxygen contact, stabilising the positive charge of O–C(5) by a charge dipole interaction [73]. It was not addressed, how this proposed H-bond to Oε2 of the catalytic nucleophile will affect the proposed H bond between C(2)–OH and Oε1 of the catalytic nucleophile20).

Hydrophobic interactions are also important in ligand-enzyme complexes, the energy for removing a hydrophobic surface of a ligand from water and binding it to a hydrophobic region of a receptor was estimated at 28 cal Å−2mol−1 (which corresponds to 0.68 kcal/mol for a methyl group) [133]. A hydrophobic "platform" stabilising the transition state appears to be present in the −1 subsite of all glycosidases [134].

Examples of substrate analogues are thioglycosides, C-glycosides, glycosylamines (or glycosyl ammonium ions, depending on the pH of the enzyme assay), and carbasugars such as 10, 11a, and 12, with $K_i$ or $IC_{50}$ values of the same order of magnitude as $K_m$ (Table 1.7.1). N-Benzyl β-glucosylamine 11b binds 3 orders of magnitude more strongly to the β-glucosidase from almonds than 11a. This difference cannot only be due to the different $pK_{HA}$ values, but the stronger binding of 11b must be due to the hydrophobic aglycon mimic. Such an increased affinity to a glycosidase is typical for inhibitors bearing a hydrophobic aglycon mimic [56] [58] [92]. Glucosyl amines are stronger inhibitors than thiobenzyl glucosides, because the basic glycosidic nitrogen interacts strongly (hydrogen bond or salt bridge) with the catalytic acid [135]. However, glucosyl amines with a $pK_{HA}$ lower than 5 do not bind more tightly than O- or S-glucosides [58]. Based on the pH dependence of their inhibition and on the fact that the (permanently charged) glucosylpyridinium ion is a weaker inhibitor than

20) By trapping the covalent sialyl-enzyme intermediate and LC-MS/MS analysis of peptic digests, Tyr342 of the trans-sialidase from Trypanosoma cruzi (family 33) was identified as the catalytic nucleophile of this enzyme [131]. See [132] for a possible explanation why sialidases may use tyrosine as the catalytic nucleophile.
β-glucosidase from sweet almonds than β-glucosylbenzene, it was assumed that glucosylamines bind to this enzyme in their unprotonated form [135] (For a few other examples of substrate analogues see [135 – 141]).

Table 1.7.1: Glycosidase Inhibitors, Substrate Analogues.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Enzyme inhibited (pH of assay), inhibition constant (inhibition type)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="10" alt="Image" /></td>
<td>β-glucosidase from almonds (6.0): ( K_i = 1.4 \text{ mM (comp.)} )</td>
<td>[135]</td>
</tr>
<tr>
<td><img src="11a" alt="Image" /></td>
<td><img src="11b" alt="Image" /> (pKHA = 5.6): β-glucosidase from almonds (6.0): ( K_i = 0.3 \text{ mM (comp.)} )</td>
<td>[135]</td>
</tr>
<tr>
<td><img src="12" alt="Image" /></td>
<td>α-glucosidase from brewer’s yeast (6.8): ( IC_{50} = 0.58 \text{ mM} ), β-glucosidase from almonds (6.8): ( IC_{50} = 1.5 \text{ mM} )</td>
<td>[31]</td>
</tr>
</tbody>
</table>

Strong inhibition is expected for transition state analogues (vide supra), and consequently numerous potential inhibitors mimicking the charge and/or the conformation of an oxycarbenium ion-like transition state have been prepared. Typical examples for analogues mimicking the coplanarity of C(5)–O–C(1)–C(2) are the lactone 13, the hydroximo lactone 14, and the lactame 15, with \( K_i \) values of the same order of magnitude as \( K_m \) (Table 1.7.2). The basic amidine 16, hydroximo lactame 17, and amidrazone 18 bind significantly (1–2 orders of magnitude) more strongly. These inhibitors are charged at the pH of the enzyme assay and are thought to interact strongly with the catalytic nucleophile. The hydroximolactone 17 is a stronger inhibitor at pH 4.5; under these conditions it is still expected to be unprotonated (for further inhibitors mimicking the coplanarity of C(5)–O–C(1)–C(2), see [66] [142 – 154]).
Table 1.7.2: Glycosidase Inhibitors, Lactone and Lactame Type.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Enzyme inhibited (pH of assay), inhibition constant (inhibition type)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image13.png" alt="Inhibitor 13" /></td>
<td>β-glucosidase from almonds (6.2): $K_i = 0.2$ mM (comp.)&lt;br&gt;β-glucosidase from almonds (4.5): $K_i = 37$ µM (comp.)</td>
<td>[57] [117] [155]</td>
</tr>
<tr>
<td><img src="image14.png" alt="Inhibitor 14" /></td>
<td>β-glucosidase from almonds (6.8): $K_i = 4.3$ mM (comp.)&lt;br&gt;β-glucosidase from almonds (4.5): $K_i = 0.1$ mM (comp.)</td>
<td>[155]</td>
</tr>
<tr>
<td><img src="image15.png" alt="Inhibitor 15" /></td>
<td>(pK HA $\approx$ 0.6):&lt;br&gt;β-glucosidase from almonds (6.8): $K_i = 0.13$ mM (comp.)</td>
<td>[57]</td>
</tr>
<tr>
<td><img src="image16.png" alt="Inhibitor 16" /></td>
<td>(pK HA = 10.6):&lt;br&gt;β-glucosidase from almonds (6.8): $K_i = 10$ µM (comp.)</td>
<td>[156]</td>
</tr>
<tr>
<td><img src="image17.png" alt="Inhibitor 17" /></td>
<td>(pK HA = 5.6):&lt;br&gt;β-glucosidase from almonds (6.8): $K_i = 16$ µM (comp.)</td>
<td>[157]</td>
</tr>
<tr>
<td><img src="image18.png" alt="Inhibitor 18" /></td>
<td>(pK HA = 8.7):&lt;br&gt;β-glucosidase from almonds (6.8): $K_i = 8.4$ µM (comp.)</td>
<td>[156]</td>
</tr>
</tbody>
</table>
An even stronger inhibition was observed for the glucose-derived fused imidazole 19a (Table 1.7.3) [14] [39] [158] which is an analogue of nagstain, an N-acetyl-β-D-glucosaminidase inhibitor isolated from the fermentation broth of *Streptomyces amakusaensis* [118]. The phenethyl derivative 19b of 19a is the strongest inhibitor of the β-glucosidases from sweet almonds and from *Caldocellum saccharolyticum* known to date. Its $K_i$ values are, however, still several orders of magnitude higher than the $K_i$ expected for an ideal transition state analogue (*vide supra*). The tight binding of these imidazoles is attributed to a synergistic interaction with the catalytic residues: the "glycosidic" N atom is protonated (or hydrogen bonded) by the catalytic acid, which potentiates a charge-dipole interaction between the catalytic nucleophile and the "anomeric" carbon [14]. This synergy between the catalytic acid and nucleophile in binding the imidazole is reminiscent of the synergistic action of these residues in the cleavage of a glycoside. However, in the presumed oxycarbenium ion-like transition state of enzymatic β-glycoside cleavage the glycosidic oxygen should be located above the pyranose ring plane, whereas in the fused imidazole it is located within the piperidine ring plane (*cf.* [130] [159]) 21). The importance of protonation (or hydrogen bonding) of the imidazoles by the catalytic acid is corroborated by the reduced affinity to the enzymes of the analogous less basic triazole 20 and tetrazole 21. It was assumed that inhibitors that bind in their unprotonated from and are protonated by the catalytic acid within the active site are particularly strong [148] [160]. Ermert determined that the tetrazole 21 is a partial (this means an imperfect) transition state analogue [38] (see also the discussion in [14] and [39]). For other inhibitors of this type see [12] [129] [161 – 168].

21) Crystal structure analysis of Cel5A in complex with a cellobiose-derived imidazole or with a distorted substrate (1$S_3$ conformation) revealed that the catalytic acid is able to bind to the axial glycosidic O atom (1.4 Å above the ring plane) of the substrate complex as well as to the "glycosidic" N atom (which is located within the ring plane) of the imidazole [129]. Similar observations were made for the family 10 Cex xylanase from *Cellulomonas fimi* [130].
### Table 1.7.3: Glycosidase Inhibitors, Imidazole Type.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Enzyme inhibited (pH of assay), inhibition constant (inhibition type)</th>
<th>Reference</th>
</tr>
</thead>
</table>
| ![Inhibitor 19a](image1) R = H, ![Inhibitor 19b](image2) R = CH₂CH₂Ph | **19a** (pKₐ = 6.1):
- β-glucosidase from almonds (6.8):
  - $K_i = 0.1 \mu M$ (comp.)
- β-glucosidase from *Caldocellum* s. (6.8):
  - $K_i = 20$ nM (mixed, $\alpha = 3.2$)

**19b** (pKₐ = 6.03):
- β-glucosidase from almonds (6.8):
  - $K_i = 1.2$ nM (comp.)
- β-glucosidase from *Caldocellum* s. (6.8):
  - $K_i = 0.11$ nM (mixed, $\alpha = 15$) | [163] [169] |
| ![Inhibitor 20](image3) | (pKₐ = 2.4):
- β-glucosidase from almonds (6.8):
  - $K_i = 19 \mu M$ (comp.)
- β-glucosidase from *Caldocellum* s. (6.8):
  - $K_i = 0.17 \mu M$ (comp.) | [163] |
| ![Inhibitor 21](image4) | (pKₐ = –4.0):
- β-glucosidase from almonds (6.8):
  - $K_i = 0.15$ mM
- β-glucosidase from *Caldocellum* s. (6.8):
  - $K_i = 5 \mu M$ (comp.) | [161] [163] |

The basic piperidines 1-deoxynojirimycin 23 and isofagomine 24 (Table 1.7.4) are relatively strong glycosidase inhibitors, mimicking the charge of an oxycarbenium ion-like transition state. Thus, they are often regarded as transition state analogues, although they do not mimic the conformation of the transition state. Varrot *et al.* determined that at the pH optimum for binding of a cellobiose-derived isofagomine to the endocellulase Cel5A from *Bacillus agaradhaerens* this enzyme is in an inactive form (catalytic acid deprotonated) [170], and from the crystal structure of the inhibitor-enzyme complex they concluded that this inhibitor rather resembles the covalent intermediate than the transition state [170]. Crystal structure analysis of the family 10 xylanase from *Cellulomonas fimi* in complex with a xylobio-isoagomine and a xylobio-deoxynojirimycin analogue revealed that this isofagomine forms a salt bridge with the catalytic nucleophile, whereas the charged N atom of the
deoxynojirimycin does not interact directly with the catalytic residues, but instead interacts with two water molecules [130]. The thermodynamics of the binding of 23 and 24 to the β-glucosidase from sweet almonds were determined by isothermal titration calorimetry [171] (cf. [172]). At 35°C and pH 7, for 1-deoxynojirimycin ΔH = –8.69 kcal/mol and TΔS = –2.35 kcal/mol, for isofagomine ΔH = –8.26 kcal/mol and TΔS = 2.54 kcal/mol, evidencing that for both inhibitors binding is enthalpically favoured, whereas the entropy contribution to binding is unfavourable for 1-DNJ, but favourable for isofagomine22). The pH dependence of the inhibition of the family 1 β-glucosidase from *Thermotoga maritima* by 23 and 24 indicated that both inhibitors bind in their protonated form to an enzyme species whose catalytic carboxylates are both deprotonated [171]. Atomic resolution crystal structure analysis of a cellobiose-derived isofagomine in complex with the endocellulase Cel5A from *Bacillus agaradhaerens* showed that the inhibitor is protonated while both catalytic carboxylates are deprotonated [170]. Quantitative analysis of the binding enthalpy of 23 and 24 to this enzyme at pH 5.8 in various buffers (both inhibitors are protonated under these conditions) revealed that upon binding one proton is released either from the glucosidase or from the inhibitor (it could not be distinguished, whether the inhibitor releases a proton to the solvent and is then protonated by the catalytic acid in the active site, or whether the protonated inhibitor binds to the active site which consequently releases a proton) [171]. (For other inhibitors of this type see [121] [174 – 189]; for indolizidines and pyrrolizidines see [27] [36] [190 – 192])

(+)-Valienamine (22, Table 1.7.4) is a non-hydrolysable carbocyclic analogue of a flattened α-glucoside. As expected, it inhibits the β-glucosidase from almonds only weakly, but is a rather strong inhibitor of the α-glucosidase from yeast. Valienamine is the key structural element of acarbose (vide supra) [28] [29], a strong inhibitor of intestinal sucrase (*K*<sub>i</sub> = 2.6 x 10<sup>−7</sup> M) which has been assessed as a transition state analogue inhibitor of cyclodextrin glycosyl-transferase [193]. As the C(4)–C(5)–C(5a)–C(1) moiety of valienamine is flattened, this provides at least some similarity to the flattened transition state (coplanarity of C(5)–O–C(1)–C(2)).

---

22) An earlier attempt to dissect the thermodynamics of binding of 23 and 24 to the β-glucosidase from sweet almonds by simple van't Hoff analysis [173] gave wrong results, as the assumption that ΔH is temperature independent is not correct [171].
Table 1.7.4: Glycosidase Inhibitors, Amines.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Enzyme inhibited (pH of assay), inhibition constant (inhibition type)</th>
<th>Reference</th>
</tr>
</thead>
</table>
| ![](image22) | β-glucosidase from almonds (6.8): \( IC_{50} = 8.8 \text{ mM} \)  
α-glucosidase from yeast (6.8): \( IC_{50} = 18 \text{ µM} \) | [31] |
| ![](image23) | (pKHA = 6.7):  
β-glucosidase from almonds (6.8): \( K_i = 26.3 \text{ µM (comp.)} \)  
α-glucosidase from yeast (6.8): \( K_i = 15 \text{ µM (comp.)} \) | [173] [174] [194] |
| ![](image24) | (pKHA = 8.6):  
β-glucosidase from almonds (6.8): \( K_i = 0.11 \text{ µM (comp.)} \) | [177] [121] |

Several pyranoside analogues mimicking high-energy reactive substrate conformers have been prepared (Table 1.7.5). The transition state for the glycosylation of enzymes distorting the substrate to a high-energy reactive conformation lies on the reaction coordinate between the reactive substrate conformation and an oxycarbenium ion (with \( \phi(C(5)–O–C(1)–C(2)) = 0^\circ \)). Inhibitors mimicking the reactive substrate conformation should be better mimics of the transition state than inhibitors with a \( ^4C_1 \) conformation and should consequently bind more tightly. Particularly strong inhibition by conformationally locked analogues of reactive substrate conformers is expected for enzymes which actually stabilise high-energy reactive conformations in the active site at the expense of binding energy, because the energy which is normally required to distort the substrate (e.g. 8 kcal/mol to distort a pyranose from a chair to a boat conformation [98] [99]) is fully available as additional binding energy.

The \( ^2^5B \) conformation was proposed as the transition state conformation for the hydrolysis of α-glucosides by the α-glucosidase from yeast [89]. However, the bicyclic deoxy-mannojirimycin derivative 25, locked in a \( ^2^5B \) conformation, is a significantly weaker inhibitor of this enzyme than 1-DNJ (23) (Table 1.7.5) [194]. Similarly, at pH 5.0 25 is a weaker inhibitor of the α-mannosidase from almonds than 1-deoxy-mannojirimycin (\( K_i = 0.24 \text{ mM} \) [174]).
The isofagomine disaccharide analogue 26a, designed to mimic the pseudoaxial orientation of the aglycon in a 1,4\(B\) distorted \(\beta\)-glucopyranoside, is only a weak inhibitor of the retaining endoglucanase Cel7B from \textit{Fusarium oxysporum} (family 7) [195], for which distortion of a substrate analogue to a boat conformation was observed in the crystal structure (\textit{vide supra}) [96]. However, it is highly unlikely that 26 actually adopts the desired conformation 26a with axial "aglycon" (conformation 26b is more likely). Isofagomine itself usually binds in a 4\(C_1\) conformation [171] [193].

In our group, the isoquinuclidines 27, 28, 29, 30, and 32, mimicking 1,4\(B\) conformers of manno-pyranose, gluco-pyranose, and GlcNAc, respectively, were first prepared as racemates by \textit{Lorthiois} and \textit{Meyyappan} and then as pure enantiomers by \textit{Boehm} via an elegant enantioselective formal [4+2] cycloaddition [196 – 199]. The mannose-analogue 27 is only a weak inhibitor of the \(\beta\)-mannosidase from snail, the \(N\) benzyl derivative 28 is 3 orders of magnitude more potent [197]. This increase in binding energy by introducing a hydrophobic aglycon mimic is similar to that observed in non-distorted substrate analogues of \(\beta\)-glucosidases (\textit{vide supra}). This might mean that the aglycon mimic adopts a similar position in the complexes of the distorted and undistorted substrate analogues, suggesting different positions for the pyranoside in subsite –1 which is at first glance counter-intuitive but is in agreement with the "bypass-binding" observed for several undistorted substrate complexes [104] [105] [107] [200] [201]. Based on an increasing affinity to the \(\beta\)-mannosidase towards higher pH values (\(\alpha\) also increases, the inhibition becomes almost fully competitive at pH 5.5), \textit{Boehm et al.} concluded that the unprotonated forms of 27 and 28 bind to the enzyme and derived \(K_i\) values of 2.2 \(\mu\)M and 2 nM, respectively, for hypothetical analogues of 27 and 28 with \(pK_{HA} = 4.5\). Whether this extrapolation is justified requires verification. The estimated \(K_i\) values of 2.2 \(\mu\)M and 2 nM for 27 and 28 would corroborate that the active site stabilises a boat(like) high-energy reactive conformation. The experimentally determined \(K_i\) values are not spectacular, but a \(K_i = 1.0\) \(\mu\)M for 28 evidences that such a conformer fits in the active site, and suggests that a related high-energy reactive conformer may be involved in catalysis.

The isoquinuclidine 29 is only a weak inhibitor of the \(\beta\)-glucosidase from almonds. Surprisingly, the \(N\)-benzyl derivative 30 binds even more weakly [198]! Apparently the hydrophobic aglycon mimic cannot adopt the same position as in a (distorted) substrate, probably because the bridged isoquinuclidine skeleton restricts the C(2)–C(1)–N–CH\(_2\) torsional angle. As the pH of the enzyme assay is close to the \(pK_{HA}\) values of 29 and 30, one cannot argue that protonation of the inhibitors corrupts binding. The reason for the weak binding of these isoquinuclidines to the \(\beta\)-glucosidase may be that hydrolysis by this enzyme proceeds \textit{via} a significantly different reactive conformation than 1,4\(B\), or that the transition state is late (and therefore a reactive boat conformer is too different from the transition state conformation to benefit from the enzyme's affinity to the transition state), or that the events of
distortion of the substrate to a reactive conformation and glycosylation are concerted. From the inhibition data for the manno and gluco isoquinuclidines Boehm et al. conclude that "the glycosidase induced lengthening of the scissile bond and rehybridisation of the anomeric centre are more strongly correlated with the change of the ground-state conformation during hydrolysis of β-glucopyranosides than of β-mannopyranosides". This means that for the reactive conformer of a β-glucopyranoside, lengthening of the glycosidic bond and rehybridisation are more advanced, therefore the isoquinuclidine with "normal" bond lengths and angles may be only a poor mimic of the reactive conformer.

The isoquinuclidine 31 is a very strong inhibitor of the N-acetyl-β-hexosaminidase from jack beans (family 18) and of the N-acetyl-β-hexosaminidase from bovine kidney23) [199]. The N-benzyl derivative 32 is a significantly weaker inhibitor of these enzymes, evidencing that the inhibition by 31 is due to specific interactions between these enzymes and the inhibitor and not to unspecific hydrophobic interactions (with the N-benzyl substituent). The 2-deoxy-analogue of 31 was only a weak inhibitor of these enzymes ($K_i = 25$ and 310 µM, respectively), evidencing a strong interaction of the enzymes with the pseudo-axial acetamido substituent. The strong inhibition by 31 evidences that hydrolysis of 2-acetamido-2-deoxy-β-D-glucopyranosides by these hexosaminidases proceeds via a $1,4\beta$ or a closely related reactive conformer and corroborates the previously made conclusion that enzymes from family 18 are capable of stabilising such a conformer by binding interactions in the –1 subsite, presumably with the acetamido substituent.

Table 1.7.5: Glycosidase Inhibitors Mimicking High-Energy Reactive Substrate Conformers.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Enzyme inhibited (pH of assay), inhibition constant (inhibition type)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure" /> 25</td>
<td>$\beta$-glucosidase from almonds (6.8): $K_i = 1$ mM (comp.)&lt;br&gt;$\alpha$-glucosidase from yeast (6.8): $K_i = 7$ mM (comp.)&lt;br&gt;$\alpha$-mannosidase from almonds (5.0): $K_i = 15$ mM (comp.)</td>
<td>[194]</td>
</tr>
</tbody>
</table>

23) The amino-acid sequence and the 3D structure of this enzyme are not known.
<table>
<thead>
<tr>
<th>Structure</th>
<th>Enzyme Activity</th>
<th>Ki</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cel7B from <em>Humicola insolens</em> (8.5):</td>
<td>$K_i = 0.2$ mM (comp.)</td>
<td></td>
<td>[195]</td>
</tr>
<tr>
<td>27 (pK$_{HA}$ = 8.4)</td>
<td>$\beta$-mannosidase from snails (4.5):</td>
<td>$K_i = 1.2$ mM (mixed, $\alpha = 1.1$)</td>
<td>[197]</td>
</tr>
<tr>
<td>28 (pK$_{HA}$ = 7.5)</td>
<td>$\alpha$-mannosidase from Jack beans (4.5):</td>
<td>$IC_{50} = 2$ mM</td>
<td></td>
</tr>
<tr>
<td>29 (pK$_{HA}$ = 7.8)</td>
<td>$\beta$-glucosidase from almonds (6.8):</td>
<td>$IC_{50} = 2.7$ mM</td>
<td>[198]</td>
</tr>
<tr>
<td>30 (pK$_{HA}$ = 6.6)</td>
<td>$\beta$-glucosidase from <em>Caldocellum</em> s. (6.8):</td>
<td>$K_i = 1.3$ mM (mixed, $\alpha = 9.0$)</td>
<td></td>
</tr>
<tr>
<td>31 (pK$_{HA}$ = 7.7)</td>
<td>$N$-Acetyl-$\beta$-hexosaminidase from Jack beans (5.0):</td>
<td>$K_i = 14$ nM (comp.)</td>
<td>[199]</td>
</tr>
<tr>
<td>32 (pK$_{HA}$ = 5.9)</td>
<td>$N$-Acetyl-$\beta$-hexosaminidase from bovine kidney (4.1):</td>
<td>$K_i = 67$ nM (comp.)</td>
<td></td>
</tr>
</tbody>
</table>
A host of other glycosidase inhibitors, especially natural compounds, are known. A few examples are shown in Table 1.7.6. Cyclophellitol (33) is a weak irreversible inhibitor of the \( \beta \)-glucosidases of sweet almonds. It is bound to the catalytic nucleophile by epoxide opening at C(1). The epoxide moiety imposes a flattened conformation on the cyclohexane ring, which thus bears some resemblance to the transition state. The aziridine corresponding to cyclophellitol is a much stronger inhibitor (see Chapter 3.1). The calystegines (e.g. calystegin C1 (34)), hydroxylated nortropanes isolated from root organs and root exudates of *Calystegia sepium* and other species, are micromolar inhibitors of several glycosidases [202 – 206]. They might be regarded as bicyclic isofagomine derivatives, suggesting interaction of their basic nitrogen with the catalytic nucleophile, although a different binding mode was suggested in the literature [204].

Several aminocyclopentitols (e.g. 35 and 36) and 1,4-dideoxy-1,4-iminofuranoses (e.g. 37) are strong glycosidase inhibitors [27] [36] [124]. This is surprising, because the structure of an (aza)-cyclcopentane differs significantly from that of a pyranoside. But the 5-membered ring is conformationally more flexible, probably allowing these inhibitors to adapt to the active site. Also, five-membered rings might be better mimics than cyclohexane chairs of a flattened pyranoside conformation (\( \Phi(C(5)–O–C(1)–C(2)) = 0^\circ \)). The exocyclic or endocyclic N atom of these inhibitors can interact strongly with the catalytic residues. The weak selectivity of both 35 and 36 for the \( \alpha \)-glucosidase is surprising. (For aminocyclopentitols see [207 – 213]; for iminofuranoses see [160] [214] [215]).

The panosialins (e.g. panosialin wA (38)) isolated from the culture broth of *Streptomyces* sp. OH-5186 are strong glycosidase inhibitors [216]. These inhibitors cannot be regarded as pyranoside analogues, but are fortuitous binders.
Table 1.7.6: Various Glycosidase Inhibitors.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Enzyme inhibited (pH of assay), inhibition constant (inhibition type)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image-url" alt="Inhibitor 33" /></td>
<td>β-glucosidase from almonds (6.8): $K_i = 0.34$ mM (irreversible, $k_i = 2.38$ min$^{-1}$)</td>
<td>[217]</td>
</tr>
</tbody>
</table>
| ![Inhibitor 34](image-url) | β-glucosidase from almonds (6.8): $K_i = 0.45$ µM (comp.)
β-glucosidase from *Caldocellum s.* (6.8): $K_i = 0.29$ µM (comp.) | [204] |
| ![Inhibitor 35](image-url) | β-glucosidase from almonds (6.8): $K_i = 6.6$ µM (comp.)
β-glucosidase from *Caldocellum s.* (6.8): $K_i = 2.6$ µM (comp.)
α-glucosidase from yeast (6.8): $K_i = 0.7$ µM (comp.) | [211] [213] |
| ![Inhibitor 36](image-url) | β-glucosidase from almonds (6.8): $K_i = 6.5$ µM (comp.)
β-glucosidase from *Caldocellum s.* (6.8): $K_i = 1.5$ µM (comp.)
α-glucosidase from yeast (6.8): $K_i = 0.5$ µM (comp.) | [213] |
| ![Inhibitor 37](image-url) | α-mannosidase from Jack beans (4.5): $K_i = 0.76$ µM (comp.) | [218] |
| ![Inhibitor 38](image-url) | β-glucosidase from almonds (6.8): $IC_{50} = 0.24$ µM | [216] |
1.8. Aims and Questions

Although glycosidases have been studied extensively and a plethora of kinetic and structural data has been collected, important details of the mechanism of action remain unclear and are the subject of controversy. As outlined in chapter 1.4, it remains elusive if glycosylation proceeds via a short-lived oxycarbenium ion rather than by an SN2-like mechanism [43] [46]. Thus, the transition state might lie on the reaction coordinate before the oxycarbenium ion-like species, and its structure might be somewhere between that of the reactive substrate and the oxycarbenium ion. Whether substrate distortion to a high-energy reactive conformation is a requirement for all glycosidases remains controversial. A conformational itinerary involving high-energy reactive conformers has been proposed but it is not fully understood, how (or if?) the enzyme stabilises such conformers, and it remains elusive whether the conformational change and glycosylation are separate processes or concerted. For glycosidases from families 5 and 7 alternative binding modes were proposed for the substrate in its ground state (bypass binding) and reactive conformation. This raises the questions whether such alternative binding modes are relevant to enzymatic catalysis or whether the bypass-binding mode observed in the crystal structure is an artifact resulting from the conditions of crystallisation. Alternative binding modes for the substrate would also suggest alternative binding modes for inhibitors mimicking the substrate in its ground state or in its reactive conformation. Although glycosylation and deglycosylation are apparently simple nucleophilic displacements, there is not yet a truly thorough understanding of the mechanism of action of glycosidases.

Structure-activity studies of both substrate and transition state analogous inhibitors provide invaluable information about how an enzyme binds the substrate and how it stabilises the transition state. The data from kinetic, structural, theoretical, and inhibition studies lead to "working hypotheses" of the mechanism, which have to be tested experimentally – be it by kinetic, structural, or further inhibition studies. The goal of such inhibition studies is to compare the activity of certain inhibitors with the predictions derived from the mechanistic hypotheses. In some cases this can be done with existing data of known inhibitors, but often mechanistic hypotheses lead to the design of novel inhibitors (e.g. distorted substrate analogues were designed to study the role of substrate distortion). Besides testing mechanistic hypotheses, the design and testing of inhibitors serves also the quest of finding strong, selective inhibitors with potential enzymological or pharmaceutical applications and the purpose of studying ligand-host interactions in a more fundamental way. A prerequisite for any structure-activity study is extensive synthetic organic chemical labour in order to prepare new potential inhibitors.
The aim of this work is the synthesis of carbasugar-derivatives as potential glycosidase inhibitors and evaluation of their activity, in the hope to obtain more information on the mechanism of action of these enzymes.

1) In the context of a research program aimed towards the synthesis and evaluation of carbo cyclic pyranoside analogues, we were in need of an efficient access to versatile carbasugar intermediates. A range of methods leads to carbasugars. Among these, ring-closing alkene metathesis (RCM) which had been applied successfully to the synthesis of complex oligofunctional molecules, appeared very promising. Indeed, RCM had been applied previously in the synthesis of a carba-pyranose from D-glucose [219] [220] and in the synthesis of a carba-furanose from D-mannose [221]. Sarabia\(^{24}\) had elaborated a synthesis of cyclohexenitols from D-glucose and D-mannose via ring-closing alkene metathesis. The aim of this work was to fully characterise the intermediates and products of these syntheses and thereby establish their configuration, which had been assigned tentatively (and as it turned out, correctly) by Sarabia. To this end I intended to repeat Sarabia’s work and establish the configuration of the key intermediates 40 and 42 (Scheme 1.8.1) by conversion into a known compound and by NMR-spectroscopy, respectively. The utility of this carbasugar synthesis should be proved by applying it to a synthesis of (+)-valienamine (22). Sarabia had transformed 40 into N-acetyl-tetra-O-benzylvalienamine (22, \(R = \text{Bn, } R' = \text{Ac}\)) by an allylic cyanate to isocyanate rearrangement, but had not attempted to deprotect this derivative. I intended to prepare \(N\)-benzyloxycarbonyl-tetra-O-benzyl valienamine and deprotect it under Birch conditions. I also intended to study the transformation of 42 into derivatives of the manno analogue of valienamine.

Scheme 1.8.1

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\(^{24}\) Prof. Francisco Sarabia, University of Malaga, Spain, post-doctoral fellow from June 1998 to October 1998.
Sarabia used benzyl protecting groups (R = Bn) in his carbasugar syntheses. In order to study the influence of the nature of the protecting group on the ring-closing alkene metathesis, we also studied the synthesis of the methoxymethyl derivative of 40 (R = MOM) from 2,3,4,6-tetra-O-methoxymethyl-D-glucopyranose. The MOM-derivative of 40 might be a more suitable intermediate than the benzyl derivative in syntheses which require hydrogenation of the double bond (e.g. the synthesis of validamines).

Remen\textsuperscript{25}) and I required a derivative of 42 with orthogonal protection of C(1)–OH (resulting from C(2)–OH of the pyranose starting material), for example for the synthesis of the bicyclic azetidine 57 (\textit{vide infra}). Attempts to prepare such an orthogonally protected derivative of 42 by selective deprotection of the tetra-O-benzyl derivative (42, R = Bn) were not successful [222]. Therefore we decided to investigate the synthesis of said derivative from a \textit{manno}-pyranose with orthogonal protection of C(2)–OH, in analogy to the synthesis of 42 from mannose.

Remen and Mohan\textsuperscript{26}) required carbafruranoses in order to prepare cyclopentanes and bicyclo[3.1.0]hexanes as potential glycosidase inhibitors. We therefore studied the synthesis of carbafruranoses from D-arabinose using ring-closing alkene metathesis as the key step. This was done by Leclerc\textsuperscript{27}).

2) Glycosylidene diaziridines of the type 44 (Scheme 1.8.2) possess trans-oriented N atom lone pairs located above and below the average plane of the glycon ring and oriented more or less parallel to the glycon ring plane. These diaziridines may, thus, inhibit both \(\alpha\)- and \(\beta\)-glycosidases. However, exploratory experiments by Weber showed that the diaziridines 44 are not sufficiently stable in aqueous solution, so that they were not evaluated as glycosidase inhibitors [223]. The goal of this work is to establish a synthesis of carbasugar-derived spiro-diaziridines 45 and to evaluate their activity as glycosidase inhibitors.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme1.8.2.png}
\end{scheme}

\textsuperscript{25}) Dr. Lubos Remen, post-doctoral fellow from March 1999 to December 2001.

\textsuperscript{26}) Dr. Halasyam Mohan, post-doctoral fellow from May 1997 to February 2002.

\textsuperscript{27}) Nathalie Leclerc, diploma student (under my supervision) from the E.N.S.C.M., France, from October 1998 to June 1999.
In complex with a β-glucosidase, the "β"-N of 45 may accept a H-bond from the catalytic acid, while the "α"-N may donate a H-bond to the catalytic nucleophile, or, in its protonated state, form a salt bridge with the catalytic nucleophile (Figure 1.8.1). An inverse situation should be present in a complex of 45 with an α-glucosidase ("α"-N accepting a H-bond from the catalytic nucleophile, "β"-N interacting with the catalytic acid). N-alkyl, N-arylalkyl, or N-(4-glucosyl) derivatives of 45 may be disaccharide analogues with improved affinity to the enzymes. Molecular modelling studies by Dr. B. Bernet revealed that N-(4-glucosyl) derivatives of 45 should be good mimics of cellobiose or maltobiose.

Figure 1.8.1: Proposed Interaction of the Diaziridine 45 with a retaining β-Glycosidase.

To differentiate between the effects of shape and charge on the inhibition by the diaziridines 45, I also required the related spiro-aziridines 46 and 47, and 1-epi-validamine (48, Scheme 1.8.3) [224]. I also included the known inhibition data for validamine (12) [31] in the comparison. The basicity of these potential inhibitors is expected to increase in the order 45 < 46, 47 < 48, 12.
The aminocyclopentitols 35 and 36 (Table 1.7.6) are much stronger glycosidase inhibitors than the aminocyclohexitols 48 and 12. In the conformation depicted in Scheme 1.8.4 – which is likely to be the binding conformation for 35 – the aminocyclopentitols resemble the 5a-amino-carbapyranoses 49 and 50 with C(1) removed. This raised the question if such 5a-aminocarbapyranoses are equally potent glycosidase inhibitors, or if the strong inhibition of the aminocyclopentitols depended on the cyclopentane scaffold. To address this question, I intended to prepare 5a-aminocarbapyranoses like 49 and 50.

Validone (51, Scheme 1.8.5), which is available by NBS-cleavage of validoxylamine A)
[225][226], appeared the starting material of choice for the synthesis of the diaziridines 45. I intended to transform a protected derivative of 51 into the corresponding derivative of 45, using Schmitz's method for the synthesis of diaziridines from ketones [227][228], and to deprotect this diaziridine under mild conditions.

**Scheme 1.8.5**

![Scheme 1.8.5](image)

Proposal for the synthesis of 45. a) i. NH₃, MeOH, then NH₂OSO₃H; ii. Deprotection.

In order to prepare the aziridines 46 and 47, I intended to first examine a direct aziridination of the alkene 53, which in turn should be available from known tetra-⁴-benzylvalidone 52 [225] by a Wittig methylenation (Scheme 1.8.6). As an alternative to the direct aziridination of 53 I also considered a synthesis of the aziridines by the robust route via epoxides and azido alcohols.

**Scheme 1.8.6**

![Scheme 1.8.6](image)

Proposal for the synthesis of 46 and 47. a) Ph₃P=CH₂, THF. b) Aziridination (e.g. chloramine T, PhMe₃NBr₃, MeCN [229], TsN₃, toluene, 110° [230][231], or TiN₃, CH₂Cl₂ [232]), deprotection; or i. mCPBA, CH₂Cl₂; ii. NaN₃, DMF; iii. Sulfonylation with TsCl or MsCl; iv. Reductive cyclisation with LiAlH₄ [233]; v. Deprotection.

28) I wish to thank Dr. A. G. O'Sullivan, Syngenta (formerly Novartis Agro), who generously provided us with validoxylamine A.
Asano et al. prepared 1-epi-validamine (48) by reductive amination of validone (51), thus obtaining 1-epi-validamine (48, 22%) and validamine (12, 36%) after separation by ion exchange chromatography [224]. To avoid such a separation of diastereoisomers, I intended to prepare 48 stereoselectively from the known axial alcohol 54 (Scheme 1.8.7) [234].

Scheme 1.8.7

Proposal for the synthesis of 48. a) i. Sulfonation; ii. NaN$_3$, DMF; iii. Hydrogenation or reduction under Birch conditions.

While one may conceive of several routes to the aminocyclohexitols 49 and 50 (cf. [226] [235]), a regioselective functionalisation of tetra-O-benzylvalidone (52) appeared as the most straightforward approach (Scheme 1.8.8). For the synthesis of the axial amines 49 I examined an azidation of 52, for the synthesis of the equatorial amines 50 I considered exploring bromination of 52 to the axial bromide, followed by a substitution with azide.

Scheme 1.8.8

Proposal for the synthesis of 49 and 50. a) LDA, THF, then 2,4,6-triisopropylbenzenesulfonyl azide [236]. b) i. Reduction of the carbonyl group (LiAlH$_4$, DIBAL-H, or NaBH$_4$); ii. Hydrogenation. c) i. PhMe$_3$NBr$_3$, camphor sulfonic acid [237] [238]; ii. NaN$_3$, DMF.
3) To study the role of substrate distortion in retaining β-glycosidases, pyranoside analogues mimicking high-energy reactive conformers of pyranosides are required. Only a few such inhibitors have been prepared to date, and of these only the isoquinuclidines prepared in our group are strong glycosidase inhibitors. These isoquinuclidines mimic a pyranoside in a $1,4^B$ conformation, but they do not feature the (partial) positive charge at the "anomeric" carbon, which develops in the transition state.

The 6-azabicyclo[3.1.1]heptane 57 (Scheme 1.8.9), a bicyclic azetidine proposed by Professor Vasella is a pyranoside analogue mimicking both a boat conformer and the (partial) positive charge at C(1), thus combining features of the distorted substrate and the transition state.

Scheme 1.8.9

This azetidine is a bicyclic derivative of the strong glycosidase inhibitor isofagomine and the azetidine N(6) should interact strongly with the catalytic nucleophile of a retaining β-glycosidase (Figure 1.8.2). The HRN–C(7) amino substituent (although on the α face of the distorted ring) should mimic the glycosidic oxygen of a pyranoside in a flattened $B$ conformation and thus interact strongly with the catalytic acid (the N of 1-aminonorbornanes appears to interact strongly with the catalytic acid [239]).

Figure 1.8.2: Proposed Interaction of 57 with a retaining β-Glycosidase.
7-Azabicyclo[2.2.1]heptanes (7-azanorbornanes) such as 58 and 59, lower homologues of the isoquinuclidine 28, are another class of potential glycosidase inhibitors (cf. [240]). They also mimic β-pyranosides in a 1.4β conformation, but the N(7) lies above the centre of the carbon ring and thus is not expected to interact strongly with the catalytic acid of a glycosidase. Nonetheless, testing these compounds as glycosidase inhibitors should provide information as to which interactions are important in the binding of pyranosides and their analogues to the active site of these glycosidases.

Originally, I intended to prepare the desired bicyclic azetidine in a "classical" way from the orthogonally protected carbasugar 60 (Scheme 1.8.10). I envisioned two routes for the transformation of 60 to 57, viz. an allylic rearrangement of 60 to 61 and introduction of the azetidine nitrogen by hydroboration-amination to 62. Removal of the MPM group, activation of C(2)–OH, and cyclisation should then provide the protected azetidine 57. Alternatively, 60 might be converted to the cyclohexanone 63; an azido group may be introduced by bromination and nucleophilic substitution to yield 64. After removal of the MPM group, cyclisation to 65 might be effected using Ph₃P. Reductive amination of the ketone 65 (or reduction to an alcohol and nucleophilic substitution) might afford 57. The last step would be hydrogenolytic removal of the benzyl protecting groups.

Scheme 1.8.10

Proposals for the synthesis of the azetidine 57. a) Allylic cyanate to isocyanate rearrangement. b) Hydroboration-amination. c) Cleavage of the MPM ether, activation of OH (e.g. sulfonylation), then base-catalysed cyclisation. d) Oxidative allylic rearrangement, then selective hydrogenation. e) Bromination, then substitution with azide. f) Cleavage of the MPM ether, then cyclisation using Ph₃P; alternatively activation of C(2)–OH, reduction of the azide group to an amino group, then base-catalysed cyclisation. g) Reductive amination; or reduction (e.g. NaBH₄), followed by substitution.
Although I prepared the carbasugar 60 from D-mannose (*vide infra*), the plan to prepare 57 from 60 was abandoned for several reasons:

- The synthesis of 60 was low yielding and would require extensive optimisation.
- There were serious doubts if 62 or 64 would cyclise to the azetidines 57 or 65. This cyclisation presumably requires an axial orientation of N and an equatorial orientation of the leaving group. However, 62 or 64 are expected to adopt a conformation with equatorial N and axial leaving group.
- The transformation of ketone 65 into 57 is not straightforward.
- Even if it were successful, the multi-step synthesis of the 6-azabicyclo[3.1.1]heptane 57 from 60 would only allow variation of the N(6) and C(7) substituents. Variation of the substituents on the other C-atoms would require starting over from a different starting material. Clearly, a more flexible approach was more attractive.

We decided to examine a general approach to 6-azabicyclo[3.1.1]heptanes and to prepare hydroxylated azetidines like 57 by hydroxylation of a simple 6-azabicyclo[3.1.1]heptane precursor. This approach should provide not only the desired glycosidase inhibitors but also interesting building blocks for combinatorial libraries in medicinal chemistry.

I intended to examine four approaches to 6-azabicyclo[3.1.1]heptanes from N-acyl-4-aminocyclohexenes, which in turn should be available from the corresponding carboxylic acids by Curtius degradation:

- Bromination of N-acyl-4-aminocyclohexenes 66 should lead to mixtures of the *trans, trans*-dibromides 67 and the *cis, trans*-dibromides 69 [241] [242] (Scheme 1.8.11). Intramolecular substitution of one Br substituent should provide 6-azabicyclo[3.1.1]heptanes 68 from 67 [243] [244] and 7-azabicyclo[2.2.1]heptanes (7-azanorbornanes) 70 from 69 [241]. I intended to examine the effect of the nature of the N-acyl group, of a substituent at C(5), and of the brominating agent on the bromination of the cyclohexenes 66, and to examine the cyclisation of the dibromides 67 and 69.
Scheme 1.8.11

Proposal for the synthesis of azetidines 68 and 7-azanorbornanes 70. 

- Bromo-cyclisation of 4-(trifluoroacetamido)cyclohexenes to 6-azabicyclo[3.1.1]heptanes [241] appeared particularly attractive, as it would provide the desired building blocks in a single step (Scheme 1.8.12).

Scheme 1.8.12

Proposed synthesis of azetidines 68. 

- A transition metal catalysed intramolecular allylic amination of an acetate 73 to the 6-azabicyclo[3.1.1]hept-2-ene 74 (Scheme 1.8.13) appeared attractive, as it allows the generation of a reactive electrophile in the presence of a nucleophilic amine or amide.
Scheme 1.8.13

Proposal for the synthesis of the azetidine \(74\). \(a)\) "Pd(0)"-catalysed intramolecular allylic amination.

- Finally I intended to examine a sigmatropic rearrangement of imidates \(75\) to \(N\)-acetyl-6-azabicyclo[3.3.1]hept-2-enes (Scheme 1.8.14).

Scheme 1.8.14

Proposal for the synthesis of the aziridine \(74\). \(a)\) Heat or Lewis acid.

For the synthesis of potential glycosidase inhibitors, I intended to transform the building blocks \(68\) and \(70\) into the diols \(76\), \(58\), and \(59\) by base-catalysed elimination of HBr, followed by dihydroxylation of the alkenes \(74\) and \(77\) and deprotection.
Proposal for the synthesis of the potential glycosidase inhibitors 76, 58, and 59. 

a) DBU. b) OsO₄, NMO; then deprotection.
2. Part 1: Carbasugars from Sugars *via* Ring-Closing Alkene Metathesis

2.1. Carbasugars and Valienamine

Carbasugars (also called pseudo-sugars [245]) are carbocyclic analogues of sugars, in which the ring oxygen has been replaced by a methylene group. In a broader sense, hydroxylated cycloalkanes of various ring-size (usually 5 to 8) are also considered as carbasugars. Carbasugars are mimics of natural sugars – humans cannot distinguish carbaglucoses from true glucoses by their taste [120] –, but, being devoid of hemiacetal or acetal character, they do not take part in many typical carbohydrate reactions. Therefore, the chemically stable carbasugars are attractive analogues of natural sugars.

A range of natural compounds belongs to the class of polyhydroxylated cyclohexanes and cyclopentanes (Figure 2.1.1). Inositols [246 – 248], (components of the cell-membrane and second messengers [249]), glycosidase inhibiting conduritols [250] and cyclophellitols [119], aminoglycoside antibiotics (*e.g.* the validamycins [34] [33]), and shikimic [251] and quinic acids [252] (intermediates in the biosynthesis of aromatic compounds) are cyclohexane derivatives. The glycosidase inhibiting allosamidines [253], trehazolins [254], and mannostatins [255], carbocyclic nucleosides such as aristeromycin [256], and even the prostaglandins [257] (*e.g.* prostaglandin $\text{F}_2\alpha$) are cyclopentanopolyols.
Owing to their biological activity, naturally occurring carbasugars and their analogues have received extensive synthetic interest, which has been reviewed comprehensively [119] [120] [124] [258 – 271]. In principle, carbasugars can be prepared \textit{de novo}, from other carbasugars, or from sugars. In the following chapter I will give a brief overview on the synthesis of carbasugars, focusing partly on established, general methods and partly on new or special methods.
2.1.1. De Novo Syntheses of Carbasugars

2.1.1.1. By Cycloadditions and Cyclisations

The (in most cases highly diastereoselective) Diels-Alder cycloaddition between some oxygen containing dienes and dienophiles provided hydroxylated cyclohexenes in a single step. Thus, conduritol D (82, Scheme 2.1.1) was prepared by the cycloaddition between trans,trans-1,4-diacetoxybutadiene (79) and vinylene carbonate (80), followed by hydrolysis of the protecting groups [272]. Shikimic acid was prepared from the cycloaddition product of trans,trans-1,4-acetoxybutadiene and methyl acrylate [273] [274] and also from 1,4-cyclohexadiene-carboxylic acid, the cycloaddition product of butadiene and propiolic acid [275]. Several 5a-carbapyranoses were prepared from the cycloaddition product of trans,trans-1,4-diacetoxybutadiene and allyl acetate [276].

Scheme 2.1.1

\[
\begin{align*}
\text{79} + \text{80} &\xrightarrow{a)} \text{81} \\
\text{81} &\xrightarrow{b)} \text{82}
\end{align*}
\]

\(a\) 205°C, autoclave; 30% [272]. \(b\) Ba(OH)\(_2\), H\(_2\)O; quant. [272].

Quinic acid was prepared from the cycloaddition product of trans,trans-1,4-dichlorobutadiene and benzyl 2-acetoxyacrylate [277]. The oxanorbornene 85 (Scheme 2.1.2), available by cycloaddition of 2-acetoxyfuran (83) to maleic anhydride (84) was transformed into several 5a-carbapyranoses. Cis dihydroxylation and hydrolysis provided 86, which upon prolonged reaction with water gave the cyclohexanone 87 [245]. Reduction of 87 gave carba-talose in a low yield. The cycloadditions between furan and vinylene carbonate [278] [279], between 2-pyrones and enol ethers, enamines [280], or vinylene carbonate [281] also provided useful carbasugar synthons.
Scheme 2.1.2

Scheme 2.1.3

a) Neat, 45%; [261]. H₂O₂, HCO₂H, H₂O; 66% [261]. c) i. LiAlH₄, THF, then Ac₂O, pyridine; 76% ii. AcOH, Ac₂O, H₂SO₄; 61%, α/β = 0.8 [261].
The cycloaddition between furan and 1-cyanovinyl (1'S)-camphanate (91, Scheme 2.1.4) provided the enantiomerically pure oxanorbornene 92 in almost quantitative yield. Hydrolysis of 92 afforded the oxanorbornenone 93. The enantiomers of 92 and 93 were prepared by using 1-cyanovinyl (1'R)-camphanate as the dienophile. These enantiomerically pure oxanorbornenes (termed "naked sugars") are highly versatile intermediates in the synthesis of carbapyranoses (e.g. conduritol C (97)) and also of carbfuranoses, furanoses, and pyranoses; they were regio- and stereoselectively functionalised at C(3), C(5), and C(6) [264] [283] [284].

Scheme 2.1.4

R* = (1'S)-camphanoyl. a) ZnI$_2$; 92% [283]. b) NaOMe, MeOH; [283]. c) i. OsO$_4$, NMO, acetone; [283]. d) TMSOTf, Et$_3$N; [283]. e) i. HF, MeOH, H$_2$O; ii. Ac$_2$O, DMAP, pyridine; iii. NaBH$_4$, CeCl$_3$, MeOH; [283]. f) i. DEAD, PPh$_3$, BzOH, THF; ii. MeOH, KOH; iii. HF, MeCN; 49% from 94 [283] (yields not given).

For further carbasugar syntheses via various oxanorbornenes see [285 – 289], for syntheses via cyclohexenes, see [290] [291].
Carbapyranoses were also prepared from 7-oxonorbornanes by Baeyer-Villiger oxidation and reductive cleavage of the resulting lactones [292] or by Grob fragmentation. Addition of methanolate to the 7-oxonorbornane 98 (Scheme 2.1.5) (prepared in five steps from 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and vinyl acetate) gave the hemiacetal anion 99 which fragmented to the cyclohexene 100 [293 – 295]. An analogous Grob fragmentation of the hemiacetal anion 103 provided the cyclopentene 104 [296].

Scheme 2.1.5

\[ \text{a, b) NaOMe, MeOH; 70%; [293]. c) i. OsO}_4, \text{NMO; 95%; ii. LiAlH}_4, \text{THF; 88%; iii. Amberlyst 15, aq. MeOH; 74% [293]. d, e) NaOMe, MeOH; 40% [297].} \]

Ozonolysis of norbornenes led to carbafularonoses [298] [299].
Carbapyranoses and carbafuranoses were prepared by formal [3+3] and [2+3] cycloadditions. Vinylogous cross aldol reaction between the 2-silyloxy furane 105 (Scheme 2.1.6) and the glyceraldehyde 106 furnished 107 (75%) which was transformed to the aldehydes 108 and 111. Intramolecular aldol reaction of these aldehydes afforded stereoselectively the cyclohexanol 109 and the cyclopentanol 112, which were elaborated into carbapyranoses (e.g. β-D-carbagulopyranose (110)) and carbafuranoses (e.g. β-D-carbaxylofuranose (113)) [300 – 304]. An analogous series of reactions starting from a 2-silyloxy pyrrole provided aminocyclohexitols and aminocyclopentitols [305].

Scheme 2.1.6

a) BF₃·OEt₂, CH₂Cl₂; 75% [301]. b) Six steps, 43%; [301]. c) i. LDA, THF; 51%; ii. TESOTf, DMAP, pyridine; 95% [301]. d) i. LiAlH₄, THF; 93%; ii. aq. HCl; 97% [301]. e) Four steps, 67% [301]. f) i. LDA, THF; 50%; ii. TESOTf, DMAP, pyridine; 95% [301]. g) i. LiAlH₄, THF; 90%; ii. Aq. HCl; 95% [301].
A sequence of an enantioselective enzymatic cross aldol reaction of the 3-cyano-3-phosphonatopropanal 114 (Scheme 2.1.7) and dihydroxyacetone phosphate (115), an intramolecular Horner-Wadsworth-Emmons reaction, and an enzymatic dephosphorylation (in one pot), followed by acetylation led to the cyclopentitol 118 in a good yield (71%) [306]. An analogous synthesis of a cyclohexitol failed, as the aldolase did not accept the homologous butanal substrate. Such reaction cascades using biochemical transformations have great potential for the commercial synthesis of specific chiral target molecules.

Scheme 2.1.7

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \\
\text{CN} & \quad \text{EtO} \\
\text{EtO} & \quad \text{EtO} \\
\text{OPO}_3^{2–} & \quad \text{HO} \\
\text{OH} & \quad \text{OPO}_3^{2–} \\
\text{OH} & \quad \text{OPO}_3^{2–} \\
\text{OH} & \quad \text{OPO}_3^{2–} \\
\text{OH} & \quad \text{OPO}_3^{2–} \\
\text{AcO} & \quad \text{AcO} \\
\text{AcO} & \quad \text{AcO} \\
\text{AcO} & \quad \text{AcO} \\
\text{AcO} & \quad \text{AcO} \\
\end{align*}
\]

\(114 \quad 115 \quad 116 \quad 117 \quad 118\)

\(a, b)\) FDP aldolase, H2O, pH 6.8 – 6.1; [306]. \(c)\) i. Phosphatase, H2O; pH 4.8; ii. Ac2O, pyridine; 71% overall [306].
2.1.1.2. From Arenes and Cycloalkanes

Catalytic hydrogenation of hexahydroxybenzene lead to a mixture of five inositol diastereoisomers, which were isolated in low yields ([307] and references cited there).

Microbial oxidation of the benzene derivatives 119 (Scheme 2.1.8, X = H, Cl, Br, I, CN, Me, and others) provided the enantiomerically pure diols 120 [308] [309]. These chirons, some of which are commercially available, have been applied in the synthesis of conduritol derivatives [310 – 312], inositols [313] [314], aminocyclohexitols [315], 5α-carbapyranoses [316] [317], (−)-6-hydroxy-shikimic acid (123) [318], and a range of other carbasugars [264] [319] [320]. The overall yield of 123 from 119 is only 17% (seven steps) due to an inefficient two-step conversion of the nitrile 121 to the carboxylic acid 122 (28%).

![Scheme 2.1.8](image)

Scheme 2.1.8

\[
\begin{align*}
119 & \xrightarrow{a)} X = \text{CN}, \text{toluene dioxygenase from} \text{Pseudomonas putida F1; 94% [318].} \\
& b) \text{i. 2,2-dimethoxypropane, TsOH, DMF; 94%; ii. OsO}_4, \text{NMO, } \text{rBuOH, THF, H}_2\text{O; 72%; iii. 2,2-dimethoxypropane, TsOH, DMF; 94% [318].} \\
& c) \text{i. DIBAL, THF; 38.7%; ii. NaClO}_2, \text{MeCN, H}_2\text{O; 72% [318].} \\
& d) \text{HCl, MeOH, H}_2\text{O; quant. [318].}
\end{align*}
\]

Another useful starting material for the synthesis of carbapyranoses is p-benzoquinone which was transformed to (±/−)-conduritol B tetraacetate (127) in four steps and 50% yield (Scheme 2.1.9) [321]. A Pd-catalysed kinetic resolution of 127 allowed the synthesis of enantiomerically pure (−)-cyclophellitol [322]. Kinetic resolution of 126 was achieved by PPL catalysed deacetylation [323]. The Diels Alder adducts of p-benzoquinone and one equivalent of cyclopentadiene or anthracene were reduced to 4-hydroxycyclohex-2-enones, or diastereoselectively to the 1,4-cis-diols, and the remaining double bond was epoxidised or dihydroxylated diastereoselectively [324] [325]. A Pd-catalysed asymmetric allylic azidation of a cis-cyclohex-2-en-1,4-diol led to enantiomerically pure aminocyclohexitols [325].
Various cyclohexitols were prepared from 1,4-cyclohexadiene by cis-dihydroxylation, epoxidation, and singulet oxygen ene reaction [326 – 330]. A concise synthesis of DL-protoquercitol (131, six steps, 14%, Scheme 2.1.10) relied on the one-pot conversion of 1,4-cyclohexadiene to the bicyclic derivative 129 by a singulet oxygen ene reaction providing the 2,4-cyclohexadiene-hydroperoxide 128, followed by a [4 + 2]-cycloaddition with singulet oxygen [331]. Landais developed an asymmetric synthesis of carbasugars using a Sharpless asymmetric dihydroxylation of 1,4-cyclohexadien-3-ylsilanes [332].

Cyclohexene was transformed into cyclohexitols and aminocyclohexitols by allylic halogenation, alkene halogenation, elimination, SN2’ substitution, hydroxylation, epoxidation, oxyselenylation, and selenoxide elimination [333 – 337].

Annulated bicyclic cyclitols were prepared from naphthalene [338] and from cyclooctatetraene [339]. Cyclooctitols were prepared from cyclooctatetraene [340]. Carbafuranooses were prepared from 2-cyclopentenone [341], from cyclopentadiene [342], and from both enantiomers of 4-hydroxy-2-cyclopentenone [343] [344]; for a review on the
synthesis of carbafruranoses, see [271].

2.1.2. Carbasugars From Naturally Occurring Carbasugars

Enantiomerically pure carbasugars were prepared by stereoselective transformations of naturally occurring hydroxylated cyclohexanes, such as myo-inositol, shikimic acid, D-(−)-quinic acid, and quebrachitol [252] [345], which are commercially available. As an example, the sialidase inhibitor 3a was prepared from shikimic acid (132) in 14 steps and 17% overall yield (Scheme 2.1.11) [25]. The advantage of the synthesis of carbasugars from naturally occurring chiral hydroxylated cyclohexanes is that they often require no changes of the carbon skeleton and that they provide enantiomerically pure products. However, the efficiency of such syntheses depends on how closely the target compound and the starting material are related. If this relation is more distant (as in the example shown), such syntheses require multiple steps including ingenious selective protections and deprotections of the functional groups. For additional examples, see chapter 2.1.4.

Scheme 2.1.11

\[
\begin{align*}
\text{132} & \rightarrow \text{a)} \rightarrow \text{MOMO} \rightarrow \text{CO}_2\text{H} \rightarrow \text{b)} \rightarrow \text{MOMO} \rightarrow \text{CO}_2\text{Me} \rightarrow \text{c)} \\
\text{135} & \rightarrow \text{d)} \rightarrow \text{MOMO} \rightarrow \text{CO}_2\text{Me} \rightarrow \text{e)} \rightarrow \text{TrN} \rightarrow \text{CO}_2\text{Me} \rightarrow \text{f)} \\
\text{138} & \rightarrow \text{g)} \rightarrow \text{AcHN} \rightarrow \text{NH}_2 \rightarrow \text{3}
\end{align*}
\]

\[a) \ i. \text{Esterification; ii. Ph}_3\text{P, DEAD, THF; 77\% [346]; iii. MOMCl, DIPEA, CH}_2\text{Cl}_2; 97\% [25]. b) i. Na}_3\text{N, NH}_4\text{Cl, MeOH, H}_2\text{O; 86\%; ii. MsCl, Et}_3\text{N, CH}_2\text{Cl}_2; 99\% [25]. c) Ph}_3\text{P, THF, then Et}_3\text{N, H}_2\text{O; 78\% [25]. d) Na}_3\text{N, NH}_4\text{Cl, DMF; 76\% [25]. e) i. HCl, MeOH; 99\%; ii. TrCl, Et}_3\text{N, CH}_2\text{Cl}_2; iii. MsCl, Et}_3\text{N, CH}_2\text{Cl}_2; 86\% from 136 [25]. f) i. 3-Pentanol, BF}_3\cdot\text{OEt}_2; ii. Ac}_2\text{O, DMAP, pyridine; 69\% from 137 [25]. g) i. Ph}_3\text{P, THF, then Et}_3\text{N, H}_2\text{O; ii. KOH, THF, H}_2\text{O; 75\% from 138 [25].} \]
2.1.3. Carbasugars From Sugars

2.1.3.1. By Intramolecular Nucleophilic Addition and Substitution

Some naturally occurring sugars are cheap chiral starting materials. Consequently, many methods were developed for the synthesis of carbasugars from sugars. This approach is particularly efficient for the synthesis of carbocyclic analogues of sugars, as the configuration of all (or most) chiral centres can be transferred into the product.

The first synthesis of a carbapyranose from a pyranose relied on the transformation of D-glucose into a 6-nitro-6-desoxy-D-glucose \([347]\), followed by an intramolecular Henry reaction to give a mixture of nitrodesoxyinositols (Scheme 2.1.12) \([348]\). Several nitro-carbasugars were prepared in an analogous way (e.g. \([349–351]\)), or by the reaction of sugar-derived dialdehydes with nitromethane \([260]\).

![Scheme 2.1.12](image)

\(a\) i. \(\text{Pb(OAc)}_4\), benzene; 80% \([347]\). \(b\) CH\(_3\)NO\(_2\), EtOH, NaOMe; 50% of a mixture of 141 and the \(ido\)-isomer \([347]\). \(c\) i. H\(_2\)SO\(_4\), H\(_2\)O; yield not given; ii. Ba(OH\(_2\)), H\(_2\)O; 90% of a mixture of 6 isomers \([348]\).

A range of related aldol and aldol-like reactions were employed in the cyclisation of sugar derivatives to cyclohexanes and cyclopentanes (reviewed in \([262]\) \([266]\)). The preparative value of such cyclisations is limited by their lack of stereo- and chemo-selectivity, as aldol reactions often lead to mixtures of diastereoisomers and to elimination products. The problem of low stereoselectivity is avoided in intramolecular stereospecific nucleophilic substitutions of sugar-derived sulfonylates or halogenides. However, these reactions can also be accompanied by eliminations \([262]\).

In contrast to inter- and intramolecular aldol reactions, the nucleophilic opening of carbohydrate-derived epoxides is highly chemoselective. Thus, carbasugars were prepared in good yields by intramolecular epoxide opening of lithiated 5,6-anhydrohexose dithioacetals.
or by the reaction of C2-symmetrical 1,2:5,6-bisanhydrohexitols (sugar-derived bisepoxides) with lithiated silylthioacetals (bisanion equivalents) [235] [353] [354]. The opening of 1,2:5,6-bisanhydrohexitols may lead to cyclohexitols or cycloheptitols, but the regioselectivity can be controlled to some extent by the choice of the protecting group for the C(3)- and C(4)-hydroxy groups. Cyclohexitols were obtained in good yield from the D-manno-1,2-5,6-bisanhydro-3,4-isopropylidene acetals 143 (Scheme 2.1.13) [354].

Scheme 2.1.13

\[ \begin{align*}
&\text{143} & & \text{144} & & \text{145} & & \text{146} \\
&\text{a)} & & & & & \\
&\text{Five eq. of 144, BuLi, Bu}_2\text{Mg, THF, HMPA; for R = isopropylidene: 67\% of 145, 24\% of 146; for R = Bn: 10\% of 145, 82\% of 146 [354].}
\end{align*} \]

6-Deoxy-hex-5-enopyranosides and 6-deoxy-hex-5-enopyranosyl esters are converted directly, efficiently, and under mild conditions to cyclohexanone derivatives of deoxyinososes by a Hg\(^{2+}\)-catalysed cascade rearrangement (the Ferrier reaction, Scheme 2.1.14) [262] [355]. This reaction proceeds via hydroxymercuration of the methylidene group, and ring opening of the resulting hemiacetal 150 with the expulsion of methanol. The presumed mercury enolate 151 then attacks the C(1) carbonyl group in an intramolecular aldol reaction, furnishing the hydroxycyclohexanone 152. The axial alcohol is formed with a high diastereoselectivity if the C(3)–OR group in the starting material is equatorial (\textit{i.e.} from glucose, mannose, and galactose derivatives) [269]. It was speculated that the bridged complex 151 may be at the root of this stereoselectivity [269]. The alcohols 152 are often converted to the corresponding cyclohexenones 153. The original procedure for the Ferrier reaction required stoichiometric amounts of the mercury salt (HgCl\(_2\) or Hg(OAc)\(_2\)) [355], but the reaction proceeds efficiently with catalytic amounts of mercury(II) trifluoroacetate [356]. Pd(II) also catalyses the reaction [357], but leads to lower yields of the cyclohexanones than Hg(II).
A useful modification of the Ferrier cyclisation is the reaction of 6-deoxyhex-5-enopyranosides with triisobutylaluminium to form cyclohexanediols [360]. This rearrangement involves cleavage of the endocyclic C–O-bond of the pyranoside 154 (Scheme 2.1.15), cyclisation of the aluminium enolate 156, and intramolecular hydride transfer to the cyclohexanone 157 with formation of the diol 158. In contrast to the Ferrier cyclisation, the aglycon is retained in the product. The configuration at C(1) is retained with high selectivity. The reduction of the carbonyl group leads to an axial OH-group in glucose and mannose derived compounds, again with high selectivity. For galactose derivatives the reduction is less selective, and the equatorial OH-group predominates. If Ti(OiPr)Cl₃ is employed as the catalyst, the rearrangement leads to a cyclohexanone with retention of the C(1)-substituent and the C(1) configuration [268].

---

29) I chose this synthesis of the benzyl derivative of 153 as an example, as I will refer to this intermediate in Chapter 2 on the synthesis of valienamine.
The starting materials for the Ferrier cyclisation are readily accessible from pyranosides by orthogonal protection, allowing to convert the C(6)–OH group to a leaving group, and elimination. The cyclisation generally proceeds in high yield and provides the versatile building blocks 152 or 153. Consequently, the Ferrier cyclisation is the most frequently used method for the conversion of sugars to cyclohexane derivatives, and has been applied to the synthesis of numerous carbasugars [262] [269]. The Al-catalysed modification has allowed the synthesis of a tris-carba-trisaccharide from a trisaccharide [361]. The Ferrier cyclisation has the disadvantage of producing a cyclohexanone that lacks the hydroxymethyl substituent of the parent pyranoside. However, a "new" hydroxymethyl substituent can be introduced by the addition of a nucleophile (e.g. a lithiated thioacetal) to the carbonyl group of 152 with good stereoselectivity, e.g. [362]. The Ferrier cyclisation is not successful in the transformation of 5-deoxy-pent-4-enofuranosides into cyclopentanones. This transformation is possible in two steps via nitrile oxide cycloaddition and reductive cleavage of the resulting spiro isoxazoline [363].

An intramolecular Nozaki-Kishi-reaction was applied as the key step in a synthesis of gabosine I (162b, Scheme 2.1.16) from tetra-O-benzyl glucose (9 steps, 17% overall yield) [364]. For other transition metal-catalysed cyclisations to carbasugars, see [265].
Scheme 2.1.16

\[
\begin{align*}
&\text{a)} \quad \text{NaBH}_4, \text{THF, H}_2\text{O}; 98\%; \hspace{1cm} \text{ii. TBDMSCl, pyridine; 97\%; \hspace{1cm} \text{iii. PCC, AcONa, MS 4Å, CH}_2\text{Cl}_2; 90\%} [364]. \\
b) \quad \text{i. Ph}_3\text{P}=\text{CHCl, THF; 92\%; \hspace{1cm} \text{ii. Bu}_4\text{NF, THF; 90\%; \hspace{1cm} \text{iii. Dess-Martin periodinane, CH}_2\text{Cl}_2; 70\%} [364]. \\
c) \quad \text{CrCl}_2, \text{NiCl}_2, \text{DMF; 61\% (1:1 mixture of diastereoisomers)} [364]. \\
d) \quad \text{i. PCC, AcONa, MS 4Å, CH}_2\text{Cl}_2; 76\%; \text{BCl}_3, \text{CH}_2\text{Cl}_2; 74\% \text{of 162b} [364].
\end{align*}
\]

Mirza and Vasella [365], Paulsen and von Deyn [366], and Fukase and Horii [367] reported syntheses of cyclohexenones from sugars applying an intramolecular Horner-Wadsworth-Emmons reaction as the key step. Thus, tetra-\textit{O}-benzylgabosine I (162, Scheme 2.1.17) was prepared from tetra-\textit{O}-benzylgluconolactone (163) in four steps and 64\% yield [366] [367]. This route is probably the most efficient access to gabosine derivatives from D-glucose and has been applied in a synthesis of (+)-valienamine (\textit{vide infra}). In a similar fashion, a cyclopentenone was prepared from a D-ribonolactone derivative and transformed into (−)-neplanocin A [368].
Scheme 2.1.17

\[
\begin{align*}
\text{163} & \quad \text{a}) \quad \text{BuLi, dimethyl methylphosphonate, THF; 95\%. [367]} \quad \text{b}) \quad \text{i. NaBH}_4, \text{ THF; 94\%; ii. (CF}_3\text{CO})_2\text{O, DMSO, Et}_3\text{N, CH}_2\text{Cl}_2; 94\% \text{ [367].} \quad \text{c}) \quad \text{K}_2\text{CO}_3, \text{ 18-K-6, toluene; 76\% [367].}
\end{align*}
\]

The reaction of 6-enopyranosides with Pd(Ph\textsubscript{3})\textsubscript{4} and SmI\textsubscript{2} [369] or with Cp\textsubscript{2}Zr and BF\textsubscript{3}·OEt\textsubscript{2} [370] [371] leads to vinylcyclopentanols (Scheme 2.1.18). The cascade reaction with Cp\textsubscript{2}Zr and BF\textsubscript{3}·OEt\textsubscript{2} involves oxidative addition to the allyl acetal, elimination of the aglycon, and addition of the allyl Zr complex to the resulting aldehyde [370]. The reaction with Pd(Ph\textsubscript{3})\textsubscript{4} and SmI\textsubscript{2} proceeds via an allyl Sm complex [369]. The vinylcyclopentanols are obtained in moderate yield. The reaction with Pd(0)/SmI\textsubscript{2} gives cis/trans mixtures with moderate to poor diastereoselectivity, the reaction with Cp\textsubscript{2}Zr/BF\textsubscript{3}·OEt\textsubscript{2} provides the cis-products with high diastereoselectivity and therefore is preparatively more useful.

Scheme 2.1.18

\[
\begin{align*}
\text{148} & \quad \text{a}) \quad \text{i. DMSO, (COCl)}_2, \text{Et}_3\text{N, CH}_2\text{Cl}_2; \text{ ii. Ph}_3\text{P=CH}_2, \text{THF; 76\% of 166a from 148; iii. Ac}_2\text{O, H}_2\text{SO}_4; 56–90\% of 166b [369].} \\
& \quad \text{b}) \quad \text{From 166a Cp}_2\text{ZrCl}_2, \text{ BuLi, BF}_3\text{·OEt}_2, \text{THF; 65\% of 168 (>98\% d.e.) [370].} \\
& \quad \text{c}) \quad \text{From 166b Pd(Ph}_3\text{P)}_4, \text{ three eq. of SmI}_2, \text{THF; 58\% of 167, 13\% of 168 [369].}
\end{align*}
\]
2.1.3.2. By Intramolecular Cycloadditions

_Bernet_ and _Vasella_ worked out a highly efficient synthesis of aminocyclopentitols from sugars [372 – 374], using a Zn-mediated reductive elimination of 6-bromo-6-deoxy pyranosides to unsaturated aldehydes and an intramolecular 1,3-dipolar cycloaddition of a nitrone (prepared _in situ_) to an alkene as the key steps (Scheme 2.1.19). Thus, the isoxazolidine 172 was obtained from methyl α-D-glucopyranoside in seven steps and 42% yield [372]. The cyclisation of the _bona fide_ nitrone 171, obtained from the crude aldehyde 170 by addition of _N_-methyl hydroxylamine, was highly diastereoselective (d.e. = 89%). The isoxazolidine 172 (and its _N_-alkyl or _N_-acyl derivatives) are readily transformed into aminocyclopentitols by hydrogenolysis (_vide infra_). This route provided the first preparatively useful access to aminocyclopentitols and is still one of the most efficient routes.

**Scheme 2.1.19**

![Scheme 2.1.19](image)

_a) i. TrCl, pyridine; 81%; ii. NaH, BnCl, DMF; 77%; iii. H2SO4, MeOH; 85% [372]. b) i. MsCl, Et3N, CH2Cl2; ii. LiBr, butanone; 95% (two steps) [372]. c) Zn, aq. EtOH [372]. d) MeNHOH·HCl, NaOMe, NaHCO3, MeOH; 84% of 172a, 5% of 172b [372].

The related intramolecular oxime olefin cycloaddition of the oxime 173 (Scheme 2.1.20) to the isoxazolidine 174 is thought to proceed _via_ the nitrone tautomer of the oxime [375]. The glycosidase inhibitor 35 was obtained by hydrogenolysis of 174. For a range of diastereoisomers of 173 the stereoselectivity and the yield of the cycloaddition depended on the configuration of the starting material [376].
Scheme 2.1.20

\[ \text{BnO} \rightarrow \begin{align*}
\text{BnO} & \xrightarrow{\text{a)}} \text{BnO} \\
\text{OH} & \xrightarrow{\text{b)}} \text{OH} \\
\text{N} & \xrightarrow{\text{c)}} \text{NH}_2
\end{align*} \]

\[ 170 \quad 173 \quad 174 \quad 35 \]

a) NH$_2$OH-HCl, pyridine, EtOH; 79% [375]. b) Toluene, 110°; quant. [375]. c) H$_2$, Pd/C, MeOH; 91%.

An intramolecular nitrone olefin cycloaddition of the D-ribose derived nitrone 177 (Scheme 2.1.21) gave in high yield the isoxazolidine 178, which was transformed into the fluorinated aminocyclohexitol 179 [377].

Scheme 2.1.21

\[ \begin{align*}
\text{HO} & \xrightarrow{\text{a)}} \text{MeNOH-HCl, pyridine; 85% [377].} \\
\text{HO} & \xrightarrow{\text{b)}} \text{i. Ac}_2\text{O, DMAP, pyridine; quant.; ii. H}_2, \text{Pd(OH)}_2/\text{C, EtOH; 92% [377].}
\end{align*} \]

Birault$^{30}$ studied the intramolecular cycloaddition of the D-glucose-derived nitrile oxide 181 (Scheme 2.1.22), which proceeded unselectively to the isoxazolines 182 and 183 (95%, 1:2) [226].

---

$^{30}$ Dr. Veronique Birault, post-doctoral fellow from January 1996 to October 1997.
A range of cycloheptenitols were prepared by intramolecular 1,3-dipolar nitrone additions [270] [378]. An α,β-unsaturated ester has also been used as the dipolarophile [379]. Intramolecular dimerisation of carbohydrate-derived bis-nitrile oxides led to [3.3.0]- and [4.3.0]-bicyclic furoxanes [380].

**2.1.3.3. By Radical Cyclisations**

Radical recombination or the addition of radicals to C=X bonds (X = C, N, O) allow the selective formation of C–C-bonds under mild conditions in the presence of a range of functional groups [381]. To avoid the epimerisations and eliminations that accompany carbanionic C–C-bond formations, several cyclopentane and cyclohexane derivatives were prepared using radical C–C-bond formation as the key step. In this chapter I will present a few examples, for reviews, see [262] [265] [267] [382] [383]. Hu [271] gives an overview for the synthesis of cyclopentanes, including radical cyclisations.

Irradiation of a 5,6-dideoxy-5-hexenose thioacetal in acetone gave the cyclohexane 185 in moderate yield by a 6-endo-trig cyclisation (Scheme 2.1.23) [384]. The reaction is initiated by hydrogen abstraction from the acetal by excited acetone.
Scheme 2.1.23

\[
\begin{align*}
\text{AcO} & \quad \text{OAc} \\
\text{SEt} & \quad \text{OAc} \\
\text{SEt} & \quad \text{SEt}
\end{align*}
\]

\[
\text{184} \rightarrow \text{185}
\]

\(a\) Acetone, H\(_2\)O, irradiation under sunlight; 40\% of \textbf{184}, 36\% of \textbf{185} [384].

\[\text{Vorwerk}\] applied a SmI\(_2\)-mediated radical 6-\textit{endo}-trig cyclisation as the key step in the synthesis of carbocyclic analogues of \(N\)-acetyl-2,3-didehydro-2-deoxy-\(D\)-neuraminic acid (Scheme 2.1.24) [138]. The cyclisation of \textbf{187} gave in high yield a 2:3 mixture of the diastereoisomers \textbf{188a} and \textbf{b}, both of which were transformed into the target compounds \textbf{190} and \textbf{191} via the common intermediate \textbf{189}.

Scheme 2.1.24

\[
\begin{align*}
\text{OH} & \quad \text{NHAc} \\
\text{O} & \quad \text{OR} \\
\text{OR} & \quad \text{NHAc}
\end{align*}
\]

\[
\text{186} \rightarrow \text{187}
\]

\(a\) 9 steps, 24\% [138]. \(b\) SmI\(_2\), THF, HMPA, \(t\)BuOH; 93\% (\textbf{188a}/\textbf{188b} = 2:3) [138]. \(c\) Three steps from \textbf{188a}, 55\%; two steps from \textbf{188b}, 78\% [138]. \(d\) Six steps; 21\% of \textbf{190}, 11\% of \textbf{191} [138].
Several cyclopentitols and cyclohexitols were prepared by the \textit{exo}-cyclisation of carbohydrate-derived 5-hexenyl or 5-hexinyl and 6-heptenyl or 6-heptinyl radicals. The radicals were generated from the corresponding halogens \cite{383} \cite{385} – \cite{391}, thiocarbonates \cite{392} \cite{393}, dithiocarbonates \cite{383}, or alkenes \cite{394} \cite{395}. Barton and coworkers generated the radical from a carbohydrate derived aryl telluride \cite{396}.

\textit{Allo}-quercitol (196) was prepared from D-ribose using a radical \textit{6-exo}-trig-cyclisation of the heptinal 194 with \text{Bu}_3\text{SnH} and AIBN as the key step (Scheme 2.1.25, 14 steps from 192, 15\%) \cite{397}. It was presumed that the reaction proceeds by the addition of a vinyl radical to the carbonyl group \cite{397}.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme2.1.25.png}
\caption{Scheme 2.1.25}
\end{figure}

A cobalt-catalysed radical-cyclisation/oxygenation of the iodide 198 (Scheme 2.1.26) with \text{NaBH}_4 under air gave the carba-pentofuranosides 199a and 199b in 69\% yield and a ratio of 12:1 \cite{387}.
Scheme 2.1.26

The pinacol-type cyclisation of carbohydrate-derived $\alpha,\omega$-dialdehydes with samarium iodide has been applied to the synthesis of inositols and conduritols [390] [398] [399] and cyclopentitols [400]. Marco-Contelles and coworkers prepared a range of aminocyclopentitols by SmI$_2$- or Bu$_3$SnH-initiated radical cyclisation of carbohydrate-derived $\omega$-halo-oxime ethers, carbonyl-tethered oxime ethers, and of oxime ethers bearing an $\alpha,\beta$-unsaturated ester in $\delta$-position [401] (see also [211] for an aminocyclopentitol synthesis). These cyclisations proceeded in moderate to good yields (50-90%) and often with high diastereoselectivity to yield cis-diols or cis-aminoalcohols.

The 1,6-diol 205 (Scheme 2.1.27), prepared from d-mannitol in five steps (yield not given), was transformed into neo-inositol (208) in four steps and 32% yield using a diastereoselective ($d.e. = 86\%$; 6% of the 1,2-cis diol were formed) SmI$_2$-mediated pinacol type cyclisation of the dione 206 as the key step [398].

Scheme 2.1.27

a) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$ [398]. b) SmI$_2$, tBuOH, THF; 79% (two steps) [398]. c) i. CF$_3$CO$_2$H, MeOH; ii. Bu$_4$NF, THF; 41% [398].
The trehalazolamine analogue **211** (Scheme 2.1.28) was prepared from tetra-\(O\)-benzylglucose (39) in four steps and 52% yield [400] [401]. Besides the intramolecular 1,3-dipolar cycloadditions, such pinacol type cyclisations provide the most efficient access to aminocyclopentitols.

![Scheme 2.1.28](image)

a) i. \(\text{BnONH}_2\cdot\text{HCl}, \text{pyridine, MeOH}\); ii. \(\text{PCC, MS 3Å, NaOAc, CH}_2\text{Cl}_2\); 81% (two steps) [401].

b) \(\text{SmI}_2, \text{THF, tBuOH}\); 80% [401].

c) \(\text{H}_2, \text{Pd(OH)}_2/\text{C, EtOH, THF, CF}_3\text{CO}_2\text{H}\); 80% [400].

**2.1.3.4. By Other Types of Cyclisations**

Several conduritols and aminoconduritols were prepared using the Ramberg-Bäcklund reaction of sugar-derived thiepane dioxides as the key step [402] [403]. Thus, the 2,3-diaminoconduritol **216** (Scheme 2.1.29) was prepared from the D-mannitol derived thiepane **213** in seven steps and 21% yield [403].

![Scheme 2.1.29](image)

a) i. \(\text{CF}_3\text{CO}_2\text{H, H}_2\text{O, MeCN}\); 95%; ii. \(\text{MsCl, pyridine}\); 92%; \(\text{NaN}_3, \text{DMSO}\); 85%; iv. \(\text{mCPBA, CH}_2\text{Cl}_2\); 98% [403].

b) \(\text{KOH, CCl}_4, \text{tBuOH, H}_2\text{O}\); 61% [403].

c) i. \(\text{Et}_3\text{N, 1,3-propanediol, MeOH}\); 68%; ii. \(\text{BCl}_3, \text{CH}_2\text{Cl}_2\); 72% [403].
A formal synthesis of d-myo-inositol involved the unusual camphorsulfonic acid-catalysed ene reaction of the d-glucose-derived alkine 217 (Scheme 2.1.30) to the allene 218 (91%) as the key step [404].

Scheme 2.1.30

a) 17 steps, 18% [404]. b) Camphorsulfonic acid, toluene; 91% [404].

Cyclohexenitols, cycloheptenitols, and cyclooctenitols were prepared by thermal or Lewis acid catalysed Claisen rearrangement of 5-vinyl-glycals, 1-methylene-4-vinyl-furanoses, and 1-methylene-5-vinyl-pyranoses (Scheme 2.1.31) [405 – 408].

Scheme 2.1.31

a) o-Dichlorobenzene, 240°C; 84% [406]. b) iBu3Al, toluene, 60°C; 76% (2:1) [408]. c) Xylene, reflux; 60% [405].
A few carbapyranoses were formed by a Prins cyclisation of an unsaturated oxycarbenium ion. Thus, the oxycarbenium ions generated from the acetals 228 (Scheme 2.1.32, R = tetra-O-benzyl-α-D-mannopyranosyl or 4-(methyl 2,3,6-tri-O-benzyl-α-D-glucoside)) added to the enol moiety to form the pseudo-disaccharides 229 (64-75%) [409]. BF₃·OEt₂-activation of the aldehyde 230 gave the conduritol derivative 231 in 86% yield [410].

**Scheme 2.1.32**

\[ \text{D-lyxose} \rightarrow 228 \rightarrow 229 \]

\[ \text{L-arabinose} \rightarrow 230 \rightarrow 231 \]

\( a) \) MeOTf, 2,6-di-tertbutyl-4-methylpyridine, CH₂Cl₂; 64 – 75\% [409].
\( b) \) BF₃·OEt₂, CH₂Cl₂; 86\% [410].

*Ohtake et al.* reported a ZnCl₂-catalysed cyclisation of the glucose-derived ketone 234 (Scheme 2.1.33) to the cyclohexanone 235 in 83\% yield (64\% overall yield from 163 in four steps) [411] [412]. Good yields were also obtained in the cyclisation of the analogous mannose and galactose derivatives. Besides the route employing a Horner-Wadsworth-Emmons reaction as the key step (*vide supra*) this appears to be one of the most efficient routes to cyclohexanones from sugars.
Scheme 2.1.33

a) 2,2-Dimethyl-3,3-propanediol, TMSOMe, TMSOTf, toluene; 94% [411]. b) AlMe₃, CH₂Cl₂; 93% [411]. c) DMSO, Ac₂O [411]. d) ZnCl₂, THF, H₂O; 73% from 233 [411].

Pauson-Khand reactions of 6,7-dideoxy-6-heptenoses led to [3.5.0]bicyclic carbasugars [270].
2.1.4. Syntheses of (+)-Valienamine

(+)-Valienamine (22, Figure 2.1.2) [33] [34] is an unsaturated aminocyclohexitol possessing the same relative configuration at C(1)–C(4) as α-D-glucopyranose. It was first isolated from the Pseudomonas denitrificans degradation products of validoxylamine A, a pseudo-aminoglycoside antibiotic isolated from Streptomyces hygroscopicus subsp. limoneus. Later it was prepared by the NBS-cleavage of validoxylamine A [225] [413]. (+)-Valienamine itself is a glycosidase inhibitor and an antibiotic, and it is the key component for the biological activity in pseudo-aminosugars and pseudo-oligosaccharides such as the validamycins, acarbose, amylostatins, adiposins, acarviosine, and trestatins. Several pseudo-aminosugars display anti-fungal, insecticidal, and antibacterial activity [33] [34]. Validamycin A is widely used in the Far East to control the sheath blight disease of rice plants.

Figure 2.1.2: (+)-Valienamine.
Since its isolation in 1972, valienamine has been synthesised several times both in racemic and enantiomerically pure form (for two recent reviews, see [33] [34]). The first synthesis of (+)-valienamine was achieved in 1980 by Paulsen and Heiker (241, Scheme 2.1.34) [414] [415]. The hydroxymethyl side chain was introduced by treating the ketone 242 with trimethyl sulfoxonium ylide, followed by hydrolysis of the resulting epoxide to give the diol 243. Further protecting group manipulations and an intramolecular substitution yielded the epoxide 245, which was reduced to the alkene 246. Substitution of the allylic alcohol 247 with HN3/Ph3P, followed by deprotection gave (+)-valienamine in an overall yield of 1% (21 steps).

Scheme 2.1.34

a) i. 2,2-Dimethoxypropane, TsOH, DMF; 85%; ii. RuO2, NaIO4, K2CO3, CH2Cl2; 81% [415]. b) i. Me3SO+I–, NaH, THF, DMSO; 57%; ii. KOH, dioxane, H2O; 89% [415]. c) Six steps, 40% [415]. d) i. MsCl, pyridine; ii. NaOMe, MeOH; iii. Ac2O, pyridine [415]. e) i. NaI, NaOAc, acetone, AcOH; ii. POCl3, pyridine; 69% from 244 [415]. f) i. NaOMe, MeOH; 93%; ii. BzCN, Et3N, MeCN; 54% [415]. g) HN3, Ph3P, toluene; 70% [415]. g) i. NaOMe, MeOH; 92%; ii. Ph3P, NH3, MeOH; 61%; iii. Na, NH3, THF; 56% [415].
Several syntheses of (+)-valienamine started from derivatives of D-glucose. Schmidt and Köhn [416] started with the cyclohexanones 249a,b (Scheme 2.1.35, prepared from D-glucose via a Ferrier rearrangement). The side chain was introduced by transformation of the ketones into thiketskals and substitution of an ethylthiogroup with a CN group. Transformation of the CN substituent into a benzoyloxymethyl group and elimination of H2O by a Mitsunobu type reaction afforded the allylic thioether 251. Treatment of 251 with chloroamine T provided the (+)-valienamine derivative 252 by a [2,3]-sigmatropic sulfimide rearrangement. Deprotection of 252 gave (+)-valienamine in 5% overall yield from methyl α-D-glucopyranoside.

**Scheme 2.1.35**

![Scheme 2.1.35]

a) Six steps (Ferrier cyclisation), 40%, 249a/249b = 4:1 [416]. b) i. EtSH, HCl, MeOH; ii. Ac2O, pyridine; 86% (two steps); iii. Me3SiCN, SnCl4, CH2Cl2; 85% [416]. c) i. DIBAH, CH2Cl2, petroleum ether; then H2O 78%; ii. LiAlH4, THF; 85%; iii. BzCN, Et3N, MeCN; 73%; iv. Ph3P, DEAD, toluene; 79% [416]. d) Chloroamine T, BnEt3NCl, CH2Cl2; 78% [416]. e) Na, NH3; 58% [416].
Nicotra et al. started with the cyclohexenone 253 (Scheme 2.1.36, prepared from methyl 2,3-O-dibenzyl-4,6-O-benzylidene-α-D-glucopyranoside via a Ferrier cyclisation) [417]. The side chain was introduced by a diastereoselective addition of benzylxymethylmagnesium chloride, providing the allylic alcohol 254. A (formal) SN2' reaction of 254 with SOCl2 gave the chloride 255, which was substituted by azide to give the valienamine derivative 256. Reduction under Birch conditions afforded (+)-valienamine in an overall yield of 12.5% (10 steps) from methyl 2,3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside. A Pd(0)-catalysed allylic azidation of the acetate 257 to the azide 258 (48%) provided access to 1-epi-valienamine derivatives.

**Scheme 2.1.36**

\[ a) \text{BnOCH}_2\text{MgCl, THF; 75\% [417].} \]
\[ b) \text{SOCl}_2, \text{Et}_2\text{O; 81\% [417].} \]
\[ c) \text{NaN}_3, \text{DMF; 83\% [417].} \]
\[ d) \text{Na, NH}_3, \text{THF; 56\% [417].} \]
\[ e) \text{From 253: BnOCH}_2\text{MgCl, THF, then Ac}_2\text{O; 73\% [417].} \]
\[ f) \text{NaN}_3, \text{Pd(PPh}_3\text{)}_4, \text{THF, H}_2\text{O; 48\% [417].} \]
Yoshikawa et al. [418] prepared (+)-valienamine from the nitro-pseudosugar 259 (Scheme 2.1.37), which was obtained from 3-O-benzyl-1,2-O-isopropylidene-α-D-glucose in 21% yield (five steps) using a nitroaldol reaction as the key step [419]. Elimination of HOAc and conjugate addition of NH₃, followed by acetylation gave the amide 260. Removal of the nitro group and elimination of H₂O provided the valienamine derivative 261, which was deprotected to give valienamine in 29% yield from 259.

Scheme 2.1.37

\[
\begin{align*}
\text{D-glucose} & \xrightarrow{a)} \text{AcO} \text{NO}_2 \text{OAc} \text{BzO} \text{BnO} \text{OH} \\
& \xrightarrow{b)} \text{AcO} \text{NHAc} \text{BzO} \text{BnO} \text{OAc} \\
& \xrightarrow{c)} \text{HOH} \text{HO} \text{NH}_2
\end{align*}
\]

\(259\) \(260\) \(261\) \(22\)

\(a\) i. NH₃, THF; ii. Ac₂O, TsOH·H₂O; 60% [418]. \(b\) i. Bu₃SnH, AIBN, benzene; 60%; ii. SOCl₂, pyridine; 89% [418]. \(c\) i. NaOMe, MeOH; ii. Na, NH₃; iii. Ac₂O, pyridine; iv. 80% aq. hydrazine; 84% (four steps) [418].

Fukase and Horii transformed the gabosine I derivative 162 (Scheme 2.1.38), obtained from tetra-O-benzyl-D-glucosonolactone using a Horner-Wadsworth-Emmons reaction as the key step (see chapter 2.1.3.1), into the valienamine derivative 263 by a stereoselective reduction to the equatorial alcohol 262, followed by a Mitsunobu reaction with phthalimide [367]. Hydrazinolysis of the imide 263 and debenzylation under Birch conditions gave (+)-valienamine in an overall yield of 12% from tetra-O-benzyl-D-glucosonolactone (8 steps). This was the most efficient synthesis of (+)-valienamine when we started our work.
Scheme 2.1.38

a) Four steps, 64% [367] (see chapter 2.1.3.1). b) NaBH₄, CeCl₃, EtOH, THF; 75% [367]. c) Ph₃P, DEAD, phthalamide, THF; 52% [367]. d) i. N₂H₄•H₂O, MeOH, THF; 74%; ii. Na, NH₃, THF; 62% [367].

Park and Danishefsky transformed the cyclohexenone 265 (Scheme 2.1.39, obtained from the glucal 264 by a Ferrier rearrangement) into a 2:1 mixture of the epoxides 266a/b [420]. Only 266a underwent an intramolecular SₐN₂'-type substitution (proceeding with a syn stereoselectivity), yielding the valienamine derivative 267. This was deprotected and acetylated to give pentaacetyl-(+)-valienamine in 3% overall yield from the glucal 264 (17 steps).

Scheme 2.1.39

a) 13 steps, 23% [420]. b) i. CH₂I₂, Zn, TiCl₄, THF, 46%; ii. mCPBA, NaHCO₃, CH₂Cl₂; 57% of 266a, 28% of 266a [420]. c) KHMDS, 18-K-6, THF; 75% [420]. d) i. Na, NH₃, THF; ii. LiOH, EtOH, H₂O; 51% [420].
Tatsuta et al. prepared valienamine from D-xylonolactone using the ring-opening reaction of the sulfone 269 (Scheme 2.1.40) with TBSOTf and the subsequent ring-closing of 270 in the presence of SnCl₄ as the key steps [421]. The hydroxymethyl side chain was introduced by treatment of 271 with Bu₃SnLi and formaldehyde; the reaction was thought to proceed by a conjugated addition of Bu₃Sn⁻ to 271, trapping of the resulting anion with formaldehyde, and elimination of Bu₃Sn and SO₂Ph [421]. Stereoselective reduction of the carbonyl group and protecting group manipulations gave the triol 272. A selective Mitsunobu reaction of the allylic alcohol 272 to the valienamine derivative 273 and deprotection furnished (+)-valienamine in 15.5% overall yield from D-xylonolactone (13 steps).

**Scheme 2.1.40**

\[ \text{Scheme 2.1.40} \]

\[ \text{268} \rightarrow \text{269} \rightarrow \text{270} \rightarrow \text{271} \rightarrow \text{272} \rightarrow \text{273} \rightarrow \text{22} \]

a) Four steps, 54% [421]. b) TBSOTf, 2,5-lutidine, CH₂Cl₂; 92% [421]. c) SnCl₄, CH₂Cl₂; 70% [421]. d) i. Bu₃SnLi, H₂CO, THF; 84%; ii. Zn(BH₄)₂, Et₂O; 80%; iii. MOMCl, Bu₄NI, iPr₂EtN, dichloroethane; 85%; iv. H₂, Raney-Ni, H₂O, dioxane; 97% [421]. e) HN₃, Ph₃P, DEAD, THF; 81% [421]. f) i. H₂, Raney-Ni, H₂O, dioxane; quant.; ii. HCl, MeOH; quant. [421].

Shing and coworkers reported two syntheses of valienamine from (−)-quinic acid (274) which was converted in 11 steps into the cyclic sulfite 275 [422] (Scheme 2.1.41). Nucleophilic displacement of this sulfite with azide led regioselectively and in high yield (97%) to the azido alcohol 276 whose deprotection furnished 2-epi-valienamine. Alternatively, inversion of the configuration of the alcohol 276 gave the valienamine derivative 277. Hydrolysis of the acetate 277, reduction of the azide, and debenzylation under Birch conditions gave valienamine in 6% overall yield from (−)-quinic acid (17 steps).
In the second synthesis (Scheme 2.1.42), (--)-quinic acid was transformed into the allylic acetate 278 [423]. Pd(0)-catalysed allylic amination of 278 to the valienamine derivative 279 and debenzylation under Birch conditions gave (+)-valienamine in 11% overall yield from (--)-quinic acid (19 steps).

Three de novo syntheses of (+)-valienamine have been reported. Ogawa et al prepared pentaacetyl-(+)-valienamine from the 7-oxanorbornene (--)-88 (Scheme 2.1.43), which was transformed into the triacetate 280 [282]. Cleavage of the ether 280 by treatment with HBr furnished the dibromide 281. This was transformed into the spiro-epoxide 283 by elimination of HBr and epoxidation. Ring opening of the epoxide 283 with HCl and acetylation provided the allylic chloride 284. An SN2' reaction (proceeding with an anti stereoselectivity) of 284 with sodium azide gave the valienamine derivative 285, which was reduced with hydrogen sulfide and acetylated to give pentaacetyl-(+)-valienamine in 6% overall yield (11 steps) from 88. Ogawa et al. had previously reported several syntheses of racemic valienamine from the
racemic oxanorbornene 88 [424 – 426].

Scheme 2.1.43

[Chemical structures and reactions]

a) i. H₂O₂, HCO₂H, H₂O; 66%; ii. LiAlH₄, THF; iii. Ac₂O, pyridine; 76% (two steps) [282]. b) HBr, AcOH; 53% [282]. c) DBU, toluene; [427]. d) mCPBA, CH₂Cl₂; 27% of 283 from 281 (plus 12% of its diastereoisomer) [427]. e) i. HCl, THF, H₂O; ii. Ac₂O, pyridine; 92% [427]. f) NaN₃, DMF; 99% [427]. g) i. H₂S, pyridine, H₂O; ii. Ac₂O, pyridine; 94% (R = Ac) [427].

Knapp and coworkers prepared valienamine from the cyclohexene 286 (Scheme 2.1.44) [428] which was transformed into the allylic alcohol 290 in 12 steps and 36% yield by series of steps involving epoxidation, epoxide opening with PhSeNa, selenide oxidation, and elimination of PhSeOH. The condensation of 290 with p-methoxybenzylisothiocyanate, followed by a MeI quench gave the carbonimidothioate 291. The key steps of the synthesis were the iodocyclisation of 291 to the oxazolidinone 292, followed by oxidation of the iodide 292 to the corresponding iodoso derivative which resulted in spontaneous elimination of HIO to give the valienamine derivative 293. This was deprotected by oxidative removal of the p-methoxybenzyl group, hydrolysis of the oxazolidinone, and debenzylation under Birch conditions, furnishing (+)-valienamine in 8% yield (18 steps) from 286.
Scheme 2.1.44

a) i. NaH, BnBr, THF, HMPA; ii. mCPBA, CH2Cl2; 83% (two steps) [428]. b) i. PhSeNa, EtOH, THF; ii. mCPBA, CH2Cl2; iii. iPr2EtN, toluene, 45°; 86% (three steps) [428]. c) i. mCPBA, CH2Cl2; ii. NaH, BnBr, THF, HMPA; 82% (two steps); iii. PhSeNa, EtOH, THF; iv. mCPBA, CH2Cl2; v. iPr2EtN, toluene, 70°, 74% (three steps) [428]. d) i. PhCO2H, DEAD, Ph3P; ii. KOH, THF, EtOH, H2O; 84% (two steps) [428]. e) KH, 4-methoxybenzylisothiocyanate, THF, then MeI [428]. f) I2, THF, molecular sieves, then aq. Na2SO3; 65% from 290 [428]. g) mCPBA, CH2Cl2; 71% [428]. h) i. CAN, SiO2, aq. MeCN; ii. KOH, MeOH, H2O; iii. Na, NH3, THF; 47% (three steps) [428].

Trost and coworkers reported an asymmetric synthesis of (+)-valienamine from the cis-cyclohexenedibenzoate 294 (Scheme 2.1.45, which was obtained from 1,3-cyclohexadiene, [312]) [429]. An asymmetric allylic alkylation with (phenylsulfonyl)nitromethane in the presence of a chiral Pd catalyst gave the cyclohexene 295, which was transformed in situ by an intramolecular allylic alkylation to the isoxazoline-N-oxide 296, obtained in 87% yield and >99% ee. The isoxazoline-N-oxide 296 was transformed into the ester 297 in three steps. Selenylation of the dianion generated from 297, oxidation to the corresponding selenoxide, and thermal elimination of ArSeOH gave the 1,4-cyclohexadiene derivative 298 which was converted in three steps to the epoxide 300. The key step of the synthesis was the Pd(0)-catalysed opening of the allylic epoxide 300 to the alkoxide 301, addition of tosylisocyanate to the alcoholate 301, and cyclisation to the oxazolidinone valienamine derivative 303. Reduction of the ester and oxazolidinone moiety of 303, cleavage of the tosyl amide under Birch conditions and removal of the silyl groups gave (+)-valienamine in an overall yield of
1-2% from the cyclohexenedibenzoate 294 (14 steps).

Scheme 2.1.45

\[
\begin{align*}
\text{PhCO}_2^+ \text{O}_2\text{CPh} & \xrightarrow{a)} \text{PhCO}_2^+ \text{SO}_2\text{Ph} \\
\text{OH} \text{CO}_2\text{CH}_3 & \xrightarrow{d)} \text{OTBS} \text{CO}_2\text{CH}_3 \xrightarrow{e)} \text{OTBS} \text{CO}_2\text{CH}_3 \\
\text{TBSO} \text{CO}_2\text{CH}_3 & \xrightarrow{f)} \text{TBSO} \text{CO}_2\text{CH}_3 \xrightarrow{g)} \text{CO}_2\text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{PO}_{3} \text{OP} & \xrightarrow{h)} \text{L}
\end{align*}
\]

\(a\) PhSO\text{CH}_2\text{NO}_2, (\text{Pd(all)}\text{Cl)}_2, (1,2,5)-\text{bis[(diphenylphosphino)benzamido]cyclohexane}, \text{NaHCO}_3, \text{THF}, \text{H}_2\text{O} [429]. \(b\) \text{Pd}_2(\text{dba})_3\text{CHCl}_3, \text{Ph}_3\text{P}, \text{THF}; 87\% \text{ (two steps)} [429]. \(c\) i. \text{SnCl}_2\text{H}_2\text{O}, \text{MeCN}, \text{then KF, Et}_2\text{O}; 88\%; \text{ii. K}_2\text{CO}_3, \text{MeOH}; 57\% \text{ from 296}; \text{iii. Mo(CO)}_6, \text{B(OH)}_3, \text{MeCN, MeOH, H}_2\text{O}; 61\% [429]. \(d\) i. LDA, \text{THF}, \text{then PhSeSePh}; 54\%; \text{ii. TBDMSCl, imidazole, DMAP, CH}_2\text{Cl}_2; 86.5\%; \text{iii. mCPBA, CaCO}_3, \text{CH}_2\text{Cl}_2; 92\% [429]. \(e\) i. mCPBA, \text{NaHCO}_3, \text{CH}_2\text{Cl}_2; 48\% \text{ from 297}; \text{ii. TBDMSCl, DBU, DMAP, CH}_2\text{Cl}_2; 90\% [429]. \(f\) mCPBA, \text{NaHCO}_3, \text{CH}_2\text{Cl}_2; 88\% [429]. \(g\) \text{Pd(OAc)}_2, \text{L} (\text{configuration of the ligand not given}), \text{BuLi, TsNCO, Me}_3\text{SnOAc, THF}; 54\% [429]. \(h\) i. \text{DIBAL-H, CH}_2\text{Cl}_2, \text{then NaOMe, MeOH}; \text{ii. HF, H}_2\text{O, MeCN}; \text{Na, NH}_3; 31\% \text{ from 303} [429].

Of these syntheses, the one by \text{Fukase} and \text{Horii} appears to be the most efficient, providing (+)-valienamine in 12\% overall yield and 8 steps from tetra-\text{O}-benzylgluconolactone.
2.2. Alkene Metathesis

Alkene metathesis converts two alkenes into two new alkenes by formal exchange of their alkylidene moieties. Thus, the swapping of alkylidene groups between two acyclic alkenes leads to two new acyclic alkenes (cross metathesis, CM, Scheme 2.2.1), the intramolecular reaction of a diene leads to a cyclic alkene and an acyclic alkene (often ethylene) (ring-closing metathesis, RCM), the reaction of a cyclic alkene and an acyclic alkene provides an acyclic diene (ring-opening metathesis, ROM, the reverse of RCM), and polymerisation of cyclic alkenes or acyclic dienes leads to polymers (ring-opening metathesis polymerisation, ROMP and acyclic diene metathesis, ADMET).

Scheme 2.2.1

Transition metal-catalysed alkene metathesis (reviews: [430 – 435]; for an example of alkene metathesis by [2+2]-cyclisation and [2+2]-ring-opening, see [436]) was discovered in the 1950's and 1960's by several industrial research groups ([437] [438]). Eleuterio et al. at E. I. Du Pont De Nemours, Petrochemicals Department discovered that propylene was converted into a mixture of propylene, ethylene, and 1-butene, when passed over a molybdenum-on-aluminium catalyst. The same group discovered polymerisation of cyclopentene, when passed over this catalyst (reviewed in [439]). Anderson and Merckling at E. I. Du Pont De Nemours reported a polymerisation of norbornene with a Ti(II) catalyst prepared in situ from TiCl4 and EtMgBr [440]. Peters and Evering at Standard Oil Co. observed that propylene yielded ethylene and butenes, when treated with a catalyst prepared from molybdenum oxide on alumina and triisobutyl aluminium [441]. Banks and Bailey of Philips Petroleum Co. reported
that Mo(CO)₆ on alumina also catalyses this "disproportionation" of propylene into ethylene and butenes [442]. At about the same time, Natta et al. at Soc. Montecatini unveiled the polymerisation of cyclobutene and cyclopentene to polybutenamer and polypentenamer, respectively, using a homogeneous Ziegler type catalyst (e.g. WCl₆/Et₃Al) [443] [444]. Calderon et al. at The Goodyear Tire and Rubber Co. reported the transformation of 2-pentene to a mixture of 2-butene, 2-pentene, and 3-hexene with a homogeneous WCl₆/Et₃Al catalyst in ethanol and termed the process "olefin metathesis". These early findings stimulated extensive research on the mechanism of this novel reaction and on the nature of the catalytic species involved (reviewed in [437] [438] [445] [446]), and in 1970, Herisson and Chauvin proposed that the key steps of alkene metathesis are the reaction of a metal carbene complex and an alkene to a metallacyclobutane and the subsequent breakdown of this metallacyclobutane to a new metal carbene and alkene (vide infra) [447].

Since the 1960's, alkene metathesis has been successfully applied in the chemical industry to the production of bulk and fine chemicals (reviewed in [437] [448], novel industrial applications of alkene metathesis using homogeneous catalysts were recently reviewed [449]). Application of the Philips triolefin process (interconversion of propylene into ethylene and butenes) was terminated in 1972. Since 1985 the reverse process has been used by Lyondell Petrochemical Co. Philips Petroleum Co. produces 3,3-dimethylbutene-1 by "ethenolysis" of diisobutene. By the Shell higher olefin process long-chain olefins and short chain olefins are converted to olefins of intermediate chain length. The Norsorex process (ROMP of norbornene), and the Hüls-Vestenamer process (ROMP of cyclooctene) are applied in the polymer industry.

For a long time alkene metathesis remained limited to such industrial applications, as the ill-defined highly Lewis acidic catalyst systems, incompatible with functional groups, were unattractive for preparative organic chemists [450]. In 1972, van Dam and coworkers reported for the first time the metathesis of functionalised alkenes, namely the cross metathesis of unsaturated fatty acid esters to alkenes and unsaturated dicarboxylic acid diesters, catalysed by a homogeneous catalyst system composed of WCl₆ and Me₄Sn [451]. This stimulated further research towards extending the scope of alkene metathesis [446] [452] [453], while the mechanistic proposal by Herisson and Chauvin led to the development of metallacyclobutanes and metal carbenes as well-defined catalysts, and by the late 1980's alkene metathesis was applied in the cross metathesis and living ROMP of functionalised alkenes [433] [445] [454] [455].
2.2.1. Ring-Closing Alkene Metathesis

The apparently first example of a ring-closing alkene metathesis (RCM) dates from 1970, when Zuech et al. at Philips Petroleum Co. reported the transformation of 1,7-octadiene into cyclohexene (91% yield determined by glpc) using a homogeneous catalyst prepared in situ from [(Ph3P)2Cl2(NO)2Mo] and Me3Al2Cl3 in chlorobenzene [456]. The same RCM (29% yield) was effected in 1971 by Kroll and Doyle at Esso Research and Engineering Co. using a homogeneous catalyst prepared in situ from the Fischer carbene Bu4N[Mo(CO)5COPh] and alkylaluminium dichlorides or alkylaluminium sesquichlorides in chlorobenzene [457]. In 1974, Verkuijlen and Boelhouwer observed the formation of cyclohexa-1,4-diene from methyl linolate in low yield (6%) [458] by RCM with the homogeneous WCl6/Me4Sn catalyst [451]. An RCM of diallyl ether to 2,5-dihydrofuran and of allyl 3-butenyl ether to 2,3-dihydro-α-pyrene in the liquid phase on an aluminium-rhenium catalyst promoted by tetraalkylstannanes was described by Bogolepova et al. in 1978 [459]. In 1980 Tsuji and Hashiguchi prepared the macrocyclic lactones 9-octadecen-18-olide (18%) and 10-eicosen-20-olide (12%) by RCM of oleyl oleate and 10-undecenyl 10-undecenoate, respectively, with WCl6 and Cp2TiMe2 in benzene [450]. RCM of di(8-heptadecenyl)ketone failed both with this catalyst and with the WCl6/Me4Sn system. In the same year, Villemin obtained the macrolides 10-pentadecen-15-olide (65%) and 10-hexadecen-16-olide (60%, both as E/Z mixtures) by RCM of 4-pentenyl 10-undecenoate and 5-hexenyl 10-undecenoate, using WCl6/SnCl4 as the catalyst [460]. These early reports on RCM did not receive much attention by synthetic organic chemists, although Tsuji and Hashiguchi made a clear statement on the preparative potential of the method [450]. Further examples of early RCM were a macrocyclisation (oleone to civetone) in the presence of Re2O7/SiO2·Al2O3 and Bu4Sn [461], the RCM of sulfur-containing dienes using the tungsten alkylidene complex 308 (Scheme 2.2.2) as catalyst [462], a synthesis of hydroazulenes via RCM [463] catalysed by MeReO3 on silica gel/aluminium oxide [464], a synthesis of 3-cyclopenteneacrylic esters from diallyl acetic acid esters using a homogeneous WCl6/1,1,3,3-tetramethyl-1,3-disilacyclobutane catalyst [465], and the syntheses of 3-methylcyclopentene from citronellene and of 3-cyclopenteneacrylic esters from diallyl acetic acid esters by RCM in the presence of the oxo-tungsten complex 309 and Et4Pb [466].
The modern use of ring-closing alkene metathesis can be traced back to a series of papers by Grubbs and coworkers who demonstrated the selective, high-yielding ring-closing alkene metathesis of functionalised dienes to unsaturated (double bond substituted) 5-, 6-, and 7-membered oxygen heterocycles (containing ether, acetal, and silylene functional groups) [467], nitrogen heterocycles (containing tertiary amino and amide groups) [468], and carbocycles with alkoxy, hydroxy, and acyl substituents [469], using the Schrock alkylidene molybdenum complex 310 (Scheme 2.2.3) [470] which had previously been applied in cross metathesis and living ROMP [471].

Although 310 proved a highly active catalyst for RCM and was extensively applied in synthesis [472 – 474], it has some drawbacks such as extreme sensitivity to air, moisture, and trace impurities, incompatibility with some functional groups (especially hydroxy and carboxylate groups), thermal instability on storage, and expense of preparation [472] [475]. Even when 310 is stored in the solid form under nitrogen using Schlenck technique, it denatures after several hours [475]. Ideally it should be stored in a refrigerated glove-box.

Consequently, less sensitive catalysts were searched for, and Grubbs and coworkers developed the ruthenium alkylidene-complexes 311 [476] and 312, known as the Grubbs’s catalysts [477 – 479]. These complexes are moderately stable to air and moisture and therefore more easy to handle than the Schrock catalyst 310. More importantly, they tolerate a large range of functional groups, except for sulfides and amines (however, ammonium ions are tolerated, allowing RCM of protonated amines) [435] [472] [475] [480]. Grubbs’s catalyst 312 catalyses the formation of 1,2-disubstituted alkenes from terminal dienes with high efficiency [431] [472], but exhibits lower propagation rates than 310, especially with sterically bulky substrates and internal alkenes. It fails to produce tetrasubstituted cycloalkenes [435] [475]. In 1999, Grubbs’s, Nolan’s, and Fürstner and Herrmann’s groups independently reported the synthesis of a new generation of ruthenium alkylidene complexes
313 [481] [482], 314 [483] [484], and 315 [485] bearing an N-heterocyclic carbene (NHC) ligand. These complexes display equal or even higher reactivity in RCM than Schrock's catalyst 310, while keeping the stability and functional group tolerance of the ruthenium alkylidene 312 [435]. Complex 315, bearing a saturated NHC ligand of the Wanzlik type, was the most reactive of these catalysts [484] and is now known as the second-generation Grubbs's catalyst.

A range of further metal-carbene complexes were developed as catalysts for alkene metathesis (Scheme 2.2.4) [435] [486]. Among these are bimetallic complexes like 316 [487], ammonium-substituted catalysts like 317 and 318, allowing to perform RCM in water [488], the cationic complex 319 [489] [490], the complex 320 with a cis arrangement of the phosphane ligands [491] [492], the recyclable catalyst 321 containing an internal metal-oxygen chelate [493], a permanently immobilised form of 315, bound to a Merrifield polymer via the NHC-ligand [494], an immobilised form of 321, bound to polyethylene glycol mono methyl ether via the ortho-alkoxyalkylidene ligand [495], and imidazolium and imidazolinium ruthenium carbene complexes generated in situ [496]. Fürstner and Ackermann reported a "most user-friendly protocol" for RCM, generating the catalytic species
in situ from \([(p\text{-cymene})\text{RuCl}_2]_2\) and PCy3 under neon light [497].

Scheme 2.2.4

2.2.2. Mechanism of the Ring-Closing Alkene Metathesis with Grubbs's Catalysts

According to the Herisson-Chauvin mechanism [447], RCM proceeds via a series of intermolecular and intramolecular [2+2]-cycloadditions between an alkene and a metal carbene to a metallacyclobutane, and cycloreversions of the metallacyclobutane (Scheme 2.2.5). Formation of the metallacyclobutane is assumed to be the rate-limiting step. The involvement of metallacyclobutanes was demonstrated by the ability of discrete metallacyclobutane complexes to act as metathesis catalysts [454] [455].
Outline of the mechanism of RCM.

Isolation and crystal structure analysis of the complex 323 (Scheme 2.2.6), corresponding to an intermediate in the catalytic cycle, further corroborates the mechanism [498].

Details of the mechanism were investigated by kinetic studies [479], NMR spectroscopy [499] [500], mass spectroscopy [501] [502], and computer simulation [503]. Kinetic studies [479] revealed that there are two competing pathways (Scheme 2.2.7). A dominant one, accounting for 95% of the activity, involves dissociation of one phosphine ligand, while both phosphine ligands remain bound in a minor pathway. This was deduced by the effect of phosphine addition, which drastically slows down the reaction: the rate law for the reaction contains one term inversely proportional to the phosphine concentration and a term independent of the phosphine concentration. It was assumed that the effect of added phosphine on the dissociative pathway is to shift the position of the equilibrium for alkene
binding which involves phosphine dissociation. However, Hofmann and coworkers later found that Grubbs's catalyst 312 reacts with a bisphosphine by attack of P at the carbene carbon, implying that there might be a more intimate role of added phosphine than equilibrium effects [491]. From stereoelectronic considerations, Grubbs and coworkers proposed the configuration of the intermediates as shown in Scheme 2.2.7 [479], and these configurations were corroborated by a simulation study [503]; however, in a later publication Grubbs and coworkers contended that the experimental data neither support nor refute these configurations [500]. The exact timing of phosphane dissociation and alkene complexing remained obscure. A $^{31}$P-NMR kinetic study of the degenerate exchange between free and bound phosphine revealed that this exchange is independent of the concentration of free phosphine and must therefore follow a dissociative mechanism [499] [500]. In addition, the reaction of ethyl vinyl ether with 312 and 315 which leads irreversibly to the Fischer carbenes [Ru]=CH(OEt) was found to be independent of the concentration of ethyl vinyl ether, and the rate constants were identical to those for the degenerate phosphine exchange, evidencing that the phosphate dissociates before the alkene is bound.

**Scheme 2.2.7**

**Dissociative pathway**

The higher activity of the second-generation ruthenium catalyst 315 as compared to the first generation catalyst 312 was examined by NMR [499] [500] and mass spectral kinetic [502] analysis. In contrast to previous assumptions, the NMR kinetic studies revealed that the dissociation of phosphine from the second-generation complex is two orders of magnitude slower. However, the ratio $k_{-1}/k_2$ is 4 orders of magnitude lower for the second generation
catalyst, meaning that once formed, the intermediate $K$ (Scheme 2.2.8) is more committed to RCM vs. phosphine binding than the intermediate $B$. These results are in agreement with a recent mass spectral kinetic study by Adharrt and Chen which revealed that in the gas phase the reaction of the intermediate $B$ with an alkene is much slower than the reaction of the intermediate $K$ [502].

![Scheme 2.2.8](image)

As all steps of the catalytic cycle are reversible, alkene metathesis will in principle lead to alkene mixtures reflecting thermodynamic control. Ring-closing alkene metathesis is entropically favoured, and removal of the volatile ethylene drives the reaction to completion. In ROMP the equilibrium is driven by using strained cycloalkenes as starting material. RCM can also be done under conditions of kinetic control, as demonstrated by kinetic resolution [504] and enantioselective RCM (see [505] for a review).

A study of the kinetics and products of catalyst decomposition revealed that the decomposition requires phosphine dissociation, but due to the complexity of the kinetics and product mixtures, a detailed mechanism was not formulated [506]. It was shown that in general methylidene ruthenium complexes (the intermediates in the RCM of terminal alkenes) decompose more quickly than higher alkylidene complexes, and that the second-generation catalyst $\text{313}$ denatures more rapidly during RCM than $\text{312}$. Recently, the dinuclear ruthenium complex $\text{M}$ (Scheme 2.2.9) and methyl tricyclohexyl phosphonium chloride were identified as products of the decomposition of the methylidene complex $\text{315a}$, and a mechanism of catalyst decomposition was postulated [507].
Of importance to any synthetic organic chemist is the question whether a catalyst will also catalyse potential side reactions. In RCM with *Grubbs's* catalyst 312, double bond migration [508], especially of allylic alcohols, leading to ethyl ketones [509] [510], and dehydrogenation [511] were observed. Hoye and Zhao observed a stoichiometric conversion of allylic alcohols to methyl ketones by 312 [512]. Maynard and *Grubbs* reported a double bond isomerisation during the distillation of an RCM product, when residual amounts of the catalyst were present [513].

*Grubbs's* catalyst 312 also catalyses the Kharasch addition of CHCl₃ and CCl₄ to alkenes [514 – 516] and atom transfer radical polymerisations, both radical processes, as corroborated by the effect of radical reaction inhibitors. Amir-Ebrahimi *et al.* demonstrated the formation of radicals from 312 and strong π-acceptors in an EPR study [517]. The decomposition product M (Scheme 2.2.9) of catalyst 315a catalyses the isomerisation of allyl benzene to 1-propenyl benzene (76%) [507]. For a recent review on non-metathesis reactions catalysed by 312 and 315, see [518].

### 2.2.3. Influence of Functional Groups and Catalyst Complexation

Studies on the synthesis of macrocycles by *Fürstner et al.* revealed that coordination of polar groups of the substrate to the *Lewis*-acidic metal carbene intermediates of the catalytic cycle is crucial in such RCM cyclisations, but – conversely – if this complexation becomes too strong, *e.g.* in 5- or 6-membered chelates, it may lead to sequestering of the catalyst in an unproductive form [519 – 521]. Thus, tetradeca-1,13-diene (324a, Scheme 2.2.10) and hexadeca-1,15-diene (324b) produced only oligomers but no RCM product in the presence of
311, whereas 2-methyl-6-heptenyl 7-octenoate (325) cyclised smoothly (72%) to 12-methyl-7-tridecen-13-olide (326) [520]. In contrast, 2-methyl-3-butenyl 10-undecenoate (327), which can sequester the catalyst in a 5-membered chelate, gave the corresponding macrolide 328 in only 10% yield [520]. Grubbs et al. observed a similar catalyst inhibition in the RCM of amides [472].

**Scheme 2.2.10**

(a) 311, CH2Cl2 [520]. b) 311, CH2Cl2; 72% [520]. c) 311, CH2Cl2; 10% [520].

An ortho-halo substituent promoted the RCM of N,N-diallylanilines with 312 by acting as a "soft" donor to ruthenium, whereas an ortho-ethyl substituent retarded the reaction due to steric effects [511].

The role of OH groups is controversial. In a comparative study, Hoye and Zhao determined that an allylic tertiary or secondary C(3)-OH group in 7-methyl-1,6-octadienes greatly accelerated the formation of cyclopentenes by RCM with 312 (Scheme 2.2.11) [522], but the reaction of secondary allylic alcohols was complicated by their conversion to ethyl ketones.
via double bond migration (see chapter 2.2.2). In contrast, a C(3)-OMe group slowed the reaction.

Scheme 2.2.11

\[
\begin{array}{ccc}
R & X & a) \\
329 & & 330 \\
\end{array}
\]

\( a) 312, \text{CDCl}_3; \text{see Table 2.2.1 [522].} \)

Table 2.2.1: RCM of 329.

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>rel. reaction rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>OH</td>
<td>60</td>
</tr>
<tr>
<td>Me</td>
<td>OH</td>
<td>12</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>8</td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>1</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>≈ 0</td>
</tr>
</tbody>
</table>

\( \text{Kirkland and Grubbs found no difference between the cyclisation of the alcohol 331 (Scheme 2.2.12) and of its acetate with 312 [523].} \)

Scheme 2.2.12

\[
\begin{array}{ccc}
\text{EtO}_2\text{C} & \text{CO}_2\text{Et} & \text{a) } \\
331a & R = H & 331b \\
332a & R = \text{Ac} & 332b \\
\end{array}
\]

\( a) 312, \text{CH}_2\text{Cl}_2; 98\% \text{ of 332a, 97}\% \text{ of 332b [523].} \)

\( \text{Maishal et al. found that the acetates of allyl 2-(but-3-en-1-olyl)ether (333b, Scheme 2.2.13) and allyl 2-hydroxybut-3-enylether (335b) were better RCM-substrates for 312 than the free alcohols 333a and 335a [524]. The TBS-group in 362 (Scheme 2.2.18, chapter 2.2.4) was} \)
required for an efficient RCM, the free alcohol was not converted by 312 [525].

Scheme 2.2.13

\[ \begin{align*}
333a \ R &= H \\
333b \ R &= Ac \\
335a \ R &= H \\
335b \ R &= Ac \\
334a \\
334b \\
336a \\
336b
\end{align*} \]

\textit{a)} 312, CH2Cl2; 79% of 334a, 98% of 334b [524]. \textit{b)} 312, CH2Cl2; 87% of 336a, 96% of 336b [524].

\textit{Fukuda et al.} studied the cyclisation of the free trienols 337a, 338a, and 339a (Scheme 2.2.14) and their benzyl, trimethylsilyl, methoxymethyl, and benzoyl derivatives 337b-e, 338b-e, and 339b-e [526]. The free alcohols gave no cyclised products with Grubbs's catalyst 312, but good yields of 1:1 mixtures of the diastereoisomeric cyclohexenes 340a, 341a, and 342a were obtained in the presence of the second-generation catalyst 315. The O-protected derivatives 337b-e, 338b-e, and 339b-e cyclised in the presence of the catalyst 312 to give the cyclopentenes 340b-e, 341b-e, and 342b-e in good yields with varying diastereoselectivity (Table 2.2.2). The influence of the protecting groups on the yield (and diastereoselectivity) was not general, but depended on the nature of R^2. A correlation between the yield and diastereoselectivity is not obvious from the data.
Scheme 2.2.14

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{337} & \quad \text{R}^2 = \text{Me} \\
\text{338} & \quad \text{R}^2 = \text{Et} \\
\text{339} & \quad \text{R}^2 = \text{Ph} \\
\end{align*}
\]

R\(^\text{1}\), see Table 2.2.2. a) 312; see Table 2.2.2 [526].

Table 2.2.2: RCM of the Dienes 337b-e, 338b-e, and 339b-e.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R(^\text{1})</th>
<th>R(^\text{2})</th>
<th>Yield (%(^\text{a}))</th>
<th>dr (1RS,4SR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>337b</td>
<td>Bn</td>
<td>Me</td>
<td>78</td>
<td>71:29</td>
</tr>
<tr>
<td>337c</td>
<td>TMS</td>
<td>Me</td>
<td>69</td>
<td>74:26</td>
</tr>
<tr>
<td>337d</td>
<td>MOM</td>
<td>Me</td>
<td>61</td>
<td>64:36</td>
</tr>
<tr>
<td>337e</td>
<td>Bz</td>
<td>Me</td>
<td>90</td>
<td>64:36</td>
</tr>
<tr>
<td>338b</td>
<td>Bn</td>
<td>Et</td>
<td>80</td>
<td>85:15</td>
</tr>
<tr>
<td>338c</td>
<td>TMS</td>
<td>Et</td>
<td>84</td>
<td>86:14</td>
</tr>
<tr>
<td>338d</td>
<td>MOM</td>
<td>Et</td>
<td>69</td>
<td>77:23</td>
</tr>
<tr>
<td>338e</td>
<td>Bz</td>
<td>Et</td>
<td>85</td>
<td>71:29</td>
</tr>
<tr>
<td>339b</td>
<td>Bn</td>
<td>Ph</td>
<td>87</td>
<td>56:44</td>
</tr>
<tr>
<td>339c</td>
<td>TMS</td>
<td>Ph</td>
<td>55</td>
<td>61:39</td>
</tr>
<tr>
<td>339d</td>
<td>MOM</td>
<td>Ph</td>
<td>88</td>
<td>62:38</td>
</tr>
<tr>
<td>339e</td>
<td>Bz</td>
<td>Ph</td>
<td>85</td>
<td>62:38</td>
</tr>
</tbody>
</table>

\(^{\text{a}}\) For the TMS, MOM, and Bz derivatives the yields given were those after removal of these protecting groups.

Hammer and Undheim reported that RCM of the allylic alcohols 343 (Scheme 2.2.15) with 312 was faster (14 h vs. 3 d) for the (S)-isomer, in which an intramolecular H-bond led to a favourable conformation for the cyclisation [527]. Both diastereoisomers of the allylic alcohol 345 cyclised smoothly to the cyclohexenes 346 (73–75%) in the presence of 312, whereas the allylic alcohols 347 did not undergo RCM. However, their acetates 349 cyclised smoothly to the cycloheptenes 350 (90–93%) [528]. It was not clear if an unfavourable conformational bias or catalyst inhibition were responsible for the failure of the RCM of the alcohols 347.
Scheme 2.2.15

\[
\begin{align*}
\text{343} & \quad \xrightarrow{a)} \quad \text{344} \\
\text{345} & \quad \xrightarrow{b)} \quad \text{346} \\
\text{347} \quad R = H & \quad \text{348} \quad R = H \\
\text{349} \quad R = \text{Ac} & \quad \text{350} \quad R = \text{Ac}
\end{align*}
\]

a) 312, benzene; 89% for the (S)-isomer of 344, 88% for the (R)-isomer of 344 [527]. b) 312, 1,2-dichloroethane; 73 – 75% for both diastereoisomers of 346 [528]. c) 312, 1,2-dichloroethane; 0% of 348, 90 – 93% for both diastereoisomers of 350 [528].

Marco-Contelles and de Opazo reported the RCM of several derivatives of the dienes 351 (Scheme 2.2.16) with 312 [529] [530]. While the (6S)-diol (R\text{1} = R\text{2} = H) cyclised in good yield (85% after 6 h), RCM of the (6R)-diastereoisomer was sluggish (45% yield after 7 days). In contrast, the diacetate (R\text{1} = R\text{2} = \text{Ac}), the dibenzylether (R\text{1} = R\text{2} = \text{Bn}), and the 3-O-TBS-6-acetoxy derivative (R\text{1} = \text{TBS}, R\text{2} = \text{Ac}) of the 6R-diastereoisomer were converted to the cycloheptenes 352 in high yield (90-99%). Again, conformational bias and catalyst complexation (both productive and inhibitive) may underlie the different reactivities. For related work, see [531 – 533].
Scheme 2.2.16

R\textsuperscript{1}, R\textsuperscript{1}, a) See text [529].

In conclusion, free (and derivatised) hydroxyl groups may accelerate RCM by complexing the catalyst, but for secondary allylic alcohols the formation of ethyl ketones via double bond migration may thwart the reaction, especially with the catalyst 312. Intramolecular H bonds may lead to favourable or to unfavourable conformations of a diene substrate. With bulky OH protecting groups, steric repulsion of the catalyst can slow RCM, while conformational changes induced by such groups can be either favourable or unfavourable.
2.2.4. Application of RCM in Organic Synthesis

RCM is an extremely useful cyclisation method, as it allows C–C bond formation in the presence of a range of functional groups under very mild conditions. This is a significant advantage over other methods such as the McMurray reaction, pinacol synthesis, intramolecular Wittig alkenylation, or aldol reaction. The only reagent required in RCM is a catalytic amount of a metal carbene, and the only byproduct formed is, in most cases, a volatile alkene such as ethylene. The power of RCM resides in its ability to transform the C–C double bond, a functional group that is unreactive towards many reagents used for the transformation of other functional groups.

The starting dienes for RCM are readily available by Wittig alkenylation or alkenyl addition to carbonyl compounds, by elimination, or by rearrangement from other alkenes. The resulting cycloalkenes are much less readily available and yet very valuable and versatile intermediates, allowing electrophilic additions to the double bond, cycloadditions, rearrangements, and allylic functionalisations.

The catalysts most frequently applied in RCM are Schrock’s molybdenum complex \(310\) (Scheme 2.2.3), and the first and second-generation Grubbs’s ruthenium complexes \(312\) and \(315\), which are available from Strem Chemicals Inc. Since the development of these catalysts and the demonstration of their utility, there has been a plethora of applications of ring-closing alkene metathesis in the synthesis of carbocyclic and heterocyclic 5-7 membered rings, medium-sized rings, and large rings (reviews: \[430 – 435\] \[472 – 475\] \[486\] \[519\] \[520\] \[534 – 537\], for a review on the use of these complexes in CM, see \[480\], for alkine-metathesis, see \[538\], for a review of en-yne-metathesis, see \[539\]). Ring-closing alkene metathesis was employed as the key-step in the synthesis of several complex molecules with multiple functionalities.

Some prominent examples (see the reviews cited above for more examples) are the synthesis of the dihydropyran \(353\) \[540\] (Scheme 2.2.17), demonstrating that vinyl ethers undergo RCM with Grubbs’s catalyst \(312\); the synthesis of frontalin \(354\), the aggregation pheromone of the southern bark beetle \(Dendroctonus frontalis\) \[541\]; the synthesis of jasmine ketolactone \(355\), a minor component of the essential oil of jasmine (\(Jasmonium grandiflorum\) L.) \[542\] (this was the first example for the synthesis of a 10-membered ring by RCM); the synthesis of epothilones \(356\) \[543\] \[544\], cytotoxic tubuline polymerising agents with a great potential in the therapy of cancer; the synthesis of Sch 38516 (fluvirucin B1, \(357\)), a member of a new class of antifungals \[545\]; the synthesis of the ABCDE ring system of manzamine A \(358\), a
complex marine alkaloid with antileukemic and antibacterial activities [546], and the synthesis of cyclic sulfonamides like 359 [547].

```
Examples of compounds prepared via RCM. The wavy line indicates the bond that was formed by RCM; the numbers in brackets indicate the catalyst used and the yield31).  
```

---

31) These and the following examples illustrate the wide scope of RCM in cyclisations leading to complex molecules. For the complete syntheses of these compounds the reader is referred to the original literature.
The synthesis of the heterospirobicyclic compound 361 [548] (Scheme 2.2.18) is an example of a diastereoselective double RCM. The diastereoselectivity of the RCM of the triene 362 to the pyrroles 363 depended on the choice of the catalyst [525]: 310 favoured formation of the syn-product, 312 formation of the anti-product.

Scheme 2.2.18

\[
\begin{align*}
360 & \xrightarrow{a} 361 \\
362 & \xrightarrow{b} 363 \quad \text{(a) CHCl₃, 74\%, 92\% d.e. [548].} \\
363 & \xrightarrow{c} 363 \quad \text{(b) benzene; 88\%, 92\% d.e. [525].} \\
363 & \xrightarrow{c} 360 \quad \text{(c) benzene; 97\%, 72\% d.e. [525].}
\end{align*}
\]

Examples for RCM in supramolecular chemistry are the synthesis of catenanes [549] and the synthesis of a peptide cyclinder from two selfassembled units of the cyclic octapeptide [(L-Phe-D-MeN-Ala-L-(3-butenyl)gly-D-MeN-Ala)₂] by a sequence of cross metathesis (in this case a pseudo-intramolecular reaction) and ring-closing metathesis [550] (for an early example of a catenane synthesis by a series of WCl₆-EtAlCl₂-EtOH-catalysed intramolecular metatheses from large-ring dienes, see [551]). RCM has also been applied in the synthesis of amino acid derivatives like 364 [552] (Scheme 2.2.19), 365 [553], and 366 [554], in the synthesis of crosslinked oligopeptides [555], and in the synthesis of the conformationally restricted dipeptide 367 and tetrapeptide 369 [552].
Examples for compounds prepared via RCM. The wavy line indicates the bond that was formed by RCM; the numbers in brackets indicate the catalyst used and the yield.

Interestingly, from a mixture of the four diastereoisomers of the diene 368 (Scheme 2.2.20), only 369 was formed. The reluctance of the other diastereoisomers to cyclise was attributed to their unfavourable conformation.

\[ a) \text{311, 60\% [552].} \]
2.2.5. Ring-Closing Alkene Metathesis in Carbohydrate Chemistry – Overview

The power of RCM has been demonstrated by numerous applications in carbohydrate chemistry (reviews: [546] [556 – 559]); examples are:

- The synthesis of bicyclic sugar derivatives [560 – 564], *e.g.* the spiro-acetal 375 [565] (Scheme 2.2.21), and the bridged bicyclic furanose 376 [566].

- The synthesis of fused bicyclic derivatives, such as pyrano-pyranoses [567 – 569] (*e.g.* 377 [570]), an oxepine annealed to a pyranose [571], cyclopentene, cyclohexene, cyclopentene, and cyclooctene fused to a pyranose [561] [562], a cyclopentene and cyclohexene fused to a furanose [510] [572], a tricyclic intermediate of an alkaloid synthesis [573], a heptenitol fused to an inositol [574], and siloxanes (*e.g.* 378 [575]), intermediates in the synthesis of C-disaccharides.

- The synthesis of a macrocyclic fused furanose [576], macrocyclic bridged glycosides [577] (*e.g.* 379 and 380 [578]) and oligoglycosides [579 – 583].

- The synthesis of glycals [584], *e.g.* 381 [585], and the synthesis of C-glycosides *via* glycals [586] [587] from pyranoses.

- The synthesis of oxepines, *e.g.* 382 [588], from pyranoses [589] [590].

- The synthesis of a phosphonosugar [591].

- The synthesis of indolizidines, pyrrolizidines, quinolizidines [546] [592 – 594] (*e.g.* castanospermine (383) [595]), calystegine B₂ [596], and other azasugars [546] from carbohydrates, and the *de novo* synthesis of piperidines [597] (*e.g.* fagomines [598] [599] and 1-deoxyiminosugars [600]), and indolizidines [601] (*e.g.* swainsonine [602]).

- The *de novo* synthesis of pyranoses and their derivatives [603 – 608], *e.g.* 384 [609], pyrano-pyranoses [540], and oxepanes [610].

- The synthesis of polyols *via* RCM of silicon-tethered allylic alcohols [611] [612], the synthesis of C–C-coupled saccharides *via* silicon-tethered RCM [613].
Examples of compounds prepared via RCM. The wavy line indicates the bond that was formed by RCM; the numbers in brackets indicate the catalyst used and the yield.

Several syntheses formed the aglycon or peripheral substituents of glycosides by RCM [614] [615]; carbohydrates also served as starting materials for syntheses involving an RCM [616 – 622].

Also cross-metathesis has been applied in carbohydrate chemistry (review: [557]), e.g. in the homodimerisation of alkenyl-glycosides [623 – 626] and nucleosides [627], in the selective en-yne cross metathesis of two saccharides [628], in the synthesis of glycopeptides [629] [630], and in the release of alkene-linked oligosaccharides from a solid phase by CM with ethylene (e.g. [631] [632]). For an example of enyne ring-closing alkene metathesis, see [633].
2.2.6. Carbasugars via Ring-Closing Alkene Metathesis

When we embarked on this project there were but a few syntheses of carbasugars using RCM as the key step. In 1996, Crimmins and King reported a synthesis of the carbanucleoside 389 (Scheme 2.2.22) from (S)-4-benzyl-2-oxazolidinone (386) [634]. RCM of the diene 387 in the presence of 0.01 eq. of *Grubbs's* catalyst 312 gave the carbafuranose 388 in 97% yield [634 – 636].

![Scheme 2.2.22](image)

\[ a) \text{i. BuLi, 4-pentenoic pivaloic mixed anhydride, THF; 99%; ii. Bu}_2\text{BOTf, Et}_3\text{N, acroleine, CH}_2\text{Cl}_2; 82\% [634]. b) 0.01 eq. of 312, CH}_2\text{Cl}_2; 97\% [634]. \]

*Ziegler* and *Wang* reported the first synthesis of a carbapyranose from a carbohydrate by RCM. With the cyclisation of the diene 390 (Scheme 2.2.23) to the cyclohexene 391 as the key step, cyclophellitol (33) was prepared in 9% overall yield (17 steps) from D-xylose [219] [220].

![Scheme 2.2.23](image)

\[ a) \text{9 steps, 32\%; [220]. b) 0.14 eq. of 312, CH}_2\text{Cl}_2; 92\% [220]. c) Seven steps, 31\% [220]. \]

*Ovaa et al.* reported the synthesis of the carbafuranose 396 (Scheme 2.2.24), a synthon for the preparation of carbanucleosides, from benzoyl-2,3:5,6-di-O-isopropylidene-α-D-mannofuranose 392 in 74% overall yield (8 steps) [221]. Selective hydrolysis of 392,
conversion of the 5,6-diol into an orthoester, and acid-catalysed thermal rearrangement (Eastwood reaction [637]) afforded the alkene 393. Hydrolysis of the benzoate and Wittig methylenation gave the diene 394 (87% overall yield). RCM in the presence of 0.005 eq. of 312 gave the cyclopentene 395 in 95% yield, which was converted into 396 by an Overman rearrangement.

Scheme 2.2.24

\[ \text{Scheme 2.2.24} \]

\[ \text{392} \rightarrow \text{393} \rightarrow \text{394} \rightarrow \text{395} \rightarrow \text{396} \]

\( a \) i. aq. AcOH; ii. HC(OEt)\(_3\), AcOH; iii. Ph\(_3\)CO\(_2\)H; 93% (three steps) [221]. \( b \) i. KOrBu, MeOH; 96%; ii. Ph\(_3\)P=CH\(_2\), THF; 98% [221]. \( c \) 0.005 eq. of 312, CH\(_2\)Cl\(_2\); 92% [221]. \( d \) i. Cl\(_3\)CCN, DBU, CH\(_2\)Cl\(_2\); ii. Xylenes, reflux; 92% (two steps) [221].

While we were about to publish our results (see below and [638]), Sellier et al. reported the synthesis of valiolamine (404) from D-arabinose via RCM in 7% overall yield (8 steps) [639]. Wittig methylenation of 2,3,5-tri-O-benzyl-D-arabinose (397, Scheme 2.2.25), followed by oxidation with CrO\(_3\)/pyridine in CH\(_2\)Cl\(_2\) gave the hexenulose 398. Addition of allylmagnesium bromide to 398 afforded in 97% yield a 7:3 mixture of the (5S) and (5R) dienols 399, which were trimethylsilylated to the derivatives 400. Treatment of this mixture with Schrock's catalyst 310 gave 97% of a mixture of the cyclohexenes 401 and 402, which were isolated in 42% and 19% yield, respectively. RCM of the dienes 400 in the presence of 0.2 eq. of Grubbs's catalyst 312 gave only 42% of the mixture of cyclohexenes. Compound 401 was further transformed into valiolamine (404) using an aminohydroxylation as the key step.
Since completion of this work, a considerable number of carbasugars have been synthesised using RCM as the key step. Asymmetric de novo syntheses led to a carbafranose from diallyl malonic acid diethyl ester [640] and to a carbafranose and a carbapyranose from ω-unsaturated acyl sultams by analogy to the synthesis by Crimmins and King (vide supra) [641].

- Carbafranoses were prepared from pentofuranoses [642 – 646], from hexopyranoses [647 – 651], from hexofuranoses [651 – 653], and from lactose [654].
- Carbapyranoses were prepared from pentofuranoses [647] [655] [656], from pentopyranoses [657], from hexopyranoses [658], from hexofuranoses [659], from hexitols [509] [660] [661], and from tartaric acid [509] [662] [663],
- Cycloheptenitols and cyclooctenitols were prepared from pentofuranoses [664], from hexopyranoses [531] [532], and from hexofuranoses [529] [530] [665] [666].

Several ways have led from carbohydrates to the required dienes: Wittig alkenylation of
pyranoses or furanoses, followed by oxidation, or Bernet-Vasella fragmentation of 6-iodopyranosides or 5-iodofuranosides lead to enuloses whose carbonyl groups allowed the introduction of a second alkene group by Wittig alkenylation or addition of alkenyl Grignard reagents. Alternatively, oxidation of the primary hydroxy group of glycitols (or glycosides) or partial reduction of the ester groups of tartrates to aldehydes, followed by alkenylation of the aldehydes or alkenyl addition provided dienes. Furthermore, the 5,6-diol moiety of hexofuranoses, or corresponding diol moieties in chain-elongated sugars were transformed into a vinyl group by elimination.

In several cases Schrock's catalyst 310 (which is incompatible with OH groups and requires handling in the glove box) or the NHC-ruthenium-complexes 315 and 313 gave better yields of 5-, 6-, 7-, and 8-membered carbasugars than the first generation Grubbs's catalyst 312, especially in the formation of trisubstituted double bonds [648 – 650], or with sterically crowded substrates [639] [643] and substrates with an unfavourable conformation [509] [647]. An exception was a synthesis of 8-membered carba-sugars, where 312 performed well, while 315 failed [66].

In the remainder of this section I will illustrate a few syntheses of carbapyranoses and carbafuranoses making use of RCM. For more examples the reader is referred to a review [556] and to the original literature cited above.

Ackermann et al. prepared the conduritol derivative 408 (Scheme 2.2.26) in six steps and 27% overall yield from D-glucitol (405) [509]. The diene 407 was obtained from the diol 406 by Swern oxidation, followed by a Tebbe methylenation (several other alkenylations failed). RCM of the diene 407 in the presence of Grubbs's catalyst 312 gave only 32% of the cyclohexene 408, while RCM in the presence of Schrock's catalyst 310, or of the second-generation ruthenium catalyst 313, proceeded in a yield of about 90%.

Scheme 2.2.26

\[ \text{HO} \]
\[ \text{OH} \]
\[ \text{OH} \]
\[ \text{OH} \]
\[ \text{a) i. Monomethoxytrityl chloride, DMAP, pyridine; 85%; ii. BnBr, NaH, THF; 96%; iii. H}_2\text{SO}_4, \text{MeOH, CH}_2\text{Cl}_2; 87\% [509]. b) i. DMSO, (COCl)_2, Et}_3\text{N, CH}_2\text{Cl}_2; quant.; ii. Cp}_2\text{Ti(Cl)(CH}_2\text{)AlMe}_3, \text{THF, pyridine; 42\% [509]. c) i. 0.05 eq. of 312, CH}_2\text{Cl}_2; 32\%; ii. 0.05 eq. of 310, CH}_2\text{Cl}_2; 92\%; iii. 0.05 eq. of 313, CH}_2\text{Cl}_2; 89\% [509].} \]
In another synthesis of conduritol derivatives, Ackermann et al. started with the tartaric acid derivative 409 Scheme 2.2.27) which was transformed into the diene 410 by reduction to the bisaldehyde, followed by addition of vinylmagnesium bromide [509]. RCM in the presence of 0.2 eq. of Grubbs's catalyst 312 gave the cyclohexene 411 in 27% overall yield (three steps) from 409. In the presence of the second-generation ruthenium catalyst 313 a much lower catalyst loading (0.01 eq.) was required, but the yield of the RCM was somewhat lower.

**Scheme 2.2.27**

![Chemical structure](image)

a) i. DIBALH, toluene, then vinylmagnesium bromide; 42%; ii. Ac₂O, pyridine, CH₂Cl₂; 83% [509].
b) i. 0.2 eq. of 312, CH₂Cl₂; 77%; ii. 0.01 eq. of 313, CH₂Cl₂; 71% [509].

Kornienko and d'Alarcao prepared the conduritol derivatives 415 (Scheme 2.2.28) from 2,3,4-tri-O-benzyl-D-xylopyranose (412) in four steps. [657] The dienes 414a,b were obtained from 412 by Wittig methylation, oxidation of C(5)–OH, and addition of vinylmagnesium bromide. RCM of these dienes in the presence of 0.1 eq. of Grubbs's catalyst 312 gave the conduritol derivatives 415a,b in high yield.

**Scheme 2.2.28**

![Chemical structure](image)

a) i. Ph₃P=CH₂, THF; ii. DMSO, (COCl)₂, CH₂Cl₂; yield not given [657].
b) vinylmagnesium bromide, MgBr₂·OEt₂, CH₂Cl₂; yield not given, 414a:414b = 8:1 [657].
c) 0.1 eq. of 312, CH₂Cl₂; 99% of 415a, 95% of 415b [657].
Hyldtoft et al. prepared cyclohexenes from methyl 5-deoxy-5-iodoribofuranosides (416)\textsuperscript{32)} [655] (Scheme 2.2.29). A domino reaction comprised of a Bernet-Vasella fragmentation and a Barbier alkylation afforded the dienes 418\textsubscript{a,b}. RCM of these dienes in the presence of 0.1 eq. of Grubbs’s catalyst 312 gave the cyclohexenes 419\textsubscript{a,b} in high yield.

\begin{itemize}
  \item \textbf{Scheme 2.2.29}
\end{itemize}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {416};
  \node (b) at (2,0) {417};
  \node (c) at (4,0) {418\textsubscript{a,b}};
  \node (d) at (6,0) {419\textsubscript{a,b}};

  \draw (a) -- (b);
  \draw (b) -- (c);
  \draw (c) -- (d);

  \node at (0,-1.5) {a) Zn, allBr, THF, H\textsubscript{2}O; 30\% of 418\textsubscript{a}, 70\% of 418\textsubscript{b} [655]. b) 0.1 eq. of 312, CH\textsubscript{2}Cl\textsubscript{2}; 96\% of 419\textsubscript{a}, 95\% of 419\textsubscript{b} [655].}
\end{tikzpicture}
\end{center}

After Leclerc\textsuperscript{27}) had finished her diploma work on the synthesis of carbafuranooses, Seepersaud et al. [642] and Sellier et al. [643] independently reported an almost identical synthesis of carbafuranooses from 2,3,5-tri-O-benzylarabinose (397, Scheme 2.2.30). The diene 421 was obtained from 397 by Wittig alkenylation, oxidation of C(4)–OH, and addition of vinylmagnesium bromide. The RCM step will be discussed in detail in chapter 2.3.5.

\textsuperscript{32}) The preparation of the starting material was neither described, nor referenced. It was probably prepared via methyl 2,3-isopropylideneribofuranoside by sulfonylation of C(5)–OH, substitution by iodide, and cleavage of the isopropylidene ketal.
Scheme 2.2.30

a) BuLi, Ph₃P=CH₂, THF; 87% [642]. b) DMSO, (COCl)₂, Et₃N, CH₂Cl₂; 90% [642]. c) i. Vinylmagnesium bromide, THF; 92% of 421 [642]; ii. 1. BnBr, NaH, Bu₄NI, DMF; 98% of 423 [642]; 2. TMSOTf, 2,6-lutidine; 94% of 422 [643]. d) 0.1 eq. of 310, CH₂Cl₂; 87% of 426 [642], or 0.1 eq. of 310, benzene; 90% of 425 [643].

Callam and Lowary prepared the methyl carba-arabinofuranoside 431 (Scheme 2.2.31) from the orthogonally protected mannopyranose 427 (prepared in 8 steps and 39% yield from D-mannose) in 8 steps and 24% overall yield [648]. The diene 429 was obtained from 427 by a Wittig methylenation, followed by oxidation of C(5)–OH and another Wittig methylenation. RCM of 429 was effected using 0.2 eq. of Schrock’s catalyst 310, yielding 74% of the cyclopentene 430. In the presence of Grubbs’s catalyst 312 this trisubstituted alkene was only formed in 12 – 18% yield.
En-yne metathesis was applied to the synthesis of vinyl-cyclohexenitols (e.g. 435 from 434, Scheme 2.2.32) [667], and a dien-yne tandem metathesis led to bicyclic carbasugar derivatives (e.g. 433 from 432) [668].
2.3. Results and Discussion

The goal of this part of my thesis was to prepare D-glucose-, D-mannose-, and D-arabinose-derived carbasugars via RCM and to demonstrate the efficiency of this approach to carbasugars by a synthesis of (+)-valienamine (22, Scheme 2.3.1).

The cyclohexene 40 (Scheme 2.3.1), possessing the same relative configuration at C(2)–C(4) as (+)-valienamine and as D-glucose, appeared as the ideal key intermediate for the synthesis of (+)-valienamine and other carbaglucoses The diene 441 was considered as an appropriate starting material for the synthesis of 40 via RCM. This diene should be readily accessible from tetra-O-benzylglucopyranose (443) via the known ketone 442 [669]. The reduction (NaBH4/CeCl3) of a similar ketone possessing a nitrile function instead of the ethenyl moiety proceeded with a diastereoselectivity of 86% [14] [161], auguring well for a diastereoselective addition of vinyl magnesium bromide to 442. The epimer 254 of 40 has been transformed by Nicotra et al. into (+)-valienamine [417] (see chapter 2.1.4) and by McAuliffe and Stick into a 1-epivalienamine derivative [670]. Protected derivatives of 40 were transformed into valiolamine derivatives by Paulsen and coworkers [671]. By analogy, the cyclohexene 42, a key intermediate for the synthesis of manno analogues of valienamine derivatives and other carba-mannoses, would be accessible from D-mannose, and the cyclopentene 424, a key intermediate for the synthesis of carba-arabinoses, from D-arabinose.

Scheme 2.3.1

The alternative key intermediate 444 (Scheme 2.3.2) appeared less attractive. RCM of the diene 445 to 444 using Grubbs's catalyst 312 would presumably be difficult (formation of a
trisubstituted double bond). Introducing the C(5) methyldiene group in 445 would require selective protection of the allylic alcohol 447. The stereoselectivity of the addition of vinylmagnesium bromide to the pyranose 443 may be low [4] [672] [673] (cf. [378] [674] for related additions to furanoses).

**Scheme 2.3.2**

2.3.1. Synthesis of (+)-Valienamine from d-Glucose via RCM

The ketone 442 was obtained in two steps and 74% yield from 2,3,4,6-tetra-O-benzyl-D-glucopyranose by Wittig methylenation [675] followed by Moffatt oxidation [669]. Addition of vinylmagnesium bromide to 442 in THF at –78° gave the epimeric dienes 441 and 450 in 86 and 1% yield, respectively (Scheme 2.3.3). The constitution of the products is evidenced by their 1H- and 13C-NMR spectra. The configuration of 441 and 450 was tentatively assigned by analogy to the above-mentioned reduction [14] [161] where the nucleophile attacked preferentially from the re face.

Ring closing alkene metathesis of the homogeneous dienes 441 and 450 in CH2Cl2 in the presence of Grubbs's catalyst 312 [477] (0.15 eq. for 441, 0.3 eq. for 450) gave the cyclohexenes 40 and 254 [417] in 58 and 66% yield, respectively. While the L-ido-isomer 254 was colourless, the D-gluco-isomer 40 was isolated as a green oil, contaminated with traces of ruthenium oxides.
Using the second-generation Grubbs's catalyst $315$ (0.1 eq.) in CH$_2$Cl$_2$ improved the yield of 40 from 441 significantly (89%). The in situ generated catalytic system developed by Fürstner and Ackermann (see chapter 2.2.1) [497] led to sluggish RCM of 441; TLC indicated only little product after several days. We also attempted the RCM of the dienes 448 and 449 (prepared in moderate yield from 441, see experimental part for details) in the presence of Schrock's catalyst $310$ in CH$_2$Cl$_2$. However, after several days, TLC did not indicate any conversion. It may be that the commercial batch of 310, although delivered in a sealed tube, did not survive shipping$^{33}$). Schrock's catalyst $310$ is extremely sensitive to air and moisture. Even stored in the solid form under nitrogen using Schlenck technique it denatures after several hours [475]. Ideally it should be stored in a refrigerated glove-box, which was not available for this investigation.

RCM of the diene 441 in the presence of Grubbs's catalyst $312$ in CH$_2$Cl$_2$ gave lower yields of the cyclohexene 40 (23%; 26% of starting material re-isolated) when the reaction was

$^{33}$) Shipping of this catalyst lot from the USA to Switzerland took more than two weeks, and apparently the sample was not refrigerated during most of the time.
carried out in the glove box under oxygen-free conditions. The colour of the solution remained purple for 2 weeks, indicating that 312 was not oxidised, whereas in the bench top reactions (58% yield), the solutions turned green after ca. one day, indicating partial oxidation of 312 (solutions of the diene 441 were FPT-degassed before the reactions; but trace amounts of oxygen might have entered the flasks during the long reaction time, especially when balloons were used). The lower yield under oxygen free conditions is surprising. Conceivably, trace oxygen may serve as a phosphine scavenger (oxidising Cy3P to Cy3PO). Dias et al. have shown that phosphine scavenging by CuCl improves RCM with Grubbs's catalyst 312 [479]. Alternatively, trace amounts of oxygen present in the bench top reactions may interfere with or catalyse radical reactions34), which have been invoked in reactions with Grubbs's catalyst 312 [515] [517].

We also wanted to study RCM of the diene 441 under microwave irradiation. In a few cases, microwave irradiation significantly enhanced the yield of RCM [676 – 679] and of ROMP [680]. Samples of 441, 421, and other dienes prepared in our group were sent to Dr. K. Ruda35) at Personal Chemistry who had offered to run the test reactions. However, after reporting promising initial results, Dr. K. Ruda refused further communication.

As the configuration at C(4) of the cyclohexenes 40 and 254 could not be determined by NMR spectroscopy, the structure was proven by converting 40 and 254 into known compounds. Benzylation of 40 and 254 gave the fully protected 451 and 454 in 88 and 49% yield, respectively. The optical rotation and 1H-NMR spectrum of 454 matched the data reported by Nicotra et al. [417], thus establishing the (4R)-configuration of 254 and the (6R)-configuration of 450, and, indirectly, the (4S)-configuration of 40 and the (6S)-configuration of 441. The data for 451, however, did not match those reported by Paulsen and coworkers for this compound [671]. These authors claimed a synthesis of 451 by benzylation of the diol 452 which they prepared by a stereoselective addition of a 2-lithio-1,3-dithiane to (3S,4R,5S)-4,5,6-tris-(benzyloxy)cyclohex-2-en-1-one. Paulsen's data for the diol 452 are also at variance with the data reported by Ogawa et al. for 452 and 455 [681]. Paulsen's data for the derivative 451 also differ from our data for 454, the origin of the difference remaining unclear36).

The vicinal coupling constants for the ring H of 40, 451, 254, and 454 indicate a $^3H_2$
conformation\textsuperscript{37}) (Table 2.3.1). The alkenyl H of 254 appear as a $s$ at 5.74 ppm, while those of 40 appear as two $dd$'s at 5.92 (H–C(6)) and 5.69 ppm (H–C(5), $J_{(5,6)} = 10.3$ Hz). The geminal coupling constants for H–C(7) of 40 and 451 (8.7 Hz) where the benzyloxymethyl groups are pseudoequatorial, are smaller than those of the epimers 254 and 454 (9.3 and 9.7 Hz, respectively) ($\Delta J = 0.6$ to 1.0 Hz), possessing pseudoaxial benzyloxymethyl groups. This is rationalised by different rotameric equilibria (Figure 2.3.1). Conformations I and II should be about equally populated in both epimeric series, while III is destabilised for 254 and 454, but not for 40 and 451. In conformation III the tertiary OR group is gauche to both methylene H. It is known [682] [683] that such an orientation of an electron withdrawing substituent leads to a decreased (absolute) geminal coupling constant. Such a dependence of the geminal coupling constant on the configuration of the quarternary centre of 1-(hydroxymethyl)-cyclohex-2-en-1-ol derivatives has been reported by Ogawa and coworkers for 452 ($J_{(7,7')}$ = 10.8 Hz) and 455 ($J_{(7,7')}$ = 11.8 Hz) [681].

Figure 2.3.1:

\[ \text{RO} \quad \text{BnO} \quad \text{OBn} \quad \text{BnO} \]
\[ \text{254} \quad \text{R} = \text{H} \]
\[ \text{454} \quad \text{R} = \text{Bn} \]
\[ \text{OBn} \quad \text{BnO} \quad \text{OBn} \quad \text{BnO} \]
\[ \text{40} \quad \text{R} = \text{H} \]
\[ \text{451} \quad \text{R} = \text{Bn} \]
\[ \text{OBn} \quad \text{BnO} \quad \text{OBn} \quad \text{BnO} \]
\[ \text{254} \quad \text{R} = \text{H} \]
\[ \text{454} \quad \text{R} = \text{Bn} \]

\textsuperscript{37) The systematic numbering differs between 40, 452, 254, and 455 on the one hand, and 451 and 454 on the other hand; the locants of the cyclohexenes in Scheme 2.3.3 used for the discussion of the conformation are those of the unprotected cyclohexenes 452 and 455 with the exception of the locant for the hydroxymethyl group that is 7. Similarly, the hydroxymethyl group of the dienes is designated as C(9).}
Table 2.3.1: Selected $^1$H- and $^{13}$C-NMR (CDCl$_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] and Optical rotations (CHCl$_3$) of 40, 451, 254, 454, 42, and 60.

<table>
<thead>
<tr>
<th></th>
<th>40</th>
<th>451$^{a)}$</th>
<th>254</th>
<th>454$^{a)}$</th>
<th>42</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>H–C(1)</td>
<td>4.20</td>
<td>4.19</td>
<td>4.20</td>
<td>4.22</td>
<td>4.16</td>
<td>4.12</td>
</tr>
<tr>
<td>H–C(2)</td>
<td>4.02</td>
<td>4.49</td>
<td>3.87</td>
<td>4.47–4.38</td>
<td>3.94</td>
<td>3.91</td>
</tr>
<tr>
<td>H–C(3)</td>
<td>3.76</td>
<td>3.97</td>
<td>3.76</td>
<td>3.97</td>
<td>4.26</td>
<td>4.22</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>5.69</td>
<td>5.76</td>
<td>5.74</td>
<td>5.67</td>
<td>5.79</td>
<td>5.76</td>
</tr>
<tr>
<td>H–C(6)</td>
<td>5.92</td>
<td>5.90</td>
<td>5.74</td>
<td>5.84</td>
<td>5.95</td>
<td>5.90</td>
</tr>
<tr>
<td>CH–C(4)</td>
<td>3.38</td>
<td>3.73</td>
<td>3.83</td>
<td>4.14</td>
<td>3.46</td>
<td>3.44</td>
</tr>
<tr>
<td>CH'–C(4)</td>
<td>3.30</td>
<td>3.53</td>
<td>3.63</td>
<td>3.76</td>
<td>3.43</td>
<td>3.41</td>
</tr>
<tr>
<td>HO–C(4)</td>
<td>2.80</td>
<td>-</td>
<td>2.74</td>
<td>-</td>
<td>3.10</td>
<td>3.07</td>
</tr>
<tr>
<td>J(1,2)</td>
<td>8.1</td>
<td>7.5</td>
<td>7.2</td>
<td>7.8</td>
<td>3.7</td>
<td>3.9</td>
</tr>
<tr>
<td>J(1,5)</td>
<td>2.2</td>
<td>1.9</td>
<td>0</td>
<td>2.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>J(1,6)</td>
<td>1.9</td>
<td>2.5</td>
<td>0</td>
<td>1.9</td>
<td>5.0</td>
<td>4.9</td>
</tr>
<tr>
<td>J(2,3)</td>
<td>10.3</td>
<td>10.6</td>
<td>10.3</td>
<td>10.3</td>
<td>9.7</td>
<td>9.7</td>
</tr>
<tr>
<td>J(5,6)</td>
<td>10.3</td>
<td>10.3</td>
<td>0</td>
<td>10.6</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>J(7,7')</td>
<td>8.7</td>
<td>8.7</td>
<td>9.3</td>
<td>9.7</td>
<td>9.3</td>
<td>9.7</td>
</tr>
<tr>
<td>C(4)</td>
<td>72.97</td>
<td>78.13</td>
<td>75.77</td>
<td>b)</td>
<td>73.08</td>
<td>73.05</td>
</tr>
<tr>
<td>[α]$^{25}$D</td>
<td>70.8</td>
<td>20.1</td>
<td>8.7</td>
<td>26c)</td>
<td>–35.2</td>
<td>b)</td>
</tr>
</tbody>
</table>

$^{a)}$ In C$_6$D$_6$

$^{b)}$ Not assigned

$^{c)}$ At 20°
The transformation of 40 into (+)-valienamine is formally an S\textsubscript{N}2\textsuperscript{'} reaction [684]. There are several methods to effect this transformation stereoselectively. One possibility is transition metal-catalysed allylic amination [685 – 689], amidation [690 – 693], or azidation [694] of an ester of the alcohol 40. A Pd(0)-catalysed azidation of the acetate of 254 was used by Nicotra et al. in their synthesis of 1-epi-valienamine [417]. Transition-metal catalysed allylic aminations are not regioselective, but one would expect a high selectivity in our case, as the double bond in the desired product is more highly substituted (thermodynamic control), and attack at the sterically less hindered centre should also lead to the desired regioisomer (kinetic control).

The stereo- and regiospecific transformation of allylic alcohols into allylic amines is also possible via [3,3]-sigmatropic rearrangements. Trichloroacetimidates of allylic alcohols (formed reversibly from the alcoholates and trichloroacetonitrile) rearrange into allylic trichloroacetamides upon heating (Overman rearrangement) or by transition metal (Hg\textsuperscript{2+}, Pd\textsuperscript{2+}) catalysis [695 – 698]. The Pd(0)-catalysed rearrangement of imidates to amides is stereo-, but not regioselective, as it proceeds via symmetrical allyl-palladium complexes [699]. N-Tosylcarbamates of allylic alcohols (prepared from the alcohols and tosyl isocyanate) undergo a Pd(II)-catalysed allylic rearrangement into N-tosyl allylamines [700]. Ichikawa et al. described the dehydration of O-allylcarbamates to allylic cyanates, which undergo a [3,3]-sigmatropic rearrangement into allylic isocyanates (cf. [701 – 705]). In contrast to the Overman rearrangement, the rearrangement precursor is formed irreversibly, and the rearrangement occurs under very mild conditions (below 0\textdegree). The versatile isocyanate products can be converted into various amine derivatives in situ.

Sarabia\textsuperscript{24}) had attempted the Overman rearrangement [695 – 698] of the trichloroacetimidate derived from 40, but obtained the desired trichloroacetamide derivative of (+)-valienamine in low yields only. The low yields were probably due to the reversibility of the trichloroacetimidation of the tertiary alcohol 40. We therefore turned our attention to the Ichikawa procedure, that had proven useful in a related synthesis of 3-deoxyvalienamine [706].

Treatment of the tertiary allylic alcohol 40 with trichloroacetyl isocyanate in CH\textsubscript{2}Cl\textsubscript{2} at 0\textdegree, followed by hydrolysis with K\textsubscript{2}CO\textsubscript{3} in aqueous MeOH gave 86\% of the carbamate 456 (Scheme 2.3.4). Dehydration of 456 with triphenylphosphine, Et\textsubscript{3}N, and tetrabromomethane in CH\textsubscript{2}Cl\textsubscript{2} at –20\textdegree led to the isocyanate 458 by spontaneous rearrangement of the bona fide cyanate 457. The isocyanate 458 was treated in situ with benzyl alcohol to yield 70\% of the protected (+)-valienamine 459. Alternatively, in situ treatment of 458 with Me\textsubscript{3}Al yielded 77\% of N-acetyl-tetra-O-benzylvalienamine (460) [225]. Its \textsuperscript{1}H- and \textsuperscript{13}C-NMR spectra were
identical to those of an authentic sample\textsuperscript{38}, confirming the (4S)-configuration of 40 and the (6S)-configuration of 441. The vicinal coupling constants for the ring H of 459 ($J_{1,2} = 4.3$ Hz, $J_{2,3} = 7.5$ Hz, $J_{3,4} = 4.7$ Hz) and 460 ($J_{1,2} = 4.1$ Hz, $J_{2,3} = 7.2$ Hz, $J_{3,4} = 4.7$ Hz) indicate an equilibrium of the $^3H_2$ and $^2H_3$ conformers. The vicinal coupling constants of the individual conformers ($^3H_2$: $J_{1,2} = 2.8$ Hz, $J_{2,3} = 4.2$ Hz, $J_{3,4} = 2.8$ Hz; $^2H_3$: $J_{1,2} = 7.8$ Hz, $J_{2,3} = 9.8$ Hz, $J_{3,4} = 4.3$ Hz) were calculated by gas-phase molecular modelling (Macromodel version 6.0, MM3* force-field [707]).

The benzyl carbamate 459 was readily deprotected under Birch conditions [367]. Workup following the procedure of Paulsen and Heiker [415] gave (+)-valienamine (22) in 78% yield as a slightly yellow solid (26% overall yield from 2,3,4,6-tetra-O-benzyl-D-glucopyranose in seven steps). The optical rotation and the $^1$H- and $^{13}$C-NMR spectra of 22 and of its pentaacetate 461 were in complete agreement with the published data [367] [417] [427] [708] [709].

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme2.3.4.png}
\caption{Scheme 2.3.4}
\end{scheme}

\begin{itemize}
\item[a)] CCl$_3$CO-NCO, CH$_2$Cl$_2$, then K$_2$CO$_3$, MeOH/H$_2$O; 86%.
\item[b)] PPh$_3$, Et$_3$N, CBr$_4$, CH$_2$Cl$_2$.
\item[c)] BnOH; 70% of 459 (from 456).
\item[d)] Me$_3$Al; 77% of 460 (from 456).
\item[e)] 459, Na, NH$_3$/THF; 78%.
\item[f)] Ac$_2$O, pyridine; 86%.
\end{itemize}

\textsuperscript{38}) The authentic sample was prepared from validoxylamine A following the protocol of Ogawa and coworkers [225]. We thank Dr. A. G. O'Sullivan, Syngenta, Basel, for a generous gift of validoxylamine A.
2.3.2. Synthesis of the MOM-Protected Glucose-Derived Carbasugar

We next examined the synthesis of the MOM-protected cyclohexene 468 from 2,3,4,6-tetra-O-methoxymethyl-D-glucopyranose (464) (Scheme 2.3.5). 2,3,4,6-tetra-O-methoxymethyl-D-glucopyranose (464) was obtained from benzyl-glucoside [352] [710] by alkylation (NaH, MOMCl, DMF, 56%) and cleavage of the benzyl glucoside 463 under Birch conditions (91%). Catalytic hydrogenolysis of the benzyl glucoside 463 was sluggish. Hydrogenation at 6 bar in the presence of 10% Pd/C in MeOH was incomplete after 5 days, and the pyranose 464 was isolated in poor yield (57%). Also with Pd(OH)2/C or Pd(CF3COO)2 as catalyst the hydrogenation could not be driven to completion. Low yields for the hydrogenolytic cleavage of benzyl-glucosides were previously reported by Achenbach and Witzke [711] and by Krohn and coworkers [352].

The pyranose 464 was transformed into the heptenitol 465 in moderate yield (63%) by treatment with one equivalent of BuLi and then two equivalents of Ph3P=CH2 (prepared from Ph3PCH3Br and BuLi). PCC oxidation of 465 gave the ketone 466 (89%). The highly stereoselective addition of vinylmagnesium bromide to the ketone 466 provided 90% of the diene 467, other products were not isolated. Ring-closing alkene metathesis of 467 in CH2Cl2 in the presence of 0.15 equivalents of Grubbs's catalyst 312 gave the desired cyclohexene 468 (54%). This yield is only slightly lower than the yield of the benzylated 40 (58%). This could either mean that there is no difference between the MOM and the benzyl groups in their influence on the RCM (in keeping with the results of Fukuda et al. [526], see chapter 2.2.3), or that incremental differences of opposite sign cancel out.

39) This work was largely done by N. Leclerc, see27).
The C(7) methylene group in 465 is evidenced in the $^1$H-NMR spectrum by a $ddd$ at 5.77 ppm for H–C(6) and $dm$ at 5.37 ppm and at 5.34 ppm for H$_2$C(7), and in the $^{13}$C-NMR spectrum by the C(6) $d$ at 134.75 ppm and the C(7) $t$ at 120.01 ppm. The constitution of the diene 467 is evidenced by signals for the two vinyl groups in the $^1$H-NMR spectrum. H–C(2) resonates as a $ddd$ at 5.78 ppm, H–C(7) resonates as a $dd$ at 6.16 ppm, H–C(8) resonates as a $dm$ at 5.52 ppm, and H$_2$–C(1) and H’–C(8) resonate as a $m$ at 5.35–5.25 ppm. In the $^{13}$C-NMR spectrum, the C(2) and C(7) $d$ resonate at 135.09 and 139.80 ppm, respectively; the C(1) and C(8) $t$ resonate at 119.66 and 115.95 ppm, respectively. The complexity of the $^1$H-NMR spectrum precluded an assignment of the configuration for 467. It was tentatively assigned as (6$S$), assuming that the addition to the ketone 466 proceeds with the same facial selectivity as the addition to the ketone 442. The complexity of the $^1$H-NMR spectrum of the cyclohexene 468 also precluded the assignment of its configuration. In the $^{13}$C-NMR spectrum, however, the C(4) $s$ resonates at 72.55 ppm, which is close to the value for 40 (72.97 ppm) and different from the value for 254 (75.77 ppm).

Chromatographic purification of the polar MOM-derivatives 463 – 468 was difficult, as the $R_f$ values of main products and by-products were similar for several eluent mixtures tested. The $^1$H-NMR spectra of these compounds were complex, so that information on the constitution was deduced mostly from $^{13}$C and DEPT spectra. Switching from benzyl to

**Scheme 2.3.5**

a) NaH, DMF, then MOMCl; 56%. b) Na, NH$_3$, THF; 91%. c) BuLi, Ph$_3$P=CH$_2$, THF; 63%. d) PCC, CH$_2$Cl$_2$; 89%. e) CH$_2$=CHMgBr, THF; 90%. f) 312, CH$_2$Cl$_2$; 54%.
MOM protecting groups did not improve the efficiency of the carbasugar synthesis from sugars via RCM.

### 2.3.3. Synthesis of Derivatives of the manno-Isomer of (+)-Valienamine from d-Mannose via RCM

For the synthesis of the d-mannose-derived L-gulo-configured cyclohexene 42 (Scheme 2.3.6), we subjected manno-heptenitol 469 [712] to a Moffatt oxidation [713] [714], similarly as described for the synthesis of the gluco-heptenitol 442 [669]. This gave the ketone 470 (87%). Addition of vinylmagnesium bromide to 470 yielded 95% of the diene 471. The diastereoselectivity of this addition was higher than that observed for the addition to 442. Only traces of a byproduct were detected on TLC. The configuration of 471 was assigned tentatively as corresponding to the one of 441.

![Scheme 2.3.6](image)

\[a\) DMSO, DCC, pyridine, CF\(_3\)CO\(_2\)H, toluene; 87\%. \(b\) H\(_2\)C=CHMgBr, THF; 95\%. \(c\) 312, CH\(_2\)Cl\(_2\), r.t.; 89\%.

RCM of 471 in CH\(_2\)Cl\(_2\) in the presence of 0.15 eq. of 312 gave the cyclohexene 42 in 89% yield as a green oil. The higher yield for the RCM of 471 as compared to the one of 441 is presumably due to the different conformational strain of the bicyclic metallacyclobutane intermediates of the cyclisation (Figure 2.3.2). If the metathesis begins by attack of the catalyst at the less hindered C(1)–C(2) double bond and the metallacyclobutane is formed \emph{cis} to the C(6)–OH group (numbering for the dienes) in the bicyclic intermediate, the proximal OBn group of the glucose-derived carbasugar will collide with the RuL\(_n\) moiety, whereas in the mannose-derived carbasugar the proximal OBn group will be \emph{trans} to the RuL\(_n\) moiety.
Remen\textsuperscript{a)} reported the unexpected formation of a 3-methylidene-cyclohexene in the RCM of a arabinose-derived 1,6-diene in toluene at 80° in the presence of 0.15 equivalents of Grubbs's catalyst 312. Subjected to these conditions for 2 d, the mannose-derived 1,7-diene 471 gave mainly re-isolated starting material (83%), the cyclohexene 42 (8.7%), and trace amounts of the enol ether 472 (1.8%) and the $\alpha,\beta$-unsaturated ketones 473 (1.6%) and 474 (1.8%) (Scheme 2.3.7). The enol ether 472 may be formed by double bond migration from 42, the enones may be formed by oxidation of the allylic ethers 42 and 472, respectively. Due to the prolonged reaction times, it remains unclear, if the formation of these products is catalysed by 312 or by degradation products of it. One may consider radical or cationic mechanisms leading to the by-products.

Scheme 2.3.7

\begin{align*}
  \text{471} & \rightarrow \text{42} + \text{472} + \text{473} + \text{474} \\
\text{471} & \rightarrow \text{42} + \text{472} + \text{473} + \text{474} \\
  \text{471} & \rightarrow \text{42} + \text{472} + \text{473} + \text{474} \\
\end{align*}

\textit{a)} 0.15 eq. of 312, toluene, 80°; 83% of 471, 8.7% of 42, 1.8% of 472, 1.6% of 473, 1.8% of 474.

\textsuperscript{a)} Dr. Lubos Remen, see\textsuperscript{25}). A report about this work is not available. This result was only communicated orally!
The C(6)–OH signals of 471 and 441 are nearly isochronous. Their chemical shift is larger than the one for C(6)–OH of 450 (Δδ ca. 0.65 ppm) (Table 2.3.2), indicating a stronger intramolecular H-bond. The IR bands (441 (3.3% in CHCl₃): 3468, 471 (1.5% in CHCl₃): 3462 cm⁻¹; these wavenumbers did not change upon dilution of the samples to 0.5%) agree well with a six-membered intramolecular H-bond to BnO–C(4), and thus with the conformations depicted in Scheme 2.3.3 and Scheme 2.3.6. The chemical shift for C(6)–OH of 450 suggests a H-bond to BnO–C(9) in a five-membered ring. This implies that H₂C(9) of 441 and 471 (but not of 450) are both gauche to the tertiary OH group (as in conformer III (Figure 2.3.1) of 40 and 451). Indeed, smaller (absolute) J(9,9') are observed for 441 and 471 (8.7 Hz) than for 450 (9.3 Hz). Thus, 471 should possess the same configuration at C(6) as 441. In keeping with that, the difference between the optical rotation of 471 and 470 (Δ[α]²⁵_D = 40.7) is very similar to that between 441 and 442 (Δ[α]²⁵_D = 34.5).
Table 2.3.2: Selected $^1$H- and $^{13}$C-NMR (CDCl$_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] and Optical rotations (CHCl$_3$) of 441, 450, 471, and 486.

<table>
<thead>
<tr>
<th></th>
<th>441</th>
<th>450</th>
<th>471</th>
<th>486</th>
</tr>
</thead>
<tbody>
<tr>
<td>H–C(1)</td>
<td>5.30</td>
<td>5.26</td>
<td>5.47–5.42</td>
<td>5.44</td>
</tr>
<tr>
<td>H'–C(1)</td>
<td>5.20</td>
<td>5.25</td>
<td>5.47–5.42</td>
<td>5.43</td>
</tr>
<tr>
<td>H–C(2)</td>
<td>5.83</td>
<td>5.94</td>
<td>6.02–5.91</td>
<td>5.95</td>
</tr>
<tr>
<td>H–C(3)</td>
<td>4.07</td>
<td>4.09</td>
<td>4.05</td>
<td>4.04</td>
</tr>
<tr>
<td>H–C(4)</td>
<td>3.88–3.84</td>
<td>3.74–3.68</td>
<td>3.90</td>
<td>3.86</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>3.88–3.84</td>
<td>3.99</td>
<td>4.07</td>
<td>4.05</td>
</tr>
<tr>
<td>CH–C(6)</td>
<td>3.63</td>
<td>3.74–3.68</td>
<td>3.73</td>
<td>3.72</td>
</tr>
<tr>
<td>CH'–C(6)</td>
<td>3.29</td>
<td>3.28</td>
<td>3.28</td>
<td>3.27</td>
</tr>
<tr>
<td>HO–C(6)</td>
<td>3.74</td>
<td>3.09</td>
<td>3.75</td>
<td>3.79</td>
</tr>
<tr>
<td>J(1,2)</td>
<td>10.3</td>
<td>17.1</td>
<td>a)</td>
<td>17.7</td>
</tr>
<tr>
<td>J(1',2)</td>
<td>17.4</td>
<td>10.6</td>
<td>a)</td>
<td>10.0</td>
</tr>
<tr>
<td>J(2,3)</td>
<td>7.8</td>
<td>7.5</td>
<td>7.5</td>
<td>7.8</td>
</tr>
<tr>
<td>J(3,4)</td>
<td>6.5</td>
<td>4.4</td>
<td>7.2</td>
<td>7.5</td>
</tr>
<tr>
<td>J(4,5)</td>
<td>3.5</td>
<td>5.9</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>J(CH,CH')</td>
<td>8.7</td>
<td>9.3</td>
<td>8.7</td>
<td>8.4</td>
</tr>
<tr>
<td>$\alpha_{	ext{D}}$</td>
<td>35.2</td>
<td>a)</td>
<td>–4.5</td>
<td>a)</td>
</tr>
</tbody>
</table>

a) Not determined
The vicinal coupling constants for the ring H of 42 indicate a $^3H_2$ conformation as in 40 (Table 2.3.1). The chemical shifts for H–C(7), H′–C(7), and C(6) of 42 show a stronger similarity to the values for 40 than to those for 254. In cyclohexanes, carbon atoms carrying an axial substituent absorb at higher field than those with equatorial substituents, and this effect is larger for oxy substituents than for alkyl substituents [715]. Thus, the upfield shift for C(6) of 40 and 42 as compared to 254 agrees with a pseudoaxial tertiary OH group. The assignment of the configuration of 42 was corroborated by a NOE experiment. Upon irradiation at 3.45 ppm (H–C(7) and H′–C(7) at 3.43 and 3.46 ppm), a NOE of 10% was observed for H–C(3), whereas no effect was observed for H–C(2).

The structure of the enol ether 472 (Scheme 2.3.7) is evident from its $^1$H-NMR spectrum where the olefinic proton resonates as a br. $t$ at 4.72 ppm and couples with H$_2$C(2) ($J = 4.4$ Hz), which appear as a br. $d$ at 2.51 and a $dd$ at 2.25 ppm, respectively. The $^1$H-NMR spectrum of the enone 474, displays an olefinic $m$, resonating at 5.73–5.69 ppm. H$_2$C(4) resonate as a $dm$ at 2.89 and as a $dd$ at 2.45 ppm and couple with the olefinic H–C(3), evidencing the position of the double bond. H–C(6) appears as a $s$ at 4.29 ppm, which confirms that the carbonyl group is located at C(1). The constitution of the enone 473 is evidenced by the olefinic $d$ at 6.71 (H–C(3)) and 6.13 ppm (H–C(2)), respectively. The H–C(5) and H–C(6) $d$ resonate as at 4.02 and 4.42 ppm, respectively. The absence of coupling between H–C(6) and the olefinic H and between H–C(5) and the olefinic H corroborates the position of the carbonyl group at C(1) and the position of the double bond. The C=O groups of 473 and 474 give rise to strong IR (CHCl$_3$) bands at 1700 and 1704 cm$^{-1}$, respectively.

By analogy to the synthesis of (+)-valienamine from 40 (Scheme 2.3.4), the allylic alcohol 42 was transformed into the manno-valienamine derivatives 43 and 479 via the Ichikawa rearrangement (Scheme 2.3.8). Treatment of 42 with trichloroacetyl isocyanate in CH$_2$Cl$_2$, followed by hydrolysis (K$_2$CO$_3$, aq. MeOH) gave the carbamate 476 (93%). Dehydration of the carbamate and spontaneous rearrangement of the bona fide cyanate 477 afforded the isocyanate 478, which was transformed in situ into the acetamide 43 by treatment with Me$_3$Al (95%) or into the methylcarbamate 479 by treatment with MeOH (91%).
a) CCl$_3$CO-NCO, CH$_2$Cl$_2$, then K$_2$CO$_3$, MeOH/H$_2$O; 93%. b) PPh$_3$, Et$_3$N, CBr$_4$, CH$_2$Cl$_2$.

The Pd(0)-catalysed allylic azidation of the acetate 475 (obtained from 42 in 73% yield) under the conditions reported by Nicotra (Pd(Ph$_3$P)$_4$, THF, aq. NaN$_3$) [417] was very sluggish. TLC indicated only little consumption of the starting material after 4 d.

The vicinal coupling constants for the ring H atoms of 43 ($J_{1,2} = 4.7$, $J_{2,3} = 2.2$, $J_{3,4} = 6.9$ Hz) and 479 ($J_{1,2} = 4.4$, $J_{2,3} = 2.2$ Hz, $J_{3,4}$ not determined) indicate an equilibrium between the $^3H_2$ and $^2H_3$ conformers. The calculated coupling constants (Macromodel version 6.0, MM3* force field) for the individual conformers are $J_{1,2} = 7.6$, $J_{2,3} = 2.1$, $J_{3,4} = 2.2$ Hz for the $^3H_2$, and $J_{1,2} = 2.1$, $J_{2,3} = 2.2$, $J_{3,4} = 9.1$ Hz for the $^2H_3$ conformer.

2.3.4. Synthesis of an Orthogonally Protected d-Mannose-Derived Carbasugar

In this chapter I describe an exploratory synthesis which was not optimised, as the project was terminated. A derivative of the mannose-derived cyclohexene 42 with orthogonal protection of C(1)–OH (resulting from C(2)–OH of the starting material) would be a very useful intermediate for the synthesis of carbocyclic GlcNAc analogues, or for introducing other
functionality at C(1). As attempts to prepare such an orthogonally protected derivative of 42 by selective deprotection were not successful [222][27], we decided to investigate the synthesis of an orthogonally protected carbasugar from a manno-pyranose orthogonally protected at C(2)–OH, following the route established for the synthesis of 42 (Scheme 2.3.6).

The 4-methoxybenzyl (4-methoxyphenylmethyl) group was chosen as the protecting group for C(2)–OH (mannose numbering). It has similar properties as the benzyl group and permits the analogous transformations to those employed in the synthesis of the tetrabenzyl derivative 42. However, it is possible to remove the 4-methoxybenzyl group by oxidative methods without affecting the benzyl groups [716]. Thus, the starting material for the Wittig methylenation would be 2-O-(4-methoxyphenylmethyl)-3,4,6-tris-O-benzyl-mannopyranose (483, Scheme 2.3.9) which in turn should be available from allyl-tris-3,4,6-O-benzyl-mannopyranoside (481 [717]) by alkylation at C(2) and acetal hydrolysis.

Remen[25] had previously prepared 483 from 481 [718], but mentioned that he was unable to effect the Wittig methylenation of 483 (no details are available). However, there was sufficient precedent for the successful methylenation of mannopyranoses [649] [712] [719] to justify a reinvestigation of this transformation. Following the route established by Remen, the allyl mannoside 481 was treated with NaH and 4-methoxybenzyl chloride to afford the orthogonally protected mannoside 482 (98%) (Scheme 2.3.9). The allyl mannoside 482 was deallylated selectively by treatment with PdCl2 in MeOH (85%) [720] [721].

Treatment of the pyranose 483 with four eq. of Ph3P=CH2 in THF at –78°, followed by heating under reflux for 50 min. gave 484 in 36% yield. This yield was improved to 44% by shortening the heating time to 12 min. At a lower temperature (50°) the reaction was slow, and a complex mixture was obtained. From the reaction of 483 with Ph3P=CH2 in THF at –78° to reflux, no significant amount of by-products was isolated (totally 12.2 wt%); on TLC no further by-products were detected, except for a "baseline spot". In order to determine whether the basic conditions of the Wittig alkenylation led to decomposition of the starting material 483 or of the product 484, solutions of 483 and 484 in THF were treated with two eq. of BuLi at 0° to r.t. TLC indicated the formation of complex mixtures after 40 min. These mixtures were more complex than any of those formed upon alkenylation and, therefore, base-catalysed decomposition of 483 and 484 appears not to be the key problem of this methylenation.

The yield was worse when the Wittig methylenation was performed under several other conditions:

- Treatment of the pyranose 483 with two eq. of Ph3P=CH2 in THF at –78° to r.t. gave the desired heptenitol 484 in 26% yield and an unidentified, impure byproduct (12 wt%).
probably a diene (\(^1\)H-NMR signals for four olefinic protons) resulting from HOBN elimination.

- Pretreatment of \(483\) with one eq. of BuLi (cf. [712]), followed by treatment with two eq. of Ph\(_3\)P=CH\(_2\) in THF at \(-78^\circ\) to r.t. did not improve the result; according to TLC it led to the formation of several by-products.

- Dropwise addition of a soln. of the pyranose \(483\) in THF to a boiling soln. of Ph\(_3\)P=CH\(_2\) in THF gave the alkene \(484\) in 38\% yield.

- The reaction of \(483\) with Ph\(_3\)P=CH\(_2\) in toluene at \(-78^\circ\) to 90\° or at 0\° to 60\° was sluggish, and led to complex mixtures.

- Treatment of \(483\) with Ph\(_3\)P=CH\(_2\) in THF and in the presence of 0.5 eq. of Bu\(_3\)SnCl (cf. [722]) was sluggish (slow, incomplete consumption of the starting material, formation of several products).

Moffatt oxidation of the heptenitol \(484\) was sluggish and 64\% of the starting material was re-isolated, along with a complex mixture, but \(485\) was not obtained. In contrast, the Swern oxidation proceeded smoothly, providing the ketone \(485\) in quantitative yield. Addition of vinylmagnesium bromide to \(485\) in THF gave the diene \(486\) (96\%); no byproduct was detected. Ring-closing alkene metathesis of \(486\) in the presence of 0.3 eq. of Grubbs's catalyst \(312\) in CH\(_2\)Cl\(_2\) afforded the cyclohexene \(60\) (49\%) and the starting material \(486\) (45\%). Further optimisations were not attempted. The project was halted at that time, and the de novo synthesis of carbasugars was examined (see Chapter 4).
2.3.9 Scheme

Scheme 2.3.9

\[
\begin{align*}
480 \quad R &= H \\
481 \quad R &= \text{All}
\end{align*}
\]

\[
\begin{align*}
482 \quad b) \\
483 \quad c) \quad d)
\end{align*}
\]

\[
\begin{align*}
484 \quad e) \\
485 \quad f) \quad g) \\
60
\end{align*}
\]

\begin{itemize}
  \item \(a)\) AllOH, CSA; 100%.
  \item \(b)\) NaH, DMF, then MPMCl; 98%.
  \item \(c)\) PdCl\(_2\), MeOH; 85%.
  \item \(d)\) Ph₃P=CH\(_2\) (prepared in THF from Ph₃PMeBr and 1.6M BuLi in Hexane), THF, \(-78^\circ\text{C}\) to reflux; 44%.
  \item \(e)\) (COCl\(_2\)), DMSO, Et\(_3\)N, CH\(_2\)Cl\(_2\); 100%.
  \item \(f)\) CH\(_2\)=CHMgBr, THF; 96%.
  \item \(g)\) 312, CH\(_2\)Cl\(_2\); 49% of 60, 45% of 486.
\end{itemize}

The \(^1\)H-NMR spectra of the compounds 486 and 60 are nearly identical to the spectra of the tetrabenzyl derivatives 471 and 42 (Table 2.3.1 and Table 2.3.2).

In conclusion, the orthogonally protected mannose-derived cyclohexene 60 was prepared in six steps and an overall yield of 16%. The low overall yield is due to the low yield of the Wittig methylation and to the sluggish RCM. The RCM might be improved by using the second-generation Grubbs's catalyst, which was not commercially available at that time. As for the Wittig reaction, other methylation procedures might lead to better results.

2.3.5. Synthesis of Carbocyclic Analogues of d-Arabinose via RCM

Leclerc\(^{27}\) worked out a synthesis of the carbafuranose 424 from 2,3,5-tri-O-benzyl-D-arabinofuranose in four steps and 47% yield, using RCM as the key step [222], but while this work was in progress, the synthesis of the carbafuranoses 425 and 426 from 2,3,5-tri-O-benzyl-D-arabinofuranose were reported by Sellier et al. [643] and by Seepersaud et al. [642], using essentially the same series of transformations (see chapter 2.2.6, Scheme 2.2.30). The
most efficient RCM was that of the TMS-derivative 422 (Scheme 2.3.10) in the presence of 0.1 eq. of Schrock's catalyst 310 in benzene, yielding 90% of the cyclohexene 425 (Table 2.3.3, Entry 4) [643]. The second-generation ruthenium catalysts were not available at the time of these studies.

Scheme 2.3.10

\[
\begin{align*}
\text{421} & \quad R = H \\
\text{422} & \quad R = \text{TMS} \\
\text{423} & \quad R = \text{Bn} \\
\text{424} & \quad R = H \\
\text{425} & \quad R = \text{TMS} \\
\text{426} & \quad R = \text{Bn}
\end{align*}
\]

(a) See Table 2.3.3.

Table 2.3.3: RCM of the Dienes 421, 422, and 423.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diene</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Yield</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>421</td>
<td>0.15 eq. of 312</td>
<td>CH₂Cl₂, r.t.</td>
<td>63%</td>
<td>[222]</td>
</tr>
<tr>
<td>2</td>
<td>421</td>
<td>0.2 eq. of 312</td>
<td>CH₂Cl₂, reflux</td>
<td>29%</td>
<td>[643]</td>
</tr>
<tr>
<td>3</td>
<td>422</td>
<td>0.2 eq. of 312</td>
<td>CH₂Cl₂, reflux</td>
<td>0%</td>
<td>[643]</td>
</tr>
<tr>
<td>4</td>
<td>422</td>
<td>0.1 eq. of 310</td>
<td>benzene, r.t.</td>
<td>90%</td>
<td>[643]</td>
</tr>
<tr>
<td>5</td>
<td>423</td>
<td>0.1 eq. of 312</td>
<td>CH₂Cl₂, r.t.</td>
<td>35%</td>
<td>[642]</td>
</tr>
<tr>
<td>6</td>
<td>423</td>
<td>0.2 eq. of 310</td>
<td>CH₂Cl₂, r.t.</td>
<td>87%</td>
<td>[642]</td>
</tr>
</tbody>
</table>
2.4. Conclusions

We have established a highly efficient synthesis of carbocyclic analogues of D-glucopyranose, D-mannopyranose, and D-arabinofuranose. The cyclohexenol 40 is a versatile chiral intermediate and allowed the currently most efficient synthesis of (+)-valienamine in 26% overall yield (seven steps) from 2,3,4,6-tetra-O-benzyl-D-glucopyranose. In comparison, Fukase and Horii obtained (+)-valienamine in 12% overall yield (eight steps) from 2,3,4,6-tetra-O-benzyl-gluconolactone [367], and Nicotra et al. obtained (+)-valienamine in an overall yield of 12.5% (10 steps) from methyl 2,3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside [417] (see [34] for a comparison of all (+)-valienamine syntheses). Similarly, 42 allowed an efficient synthesis of derivatives of the manno-analogue of (+)-valienamine. The cyclohexenols 40 and 42 have been used by Boehm in the synthesis of 1-epi-valienamine derivatives, of 2,3,4,6-tetra-O-benzyl-α-D-5a-carba-glucopyranose, and of pseudo-disaccharides [723]. Remen25) has scaled up the preparation of the cyclopentene 424 and applied it in the synthesis of potential glycosidase inhibitors.

In these carbapyranose syntheses via RCM the C(6) hydroxymethyl group of the starting hexopyranose is transformed into the (protected) hydroxymethyl side chain of the product. The additional C of the cyclohexene ring is introduced by the addition of vinylmagnesium bromide to the heptenulose intermediate before the RCM. The high stereoselectivity of this addition results in a transfer of the chirality of C(5) of the hexopyranose starting material into the cyclohexene product. Thus, for carba-hexopyranoses, the synthesis via RCM is more efficient than syntheses via the Ferrier rearrangement, as demonstrated by the high-yielding synthesis of (+)-valienamine (this work) and by syntheses of a few carbapyranoses [723]. The Ferrier rearrangement leads to unbranched carbapyranoses, and C(6) of the starting pyranose is incorporated into the cyclohexane ring. Introduction of a (protected) hydroxymethyl side chain requires several steps and often proceeds with low diastereoselectivity. However, the cyclohexanones prepared by the Ferrier rearrangement allow the addition of a large variety of nucleophiles [262] [266].

It is clear that the synthesis of carbasugars via RCM is not universally the best method, as the high price for the catalyst and the requirement of chromatographic purification of all intermediates for the time being limits this route to laboratory and kilogram scales. Also, the carbasugars 40, 42, and 424 are not appropriate intermediates for the synthesis of unbranched carbasugars. Thus, the synthesis of carbasugars via RCM complements the other available methods. The specific method of choice depends on the targeted carbasugar. For ketones like 52 and 162 the synthesis via intramolecular Horner-Wadsworth-Emmons reaction [366] [367]
will be more efficient. For the synthesis of unbranched aminocyclitols, the *Ferrier* rearrangement provides the appropriate intermediates and will remain the method of choice. For the synthesis of multi-kilogram quantities of some carbasugars, *Diels-Alder* and biocatalytic approaches appear attractive. For the synthesis of aminocyclopentitols, *Bernet* and *Vasella's* synthesis by intramolecular nitrone addition remains the method of choice.
3. Part 2: Synthesis of Carbasugar-Derived \textit{spiro}-Diaziridines and \textit{spiro}-Aziridines, of 1-\textit{epi}-Validamine, and of 5a-Amino-5a-carba-pyranoses

3.1. Introduction

The goal of this part of my thesis was to synthesise the carbasugar-derived \textit{spiro}-diaziridines \textbf{45} and the \textit{spiro}-aziridines \textbf{46} and \textbf{47} (Scheme 3.1.1), to evaluate their activity against glycosidases, and to compare this activity to that of 1-\textit{epi}-validamine (\textbf{48}), validamine (\textbf{12}), and the aminocyclopentitols \textbf{35} and \textbf{36}. I also intended to synthesise and evaluate the 5a-amino-cyclohexitols \textbf{49} and \textbf{50}.

Scheme 3.1.1

At the beginning of this project, there were no known diaziridine glycosidase inhibitors. Some aziridine (but no \textit{spiro}-aziridine) glycosidase inhibitors are known [59]. The aziridine \textbf{492} (Figure 3.1.1) inhibits the $\alpha$-galactosidase from coffee beans irreversibly ($K_i = 7 \mu$M) [724]. Conduritol aziridine \textbf{493} is a weak irreversible inhibitor of the $\beta$-glucosidase from \textit{Alcaligenes faecalis} ($K_i = 3.0$ mM) and the $\alpha$-glucosidase from yeast ($K_i = 9.5$ mM) [725].
Tatsuta et al. prepared the cyclophellitol analogue **494**, a strong inhibitor of the β-glucosidases from almonds (IC₅₀ = 0.22 µg/ml, i.e. 1.2 µM), and the 1,6-epi-cyclophellitol analogue **495** [118] [119]. No inhibition data were reported for the potential glycosidase inhibitors **496** [726], **497** [727], and **498** [728]. The [3.1.0]bicyclic aziridine (±)-**500** is a reversible, competitive inhibitor of the α-mannosidase from jack beans (Kᵢ = 8.0 µM), whereas (±)-**499** does not inhibit several α- and β-glycosidases.

Figure 3.1.1: Aziridine Glycosidase Inhibitors.

1-Epi-validamine (**48**, Scheme 3.1.1) is a competitive inhibitor of pig kidney trehalase (Kᵢ = 1.2 µM) [224]. In a comprehensive literature search, no inhibition data for this compound against the enzymes studied here were found. Likewise, no inhibition data for 5a-aminocyclohexitols like **49** and **50** (Scheme 3.1.1) were found in the literature. Some 5a-amino-1-deoxycarbapyranoses were prepared as aminocyclitol analogues, but no inhibition data were given [235].

### 3.1.1. Synthesis of Diaziridines

Diaziridines were prepared by N–N-bond formation (intramolecular nucleophilic substitution, elimination of N₂ from Δ²-tetrazolines, or intramolecular nitrene insertion into an NH bond), by C–N-bond formation (intramolecular addition or substitution from hydrazones or hydrazines, or electrocyclisation from azomethine imines), by addition of carbenes to azo-
compounds, or from diazirines by selective reduction of, or nucleophilic addition to the N−N double bond (Scheme 3.1.2) (for reviews, see [729 – 732]). The addition of nitrenes to imines might also lead to diaziridines, but has not yet been successful (for an example where such an addition was attempted with a nitrene generated from ethyl azidoformate, see [733]).

Scheme 3.1.2

Most diaziridines were prepared by N−N bond formation by intramolecular substitution of an N,N-acetal bearing a leaving group on one of the N. Such N,N-acetals are generated from a carbonyl compound, an amine, and a nitrenoid (for reviews, see [729] [731] [732] and the PhD thesis of Briner [734]). The various procedures differ mainly by the order of mixing the three components. The first diaziridine syntheses involved the condensation of a ketone and ammonia in the presence of Cl₂ or tBuOCl (in situ formation of ClNH₂ as the nitrenoid) in the gas phase (reported by Abendroth and Henrich [735]) or in the liquid phase (reported by Paulsen [736] and by Schmitz [227] (see also [737])), or the condensation of an imine and a nitrenoid (e.g. a haloamine or hydroxylamine-O-sulfonic acid [738] [739]). The synthesis of diaziridines by the condensation of a ketone with ammonia (or an amine) in water, followed by treatment of the resulting imine with hydroxylamine-O-sulfonic acid [227] [228] is known as the Schmitz method. A range of 3,3-dialkyl diaziridines was made in this way [731]. The scope of this method is limited by the failure of anilines to provide N-aryl diaziridines. The diaziridines formed from aldehydes, ammonia, and hydroxylamine-O-sulfonic acid condense with additional aldehyde and ammonia to give 1,3,5-triazabicyclo[3.1.0]hexanes, from which the 3-alkyldiaziridines may be generated only in poor yield by acid hydrolysis [731].

For the synthesis of sterically hindered diaziridines it is advantageous to use an N-alkyl imine.
instead of a ketone as the starting material in order to avoid the formation of water in the reaction medium which results in the equilibration of imine and water to ketone and ammonia [227] [740]. The synthesis of diaziridines from imines proved particularly useful in the formation of diaziridines in the neopentylic 17-position of steroids (such as 502) [741] [742] (Scheme 3.1.3).

Scheme 3.1.3

![Scheme 3.1.3](image)

a) NH₃, MeOH, then NH₂SO₃H; 58% [741]. b) Br₂, Et₃N, CHCl₃, then NaI, acetone; 97% [741].

2-Hydrazicamphane (506, Scheme 3.1.4) is an intermediate in the synthesis of 2-azicamphane (507), which is of interest as a carbene precursor. The diaziridine 506 could not be obtained by the standard Schmitz method. However, it was prepared from the corresponding imminium salt in a satisfactory yield (48%) [743] (Scheme 3.1.4). The reaction of N-trimethylsilylimines of non-enolisable aldehydes provided 3-alkyldiaziridines [744], which were difficult to obtain from the aldehydes themselves by the standard procedure.

Scheme 3.1.4

![Scheme 3.1.4](image)

a) i. NH₂OH; 90%; ii. NaNO₂, H₂SO₄; iii. NH₃, then HCl; 60% (two steps) [743]. b) NH₂OSO₃H, NH₃, MeOH, H₂O [743]. c) I₂, Et₃N, MeOH; 48% (two steps) [743].

A complementary diaziridine synthesis is based on the addition of ammonia or primary
amines to \(N\)-chloroimines or ketoimine-\(O\)-sulfonates [729] [745 – 747]. This method is useful in the preparation of diaziridines with electron-withdrawing C(3)-substituents [731], \(e.g.\) 3-trifluoromethyl diaziridines [748] and diaziridine-3,3-dicarboxylates [749]. Oxime sulfonates without electron withdrawing groups undergo a Beckmann rearrangement in competition with diaziridine formation. Aldoxime-\(O\)-sulfonic acids and \(O\)-acyl aldoximes decompose to nitriles and the corresponding sulfonic or carboxylic acids, but triethylammonium salts of aldoxime-\(O\)-sulfonic acids are stable and were converted in moderate yield to diaziridines by treatment with ammonia or primary amines [750].

Both the Schmitz and the oxime sulfonate syntheses of diaziridines proceed via a derivative of an \(N, N\)-acetal, which is formed by nucleophilic addition of a nitrenoid to an imine, or by nucleophilic addition of an amine to an oxime ester, respectively (Scheme 3.1.5). An intramolecular substitution then provides the diaziridine. Cyclisation of the aminal intermediate via a nitrene (formed by \(\alpha\)-elimination) was discussed in earlier work [739], but can be excluded, as optically active diaziridines were obtained from oxime esters of camphorsulfonic acid, evidencing that the sulfonylate leaving group participates in the cyclisation step [751].

**Scheme 3.1.5**

![Scheme 3.1.5](https://example.com/scheme.png)

3,3-Disubstituted diazirines are generally prepared by oxidation of diaziridines with I₂ in the presence of Et₃N or Me₃N [752] [753], or Ag₂O [227]. In earlier examples, HgO, KMnO₄, dichromate, cupric salts, Br₂, \(t\)BuOCl, or chloramine were used as oxidant [729] [731]. 3-Halo-3-alkyl- and 3-halo-3-aryl-diazirines are prepared by Graham’s method which involves treatment of alkyl or aryl amidines with sodium hypochlorite or hypobromite [754]. The reduction of tetrafluoroformamidine and pentafluoroguanidine with ferrocene yielded 3,3-difluorodiazirine and 3-(difluoramino)-3-fluorodiazirine [755]. Electrocyclisation of diazoacetamides by irradiation with visible light provided 3-aminocarbonyldiazirines [756]. For reviews on diazirine synthesis, see [729] [731] [732] and the PhD thesis of Briner [734].
Diaziridines were also prepared by several other methods. In the remainder of this chapter I will illustrate these methods by providing a few examples. For comprehensive reviews, see [729] [731] [732] and the PhD thesis of Briner [734].

The formation of the explosive 1,2,3,3-tetrafluorodiaziridine (509) and 1,2,3-trifluoro-3-difluoroaminodiaziridine (511) from tetrafluoroamidine and pentafluoroguanidine by treatment with KF, CsF or RbF (Scheme 3.1.6) [757] presumably proceeded by intramolecular nucleophilic N-N bond formation.

### Scheme 3.1.6

\[
\begin{align*}
\text{FF} \text{NF} & \quad \text{a)} \quad \text{FF} \text{NF} \\
\text{F}_2\text{N} & \quad \text{508} \\
\text{F} & \\
\text{NF} \text{F}_2\text{N} & \quad \text{b)} \quad \text{NF} \text{F}_2\text{N} \\
\text{F} & \\
\text{F} \text{NF}_2\text{N} & \quad \text{510} \\
\text{F} & \\
\text{F} \text{NF}_2\text{N} & \quad \text{511}
\end{align*}
\]

\(\text{a)}\) KF, CF(\text{NF}_2)_2; not isolated [757]. \(\text{b)}\) RbF; 25% [757].

Photolysis of the \(\Delta^2\)-tetrazolines 512 provided in good yields (60–70%) the \(N\)-phenyldiaziridines 513 (Scheme 3.1.7) [758], which are difficult to obtain by other methods [729]. The \(\Delta^2\)-tetrazolines were prepared from 1-methyl-5-phenyl- or 1,5-diphenyl-5-tetrazole by methylation at N(4) and NaBH₄ reduction.

### Scheme 3.1.7

\[
\begin{align*}
\text{R} \quad \text{N} \quad \text{N} & \quad \text{hv} \quad \text{R} \quad \text{N} \\
\text{H} \quad \text{N} \quad \text{N} & \quad \text{512} \\
\text{H}_3\text{C} & \quad \text{513}
\end{align*}
\]

Photolysis of the amino azide 515 (Scheme 3.1.8), obtained from hexafluoroisopropylidene imine (514) by addition of hydrazoic acid, led to the diaziridine 517 (43%), presumably via the \(\alpha\)-amino nitrene 516 [759]. Pyrolysis of 515 gave the hydrazone 518 as the main product.
(60%) and only 11% of the diaziridine.

**Scheme 3.1.8**

\[
\begin{align*}
\text{F}_3\text{C} & \quad \xrightarrow{a)} \quad \text{F}_3\text{C} & \quad \xrightarrow{b)} \quad \left[ \begin{array}{c}
\text{F}_3\text{C} \\
\text{N} \quad \text{N} \\
\text{F}_3\text{C} \\
\text{N} \quad \text{N} \\
\text{F}_3\text{C}
\end{array} \right] \\
514 & \quad \xrightarrow{a)} \quad 515 & \quad \xrightarrow{b)} \quad 516 & \quad \xrightarrow{517} \quad 518
\end{align*}
\]

*a) HN₃, CH₂Cl₂; 52% [759]. b) hν or Δ; see text [759].

The reaction of benzaldehyde with methylhydrazine and diborane in the presence of acetic acid gave the diaziridine 520 (60%) (Scheme 3.1.9) [760]. The reaction was proposed to proceed via the carbinolamine 519 [760]. This might cyclise by an S_N1-like intramolecular substitution.

**Scheme 3.1.9**

\[
\begin{align*}
\text{PhCHO} & \quad + \quad \text{H}_2\text{N}–\text{NHCH}_3 \quad \xrightarrow{a)} \quad \left[ \begin{array}{c}
\text{Ph} \\
\text{H} \quad \text{N} \quad \text{N} \\
\text{H} \quad \text{H} \\
\text{C} \\
\text{NCH}_2\text{Ph}
\end{array} \right] \\
& \quad \xrightarrow{519} \quad \text{Ph} & \quad \xrightarrow{520}
\end{align*}
\]

*a) BH₃, AcOH, THF; 60% [760].

Electrocyclisation of the azomethine imine 521 upon irradiation with sunlight at –80° gave the diaziridine 522 (70%) (Scheme 3.1.10) [761]. An analogous electrocyclisation of iminopyridinium ylides to 1,7-diaza-bicyclo[4.1.0]heptanes is the first step in the
photochemical ring-expansion of iminopyridinium ylides to 1,2-diazepines [762].

Scheme 3.1.10

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C} \quad \text{N} \\
\text{H}_3\text{C} \\
\end{array}
\quad \xrightarrow{\text{a)}}
\quad
\begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C} \quad \text{O} \\
\text{H}_3\text{C} \\
\end{array}
\]

521

522

\(a) \text{hv, CHCl}_3, \text{MeOH; 70\% [761].}\)

The reaction of diazomethane with diethyl azodicarboxylate leads to oxadiazolines (1,4-addition), and not to diaziridines (Scheme 3.1.11) [731] [763] [764].

Scheme 3.1.11

In contrast, the addition of ethyl diazoacetate to 4-phenyl-1,2,4-triazolin-2,4-dione (523, \(R = \text{Ph}\)) provided the diaziridine 524 (\(R = \text{Ph}\)) in nearly quantitative yield (Scheme 3.1.12) [765]. A range of derivatives of 524 was prepared by the reaction of alkyl diazoacetates with 4-substituted 1,2,4-triazolin-2,4-diones [766]. Because of the mild reaction conditions (0°), it was proposed that the reaction proceeded by a 1,3-dipolar cycloaddition of the diazoacetate followed by N2-elimination, rather than by addition of a free carbene (its formation generally requiring temperatures above 100°).
Some diaziridines were prepared from diazirines by reduction with sodium amalgam or with one equivalent of hydrogen in the presence of Pd/C, or by addition of Grignard reagents [227] [763]. These reactions are, however, of limited use for the preparation of 3,3-dialkyldiaziridines, as 3,3-dialkyldiazirines are usually prepared by oxidation of the corresponding diaziridines.

3.1.2. Properties of Diaziridines

The nitrogen substituents (and also the nitrogen lone pairs) of diaziridines are usually trans oriented unless the molecular skeleton restricts the diaziridine moiety to a cis configuration (as in 1,5-diazabicyclo[3.1.0]hexanes) [767]. The 1,2-cis configuration is destabilised by n-n interaction of the nitrogen lone pairs and by steric interactions of the N substituents [767]. An exception is 1,2-dimethyl-3-tertbutyldiaziridine, for which the 2-c-3-t configuration A (Scheme 3.1.13) dominates over the 1-t configuration B in water (2:1 ratio of A:B; in CHCl₃ the ratio is 1:2) [768]. Steric interactions between the methyl groups and the tertbutyl group destabilise the configuration B; in water, the repulsive n-n interaction between the nitrogen lone pairs is reduced by hydrogen bonding and also the higher solvent polarity might stabilise the more polar configuration A [768].
ergo via the cis diaziridine [767]. The inversion barrier $\Delta G^\neq$ is larger than 23 kcal/mol (as a rule, 22–28 kcal/mol) [769] [770]. This has allowed the isolation of pure diastereoisomers of diaziridines [771], and of the pure enantiomers of $C_2$-symmetric diaziridines with only the N atoms as chiral centres [751] [772].

Diaziridines are weak bases as illustrated by the following $pK_{HA}$ values (acetone): 3,3-pentamethylenediaziridine 4.6; 1-methyl-3,3-pentamethylenediaziridine 5.4; 1-butyl-3,3-pentamethylenediaziridine 6.4 [773]. Although they structurally resemble N,N-acetals, diaziridines are stable even in hot aqueous bases, and hydrolysis with dilute acids at room temperature requires long reaction times (hours for 3,3-dialkyldiaziridines, days for 3-monoalkyldiaziridines, weeks for diaziridines derived from formaldehyde) [227] [729]. Some diaziridines were extracted from organic solvents with aqueous mineral acids and regenerated by the action of a base [763]. The reason for the relative stability of diaziridines is that the N lone pair is at an angle of 60° with respect to the ring plane, and therefore cannot participate in the cleavage of the C–N bond by delocalising electrons into the $\sigma^*$ orbital of this bond [774] (cf. [79]). Nevertheless, the hydrolysis of diaziridines made their purification difficult or impossible in some cases [752].

3.1.3. Carbohydrate-Derived Diaziridines and Diazirines

Lehmann and coworkers prepared a range of pyranoside-derived diazirines (Scheme 3.1.14) with the azi substituent on C(6), on the aglycon of O, S, and C glycosides, and in one case with the azi substituent spiro-linked to C(4) [126] [775 – 781]. These diazirines were prepared from the corresponding ketones which were transformed into diaziridines by the Schmitz method. The crude diaziridines were oxidised with I$_2$ and Et$_3$N. The resulting diazirines were used to photolabel glycosidases. The spiro-diazirine 531 was prepared from the trimethylsilylated uloside 529 via the spiro-diaziridine 530 in 13% yield [782] [783]. The diaziridine was not purified. The trimethylsilyloxy groups were cleaved in parallel to the diaziridine formation, but they were crucial for the formation of the diaziridine. Thus, treatment of the free uloside with NH$_3$ and hydroxylamine-O-sulfonic acid in MeOH led to a number of compounds, none of which could be oxidised to the desired diazirine [783]. Thieme assumed that the basic reaction conditions led to decomposition of the unprotected uloside, and that the role of the trimethylsilyloxy groups of 529 was to protect the uloside against decomposition [783].
Vasella and coworkers prepared pyranosylidene- and furanosylidene spiro-diaziridines and spiro-diazirines [784 – 815]. The diaziridines, which are the first examples of 3-alkyl-3-alkoxydiaziridines, were prepared in high yield by the reaction of [(glycopyranosylidene)amino]methanesulfonates with a saturated solution of NH$_3$ in MeOH. For example, the glucose-derived diaziridine 533 (Scheme 3.1.15) was obtained in 82% yield from the oxime methanesulfonate 532 (prepared from tetra-$O$-benzylglucuronolactone oxime). The reaction of the corresponding glycosylidene imine (generated in situ by deoxygenation of the hydroximolactone) with hydroxylamine-$O$-sulfonic acid in MeOH did not furnish a diaziridine. The glycosylidene diaziridines were oxidised with Et$_3$N (or the more volatile Me$_3$N) and I$_2$ to glycosylidene diazirines (e.g. 534, 91%). These diazirines – by the virtue of being precursors of glycosylidene carbenes – are mild, selective glycosidation agents [815], and have recently been used e.g. for the glycosidation of C$_{60}$ fullerene [792] [803], and of
TiO$_2$ surfaces [810], and for the synthesis of glycosylborinates, -boranes, and -alanes [812].

**Scheme 3.1.15**

\[ \text{Scheme 3.1.15} \]

\[ \text{532} \quad \text{a)} \quad \text{533} \quad \text{b)} \quad \text{534} \]

\[ a) \text{NH}_3, \text{MeOH, r.t.; 82\% [784].} \quad b) \text{I}_2, \text{Et}_3\text{N, MeOH; 91\% [784]} \]

The synthesis of the free diaziridine 539 and the diazirine 540 was briefly examined by Weber (Scheme 3.1.16) [223]. The triethylsilyl protected lactone oxime mesylate 536 (obtained from the lactone oxime 535 in three steps and 59\% yield) did not react with NH$_3$ in methanol, 2,2,2-trifluoroethanol, or 2-methoxyethanol at temperatures of up to 45°, while the triflate 537 (obtained from 535 in three steps and 55\% yield) decomposed rapidly. Treatment of the unprotected lactone oxime mesylate 538 (obtained in 76\% yield from 536) with NH$_3$ in MeOH at 25° gave the crude diaziridine 539 in yields up to 30\%, but purification was not straightforward. Finally, treatment of the acetyl protected lactone oxime triflate 541 with NH$_3$ in CH$_2$Cl$_2$/MeOH gave the acetyl protected diaziridine 542 in 71\% yield. Hydrolysis of 542 (NH$_3$, MeOH, H$_2$O) and crystallisation of the crude product from MeOH gave 539 in 72\% yield as a white solid. This diaziridine was rather unstable; in aqueous solution it decomposed within hours. Oxidation of 542 gave a mixture of D-glucose and methyl $\alpha$- and $\beta$-D-glucosides, most probably via the diazirine 540.
Scheme 3.1.16

\[ \text{Scheme 3.1.16} \]

\[ \text{Scheme 3.1.16} \]

\[ 535 \quad R^1 = R^2 = H \]
\[ 536 \quad R^1 = \text{TES}, R^2 = \text{Ms} \]
\[ 537 \quad R^1 = \text{TES}, R^2 = \text{Tf} \]

\[ a) \text{HF, pyridine, THF; } 76\% \text{ from } 536 \text{ [223].} \]
\[ b) \text{NH}_3, \text{MeOH, 25}\degree; 31\% \text{ of crude } 539 \text{ [223].} \]
\[ c) \text{NH}_3, \text{MeOH, CH}_2\text{Cl}_2, -20\degree; 71\% \text{ [223].} \]
\[ d) \text{NH}_3, \text{MeOH, H}_2\text{O, 25}\degree; 72\% \text{ [223].} \]
\[ e) \text{I}_2, \text{Et}_3\text{N, H}_2\text{O, MeOH; mixture of D-glucose and methyl } \alpha-\text{ and } \beta-\text{D-glucopyranoside formed via bona fide } 540 \text{ (yield not given) [223].} \]

3.1.4. Previous Work Directed at the Synthesis of Carbasugar-Derived spiro-Diaziridines

Birault\(^{30}\) had previously attempted the synthesis of carbasugar-derived spiro-diaziridines without success. The reaction of the gluco- and ido-configured ketones 543 and 546 (Scheme 3.1.17, prepared in a multi-step synthesis from D-glucose, see Scheme 2.1.22) with NH\(_3\) and hydroxylamine-\(O\)-sulfonic acid in MeOH did not provide diaziridines. Only the starting materials were isolated from the reaction mixture. Treatment of the gluco-configured oxime methanesulfonate 544 with NH\(_3\) in MeOH gave the starting material after evaporation and none of the diaziridine 545. The ido-configured oxime methanesulfonate 547 was not isolated, as it underwent a Beckmann fragmentation to the nitrile 548 under the conditions of its formation.

The failure to obtain diaziridines was not commented upon. Conceivably, the bulky protecting groups impeded the formation of the tetrahedral N,N acetal intermediates. Alternatively, ammonia might attack the S atom of the sulfonyl-group [747], leading to the oxime and a sulfonamide. It is not clear from Birault’s report if the oximesulfonate or the oxime was re-
isolated. The contrasting stability of 544 vs. 547 might be due to different configurations (E/Z) or conformations of these oxime-sulfonates, neither of which was analysed.

Scheme 3.1.17

Birault also prepared the oxime 550 from validone (51, Scheme 3.1.18) and proposed a diaziridine synthesis via the corresponding methanesulfonate. Due to a lack of time the proposal was not put to an experimental test. Birault prepared validone (51) by NBS-cleavage of validoxylamine A (549) [225], followed by purification by FC in a yield of 50%. Ogawa and coworkers had reported the NBS-cleavage of validoxylamine A, but not the isolation of 51 from the cleavage products.

Scheme 3.1.18

\[ \text{549} \xrightarrow{\text{a) NBS, MeCN, H}_2\text{O; 50\% [226]}} \text{51} \xrightarrow{\text{b) i. NH}_2\text{OH, MeOH; 97\%; ii. Acetylation [226].}} \text{550} \]
3.1.5. Synthesis of Aziridines

Aziridines are made by C–N-bond formation, C–C-bond formation, addition of nitrenes to alkenes, addition of carbenes to imines, and ring contraction of 1,2,3-triazolines (Scheme 3.1.19) [816 – 820].

![Scheme 3.1.19](image)

Aziridines were prepared under mild conditions by C–N-bond formation of β-haloamines, β-amino-sulfonylates, or the corresponding amides, and β-hydroxy-amines (reviewed in [816] [818 – 820]). The Sharpless aziridination of alkenes with chloramine T and catalytic amounts of PhMe₃NBr₃ [229] proceeds via β-bromotosylamides (Scheme 3.1.20). The conjugate addition of amines to α-bromo-acrylates furnishes α-bromo-β-amino-carboxylates which cyclise in situ to aziridines [821] [822]. Aziridines were also prepared in one pot from alkenes by addition of iodine isocyanate to give β-iodoisocyanates, methanolysis to the corresponding methyl carbamates, and base catalysed cyclisation [823]. β-Azidoalcohols, readily available by epoxide opening with azide, undergo a Staudinger reaction to iminophosphanes which form aziridines and phosphane oxides [824]. Similarly, the reductive cyclisation of β-halo azides, obtained from alkenes by addition of iodoazide or bromoazide, furnishes aziridines [825 – 827].
Aziridine synthesis by C–C-bond formation (route (B) in Scheme 3.1.19) is limited to the Kaplan synthesis of N-methyl-6-azabicyclo[3.1.0]hex-3-en-2-ol (565) by photoinduced rearrangement of N-methylpyridinium chloride in water (564) [828] (Scheme 3.1.21) and to the valence tautomerism of pyrroles or azacyclononatrienes, leading to azabicyclo[2.1.0]pentanes and azabicyclo[6.1.0]nonanes, respectively (see [816] and references cited there). Thermal or photolytic electrocyclic ring opening of aziridines is used in the preparation of azomethine ylides. The reverse process has been applied to the synthesis of only a few aziridines [816].
Nitrene or nitrenoid addition to alkenes and related processes (route (D) in Scheme 3.1.19) provide aziridines in a single step (for reviews, see [816 – 820]). The reaction of acyl nitrenes – generated by thermolysis or photolysis from acyl azides – is complicated by the fact that the nitrenes exist as a mixture of singulet and triplet species, and by the lack of chemoselectivity due to the high reactivity. The yields of aziridines are often low. The high reactivity of nitrenes precludes the application of these reactions to the synthesis of highly functionalised aziridines [816]. Transition metal-catalysed reaction of alkenes with nitrene precursors, such as N-tosyliminophenyliodinane, are highly attractive, as they allow diastereoselective and also enantioselective aziridinations [820] [829 – 831]. However, these procedures require a large excess of the alkene substrates (for some recent examples, see [832 – 835]), and, therefore, are inadequate for a straightforward aziridination of precious alkenes. N-acetoxyaminoquinazolone or N-acetoxyaminophthalimide, generated from aminoquinazolone (567) or N-aminophthalimide and Pb(OAc)$_4$ convert alkenes into N-quinazolinyl or N-phthaloylamido aziridines in a reaction analogous to the peracid epoxidation of alkenes [836] [837] (Scheme 3.1.22).
Similarly, the scope of the synthesis of aziridines by addition of carbenes or carbenoids (route (C) in Scheme 3.1.19) to imines is limited due to the high reactivity of carbenes (for reviews, see [816] [820] [838 – 843]). The alternative transition metal catalysed addition of diazo alkanes to imines is more promising, especially in view of developing enantioselective reactions, but has been applied mostly to the synthesis of rather simple aziridines from hydrocarbons bearing no or only a few functional groups.

The [3 + 2]-cycloaddition of alkyl- and aryl-azides to alkenes yields 1,2,3-triazolines, which are thermolysed or pyrolysed in situ, or in a separate step to form aziridines and N₂ (route (E) in Scheme 3.1.19). However, the electron rich alkyl azides will only add to electron deficient alkenes, and for simple alkenes only intramolecular reactions are preparatively useful [817].

The majority of carbohydrate-derived aziridines were prepared by base-induced cyclisation of β-amino sulfonylates (e.g. 569 to 570 [726] (Scheme 3.1.23), [844] [845]), by intramolecular Mitsunobu reaction from β-amino alcohols ([846]), by reductive cyclisation of β-azido sulfonylates (e.g. 572 to 573 [847], [233] [848] [849]), by Staudinger reaction of β-azido alcohols (e.g. 575a b to 494 [850], [118] [851] [852]), or from the cyclic sulfates of diols by an intermolecular and then an intramolecular substitution (e.g. 577 to 578 [853], [851] [854]).
A few carbohydrate-derived aziridines were prepared by intramolecular azide addition to a C=C double bond [855] [856]. Thus, Murty in our group prepared the bicyclic aziridine 581 (Scheme 3.1.24) from the D-GlucNAc-derived azide 579 via the triazole 580 [857].
In the context of the synthesis of conduritol analogues, Desjardins et al. reported the Cu(acac)2-catalysed aziridination of the alkene 582 (Scheme 3.1.25) with PhI=NTs, yielding not more than 30% of 583 [858].

Carbohydrate derived spiro-aziridines were prepared as intermediates in the syntheses of C(3)-branched 3-aminosugars, as reviewed in [859]. Thus, spiro-aziridines were made by cyanomesylation of 3-uloses followed by reductive cyclisation with LiAlH4 [860 – 865] (as exemplified by the transformation of the ulose 584 (Scheme 3.1.26) via 585 into the aziridine 586 (45% overall yield) [866]), by opening of the corresponding spiro-epoxides with azide, mesylation of the resulting tertiary alcohol, and reductive cyclisation [867] (as exemplified by the transformation of the epoxide 587 into the branched aminosugar 590 (25% overall yield) via the aziridine 589 [868]), and from 3-methylene sugars by addition of iodine azide,
followed by LiAlH₄ reduction [869] (as exemplified by the transformation of the alkene 591 into the aziridine 593 (12% overall yield) [870]), or by addition of iodine isocyanate, followed by methanolysis and base catalysed cyclisation (as exemplified by the transformation of the enolether 594 into 596 [871]).

Scheme 3.1.26

a) KCN, NaHCO₃, CH₂Cl₂/H₂O, then MsCl, Et₃N, DMAP; 87% [866]. b) LiAlH₄, Et₂O; 50% [866]. c) NaN₃, DMF, then MsCl, pyridine; 46% [868]. d) H₂/Pd, MeOH, then Ac₂O, pyridine; 55% [868]. e) IN₃, MeCN; 24% [870]. f) LiAlH₄, Et₂O, then Ac₂O, pyridine; 52% [870]. g) I-NCO, THF, then MeOH; 12%, along with 36% of the diastereoisomer [871]. h) KOH, H₂O, MeOH; 68% [871].
3.2. Results and Discussion

3.2.1. Diaziridines

The goal of this part of my thesis was to establish a synthesis of the carbasugar derived spiro-diaziridines 45 (Scheme 3.2.1). Validone (51) appeared as the starting material of choice for a synthesis of 45 and its derivatives by the Schmitz method. I intended to prepare a protected derivative of 45 from the corresponding validone derivative and to deprotect it under mild conditions to 45. I considered isopropylidene groups, benzylidene groups, and trialkylsilyl groups as suitable protecting groups, as their cleavage should be possible under mild conditions not affecting the diaziridine ring.

Scheme 3.2.1

\[
\begin{array}{c}
\text{RO} \\
\text{RO} \\
\text{a)} \\
\text{RO} \\
\text{RO} \\
\end{array}
\]

Proposal for the synthesis of 45. a) i. NH₃, MeOH, then NH₂OSO₃H; ii. Deprotection.

Benzyl groups did not appear suitable, as the diaziridine ring is not expected to survive the conditions which are applied for removing the benzyl groups [783]. Nonetheless, while working on the synthesis of 45 from a differently protected derivative of 51, I briefly examined the synthesis of the benzyl-protected diaziridines 602 (Scheme 3.2.2) and diazirine 603 from the readily available tetra-O-benzylvalidone (52) in a model study to determine the feasibility of the synthesis.

The cyclohexanone 52 (Scheme 3.2.2) was obtained from octa-O-benzyl valdoxylamine A²⁸ in two steps (benzylation followed by NBS cleavage) and in a yield of 50%, following a known procedure [225].

Saturation of a solution of 52 in MeOH at −20° with NH₃, followed by treatment with hydroxylamine-\(O\)-sulfonic acid [227] [228] [752] [782] gave the spiro-diaziridine 602 (35%) (Scheme 3.2.2) which was oxidised with I₂ in the presence of Et₃N [753] to the spiro-diazirine 603 (85%). Both 602 and 603 were readily purified by flash chromatography.
The diaziridine 602 oxidises iodide to iodine in acidic medium, a reaction characteristic for diaziridines [735] [739] [774]. The IR N–H band at 3259 cm⁻¹ (CHCl₃) is characteristic for diaziridines [731] [872] (3,3-pentamethylenediaziridine [872] shows a band at 3266 cm⁻¹). The ¹H-NMR spectrum (CDCl₃) (see Table 3.2.3) shows that 602 is a ca. 4:1 mixture of diastereoisomers. The NH signals exchanged with D₂O; the signals of the major diastereoisomer resonate as two d at 2.64 and 1.57 ppm, respectively (J = 7.9 Hz), while only one d, resonating at 1.44 ppm (J = 8 Hz) could be observed for the other isomer (the other signal is hidden behind other signals at 2.26–2.06 ppm). In the ¹³C-NMR C(3) resonates as a s at 57.06 ppm (cf. [873]).

The UV spectrum of the diazirine 603 in CH₂Cl₂ shows a typical maximum at 340 nm (ε = 92) [731] [754]. The IR N=N band (CHCl₃) at 1590 cm⁻¹ is characteristic for diazirines [731] [754]. A large chemical shift difference was observed for the two H–C(8) (Δδ = 1.38 ppm). The signal for the equatorial H is shifted upfield, an observation characteristic for spiro-diazirines [731] [753] [874]. The C(3) s of 603 (28.82 ppm) is shifted upfield by 28.2 ppm as compared to 602 (for similar upfield shifts of 1-azipyranoses, see [784]). The vicinal coupling constants for the ring H of 602 and 603 evidence a ⁶C₃ conformation.

Scheme 3.2.2

52 → a) NH₃, MeOH, then NH₂OSO₃OH; 35%. b) I₂, Et₃N, MeOH, CH₂Cl₂; 85%.

The question may be justified whether this model study was useful or a waste of time and resources. In view of the negative results of Birault [226] and of the low yields obtained by Kurz et al. [782] in the synthesis of related spiro-diaziridines, and in view of the difficulties encountered in the synthesis of 45 (vide infra) this model study proved very useful indeed as it showed that the synthesis of derivatives of 45 is feasible. The benzyl-derivatives 602 and 603 were also useful for spectral studies.

The successful model study augured well for a synthesis of 45 from other derivatives of validone. However, attempts to prepare the tetra-O-TBS-derivative, the di-isopropylidene-derivative, and the 4,6-benzylidene-derivative failed. The reaction of validone with TBSCl and Li₂S in MeCN [875] led to decomposition of the starting material. The reaction with
TBSCI and imidazole in DMF [876] provided the di-TBS derivative 604 in low yield (9%) (Scheme 3.2.3). Treatment of validone with benzaldehyde dimethylacetal and toluenesulfonic acid monohydrate in DMF at 60°C (cf. [877 – 879]) gave the 4,6-benzylidene derivative 605 in only 10% yield. The reaction of 51 with 2-propenyl-trimethylsilyl ether and HCl (g) in MeCN [880] [881] did not provide the isopropylidene derivative, but in low yield (33% after FC) the tetra-O-trimethylsilyl derivative 606.

Scheme 3.2.3

![Scheme 3.2.3](image)

a) TBSCI, DMF, imidazole; 9%. b) PhCH(OMe)₂, pTsOH·H₂O, DMF; 8%. c) 2-Trimethylsilyloxy-propene, HCl, MeCN; 33%.

Sarabia²⁴ had tried to prepare tetra-O-TBS validone by NBS-cleavage of the octa-O-TBS derivative of validoxylamine A, obtained in 40% yield from validoxylamine A. However, this derivative was inert to NBS, presumably because the bulky TBS-groups protected the N atom from attack of bromine [882].

The synthesis of di-O-isopropylidene validone by NBS-cleavage of tetra-O-isopropylidene validoxylamine A (607) was examined next. Racemic 609 had been prepared by Ogawa et al. by oxidation of the corresponding equatorial alcohol, which in turn was prepared in a de novo carbasugar synthesis [883]. Treatment of validoxylamine A²⁸ with 2-methoxypropene and 1.2 equivalents of toluenesulfonic acid monohydrate in DMF gave the crystalline tetra-O-isopropylidene derivative 607 in a good yield (55%) (Scheme 3.2.4). Excess acid was necessary, as one equivalent was consumed by protonation of the starting material. Cleavage
of 607 with NBS in aqueous MeCN gave 2,3:4,6-di-O-isopropylidene gabosine I (608, 23%) and 2,3:4,6-di-O-isopropylidene validone (609, 63%). Basic workup was a prerequisite for the isolation of 609, otherwise the crude product decomposed during evaporation.

Treatment of a methanol solution of 609, saturated with NH₃ at –20°, with hydroxylamine-O-sulfonic acid led to a complex product mixture (acc. to TLC). FC gave in low yield (11 mg from 100 mg) a fraction which oxidised iodide in acidic solution, and which stained yellow with vanillin on the TLC plate. According to its ¹H-NMR spectrum, however, this fraction was a complex mixture.

Therefore the diaziridine synthesis via the oxime methanesulfonylate of 609 was studied. Condensation of 609 with hydroxylamine in MeOH gave the oxime 610 (66%). Treatment of 610 with Et₃N and MsCl in CH₂Cl₂ at 0° afforded in quantitative yield the crude bona fide oxime methanesulfonylate 611, which decomposed rapidly, and, therefore, was immediately used in the subsequent step. The reaction of crude 611 with a solution of NH₃ in MeOH at –20° to 25° gave a mixture, which oxidised iodide in acidic solution. However, after FC only a mixture (acc. to TLC and ¹H-NMR) was obtained in low yield (10 mg in two steps from 59 mg of 610). This mixture also oxidised iodide in acidic solution.

Scheme 3.2.4

\[ \text{Scheme 3.2.4} \]

\[ \begin{align*}
\text{549} & \xrightarrow{a)} \text{607} \\
\text{608} & \xrightarrow{c)} \text{609} \\
\text{610} & \xrightarrow{e)} \text{611} \\
\text{612} & \xrightarrow{f)} \text{611, } R = \text{Ms} \\
\end{align*} \]

\( a) \) 2-Methoxypropene, pTsOH, DMF; 55%. \( b) \) NBS, MeCN, H₂O; 23% of 608, 58% of 609. \( c) \) NH₃, MeOH, then NH₂OSO₃H; see text. \( d) \) NH₂OH, MeOH; 66%. \( e) \) MsCl, Et₃N, CH₂Cl₂; quant. crude. \( f) \) NH₃, MeOH; see text.
The structure of the di-TBS derivative 604 is evidenced by its $^1$H-NMR spectrum (Table 3.2.1), showing signals for two TBS groups. The position of the TBS groups is evidenced by a deuterium exchange upon which the H–C(3) $td$ and the H–C(4) $br. t$ become triplets. The benzylidene group of 605 gives rise to a s at 5.62 ppm and to signals for 5 PhH. The position of the benzylidene group was not proven. The structure of the trimethylsilyl ether 606 is evidenced by its MS and by the $^1$H- and $^{13}$C-NMR spectra.

The structure of tetra-$O$-isopropylidene validoxylamine A 607 is evidenced by its MS and $^{13}$C-NMR spectrum. The CMe2 s resonate at 111.47 and 110.61 for the dioxolane rings and at 99.17 and 99.00 for the dioxane rings (cf. [258] [884]). H–C(6) of the gabosine I derivative 608 resonates at 5.80 ppm. The large vicinal coupling constants for the ring H ($J(2,3) = 10.6$ Hz, $J(3,4) = 8.4$ Hz) evidence a $^2$$H_3$ conformation and a pseudo-equatorial orientation of the C(2), C(3), and C(4) substituents. The isopropylidene groups resonate as s at 1.56 (3 H), 1.48 (6 H), and 1.43 ppm (3 H).

H–C(2) and H–C(3) of the validone derivative 609 resonate as a $m$ ($\tau_{1/2} \approx 18$ Hz), precluding a proof of the configuration at C(2). The vicinal coupling constant for the H–C(2) $d$ of the oxime 610 (6.2 Hz) is smaller than expected. This could be due to an epimerisation at C(2) leading to the mannose analogue of 609 and reducing ring strain. An axial C(2)–O, however, should lead to a downfield shift for H–C(4) and H$_{ax}$–C(6), which is not observed. Briner observed small coupling constants for H–C(2) of D-gluconolactone oxime and concluded that it adopts a non-chair conformation [734]. For 610, in conjunction with the relatively small $J(3,4) = 7.8$ Hz, the small $J(2,3)$ suggests a decreased O–C(2)–C(3)–O torsional angle which is probably due to the ring strain induced by the trans-diequatorially annulated dioxolane ring. The downfield shift for H$_{eq}$–C(6) and the upfield shift for C(6) evidence the ($E$) configuration of the oxime. The dioxolane and dioxane CMe2 of 609 resonate at 110.88 and 98.76 ppm, respectively, those of 610 at 110.61 and 99.35 ppm, respectively.
Table 3.2.1: Selected $^1$H-NMR (CDCl$_3$) Chemical Shifts [ppm] and Coupling Constants for the Cyclohexanes 51, 604, 605, 606, 608, 609, and 610.

<table>
<thead>
<tr>
<th></th>
<th>51$^a$</th>
<th>604</th>
<th>605$^b$</th>
<th>606</th>
<th>608</th>
<th>609</th>
<th>610</th>
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<td>4.25</td>
<td>4.10</td>
<td>4.17</td>
<td>4.03</td>
<td>4.15</td>
<td>4.61–4.53</td>
<td>4.68</td>
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<tr>
<td>H–C(3)</td>
<td>3.50–3.30</td>
<td>3.54</td>
<td>3.76</td>
<td>3.46</td>
<td>3.96</td>
<td>4.61–4.53</td>
<td>4.15</td>
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<tr>
<td>H–C(4)</td>
<td>3.84–3.60</td>
<td>3.88</td>
<td>3.88</td>
<td>3.76</td>
<td>4.78</td>
<td>3.70</td>
<td>3.76</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>2.00–1.44</td>
<td>1.94–1.78</td>
<td>2.12–1.94</td>
<td>1.70–1.56</td>
<td>–</td>
<td>2.33–2.15</td>
<td>1.71–1.58</td>
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<tr>
<td>H–C(6)</td>
<td>2.63–2.41</td>
<td>2.49–2.31</td>
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<td>2.40 (ax)</td>
<td>5.80</td>
<td>2.50 (eq)</td>
<td>2.94 (eq)</td>
</tr>
<tr>
<td>H–C(6$'$)</td>
<td>2.63–2.41</td>
<td>2.49–2.31</td>
<td>2.19 (ax)</td>
<td>2.30 (eq)</td>
<td>–</td>
<td>1.99 (ax)</td>
<td>1.85 (ax)</td>
</tr>
<tr>
<td>H–C(7)</td>
<td>3.84–3.60</td>
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<td>4.25</td>
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<td>4.56</td>
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<td>3.47</td>
<td>4.43</td>
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<td>$J$(2,3)</td>
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<td>10.0</td>
<td>9.3</td>
<td>9.5</td>
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<td>c)</td>
<td>6.2</td>
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<tr>
<td>$J$(3,4)</td>
<td>c)</td>
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<td>9.0</td>
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<td>–</td>
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<td>c)</td>
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<td>4.7</td>
<td>–</td>
<td>11.2</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>$J$(5,7)</td>
<td>c)</td>
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<td>–</td>
<td>5.6</td>
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</tr>
<tr>
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<td>10.7</td>
<td>2.5</td>
<td>–</td>
<td>11.2</td>
<td>11.2</td>
</tr>
<tr>
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<td>c)</td>
<td>13.7</td>
<td>14.0</td>
<td>–</td>
<td>17.7</td>
<td>16.4</td>
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</tr>
<tr>
<td>$J$(7,7)</td>
<td>c)</td>
<td>10.0</td>
<td>11.2</td>
<td>10.0</td>
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<td>203.05</td>
<td>c)</td>
<td>207.24</td>
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<td>220.88</td>
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<td></td>
<td>80.8</td>
<td>76.53</td>
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<td>79.76</td>
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<td></td>
<td>74.4</td>
<td>69.61</td>
<td>c)</td>
<td>73.50</td>
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<tr>
<td>C(5)</td>
<td>43.6</td>
<td>36.47d)</td>
<td>c)</td>
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<td>38.25d)</td>
<td>c)</td>
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<td>C(7)</td>
<td>64.3</td>
<td>60.88</td>
<td>c)</td>
<td>61.76</td>
<td>c)</td>
<td>63.58</td>
<td>64.17</td>
</tr>
</tbody>
</table>

$^a$) In D$_2$O.

$^b$) In CDCl$_3$ + D$_2$O.

$^c$) Not determined.

$^d$) Assignment may be pairwise interchanged.
After the successful model study with the benzyl derivatives, these results were a major setback. Encouraged by the results of Kurz et al. [782] and of Thieme [783], who obtained the related diazirine 531 – albeit in low yield – from the trimethylsilyl ether 529 (Scheme 3.1.14), the transformation of the tetra-O-TMS derivative 606 to the diaziridine 45 by the Schmitz method was studied.

Trimethylsilylation [885] of 51 gave crude 606 (94%) that was isolated by chromatography (27%) (Scheme 3.2.5). An attempt to purify 606 by kugelrohr distillation (130°, 0.5 bar) resulted in partial decomposition. Only chromatographically purified samples of 606 gave good results in the subsequent step. Treatment of a solution of 606 in MeOH, saturated at −20° with NH₃, with hydroxylamine-O-sulfonic acid gave crude 45 (69%) which oxidised iodide in acidic solution. Flash chromatography gave a solution of 45, pure by TLC, but complete evaporation of the solvent (AcOEt, iPrOH, H₂O), even below 10°, resulted in partial decomposition. Pure 45 was obtained in 50% yield by partial evaporation of the column eluate, application of the residual colourless solution of pure 45 to a strong acid ion exchanger, elution with 2% aqueous ammonia solution, and lyophilisation. The stability of 45 on the strong acid ion exchanger is in contrast to its sensitivity to aqueous HCl: although TLC experiments indicated that 45 is stable in aqueous buffers at pH 4.2, pH 5.0, and in pure water, addition of 1 M HCl to a methanol solution of 45 (to pH 1) led to rapid decomposition to a complex mixture41). Pure 45 hydrolysed partially to validone (according to TLC), when it was submitted to Sephadex G-10 chromatography (eluent water)42).

---

41) The higher sensitivity to HCl than to the strong ion exchanger (R–SO₃H) may be due to the higher nucleophilicity of Cl⁻ as compared to that of R–SO₃⁻.

42) This is very surprising. The resin was washed extensively with water. Therefore, the sensitivity to Sephadex G10 must be due to the resin itself, not to water-soluble contaminations.
The diaziridine 45 was also obtained by treating validone (51) with NH₃ and hydroxylamine-O-sulfonic acid in MeOH. However – in agreement with the results of Kurz et al. [782] and of Thieme [783] – the yield of 45 was lower (28% of crude 45), and the reaction less clean, so that 45 could not be obtained pure.

The yield for the transformation of the trimethylsilyl derivative 606 of validone into the diaziridine 45 (50%) is higher than that for the transformation of the benzyl derivative 52 of validone into the diaziridine 602 (35%, Scheme 3.2.2). This suggests that the trimethylsilyl groups of 606 which are cleaved off during the diaziridine synthesis play an active role in the diaziridine formation rather than just blocking the OH groups. This role of the silyl groups might involve the in situ formation of hexamethyldisilazane, or the sequestration of H₂O formed in the condensation of NH₃ with the ketone. To address this issue, I examined the transformation of validone (51) into 45 in the presence of hexamethyldisilazane, and the transformation of the benzylated validone 52 into 602 in the presence of hexamethyldisilazane or TMSCl (Table 3.2.2). Treatment of 51 with hexamethyldisilazane and then with hydroxylamine-O-sulfonic acid led to a lower yield of the diaziridine (Entry 2, 20% of crude 45) than the reaction with NH₃/hydroxylamine-O-sulfonic acid (Entry 1, 28%). Using hexamethyldisilazane and NH₃ improved the yield somewhat (Entry 3, 38%), but it was still significantly lower than the one realised from 606 (Entry 4, 69%). Treating the benzylated validone 52 with hexamethyldisilazane and NH₃/hydroxylamine-O-sulfonic acid
provided 602 in 29% yield (Entry 6). Treating 52 with excess chlorotrimethylsilane and NH3/hydroxylamine-O-sulfonic acid resulted in a significantly higher yield (Entry 7, 50%), suggesting that the trimethylsilyl ether 606 acts as a H2O scavenger.

**Table 3.2.2: Synthesis of 45 and 602 in the Presence of Various Silylating Agents.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Reagents</th>
<th>Product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>NH3, then NH2OSO3H</td>
<td>45 (28%b)</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
<td>HN(SiMe3)2 (four eq.), then NH2OSO3H</td>
<td>45 (20%b)</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>HN(SiMe3)2 (two eq.), NH3, then NH2OSO3H</td>
<td>45 (38%b)</td>
</tr>
<tr>
<td>4</td>
<td>606</td>
<td>NH3, then NH2OSO3H</td>
<td>45 (69%b)</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>NH3, then NH2OSO3H</td>
<td>602 (35%)</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>HN(SiMe3)2 (two eq.), NH3, then NH2OSO3H</td>
<td>602 (29%)</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>Me3SiCl (four eq.), NH3, then NH2OSO3H</td>
<td>602 (52%)</td>
</tr>
</tbody>
</table>

a) Conditions: A soln. of the starting material in MeOH was treated with HN(SiMe3)2 at r.t. (entries 2, 3, and 6) or with Me3SiCl at –20° (entry 7), saturated with NH3 at –20° (except for entry 2), treated dropwise with NH2OSO3H (one eq.), stirred at –20° for 3 h, and allowed to warm to r.t. overnight. b) Crude product after FC.

Oxidation of the diaziridine 45 with I2 in MeOH in the presence of Et3N gave a mixture of the diazirine 613 and Et3N (2.5:1) (Scheme 3.2.5), which could not be separated even by repeated FC. Replacing Et3N with the more volatile Me3N, which was successfully used in the synthesis of pyranosylidene diazirines, led to a mixture of 613 and several unidentified by-products. Acetylation of the mixture of 613 and Et3N gave the tetraacetate 614b) (84% from 45). Pure diazirine 613 (89%) was obtained from 613-Et3N by weak acid ion exchange chromatography. Chromatography of 613 on a strong acid ion exchanger led to decomposition to a complex mixture. This is in agreement with the known sensitivity of β-hydroxydiazirines and – more general – of diazirines bearing a (partial) positive charge at a carbon atom adjacent to the three-membered ring [729] [886].

43) This acetate of 613 was only prepared for analytical reasons. Deacetylation of 614 was not attempted.
Treatment of the silylated validone 606 with BnNH₂ in MeOH and then with hydroxylamine-O-sulfonic acid in MeOH gave, after FC, a ca. 1:4 mixture of the N-benzyl diaziridine 615 and BnNH₂, from which pure 615 (27%) was obtained by chromatography on a weak acid ion exchanger (Scheme 3.2.6). The configuration of 615 may result from an equatorial attack of hydroxylamine-O-sulfonic acid on an (E)-configured N-benzyl imine formed in situ from 606 and benzylamine (the (Z)-configured N-benzylimine is expected to be disfavoured by a repulsive 1,5-interaction between BnO–C(2) and Bn–N). Equatorial attack of hydroxylamine-O-sulfonic acid on an intermediary imine has been observed by Shustov et al. in the synthesis of 5-methyl-3,3-pentamethylenediaziridine [887]. For a discussion of the diastereoselective addition of NH₃ or H₂NMe to glyconolactone oxime mesylates in the formation of alkoxydiaziridines, see [813].

Scheme 3.2.6

![Scheme 3.2.6](image)

a) BnNH₂, MeOH, then NH₂OSO₃H; 27%.
The diaziridines 45 and 615 oxidise iodide to iodine in acidic medium. According to its $^1$H-NMR spectrum in (D$_6$)DMSO (Table 3.2.3), 45 is a ca. 3:2 mixture of two diastereoisomers. The NH signals of the major isomer appear as two $d$ at 2.30 and 2.13 ppm ($J = 8.1$ Hz) and the NH signals of the minor isomer as two $d$ at 2.24 and 2.07 ppm, respectively ($J = 8.1$ Hz). Upon addition of trifluoroacetic acid, the two diastereoisomers equilibrate rapidly, and the spectrum of a single compound is observed. C(3) of 45 appears as a $s$ at 60.02 ppm (cf. [873]).

According to its $^1$H-NMR spectrum (D$_2$O), the $N$-benzyl diaziridine 615 is a single stereoisomer. Its configuration was determined by NOE difference spectra. Upon irradiation at 2.04 ppm (H$_{eq}$–C(8)) a NOE of 4% and 6%, respectively, was observed for the benzylic H. Upon simultaneous irradiation of the benzylic H at 3.92 and 3.81 ppm, a NOE of 6% for H$_{eq}$–C(8) and one of 8% for H–C(7) were observed. Irradiation at 3.62 ppm (H–C(4)) did not lead to a NOE of the benzylic H. C(3) appears as a $s$ at 62.90 ppm and PhCH$_2$ as a $t$ at 57.27 ppm (compare [772]).

The UV spectrum of 613 (H$_2$O) shows a typical maximum at 340 nm ($\varepsilon = 68$) [731] [754]. A large chemical shift difference is observed for the two H–C(8) ($\Delta\delta \approx 1.2$ ppm). The signal for the equatorial H is shifted upfield as in 603. The C(3) $s$ (32.34 ppm) is shifted upfield by 27.7 ppm as compared to that of 45 (for similar upfield shifts of 1-azipyranoses, see [784]).

The vicinal coupling constants for the ring H of 45, 613, 614, and 615 evidence a $^6$C$_3$ conformation.
Table 3.2.3: Optical Rotation and Selected $^1$H- and $^{13}$C-NMR Chemical Shifts [ppm] and Coupling Constants [Hz] for 602, 45, 615, 603, 613, and 614.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>602</th>
<th>45</th>
<th>615</th>
<th>603</th>
<th>613</th>
<th>614</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent</td>
<td>CDCl$_3$</td>
<td>a)</td>
<td>b)</td>
<td>CDCl$_3$</td>
<td>D$_2$O</td>
<td>CDCl$_3$</td>
</tr>
<tr>
<td>$[^{25}\alpha]D_2$</td>
<td>29.4</td>
<td>22.2</td>
<td>59.7</td>
<td>49.7</td>
<td>37.2</td>
<td>47.4</td>
</tr>
<tr>
<td>H–C(4)</td>
<td>3.90</td>
<td>3.70</td>
<td>3.62</td>
<td>3.70</td>
<td>3.86</td>
<td>5.15</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>3.56</td>
<td>3.06</td>
<td>3.36</td>
<td>3.82</td>
<td>3.54</td>
<td>5.33</td>
</tr>
<tr>
<td>H–C(6)</td>
<td>3.69</td>
<td>3.16</td>
<td>3.43</td>
<td>3.65–3.57</td>
<td>3.48</td>
<td>5.13</td>
</tr>
<tr>
<td>H–C(7)</td>
<td>2.19–2.06</td>
<td>1.52–1.47</td>
<td>1.53–1.40</td>
<td>2.13–2.05</td>
<td>2.00–1.85</td>
<td>2.40–2.29</td>
</tr>
<tr>
<td>H–C(8)</td>
<td>2.26 (ax)</td>
<td>1.95 (ax)</td>
<td>2.04 (eq)</td>
<td>2.05 (ax)</td>
<td>2.00–1.85</td>
<td>2.02 (ax)</td>
</tr>
<tr>
<td>H$^-$–C(8)</td>
<td>1.35 (eq)</td>
<td>1.52–1.47 (eq)</td>
<td>1.93 (ax)</td>
<td>0.67 (eq)</td>
<td>0.72 (eq)</td>
<td>0.79 (eq)</td>
</tr>
<tr>
<td>CH–C(7)</td>
<td>3.77</td>
<td>3.56</td>
<td>3.75</td>
<td>3.63</td>
<td>3.77</td>
<td>4.07</td>
</tr>
<tr>
<td>CH$^-$–C(7)</td>
<td>3.48</td>
<td>3.38</td>
<td>3.64</td>
<td>3.42</td>
<td>3.66</td>
<td>3.90</td>
</tr>
<tr>
<td>N–H</td>
<td>2.64</td>
<td>2.30/2.24</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>N$^-$–H</td>
<td>1.57</td>
<td>2.13/2.07</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>J(4,5)</td>
<td>9.6</td>
<td>9.0</td>
<td>9.3</td>
<td>9.2</td>
<td>9.3</td>
<td>9.7</td>
</tr>
<tr>
<td>J(5,6)</td>
<td>9.6</td>
<td>9.0</td>
<td>9.0</td>
<td>9.2</td>
<td>9.3</td>
<td>9.7</td>
</tr>
<tr>
<td>J(6,7)</td>
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<td>9.0</td>
<td>9.0</td>
<td>9.3</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>J(7,8)</td>
<td>12.9</td>
<td>14.9</td>
<td>4.1</td>
<td>12.8</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>J(7,8$^-$)</td>
<td>2.9</td>
<td>c)</td>
<td>14.0</td>
<td>ca. 1</td>
<td>2.8</td>
<td>4.4</td>
</tr>
<tr>
<td>J(8,8$^-$)</td>
<td>12.9</td>
<td>14.9</td>
<td>14.3</td>
<td>12.8</td>
<td>13.1</td>
<td>15.1</td>
</tr>
<tr>
<td>J(7,CH)</td>
<td>3.7</td>
<td>3.1</td>
<td>3.4</td>
<td>4.4</td>
<td>3.1</td>
<td>5.6</td>
</tr>
<tr>
<td>J(7,CH$^-$)</td>
<td>2.5</td>
<td>6.2</td>
<td>5.9</td>
<td>3.4</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>J(CH,CH$^-$)</td>
<td>9.1</td>
<td>10.6</td>
<td>11.5</td>
<td>9.0</td>
<td>11.2</td>
<td>11.5</td>
</tr>
<tr>
<td>J(NH,N'H)</td>
<td>7.9</td>
<td>8.1/8.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C(3)</td>
<td>57.06</td>
<td>60.02</td>
<td>62.90</td>
<td>28.82</td>
<td>32.34</td>
<td>26.75</td>
</tr>
<tr>
<td>C(7)</td>
<td>39.96</td>
<td>43.50</td>
<td>43.05</td>
<td>39.66</td>
<td>43.46</td>
<td>37.28</td>
</tr>
<tr>
<td>C(8)</td>
<td>34.80</td>
<td>34.91</td>
<td>27.55</td>
<td>30.21</td>
<td>31.76</td>
<td>29.67</td>
</tr>
<tr>
<td>CH$_2$–C(7)</td>
<td>c)</td>
<td>c)</td>
<td>64.02</td>
<td>c)</td>
<td>c)</td>
<td>c)</td>
</tr>
</tbody>
</table>

a) $^1$H-NMR spectrum in D$_6$-DMSO/TFA (NH signals from D$_6$-DMSO spectrum). $^{13}$C-NMR spectrum in D$_2$O.

b) $^1$H-NMR spectrum in D$_2$O. $^{13}$C-NMR spectrum in CD$_3$OD. PhCH: 3.92, PhCH$^-$: 3.81; J (PhCH,PhCH$^-$) = 14.5.

c) Not determined.
d) Assignment may be interchanged.
3.2.2. Aziridines

For the synthesis of the aziridines 46 and 47 (Scheme 3.2.7) I intended to first study an aziridination of the alkene 53 and then a synthesis by the robust route via epoxides and azido alcohols. The alkene 53 should be readily available from tetra-O-benzylvalidone (52).

Scheme 3.2.7

Proposal for the synthesis of the aziridines 46 and 47. a) Methylenation. b) Aziridination, followed by deprotection; or epoxidation, azide-opening, O-mesylation, and reductive cyclisation.

Wittig methylenation of the cyclohexanone 52 gave the alkene 53 (77%) (Scheme 3.2.8). Of the attempts to transform 53 into an aziridine, only the reaction with chloramine T and phenyltrimethylammonium tribromide in MeCN [229] gave the N-tosyl aziridine 616 (15%) besides 2% of the ring-opened tosylamide 617.
Scheme 3.2.8

\[ \text{Scheme 3.2.8} \]

\begin{align*}
52 & \xrightarrow{a)} \ 53 \\
\text{a) Ph}_3\text{P}=\text{CH}_2, \text{THF; 77\%. } & \text{b) Chloramine T, PhMe}_3\text{NBr}_3, \text{MeCN; 18\% of } 616, \ 2\% \text{ of } 617.
\end{align*}

The alkene 53 did not react with TsN3 in toluene at 110° ([230] [231]), with TfN3 in CH2Cl2 ([232]), with diphenylphosphoryl azide in toluene at 70°, with NBS and NaN3 in DME/H2O (or DMF) ([827]), nor with I-NCO in Et2O, followed by treatment with KOH in MeOH ([823] [871] [888]). The reaction with I-NCO in MeCN, followed by treatment with KOH in MeOH gave the epoxide 618 (36\%) and unidentified by-products. The epoxide may have been formed via a iodohydroxylation, or (less probable) by substitution of NCO by OH. The reaction of 53 with ICl and NaN3 in MeCN ([825] [869] [870] [889]) gave 34\% of a mixture of IN3 addition products which on treatment with LiAlH4 gave 53 (43\%, see exp. part). Such an elimination of a \( \beta \)-iodoazide by LiAlH4 was also observed by Hassner et al. [825] and probably proceeds by attack of hydride at the iodine substituent.

Due to the poor yield of the aziridination, I investigated a synthesis of the aziridines 46 and 47 via the epoxides 618 and 619 (Scheme 3.2.9) (cf. [867] [868]). These epoxides were prepared by treating the alkene 53 with mCPBA/NaHCO3 and isolated in 25 and 61\% yield, respectively, after FC. On a scale of 700 mg their separation required HPLC, and the yields were somewhat lower (19\% and 48\%, respectively). Treatment of 618 and 619 with NaN3 in DMF gave the azido-alcohols 620 (91\%) and 623 (88\%), respectively. Mesylation (MsCl, DMAP, 2,5-lutidine) [890] of 620 yielded 95\% of the mesylate 621 besides 4\% of the elimination product 626, while mesylation of 623 gave exclusively the mesylate 624 (99\%). The higher propensity of 620 towards elimination probably results from the steric strain of the axial azidomethyl group which is relieved in the elimination. The azido-mesylates 621 and 624 were transformed into the aziridines 622 (83\%) and 625 (74\%) by reductive cyclisation with LiAlH4 in THF (cf. [233]). Debenzylation of the aziridine 625 under Birch conditions gave the aziridine 46 that was isolated in a yield of 45\% by chromatography first on a strong
Birch debenzylolation of the aziridine 622, followed by ion exchange chromatography led to the crude aziridine 47 that decomposed on the CN phase column. Even just evaporating a methanolic solution of some batches of 47 led to decomposition 46. Crude 47 (containing small amounts of an unidentified byproduct and some salts) was obtained by chromatography of the reaction product on a Sephadex G 10 column, and used for the enzyme assay. Hydrogenation of the benzylated aziridine 622 over Pd-C in MeOH/HCl gave a mixture of the ring-opened 627 and 628 as their hydrochlorides (1.6:1). Based on a mass-spectrum of this mixture, showing a peak at m/e = 190, the structure of 627 was first incorrectly assigned as 47·HCl, but later Poisson 47) obtained pure 627, allowing an unambiguous structural assignment (vide infra).

44) The CN phase is a "reversed phase" silica gel prepared by derivatising Si–OH groups at the surface of the silica with a cyanopropyl group attached to a linker, a process called modification. Demodification involves cleavage of the cyanopropyl group (along with the spacer?) from the silica gel. As the nature of the spacer is a trade secret, I cannot apply a chemical term (such as dealkylation or desilylation) instead of demodification.

45) I thank Dr. Riering, Machery-Nagel, Düren, Germany, for a pertinent discussion on the properties of the CN phase.

46) The relative instability of the aziridine 47 is not without precedent. The oligohydroxylated aziridines 496 [726] and 498 [728] also were unstable (Figure 3.1.1). Hassner reported that some aziridines decompose upon concentration of their solution in organic solvents, unless scrupulously dried [825].

Scheme 3.2.9

a) mCPBA, NaHCO₃, CH₂Cl₂; 25% of 618, 61% of 619. b) NaN₃, DMF; 91% of 620; 88% of 623. c) MsCl, DMAP, 2,5-lutidine; 95% of 621, 4% of 626; 99% of 624. d) LiAlH₄, THF; 83% of 622; 74% of 625. e) Na, NH₃, THF; 45% of 46; (yield of 47: see text).

Poisson⁴⁷), convinced that 47 should be stable, re-examined its synthesis. His attempts to improve the synthesis of the protected derivative 622 from 52 were not fruitful. He then attempted to prepare 47 via the trifluoroacetamide of 622, but was unable to obtain the pure amide. Finally, he claimed a preparation of 47·HCl by elution of crude 47 from a Sephadex C 25 column with aqueous HCl. However, from the ¹H-NMR data and from a re-inspection of the mass spectral data (vide infra), I could show that Poisson's product is the ring-opened 627·HCl.
The configuration of the epoxides was determined by NOE difference spectra. Irradiation of H–C(2) of 618 at 3.18 ppm caused a NOE of 1% for H–C(5). Upon irradiation at 2.56 ppm (H'–C(2)), a NOE of 7% was observed for H_{eq}–C(8). For 619, irradiation at 2.98 ppm (H–C(2)) led to a NOE of 1% for H–C(4). Irradiation at 2.59 ppm (H'–C(2)) led to a NOE of 4% for H_{eq}–C(8). The pseudo-axial O–C(3) of 619 leads to a downfield shift for H–C(5) (Δδ = 0.29 ppm) and H–C(7) (Δδ ≈ 0.2 ppm), as compared to 618. This shift confirms the assignment of the configuration of 618 and 619.

The 1H-NMR spectrum of the N-tosyl aziridine 616 shows two br. s at 2.63 and 2.59 ppm (H_{2}–C(2)) (Table 3.2.4). Their small coupling constants are typical for aziridines [715]. C(3) appears as a s at 51.73 ppm and C(2) as a t at 28.77 ppm. The configuration of 616 was determined by NOE difference spectra. Upon irradiation at 2.63 ppm (H–C(2)), a NOE of 2% was observed for H–C(5), and irradiation at 2.59 ppm (H'–C(2)) led to a NOE of 1% for H–C(7) and for the H_{2}–C(8) multiplet. Irradiation at 3.78 ppm (H–C(4)) did not lead to an observable NOE for H_{2}–C(2). Irradiation at 3.39 ppm (H–C(5)) caused an NOE of 1.5% for H–C(2). The vicinal coupling constants for the ring H evidence a 6C_{3} conformation.

H_{2}–C(2) of the aziridines 622 and 625 appear as two br. s at 1.87 and 1.40 ppm for 622 and at 1.98 and 1.29 ppm for 625. NH of 622 and 625 appear as a broad signal at 1.17–0.87 and 1.18–0.85 ppm, respectively. C(3) resonates as a s at 37.42 ppm for 622 and at 37.86 ppm for 625, and C(2) as a t at 27.17 ppm for 622 and at 26.97 ppm for 625. The coupling constants for the ring H of 622 evidence a 6C_{3} conformation. Signal overlap for the ring H of 625 prevented a conformational analysis. H_{2}–C(2) of the aziridine 46 resonate as two br. s at 2.02 and 1.34 ppm, respectively. C(3) appears as a s at 39.90 ppm and C(2) as a t at 27.36 ppm. The coupling constants for the ring H evidence a 6C_{3} conformation. The pK_{HA} of 46 is 6.8, and equilibration of the N configurational isomers should be fast at pH 7.

H_{2}–C(2) of the crude aziridine 47 resonate as two br. s at 1.96 and 1.53 ppm, respectively. The coupling constants evidence a 6C_{3} conformation. In the HR-MS, the [M + 1]^{+}-peak appears at 190.1076 (calc. 190.1079).
Table 3.2.4: Optical Rotation and Selected $^1$H- and $^{13}$C-NMR Chemical Shifts [ppm] and Coupling Constants [Hz] (CDCl$_3$) for 616, 618, 619, 622, 625, 47, and 46.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>618</th>
<th>619</th>
<th>616</th>
<th>622</th>
<th>625</th>
<th>47</th>
<th>46</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDCl$_3$</td>
<td>36.0</td>
<td>16.5</td>
<td>-9.2</td>
<td>32.1</td>
<td>8.8</td>
<td>a)</td>
<td>6.0</td>
</tr>
<tr>
<td>H–C(2)</td>
<td>3.18</td>
<td>2.98</td>
<td>2.63</td>
<td>1.87</td>
<td>1.98</td>
<td>1.96</td>
<td>2.02</td>
</tr>
<tr>
<td>H–C’(2)</td>
<td>2.56</td>
<td>2.59</td>
<td>2.59</td>
<td>1.40</td>
<td>1.29</td>
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</tr>
<tr>
<td>H–C(4)</td>
<td>3.73</td>
<td>3.69</td>
<td>3.78</td>
<td>3.78</td>
<td>3.65–3.57</td>
<td>3.80</td>
<td>3.48</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>3.54</td>
<td>3.83</td>
<td>3.39</td>
<td>3.60</td>
<td>3.65–3.57</td>
<td>3.36</td>
<td>3.22</td>
</tr>
<tr>
<td>H–C(7)</td>
<td>1.93–1.81</td>
<td>2.09–2.00</td>
<td>1.88–1.78</td>
<td>2.15–2.06</td>
<td>1.93–1.81</td>
<td>1.87–1.78</td>
<td>1.68–1.57</td>
</tr>
<tr>
<td>H–C(8)</td>
<td>2.09</td>
<td>2.09–2.00</td>
<td>2.42–2.35</td>
<td>2.01</td>
<td>2.00</td>
<td>1.87–1.78</td>
<td>1.73</td>
</tr>
<tr>
<td>H–C’(8)</td>
<td>1.46</td>
<td>1.36</td>
<td>2.42–2.35</td>
<td>1.29–1.21</td>
<td>1.31–1.25</td>
<td>1.26</td>
<td>1.29</td>
</tr>
<tr>
<td>CH–C(7)</td>
<td>3.61–3.54</td>
<td>3.75</td>
<td>3.70</td>
<td>3.79</td>
<td>3.65–3.57</td>
<td>3.78</td>
<td>3.75</td>
</tr>
<tr>
<td>CH–C(7)</td>
<td>3.50</td>
<td>3.41</td>
<td>3.51</td>
<td>3.45</td>
<td>3.49</td>
<td>3.70</td>
<td>3.58</td>
</tr>
<tr>
<td>N–H</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.17–0.85</td>
<td>1.18–0.85</td>
<td>–</td>
</tr>
<tr>
<td>OH</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>$J$(2,2’)</td>
<td>5.3</td>
<td>5.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>ca. 0.5</td>
</tr>
<tr>
<td>$J$(4,5)</td>
<td>9.3</td>
<td>9.6</td>
<td>9.3</td>
<td>9.0</td>
<td>a)</td>
<td>9.3</td>
<td>9.0</td>
</tr>
<tr>
<td>$J$(5,6)</td>
<td>9.3</td>
<td>9.2</td>
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<td>a)</td>
<td>9.2</td>
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<td>9.6</td>
<td>10.6</td>
<td>9.5</td>
<td>9.5</td>
<td>a)</td>
<td>9.5</td>
<td>9.2</td>
</tr>
<tr>
<td>$J$(7,8)</td>
<td>13.1</td>
<td>a)</td>
<td>a)</td>
<td>12.9</td>
<td>a)</td>
<td>a)</td>
<td>12.5</td>
</tr>
<tr>
<td>$J$(7,8’)</td>
<td>3.4</td>
<td>ca. 1</td>
<td>a)</td>
<td>a)</td>
<td>a)</td>
<td>a)</td>
<td>2.8</td>
</tr>
<tr>
<td>$J$(8,8’)</td>
<td>13.4</td>
<td>10.0</td>
<td>a)</td>
<td>12.9</td>
<td>12.5</td>
<td>10.6</td>
<td>12.5</td>
</tr>
<tr>
<td>$J$(7,71)</td>
<td>a)</td>
<td>3.4</td>
<td>4.4</td>
<td>3.7</td>
<td>a)</td>
<td>3.1</td>
<td>3.7</td>
</tr>
<tr>
<td>$J$(7,71’)</td>
<td>2.8</td>
<td>1.9</td>
<td>2.5</td>
<td>2.2</td>
<td>2.8</td>
<td>5.0</td>
<td>5.9</td>
</tr>
<tr>
<td>$J$(71,71’)</td>
<td>8.7</td>
<td>9.0</td>
<td>9.0</td>
<td>9.0</td>
<td>9.0</td>
<td>11.3</td>
<td>10.9</td>
</tr>
<tr>
<td>C(2)</td>
<td>49.61</td>
<td>49.70</td>
<td>28.77</td>
<td>27.17</td>
<td>26.97</td>
<td>a)</td>
<td>27.36</td>
</tr>
<tr>
<td>C(3)</td>
<td>59.77</td>
<td>58.76</td>
<td>51.73</td>
<td>37.42</td>
<td>37.86</td>
<td>a)</td>
<td>39.90</td>
</tr>
<tr>
<td>C(7)</td>
<td>40.06</td>
<td>39.80</td>
<td>41.58</td>
<td>40.29</td>
<td>40.92</td>
<td>a)</td>
<td>43.77</td>
</tr>
<tr>
<td>C(8)</td>
<td>32.64</td>
<td>32.17</td>
<td>35.28</td>
<td>33.62</td>
<td>34.32</td>
<td>a)</td>
<td>34.27</td>
</tr>
</tbody>
</table>

a) Not determined.
The MS spectrum of the ring-opened tosylamide 617 shows two \([M + Na]^+\) peaks at \(m/z = 808\) and 806 of about equal intensity, evidencing a Br substituent. CH2–C(1) resonate as two \(dd\) at 3.18 ppm \((J = 13.4, 6.5\) Hz) and 3.04 ppm \((J = 13.4, 8.1\) Hz), and NH as a \(dd\) at 3.62 ppm \((J = 7.8, 6.2\) Hz) (Table 3.2.5), evidencing that the NHTs moiety is bound to CH2–C(1) and not to C(1). H–C(2) appears as a \(d\) at 3.13 ppm \((J = 9.0\) Hz), indicating that C(1) is fully substituted. The configuration of C(1) was deduced from the large chemical shifts for H–C(5) \((2.29–2.15\) ppm) and H–C(3) \((4.03\) ppm) that indicate that Br–C(1) is axial.

The azidoalcohols 620 and 623 show strong IR bands for the N3 and OH groups. CH2–N3 resonate as two \(d’s\) at 3.74 and 3.34 ppm \((J = 12.8\) Hz) for 620, at 3.29 and 3.22 ppm \((J = 11.8\) Hz) for 623, at 4.10 and 3.45 ppm \((J = 14.0\) Hz) for the mesylate 621, and at 4.17 and 3.90 ppm \((J = 12.1\) Hz) for the mesylate 624. H–C(3) and H–C(5) of 623 and 624 (axial O–C(1)) are shifted downfield as compared to 620 \((\Delta \delta = 0.3\) ppm for H–C(3) and \(\Delta \delta = 0.4\) ppm for H–C(5)) and 621 \((\Delta \delta = 0.37\) ppm for H–C(3) and \(\Delta \delta = 0.4\) ppm for H–C(5)). H–C(2) \((\Delta \delta = 0.8\) ppm) and Hax–C(6) \((\Delta \delta = 0.94\) ppm) of 621 are shifted downfield as compared to 620. A downfield shift of ca. 20 ppm is observed for the C(1)s of 621 \((95.31\) ppm) and 624 \((94.00\) ppm) as compared to 620 and 623, confirming that the OMs group is bound to C(1). The coupling constants for the ring H evidence a \(4C_1\) conformation for 620, 623, 621, and 624. The geminal coupling constants for the axial CH2–N3 substituent of 620 and 621 are larger than those of the equatorial CH2–N3 of 623 and 624 \((\Delta J = 1.0\) to 1.9 Hz). The tertiary alcohol 623 and the mesylate 624 can adopt a conformation in which the OR group is gauche to both vicinal methylene H, an orientation of an electron withdrawing substituent that leads to a decreased (absolute) geminal coupling constant [682] [683].

The structure of the elimination product 626 is evidenced by a strong IR band at 2109 cm\(^{-1}\) for the N3 group, by a br. \(t\) at 6.36 ppm \((J = 1.2\) Hz) for CH–N3, and by the MS spectrum \((m/z = 570\) corresponding to \([M + Na – N2]^+\)). The \(^{13}\)C-NMR spectrum shows alkene signals at 126.55 and 120.32 ppm. The coupling constants for the ring H evidence a flattened \(4C_1\)\(^{as}\). The \((E)\) configuration of the olefinic double bond was not proven, but tentatively assigned. The \((Z)\)-diastereoisomer would suffer from a severe 1,5-strain and thus probably adopt a different conformation.

\(^{as}\) Generic locants are used in the \textit{Scheme} and \textit{Table} to describe 626. IUPAC nomenclature is used in the experimental part.
Table 3.2.5: Optical Rotation and Selected $^1$H- and $^{13}$C-NMR Chemical Shifts [ppm] and Coupling Constants [Hz] for 617, 620, 623, 621, 624, and 626.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>617</th>
<th>620</th>
<th>623</th>
<th>621</th>
<th>624</th>
<th>626</th>
</tr>
</thead>
<tbody>
<tr>
<td>[α]$_D^{25}$</td>
<td>a)</td>
<td>16.2</td>
<td>9.1</td>
<td>a)</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>CH–C(1)</td>
<td>3.18</td>
<td>3.74</td>
<td>3.29</td>
<td>4.10</td>
<td>4.17</td>
<td>6.36</td>
</tr>
<tr>
<td>CH′–C(1)</td>
<td>3.04</td>
<td>3.34</td>
<td>3.22</td>
<td>3.45</td>
<td>3.90</td>
<td>-</td>
</tr>
<tr>
<td>H–C(2)</td>
<td>3.13</td>
<td>3.62–3.49</td>
<td>3.46</td>
<td>4.38</td>
<td>3.54</td>
<td>3.92</td>
</tr>
<tr>
<td>H–C(3)</td>
<td>4.03</td>
<td>3.62–3.49</td>
<td>3.87</td>
<td>3.53</td>
<td>3.90</td>
<td>3.45</td>
</tr>
<tr>
<td>H–C(4)</td>
<td>3.57</td>
<td>3.62–3.49</td>
<td>3.54</td>
<td>3.66</td>
<td>3.62</td>
<td>3.58</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>2.29–2.15</td>
<td>1.75–1.62</td>
<td>2.21–2.09</td>
<td>1.79–1.66</td>
<td>2.25–2.13</td>
<td>1.72–1.60</td>
</tr>
<tr>
<td>H–C(6)</td>
<td>2.09–1.91</td>
<td>2.06</td>
<td>1.80</td>
<td>2.66</td>
<td>2.40</td>
<td>2.73</td>
</tr>
<tr>
<td>H′–C(6)</td>
<td>2.09–1.91</td>
<td>1.58</td>
<td>1.67</td>
<td>2.52</td>
<td>1.89</td>
<td>1.80</td>
</tr>
<tr>
<td>CH–C(5)</td>
<td>3.70</td>
<td>3.66</td>
<td>3.76</td>
<td>3.46</td>
<td>3.92</td>
<td>3.65</td>
</tr>
<tr>
<td>CH′–C(5)</td>
<td>3.40</td>
<td>3.45</td>
<td>3.43</td>
<td>3.51</td>
<td>3.43</td>
<td>3.52–3.47</td>
</tr>
<tr>
<td>N–H</td>
<td>3.62</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>OH</td>
<td>–</td>
<td>2.13</td>
<td>2.41</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>$J(1^1,1^1')$</td>
<td>13.4</td>
<td>12.8</td>
<td>11.8</td>
<td>14.0</td>
<td>12.1</td>
<td>(1.2)</td>
</tr>
<tr>
<td>$J(2,3)$</td>
<td>9.0</td>
<td>a)</td>
<td>9.3</td>
<td>9.3</td>
<td>9.7</td>
<td>7.5</td>
</tr>
<tr>
<td>$J(3,4)$</td>
<td>9.2</td>
<td>a)</td>
<td>9.3</td>
<td>9.3</td>
<td>9.3</td>
<td>8.7</td>
</tr>
<tr>
<td>$J(4,5)$</td>
<td>10.9</td>
<td>a)</td>
<td>10.9</td>
<td>9.3</td>
<td>10.9</td>
<td>9.5</td>
</tr>
<tr>
<td>$J(5,6)$</td>
<td>a)</td>
<td>2.5</td>
<td>4.1</td>
<td>3.7</td>
<td>3.4</td>
<td>3.7?</td>
</tr>
<tr>
<td>$J(5,6')$</td>
<td>a)</td>
<td>13.1</td>
<td>14.3</td>
<td>13.1</td>
<td>13.4</td>
<td>13.4</td>
</tr>
<tr>
<td>$J(6,6')$</td>
<td>a)</td>
<td>12.8</td>
<td>14.3</td>
<td>13.4</td>
<td>14.8</td>
<td>13.7</td>
</tr>
<tr>
<td>$J(5,5^1)$</td>
<td>4.1</td>
<td>4.1</td>
<td>4.1</td>
<td>4.7</td>
<td>3.7</td>
<td>4.7</td>
</tr>
<tr>
<td>$J(5,5^1')$</td>
<td>2.2</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>$J(5,5^1,5^1')$</td>
<td>9.0</td>
<td>9.0</td>
<td>9.0</td>
<td>9.0</td>
<td>9.3</td>
<td>9.0</td>
</tr>
<tr>
<td>CH$_2$–C(1)</td>
<td>a)</td>
<td>54.49</td>
<td>57.89</td>
<td>52.94</td>
<td>53.46</td>
<td>–</td>
</tr>
<tr>
<td>C(1)</td>
<td>a)</td>
<td>75.68</td>
<td>74.67</td>
<td>95.31</td>
<td>94.00</td>
<td>a)</td>
</tr>
<tr>
<td>C(5)</td>
<td>a)</td>
<td>38.64</td>
<td>37.39</td>
<td>38.64</td>
<td>37.83</td>
<td>42.24</td>
</tr>
<tr>
<td>C(6)</td>
<td>a)</td>
<td>33.80</td>
<td>33.02</td>
<td>30.94</td>
<td>32.67</td>
<td>30.39</td>
</tr>
</tbody>
</table>

a) Not determined.
The structure of the ring-opened 627-HCl and 628-HCl (Scheme 3.2.10) was assigned on the basis of MS and 1H-NMR data. The ESI+-MS spectrum of the mixture of 627-HCl and 628-HCl shows peaks at 224 ([M + MeOH + 1]+) and 192 ([M + 1]+) for 628, and pairs of peaks with an intensity ratio of 1:2 (typical for chloro compounds) at 250 and 248 ([M + Na]+) and 228 and 226 ([M + 1]+), and peaks at 222 ([M – Cl + MeOH]+) and 190 ([M – Cl]+, i.e. [M(47) + 1]+) for 627.

Scheme 3.2.10

In the 1H-NMR spectrum of the mixture 627-HCl/628-HCl, CH3 of 628-HCl resonates as a s at 1.43 ppm. CH2–C(1) of 627-HCl resonates as two d (J = 12.3 Hz) at 4.11 and 3.85 ppm. The large geminal coupling constant excludes the structure of an aziridinium ion. The large chemical shift indicates that Cl and not NH3+ is bound to CH₂–C(1) (cf. the CH₂–C(1) signals of aminomethylcyclohexane hydrochloride (2.94 ppm) [891] vs. chloromethyl-cyclohexane (3.31 ppm) [892], 1-aminomethyl-1-chloro-cyclohexane hydrochloride (3.04 ppm) [893] vs. 1-chloromethylcyclohexylamine hydrochloride (3.43 ppm) [894], and 1-aminomethyl-1-bromocyclohexylamine hydrobromide (3.1 ppm) vs. 1-bromomethyl-cyclohexylamine hydrobromide (3.33 ppm) [895]). The product 627-HCl is the result of an acid-catalysed regioselective attack of Cl⁻ on the less highly substituted carbon atom of the aziridine, cf. [894 – 897].
3.2.3. 1-epi-Validamine

1-Epi-validamine (48) which I wanted to include as a reference compound in the inhibition studies of the diaziridines and aziridines was prepared stereoselectively from the known axial alcohol 54 [234] (Scheme 3.2.11). Mesylation of 54 (93%), followed by substitution of the mesylate group with NaN₃ in DMF gave the azide 630 (94%) which was hydrogenated over Pd-C in MeOH/HCl to yield 1-epi-validamine (48) in an almost quantitative yield.

Scheme 3.2.11

\[
\text{Scheme 3.2.11}
\]

\[
\begin{align*}
&\text{54 } R = \text{ H} \\
&\text{629 } R = \text{ Ms} \\
&\text{630} \\
&\text{48}
\end{align*}
\]

\( a) \text{ MsCl, pyridine; 93\%}. \quad b) \text{ NaN}_3, \text{ DMF; 94\%}. \quad c) \text{ H}_2 (6 \text{ bar}), \text{ Pd-C, MeOH, HCl; 100\%}. \)
3.2.4. Inhibition of the β-Glucosidase from *Caldocellum saccharolyticum*, the β-Glucosidases from Sweet Almonds, and the α-Glucosidase from Brewer’s Yeast by the Diaziridines 45 and 615, the Aziridines 46 and 47, and 1-Epi-Validamine (48)

The diaziridines 45 and 615, the aziridines 46 and 47, and 1-epi-validamine (48) were evaluated as inhibitors of the β-glucosidase from *Caldocellum saccharolyticum*, the β-glucosidases from sweet almonds, and the α-glucosidase from brewer’s yeast. To this end, I measured the rate of hydrolysis of 4-nitrophenyl β-D-glucoside by the β-glucosidases and of 4-nitrophenyl α-D-glucoside by the α-glucosidase in the presence of various concentrations of the potential inhibitors. The diaziridines, the aziridines, and 1-epi-validamine are, at best, weak inhibitors of these enzymes (Table 3.2.6).

At pH 6.8, 45 did not inhibit any of these glucosidases. At pH 4.2, 45 inhibited the β-glucosidase from *C. saccharolyticum* very weakly and proved inactive against the sweet almond β-glucosidases. At pH 6.8, the N-benzyl diaziridine 615 was a weak inhibitor of the α-glucosidase (IC₅₀ = 1.7mM); as expected, the hydrophobic aglycon mimic leads to a (slightly) stronger inhibition [92]. The diazirine 613 did not significantly inhibit any of the enzymes tested.
Table 3.2.6: Inhibition of the β-Glucosidases from Sweet Almonds, the β-Glucosidase from *Caldocellum saccharolyticum* and the α-Glucosidase from Brewer’s Yeast ([IC₅₀] in mM at pH 6.8) by the Diaziridines 45 and 615, the Diazirine 613, the Aziridines 47 and 46, 1-epi-Validamine (48), Validamine (12) [31], and the Cyclopentylamines 35 and 36 [211] [213].

<table>
<thead>
<tr>
<th>Inhibitor (pKHA)</th>
<th>β-Glucosidase (Sweet Almonds)</th>
<th>β-Glucosidase (C. saccharolyticum)</th>
<th>α-Glucosidase (Brewer’s Yeast)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 (2.6) j)</td>
<td>no inh. at 8.8mM</td>
<td>no inh. at 2.2mM a)</td>
<td>no inh. at 8.8mM</td>
</tr>
<tr>
<td>615</td>
<td>no inh. at 3.7mM b)</td>
<td>≈ 1.7</td>
<td></td>
</tr>
<tr>
<td>613</td>
<td>no inh. at 5.8mM b)</td>
<td>no inh. at 11.6mM</td>
<td></td>
</tr>
<tr>
<td>47 c)</td>
<td>ca. 30% inh.</td>
<td>ca. 10% inh.</td>
<td>ca. 50% inh. d)</td>
</tr>
<tr>
<td>46 (6.8)</td>
<td>no inh. at 1.3mM 3e) (irreversible)</td>
<td>≈ 1 f)</td>
<td></td>
</tr>
<tr>
<td>48 (8.4)</td>
<td>1.7</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>12 g)</td>
<td>1.5</td>
<td>–</td>
<td>0.58</td>
</tr>
<tr>
<td>35 h) (7.9)</td>
<td>0.0034 e)</td>
<td>0.00018 e)</td>
<td>0.013 e)</td>
</tr>
<tr>
<td>36 i)</td>
<td>0.0065 e)</td>
<td>0.0015 e)</td>
<td>0.0006 e)</td>
</tr>
</tbody>
</table>

a) At pH 4.2 ca. 20% inhibition at 6.6mM. b) Not determined. c) Ca. 100 µM solution. d) After 20 min., irreversible. e) Ki value. f) At pH 5.0: no inhibition at 1.3mM. g) Data from [31]. h) Inhibition data from [211]. i) [213]. j) The author is indebted to Dr. N. Panday for double checking and confirming the very weak inhibition by 45.

The aziridine 46 did not inhibit the almond β-glucosidases (pH 6.8). It proved a weak irreversible inhibitor of the β-glucosidase from *C. saccharolyticum* (Figure 3.2.1), and a weak reversible inhibitor of the α-glucosidase from brewer’s yeast. The inhibition of the α-glucosidase was abolished at pH 5.0, likely due to protonation of both the inhibitor and the catalytic acid. The crude aziridine 47 appears to be a weak reversible inhibitor of the β-glucosidases, and a weak irreversible inhibitor of the α-glucosidase 49). Irreversible inhibition by the aziridines most likely results from an acyloxylation aziridine ring opening.

49) The concentration of 47 in the enzyme tests was assumed to be 100 µM. This is an upper limit, as this concentration implies a quantitative yield of the Birch reduction of 622.
**Figure 3.2.1:** Inactivation of the $\beta$-Glucosidase from *Caldocellum saccharolyticum* by 46. Plot of the ln of the residual activity vs. time.

Also 1-*epi*-validamine (48) proved a weak inhibitor of all three enzymes, with $IC_{50}$ values in the millimolar range, similar as its epimer validamine (12) [31].

The very low inhibition by the diaziridines, aziridines, and *epi*-validamine suggests that structural factors rather than basicity are at the root of the weak interaction of the glycosidases tested. Basicity does have some effect and the lower basicity of the diaziridine 45 as compared to the one of the aziridine 46 may contribute to the lower inhibition by 45. Legler has reported that only glycosylamines with a $pK_{HA}$ higher than 5 are strong glycosidase inhibitors [58]. The particularly low inhibition of the $\beta$-glucosidase by 45 and 46 is probably due to steric crowding due to the relatively bulky (as compared to H) NH or CH$_2$ "$\alpha$-anomeric" substituent and the catalytic nucleophile. Superimposing the diaziridine 45 over the imidazole 19 in complex with the $\beta$-glucosidase from white clover ([14]) (the ring atoms C(3), C(4), and C(5) (sugar nomenclature) were superimposed) suggested a steric clash between the diaziridine and the catalytic nucleophile (1.45 Å distance between N of the inhibitor and O of the catalytic nucleophile vs. 3.16 Å distance between the pseudoanomeric C of the imidazole and O of the nucleophile, Figure 3.2.2; the sum of the *Van der Waals* radii of O and N is 2.9 Å). In an attempt to minimise this structure (constraining all the atoms belonging to the enzyme), the diaziridine was pushed away from the catalytic nucleophile (not shown), presumably to alleviate the steric interaction between the diaziridine and the catalytic nucleophile.
Figure 3.2.2: (a) Modelled Complex of the Imidazole 19 and the Active Site of White Clover β-Glucosidase ([14]). (b) The Diaziridine 45 in the Position of the Imidazole in (a) (See Text). A Clash Between the "α"-NH-Moiety and the Catalytic Nucleophile is Evident.

(a)

(b)

The importance of shape vs. basicity is further highlighted by the striking difference between the inhibitory action of the cyclohexylamine 48 ($IC_{50}$ ca 1 mM; $pK_{HA} = 8.4$) and the
cyclopentylamine 35 \([372]\) \((K_i \text{ between } 0.2 \text{ and } 13 \mu \text{M} \text{ [211] [213]; } pK_{HA} = 7.9)\). The small difference between the \(pK_{HA}\) values of the two compounds cannot account for this difference in the affinity to the enzymes. Both inhibitors will be mostly in the protonated form at pH 6.8.

To further study the inhibition of the \(\beta\)-glucosidases from almonds by the cyclopentylamine 35, I examined the pH dependence of the inhibition between pH 5.0 and pH 7.8 (Figure 3.2.3\(^50\)). Between pH 6.2 and 7.8, the inhibition was nearly constant, but it was significantly reduced at pH 5.0. This behaviour, similar to the one of \(\beta\)-glucosyl pyridinium ion \([135]\), suggests that the protonated form of 35 binds to the enzyme. The stronger inhibition at higher pH values might alternatively suggest binding of the unprotonated amine, but the kink in the curve shown below does not correspond to the \(pK_{HA}\) value of 7.9 for 35 in water; it might, however, correspond to a decreased \(pK_{HA}\) value of 35 in the active site.

**Figure 3.2.3:** pH-Dependent Inhibition of the \(\beta\)-Glucosidases from Sweet Almonds by 35.

The stronger inhibition by the cyclopentylamine 35 may be traced back to its relative conformational flexibility, allowing it to adapt to the enzyme's active site, whereas the cyclohexane derivatives are fixed in a \(^4C_1\) conformation. The cyclopentylamine probably binds in a conformation with a pseudoaxial amino group, rendering it a better mimic of a distorted reactive substrate conformation or of the transition state. In contrast, the cyclohexane derivatives are undistorted substrate or product analogues. Their distortion to a

\(^{50}\text{I thank Dr. B. Bernet for generously providing a sample of 35.}\)
or flattened conformation requires too much energy.

For some endo-glycosidases from families 5 and 7 it was proposed that the substrate first binds in a $^{4}C_1$ conformation, bypassing the active site, and then is pulled into the active site and simultaneously distorted to a boat-like reactive conformation (see Chapter 1.6). There is no evidence for a similar “bypass binding” in exo-glycosidases. However, this does not mean that such a “bypass binding” must be ruled out for exo-glycosidases. If the $\beta$-glucosidases studied here bound their substrates in a "bypassing" mode the substrate analogous cyclohexanes might bind in such a bypass fashion.
3.3. Synthesis and Evaluation as Glycosidase Inhibitors of 5a-Amino-5a-Carbaglucopyranoses

3.3.1. Introduction

The much stronger glycosidase inhibition by the aminocyclopentitols 35 and 36 as compared to the aminocyclohexitols 48 and 12 (Table 3.2.6) justified further scrutiny. In the conformation depicted in Scheme 3.3.1 – which is likely to be the binding conformation for 35 (vide supra) – the aminocyclopentitols resemble the 5a-amino-carbapyranooses 49 and 50 with C(1) removed. This raised the question if such 5a-aminocarbapyranooses are equally potent glycosidase inhibitors, or if the strong inhibition of the aminocyclopentitols depended on the cyclopentane scaffold. To address this question, I embarked upon the synthesis of 5a-aminocarbapyranooses like 49 and 50. In the literature, no inhibition data for such aminocyclohexitols was found. Some 5a-amino-1-deoxycarbapyranooses were prepared as aminocyclitol analogues, but no inhibition data were given [235].

Scheme 3.3.1

3.3.2. Results and Discussion

While one may conceive several routes to the desired aminocyclohexitols (cf. [226] [235]), a regioselective electrophilic functionalisation of tetra-\(O\)-benzylvalidone (52) appeared the most straightforward approach.
Bromination of 52 with PhMe$_3$NBr$_3$ in the presence of camphorsulfonic acid (CSA) [237] [238] gave the axial bromide 631 (58%), which was transformed into the equatorial azide 56 by nucleophilic substitution (NaN$_3$, DMF, 91%) (Scheme 3.3.2). Attempts to prepare the corresponding axial azide by enolisation of 52 and azidation of the enolate with 2,4,6-triisopropylbenzenesulfonyl azide [236] failed (the starting material was re-isolated). Other routes to the axial epimers 49 were not examined, as time ran out. DIBALH reduction of the ketone 56 and chromatography gave the equatorial alcohol 632 (44%) and a ca. 1:1 mixture of 632 and the axial alcohol 633 (47%). NaBH$_4$ reduction of 56 gave the axial alcohol 633 exclusively (73%). Catalytic hydrogenation of 632 and 633 in acidic MeOH afforded the aminocyclohexitols 634 and 635 as their hydrochlorides in nearly quantitative yield.

Scheme 3.3.2

\[ \text{52} \xrightarrow{a)} \text{631} \xrightarrow{b)} \text{56} \]
\[ \text{632} \xrightarrow{d)} \text{634} \xrightarrow{d)} \text{635} \]
\[ \text{633} \]

a) PhMe$_3$NBr$_3$, camphorsulfonic acid, THF; 58%. b) NaN$_3$, DMF; 91%. c) i. iBu$_2$AlH, CH$_2$Cl$_2$; 44% of 632 and 47% of a ca. 1:1 mixture of 632 and 635. ii. NaBH$_4$, THF; 73% of 635. d) H$_2$, Pd/C, MeOH; 100% of 634·HCl·H$_2$O·MeOH; 100% of 635·HCl·H$_2$O.

The 5a-aminocarbapyranoses 634 and 635 are only weak inhibitors of the $\beta$-glucosidases of sweet almonds and the $\alpha$-glucosidase from brewer's yeast (Table 3.3.1), in contrast to the micromolar inhibition of these enzymes by the aminocyclopentitol 36 [213]. Interestingly, 634 displayed sigmoidal binding to the $\alpha$-glucosidase, indicating cooperative binding. Shortage of time did not allow me to study the inhibition by 634 in more detail, so as to
establish the type of inhibition. A literature search on cooperative or sigmoidal binding to the \( \alpha \)-glucosidase from brewer’s yeast returned no hits. 5a-aminocarbapyranoses of the type 49 with an axial NH\(_2\) group have not yet been prepared.

The much stronger inhibition by the aminocyclitol 35 [213] as compared to the 5a-aminocarbapyranoses suggests that the potency of 36 depends largely on the cyclopentane scaffold. The cyclopentane scaffold – as discussed before (\textit{vide supra}) – may allow a better mimicry of a distorted reactive substrate conformation in so far as 35 may adopt a conformation with pseudoaxial NH. Why 36 with an "\( \alpha \)"-NH\(_2\) substituent is such a good inhibitor of the \( \beta \)-glucosidase is not evident – its NH\(_2\) group might interact with the catalytic nucleophile. The cyclohexanes differ significantly from the cyclopentanes by the presence of C(1) which, in a chair conformation, may interact unfavourably with the catalytic nucleophile of a \( \beta \)-glycosidase. The cyclopentanes ("no C(1)") may be better mimics of an oxycarbenium ion like transition state (\( \Phi(C(5)–O–C(1)–C(2)) \approx 0^\circ \)) than the cyclohexanes (\( \Phi(C(5)–C(5a)–C(1)–C(2)) \approx 60^\circ \)).

![Chemical structures](image)

**Table 3.3.1:** Inhibition of the \( \beta \)-Glucosidases from Sweet Almonds and of the \( \alpha \)-Glucosidase from Brewer’s Yeast by the 5a-Aminocarbapyranoses 634 and 635 (\( IC_{50} \) Values in mM) and by the Aminocyclopentitol 36 (\( K_i \) Values in mM [213]).

<table>
<thead>
<tr>
<th></th>
<th>634</th>
<th>635</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta )-Glucosidase (Almonds)</td>
<td>\textit{ca.} 1</td>
<td>&gt; 1</td>
<td>0.0065</td>
</tr>
<tr>
<td>( \alpha )-Glucosidase (Yeast)</td>
<td>\textit{ca.} 0.4 a)</td>
<td>&gt; 1</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

a) Sigmoidal binding.

In the following discussion arbitrary locants are used; IUPAC nomenclature is used in the experimental part.

The vicinal coupling constants for the ring H (Table 3.3.2) evidence a \( 4C_1 \) conformation for 631, 56, 632, 633, 634, and 635.

H–C(6) of the bromide 631 resonates as a \( d \) at 4.67 ppm. The small \( J(5,6) = 3.4 \) Hz) evidences that Br is axial.
The azide 56 gives rise to a strong IR (CHCl₃) band at 2110 cm⁻¹. In the ¹H-NMR spectrum, H–C(6) resonates as a dd at 4.24 ppm. J(5,6) = 12.5 Hz evidences that N₃ is equatorial. Long-range coupling is observed between the 1,3-diaxial H–C(2) and H–C(6) (1.5 Hz).

The azidoalcohols 632 and 633 give rise to IR (CHCl₃) OH bands at 3588 and 3579 cm⁻¹, respectively, and N₃ bands at 2108 and 2105 cm⁻¹, respectively. H–C(1) of 632 resonates as a td at 3.51 ppm, H–C(2) and H–C(6) resonate as t at 3.38 and 3.59 ppm, respectively. The large J(1,2) = 9.2 Hz and J(1,6) = 10.0 Hz evidence that N₃ and HO–C(1) are equatorial. The H–C(1) m of 633 resonates at 4.29–4.20 ppm, H–C(2) resonates as a dd at 3.41 ppm, and H–C(6) resonates as a ddd at 3.46 ppm. J(1,2) = 2.6 Hz and J(1,6) = 2.5 Hz evidence that HO–C(1) is axial. The large J(5,6) = 11.8 Hz evidences that N₃ is equatorial. Weak w coupling is observed between HO–C(1) and H–C(6) (1.3 Hz).

The ¹H-NMR spectrum (CD₃OD) of 634 is complex, precluding a detailed analysis. For 635, H–C(1) resonates as a t at 4.02 ppm, H–C(2) and H–C(6) appear as a m at 3.36–3.28 ppm. The small J(1,2) = J(1,6) = 2.6 Hz evidence that HO–C(1) is axial.

Interestingly, the vicinal coupling constants between H–C(5) and CH₂–C(5) of 631, 56, and 633 differ in a characteristic way (Table 3.3.2). In the bromide 631, the coupling constant between H–C(5) and CH–C(5) (2.2 Hz) is smaller than that between H–C(5) and CH'–C(5) (4.0 Hz). This is consistent with a preferred gt conformation of the benzyloxyethyl group as shown. For the equatorial azide 56, the coupling constants are similar to each other (1.7 and 2.3 Hz, respectively), consistent with a gg conformation, as shown. This conformational change may be due to a 1,3-strain between N₃ and OBn in the gt conformation of 56. The coupling constants for the axial alcohol 633 (J(5,7) = 1.6 Hz, J(5,7') = 5.0 Hz), but not those for the equatorial alcohol 632, are, in turn, similar to those of 631, again suggesting a gt conformation. This conformational difference between the benzyloxyethyl groups of the ketone 56 and the axial alcohol 633 could be the result of a destabilising long range interaction between OBn and OH in the gg conformation, or of a stabilising long range interaction in the observed gt conformation. However, for 1,4-difluorobutane, the G⁺AG⁻ conformer (corresponding to the gg conformer of 633) is the most stable, followed by the ca. 0.5 kcal/mol less stable G⁺AG⁺ conformer (corresponding to gt) [898]. The conformational change of the BnO–CH₂–C(5) moiety could also be induced by the conformational changes resulting from the rehybridisation of C(1) from sp² to sp³.
Table 3.3.2: Selected $^1$H and $^{13}$C NMR Shifts [ppm] and Coupling Constants [Hz] for 631, 56, 632, 633, 634-HCl, and 635-HCl.

<table>
<thead>
<tr>
<th></th>
<th>631</th>
<th>56</th>
<th>632</th>
<th>633</th>
<th>634</th>
<th>635</th>
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<tr>
<td>H–C(1)</td>
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<td>–</td>
<td>3.51</td>
<td>4.29–4.20</td>
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<td></td>
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<tr>
<td>H–C(2)</td>
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<td>4.16</td>
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<td>3.37–3.13</td>
<td>3.41</td>
<td>3.36–3.28</td>
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<td>3.70</td>
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<td>3.90</td>
<td>3.61</td>
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<td>4.00</td>
<td>3.72</td>
<td>3.37–3.13</td>
<td>3.61</td>
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<tr>
<td>H–C(5)</td>
<td>2.17</td>
<td>1.73</td>
<td>1.50</td>
<td>1.70</td>
<td>2.24</td>
<td>2.04</td>
</tr>
<tr>
<td>H–C(6)</td>
<td>4.67</td>
<td>4.24</td>
<td>3.59</td>
<td>3.05</td>
<td>3.46</td>
<td>3.36–3.28</td>
</tr>
<tr>
<td>CH–C(5)</td>
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<td>4.02</td>
<td>3.89</td>
<td>3.93</td>
</tr>
<tr>
<td>CH’–C(5)</td>
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<td>J(1,2)</td>
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<td>9.2</td>
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</tr>
<tr>
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<td>a)</td>
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</tr>
<tr>
<td>J(5,7)</td>
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<tr>
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<tr>
<td>J(7,7')</td>
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<td>9.3</td>
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<td>a)</td>
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<td>a)</td>
</tr>
<tr>
<td>J(6,OH)</td>
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<td>a)</td>
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<tr>
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</tr>
<tr>
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<tr>
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<td>63.05</td>
<td>61.49</td>
<td>54.58</td>
<td>58.69</td>
<td>52.80</td>
</tr>
</tbody>
</table>

a) Not assigned. b) Assignment by analogy, not proven.
3.4. Conclusions and Outlook

Using the Schmitz method, I have established a straightforward synthesis of the carbasugar-derived spiro-diaziridines 45 and 615 from validoxylamine A. While Birault tried without success to attach the hydrazi group to C(5a) of an O–TBS-protected 5a-carbapyranose, I attached the hydrazi group to the less hindered C(1) of an O–TMS-protected 5a-carbaglucose. I showed that the trimethylsilyl ethers play an active role in the formation of 45 by sequestering H2O.

Attempts to prepare the carbasugar-derived aziridines 46 and 47 by aziridination of the validoxylamine A-derived alkene 53 were not successful. However, 46 and 47 were obtained in reasonable yields via the epoxides 619 and 618.

The stereoselective synthesis of epi-validamine (48) from 54 allowed for a ready isolation of the unprotected inhibitor, whereas the previous synthesis gave validamine (12) along with 48 and required separation of the epimers by ion exchange chromatography [224].

The diaziridines 45 and 615, the aziridines 46 and 47, and epi-validamine (48) are pyranoside analogues with pK_HA values ranging from 2.6 (45) to 6.8 (46) to 8.4 (48). These cyclohexane derivatives are only weak inhibitors of the glycosidases tested, in contrast to the strong inhibition by the cyclopentylamines 35 (pK_HA = 7.9) and 36 [211] [213]. Carbafulanose-derived spiro-diaziridines and -aziridines corresponding to 35 and 36 might be the subject of future studies. They would allow examining the effect of structure and basicity on glycosidase inhibition within the context of the cyclopentane scaffold.

To obtain deeper insight into the strong inhibition by the cyclopentylamine 36, I prepared the related 5a-amino-5a-carbapyranoses 634 and 635. The weak inhibition by 634 and 635 suggested that the strong inhibition by 36 depends on the cyclopentane scaffold. The cyclopentanes ("no C(1)") may be better mimics of an oxycarbenium ion like transition state (Φ(C(5)–O–C(1)–C(2)) = 0°) than the cyclohexanes (Φ(C(5)–C(5a)–C(1)–C(2)) = 60°). The sigmoidal binding of 634 to the α-glucosidase from yeast may warrant further studies.

4.1. Introduction

The goal of this part of my thesis was the synthesis of 6-azabicyclo[3.1.1]heptanes such as 57 (Figure 4.1.1) and of 7-azabicyclo[2.2.1]heptanes such as 58 and 59 as potential glycosidase inhibitors.

Figure 4.1.1: Potential Glycosidase Inhibitors.

6-Azabicyclo[3.1.1]heptanes have never been examined as glycosidase inhibitors. The only 7-azanorbornanes that are known to act as glycosidase inhibitors are the aminodiols (–)-641 and (+)-641 (Figure 4.1.2). They were prepared by Vogel et al. as rigid bicyclic analogues of 2-aminomethylpyrrolidines, known glycosidase inhibitors [240]. The aminodiols (–)-641 and (+)-641 inhibited the β-glucosidases from almonds (\(K_i = 55\) and 117 \(\mu\)M, respectively), the β-galactosidase from bovine liver (65% and 90% inhibition at 1 mM, respectively) and the \(\alpha\)-glucosidase from baker yeast (82% and 74% inhibition at 1 mM, respectively). These 7-azanorbornanes were, however, weaker inhibitors than the conformationally flexible 2-aminomethylpyrrolidines.


**Figure 4.1.2:** Known 7-Azanorbornane Inhibitor.

![Figure 4.1.2](image)

4.1.1. Synthesis of 6-Azabicyclo[3.1.1]heptanes

Azetidines are prepared by intramolecular substitution forming the C–N or (in far fewer cases) the C(2)–C(3) bond, by thermal or photochemical [2+2] cycloaddition of imines and alkenes, by [3+1] cycloaddition between azomethine ylides and sulfonium or sulfoxonium ylides or isonitriles, and by ring contraction of azacycloalkanes, or by ring expansion of aziridines (for reviews, see [899 – 901]).

Only a few 6-azabicyclo[3.1.1]heptanes have been reported in the literature. The parent compound, 6-azabicyclo[3.1.1]heptane (644, Scheme 4.1.1) was synthesised in low yield by base-catalysed intramolecular nucleophilic substitution (NaOH, H2O) from t-3-bromocyclohexylamine (643), which in turn was obtained from resorcine in seven steps [243]. Parcell et al. reported the formation of the 6-azabicyclo[3.1.1]heptanes 646 (55%) and 647 (28%) upon treatment of the trans-2-(methylamino)-6-bromocyclohexanone 645 with NaBH4 in refluxing THF [244]. The reaction was assumed to proceed by reduction of the carbonyl group of 645, followed by cyclisation of the resulting alcohols. A Staudinger reaction of the azidodiol 649 with Ph3P led to the aziridine 650 (40%) besides 24% of the 6-aza-bicyclo[3.1.1]heptane 651 [902]. The reaction of the mesylate 652 with NaN3 in DMF at 93° gave 12% of the desired azide 653 besides 22% of the azetidine 654 [903]. The amines 645 and 652 and the azide 649 are expected to adopt a conformation with axial N nucleophile and equatorial leaving group, which is expected to favour cyclisation to the bicyclic azetidines. An N,N-dimethyl azoniabicyclo[3.1.1]heptane was formed in 8% yield in the fragmentation of trans-3-(dimethylamino)cyclohexyltosylate [904]. A 6-azabicyclo[3.1.1]hept-2-ene was formed as a byproduct in the radical detosylation of a 3-toluenesulfonyl 7-azabicyclo[2.2.1]hept-2-en [905].
In the context of a synthesis of epibatidine, Corey and coworkers reported the formation of the bicyclic azetidine 656 (Scheme 4.1.2) in a yield of 85% upon treatment of the trifluoroacetamide 655 with NBS in AcOH [241]. The postulated transformation of 655 to 656 is remarkable in that it implies N- rather than O-alkylation of an amide by a bona fide epibromonium ion, and in that N-alkylation should lead to a four- rather than to a five-membered ring, i.e. to a 6-azabicyclo[3.1.1]heptane rather than to a 7-aza-
bicyclo[2.2.1]heptane. As a rule, electrophilic cyclisations of \( N \)-alkenylated amides involve the carbonyl oxygen and lead to oxazolines and dihydrooxazines [906]. In keeping with this rule, \( N \)-benzoyl-4-aminocyclohexene (657) cyclised to the bicyclic dihydro-1,3-oxazine 658 upon treatment with NBS in AcOH [907]. The formation of cyclic amides by \( N \)-alkylation is preferred if \( O \)-alkylation would lead to a strained product, or if the NH group is deprotonated [906].

Scheme 4.1.2

\[
\begin{align*}
\text{655} & \quad \xrightarrow{a)} \quad \text{656} \\
\text{657} & \quad \xrightarrow{b)} \quad \text{658}
\end{align*}
\]

\( a \) NBS, AcOH, 0\(^\circ\) to 23\(^\circ\); 85\% [241]. \( b \) NBS, AcOH, r.t.; 26\% [907].

A related 5-azabicyclo[2.1.1]hexane 661 (Scheme 4.1.3) was prepared in 84\% yield by cyclisation (KOrBu, DMF, benzene) of \( N \)-benzoyl \( t \)-3-chlorocyclopentylamine (660) which in turn was obtained in three steps from 659, the Diels-Alder adduct of cyclopentadiene and nitrosyl benzoate [908].

Scheme 4.1.3

\[
\begin{align*}
\text{659} & \quad \xrightarrow{a)} \quad \text{660} \quad \xrightarrow{b)} \quad \text{661}
\end{align*}
\]

\( a \) i. H\(_2\), Pd/C, EtOH; 95\%; ii. Al(Hg), THF, H\(_2\)O; 95\%; iii. SOCl\(_2\), Et\(_3\)N, CHCl\(_3\); 65\% [908]. \( b \) KOrBu, DMF, benzene; 83\% [908].
4.1.2. Synthesis of 7-Azabicyclo[2.2.1]heptanes

As the scaffold of the alkaloid epibatidine (668, Scheme 4.1.4) [909] and of several pharmacological agents [910] 7-azanorbornanes have received much synthetic interest (for recent reviews, see [910 – 912]). 7-Azanorbornanes and 7-azanorbornenes have been synthesised by Diels-Alder reaction of pyrrole derivatives with appropriate dienophiles, by 1,3-dipolar addition of pyrrole-derived azomethine-ylides with dipolarophiles, by cyclisation of cyclohexylamine derivatives forming the C-N-bond, by cyclisation of pyrrolidine-derivatives forming the C–C-bond [913] [914], or by ring contraction of tropinone derivatives [915 – 917].

The [4+2]-cycloadditions yield 7-azanorbornanes in a single step, but these reactions are often low yielding (see [910 – 912]). They require high pressure [918] or activated reagents that have to be synthesised, and additional steps may be necessary to remove activating groups [240] [919 – 924]. These issues are illustrated by the first and very straightforward synthesis of epibatidine (five steps, 4% overall yield) reported by Clayton and Regan [925]. Thus, the Diels-Alder cycloaddition between N-methoxycarbonylpyrrole (662) and tosyl-acetylene (663) gave in moderate yield (35%) the 7-azanorbornadiene 664, which was hydrogenated to the 7-azanorbornene 665 (99%) [925]. The tosyl group of 665 was removed using Na-Hg (39%) [925]. Pd-catalysed reductive coupling between 666 and the pyridyl iodide 667 (35%), followed by deprotection gave epibatidine (668) in 26% yield (for an enantioselective variant of the Pd-coupling, see [926]).

Scheme 4.1.4

\[ \text{CO}_2\text{Me} \quad + \quad \text{Ts} \quad \rightarrow \quad \text{CO}_2\text{Me} \quad \text{Ts} \quad \rightarrow \quad \text{CO}_2\text{Me} \quad \text{Ts} \quad \rightarrow \quad \text{CO}_2\text{Me} \quad \text{Cl} \quad \rightarrow \quad \text{CO}_2\text{Me} \quad \text{Cl} \]

\[ a) \text{Neat, 80 – 85°C; 36% [925] or CH}_2\text{Cl}_2, 12 \text{kbar, 85 – 87°C; 81% [927].} \]
\[ b) \text{H}_2, \text{Pd/C, MeCN; 99% [925].} \]
\[ c) \text{Na-Hg, Na}_2\text{HPO}_4, \text{NaH}_2\text{PO}_4, \text{MeOH, THF; 39% [925].} \]
\[ d) i. \text{(Ph}_3\text{P)}_2\text{Pd(OAc)}_2, \text{DMF, piperidine, HCO}_2\text{H; 35%}; \text{ii. HBr, AcOH; 74% [925].} \]
The yield of the cycloaddition to 664 was improved to 81% by performing the Diels-Alder reaction under high pressure (12 kbar) [927]. Similarly, the Diels-Alder reaction between 662 and phenyl vinyl sulfone at 12 kbar furnished a 1:1 mixture of endo- and exo-N-methoxycarbonyl 5-phenylsulfonyl-7-azanorbornene (670, Scheme 4.1.5) in a yield of 95% [905].

Scheme 4.1.5

\[ \text{CO}_2\text{Me} \]
\[ \text{N} \]
\[ \text{662} \]
\[ + \]
\[ \text{SO}_2\text{Ph} \]
\[ \text{a)} \]
\[ \text{CO}_2\text{Me} \]
\[ \text{N} \]
\[ \text{670} \]
\[ \text{SO}_2\text{Ph} \]
\[ \text{MeCN, 12 kbar, 50°; 95% (endo/exo 1:1)} [905]. \]

A more efficient conversion of 665 to 666 (83% overall yield) was achieved by silylation of 665 to 671, diimide reduction to 672, and fragmentation with TBAF [927] (Scheme 4.1.6). An alternative transformation of 665 to 666 (72 – 89% overall yield) involved conjugated radical addition of tributyltin hydride to 665, followed by TBAF-induced fragmentation of 673 [928]. These appear to be the most efficient syntheses of 7-azanorbornanes and of epibatidine by the Diels-Alder cycloaddition of pyrroles.

Scheme 4.1.6

\[ \text{CO}_2\text{Me} \]
\[ \text{N} \]
\[ \text{665} \]
\[ \text{Ts} \]
\[ \text{a)} \]
\[ \text{CO}_2\text{Me} \]
\[ \text{N} \]
\[ \text{671} \]
\[ \text{Ts} \]
\[ \text{SiMe}_3 \]
\[ \text{b)} \]
\[ \text{CO}_2\text{Me} \]
\[ \text{N} \]
\[ \text{672} \]
\[ \text{Ts} \]
\[ \text{SiMe}_3 \]
\[ \text{c)} \]
\[ \text{CO}_2\text{Me} \]
\[ \text{N} \]
\[ \text{666} \]
\[ \text{a)} \text{LDA, THF, then Me}_3\text{SiCl; 97% [927].} \]
\[ \text{b)} \text{KO}_2\text{CN=NCO}_2\text{K, AcOH, MeOH; 99% [927].} \]
\[ \text{c)} \text{Bu}_4\text{NF, THF; 86% [927].} \]
\[ \text{d)} \text{Bu}_3\text{SnH, AIBN, benzene; 78 – 91% depending on the scale [928].} \]
\[ \text{e)} \text{Bu}_4\text{NF, THF; 93 – 98% [928].} \]
*Pandey et al.* reported the synthesis of a 7-azanorbornane by a [3+2]-cycloaddition [929]. Treatment of the pyrrolidine 674 (Scheme 4.1.7, prepared in four steps and 51% yield from N-Boc pyrrolidine) with AgF in acetonitrile generated the azomethine ylide 675 which reacted with phenyl vinyl sulfone to yield 90% of the 7-azanorbornane 676 [929]. For a few further examples of [3+2] cycloadditions to 7-azanorbornanes, see [910] [912].

### Scheme 4.1.7

![Scheme 4.1.7](image)

*a* AgF, MeCN, 669; 90% [929]

Cyclisation of cyclohexylamines remains a competitive route to 7-azanorbornanes. The required precursors possessing a 1,4-trans relation between nitrogen and a leaving group\(^{51}\) have been prepared by a (in some cases poorly) stereoselective reduction of 4-oxo-cyclohexylamines [930 – 938], by stereospecific transformations of 1,4-cis-cyclohexane derivatives ([312] [939 – 941]), by stereospecific transformations of natural cyclohexanes [942] [943], or *via* epoxidation [944 – 946], halocyclisation [947], halohydroxylation [948], and halogenation of cyclohex-3-enylamines [241] [242]. These transformations shall be illustrated by the following examples.

*Evans et al.* reported an asymmetric synthesis of epibatidine (668) from 677 and 678 in 12 steps and 14% overall yield *via* the aminocyclohexanone 680 [937] (Scheme 4.1.8). The diastereoselective (d.e. = 84%) reduction of 680 with NaBH\(_4\) in MeOH gave 82% of the equatorial alcohol 681. Stereospecific substitution of OH by Br and deboclylation afforded the \(t\)-4-bromocyclohexylamine 682 which cyclised to epibatidine in boiling CHCl\(_3\).

---

\(^{51}\) \(t\)-4-aminocyclohexanol hydrochloride is commercially available and has been transformed into 7-azanorbornane [908].
Aoyagi et al. reported an asymmetric synthesis of epibatidine (668) in eight steps and 7% overall yield via the 2-oxa-3-azabicyclo[2.2.2]octane 685 (prepared by an asymmetric hetero Diels-Alder cycloaddition) [939] (Scheme 4.1.9). Reductive cleavage of the N–O bond of 685 gave the alcohol 681 which was transformed into epibatidine in a similar way as shown in the preceding Scheme [937].
The amine 686, obtained from D-(-)-quinic acid in 12 steps, cyclised to the azanorbornane 687 (95%) in boiling toluene [942] (Scheme 4.1.10). In contrast, the isomeric amine 688 did not cyclise to the azetidine 689, but decomposed when heated in toluene or xylene under reflux.

Scheme 4.1.10

![Scheme 4.1.10]

\[ \text{D(-)-Quinic acid} \rightarrow 686 \rightarrow 688 \rightarrow \text{a) Toluene, reflux; 95\% [942].} \]

Corey and coworkers prepared epibatidine in 9 steps and 47% overall yield from the alkene 690 (Scheme 4.1.11). Key steps of the synthesis were a stereoselective bromination (Br₂ in the presence of 10 eq. of Bu₄NBr) of the N-acyl-4-aminocyclohexene 655 to 692 (96%), followed by base-catalysed cyclisation to the azanorbornane 693 [241]. Resolution of the racemate 655 allowed the first synthesis of (–)-epibatidine.

Scheme 4.1.11

\[ \text{690} \rightarrow 691 \rightarrow 655 \rightarrow 692 \rightarrow 693 \rightarrow 668 \]

\[ a) \text{ i. Toluene, 190°; 95\%. b) i. LiOH, THF; 100\%; ii. Et₃N, DPPA, toluene, then TMSCH₂CH₂OH; 95\%; iii. Bu₄NF, THF; iv. (CF₃CO)₂O, Et₃N, CH₂Cl₂; 80\% (two steps) [241]. c) 10 eq. of Et₄NBr, Br₂, CH₂Cl₂, –78°; 96\% [241]. d) KOtBu, THF; 75\% [241]. e) i. Bu₃SnH, AIBN, benzene; 95\%; ii. NaOMe, MeOH; 96\% [241].} \]
Bastable et al. reported a synthesis of N-methyl-2-exo-chloro-7-azanorbornane (696, Scheme 4.1.12) from N-methyl-cyclohex-3-enylamine (694) in two steps and 13% yield by chlorination (Cl2) to give a 1:1-mixture of 695 and 697, followed by cyclisation of 695 in DMF at 100°C [242]. The diastereoisomeric dichloride 697 did not cyclise to the azetidine 698 under these conditions, and more forcing conditions resulted in the formation of alkenes. No attempts were made to improve the stereoselectivity of the chlorination. HCl-elimination from the 2-chloro-7-azanorbornane was not investigated by these authors, but Fraser and Swingle reported their failure to eliminate HCl from exo-2-chloro-7-azanorbornane (which they obtained by radical chlorination of N-trichloroacetyl 7-azanorbornane) [930].

![Scheme 4.1.12](image)

\[ a \) 694-HCl, Cl₂, CH₂Cl₂, then aq. NaOH; 59% of a 1:1 mixture of 695 and 697 [242]. \( b \) DMF, 100°, then NaOH; 44% [242].

Avenoza et al. reported several syntheses of 7-azanorbornanes from branched N-acyl-4-amino-cyclohexenes, establishing the 1,4-trans relation between the amino substituent and a leaving group by iodocyclisation. Thus, treatment of 699 with NIS in CH₂Cl₂ gave the dihydro-1,3-oxazine 700 in quantitative yield [949] (Scheme 4.1.13). Hydrolysis of 700, followed by base-catalysed cyclisation gave the 7-azanorbornane 702 [947].

![Scheme 4.1.13](image)

\( R = (-)-(8\text{-}\text{phenylmenthyl}) \) \( a \) NIS, CH₂Cl₂; 100% [949]. \( b \) CF₃CO₂H, THF, H₂O; 99% [947]. \( c \) Na₂CO₃, EtOH; 94% [947].
Several N-chloro-cycloalkenylamines were transformed into bridged azabicycloalkanes by radical reactions [950 – 953], e.g. N-chloro-N-methyl-cyclooct-4-enylamine (703) into the azabicyclo[4.2.1]nonanes 704 and the azabicyclo[3.3.1]nonanes 705 [954] (Scheme 4.1.14). 7-Azabicyclo[2.2.1]heptanes and 6-azabicyclo[3.3.1]heptanes, however, have not been made in this way.

Scheme 4.1.14

\[
\begin{align*}
703 & \rightarrow 704 + 705 \\
\text{Cl} & \text{N}\text{Me} \\
\text{N}\text{Me} & \text{Cl}
\end{align*}
\]

\(a)\) AIBN, cyclohexane, 60°; 30% of 704, 17% of 705 [954].

4.2. Results and Discussion

4.2.1. Electrophilic Bromination of N-Acyl-4-Aminocyclohexenes

A bromocyclisation of N-acyl-4-aminocyclohexenes, such as the transformation of 655 into 656 [241], appeared the most attractive approach to the desired bicyclic azetidines. A Br substituent in the key intermediate would allow further transformations by substitution, or elimination-electrophilic addition, or elimination-allylic substitution-electrophilic addition. Alternatively, dibromination of N-acyl-aminocyclohex-3-enes followed by intramolecular substitution of one Br substituent should lead to 2-bromo-6-azabicyclo[3.1.1]heptanes in two steps. 7-Azanorbornanes should be available by dibromination of N-acylaminocyclohex-3-enes followed by intramolecular substitution of one Br substituent (cf. [242]).

Therefore, I decided to study the effect of the nature of the N-acyl group, of a substituent at C(6), and of the brominating agent on the bromocyclisation and dibromination-cyclisation of N-acylaminocyclohex-3-enes.

The starting cyclohexenes 712 [955] [956] and 71 [957] were prepared in one pot by Curtius rearrangement (Et₃N, DPPA) of commercial cyclohex-3-enecarboxylic acid (711)⁵,⁵

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⁵) All compounds prepared in this part of my thesis are racemates. Only one enantiomer is presented in the Schemes for each compound.
followed by treatment of the resulting isocyanate either with \( tBuOH \) in the presence of \( CuCl \) [958] to yield 92\% of 712, or with \( CF_3COOH \) [957] to yield 84\% of 71 (Scheme 4.2.1). Previously, the amide 71 had been prepared from cyclohex-3-enecarboxylic acid via cyclohex-3-encarboxyl chloride. The Curtius rearrangement of cyclohex-3-encarboxyl chloride with NaN3 required isolation of the reactive acyl azide and gave 71 in a yield of 86\% [957]. The procedure using DPPA is more efficient (one step less) and safer (no isolation of the acyl azide). This method for the Curtius rearrangement is also used in the chemical industry on a multi-kg scale. The reduced cost for equipment and labour compensates for the relatively high price of DPPA.

**Scheme 4.2.1**

![Scheme 4.2.1](image)

\( a) \) DPPA, \( Et_3N \), toluene, then \( tBuOH \), \( CuCl \); 92\% of 712. \( b) \) DPPA, \( Et_3N \), toluene, then \( CF_3COOH \); 84\% of 71.

The racemic C(6)-substituted \( N \)-acylaminocyclohex-3-enes 714, 716, 72, and 718 were prepared from the monoester 713 (Scheme 4.2.2), prepared in two steps (95\% yield) from butadiene and maleic anhydride [959]. Curtius rearrangement (\( Et_3N \), DPPA) of 713 and treatment of the resulting isocyanate with \( tBuOH/CuCl \) [958] gave the \( \beta \)-amino-acid derivative 714 (90\%) which was reduced to the alcohol 715 (74\%).

Selective benzylation of the hydroxy group of 715 required treatment of its dianion with 1.0 eq. of \( BnBr \) (cf. [960 – 962]), and yielded 95\% of 716 besides 5\% of the oxazin-2-one 717. The dianion was generated by adding 715 to 2.0 eq. of \( NaH \) in DMF. Inverse addition of 1.2 eq. of \( NaH \) to 715 in DMF, followed by treatment with 1.5 eq. of \( BnBr \) gave 716 (55\%), 717 (33\%), and the \( N,O \)-dibenzyl derivative 718 (12\%). The trifluoroacetamide 72 was obtained in a yield of 84\% from the carbamate 716 by debocylation and trifluoroacetylation.
Scheme 4.2.2

![Diagram](image)

a) DPPA, Et₃N, toluene, then iBuOH, CuCl; 90%. b) LiBH₄, THF; 74%. c) Addition to NaH, DMF, then BnBr; 95% of 716, 5% of 717. d) NaH, DMF, then BnBr; 12% of 718, 55% of 716, 33% of 717. e) i: CF₃COOH, CH₂Cl₂; ii: (CF₃CO)₂O, Et₃N, CH₂Cl₂; 84%.

The coupling constants for the H–C(1) td of the carbamate 714 (J(1,2) = J(1,2') = 6.2 Hz, J(1,6) = 3.1 Hz) evidence an equilibrium between the 1H6, 6H1, 2,5B, and B2,5 conformers (calculated coupling constants (Macromodel version 6.0, MM3* force field [707]) for 1H6: J(1,2) = 5.2 Hz, J(1,2') = 1.7 Hz, J(1,6) = 2.6 Hz; for 6H1: J(1,2) = 4.7 Hz, J(1,2') = 11.9 Hz, J(1,6) = 2.1 Hz; for 2,5B: J(1,2) = 3.9 Hz, J(1,2') = 12.3 Hz, J(1,6) = 9.2 Hz; for B2,5: J(1,2) = 4.2 Hz, J(1,2') = 2.2 Hz, J(1,6) = 9.0 Hz). The complexity of the NMR signals for the ring H precluded a straightforward conformational analysis for 715 – 718. CH₂(4) of the oxazin-2-one 717 resonates as a t at 4.27 ppm (J = 11.4 Hz) and as a ddd at 4.13 ppm (J = 10.6, 4.7, 1.9 Hz), the small coupling constant for the ddd resulting from a w coupling with H–C(8a). Modelling shows that this is consistent only with a 4aH8a conformation of the carbocycle.

I first examined the transformation of the unsaturated trifluoroacetamides 71 and 72 with NBS in AcOH, i.e. under the conditions described by Corey et al. [241], but at 10° rather than 0° to avoid freezing of AcOH. Under these conditions, the trifluoroacetamide 71 reacted to give the dihydro-1,3-oxazine 720 (31%) and the bromo-acetate 721 (24%) (Scheme 4.2.3). Treatment of 721 with NaH in THF gave the epoxide 722 (28%) and the dihydro-1,3-oxazine 723 (34%) which was also obtained (89%) by treatment of 721 with K₂CO₃ in MeOH/H₂O. NBS in THF transformed 71 mostly into the bromo-ether 719 (31%), resulting from solvent capture of the bona fide epibromonium ion. Also treatment of the trifluoroacetamide 72 with NBS in AcOH led to a dihydro-1,3-oxazine, and 724 was readily isolated in a yield of 79%.
In view of these results I decided to re-examine the reaction of the trifluoroacetamide \textbf{655} with NBS in AcOH which according to \textit{Corey et al.} yielded the bicyclic azetidine \textbf{656} [241]. Treatment of \textbf{655} (prepared as described in [241]) with NBS in AcOH yielded 81\% of a single product \textbf{725} (Scheme 4.2.4). Its $^{13}$C-NMR data could not be distinguished from those reported by \textit{Corey et al.} for their main product to which they assigned structure \textbf{656}. Also the chemical shift values for the $^1$H signals of \textbf{725} (NMR spectrum registered at 300 MHz) were indistinguishable from those reported by \textit{Corey et al.} (NMR spectrum registered at 500 MHz). Coupling constants, however, could not be compared, as the resolution of the reported spectrum and the one registered by me appear to differ. To substantiate the contention that the cyclisation product possesses structure \textbf{725} rather than \textbf{656}, I hydrolysed the cyclisation product with aqueous CF$_3$COOH in THF, and obtained the trifluoroacetate \textbf{726}:CF$_3$COOH in a nearly quantitative yield.
The MS of the bromo-ether 719 shows the presence of two Br substituents. The C(3) \( d \) resonates at 78.01 ppm, and the C(1) and C(4) \( d \) resonate at 49.38 and 44.74 ppm. The bromobutoxy substituent is evidenced by the C(1') and C(4') \( t \) resonating at 68.81 and 33.69 ppm, respectively, and by two additional \( t \) in the region between 30.68 and 26.54 ppm. The small coupling constants for the H–C(3) \( q \) (3.2 Hz) and the H–C(4) \( q \) (3.1 Hz) indicate the axial orientation of the C(3) and C(4) substituents. In keeping with the relative configuration, the large \( \tau_{1/2} \) of ca. 21 Hz for the H–C(1) \( m \) evidences that NHCOF\(_3\) is equatorial.

Similarly, the C(3) \( d \) of the bromo-acetate 721 resonates at 71.96 ppm, and the C(1) and C(4) \( d \) resonate at 47.53 and 44.75 ppm. The coupling constants for the H–C(3) and H–C(4) \( q \) (both 3.4 Hz) and the \( \tau_{1/2} \) of the H–C(1) \( m \) (ca. 20 Hz) are very similar to those of 719 and evidence the same relative configuration of 719 and 721.

The chemical shift values for the H–C(3) \( m \) (3.26–3.23 ppm) and the H–C(4) \( td \) (3.18 ppm), and the C(3) and C(4) \( d \) (51.98 and 50.80 ppm) of 722 are typical of epoxides. The configuration of 722 is not strictly proven, but derived from its mode of formation.
The MS of the dihydro-1,3-oxazines 720, 724, and 725 show the presence of only one Br substituent. The IR C=N bands of 720, 723, 724, and 725 at 1686, 1689, 1688, and 1688 cm\(^{-1}\) are in agreement with the dihydro-1,3-oxazine structure (see [963] [964] for the IR spectra of related 1,3-oxazines). Only 723 shows an OH band, but none of the dihydro-1,3-oxazines give rise to an NH band. The chemical shift (Table 4.2.1) for the C(1) of 720 (74.47), 723 (74.26), 724 (74.33), and 725 (73.82) evidences that C(1) is bound to O and not to N. The δ values are similar to each other and similar to those of related 2-(trifluoromethyl)dihydro-1,3-oxazines (78.6 and 75.7 ppm [965]), of a 2-methyl-dihydro-1,3-oxazine (72.26 ppm [963]), and of a 2-phenyl-dihydro-1,3-oxazine (74.2 ppm [966]). The chemical shift values for the C(5) and C(8) of the bromo-1,3-oxazines 720, 724, and 725 are similar to each other (46.73–51.26 ppm) and were not assigned separately. The C(5) and C(8) of the hydroxy-dihydro-1,3-oxazine 723 resonate at 46.94 and 67.39 ppm, respectively. For the azetidine 656 (N bound to C(1)), one expects that the chemical shift values for C(1) and C(5) are similar to each other. 13C chemical shift values for similar azetidine trifluoroacetamides have not been reported. The C–N δ of the azetidine moiety of a tricyclic azetidine acetamide resonate at 62.8 and 60.6 ppm [967]. Similarly, the C–N δ of N-acetyl 5-azabicyclo[2.1.1]hexane resonate at 63.0 ppm [968]. The identical value for the vicinal coupling constants for the H–C(9) dt (J(1,9) = J(5,9)) for 720 (1.6 Hz), 723 (1.5 Hz), 724 (1.6 Hz), and 725 (1.6 Hz) are in keeping with the bicyclic structure. A w coupling between H–C(8) and the equatorial H'–C(9) (1.9, 1.6, and 1.6 Hz, respectively) evidences that the Br substituent of 720, 724, and 725 is axial. For 723, the small J(7ax,8) = 3.4 Hz evidences the axial orientation of HO–C(8). The large J(6,7ax) for 724 and 725 (12.1 and 10.3 Hz, respectively) evidences that the benzoxymethyl and the pyridyl groups are equatorial.

The δ value for the C(1) δ (68.14 ppm) of the salt 726-CF3COOOH is typical for a secondary alcohol. The δ values for the C(3) and C(6) δ are similar to each other (51.09 and 50.29 ppm) and were not assigned separately. The vicinal coupling constants for the ring H evidence a \(^1\)C\(_4\) conformation. The small vicinal coupling constants for the H–C(1) q (3.4 Hz) and the H–C(6) m (3.4 Hz) evidence the axial orientation of the Br and OH substituents. The identical coupling constants J(1,2ax) = J(2ax,3) = 3.4 Hz evidence the syn configuration at C(1) and C(3). The large J(4,5ax) = 12.1 Hz evidences the equatorial orientation of the pyridyl group.
Table 4.2.1: Selected IR Bands [cm\(^{-1}\)], \(^1\)H- and \(^{13}\)C-NMR (CDCl\(_3\)) Chemical Shifts [ppm], and Coupling Constants [Hz] of 720, 723, 724, 725, and 762.

<table>
<thead>
<tr>
<th></th>
<th>720</th>
<th>723</th>
<th>724</th>
<th>725</th>
<th>762</th>
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<tbody>
<tr>
<td>(\nu(C=\text{N}))</td>
<td>1686</td>
<td>1689</td>
<td>1688</td>
<td>1688</td>
<td>1689</td>
</tr>
<tr>
<td>H–C(1)</td>
<td>4.75–4.70</td>
<td>4.59–4.55</td>
<td>4.74–4.69</td>
<td>4.79</td>
<td>4.79–4.75</td>
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<tr>
<td>H–C(6)</td>
<td>2.18–2.01</td>
<td>2.02</td>
<td>2.65–2.54</td>
<td>3.52</td>
<td>2.28–2.16</td>
</tr>
<tr>
<td>H—C(6)</td>
<td>1.99–1.83</td>
<td>1.88–1.78</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>H–C(7)</td>
<td>1.99–1.83</td>
<td>1.73–1.62</td>
<td>2.12</td>
<td>2.21–2.08</td>
<td>2.36</td>
</tr>
<tr>
<td>H—C(7)</td>
<td>1.99–1.83</td>
<td>1.53</td>
<td>1.57</td>
<td>2.21–2.08</td>
<td>1.52</td>
</tr>
<tr>
<td>H–C(9)</td>
<td>2.59</td>
<td>2.26</td>
<td>2.54</td>
<td>2.74</td>
<td>2.11</td>
</tr>
<tr>
<td>H—C(9)</td>
<td>1.77</td>
<td>1.73–1.62</td>
<td>1.83</td>
<td>1.95</td>
<td>1.86</td>
</tr>
<tr>
<td>CH–C(6)</td>
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<td>3.56</td>
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<tr>
<td>CH—C(6)</td>
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<td>–</td>
<td>3.29</td>
<td>–</td>
<td>3.27</td>
</tr>
<tr>
<td>J (1,5)</td>
<td>a)</td>
<td>a)</td>
<td>a)</td>
<td>2.2</td>
<td>a)</td>
</tr>
<tr>
<td>J (1,8)</td>
<td>a)</td>
<td>a)</td>
<td>a)</td>
<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td>J (1,9)</td>
<td>1.6</td>
<td>1.5</td>
<td>1.6</td>
<td>1.6</td>
<td>4.1</td>
</tr>
<tr>
<td>J (1,9')</td>
<td>3.7</td>
<td>a)</td>
<td>3.9</td>
<td>4.0</td>
<td>1.6</td>
</tr>
<tr>
<td>J (5,6)</td>
<td>a)</td>
<td>3.1</td>
<td>a)</td>
<td>2.2</td>
<td>a)</td>
</tr>
<tr>
<td>J (5,6')</td>
<td>a)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>J (5,9)</td>
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<td>1.5</td>
<td>1.6</td>
<td>1.6</td>
<td>4.1</td>
</tr>
<tr>
<td>J (5,9')</td>
<td>3.7</td>
<td>a)</td>
<td>3.9</td>
<td>4.0</td>
<td>1.6</td>
</tr>
<tr>
<td>J (6,7)</td>
<td>a)</td>
<td>4.7</td>
<td>ca. 3.6</td>
<td>6.5</td>
<td>4.7</td>
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<tr>
<td>J (6,7')</td>
<td>a)</td>
<td>13.4</td>
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<tr>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>J (6,7)</td>
<td>a)</td>
<td>5.3</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>J (6,7')</td>
<td>a)</td>
<td>13.6</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>J (6,10)</td>
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<td>7.5</td>
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<td>7.2</td>
</tr>
<tr>
<td>J (6,10')</td>
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<td>–</td>
<td>6.5</td>
<td>–</td>
<td>6.9</td>
</tr>
<tr>
<td>J (7,8)</td>
<td>a)</td>
<td>a)</td>
<td>a)</td>
<td>a)</td>
<td>5.3</td>
</tr>
<tr>
<td>J (7,8')</td>
<td>a)</td>
<td>3.4</td>
<td>4.0</td>
<td>a)</td>
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</tr>
<tr>
<td>J (7,7)</td>
<td>a)</td>
<td>15.3</td>
<td>15.9</td>
<td>a)</td>
<td>14.0</td>
</tr>
<tr>
<td>J (8,9')</td>
<td>1.9</td>
<td>a)</td>
<td>1.6</td>
<td>1.6</td>
<td>0</td>
</tr>
<tr>
<td>J (9,9')</td>
<td>14.0</td>
<td>14.0</td>
<td>14.3</td>
<td>14.3</td>
<td>14.0</td>
</tr>
<tr>
<td>J (10,10')</td>
<td>–</td>
<td>–</td>
<td>9.0</td>
<td>–</td>
<td>9.0</td>
</tr>
<tr>
<td>C(1)</td>
<td>74.47</td>
<td>74.26</td>
<td>74.33</td>
<td>73.82</td>
<td>74.99</td>
</tr>
<tr>
<td>C(3)</td>
<td>a)</td>
<td>a)</td>
<td>147.62</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>C(5)</td>
<td>46.73b</td>
<td>46.94</td>
<td>47.80b</td>
<td>51.26b</td>
<td>46.50b</td>
</tr>
<tr>
<td>C(8)</td>
<td>48.17b</td>
<td>67.39</td>
<td>47.68b</td>
<td>47.62b</td>
<td>44.26b</td>
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<tr>
<td>CF(_3)</td>
<td>a)</td>
<td>–73.43</td>
<td>–73.10</td>
<td>–73.54</td>
<td>–73.69</td>
</tr>
</tbody>
</table>

\(^a\) Not determined.

\(^b\) Assignment may be interchanged.
Not unexpectedly, bromination of the N-trifluoroacetaminocyclohexenes 71 and 72 under conditions favouring anchimeric assistance provided neither azetidines nor 7-azanorbornanes. I, therefore, also examined the dibromination of the N-acylaminocyclohex-3-enes 712, 71, 714, 716, 72, and 718, followed by intramolecular substitution of one of the Br substituents. For this, I compared three reaction conditions: bromination with two eq. of Br2 in the presence of 10 eq. of Et4NBr (cf. [241]), bromination with two eq. of PhMe3NBr3, and bromination with excess Br2.

I first examined the bromination of the carbamate 712 and the amide 71. The crude products were analysed by 1H-NMR spectroscopy; pure products were only isolated in a few cases. Bromination of 712 and 71 led to two major products, the c-3,t-4 dibromide 727 and its t-3,c-4 diastereoisomer 728 from 712, and the c-3,t-4 dibromide 729 and its t-3,c-4 diastereoisomer 730 from 71 (Scheme 4.2.5). The stereoselectivity of the bromination depended on the nature of the N-protecting group and on the reaction conditions (Table 4.2.2). Bromination of the amide 71 showed a greater tendency to provide the c-3,t-4 diastereoisomer than bromination of the carbamate 712, as seen by comparing Entries 1 to 11, 2 to 12, 5 to 13, and 10 to 14. The highest ratios in favour of the c-3,t-4 product resulted from treating the amide 71 with PhMe3NBr3 in CH2Cl2 (6:1, Entry 14) or with Br2/Et4NBr in CH2Cl2 (5.5:1, Entry 11). On a 10 g scale, bromination of 71 with PhMe3NBr3 in CH2Cl2 followed by chromatography led to 79% of 729 and 15% of 730. The highest ratios in favour of the c-3,t-4 diastereoisomer derived from the carbamate 712, as seen by comparing Entries 1 to 11, 2 to 12, 5 to 13, and 10 to 14. Conversely, the highest ratio in favour of the t-3,c-4 diastereoisomer resulted from treating 712 with Br2 in Et2O at –78° (< 1:10, Entry 3). Among the conditions that were used for the bromination of both 712 and 71, Br2 in CH2Cl2 led to the highest proportion of the t-3,c-4 products 728 (1:5, Entry 2) and 730 (1:3.3, Entry 12).

The bromination of 712 with PhMe3NBr3 in Et2O, cyclohexane, and toluene (Entries 7 – 9) led to a higher proportion of the diaxial dibromide 728 than the reaction in CH2Cl2, CHCl3, or MeCN (Entries 5, 6, and 10). This probably reflects the lower solubility of PhMe3NBr in Et2O, cyclohexane, and toluene, and the bromination by PhMe3NBr3 in these solvents may be mostly due to free Br2. This hypothesis is corroborated by the similar selectivity of the bromination of 712 with PhMe3NBr3 in Et2O and with Br2 in Et2O (compare Entries 4 and 7).
Scheme 4.2.5

\[
\begin{align*}
\text{712 } R &= \text{ Boc} \\
\text{71 } R &= \text{ COCF}_3 \\
\text{727 } R &= \text{ Boc} \\
\text{729 } R &= \text{ COCF}_3 \\
\text{728 } R &= \text{ Boc} \\
\text{730 } R &= \text{ COCF}_3
\end{align*}
\]

\textit{a}) \text{Et}_4\text{NBr, then Br}_2, \text{ or Br}_2, \text{ or PhMe}_3\text{NBr}_3; \text{ see Table 4.2.2.}

Table 4.2.2: Stereoselectivities of the Dibromination of the Alkenes 712 and 71.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Reagents</th>
<th>Solvent</th>
<th>T</th>
<th>727 / 728 or 729 / 730</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>712</td>
<td>Et4NBr, Br2</td>
<td>CHCl2</td>
<td>–78°</td>
<td>1.3:1</td>
</tr>
<tr>
<td>2</td>
<td>712</td>
<td>Br2</td>
<td>CHCl2</td>
<td>–78°</td>
<td>1:5</td>
</tr>
<tr>
<td>3</td>
<td>712</td>
<td>Br2</td>
<td>Et2O</td>
<td>–78°</td>
<td>&lt; 1:10</td>
</tr>
<tr>
<td>4</td>
<td>712</td>
<td>Br2</td>
<td>Et2O</td>
<td>0°</td>
<td>1:6</td>
</tr>
<tr>
<td>5</td>
<td>712</td>
<td>PhMe3NBr3</td>
<td>CHCl2</td>
<td>0°</td>
<td>1:1.3</td>
</tr>
<tr>
<td>6</td>
<td>712</td>
<td>PhMe3NBr3</td>
<td>CHCl3</td>
<td>0°</td>
<td>1:1.7</td>
</tr>
<tr>
<td>7</td>
<td>712</td>
<td>PhMe3NBr3</td>
<td>Et2O</td>
<td>0°</td>
<td>1:6</td>
</tr>
<tr>
<td>8</td>
<td>712</td>
<td>PhMe3NBr3</td>
<td>cyclohexane</td>
<td>r.t.</td>
<td>1:5</td>
</tr>
<tr>
<td>9</td>
<td>712</td>
<td>PhMe3NBr3</td>
<td>toluene</td>
<td>r.t.</td>
<td>1:3</td>
</tr>
<tr>
<td>10</td>
<td>712</td>
<td>PhMe3NBr3</td>
<td>MeCN</td>
<td>0°</td>
<td>\textit{ca.} 1:1.5</td>
</tr>
<tr>
<td>11</td>
<td>71</td>
<td>Et4NBr, Br2</td>
<td>CHCl2</td>
<td>–78°</td>
<td>5.5:1</td>
</tr>
<tr>
<td>12</td>
<td>71</td>
<td>Br2</td>
<td>CHCl2</td>
<td>–78°</td>
<td>1:3.3</td>
</tr>
<tr>
<td>13</td>
<td>71</td>
<td>PhMe3NBr3</td>
<td>CHCl2</td>
<td>0°</td>
<td>6:1</td>
</tr>
<tr>
<td>14</td>
<td>71</td>
<td>PhMe3NBr3</td>
<td>MeCN</td>
<td>0°</td>
<td>3.5:1</td>
</tr>
</tbody>
</table>

Conditions: Two eq. of Br2. For Et4NBr, Br2 see method A in the exp. part. For PhMe3NBr3 see method B in the exp. part.
Bromination of the β-amino ether 716 led to several products (Scheme 4.2.6). The reaction with two eq. of PhMe₃NBr₃ in CH₂Cl₂ gave the dibromide 731 (46%) and the dihydrooxazin-2-one 733 (49%). A yield of 82% of 731 was realised by treating a more highly concentrated solution of 716 in CH₂Cl₂ with two eq. of PhMe₃NBr₃ in the presence of 10 eq. of Et₄NBr. Bromination of 716 with Br₂ in CH₂Cl₂ yielded the dibromides 731 (18%) and 732 (6%), the dihydrooxazin-2-one 733 (43%), and the bicyclic ether 734 (32%). No conditions were found to produce the isomeric dibromide 732 selectively.

Bromination of the analogous trifluoroacetamide 72 with two eq. of PhMe₃NBr₃ and 10 eq. of Et₄NBr in CH₂Cl₂ gave the dibromide 735 as the only product in a yield of 89%, while bromination of 72 with Br₂ in CH₂Cl₂ led to the dibromides 735 (42%) and 736 (32%) and also to 19% of the dihydro-1,3-oxazine 724.

Bromination of the protected β-amino acid 714 with two eq. of PhMe₃NBr₃ and 10 eq. of Et₄NBr in CH₂Cl₂ gave the dibromides 737 (84%) and 738 (6%). Bromination with Br₂ in CH₂Cl₂ gave lower yields of 737 (28%) and 738 (30%) and the dihydrooxazin-2-one 739 (36%).

Finally, bromination of the Boc-protected benzylamine 718 with Br₂ in CH₂Cl₂ gave the bicyclic ether 741 (26%) and the oxazin-2-one 740 (32%). According to TLC, bromination of 718 with two eq. of PhMe₃NBr₃ and 10 eq. of Et₄NBr in CH₂Cl₂ gave the oxazin-2-one 740 as the main product; 741 was not detected.

---

53) For a related bromo-carbamoylation, see [955].
Scheme 4.2.6

The results of the bromination of the cyclohexenes 712, 71, 714, 716, 72, and 718 depended on the structure of the starting material and on the reaction conditions.

Bromination of 714, 716, and 72 displayed a higher tendency to provide the dibromide with a 1,3-cis relation between the N and the proximal Br substituents than bromination of 712 and
Similarly as observed in the bromination of 712 and 71, the highest proportion of the products with a 1,3-cis relation between the N and proximal Br substituents was obtained with PhMe₃NBr₃/Et₄NBr as the brominating agent. Substituting the benzylxoymethyl by the methoxycarbonyl group such as in 714 led to a slightly decreased diastereoselectivity of the brominations with PhMe₃NBr/Et₄NBr and with Br₂.

In addition to dibromides, bromination of 714, 716, and 72 led also to bicyclic dihydrooxazin-2-ones and bicyclic oxolanes. The N-benzylated 718 did not form a dibromo compound at all, but only the dihydrooxazin-2-one 740 and the oxolane 741. The dihydrooxazin-2-ones 733 and 740 were formed both in the brominations with Br₂ and with PhMe₃NBr₃. The oxolanes 734 and 741 and the dihydro-1,3-oxazine 724 were only formed in the reaction with Br₂. Preparatively significant is the addition of excess Br⁻ in the PhMe₃NBr₃ bromination, leading to 84% of the dibromide 737 from 714, to 82% of the analogous dibromide 731 from 716, and to 89% of 735 from 72.

These observations suggest a different reaction mechanism for the brominations by PhMe₃NBr₃/Et₄NBr and by Br₂ in CH₂Cl₂, as it is known from kinetic studies of brominations with Br₂ and with Br₃⁻ (see [969 – 972] and references cited there). With Br₂, the rate-limiting ionisation of a 2:1 π-complex between Br₂ and the alkene leads to an epibromonium tribromide ion pair which collapses rapidly to the dibromide and Br₂. Bromination with tribromides is characterised by a rate-limiting nucleophilic attack of Br⁻ on a 1:1 π-complex between Br₂ and the alkene, leading to the dibromide and Br⁻ without proceeding through an intermediate. The formation of the bicyclic oxolanes 734 and 741 and the dihydro-1,3-oxazine 724 upon bromination by Br₂ but not by Br₃⁻ correlates with the higher reactivity of an epibromonium ion as compared to a Br₂-alkene π-complex [973].

The dibromides 728 and 730 are almost certainly formed by diaxial bromination of the pseudoequatorial conformer of 712 and 71, in accord with the Fürst-Plattner rule. The dibromides 727 and 729 must result from the diaxial bromination of the pseudoaxial conformer of 712 and 71.

In the bromination by Br₂, ionisation of a (Br₂)₂:alkene complex on either face of the pseudoequatorial (A) and pseudoaxial conformer (B) might yield the epibromonium ions C, D, E, and F (Scheme 4.2.7). Nucleophilic attack of Br⁻ will lead to the dibromide G from C and D and to the dibromide H from E and F. The ratio of G and H presumably reflects the

54) A similar formation of bicyclic products in the bromination of 712 and 71 by Br₂ cannot be excluded; side products were observed, but not isolated.

55) Br₂ and Br⁻ are in equilibrium with Br₃⁻; Br₃⁻ predominates: \( K \approx 2 \times 10^7 \text{ l/mol (dichloroethane)}; K = 1.2 \times 10^5 \text{ l/mol (chloroform)} \) (see [970] and references cited there).
ratios between the conformers C and E, and D and F. Bicyclic oxolanes (I) will be formed from D, and dihydrooxazin-2-ones (J) from F by intramolecular interception of the epibromonium ion.

Proposed conformational itinerary for the bromination by Br2 in CH2Cl2. The dashed arrows indicate the trajectories for nucleophilic attack on the epibromonium ions according to the Fürst-Plattner rule.

Similarly, bromination by Br3− will proceed via the 1:1 Br2 alkene π complexes K, L, M, and N (Scheme 4.2.8). Nucleophilic attack of Br− will lead to the formation of the dibromide G from K and M, and to the formation of the dibromide H from L and N. The increased proportion of the dibromide 727 and the selective formation of 729 (corresponding to H) resulting from the bromination by Br3− indicate that under these conditions bromination via the pseudoaxial conformers L and N is favoured, suggesting a neighbouring group
participation by the NHR group\textsuperscript{56}). Both NHBOc and NHCO\textsubscript{CF}\textsubscript{3} can act as hydrogen bond donor to Br\textsuperscript{−} acting as nucleophile (in the reaction \textit{via N}) (cf. [975]) or as leaving group (in the reaction \textit{via L}) (cf. [969] [971] [976 – 978]). Alternatively, a H-bonded complex of Br\textsubscript{3}\textsuperscript{−} (cf. [979] [980]) with the pseudoaxial conformer B may promote the liberation of Br\textsubscript{2} and lead to a pseudointramolecular bromination of this conformer (not shown in Scheme 4.2.8). The higher proportion of the diastereoisomers H resulting from the bromination of trifluoroacetamides indeed correlates with the better H-bond donating properties of the more highly acidic trifluoroacetamido group. A neighbouring group participation by NHR appears to be significant only in the bromination by Br\textsubscript{3}\textsuperscript{−} but not in the bromination by Br\textsubscript{2}. This may correlate with the higher reactivity of Br\textsubscript{2} as compared to Br\textsubscript{3}\textsuperscript{−}.

\textbf{Scheme 4.2.8}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {$ \text{Br}_2 + \text{Br}^{-} $};
\node at (-1.5,-3) {$ \text{K} $};
\node at (1.5,-3) {$ \text{L} $};
\node at (-4.5,-6) {$ \text{A} $};
\node at (4.5,-6) {$ \text{H} $};
\node at (-3.5,-9) {$ \text{G} $};
\node at (-3.5,-7) {$ \text{I} $};
\node at (3.5,-9) {$ \text{J} $};
\node at (3.5,-7) {$ \text{M} $};
\node at (-0.5,-9) {$ \text{B} $};
\node at (0.5,-9) {$ \text{N} $};
\node at (0,-12) {$ \text{H} $};
\end{tikzpicture}
\end{center}

Proposed conformational itinerary for the bromination by Br\textsubscript{3}\textsuperscript{−} in CH\textsubscript{2}Cl\textsubscript{2}. The dashed arrows indicate the trajectories for nucleophilic attack on the $\pi$ complexes according to the Fürst-Plattner rule.

\textsuperscript{56}) Similarly, the \textit{syn}-selectivity of the \textit{cis}-dihydroxylation of $N$-(trifluoroacetylamino)cyclohex-3-enes was rationalised by neighbouring group participation in the pseudoaxial conformer [974].
Intramolecular attack of the Br$_2$ alkene π complex N by NHCO$_2$R will lead to the formation of the dihydrooxazin-2-one J. Interestingly, excess Br$^-$ has a significant effect on the chemoselectivity of the bromination of 716 by Br$_3^-$, completely suppressing the formation of the dihydrooxazin-2-one 733, but it does not significantly influence the stereoselectivity of the bromination of 716 (and also of 71).

4.2.2. Cyclisation of 3,4-Dibromocyclohexylamines

I next studied the transformation of the dibromides 727, 729, 731, and 737 into 7-azabicyclo[2.2.1]heptanes, and the transformation of the dibromides 728, 738, and 736 into 6-azabicyclo[3.1.1]heptanes.

Deboclylation of the carbamates 727 and 728 (CF$_3$CO$_2$H) gave the crude amines 742 and 747 in quantitative yield (Scheme 4.2.9). Heating 742 in CHCl$_3$ under reflux in the presence of K$_2$CO$_3$ for 12 d gave the crude azanorbornane 743 (quant.), which was carbamoylated to 744 (83% from 727). On a 10 g scale, 744 was prepared in 93% yield from 729 by hydrolysis (K$_2$CO$_3$, MeOH, H$_2$O) of the amide, cyclisation, and carbamoylation without isolation of the intermediates 742 and 743. For the cyclisation, the solution of the amine 742 had to be free of MeOH. Although MeOH apparently accelerated the cyclisation, it also led to the formation of by-products, thwarting the reaction. Base-catalysed elimination of HBr transformed 744 into the known [981] 7-azanorbornene 745 (87%). Dihydroxylation (OsO$_4$, NMO, acetone/H$_2$O, cf. [982]) of 745 provided the diol 746 that was isolated in 56% yield by chromatography (82%), followed by crystallisation. Deboclylation (CF$_3$COOH, CH$_2$Cl$_2$) of the dihydroxycarbamate 746 yielded 97% of the ammonium salt 58-HCl (30% overall yield (8 steps) from cyclohex-3-enecarboxylic acid).

The amine 747 did not cyclise to a 6-aza-bicyclo[3.1.1]heptane, i.e. to an azetidine. It did not react in the presence of K$_2$CO$_3$ in boiling CHCl$_3$ or in 1,3-dichlorobenzene up to 120°; at 130°, a new compound formed, which upon carbamoylation gave the 7-azanorbornane 744 (62%). Presumably, at this temperature the diaxial dibromide 747 rearranged into the diequatorial 742 (cf. [983] [984]), which cyclised to the 7-azanorbornane 743.
Treating 747 with K₂CO₃ in DMF at 80° led to the formation of a new compound which was car bamoylated in situ (Boc₂O) to yield the 1,3-oxazolidinone 749 (28%) (Scheme 4.2.10). NMR-analysis did not allow me to unambiguously establish the structure of 749. Attempts to crystallise 749 failed, therefore I prepared the dibromides 750 and 751. The structure of 751 which readily crystallised from CH₂Cl₂ / hexane was determined by crystal structure analysis.

The transformation of the amine 747 into 749 requires C(2) to become electrophilic. Conceivably, elimination of HBr might lead to the allylic bromide A. The carbamic acid B derived form A might then be transformed into C by an intramolecular SN₂¹ like reaction.
Debocylation (CF₃COOH, CH₂Cl₂) of the carbamate 731 gave the amine 752 in quantitative yield (Scheme 4.2.11). According to its ¹H-NMR spectrum, it partially cyclised to the azanorbornane 753 during isolation. The cyclisation was completed by boiling a solution of the mixture 752/753 in CHCl₃ in the presence of K₂CO₃ for 40 h. The amine 753 was isolated in nearly quantitative yield from 731 and carbamoylated to 754 (84% from 731). Elimination of HBr gave the azanorbornene 755 (92%) which was dihydroxylated (OsO₄, NMO, acetone/H₂O, cf. [982]) to the diol 756 (81%). Hydrogenolytic debenzylation of 756, followed by debocylation gave the ammonium salt 59·HCl in 60% yield (18% overall yield (13 steps) from butadiene and maleic anhydride).
Scheme 4.2.11

\[
\begin{align*}
\text{a)} & \quad CF_3COOH, CH_2Cl_2; \text{ quant.} \\
\text{b)} & \quad K_2CO_3, CHCl_3; \text{ quant.} \\
\text{c)} & \quad \text{Boc}_2O, K_2CO_3, CHCl_3; 84\% \text{ from } 731. \\
\text{d)} & \quad \text{KOrBu, THF; 92\%. } \\
\text{e)} & \quad \text{OsO}_4, \text{NMO, acetone, H}_2\text{O; 81\%.} \\
\text{f)} & \quad \text{H}_2\text{-Pd/C, MeOH; 90\% crude, 60\% after repeated chrom.} \\
\text{g)} & \quad \text{0.1N HCl; 100\%.} \\
\end{align*}
\]

Debocylation of the carbamates 737 and 738 gave the amines 758 and 759, respectively, in quantitative yield (Scheme 4.2.12). Boiling 758 in CHCl₃ in the presence of K₂CO₃ gave the azanorbornane 760 which upon carbamoylation furnished the bicyclic amino acid derivative 761 (62% from 737).

We had hoped that the amine 759, adopting a conformation with axial N and equatorial Br substituents (vide infra), would be more prone to cyclise to a 6-aza-bicyclo[3.1.1]heptane than the amine 747. However, 759 did not react in the presence of K₂CO₃ in boiling CHCl₃ and in 1,3-dichlorobenzene up to 100°. At 120°, a slow conversion to a new compound was observed by TLC. Carbamoylation (Boc₂O, K₂CO₃) of the new product afforded the 7-azanorbornane 761 (21%), i.e. 759 behaved similarly as 747.
An attempt to hydrolyse the amide 736 (K$_2$CO$_3$, MeOH/H$_2$O) led to the 1,3-oxazine 762 (Scheme 4.2.13). A similar formation of a dihydro-1,3-oxazine from N-(1,3-trans-1,4-cis-3,4-dibromo-cyclohexyl)benzamide upon treatment with AgOAc in AcOH was reported by Della and Jefferies [907].
The configuration and conformation of the dibromides 727, 728, 729, 730, 742, and 747 were deduced from their proton NMR spectra.

In these bromides, the N substituent is equatorial, as evidenced by the large $J(1,2_{ax})$ and $J(1,6_{ax})$ values (Table 4.2.3) for 742, 728, 729, 730, and 747 and by the large $\tau_{1/2}$ of ca. 20 Hz for the H–C(1) $m$ of 727. The small $\tau_{1/2}$ values for the H–C(3) and H–C(4) $m$ of the dibromides 728, 730, and 747 evidence an axial orientation of the Br atoms. This is corroborated by the small $J(4,5_{ax})$ (3.1 – 3.4 Hz). This conformation of 728, 730, and 747 with equatorial NHR and axial Br is not surprising, as the A value of Br is lower ($\approx$ 0.4 kcal/mol) [986] than the one expected for NHR (A(NHBz) = 1.6 kcal/mol) [988], and in solvents of low polarity trans-cyclohexane-1,2-dibromides prefer the diaxial conformation [985] [986]. The large $J(3,4)$ for the dibromides 727 and 742 (9.3 Hz and 10.6 Hz, respectively) and the large $\tau_{1/2}$ of the H–C(3) and H–C(4) $m$ of 729 evidence the equatorial orientation of the Br atoms.
<table>
<thead>
<tr>
<th></th>
<th>727</th>
<th>728</th>
<th>729</th>
<th>730</th>
<th>742</th>
<th>747</th>
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</tr>
<tr>
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<td>2.79–2.69</td>
<td>2.33–2.18</td>
<td>2.80 (eq)</td>
<td>2.46 (ax)</td>
<td>2.59 (eq)</td>
<td>2.33 (ax)</td>
</tr>
<tr>
<td>H’–C(2)</td>
<td>2.06–1.73</td>
<td>2.33–2.18</td>
<td>2.16–1.91</td>
<td>2.25 (eq)</td>
<td>1.98–1.72</td>
<td>2.17 (eq)</td>
</tr>
<tr>
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<td>4.10b)</td>
<td>4.64–4.60b</td>
<td>4.33–4.19</td>
<td>4.69–4.64</td>
<td>4.06c)</td>
<td>4.70–4.65</td>
</tr>
<tr>
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<td>4.02b)</td>
<td>4.60–4.55b</td>
<td>4.33–4.19</td>
<td>4.64–4.59</td>
<td>3.98c)</td>
<td>4.60–4.56</td>
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<td>2.55 (ax)</td>
<td>2.51 (eq)</td>
<td>2.61 (ax)</td>
<td>2.47 (eq)b)</td>
<td>2.51 (ax)</td>
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<td>2.04–1.94</td>
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<td>2.05 (eq)</td>
<td>1.98–1.72</td>
<td>2.04 (eq)</td>
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<td>1.93–1.83</td>
<td>2.16–1.91</td>
<td>1.98 (eq)</td>
<td>1.98–1.72</td>
<td>1.88–1.69</td>
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<td>1.71 (ax)</td>
<td>1.65–1.53</td>
<td>1.86 (ax)</td>
<td>1.32–1.18</td>
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<td>NH</td>
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<td>7.13–7.00</td>
<td>6.41–6.29</td>
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<td>a)</td>
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<td>J (1,2)</td>
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<td>a)</td>
<td>4.1</td>
<td>11.7</td>
<td>3.7</td>
<td>10.9</td>
</tr>
<tr>
<td>J (1,2')</td>
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<td>8.1</td>
<td>4.1</td>
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<td>4.4</td>
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<td>a)</td>
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<td>3.4</td>
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<tr>
<td>J (2',3)</td>
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<td>a)</td>
<td>a)</td>
<td>a)</td>
<td>10.6</td>
<td>a)</td>
</tr>
<tr>
<td>J (3,4)</td>
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<td>a)</td>
<td>a)</td>
<td>a)</td>
<td>10.6</td>
<td>a)</td>
</tr>
<tr>
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<td>3.4</td>
<td>3.4</td>
<td>4.1 or 3.1</td>
<td>4.4</td>
<td>4.4 or 3.1</td>
</tr>
<tr>
<td>J (4,5')</td>
<td>9.3</td>
<td>a)</td>
<td>a)</td>
<td>a)</td>
<td>10.6</td>
<td>a)</td>
</tr>
<tr>
<td>J (5,5')</td>
<td>15.6</td>
<td>14.6</td>
<td>15.3</td>
<td>14.0</td>
<td>15.3</td>
<td>a)</td>
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<tr>
<td>J (5,6)</td>
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<td>4.1 or 3.1</td>
<td>7.8</td>
<td>4.4 or 3.1</td>
<td>a)</td>
<td>12.1</td>
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<tr>
<td>J (5,6')</td>
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<td>12.5</td>
<td>a)</td>
<td>12.1</td>
<td>a)</td>
</tr>
<tr>
<td>J (5',6)</td>
<td>3.4</td>
<td>a)</td>
<td>3.7</td>
<td>a)</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>J (6,6')</td>
<td>12.3</td>
<td>a)</td>
<td>12.1</td>
<td>a)</td>
<td>12.1</td>
<td>a)</td>
</tr>
<tr>
<td>J (6,1)</td>
<td>4.1</td>
<td>4.1</td>
<td>3.7</td>
<td>4.4</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>J (6',1)</td>
<td>12.3</td>
<td>8.1</td>
<td>12.1</td>
<td>11.2</td>
<td>10.6</td>
<td>a)</td>
</tr>
<tr>
<td>C(1)</td>
<td>48.18</td>
<td>44.95</td>
<td>46.61</td>
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<td>50.03</td>
<td>45.33</td>
</tr>
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<td>52.36c)</td>
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<td>C(4)</td>
<td>53.44b)</td>
<td>51.79c)</td>
<td>51.66b)</td>
<td>50.58b)</td>
<td>54.57b)</td>
<td>52.71b)</td>
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</table>

a) Not determined. b), c) Assignment may be interchanged. Values in italics: assignment by comparison, not proven.
The identical $J(1,6) = J(5,6) = 4.4$ Hz and $J(1,6') = J(5,6') = 7.1 - 7.3$ Hz of the dibromides 731 and 735 (Table 4.2.4) evidence the 1,5-\textit{cis} configuration. The identical coupling pattern for the H–C(3) and H'–C(3) \textit{ddd} resonating at 2.34 ($J = 14.6, 7.6, 3.6$ Hz) and 2.08 ppm ($J = 14.6, 7.6, 4.0$ Hz) (731) and at 2.46 ($J = 14.3, 8.3, 3.6$ Hz) and 2.06 ppm ($J = 13.7, 7.8, 2.8$ Hz) (735) and the coupling constants evidence the 2,4-\textit{trans} configuration and an equilibrium of the $4C_1$ and $1C_4$ conformers.

![Chemical structures](image)

The large $J(2,3_{ax} = J(3_{ax},4) = 9.7$ Hz and $J(5,6_{ax}) = 10$ Hz of the dibromide 736 evidence an equatorial orientation of the benzyloxymethyl and Br substituents and a $1C_4$ conformation. The small $J(1,6_{ax}) = 3.6$ Hz evidences the axial orientation of NHCOCF$_3$–C(1). The structure of 732 was tentatively assigned as the diastereoisomer of 731, assuming that only \textit{trans}-dibromides are obtained. Due to the complexity of the proton NMR signals, the structure could not be proven.
Table 4.2.4: Selected $^1$H- and $^{13}$C-NMR (CDCl$_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] of $^{731}$, $^{732}$, $^{735}$, and $^{736}$.

<table>
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<th>$^{736}$</th>
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<td>4.00–3.94</td>
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<td>4.27–4.16</td>
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<td>H–C(2)</td>
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<td>?</td>
<td>2.53</td>
<td>2.21–2.11</td>
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<td>H–C(3)</td>
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<td>2.46</td>
<td>2.57</td>
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<tr>
<td>H′–C(3)</td>
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<td>?</td>
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<td>2.27</td>
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<tr>
<td>H–C(4)</td>
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<td>4.26–4.05</td>
<td>4.48–4.24</td>
<td>4.27–4.16</td>
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<tr>
<td>H–C(5)</td>
<td>4.37–4.29</td>
<td>4.26–4.05</td>
<td>4.48–4.24</td>
<td>4.27–4.16</td>
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<tr>
<td>H–C(6)</td>
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<td>?</td>
<td>2.74</td>
<td>2.91</td>
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<td>H′–C(6)</td>
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<td>2.30</td>
<td>2.14</td>
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<td>CH–C(2)</td>
<td>3.67</td>
<td>3.54</td>
<td>3.73</td>
<td>3.83</td>
</tr>
<tr>
<td>CH′–C(2)</td>
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<td>3.41</td>
<td>3.54</td>
<td>3.58</td>
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<td>a)</td>
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<td>a)</td>
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<td>a)</td>
<td>4.4</td>
<td>4 or 5</td>
</tr>
<tr>
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<td>a)</td>
<td>7.1</td>
<td>3.6</td>
</tr>
<tr>
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<td>a)</td>
<td>8.3</td>
<td>3.9</td>
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<tr>
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<td>a)</td>
<td>2.8</td>
<td>9.7</td>
</tr>
<tr>
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<td>a)</td>
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<tr>
<td>$J$(3,4)</td>
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<td>a)</td>
<td>3.6</td>
<td>3.9</td>
</tr>
<tr>
<td>$J$(3′,4)</td>
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<td>a)</td>
<td>7.8</td>
<td>9.7</td>
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<tr>
<td>$J$(4,5)</td>
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<td>a)</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>$J$(5,6)</td>
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<td>4 or 5</td>
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<tr>
<td>$J$(5,6′)</td>
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<td>a)</td>
<td>7.1</td>
<td>10.0</td>
</tr>
<tr>
<td>$J$(6,6′)</td>
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<td>a)</td>
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<td>14.6</td>
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<tr>
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</tr>
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<td>$J$(2,7′)</td>
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<td>4.4</td>
<td>3.6</td>
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<td>$J$(7,7′)</td>
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<td>–75.80</td>
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</table>

a) Not determined. b) Assignment may be interchanged.
Values in *italics*: assignment by comparison; not proven.
The large $J(2,3_{ax}) = J(3_{ax},4) = 9.0$ Hz and $J(5,6_{ax}) = 9.3$ Hz for the dibromide 737 (Table 4.2.5) evidence an equatorial orientation of the NHBoc and Br substituents. The small $J(1,6) = 4.7$ Hz evidences an axial orientation of the methoxycarbonyl group. The ring adopts a $^{1}C_{4}$ conformation. The similar coupling pattern for H–C(6) and H'–C(6) of the amine 758 resonating as $ddd$ at $2.77 \ (J = 14.8, 7.6, 3.7$ Hz) and $2.13$ ppm ($J = 14.8, 8.8, 4.4$ Hz) and the values of the coupling constants evidence an equilibrium of the $^{1}C_{4}$ and $^{4}C_{1}$ conformers.

The complexity of the $^{1}H$-NMR spectrum of 738 precluded a straightforward conformational analysis. The large $J(3_{ax},4) = 11.2$ Hz $J(4,5) = 9.8$ Hz and the small $J(2,3_{ax}) = 3.1$ Hz of the amine 759 evidence the equatorial orientation of the Br atoms and the axial orientation of H$_2$N–C(2) and a $^{4}C_{1}$ conformation.
Table 4.2.5: Selected $^1$H- and $^{13}$C-NMR (CDCl₃) Chemical Shifts [ppm] and Coupling Constants [Hz] of 737, 738, 758, and 759.

<table>
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<th>759</th>
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<tr>
<td>H–C(2)</td>
<td>4.10–3.94</td>
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<td>3.42–3.31</td>
<td>2.68–2.58</td>
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<td>H–C(3)</td>
<td>2.58 (eq)</td>
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<td>2.52 (eq)</td>
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<td>H'–C(3)</td>
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<td>2.34</td>
<td>2.08 (ax)</td>
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<td>4.35–4.26$^b$</td>
<td>4.50</td>
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<tr>
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<td>a)</td>
<td>a)</td>
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<tr>
<td>J (1,6)</td>
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</tr>
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<td>J (1,6')</td>
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<td>a)</td>
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<tr>
<td>J (5,6')</td>
<td>9.3</td>
<td>a)</td>
<td>8.0</td>
<td>a)</td>
</tr>
<tr>
<td>J (6,6')</td>
<td>14.5</td>
<td>a)</td>
<td>14.8</td>
<td>a)</td>
</tr>
<tr>
<td>C(1)</td>
<td>38</td>
<td>42.20</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>C(2)</td>
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<td>45.49</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>C(4)</td>
<td>47.84$^b$</td>
<td>52.13</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>C(5)</td>
<td>43.37$^b$</td>
<td>50.39</td>
<td>a)</td>
<td>a)</td>
</tr>
</tbody>
</table>

$^a$) Not determined.

$^b$) Assignment may be interchanged.

Values in italics: assignment by comparison; not proven.
The MS of the dihydrooxazin-2-ones 733, 739, and 740 show the presence of only one Br substituent. Strong IR bands at 1715, 1715, and 1687 cm\(^{-1}\), respectively, evidence the carbonyl group. No signals for a \(\text{tert}\)-butyl group were observed in the NMR spectra (Table 4.2.6). The chemical shift value for the C(1) \(d\) of 733 (75.49 ppm) and 740 (76.03 ppm) (a \(^{13}\text{C}\)-NMR spectrum of 739 was not registered) evidence that C(1) is bound to O.

The similar \(J(1,9_{\text{ax}}) = 1.6\) Hz and \(J(5,9_{\text{ax}}) = 2.2\) Hz are in agreement with the bicyclic structure. A \(\sigma\) coupling (1.6 Hz) was observed between NH and the axial H–C(9) of 733 and 739. A \(\sigma\) coupling between H–C(8) and the equatorial H'–C(9) (1.6 Hz for 733, 739, and 740) evidences an axial orientation of the Br substituent. The large \(J(6,7_{\text{ax}})\) (10.9 Hz (739), 12.1 Hz (740), not measured for 733 due to the complexity of the spectrum) evidences the equatorial orientation of the methoxycarbonyl and the benzlyoxymethyl substituents.
Table 4.2.6 Selected IR Bands [cm\(^{-1}\)], \(^1\)H- and \(^13\)C-NMR (CDCl\(_3\)) Chemical Shifts [ppm], and Coupling Constants [Hz] of 733, 739, 740, 795, and 799.

<table>
<thead>
<tr>
<th></th>
<th>733</th>
<th>739</th>
<th>740</th>
<th>795</th>
<th>799</th>
</tr>
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<tbody>
<tr>
<td>(\nu(C=O))</td>
<td>1715</td>
<td>1715</td>
<td>1687</td>
<td>1721</td>
<td>1713</td>
</tr>
<tr>
<td>H–C(1)</td>
<td>4.68–4.64</td>
<td>4.67–4.63(^a)</td>
<td>4.64</td>
<td>4.72–4.68(^a)</td>
<td>4.72–4.68(^a)</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>3.78–3.73</td>
<td>4.06–4.01</td>
<td>3.80–3.76</td>
<td>3.65</td>
<td>3.74–3.69</td>
</tr>
<tr>
<td>H–C(6)</td>
<td>2.41–2.30</td>
<td>3.00</td>
<td>2.50–2.42</td>
<td>?</td>
<td>2.35</td>
</tr>
<tr>
<td>H(^1)–C(6)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>?</td>
<td>(-)</td>
</tr>
<tr>
<td>H–C(7)</td>
<td>1.97–1.90</td>
<td>2.43–2.37</td>
<td>1.98</td>
<td>?</td>
<td>1.86</td>
</tr>
<tr>
<td>H(^1)–C(7)</td>
<td>1.97–1.90</td>
<td>2.43–2.37</td>
<td>1.88</td>
<td>?</td>
<td>1.89–1.83</td>
</tr>
<tr>
<td>H–C(8)</td>
<td>4.50–4.46</td>
<td>4.56–4.51(^a)</td>
<td>4.51–4.47</td>
<td>4.66–4.61(^a)</td>
<td>4.66–4.61(^a)</td>
</tr>
<tr>
<td>H–C(9)</td>
<td>2.53</td>
<td>2.56</td>
<td>2.43</td>
<td>2.69</td>
<td>2.66</td>
</tr>
<tr>
<td>H(^1)–C(9)</td>
<td>2.04</td>
<td>2.10</td>
<td>1.74</td>
<td>?</td>
<td>2.08</td>
</tr>
<tr>
<td>CH(^1)–C(6)</td>
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<td>(-)</td>
<td>3.42–3.37</td>
<td>(-)</td>
<td>3.39–3.30</td>
</tr>
<tr>
<td>NH</td>
<td>5.33–5.28</td>
<td>5.76–5.68</td>
<td>(-)</td>
<td>6.31–6.23</td>
<td>6.00–5.75</td>
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<td>(J(1,8))</td>
<td>(b)</td>
<td>(b)</td>
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<td>(b)</td>
<td>(b)</td>
</tr>
<tr>
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<td>1.6</td>
<td>1.6</td>
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<td>0</td>
</tr>
<tr>
<td>(J(1,9'))</td>
<td>4.0</td>
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<td>4.0</td>
<td>(b)</td>
<td>(b)</td>
</tr>
<tr>
<td>(J(5,6))</td>
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<td>(b)</td>
<td>0</td>
<td>(b)</td>
</tr>
<tr>
<td>(J(5,6'))</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>0</td>
<td>(-)</td>
</tr>
<tr>
<td>(J(5,9))</td>
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<td>2.2</td>
<td>2.2</td>
<td>2.3</td>
<td>0</td>
</tr>
<tr>
<td>(J(5,9'))</td>
<td>4.0</td>
<td>4.1</td>
<td>4.0</td>
<td>0</td>
<td>(b)</td>
</tr>
<tr>
<td>(J(6,6'))</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(b)</td>
<td>(-)</td>
</tr>
<tr>
<td>(J(6,7))</td>
<td>(b)</td>
<td>10.9</td>
<td>12.1</td>
<td>(b)</td>
<td>3.6 or 0</td>
</tr>
<tr>
<td>(J(6,7'))</td>
<td>(b)</td>
<td>5.9</td>
<td>(b)</td>
<td>(b)</td>
<td>(b)</td>
</tr>
<tr>
<td>(J(6',7))</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(b)</td>
<td>(-)</td>
</tr>
<tr>
<td>(J(6,10))</td>
<td>5.1</td>
<td>(-)</td>
<td>(b)</td>
<td>(-)</td>
<td>(b)</td>
</tr>
<tr>
<td>(J(6,10'))</td>
<td>9.2</td>
<td>(-)</td>
<td>(b)</td>
<td>(-)</td>
<td>(b)</td>
</tr>
<tr>
<td>(J(7,7'))</td>
<td>(b)</td>
<td>(b)</td>
<td>15.8</td>
<td>(b)</td>
<td>9.2</td>
</tr>
<tr>
<td>(J(7,8))</td>
<td>(b)</td>
<td>(b)</td>
<td>4.0</td>
<td>(b)</td>
<td>3.6 or 0</td>
</tr>
<tr>
<td>(J(7,8'))</td>
<td>(b)</td>
<td>(b)</td>
<td>(b)</td>
<td>(b)</td>
<td>(b)</td>
</tr>
<tr>
<td>(I(8,9'))</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
<td>(b)</td>
<td>(b)</td>
</tr>
<tr>
<td>(J(9,9'))</td>
<td>14.0</td>
<td>14.2</td>
<td>14.0</td>
<td>13.9</td>
<td>14.0</td>
</tr>
<tr>
<td>(J(9,NH))</td>
<td>1.6</td>
<td>1.6</td>
<td>(-)</td>
<td>1.6</td>
<td>(b)</td>
</tr>
<tr>
<td>(J(10,10'))</td>
<td>9.4</td>
<td>(-)</td>
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<td>(-)</td>
<td>(b)</td>
</tr>
<tr>
<td>C(1)</td>
<td>75.49</td>
<td>(b)</td>
<td>76.03</td>
<td>76.64</td>
<td>76.81</td>
</tr>
<tr>
<td>C(3)</td>
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<td>(b)</td>
<td>(b)</td>
<td>154.02</td>
<td>(b)</td>
</tr>
<tr>
<td>C(5)</td>
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<td>(b)</td>
<td>49.26(^a)</td>
<td>45.24</td>
<td>46.20</td>
</tr>
<tr>
<td>C(8)</td>
<td>46.00(^a)</td>
<td>(b)</td>
<td>47.73(^a)</td>
<td>27.73</td>
<td>26.74</td>
</tr>
</tbody>
</table>

\(^a\) Assignment may be interchanged.
\(^b\) Not determined.
The MS of the bicyclic oxolanes 734 and 741 show the presence of only one Br substituent. According to the NMR spectra (Table 4.2.7), 734 and 741 are devoid of O-benzyl groups.

The chemical shift values for the C(5) of 734 (77.11 ppm) and 741 (77.23 ppm) and $J(7,7')$ evidence the oxolane moiety. The values of $J(2,3_{eq})$ (5.5 and 4.8 Hz, respectively), $J(2,3_{ax})$ (12.1 and 13.2 Hz, respectively), $J(3_{eq},4)$ (0 Hz), and $J(3_{ax},4)$ (5.3 and 5.1 Hz, respectively) evidence an equatorial C(2) tert-butoxycarbonylamino and an axial Br–C(4) substituent and a chair conformation of the cyclohexane ring. A $w$ coupling between H–C(4) and the equatorial H'–C(8) (1.2 and 1.6 Hz, respectively) corroborates the axial orientation of the Br substituent. The bridgehead H–C(1) couples with H$_{exo}$–C(7) (4.0 and 4.1 Hz, respectively) but not with the endo H$_{endo}$–C(7), similarly to levoglucosans. The bridgehead H–C(1) and H–C(5) do not couple with the axial H–C(8), but with the equatorial H'–C(8) (5.6 Hz).
Table 4.2.7: Selected $^1$H- and $^{13}$C-NMR (CDCl$_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] of 734 and 741.

<table>
<thead>
<tr>
<th></th>
<th>734</th>
<th>741</th>
</tr>
</thead>
<tbody>
<tr>
<td>H–C(1)</td>
<td>2.59–2.54</td>
<td>2.54–2.48</td>
</tr>
<tr>
<td>H–C(2)</td>
<td>4.05–3.93</td>
<td>4.57–4.49</td>
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<tr>
<td>H–C(3)</td>
<td>2.20 (eq)</td>
<td>2.43 (ax)</td>
</tr>
<tr>
<td>H’–C(3)</td>
<td>1.97 (ax)</td>
<td>1.99 (eq)</td>
</tr>
<tr>
<td>H–C(4)</td>
<td>4.14</td>
<td>4.16–4.12</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>4.29</td>
<td>4.24</td>
</tr>
<tr>
<td>H–C(7)</td>
<td>3.86</td>
<td>3.86</td>
</tr>
<tr>
<td>H’–C(7)</td>
<td>3.79</td>
<td>3.64</td>
</tr>
<tr>
<td>H–C(8)</td>
<td>2.52 (ax)</td>
<td>2.55 (ax)</td>
</tr>
<tr>
<td>H’–C(8)</td>
<td>1.87 (eq)</td>
<td>1.84 (eq)</td>
</tr>
<tr>
<td>NH</td>
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<td>–</td>
</tr>
<tr>
<td>$J$ (1,2)</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>$J$ (1,7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$J$ (1,7’)</td>
<td>4.0</td>
<td>4.1</td>
</tr>
<tr>
<td>$J$ (1,8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$J$ (1,8’)</td>
<td>5.6</td>
<td>5.4</td>
</tr>
<tr>
<td>$J$ (2,3)</td>
<td>5.5</td>
<td>13.2</td>
</tr>
<tr>
<td>$J$ (2,3’)</td>
<td>12.1</td>
<td>4.8</td>
</tr>
<tr>
<td>$J$ (2,NH)</td>
<td>6.9</td>
<td>–</td>
</tr>
<tr>
<td>$J$ (3,4)</td>
<td>0</td>
<td>5.1</td>
</tr>
<tr>
<td>$J$ (3’,4)</td>
<td>5.3</td>
<td>0</td>
</tr>
<tr>
<td>$J$ (3,3’)</td>
<td>15.0</td>
<td>14.5</td>
</tr>
<tr>
<td>$J$ (4,5)</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>$J$ (4,8’)</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td>$J$ (5,8)</td>
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<td>0</td>
</tr>
<tr>
<td>$J$ (5,8’)</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>$J$ (7,7’)</td>
<td>8.7</td>
<td>8.9</td>
</tr>
<tr>
<td>$J$ (8,8’)</td>
<td>12.7</td>
<td>12.5</td>
</tr>
<tr>
<td>C(1)</td>
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<td>40.63</td>
</tr>
<tr>
<td>C(2)</td>
<td>47.80$^b)$</td>
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</tr>
<tr>
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<td>47.47$^b)$</td>
<td>48.58</td>
</tr>
<tr>
<td>C(5)</td>
<td>77.11</td>
<td>77.23</td>
</tr>
<tr>
<td>C(7)</td>
<td>68.52</td>
<td>69.61</td>
</tr>
</tbody>
</table>

a) Not determined. b) Assignment may be interchanged.
The *exo*-orientation of Br–C(2) of the azanorbornanes **743** and **744** is evidenced by the absence of coupling between the H–C(2) *dd* and the bridgehead H–C(1) (*cf.* [989]) (Table 4.2.8). Similarly, H–C(2) and H–C(3) of the *meso* diols **746** and **58·HCl** do not couple with the bridgehead H–C(1) and H–C(4).
Table 4.2.8: Selected $^1$H- and $^{13}$C-NMR (CDCl$_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] of 743, 744, 746, and 58.

<table>
<thead>
<tr>
<th></th>
<th>743</th>
<th>744</th>
<th>746</th>
<th>58</th>
</tr>
</thead>
<tbody>
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<td>H–C(1)</td>
<td>3.73–3.67$^a$</td>
<td>4.41–4.36$^a$</td>
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<td>4.06</td>
</tr>
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<td>H–C(2)</td>
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<td>3.99</td>
<td>3.79</td>
<td>4.16</td>
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<td>H–C(3)</td>
<td>2.18 (endo)</td>
<td>2.33–2.23 (exo)</td>
<td>3.79</td>
<td>4.16</td>
</tr>
<tr>
<td>H'–C(3)</td>
<td>2.00</td>
<td>2.17 (endo)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>H–C(4)</td>
<td>3.64–3.56$^a$</td>
<td>4.34–4.27$^a$</td>
<td>4.11</td>
<td>4.06</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>1.64–1.52</td>
<td>1.78–1.63</td>
<td>1.73–1.65</td>
<td>1.95–1.88</td>
</tr>
<tr>
<td>H'–C(5)</td>
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<td>1.69</td>
</tr>
<tr>
<td>H–C(6)</td>
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<td>H'–C(6)</td>
<td>1.28–1.09</td>
<td>1.43–1.25</td>
<td>1.81</td>
<td>1.69</td>
</tr>
<tr>
<td>CH–C(5)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CH'–C(5))</td>
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<tr>
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<td>b$^b$</td>
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<td>b$^b$</td>
<td>8.1?</td>
<td>8.1</td>
</tr>
<tr>
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<td>b$^b$</td>
<td>b$^b$</td>
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</tr>
<tr>
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<td>b$^b$</td>
<td>8.1?</td>
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<td>b$^b$</td>
<td>8.1?</td>
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<tr>
<td>J (5',6')</td>
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<tr>
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<td>b$^b$</td>
<td>8.1?</td>
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</tr>
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<td>b$^b$</td>
<td>?</td>
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<td>?</td>
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<tr>
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<td>–</td>
<td>–</td>
</tr>
<tr>
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<tr>
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<td>64.32</td>
</tr>
<tr>
<td>C(2)</td>
<td>53.84</td>
<td>49.71</td>
<td>74.24</td>
<td>71.47</td>
</tr>
<tr>
<td>C(4)</td>
<td>56.74</td>
<td>55.61</td>
<td>62.26</td>
<td>64.32</td>
</tr>
<tr>
<td>C(6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$) Assignment maybe interchanged.

$^b$) Not determined.

Values in *italics*: assignment by comparison; not proven.
Similarly, the \textit{exo}-orientation of the C(2) and C(5) substituents of the azanorbornanes 753, 754, 760, and 761 (Table 4.2.9) is evidenced by the absence of coupling between the corresponding H and the bridgehead H.
Table 4.2.9: Selected $^1$H- and $^{13}$C-NMR (CDCl$_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] of 753, 754, 760, and 761.

<table>
<thead>
<tr>
<th></th>
<th>753</th>
<th>754</th>
<th>760</th>
<th>761</th>
</tr>
</thead>
<tbody>
<tr>
<td>H–C(1)</td>
<td>3.84$^a$</td>
<td>4.37</td>
<td>3.92</td>
<td>4.60–4.43</td>
</tr>
<tr>
<td>H–C(2)</td>
<td>1.84</td>
<td>1.98–1.85</td>
<td>2.36</td>
<td>1.82</td>
</tr>
<tr>
<td>H–C(3)</td>
<td>1.55 (endo)</td>
<td>1.55 (endo)</td>
<td>2.05 (exo)</td>
<td>2.24 (exo)</td>
</tr>
<tr>
<td>H’–C(3)</td>
<td>1.45</td>
<td>1.47–1.35 (exo)</td>
<td>1.58 (endo)</td>
<td>0.87 (endo)</td>
</tr>
<tr>
<td>H–C(4)</td>
<td>3.88$^a$</td>
<td>4.50</td>
<td>3.80</td>
<td>4.38–4.25</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>4.07</td>
<td>4.00</td>
<td>4.00</td>
<td>3.29</td>
</tr>
<tr>
<td>H–C(6)</td>
<td>2.31–2.17</td>
<td>2.31 (exo)</td>
<td>2.17 (endo)</td>
<td>2.01 (exo)</td>
</tr>
<tr>
<td>H’–C(6)</td>
<td>2.31–2.17</td>
<td>2.21 (endo)</td>
<td>2.12–2.01 (exo)</td>
<td>1.46 (endo)</td>
</tr>
<tr>
<td>CH–C(2)</td>
<td>3.46</td>
<td>3.30</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CH’–C(2)</td>
<td>3.31</td>
<td>3.17</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>NH</td>
<td>4.20–3.90</td>
<td>–</td>
<td>b) 4.20–3.90</td>
<td>b) 4.20–3.90</td>
</tr>
<tr>
<td>$J$ (1,2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$J$ (1,6)</td>
<td>3.4</td>
<td>5.3</td>
<td>0</td>
<td>5.0</td>
</tr>
<tr>
<td>$J$ (1,6')</td>
<td>0</td>
<td>4.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$J$ (2,3)</td>
<td>8.4</td>
<td>8.3</td>
<td>4.4</td>
<td>4.7</td>
</tr>
<tr>
<td>$J$ (2,3')</td>
<td>5.0</td>
<td>8.7</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>$J$ (2,7)</td>
<td>8.9</td>
<td>8.9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>$J$ (2,7')</td>
<td>5.3</td>
<td>6.4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>$J$ (3,3')</td>
<td>13.1</td>
<td>12.9</td>
<td>13.1</td>
<td>13.1</td>
</tr>
<tr>
<td>$J$ (3,4)</td>
<td>0</td>
<td>0</td>
<td>5.3</td>
<td>5.1</td>
</tr>
<tr>
<td>$J$ (3,4')</td>
<td>3.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$J$ (4,5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$J$ (5,6)</td>
<td>4.5</td>
<td>3.7</td>
<td>7.9</td>
<td>3.5</td>
</tr>
<tr>
<td>$J$ (5,6')</td>
<td>6.1</td>
<td>7.3</td>
<td>3.4</td>
<td>7.5</td>
</tr>
<tr>
<td>$J$ (6,6')</td>
<td>b) 14.0</td>
<td>14.3</td>
<td>14.0</td>
<td></td>
</tr>
<tr>
<td>$J$ (7,7')</td>
<td>9.3</td>
<td>9.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>C(1)</td>
<td>59.42$^a$</td>
<td>57.65,57.18$^a$</td>
<td>60.53$^a$</td>
<td>59.51$^a$</td>
</tr>
<tr>
<td>C(2)</td>
<td>40.95</td>
<td>42.71,41.91</td>
<td>50.95</td>
<td>46.15$^c$</td>
</tr>
<tr>
<td>C(4)</td>
<td>65.26$^a$</td>
<td>63.79,62.91$^a$</td>
<td>64.63$^a$</td>
<td>64.18$^a$</td>
</tr>
<tr>
<td>C(5)</td>
<td>50.68</td>
<td>49.73,48.88</td>
<td>45.95</td>
<td>48.36$^c$</td>
</tr>
</tbody>
</table>

$^a$) Assignment may be interchanged.

$^b$) Not determined.

Values in *italics*: assignment by comparison; not proven.
The chemical shift value for H–C(2) and H–C(3) of the azanorborene 755 resonating as a br. d at 6.29 ppm is typical of alkenes (Table 4.2.10). H–C(5) resonates as a m at 1.90–1.79 ppm, precluding a straightforward assignment of the configuration at C(5).

\[
\begin{align*}
\text{BnO} & \quad \text{N} & \quad \text{Boc} \\
5 & \quad 4 & \quad 3 & \quad 2 \\
\text{755} \\
\end{align*}
\[
\begin{align*}
\text{R}^1 & \quad \text{OH} & \quad \text{OH} \\
6 & \quad 5 & \quad 4 & \quad 3 \\
\text{756} & \quad \text{R}^1 = \text{Boc}, \text{R}^2 = \text{Bn} \\
\text{757} & \quad \text{R}^1 = \text{Boc}, \text{R}^2 = \text{H} \\
\text{59} & \quad \text{R}^1 = \text{HCl}, \text{R}^2 = \text{H} \\
\end{align*}
\]

Also, the configuration of the diol 756 could not be determined due to the complexity of its $^1$H-NMR spectrum. The CDCl$_3$ solution of the triol 757 became a gel, therefore the NMR spectra were recorded of solutions in CD$_3$OD. The exo orientation of the C(2), C(3), and C(5) substituents of 757 and 59-HCl is evidenced by the absence of coupling between the corresponding H and the bridgehead H.
## Table 4.2.10: Selected $^1$H- and $^{13}$C-NMR (CDCl$_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] of 755, 756, 757, and 59.

<table>
<thead>
<tr>
<th></th>
<th>755</th>
<th>756</th>
<th>757</th>
<th>59</th>
</tr>
</thead>
<tbody>
<tr>
<td>H–C(1)</td>
<td>4.70–4.51</td>
<td>4.02–3.97$^a$</td>
<td>3.99</td>
<td>3.93</td>
</tr>
<tr>
<td>H–C(2)</td>
<td>6.29</td>
<td>3.46–3.41$^b$</td>
<td>3.80$^a$</td>
<td>4.10–4.06</td>
</tr>
<tr>
<td>H–C(3)</td>
<td>6.29</td>
<td>3.39–3.33$^b$</td>
<td>3.77$^a$</td>
<td>4.10–4.06</td>
</tr>
<tr>
<td>H'–C(3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>H–C(4)</td>
<td>4.70–4.51</td>
<td>4.25–4.17$^a$</td>
<td>4.02</td>
<td>3.91</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>1.90–1.79</td>
<td>1.46</td>
<td>1.82</td>
<td>2.09</td>
</tr>
<tr>
<td>H–C(6)</td>
<td>1.38–1.28</td>
<td>0.83–0.76</td>
<td>1.48 (endo)</td>
<td>1.86 (endo)</td>
</tr>
<tr>
<td>H'–C(6)</td>
<td>1.38–1.28</td>
<td>0.83–0.76</td>
<td>1.09 (exo)</td>
<td>1.67</td>
</tr>
<tr>
<td>CH–C(5)</td>
<td>3.51</td>
<td>3.08</td>
<td>3.32–3.24</td>
<td>3.65</td>
</tr>
<tr>
<td>CH'–C(5)</td>
<td>3.51–3.37</td>
<td>2.91</td>
<td>3.32–3.24</td>
<td>3.48</td>
</tr>
<tr>
<td>NH</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4.94</td>
</tr>
<tr>
<td>J(1,2)</td>
<td>c)</td>
<td>c)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>J(2,3)</td>
<td>10.0</td>
<td>c)</td>
<td>8.7 or 6.2?</td>
<td>c)</td>
</tr>
<tr>
<td>J(2,3')</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>J(3,3')</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>J(3,4)</td>
<td>c)</td>
<td>c)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>J(3',4)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>J(4,5)</td>
<td>c)</td>
<td>c)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>J(5,6)</td>
<td>c)</td>
<td>7.0</td>
<td>8.4</td>
<td>9.2</td>
</tr>
<tr>
<td>J(5,6')</td>
<td>c)</td>
<td>7.0</td>
<td>4.7</td>
<td>5.1</td>
</tr>
<tr>
<td>J(6,6')</td>
<td>c)</td>
<td>c)</td>
<td>12.7</td>
<td>13.5</td>
</tr>
<tr>
<td>J(6,1)</td>
<td>c)</td>
<td>c)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>J(6',1)</td>
<td>c)</td>
<td>c)</td>
<td>5.3</td>
<td>5.0</td>
</tr>
<tr>
<td>J(5,7)</td>
<td>6.1</td>
<td>9.0</td>
<td>7.9</td>
<td>4.5</td>
</tr>
<tr>
<td>J(5,7')</td>
<td>c)</td>
<td>6.5</td>
<td>7.9</td>
<td>5.9</td>
</tr>
<tr>
<td>J(7,7')</td>
<td>9.2</td>
<td>9.0</td>
<td>8.1</td>
<td>10.7</td>
</tr>
<tr>
<td>C(1)</td>
<td>61.56$^a$</td>
<td>64.64$^a$</td>
<td>c)</td>
<td>c)</td>
</tr>
<tr>
<td>C(2)</td>
<td>136.55, 136.26</td>
<td>74.62 or 74.01</td>
<td>c)</td>
<td>c)</td>
</tr>
<tr>
<td>C(4)</td>
<td>60.12,59.08</td>
<td>62.99, 60.89$^a$</td>
<td>c)</td>
<td>c)</td>
</tr>
<tr>
<td>C(5)</td>
<td>39.62,38.79</td>
<td>38.44</td>
<td>40.99</td>
<td>37.46</td>
</tr>
</tbody>
</table>

$^a$, $^b$ Assignment may be interchanged.

$^c$ Not determined.

Values in *italics*: assignment by comparison; not proven.
The IR (CHCl₃) C= N band of the dihydro-1,3-oxazine 762 (1689 cm⁻¹) and the chemical shift values for the C(1), C(5), and C(8) d (74.99, 50.15 and 46.50 ppm, respectively) are similar to the corresponding values for the dihydro-1,3-oxazines 720, 724, and 725 (Table 4.2.1, chapter 4.2.1). H–C(8) of 762 resonates as a ddd at 4.16 ppm. The large $J(\gamma_{ax},8) = J(6,7_{ax}) = 12.5$ Hz evidence the equatorial orientation of Br–C(8) and of the C(6) benzyloxymethyl substituent. Due to a $\gamma$-effect, $\delta_{ax}$–C(9) of the dihydro-1,3-oxazines 720, 724, and 725 ($\delta_{ax}$–C(9)) = 2.26–2.74 ppm) with axial Br is shifted downfield as compared to 762 (Br equatorial, $\delta_{ax}$–C(9)= 1.86 ppm). The geminal $J(7,7')$ of 724, where the axial Br is gauche to H–C(7) and anti to H'–C(7), is larger (15.9 Hz) than that of 762 (14.0 Hz), where a gauche relation between the equatorial Br and both H–C(7) leads to a decreased (absolute) value of the geminal coupling constant (cf. [682] [683]).
The MS and $^1$H-NMR spectrum of 749 were consistent with both the structure 748 and 749. A (H,H)-COSY spectrum revealed strong coupling between the two methylene groups. The $^{13}$C-NMR spectrum displayed two $d$ at 69.27 and 54.51 ppm. These observations were hardly consistent with structure 748. The structure of 749 was established indirectly by X-ray crystallography of the dibromide 751 (Figure 4.2.1) derived from 749. The large $J(3a,4) = 11.2$ Hz) of 749 evidences the equatorial orientation of N–C(3a) and thus a 4H$_{3a}$ conformation of the cyclohexene ring. Several analogues of 749 with no or another N substituent are known [948] [990] [991].

Figure 4.2.1: Crystal Structure of 751.

<table>
<thead>
<tr>
<th>Bond Lengths [Å]</th>
<th>Bond Angles [°]</th>
<th>Torsional Angles [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(6)–Br(6)</td>
<td>1.963(6)</td>
<td>O(1)–C(7a)–C(3a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>102.4(4)</td>
</tr>
<tr>
<td>C(7)–Br(7)</td>
<td>1.947(7)</td>
<td>O(1)–C(7a)–C(7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>111.5(5)</td>
</tr>
<tr>
<td>C(7a)–O(1)</td>
<td>1.461(7)</td>
<td>C(3a)–C(7a)–C(7a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>116.7(5)</td>
</tr>
<tr>
<td>C(3a)–O(1)</td>
<td>1.514(8)</td>
<td>C(7a)–O(1)</td>
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<tr>
<td></td>
<td></td>
<td>1.461(7)</td>
</tr>
<tr>
<td>C(3a)–N(3)</td>
<td>1.475(7)</td>
<td>C(3a)–C(7a)–C(7a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>116.7(5)</td>
</tr>
<tr>
<td>C(2)–N(3)</td>
<td>1.385(7)</td>
<td>C(2)–N(3)–C(31)</td>
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<tr>
<td></td>
<td></td>
<td>123.0(5)</td>
</tr>
<tr>
<td>N(3)–C(7')</td>
<td>1.395(7)</td>
<td>C(2)–O(C(2))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.201(7)</td>
</tr>
<tr>
<td>C(2)–O(C(2))</td>
<td>1.199(7)</td>
<td>O(1)–C(2)–C(2)–O(1)</td>
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<tr>
<td></td>
<td></td>
<td>123.1(5)</td>
</tr>
<tr>
<td>C(2)–O(1)</td>
<td>1.357(7)</td>
<td>O(1)–C(2)–N(3)</td>
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<td></td>
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<td>129.0(6)</td>
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<tr>
<td>C(31)–O(C(31))</td>
<td>1.201(7)</td>
<td>C(2)–O(1)–C(7a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>108.4(4)</td>
</tr>
</tbody>
</table>

Table 4.2.11: Selected Bond Lengths [Å], Bond Angles, and Torsional Angles [°] of 751.
Table 4.2.12: Selected Torsional Angles [°] of 751

<table>
<thead>
<tr>
<th>Torsional Angle</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)–C(7a)–C(7)–C(6)</td>
<td>-78.8(7)</td>
</tr>
<tr>
<td>O(1)–C(7a)–C(3a)–C(4)</td>
<td>84.2(5)</td>
</tr>
<tr>
<td>N(3)–C(3a)–C(4)–C(5)</td>
<td>158.5(5)</td>
</tr>
<tr>
<td>N(3)–C(3a)–C(7a)–C(7)</td>
<td>-156.3(4)</td>
</tr>
<tr>
<td>O(1)–C(7a)–C(3a)–N(3)</td>
<td>-34.2(4)</td>
</tr>
<tr>
<td>C(7a)–C(3a)–N(3)–C(2)</td>
<td>28.5(5)</td>
</tr>
<tr>
<td>C(3a)–N(3)–C(2)–O(1)</td>
<td>-10.7(6)</td>
</tr>
<tr>
<td>N(3)–C(2)–O(1)–C(7a)</td>
<td>-13.3(6)</td>
</tr>
<tr>
<td>C(2)–O(1)–C(7a)–C(3a)</td>
<td>31.0(5)</td>
</tr>
<tr>
<td>C(4)–C(3a)–C(7a)–C(7)</td>
<td>-37.9</td>
</tr>
<tr>
<td>C(3a)–C(7a)–C(7)–C(6)</td>
<td>38.5(7)</td>
</tr>
<tr>
<td>C(5)–C(4)–C(3a)–C(7a)</td>
<td>47.9(7)</td>
</tr>
<tr>
<td>Br(7)–C(7)–C(6)–C(5)</td>
<td>-175.1(4)</td>
</tr>
<tr>
<td>Br(7)–C(7)–C(6)–Br(6)</td>
<td>65.3(5)</td>
</tr>
<tr>
<td>Br(6)–C(6)–C(5)–C(4)</td>
<td>-178.9(4)</td>
</tr>
<tr>
<td>C(3\textsuperscript{1})–N(3)–C(2)–O(C(2))</td>
<td>-1.5(9)</td>
</tr>
<tr>
<td>C(3a)–N(3)–C(2)–O(C(2))</td>
<td>166.5(6)</td>
</tr>
<tr>
<td>C(3\textsuperscript{1})–N(3)–C(2)–O(1)</td>
<td>-178.8(4)</td>
</tr>
<tr>
<td>C(2)–N(3)–C(3\textsuperscript{1})–O(C(3\textsuperscript{1}))</td>
<td>-19.4(8)</td>
</tr>
</tbody>
</table>

The crystal structure of 751 revealed a $7^aC_5$ conformation of the cyclohexane with equatorial Br substituents, a pseudoaxial orientation of C(7a)–O, and a pseudoequatorial orientation of C(3a)–N. The conformation of the dihydrooxazol-2-one is somewhere between $E_{7a}$ and $3^aE$.

The structure of the dibromide 750 obtained along with 751 was tentatively assigned as the diastereoisomer of 751. In the $^1$H-NMR spectrum of 751 $J(6,7) = 10.0$ Hz, corroborating the equatorial orientation of the Br substituents. The small $J(6,7) = ca. 6.5$ Hz for 750 evidences the axial orientation of the Br substituents.

The low stereoselectivity of the bromination of 749 is surprising. From a diaxial dibromination of the $4H_{3a}$ conformer of 749 one would expect a selective formation of 750. Cabanal-Duvillard et al. studied the dibromination and the bromohydroxylation of the analogous oxazolidinones 763 (Scheme 4.2.14, Table 4.2.13) [948]. The dibromination of the N-tosyl derivative 763b yielded 765b as the only product, but the dibromination of the N-benzyl derivative 763c was unselective. The bromohydroxylation of 763a and 763c with NBS
furnished 766a and 766c as the major products, resulting from nucleophilic attack of water on the trans-epibromonium ion. The bromohydroxylation of 763a with Br2 gave 766a as the major product, while the major product of the bromohydroxylation of 763b was 767b, resulting from the cis-epibromonium ion. These selectivities were not explained convincingly in [948].

In order to rationalise the results of the dibromination and bromohydroxylation of 763 one has

Table 4.2.13: Dibromination and Bromohydroxylation of 763a - c [948].

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Conditions</th>
<th>Combined yield</th>
<th>764 / 765 or 766 / 767</th>
</tr>
</thead>
<tbody>
<tr>
<td>763a</td>
<td>Br2, CH2Cl2, r.t.</td>
<td>95%</td>
<td>a)</td>
</tr>
<tr>
<td>763b</td>
<td>Br2, CH2Cl2, r.t.</td>
<td>96%</td>
<td>&lt;5:95</td>
</tr>
<tr>
<td>763c</td>
<td>Br2, CH2Cl2, r.t.</td>
<td>90%</td>
<td>50:50</td>
</tr>
<tr>
<td>763a</td>
<td>two eq. of NBS, DMSO / H2O (1:1), r.t.</td>
<td>50%</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>763c</td>
<td>two eq. of NBS, DMSO / H2O (1:1), r.t.</td>
<td>72%</td>
<td>80:20</td>
</tr>
<tr>
<td>763a</td>
<td>two eq. of Br2, DME / H2O, r.t.</td>
<td>70%</td>
<td>65:35</td>
</tr>
<tr>
<td>763b</td>
<td>two eq. of Br2, DME / H2O, r.t.</td>
<td>75%</td>
<td>20:80</td>
</tr>
</tbody>
</table>

a) 30% d.e., the structure of the major product was not determined.
to look at the possible epibromonium ions (Scheme 4.2.15). These are the trans-epibromonium ions A and B and the cis-epibromonium ions C and D. The dashed arrows indicate the trajectories of a nucleophilic attack on these epibromonium ions according to the Fürst-Plattner rule.

**Scheme 4.2.15**

\[ \text{Scheme 4.2.15} \]

R: see Table 4.2.13.

The bromoalcohols 766 must be formed from A, and the bromoalcohols 767 from D. In NBS bromohydroxylations, formation of the epibromonium ion is reversible, and the attack of H\textsubscript{2}O on the bromonium ion is the rate-determining step (see [977] [983] [992] and references cited there). If this is true also for the NBS bromohydroxylation of 763, the relative energies of the transition states for the attack of water on A, B, C, and D will govern the selectivity. The selective formation of 766 in the NBS bromohydroxylation means that the dialxial opening of A is the one which is kinetically most favourable. Dialxial opening of B may be disfavoured by steric hindrance and electronically (in the transition state of opening of the epibromonium ion, bond breaking is expected to be more advanced than bond making, resulting in a build-up of positive charge on the C-atom; this is unfavourable in the \( \alpha \)-position of the positively polarised C–O atom). The build-up of 1,3-dialxial interactions between Br and O and between Br and N in the transition states might disfavour the opening of C and D. The selective formation of 766 might also be rationalised by an irreversible formation of the trans-epibromonium ion under kinetic control, followed by a preferred attack on A.
In Br₂ bromohydroxylations, the formation of the epibromonium ion is rate-determining and irreversible (see [969 – 973] [992] and references cited there). Thus, the selectivity in favour of 766a in the Br₂ bromohydroxylation of 763a must result from a selective formation of the epibromonium ion on the less hindered trans face of the alkene. Diamaxial nucleophilic opening of the conformer A yields 766a (vide supra). The minor product 767a results from diaxial opening of the cis-epibromonium ion D (vide infra).

The inverse selectivity in the Br₂ bromohydroxylation of 763b (yielding 767b as the major product) must in turn result from a selective formation of the cis-epibromonium ion and the exclusive diaxial opening of the conformer D. The selective formation of the cis epibromonium ion means that the endo attack of Br₂ on 763b is favoured or that the exo attack is disfavoured. The endo attack might be favoured by dipole-dipole or charge donor-acceptor interactions between NTs and Br₂ [976] [977]. The exo attack might be disfavoured by stereoelectronic effects. The more strongly electron withdrawing tosyl group (compared to H) lowers the orbital energies of the oxazolidinone moiety and might deform the (frontier) orbitals. The high regioselectivity of the nucleophilic attack on the cis-epibromonium ion can be rationalised by stereoelectronic effects. In the transition state of this reaction, bond breaking is expected to be more advanced than bond making, resulting in a build-up of positive charge on the C-atom. This build-up of positive charge is unfavourable in the α-position of the positively polarised C–O atom.

The diastereoselectivity of the dibromination of 763 can be similarly explained by reflecting the selectivity of epibromonium ion formation and diaxial opening of A and D.

A rationalisation of the low selectivity of my own PhMe₃NBr₃ dibromination of 749 must take account of the different reaction mechanism: The rate-limiting step is the attack of Br⁻ on a 1:1 Br₂-alkene π-complex ([969 – 972], see chapter 4.2.1). The possible π-complexes may also be represented by the formulae A - D, except that Br⁺ has to be replaced with Br₂. The attack of Br⁻ on these π-complexes must also follow the shown trajectories. The low selectivity of the reaction must result from a competition of A (and/or C) and D (and/or B). Again, some stereoelectronic effect must be invoked to explain the unexpected formation of 751.
4.2.3. Glycosidase Inhibition by the 7-Azanorbornanes 58-HCl and 59-HCl

The azanorbornanes 58-HCl and 59-HCl were tested against the β-mannosidase from snail acetone powder (sequence not known), the α-mannosidase from Jack beans (family 38) (both at pH 4.5), the β-glucosidases from sweet almonds (family 1), the β-glucosidase from *Caldocellum saccharolyticum* (family 1), and the α-glucosidase from brewer's yeast (family 13) (all three at pH 6.8) (Table 4.2.14). The 7-azanorbornanes proved at best weak inhibitors of these enzymes.

![Structural formulas of 58, 59, 27, and 29](image)

Table 4.2.14: Inhibition of Several Glycosidases by the 7-Azanorbornanes 58 and 59 (IC₅₀ Values in mM).

<table>
<thead>
<tr>
<th>Enzyme Type</th>
<th>(±)-58</th>
<th>(±)-59</th>
<th>(±)-27 [197]</th>
<th>29 [198]</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-mannosidase (snail)</td>
<td>no inh. at 2 mM</td>
<td>ca. 25% inh. at 2.7</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>α-mannosidase (Jack beans)</td>
<td>no inh. at 2 mM</td>
<td>0.55</td>
<td>3.9</td>
<td>a)</td>
</tr>
<tr>
<td>β-glucosidases (almonds)</td>
<td>1.74</td>
<td>2.05</td>
<td>a)</td>
<td>2.7</td>
</tr>
<tr>
<td>β-glucosidase (C. sacch.)</td>
<td>2.2</td>
<td>1.95</td>
<td>4.3</td>
<td>1.9</td>
</tr>
<tr>
<td>α-glucosidase (brewer's yeast)</td>
<td>ca. 10% inh. at 1.6 mM</td>
<td>no inh. at 2 mM</td>
<td>a)</td>
<td>a)</td>
</tr>
</tbody>
</table>

a) Not determined.

The meso-diol 58-HCl weakly inhibited the β-glucosidases from sweet almonds and the β-glucosidase from *Caldocellum saccharolyticum*, but not the mannosidases. The triol 59-HCl weakly inhibited the β-glucosidases from sweet almonds and *Caldocellum saccharolyticum* and the α-mannosidase from Jack beans, but not the β-mannosidase from snail. Thus, the azanorbornane 59-HCl is a weaker inhibitor of the β-mannosidase from snail than the isoquinuclidine (±)-27, but a stronger inhibitor of the α-mannosidase from Jack beans. The IC₅₀ value for the inhibition by racemic 59-HCl of the β-glucosidases is similar to that of enantiomerically pure 29. The observed weak selectivity of 59-HCl for the α-mannosidase is surprising. An interaction of the protonated N(7) with the (deprotonated?) catalytic nucleophile of the α-mannosidase may be at the root of this weak binding, and the boat conformation of the cyclohexane ring may place the C(2)–OH group in a similar orientation.
as in an oxycarbenium ion like transition state with \( \phi(C(5)-O-C(1)-C(2)) \approx 0^\circ \). Inhibition of the \( \beta \)-glucosidases by the manno-configured 58-HCl and 59-HCl correlates with the notion that mannose in a boat conformation is analogous to glucose in a chair conformation (see [189] and references cited there). However, these 7-azanorbornanes, especially the meso-diol 58-HCl, may bind in a different orientation from that resembling a distorted glycoside in the active site of a glycosidase. Considering the weak inhibition by 58-HCl and 59-HCl an interpretation may not be meaningful.

The weak inhibition of these \( \beta \)-glycosidases by 58-HCl and 59-HCl and also by the isoquinuclidines 27 and 29 (Table 4.2.14) evidences that such conformers are not stabilised in the –1 subsites of these enzymes. Conceivably, the conformational itinerary of these enzymes involves another reactive substrate conformation that is in accord with the requirements of stereoelectronic control (see chapter 1.5). It is also conceivable that glycolysis by these enzymes does not involve a high-energy reactive substrate conformation at all, but proceeds from the \( ^4C_1 \) substrate conformation to the transition state, as argued for by Fraser-Reid et al. [83] (see chapter 1.5).

As suggested by Boehm et al., the weak inhibition of these enzymes by boat-like inhibitors may also be due to a strong correlation of substrate distortion with lengthening of the glycosidic bond and rehybridisation of the anomic carbon [197] [198], such that a boat type inhibitor with "normal" bond lengths and angles may only poorly mimic a reactive conformer or a transition state with lengthened glycosidic bond and rehybridised anomic centre.

For some endo-glycosidases from families 5 and 7 it was proposed that the substrate first binds in a \( ^4C_1 \) conformation, bypassing the active site, and then is pulled into the active site and simultaneously distorted to a boat-like reactive conformation [104] [105] [107] (see chapter 1.6)\(^57\). It was assumed that this translocation and conformational change of the substrate precede glycolysis. However, it is conceivable that glycolysis is correlated with the conformational change and translocation of the substrate, such that translocation towards the catalytic nucleophile and the catalytic acid, and conformational change towards a conformation with \( \phi(C(5)-O-C(1)-C(2)) \approx 0^\circ \) leads to lengthening of the glycosidic bond (i.e. towards the transition state) and finally to breaking of the glycosidic bond and glycosylation of the catalytic nucleophile, rather than to binding of a high-energy conformer in the active site. These suggestions are, of course, highly speculative.

\(^57\) There is no evidence for a similar “bypass binding” in exo-glycosidases. However, this does not mean that an analogy to such a “bypass binding” must be ruled out for exo-glycosidases.
4.3. Attempts Towards the Synthesis of 6-Azabicyclo[3.1.1]heptanes

4.3.1. By Pd-Catalysed Intramolecular Allylic Amination

4.3.1.1. Introduction

As the attempts to prepare the bicyclic azetidines by intramolecular nucleophilic substitution of the dibromides failed, I examined alternative routes. As we were interested in a general and highly efficient access to 6-azabicyclo[3.1.1]heptanes we were looking for a synthesis from readily available starting materials in a few steps, rather than devising a multi-step synthesis.

Transition metal catalysed intramolecular amination of an acetate 73 (Scheme 4.3.2) appeared as a particularly attractive route to the azetidines 74, as it allows the generation of a reactive electrophile in the presence of a nucleophilic amine or amide. The nucleophilic nitrogen species used in Pd(0)-catalysed allylic aminations are primary and secondary amines [686] [993 – 995], 4,4’-dimethoxybenzhydrylamine [996], azide [694], sulfonamides [690], phthalimide [997], di-t-butyl iminodicarbonate [998], and N-(t-butoxycarbonyl)phosphoramides [999] (see [1000] for the comparison of a range of nitrogen nucleophiles, for reviews on allyl-Palladium chemistry see [685] [687] [1001 – 1003]).

Acetates and carbonates are the most common leaving groups for generation of π-allyl-palladium species by oxidative addition, but also hydroxide [993], halides [417] [690] [1004], phenolates and isoureas [997], epoxides [429], carbamates [1005 – 1008], phosphates [694] [995], sulfonylaziridines and -azetidines [1009], or benzotriazole [1010] can serve as the leaving group. There are also examples for a Pd(II)-catalysed allylic amination (with secondary amines) [1011] or amidation [1012] [1013], for Rh-catalysed allylic sulfonamidation [691], and for Ir-catalysed allylic aminations [688]. Intramolecular Pd-catalysed allylic aminations [686] [687] [689] [1010] [1014 – 1016] and amidations [692] [1009] have led to several azacycloalkanes. Of particular interest in the context of my own work is the intramolecular allylic amination of the cyclohexene 773 (Scheme 4.3.1), which under conditions of kinetic control yielded the strained bicyclic azetidine 774 [687]. Under conditions of thermodynamic control (longer reaction times) the more stable isoquinuclidine 775 was obtained. The azetidine 774 is formed from an intermediate with pseudoequatorial aminomethyl group, whereas the isoquinuclidine 775 is formed from a high-energy conformer with pseudoaxial aminomethyl group.
Scheme 4.3.1

\[
\begin{align*}
\text{OAc} & \quad \text{NH} & \quad \text{Bn} \\
\text{773} & \quad \xrightarrow{a) \ \text{or} \ b)} & \quad \text{774} & \quad \text{or} \quad \text{775}
\end{align*}
\]

\(a)\) Formation of 774 under conditions of kinetic control; conditions and yield not given [687].

\(b)\) (Ph3P)4Pd, Et3N, MeCN, 70°; 56% of 775 [1014].

The required acetates 73 (Scheme 4.3.2) should be available from \(N\)-acylamino-cyclohex-3-enes via the bicyclic dihydrooxazin-2-ones 777 or dihydro-1,3-oxazines 75. These in turn may be prepared by halocyclisation [906] [907] [955] [966] of \(N\)-acyl-cyclohex-3-enylamines, respectively, followed by elimination of H-Hal [1017] [1018].

Scheme 4.3.2

\[
\begin{align*}
\text{N} & \quad \xrightarrow{\text{R}} & \quad \text{74} & \quad \xrightarrow{\text{AcO}} & \quad \text{73} & \quad \xrightarrow{\text{R'}} & \quad \text{777} & \quad \xrightarrow{\text{N}} & \quad \text{75} & \quad \xrightarrow{\text{NHR}} & \quad \text{74}
\end{align*}
\]

Retrosynthetic analysis of the azetidine 74.

It was most intriguing that the dihydrooxazin-2-ones 777 themselves might serve as substrates for the Pd-catalysed intramolecular amination, as allylic carbamates are suitable substrates for Pd-catalysed allylations (\textit{vide supra}). Oxidative addition of 777 to Pd(0) should lead to a carbamate A (Scheme 4.3.3) which might lose CO₂, liberating an amide B. Intramolecular attack of this amide at the allyl moiety might yield the azetidine 776. In this way the steps required to transform the dihydrooxazin-2-ones 777 into the acetates 73 would most elegantly be bypassed. Therefore, I embarked upon a study of Pd(0)-catalysed conversions of the oxazin-2-ones 777 to the azetidines 74.
In the literature, there are only few examples for a related Pd(0)-catalysed conversion of allyl-carbamates to allylamines by extrusion of CO₂. Genet et al. obtained 70% of 780 (Scheme 4.3.4) upon deprotecting 778 [1006]. The formation of this undesired product was suppressed by using an excess of Et₂NH. In the analogous deprotection of Alloc-protected morpholine 781, 2% of N-allylmorpholine 783 were obtained [1006]. Minami et al. obtained 60% of N-allylmorpholine 783 from 781 in an attempted allylic C-allylation (Pd₂(dba)₃·CHCl₃, PPh₃, THF) of methyl 2-methyl-3-oxopentanoate [1019]. For additional examples of such decarboxylative allylic carbamate to allylic amine conversions, see [1020 – 1022].
Some related Pd-catalysed allylic substitutions have been reported, where the leaving group (or a product derived from it) also acts as nucleophile. Treatment of the carbamate 784 with Pd$_2$(dba)$_3$·CHCl$_3$/Ph$_3$P in CH$_2$Cl$_2$ in the presence of diethyl malonate gave the 1,3-oxazoline 785 (quant.) [1007] (Scheme 4.3.5). In the presence of benzylamine (instead of diethylmalonate), the oxazoline 785 and the diene 786 were formed in a ratio of 10:90 (quant.). The allylic amine 787 was obtained selectively by treating a THF solution of 784 with benzylamine and 0.1 equivalents of Pd$_2$(dba)$_3$·CHCl$_3$/dppp in the presence of 0.36 equivalents of LiCl ("low yield"). It was speculated that Cl$^-$ suppresses elimination by replacing a phosphine ligand of the Pd(II)-allyl complex, thereby neutralising the charge on Pd and moderating the reactivity of the complex.

**Scheme 4.3.5**

\[
\begin{array}{c}
\text{784} \quad \text{a), b), or c)} \\
\text{O} \quad \text{Ph} \\
\text{O} \\
\text{N} \\
\text{Ph} \\
\end{array}
\quad \begin{array}{c}
\text{785} \\
\text{N} \\
\text{Ph} \\
\text{O} \\
\end{array}
\quad \begin{array}{c}
\text{786} \\
\text{NHCOPh} \\
\text{Ph} \\
\end{array}
\quad \begin{array}{c}
\text{787} \\
\text{NHCOPh} \\
\text{BnN} \\
\end{array}
\]

a) Diethyl malonate, Pd$_2$(dba)$_3$·CHCl$_3$, Ph$_3$P, CH$_2$Cl$_2$; 785 (quant.) [1007]. b) BnNH$_2$, Pd$_2$(dba)$_3$·CHCl$_3$, Ph$_3$P, CH$_2$Cl$_2$; 10% of 785, 90% of 786 [1007]. c) BnNH$_2$, Pd$_2$(dba)$_3$·CHCl$_3$, dppp, LiCl, THF; low yield of 787 [1007] or BnNH$_2$, (AllPdCl)$_2$, dppp, THF; 86% of 787 [1007].

Fugami et al. reported a Pd(0)-catalysed rearrangement of N-sulfonyl-2-(buta-1,3-dienyl)-aziridines to vinyl pyrrolines (e.g. 788 to 789, Scheme 4.3.6) and of N-sulfonyl-2-(buta-1,3-dienyl)azetidines to vinyl piperidines (e.g. 790 to 791) [1009].
Suzuki et al. reported a Pd(0)-catalysed decarboxylative ring-opening polymerisation of 4-vinyl-1,3-oxazin-2-ones [1008] (Scheme 4.3.7). Allylic substitution of the carbamate by Pd$_2$(dba)$_3$·CHCl$_3$/8 Ph$_3$P in CH$_2$Cl$_2$ and decarboxylation of the carbamoyl leaving group generated the allyl-π-complex 793, the propagating species of the polymerisation to 794.

Another example is the transformation of 300 to 303 applied in Trost's synthesis of (+)-valienamine (see Scheme 2.1.45 in chapter 2.1.4).
4.3.1.2. Results and Discussion

Iodocyclisation of the carbamate 712 to the dihydrooxazin-2-one 795 (> 100% crude) according to [955], followed by elimination of HI (DBU, THF) (cf. [1017]) gave the alkene 796 (75% from 712) (Scheme 4.3.8). This was benzylated (BuLi, THF, then BnBr [1023]) to give 797 (92%), ortosylated (NaH, THF, then TsCl [1024]) to give 798 (89%).

Similarly, the carbamate 716 was transformed into the alkene 800 (78%) byiodocarbamoylation (> 100% crude), followed by elimination of HI. Tosylation gave the N-tosyl derivative 801 (86%), and p-nitrobenzylation (NaH, DMF, pNBnBr) afforded the N-p-nitrobenzyl derivative 802 (58%).

The free carbamate 796 did not react with Pd(0) at r.t. (Table 4.3.1, Entry 1). Also the benzyl derivative 797 was inert to Pd(0) in several solvents at r.t. or under reflux (Entries 2 – 5) in agreement with a literature report that N-benzyl allylic carbamates are inert to (Ph3P)4Pd, Pd(OAc)2(PPh3)2, and Pd2(dba)3-benzene/Ph3P [1005]. Even when the carbamate 797 was
activated with In(OTf)$_3$\textsuperscript{58}), it was inert to Pd(0) at r.t., and the reaction under reflux (THF) was sluggish (according to TLC incomplete conversion to a complex mixture).

In contrast, upon treatment with Pd(PPh$_3$)$_4$ in THF at r.t. the $N$-tosyl carbamate \textbf{798} was readily transformed into a new compound, the diene \textbf{803} (\textit{Entry 6}) (this volatile compound was isolated in 15% yield after FC and evaporation) (Scheme 4.3.9). Treatment of \textbf{798} with Pd(PPh$_3$)$_4$ in EtOH at r.t. gave the diene \textbf{803} (22%) besides the ethyl allyl-ether \textbf{804} (28%) (\textit{Entry 7}), whereas the analogous reaction in MeCN afforded only the diene according to TLC (\textit{Entry 8}). At r.t., \textbf{798} did not react with Pd(PPh$_3$)$_4$ in THF in the presence of LiCl (\textit{cf.} [1007]) (\textit{Entry 9}), while a new, more polar compound formed upon heating to reflux. However, after FC and evaporation of the corresponding fractions, this compound could no longer be detected on TLC. Treatment of an EtOH solution of \textbf{798} with Pd(PPh$_3$)$_4$ in the presence of LiCl at r.t. gave the diene \textbf{803} and the ethyl allyl ether \textbf{804} (TLC) (\textit{Entry 10}). Conceivably, in EtOH Cl$^-$ is hydrogen bonded to Et–O–H, and may thus not be able to interfere with the Pd complexes.

I had hoped that Pd(0)-catalysed intramolecular allylic amination of the C(6)-substituted $N$-tosyl carbamate \textbf{801} to an azetidine has a higher chance of succeeding, as the benzylxoymethyl substituent should favour a conformation with an axial sulfonylamino group. However, the reaction of \textbf{801} with Pd(PPh$_3$)$_4$ in THF at r.t. gave the diene \textbf{805} (70%) (\textit{Entry 11}). In the presence of LiCl, \textbf{801} did not react with Pd(PPh$_3$)$_4$ in THF at r.t., while in boiling THF it was transformed into the diene \textbf{806} (39%) (\textit{Entry 12}).

The $N$-p-nitrobenzyl carbamate \textbf{802} was inert to Pd(0) in THF at r.t. and under reflux (\textit{Entry 14}). The reactivity of the carbamates \textbf{796}, \textbf{797}, \textbf{798}, \textbf{801}, and \textbf{802} towards Pd(0) correlates with their IR C=O bands. For the reactive carbamates \textbf{798} and \textbf{801}, bearing the strongly electron withdrawing tosyl group, the IR C=O band is observed at 1721 cm$^{-1}$. For the inert carbamates \textbf{796}, \textbf{797}, and \textbf{802} the IR C=O band is observed at 1701, 1680, and 1680 cm$^{-1}$, respectively, indicating that the $p$-nitro-group does not significantly enhance the $\sigma$-acceptor properties of the benzyl groups.

\textsuperscript{58}) As suggested by Professor B. Trost (personal communication). I thank Professor B. Trost for a discussion of the Pd chemistry.
When neat carbamate 801 was heated to 160° under Ar, it slowly rearranged to the isomeric carbamate 807, isolated in 52% yield (Entry 13). Presumably, this transformation of 801 to 807 is a concerted [3,3]-sigmatropic rearrangement. For an ionic or radical mechanism one would expect loss of CO₂. The driving force for this rearrangement (all starting material is consumed according to TLC) may be a less hindered position of the benzyloxymethyl group in the product 807 as compared to 801.

Scheme 4.3.9

\[ a) \text{ See text and Table 4.3.1; } b) 160°, neat; 52\%. \]
Table 4.3.1: Pd-Catalysed and Thermal Reactions of the Carbamates 796, 797, 798, 801, and 802.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>R</th>
<th>Catalyst/additive</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>796</td>
<td>H</td>
<td>10% Pd(PPh₃)₄</td>
<td>THF, r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>797</td>
<td>Bn</td>
<td>10% Pd(PPh₃)₄</td>
<td>THF, r.t.–&gt;reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>797</td>
<td>Bn</td>
<td>10% Pd(PPh₃)₄</td>
<td>MeCN, r.t.–&gt;80°</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>797</td>
<td>Bn</td>
<td>25% Pd(acac)₂, 25% PBP₃</td>
<td>THF, r.t.–&gt;reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>797</td>
<td>Bn</td>
<td>10% Pd(PPh₃)₄, 10% In(OTf)₃</td>
<td>THF, r.t.–&gt;reflux</td>
<td>no reaction; mixture (TLC)</td>
</tr>
<tr>
<td>6</td>
<td>798</td>
<td>Ts</td>
<td>10% Pd(PPh₃)₄</td>
<td>THF, r.t.</td>
<td>15% of 803</td>
</tr>
<tr>
<td>7</td>
<td>798</td>
<td>Ts</td>
<td>10% Pd(PPh₃)₄</td>
<td>EtOH, r.t.</td>
<td>22% of 803, 28% of 804</td>
</tr>
<tr>
<td>8</td>
<td>798</td>
<td>Ts</td>
<td>10% Pd(PPh₃)₄</td>
<td>MeCN, r.t.</td>
<td>803 (TLC)</td>
</tr>
<tr>
<td>9</td>
<td>798</td>
<td>Ts</td>
<td>10% Pd(PPh₃)₄, 20% LiCl</td>
<td>THF, r.t.–&gt;reflux</td>
<td>see text</td>
</tr>
<tr>
<td>10</td>
<td>798</td>
<td>Ts</td>
<td>10% Pd(PPh₃)₄, 20% LiCl</td>
<td>EtOH, r.t.</td>
<td>803, 804 (TLC)</td>
</tr>
<tr>
<td>11</td>
<td>801</td>
<td>Ts</td>
<td>10% Pd(PPh₃)₄</td>
<td>THF, r.t.</td>
<td>70% of 805</td>
</tr>
<tr>
<td>12</td>
<td>801</td>
<td>Ts</td>
<td>10% Pd(PPh₃)₄, 15% LiCl</td>
<td>THF, r.t.–&gt;reflux</td>
<td>no reaction; 39% of 806</td>
</tr>
<tr>
<td>13</td>
<td>801</td>
<td>Ts</td>
<td>none</td>
<td>160°, neat</td>
<td>52% of 807</td>
</tr>
<tr>
<td>14</td>
<td>802</td>
<td>pNBn</td>
<td>10% Pd(PPh₃)₄</td>
<td>THF, r.t.–&gt;reflux</td>
<td>no reaction</td>
</tr>
</tbody>
</table>
The structure of the iodocarbamates 795 and 799 is evident from their MS and $^1$H-NMR spectra (Table 4.2.6, chapter 4.2.2).

Conversion to the unsaturated carbamates 796 and 800 is evidenced by typical olefinic signals in the $^1$H- and $^{13}$C-NMR spectra (Table 4.3.2). The $\text{H–C}(8)$ $dddd$ resonate at 5.94 and 6.06 ppm, respectively. $\text{H–C}(7)$ resonates as a $m$ at 6.09–6.02 ppm for 796 and as a $dt$ at 5.54 ppm for 800. The upfield shift of the latter is presumably due to a field effect of the neighbouring phenyl group. $w$ coupling is observed between the equatorial $\text{H–C}(9)$ and $\text{H–C}(8)$ (1.3 Hz) and between the axial $\text{H'}–\text{C}(9)$ and NH (1.9 Hz).

![Chemical structures](image)

The constitution of the rearranged carbamate 807 is evidenced by the different coupling pattern for the axial $\text{H–C}(9)$ as compared to 801. The $\text{H–C}(9)$ $ddt$ resonating at 2.39 ppm couples with $\text{H–C}(1)$ and $\text{H–C}(5)$ (2.0 Hz), and with $\text{CH–C}(9)$ (6.5 Hz) and $\text{CH'–C}(9)$ (8.4 Hz). $\text{H–C}(5)$ couples with $\text{H–C}(6)$ (2.5 Hz) and with $\text{H'}–\text{C}(6)$ (4.0 Hz).
**Table 4.3.2:** Selected IR Bands [cm$^{-1}$], $^1$H- and $^{13}$C-NMR (CDCl$_3$) Chemical Shifts [ppm], and Coupling Constants [Hz] of 796, 797, 798, 800, 801, 802, and 807.

<table>
<thead>
<tr>
<th></th>
<th>796</th>
<th>797</th>
<th>798</th>
<th>800</th>
<th>801</th>
<th>802</th>
<th>807</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nu$(C=O)</td>
<td>1701</td>
<td>1680</td>
<td>1721</td>
<td>1705</td>
<td>1721</td>
<td>1680</td>
<td>1725</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>5.94</td>
<td>5.91</td>
<td>6.05–6.02</td>
<td>5.54</td>
<td>6.16</td>
<td>5.63</td>
<td>6.07–6.04</td>
</tr>
<tr>
<td>H–C(8)</td>
<td>6.09–6.02</td>
<td>6.11–6.04</td>
<td>6.05–6.02</td>
<td>6.06</td>
<td>6.05</td>
<td>6.12</td>
<td>6.07–6.04</td>
</tr>
<tr>
<td>H–C(9)</td>
<td>2.21(eq)</td>
<td>2.24–2.13</td>
<td>2.25(eq)</td>
<td>2.25</td>
<td>2.23–2.11</td>
<td>2.11</td>
<td>–</td>
</tr>
<tr>
<td>$\delta$(C–C(6))</td>
<td>67.99</td>
<td>67.69</td>
<td>68.61</td>
<td>68.05</td>
<td>69.16</td>
<td>68.17</td>
<td>67.76</td>
</tr>
<tr>
<td>$\delta$(C–C(3))</td>
<td>154.99</td>
<td>153.67</td>
<td>156.83</td>
<td>153.52</td>
<td>148.59</td>
<td>153.77</td>
<td>144.71</td>
</tr>
<tr>
<td>$\delta$(C–C(5))</td>
<td>44.27</td>
<td>48.30</td>
<td>50.74</td>
<td>45.41</td>
<td>52.82</td>
<td>49.67</td>
<td>52.45</td>
</tr>
</tbody>
</table>

$^a$) Not determined.
The structure of the diene 803 is evidenced by signals for 4 olefinic H. H–C(1) resonates as a $\text{ddd}$ at 3.93 ppm and CH$_2$(6) as a $\text{ddd}$ at 2.38 ppm.

The ethoxy group of the ether 804 is evidenced by 2 $\text{dq}$ at 3.51 and 3.46 ppm and a $\text{t}$ at 1.21 ppm. The constitution of 804 is evidenced by coupling of CH$_2$(2) with the olefinic protons, coupling of CH$_2$(6) with H–C(1) and H–C(5), and coupling of H–C(1) with both CH$_2$(2) and CH$_2$(6). The configuration is evidenced by the large $J(1,2_{\text{ax}}) = J(1,6_{\text{ax}})$ = 8.9 Hz and by the large width of the H–C(5) signal (18 Hz).

The $^1$H-NMR spectrum of the diene 805 shows signals for 4 olefinic H. H–C(1) and H–C(6) resonate as $\text{m}$ at 4.07–3.89 and 2.64–2.55 ppm, respectively. The configuration was assigned tentatively, assuming that C(1) and C(6) were unaffected by the reaction. For the diene 806, the $^1$H-NMR spectrum displays only 3 signals for olefinic H. H–C(1) resonates as a $\text{ddd}$ at 3.95 ppm. The CH$_2$–C(2) resonate as $\text{d}$ at 3.84 and 3.76 ppm ($J = 12.3$ Hz), confirming the absence of a proton at C(2). CH$_2$(6) resonates as a $\text{m}$ at 2.50–2.29 ppm.
4.3.2. Attempted Synthesis of Azetidines by [3.3]Sigmatropic Rearrangements

The facile rearrangement of the oxazin-2-one 801 into 807 (vide supra) stimulated an investigation of the synthesis of the desired azetidines 74 by a [3.3]-sigmatropic rearrangement of imidates 808 to amides 776 (Scheme 4.3.10). Such rearrangements have been reviewed by Ritter [698], by Schenck and Bosnich [699], and by Overman [697]. Below I will describe some examples of particular interest in the context of my own work.

Scheme 4.3.10

\[
\begin{align*}
\text{808} & \quad \xrightarrow{a)} \quad \text{776} \\
\end{align*}
\]

*a) [3.3]-Sigmatropic rearrangement.

*Synerholm et al.* [1025] reported the decarboxylative rearrangement of O-allyl-N-phenyl carbamates 809 to N-phenylallylamines 812 (24–76%) at 200–240° in the presence of catalytic amounts of NaH (Scheme 4.3.11). NaH is believed to facilitate the tautomerisation of the carbamates 809 to the isocarbamates 810, which undergo the sigmatropic rearrangement. The loss of CO₂ provides the driving force for this rearrangement.

Scheme 4.3.11

\[
\begin{align*}
\text{809} & \quad \xrightleftharpoons{a)} \quad \text{810} & \quad \xrightarrow{\text{a)}} \quad \text{811} & \quad \xrightarrow{\text{a)}} \quad \text{812} \\
\end{align*}
\]

*a) 2% NaH, 210 – 230°; 24% [1025].
Wang and Calabrese described a related decarboxylative rearrangement of allylic carbamates 813 to piperidines 814 under much milder conditions by treatment with BF$_3$·OEt in CH$_2$Cl$_2$ at r.t. [1026] (Scheme 4.3.12). The best yields (75–85%) were obtained when R$^1$ is a phenyl, or when R$^2$ is a trimethylsilyl group, stabilising a carbenium ion. This indicated that the rearrangement follows a stepwise cationic and not an electrocyclic mechanism.

Scheme 4.3.12

![Scheme 4.3.12](image)

\[a\) BF$_3$·OEt$_2$, CH$_2$Cl$_2$, r.t.; 20% (R$^1$ = n-hexyl, R$^2$ = H); 76% (R$^1$ = n-hexyl, R$^2$ = SiMe$_3$); 85% (R$^1$ = Ph, R$^2$ = H) [1026].

Knapp and Patel reported a sigmatropic rearrangement of the isocarbamate 816 to the carbamate 817 (96%) in boiling toluene [1027] [1028] (Scheme 4.3.13). The isocarbamate 816 was obtained in quantitative yield by treatment of the allylic alcohol with KH and methyl N-benzyl chloroformimidate in THF. Similarly, the rearrangement of 2-allyloxy-1,3-oxazoles gave N-allyl-1,3-oxazolidin-2-ones [1029] [1030]. Analogous rearrangements of O-allyl-O'-silyl isocarbamates are not known.

Scheme 4.3.13

![Scheme 4.3.13](image)

\[a\) KH, ClC(=NBn)(OMe), THF; [1027]. \[b\) 110°, CCl$_4$, 24 h; 88% (two steps) [1027].

The rearrangement of the imidates 808 (R = alkyl or aryl) to the desired azetidines 776 is an N-alkyl/aryl analogue of the Overman rearrangement or of transition metal catalysed allylic rearrangements [695 – 699] [1031]. Thermal rearrangements of this kind were reported for R
= phenyl [1032] (e.g. 818 to 819, Scheme 4.3.14) [1033]. Transition metal catalysed variants were reported by Schenck and Bosnich (e.g. 820 to 821) [699]. The imidates employed in the Overman rearrangement are usually prepared by the addition of allylic alcohols to trichloroacetonitrile, precluding additional substitution at N.

![Scheme 4.3.14](image)

**Scheme 4.3.14**

\[ a) 250^\circ; 58\% [1033]. b) (Ph_3P)_4Pd, CDCl_3; 90\% conversion [699]. \]

Stereoelectronically the rearrangement of the imidates 808 to the azetidines 776 should be possible, as there is precedent for a corresponding ketone to enol ether rearrangement: neat [3.1.1]bicyclohept-2-enyl methyl ketone 822 rearranges at 180° into the bicyclic enol ether 823 (85%) [1034] (Scheme 4.3.15). The driving force for this rearrangement is the release of ring strain, which outbalances the energy required for the conversion of a ketone to an enol ether. In the rearrangement of 808 to 776 the ring strain would increase by ca. 20 kcal/mol, whereas the conversion of the imidate to the amide would deliver ca. 15 kcal/mol [698], indicating that the free energy for this reaction would be positive. However, placing the benzyloxymethyl group into a sterically less hindered position may provide some additional driving force (vide supra). Additional driving force would be gained for R = OH or R = OSiR₃, as the rearrangement of 808 to 776 would be followed by an irreversible decarboxylation. Michels et al. reported the acid-catalysed transformation of N-alkyl 4-aza-2-oxabicyclo[4.2.0]octa-3,7-dienes (824) into N-acyl 2-azabicyclo[2.2.0]hex-5-enes (825) [1035]. The driving force for this reaction was not commented upon, but is probably delivered by the relief of repulsive interactions between the phenyl group and the proximal tert-butyl group in 824.
I first tried a BF₃·OEt₂ catalysed rearrangement of the carbamate 800 (Scheme 4.3.16). In CH₂Cl₂ no reaction was observed in the presence of one equivalent of BF₃·OEt₂ at r.t. or under reflux. In boiling THF, 800 did not react with two equivalents BF₃·OEt₂. When 800 was treated with two equivalents BF₃·OEt₂ in diglyme at 150°, NMR and TLC⁵⁹) indicated consumption of the starting material. However, after carbamoylation (Boc₂O, K₂CO₃) no product could be isolated by FC.

Therefore, I turned my attention towards the rearrangement of an O-allyl-O’-silyl isourethane derived from 800. Trimethylsilylation (Et₃N, Me₃SiCl) [1036] of 800 was incomplete after 1 d, according to a ¹H-NMR spectrum of the crude reaction mixture. After workup, only the starting material could be detected by NMR. Obviously the desired trimethylsilyl isocarbamate was too labile to allow for its synthesis or even isolation. Therefore I examined the tert-butyldimethylsilylation of 800, followed by in situ rearrangement. Treatment of 800 with TBSOTf and Et₃N in CH₂Cl₂ did not result in consumption of the starting material, as judged by TLC. When the reaction was performed in toluene at 80°, the starting material was consumed, but according to the ¹H-NMR spectrum, a complex mixture was obtained. The reaction in diglyme at 150°, followed by trifluoroacetylation ((CF₃CO)₂O, Et₃N) and FC, did not afford any isolated product.

⁵⁹) A smear was observed on TLC.
Scheme 4.3.16

\[
\text{ON H} \quad \begin{array}{c}
\text{CH}_2\text{OBn} \\
\text{N} \\
R \\
(800)
\end{array}
\]

\[
\text{ON} \quad \begin{array}{c}
\text{CH}_2\text{OBn} \\
\text{N} \\
(826)
\end{array} \xrightarrow{b) BF_3\cdot\text{OEt}_2, \text{see text.}} \quad \begin{array}{c}
\text{ON} \quad \begin{array}{c}
\text{CH}_2\text{OBn} \\
\text{N} \\
(776)
\end{array}
\end{array}
\]

\[
\text{ON} \quad \begin{array}{c}
\text{CH}_2\text{OBn} \\
\text{N} \\
(800)
\end{array} \xrightarrow{a) \text{Me}_3\text{SiCl, Et}_3\text{N or TBSOTf, Et}_3\text{N, see text.}} \quad \begin{array}{c}
\text{ON} \quad \begin{array}{c}
\text{CH}_2\text{OBn} \\
\text{N} \\
(776)
\end{array}
\end{array}
\]

\(a) \text{BF}_3\cdot\text{OEt}_2, \text{see text.} \quad b) \text{Me}_3\text{SiCl, Et}_3\text{N or TBSOTf, Et}_3\text{N, see text.}\)

O-Silyl isocarbamates were not a good choice as the starting material of the desired 1-aza-3-oxa-Cope rearrangement. It was impossible to obtain them in pure form, and they were apparently not stable enough to survive the high temperatures required to effect the sigmatropic rearrangement. Therefore, I briefly examined the rearrangement of acetimidates of the type \(808\) (\(R = \text{alkyl}, \text{Scheme 4.3.10}\)). The derivative of choice was the trifluoroacetimidate \(827\) (Scheme 4.3.17), as a trifluoromethyl group facilitates the imidate to amide rearrangement [698], and \(827\) should be easily available from \(724\) (Scheme 4.2.6, page 225) by elimination of HBr. However, this elimination turned out to be sluggish (DBU, THF: no reaction; KOrBu, THF: low yield (19%), diene formation). In contrast, the iodide \(828\), prepared from \(72\) by treatment with NIS in AcOH (86%), was readily dehydrohalogenated by treatment with DBU in boiling THF (86%). Heating neat trifluoromethylimidate \(827\) under Ar at temperatures up to 180° did not result in consumption of the starting material. At 210° the starting material was consumed, but according to \(^1\)H-NMR a complex product mixture was formed. This means either that \(827\) decomposed below the temperatures required for the rearrangement, or that the equilibrium of the rearrangement lies completely on the left side, and therefore the desired azetidine cannot be detected.
The structure of the iodide 828 is evidenced by its NMR data that are very similar to those of the bromide 724 (Table 4.3.3). The C=C double bond in 827 is evidenced by the typical signals for the olefinic H in the $^{1}H$-NMR spectrum.
Table 4.3.3: Selected $^1$H- and $^{13}$C-NMR (CDCl$_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] of 724, 828, and 827.

<table>
<thead>
<tr>
<th></th>
<th>724</th>
<th>828</th>
<th>827</th>
</tr>
</thead>
<tbody>
<tr>
<td>H–C(1)</td>
<td>4.74–4.69</td>
<td>4.76–4.72</td>
<td>4.94–4.89</td>
</tr>
<tr>
<td>H–C(5)</td>
<td>4.94–4.89</td>
<td>4.00–3.96</td>
<td>4.11–4.06</td>
</tr>
<tr>
<td>H–C(6)</td>
<td>2.65–2.54</td>
<td>2.65–2.54</td>
<td>2.92–2.84</td>
</tr>
<tr>
<td>H'–C(6)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>H–C(7)</td>
<td>2.12</td>
<td>2.11–2.03</td>
<td>6.07</td>
</tr>
<tr>
<td>H'–C(7)</td>
<td>1.57</td>
<td>1.48</td>
<td>–</td>
</tr>
<tr>
<td>H–C(8)</td>
<td>4.51–4.47</td>
<td>4.68–4.64</td>
<td>5.98</td>
</tr>
<tr>
<td>H–C(9)</td>
<td>2.54</td>
<td>2.68</td>
<td>2.07</td>
</tr>
<tr>
<td>H'–C(9)</td>
<td>1.83</td>
<td>1.88</td>
<td>1.86</td>
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<tr>
<td>CH–C(6)</td>
<td>3.56</td>
<td>3.58</td>
<td>3.74</td>
</tr>
<tr>
<td>CH'–C(6)</td>
<td>3.29</td>
<td>3.30</td>
<td>3.42</td>
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<tr>
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<td>a)</td>
<td>a)</td>
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</tr>
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<td>J(1,8)</td>
<td>a)</td>
<td>a)</td>
<td>5.3</td>
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<tr>
<td>J(1,9)</td>
<td>1.6</td>
<td>1.6</td>
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<td>J(1,9')</td>
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<td>3.9</td>
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</tr>
<tr>
<td>J(5,6)</td>
<td>a)</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>J(5,6')</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>J(5,9)</td>
<td>1.6</td>
<td>1.6</td>
<td>3.4</td>
</tr>
<tr>
<td>J(5,9')</td>
<td>3.9</td>
<td>3.9</td>
<td>1.2</td>
</tr>
<tr>
<td>J(6,7)</td>
<td>ca. 3.6</td>
<td>a)</td>
<td>1.6</td>
</tr>
<tr>
<td>J(6,7')</td>
<td>12.1</td>
<td>12.5</td>
<td>–</td>
</tr>
<tr>
<td>J(6',7)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>J(6',7')</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>J(6,10)</td>
<td>7.5</td>
<td>7.5</td>
<td>6.9</td>
</tr>
<tr>
<td>J(6,10')</td>
<td>6.5</td>
<td>6.9</td>
<td>9.0</td>
</tr>
<tr>
<td>J(7,8)</td>
<td>a)</td>
<td>a)</td>
<td>10.0</td>
</tr>
<tr>
<td>J(7,8')</td>
<td>4.0</td>
<td>4.7</td>
<td>–</td>
</tr>
<tr>
<td>J(7,9')</td>
<td>15.9</td>
<td>16.2</td>
<td>–</td>
</tr>
<tr>
<td>J(8,9')</td>
<td>1.6</td>
<td>1.9</td>
<td>1.2, J(8,9)</td>
</tr>
<tr>
<td>J(9,9')</td>
<td>14.3</td>
<td>14.3</td>
<td>13.4</td>
</tr>
<tr>
<td>J(10,10')</td>
<td>9.0</td>
<td>9.0</td>
<td>9.0</td>
</tr>
<tr>
<td>C(1)</td>
<td>74.33</td>
<td>73.65</td>
<td>73.61</td>
</tr>
<tr>
<td>C(3)</td>
<td>147.62</td>
<td>a)</td>
<td>a)</td>
</tr>
<tr>
<td>C(5)</td>
<td>47.80b)</td>
<td>48.04</td>
<td>47.66</td>
</tr>
<tr>
<td>C(8)</td>
<td>47.68b)</td>
<td>26.66 a)</td>
<td>a)</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>–73.10</td>
<td>a)</td>
<td>a)</td>
</tr>
</tbody>
</table>

a) Not determined.
b) Assignment may be interchanged.
4.4. Conclusions and Outlook

I have established an efficient synthesis of 7-azanorbornanes from aminocyclohex-3-enes using a highly stereoselective dibromination and an intramolecular substitution as the key steps. This synthesis uses readily available starting materials and reagents and does not require special techniques (such as high pressure). It complements the existing methods for the synthesis of 7-azanorbornanes and might also be applied on kg-scale. The 7-azanorbornanes 744 and 754 and the 7-azanorborenes 745 and 755 are of interest as building blocks for the synthesis of potential drugs, such as epibatidine and its analogues.

My attempts to prepare 6-azabicyclo[3.1.1]heptanes (bicyclic azetidines) were not successful. The cyclisation of 747 and 759 was probably hindered by repulsive interactions between the vicinal Br substituents, in contrast to the successful cyclisation of 3-bromocyclohexylamine by von Braun et al. [243]. In the attempted Pd-catalysed rearrangement of 798 and 801, intramolecular substitution could not successfully compete with elimination. However, an extensive catalyst screening may be worthwhile. Finally, a sigmatropic rearrangement of imidates 808 to azetidines 776 could not be effected, even under conditions where decarboxylation of the azetidines 776 should provide the driving force required for the rearrangement.

The 7-azanorbornanes 58 and 59 are only weak inhibitors of the β-mannosidase from snail and of the β-glucosidases from sweet almonds and from Caldocellum saccharolyticum, suggesting that these enzymes do not stabilise $^{14}B$ conformers in their active site. The 7-azanorbornanes are lower homologues of the isoquinuclidines prepared by Böhm et al. [197 – 199]. Higher homologues of the isoquinuclidines (e.g. 1-azabicyclo[3.2.2]nonanes) are also of interest as potential glycosidase inhibitors. They should be conformationally more flexible than the isoquinuclidines and the 7-azanorbornanes and thus might be better mimics of distorted boat conformers. The synthesis of such higher homologues of the isoquinuclidines has been accomplished by Buser [239].
5. Part 4: Varia

5.1. 1-C-(Benzyloxy)methyl)cyclohex-3-enylamine

In the context of the attempted synthesis of bicyclic azetidines, I briefly examined the synthesis of the C(1)-branched \(N\)-cyclohex-3-enylamine 834 from methyl cyclohex-3-enecarboxylate (Scheme 5.1.1). Hydroxymethylation [1037] of 829 [1038] gave the branched cyclohexene 830 (47%). Benzylation of 830 gave the benzyl ether 831 (31%) besides the benzyl ester 832 (12%). Hydrolysis of the methyl ester 831 afforded the carboxylic acid 833 (89%). Curtius degradation of 833 gave the corresponding isocyanate, which - even in the presence of CuCl - reacted only very slowly with \(t\)BuOH, yielding only 28% of the branched \(N\)-cyclohex-3-enylamine 834 after 6 days. Presumably most of the neopentylic isocyanate was converted to the free amine (see experimental part). No attempts were made to improve this synthesis of 834, as this synthetic route was given up. A more ready access to the desired branched \(N\)-cyclohex-3-enylamines would be Diels-Alder cycloadditions of \(\alpha\)-acetamido acrylates or 2-alkylidene-5(4H)-oxazolones to butadiene [931] [938].

Scheme 5.1.1

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
829 & \quad \text{CH}_2\text{OH} \\
830 & \quad \text{CO}_2\text{Me} \\
831 & \quad \text{CH}_2\text{OBn} \\
832 & \quad \text{CO}_2\text{Me} \\
833 & \quad \text{CO}_2\text{H} \\
834 & \quad \text{NH}Boc
\end{align*}
\]

\(a)\) LDA, THF, then \(\text{CH}_2\text{O}; 53\%. \) \(b)\) NaH, THF, then \(\text{Bu}_4\text{NI}, \text{BnBr}; 31\%\) of 831, 12% of 832. \(c)\) LiOH, H\(_2\)O; 89%. \(d)\) \(\text{Et}_3\text{N}, \text{DPPA, toluene, then } \text{tBuOH, CuCl}; 28\%.\)
5.2. Concerning The Ideal Transition State Analogue

The lower limit for the $K_i$ of an ideal (or perfect) transition state analogue is given by $K_{\text{tx}}$, which is estimated at $10^{-14}$ to $10^{-18}$ M for a retaining $\beta$-glucosidase (vide supra). However, even the strongest inhibitor known to date, the phenethyl-substituted imidazole 19b (vide supra), has "only" a $K_i$ of $10^{-10}$ M against the $\beta$-glucosidase from Caldocellum saccharolyticum [169]. Although this inhibitor mimics the flattened conformation of an oxycarbenium ion-like transition state and exploits the synergistic action of the catalytic residues in its binding to the active site, its structure differs significantly from that of the transition state, especially in lacking the apical aglycon leaving group.

The ideal transition state analogue must perfectly mimic the shape and charge of the transition state, i.e. the bond and torsional angles and the bond length and strength. Such a perfect mimicry, however, is only possible for the transition state itself, as any substitution of an element by another element will alter these parameters. In other words: the preparation of a compound with the structure of the transition state is per definitionem impossible [58], or "by definition a 'transition-state mimic' is never perfect and will not capture all of the binding energy available in an enzyme active site for the reaction transition state" [171]. It is still tempting, however, to contemplate a nearly ideal transition state analogue.

Such a nearly ideal transition state analogue should mimic the shape and charge of the transition state as well as possible. Therefore, it should include the aglycon leaving group in an appropriate position. An important feature of the transition state is the pentacoordinated trigonal-bipyramidal anomeric carbon. As pentacoordinated carbon is not stable, the anomeric carbon has to be replaced by a heteroatom X, which forms stable, pentacoordinated trigonal-bipyramidal molecules or complexes. An intriguing example for such a mimicry of a transient pentacoordinated species by a stable pentacoordinated species is provided by the complex of cAMP-dependent protein kinase with ADP, aluminium fluoride, and a substrate peptide [1039]. In this complex, Al forms a pentacoordinated trigonal-bipyramidal coordination compound, with the F atoms in the equatorial positions and an oxygen each of ADP and of the substrate peptide in the apical positions, thus mimicking the transition state for phosphoryl transfer from ATP to the substrate peptide (for a similar complex see [1040] [1041]).

In a nearly ideal glycosidase inhibitor, X might be a heavy element from the 5th main group (e.g. P), silicon, or a transition metal. In order to mimic the (partial) protonation of the glycosidic oxygen without breaking the glycosidic bond, this oxygen probably has to be replaced by a heteroatom Y (e.g. nitrogen). The quest is now to choose a heteroatom X (and
also Y), for which the corresponding pyranoside analogue and the complex with the enzyme are stable.

**Figure 5.2.1:** Design of a Nearly Ideal Transition State Analogue.

![Diagram](image)

Although such an inhibitor may remain inaccessible, it is still worthwhile to look at the binding characteristics of its complex with a retaining glycosidase (Figure 5.2.1). An important requirement for this nearly ideal transition state analogue is to mimic the developing bond between the catalytic nucleophile and the anomeric atom, either by a coordination bond or by a covalent bond! This requirement of a bond (be it covalent or coordinative) between the inhibitor and the catalytic nucleophile raises the question if such a nearly ideal transition state analogue is a reversible or irreversible inhibitor. This depends on the strength of the bond and on how one defines “irreversible inhibition”. The term “irreversible inhibition” is defined as an inactivation of an enzyme that cannot be reversed by dialysis. Usually, such irreversible inhibition results from covalent binding of the inhibitor to the enzyme. However, covalent binding to the enzyme is sometimes reversible.
6. Experimental Part

General. Solvents were freshly distilled from CaH₂ (CH₂Cl₂, MeOH, DMF, Et₃N) or Na/benzophenone (THF, toluene), Na (BnNH₂), or BaO (2,6-lutidine). Pyridine, DMSO, and DMF were dried by standing over molecular sieves 4 Å. For multigram scale operations, toluene was dried by standing over molecular sieves 4 Å, and CHCl₃ was dried by filtration through Al₂O₃.

Camphorsulphonic acid was recrystallised from AcOEt.

NH₄OH = 25% aq. NH₃ soln.

The β-glucosidase from almonds (Fluka), the β-glucosidase from Caldocellum saccharolyticum (Sigma), the α-glucosidase from brewer's yeast (Sigma), the β-mannosidase from snail (Sigma), and the α-mannosidase from jack beans (Sigma) were used without further purification.

All reactions were carried out under an atmosphere of argon, unless stated otherwise.

Anal. TLC: Merck precoated silica gel 60 F-254 plates; detection by treatment with a soln. of 5% (NH₄)₆Mo₇O₂₆ · 4 H₂O, 0.1% Ce(SO₄)₂ · H₂O, in 10% H₂SO₄ soln. or by treatment with a 1% soln. of KMnO₄ in a 6% aq. K₂CO₃ soln. or with a soln. of vanillin in ethanol.

Flash chromatography (FC): silica gel 60 (40–63 μm); 0.05 – 0.5 bar N₂.

M.p.: open capillary, uncorrected.

Optical rotations: c in g / 100 ml, 1-dm cell, 589 nm.

FT-IR spectra: absorption in cm⁻¹.

NMR spectra: recorded at 23 – 26°, unless stated otherwise. Chemical shifts in ppm relative to TMS (¹H, ¹³C); coupling constants in Hz. Multiplicities of ¹³C signals were determined by DEPT. NOE experiments allowed unambiguous assignments of all ¹H-NMR signals of 40 and 42, and HSQC.GRASP spectra unambiguous assignments of the ¹³C-NMR signals of 40 and 42. An * indicates, that the assignments may be reversed.

Mass spectra: FAB-MS in 3-nitrobenzyl alcohol (NOBA) matrix. HR-MALDI-MS in 2,5-dihydroxybenzoic acid (DHB) matrix.
The pK$_{HA}$ values of 46, 48, and 35 were determined by potentiometric titration in H$_2$O. The pK$_{HA}$ of 45 was estimated as the pH, at which $c(45) = c(45'HCl)$ as described in [135].

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Part 1.

3,4,5-Tri-O-benzyl-6-C-(benzyloxymethyl)-1,2,7,8-tetradeoxy-D-gluco-octa-1,7-dienitol (441) and 3,4,5-Tri-O-benzyl-6-C-(benzyloxymethyl)-1,2,7,8-tetradeoxy-L-ido-octa-1,7-dienitol (450).

A cooled (–78 °C) soln. of 442 (2.32 g, 4.32 mmol) in THF (43 ml) was treated dropwise with 1M vinylmagnesium bromide in THF (6.5 ml, 6.5 mmol), stirred for 45 min at this temperature, warmed to 0 °C, and treated with Et2O (80 ml) and sat. aq. NH4Cl soln. (80 ml). The organic phase was separated, washed with brine (50 ml), dried (MgSO4), and evaporated. FC (300 g of silica gel, hexane/AcOEt 6:1) of the oily residue (2.7 g) gave 450 (22 mg, 1%) and 441 (2.11 g, 86%).

Data of 441: colourless oil. Rf (hexane/AcOEt 3:1) 0.57. [α]D 25 = 35.2 (c 3.3, CHCl3). FT-IR (3%, CHCl3): 3448 m, 3089 w, 3066 w, 3007 m, 2911 w, 2866 m, 1951 w, 1873 w, 1811 w, 1732 w, 1639 w, 1604 w, 1496 m, 1454 m, 1422 w, 1398 w, 1351 m, 1313 m, 1289 m, 1261 m, 1222 m, 1193 s, 1161 s, 1131 m, 1094 m, 1066 m, 1008 m, 996 m, 934 m, 822 w, 606 w, 515 w. 1H-NMR (300 MHz, CDCl3): 7.36–7.23 (m, 20 arom. H); 6.07 (dd, J = 17.1, 10.6, H–C(7)); 5.94 (ddd, J = 17.1, 10.3, 7.8, H–C(2)); 5.45 (dd, J = 17.4, 1.9, H–C(8)); 5.30 (br. dd, J = 10.3, 1.9, H–C(1)); 5.26 (br. dd, J = 17.4, 1.9, H–C(1)); 5.23 (dd, J = 10.9, 2.2, H–C(8)); 4.82 (d, J = 11.5, PhCH); 4.68 (d, J = 11.8, PhCH); 4.65–4.61 (m, 3 PhCH); 4.48 (d, J = 12.1, PhCH); 4.43 (d, J = 11.8, PhCH); 4.35 (d, J = 11.8, PhCH); 4.07 (br. dd, J = 10.6, 1.9, H–C(8)); 3.88–3.84 (m, H–C(4), H–C(5)); 3.74 (s, OH); 3.63 (d, J = 8.7, CH–C(6)); 3.29 (d, J = 8.7, CH–C(6)). 13C-NMR (75 MHz, CDCl3): 140.32 (d, C(7)); 139.05 (s); 138.56 (s); 138.47 (s); 138.34 (s); 135.67 (d, C(2)); 128.65–127.62 (several d); 119.66 (t, C(1)); 114.88 (t, C(8)); 81.83 (d); 81.23 (d); 78.35 (d); 77.98 (s, C(6)); 74.76 (t); 74.49 (t); 73.52 (t); 70.70 (t). FAB-MS (NOBA): 587 (9, [M + Na]+), 565 (53, [M + 1]+), 457 (18, [M – BnO]+), 267 (7), 241 (9), 197 (10), 181 (100), 173 (16), 154 (11), 147 (15), 107 (9). Anal. calc. for C37H40O5 (564.72): C 78.70, H 7.14; found: C 78.87, H 7.35.

Data of 450: colourless oil. Rf (hexane/AcOEt 3:1) 0.62. 1H-NMR (300 MHz, CDCl3): 7.36–7.21 (m, 20 arom. H); 6.07 (dd, J = 17.4, 10.9, H–C(7)); 5.94 (ddd, J = 17.1, 10.6, 7.5, H–C(2)); 5.45 (dd, J = 17.4, 2.2, H–C(8)); 5.26 (br. dd, J = 17.1, 1.0, H–C(1)); 5.25 (br. dd, J = 10.6, 1.0, H–C(1)); 5.23 (dd, J = 10.9, 2.2, H–C(8)); 4.82 (d, J = 11.5, PhCH); 4.68 (d, J =
11.5, PhCH); 4.64 (d, J = 11.8, PhCH); 4.62–4.43 (m, 4 PhCH); 4.35 (d, J = 11.8, PhCH);
4.09 (br. dd, J = 7.5, 4.4, H–C(3)); 3.99 (d, J = 5.9, H–C(5)); 3.74–3.68 (m, H–C(4),
CH–C(6)); 3.28 (d, J = 9.3, CH–C(6)); 3.09 (s, OH). 13C-NMR (75 MHz, CDCl 3): 139.43, 138.99, 138.52, 138.34, 138.03 (C(7)); 136.09 (C(2)); 128.62–127.45; 118.96 (C(1)); 115.92 (C(8)); 81.67; 80.83; 79.32; 74.78; 74.75; 74.65; 73.52; 70.64; s of C(6) hidden by noise or
other signals.

3,4,5-Tri-O-benzyl-6-C-((benzyloxymethyl)-6-O-(methoxymethyl)-1,2,7,8-tetradeoxy-D-gluco-
octa-1,7-dienitol (448):
A suspension of NaH (17 mg, 0.708 mmol, washed with hexane) in DMF (5 ml) was treated
at 0° with a soln. of 441 (200 mg, 0.354 mmol) in DMF (5 ml), stirred at 0° for 30 min.,
treated with MOMCl (57 mg, 0.708 mmol), and stirred for 20 h while warming to r.t.. The
mixture was treated with MeOH (0.5 ml) and 10% aq. NaCl soln. (20 ml) and extracted with
AcOEt (3 x 30 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC
(30 g of silica gel, cyclohexane/ACOEt 15:1) of the residue (284 mg, yellow oil) gave 448
(105 mg, 48%) and 448 contaminated with 441 (103 mg, 47%) as colourless oils. Rf
cyclohexane/ACOEt 3:1) 0.75. 1H-NMR (300 MHz, CDCl3): 7.36–7.18 (20 arom. H); 5.92–5.82 (m, H–C(2)); 5.84 (dd, J = 17.7, 10.9, H–C(7)); 5.25–5.11 (m, CH2(1), CH2(8));
4.84–4.79 (m, PhCH, OCHO); 4.82 (d, J = 11.5, PhCH); 4.68–4.64 (m, PhCH, OCHO); 4.68
(d, J = 11.8, PhCH); 4.62 (d, J = 11.8, PhCH); 4.47 (d, J = 11.5, PhCH); 4.42 (d, J = 12.1,
PhCH); 4.32 (d, J = 11.8, PhCH); 3.95 (br. dd, J = 8.1, 5.0, H–C(3)); 3.90 (d, J = 4.4,
H–C(5)); 3.90 (d, J = 9.7, CH–C(6)); 3.84 (dd, J = 5.0, 4.4, H–C(4)); 3.66 (d, J = 10.0,
CH–C(6)); 3.36 (s, MeO).

3,4,5-Tri-O-benzyl-6-C-((benzyloxymethyl)-6-O-methyl-1,2,7,8-tetradeoxy-D-gluco-octa-1,7-
dienitol (449):
A cold (0°) soln. of 441 (220 mg, 0.39 mmol) in DMF (10 ml) was treated with NaH (47 mg
of a 55% suspension in oil, 0.97 mmol), stirred for 30 min., treated with MeI (0.06 ml, 0.97
mmol), and stirred for 16 h while warming to r.t.. The mixture was treated with MeOH (4 ml)
and diluted with AcOEt (40 ml). The resulting solution was washed with brine (2 x 15 ml),
dried (Na₂SO₄), and evaporated. FC (30 g of silica gel, cyclohexane/AcOEt 50:1) of the
residue (290 mg, yellow oil) gave 449 (125 mg, 55%) as a colourless oil and 449
contaminated with 441 (58.7 mg, 26%).

\[ R_f (\text{cyclohexane/AcOEt 9:1}) = 0.29 \]

1H-NMR (300 MHz, CDCl₃):

- 7.37–7.19 (20 arom. H);
- 5.83 (\text{ddd}, J = 17.3, 10.4, 8.0, H–C(2));
- 5.72 (\text{dd}, J = 17.3, 11.7, H–C(7));
- 5.27–5.11 (m, CH₂(1), CH₂(8));
- 4.75 (\text{d}, J = 11.8, PhCH);
- 4.70 (\text{d}, J = 11.8, PhCH);
- 4.68 (d, J = 11.5, PhCH);
- 4.62 (d, J = 11.5, PhCH);
- 4.48 (d, J = 10.9, PhCH);
- 4.44 (d, J = 12.1, PhCH);
- 3.82 (dd, J = 6.9, 4.4, H–C(4));
- 3.71 (d, J = 10.9, CH–C(6));
- 3.62 (d, J = 10.3, CH'–C(6));
- 3.27 (s, MeO).

A soln. of 441 (2.20 g, 3.89 mmol) in CH₂Cl₂ (200 ml) was degassed by purging with N₂,
treated with 312 (0.48 g, 0.54 mmol), stirred at r.t. for 7 d, and evaporated. FC (300 g of silica
gel, hexane/AcOEt 3:1) of the residual oil gave 441 (0.5 g, 23%) as a dark green oil and 40
(1.25 g) as a dark green oil. An additional FC (150 g of silica gel, as above) of the latter gave
40 (1.2 g, 58%).

\[ R_f (\text{hexane/AcOEt 3:1}) = 0.33 \]

\[ [\alpha]_{D}^{25} = 70.8 \] (c = 1.51, CHCl₃).

FT-IR (1.5%, CHCl₃):

- 3538 \text{m}, 3089 \text{m}, 3066 \text{m}, 3008 \text{m}, 2863 \text{m}, 1951 \text{w}, 1875 \text{w}, 1811 \text{w},
- 1604 \text{w}, 1496 \text{m}, 1454m, 1393w, 1361m, 1294w, 1136m, 1064s, 1028m, 929w, 912w,
- 857w, 628w, 609w, 548w, 537w, 525w, 518w, 503w. 1H-NMR (300 MHz, CDCl₃):

- 7.37–7.16 (m, 20 arom. H);
- 5.92 (\text{dd}, J = 10.3, 1.9, H–C(6));
- 4.95 (d, J = 10.9, PhCH);
- 4.93 (d, J = 10.9, PhCH);
- 4.86 (d, J = 11.2, PhCH);
- 4.72 (s, PhCH₂);
- 4.48 (d, J = 12.5, PhCH);
- 4.46 (d, J = 10.9, PhCH);
- 4.38 (d, J = 12.1, PhCH);
- 4.20 (dt, J = 8.1, 2.1, irr. at 5.92 --- NOE of 6%, H–C(1));
- 3.76 (d, J = 10.3, H–C(3));
- 3.38 (d, J = 8.7, CH–C(4));
- 3.30 (d, J = 8.7, irr. at 5.69 --- NOE of 3%, CH'–C(4));

\[ 1^3C-\text{NMR} (75 \text{ MHz, CDCl₃}, \text{assignment based on HSQC.GRASP}) : 139.09 (s);
- 138.75 (s); 138.34 (s); 138.03 (s); 131.24 (d, C(6)); 129.86 (d, C(5));
- 128.67–127.79 (several d);
- 81.57 (d, C(2)); 80.28 (d, C(1)); 78.39 (d, C(3)); 75.85 (t);
- 75.51 (t); 73.53 (t, CH₂–C(4));
- 73.47 (t);
- 72.97 (s, C(4)); 72.01 (t). FAB-MS (NOBA): 559 (6, [M + Na]⁺), 535 (15, [M – 1]⁺),

\( (1\text{D})-(1,3,4/2)-1,2,3-Tri-O-benzyl-4-C-(benzyloxy)methyl)cyclohex-5-ene-1,2,3,4-tetrol (40) \)
A cooled (0°) suspension of oil-free NaH (washed with hexane, 25 mg, 1.04 mmol) in DMF (5 ml) was treated with a soln. of 40 (257 mg, 0.48 mmol) in DMF (6 ml) and stirred for 30 min. After warming to r.t., the mixture was treated with BnBr (85 µl, 0.72 mmol), stirred for 3.5 h, treated carefully with MeOH (0.3 ml), and diluted with AcOEt (40 ml). The organic phase was separated, washed with H2O (3 6 10 ml), dried (Na2SO4), and evaporated. FC (40 g of silica gel, hexane/AcOEt 10:1) of the oily residue gave 451 (264 mg, 88%). Colourless oil. Rf (hexane/AcOEt 9:1) 0.20. [α]20D = 20.1 (c = 0.50, CHCl3). FT-IR (1.5%, CHCl3): 3089 w, 3066 m, 3008 m, 2913 m, 2865 m, 1951 w, 1876 w, 1811 w, 1711 w, 1604 w, 1496 m, 1454 m, 1361 m, 1309 w, 1140 m, 1093 s, 1067 s, 1028 m, 911 w, 855 w, 607 w, 552 w, 530 w, 514 w. 1H-NMR (300 MHz, C6D6): 7.42–7.04 (25 arom. H); 5.90 (dd, J = 10.3, 2.5, H–C(5)); 5.76 (dd, J = 10.3, 1.9, H–C(6)); 5.07 (d, J = 11.5, PhCH); 4.96 (d, J = 11.5, PhCH); 4.89 (d, J = 11.5, PhCH); 4.76–4.64 (m, 3 PhCH); 4.61 (d, J = 12.1, PhCH); 4.55 (d, J = 12.1, PhCH); 4.49 (dd, J = 10.6, 7.5, H–C(3)); 4.23 (d, J = 12.1, PhCH); 4.19 (dt, J = 7.5, 2.2, H–C(4)); 4.18 (d, J = 12.1, PhCH); 3.97 (d, J = 10.6, H–C(2)); 3.73 (d, J = 8.7, CH–C(1)); 3.53 (d, J = 8.7, CH–C(1)). 13C-NMR (75 MHz, CDCl3): 140.33 (s); 139.91 (s); 139.15 (s); 138.79 (s); 138.16 (s); 132.40 (d, C(5)); 129.72 (d, C(6)); 128.65–127.44 (several d); 81.98 (d); 80.73 (d); 80.00 (d); 78.13 (s, C(1)); 75.75 (t); 75.30 (t); 73.40 (t); 72.13 (t); 71.69 (t); 66.84 (t). FAB-MS (NOBA): 625 (11, [M – 1]+), 519 (18, [M – BnO]+), 412 (25, [M – BnO – BnO]+), 321 (17), 291 (7), 271 (19), 213 (14), 197 (20), 181 (100). Anal. calc. for C42H42O5 (626.79): C 80.48, H 6.75; found: C 80.35, H 6.61.

(1L)-(1,2,4/3)-1,2,3,4-Tetra-O-benzyl-1-C-(benzyloxymethyl)-cyclohex-5-ene-1,2,3,4-tetrol (451).
(1D)-(1,3/2,4)-1,2,3-Tri-O-benzyl-4-C-(benzyloxymethyl)cyclohex-5-ene-1,2,3,4-tetrol (254) [417].

A soln. of 450 (22 mg, 0.04 mmol) in CH$_2$Cl$_2$ (5 ml) was degassed by purging with N$_2$, treated with 312 (10 mg, 0.012 mmol), stirred at r.t. for 5 d, and evaporated. FC (5 g of silica gel, hexane/AcOEt 4:1) of the residual oil gave 18 mg of a green oil, which was subjected to an additional FC (as above) yielding 254 (14 mg, 66%). Colourless oil. $R_f$ (hexane/AcOEt 3:1) 0.31. $[\alpha]_{D}^{25} = 8.7$ ($c = 1.01$, CHCl$_3$; [417]: $[\alpha]_D = 8.5$ ($c = 1$, CHCl$_3$)). FT-IR (1%, CHCl$_3$): 3553 m, 3089 w, 3066 w, 3007 m, 2866 m, 1951 w, 1811 w, 1603 w, 1497 m, 1454 m, 1360 m, 1329 w, 1090 s, 1069 s, 1028 m, 930 w, 911 w, 609 w, 515 w, 507 w. $^1$H-NMR (300 MHz, CDCl$_3$): see [417]. $^{13}$C-NMR (75 MHz, CDCl$_3$): 138.79 (s); 138.61 (s); 138.34 (s); 137.93 (s); 131.93 (d, C(6)*); 128.42–127.60 (several d); 126.59 (d, C(5)*); 83.97 (d); 81.69 (d); 79.68 (d); 75.77 (s, C(4)); 75.69 (d); 75.14 (d); 73.78 (d); 73.13 (d). FAB-MS (NOBA): 756 (7), 663 (11), 559 (15, [M + Na]+), 535 (29, [M – 1]+), 519 (100, [M – OH]+), 429 (11, [M – BnO]+), 412 (17, [M – BnO – OH]+), 321 (14), 296 (10), 271 (12), 231 (6), 213 (8), 181 (89).

(1D)-(1,3/2,4)-1,2,3,4-Tetra-O-benzyl-1-C-(benzyloxymethyl)-cyclohex-5-ene-1,2,3,4-tetrol (454).

A cooled (0 °C) solution of 254 (7.5 mg, 14 µmol) in DMF (1.5 ml) was treated with NaH (60% suspension in oil, 5 mg, 125 µmol), stirred for 30 min, treated with BnBr (30 µl, 250 µmol), allowed to warm to r.t., and stirred for 4 h. The mixture was treated with MeOH (0.1 ml), diluted with EtOAc (20 ml), washed with H$_2$O (2 6 5 ml), brine (5 ml), dried (Na$_2$SO$_4$), and evaporated. FC (10 g of silica gel, hexane/AcOEt 10:1) gave 454 (4.3 mg, 49%). Colourless oil. $R_f$ (hexane/AcOEt 9:1) 0.24. $[\alpha]_{D}^{20} = 26$ ($c = 0.2$, CHCl$_3$). $^1$H-NMR (300 MHz, C$_6$D$_6$): 7.42–7.08 (25 arom. H); 5.84 (dd, $J = 10.6, 1.9$, H–C(5)); 5.67 (dd, $J = 10.6, 2.2$, H–C(6));
5.04 (d, J = 11.5, PhCH); 4.91 (d, J = 11.5, PhCH); 4.86 (s, PhCH$_2$); 4.65 (d, J = 12.1, PhCH); 4.59 (d, J = 12.1, PhCH); 4.47-4.38 (m, 2 PhCH, H-C(3)); 4.36 (d, J = 11.8, PhCH); 4.27 (d, J = 11.8, PhCH); 4.22 (dt, J = 7.8, 2.2, H–C(4)); 4.14 (d, J = 9.7, CH–C(1)); 3.97 (s, PhC$_2$H); 4.27 (d, J = 11.8, PhCH); 4.22 (dt, J = 7.8, 2.2, H–C(4)); 4.14 (d, J = 9.7, CH–C(1)); 3.97 (d, J = 10.3, H–C(2)); 3.76 (d, J = 9.7, CH'–C(1)).

(1D)-(1,3,4/2)-1,2,3-Tri-O-benzyl-4-C-(benzoyloxyethyl)-4-O-carbamoylcyclohex-5-ene-1,2,3,4-tetrol (456).

A cooled (0˚C) soln. of 40 (300 mg, 0.56 mmol) in CH$_2$Cl$_2$ (5 ml) was treated dropwise with trichloroacetyl isocyanate (133 µl, 1.12 mmol), stirred for 30 min at this temperature, and evaporated. The residue, dissolved in MeOH (10 ml) and H$_2$O (1 ml), was cooled to 0˚C, treated with K$_2$CO$_3$ (0.24 g, 1.72 mmol), and stirred for 100 min at 0˚C and 100 min at r.t.. After evaporation of MeOH, the aqueous soln. was diluted with H$_2$O (10 ml) and extracted with CH$_2$Cl$_2$ (4 6 15 ml). The combined organic phases were washed with brine (10 ml), dried (MgSO$_4$) and evaporated. FC (30 g of silica gel, hexane/AcOEt 5:2) of the resulting oil (394 mg) gave 456 (281 mg, 86%). Colourless oil. $R_f$ (hexane/AcOEt 2:1) 0.24. $\left[\alpha\right]_{D}^{25} = 36.6$ (c = 0.50, CHCl$_3$). FT-IR (0.5%, CHCl$_3$): 3543 m, 3428 m, 3089 w, 3066 w, 3008 m, 2939 m, 2866 m, 1952, 1810, 1729 s, 1582 s, 1497 m, 1454 m, 1357 s, 1281 w, 1175 w, 1143 s, 1091 s, 1059 s, 1028 m, 930 w, 911 w, 629 w, 606 w, 554 w. $^1$H-NMR (300 MHz, CDCl$_3$): 7.38–7.20 (m, 20 arom. H); 6.34 (dd, J = 10.3, 1.9, H–C(6)); 5.95 (dd, J = 10.3, 2.5, H–C(5)); 4.91 (s, PhCH$_2$); 4.90 (d, J = 10.9, PhCH); 4.70 (s, PhCH$_2$); 4.58 (d, J = 10.9, PhCH); 4.51 (d, J = 12.1, PhCH); 4.40 (d, J = 12.1, PhCH); 4.60–4.49 (br., NH$_2$); 4.23 (d, J = 8.1, CH–C(4)); 4.22 (dt, J = 7.2, 2.2, H–C(1)); 4.16 (dd, J = 10.0, 7.2, H–C(2)); 3.90 (d, J = 10.0, H–C(3)); 3.85 (d, J = 8.1, CH'–C(4)). $^{13}$C-NMR (75 MHz, CDCl$_3$): 155.60 (s, C=O); 139.12 (s); 138.62 (s); 138.52 (s); 138.02 (s); 131.58 (d, C(6)); 129.52 (d, C(5)); 128.72–127.79 (several d); 81.56 (d, C(2)); 81.02 (s, C(4)); 80.55 (d, C(1)); 78.77 (d, C(3)); 76.17 (t); 75.26 (t); 73.61 (t); 72.13 (t); 69.02 (t). FAB-MS (NOBA): 602 (11, [M + Na]$^+$), 580 (7, [M + 1]$^+$), 519 (59, [M – NH$_2$CO$_2$]$^+$), 472 (95, [M – BnO]$^+$), 411 (66, [M – BnOH – NH$_2$CO$_2$]$^+$), 321 (19), 213 (23), 197 (13), 181 (100), 154 (45), 136 (34), 123 (18), 107 (19). Anal. calc. for C$_{36}$H$_{37}$NO$_6$ (579.69): C 74.59, H 6.43, N 2.42; found: C 74.52, H 6.49, N 2.41.
(II)-(1,3,4/2)-1,2,3-Tri-O-benzyl-4-(benzyloxy carbonylamino)-6-(benzyloxymethyl)cyclohex-5-ene-1,2,3-triol (459).

A cooled (–20˚) soln. of 456 (228 mg, 0.39 mmol), PPh3 (258 mg, 0.98 mmol) and Et3N (110 µl, 0.79 mmol) in CH2Cl2 (4.5 ml) was treated dropwise with a soln. of CBr4 (365 mg, 1.10 mmol) in CH2Cl2 (2.1 ml), stirred for 1 h at –20˚, treated dropwise with BnOH (326 µl, 3.15 mmol), and allowed to warm to r.t. overnight. The mixture was poured into H2O (10 ml). The organic phase was separated and the aqueous phase extracted with CH2Cl2 (4 6 10 ml). The combined organic phases were washed with brine (10 ml), dried (Na2SO4), and evaporated. FC (35 g of silica gel, hexane/AcOEt 9:2) of the resulting oil (1.4 g) gave a mixture of 459 and BnOH. Removal of BnOH in h.v. at 60˚ gave pure 459 (184 mg, 70%). Colourless oil. \[\alpha\]D = 30.9 (c = 1.51, CHCl3). FT-IR (1.5%, CHCl3): 3439 m, 3089 w, 3067 m, 3008 m, 2865 m, 1952 w, 1876 w, 1810 w, 1717 s, 1604 w, 1498 s, 1454 m, 1366 w, 1331 m, 1294 m, 1144 m, 1068 s, 1028 m, 911 w, 604 w, 544 w, 536 w, 520 w. 1H-NMR (300 MHz, CHCl3): 7.38–7.23 (m, 25 arom. H); 5.81 (br. d, J = 3.1, H–C(5)); 5.11 (s, PhCH2OC=O); 5.07 (d, J = 9.7, NH); 4.77–4.63 (m, 2 PhCH, H–C(4)); 4.60 (s, PhCH2); 4.59 (d J = 11.2, PhCH); 4.57 (d, J = 11.5, PhCH); 4.49 (d, J = 11.8, PhCH); 4.40 (d, J = 11.8, PhCH); 4.24 (d, J = 12.1, CH–C(6)); 4.05 (br. d, J = 4.3, H–C(1)); 3.90 (d, J = 12.1, CH–C(6)); 3.81 (dd, J = 7.5, 4.7, H–C(3)); 3.73 (br. dd, J = 7.5, 4.3, H–C(2)). 13C-NMR (75 MHz, CDCl3): 156.41 (s, C=O); 138.50 (s); 138.41 (s); 138.12 (s); 137.35 (s); 136.80 (s); 1 s hidden by noise or other signals; 128.76–127.87 (several d); 125.40 (d, C(5)); 77.26 (d); 76.33 (d); 75.96 (d); 74.42 (t); 73.84 (t); 72.30 (t); 72.13 (t); 70.62 (t, CH2–C(6)); 66.92 (t, COOCH2Ph); 47.20 (d, C(4)). FAB-MS (NOBA): 670 (9, [M + 1]+), 562 (100, [M – BnO]+), 534 (6), 518 (7, [M – BnO2]3+), 472 (9), 429 (12), 181 (33). Anal. calc. for C43H43NO6 (669.82): C 77.11, H 6.47, N 2.09; found: C 77.10, H 6.25, N 2.09.
(1L)-(1,3,4/2)-4-Acetamido-1,2,3-tri-O-benzyl-6-(benzyloxymethyl)cyclohex-5-ene-1,2,3-triol (460) [225].

A cooled (−20°C) soln. of 456 (260 mg, 0.45 mmol), PPh3 (296 mg, 1.13 mmol) and Et3N (126 µl, 0.90 mmol) in CH2Cl2 (5 ml) was treated dropwise with a soln. of CBr4 (420 mg, 1.27 mmol) in CH2Cl2 (2.4 ml), stirred for 1 h at this temperature, and treated dropwise with 2.0M Me3Al in heptane (1.8 ml, 3.62 mmol). After stirring for 1 h at −20°C, the mixture was treated carefully with MeOH (2 ml), CH2Cl2 (5 ml), and 0.2M HCl (10 ml) and allowed to warm to 0°C. The organic phase was separated and the aqueous phase extracted with CH2Cl2 (6×10 ml). The combined organic phases were washed with brine (10 ml), dried (MgSO4), and evaporated. FC (30 g of silica gel, hexane/AcOEt 1:1) of the resulting oil (1.1 g) gave 460 (200 mg, 77%). Colourless oil. Rf (hexane/AcOEt 1:1) 0.21. [α]23D = 23.4 (c = 1.01, CHCl3; [225]: [α]23D = 22 (c = 1, CHCl3)). FT-IR (0.6%, CHCl3): 3438 m, 3065 w, 3008 m, 2976 m, 2895 m, 1667 m, 1603 w, 1498 m, 1454 m, 1390 m, 1370 m, 1297 w, 1146 w, 1048 s, 877 m, 847 w, 600 w, 522 w, 506 w. 1H-NMR (300 MHz, CDCl3): 7.36–7.25 (m, 20 arom. H); 5.76 (d, J = 3.7, H–C(5)); 5.69 (d, J = 9.0, NH); 4.96–4.93 (m, H–C(4)); 4.74 (d, J = 11.5, PhCH); 4.70 (d, J = 10.3, PhCH); 4.62 (d, J = 11.2, PhCH); 4.60 (d, J = 12.1, PhCH); 4.58 (d, J = 11.5, PhCH); 4.54 (d, J = 11.5, PhCH); 4.49 (d, J = 12.1, PhCH); 4.40 (d, J = 11.8, PhCH); 4.27 (d, J = 12.1, CH–C(6)); 4.07 (br. d, J = 4.1, H–C(1)); 3.90 (d, J = 12.1, CH–C(6)); 3.82 (dd, J = 7.2, 4.1, H–C(2)); 3.73 (dd, J = 7.2, 4.7, H–C(3)); 1.93 (s, Ac). 13C-NMR (75 MHz, CDCl3): 169.92 (s, C=O); 138.49 (s); 138.45 (s); 138.41 (s); 138.07 (s); 137.01 (s, C(6)); 128.73–127.86 (several d); 125.61 (d, C(5)); 76.91 (d); 75.94 (d); 75.62 (d); 74.50 (t); 73.65 (t); 72.16 (t); 72.04 (t); 70.67 (t, CH2–C(6)); 45.19 (d, C(4)); 23.49 (q, Me). FAB-MS (NOBA): 1155 (8, [2 M + 1], 600 (11, [M + Na]+), 578 (98, [M + 1]+), 471 (100, [M + 1–BnO]+), 380 (46), 363 (20), 337 (20), 272 (16), 254 (41), 242 (11), 228 (19), 212 (32), 181 (87), 164 (61), 154 (75), 150 (42), 138 (58), 136 (74), 107 (23).
At –78°, NH₃ (20 ml) was condensed into a soln. of 459 (145 mg, 0.22 mmol) in THF (5 ml). The solution was treated with Na in small pieces (ca. 30 mg), until the blue colour of the soln. persisted. After stirring for 2 h at -78°, the mixture was treated with NH₄Cl (220 mg), stirred at r.t. overnight, and evaporated. The residue was dried in h.v., extracted with abs. MeOH, filtered, and evaporated. The resulting residue was extracted with EtOH, filtered, and evaporated. The residue (66 mg) was adsorbed on 3 ml of neutral Dowex 50-WX-8 (washed with H₂O). After washing with water (30 ml), elution with 2% aq. NH₃ gave 22 (30 mg, 78%). Slightly yellow solid. [α]₂₅° = 79.3 (c = 1.5, H₂O; [708]: [α]₂₅° = 81.6 (H₂O)). ¹H-NMR (300 MHz, D₂O): see [367]. ¹³C-NMR (75 MHz, D₂O): see [708]. Conventional acetylation of 22 gave, after FC 461 (55 mg, 86%). Colourless crystals (Et₂O). Rf (toluene/acetone 7:2) 0.08. M.p. 94–95° ([427]: 92.5-95° (EtOH/toluene)). [α]₂₅° = 26.3 (c = 1.02, CHCl₃; [417]: [α]₀ = 24 (c = 1, CHCl₃)). ¹H-NMR (300 MHz, CDCl₃) and ¹³C-NMR (75 MHz, CDCl₃): see [429]. FAB-MS (NOBA): 771 (21, [2 M + 1]+), 386 (41, [M + 1]+), 326 (100, [M – AcO]+), 284 (7), 206 (7), 164 (12), 122 (12).

Oxidative rearrangement of 40 to 162.
A soln. of 40 (100 mg, 0.186 mmol) in CH₂Cl₂ (2 ml) was treated with PCC (160 mg, 0.74 mmol), stirred at r.t. for 1 month, and evaporated. The residue was suspended in Et₂O (10 ml), filtered through Celit, and evaporated. FC (15 g of silica gel, cyclohexane/AcOEt 6:1) of the residue (41 mg) gave 162 (6.8 mg, 6.5%) as a colourless oil.
MOMO O

Benzyl 2,3,4,6-tetra-O-methoxymethyl-D-glucopyranoside (463).

A cooled (0°) suspension of oil-free NaH (0.62 g, 25.9 mmol, washed with hexane) was treated dropwise with a solution of Benzyl-D-glucopyranoside (1.69 g, 6.25 mmol) in DMF (40 ml) over 30 min, then treated dropwise with methylichloromethyl ether (2.9 ml, 37.2 mmol), stirred at 23° for 65 h, treated with MeOH (10 ml), and poured into 500 ml of distilled water. The org. phase was separated, the aq. phase was extracted with AcOEt (3*60 ml), the combined organic phases were washed with brine, dried (Na₂SO₄) and evaporated. FC of the yellow oily residue (hexane/acetone 4:1) afforded 463 (1.55 g, 34.7 mmol, 56 %) as a colourless oil. Rf (hexane/acetone 3:2) 0.58. 1H-NMR (CDCl₃): 7.40–7.28 (m, 5 arom. H); 4.98 (m, H–C(1)); 4.90–4.54 (m, 12 H, (O-CH₂-O-CH₃, PhCH₂); 4.03–3.94 (m, 1 H); 3.77–3.64 (m, 3 H); 3.61–3.50 (m, 2 H); 3.45–3.32 (m, 10 H) and 3.26 (s, 2 H, O-CH₂-O-CH₃). 13C-NMR (CDCl₃): 137.39 (s); 127.84–128.6 (several d); 98.74 (t, (O-CH₂-O-CH₃)); 98.66 (t, (O-CH₂-O-CH₃)); 98.58 (t, (O-CH₂-O-CH₃)); 97.59 (t, (O-CH₂-O-CH₃)); 97.07 (d); 96.73 (d, C(1)); 78.89 (d); 78.81 (d); 78.76 (d); 78.75 (d); 69.65 (t, (PhCH₂); 66.37 (t, C(6)); 56.53 (q, (O-CH₂-O-CH₃)); 56.32 (q, (O-CH₂-O-CH₃)); 55.74 (q, (O-CH₂-O-CH₃)); 55.49 (q, (O-CH₂-O-CH₃)). CI-MS (NH₄·DCI): 464 (16, [M + NH₄]+), 263 (40, [M – 3 OMOM ]+), 217 (81), 161 (80), 148 (80), 91 (80), 45 (86).

2,3,4,6-Tetra-O-methoxymethyl-D-glucopyranose (464).

Na (200 mg, 8.7 mmol) was dissolved in NH₃ (25 ml) at -78°. The blue solution was treated dropwise with a solution of 463 (1.75 g, 3.92 mmol) in THF (25 ml), stirred for 15 min at -78°, treated with NH₄Cl (2g), stirred for 2 h at r.t., and treated with Et₂O (70 ml) and saturated NH₄Cl soln. (30 ml). The org. phase was separated, the aq. phase was extracted with Et₂O (3*40 ml). The combined organic phases were washed with brine, dried over MgSO₄, and evaporated. FC of the yellow oily residue (hexane/acetone 3:1) afforded 464 (1.26 g, 3.55 mmol, 91 %) as a colourless oil. Rf (hexane/acetone 3:2) 0.39. 1H-NMR (CDCl₃): 5.35 (s, 1
H, OH); 4.97 (m, 1 H, H–C(1)); 4.89–4.68 (m, 8 H, (O-CH₂-O-CH₃)); 4.03–3.93 ((m, 2 H H–C(6)); 3.83 (m, 1 H); 3.74–3.68 (m, 1 H); 3.55–3.52 (m, 2 H); 3.45–3.36 (m, 12 H, (O-CH₂-O-CH₃)). ¹³C-NMR (CDCl₃): 98.64 (t, (O-CH₂-O-CH₃)); 98.51 (t, (O-CH₂-O-CH₃)); 97.59 (t, (O-CH₂-O-CH₃)); 96.94 (d, C(1)); 78.37 (d, C(2)); 78.24 (d); 76.91 (d); 69.88 (d); 66.74 (t, C(6)); 56.50 (q, (O-CH₂-O-CH₃)); 56.30 (q, (O-CH₂-O-CH₃)); 55.79 (q, (O-CH₂-O-CH₃)); 55.45 (q, (O-CH₂-O-CH₃)). FAB-MS (NOBA.): 355 (10, [M + 1]+), 291 (41), 247 (51), 215 (100, [M – 2 OMOM – OH]+), 185 (84), 155 (40).

1,3,4,5-Tetra-O-methoxymethyl-6,7-dideoxy-L-gulo-hept-6-enitol (465).

A cooled (-78°) solution of 464 (1.08 g, 3.04 mmol) in THF (15 ml) was treated dropwise with 1.6M butyl lithium in hexane (1.9 ml, 3.04 mmol), stirred for 5 min at 0°, cooled to -78°, and treated with PH₃P=CH₂ (prepared from a solution of methyl triphenyl phosphonium bromide (2.17 g, 6.04 mmol) in THF (20 ml) treated by dropwise addition of 1.6 M butyl lithium in hexane (3.8 ml, 24 mmol)). The resulting mixture was stirred at 23° for 20 h and poured into sat. NaHCO₃ soln. (50 ml)). The org. phase was separated and the aq. phase was extracted with AcOEt (3×40 ml). The combined org. phases were washed with brine (20 ml), dried (MgSO₄), and evaporated. FC of the oily residue (hexane/acetone 3:1) afforded 465 (0.682 g, 1.92 mmol, 63%) as a colourless oil. Rf (hexane/acetone 3:2) 0.52. IR (CH₂Cl₂): 3462 w, 3041 w, 2935 m, 2894 m, 2825 m 1467 w, 1442 w, 1422 w, 1213 w, 1151 s, 1026 s, 992 s, 920 m. ¹H-NMR (CDCl₃): 5.77 (ddd, J = 17.43, 10.27, 7.47, H–C(6)); 5.37 (dm, J = 17.4, H–C(7)); 5.34 (dm, J = 10.3, H’–C(7)); 4.92–4.53 (m, 8 H, (O-CH₂-O-CH₃)); 4.38–4.31 (m, 1 H); 3.92–3.61 (m, 6 H); 3.41–3.33 (m, 12 H, (O-CH₂-O-CH₃)). ¹³C-NMR (CDCl₃): 134.75 (d, C(6)); 120.01 (t, C(7)); 99.17 (t, (O-CH₂-O-CH₃)); 98.93 (t, (O-CH₂-O-CH₃)); 97.14 (t, (O-CH₂-O-CH₃)); 94.18 (t, (O-CH₂-O-CH₃)); 80.68 (d); 79.97 (d); 77.50 (d); 69.81 (d, C(2)); 69.05 (d, C(1)); 56.50 (q, (O-CH₂-O-CH₃)); 56.34 (q, (O-CH₂-O-CH₃)); 55.92 (q, (O-CH₂-O-CH₃)); 55.48 (q, (O-CH₂-O-CH₃)). FAB-MS (NOBA.): 355 (8, [M – 1]+), 293 (28, [M – OMOM ]+), 263 (100, [M – 2 MOM]+), 233 (27, [ M – 2 OMOM ]+), 249 (41), 217 (70), 187 (42), 171 (48), 157 (40), 127 (28).
1,3,4,5-Tetra-O-methoxymethyl-6,7-dideoxy-L-xylo-hept-6-en-2-ulose (466).

A suspension of molecular sieves (3 Å, 0.5 g) and pyridinium chlorochromate (PCC) (0.334 g, 1.56 mmol, 2.2 eq) in CH₂Cl₂ (15 ml) at 22° was treated with a soln. of 465 (0.251 g, 0.711 mmol) in CH₂Cl₂ (5 ml), stirred for 2 h, filtered through celite, and evaporated. FC of the crude product (cyclohexane/acetone 3:1) afforded 466 (0.223 g, 0.632 mmol, 89%) as a colourless oil. Rf (cyclohexane/acetone 3:2) 0.53. ¹H-NMR (CDCl₃): 5.84 (ddd, J = 17.43, 9.96, 7.78, H–C(6)); 5.41–5.33 (m, H₂–C(7)); 4.77–4.50 (m, 8 H, (O-CH₂-O-CH₃)); 4.49–4.45 (m, 2 H); 4.36 (d, J = 3.4, H–C(3)); 4.33 (dd, J = 5.3, 1.9, 1 H); 4.04 (br. dd, J = 6.9, 3.4, H–C(4)); 3.40–3.32 (m, 12 H, (O-CH₂-O-CH₃)). ¹³C-NMR (CDCl₃): 206 (s, (C(2)); 134.35 (d, (C(6))); 120.01 (t, (C(7))); 98.45 (t, (O-CH₂-O-CH₃)); 98.03 (t, (O-CH₂-O-CH₃)); 96.70 (t, (O-CH₂-O-CH₃)); 93.76 (t, (O-CH₂-O-CH₃)); 80.88 (d); 79.44 (d); 77.16 (d); 71.46 (t, (C(1))); 56.72 (q, (O-CH₂-O-CH₃)); 56.48 (q, (O-CH₂-O-CH₃)); 55.93 (q, (O-CH₂-O-CH₃)); 55.77 (q, (O-CH₂-O-CH₃)). FAB-MS (NOBA.): 351 (19, [M – 1]+), 291 (66, [M – OMOM]⁺), 275 (30), 245 (100), 215 (29), 183 (36), 153 (32), 85 (36).

3,4,5-Tri-O-methoxymethyl-1,2,7,8-tetradeoxy-6-C-[methoxymethyloxymethyl]-D-gluco-octa-1,7-dienitol (467).

A cooled (-78°) soln. of 466 (0.159 g, 0.45 mmol) in THF (10 ml) was treated dropwise with 1M vinylmagnesium bromide in THF (0.68 ml, 0.68 mmol), stirred for 60 min, treated with Et₂O (20 ml), warmed to 0°, and treated with sat. aq. NH₄Cl soln. (10 ml). The org. phase was separated and the aq. phase extracted with Et₂O (2*20ml). The combined org. phases were washed with brine (10 ml), dried (MgSO₄), and evaporated. FC of the oily residue (cyclohexane/acetone 10:1) afforded 467 (0.155 g, 0.41 mol, 90 %) as a colourless oil. Rf (cyclohexane/acetone 3:2) 0.54. ¹H-NMR (CDCl₃): 6.16 (dd, J = 17.4, 10.9, H–C(7)); 5.78 (ddd, J = 17.7, 10.0, 7.8, H–C(2)); 5.52 (dm, J = 17.43 H–C(8)); 5.35–5.25 (m, H₂–C(1),
H’–C(8)); 4.86–4.55 (m, 8 H, (O-CH$_2$-O-CH$_3$)); 4.26 (q, J = 6.8, 1 H, not assigned, impurity?); 4.05 (d, J = 3.1, H–C(5)); 3.98 (dd, J = 6.2, 2.8 Hz, 1 H); 3.86 (t, J = 2.8, 1 H); 3.68–3.64 (m, 2 H); 3.44–3.33 (m, 13 H, (O-CH$_2$-O-CH$_3$), 1 H). $^{13}$C-NMR (CDCl$_3$): 139.80 (d, (C(7))); 135.09 (d, (C(2))); 119.66 (t, (C(1))); 115.95 (t, (C(8))); 98.98 (t, (O-CH$_2$-O-CH$_3$)); 98.77 (t, (O-CH$_2$-O-CH$_3$)); 97.38 (t, (O-CH$_2$-O-CH$_3$)); 94.37 (t, (O-CH$_2$-O-CH$_3$)); 78.66 (d); 77.90 (d); 77.16 (d); 72.58 (t, CH$_2$–C(6)); 56.72 (q, (O-CH$_2$-O-CH$_3$)); 56.48 (q, (O-CH$_2$-O-CH$_3$)); 55.93 (q, (O-CH$_2$-O-CH$_3$)); 55.77 (q, (O-CH$_2$-O-CH$_3$)); C(6) is hidden by noise or other signal. FAB-MS (NOBA.): 381 (4, [M + 1]$^+$), 273 (41), 241 (100), 211 (33), 181 (29), 99 (38).

(1D)-(1,3,4/2)-1,2,3-tri-O-methoxymethyl-4-C-[methoxymethyloxymethyl] cyclohex-5-ene-1,2,3,4-tetrol (468).

A solution of 467 (0.130 g, 0.34 mmol) in CH$_2$Cl$_2$ (30 ml) degassed by 3 cycles of freeze pump thaw was added via cannula to a flask containing the Grubbs catalyst (60.9 mg, 0.068 mmol), under N$_2$. The resulting mixture was refluxed for 7 days under N$_2$ and evaporated..FC of the dark, green, oily residue (cyclohexane/acetone 3:1) afforded 468 (0.065 g, 0.185 mmol, 54 %, after 2 columns) as a green oil. $R_f$(cyclohexane/acetone 2:1) 0.29. $^1$H-NMR (CDCl$_3$): 5.84 (dt, J = 10.3, 1.9, H–C(6)); 5.69 (dt, J = 10.3, 1.9 Hz H–C(5)); 5.02 (d, J = 6.5, O–C–O–CH$_3$); 4.97 (d, J = 6.5, O–C–O–CH$_3$); 4.84–4.62 (m, 6 H, (O-CH$_2$-O-CH$_3$)); 4.59 (m, 2 H, CH$_2$–C(4)); 4.14 (dt, J = 8.1, 1.9, H–C(1)); 4.04–3.96 (m, H–C(2)); 3.72 (dd, J = 10.3, = 2, H–C(3)); 3.54–3.51 (m, CH$_2$–C(4)); 3.46–3.36 (m, 13 H, (O-CH$_2$-O-CH$_3$)), OH). $^{13}$C-NMR (CDCl$_3$): 131.38 (d); 129.61 (d); 98.90 (t, (O-CH$_2$-O-CH$_3$)); 98.27 (t, (O-CH$_2$-O-CH$_3$)); 97.10 (t, (O-CH$_2$-O-CH$_3$)); 97.05 (t, (O-CH$_2$-O-CH$_3$)); 78.34 (d); 77.05 (d); 72.55 (s); 71.53 (t, CH$_2$–C(4)); 56.27 (q, (O-CH$_2$-O-CH$_3$)); 56.64 (q, (O-CH$_2$-O-CH$_3$)); 55.66 (q, (O-CH$_2$-O-CH$_3$)); 55.49 (q, (O-CH$_2$-O-CH$_3$)).
1,3,4,5-Tetra-O-benzyl-6,7-dideoxy-D-arabino-hept-6-en-2-ulose (470).

A solution of 469 [712] (1.86 g, 3.45 mmol) in toluene (6.7 ml) was treated with dicyclohexyl carbodiimide (1.67 g, 8.09 mmol), DMSO (0.93 ml, 17.60 mmol), and pyridine (0.37 ml, 4.58 mmol), and then dropwise with trifluoroacetic acid (0.37 ml, 3.32 mmol), and stirred for 4 h. The mixture was treated with H2O (2 ml), Et2O (9.5 ml), and filtered through Celite. The filtrate residue was washed with Et2O (25 ml). The filtrate was washed with 1 M HCl (2.6 10 ml), sat. aq. NaHCO3 soln. (20 ml), and brine (20 ml), dried (Na2SO4), and evaporated. FC (110 g of silica gel, hexane/AcOEt 6:1) of the residue (2.6 g) gave 470 (1.58 g, 87%). Colourless oil. Rf (hexane/AcOEt 3:1) 0.59. [α]D25 = –39.8 (c = 1.52, CHCl3). FT-IR (1.5%, CHCl3): 3089 m, 3067 m, 3008 m, 2868 m, 1952 w, 1874 w, 1811 w, 1728 s, 1604 w, 1497 m, 1454 m, 1422 w, 1391 w, 1336 w, 1306 w, 1171 w, 1072 s, 1028 m, 996 m, 936 m, 908 w, 818 w, 651 w, 601 w, 538 w, 520 w. 1H-NMR (300 MHz, CDCl3): 7.35–7.16 (20 arom. H); 5.89 (ddd, J = 17.4, 10.3, 7.8, H–C(6)); 5.50–5.41 (m, 2 H–C(7)); 4.61–4.55 (m, 2 H); 4.48-4.29 (m, 7 H); 4.23–4.17 (m, 2 H); 4.08 (br. t, J = 8.1, H–C(5)); 3.92 (dd, J = 8.4, 3.4, H–C(4)). 13C-NMR (75 MHz, CDCl3): 209.33 (s, C(2)); 138.34 (s); 137.82 (s); 137.63 (s); 137.29 (s); 136.17 (d, C(6)); 128.75–127.84 (several d); 120.69 (t, C(7)); 84.37 (d); 82.56 (d); 79.60 (d); 75.09 (t); 74.71 (t); 74.55 (t); 73.37 (t); 70.17 (t). FAB-MS (NOBA): 559 (86, [M + Na]+), 537 (43, [M + 1]+), 536 (26, [M – 1]+), 429 (96, [M – BnO]+), 271 (31), 181 (100). Anal. calc. for C35H36O5 (536.67): C 78.33, H 6.76; found: C 78.29, H 6.75.

3,4,5-Tri-O-benzyl-6-C-(benzyloxymethyl)-1,2,7,8-tetrahydroxy-a-manno-octa-1,7-dienitol (471).

A cooled (−78˚) solution of 470 (1.49 g, 2.77 mmol) in THF (31 ml) was treated dropwise with 1M vinylmagnesium bromide in THF (4.15 ml, 4.15 mmol), stirred for 85 min, treated
with Et₂O (40 ml), warmed to 0°, and treated with sat. aq. NH₄Cl soln. (40 ml). The organic phase was separated and the aqueous phase extracted with Et₂O (2.6 20 ml). The combined organic phases were washed with brine (30 ml), dried (Na₂SO₄), and evaporated. FC (110 g of silica gel, hexane/AcOEt 6.5:1) of the oily residue (1.85 g) gave 471 (1.49 g, 95%). Colourless oil. Rt (hexane/AcOEt 3:1) 0.64. [α]₀^25 = −4.5 (c = 1.5, CHCl₃). FT-IR (1.5%, CHCl₃): 3462 (w, νOH); 1740 (m, νC=O); 1129 (3, [M + Na]⁺), 1067 (100, [M + 1]⁺). Anal. calc. for C₃₇H₄₀O₅ (564.72): C 78.70, H 7.14; found: C 78.60, H 7.09.

A solution of 471 (2.20 g, 3.89 mmol) in CH₂Cl₂ (200 ml, degassed by purging with N₂) was treated with 312 (480 mg, 0.58 mmol), stirred for 4 d under N₂, and concentrated. FC (250 g of silica gel, hexane/AcOEt 4:1) of the oily residue gave 42 (1.85 g, 89%). Green oil. Rt (cyclohexane/AcOEt 3:1) 0.44. [α]₀^25 = −35.2 (c = 1.5, CHCl₃). FT-IR (1.5%, CHCl₃): 3532 (m), 3089 (m), 3066 (m), 3008 (m), 2864 (m), 1951 (w), 1877 (w), 1811 (w), 1737 (w), 1604 (w), 1496 (m), 1454 (m), 1368 (m), 1306 (s), 1098 (s), 1028 (m), 913 (w), 855 (w), 636 (w), 601 (w), 563 (w), 536 (m), 524 (w). ¹H-NMR (300 MHz, CDCl₃): 7.41–7.22 (20 arom. H); 5.95 (d, J = 10.0, 5.0, H–C(5)); 5.26 (d, J = 10.0, H–C(4)); 4.77 (d, J = 12.1, PhCH); 4.75–4.67 (m, 3 PhCH); 4.59 (d, J = 10.9, PhCH); 4.57 (d, J = 12.1, PhCH); 4.46 (d, J = 12.1, PhCH); 4.26 (d, J = 9.7, irrad. at 3.45 → NOE of 10%, H–C(3)); 4.16 (dd, J = 5.0, 3.7, irrad. at 5.95 → NOE of 15%, H–C(1)); 3.94 (dd, J = 9.7, 3.7, H–C(2)); 3.46 (d, J = 9.3,
CH–C(4)); 3.43 (d, J = 9.3, CH‘–C(4)); 3.10 (s, OH). 13C-NMR (75 MHz, CDCl3): 139.10 (s); 138.88 (s); 138.52 (s); 138.39 (s); 132.84 (br. d, C(5)); 128.59-127.81 (several d, incl. C(6)); 78.16 (d, C(2)); 75.98 (d, C(3)); 75.57 (t); 74.55 (t, CH2–C(4)); 73.58 (t); 73.08 (s, C(4)); 72.87 (t); 71.88 (t); 71.69 (d, C(1)). Anal. calc. for C35H36O5 (536.67): C 78.33, H 6.76; found: C 78.42, H 6.87.

Metathesis of 471 in toluene at 80°; isolation of byproducts

A solution of 471 (217 mg, 0.38 mmol) in toluene (30 ml) was degassed by three cycles of FPT, treated with Grubbs's catalyst (48 mg, 0.06 mmol), stirred under N2 at 80º for 2 d, and evaporated. FC (40 g of silica gel; cyclohexane/AcOEt 5:1) gave 471 (180 mg, 83%), 472 (3.8 mg, 2%), 473 (18 mg, 9%), 474 (2.6 mg, 2%), and 474 (3.0 mg, 2%).

Data of (1S,5S,6S)-4,5,6-Tris-benzyloxy-1-(benzyloxymethyl)cyclohex-3-enol (472): Colourless oil. Rf (cyclohexane/AcOEt 3:1) 0.48. 1H-NMR (300 MHz, CDCl3): 7.38–7.24 (20 arom. H); 4.86 (d, J = 11.2, PhCH); 4.81 (d, J = 11.2, PhCH); 4.78 (s, PhCH2); 4.72 (br. t, J = 4.0, H–C(3)); 4.65 (d, J = 11.5, PhCH); 4.62 (d, J = 11.5, PhCH); 4.54 (d, J = 12.1, PhCH); 4.48 (d, J = 12.1, PHCH); 4.32 (br. d, J = 5.6, H–C(5)); 3.93 (d, J = 5.9, H–C(6)); 3.58 (d, J = 9.0, CH–C(1)); 3.45 (d, J = 9.0, CH‘–C(1)); 2.51 (br. d, J = 17.1, H–C(2)); 2.43 (s, OH); 2.25 (dd, J = 16.8, 4.4, H’–C(2)). HR-MS (MALDI): 559.2455 (100, C35H36NaO5+, [M + Na]+; calc. 559.2460).

Data of (4S,5S,6S)-5,6-Bis-benzyloxy-4-(benzyloxymethyl)-4-hydroxycyclohex-2-enone (473): Rf (cyclohexane/AcOEt 3:1) 0.30. FT-IR (0.5%, CHCl3): 1700s (C=O). 1H-NMR (300 MHz, CDCl3): 7.45–7.19 (15 arom. H); 6.71 (d, J = 10.3, H–C(3)); 6.13 (d, J = 10.3, H–C(2)); 5.08

O
OH

BnO

5

1

4

3

2

O

BnO

6

1

4

5

2

3

6

O

BnO

6

1

4

5

2

3

6

O
(d, J = 11.2, PhCH); 4.94 (d, J = 10.9, PhCH); 4.70 (d, J = 11.5, PhCH); 4.49 (d, J = 11.2, PhCH); 4.46 (d, J = 11.2, PhCH); 4.42 (d, J = 9.7, H–C(6)); 4.36 (d, J = 11.8, PhCH); 4.02 (d, J = 10.0, H–C(5)); 3.46 (d, J = 9.0, CH–C(4)); 3.41 (d, J = 9.0, CH’–C(4)); 2.97 (s, OH). HR-MS (MALDI): 467.1829 (100%, C28H28NaO5+, [M + Na]+; calc. 467.1834).

Data of (5S,6R)-2,6-Bis-benzyloxy-5-(benzyloxymethyl)-5-hydroxy-cyclohex-2-enone (474):

Rf (cyclohexane/AcOEt 3:1) 0.23. FT-IR (0.5%, CHCl3): 1703 s (C=O). 1H-NMR (300 MHz, CDCl3): 7.37–7.21 (15 arom. H); 5.73–5.69 (m, H–C(3)); 5.09 (d, J = 10.9, PhCH); 4.91 (d, J = 12.5, PhCH); 4.82 (d, J = 12.1, PhCH); 4.69 (d, J = 10.9, PhCH); 4.47 (s, PhCH2); 4.29 (s, H–C(6)); 3.56 (d, J = 9.0, CH–C(5)); 3.27 (d, J = 8.7, CH’–C(5)); 2.89 (dm, J = 18.7, H–C(4)); 2.45 (dd, J = 18.7, 5.6, H’–C(4)); 2.38 (s, OH). HR-MS (MALDI): 467.1829 (100%, C28H28NaO5+, [M + Na]+; calc. .647.1834).

(1L)-(1,2/3,4)-1,2,3-Tri-O-benzyl-4-C-[(benzyloxy)methyl]-4-O-carbamoylcyclohex-5-ene-1,2,3,4-tetrol (476).

A solution of 42 (140 mg, 0.26 mmol) in CH2Cl2 (2.5 ml) was cooled to 0°, treated dropwise with CCl3CONCO (62 µl, 0.52 mmol), stirred for 30 min, and evaporated. A solution of the residue in MeOH (3.5 ml) and H2O (0.5 ml) was cooled to 0°, treated with K2CO3 (120 mg, 0.86 mmol), and stirred at 0° for 100 min and at r.t. for 14 h. After evaporation of MeOH, the residue was diluted with H2O (20 ml) and extracted with CH2Cl2 (3 x 30 ml). The combined organic phases were washed with brine (20 ml) and dried (Na2SO4). Evaporation and FC (30 g of silica gel, cyclohexane/AcOEt 5:2) gave 476 (141 mg, 93%). Colourless oil. Rf (cyclohexane/AcOEt 3:1) 0.07. 1H-NMR (300 MHz, CDCl3): 7.81–7.25 (20 arom. H); 6.29 (br. d, J = 10.3, H–C(5)); 5.96 (dd, J = 10.3, 4.4, H–C(6)); 4.83 (d, J = 11.2, PhCH); 4.72 (d,
\[ J = 12.1, \text{PhCH}; 4.70–4.63 \ (m, 4 \text{PhCH}); 4.56–4.43 \ (\text{br. s, NH}_2); 4.54 \ (d, J = 12.1, \text{PhCH}); 4.44 \ (d, J = 12.1, \text{PhCH}); 4.37 \ (d, J = 9.0, \text{H–C(3)}); 4.22 \ (\text{br. t, } J = 4.1, \text{H–C(1)}); 4.13 \ (d, J = 9.0, \text{CH–C(4)}); 4.02 \ (dd, J = 9.0, 4.0, \text{H–C(2)}); 3.84 \ (d, J = 9.0, \text{CH'}–\text{C(4)}) \].

\[ (1L)-(1,4/2,3)-4\text{-Acetamido-1,2,3-tri-O-benzyl-6-}[(\text{benzyloxy})\text{methyl}]\text{cyclohex-5-ene-1,2,3-triol (43)}. \]

A solution of 476 (139 mg, 0.24 mmol), Ph\textsubscript{3}P (157 mg, 0.60 mmol), and Et\textsubscript{3}N (66 µl, 0.48 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (2.5 ml) was cooled to –20°, treated dropwise with a solution of CBr\textsubscript{4} (223 mg, 0.67 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1.2 ml), stirred for 1 h, treated dropwise with 2.0 M Me\textsubscript{3}Al in heptane (0.96 ml, 1.92 mmol), stirred for 1 h, treated carefully with MeOH (1 ml), CH\textsubscript{2}Cl\textsubscript{2} (2.5 ml), and 0.1 M HCl (10 ml), and allowed to warm to 0°. The organic phase was separated and the aqueous phase extracted with CH\textsubscript{2}Cl\textsubscript{2} (6 x 15 ml). The combined organic phases were washed with brine (30 ml) and dried (Na\textsubscript{2}SO\textsubscript{4}). Evaporation and FC (30 g of silica gel, cyclohexane/\text{AcOEt} 1:1) gave 43 (132 mg, 95%). \( R_f \) (cyclohexane/\text{AcOEt} 1:1) 0.24. \( \text{^1H-NMR (300 MHz, CDCl}_3\text{):} \) 7.36–7.22 (20 arom. H); 5.69 (d, \( J = 3.1, \text{H–C(5)}\)); 5.08 (br. d, \( J = 8.4, \text{AcNH}\)); 4.88–4.79 (m, \text{H–C(4)}); 4.67 (d, \( J = 11.5, 2 \text{PhCH}\)); 4.62 (d, \( J = 11.5, \text{PhCH}\)); 4.55 (d, \( J = 12.1, 2 \text{PhCH}\)); 4.49 (d, \( J = 11.8, \text{PhCH}\)); 4.48 (d, \( J = 12.5, \text{PhCH}\)); 4.36 (d, \( J = 11.8, \text{PhCH}\)); 4.16 (br. d, \( J = 4.7, \text{H–C(1)}\)); 4.15 (br. d, \( J = 11, \text{CH–C(6)}\)); 3.87 (br. d, \( J = 12.8, \text{CH'}–\text{C(6)}\)); 3.83 (dd, \( J = 5.0, 2.2, \text{H–C(2)}\)); 3.70 (dd, \( J = 6.9, 2.2, \text{H–C(3)}\)); 1.89 (s, Ac). MALDI-MS: 600 (100, [\( M + \text{Na} \text{]}}^+\).

\[ (1L)-(1,4/2,3)-1,2,3\text{-Tri-O-benzyl-6-}[(\text{benzyloxy})\text{methyl}]\text{-4-}[(\text{methoxycarbonyl})\text{amino}]\text{cyclohex-5-ene-1,2,3-triol (479)}. \]

A solution of 476 (144 mg, 0.25 mmol), Ph\textsubscript{3}P (163 mg, 0.62 mmol), and Et\textsubscript{3}N (70 µl, 0.50 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (3 ml) was cooled to –20°, treated dropwise with a solution of CBr\textsubscript{4} (231 mg, 0.70 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1.3 ml), stirred for 1 h, treated dropwise with MeOH (0.5 ml),
allowed to warm to r.t., stirred for 15 h, and poured into ice-water (20 ml). The aqueous phase was extracted with CH₂Cl₂ (4 x 20 ml), and the combined organic phases were washed with brine (30 ml) and dried (Na₂SO₄). Evaporation and FC (30 g of silica gel, cyclohexane/AcOEt 4:1) gave 479 (136 mg, 91%). R_f (cyclohexane/AcOEt 3:1) 0.28. ¹H-NMR (300 MHz, CDCl₃): 7.36–7.20 (20 arom. H); 5.74–5.70 (m, H–C(5)); 4.69 (d, J = 12.1, PhCH); 4.67–4.54 (m, 2 PhCH, H–C(4), NH); 4.62 (d, J = 11.8, PhCH); 4.58 (d, J = 12.1, PhCH); 4.53 (d, J = 12.1, PhCH); 4.49 (d, J = 11.8, PhCH); 4.36 (d, J = 11.8, PhCH); 4.19–4.10 (m, CH–C(6), H–C(1)); 3.90–3.81 (m, CH'–C(6)); 3.85 (dd, J = 4.4, 2.2, H–C(2)); 3.72–3.67 (m, H–C(3)); 3.69 (s, MeO). ¹³C-NMR (75 MHz, CDCl₃): 157.01 (s, C=O); 138.68, 138.52, 136.11 (3s); 128.72–127.49 (several d); 77.46 (d); 75.22 (2d); 74.16, 72.61, 71.83, 70.48 (4t, 1t hidden); 52.34 (q, MeO); 49.83 (d, C(4)). HR-MS (MALDI): 616.2667 (100%, C₃₇H₃₉NaNO₆+, [M + Na]+; calc. 616.2675).

A soln. of 475 (220.7 mg, 73%) as a colourless oil and 42 (42.8 mg, 15%) as a colourless oil. R_f (hexane/AcOEt 3:1) 0.53. ¹H-NMR (300 MHz, CDCl₃): 7.36–7.17 (20 arom. H); 6.22 (d, J = 10.3, H–C(6)); 5.92 (dd, J = 10.3, 4.4, H–C(5)); 4.81 (d, J = 11.5, PhCH); 4.73 (d, J = 12.1, PhCH); 4.72–4.65 (m, 3 PhCH); 4.64 (d, J = 11.8, PhCH); 4.51 (d, J = 11.8, PhCH); 4.44 (d, J = 12.1, PhCH); 4.33 (d, J = 8.7, H–C(2)); 4.19 (t, J = 4.4, H–C(4)); 4.05 (d, J = 9.0, CH–C(1)); 4.01 (dd, J = 8.7, 3.7, H–C(3)); 3.79 (d, J = 9.0, CH'–C(1)); 1.98 (s, Ac).

**Reaction of 475 with Pd(PPh₃)₄ and NaN₃ (cf. [417]).**

A soln. of 475 (80 mg, 0.138 mmol) in THF (2.5 ml) was treated with Pd(PPh₃)₄ (20 mg, 0.017 mmol) and 1 M aq. NaN₃ soln. (1 ml, 1 mmol) and refluxed for 4 d. TLC (hexane/AcOEt 3:1) indicated starting material and little conversion to a new component (R_f 0.66).
(1L)-(1,2,3,4)-1,2,3-Tri-O-benzyl-4-tert-butyl-dimethyl-silyl-4-C-[(benzyloxy)methyl] cyclohex-5-ene-1,2,3,4-tetrol (836).

A cooled (0°) solution of 42 (0.623 g, 1.16 mmol) in CH₂Cl₂ (12 ml) was treated dropwise with 2,6-lutidine (0.31 ml, 2.32 mmol, 2.0 eq) and tert-butyl-dimethylsilyl trifluoromethane sulfonate (0.54 ml, 2.32 mmol, 2.0 eq), stirred for 30 min, and treated with sat. aq. NH₄Cl soln. (20 ml). The org. phase was separated and the aq. phase was extracted with CH₂Cl₂ (3*30 ml). The combined organic phases were washed with brine (20 ml), dried (MgSO₄), and evaporated. FC of the yellow oily residue (Cyclohexane/AcOEt 20:1) afforded 836 (0.746 g, 1.147 mmol, 99 %) as a colourless oil. 

\[ R_f (\text{Cyclohexane/AcOEt 10:1}) = 0.72 \]

1H-NMR (CDCl₃): 7.43–7.25 (m, 20 arom. H); 5.86 (d, \( J = 9.96 \) Hz, H–C(5)); 5.80 (dd, \( J = 9.96, 4.67 \) Hz, H–C(6)); 5.09 (d, \( J = 11.83 \) Hz, PhCH); 4.87 (d, \( J = 12.45 \) Hz, PhCH); 4.81 (d, \( J = 12.45 \) Hz, PhCH); 4.75 (s, PhCH₂); 4.61 (d, \( J = 10.27 \) Hz, H–C(3)); 4.11 (dd, \( J = 4.67, 4.05 \) Hz, H–C(1)); 4.01 (dd, \( J = 10.27, 4.05 \) Hz, H–C(2)); 3.48 (dd, \( J = 8.72 \) Hz, CH₂–C(4)); 0.89 (s, 9 H, C(CH₃)₃); 0.04 (s, 3H, Si–CH₃); 0.08 (s, 3H, Si–CH₃). 13C-NMR (CDCl₃) 139.91 (s); 139.47 (s); 139.26 (s); 138.53 (s); 134.49 (d, C(5)); 128.52-127.89 (several Ph); 127.66 (d, C(6)); 77.85 (d, C(2)); 76.77 (d, C(2)); 74.97 (t, CH₂–C(4)); 74.02 (t, PhCH₂); 73.39 (t, PhCH₂); 72.69 (t, PhCH₂); 25.91 (q); 18.54 (s); – 2.21 (q); – 2.47 (q). FAB-MS (NOBA) 650 (6, [\( M^+ \]), 181 (17), 91 (100), 73 (15).

(1L)-(1,2,3,4)-2,3-Di-O-benzyl-1-O-acetyl-4-tert-butyl-dimethyl-silyl-4-C-[(benzyloxy)methyl] cyclohex-5-ene-1,2,3,4-tetrol (837) and (1D)-(1,3,4/2)-2,3-Di-O-benzyl-1-O-acetyl-4-tert-butyl-dimethyl-silyl-4-C-[(benzyloxy)methyl] cyclohex-5-ene-1,2,3,4-tetrol (838).

A solution of 836 (30.05 mg, 0.046 mmol) was treated with Zn(OTf)₂ (51.4 mg, 0.141 mmol), Ac₂O (1 ml), stirred at 24° for 2 h, treated with CH₂Cl₂ (10 ml), and sat. aq. NH₄Cl soln. (20
The org. phase was separated and the aq. phase was extracted with CH$_2$Cl$_2$ (3*10 ml). The combined organic phases were washed with brine (5 ml), dried (MgSO$_4$), and evaporated. FC of the yellow oily residue (Cyclohexane/AcOEt 20:1) afforded a mixture of the epimers 837 and 838 (20.93 mg, 0.034 mmol, 74%) as a colourless oil.

Data of 837 (57%): $^1$H-NMR (CDCl$_3$): 7.34–7.25 (m, 15 arom. H); 5.92 (d, $J$ = 9.65, H–C(5)); 5.76–5.74 (dd, $J$ = 9.65, 4.05, H–C(6)); 5.67 (d, $J$ = 4.05 Hz, 4.04 Hz H–C(1)); 5.00 (d, $J$ = 11.51, PhCH); 4.83–4.33 (m, 5 PhCH); 4.03 (dd, $J$ = 10.58, 4.04, H–C(2)); 3.96 (d, $J$ = 10.58, H–C(3)); 3.58 (d, $J$ = 8.41, CH–C(4)); 3.33 (d, $J$ = 8.41 Hz, CH'–C(4)); 2.12 (s, OAc); 0.89 (s, 9 H, Si C(CH$_3$)$_3$); 0.04 (s, 3 H, Si–CH$_3$); – 0.08 (s, 3 H, Si–CH$_3$).

Data for 838 (43%): $^1$H-NMR (CDCl$_3$): 7.34–7.25 (m, 15 arom. H); 5.81-5.77 (dd, $J$ = 9.96, 4.36, H–C(6)); 5.61 (d, $J$ = 9.96, H–C(5)); 5.47 (dd, $J$ = 8.09, 4.36, H–C(1)); 4.98 (d, $J$ = 11.51, PhCH); 4.83–4.33 (m, 5 PhCH); 4.11–4.05 (dd, $J$ = 10.59, 8.1, H–C(2)); 3.72 (d, $J$ = 10.59 Hz, H–C(3)); 3.54 (d, $J$ = 8.41 Hz, CH–C(4)); 3.29 (d, $J$ = 8.41, CH'–C(4)); 1.95 (s, OAc); 0.81 (s, 9 H, Si C(CH$_3$)$_3$); 0.003 (s, 3 H, Si–CH$_3$); – 0.002 (s, 3 H, Si–CH$_3$).
**Allyl 3,4,6-Tri-O-benzyl-α-D-mannopyranoside (481).**

A solution of 480 (2.0 g, 4.44 mmol) in allylic alcohol (15 ml) was treated with camphorsulfonic acid (0.5 g) and stirred at 90° for 2 d. Evaporation and FC (20 g of silica gel, cyclohexane/AcOEt 3:1) gave 481 (2.29 g, 100%). Colourless oil. Rf (cyclohexane/AcOEt 1:1) 0.73. 1H-NMR (300 MHz, CDCl3): 7.39−7.18 (15 arom. H); 5.91 (ddt, J = 17.1, 10.3, 5.1, H−C(2´)); 5.28 (dq, J = 17.1, 1.6, H−C(3´)); 5.20 (dq, J = 10.3, 1.3, H´−C(3´)); 4.98 (d, J = 1.9, H−C(1)); 4.85 (d, J = 10.9, PhCH); 4.74 (d, J = 11.5, PhCH); 4.69 (d, J = 11.5, PhCH); 4.68 (d, J = 12.1, PhCH); 4.55 (d, J = 12.1, PhCH); 4.53 (d, J = 10.6, PhCH); 4.20 (ddt, J = 13.1, 5.3, 1.6, H−C(1´)); 4.08 (br. dd, J = 4.4, 2.8, H−C(2)); 4.01 (ddt, J = 13.1, 6.2, 1.3, H´−C(1´)); 3.93−3.91 (m, 1 H); 3.88 (t, J = 8.7, H−C(4)); 3.84−3.70 (m, 3 H); 2.52 (d, J = 2.5, OH). 13C-NMR (75 MHz, CDCl3): 138.57 (2s); 138.24 (1s); 134.01 (d, C(2´)); 128.80−127.83 (several d); 117.73 (t, C(3´)); 98.61 (d, C(1)); 80.42 (d); 75.31 (t); 74.50 (d); 73.61 (t); 72.16 (t); 71.32 (d); 69.08 (t); 68.52 (d); 68.10 (t). HR-MS (MALDI): 513.2245 (100, C30H34NaO6+, [M + Na]+; calc. 513.2253), 471 (20, [M + Na − C3H6]+).

**Allyl 3,4,6-Tri-O-benzyl-2-O-(4-methoxybenzyl)-α-D-mannopyranoside (482).**

A solution of 481 (2.03 g, 4.14 mmol) in DMF (50 ml) was cooled to 0°, treated with NaH (0.36 g, 55% in oil, 8.28 mmol), stirred for 40 min, treated with 4-methoxybenzyl chloride (1.12 ml, 8.28 mmol), warmed to r.t., stirred for 15 h, cooled to 0°, treated with MeOH (1 ml), stirred for 20 min, and diluted with AcOEt (100 ml). The organic phase was separated, washed with H2O (70 ml) and brine (70 ml), and dried (Na2SO4). Evaporation and FC (100 g of silica gel, cyclohexane/AcOEt 6:1) gave 482 (2.49 g, 98%). Colourless oil. Rf (cyclohexane/AcOEt 3:1) 0.63. 1H-NMR (300 MHz, CDCl3): 7.43−7.18 (17 arom. H); 6.85 (d, J = 8.7, 2 arom. H); 5.88 (ddt, J = 17.1, 10.6, 5.1, H−C(2´)); 5.24 (dq, J = 17.1, 1.6, H−C(3´)); 5.17 (dq, J = 10.6, 3.1, H´−C(3´)); 4.93 (d, J = 1.9, H−C(1)); 4.91 (d, J = 10.6, PhCH); 4.70 (d, J = 12.1, PhCH); 4.69 (s, PhCH2); 4.63 (s, PhCH2); 4.61 (d, J = 11.5,
PhCH); 4.53 (d, J = 10.6, PhCH); 4.19 (dddt, J = 13.1, 5.0, 1.6, H–C(1')); 4.01–3.92 (m, 3 H); 3.83–3.73 (m, 4 H); 3.81 (s, MeO). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): 159.52 (s); 138.91, 138.81, 138.76 (3s); 134.14 (d, C(2')); 130.69–127.71 (several d); 117.42 (t, C(3')); 113.96 (2d); 97.30 (d, C(1')); 80.39 (d); 75.31 (t, PhCH\(_2\)); 75.17 (d); 74.29 (d); 73.52, 72.30, 72.22 (3t, 2 PhCH\(_2\), MeOC\(_6\)H\(_4\)CH\(_2\)); 72.04 (d); 69.47 (t); 67.94 (t); 55.38 (q, MeO). HR-MS (MALDI): 633.2817 (100, C\(_{38}\)H\(_{42}\)NaO\(_7\)+,[M + Na]+; calc. 633.2828)., 519 (47, [M + Na – C\(_3\)H\(_6\)]+).

3,4,6-Tri-O-benzyl-2-O-(4-methoxybenzyl)-D-mannopyranose (483).

A solution of 482 (2.26 g, 3.71 mmol) in MeOH (50 ml) was treated with PdCl\(_2\) (96 mg, 0.54 mmol), stirred for 4.5 h, treated with Et\(_3\)N (1 ml), and filtered through Celite. Evaporation and FC (30 g of silica gel, cyclohexane/AcOEt 3:1) gave 483 (1.80 g, 85%). Colourless oil. R\(_f\) (cyclohexane/AcOEt 3:1) 0.18. \(^1\)H-NMR (300 MHz, CDCl\(_3\), mixture of diastereoisomers, >6:1, therefore only the signals of the major diastereoisomer could be analysed): 7.36–7.16 (17 arom. H); 6.84 (d, J = 8.7, 2 arom. H); 5.24–5.22 (br. s, H–C(1)); 4.90 (d, J = 10.9, PhCH); 4.67 (s, PhCH\(_2\)); 4.61 (s, PhCH\(_2\)); 4.59 (d, J = 10.0, PhCH); 4.53 (d, J = 12.1, PhCH); 4.51 (d, J = 10.9, PhCH); 4.05 (dddt, J = 9.7, 6.1, 2.1, H–C(5)); 3.96 (dd, J = 9.3, 3.1, H–C(3)); 3.85 (t, J = 9.7, H–C(4)); 3.81–3.78 (m, H–C(2)); 3.79 (s, MeO); 3.73 (dd, J = 10.6, 2.2, H–C(6)); 3.67 (dd, J = 10.6, 6.2, H’–C(6)); 3.45 (d, J = 3.1, OH). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): 159.52 (s); 138.84 (2s), 138.71 (1s); 130.67–127.79 (several d); 113.98 (2d); 92.96 (d, C(1')); 79.89 (d); 75.41 (d); 75.18 (t, 2 PhCH\(_2\)); 74.42 (d); 73.44, 72.38, 72.24 (3t, 2 PhCH\(_2\), MeOC\(_6\)H\(_4\)CH\(_2\)); 71.66 (d); 69.80 (t); 55.37 (q, MeO). HR-MS (MALDI): 593.2508. (100, C\(_{35}\)H\(_{38}\)NaO\(_7\)+,[M + Na]+; calc. 593.2515).
1,3,4-Tri-O-benzyl-6,7-dideoxy-5-(4-methoxybenzyl)-D-manno-hept-6-enitol (484).

A solution of 483 (115 mg, 0.20 mmol) in THF (5 ml) was cooled to −78°, treated dropwise with a solution of Ph₃P=CH₂ (prepared at 0° from Ph₃PMeBr (287 mg, 0.80 mmol) and 1.6M BuLi in hexane (0.5 ml) in THF (5 ml)), heated under reflux for 12 min, cooled to 0°, and poured into sat. aqueous NaHCO₃ solution (50 ml). The mixture was extracted with AcOEt (60 ml). The organic phase was washed with brine (2 × 50 ml) and dried (Na₂SO₄). Evaporation and FC (20 g of silica gel, cyclohexane/AcOEt 6:1) gave 484 (51 mg, 44%). Colourless oil. \( R_f \) (cyclohexane/AcOEt 3:1) 0.48. \( ^1H \)-NMR (300 MHz, CDCl₃): 7.38−7.19 (17 arom. H); 6.85 (\( d, J = 8.7 \), 2 arom. H); 5.97 (\( ddd, J = 17.4, 10.3, 7.8, \) H–C(6)); 5.44 (\( ddd, J = 17.4, 1.9, 0.6, \) H–C(7)); 5.41 (\( ddd, J = 10.0, 1.6, 0.6, \) H'–C(7)); 4.72 (\( d, J = 11.2, \) PhCH); 4.63 (\( d, J = 11.2, \) PhCH); 4.55 (\( d, J = 11.2, \) PhCH); 4.54 (\( dd, J = 11.8, \) PhCH); 4.50 (s, PhCH₂); 4.47 (\( d, J = 10.6, \) PhCH); 4.20 (\( d, J = 11.5, \) PhCH); 4.11 (br. t, \( J = 7.2, 1 \) H); 4.05–3.97 (m, 1 H); 3.88–3.84 (m, 2 H); 3.79 (s, MeO); 3.64 (\( dd, J = 9.7, 3.4, \) H–C(1)); 3.58 (\( dd, J = 9.7, 5.3, \) H'–C(1)); 2.66 (\( d, J = 5.3, \) OH). \( ^{13}C \)-NMR (75 MHz, CDCl₃): 159.44 (s); 138.68 (2s); 138.34 (1s); 136.68 (\( d, C(6) \)); 130.69−127.75 (several \( d \)); 119.87 (t, C(7)); 113.98 (2d); 81.04, 80.04, 78.74 (3d); 74.44, 74.07, 73.47, 71.43 (4t, 3 PhCH₂, MeOC₆H₄CH₂); 70.35 (d); 69.75 (t, C(1)); 55.37 (q, MeO).

1,3,4-Tri-O-benzyl-6,7-dideoxy-5-(4-methoxybenzyl)-D-arabino-hept-6-en-2-ulose (485).

A solution of oxalyl chloride (9 µl, 100 µmol) in CH₂Cl₂ was cooled to −50°, treated with DMSO (11 µl, 200 µmol), stirred for 15 min, treated with a solution of 484 (20 mg, 35 µmol) in CH₂Cl₂ (1 ml), stirred for 30 min, allowed to warm to −25°, treated with Et₃N (70 µl, 500 µmol), warmed to 0°, stirred for 90 min, and poured into ice-cold sat. aqueous NaHCO₃
solution (20 ml). The mixture was extracted with Et2O (2 × 20 ml). The organic phase was washed with brine (20 ml) and dried (Na2SO4). Evaporation and FC (6 g of silica gel, cyclohexane/AcOEt 6:1) gave 485 (20 mg, 100%). Colourless oil. Rf (cyclohexane/AcOEt 3:1) 0.53. 1H-NMR (300 MHz, CDCl3): 7.34–7.17 (17 arom. H); 6.83 (d, J = 8.7, 2 arom. H); 5.88 (ddd, J = 17.1, 10.0, 7.8, H–C(6)); 5.46 (br. dd, J = 17.1, 0.9, H–C(7)); 5.43 (br. dd, J = 10.0, 1.6, H′–C(7)); 4.58 (d, J = 10.6, PhCH); 4.50 (d, J = 11.2, PhCH); 4.46 (d, J = 10.0, PhCH); 4.43 (s, PhCH2); 4.38 (d, J = 10.9, PhCH); 4.36 (d, J = 11.8, PhCH); 4.32 (d, J = 18.4, H–C(1)); 4.31 (d, J = 3.4, H–C(3)); 4.20 (d, J = 18.4, H′–C(1)); 4.13 (d, J = 11.2, PhCH); 4.07 (br. t, J = 8.1, H–C(5)); 3.89 (dd, J = 8.4, 3.4, H–C(4)); 3.77 (s, MeO). 13C-NMR (75 MHz, CDCl3): 209.27 (s, C(2)); 159.49 (s); 137.84, 137.65, 137.34 (3 s); 136.30 (d, C(6)); 130.37 – 128.07 (several d); 120.63 (t, C(7)); 113.98 (2 d); 84.47, 82.56, 79.26 (3d, C(3), C(4), C(5)); 75.09, 74.68, 74.52, 73.35 (4t, 3 PhC6H4C2); 69.81 (t, C(1)); 55.37 (q, MeO). HR-MS (MALDI): 589.2560. (100, C36H38NaO6+, [M + Na]+; calc. 589.2561), 453 (21), 347 (10).

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\begin{align*}
\text{4,5-Di-O-benzyl-6-C-[(benzyloxy)methyl]-1,2,7,8-tetradeoxy-3-(4-methoxybenzyl)-D-manno-octa-1,7-dienitol (486).}
\end{align*}
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A solution of 485 (19 mg, 33 µmol) in THF (2 ml) was cooled to –78°, treated dropwise with a solution of 1M vinylmagnesium bromide in THF (50 µl), stirred for 45 min, allowed to warm to 0°, diluted with Et2O (20 ml), and treated with sat. aqueous NH4Cl solution (20 ml). The organic phase was separated, washed with brine (20 ml), and dried (Na2SO4). Evaporation and FC (10 g of silica gel, cyclohexane/AcOEt 6:1) gave 486 (19 mg, 96%). Colourless oil. Rf (cyclohexane/AcOEt 3:1) 0.64. 1H-NMR (300 MHz, CDCl3): 7.36–7.21 (17 arom. H); 6.82 (d, J = 8.7, 2 arom. H); 6.17 (dd, J = 17.1, 10.6, H–C(7)); 5.95 (ddd, J = 17.7, 10.0, 7.8, H–C(2)); 5.56 (dd, J = 17.1, 1.9, H–C(8)); 5.44 (br. d, J = 15.9, H–C(1)); 5.43 (br. d, J = 11.5, H′–C(1)); 5.25 (dd, J = 10.9, 1.9, H′–C(8)); 4.69 (d, J = 10.6, PhCH); 4.59–4.51 (m, 4 PhCH); 4.48 (d, J = 11.8, PhCH); 4.42 (d, J = 12.1, PhCH); 4.18 (d, J = 11.51, PhCH); 4.05 (d, J = 2.5, H–C(5)); 4.04 (t, J = 7.5, H–C(3)); 3.86 (dd, J = 7.2, 2.5, H–C(4)); 3.79 (s, OH); 3.78 (s, MeO); 3.72 (d, J = 8.4, CH–C(6)); 3.27 (d, J = 8.4, CH′–C(6)). 13C-NMR (75 MHz, CDCl3): 140.49 (d, C(7)); 138.73 (2s); 138.24 (1s); 136.24 (d, C(2)); 130.27–127.36 (several d); 119.98 (t, C(1)); 114.61 (t, C(8)); 113.78 (2d); 81.32,
80.35, 78.28 (3d, C(3), C(4), C(5)); 77.94 (s, C(6)); 74.91, 74.85, 73.42, 73.20 (4t, 3 PhCH₂, MeOC₆H₄CH₂); 69.51 (t, CH₂–C(6)); 55.27 (q, MeO). HR-MS (MALDI): 617.2856 (100, C₃₈H₄₂NaO₆⁺, [M + Na]⁺; calc. 617.2874), 481 (40), 376 (32).

A soln. of 486 (19 mg, 32 µmol) in CH₂Cl₂ (5 ml) was degassed by purging with N₂ and added via cannula to 312 (8 mg, 10 µmol). The mixture was stirred under N₂ for 4 d and evaporated. FC (12 g of silica gel, cyclohexane/AcOEt 6:1) gave 60 (9.4 mg, 49%) as a green oil and 486 (8.2 mg, 45%) as a green oil. Rₐ (cyclohexane/AcOEt 3:1) 0.58. ¹H-NMR (300 MHz, CDCl₃): 7.37–7.20 (17 arom. H); 6.86 (dm, J = 8.7, 2 arom. H); 5.90 (dd, J = 10.0, 5.0, H–C(6)); 5.76 (d, J = 10.0, H–C(5)); 4.95 (d, J = 10.9, PhCH); 4.70–4.63 (m, 4 PhCH); 4.58 (d, J = 11.2, PhCH); 4.55 (d, J = 12.1, PhCH); 4.45 (d, J = 12.1, PhCH); 4.22 (d, J = 9.7, H–C(3)); 4.12 (dd, J = 4.7, 4.1, H–C(1)); 3.91 (dd, J = 9.7, 3.7, H–C(2)); 3.81 (s, MeO); 3.44 (d, J = 9.7, CH–C(4)); 3.41 (d, J = 9.7, CH′–C(4)); 3.07 (s, OH). ¹³C-NMR (75 MHz, CDCl₃): 138.39 (3s); 132.65–127.79 (several d, including C(5) and C(6)); 113.95 (2d); 78.13 (d, C(2)); 76.04 (d, C(3)); 75.52 (t); 74.60 (t, CH₂–C(4)); 73.58 (t); 73.05 (s, C(4)); 72.79 (t); 71.43 (t); 71.19 (d, C(1)); 55.40 (q, MeO). HR-MS (MALDI): 589.2558 (100, C₃₆H₃₈NaO₆⁺, [M + Na]⁺; calc. 589.2561).
1,3,4-Tri-O-benzyl-5,6 dideoxy-D-threo-hex-5-en-2-ulose (420).

A soln. of 2,3,5-tri-O-benzyl-D-arabinofuranose (commercially available, 5 g, 11.89 mmol) in THF (70 ml) was cooled to −78°, treated with PH₃P=CH₂ (prepared from a solution of Ph₃PMeBr (8.50 g, 23.8 mmol) in THF (80 ml) by dropwise addition of 1.6M butyllithium in hexane (15 ml, 24 mmol)), refluxed for 3 h, cooled to r.t., treated with acetone (50 ml) and with sat. aq. NH₄Cl soln. (50 ml), and diluted with Et₂O (100 ml). The org. phase was separated and the aq. phase extracted with AcOEt (3 x 50 ml). The combined org. phases were washed with brine (30 ml), dried (MgSO₄), and evaporated. FC of the residue (cyclohexane/AcOEt 9:1) afforded 420 (3.98 g, 80 %) as a colourless oil. \( R_f \) (cyclohexane/AcOEt 3:1) 0.46. \([\alpha]_{25}^D = -8.4 \) (c = 1.48, CHCl₃). IR (CHCl₃): 3570–3480 m, 3090 m, 3070 m, 3000 m, 2920 s, 2870 s, 1500 s, 1450 s, 1400 m, 1350 m, 1300 s, 1250 m, 1090 s, 930 s. \(^1\)H-NMR (CDCl₃): 7.23–7.37 (m, 15 arom. H); 5.96 \((ddd, J = 16.5, 11.2, 7.5, \text{H–C}(5))\); 5.34 \((dm, J = 11.2, \text{H–C}(6))\); 5.32 \((dm, J = 16.5, \text{H}^1\text{C}(6))\); 4.64 \((d, J = 12.1, 2 \text{PhCH})\); 4.56 \((d, J = 11.51, \text{PhCH})\); 4.51 \((s, \text{PhCH}2)\); 4.37 \((d, J = 12.1, \text{PhCH})\); 4.11 \((\text{br. } dd, J = 7.5, 4.1, \text{H–C}(4))\); 4.01 \((dt, J = 7.2, 4.4, \text{H–C}(2))\); 3.63 \((dd, J = 7.2, 4.1, \text{H–C}(3))\); 3.61–3.56 \((m, \text{CH}2(1))\). \(^{13}\)C-NMR (CDCl₃): 138.45; 138.21; 137.81; 135.46 \((\text{C}(5))\); 128.57–127.87 \((\text{several } d)\); 118.98 \((\text{C}(6))\); 80.88, 80.49 \((\text{C}(3), \text{C}(4))\); 74.21; 73.47; 71.17; 70.85; 70.47. FAB-MS (NOBA) 419 \((22,[M + 1]^+)\), 311 \((5)\), 219 \((8)\), 181 \((35)\), 154 \((5)\), 91 \((100)\). Anal. calc. for C₂₇H₃₀O₄ (418.52): C 77.48, H 7.22; found: C 77.48, H 7.02.

1,3,4-Tri-O-benzyl-5,6 dideoxy-D-threo-hex-5-en-2-ulose (398).

A soln. of 420 (3.71 g, 8.85 mmol) in CH₂Cl₂ (50 ml) was treated with a solution of Dess Martin's periodinane (4.5 g, 10.58 mmol) in CH₂Cl₂ (50 ml), stirred at 24° for 30 min, diluted with Et₂O (150 ml), treated with 1.3M NaOH (50 ml), stirred for 15 min, and treated with sat. aq. NH₄Cl soln. (40 ml). The org. phase was separated, washed with H₂O (40 ml), dried (MgSO₄), and evaporated. FC of the residue (cyclohexane/AcOEt 5:1) afforded 398 (3.53 g 96%) as a colourless oil. \( R_f \) (cyclohexane/AcOEt 3:1) 0.51. \([\alpha]_{25}^D = -36.58° \) (c = 0.55,
CHCl$_3$). IR (CHCl$_3$): 3033 $m$, 2867 $m$, 1733 $s$, 1700 $m$, 1606 $w$, 1495 $w$, 1450 $m$, 1389 $m$, 1339 $m$, 1322 $m$, 1205 $m$, 1106 $s$, 1022 $s$, 995 $m$, 939 $m$, 828 $w$. $^1$H-NMR (CDCl$_3$): 7.23–7.37 ($m$, 15 arom. H); 5.96 ($m$, $J = 17.1$, 11.8, 7.8, H–C(5)); 5.34 ($dm$, $J = 11.8$, H–C(6)); 5.33 ($dm$, $J = 17.1$, H′–C(6)); 4.59 ($d$, $J = 11.8$, PhCH); 4.58 ($d$, $J = 11.8$, PhCH); 4.51 ($d$, $J = 11.8$, PhCH); 4.50 ($d$, $J = 11.8$, PhCH); 4.43 ($d$, $J = 11.8$, PhCH); 4.33 (br. $s$, CH$_2$(1)); 4.29 ($d$, $J = 11.8$, PhCH); 4.18 (br. $dd$, $J = 7.8$, 3.4, H–C(4)); 4.00 ($d$, $J = 3.4$, H–C(3)). $^{13}$C-NMR (CDCl$_3$): 207.87 (C(2)); 138.45; 138.21; 137.81; 134.38 (C(5)); 128.75–128.00 (several $d$); 119.98 (C(6)); 85.99, 81.06 C(3), C(4); 74.68, 74.45, 73.40 (3 PhC$_2$); 71.01 (C(1)). FAB-MS (NOBA) 439 (8, [M + Na]$^+$), 415 (9), 360 (5), 309 (4), 271 (5), 219 (9), 181 (53), 147 (10), 91 (100).

3,4-Di-O-benzyl-1,2,6,7-tetradeoxy-5-C-[(benzyloxy)methyl]-D-arabino-hepta-1,6-dienitol (421).

A soln. of 398 (3.858 g, 9.24 mmol) in THF (80 ml) was cooled to $-78^\circ$, treated dropwise with 1M vinylmagnesium bromide in THF (13.9 ml, 13.9 mmol), stirred for 60 min, treated with Et$_2$O (100 ml), warmed to 0$^\circ$, and treated with sat. aq. NH$_4$Cl soln. (40 ml). The org. phase was separated and the aq. phase extracted with Et$_2$O (2 x 40 ml). The combined org. phases were washed with brine (40 ml), dried (MgSO$_4$), and evaporated. FC of the residue (cyclohexane/AcOEt 7:1) afforded 421 (4.05 g, 98%) as a colourless oil. $R_f$ (cyclohexane/AcOEt 3:1) 0.61. [a]$_D^{25} = -25.2$ ($c = 0.6$, CHCl$_3$). IR (CHCl$_3$): 3456 $m$, 3078 $m$, 3022 $s$, 2867 $s$, 1956 $w$, 1872 $w$, 1811 $w$, 1639 $w$, 1605 $w$, 1494 $m$, 1450 $s$, 1394 $s$, 1344 $s$, 1205 $m$, 1083 $s$, 1028$s$, 1000$s$, 928$s$, 817$w$. $^1$H-NMR (CDCl$_3$): 7.36–7.63 ($m$, 15 arom. H); 6.14 ($dd$, $J = 17.1$, 10.9, H–C(6)); 5.97 ($ddd$, $J = 17.4$, 10.6, 8.1, H–C(2)); 5.44 ($dd$, $J = 17.1$, 2.2, H–C(7)); 5.29 ($dm$, $J = 18.0$, H–C(1)); 5.28 ($dm$, $J = 10.3$, H′–C(1)); 5.16 ($dd$, $J = 10.6$, 2.2, H′–C(7)); 4.70 ($d$, $J = 11.2$, PhCH); 4.63 ($d$, $J = 11.2$, PhCH); 4.56 ($d$, $J = 11.2$, PhCH); 4.46, 4.42 ($2d$, $J = 11.8$, PhCH$_2$); 4.23 ($d$, $J = 11.5$, PhCH); 4.22 ($s$, OH); 4.17 ($dd$, $J = 8.1$, 2.5, H–C(3)); 3.77 ($d$, $J = 8.7$, CH–C(5)); 3.70 ($d$, $J = 2.5$, H–C(4)); 3.24 ($d$, $J = 8.7$, CH′–C(5)). $^{13}$C-NMR (CDCl$_3$): 140.52 (C(6)); 138.55; 138.36; 137.56; 136.35 (C(2)); 128.81–127.89 (several signals); 118.93 (C(1)); 114.62 (C(7)); 82.03, 81.82 (C(3), C(4)); 78.52 (C(5)); 76.02, 74.50, 73.53 (3 PhCH$_2$); 70.67 (CH$_2$–C(6)). FAB-MS (NOBA) 445 (7, [M+1]$^+$), 229 (9), 181 (51), 147 (15), 91 (100). Anal. calc. for C$_{29}$H$_{32}$O$_4$ (444.56): C 78.35, H 7.26; found: C 78.23, H 7.41.
(1L)-(1,2,3)-1,2-Di-O-benzyl-3-C-[(benzyloxy)methyl]-cyclopent-4-ene-1,2,3-triol (424).

A soln. of 421 (109 mg, 0.245 mmol) in CH₂Cl₂ (15ml) was degassed by 3 cycles of freeze pump thaw, treated with Grubbs's catalyst 312 (30 mg, 0.037 mmol), refluxed for 4 days under N₂, and evaporated. Two FC's (cyclohexane/AcOEt 7:1) of the dark-green oily residue afforded 424 (64.7 mg, 63%) as a green oil. Rf (cyclohexane/AcOEt 3:1) 0.70. [α]D²⁵ = –46.4 (c = 0.44, CHCl₃). IR (CHCl₃): 3528 m, 3066 m, 3008 s, 2663 m, 1711 s, 1496 m, 1454 m, 1362 s, 1093 s, 1028 m. ¹H-NMR (CDCl₃): 7.37–7.26 (m, 15 arom. H); 6.02 (dd, J = 6.2, 1.6, H–C(5)); 5.90 (dd, J = 6.2, 1.1, H–C(4)); 4.73 (d, J = 11.5, PhCH); 4.66 (d, J = 11.5, PhCH); 4.66–4.64 (m, H–C(1)); 4.57 (s, PhCH₂); 4.55 (d, J = 11.8, PhCH); 4.51 (d, J = 11.8, PhCH); 3.97 (d, J = 3.7, H–C(2)); 3.51 (d, J = 9.7, CH–C(3)); 3.47 (d, J = 9.7, CH–C(3)); 3.22 (s, OH). ¹³C-NMR (CDCl₃): 138.92; 138.39; 137.77; 136.19, 133.79 (C(4), C(5)); 128.67–127.91 (several signals); 87.93, 84.27 (C(1), C(2)); 74.76, 73.74, 73.21 (3 PhCH₂); 71.79 (CH₂–C(3)) (C(3) signal hidden by noise). FAB-MS (NOBA) 400 (100, [M – OH]+), 309 (15), 281 (5), 201 (10), 181 (16), 154 (19), 136 (14), 107 (7), 91 (100), 69 (8).
Part 2.

\[(4S,5S,6R,7R)-4,5,6-Tris(benzoxly)-7-(benzyloxymethyl)-1,2-diazaspiro[2.5]octane (602)\].

At \(-20^\circ\), a suspension of 52 [225] (115 mg, 0.21 mmol) in MeOH (5 ml) was saturated with \(\text{NH}_3\), treated dropwise with a soln. of hydroxylamine-\(O\)-sulfonic acid (24.3 mg, 0.21 mmol) in MeOH (2.5 ml), stirred for 3 h, allowed to warm to r.t., and stirred overnight. Filtration, evaporation, and FC (17 g of silica gel; hexane/AcOEt 3:1) gave 602 (41 mg, 35%). Colourless, amorphous. \(R_f\) (hexane/AcOEt 1:1) 0.49. M.p. 76–78°. \([\alpha]_{25}^{25}D = 29.4\) (\(c = 0.98, \text{CHCl}_3\)). FT-IR (1%, CHCl\(_3\)): 3259 \(w\), 3089 \(w\), 3066 \(w\), 3008 \(s\), 2908 \(m\), 2862 \(m\), 1951 \(w\), 1876 \(w\), 1811 \(w\), 1730 \(w\), 1603 \(w\), 1497 \(m\), 1454 \(s\), 1404 \(w\), 1358 \(s\), 1274 \(w\), 1175 \(m\), 1149 \(s\), 1097 \(s\), 1028 \(s\), 1016 \(w\), 913 \(w\), 872 \(w\), 855 \(w\). \(^1\)H-NMR (200 MHz, CDCl\(_3\), 4:1 mixture of diastereoisomers) 7.35–7.22 (\(m\), 20 arom. H); 5.00 (\(d\), \(J = 10.0, \text{PhCH}\)); 4.91 (\(d\), \(J = 10.8, \text{PhCH}\)); 4.89 (\(d\), \(J = 11.6, \text{PhCH}\)); 4.82 (\(d\), \(J = 10.8, \text{PhCH}\)); 4.70 (\(d\), \(J = 10.4, \text{PhCH}\)); 4.59 (\(d\), \(J = 11.2, \text{PhCH}\)); 4.47 (s, \(\text{PhCH}_2\)); 3.90 (\(d\), \(J = 9.6, \text{H–C(4)}\)); 3.77 (\(dd\), \(J = 9.1, 3.7, \text{CH–C(7)}\)); 3.69 (\(t\), \(J = 10.0, \text{H–C(6)}\)); 3.56 (\(t\), \(J = 9.6, \text{H–C(5)}\)); 3.48 (\(dd\), \(J = 9.1, 2.5, \text{CH’–C(7)}\)); 2.64 (br. \(d\), \(J = 7.9, 0.8 \text{H, exchange with D}_2\text{O, NH}\)); 2.26–2.06 (0.2 \(H\), exchange with D\(_2\)O, NH); 2.26 (br. \(t\), \(J = 12.9, \text{H}_{\text{ax}}–\text{C(8)}\)); 2.19–2.06 (\(m\), \(\text{H–C(7)}\)); 1.57 (\(d\), \(J = 7.9, 0.8 \text{H, exchange with D}_2\)O, NH); 1.44 (\(d\), \(J = 8, 0.2 \text{H, exchange with D}_2\)O, NH); 1.35 (\(dd\), \(J = 12.9, 2.9, \text{H}_{\text{eq}}–\text{C(8)}\)). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\), one set of signals): 139.00, 138.88, 138.62, 138.50 (4s); 128.62–127.79 (several \(d\)); 88.20, 80.33, 79.49 (3d, C(4), C(5), C(6)); 76.38, 76.01, 75.51, 73.21 (4t, 4 \(\text{PhCH}_2\)); 69.42 (\(t\), \(\text{CH}_2–\text{C(7)}\)); 57.06 (s, C(3)); 39.96 (\(d\), C(7)); 34.80 (\(t\), C(8)). FAB-MS (NOBA): 551 (100, \([M + 1]^+\)), 534 (14, \([M – \text{NH}_2]^+\)), 531 (10), 461 (18), 459 (22, \([M – \text{Bn}]^+\)), 443 (96, \([M – \text{BnO}]^+\)), 428 (27). Anal. calc. for C\(_{35}\)H\(_{38}\)N\(_2\)O\(_4\) (550.70): C 76.34, H 6.95, N 5.09; found: C 76.04, H 6.66, N 4.98.
At 0°, a soln. of 602 (61 mg, 0.11 mmol) in MeOH (10 ml) and CH₂Cl₂ (10 ml) was treated with Et₃N (0.1 ml, 0.72 mmol) and dropwise with a soln. of iodine (ca. 30 mg) in MeOH (1 ml), until the brown colour persisted. Evaporation and FC (10 g of silica gel, hexane/AcOEt 10:1) gave 603 (52 mg, 85%). Colourless, amorphous. Rf (hexane/AcOEt 3:1) 0.73. M.p. 59–61°. [α]²⁵D = 49.7 (c = 1.03, CHCl₃). UV (CH₂Cl₂): 232 (846), 252 (846), 258 (906), 340 (92). FT-IR (1%, CHCl₃): 3089 w, 3066 w, 3007 m, 2907 m, 2864 m, 2791 w, 1950 w, 1869 w, 1810 w, 1750 w, 1590 m, 1558 w, 1497 m, 1454 s, 1400 w, 1357 m, 1329 w, 1309 w, 1150 m, 1131 s, 1096 s, 1043 s, 1028 s, 1005 m, 912 w, 868 w. $^1$H-NMR (300 MHz, CDCl₃): 7.37–7.19 (m, 20 arom. H); 4.93 (d, J = 10.9, PhCH); 4.88 (d, J = 10.9, PhCH); 4.82 (d, J = 10.9, PhCH); 4.57 (d, J = 10.9, PhCH); 4.42 (s, PhCH₂); 4.26 (d, J = 11.2, PhCH); 4.21 (d, J = 11.2, PhCH); 3.82 (t, J = 9.2, H–C(5)); 3.70 (d, J = 9.2, H–C(4)); 3.65–3.57 (hidden by other signals, H–C(6)); 3.63 (dd, J = 9.0, 4.4, CH–C(7)); 3.42 (dd, J = 9.0, 3.4, CH–C(7)); 2.13–2.05 (m, H–C(7)); 2.05 (br. t, J = 12.8, Hax–C(8)); 0.67 (br. d, J = 10.6, Heq–C(8)). $^{13}$C-NMR (75 MHz, CDCl₃): 138.94, 138.79, 138.49, 137.39 (4 s); 128.67–127.75 (several d); 86.39, 80.55, 78.10 (3d, C(4), C(5), C(6)); 75.86, 75.57, 73.23, 73.19 (4t, 4 PhCH₂); 69.46 (t, CH₂–C(7)); 39.66 (d, C(7)); 30.21 (t, C(8)); 28.82 (s, C(3)). FAB-MS (NOBA): 549 (60, [M + 1]⁺), 457 (15, [M – Bn]⁺), 441 (18, [M – BnO]⁺), 413 (22, [M – BnO – N₂]⁺), 307 (33). Anal. calc. for C₃₅H₃₆N₂O₄ (548.68): C 76.62, H 6.61, N 5.11; found: C 76.75, H 6.73, N 4.88.
(2R,3S,4R,5R)-2,3,4-Trihydroxy-5-(hydroxymethyl)-cyclohexanone (51).

A suspension of 549 (2.0 g, 5.96 mmol) in MeCN (30 ml) and H2O (6 ml) was treated with NBS (1.6 g, 8.98 mmol), stirred for 15 h, and evaporated. FC (90 g of silica gel, AcOEt/iPrOH/H2O 8:2:1) gave 51 (520 mg, 50%) as a brown amorphous solid. A pure sample (14 mg) was obtained by reversed phase C8 HPLC (H2O) and lyophilisation. Rf (nPrOH/AcOH/H2O 4:1:1) 0.53. 1H-NMR (200 MHz, D2O): 4.25 (d, J = 10, H–C(2)); 3.84–3.60 (m, H–C4), CH–C(5), CH′–C(5)); 3.50–3.30 (m, H–C(3)); 2.63–2.41 (m, 2 H–C(6)); 2.00–1.44 (m, H–C(5)). 13C-NMR (50 MHz, D2O): 212.9 (s, C(1)); 81.1, 80.8, 74.4 (3d, C(2), C(3), C(4)), 64.3 (t, CH2–C(5)); 43.6 (d, C(5)); 41.7 (t, C(6)). CI-MS (NH3): 194 (77, [M + NH4]+), 176 (7, [M]+), 141 (26, [M +1 – 2 H2O]+), 123 (100, [M + 1 – 3 H2O]+), 110 (75), 98 (16), 86 (17), 73 (22), 55 (19).

(tertButyl)dimethylsilylation of 51.

A solution of 51 (45 mg, 0.26 mmol) in DMF (0.6 ml) was treated with imidazole (174 mg, 2.56 mmol) and TBSCl (185 mg, 1.23 mmol), stirred at 35° for 10 h, and poured into ice-water. The mixture was extracted with AcOEt (3 x 30 ml). The combined organic phases were washed with brine (2 x 30 ml) and dried (Na2SO4). Evaporation and FC (6 g of silica gel, hexane/AcOEt 6:1) gave 604 (9.7 mg, 9%). Colourless amorphous solid. Rf (hexane/AcOEt 3:1) 0.32. 1H-NMR (200 MHz, CDCl3): 4.10 (dd, J = 10.0, 0.8, H–C(2)); 3.95 (dd, J = 10.0, 4.2, CH–C(5)); 3.88 (br, t, J = 10.0, addn. of D2O -> t, J = 10.0, H–C(4)); 3.65 (dd, J = 10.0, 4.6, CH′–C(5)); 3.54 (td, J = 10.0, 2.1, addn. of D2O -> t, J = 10.0, H–C(3)); 3.19 (d, J = 1.2, exchanged with D2O, HO–C(4)); 2.73 (d, J = 2.1, exchanged with D2O, HO–C(3)); 2.49–2.31 (m, CH2(6)); 1.94–1.78 (m, H–C(5)); 0.96, 0.92 (2s, 2 Me3C); 0.19, 0.10, 0.09, 0.07 (4s, 2 Me2Si). 13H-NMR (50 MHz, CDCl3): 203.05 (C(1)); 77.38, 76.53, 69.61 (C(2), C(3), C(4)); 60.88 (CH2–C(5)); 38.25, 36.47 (C(5), C(6)); 23.39 (2 Me3CSi); 16.06, 15.77 (2 Me3CSi); –6.89, –7.9 (2 Me2Si).
Benzylidenaion of 51.
A soln. of 51 (80 mg, 0.454 mmol) in DMF (5 ml) was treated with benzaldehyde dimethyl acetal (86 µl, 0.59 mmol) and TsOH-H2O (7 mg, 37 µmol), stirred at r.t. for 5 d, treated with ice-water (10 ml), and extracted with AcOEt (3 x 20 ml). The combined organic phases were washed with brine (50 ml), dried (Na2SO4), and evaporated. FC (6 g of silica gel, hexane/AcOEt 1:2) of the orange-brown oil (63 mg) gave 605 (10 mg, 8%) as a colourless oil. Rf (AcOEt(iPrOH/H2O 8:2:1) 0.58. 1H-NMR (300 MHz, CDCl3/D2O): 7.55–7.47 (m, 2 arom. H); 7.43–7.33 (m, 3 arom. H); 5.62 (s, PhC–H); 4.25 (dd, J = 11.2, 4.3, C–CHeq–C(5)); 4.17 (dd, J = 9.3, 1.2, H–C(2)); 3.88 (t, J = 9.4, H–C(4)); 3.76 (t, J = 9.5, H–C(3)); 3.71 (t, J = 10.7, CHax–C(5)); 2.47 (dd, J = 13.7, 3.7, H–C(6)); 2.19 (td, J = 13.7, 1.3, Hax–C(6)); 2.12–1.94 (m, H–C(5)).

Isopropylidenaion of 51 with (propen-2-yl)trimethylsilyl ether (IPOTMS) (cf [881] [880]).
A soln. of 51 (56.6 mg, 0.32 mmol) in MeCN (2 ml) was treated with IPOTMS (295 µl, 1.60 mmol) and a sat. soln. of gaseous HCl in MeCN (0.1 ml), stirred at r.t. for 15 h, and poured onto ice-water. The mixture was extracted with AcOEt (3 x 25 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (6 g of silica gel, hexane/AcOEt 100:3) of the yellow oil (117 mg) gave 606 (49.3 mg, 33%) as a colourless oil. Colourless oil. Rf (hexane/AcOEt 9:1) 0.63. 1H-NMR (300 MHz, CDCl3): 4.03 (dd, J = 9.5, 1.1, H–C(2)); 3.76 (t, J = 9.8, H–C(4)); 3.76 (dd, J = 10.0, 3.1, CH–C(5)); 3.47 (dd, J = 10.0, 2.5, CH–C(5)); 3.46 (t, J = 9.0, H–C(3)); 2.40 (td, J = 14.0, 1.1, Hax–C(6)); 2.30 (dd, J = 14.0, 4.7, Heq–C(6)); 1.70–1.56 (m, H–C(5)); 0.19, 0.15, 0.14, 0.09 (4s, 4 Me3Si). 13C-NMR (75 MHz, CDCl3): 207.24 (s, C=O); 80.20, 79.76, 73.50 (3d, C(2), C(3), C(4)); 61.76 (t, CH2–C(5)); 41.57 (t, C(6)); 39.45 (d, C(5)). FAB-MS (NOBA): 465 (14, [M + 1]+), 464 (31, M+), 447 (42, [M – OH]+), 359 (68, [M – TMS–O2]+), 331 (32), 305 (13).
2,3:4,6:2',3':4',6'-Tetra-O-isopropylidenevalidoxylamine A (607).

At 0° a solution of 549 (2.0 g, 5.97 mmol) in DMF (40 ml) was treated with pTsOH (1.36 g, 7.15 mmol) and dropwise with 2-methoxypropene (10 ml, 106 mmol), allowed to slowly warm to r.t., stirred for 5 d, treated with K$_2$CO$_3$ (2.5 g), and filtered. Evaporation and FC (100 g of silica gel; cyclohexane/AcOEt 3:1) gave 607 (1.76 g, 59%) as a yellow oil. Crystallisation from AcOEt gave pure 607 (1.65 g, 55%). Colourless crystals. R$_f$ (cyclohexane/AcOEt 3:1) 0.17. M.p. > 200°. [α]$^2_{D}$ = 100.2 (c = 1.78, CHCl$_3$). FT-IR (1.8%, CHCl$_3$): 3494 w, 3340 w, 2992 s, 2936 m, 2911 m, 2862 m, 1731 w, 1455 m, 1383 s, 1374 s, 1342 w, 1327 w, 1269m, 1171s, 1095s, 1039s, 1012m, 990w, 981w, 966w, 908w, 867m, 851s, 835m. $^1$H-NMR (300 MHz, CDCl$_3$): 5.54 (br. d, J = 4.4 H–C(6´)); 4.48–4.42 (m, 2 H); 4.16 (br. d, J = 14.3, 1 H); 3.99 (t, J = 9.0, 1 H); 3.91 (dd, J = 10.0, 8.1, 1 H); 3.76–3.45 (m, 7 H); 2.33–2.15 (m, H–C(5)); 1.69 (td J = 14.0, 3.1, H–C(6)); 1.55, 1.49, 1.49, 1.46, 1.44, 1.43, 1.43, 1.41 (8 s, 8 Me); 1.05 (dt, J = 14.0, 3.1, H´–C(6)); NH signal hidden. $^{13}$C-NMR (75 MHz, CDCl$_3$): 133.04 (d, C(6´)); 122.00 (s, C(5´)); 109.57, 110.61 (2s, CMe$_2$ in dioxolane rings); 99.17, 99.00 (2s, CMe$_2$ in dioxane rings); 80.63 (d); 77.69 (d); 75.20 (d); 74.47 (d); 71.69 (d); 64.42, 62.97 (2t, CH$_2$-O); 54.62, 54.31 (2d, CH–N); 33.67 (d, C(5)); 29.80 (q); 29.48 (t, C(6)); 28.19 (q); 27.23 (q); 27.04 (q); 26.89 (q); 20.02 (q); 19.30 (q); 1q hidden. FAB-MS (NOBA): 496 (100, [M + 1]$^+$), 480 (39), 438 (36), 422 (11), 380 (13), 337 (7). Anal. calc. for C$_{26}$H$_{41}$NO$_8$ (496.61): C 63.01, H 8.34, N 2.83; found: C 63.05, H 8.31, N 2.87.

2,3:4,6-Di-O-isopropylenegabosine 1 and 2,3:4,6-Di-O-isopropylidenevalidone (609).

A solution of 607 (1.72 g, 3.47 mmol) in MeCN (50 ml) and H$_2$O (12 ml) was treated with NBS (0.93 g, 5.21 mmol), stirred for 2 h at r.t., poured on saturated aq. NaHCO$_3$ solution/ ice (100 ml), and extracted with AcOEt (4 x 100 ml). The combined organic phases were washed with brine (100 ml), dried (Na$_2$SO$_4$), treated with Et$_3$N (1 ml), and evaporated. FC (80 g of silica gel, cyclohexane/AcOEt/Et$_3$N 4:1:0.01) gave 609 (565 mg, 63%). According to the same procedure, 607 (708 mg, 1.43 mmol) was transformed into 608 (86 mg, 23%) and 609 (213 mg, 58%).
Data of 608:
Brown, amorphous. \( R_f \) (cyclohexane/AcOEt 3:1) 0.17. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): 5.80 \((dt, J = 1.9, 1.6, H–C(6))\); 4.78 \((ddt, J = 8.4, 1.9, 1.2, H–C(4))\); 4.56 \((dd, J = 16.2, 1.6, 1.2, CH–C(5))\); 4.43 \((ddd, J = 16.2, 1.9, 1.6, CH'–C(5))\); 4.15 \((d, J = 10.6, H–C(2))\); 3.96 \((dd, J = 8.4, 10.6, H–C(3))\); 1.56 \((s, Me)\), 1.48 \((s, 2 Me)\), 1.43 \((s, Me)\).

Data of 609:
Colourless foam. \( R_f \) (cyclohexane/AcOEt 3:1) 0.13. \([\alpha]_{D}^{25} = 39.4 \( (c = 1.6, CHCl_3)\). FT-IR (1.6%, CHCl\(_3\)): 2996s, 2941m, 2868m, 1735s (C=O), 1457m, 1411w, 1385s, 1376s, 1161m, 1104s, 1091s, 1050m, 1018m, 999m, 966w, 948w, 932w, 886m, 856m. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): 4.61–4.53 \((m, H–C(2), H–C(3))\); 3.89 \((dd, J = 11.8, 5.6, CH_{eq}–C(5))\); 3.70 \((dd, J = 11.8, 6.2, H–C(4))\); 3.62 \((t, J = 11.2, CH_{ax}–C(5))\); 2.50 \((dd, J = 17.7, 6.9, Heq–C(6))\); 2.33–2.15 \((m, H–C(5))\); 1.99 \((dd, J = 17.7, 11.2, H_{ax}–C(6))\); 1.52, 1.50, 1.47, 1.39 \((4 s, 2 Me_2C)\). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)): 220.88 \((s, C=O)\); 110.88 \((s, Me_2C\) of dioxolane ring); 98.76 \((s, Me_2C\) of dioxane ring); 79.39, 78.09 \((2d, C(2), C(3))\); 73.36 \((d, C(4))\); 63.58 \((t, CH_2–C(5))\); 36.38 \((t, C(6))\); 30.09 \((d, C(5))\); 29.11, 26.63, 24.73, 18.53 \((4 q, 2 Me_2C)\). FAB-MS (NOBA): 257 \((24, [M + 1]^+)\), 241 \((100)\), 199 \((20)\). Anal. calc. for C\(_{13}\)H\(_{20}\)O\(_5\) (256.30): C 60.92, H 7.87; found: C 60.77, H 7.75.

Reaction of 609 with NH\(_3\)/NH\(_2\)OSO\(_3\)H.
A soln. of 609 \((100 \text{ mg}, 0.39 \text{ mmol})\) in MeOH \((5 \text{ ml})\) was saturated at \(–20^\circ\) with gaseous NH\(_3\), treated dropwise with a soln. of hydroxylamin-O-sulfonic acid \((44 \text{ mg}, 0.39 \text{ mmol})\) in MeOH \((5 \text{ ml})\), stirred for 3 h at \(–20^\circ\), and allowed to warm to r.t. overnight. The mixture was filtered and evaporated. TLC indicated a new component with \( R_f = 0 \) (cyclohexane/AcOEt 1:1), which stained yellow with vanillin. This component was purified by FC \((15 \text{ g of silica gel, cyclohexane/AcOEt 3:1 \rightarrow AcOEt})\). It oxidised I\(–\) in acidic soln. According to its \(^1\)H-NMR spectrum it was not a single compound, but a mixture. Presumably, the isopropylidene acetals had been cleaved.
2,3:4,6-Di-O-isopropylidenevalionoxime (610).
The ketone 609 (259 mg, 1.01 mmol) was treated with a ca. 0.2M solution of NH₂OH in MeOH (40 ml, 8 mmol), stirred for 3 d, and evaporated. FC (25 g of silica gel, cyclohexane/AcOEt/Et₃N 6:2:0.01) gave 610 (133 mg, 48%) and a mixture of 610 and 609 (62 mg). Treatment of the latter with NH₂OH for 10 d gave more 610 (47 mg, 18%). Colourless foam. Rf (cyclohexane/AcOEt 1:1) 0.54. [α]D²⁵ = 13.0 (c = 1.49, CHCl₃). FT-IR (1.5%, CHCl₃): 3315 m (br.), 2995 s, 2939 m, 2906 m, 2868 m, 1710 w, 1652 w, 1458 m, 1435 w, 1384 s, 1374 s, 1327 w, 1302 w, 1261 s, 1162 s, 1141 w, 1097 s, 1078 m, 1064 s, 1055 s, 1020 m, 964 m, 940 m, 928 m, 878 m, 867 m, 853 m. ¹H-NMR (300 MHz, CDCl₃): 4.68 (d, J = 6.2, H–C(2)); 4.15 (dd, J = 7.8, 6.2, H–C(3)); 3.86 (dd, J = 11.5, 5.0, CHeq–C(5)); 3.76 (dd, J = 11.5, 8.1, H–C(4)); 3.66 (t, J = 11.2, CHax–C(5)); 2.94 (dd, J = 16.5, 4.4, Heq–C(6)); 1.85 (ddd, J = 16.2, 13.4, 0.9, Haax–C(6)); 1.71–1.58 (m, H–C(5)); 1.55, 1.50, 1.45, 1.40 (4 s, 2 Me₂C); OH hidden. ¹³C-NMR (75 MHz, CDCl₃): 154.0 (s, C=N); 110.61 (s, Me₂C of the dioxolane ring); 99.35 (s, Me₂C of the diolane ring); 79.07 (d, C(3)); 75.02, 74.42 (2d, C(2), C(4)); 64.17 (t, CH₂–C(5)); 32.44 (d, C(5)); 29.64 (q); 28.07 (q); 26.03 (q); 21.81 (t, C(6)); 18.85 (q). ESI-MS (MeOH): 565 (81, [2 M + Na]+), 543 (6, [2 M + 1]+), 392 (18), 326 (100, [M + Na + MeOH]⁺), 294 (65, [M + Na]⁺), 272 (12, [M + 1]⁺). Anal. calc. for C₁₃H₂₁NO₅ (271.31): C 57.55, H 7.80, N 5.16; found: C 57.59, H 7.84, N 5.05.

2,3:4,6-Di-O-isopropylidenevalionoxime-mesylate (611).
A soln. of 610 (59 mg, 0.217 mmol) in CH₂Cl₂ (5 ml) was cooled to 0°, treated with Et₃N (80 µl, 0.543 mmol) and MsCl (22 µl, 0.282 mmol), and stirred for 45 min. The mixture was diluted with CH₂Cl₂ (20 ml) and washed with 1M aq. NaHCO₃ soln. (12 ml) and H₂O (10 ml). Drying (Na₂SO₄) and evaporation gave crude 611 (144 mg, quant.) as a yellow oil, which rapidly became brown and therefore was immediately used in the subsequent step. Rf (cyclohexane/AcOEt 1:1) 0.47.
Reaction of 611 with NH₃.

A soln. of crude 611 (144 mg, ca. 0.21 mmol) in MeOH (10 ml) was cooled to 0°, treated dropwise with a soln. of NH₃ in MeOH (10 ml, saturated at −20°), stirred for 20 h while warming to r.t., and evaporated. FC (25 g of silica gel, cyclohexane/AcOEt/Et₃N 5:1:0.1) of the residue gave a crude product (10 mg), which oxidised I⁻ in acidic solution but was a complex mixture according to its ¹H-NMR spectrum. Rₕ (cyclohexane/AcOEt 1:1) 0.16.

(2R,3S,4R,5R)-2,3,4-Tris(trimethylsilyloxy)-5-(trimethylsilyloxymethyl)cyclohexanone (606).

At 25°, a soln. of 51 (630 mg, 3.59 mmol) was treated with hexamethyldisilazane (HMDS, 10 ml, 48.0 mmol) and Me₃SiCl (5 ml, 39.5 mmol), stirred for 6.5 h, evaporated, and dried in h.v. The residue was digested with CH₂Cl₂ (3 x 50 ml) and filtered. The organic phase was washed with ice-cold H₂O (75 ml), dried (MgSO₄), and evaporated. FC (30 g of silica gel, hexane/AcOEt/Et₃N 400:10:0.4) of the residue (1.28 g, brown oil) gave 606 (448 mg, 27%). Colourless oil. Rₕ (hexane/AcOEt 9:1) 0.63. ¹H-NMR (300 MHz, CDCl₃): 4.03 (dd, J = 9.5, 1.1, H–C(2)); 3.76 (t, J = 9.8, H–C(4)); 3.76 (dd, J = 10.0, 3.1, CH–C(5)); 3.47 (dd, J = 10.0, 2.5, CH–C(5)); 3.46 (t, J = 9.0, H–C(3)); 2.40 (td, J = 14.0, 1.1, H₆ax–C(6)); 2.30 (dd, J = 14.0, 4.7, H₆eq–C(6)); 1.70–1.56 (m, H–C(5)); 0.19, 0.15, 0.14, 0.09 (4s, 4 Me₃Si). ¹³C-NMR (75 MHz, CDCl₃): 207.24 (s, C=O); 80.20, 79.76, 73.50 (3d, C(2), C(3), C(4)); 61.76 (t, CH₂–C(5)); 41.57 (t, C(6)); 39.45 (d, C(5)). FAB-MS (NOBA): 465 (14, [M + 1]⁺), 464 (31, M⁺), 447 (42, [M − OH]⁺), 359 (68, [M − TMS–O₂]⁺), 331 (32), 305 (13).

(4S,5S,6R,7R)-7-(Hydroxymethyl)-1,2-diazaspiro[2.5]octane-4,5,6-triol (45).

At −20°, a soln. of 606 (260 mg, 0.56 mmol) in MeOH (15 ml) was saturated with NH₃, treated dropwise with a soln. of hydroxylamine-O-sulfonic acid (63 mg, 0.56 mmol) in MeOH (5 ml), stirred for 3 h, allowed to warm to r.t., and stirred overnight. Filtration, evaporation, and FC (60 g of silica gel, AcOEt/iPrOH/H₂O 4:2:1) gave a colourless soln. of
After removal of most of the AcOEt in vacuo below 30°, this soln. was applied to an ion exchange column (5 ml of Dowex 50-WX-8, H⁺-form, washed with MeOH (50 ml) and H₂O to pH 7). After washing with H₂O (200 ml), elution with 2% aq. NH₃ and lyophilisation gave colourless, amorphous 45 (53 mg, 50%). Rᵥ (AcOEt/iPrOH/H₂O 4:2:1) 0.13. Rᵥ (acetone/H₂O 2:1) 0.16. Rᵥ (acetone/H₂O 2:1) 0.72. Rᵥ (iPrOH/H₂O 4:1) 0.43. M.p. 68–76°. [α]²⁵D = 22.2 (c = 1.50, H₂O). pK(HA) = 2.6. ¹H-NMR (300 MHz, (D₆)-DMSO, 3:2 mixture of diastereoisomers): 4.87–4.68 (m, 1.4 OH); 4.61–4.52 (m, 1.2 OH); 4.41–4.27 (m, 1.4 OH); 3.61–2.85 (m, H–C(4), H–C(5), H–C(6), CH₂–C(7)); 2.30 (br. d, J = 8.1, 0.6 H), 2.24 (br. d, J = 8.1, 0.4 H), 2.13 (br. d, J = 8.1, 0.6 H), 2.07 (br. d, J = 8.1, 0.4 H) (2 NH); 1.80 (t, J = 13.4, 0.4 Hax–C(8)); 1.60 (t, J = 13.0, 0.6 Heq–C(8)); 1.57–1.37 (m, H–C(7)); 1.27–1.15 (m, Heq–C(8)). ¹H-NMR (300 MHz, (D₆)DMSO/CF₃COOH): 3.70 (d, J = 9.0, H–C(4)); 3.56 (dd, J = 10.6, 3.1, CH–C(7)); 3.38 (dd, J = 10.6, 6.2, CH–C(7)); 3.16 (t, J = 9.0, H–C(6)); 3.06 (t, J = 9.0, H–C(5)); 1.95 (br. t, J = 14.9, Hax–C(8)); 1.52–1.47 (m, H–C(7), Heq–C(8)). ¹H-NMR (500 MHz, CD₃OD, 4:3 mixture of diastereoisomers): 3.74–3.63 (m, 2.57 H); 3.48 (d, J = 9.1, 0.43 H–C(4)); 3.38–3.34 (m, 1.43 H); 3.19 (t, J = 9.3, 0.57 H); 2.04 (t, J = 13.6, 0.43 H–C(8)); 1.89 (t, J = 13.3, 0.57 H–C(8)); 1.80–1.71 (m, 0.57 H–C(5)); 1.71–1.63 (m, 0.43 H–C(5)); 1.37 (td, J = 14.5, 3.9, H–C(6)). ¹³C-NMR (75 MHz, D₂O, ca. 1:1 mixture of diastereoisomers): 80.37, 79.87 (2d); 75.50, 75.21 (2d); 72.19 (d); 64.70 (t, CH₂–C(7)); 60.02 (s, C(3)); 43.78, 43.50 (2d, C(7)); 34.91 (t, C(8)). ESI-MS: 445 (4, [2M + 1 + 2 MeOH]⁺). 419 (8, [2M + K]⁺), 403 (100, [2M + Na]⁺), 381 (12, [2M + 1]⁺), 360 (6), 338 (4), 245 (16, [M + Na + MeOH]⁺), 229 (10, [M + K]⁺), 213 (26, [M + Na]⁺), 191 (23, [M + 1]⁺). HR-FAB-MS (NOBA): 213.0858 (C₇H₁₄N₂NaO₄⁺, [M + Na]⁺; calc. 213.0851); 191.1026 (C₇H₁₅N₂O₄⁺, [M + H]⁺; calc. 191.1027).

(4S,5S,6R,7R)-7-(Hydroxymethyl)-1,2-diazaspiro[2.5]oct-1-ene-4,5,6-triol (613).

A soln. of I₂ (ca. 30 mg) in MeOH (1 ml) was added dropwise at 25° to a soln. of 45 (55 mg, 0.29 mmol) in MeOH (8 ml) and Et₃N (0.1 ml, 0.72 mmol) until the brown colour persisted. Evaporation and FC (20 g of silica gel, CH₂Cl₂/MeOH 9:1) gave a mixture of 613 and Et₃N (2.5:1, 60 mg). This mixture was applied to an ion exchange column (7 ml of Dowex-CCR-2, H⁺-form, washed with MeOH (100 ml) and H₂O to pH 7). Elution with H₂O and lyophilisation gave 613 (48.8 mg, 89%). Colourless syrup. Rᵥ (AcOEt/iPrOH/H₂O 4:2:1) 0.75. [α]²⁵D = 37.2 (c = 1.03, H₂O). UV (H₂O): 340 (68). ¹H-NMR (300 MHz, D₂O): 3.86...
(d, J = 9.3, H–C(4)); 3.77 (dd, J = 11.2, 3.1, CH–C(7)); 3.69–3.66 (m, CH´–C(7)); 3.54 (t, J = 9.3, H–C(5)); 3.48 (t, J = 9.3, H–C(6)); 2.00–1.85 (m, H–C(7), Hax–C(8)); 0.72 (dd, J = 13.1, 2.8, Heq–C(8)). 13C-NMR (75 MHz, D2O): 80.60, 75.38, 71.93 (3d, C(4), C(5), C(6)); 64.68 (t, CH2–C(7)); 43.46 (d, C(7)); 32.34 (s, C(3)); 31.76 (t, C(8)). HR-ESI-MS (MeOH): 211.069 (C7H12NaN2O4, [M + Na]+; calc. 211.0695).

(4S,5S,6R,7R)-4,5,6-Tris(acetyloxy)-7-(acetyloxymethyl)-1,2-diazaspiro[2.5]oct-1-ene (614).

At 0°, a soln. of a mixture of 613 and Et3N (84 mg, prepared as described above from 45 (79 mg, 0.42 mmol)) in pyridine (10 ml) was treated with Ac2O (1 ml), allowed to warm to r.t. overnight, and poured into ice-water (50 ml). The aq. phase was extracted with CH2Cl2 (4 x 50 ml). Drying (Na2SO4), evaporation, and FC (30 g of silica gel, hexane/AcOEt 3:1) gave 614 (124 mg, 84%). Colourless oil. Rf (hexane/AcOEt 3:1) 0.15. \([\alpha]_{D}^{25} = 47.4\) (c = 1.54, CHCl3). FT-IR (1.5%, CHCl3): 3038 w, 2954 w, 1751 s, 1594 w, 1443 m, 1377 m, 1248 s, 1131 w, 1064 m, 1033 m, 978 w, 932 w, 896 w, 846 w. UV (CH2Cl2): 229 (130), 334 (83). 1H-NMR (300 MHz, CDCl3): 5.33 (t, J = 9.7, H–C(5)); 5.15 (d, J = 9.7, H–C(4)); 5.13 (dd, J = 10.6, 9.3, H–C(6)); 4.07 (dd, J = 11.5, 5.6, CH–C(7)); 3.90 (dd, J = 11.5, 3.1, CH´–C(7)); 2.40–2.29 (m, H-C(7)); 2.05, 2.03, 1.98, 1.87 (4s, 4 AcO); 2.02 (dd, J = 15.1, 9.0, Hax–C(8)); 0.79 (dd, J = 15.1, 4.4, Heq–C(8)). 13C-NMR (300 MHz, CDCl3): 170.86, 170.11, 170.00, 169.03 (4s, 4 C=O); 73.69, 71.07, 68.26 (3d, C(4), C(5), C(6)); 62.66 (t, CH2–C(7)); 37.28 (d, C(7)); 29.67 (t, C(8)); 26.75 (s, C(3)); 20.68, 20.58, 20.55, 20.11 (4q, 4 Me). FAB-MS (NOBA): 379 (11, [M + Na]+), 357 (24, [M + 1]+), 297 (9, [M – AcO]+), 269 (100, [M – AcO – N2]+), 227 (21), 208 (11), 167 (93). Anal. calc. for C15H20N2O8 (356.33): C 50.56, H 5.66, N 7.86; found: C 50.80, H 5.58, N 7.64.
A soln. of 606 (466 mg, 1.0 mmol) in MeOH (30 ml) was treated at 25° with BnNH$_2$ (4.5 ml, 41.2 mmol), stirred for 1 h, cooled to 0°, treated dropwise with a soln. of hydroxylamine-O-sulfonic acid (116 mg, 1.00 mmol) in MeOH (5 ml), allowed to warm to r.t. and stirred overnight. Filtration, evaporation, and repeated FC (50 g of silica gel, AcOEt/MeOH 1:0 –> 4:1) gave a mixture of 615 and BnNH$_2$ (1:4, 487 mg), which was dissolved in H$_2$O, applied on an ion exchange column (15 g of Dowex-CCR-2, H$^+$-form, washed with MeOH (100 ml) and H$_2$O to pH = 7), and eluted with H$_2$O. Lyophilisation gave colourless, amorphous 615 (76 mg, 27%). $R_f$ (AcOEt/iPrOH/H$_2$O 4:2:1) 0.51. M.p. 52–58°. [$\alpha$]$^D_{25}$ = 59.7 (c = 1.53, H$_2$O). $^1$H-NMR (300 MHz, D$_2$O): 7.49–7.38 (m, 5 arom. H); 3.92 (d, $J$ = 14.0, irrad. at 2.04 -> NOE of 4%, PhCH); 3.81 (d, $J$ = 14.0, irradi. at 2.04 -> NOE of 6 %, PhCH); 3.75 (dd, $J$ = 11.5, 3.4, CH–C(7)); 3.64, (dd, $J$ = 11.5, 5.9, CH'–C(7)); 3.62 (d, $J$ = 9.3, H–C(4)); 3.43 (t, $J$ = 9.0, irradi. at 3.62 -> NOE of 9%, H–C(6)); 3.36 (t, $J$ = 9.0, H–C(5)); 2.04 (dd, $J$ = 14.6, 4.1, irradi. at 3.92 and 3.81 -> NOE of 6%, H$_2$–C(8)); 1.93 (br. t, $J$ = 14.0, irradi. at 3.62 -> NOE of 4%, H$_{ax}$–C(8)); 1.53–1.40 (m, irradi. at 3.81 and 3.75 -> NOE of 8%, H–C(7)). $^{13}$C-NMR (75 MHz, CD$_3$OD): 140.07 (s); 129.83 (d, 2 C); 129.65 (d, 2 C); 128.52 (d); 79.66, 74.45, 73.10 (3d, C(4), C(5), C(6)); 63.96 (t, CH$_2$–C(7)); 62.87 (s, C(3)); 57.19 (t, PhCH$_2$); 43.02 (d, C(7)); 27.44 (t, C(8)). HR-MALDI-MS (DHB): 303.1310 (C$_{14}$H$_{20}$NaN$_2$O$_4$+, [M + Na]$^+$; calc. 303.1316); calc. for ; found: 281.1492 (C$_{14}$H$_{21}$N$_2$O$_4$+, [M + H]$^+$; calc. 281.1496). Anal. calc. for C$_{14}$H$_{20}$N$_2$O$_4$·0.25 H$_2$O: C 59.04 , H 7.26, N 9.84; found: C 58.79, H 7.31, N 10.00.
(1S,2S,3R,4R)-1,2,3-Tris(benzyloxy)-4-(benzyloxymethyl)-6-methylene-cyclohexane (53).

A soln. of 52 (1.17 g, 2.18 mmol) in THF (20 ml) was treated dropwise at –20° with a soln. of Ph3P=CH2 (prepared at 0° from Ph3PMeBr (1.17 g, 3.27 mmol) and BuLi (2.05 ml, 1.6M in hexane) in THF (15 ml)), allowed to warm slowly for 3 h, treated with acetone (5 ml), and poured into sat. aq. NH4Cl soln. (150 ml). The aq. phase was extracted with CH2Cl2 (3 x 100 ml), and the extract dried (Na2SO4), and evaporated. FC (150 g of silica gel, cyclohexane/AcOEt 20:1) gave 53 (0.90 g, 71%). Colourless oil. Rf (cyclohexane/AcOEt 3:1) 0.75. [α]25D = 56.7 (c = 1.53, CHCl3). FT-IR (1.5%, CHCl3): 3089 w, 3066 m, 3008 m, 2908 m, 2862 m, 2789 w, 1951 w, 1876 w, 1811 w, 1657 w, 1544 s, 1496 m, 1454 s, 1400 w, 1356 m, 1309 w, 1149 m, 1100 s, 1028 s, 912 m, 865 w. 1H-NMR (300 MHz, CDCl3): 7.45–7.24 (20 arom. H); 5.22 (br. d, J = 0.9, CH=C(6)); 5.05 (d, J = 10.9, PhCH); 4.99 (d, J = 1.6, CH´=C(6)); 4.96 (d, J = 10.9, PhCH); 4.86 (d, J = 10.9, PhCH); 4.81 (d, J = 11.5, PhCH); 4.73 (d, J = 11.2, PhCH); 4.58 (d, J = 10.9, PhCH); 4.50 (s, PhCH2); 3.96 (br. d, J = 9.0, 1.9, CH–C(6)); 3.64 (dd, J = 9.0, 7.2, H–C(3)); 3.56 (dd, J = 9.0, 2.8, CH´–C(4)); 3.53 (t, J = 9.0, H–C(2)); 2.48 (dd, J = 13.4, 4.4, Heq–C(5)); 2.16 (br. t, J = 13.4, Hax–C(5)); 1.84–1.75 (m, H–C(4)). 13C-NMR (75 MHz, CDCl3): 144.38 (s, C(6)); 139.34 (s); 139.09 (s); 138.83 (s, 2 C); 128.65–127.72 (several d); 108.28 (t, CH2=C(6)); 88.37, 83.82, 81.23 (3d, C(1), C(2), C(3)); 75.81, 75.44, 73.68, 73.26 (4t, 4 PhCH2); 70.31 (t); 43.36 (d, C(4)); 33.95 (t, C(5)). FAB-MS (NOBA): 535 (3, [M + 1]+), 335 (9), 280 (15), 279 (17), 263 (13), 262 (10), 221 (13), 207 (22). Anal. calc. for C36H38O4 (534.69): C 80.87, H 7.16; found: C 80.60, H 7.17.

(3S,4S,5S,6R,7R)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-1-(toluene-4-sulfonyl)-1-azaspiro[2.5]octane (616) and 4-Methyl-N-[(1S,2R,3S,4R,5R)-2,3,4-tris(benzyloxy)-5-(benzyloxymethyl)-1-bromo-cyclohexylmethyl]-benzenesulfonamide (617).

A soln. of 53 (500 mg, 0.94 mmol) in MeCN (50 ml) was treated with chloramine T (2.13 g, 9.35 mmol) and PhMe3N·Br3 (123 mg, 0.33 mmol). The mixture was stirred for 4.5 h, diluted
with AcOEt (250 ml), washed with H2O (150 ml) and brine (150 ml), dried (Na2SO4), and evaporated. FC (80 g of silica gel, cyclohexane/AcOEt 9:1) of the residue (1.2 g) gave a mixture of 616 and 617 (283 mg), which was separated by prep. HPLC (silica gel, toluene/AcOEt 40:1), yielding 616 (120 mg, 18%) and 617 (15 mg, 2%).

Data of 616: Colourless oil. Rf (toluene/AcOEt 10:1) 0.47. Prep. HPLC tR (toluene/AcOEt 40:1) 22.8 min. [α]D25 = −9.2 (c = 1.56, CHCl3). FT-IR (1.5%, CHCl3): 3064 w, 3008 m, 2866 m, 1952 w, 1810 w, 1599 w, 1496 w, 1454 m, 1357 m, 1321 s, 1158 s, 1099 s, 995 s, 910 w, 859 m. 1H-NMR (300 MHz, CDCl3): 7.84 (d, J = 8.4, 2 arom. H); 7.40–7.08 (22 arom. H); 4.87 (d, J = 10.6, PhCH); 4.84 (d, J = 10.0, PhCH); 4.74 (d, J = 10.6, PhCH); 4.73 (d, J = 10.3, PhCH); 4.59 (d, J = 10.3, PhCH); 4.53 (d, J = 10.9, PhCH); 4.51 (d, J = 11.8, PhCH); 4.44 (d, J = 12.1, PhCH); 3.78 (d, J = 9.3, H–C(4)); 3.70 (dd, J = 9.0, 4.4, CH–C(7)); 3.63 (dd, J = 9.3, 10.6, irr. at 3.78 -> NOE of 3%, H–C(6)); 3.51 (dd, J = 9.0, 2.5, CH´–C(7)); 3.39 (t, J = 9.2, irr. at 2.63 -> NOE of 2%, H–C(5)); 2.63 (br. s, irr. at 3.39 -> NOE of 1.5%, H–C(2)); 2.59 (br. s, irr. at 2.63 -> NOE of 19%, H–C(2)); 2.45 (s, Me); 2.42–2.35 (m, irr. at 3.78 -> NOE of 1%, irr. at 2.59 -> NOE of 1%, 2 H–C(8)); 1.88–1.78 (m, irr. at 3.39 -> NOE of 9%, irr. at 2.59 -> NOE of 1%, H–C(7)). 13C-NMR (75 MHz, CDCl3): 144.25 (s); 138.83, 138.55, 138.16 (3 s, 1s hidden by noise or other signals); 129.82–127.58 (several d); 86.49, 80.96, 80.18 (3d, C(4), C(5), C(6)); 76.11, 75.93, 75.54, 73.35 (4 t, 4 PhCH2); 69.50 (t, CH2–C(7)); 51.73 (s, C(3)); 41.58 (d, C(7)); 35.82 (t, C(8)); 28.77 (t, C(2)); 21.65 (q, Me). MALDI-MS (DHB): 742 (67, [M + K] +), 726 (100, [M + Na] +). Anal. calc. for C43H45NO6S (703.90): C 73.37, H 6.44, N 1.99; found: C 73.36, H 6.44, N 1.96.

Data of 617: Colourless oil. Rf (toluene/AcOEt 10:1) 0.45. Prep. HPLC tR (toluene/AcOEt 40:1) 27.2 min. 1H-NMR (300 MHz, CDCl3): 7.56 (d, J = 8.4, 2 arom. H); 7.40–7.18 (22 arom. H); 4.94 (d, J = 10.9, PhCH); 4.92 (d, J = 11.8, PhCH); 4.89 (d, J = 11.2, PhCH); 4.87 (d, J = 10.9, PhCH); 4.73 (d, J = 12.1, PhCH); 4.55 (d, J = 10.9, PhCH); 4.44 (s, PhCH2); 4.03 (t, CH2–C(7)); 3.70 (dd, J = 9.0, 4.1, CH–C(5)); 3.62 (dd, J = 7.8, 6.2, irr. at 3.04 -> d, NH); 3.57 (dd, J = 10.9, 9.3, H–C(4)); 3.40 (dd, J= 9.0, 2.2, CH–C(5)); 3.18 (dd, J = 13.4, 5.6, CH–C(1)); 3.13 (d, J = 9.0, irr. at 4.03 -> s, H–C(2)); 3.04 (dd, J = 13.4, 8.1, CH´–C(1)); 2.34 (s, Me); 2.29–2.15 (m, H–C(5)); 2.09–1.91 (m, 2 H–C(6)). FAB-MS (NOBA): 808 (9, [M81Br] + Na)+, 806 (8, [M79Br] + Na)+, 786 (59, [M81Br] + H)+, 784 (100, [M81Br] – H)+, [M79Br] + H)+, 782 (51, [M79Br] – H)+, 695 (14), 694 (33), 693 (12), 692 (29), 614 (11), 613 (23), 461 (15), 460 (54).
**Iodoazidation and reduction of 53.**

A soln. of NaN₃ (61 mg, 94 µmol) in MeCN (1 ml) at 0° was treated with ICl (7.3 mg, 45 µmol), stirred for 10 min, treated with 53 (20 mg, 37 µmol), allowed to warm to r.t., stirred for 20 h, and poured into H₂O (20 ml). The aq. phase was extracted with AcOEt (2 × 20 ml), and the combined organic phases were washed with 5% Na₂S₂O₃ (20 ml) and H₂O (2 × 20 ml), and dried (Na₂SO₄). Evaporation and FC (20 g of silica gel, cyclohexane/AcOEt 20:1) gave a mixture (¹H-NMR) of iodo-azides (9 mg, 34%). Colourless oil. Rᶠ (toluene/AcOEt 10:1) 0.69. FT-IR (1%, CHCl₃): 2106 s (N₃). HR-MS (MALDI): Calc. for, found: 726.1802 ([M +Na]⁺; calc 726.1805).

A soln. of this mixture (9 mg, 13 µmol) in THF (2 ml) was treated at 0° with LiAlH₄ (2.5 g, 64 µmol), stirred for 70 min, and treated with MeOH (1 ml) and 1M NaOH (0.5 ml). Filtration through Celite, evaporation, and FC (20 g of silica gel, cyclohexane/AcOEt 20:1) gave 53 (3 mg, 43%).

\[ \text{(3S,4R,5S,6R,7R)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-1-oxaspiro[2.5]octane (618)} \]

\[ \text{and (3R,4R,5S,6R,7R)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-1-oxaspiro[2.5]octane (619).} \]

A soln. of 53 (20 mg, 37.4 mmol) in CH₂Cl₂ (1 ml) was treated with NaHCO₃ (7 mg, 84.2 mmol) and mCPBA (23 mg, 93.5 mmol), and stirred for 220 min. The mixture was diluted with CH₂Cl₂ (25 ml), washed with sat. aq. NaHCO₃ soln. (3 x 20 ml) and brine (20 ml), dried (Na₂SO₄), and evaporated. FC (20 g of silica gel, cyclohexane/AcOEt 9:1) gave 618 (5.2 mg, 25%) and 619 (61%)

Data of 618: Colourless oil. Rᶠ (cyclohexane/AcOEt 3:1) 0.66. [α]²⁵_D = 36.0 (c = 1.32, CHCl₃). FT-IR (1.3%, CHCl₃): 3065w, 3008m, 2922m, 2863m, 1953w, 1877w, 1811w, 1726w, 1603w, 1496w, 1454m, 1358m, 1099s, 841w. ¹H-NMR (300 MHz, CDC1₃): 7.37–7.19 (20 arom. H); 4.91 (d, J = 10.9, 2 PhCH); 4.78 (d, J = 10.9, PhCH); 4.77 (d, J = 10.9, PhCH); 4.62 (d, J = 10.9, PhCH); 4.54 (d, J = 10.9, PhCH); 4.45 (s, PhCH₂); 3.73 (br. d, J = 9.3 H–C(4)); 3.61–3.54 (m, H–C(5), H–C(6), CH–C(7), irrad. at 3.18 -> NOE of 1% for
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t at 3.54 of H–C(5)); 3.50 (dd, J = 8.7, 2.8, CH´–C(7)); 3.18 (dd, J = 5.3, 1.3, H–C(2)); 2.56 (d, J = 5.3, H–C(2)); 2.09 (td, J = 13.1, 2.0, Hax–C(8)); 1.93–1.81 (m, H–C(7)); 1.46 (dd, J = 13.4, 3.4, irrad. at 2.56 -> NOE of 7%, H eq–C(8)). 13C-NMR (75 MHz, CDCl3): 138.81 (br. s); 128.62–127.79 (several d); 86.83, 80.75, 80.26 (3d, C(4), C(5), C(6)); 75.93, 75.56, 75.51, 73.23 (4t, 4 PhCH2), 69.89 (t, CH2–C(7)); 59.77 (s, C(3)); 49.61 (t, C(2)); 40.06 (d, C(7)); 32.64 (t, C(8)). FAB-MS (NOBA): 1213 (21), 663 (35), 647 (19), 572 (16, [M + Na – 1] +), 550 (44, [M] +), 549 (20, [M – 1] +), 548 (84, [M – 2] +), 480 (20), 459 (13), 458 (30), 444 (15), 442 (36), 391 (12), 338 (14), 306 (19), 288 (15), 271 (13), 260 (11), 259 (40), 245 (16), 242 (12), 219 (47), 217 (12), 203 (13), 197 (12), 181 (100).

Data of 619: Colourless, amorphous. Rf (cyclohexane/AcOEt 3:1) 0.55. [α]25D = 16.5 (c = 1.47, CHCl3). FT-IR (1.5%, CHCl 3): identical to that of 618. 1H-NMR (300 MHz, CDCl 3): 7.36–7.22 (20 arom. H); 4.94 (d, J = 10.9, PhCH); 4.92 (d, J = 10.9, PhCH); 4.88 (d, J = 10.9, PhCH); 4.86 (d, J = 11.5, PhCH); 4.61 (d, J = 11.5, PhCH); 4.58 (d, J = 10.9, PhCH); 4.43 (s, PhCH2); 3.83 (t, J = 9.3, H–C(5)); 3.75 (dd, J = 9.0, 3.4, CH–C(7)); 3.69 (br. t, J = 9.6, H–C(6)); 3.66 (br. t, J = 9.6, H–C(6)); 3.41 (dd, J = 9.0, 1.9, CH´–C(7)); 2.98 (d, J = 5.0, H–C(2)); 2.59 (d, J = 5.0, H–C(2)); 2.09–2.00 (m, H–C(7), Hax–C(8)); 1.36 (br. d, J = 10.0, irrad. at 2.59 -> NOE of 4%, H eq–C(8)). 13C-NMR (75 MHz, CDCl3): 138.94, 138.70, 138.07 (3s, 1 s hidden by other signal or noise); 128.68–127.79 (several d); 86.75, 80.81, 78.55 (3d, C(4), C(5), C(6)); 75.93, 75.47, 75.38, 73.18 (4t, 4 PhCH2); 69.54 (t, CH2–C(7)); 58.76 (s, C(3)); 49.70 (t, C(2)); 39.80 (d, C(7)); 32.17 (t, C(8)). FAB-MS (NOBA): 662 (16), 646 (12), 572 (22, [M + Na – 1] +), 550 (32, [M] +), 549 (26, [M – 1] +), 548 (77, [M – 2] +), 459 (10), 458 (24), 442 (28), 335 (9), 288 (8), 271 (17), 260 (8), 259 (32), 245 (14), 241 (8), 219 (32), 217 (8), 203 (9), 197 (11), 181 (100). Anal. calc. for C36H38O5 (550.69): C 78.52, H 6.95; found: C 78.67, H 6.99.

(1S,2R,3S,4R,5R)-1-(Azidomethyl)-2,3,4-tris(benzyloxy)-5-(benzyloxymethyl)-cyclohexan-1-ol (620).

A soln. of 618 (174 mg, 0.32 mmol) in DMF (25 ml) was treated with NaN3 (255 mg, 3.93 mmol), stirred at 100° for 20 h, cooled, diluted with AcOEt (200 ml), washed with H2O (100
ml) and brine (100 ml), dried (Na$_2$SO$_4$), and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 9:1) gave colourless, amorphous **620** (170 mg, 91%). $R_f$ (cyclohexane/AcOEt 3:1) 0.52. M.p. 79–80°. [α]$^D_{25}$ = 16.2 ($c$ = 1.50, CHCl$_3$). FT-IR (1.5%, CHCl$_3$): 3555 w, 3066 w, 3008 m, 1954 w, 1812 w, 1599, 1496 w, 1453 m, 1359 m, 1282 m, 1065 s, 912 w, 871. H-NMR (300 MHz, CDCl$_3$): 7.61–7.20 (20 arom. H); 4.98 ($d$, $J$ = 10.9, PhCH); 4.95 ($d$, $J$ = 11.2, PhCH); 4.85 ($d$, $J$ = 11.1, 2 PhCH); 4.62 ($d$, $J$ = 11.2, PhCH); 4.57 ($d$, $J$ = 10.9, PhCH); 4.48 ($d$, $J$ = 12.1, PhCH); 4.44 ($d$, $J$ = 12.1, PhCH); 3.87 ($t$, $J$ = 9.3, H–C(5)); 3.76 ($dd$, $J$ = 9.0, 4.1, CH–C(5)); 3.54 ($dd$, $J$ = 10.9, 9.3, H–C(4)); 3.46 ($d$, $J$ = 9.3, H–C(2)); 3.43 ($dd$, $J$ = 9.0, 2.5, CH´–C(5)); 3.29 ($d$, $J$ = 11.8, CHN3); 3.22 ($d$, $J$ = 11.8, CH´–C(5)); 2.41 ($d$, $J$ = 2.2, OH); 2.21–2.09 (m, H–C(5)); 1.80 ($dd$, $J$ = 14.3, 4.1, H$_{eq}$–C(6)); 1.67 ($td$, $J$ = 14.3, 2.2, H$ax$–C(6)). **13C-NMR** (75 MHz, CDCl$_3$): 138.76, 138.60 (2 br. s); 128.88–127.86 (several d); 85.67, 81.54, 81.01 (3d, C(2), C(3), C(4)); 75.78 (2t, 2 PhC$_2$H); 75.31 (t, 3PhC$_2$H); 74.67 (s, C(1)); 73.27 (t, PhCH$_2$); 69.62 ($t$, C$_2$H$_2$–C(5)); 57.89 ($t$, C$_2$H$_2$N$_3$); 37.39 (d, C(5)); 33.02 (t, C(6)). MALDI-MS (DHB): 616 (47, [M + Na]$^+$), 590 (34), 588 (45, [M + Na – N$_2$]$^+$), 573 (19), 566 (20, [M + 1 – N$_2$]$^+$), 559 (100), 480 (20, [M + Na – N$_2$ – BnOH]$^+$), 460 (19), 458 (60, [M + 1 – N$_2$ – BnOH]$^+$). Anal. calc. for C$_{36}$H$_{39}$N$_3$O$_5$ (593.72): C 72.83, H 6.62, N 7.08; found: C 72.65, H 6.62, N 6.91.

Similarly as described above for **620**, **623** (186 mg, 88%) was obtained from **619** (195 mg, 0.35 mmol) and NaN$_3$ (280 mg, 4.31 mmol). Colourless oil. $R_f$ (cyclohexane/AcOEt 3:1) 0.45. [α]$^D_{25}$ = 9.1 ($c$ = 1.50, CHCl$_3$). FT-IR (1.5%, CHCl$_3$): apart from a band at 3559 m identical to the spectrum of **620**. H-NMR (300 MHz, CDCl$_3$): 7.61–7.20 (20 arom. H); 4.98 ($d$, $J$ = 10.9, PhCH); 4.95 ($d$, $J$ = 11.2, PhCH); 4.85 ($d$, $J$ = 11.1, 2 PhCH); 4.62 ($d$, $J$ = 11.2, PhCH); 4.57 ($d$, $J$ = 10.9, PhCH); 4.48 ($d$, $J$ = 12.1, PhCH); 4.44 ($d$, $J$ = 12.1, PhCH); 3.87 ($t$, $J$ = 9.3, H–C(3)); 3.76 ($dd$, $J$ = 9.0, 4.1, CH–C(5)); 3.54 ($dd$, $J$ = 10.9, 9.3, H–C(4)); 3.46 ($d$, $J$ = 9.3, H–C(2)); 3.43 ($dd$, $J$ = 9.0, 2.5, CH´–C(5)); 3.29 ($d$, $J$ = 11.8, CHN3); 3.22 ($d$, $J$ = 11.8, CH´–C(5)); 2.41 ($d$, $J$ = 2.2, OH); 2.21–2.09 (m, H–C(5)); 1.80 ($dd$, $J$ = 14.3, 4.1, H$_{eq}$–C(6)); 1.67 ($td$, $J$ = 14.3, 2.2, H$_ax$–C(6)). **13C-NMR** (75 MHz, CDCl$_3$): 139.02, 138.73, 138.13 (3s, 1 s hidden by noise or other signals); 128.76–127.81 (several d); 85.67, 81.54, 81.01 (3d, C(2), C(3), C(4)); 75.78 (2 t), 75.31 (t, 3PhCH$_2$); 74.67 (s, C(1)); 73.27 (t, PhCH$_2$); 69.71 (t, CH$_2$–C(5)); 57.89 (t, CH$_2$N3); 37.39 ($d$, C(5)); 33.02 (t, C(6)). MALDI-MS (DHB): 616 (47, **623**).
Mg + Na\(^{+}\), 590 (37), 588 (72, [M + Na – N\(_2\)]\(^{+}\)), 573 (24), 566 (12, [M + 1 – N\(_2\)]\(^{+}\)), 559 (100), 480 (18, [M + Na – N\(_2\) – BnOH\(^{+}\)], 460 (8), 458 (14, [M + 1 – N\(_2\) – BnOH\(^{+}\)]). Anal. calc. for C\(_{36}\)H\(_{39}\)N\(_3\)O\(_5\) (593.72): C 72.83, H 6.62, N 7.08; found: C 72.81, H 6.66, N 6.99.

(1S,2R,3S,4R,5R)-1-(Azidomethyl)-2,3,4-tris(benzyloxy)-5-(benzyloxymethyl)-cyclohex-1-yl methanesulfonate (621) and (1S,2S,3R,4R)-6-(Azidomethylen)-1,2,3-tris(benzyloxy)-4-(benzyloxymethyl)-cyclohexane (626).

A soln. of 620 (165 mg, 0.28 mmol) in 2,6-lutidine (2.2 ml) was treated at 0\(^\circ\)C with MsCl (0.1 ml, 1.25 mmol) and DMAP (2 mg), stirred for 7.5 h, diluted with Et\(_2\)O (120 ml), washed with cold brine (2 x 60 ml), dried (Na\(_2\)SO\(_4\)), and evaporated. FC (25 g of silica gel, cyclohexane/AcOEt 9:1) gave 626 (6 mg, 4%) and 621 (177 mg, 95%).

Data of 621: Colourless oil. R\(_f\) (toluene/AcOEt 10:1) 0.49. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): 7.41–7.17 (20 arom. H); 4.98 (d, J = 10.9, PhCH); 4.92 (d, J = 10.9, PhCH); 4.88 (d, J = 10.3, PhCH); 4.87 (d, J = 10.9, PhCH); 4.84 (d, J = 11.2, PhCH); 4.55 (d, J = 10.9, PhCH); 4.54 (d, J = 12.5, PhCH); 4.49 (d, J = 12.1, PhCH); 4.38 (d, J = 9.3, H–C(2)); 4.10 (br. d, J = 13.4, CHN\(_3\); 3.67 (dd, J = 9.0, 4.7, CH–C(5)); 3.66 (t, J = 9.2, H–C(4)); 3.53 (t, J = 9.3, H–C(3)); 3.51 (dd, J = 9.0, 2.5, CH–C(5)); 3.45 (d, J = 14.0, CH\(_3\)N); 3.02 (s, MsO); 2.66 (dd, J = 13.4, 3.7, H\(_{eq}\)–C(6)); 2.52 (br. t, J = 13.1, H\(_ax\)–C(6)); 1.79–1.66 (m, H–C(5)). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): 138.62, 138.47 (2 br. s), 128.70–127.79 (several d), 95.31 (s, C(1)); 85.91, 84.70, 80.28 (3 d, C(2), C(3), C(4)); 76.22, 75.91, 75.59, 73.26 (4 t, 4 PhCH\(_2\)); 69.18 (t, CH\(_2\)–C(5)); 52.94 (t, CH\(_2\)N); 41.14 (q, MsO); 38.64 (d, C(5)); 30.94 (t, C(6)). MALDI-MS (DHB): 570 (100, [M + Na – HOMs – N\(_2\)]\(^{+}\)).

Data of 626: Colourless oil. R\(_f\) (toluene/AcOEt 10:1) 0.67. FT-IR (1.5%, CHCl\(_3\)): 3089 w, 3067 w, 3008 m, 2914 w, 2862 m, 2109 s, 1950 w, 1732 w, 1668 w, 1604 w, 1496 w, 1454 m, 1385 m, 1327 w, 1275 w, 1151 m, 1130 m, 1095 m, 1028 m, 909 w, 843 w. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): 7.36–7.18 (20 arom. H); 6.36 (br. t, J = 1.2, CHN\(_3\)); 4.93 (d, J = 10.9, PhCH); 4.87 (d, J = 10.9, PhCH); 4.81 (d, J = 10.9, PhCH); 4.75 (d, J = 11.5, PhCH); 4.69 (d, J = 11.5, PhCH); 4.53 (d, J = 10.9, PhCH); 4.46 (s, PhCH\(_2\)); 3.92 (br. d, J = 7.5, H–C(1)); 3.65 (dd, J = 9.0, 4.7, CH–C(4)); 3.58 (t, J = 9.5, H–C(3)); 3.52–3.47 (dd, J = 9.9, 2.5, partly hidden by other signals, CH–C(4)); 3.45 (t, J = 8.7, H–C(2)); 2.73 (dd, J = 13.7, 3.7, H\(_{eq}\)–C(5)); 1.80.
(br. \( t, J = 13.4, H_{ax}–C(5) \)); 1.72–1.60 (\( m, H–C(4) \)). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): 139.07; 138.73; 138.39; 128.73–127.81; 126.55; 120.32; 88.59; 82.58; 80.80; 75.67; 75.36; 74.02; 73.24; 69.93; 42.24; 30.39. MALDI-MS (DHB): 588 (5), 586 (1, \([M + K – N_2]^+\)), 570 (100, \([M + Na – N_2]^+\)), 566 (4), 548 (17, \([M + 1 – N_2]^+\)).

\[
\begin{align*}
\text{OBn} & \quad \text{BnO} \\
& \quad \text{OMs} \\
\text{N}_3 & \quad \text{BnOBnO}
\end{align*}
\]

\((1R,2R,3S,4R,5R)-1-(Azidomethyl)-2,3,4-tris(benzyloxy)-5-(benzyloxymethyl)cyclohex-1-yl methanesulfonate (624)\).

Similarly as described above, treatment of 623 (103 mg, 0.17 mmol) with MsCl (0.06 ml, 0.77 mmol) and DMAP (1 mg) in 2,6-lutidine (3 ml) at 0° gave 624 (116 mg, 99%). Colourless oil. \( R_f \) (toluene/AcOEt 10:1) 0.38. \(^1\)H-NMR (300 MHz, CDCl\(_3\)): 7.42–7.19 (20 arom. H); 4.96 (\( d, J = 11.2, \text{PhCH} \)); 4.91 (\( d, J = 10.9, \text{PhCH} \)); 4.89 (\( d, J = 10.6, \text{PhCH} \)); 4.85 (\( d, J = 10.9, \text{PhCH} \)); 4.69 (\( d, J = 11.2, \text{PhCH} \)); 4.56 (\( d, J = 10.9, \text{PhCH} \)); 4.48 (\( d, J = 11.8, \text{PhCH} \)); 4.43 (\( d, J = 12.1, \text{PhCH} \)); 4.17 (\( d, J = 11.8, \text{CHN}_3 \)); 3.90 (\( t, J = 9.3, H–C(3) \)); 3.90 (\( d, J = 12.1, \text{CH’N}_3 \)); 3.79 (\( dd, J = 9.3, 3.7, \text{CH–C(5)} \)); 3.62 (\( dd, J = 10.9, 9.3, \text{H–C(4)} \)); 3.54 (\( d, J = 9.7, \text{H–C(2)} \)); 3.43 (\( dd, J = 9.3, 2.5, \text{CH’–C(5)} \)); 3.07 (\( s, \text{MsO} \)); 2.40 (\( dd, J = 14.9, 3.4, \text{Heq–C(6)} \)); 2.25–2.13 (\( m, H–C(5) \)); 1.89 (\( dd, J = 14.6, 13.4, H_{ax}–C(6) \)). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): 138.83, 138.76, 138.55, 138.29 (4s); 128.70–127.87 (several \( d \)); 94.00 (\( s, \text{C(1)} \)); 84.66, 81.06, 80.54 (3\( d, \text{C(2)}, \text{C(3)}, \text{C(4)} \)); 76.04, 75.77, 75.62, 73.34 (4\( r, 4\text{ PhCH}_2 \)); 69.00 (\( t, \text{CH}_2–C(5) \)); 53.46 (\( t, \text{CH}_2\text{N}_3 \)); 40.71 (\( q, \text{MsO} \)); 37.83 (\( d, \text{C(5)} \)); 32.67 (\( t, \text{C(6)} \)). MALDI-MS (DHB): 570 (100, \([M + Na – HOMs – N_2]^+\)).

(\(3R,4S,5S,6R,7R\))-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-1-aza-spiro[2.5]octane (622).

A soln. of 621 (165 mg, 0.25 mmol) in THF (15 ml) was treated at 0° with LiAlH\(_4\) (49 mg, 1.2 mmol), stirred for 3.5 h, treated with MeOH (14 ml) and 1M NaOH, filtered through Celite, and evaporated. FC (20 g of silica gel, cyclohexane/AcOEt 1:1) gave 622 (112 mg, 83%). Colourless oil. \( R_f \) (cyclohexane/AcOEt 1:1) 0.14. \([\alpha]_D^{25} = 32.1 (c = 1.50, \text{CHCl}_3)\). FT-
IR (1.5%, CHCl₃): 3296 w, 3066 m, 2911 m, 2863 m, 1952 w, 1877 w, 1811 w, 1725 w, 1585 w, 1497 m, 1453 m, 1359 m, 1095 s, 909 m, 869 w. ¹H-NMR (300 MHz, CDCl₃): 7.38–7.24 (20 arom. H); 4.94 (d, J = 10.9, PhCH); 4.92 (br. d, J = 12.1, 2 PhCH); 4.86 (d, J = 10.9, PhCH); 4.62 (d, J = 10.9, PhCH); 4.57 (d, J = 11.2, PhCH); 4.48 (d, J = 12.1, PhCH); 4.44 (d, J = 12.1, PhCH); 3.79 (dd, J = 9.0, 3.7, CH–C(7)); 3.78 (d, J = 9.0, H–C(4)); 3.68 (t, J = 9.5, H–C(6)); 3.60 (t, J = 9.2, H–C(5)); 3.45 (dd, J = 9.0, 2.2, CH–C(7)); 2.15–2.06 (m, H–C(7)); 2.01 (t, J = 12.9, Hax–C(8)); 1.87 (br. s, H–C(2)); 1.40 (br. s, H′–C(2)); 1.29–1.21 (m, Heq–C(8)); 1.17–0.87 (br. s, NH). ¹³C-NMR (75 MHz, CDCl₃): 139.05, 138.86, 138.21 (3 s, 1 s hidden by noise or other signals); 128.72–127.75 (several d); 87.79, 81.25, 79.20 (3d, C(4), C(5), C(6)); 75.96, 75.88, 75.44, 73.19 (4t, 4 PhCH₂); 69.84 (t, CH₂–C(7)); 40.29 (d, C(7)); 37.42 (s, C(3)); 33.62 (t, C(8)); 27.17 (br. s, NH). MALDI-MS (DHB): 588 (2, [M + K]+), 572 (100, [M + Na]+), 550 (4, [M + 1]+). Anal. calc. for C₃₆H₃₉NO₄ (549.71): C 78.66, H 7.15, N 2.55; found: C 78.57, H 7.12, N 2.48.

Similarly as described above, a soln. of 624 (116 mg, 0.17 mmol) in THF (11 ml), was treated with LiAlH₄ (35 mg, 0.86 mmol) at 0° for 9 h to yield 625 (70 mg, 74%). Colourless oil. Rf (cyclohexane/AcOEt 1:1) 0.22. [α]25D = 8.8 (c = 1.42, CHCl₃). FT-IR (1.4%, CHCl₃): identical to that of 622. ¹H-NMR (300 MHz, CDCl₃): 7.38–7.23 (20 arom. H); 4.93 (d, J = 10.9, PhCH); 4.92 (d, J = 11.8, PhCH); 4.91 (d, J = 10.9, PhCH); 4.86 (d, J = 10.9, PhCH); 4.59 (d, J = 10.9, PhCH); 4.58 (d, J = 11.5, PhCH); 4.46 (s, PhCH₂); 3.65–3.57 (m, H–C(4), H–C(5), H–C(6), CH–C(7)); 3.49 (dd, J = 9.0, 2.8, CH–C(7)); 2.00 (br. s, J = 12.5, Hax–C(8)); 1.98 (br. s, H–C(2)); 1.93–1.81 (m, H–C(7)); 1.31–1.25 (m, Heq–C(8)); 1.29 (br. s, H′–C(2)); 1.18–0.85 (br. s, NH). ¹³C-NMR (75 MHz, CDCl₃): 138.89, 138.71, 138.45 (3s, 1 s hidden); 128.85–127.78 (several d); 88.61, 81.54, 79.60 (3d, C(4), C(5), C(6)); 75.75, 75.64, 75.51, 73.21 (4t, 4 PhCH₂); 70.02 (t, CH₂–C(8)); 40.92 (d, C(7)); 37.86 (s, C(3)); 34.32 (t, C(8)); 26.97 (t, C(2)). MALDI-MS (DHB): identical to that of 622. Anal. calc. for C₃₆H₃₉NO₄ (549.71): C 78.66, H 7.15, N 2.55; found: C 78.86, H 7.32, N 2.60.

A soln. of 622 (10 mg, 18 mmol) in NH₃ (5 ml) and THF (2 ml) at −78° was treated with Na in small pieces (ca. 20 mg), until the blue colour persisted for 1 h, treated with NH₄Cl (ca. 40 mg), until the blue colour disappeared, allowed to warm to r.t. overnight, and evaporated. The residue was dried in h.v., suspended in abs. MeOH, and filtered. After evaporation, the suspension of the residue in abs. EtOH was filtered. Evaporation and chromatography on Sephadex G-10 (20 x 1 cm, eluant H₂O), and lyophilisation gave a mixture of 47, an unidentified byproduct, and inorganic material (13 mg, colourless powder). Rf (nPrOH/AcOH/H₂O 4:1:1) 0.31. ¹H-NMR (300 MHz, D₂O): 3.80 (d, J = 9.3, H–C(4)); 3.78 (dd, J = 11.5, 3.1, CH–C(7)); 3.70 (dd, J = 11.2, 5.0, CH′–C(7)); 3.45 (d, J = 9.5, H–C(6)); 3.36 (t, J = 9.2, H–C(5)); 1.96 (br. s, H–C(2)); 1.94 (s, ?); 1.87–1.78 (m, H–C(7), H₉C–C(8)); 1.53 (br. s, H′–C(2)); 1.35 (d, J = 6.9, ?); 1.26 (br. d, J = 10.6, Hₑq–C(8)). HR-MALDI-MS (DHB): Calc. for C₈H₁₆NO₄⁺, found: 190.1076 (C₈H₁₆NO₄⁺, [M + H]⁺; calc. 190.1079).

(1S,2S,3S,4R,5R)-1-Amino-1-(chloromethyl)-5-(hydroxymethyl)-cyclohexane-2,3,4-triol Hydrochloride (627·HCl) and (1S,2S,3S,4R,5R)-1-Amino-1-methyl-5-hydroxymethyl-cyclohexane-2,3,4-triol Hydrochloride (628·HCl).

A soln. of 622 (12 mg, 21.8 mmol) in MeOH (2 ml) was acidified (pH 4) by the dropwise addition of a soln. of conc. HCl (1 drop) in MeOH (1 ml) (20 drops), treated with 10% Pd on C (10 mg), and stirred under a H₂ atmosphere for 110 min. Filtration through a pad of Celite (washed with 20 ml of 0.1N HCl in MeOH and with 50 ml of MeOH) with MeOH, and evaporation gave a mixture of 627·HCl and 628·HCl (7.6 mg, 3:2). Rf (nPrOH/AcOH/H₂O 4:1:1) 0.35. ¹H-NMR (300 MHz, D₂O, 627·HCl/628·HCl 3:2): 4.06, 3.79 (2 d, J = 11.8, 1.2 H); 3.83–3.33 (m, 5 H); 2.32 (br. d, J = 12.1, 0.6 H, H–C(6)); 2.04 (dd, J = 14.8, 3.3, 0.4 H, H–C(6)); 1.81–1.57 (m, 2 H, H–C(5), H’–C(6)); 1.43 (s, 1.2 H, Me). ESI⁺-MS: data for 627: 250 (6, [M(37Cl) + Na]⁺), 248 (11, [M(35Cl) + Na]⁺), 228 (14, [M(37Cl) + 1]⁺), 226 (34,
(1S,2S,3S,4R,5R)-1-Amino-1-(chloromethyl)-5-(hydroxymethyl)-cyclohexane-2,3,4-triol Hydrochloride (627·HCl) (This experiment was done by Dr. Poisson).

At –60°, Na (70 mg, 2 mmol) was dissolved in NH₃ (3 ml) and THF (5 ml), stirred for 15 min., treated dropwise with a soln. of 622 (31 mg, 0.05 mmol) in THF (1 ml), and stirred for 30 min. at –50°. The blue mixture was treated with NH₄Cl in small portions, until it became colourless, and NH₃ was allowed to evaporate. The remaining soln. was diluted with MeOH, filtered through Celite, and evaporated. The residue was purified by chromatography on Sephadex C-25 (elution with HCl 0.01M - 1M). Lyophilisation of the eluate gave a mixture of 627·HCl and NH₄Cl (64 mg). ¹H-NMR (300 MHz, D₂O): 4.11 (d, J = 12.3, CH–C(1)); 3.85 (d, J = 12.3, CH'–C(1)); 3.81 (dd, J = 11.4, 3.3, CH–C(5)); 3.75 (dd, J = 11.1, 5.4, CH'–C(5)); 3.71–3.61 (m, 2 H); 3.44 (ddd, J = 9.6, 7.8, 1.5, 1 H); 2.37 (dd, J = 14.1, 2.4, H–C(6)); 1.87–1.65 (m, H–C(5), H'–C(6)).

A soln. of 625 (33 mg, 60 mmol) in NH₃ (10 ml) and THF (2.5 ml) was treated at –78° with Na in small pieces (ca. 30 mg), until the blue colour persisted for 1 h, treated with NH₄Cl (ca. 50 mg), until the blue colour disappeared, and allowed to warm to r.t. overnight. The solvent was evaporated, the residue dried in h.v., suspended in abs. MeOH, and filtered. After evaporation, the suspension of the resulting residue in abs. EtOH was filtered, and the filtrate evaporated. The residue (138 mg) was adsorbed on neutral Dowex 50-WX-8 (3 ml, washed with H₂O). After washing with H₂O (50 ml), elution with 2% aq. NH₃ gave crude 46 (6 mg). Chromatography (25 g of Nucleoprep 20 CN, MeOH) gave colourless, amorphous 46 (5.2 mg, 45%). Rf (nPrOH/AcOH/H₂O 4:1:1) 0.26. [α]D²⁵ = 6.0 (c = 0.31, H₂O). pKₐ = 6.78. ¹H-NMR (300 MHz, CD₃OD): 3.75 (dd, J = 10.9, 3.7, CH–C(7)); 3.58 (dd, J = 10.9, 5.9, CH'–C(7)); 3.48 (d, J = 9.0, H–C(4)); 3.30 (t, J = 9.2, H–C(6)); 3.22 (t, J = 9.0, H–C(5)); 2.02 (br. s, H–C(2)); 1.73 (br. t, J = 12.5, H₂ax–C(8)); 1.68–1.57 (m, H–C(7)); 1.34 (br. s, H'–C(2)); 1.29 (dd, J = 12.5, 2.8, H₂eq–C(8)). ¹³C-NMR (75 MHz, CD₃OD): 80.44, 75.30,
72.11 (3\(d\), C(4), C(5), C(6)); 64.25 (\(t\), CH\(_2\)–C(7)); 43.77 (\(d\), C(7)); 39.90 (s, C(3)); 34.27 (\(t\), C(8)); 27.36 (\(t\), C(2)). HR-MALDI-MS (DHB): 401 (69, [2 \(M + \text{Na}\)]\(^{+}\)), 379 (71, [2 \(M + 1\)]\(^{+}\)), 212.0891 (19, C\(_8\)H\(_{15}\)NO\(_4\)Na\(^{+}\), [\(M + \text{Na}\)]\(^{+}\); calc. 212.0899), 207.1337 (23, C\(_8\)H\(_{19}\)N\(_2\)O\(_4\)\(^{+}\), [\(M + \text{NH}_4\)]\(^{+}\); calc. 207.1345), 190.1074 (100, C\(_8\)H\(_{16}\)NO\(_4\)\(^{+}\) [\(M + \text{H}\)]\(^{+}\); calc. 190.1079).
(1S,2S,3S,4R,5R)-2,3,4-Tris(benzyloxy)-5-(benzyloxymethyl)-1-cyclohex-1-yl methanesulfonate (629).

A soln. of 54 [234] (200 mg, 0.37 mmol) in pyridine (6 ml) at 0° was treated with MsCl (0.12 ml, 1.49 mmol), stirred for 45 min at 0° and for 90 min at r.t., diluted with AcOEt (100 ml), washed with H2O (100 ml) and brine (100 ml), dried (Na2SO4), and evaporated. FC (20 g of silica gel, cyclohexane/AcOEt 9:1) gave colourless, amorphous 629 (212 mg, 93%). Rf (cyclohexane/AcOEt 3:1) 0.40. M.p. 137–138°. 1H-NMR (300 MHz, CDCl3): 7.38–7.21 (20 arom. H); 5.22–5.18 (m, H–C(1)); 4.94 (d, J = 10.9, PhCH); 4.90 (d, J = 9.7, PhCH); 4.84 (d, J = 10.6, PhCH); 4.78 (d, J = 11.2, PhCH); 4.69 (d, J = 10.9, PhCH); 4.55 (d, J = 10.9, PhCH); 4.43 (s, PhCH2); 3.84 (t, J = 9.3, H–C(3)); 3.77 (dd, J = 9.0, 3.4, CH–C(5)); 3.59 (dd, J = 10.9, 9.3, H–C(4)); 3.49 (dd, J = 9.7, 2.8, H–C(2)); 3.40 (dd, J = 9.3, 2.2, CH–C(5)); 3.01 (s, MsO); 2.18–2.05 (m, H–C(5), Heq–C(6)); 1.77 (br. t, J = 13.7, Haax–C(6)). 13C-NMR (75 MHz, CDCl3): 138.9, 138.55, 137.78 (3s, 1s hidden by other signals); 128.76–127.84 (several d); 83.39, 81.20, 80.34, 79.07 (4d, C(1), C(2), C(3), C(4)); 75.89, 75.54, 73.40, 73.21 (4t, 4PhCH2); 69.08 (t, CH2–C(5)); 39.03 (d, C(5)); 37.42 (q, MsO); 30.32 (t, C(6)).


A soln. of 629 (210 mg, 0.34 mmol) in DMF (15 ml) was treated with NaN3 (221 mg, 3.4 mmol), stirred at 120° for 3 h, cooled to r.t., diluted with AcOEt (60 ml), washed with H2O (50 ml) and brine (50 ml), dried (Na2SO4), and evaporated. FC (30 g of silica gel, cyclohexane/AcOEt 20:1) gave colourless, amorphous 630 (181 mg, 94%). Rf (cyclohexane/AcOEt 9:1) 0.36. M.p. 69–70°. [α]25D25 = 49.5 (c = 1.49, CHCl3). FT-IR (1.5%, CHCl3): 3066 w, 3006 w, 2865 w, 2103 s, 1497 w, 1454 m, 1359 m, 1260 w, 1089 m, 1028 m, 910 w.

1H-NMR (300 MHz, CDCl3): 7.38–7.18 (20 arom. H); 4.93–4.83 (m, 5 PhCH); 4.53 (d, J = 10.9, PhCH); 4.46 (s, PhCH2); 3.60 (dd, J = 9.0, 5.0, CH–C(5)); 3.59–3.35 (m, 5 H); 2.04 (dt,
$J = 13.4, 3.7, \text{H}_{\text{eq}}–\text{C}(6); 1.82–1.69 (m, \text{H}–\text{C}(5)); 1.48 (q, J = 13.0, \text{H}_{\text{ax}}–\text{C}(6))$. $^{13}$C-NMR (75 MHz, CDCl₃): 138.84, 138.63, 138.50, 138.24 (4s); 128.67–127.86 (several d); 86.91, 85.05, 80.62 (3d, C(2), C(3), C(4)); 75.91 (t, 2 PhCH₂); 75.52, 73.34 (2t, 2 PhCH₂); 69.71 (t, CH₂–C(5)); 63.21 (d, C(1)); 40.01 (d, C(5)); 30.68 (t, C(6)). FAB-MS (NOBA): 614 (29), 565 (38, [M + 2]+), 554 (13), 540 (11), 496 (12), 461 (100), 452 (13), 444 (20), 429 (19), 422 (17), 408 (14), 392 (10), 339 (29), 329 (12). Anal. calc. for C₃₅H₃₇N₃O₄ (563.70): C 74.58, H 6.62, N 7.45; found: C 74.61, H 6.71, N 7.23.

(1R,2S,3S,4R,6R)-4-Amino-6-(hydroxymethyl)-cyclohexane-1,2,3-triol (48).

A soln. of 630 (50 mg, 88 mmol) in MeOH (12 ml) was treated with conc. aq. HCl (2 drops) and Pd on C (10%, 40 mg), stirred in a H₂-atmosphere (6 bar) for 15 h, filtered through Celite, and evaporated. The residue was adsorbed on neutral Dowex 50 WX8 (3 ml, washed with H₂O). After washing with H₂O (70 ml), elution with 2% aq. NH₃ gave 48 (16 mg, 100%). $R_f$ (nPrOH/AcOH/H₂O 4:1:1) 0.31. $[\alpha]^{25}_D = 17$ (c = 0.42, H₂O; [224]: 17.2 (c = 0.57, H₂O)). $^1$H-NMR (300 MHz, D₂O): 3.77 (dd, $J = 11.2, 3.4, \text{CH}–\text{C}(6)$); 3.62 (dd, $J = 11.2, 6.2, \text{CH}–\text{C}(6)$); 3.31–3.26 (m, 2 H); 3.14–3.08 (m, 1 H); 2.74 (ddd, $J = 13.1, 9.65, 4.0, \text{H}–\text{C}(4)$); 1.92 (dt, $J = 13.1, 4.0, \text{H}_{\text{eq}}–\text{C}(5)$); 1.75–1.60 (m, H–C(6)); 1.15 (br. $q, J = 12.6, \text{H}_{\text{ax}}–\text{C}(5)$). $^{13}$C-NMR (75 MHz, D₂O): 80.26, 80.10, 75.68 (3d, C(1), C(2), C(3)); 65.09 (t, CH₂–C(6)); 54.81 (d, C(4)); 44.05 (d, C(6)); 33.77 (t, C(5)).

**Inhibition Studies.** The IC₅₀ values were determined based on a range of inhibitor concentrations (typically 4–8 concentrations) which bracket the IC₅₀ value.

a) **Inhibition of the β-Glucosidase from almonds in the pH range of 6.2–7.8.** IC₅₀ values were determined at 37° in 0.08M KH₂PO₄/K₂HPO₄ or NaH₂PO₄/Na₂HPO₄ buffer, using 4-nitrophenyl β-D-glucopyranoside as the substrate ([S] ≈ $K_M$). The enzymatic reaction was started after incubation of the enzyme for 10–60 min in the presence of the inhibitor by the addition of substrate. The increase of absorption per min at 400 nm was taken as the relative rate for the hydrolysis of the substrate. The increase was linear during all measurements (1 min). IC₅₀ values were determined by plotting the relative rate of substrate hydrolysis vs. the inhibitor concentration. Determination of the inhibitor concentration corresponding to half the relative rate measured in the absence of the inhibitor gave the appropriate IC₅₀ value. To
check for slow inhibition, the dependence of the inhibition on the incubation time was determined.

b) Inhibition of the β-Glucosidase from almonds at pH 4.2. See a). IC50 values were determined at 37° in 0.08M citric acid/Na2HPO4 buffer (pH 4.2). The enzymatic reaction was started after incubation of the enzyme for 15 min in the presence of the inhibitor by the addition of substrate. The mixture was incubated at 37° for 5 min and the reaction quenched by the addition of 0.2M borate buffer (pH 9.0). The absorption at 400 nm was measured immediately and taken as the relative rate for the hydrolysis of the substrate.

c) Inhibition of the β-Glucosidase from Caldocellum saccharolyticum. As described in a) or b), respectively. All measurements were performed at 55°.

d) Inhibition of the α-Glucosidase from brewer's yeast at pH 6.8. As described in a) . All measurements were performed at 37°, using 4-nitrophenyl α-D-glucopyranoside as substrate.

e) Inhibition of the α-Glucosidase from brewer's yeast and the β-Glucosidase from almonds at pH 5.0. As described in a), b) and d), using 0.08M AcOH/AcONa buffer (pH 5.0).

f) Determination of Ki and ki for the Irreversible Inhibition of the β-Glucosidase from Caldocellum saccharolyticum by 46. cf. [725] [217] [1042]. The enzyme was incubated with various concentrations of inhibitor (5.0–0.5 mM) at 55° in 0.08M KH2PO4/K2HPO4 buffer (pH 6.8). Aliquots (50 µl) were taken at appropriate time intervals, diluted into 900 µl of buffer, and the residual enzyme activity was measured by the increase of the absorbance at 400 nm, which was observed after the addition of substrate. For each inhibitor concentration, ln of the residual activity was plotted vs. time, fitted to a straight line, and the first order rate constant for the inactivation determined from the slope of the line. Replotting the reciprocal of these rate constants vs. the reciprocal of the inhibitor concentrations gave a straight line, from which Ki and ki were determined.
(2R,3S,4R,5R,6R)-2,3,4-Tris-(benzyloxy)-5-(benzyloxy)methyl)-6-bromocyclohexanone (631).

A soln. of 52 (228 mg, 0.425 mmol) in THF (50 ml) was cooled to 0°, treated with PhMe3NBr3 (176 mg, 0.467 mmol) and CSA (10 mg, 43 µmol), stirred at 0° for 5 min, and for 7 h while warming to r.t., and treated with sat. aq. Na2S2O5 soln. (50 ml). The mixture was extracted with Et2O (2 x 60 ml). The combined organic phases were dried (Na2SO4) and evaporated. Repeated FC (30 g of silica gel, cyclohexane/AcOEt 12:1) of the orange oil gave 631 (151 mg, 58%) as a colourless oil, which crystallised upon standing. Rf (cyclohexane/AcOEt 3:1) 0.66. M.p.: 83.4–89.5°. FT-IR (0.5%, CHCl3): 3038 w, 2868 w, 1731 m (C=O), 1496 w, 1451 m, 1359 w, 1094 s, 1046 m, 993 w, 911 w. 1H-NMR (300 MHz, CDCl3): 7.48–7.12 (20 arom. H); 5.08 (d, J = 10.0, H−C(2)); 5.00 (d, J = 10.6, PhCH); 4.97 (d, J = 11.2, PhCH); 4.94 (d, J = 10.9, PhCH); 4.79 (d, J = 10.6, PhCH); 4.67 (d, J = 3.4, H−C(6)); 4.63 (d, J = 11.2, PhCH); 4.55 (d, J = 10.9, PhCH); 4.52 (s, PhCH2); 3.92 (dd, J = 8.7, 2.2, CH−C(5)); 3.87 (dd, J = 8.7, 4.0, CH′−C(5)); 3.76 (t, J = 9.3, H−C(3)); 3.48 (t, J = 9.3, H−C(4)); 2.17 (tt, J = 10.0, 4.0, H−C(5)). 13C-NMR (75 MHz, CDCl3): 199.83 (s, C=O); 138.30, 138.00, 137.92, 137.55 (4 s); 128.72–128.05 (several d); 86.27, 81.99, 77.94 (3 d, C(2), C(3), C(4)); 76.36, 75.86, 74.07, 73.65 (4t, 4 PhCH2); 67.70 (t, CH2−C(5)); 51.41 (d, C(5)). HR-MS (MALDI): 639 (100), 637.1567 (95, [M + Na]+; calc. 637.1566); 559 (47, [M + Na + H − Br]+).

(2S,3R,4R,5S,6R)-2-Azido-4,5,6-tris-(benzyloxy)-3-(benzyloxy)methyl)cyclohexanone (56).

A soln. of 631 (133 mg, 216 µmol) in DMF (13 ml) was cooled to 0°, treated with NaN3 (140 mg, 2.16 mmol), stirred for 65 min, and poured into ice-water (150 ml). The mixture was extracted with AcOEt (2 x 150 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (30 g of silica gel, cyclohexane/AcOEt 12:1) of the yellow oil (139 mg) gave colourless amorphous 56 (114 mg, 91%). Rf (toluene/AcOEt 10:1) 0.71. FT-IR (0.5%, CDCl3): 3067w, 3033w, 3013w, 2925w, 2873w, 2110s (N3), 1742m (C=O), 1497s, 1454w, 1359w, 1146m, 1090s, 1072m, 1055m, 1028m, 1005w, 909s. 1H-NMR (300 MHz, CDCl3): 7.42–7.15 (20 arom. H); 5.01 (d, J = 10.9, PhCH); 4.98 (d, J = 10.6, PhCH); 4.98 (d, J = 11.5, PhCH); 4-81 (d, J = 10.6, PhCH); 4.60 (d, J = 11.5, PhCH); 4.59 (d, J = 10.9, PhCH); 4.54 (d, J = 11.5, PhCH); 4.46 (d, J = 11.8, PhCH); 4.24 (dd, J = 12.5, 1.3, H−C(2)); 4.16 (dd, J = 10.0, 1.6, H−C(6)); 4.00 (dd, J = 10.7, 9.2, H−C(4)); 3.87 (dd, J = 9.2, 1.7, CH−C(3)); 3.70
(dd, J = 10.0, 9.3, H–C(5)); 3.62 (dd, J = 9.7, 2.3, CH'–C(3)); 1.73 (ddt, J = 12.5, 10.9, 2.0, H–C(3)). 13C-NMR (75 MHz, CDCl3): 201.68 (s, C=O); 138.36, 138.27, 138.02, 137.48 (4s); 128.73–128.05 (several d); 85.77, 84.48, 76.80 (3d, C(4), C(5), C(6)); 76.20, 76.07, 73.78, 73.52 (4t, PhCH2); 64.80 (t, C(3)). HR-MS (MALDI): 600.2475 (55, C35H35N3NaO5+, [M + Na]+; calc. 600.2474) ; 572 (100, [M + Na – N2]+).

BnOBnO
BnO
OBn
N3
OH

(1S,2S,3R,4R,5S,6S)-2-Azido-4,5,6-(benzyloxy)-3-(benzyloxymethyl)cyclohexanol (633).
A soln. of 56 (49 mg, 84.8 µmol) in MeOH (12 ml) was cooled to 0°, treated with NaBH4 (19.3 mg, 509 µmol), stirred for 55 min, and evaporated. A soln. of the residue in AcOEt (50 ml) was washed with sat. aq. NH4Cl soln. and brine (40 ml of each). The aq. phases were extracted with AcOEt (50 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (15 g of silica gel, cyclohexane/AcOEt 6:1) of the yellow oil (73 mg) gave 633 (36 mg, 73%) as a colourless oil and a mixture of 633 and an unidentified byproduct (8.3 mg). Rf (cyclohexane/AcOEt 3:1) 0.51. FT-IR (1%, CHCl3): 3579 w (OH), 3034 w, 3011 w, 2873 w, 2105 s (N3), 1496 w, 1454 w, 1360 w, 1126 w, 1093 m, 1066 m, 1028 m, 909 s. 1H-NMR (300 MHz, CDCl3): 7.44–7.15 (20 arom. H); 4.91 (d, J = 10.9, PhCH); 4.88 (d, J = 10.9, PhCH); 4.83 (d, J = 10.6, PhCH); 4.73 (d, J = 11.5, PhCH); 4.69 (d, J = 11.5, PhCH); 4.51 (d, J = 11.5, PhCH); 4.50 (d, J = 9.3, PhCH); 4.39 (d, J = 11.8, PhCH); 4.29–4.20 (m, H–C(1)); 3.90 (t, J = 9.5, H–C(5)); 3.89 (dd, J = 9.6, 1.6, CH–C(3)); 3.62 (dd, J = 9.3, 5.0, CH1–C(3)); 3.61 (t, J = 8.9, H–C(4)); 3.46 (ddd, J = 11.8, 2.5, 1.3, H–C(2)); 3.41 (dd, J = 9.5, 2.6, H–C(6)); 2.46 (t, J = 1.3, irradiation at 4.25 ppm -> d, irradiation at 3.46 ppm -> d, OH); 2.24 (tm, J = 11.4, H–C(3)). 13C-NMR (75 MHz, CDCl3): 138.59; 138.32; 138.00; 137.51; 128.50–127.49 (several signals); 82.84; 80.48; 77.80; 75.77; 75.57; 73.15; 72.80; 69.88; 65.21; 58.69 (C(2)); 41.42 (C(3)). HR-MS (MALDI): 602.2620 (52, C35H37N3NaO5+, [M + Na]+; calc. 602.2631), 574 (100, [M + Na – N2]2+), 554 (48).

(1R,2S,3S,4S,5S,6R)-5-Amino-6-(hydroxymethyl)cyclohexane-1,2,3,4-tetrol Hydrochloride Monohydrate (635-HCl-H2O).
A suspension of 10% Pd/C (25 mg) in MeOH (2 ml) was treated with 3 drops of conc. HCl and with a soln. of 633 (36 mg, 62 µmol) in MeOH (10 ml), and stirred under H2 at r.t. for 14 h. Filtration and evaporation gave colourless glassy 635-HCl-H2O (15.4 mg, 100%). Rf
(nPrOH/AcOH/H₂O 4:1:1) 0.31. ¹H-NMR (300 MHz, CD₃OD): 4.02 (t, J = 2.6, H–C(4)); 3.93 (dd, J = 11.2, 3.4, CH–C(6)); 3.82 (dd, J = 11.2, 6.2, CH'–C(6)); 3.61 (t, J = 9.3, H–C(2)); 3.36–3.28 (m, H–C(3), H–C(5)); 3.20 (dd, J = 10.6, 9.0, H–C(1)); 2.04 (ttdd, J = 10.9, 6.2, 3.4, H–C(6)). ¹³C-NMR (75 MHz, CD₃OD): 74.68; 73.07; 71.37; 70.88 (C(1), C(2), C(3), C(4)); 60.82 (C₇H₅–C(6)); 52.80 (C(5)); 42.34 (C(6)). ESI-MS: 409 (56 [2M + Na]⁺), 360 (21), 338 (30), 248 (14, [M + Na + MeOH]⁺), 216 (22, [M + Na]⁺), 194 (100, [M + 1]⁺).

A soln. of 56 (38 mg, 65 µmol) in CH₂Cl₂ (5 ml) was cooled to –78°, treated with 1.5 M diisobutylaluminium hydride in toluene (0.066 ml, 98 µmol), stirred for 35 min, treated with AcOEt (0.5 ml), stirred for 15 min, treated with sat. aq. Na₂SO₄ soln., allowed to warm to r.t., and filtered. Evaporation and two FC's (15 g of silica gel, cyclohexane/AcOEt 8:1) of the colourless amorphous residue (42 mg) gave 632 (16.5 mg, 44%) as a colourless oil and a ca. 1:1 mixture of 632 and 633 (17.8 mg, 47%). Rf (cyclohexane/AcOEt 3:1) 0.54. FT-IR (0.5%, CHCl₃): 3588 w (OH), 3033 w, 3011 w, 2914 w, 2874 w, 2108 s (N 3), 1497 w, 1454 w, 1360 w, 1264 w, 1134 w, 1094 w, 1058 m, 1028 w, 1003 w, 909 w. ¹H-NMR (300 MHz, CDCl₃): 7.39–7.18 (20 arom. H); 4.97 (d, J = 11.2, PhCH); 4.90 (s, PhCH₂); 4.88 (d, J = 9.3, PhCH); 4.73 (d, J = 11.2, PhCH); 4.55 (d, J = 11.2, PhCH); 4.51 (d, J = 12.1, PhCH); 4.44 (d, J = 11.8, PhCH); 3.80 (dd, J = 9.2, 2.0, CH–C(3)); 3.72 (dd, J = 10.7, 9.2, H–C(4)); 3.67 (dd, J = 9.3, 2.5, CH–C(3)); 3.59 (t, J = 10.4, H–C(2)); 3.53 (t, J = 9.3, H–C(5)); 3.51 (td, J = 10.0, 2.2, H–C(1)); 3.38 (t, J = 9.2, H–C(6)); 2.53 (d, J = 2.2, OH); 1.50 (tt, J = 10.9, 2.0, H–C(3)). ¹³C-NMR (75 MHz, CDCl₃): 138.40; 128.88–127.87 (several signals); 85.67; 83.13; 77.86; 76.12; 75.89; 75.81; 75.72; 73.32; 64.84; 61.49; 44.80. HR-MS (MALDI): 602.2619 (49, C₃₅H₃₇N₃NaO₅⁺, [M + Na]⁺; calc. 602.2631), 574 (100, [M + Na – N₂]⁺), 554 (57).

(1R,2S,3R,4R,5S,6S)-2-Azido-4,5,6-tris-(benzylloxy)-3-(benzyloxymethyl)cyclohexanol (632).

(1R,2S,3S,4R,5S,6R)-5-Amino-6-(hydroxymethyl)cyclohexane-1,2,3,4-tetrol Hydrochloride Monohydrate (634·HCl·H₂O).

A suspension of 10% Pd/C (10 mg) in MeOH (1 ml) was treated with 3 drops of conc. HCl and a soln. of 632 (15.5 mg, 26.7 µmol) in MeOH (5 ml), stirred under H₂ at r.t. for 29 h, and filtered. Evaporation gave colourless glassy 634·HCl·H₂O-MeOH (9.3 mg, quant.). Rf (nPrOH/AcOH/H₂O 4:1:1) 0.32. ¹H-NMR (300 MHz, CD₃OD): 4.02 (dd, J = 10.9, 3.4, 2.2, 1.5, H–C(6)); 3.80 (dd, J = 10.7, 9.2, H–C(4)); 3.67 (dd, J = 9.3, 2.5, CH–C(3)); 3.59 (t, J = 10.4, H–C(2)); 3.53 (t, J = 9.3, H–C(5)); 3.51 (td, J = 10.0, 2.2, H–C(1)); 3.38 (t, J = 9.2, H–C(6)); 2.53 (d, J = 2.2, OH); 1.50 (tt, J = 10.9, 2.0, H–C(3)). ¹³C-NMR (75 MHz, CDCl₃): 138.40; 128.88–127.87 (several signals); 85.67; 83.13; 77.86; 76.12; 75.89; 75.81; 75.72; 73.32; 64.84; 61.49; 44.80. HR-MS (MALDI): 602.2619 (49, C₃₅H₃₇N₃NaO₅⁺, [M + Na]⁺; calc. 602.2631), 574 (100, [M + Na – N₂]⁺), 554 (57).
CH–C(6)); 3.79 (dd, J = 10.9, 6.8, CH’–C(6)); 3.37 (dd, J = 10.3, 8.4, 1 H); 3.24–3.13 (m, 3 H); 3.05 (t, J = 10.9, H–C(5)); 1.70 (tdd, J = 10.9, 7.3, 3.6, H–C(6)). $^{13}$C-NMR (75 MHz, CD$_3$OD): 76.56; 74.74; 72.91; 70.18 (C(1), C(2), C(3), C(4)); 60.45 (CH$_2$–C(6)); 54.58 (C(5)); 43.55 (C(6)). ESI-MS: 409 ([2M + Na]$^+$), 360 (57), 338 (84), 248 (10, [M + Na + MeOH]$^+$), 216 (16, [M + Na]$^+$), 194 (42, [M + 1]$^+$).
Part 3.

O-tertButyl N-(cyclohex-3-enyl)carbamate (712) [955] [956].
At r.t., a solution of cyclohex-3-enecarboxylic acid (2 g, 1.85 ml, 15.85 mmol) in toluene (50 ml) was treated with Et3N (2.43 ml, 17.44 mmol) and diphenylphosphoryl azide (3.59 ml, 16.65 mmol), stirred for 30 min, slowly warmed to 80°, and stirred under reflux for 3 h (IR control). After cooling to r.t., the mixture was treated with tBuOH (7.44 ml, 79.3 mmol) and CuCl (50 mg, 0.51 mmol) and stirred at 100° for 2 h. The mixture was cooled, diluted with sat. aq. NaHCO3 soln. (100 ml) and extracted with Et2O (3 x 100 ml). The organic phases were dried (Na2SO4) and evaporated. FC (50 g of silica gel, cyclohexane/AcOEt 12:1) gave 712 (2.88 g, 92%) as colourless crystals. Rf (cyclohexane/AcOEt 3:1) 0.71. M.p. 52–54°. 1H-NMR (300 MHz, CDCl3): 5.71–5.63, 5.63–5.55 (2m, H–C(3), H–C(4)); 4.59–4.49 (m, NH); 3.84–3.70 (m, H–C(1)); 2.43–2.32 (m, 1 H); 2.17–2.08 (m, 2 H); 1.92–1.79 (m, 2 H); 1.57–1.49 (m, 1 H); 1.45 (s, Me3C). 13C-NMR (75 MHz, CDCl3): 127.21, 124.75 (2d, C(3), C(4)); 79.21 (s, Me3C); 45.77 (d, C(1)); 32.15 (t); 28.49 (q, Me3C); 23.67 (t, 2 C).

NHCOCF3

N-(Cyclohex-3-enyl)-2,2,2-trifluoroacetamide (71) [957].
At r.t., a solution of cyclohex-3-enecarboxylic acid (10 g, 9.3 ml, 79.3 mmol) in toluene (250 ml) was treated with Et3N (13 ml, 95 mmol) and DPPA (17.9 ml, 83.2 mmol), stirred for 30 min, slowly heated to 80°, and stirred under reflux for 5 h (IR control). After cooling to r.t., the mixture was treated with trifluoroacetic acid (15.2 ml, 119 mmol) and stirred at 80° for 16 h. After cooling to r.t., the solution was washed with sat. aq. NaHCO3 soln. (2 x 400 ml), dried (Na2SO4), and evaporated. FC (60 g of silica gel, cyclohexane/AcOEt 12:1) gave 71 (12.91 g, 84%) as colourless crystals. Rf (cyclohexane/AcOEt 3:1) 0.70. M.p. 59–60° (957): 62–63°. FT-IR (1.5%, CHCl3): 3428m (NH), 3008w, 2926w, 2845w, 1723s (C=O), 1532m, 1439w, 1372w, 1337w, 1290m, 1171s, 1045w, 940w, 865w. 1H-NMR (300 MHz, CDCl3): 6.28–6.14 (m, NH, exch. with D2O); 5.79–5.71, 5.67–5.59 (2m, H–C(3), H–C(4)); 4.25–4.13 (m, H–C(1)); 2.52–2.40 (dm, J = 17.7, 1 H); 2.27–2.07 (m, 2 H); 2.04–1.86 (m, 2 H); 1.77–1.64 (m, 1 H). 13C-NMR (75 MHz, CDCl3): 127.49, 124.75 (2d, C(3), C(4)); 45.55 (d, C(1)); 30.95, 27.17, 22.93 (3t, C(2), C(5), C(6)). 19F-NMR (282 MHz, CDCl3): −75.75 (s).
Methyl cis-6-(tert-Butoxycarbonylamino)-cyclohex-3-ene carboxylate (714).

A soln. of 713 [959] (25 g, 136 mmol) in toluene (450 ml) was treated with Et3N (22.7 ml, 163 mmol) and diphenylphosphoryl azide (30.7 ml, 143 mmol), heated slowly to 80°, kept at this temperature until N2 evolution ceased, and refluxed for 200 min. After cooling to r.t., the mixture was treated with tBuOH (64 ml, 678 mmol) and CuCl (500 mg, 5.1 mmol) and stirred at 100° for 15 h. The mixture was cooled, washed with sat. aq. NaHCO3 soln. (2 x 400 ml). The aq. phases were extracted with Et2O (2 x 400 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (230 g of silica gel, cyclohexane/AcOEt 9:1) gave 714 (31.4 g, 90%) as a slightly yellow oil, which crystallised upon standing at –20°. Rf (cyclohexane/AcOEt 3:1) 0.52. M.p. 51.8–55.5°. FT-IR (1%, CHCl3): 3442 w (NH), 3019 m, 2982 w, 1708 s (C=O), 1501 s, 1438 m, 1393 w, 1368 m, 1305 m, 1066 w, 850 w. 1H-NMR (300 MHz, CDCl3): 5.67 (dtd, J = 10.3, 3.1, 1.6), 5.60 (dtd, J = 10.3, 3.1, 1.6) (H–C(3), H–C(4)); 5.14 (br. d, J = 9.0, NH); 4.23–4.14 (m, H–C(6)); 3.69 (s, MeO); 2.80 (td, J = 6.2, 3.1, H–C(1)); 2.57–2.46 (dm, J = 18, H–C(2)); 2.42–2.25 (m, H–C(2), H–C(5)); 2.22–2.10 (dm, J = 18, H–C(5)); 1.43 (s, Me3C). 13C-NMR (75 MHz, CDCl3): 173.78 (s, C=O2Me); 155.17 (s, CO2CMe3); 124.85, 124.68 (2d, C(3), C(4)); 79.30 (s, Me3C); 51.92 (q, MeO); 46.21 (d, C(1)); 42.18 (d, C(6)); 30.81 (t); 28.46 (q, Me3C); 25.45 (t). EI-MS: 255 (1, M+), 201 (7, [M–C4H6]+), 199 (9, [M–C4H8]+), 182 (13), 168 (14), 155 (18, [M–C4H8–CO2]+), 150 (16), 145 (14, [M–C4H8–C4H6]+), 142 (8), 138 (61), 101 (87, [M–C4H8–C4H6– CO2]+). Anal. calc. for C13H21NO4 (255.31): C 61.16, H 8.29, N 5.49; found: C 61.06, H 8.20, N 5.41.

O-tertButyl-N-/cis-6-(hydroxymethyl)-cyclohex-3-enyl]-carbamate (715).

A cold (0°) soln. of 714 (27.6 g, 108 mmol) in THF (350 ml) was treated with LiBH4 (3.5 g, 162 mmol), stirred at r.t. for 19 h. After cooling to 0°, the mixture was treated with sat. aq. NH4Cl soln. (40 ml) and diluted with AcOEt (400 ml). The organic phase was separated, washed with sat. aq. NaHCO3 soln. (2 x 400 ml), dried (Na2SO4), and evaporated. FC (125 g of silica gel, cyclohexane/AcOEt 3:1) gave colourless crystalline 715 (18.3 g, 74%). Rf (cyclohexane/AcOEt 3:1) 0.26. M.p. 105.0–105.9°. FT-IR (0.5%, CHCl3): 3611 w, 3435 w, 2983 w, 1684 m (C=O), 1502 s, 1368 m, 1062 w, 921 w, 843 m. 1H-NMR (300 MHz, CDCl3): 5.70 (dm, J = 10.0), 5.60 (dm, J =10.0) (H–C(3), H–C(4)); 4.74 (d, J = 8.4, NH); 4.22–4.15 (m, H–C(1)); 4.15–3.85 (br. s, OH); 3.48 (dd, J = 12.1, 4.7), 3.22 (t, J = 11.2) (CH2–OH);
2.44 (dm, J = 18.0, H–C(2)); 2.09 (dm, J = 18, H'–C(2)); 2.05–1.88 (m, H–C(5), H–C(6));
1.66–1.51 (m, H'–C(5)); 1.44 (s, Me₃C). ¹³C-NMR (75 MHZ, CDCl₃): 157.26 (s, C=O); 126.45, 123.49 (2d, C(3), C(4)); 79.89 (s, Me₃C); 63.57 (t, CH₂OH); 43.26 (d, C(1)); 38.90 (d, C(6)); 31.16 (t, C(5)); 28.39 (q, Me₃C); 23.40 (t, C(2)).


O-tert-Butyl-N-benzyl-N-[cis-6-(benzyloxymethyl)-cyclohex-3-enyl]-carbamate (718), O-tertButyl-N-[cis-6-(benzyloxymethyl)-cyclohex-3-enyl]-carbamate (716), and 1-Benzyl-1,4,4a,5,8,8a-hexahydro-cis-benzo[d][1.3]oxazin-2-one (717)
a) A cold (–30°) suspension of NaH (6.19 g of a 60% suspension in oil, 155 mmol) in DMF (225 ml) was treated dropwise with a soln. of 715 (17.6 g, 77.4 mmol) in DMF (50 ml), warmed to –20°, treated dropwise with BnBr (9.19 ml, 77.4 mmol), and stirred for 45 min. After treatment with MeOH (9 ml), the mixture was stirred at –30° for 30 min. and diluted with AcOEt (1000 ml). The organic phase was washed with H₂O (2 x 500 ml), dried (Na₂SO₄), and evaporated. FC (27.3 g of silica gel, cyclohexane/AcOEt 9:1 → 3:2) gave 716 (23.5 g, 95%) as a colourless oil, which crystallised upon standing, and 717 (980 mg, 5%) as a yellow oil, which crystallised upon standing.

b) A cold (0°) soln. of 715 (380 mg, 1.67 mmol) in DMF (5 ml) was treated with NaH (88 mg of a 55% suspension in oil, 2.00 mmol), stirred for 30 min. at 0°, treated dropwise with BnBr (0.30 ml, 2.51 mmol), stirred for 5 min, allowed to warm to r.t., and stirred for 19 h. The mixture was cooled to 0°, treated with MeOH (0.15 ml), stirred at 0° for 30 min, diluted with AcOEt (50 ml), and washed with H₂O (2 x 30 ml). The organic phase was dried (Na₂SO₄) and evaporated. FC (60 g of silica gel, cyclohexane/AcOEt 10:1) gave 718 (85 mg, 12%, colourless oil) and 716 (293 mg, 55%, colourless oil, which crystallised upon standing). Elution of the column with MeOH gave 717 (134 mg, 33%, yellow oil).

Data of 718:
Colourless oil. Rᶠ (cyclohexane/AcOEt 3:1) 0.74. FT-IR (3%, CHCl₃): 3089w, 3067w, 3030m, 3013s, 2980m, 2931m, 2862m, 1681s, 1496m, 1477m, 1454s, 1405m, 1392m, 1367s, 1351m, 1339m, 1272m, 1123m, 1076m, 1028w, 1012w, 971w, 904w, 884w, 857w, 853w. ¹H-NMR (300 MHZ, CDCl₃): 7.42–7.13 (10 arom. H); 5.64 (dm, J = 10.3), 5.56 (dm, J = 10.0)
(H–(3), H–C(4)); 4.65 (br. d, J = 17, PhCHN); 4.54–4.45 (m, H–C(1)); 4.51 (d, J = 11.8). 4.45 (d, J = 11.8) (PhCH₂O); 4.29 (d, J = 16.8, PhCHN'); 3.64 (dd, J = 9.2, 4.8, CH–C(6)); 3.43 (t, J = 8.9, CH–C(6)); 2.47–2.29 (m, 2 H); 2.23–2.07 (m, 3 H); 1.38 (s, Me₃C).

1³C-NMR (75 MHz, CDCl₃): 155.90 (s, C=O); 140.53, 138.42 (2s); 128.87–125.90 (several d); 125.77, 125.11 (2d, C(3), C(4)); 79.67 (s, Me₃C); 73.07, 70.26 (2t, PhCH₂O, CH₂–C(6)); 52.54 (d, C(1)); 48.22 (t, PhCH₂N); 37.77 (d, C(6)); 28.35 (q, Me₃C); 27.55 and 27.26 (2t, C(2), C(5)).


Data of 716:

Rf (cyclohexane/AcOEt 3:1) 0.66. M.p. 62.8–65.8. FT-IR (3%, CHCl₃): 3438 m (NH), 3090 w, 3067 w, 3067 w, 3020 m, 2981 m, 2922 m, 2866 m, 1706 s (C=O), 1501 s, 1455 m, 1392 m, 1367 s, 1337 w. 1H-NMR (300 MHz, CDCl₃): 7.37–7.25 (5 arom. H); 5.67–5.54 (m, H–C(3), H–C(4)); 5.20 (d, J = 8.4, NH); 4.54; 4.48 (2d, J = 11.8, PhCH₂); 4.10–4.01 (m, H–C(1)); 3.58 (t, J ≈ 8.7, CH–C(6)); 3.36 (dd, J = 9.3, 5.6, CH–C(6)); 2.43–2.19 (m, 3 H); 2.08–1.98 (m, 1 H); 1.85–1.75 (m, 1 H); 1.44 (s, Me₃C). 1³C-NMR (75 MHz, CDCl₃): 155.56 (s, C=O); 138.23 (s); 128.28 (2 d, C); 127.52 (d, 2 C), 127.47 (d); 125.55, 124.59 (2d, C(3), C(4)); 78.84 (s, Me₃C); 73.36, 72.05 (2t, PhCH₂, CH₂–C(6)); 46.41 (d, C(1)); 36.48 (d, C(6)); 30.97 (t, C(5)); 28.55 (q, Me₃C); 26.33 (t, C(2)). ESI-MS: 657 (14, [2M + Na]⁺), 377 (6), 356 (4, [M + K]⁺), 340 (36, [M + Na]⁺), 318 (60, [M + 1]⁺), 262 (13, [M + 1 – C₄H₈]⁺), 218 (4, [M + 1 – C₄H₈ – CO₂]⁺). Anal. calc. for C₁₉H₂₇NO₃ (317.43): C 71.89, H 8.57, N 4.41; found: C 71.78, H 8.54, N 4.37.

Data of 717:

Colourless amorphous. Rf (cyclohexane/AcOEt 3:1) 0.12. M.p. 79.8–81.6°. FT-IR (1.5%, CDCl₃): 3028 w, 3015 m, 2915 w, 2851 w, 1682 s (C=O), 1604 w, 1486 w, 1451 m, 1361 w, 1129 m, 1075 w, 1035 w, 963 w. 1H-NMR (300 MHz, CDCl₃): 7.38–7.24 (5 arom. H); 5.60–5.49 (m, H–C(6), H–C(7)); 5.03 (d, J = 15.3, PhCH); 4.27 (t, J = 11.4, H–C(4)); 4.19 (d, J = 15.3, PhCH); 4.13 (ddd, J = 10.6, 4.7, 1.9, H–C(4)); 3.43–3.35 (m, H–C(8a)); 2.50–2.31 (m, H–C(4a), H–C(5), H–C(8)); 2.15–2.03 (m, H–C(8)); 1.89 (dm, J = 18, H–C(5)). 1³C-NMR (75 MHz, CDCl₃): 153.12 (s, C=O); 137.14 (s); 128.55 (d, 2 C); 127.82 (d, 2 C); 127.49 (d); 123.99, 122.20 (2d, C(6), C(7)); 67.77 (t, C(4)); 50.87 (t, PhCH₂); 50.80 (d, C(8a)); 29.90
N-(cis-6-[Benzyloxymethyl]-cyclohex-3-enyl)-2,2,2-trifluoroacetamide (72).

A soln. of 716 (1 g, 3.15 mmol) in CH2Cl2 (25 ml) was treated with CF3CO2H (4 ml, 52 mmol), stirred at r.t. for 1.5 h, and evaporated. The soln. of the residue (milky oil) in CH2Cl2 (10 ml) was treated with Et3N (4 ml, 28.7 mmol) and trifluoroacetic acid anhydride (1.7 ml, 12.2 mmol), stirred at r.t. for 19 h, and evaporated. FC (cyclohexane/AcOEt 9:1) of the residue (orange oil) gave 72 (848 mg, 84%) as a yellow oil. 

\[ R_f (\text{cyclohexane/AcOEt 3:1}) 0.66. \]

FT-IR (1%, CHCl3): 3363 w (NH), 3033 w, 2920 w, 2868 w, 2848 w, 1718 s (C=O), 1583 m, 1455 w, 1440 w, 1373 w, 1290 w, 1093 w, 1074 w, 1004 w, 911 w. 1H-NMR (300 MHz, CDCl3): 7.92–7.82 (br.s, NH); 7.40–7.28 (5 arom. H); 5.61 (dm, J = 11.8, H–C(4)); 5.57 (dm, J = 11.5, H–C(3)); 4.52, 4.48 (2d, J = 11.5, PhCH2); 4.33 (tdd, J = 8.4, 5.6, 2.8, H–C(1)); 3.72 (t, J = 9.8, CH–C(6)); 3.48 (dd, J = 9.7, 4.4, CH’–C(6)); 2.50–2.32 (m, H–C(2), H–C(5), H–C(6)); 2.02 (ddm, J = 17, 9, H’–C(2)); 1.82 (dm, J = 18, H’–C(5)). 13C-NMR (75 MHz, CDCl3): 137.10 (s); 128.41 (d, 2 C); 127.75 (d, 2 C); 124.91, 123.98 (2d, C(3), C(4)); 73.85, 71.51 (2r, PhCH2,CH2–C(6)); 47.76 (d, C(1)); 34.94 (d, C(6)); 28.16, 27.37 (2t, C(2), C(5)); signals for COCF3 hidden by noise. 19F-NMR (282 MHz, CDCl3): -76.14 (s). ESI-MS: 368 (7, [M + Na + MeOH]+), 352 (18, [M + K]+), 336 (100, [M + Na]+), 314 (60, [M + 1]+).

PT-IR (1%, CHCl3): 3363 w (NH), 3033 w, 2920 w, 2868 w, 2848 w, 1718 s (C=O), 1583 m, 1455 w, 1440 w, 1373 w, 1290 w, 1093 w, 1074 w, 1004 w, 911 w. 1H-NMR (300 MHz, CDCl3): 7.92–7.82 (br.s, NH); 7.40–7.28 (5 arom. H); 5.61 (dm, J = 11.8, H–C(4)); 5.57 (dm, J = 11.5, H–C(3)); 4.52, 4.48 (2d, J = 11.5, PhCH2); 4.33 (tdd, J = 8.4, 5.6, 2.8, H–C(1)); 3.72 (t, J = 9.8, CH–C(6)); 3.48 (dd, J = 9.7, 4.4, CH’–C(6)); 2.50–2.32 (m, H–C(2), H–C(5), H–C(6)); 2.02 (ddm, J = 17, 9, H’–C(2)); 1.82 (dm, J = 18, H’–C(5)). 13C-NMR (75 MHz, CDCl3): 137.10 (s); 128.41 (d, 2 C); 127.75 (d, 2 C); 124.91, 123.98 (2d, C(3), C(4)); 73.85, 71.51 (2r, PhCH2,CH2–C(6)); 47.76 (d, C(1)); 34.94 (d, C(6)); 28.16, 27.37 (2t, C(2), C(5)); signals for COCF3 hidden by noise. 19F-NMR (282 MHz, CDCl3): -76.14 (s). ESI-MS: 368 (7, [M + Na + MeOH]+), 352 (18, [M + K]+), 336 (100, [M + Na]+), 314 (60, [M + 1]+).

(±)-(1R*,5R*,8R*)-8-Bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene (720) and N-(t-3-acetoxy-c-4-bromocyclohexyl)-2,2,2-trifluoroacetamide (721).

a) A soln. of 71 (210 mg, 1.09 mmol) in AcOH (10 ml) was treated with NBS (580 mg, 3.26 mmol), stirred at r.t. for 85 min., and evaporated. The residue, suspended in AcOEt (25 ml) was washed with sat. aq. NaHCO3 soln. (20 ml) and brine (20 ml). The aq. phases were extracted with AcOEt (25 ml), and the combined organic phases were dried (Na2SO4) and evaporated. FC (cyclohexane/AcOEt 9:1) of the residue (520 mg) gave 720 (91.5 mg, 31%) and 721 (86.3 mg, 24%), as red oils.

b) A soln. of 71 (31 mg, 0.16 mmol) in AcOH (1.6 ml) was treated at 5° with NBS (88.5 mg, 0.50 mmol), stirred at r.t. for 1.5 h, and evaporated. A suspension of the residue in AcOEt (25 ml) was washed with sat. aq. NaHCO3 soln. (20 ml) and brine (20 ml), dried (Na2SO4), and evaporated. Two FC (2 g of silica gel, cyclohexane/AcOEt 9:1) of the residue (72 mg, yellow, amorphous) gave 721 (9.3 mg, 17%) as a colourless oil.
Data of 720:

Rf (cyclohexane/AcOEt 3:1) 0.68. FT-IR (1.5%, CHCl3): 2953w, 1788w, 1686m, 1443w, 1391w, 1369w, 1349m, 1332w, 1288m, 1159s, 1124s, 1114m, 1090w, 1051m, 1021m, 981w, 903w, 851w.

1H-NMR (300 MHz, CDCl3): 4.75–4.70 (m, H–C(1)); 4.50–4.45 (m, H–C(8)); 3.93–3.88 (m, H–C(5)); 2.59 (dt, J = 14.0, 1.6, H–C(9)); 2.18–2.01 (m, H–C(6)); 1.99–1.83 (m, H’–C(6), CH2(7)); 1.77 (dtt, J = 14.0, 3.7, 1.9, H’–C(9)).

13C-NMR (75 MHz, CDCl3): 74.47 (d, C(1)); 48.17, 46.73 (2d, C(5), C(8)); 25.02, 24.90, 22.85 (3t, C(6), C(7), C(9)); q for CF3CO hidden by noise.

ESI-MS: 196 (10), 194 (10, [M – CCF3 + 4 H]+); 87 (100).

Data of 721:

Rf (cyclohexane/AcOEt 3:1) 0.49. FT-IR (1.5%, CHCl3): 3426w (NH), 3034w, 3008w, 2959w, 1727s (C=O), 1537m, 1457w, 1436w, 1374m, 1260m, 1095w, 1063w, 1036m, 1018m, 983w, 909w.

1H-NMR (300 MHz, CDCl3): 6.25–6.16 (br. s, NH); 5.21 (q, J = 3.4, H–C(3)); 4.27 (q, J = 3.4, H–C(4)); 4.24–4.11 (m, H–C(1)); 2.32–1.73 (m, 6 H); 2.11 (s, MeO).

13C-NMR (75 MHz, CDCl3): 169.89 (s, COMe); 156.85 (q, J = 37.6, COCF3); 115.91 (q, J = 289.3, CF3); 71.96 (d, C(3)); 47.53, 44.75 (2d, C(1), C(4)); 30.81, 28.43, 26.55 (3t, C(2), C(5), C(6)); 21.07 (q, Me).

19F-NMR (282 MHz, CDCl3): –75.70 (s).

ESI-MS: 388 (35), 386 (34, [M + Na + MeOH]+); 356 (97), 354 (100, [M + Na]+).

N-(trans-3,4-epoxycyclohexyl)-2,2,2-trifluoroacetamide (722) and (+)-(1R*,5R*,8R*)-3-Trifluoromethyl-2-oxa-4-azabicyclo[3.3.1]non-3-en-8-ol (723).

a) A cold (0°) soln. of 721 (17 mg, 51 µmol) in THF (1.5 ml) was treated with NaH (3.7 mg of a 50% suspension in oil, 77 µmol), stirred at 0° for 1 h, stirred for 20 h while warming to r.t., and poured into H2O (10 ml). The mixture was extracted with CH2Cl2 (4 x 15 ml). The combined organic phases were dried (Na2SO4), and evaporated. FC (2 g of silica gel, cyclohexane/AcOEt 2:1) of the residue (11.9 mg, colourless oil) gave 722 (3.0 mg, 28%) and 723 (3.6 mg, 33%), both as colourless volatile oils.

b) 723 (16.7 mg, 89%) was obtained by hydrolysis of 721 (30 mg, 90 µmol) in MeOH (1 ml) and H2O (0.2 ml) with K2CO3 (30 mg, 217 µmol).
Data of 722:

$R_f$ (cyclohexane/AcOEt 1:1) 0.59. FT-IR (0.2%, CHCl$_3$): 3410 w (NH), 2950 w, 1727 s (C=O), 1528 w, 1262 s, 1171 s, 1093 m, 1020 m, 974 w, 928 w, 822 m. $^1$H-NMR (300 MHz, CDCl$_3$): 6.13–5.99 (br. s, NH); 4.08–3.96 (m, H–C(1)); 3.26–3.23 (m, J = 2.2, 1.9, irr. at 2.46 pp, $\rightarrow$ dd, J = 3.7, 2.2, H–C(3)); 3.18 (td, J = 3.7, 1.6, H–C(4)); 2.46 (ddt, J = 14.6, 5.3, 1.5, H–C(2)); 2.10–2.03 (m, CH$_2$(5)); 1.81–1.70 (H–C(6)); 1.75 (dddd, J = 14.6, 8.6, 2.7, H’–C(2)); 1.38 (ddt, J = 12.7, 10.0, 7.2, H’–C(6)). $^{13}$C-NMR (75 MHz, CDCl$_3$): 51.98, 50.80 (C(3), C(4)); 43.68 (C(1)); 30.84, 25.65, 21.99 (C(2), C(5), C(6)); signals for CF$_3$CO hidden by noise. $^{19}$F-NMR (282 MHz, CDCl$_3$): –75.72. ESI-MS (neg. mode): 254 (65, [M + HCOO]$^-$), 208 (60, [M – 1]$^-$), 91 (68), 45 (100).

Data of 723:

$R_f$ (cyclohexane/AcOEt 1:1) 0.47. FT-IR (0.5%, CHCl$_3$): 3618 w (OH), 2998 w, 2948 w, 1689 m, 1446 w, 1393 w, 1322 w, 1290 m, 1262 w, 1153 s, 1100 s, 1080 m, 1023 m, 1004 m, 970 w, 936 w, 851 w. $^1$H-NMR (300 MHz, CDCl$_3$): 4.59–4.55 (m, H–C(1)); 4.18–4.13 (m, H–C(8)); 3.90–3.84 (m, H–C(5)); 2.26 (dt, J = 14.0, 1.5, H–C(9)); 2.02 (ddt, J = 13.6, 4.7, 3.1, H–C(6)); 1.88–1.78 (m, H’–C(6)); 1.73–1.62 (m, H–C(7), H’–C(9)); 1.53 (dddd, J = 15.3, 13.4, 5.3, 3.4, H’–C(7)); (OH hidden between 1.73 and 1.47). $^{13}$C-NMR (75 MHz, CDCl$_3$): 74.26 (d, C(1)); 67.39 (d, C(8)); 46.94 (d, C(5)); 25.02, 23.92, 22.46 (3t, C(6), C(7), C(9)). $^{19}$F-NMR (282 MHz, CDCl$_3$): –74.33 (s). EI-MS: 209 (24, [M]$^+$); 153 (99, [M – 56]$^+$).

N-[c-4-Bromo-t-3-(4-bromobutoxy)-cyclohexyl]-2,2,2-trifluoroacetamide (719).

A cold (0°) soln. of 71 (59 mg, 0.33 mmol) in THF (2 ml) was treated with NBS (29 mg, 0.16 mmol) and stirred for 25 h while allowed to warm to r.t. The mixture was diluted with Et$_2$O (10 ml), washed with sat. aq. Na$_2$S$_2$O$_5$ soln. (3 x 10 ml) and brine (10 ml), dried (Na$_2$SO$_4$), and evaporated. FC (2 g of silica gel, cyclohexane/AcOEt 12:1) of the residue (31 mg, colourless oil) gave 719 (14.7 mg, 31%) as a colourless oil and an unidentified byproduct(3.2
mg. *R* (toluene/AcOEt 10:1) 0.58. FT-IR (1.5%, CHCl3): 3428 w (NH), 2953 w, 1725 s (C=O), 1536 m, 1435 w, 1384 w, 1357 w, 1097 m, 968 w. 1H-NMR (300 MHz, CDCl3): 6.14–6.07 (br. s, NH); 4.32 (q, J = 3.2, H–C(3)); 4.22–4.08 (m, H–C(1)); 3.76 (q, J = 3.1, H–C(4)); 3.59–3.49 (m, 2 H); 3.45 (t, J = 6.5, 2 H) (CH2(1’), CH2(4’)); 2.30 (ddt, J = 15.4, 12.1, 3.5, H–C(5)); 2.10–1.65 (m, CH2(2), H’–C(5), CH2(6), CH2(2’), CH2(3’)). 13C-NMR (75 MHz, CDCl3): 78.01 (d, C(3)); 68.81 (t, C(1’)); 49.38, 44.74 (2 d, C(1), C(4)); 33.69 (t, C(4’)); 30.68, 29.58, 28.59, 28.14, 26.54 (5 t, C(2), C(5), C(6), C(2’), C(3’)). 19F-NMR (282 MHz, CDCl3): –75.74 (s).

**BnOH2C** (±)-(1*R*,5*S*,6R*,8R*)-6-(Benzyloxymethyl)-8-bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene (**724**).

A solution of **72** (36 mg, 115 µmol) in AcOH (3 ml) was treated at 10° with NBS (61 mg, 345 µmol), stirred for 90 min at r.t., and evaporated. The residue was suspended in AcOEt (20 ml) and washed with sat. aq. NaHCO3 soln. (20 ml) and brine (20 ml). The aq. phases were extracted with AcOEt (20 ml). The combined organic phases were dried (Na2SO4), and evaporated. FC (2 g of silica gel, hexane/AcOEt 8:1) of the residue (85 mg, yellow oil) gave **724** (36 mg, 79%) as a colourless oil. *R* (cyclohexane/AcOEt 3:1) 0.68. FT-IR (0.5%, CHCl3): 3008 w, 2927 m, 2857 w, 1728 w, 1688 m, 1602 w, 1454 w, 1442 w, 1390 w, 1362 w, 1166 s, 1130 s, 1100 m, 1076 m, 1040 w, 914 w. 1H-NMR (300 MHz, CDCl3): 6.76–6.75 (5 arom. H); 4.74–4.69 (m, H–C(1)); 4.57 (d, J = 11.8, PhCH); 4.51–4.47 (m, H–C(8)); 4.49 (d, J = 11.8, PhCH); 4.04–3.99 (m, H–C(5)); 3.56 (dd, J = 9.0, 7.5, CH–C(6)); 3.29 (dd, J = 9.0, 6.5, CH–C(6)); 2.65–2.54 (m, H–C(6)); 2.54 (dt, J = 14.3, 1.6, Hax–C(9)); 2.12 (br. dd, J = 15.9, 2.5, Heq–C(7)); 1.83 (ddtt, J = 14.3, 3.9, 1.6, Heq–C(9)); 1.57 (ddd, J = 15.9, 12.1, 4.0, Hax–C(7)). 13C-NMR (75 MHz, CDCl3): 147.62 (q, J = 38.4, O–C=N); 138.05 (s); 128.30 (d, 2 C); 127.56 (d, 3 C); 116.26 (q, J = 275.9, CF3); 74.33 (d, C(1)); 73.28 (t, PhCH2); 71.34 (t, CH2–C(6)); 47.80, 47.68 (2d, C(5), C(8)); 38.04 (d, C(6)); 28.88 (t, C(7)); 23.32 (t, C(9)). 19F-NMR (282 MHz, CDCl3): –73.10 (s). HR-MS (MALDI): 412 (86), 410.0578 (100) (C16H20BrF3NO3+ [M + H3O]+; calc. 410.0579); 394 (1); 382.0475 (1) (C16H18BrF3NO2+, [M + Na]2+; calc. 392.0473); 298 (6), 296 (6, [M + 2 – COCF3]2+).
(-)-(1R*,5S*,6S*,8R*)-6-(6-Chloropyrid-3-yl)-8-bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene 725

A soln. of 655 (50 mg, 167 µmol) in AcOH (3 ml) was treated at 10° with NBS (89 mg, 501 µmol), stirred for 90 min. at r.t., and evaporated. A suspension of the residue in AcOEt (20 ml) was washed with sat. aq. NaHCO₃ soln. (20 ml) and brine (20 ml), dried (Na₂SO₄), and evaporated. FC (2 g of silica gel, hexane/AcOEt 6:1) of the residue (99 mg, yellow, amorphous) gave 725 (52 mg, 81%) as a colourless oil. Rf (toluene/AcOEt 10:1) 0.42. FT-IR(1%, CHCl₃): 3003 w, 2945 w, 1688 m, 1586 w, 1565 w, 1461 m, 1441 w, 1387 w, 1363 w, 1335 w, 1161 s, 1128 s, 1106 m, 1087 w, 1053 w, 1025 w, 1001 w, 967 w, 929 w, 915 w, 875 w. ¹H-NMR (300 MHz, CDCl₃): 8.33 (d, J = 2.5, 1 arom. H); 7.62 (dd, J = 8.4, 2.8, 1 arom. H); 7.28 (d, J = 8.4, 1 arom. H); 4.79 (tt, J = 3.5, 1.7, irr. at 4.02–3.97 → td, J = 3.5, 1.6, irr. at 2.74 → td, J = 3.6, 2.2, H–C(1)); 4.62–4.57 (m, H–C(8)); 4.02–3.97 (m, H–C(5)); 3.52 (ddd, J = 10.3, 6.5, 2.2, H–C(6)); 2.74 (dt, J = 14.3, 1.6, H–C(9)); 2.21–2.08 (m, CH₂(7)); 1.95 (dd, J = 14.3, 4.0, 1.6, H'–C(9)). ¹³C-NMR (75 MHz, CDCl₃): 150.54 (s); 149.54 (s); 138.42 (d); 135.87 (s); 124.35 (d); 73.82 (d, C(1)); 51.26, 47.62 (2 d, C(5), C(8)); 40.45 (d, C(6)); 32.12, 24.18 (2t, C(7), C(9)). ¹⁹F-NMR (282 MHz, CDCl₃): –73.54 (s).

Hydrolysis of 725 to c-3-Ammonia-t-6-bromo-c-3-(6-chloro-3-pyridinium)-cyclohexane trifluoroacetamide 726-CF₃COOH.

A soln. of 725 (5.6 mg, 14.6 µmol) in THF (1 ml) and H₂O (0.33 ml) was treated with CF₃COOH (1 drop), stirred at r.t. for 50 min, and evaporated. The residue was coevaporated with MeOH to yield crude 726-CF₃COOH (7.8 mg, quant.) as a colourless oil. Rf (CH₂Cl₂/MeOH 9:1) 0.40. ¹H-NMR (300 MHz, D₂O): 8.33 (d, J = 2.5, 1 arom. H); 7.83 (dd, J = 8.4, 2.5, 1 arom. H); 7.52 (d, J = 8.4, 1 arom. H); 4.61–4.56 (qd, J = 3.4, 2, irr. at 2.09 → q, J = 3.4, H–C(6)); 4.25 (q, J = 3.4, irr. at 2.64 → q, J = 3.4, H–C(1)); 4.61–4.56 (qd, J = 3.4, 2, irr. at 2.64 → q, J = 3.4, H–C(6)); 4.25 (q, J = 3.4, irr. at 2.64 → q, J = 3.4, H–C(1)); 3.86–3.78 (m, H–C(3), H–C(4)); 2.90 (ddd, J = 15.6, 12.1, 3.4, H–C(5)); 2.64 (dt, J = 15.6, 3.4, H–C(2)); 2.23 (br. dt, J = 15.6, 3.1, H'–C(5)); 2.09 (dm, J = 15.5, H'–C(2)). ¹³C-NMR (75 MHz, D₂O): 149.64; 148.35; 139.65; 133.89; 124.86; 68.14 (C(1)); 51.09, 50.29 (C(3), C(6)); 43.02 C(4)); 35.34, 30.20 (C(2), C(5)). ¹⁹F-NMR (282 MHz, D₂O): –76.08 (s). HR-MS (MALDI): 425 (24), 423.
O-tertButyl N-(t-3,c-4-dibromocyclohexyl)carbamate (728) and O-tertButyl N-(c-3,t-4-dibromocyclohexyl)carbamate (727).

Method A)
A solution of 712 (849 mg, 4.3 mmol) in CH₂Cl₂ (50 ml) was treated with Et₄NBr (9.0 g, 43 mmol) at r.t., cooled to –78°, treated with Br₂ (0.44 ml, 1.38 g, 8.6 mmol) over a period of 10 min, stirred at –78° for 2 h, and poured into sat. aq. Na₂S₂O₅ soln. (50 ml). The mixture was extracted with AcOEt (4 x 50 ml), and the combined organic phases dried (Na₂SO₄) and evaporated. FC (60 g of silica gel, cyclohexane/AcOEt 12:1) gave 728 (590 mg, 38%) and 727 (775 mg, 50%).

Data of 728:
Colourless crystals. Rf (cyclohexane/AcOEt 3:1) 0.67. M.p. 105–106°. FT-IR (1.5%, CHCl₃): 3442 m (NH), 3008 m, 2980 m, 1709 s (C=O), 1503 m, 1454 w, 1435 m, 1392 m, 1368 m, 1323 w, 1313 m (H–C(5)); 2.04–1.94 (dm, J = 15.3, 1 H); 1.93–1.83 (dm, J = 12.8, 1 H); 1.71 (qd, J = 12.3, 3.4, H–C(6)); 1.44 (s, Me₃C). ¹³C-NMR (75 MHz, CDCl₃): 155.30 (s, C=O); 79.66 (s, Me₃C); 52.36, 51.79 (2d, C(3), C(4)); 44.95 (d, C(1)); 35.24 (t, C(2)); 28.45 (q, Me₃C); 28.38, 27.59 (2t, C(5), C(6)). ESI-MS: 414 (48), 412 (100), 410 (50, [M + Na + MeOH]⁺); 398 (17), 396 (32), 394 (14, [M + K]⁺); 382 (26), 380 (53), 378 (27, [M + Na]⁺).

Data of 727:
Colourless crystals. Rf (cyclohexane/AcOEt 3:1) 0.60. M.p. 128–129°. FT-IR (1.5%, CHCl₃): 3441 w (NH), 3008 m, 2980 m, 1708 s (C=O), 1503 w, 1454 w, 1435 m, 1392 w, 1368 m, 1314 m, 1274 m, 1164 s, 1076 w, 1045 m, 1012 w, 949 w, 917 w, 860 w. ¹H-NMR (300 MHz, CDCl₃): 4.67–4.57 (br. s, NH); 4.10 (td, J = 9.3, 4.1); 4.02 (td, J = 9.3, 4.1), H–C(3), H–C(4); 3.66–3.53 (br. s, HW₅₀ = 20 Hz, H–C(1)); 2.79–2.69 (br. d, J = 13.4, 1 H); 2.52–2.43 (m, 1 H); 2.06–1.97 (m, 1 H); 1.95–1.73 (m, 2 H); 1.42 (br. s, Me₃C); 1.38–1.21 (m, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 155.13 (s, C=O); 79.91 (s, Me₃C); 55.33, 53.44 (2d, C(3), C(4)); 48.18 (d, C(1)); 42.99 (t, C(2)); 34.33, 32.12 (2t, C(5), C(6)); 28.43 (q, Me₃C). ESI-MS: 414
N-((t-3,c-4-Dibromocyclohexyl)-2,2,2-trifluoroacetamide (730) and N-((c-3,t-4-Dibromocyclohexyl)-2,2,2-trifluoroacetamide (729).

Method B)
At 0°, a solution of 71 (11.61 g, 60.1 mmol) in CH2Cl2 (250 ml) was treated with phenyltrimethylammonium tribromide (45.2 g, 120.2 mmol), stirred for 2.5 h, and poured into ice-cold sat. aq. Na2S2O5 soln. (600 ml). The aqueous phase was extracted with AcOEt (2 x 500 ml), and the combined organic phases were dried (Na2SO4) and evaporated. FC (200 g of silica gel, cyclohexane/AcOEt 12:1) gave 730 (3.27 g, 15%) and 729 (16.79 g, 79%).

Method A)
Conversion of 71 (102 mg, 0.53 mmol) acc. to Method A (vide supra) gave 730 (51 mg, 27%) and 729 (120 mg, 64%).

Data of 730:
Amorphous solid. Rf (cyclohexane/AcOEt 3:1) 0.59. M.p. 114–115°. FT-IR (1.5%, CHCl3): 3426m (NH), 3011w, 2957w, 2908w, 1728s (C=O), 1536m, 1454w, 1436w, 1385w, 1395m, 1298w, 1278w, 1259m, 1171s, 1027w, 962w, 899w, 849w. 1H-NMR (300 MHz, CDCl3): 6.41–6.29 (m, NH); 4.69–4.64 (m, H–C(3)); 4.64–4.59 (m, H–C(4)); 4.40 (tdt, J = 11.8, 8.1, 4.1, H–C(1)); 2.61 (ddddd, J = 15.6, 12.5, 4.1, 3.1, H–C(5)); 2.46 (ddd, J = 14.2, 11.7, 3.4, H–C(2)); 2.25 (dm, J = 14.3, H'–C(2)); 2.05 (dm, J = 14.9, H'–C(5)); 1.98 (dm, J = 13.3, H–C(6)); 1.86 (qd, J = 12.1, 3.7, H’–C(6)). 13C-NMR (75 MHz, CDC13): 51.30, 50.58 (2d, C(3), C(4)); 44.83 (d, C(1)); 33.82 (t, C(2)); 27.18, 26.49 (2t, C(5), C(6)). ESI-MS (neg. mode): 390 (36), 388 (50), 386 (23, [M + Cl]–): 354 (47), 352 (100), 350 (49, [M − H]–).

Anal. calc. for C8H10Br2NO2F3 (352.98): C 27.22, H 2.86, N 3.97; found: C 27.33, H 2.96, N 3.84.

Data of 729:
Amorphous solid. Rf (cyclohexane/AcOEt 3:1) 0.48. M.p. 99–100°. FT-IR (1.5%, CHCl3): 3426w (NH), 3400w, 3008w, 2957w, 2862w, 1727s (C=O), 1535m, 1448w, 1438w, 1424w, 1381w, 1344w, 1293w, 1263m, 1170s, 1082w, 997w, 950w, 928w, 878w. 1H-NMR (300 MHz, CDCl3): 7.13–7.00 (m, NH); 4.33–4.19 (m, H–C(3), H–C(4)); 4.08 (qt, J = 8.1, 4.0,
H–C(1)); 2.80 (dd, J = 14.0, 4.1, H–C(2)); 2.51 (dd, J = 14.6, 7.2, 3.4, H–C(5)); 2.16–1.91 (m, H–C(6), H–C(2), H–C(5)); 1.65–1.53 (m, H–C(6)). 13C-NMR (75 MHz, CDCl3): 156.77 (q, J = 37, C=O); 115.89 (q, J = 288, CF3); 53.54, 51.66 (2d, C(3), C(4)); 46.61 (d, C(1)); 38.20 (t, C(2)), 30.84, 28.85 (2t, C(5), C(6)). ESI-MS (neg. mode): 390 (37), 388 (53), 386 (23, [M + Cl]–); 354 (46), 352 (100), 350 (47, [M – H]+). Anal. calc. for C8H10Br2NOF3 (352.98): C 27.22, H 2.86, N 3.97; found: C 27.34, H 2.50, N 3.91.


a) At 0°, soln. of 716 (130 mg, 0.41 mmol) in CH2Cl2 (10 ml) was treated with PhMe3NBr3 (310 mg, 0.82 mmol), stirred for 160 min., treated with sat. aq. Na2S2O5 soln. (20 ml), and extracted with Et2O (2 x 20 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (15 g of silica gel, cyclohexane/AcOEt 10:1) gave 731 (91 mg, 46%). Elution of the column with MeOH gave 733 (69 mg, 49%).
b) At –78°, a soln. of 716 (140 mg, 0.44 mmol) in CH2Cl2 (10 ml) was treated with Br2 (0.07 ml, 1.32 mmol), stirred for 160 min, and worked up as described in a). FC (15 g of silica gel, cyclohexane/AcOEt 10:1) gave 731 (37.5 mg, 18%), 732 (14 mg, 6%), and 734 (43.4 mg, 32%). Elution of the column with MeOH gave 733 (58 mg, 43%).
c) At –78°, a suspension of 716 (2.0 g, 6.5 mmol) and Et4NBr (13.2 g, 63 mmol) in CH2Cl2 (20 ml) was treated with PhMe3NBr3 (4.79 g, 12.6 mmol), and allowed to warm to r.t. within 20 h. Workup as described in a) and FC (100 g of silica gel, cyclohexane/AcOEt 10:1) gave 731 (2.48 g, 82%) as colourless crystals.

Data of 731:
Colourless crystals. Rf (toluene/AcOEt 10:1) 0.58. M.p.: 117° (decomp.). FT-IR (2%, CHCl3): 3433w (NH), 3020m, 2981m, 2932w, 2868w, 1707s (C=O), 1502s, 1455m, 1393m, 1377m, 1323w, 1280w, 1090m, 1040w, 1028w, 981w, 857w. 1H-NMR (300 MHz, CDCl3): 7.39–7.26 (5 arom. H); 5.60 (br. d, J = 8.1, NH); 4.54, 4.46 (2d, J = 11.8, PhCH2); 4.50–4.41 (m, H–C(4)); 4.37–4.29 (m, H–C(5)); 4.03–3.93 (m, H–C(1)); 3.67 (dd, J = 9.7, 7.2, CH–C(2)); 3.47 (dd, J = 9.7, 5.3, CH–C(2)); 2.66 (dt, J = 14.6, 4.4, H–C(6)); 2.49–2.40 (m, H–C(2)); 2.34 (ddd, J = 14.6, 7.6, 3.6, H–C(3)); 2.22 (dt, J = 14.6, 7.3, H–C(6)); 2.08 (ddd, J = 14.6, 7.6, 4.0, H–C(3)); 1.43 (s, Me3C). 13C-NMR (75 MHz, CDCl3): 155.07 (s, C=O);
137.65 (s); 128.41 (d, 2 C); 127.34 (d); 127.58 (d, 2 C); 79.35 (s, Me3C); 73.46 (t, PhCH2); 70.69 (t, CH2–C(2)); 53.06, 52.06, 48.33 (3d, C(1), C(4), C(5)); 36.43 (d, C(2)); 28.54 (q, Me3C); 2 t hidden (probably at 28.54 ppm). ESI-MS: 518 (14), 516 (29), and 514 (15, [M + K]+); 502 (49), 500 (100), and 498 (57, [M + Na]+); 446 (19), 444 (19), and 442 (7, [M + Na – C4H8]+); 380 (5), 378 (10), and 376 (7, [M + 1 – C4H8 –CO2]+). Anal. calc. for C19H27Br2NO3 (477.24): C 47.82, H 5.70, N 2.93; found: C 47.94, H 5.76, N 2.86.

Data of 732:
Colourless oil. Rf (toluene/AcOEt 10:1) 0.56. 1H-NMR (300 MHz, CDCl3): 7.38–7.12 (5 arom. H); 5.21 (br. s, NH); 4.49 (d, J = 12.1), 4.44 (d, J = 11.8) (PhCH2); 4.26–4.05 (5, 2 H); 4.00–3.94 (m, 1 H); 3.54 (br. dd, J = 9.5, 5.1, CH–C(2)); 3.41 (br. dd, J = 9.0, 4.4, CH’–C(2)); 2.92 (d, J = 14.0, 1 H); 2.58–2.39 (m, 2 H); 2.09–1.96 (m, 2 H); 1.46 (s, Me3C). 13C-NMR (75 MHz, CDCl3): 155.32 (C=O); 137.48; 128.35 (2 C); 137.73; 127.61 (2 C); 80.35 (Me3C); 73.59 (PhCH2); 71.56 (C=CH2–C(2)); 52.78, 49.67, 48.54 (C(1, C(4), C(5)); 40.62 (C(2)); 38.86; 28.47 (Me3C); 1 signal hidden by other signal. ESI-MS+: 518 (16), 516 (35), 514 (21, [M + K]+); 502 (43), 500 (100), 498 (44, [M + Na]+).

Data of 734:
Colourless amorphous. Rf (toluene/AcOEt 10:1) 0.25. M.p.: 153.3–155.0. FT-IR (1%, CHCl3): 3445 w (NH), 3031 w, 3011 m, 2981 m, 2885 w, 1711 s (C=O), 1501 s, 1454 w, 1368 m, 1326 w, 1278 m, 1087 w, 1053 m, 1030 m, 1000 w, 971 w, 945 w, 923 w, 83 w, 819 w. 1H-NMR (300 MHz, CDCl3): 4.51 (br. d, J = 6.9, NH); 4.29 (dd, J = 5.6, 4.4, H–C(5)); 4.14 (t, J = 4.7, H–C(4)); 4.05–3.93 (m, HW50 = 20 Hz, H–C(2)); 3.86 (d, J = 8.7, Hendo–C(7)); 3.79 (dd, J = 8.7, 4.0, Hexo–C(7)); 2.59–2.54 (m, H–C(1)); 2.52 (d, J = 12.8, Hax–C(8)); 2.20 (dd, J = 15.1, 5.5, irr. at 3.99 -> d, J = 15.1, Heq–C(3)); 1.97 (ddd, J = 14.9, 12.1, 5.3, irr. at 3.99 -> dd, J = 14.9, 5.3, Hax–C(3)); 1.87 (dt, J = 12.5, 5.6, 1.2, Heq–C(8)); 1.43 (s, Me3C). 13C-NMR (75 MHz, CDCl3): 154.70 (s, C=O); 79.71 (s, Me3C); 77.13 (d, C(5)); 68.52 (t, C(7)); 47.80, 47.47 (2d, C(2), C(4)); 40.37 (d, C(1)); 34.54, 31.94 (2r, C(3), C(8)); 28.43 (q, Me3C). ESI-MS: 356 (100); 346 (12), 344 (12, [M + K]+); 330 (37), 328 (29, [M + Na]+).
Data of 733:

Yellow amorphous. \( R_f \) (toluene/AcOEt 10:1) 0.02. M.p.: 136–141\(^\circ\). FT-IR (1%, CHCl\(_3\)): 3443 \( w \)(NH), 3033 \( w \), 3010 \( m \), 2867 \( w \), 1715 \( s \)(C=O), 1604 \( w \), 1436 \( m \), 1409 \( w \), 1369 \( w \), 1294 \( w \), 1102 \( m \), 1038 \( w \), 904 \( w \). 1H-NMR (300 MHz, CDCl\(_3\)): 7.41–7.29 (5 arom. H); 5.33–5.28 (m, NH); 4.68–4.64 (m, H–C(1)); 4.54 (d, \( J = 12.1 \), PhCH\(_2\)); 4.50–4.46 (m, H–C(8)); 4.45 (d, \( J = 12.1 \), PhCH\(_2\)); 3.78–3.73 (m, H–C(5)); 3.37 (dd, \( J = 9.5, 5.1 \), CH–C(6)); 3.31 (t, \( J = 9.2 \), CH\(^\prime\)–C(6)); 2.53 (ddt, \( J = 14.0, 2.2, 1.6 \), H\(_{ax}\)–C(9)); 2.41–2.30 (m, H–C(6)); 2.04 (dt, \( J = 14.0, 4.0, 1.6 \), irr. at 4.48 \( \rightarrow dt \), H\(_{eq}\)–C(9)); 1.97–1.90 (m, CH\(_2\)(7)). 13C-NMR (75 MHz, CDCl\(_3\)): 153.72 (s, C=O); 137.80 (s); 128.45 (d, 2 C); 127.82 (d, 2 C); 75.49 (d, C(1)); 73.30 (t, PhCH\(_2\)); 70.35 (t, CH\(_2\)–C(6)); 47.68, 46.00 (2d, C(5), C(8)); 36.92 (d, C(6)); 28.19, 24.30 (2t, C(7), C(9)). ESI-MS: 705 (31), 703 (23), 701 (16, [2 \( M + Na \)]\(^+\)); 364 (19), 362 (23, [\( M + Na \)]\(^+\)); 342 (15), 340 (15, [\( M + 1 \)]\(^+\)); 298 (75), 296 (100, [\( M + 1 – CO_2 \)]\(^+\)).

(\( \pm \)-IR\(^*\),SS\(^*\),6R\(^*\),8R\(^*\))-6-(Benzyloxymethyl)-8-bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene (724), N-[c-2-(Benzyloxymethyl)-t-4,c-5-dibromocyclohexyl]-2,2,2-trifluoroacetamide (735), and N-[c-2-(Benzyloxymethyl)-c-4,t-5-dibromocyclohexyl]-2,2,2-trifluoroacetamide (736).

a) A cold (0\(^\circ\)) soln. of 72 (31 mg, 98.9 µmol) in CH\(_2\)Cl\(_2\) (1 ml) was treated with Et\(_4\)NBr (208 mg, 989 µmol) and PhMe\(_3\)NBr\(_3\) (75 mg, 198 µmol), stirred for 1 h, and treated with sat. aq. Na\(_2\)S\(_2\)O\(_5\) soln. (2 ml). The mixture was extracted with Et\(_2\)O (2 x 20 ml), and the combined organic phases were dried (Na\(_2\)SO\(_4\)), and evaporated. FC (2 g of silica gel, cyclohexane/AcOEt 10:1) of the residue (62 mg, colourless oil) gave 735 (42 mg, 89%) as a colourless oil.

b) At –78\(^\circ\), a solution of 72 (52.5 mg, 167 µmol) in CH\(_2\)Cl\(_2\) (2 ml) was treated with Br\(_2\) (25 µl, 502 µmol), stirred for 1 h, and treated with sat. aq. Na\(_2\)S\(_2\)O\(_5\) soln. (15 ml). The mixture was extracted with Et\(_2\)O (2 x 20 ml), and the combined organic phases were dried (Na\(_2\)SO\(_4\)), and evaporated. FC (12 g of silica gel, hexane/AcOEt 10:1) of the residue (91 mg, yellow oil) gave 724 (12.6 mg, 19%), 735 (33.2 mg, 42%), and 736 (25 mg, 32%) as colourless oils.
Data of 724:

Rf (cyclohexane/AcOEt 3:1) 0.68. FT-IR (0.5%, CHCl3): 3008w, 2927m, 2857w, 1728w, 1688m, 1602w, 1454w, 1442w, 1390w, 1362w, 1166s, 1130s, 1110m, 1076m, 1040w, 914w.

1H-NMR (300 MHz, CDC13): 7.36–7.26 (5 arom. H); 4.74–4.69 (m, H–C(1)); 4.57 (d, J = 11.8, PhCH); 4.51–4.47 (m, H–C(8)); 4.49 (d, J = 11.8, PhCH); 4.04–3.99 (m, H–C(5)); 3.56 (dd, J = 9.0, 7.5, CH–C(6)); 3.29 (dd, J = 9.0, 6.5, CH’–C(6)); 2.65–2.54 (m, H–C(6)); 2.12 (br. dd, J = 15.9, 2.5, Heq–C(7)); 1.83 (dd, J = 14.3, 3.9, 1.6, Hax–C(9)); 1.57 (ddd, J = 15.9, 12.1, 4.0, Hax–C(7)). 13C-NMR (75 MHz, CDCl3): 147.62 (q, J = 38.4, O–C=N); 138.05; 128.30 (2 C); 116.26 (q, J = 275.9, CF3); 74.33 (d, C(1)); 73.28 (t, PhC2); 71.34 (t, CH2–C(6)); 47.80, 47.68 (2 d, C(5), C(8)); 38.04 (d, C(6)); 28.88 (t, C(7)); 23.32 (t, C(9)). 19F-NMR (282 MHz, CDCl3): –73.10.

HR-MS (MALDI): 412 (86), 410.0578 (100) (C16H20BrF3NO3+ [M + H]+ 3O); calc. 410.0579; 394 (1); 392.0475 (1) (C16H18BrF3NO2+, [M + 1]⁺; calc. 392.0473); 316 (16), 314 (16, [M + 4 – CF3C]⁺); 312 (14), 310 (14); 298 (6), 296 (6, [M + 2 – COCF3]⁺).

Data of 735:

Rf (toluene/AcOEt 10:1) 0.62. FT-IR (0.5%, CHCl3): 3389w (NH), 3339w (NH), 2928w, 2857w, 1722s, 1603w, 1541m, 1452w, 1427w, 1369w, 1292w, 1278w, 1102w, 1091w, 1027w, 987w, 929w, 906w, 856w.

1H-NMR (300 MHz, CDC13): 8.01–7.91 (br. s, NH); 7.41–7.27 (5 arom. H); 4.52 (d, J = 12.4), 4.48 (d, J = 12.1) (PhCH2); 4.48–4.41, 4.41–4.33, 4.33–4.24 (3m, H–C(1), H–C(4), H–C(5)); 3.73 (t, J = 8.6, CH–C(2)); 3.54 (dd, J = 9.7, 3.6, CH–C(2)); 2.74 (dt, J = 14.9, 4.4, H–C(6)); 2.53 (tt, J = 8.1, 4.0, H–C(2)); 2.46 (dd, J = 14.3, 8.3, 3.6, H–C(3)); 2.30 (dt, J = 14.9, 7.1, H′–C(6)); 2.06 (dd, J = 13.7, 7.8, 2.8, H′–C(3)). 13C-NMR (75 MHz, CDC13): 156.85 (q, J = 36.6, C=O); 137.07; 128.83 (2 C); 128.43; 128.16 (2 C); CF3 hidden by noise; 74.10 (PhCH2); 70.88 (CH2–C(2)); 52.18 (C(1)); 50.71, 48.55 (C(4), C(5)); 35.58 (C(2)); 27.13 (C(3), C(6)). 19F-NMR (282 MHz, CDCl3): −76.68. ESI-MS: 530 (4), 528 (9), 526 (6, [M + Na + MeOH]⁺); 514 (24), 512 (40), 510 (18, [M + K]⁺); 498 (54), 496 (100), 494 (53, [M + Na]⁺).
Data of 736:

\[ \text{Rf (cyclohexane/\text{AcOEt} 3:1) 0.51. FT-IR (1\%, CHCl}_3\): 3331\,\text{w} (\text{NH}), 3033\,\text{w}, 3013\,\text{w}, 2868\,\text{w}, 1725\,\text{s} (\text{C} = \text{O}), 1602\,\text{w}, 1499\,\text{s}, 1446\,\text{w}, 1309\,\text{m}, 1065\,\text{w}, 1012\,\text{w}. } ^1\text{H-NMR (300 MHz, CDCl}_3\): 7.90–7.81 (br. s, NH); 7.40–7.24 (5 arom. H); 4.52, 4.48 (2 d, J = 11.8, PhCH\textsubscript{2}); 4.27–4.16 (m, H–C(1), H–C(4), H–C(5)); 3.83 (dd, J = 9.3, 6.2, CH–C(2)); 3.58 (dd, J = 9.8, 2.3, CH'–C(2)); 2.91 (br. \textit{ddd}, J \approx 15, 5, 4, H–C(6)); 2.57 (br. dt, J = 14.6, 3.9, H–C(3)); 2.27 (dt, J = 14.4, 9.7, H'–C(3)); 2.21–2.11 (m, H–C(2)); 2.14 (\textit{ddd}, J = 14.6, 10.0, 3.6, H'–C(6)). ^{13}\text{C-NMR (75 MHz, CDCl}_3\): 136.39; 128.54 (2 C); 128.23; 127.95 (2 C); 74.02 (PhCH\textsubscript{2}); 71.86 (CH\textsubscript{2}–C(2)); 53.00 (br., CBr); 51.30 (C(1)); 50.65 (br., CBr); 38.61 (C(2)); 34.76 (C(3)); 27.02 (C(6)); COCF\textsubscript{3} signals hidden by noise. ^{19}\text{F-NMR (282 MHz, CDCl}_3\): –75.80 (s). ESI-MS: 514 (70), 512 (100), 510 (37, [M + K]+); 498 (40), 496 (84), 494 (40, [M + Na]+).

\textbf{Methyl-c-4,t-5-dibromo-c-2-(tertbutoxycarbonylamino)-cyclohexanecarboxylate (737), Methyl-t-4,c-5-dibromo-c-2-(tertbutoxycarbonylamino)-cyclohexanecarboxylate (738), and Methyl (±)-(IR\textsuperscript{*},5S\textsuperscript{*},6R\textsuperscript{*},8R\textsuperscript{*})-8-Bromo-3-oxo-2-oxa-4-aza-bicyclo[3.3.1]nonane-6-carboxylate (739)}

\textbf{a)} At 0°, a suspension of 714 (110 mg, 0.43 mmol) and Et\textsubscript{4}NBr (905 mg, 4.3 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1 ml) was treated with PhMe\textsubscript{3}NBr\textsubscript{3} (323 mg, 0.86 mmol), stirred for 2 h, treated with sat. aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{5} soln. (10 ml), and extracted with Et\textsubscript{2}O (2 x 10 ml). The combined organic phases were dried (Na\textsubscript{2}SO\textsubscript{4}) and evaporated. FC (12 g of silica gel, cyclohexane/\text{AcOEt} 9:1) gave 737 (151 mg, 84%) and 738 (11 mg, 6%).

\textbf{b)} At –78°, a solution of 714 (210 mg, 0.795 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (2 ml) was treated with Br\textsubscript{2} (0.2 ml, 3.9 mmol), stirred for 75 min, treated with sat. aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{5} soln. (10 ml), and warmed to 0°. Workup as described in a) and FC (50 g of silica gel, cyclohexane/\text{AcOEt} 9:1) of the residue (293 g, colourless amorphous) gave 737 (92 mg, 28%) and 738 (99.5 mg, 30%). Elution of the column with MeOH gave 739 (81 mg, 36%).

Data of 737:

Colourless crystals. \textbf{Rf (toluene/\text{AcOEt} 10:1) 0.47. M.p.: 148.8–150.0°. FT-IR (0.5\%, CHCl\textsubscript{3})}: 3437\,\text{w} (\text{NH}), 3019\,\text{s}, 2980\,\text{w}, 2952\,\text{w}, 1728\,\text{s} (\text{C} = \text{O}), 1709\,\text{s} (\text{C} = \text{O}), 1602\,\text{w}, 1499\,\text{s}, 1446\,\text{w}, 1367\,\text{m}, 1309\,\text{m}, 1065\,\text{w}, 1012\,\text{w}. ^1\text{H-NMR (300 MHz, CDCl}_3\): 5.50 (br. d, J = 9.3,
NH); 4.34–4.10 (br. s, 2 H), 4.10–3.94 (br. s, 1 H) (H–C(2), H–C(4), H–C(5)); 3.72 (s, MeO); 3.01 (br. dt, J = 5.0, 4.4, H–C(1)); 2.78 (br. ddd, J = 14.6, 5.6, 3.4, H–C(6)); 2.58 (br. d, J = 14.0, H–C(3)); 2.28 (dt, J = 14.0, 9.0, H'–C(3)); 2.09 (dd, J = 14.3, 9.3, 4.7, H'–C(6)); 1.40 (s, C(CH3)3). 13C-NMR (75 MHz, CDCl 3): 172.30 (s, CO2Me); 154.70 (s, CO2CMe3); 79.77 (s, Me3C); 52.27 (q, OCH3); 52.02 (d, C(2)); 47.84, 43.37 (2d, C(4), C(5)); 38 (br. d, C(1)); 28.39 (q, Me3) (the C(3) and C(6) t are hidden, presumably under the Me3C q). ESI-MS: 418 (45), 416 (100), 414 (52, [M + 1]+); 362 (14), 360 (32), 358 (15, [M + 1 – C4H8]+).

Data of 738:
Colourless crystals. Rf (toluene/AcOEt 10:1) 0.43. M.p.: 101.5–109.0. FT-IR (0.5%, CHCl3): 3440 w (NH), 3030 m, 2981 w, 2955 w, 1725 s (C=O), 1709 s (C=O), 1602 w, 1500 s, 1439 m, 1367 m, 1280 m, 1096 w, 1053 w, 1007 m. 1H-NMR (300 MHz, CDCl3): 5.62–5.45 (m, NH); 4.63–4.53 (m, 1 H), 4.40–4.28 (m, 2 H) (H–C(2), H–C(4), H–C(5)); 3.71 (s, MeO); 2.87–2.75 (m, 3 H); 2.61–2.50 (m, 1 H); 2.04 (dt, J = 14.6, 4.7, 1 H); 1.44 (s, Me3C). 13C-NMR (75 MHz, CDCl3): 155.20 (C O2CMe3) (one signal hidden by noise); 79.94 (Me3C); 52.13, 50.39, 45.49 (C(2), C(4), C(5)); 42.20 (C(1)); 31.95, 27.08 (C(3), C(6); 28.54 (Me3C). ESI-MS: 472 (11), 470 (21), 468 (9, [M + Na + MeOH]+); 456 (10), 454 (21), 452 (10, [M + K]+); 440 (52), 438 (100), 436 (58, [M + Na]+); 418 (7), 416 (17), 414 (8, [M + 1]+); 362 (13), 360 (28), 358 (12, [M + 1 – C4H8]+); 318 (5), 316 (9), 314 (5, [M + 1 – C4H8 – CO2]+).

Data of 739:
Yellowish, amorphous. Rf (cyclohexane/AcOEt 3:1) 0.0. mp.: 190–197° (dec.). FT-IR (1.5%, CHCl3): 3438 w (NH), 3025 w, 2911 w, 2952 w, 1715 s (C=O), 1502 w, 1438 m, 1407 w, 1367 w, 1347 w, 1326 w, 1154 w, 1101 m, 1062 w, 1040 w, 1005 w, 978 w, 953 w, 891 w. 1H-NMR (300 MHz, CDCl3): 5.76–5.68 (br. s, NH); 4.67–4.63 (m), 4.56–4.51 (m) (H–C(1), H–C(8)); 4.06–4.01 (m, H–C(5)); 3.73 (s, MeO); 3.00 (ddd, J = 10.9, 5.9, 1.6, H–C(6)); 2.56 (ddt, J = 14.0, 2.2, 1.6, irr. at 5.72 → dt, J = 14.0, 1.6, Hax–C(9)); 2.43–2.37 (m, CH2(7)); 2.10 (dt, J = 14.3, 4.1, 1.6, Heq–C(9)). ESI-MS+: 329 (33), 327 (34, [M + MeOH + NH4]+); 312 (19), 310 (18, [M + MeOH + 1]+); 280 (100), 278 (80, [M + 1]+).
(±)-(1R*, 2S*, 4S*, 5S*)-2-{(N-{(tert-Butyloxy)carbonyl}benzylamino)-4-bromo-6-oxabicyclo[3.2.1]octane (741) and (±)-(1R*, 5S*, 6R*, 8R*)-4-Benzyl-6-(benzyloxymethyl)-8-bromo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (740).

At –78°, a soln. of 718 (30 mg, 73 µmol) in CH2Cl2 (3 ml) was treated with Br2 (7.5 µl, 146 µmol), stirred for 3 h, and treated with sat. aq. Na2S2O5 soln. The mixture was extracted with Et2O (2 x 20 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (2 g of silica gel, cyclohexane/AcOEt 6:1) of the residue (36 mg, orange oil) gave 741 (7.6 mg, 26%) as a colourless oil and 740 (10.2 mg, 32%) as a colourless oil, which became a glass upon standing.

Data of 741:
Rf (cyclohexane/AcOEt 3:1) 0.49. FT-IR (1.5%, CHCl3): 3027 w, 3013 m, 2979 m, 2887 w, 1683 s (C=O), 1604, 1591, 1566, 1539, 1529, 1492, 1481, 1453, 1428, 1397, 1377, 1350, 1327, 1278, 1252, 1222, 1191, 1166, 1117, 1093, 1052, 1018, 977, 950, 922, 884, 864, 844, 821, 801, 780, 760, 741, 721, 703, 685, 666, 647, 628, 610, 592, 574, 555, 537, 518, 499, 481, 462, 443, 424, 405, 386, 367, 348, 329, 310, 291, 272, 253, 234, 215, 196, 177, 158, 140, 121, 101, 81, 61, 41, 21. 1H-NMR (300 MHz, CDCl3): 7.34–7.11 (5 arom H); 4.57 (d, J = 17.1, PhCH); 4.57–4.49 (m, H–C(2)); 4.49 (d, J = 16.8, PhCH′); 4.24 (t, J = 5.0, H–C(5)); 4.16–4.12 (m, H–C(4)); 3.86 (d, J = 8.7, Hendo–C(7)); 3.64 (dd, J = 9.0, 4.1, Hexo–C(7)); 2.55 (d, J = 12.5, Hax–C(8)); 2.54–2.48 (m, H–C(1)); 2.43 (br. td, J = 13.2, 5.1, Hax–C(3)); 1.99 (br. dd, J = 14.5, 4.8, Heq–C(3)); 1.84 (dd, J = 12.5, 5.4, 1.6, Heq–C(8)); 1.45 (s, Me3C). 13C-NMR (75 MHz, CDCl3): 155.66 (s, C=O); 139.58 (s); 128.45 (d, 2 C); 126.76 (d, 1 C); 126.08 (d, 2 C); 80.38 (s, Me3C); 77.23 (d, C(5)); 69.61 (t, C(7)); 53.04 (d, C(2)); 48.58 (d, C(4)); 47.12 (t, PhCH2); 40.63 (d, C(1)); 34.00, 32.66 (2r, C(3), C(8)); 28.46 (q, Me3C). ESI-MS: 817 (10), 815 (15), 813 (9, [2M+Na]+); 452 (26), 450 (25, [M+Na+MeOH]+); 436 (39), 434 (34, [M+K]+); 420 (100), 418 (98, [M+Na]+); 398 (6), 396 (5, [M+1]+); 342 (15), 340 (13, [M+1–C4H8]+).

Data of 740:
Rf (cyclohexane/AcOEt 3:1) 0.21. FT-IR (0.5%, CHCl3): 3014, 2952, 2862, 1687 s (C=O), 1604, 1596, 1545, 1362, 1309, 1123, 1106, 1074, 1046, 1001. 1H-NMR (300 MHz, CDCl3): 7.42–7.19 (10 arom. H); 5.27 (d, J = 14.9, PhCHN); 4.64 (br. t, J = 3.4, H–C(1)); 4.67 (s, PhCH2O); 4.51–4.47 (m, H–C(8)); 3.80–3.76 (m, H–C(5)); 3.76 (d, J =
14.9, PhCH‘N); 3.42–3.37 (m, CH₂–C(6)); 2.50–2.42 (m, H–C(6)); 2.43 (ddd, J = 14.0, 2.2, 1.6 Hax–C(9)); 1.98 (ddd, J = 15.6, 12.1, 4.0, Hax–C(7)); 1.88 (dtm, J = 15.9, Heq–C(7)); 1.74 (dt, J = 14.0, 4.0, 1.6, Heq–C(9)). ¹³C-NMR (75 MHz, CDCl₃): 137.61, 137.24 (2s); 128.84, 128.40, 128.30, 128.22, 127.94 (5d); 76.03 (d, C(1)); 73.61 (t, PhCH₂O); 70.49 (t, C₂H₂–C(6)); 52.92 (t, PhCH₂N); 49.26, 47.73 (2d, C(5), C(8)); 37.19 (d, C(6)); 28.39, 25.73 (2t, C(7), C(9)). ESI-MS: 901 (4), 899 (8), 897 (3, [2M + K]+); 885 (59), 883 (100), 881 (49, [2M + Na]+); 486 (10), 484 (9, [M + Na + MeOH]+); 470 (27), 468 (23, [M + K]+); 454 (92), 452 (95, [M + Na]+); 432 (7), 430 (6, [M + 1]+).

c-3,t-4-Dibromocyclohexylamine (742).
At r.t., a solution of 727 (350 mg, 0.98 mmol) in CH₂Cl₂ (20 ml) was treated with trifluoroacetic acid (1.5 ml, 19.3 mmol), stirred for 3.5 h, and evaporated. The residual oil, dissolved in sat. aq. K₂CO₃ soln. (15 ml), was extracted with CHCl₃ (4 x 40 ml), and the combined organic phases were dried (K₂CO₃), and evaporated to yield crude 742 (266 mg, 100%). Colourless oil. Rf (CH₂Cl₂/MeOH/NH₄OH 9:1:0.1) 0.49. ¹H-NMR (300 MHz, CDCl₃): 4.06, 3.98 (2td, J = 10.6, 4.4, H–C(3), H–C(4)); 2.84 (tt, J = 11.2, 3.7, H–C(1)); 2.59 (ddd, J = 13.1, 6.5, 4.1, 1 H); 2.47 (ddd, J = 14.0, 7.8, 3.4 1 H); 1.98–1.72 (m, 3 H); 1.32–1.18 (m, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 56.29, 54.57 (2d, C(3), C(4)); 50.03 (d, C(1)); 47.75 (t, C(2)), 35.97, 35.89 (2t, C(5), C(6)). ESI-MS: 260 (46), 258 (100), 256 (51, [M + 1]+); 178 (50), 176 (53, [M – Br]+).

t-3,c-4-Dibromocyclohexylamine (747).
According to the preparation of 742, 728 (295 mg, 0.826 mmol) yielded 747 (226 mg, quant.) as a colourless oil. Rf (CH₂Cl₂/MeOH/NH₄OH 9:1:0.1) 0.47. ¹H-NMR (300 MHz, CDCl₃): 4.70–4.65 (m, H–C(3)); 4.60–4.56 (m, H–C(4)); 3.33 (tt, J = 10.6, 4.4, H–C(1)); 2.51 (dddd, J = 15.3, 12.1, 4.4, 3.1, Hax–C(5)); 2.33 (ddd, J = 14.3, 10.9, 3.4, Hax–C(2)); 2.17 (dm, J = 14.3, Heq–C(2)); 2.04 (dm, J = 15.3, Heq–C(5)); 1.88–1.69 (m, CH₂(6)). ¹³C-NMR (75 MHz, CDCl₃): 52.78, 52.71 (2d, C(3), C(4)); 45.33 (d, C(1)); 38.65 (t, C(2)); 30.98, 28.48 (2t, C(5), C(6)). ESI-MS: 355 (28), 353 (58), 351 (29); 292 (8), 290 (17, 288 (8, [M + MeOH + 1]+); 260 (48), 258 (100), 256 (51, [M + 1]+).
(±)-(1R*,2S*,4S*)-2-Bromo-7-aza-bicyclo[2.2.1]heptane (743).

A solution of 742 (266 mg, 0.98 mmol) in CHCl₃ (20 ml) was treated with K₂CO₃ (140 mg, 0.98 mmol), stirred under reflux for 12 d, cooled to r.t., and treated with 10% aq. K₂CO₃ soln. (10 ml). The organic phase was separated, and the aqueous phase extracted with CHCl₃ (4 x 20 ml). The combined organic phases were dried (K₂CO₃), and evaporated to give crude 743 (200 mg, 100%). Brown oil. Rᵥ (CH₂Cl₂/MeOH/NH₄OH 9:1:0.1) 0.56. ¹H-NMR (300 MHz, CDCl₃): 4.08 (dd, J = 7.2, 2.8, H–C(2)); 3.73–3.67, 3.64–3.56 (2m, H–C(1), H–C(4)); 2.18 (dd, J = 14.3, 6.9, H–C(3)); 2.00 (ddt, J = 14.3, 5.3, 2.5, H'–C(3)); 1.73 (tdd, J = 11.8, 5.3, 3.7, 1 H); 1.64–1.52 (m, 1 H); 1.28–1.09 (m, 2 H). ¹³C-NMR (75 MHz, CDCl₃): 64.97 (d, C(1)); 56.74 (d, C(4)); 53.84 (d, C(2)); 44.83 (t, C(3)); 28.56, 27.04 (2t).

N Br

Boc

(±)-(1R*,2S*,4S*)-2-Bromo-7-tert-Butyloxycarbonyl-7-azabicyclo[2.2.1]heptane (744).

At r.t., a solution of 743 (200 mg, 0.98 mmol) in CHCl₃ (10 ml) was treated with K₂CO₃ (140 mg, 0.98 mmol) and Boc₂O (855 mg, 3.92 mmol), and stirred for 19 h. The mixture was washed with water, and the aqueous phase extracted with CHCl₃ (2 x 25 ml). The combined organic phases were dried (Na₂SO₄) and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 12:1) gave 744 (224 mg, 83% from 727). Colourless oil. Rᵥ (cyclohexane/AcOEt 3:1) 0.61. FT-IR (0.7%, CHCl₃): 3008 m, 2980 m, 2879 w, 1694 s (C=O), 1550 w, 1477 w, 1454 w, 1392 s, 1368 s, 1321 m, 1177 m, 1153 s, 1134 m, 1101 m, 1048 w, 983 w, 907 w, 886 w, 872 w, 849 w. ¹H-NMR (300 MHz, CDCl₃): 4.41–4.36, 4.34–4.27 (2m, H–C(1), H–C(4)); 3.99 (dd, J = 7.2, 3.4, H–C(2)); 2.33–2.23 (br. d, J = 14, Hexo–C(3)); 2.17 (dd, J = 13.7, 7.5, Hendo–C(3)); 1.94–1.82 (m, H–C(6)); 1.78–1.63 (m, H–C(5)); 1.46 (s, Me₃C); 1.43–1.25 (m, H–C(6), H–C(5)). ¹³C-NMR (75 MHz, CDCl₃): 155.00 (s, C=O); 79.93 (s, Me₃C); 63.89 (d, C(1)); 55.61 (br. d, C(4)); 49.71 (br. d, C(2)); 43.61 (t, C(3)); 28.52, 28.00 (2t, C(5), C(6)); 28.27 (q, Me₃C). ESI-MS: 332 (97), 330 (100, [M + Na + MeOH]⁺); 316 (50), 314 (45, [M + K]⁺); 300 (45), 298 (46, [M + Na]⁺). Anal. calc. for C₁₁H₁₈BrNO₂ (276.17): C 47.84, H 6.57, N 5.07; found: C 47.78, H 6.47, N 5.16.

Transformation of 729 into 744.

At r.t., a solution of 729 (15.28 g, 43.3 mmol) in MeOH (500 ml) and H₂O (200 ml) was treated with K₂CO₃ (29.9 g, 216 mmol) and stirred for 13.5 h. MeOH was removed in vacuo
below 40°. The residue was treated with sat. aq. K₂CO₃ soln. (100 ml) and extracted with CHCl₃ (5 x 300 ml). The combined organic phases were dried (K₂CO₃) and evaporated. The residue (crude 742 (11.1 g, 43.2 mmol) was dissolved in CHCl₃ (1 l), treated with K₂CO₃ (5.97 g, 43.2 mmol), heated under reflux for 13 d, cooled to r.t., treated with Boc₂O (60 ml, 0.26 mol) and K₂CO₃ (5.97 g, 43.2 mmol), and stirred at r.t. for 3 d. The mixture was washed with H₂O (500 ml), and the aqueous phase extracted with CHCl₃ (500 ml). The combined organic phases were dried (Na₂SO₄) and evaporated. FC (300 g of silica gel, toluene/AcOEt 40:1) gave 744 (11.27 g, 93% from 729).

Attempted cyclisation of 747
A solution of 747 (49 mg, 0.19 mmol) in 1,3-dichlorobenzene (10 ml) was treated with K₂CO₃ (26 mg, 0.19 mmol) and heated slowly to 120°. TLC indicated no change. Then the mixture was heated at 130° for 2 d, when TLC indicated the formation of a new compound (Rᵣ (CH₂Cl₂/MeOH/NH₄OH 9:1:0.1) 0.56). The mixture was cooled to r.t., treated with Boc₂O (0.21 ml, 0.95 mmol), stirred for 3 d, and washed with sat. aq. K₂CO₃ soln. (25 ml). The aqueous phase was extracted with CHCl₃ (3 x 25 ml) and the combined organic phases were dried (Na₂SO₄) and evaporated. FC (15 g of silica gel, cyclohexane/AcOEt 12:1) gave 744 (32.5 mg, 62%) as a colourless oil.

7-(tertButyloxycarbonyl)-7azabicyclo[2.2.1]hept-2-ene (745) ([981]).
A soln. of 744 (1.058 g, 3.83 mmol) in THF (50 ml) was treated with KOtBu (473 mg, 4.21 mmol), heated under reflux for 3 h, cooled, and poured into brine (50 ml). The resulting mixture was extracted with Et₂O (3 x 100 ml). The combined organic phases were dried (Na₂SO₄) and evaporated. FC (35 g of silica gel, cyclohexane/AcOEt 12:1) gave 745 (652 mg, 87%) as a colourless oil. Data see [981].

(±)-(1R*,2R*,3S*,4S*)-7-[(tert-Butyloxy)carbonyl]-7-azabicyclo[2.2.1]heptane-2,3-diol (746).
A soln. of 745 (98 mg, 0.50 mmol) in acetone (23 ml) and water (2.5 ml) was treated with N-methylmorpholineoxide monohydrate (102 mg, 0.75 mmol) and 2.5% OsO₄ in rBuOH (0.5 ml, 40 µmol), stirred at r.t. for 22 h, diluted with sat. aq. Na₂S₂O₅ soln. (50 ml), and
extracted with CHCl₃ (4 x 100 ml). The combined organic phases were dried (Na₂SO₄) and evaporated. FC (30 g of silica gel, cyclohexane/AcOEt 1:1) gave 746 (93.5 mg, 82%) as a yellow oil. Crystallisation from hexane/CH₂Cl₂ gave colourless needles of 746 (64 mg, 56%).

\[ R_f (cyclohexane/AcOEt 1:1) 0.19. \]
\[ M.p. 82°. \]
\[ FT-IR (0.5%, CHCl₃): 3502 \text{ w} (OH), 3004 \text{ m}, 2988 \text{ m}, 2988 \text{ w}, 2884 \text{ w}, 1697 \text{ s} (C=O), 1466m, 1368s, 1318m, 1170s, 1141s, 1111m, 1056s, 1010w, 972w, 931w, 803w. \]
\[ 1H-NMR (300 MHz, CDCl₃): 4.11 (br. s, H–C(1), H–C(4)); 3.79 (br. s, H–C(2), H–C(3)); 3.28–3.08 (br. s, 2 OH); 1.73–1.65 (m, H–C(5), H–C(6)); 1.45 (s, Me₃C); 1.81 (d \( J = 8.1 \), H’–C(5), H’–C(6)). \]
\[ 13C-NMR (75 MHz, CDCl₃): 157.22 (s, C=O); 80.25 (s, Me₃C); 74.24 (d, C(2), C(3)); 62.26 (d, C(1), C(4)); 28.26 (q, Me₃C); 24.27 (t, C(5), C(6)). \]

Anal. calc. for C₁₁H₁₉NO₄ (229.28): C 57.63, H 8.35, N 6.11; found C 57.78, H 8.25, N 6.10.

\( \text{OH} \)
\( \text{NH} \)
\( \text{HCl} \)

\( \text{N} \)
\( \text{Br} \)

\( \text{r-1-Amino-c-2-(benzyloxymethyl)-t-4c-5-dibromocyclohexane (752)}. \)

A soln. of 731 (290 mg, 0.607 mmol) in CH₂Cl₂ (15 ml) was treated with CF₃CO₂H (0.93 ml, 12.1 mmol), stirred at r.t. for 3 h, and evaporated. The residue was taken up in sat. aq. K₂CO₃ soln. (20 ml) and extracted with CHCl₃ (3 x 25 ml). The combined organic phases were dried (K₂CO₃) and evaporated to give crude 752 as a colourless oil (250 mg, quant.).

\[ R_f (CH₂Cl₂/MeOH/NH₄OH 9:1:0.1) 0.61. \]
\[ ESI-MS: 380 (1), 378 (2), 376 (1, \([M+1]^+\]), 298 (96), 296 (100, \([M–Br]^+\]). \]
A solution of crude 752 (250 mg) in CHCl₃ (20 ml) was treated with K₂CO₃ (83 mg, 0.607 mmol), heated under reflux for 40 h, cooled to r.t., treated with K₂CO₃ (ca. 100 mg), and filtered. Evaporation of the filtrate gave crude 753 (268 mg, quant.) as a slightly yellow oil.

Rᵥ (CH₂Cl₂/MeOH/NH₄OH 9:1:0.1) 0.88. 1H-NMR (300 MHz, CDCl₃): 7.38–7.25 (5 arom. H); 4.54 (d, J = 12.1), 4.48 (d, J = 11.8) (PhCH₂); 4.50 (br. s, H–C(4)); 4.45 (d, J = 11.8, PhCH'); 4.37 (d, J = 5.3, H–C(1)); 4.00 (dd, J = 7.2, 3.7, H–C(5)); 3.30 (t, J = 8.9, CH–C(2)); 1.98–1.85 (m, H–C(2)); 1.55 (dd, J = 12.9, 8.3, H–C(3)); 1.48 (s, C(CH₃)₃); 1.47–1.35 (m, H–C(3)); signals for the minor diastereoisomer: 4.48 (br. s, H–C(4)); 4.31 (d, J = 4.7, H–C(1)); the other signals are hidden by the signals of the major diastereoisomer. 13C-NMR (75 MHz, CDCl₃) (ca. 2:1 mixture of diastereoisomers): signals for the major diastereoisomer: 138.01 (s); 128.35, 128.27, 127.61, 127.49 (4d); 80.05 (d, Me₃C); 73.25 (t, PhCH₂); 72.42 (t,
CH$_2$–C(2)); 63.79, 57.18 (2d, C(1), C(4)); 49.73 (d, C(5)); 42.99 (t); 41.91 (d, C(2)); 32.79 (t); 28.39 (q, Me$_3$C); signals for the minor diastereoisomer: 138.01 (s); 128.35, 128.27, 127.61, 127.49 (4d); 79.92 (d, Me$_3$C); 73.34 (t, PhCH$_2$); 72.30 (t, CH$_2$–C(2)); 62.91, 57.65 (2d, C(1), C(4)); 48.88 (d, C(5)); 43.61 (t); 42.71 (d, C(2)); 31.66 (t); 28.46 (q, Me$_3$C). ESI-MS: 420 (100), 418 (94, [M + Na]$^+$); 364 (72), 362 (67, [M + Na – C$_4$H$_8$]$^+$); 298 (8), 296 (8).

Anal. calc. for C$_{19}$H$_{26}$BrNO$_3$ (396.32): C 57.58, H 6.61, N 3.53; found: C 57.88, H 6.51, N 3.61.

A soln. of 754 (167 mg, 0.42 mmol) in THF (12 ml) was treated with KOrBu (71 mg, 0.63 mmol), heated under reflux for 25 h, cooled to 0$^\circ$, diluted with Et$_2$O (20 ml), and washed with brine (25 ml). The aqueous phase was extracted with Et$_2$O (25 ml). The combined organic phases were dried (Na$_2$SO$_4$) and evaporated. FC (15 g of silica gel, cyclohexane/AcOEt 10:1) gave 755 (123 mg, 92%). Colourless oil. $R_f$ (cyclohexane/AcOEt 3:1) 0.58. FT-IR (1.5%, CHCl$_3$): 3028 $w$, 3012 $m$, 2981 $m$, 2939 $w$, 2864 $w$, 1694 $s$ (C=O), 1496 $w$, 1477 $w$, 1455 $w$, 1393 $m$, 1368$s$, 1298$m$, 1110$m$, 1029$w$, 949$w$, 912$w$, 876$w$, 861$w$. $^1$H-NMR (300 MHz, CDCl$_3$): 7.37–7.25 (5 arom. H); 6.29 (br. d, $J = 10.0$, H– C(2), H–C(3)); 4.70–4.51 (m, PhCH$_2$, H–C(1), H–C(4)); 3.51 (dd, $J = 9.2$, 6.1, CH–C(5)); 3.51–3.37 (m, CH$^+$–C(5)); 1.90–1.79 (m, H–C(5)); 1.42 (s, Me$_3$C); 1.38–1.28 (m, CH$_2$(6)). $^{13}$C-NMR (75 MHz, CDCl$_3$, ca. 6:5 mixture of diastereoisomers): 138.25 (s); 136.55 (d, 0.55 C), 136.26 (d, 0.45 C), 135.12 (d, 0.45 C), 134.70 (d, 0.55 C) (C(2), C(3)); 128.28 (d, 2 C); 127.56 (d, 2 C); 127.47 (d); 79.69 (s, Me$_3$C); 72.23 (t, PhCH$_2$, CH$_2$–C(5)); 61.56 (d), 60.12 (d, 0.45 C), 59.08 (d, 0.55 C) (C(1), C(4)); 39.62 (d, 0.55 C), 38.79 (d, 0.45 C) (C(5)); 29.63 (t, C(6)); 28.36 (q, Me$_3$C). ESI-MS: 370 (3, [M + Na + MeOH]$^+$) 354 (22, [M + K]$^+$) 338 (100, [M + Na]$^+$) 316 (8, [M + 1]$^+$) 260 (33, [M + 1 – C$_4$H$_8$]$^+$) 216 (8, [M + 1 – C$_4$H$_8$ – CO$_2$]$^+$). Anal. calc. for C$_{19}$H$_{25}$NO$_3$ (315.41): C 72.35, H 7.99, N 4.44; found: C 72.41, H 8.02, N 4.52.
(±)-(1R*,2R*,3S*,4S*,5S*)-5-(Benzyloxymethyl)-7-[(tert-butoxycarbonyl)-7-azabicyclo[2.2.1]heptane-2,3-diol (756).

A soln. of 755 (114 mg, 0.36 mmol) in acetone (23 ml) and water (2.5 ml) was treated with N-methylmorpholineoxide monohydrate (73 mg, 0.54 mmol) and 2.5% OsO₄ in tBuOH (0.5 ml), stirred at r.t. for 13 h, diluted with sat. aq. Na₂S₂O₅ soln. (50 ml), and extracted with CHCl₃ (2 x 100 ml). The combined organic phases were dried (Na₂SO₄) and evaporated. FC (12 g of silica gel, cyclohexane/AcOEt 1:1) gave 756 (102 mg, 81%) as a yellow oil. Rf (cyclohexane/AcOEt 1:1) 0.19. FT-IR (1%, CHCl₃): 3488 w (br., OH), 3028 w, 3013 m, 2981 m, 2932 w, 2864 w, 1727 w, 1692s, 1500 w, 1478 w, 1455 m, 1386 s, 1368 s, 1318 m, 1112 m, 1091 m, 1051 m, 909 w, 870 w.

1H-NMR (300 MHz, C₆D₆, 50°): 7.24–7.02 (5 arom. H); 4.26 (d, J = 12.1, PhCH₂); 4.20 (d, J = 11.2, PhCH₂'); 4.21–4.17 (m, H–C(1*)); 4.02–3.97 (m, H–C(4*)); 3.46–3.41, 3.39–3.33 (2 m, H–C(2), H–C(3)); 3.16–2.95 (m, 2 OH); 3.08 (t, J = 9.0, CH–C(5)); 2.91 (dd, J = 9.0, 6.5, CH'–C(5)); 1.46 (br. qi, J ≈ 7.0, H–C(5)); 1.37 (s, Me₃C); 0.83–0.76 (m, CH₂(6)). 13C-NMR (75 MHz, CDCl₃, ca. 1:1 mixture of diastereoisomers, most signals isochronic for both diastereoisomers): 155.76 (s, C=O); 137.91 (s); 128.31, 127.58 (2d) (1 d hidden by noise or other signal); 80.30 (s, Me₃C); 74.62, 74.01 (2d, C(2), C(3)); 73.25 (t, PhCH₂); 72.17 (t, CH₂–C(5)); 64.64 (ca.0.47 C), 62.99, 60.89 (2d, ca. 0.53 C) (C(1), C(4)); 38.44 (d, C(5)); 28.77 (t, C(6)); 28.34 (q, Me₃C). HR-MALDI-MS (DHB): 372.1783 (80) (C₁₉H₂₇NNaO₅+, [M + Na]+; calc. 372.1787), 316 (66, [M + Na –C₄H₈]+), 272 (28, [M + Na –C₄H₈–CO₂]+), 250 (100, [M + 1–C₄H₈–CO₂]+).

(±)-(1R*,2R*,3S*,4S*,5S*)-7-(tert-Butyloxycarbonyl)-5-(hydroxymethyl)-7-azabicyclo[2.2.1]heptane-2,3-diol (757).

A suspension of 10% Pd/C (30 mg) in MeOH (5 ml) was treated with a solution of 756 (91 mg, 0.26 mmol) in MeOH (5 ml), put under a H₂ atmosphere (balloon), and stirred at r.t. for 19 h. Filtration through a membrane filter and evaporation gave crude 757 as a yellow oil (61 mg, 90%). Repeated FC (12 g of silica gel, CH₂Cl₂/MeOH 12:1) gave 757 as a colourless oil (41 mg, 60%). Rf (CH₂Cl₂/MeOH 9:1) 0.46. FT-IR (1%, CHCl₃): 3693w, 3623w, 3489w (br., OH), 3028w, 3011m, 2972s, 2875w, 1674s (C=O), 1603w, 1475m, 1456m, 1393s, 1369s, 1318m, 1115m, 1050m, 911w, 872w. 1H-NMR (300 MHz, CD₃OD, ca. 1:1 mixture of...
diastereoisomers): 4.02 (br. s, H–C(4)); 3.99 (br. d, J = 5.3, H–C(1)); 3.80 (br. d, J = 6.2), 3.77 (d, J = 6.2) (H–C(2), H–C(3)); 3.32–3.24 (m, CH₂–C(5)); 1.82 (dd, J = 8.1, 7.9, 4.7, H–C(5)); 1.48 (dd, J = 12.8, 8.4, H–C(6)); 1.45 (s, C(CH₃)₃); 1.48 (ddd, J = 12.8, 8.4, H–C(6)); 1.45 (s, C(CH₃)₃); 1.10, 1.09 (2 dt, J = 12.5, 5.3, H'–C(6)). 13C-NMR (75 MHz, CD₃OD, ca. 1:1 mixture of diastereoisomers): 156.61 (C=O); 79.92, 79.80 (Me₃C); 73.67, 73.46, 73.37 73.16 (C(2), C(3)); 63.97 (2 C), 63.83, 62.95, 62.41, 61.22 (C(1), C(4), CH₂–C(5)); 40.99 (2 C, C(5)); 28.25, 27.94 (C(6); 27.43 (Me₃C).

HR-MALDI-MS (DHB): 314.1745 (49) (C₁₃H₂₅NNaO₆⁺, [M + Na + MeOH]⁺; calc. 314.1580), 224 (11).

![Chemical structure of 159-HCl](image)

(±)-(1R*,2R*,3S*,4S*,5S*)-2,3-Dihydroxy-5-(hydroxymethyl)-7-azoniabicyclo[2.2.1]heptane Chloride (59-HCl)

A solution of 757 (40 mg, 0.154 mmol) in 0.1N HCl (5 ml) was stirred at r.t. for 43 h and lyophilised to give colourless amorphous 59-HCl·H₂O (33.2 mg, 100%). Rf (nPrOH/AcOH/H₂O 4:1:1) 0.52. 1H-NMR (300 MHz, CD₃OD): 4.10–4.06 (m, H–C(2), H–C(3)); 3.93 (d, J = 5.0, H–C(1)); 3.91 (br. s, H–C(4)); 3.65 (dd, J = 10.7, 4.5, CH–C(5)); 3.48 (dd, J = 10.6, 5.9, CH'–C(5)); 2.09 (hexet, J = 4.9, H–C(5)); 1.86 (dd, J = 13.5, 9.2, H–C(6)); 1.67 (dt, J = 13.5, 5.1, H'–C(6)). 13C-NMR (75 MHz, CD₃OD): 72.11 (C(2), C(3)); 68.48 (CH₂–C(5)); 66.03 C(4); 63.21 (C(1)); 37.46 (C(5)); 26.74 (C(6)). HR-ESI-MS: 160.09655 (C₇H₁₄NO₃⁺, [M + 1]⁺; calc. 160.09682).

![Chemical structure of 758](image)

Methyl-c-2-amino-c-4-t-5-dibromocyclohexanecarboxylate (758)

A solution of 737 (147 mg, 0.356 mmol) in CH₂Cl₂ (7.5 ml) was treated with CF₃CO₂H (0.5 ml), stirred at r.t. for 13 h, and evaporated. The residue was suspended in sat. aq. K₂CO₃ soln. (15 ml) and extracted with CHCl₃ (3 x 20 ml). The combined organic phases were dried (K₂CO₃) and evaporated to give 758 (140 mg, quant.) as a slightly yellow oil. Rf (CH₂Cl₂/MeOH 9:1) 0.72. 1H-NMR (300 MHz, CDCl₃): 4.61–4.52 (m, 1 H), 4.35–4.26 (m, 1 H) (H–C(4), H–C(5)); 3.74 (s, MeO); 3.42–3.31 (m, H–C(2)); 3.02–2.98 (m, H–C(1)); 2.77 (ddd, J = 14.8, 7.6, 3.7, H–C(6)); 2.62 (dm, J = 13.7, H–C(3)); 2.34 (dt, J = 14.6, 7.4, H'–C(3)); 2.13 (ddd, J = 14.8, 8.0, 4.4, H'–C(6)). ESI-MS: 318 (49), 316 (100), 314 (46, [M + 1]⁺); 236 (49), 234 (48, [M – Br]⁺).
Methyl-c-2-amino-t-4,c-5-dibromocyclohexanecarboxylate (759).
According to the preparation of 758, 738 (84 mg, 0.20 mmol) was transformed into 759 (93 mg, quant.). Slightly yellow oil. Rf (CH$_2$Cl$_2$/MeOH 9:1) 0.62. $^1$H-NMR (300 MHz, CDCl$_3$): 4.50 (ddd, $J = 11.1, 9.8, 4.4$, H–C(4)); 4.12–4.03 (m, H–C(5)); 3.70 (s, MeO); 2.68–2.56 (m, 4 H); 2.52 (dt, $J = 14.3, 4.4$, H–C(3)); 2.08 (ddd, $J = 14.3, 11.2, 3.1$, H–C(3)).

Methyl (±)-(1R*,2S*,4R*,5S*)-5-Bromo-7-azabicyclo[2.2.1]heptane-2-carboxylate (760).
A solution of 758 (133 mg, ca. 0.35 mmol) in CHCl$_3$ (10 ml) was treated with K$_2$CO$_3$ (0.35 mmol), heated under reflux for 30 d, allowed to cool to r.t., and washed with sat. aq. K$_2$CO$_3$ soln. (15 ml). The aqueous phase was extracted with CHCl$_3$ (2 x 25 ml). The combined organic phases were dried (K$_2$CO$_3$) and evaporated to give crude 760 (122 mg) as a yellow oil. Rf (CH$_2$Cl$_2$/MeOH 9:1) 0.74. $^1$H-NMR (300 MHz, CDCl$_3$): 4.00 (dd, $J = 8.9, 3.4$, H–C(5)); 3.92 (d, $J = 4.7$, H–C(1)); 3.80 (d, $J = 5.3$, H–C(4)); 3.66 (s, MeO); 2.36 (dd, $J = 8.7, 4.4$, H–C(2)); 2.17 (dd, $J = 14.3, 6.9$, H–C(6)); 2.12–2.01 (m, H–C(6)); 2.05 (dt, $J = 13.0, 4.9$, H–C(3)); 1.58 (dd, $J = 13.2, 8.9$, H–C(3)). $^{13}$C-NMR (75 MHz, CDCl$_3$): 174.49 (s, C=O); 64.63, 60.53 (2d, C(1), C(4)); 52.18 (q, MeO); 50.95 (d, C(5)); 45.95 (d, C(2)); 43.53, 32.45 (2r, C(3), C(6)).

Methyl (±)-(1R*,2S*,4R*,5S*)-5-Bromo-7-[(tert-butyloxy)carbonyl]-7-azabicyclo[2.2.1]heptane-2-carboxylate (761).
A soln. of 760 (122 mg, ca. 0.35 mmol) in CHCl$_3$ (15 ml) was treated with K$_2$CO$_3$ (48 mg, 0.35 mmol) and Boc$_2$O (0.32 ml, 1.4 mmol), stirred at r.t. for 16 d, and washed with H$_2$O (20 ml). The aqueous phase was extracted with CHCl$_3$ (2 x 20 ml). The combined organic phases were dried (K$_2$CO$_3$) and evaporated. FC (15 g of silica gel, cyclohexane/AcOEt 6:1) gave colourless crystalline 761 (74 mg, 62% from 737). Rf (cyclohexane/AcOEt 3:1) 0.35. M.p.: 56.7–58.6°. FT-IR (1.5%, CHCl$_3$): 3027w, 3012w, 2982w, 2954w, 1737s (COOMe), 1697s (COOBU), 1477w, 1437m, 1392m, 1368s, 1323m, 1303w, 1145s, 1104w, 1039w, 979w, 916w, 883w. $^1$H-NMR (300 MHz, C$_6$D$_6$, 50°): 4.60–4.43 (br. s, H–C(1)); 4.38–4.25 (br. s,
H–C(4)); 3.34 (s, MeO); 3.29 (dd, J = 7.5, 3.5, H–C(5)); 2.24 (dt, J = 13.1, 5.1, H–C(3)); 2.01 (dd, J = 13.9, 5.0, 3.6, H–C(6)); 1.82 (dd, J = 8.7, 4.7, H–C(2)); 1.46 (dd, J = 14.0, 7.5, H–C(6)); 1.42 (s, Me3C); 0.87 (dd, J = 13.1, 8.7, H'–C(3)). 13C-NMR (75 MHz, C6D6, 50°): 172.23 (s, C O2Me); 153.99 (s, C O2CMe3); 79.83 (s, Me3C); 64.18, 59.51 (2d, C(1), C(4)); 51.63 (q, MeO); 48.36, 46.15 (2d, C(2), C(5)); 43.25 (t), 31.67 (2t, C(3), C(6)); 28.29 (q, Me3C). ESI-MS: 693 (35), 691 (65), 689 (32, [2M + Na]+); 390 (14), 388 (14, [M + Na + MeOH]+); 374 (22), 372 (20, [M + K]+); 358 (100), 356 (96, [M + Na]+); 336 (18), 334 (22, [M + 1]+); 280 (22), 278 (20, [M + 1 – C4H8]+); 236 (16), 234 (18, [M + 1 – C4H8 – CO2]+).

Attempted Cyclisation of 759.
A soln. of 759 (93 mg, ca. 0.20 mmol) in 1,3-dichlorobenzene (15 ml) was treated with K2CO3 (27.6 mg, 0.20 mmol), stirred for 28 d at 120°, allowed to cool to r.t., treated with K2CO3 (27.6 mg, 0.20 mmol) and Boc2O (0.3 ml, 1.3 mmol), stirred at r.t. for 10 d, and washed with H2O (30 ml). The aqueous phase was extracted with CHCl3 (2 x 20 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (12 g of silica gel, hexane/AcOEt 4:1) of the oily residue gave 761 (14 mg, 21%) as a yellow oil.

A soln. of 736 (9.3 mg, 19.7 µmol) in MeOH (1.5 ml) and H2O (0.6 ml) was treated with K2CO3 (27.6 mg, 0.20 mmol), stirred at r.t. for 26 h, and evaporated. The residue was suspended in sat. aq. K2CO3-soln. (10 ml), and extracted with CHCl3 (3 x 10 ml). The combined organic phases were dried (K2CO3) and evaporated to yield crude 762 (1.6 mg, quant.) as a colourless oil. Rf (toluene/AcOEt 10:1) 0.36. FT-IR (1%, CHCl3): 3008 m, 2871 m, 1689 m, 1455 w, 1393 w, 1373 w, 1319 w, 1300 w, 1128 s, 1107 s, 1090 s, 909 s. 1H-NMR (300 MHz, CDCl3): 7.38–7.27 (5 arom. H); 4.79–4.75 (m, H–C(1)); 4.54, 4.48 (2d, J = 11.8, PhCH2); 4.16 (ddd, J = 12.5, 5.3, 2.2, H–C(8)); 4.06–4.02 (m, H–C(5)); 3.55 (dd, J = 9.0, 7.2, CH–C(6)); 3.27 (dd, J = 9.0, 6.9, CH’–C(6)); 2.36 (dt, J = 13.9, 4.7, Heq–C(7)); 2.28–2.16 (m, Hax–C(7)). 13C-NMR (75 MHz, CDCl3): 137.88 (s); 128.33, 127.60 (2d); 75.65 (d, C(1)); 73.41 (t, PhCH2)); 71.38 (t, C(2)); 50.15, 46.50 (2d, C(5), C(8)); 44.27 (d, C(6)); 31.65 (t, C(9)); 28.82 (t, C(7)); 19F-NMR (282 MHz, CDCl3): −73.69 (s). ESI-MS: 448 (1), 446 (1, [M + Na + MeOH]+); 432 (16), 430 (15, [M + K]+); 416 (97), 414 (100, [M +
Inhibition studies

Determination of the $IC_{50}$ values was performed with a range of inhibitor concentrations (typically 4–8 concentrations) which bracket the $IC_{50}$ value, using $[S] = KM$.

$\beta$-Glucosidase from almonds (pH 6.8, 37°), $\beta$-Glucosidase from Caldocellum saccharolyticum (pH 6.8, 55°), and $\alpha$-Glucosidase from brewer's yeast (pH 6.8, 37°) as described previously [1043].

$\beta$-Mannosidase from snail acetone powder (pH 4.5, 27°) using 4-nitrophenyl-$\beta$-D-mannopyranoside as substrate [197].

$\alpha$-Mannosidase from jack bean (pH 4.5, 25°) using 4-nitrophenyl-$\alpha$-D-mannopyranoside as substrate [197].

\[
\text{N-Benzyll-N-[c-6-(benzyloxymethyl)cyclohex-3-enyl]-2,2,2-trifluoroacetamide (839)}.
\]

A soln. of 718 (1.248 g, 3.06 mmol) in CH$_2$Cl$_2$ (25 ml) was treated with CF$_3$CO$_2$H (4 ml, 52 mmol), stirred at r.t. for 95 min, and evaporated. A soln. of the residue in CH$_2$Cl$_2$ (20 ml) was treated with Et$_3$N (4.6 ml, 33 mmol) and (CF$_3$CO)$_2$O (1.7 ml, 12.2 mmol), stirred at r.t. for 20 h, and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 10:1) of the orange oil gave 839 (1.00 g, 81%) as a slightly yellow oil, which became amorphous on standing. $R_f$ (cyclohexane/AcOEt 3:1) 0.61. M.p.: 56.3–59.7°. FT-IR (1%, CHCl$_3$): 3031 w, 3015 w, 2860 w, 1681 s (C=O), 1603 w, 1497 w, 1453 m, 1434 w, 1356 w, 1286 w, 1106 w, 1029 w, 993 w.

$^1$H-NMR (300 MHz, CDCl$_3$, 7:3 mixture of diastereoisomers): 7.39–7.28 (8 arom. H); 7.08 (d, $J = 7.2$, 2 arom. H); 5.69–5.61 and 5.49–5.41 (2m, H–C(3), H–C(4)); 4.96 (br. $d$, $J = 16.2$, 0.3 H); 4.72 (br. $d$, $J = 18.4$, 0.7 H); 4.61 (br. $d$, $J = 19.3$, 0.7 H); 4.60–4.52 (m, H–C(1)); 4.50–4.37 (m, 2.3 H); 3.66 (dd, $J = 9.3$, 7.5, CH–C(6)); 3.46 (dd, $J = 9.7$, 6.8, CH–C(6)); 2.63–2.54 (m, 0.7 H), 2.46–2.32 (m, 2.2 H), 2.27–2.03 (m, 1.4 H), 2.00–1.89 (m, 0.7 H) (CH$_2$(2), CH$_2$(5), H–C(6)). $^{13}$C-NMR (75 MHz, CDCl$_3$, only the signals for the major diastereoisomer are reported, those of the minor diastereoisomer are hidden by noise): 137.79; 128.54, 128.30, 127.58, 127.22, 126.16, 125.61, 125.33, 124.35 (several arom. CH); 73.22 (PhCH$_2$O); 69.85 (CH$_2$–C(6)); 55.67, 49.39 (C(1), PhCH$_2$N); 35.55 (C(6)); 28.47, 25.33 (C(2), C(5)); signals for CF$_3$CO hidden by noise. $^{19}$F-NMR (282 MHz, CDCl$_3$, 7:3 mixture

tert-Butyl cis-2-Oxo-3a,4,5,7a-tetrahydrobenzoxazole-3-carboxylate (749).
A soln. of 747 (320 mg, 1.25 mmol) in DMF (30 ml) was treated with K2CO3 (172 mg, 1.25 mmol) and stirred at 80° for 4 d. The mixture was cooled to r.t., treated with Boc2O (1.6 ml, 7.18 mmol), stirred for 3 d, diluted with AcOEt (250 ml), and washed with H2O (150 ml) and brine (150 ml). The aqueous phases were extracted with AcOEt (200 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 5:1) of the orange oil gave colourless crystalline 749 (86 mg, 28%). Rf (cyclohexane/AcOEt 3:1) 0.28. M.p.: 116.0–118.5°. FT-IR (1%, CHCl3): 3000 w, 2989 w, 1811 s (C=O), 1784 s (C=O), 1718 m, 1360 s, 1336 m, 1289 w, 1258 w, 1159 m, 1115 m, 1078 m, 1010 w, 935 w, 873 w, 847 w. 1H-NMR (300 MHz, CDCl3): 6.27–6.20 (m, H–C(6)); 5.88 (dddd, J = 10.0, 3.8, 2.5, 1.2, H–C(7)); 4.78–4.72 (m, H–C(7a)); 4.25 (ddd, J = 11.2, 7.2, 4.4, H–C(3a)); 2.29–2.18 (m, H–C(4), H–C(5)); 2.09–1.96 (m, H’–C(5)); 1.67–1.58 (m, H’–C(4)); 1.56 (s, Me3C). 13C-NMR (75 MHz, CDCl3): CO signals hidden by noise; 135.19 (d, C(7)); 121.37 (d, C(6)); 83.72 (s, Me3C); 69.27 (d, C(7a)); 54.51 (d, C(3a)); 28.15 (q, Me3C); 24.07, 22.20 (2t, C(4), C(5)). ESI-MS: 501 (40, [2 M + Na]+), 294 (28, [M + Na + MeOH]+), 262 (71, [M + Na]+), 132 (65), 116 (100).

tert-Butyl cis-c-6,t-7-dibromo-2-oxohexahydrobenzoxazole-3-carboxylate (750) and tert-Butyl cis-t-6,c-7-dibromo-2-oxohexahydrobenzoxazole-3-carboxylate (751).
A soln. of 749 (61 mg, 0.31 mmol) in CH2Cl2 (7 ml) was cooled to 0°, treated with PhMe3NBr3 (470 mg, 1.26 mmol), stirred for 18 h while slowly warming to r.t., and poured into ice-cold sat. aq. Na2S2O5 soln. (20 ml). The mixture was extracted with AcOEt (3 x 25 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (30 g of silica gel, cyclohexane/AcOEt 6:1) of the orange oil (123 mg) gave 750 (48 mg, 38%) and 751 (38 mg, 30%).
Data of 750:
Colourless oil. Rf (cyclohexane/AcOEt 3:1) 0.46. FT-IR (1.5%, CHCl3): 3030v, 2984w, 1819s (C=O), 1721m, 1477w, 1456w, 1437w, 1370s, 1358s, 1346m, 1330m, 1301m, 1283w, 1158m, 1075s, 1035w, 984w, 909w, 846w. 1H-NMR (300 MHz, CDCl3): 4.83–4.79 (m, H–C(7)); 4.77 (br. dd, J = 6.1, 2.0, H–C(7a)); 4.55 (br. dd, J = 7.2, 3.1, H–C(6)); 4.45 (dt, J = 9.3, 6.2, H–C(3a)); 2.46–2.25 (m, 2 H); 2.16–1.97 (m, 2 H); 1.55 (s, Me3C). 13C-NMR (300 MHz, CDCl3): 150.22, 148.84 (2 C=O); 84.31 (Me 3C); 74.77 (C(7a)); 52.00 (C(3a)); 47.21, 45.94 (C(6), C(7)); 28.07 (Me3C); 25.25, 22.73 (C(4), C(5)). ESI-MS: 841 (1), 839 (2), 837 (4), 835 (2), 833 (1, [2 M + K+]4); 825 (17), 823 (65), 821 (100), 819 (64), 817 (14, [2 M + Na+]4); 456 (11), 454 (24), 452 (12, [M + Na + MeOH]+); 440 (28), 438 (53), 436 (24, [M + K]+); 424 (32), 422 (71), 420 (36, [M + Na]4+); 400 (3), 398 (6), 396 (2, [M + Na + MeOH – C4H8]+); 368 (4) 366 (9), 364 (4, [M + Na – C4H8]+).

Data of 751:
Colourless needles. Rf (cyclohexane/AcOEt 3:1) 0.39. M.p.: 168°. FT-IR (1%, CHCl3): 3031w, 2985w, 2933v, 1819s (C=O), 1722m, 1477w, 1455w, 1449w, 1383m, 1371m, 1353s, 1321m, 1287w, 1159m, 1139m, 1077s, 1062m, 1046w, 1006w, 952w, 915w, 843w. 1H-NMR (300 MHz, CDCl3): 4.75 (dd, J = 6.2, 3.1, H–C(7a)); 4.33 (dt, J = 8.1, 6.1, H–C(3a)); 4.25 (dd, J = 10.3, 8.3, 4.5, H–C(6)); 4.19 (dd, J = 10.0, 3.4, H–C(7)); 2.51 (ddt, J = 14.6, 6.8, 3.8, Heq–C(5)); 2.32 (dt, J = 14.6, 6.2, 3.1, Hax–C(5)); 1.98 (dd, J = 14.6, 6.2, 3.1, Heq–C(4)); 1.69 (dd, J = 14.6, 11.5, 8.1, 3.4, Hax–C(4)); 1.53 (s, Me3C). 13C-NMR (75 MHz, CDCl3): 150.00, 148.62 (2 C=O); 84.55 (Me3C); 75.72 (C(7a)); 54.44 (C(3a)); 51.47, 49.49 (C(6), C(7)); 31.98, 26.00 (C(4), C(5)); 28.05 (Me3C). ESI-MS: 825 (2), 823 (8), 821 (13), 819 (8), 817 (2, [2 M + Na]+)); 456 (6), 454 (12), 452 (7, [M + Na + MeOH]+); 440 (14), 438 (25), 436 (13, [M + K]+); 424 (36), 422 (73), 420 (37, [M + Na]+); 368 (5) 366 (11), 364 (5, [M + Na – C4H8]+). Anal. calc. for C12H17Br2NO4 (399.08): C 36.12, H 4.29, N 3.51; found: C 36.34, H 4.53, N 3.38.
X-ray crystal structure analysis of 751.
Compound 751 was recrystallised from hexane/CH2Cl2.

Table 1. Selected crystal structure data for 751.

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Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3).

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Table 3. Bond lengths [Å].

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Table 4. Bond angles [°].

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Table 5. Torsion angles [°].

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A soln. of 729 (51 mg, 144 µmol) in THF (2.5 ml) was cooled to 0°, treated with NaH (9.5 mg of a 55% suspension in oil, 217 µmol), allowed to warm to r.t., stirred at 50° for 21 h and under reflux for 22 h, cooled to r.t., and poured into H₂O (10 ml). The mixture was extracted with CH₂Cl₂ (4 x 15 ml). The combined organic phases were washed with brine (10 ml), and the aq. phase was extracted with CH₂Cl₂ (10 ml). The combined organic phases were dried (Na₂SO₄) and evaporated. FC (10 g of silica gel, cyclohexane/acetone 9:1) of the colourless oil (43.6 mg) gave 840 (10 mg, 25%) as a colourless oil. Rf (cyclohexane/acetone 3:1) 0.37.

1H-NMR (300 MHz, CDCl₃, ca. 3:2 mixture of rotamers): 4.92 (br. dd, J = 5.3, 0.9, 0.4 H) and 4.86–4.81 (m, 0.6 H) (H–C(1)); 4.63 (dm, J = 5.3, 0.4 H) and 4.62–4.57 (m, 0.6 H) (H–C(4)); 4.10 (br. t, J = 5.4, 0.6 H) and 4.07 (br. t, J = 5.3, 0.4 H) (H–C(2)); 2.42–2.37 (m, 1 H); 2.33–2.28 (m, 1 H); 2.06–1.78 (m, 2 H); 1.68–1.42 (m, 2 H). 13C-NMR (75 MHz, CDCl₃, ca. 3:2 mixture of diastereoisomers, minor diastereoisomer in italics): 64.94, 63.02 (2d, C(1)); 57.2, 55.35 (2d, C(4)); 47.83, 46.39 (2d, C(2)); 44.22, 42.36 (2t, C(3)); 29.43, 28.72, 27.25, 26.50 (4t, C(5), C(6)). 19F-NMR (282 MHz, CDCl₃, ca. 3:2 mixture of diastereoisomers): –70.13 (d, J = 1.3, 0.6 F); –71.45 (d, J = 1.8, 0.4 F). ESI-MS: 328 (98), 326 (100, [M + Na + MeOH]⁺); 312 (9), 310 (8, [M + K]⁺); 296 (10), 294 (10, [M + Na]⁺).
(±)-(1R*,5R*,8R*)-8-Iodo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (795).

A soln. of 712 (1 g, 5.06 mmol) in Et2O (50 ml) was treated with K2CO3 (1.4 g, 10.14 mmol) and I2 (2.58 g, 10.14 mmol), stirred at r.t. for 24 h, diluted with AcOEt (150 ml), and washed with sat. aq. Na2S2O5 soln. The aq. phase was extracted with AcOEt (2 x 150 ml). Drying (Na2SO4) and evaporation of the combined organic phases gave brown amorphous 795 (1.42 g, quant.). Rf (cyclohexane/AcOEt 3:1) 0.03. FT-IR (1%, CDCl3): 3445 w (NH), 3002 w, 2940 w, 2922 w, 1721 s (C=O), 1439 m, 1410 w, 1273 w, 1097 s, 1042 m, 838 w. 1H-NMR (300 MHz, CDCl3): 6.31–6.23 (br. s, NH); 4.72–4.68, 4.66–4.61 (2 m, H–C(1), H–C(8)); 3.65 (br. d, J = 3.7, H–C(5)); 2.69 (ddt, J = 13.9, 2.3, 1.6, H–C(9)); 2.32–2.17 (m, 1 H); 2.05–1.92 (m, 3 H); 1.76–1.67 (dm, J = 13.7, 1 H). 13C-NMR (75 MHz, CDCl3): 154.02 (s, C=O); 76.64 (d, C(1)); 45.24 (d, C(5)); 27.73 (d, C(8)); 27.65, 26.32, 25.02 (3 t, C(6), C(7), C(9)). EI-MS: 267 (3, M+), 154 (6), 140 (100, [M – I]+), 96 (69, [M – I – CO2]+).

2-Oxa-4-azabicyclo[3.3.1]non-7-en-3-one (796).

A soln. of 795 (1.42 g, 5.06 mmol) in THF (50 ml) was treated with DBU (1.16 ml, 7.76 mmol), refluxed for 22 h, allowed to cool to r.t., and evaporated. Two FC's (70 g of silica gel, CH2Cl2/acetone 5:2) of the residue gave colourless crystalline 796 (533 mg, 75%). Rf (CH2Cl2/Methanol 9:1) 0.53. M.p.: 202.9–204.5°. FT-IR (0.5%, CHCl3): 3442 w, 3008 w, 1701 s (C=O); 1452 w, 1450 m, 1420 m, 1412 m, 1350 w, 1296 w, 1259 w, 1107 m, 1058 m, 1019 w, 976 w, 966 w, 913 w, 849 w. 1H-NMR (300 MHz, CDCl3): 6.09–6.02 (m, H–C(8)); 5.99–5.84 (br. s, NH); 5.94 (dddd, J = 10.0, 4.0, 2.8, 1.3, H–C(7)); 4.77–4.73 (m, H–C(1)); 3.88–3.82 (m, H–C(5)); 2.41–2.25 (m, CH2C(6)); 2.21 (dddd, J = 13.2, 4.5, 3.3, 1.2, H–C(9)); 1.90 (ddq, J = 13.4, 2.3, 1.9, H’–C(9)). 13C-NMR (75 MHz, CDCl3): 154.99 (s, C=O); 129.96, 125.59 (2d, C(7), C(8)); 67.99 (d, C(1)); 44.27 (d, C(5)); 34.87, 26.85 (2t, C(6), C(9)). EI-MS: 139 (100, M+), 94 (18), 80 (57), 67 (28), 43 (34).
4-Benzyl-2-oxa-4-azabicyclo[3.3.1]non-7-en-3-one (797).
A suspension of 796 (115 mg, 0.83 mmol) in THF (10 ml) was cooled to –78°, treated dropwise with 1.5M BuLi in hexane (0.6 ml, 0.91 mmol), stirred for 15 min, treated with BnBr (0.29 ml, 2.47 mmol), stirred for 22 h while warming to r.t., and poured into sat. aq. NH4Cl soln. The mixture was extracted with AcOEt (3 x 50 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 1:1) of the orange oil (420 mg) gave colourless crystalline 797 (175 mg, 92%).

M.p.: 93.5–94.0°. FT-IR (1.5%, CHCl3): 3008 w, 2944 w, 1680 s (C=O), 1496 w, 1448 m, 1422 w, 1393 m, 1358 w, 1330 w, 1291 w, 1144 w, 1126 m, 1067 w, 1039 w, 977 w, 942 w, 847 w. 1H-NMR (300 MHz, CDCl3): 7.36–7.24 (5 arom. H); 6.11–6.04 (m, H–C(8)); 5.91 (dddd, J = 9.7, 4.7, 2.2, 1.3, H–C(7)); 5.09 (d, J = 15.3, PhCH); 4.75-4.71 (m, H–C(1)); 4.07 (d, J = 15.6, PhCH2); 3.67–3.62 (m, H–C(5)); 2.42 (dddt, J = 18.7, 4.7, 2.0, 1.6, H–C(6)); 2.24–2.13 (m, H–C(6), H–C(9)); 1.91 (dt, J = 13.1, 2.2, H–C(9)). 13C-NMR (75 MHz, CDCl3): 153.67 (s, C=O); 137.24 (s); 129.25 (d), 128.58 (2d), 127.56 (2d), 127.44 (d), 125.69 (d) (arom. C, C(7), C(8)); 67.69 (d, C(1)); 50.97 (t, PhCH2); 48.30 (d, C(5)); 31.18, 28.10 (2t, C(6), C(9)). ESI-MS: 481 (100, [2M + Na]+), 284 (11, [M + Na + MeOH]+), 268 (9, [M + K]+), 252 (61, [M + Na]+), 230 (13 (M + 1)+).

4-(Toluene-4-sulfonyl)-2-oxa-4-azabicyclo[3.3.1]non-7-en-3-one (798).
A suspension of 796 (100 mg, 0.72 mmol) in THF (8 ml) was cooled to 0°, treated with NaH (78 mg, of a 55% suspension in oil, 1.79 mmol), stirred for 0.5 h, treated with TsCl (164 mg, 0.86 mmol), and stirred for 2.5 h while warming to r.t. The mixture was acidified with 1M HCl to pH 4.5, diluted with H2O (20 ml), and extracted with Et2O (3 x 25 ml) and CH2Cl2 (3 x 30 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (30 g of silica gel, cyclohexane/AcOEt 2:1) of the residue (262 mg, colourless solid) gave colourless crystalline 798 (189 mg, 89%). Rf (cyclohexane/AcOEt 1:1) 0.49. M.p.: 174.0–174.7°. FT-IR (1%, CHCl3): 3008 w, 1721 s (C=O), 1650 w, 1598 w, 1558 w, 1507 w, 1494 w, 1441 w, 1398 m, 1390 m, 1361 m, 1294 w, 1171 s, 1142 m, 1131 s, 1090 m, 1070 m, 1034 w, 979 w, 986 w, 937 w, 893 m, 861 w, 843 w. 1H-NMR (300 MHz, CDCl3): 7.87 (d, J = 8.4, 2 arom. H); 7.30 (d, J =
N-((Cyclohexa-2,4-dienyl)-(4-methylbenzene)sulfonamide (803).

A soln. of 798 (10.9 mg, 37 µmol) in THF (5 ml) was purged with Ar, treated with Pd(PPh3)4 (4 mg, 3.7 µmol), purged with Ar, stirred at r.t. for 22 h, and evaporated. FC (2 g of silica gel, cyclohexane/AcOEt 4:1) of the yellow oil gave 803 (1.4 mg, 15%) as a volatile colourless oil. Rf (cyclohexane/AcOEt 9:1) 0.90. FT-IR (0.5%, CHCl3): 3379 w (NH), 3009 w, 2927 w, 1599 w, 1403 m, 1334 m, 1305 w, 1158 w, 1094 m, 1034 m, 909 s. 1H-NMR (300 MHz, CDCl3): 7.75 (dt, J = 8.4, 2.0, 2 arom. H); 7.31 (dd, J = 8.7, 0.6, 2 arom. H); 6.01–5.92 (m, 2 H); 5.80–5.73 (m, 1 H); 5.59–5.52 (m, 1 H); 4.58 (d, J = 9.3, NH); 3.93 (br. ddd, J = 12.1, 9.2, 6.2, H–C(1)); 2.44 (s, Me); 2.38 (ddd, J = 6.5, 5.4, 1.6, CH2(6)). ESI-MS: 537 (7, [2 M + K]+), 521 (23, [2 M + Na]+), 304 (22, [M + Na + MeOH]+), 288 (10, [M + K]+), 272 (11, [M + Na]+), 267 (3, [M + 1]+).

N-((c-5-Ethoxycyclohex-3-enyl)-(4-methylbenzene)sulfonamide (804).

A soln. of 798 (9.7 mg, 33 µmol) in EtOH (6 ml) was purged with Ar, treated with Pd(PPh3)4 (3.8 mg, 3.3 µmol), stirred at r.t. for 2 d, and evaporated. FC (2 g of silica gel, cyclohexane/AcOEt 4:1) of the residue gave 803 (1.8 mg, 22%) and 804 (2.7 mg, 28%) as colourless oils. Rf (cyclohexane/AcOEt 1:1) 0.66. FT-IR (1%, CHCl3): 3312 w, 3009 w, 2977 w, 2928 w, 2872 w, 1599 w, 1440 w, 1426 w, 1335 m, 1305 m, 1159 s, 1094 s, 1077 m, 1020 w, 963 w, 931 w, 884 w, 843 w. 1H-NMR (300 MHz, CDCl3): 7.75 (br. d, J = 8.4, 2 arom. H); 7.29 (br. d, J = 8.4, 2 arom. H); 5.91–5.82 (m, H–C(4), NH); 5.72 (dt, J = 10.1, 3.6, H–C(3)); 3.87–3.81 (m, H–C(5)); 3.65 (tt, J = 8.9, 4.6, H–C(1)); 3.51, 3.46 (2 dq, J = 9.0, 6.9, MeCH2O); 2.43 (s, PhMe); 2.18–2.14 (m, CH2(2)); 1.74 (t, J = 4.5, CH2(6)); 1.21 (t, J = 7.0, MeCH2O). ESI-MS: 629 (3, [2 M + K]+), 613 (30, [2 M + Na]+), 313 (5, [M + NH4]+), 296 (35, [M + 1]+).

A soln. of 716 (1.0 g, 3.15 mmol) in Et₂O (50 ml) was treated with K₂CO₃ (0.87 g, 6.30 mmol) and I₂ (1.6 g, 6.3 mmol), stirred at r.t. for 42 h, diluted with AcOEt (150 ml), and washed with sat. aq. Na₂S₂O₅ soln. (150 ml). The aq. phase was extracted with AcOEt (2 x 150 ml). Drying (Na₂SO₄) and evaporation of the combined organic phases gave orange amorphous 799 (1.48 g, quant.).

Rf (CH₂Cl₂/MeOH 9:1) 0.71. M.p.: 134–136°. FT-IR (1.5%, CHCl₃): 3443 w (NH), 3019 m, 2927 m, 2857 w, 1713 s (C=O), 1497 w, 1436 m, 1409 w, 1367 w, 1308 w, 1292 w, 1100 m, 1036 w, 1093 w. 1H-NMR (300 MHz, CDCl₃): 7.41–7.28 (5 arom. H); 6.00–5.75 (br. s, NH); 4.72–4.68, 4.66–4.61 (2 m, H–C(1), H–C(8)); 4.52 (d, J = 12.1), 4.47 (d, J = 12.8) (PhCH₂); 3.74–3.69 (m, H–C(5)); 3.39–3.30 (m, CH₂–C(6)); 2.66 (br. d, J = 14.0, H–C(9)); 2.35 (br. quint., J = 8.0, H–C(6)); 2.08 (dm, J = 14.0, H'–C(9)); 1.86 (dd, J = 9.2, 3.6, H–C(7)); 1.89–1.83 (m, H'–C(7)). 13C-NMR (75 MHz, CDCl₃): 128.46 (2 d), 127.88 (d), 127.68 (2d), 76.81 (d, C(1)); 73.28 (t, PhCH₂); 70.08 (t, CH₂–C(6)); 46.20 (d, C(5)); 37.52 (d, C(6)); 29.58 (t, C(9)); 25.91 (t, C(7)). ESI-MS: 797 (13, [2M + Na]+), 426 (10, [M + K]+), 410 (100, [M + Na]+).

(±)-(IR*,5S*,6R*)-6-(Benzyloxymethyl)-2-oxa-4-azabicyclo[3.3.1]nonan-7-en-3-one (800).

A soln. of 799 (1.48 g, ca. 3.15 mmol) in THF (50 ml) was treated with DBU (0.56 ml, 3.78 mmol), refluxed for 50 h, and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 2:5) of the brown residue gave yellow amorphous 800 (640 mg, 78%). Rf (CH₂Cl₂/MeOH 9:1) 0.62. M.p.: 164.0–165.0°. FT-IR (1%, CHCl₃): 3442 w (NH), 3015 m, 2866 w, 1713 s (C=O), 1497 w, 1436 m, 1409 w, 1308 w, 1292 w, 1100 m, 1036 w, 903 w. 1H-NMR (300 MHz, CDCl₃): 129.84, 126.67 (2d, C(7), C(8));128.49 (2d), 127.93 (d), 127.65 (2d), 76.81 (d, C(1)); 73.28 (t, PhCH₂); 70.08 (t, CH₂–C(6)); 46.20 (d, C(5)); 37.52 (d, C(6)); 29.58 (t, C(9)); 25.91 (t, C(7)). ESI-MS: 797 (13, [2 M + Na]+), 426 (10, [M + K]+), 410 (100, [M + Na]+).
68.05 (d, C(1)); 45.41, 43.24 (2d, C(5), C(6)); 27.19 (t, C(9)). ESI-MS: 541 (7, [2 M + Na]+), 298 (3, [M + K]+), 282 (100, [M + Na]+). Anal. calc. for C15H17NO3 (259.30): C 69.48, H 6.61, N 5.40; found: C 69.45, H 6.42, N 5.36.

(±)-(IR*,5S*,6R*)-6-(Benzyloxymethyl)-4-(toluene-4-sulfonyl)-2-oxa-4-azabicyclo[3.3.1]non-7-en-3-one (801).

A suspension of 800 (100 mg, 0.386 mmol) in THF (8 ml) was cooled to 0°, treated with NaH (42 mg of a 55% suspension in oil, 0.964 mmol), stirred for 30 min, treated with TsCl (88 mg, 0.463 mmol), stirred at r.t. for 3.5 h, refluxed for 24 h, cooled to r.t., neutralised with 1M HCl, and diluted with H2O (25 ml) and CH2Cl2 (25 ml). The organic phase was separated and the aq. phase was extracted with CH2Cl2 (25 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (15 g of silica gel, cyclohexane/AcOEt 2:1) of the yellow oil (242 mg) gave yellow amorphous 801 (138 mg, 86%). Rf (cyclohexane/AcOEt 1:1) 0.50. M.p.: 175.6–177.1°. FT-IR (0.5%, CHCl3): 3068 w, 2975 w, 2925 w, 2863 w, 1721 s (C=O), 1597 w, 1496 w, 1455 w, 1441 w, 1402 w, 1377 w, 1359 m, 1135 s, 1090 m, 929 w, 876 w, 857 w.

1H-NMR (300 MHz, CDCl3): 7.82 (d, J = 8.4, 2 arom. H); 7.41–7.30 (5 arom. H); 7.28 (d, J = 8.1, 2 arom. H); 6.16 (br. d, J = 10.0, H–C(7)); 6.05 (ddd, J = 9.9, 5.4, 2.7, H–C(8)); 5.10–5.05 (m, H–C(5)); 4.75–4.69 (m, H–C(1)); 4.64, 4.56 (2d, J = 11.5, PhCH2); 4.41 (dd, J = 9.0, 5.9, CH–C(6)); 3.62 (t, J = 9.2, CH’–C(6)); 2.91–2.81 (m, H–C(6)); 2.41 (s, Me); 2.19 (t, J = 3.0, CH2(9)).

13C-NMR (75 MHz, CDCl3): 148.59 (s, C=O); 144.71, 138.00, 135.89 (3s); 132.07, 124.69 (2d, C(7), C(8)); 129.17 (2d), 128.71 (2d), 128.30 (2d), 127.82 (2d), 127.60 (d) (Ph, Ts); 73.50 (t, PhCH2); 70.67 (t, CH2–C(6)); 69.16 (d, C(1)); 52.82 (d, C(5)); 43.66 (d, C(6)); 28.75 (t, C(9)); 21.75 (q, Me). ESI-MS: 849 (5, [2 M + Na]+), 452 (22, [M + K]+), 436 (100, [M + Na]+), 414 (6, [M + 1]+).
(±)-(IR*,SS*,6R*)-6-(Benzyloxymethyl)-4-(4-nitrobenzyl)-2-oxa-4-azabicyclo[3.3.1]non-7-en-3-one (802).

A soln. of 800 (45 mg, 173 µmol) in DMF (2 ml) was cooled to 0°, treated with NaH (9.1 mg of a 55% suspension in oil, 208 µmol), stirred at 0° for 30 min, treated with 4-nitrobenzyl bromide (75 mg, 347 µmol), stirred for 23 h while warming to r.t., and poured into sat. aq. NH₄Cl soln. The mixture was extracted with AcOEt (3 x 10 ml). The combined organic phases were dried (Na₂SO₄) and evaporated. FC (cyclohexane/AcOEt 1:1) of the yellow oil (458 mg) gave 802 (40 mg, 58%) as a yellow oil. \( R_f \) (cyclohexane/AcOEt 1:1) 0.28. FT-IR (0.5%, CHCl₃): 3023 \( \text{w} \), 3011 \( \text{w} \), 2970 \( \text{w} \), 2864 \( \text{w} \), 1680 \( \text{s} \) (C=O), 1606 \( \text{w} \), 1523 \( \text{m} \), 1491 \( \text{w} \), 1454 \( \text{m} \), 1415 \( \text{w} \), 1347 \( \text{s} \), 1134 \( \text{w} \), 1122 \( \text{w} \), 1110 \( \text{w} \), 1086 \( \text{w} \), 1005 \( \text{w} \), 909 \( \text{w} \), 857 \( \text{w} \). 1H-NMR (300 MHz, CDCl₃): 8.07 (d, \( J = 8.4 \), 2 arom. H); 7.42–7.26 (5 arom. H); 7.30 (d, \( J = 8.7 \), 2 arom. H); 6.12 (br. \( \text{ddd} \), \( J = 9.5, 5.9, 3.3 \), H–C(8)); 5.63 (br. d, \( J = 9.7 \), H–C(7)); 5.23 (d, \( J = 15.3 \), ArCH); 4.81–4.76 (m, H–C(1)); 4.61, 4.55 (2d, \( J = 11.5 \), PhCH₂O); 4.13 (d, \( J = 15.6 \), ArCH); 3.85–3.80 (m, H–C(5)); 3.63 (dd, \( J = 9.7, 5.3 \), CH–C(6)); 3.54 (t, \( J = 10.4 \), CH′–C(6)); 2.87–2.79 (m, H–C(6)); 2.11 (br. dt, \( J = 13.5, 3.8 \) (H–C(9)); 1.95 (br. d, \( J = 13.4 \), H′–C(9)). \(^{13}\)C-NMR (75 MHz, CDCl₃): 153.77 (s, C=O); 147.11, 145.12, 136.97 (3s, Ph); 129.42, 126.76 (2d, C(7), C(8)); 128.53 (2d), 128.49 (2d), 128.16 (d), 127.91 (2d), 123.60 (2d) (Ar, Ph); 73.34 (t, PhCH₂O); 69.66 (t, CH₂–C(6)); 68.17 (d (C(1))); 51.35 (t, PhCH₂N); 49.67 (d, C(5)); 44.22 (d, C(6)); 28.70 (t, C(9)). ESI-MS: 827 (21, [2 \( M + K \)]\(^+ \)), 811 (94, [2 \( M + Na \)]\(^+ \)), 426 (50, \( [M + MeOH] \)]\(^+ \)), 417 (18, \( [M + Na] \)]\(^+ \)).

CH₂OBn
NHTs

N-[c-6-(Benzyloxymethyl)cyclohexa-2,4-dienyl)-(4-methylbenzene)sulfonamide (805).

A degassed (purged with Ar) soln. of 801 (10 mg, 24 µmol) in THF (5 ml) was treated with Pd(PPh₃)₄ (3 mg, 2.4 µmol), degassed, stirred at r.t. for 21 h, and evaporated. FC (2 g of silica gel, cyclohexane/AcOEt 4.5:1) of the brown oil gave 805 (6.2 mg, 70%) as a colourless oil. \( R_f \) (cyclohexane/AcOEt 1:1) 0.81. FT-IR (0.5%, CHCl₃): 3367m (NH), 3032s, 3011s, 2927s, 2864m, 1694s, 1599m, 1496m. \(^{1}H\)-NMR (300 MHz, CDCl₃): 7.72 (dt, \( J = 8.4 \), 1.9, 2 arom. H); 7.40–7.30 (5 arom. H); 7.26 (dm, \( J = 8.7 \), 2 arom. H); 5.96 (dddd, \( J = 9.3, 5.0, 2.2, 1.3 \)), 5.89 (dddt, \( J = 9.3, 5.0, 1.3 \) (H–C(2), H–C(5))); 5.64 (br. td, \( J = 8.9, 4.3 \), H–C(3), H–C(4)); 5.32 (br. d, \( J = 9.0 \), NH); 4.50 (d, \( J = 11.5 \), PhCH); 4.41 (d, \( J = 11.8 \), PhCH)
4.07–3.98 (m, H–C(1)); 3.71 (t, J = 8.9, CH–C(6)); 3.45 (dd, J = 9.3, 5.6, CH–C(6));
2.64–2.55 (m, H–C(6)); 2.41 (s, Me). ESI-MS (the sample was contaminated with HCl): 867
(11), 865 (12, [2 (M + HCl) + MeOH + Na]+); 462 (6), 460 (10, [M + HCl + MeOH + Na]+);
446 (12), 444 (25, [M + HCl + K]+).

N-[2-(Benzoyloxymethyl)cyclohexa-2,4-dienyl]-(4-methylbenzene)sulfonamide (806).
A degassed (purged with Ar) soln. of 801 (10 mg, 24 µmol) in THF (5 ml) was treated with
LiCl (1 mg, 23 µmol) and Pd(PPh3)4 (3 mg, 2.4 µmol), degassed, stirred at r.t. for 1 h,
refluxed for 22 h, cooled to r.t., and evaporated. FC (2 g of silica gel, cyclohexane/AcOEt 9:2)
of the yellow oil gave 806 (3.5 mg, 39%) as a colourless oil. Rf (cyclohexane/AcOEt 1:1) 0.78.
FT-IR (0.5%, CHCl3): 3374 w (NH), 3031 m, 3015 m, 2927 w, 2867 w, 1599 w,
1496 w, 1454 w, 1416 m, 1338 m, 1092 s, 914 w, 843 s. 1H-NMR (300 MHz, CDCl3): 7.73
dt, J = 8.4, 1.9, 2 arom. H); 7.39–7.25 (7 arom. H); 6.03–5.96 (m, 2 H) und 5.78–5.71 (m, 1 H) (H–C(3),
H–C(4), H–C(5)); 4.82 (d, J = 8.7, NH); 4.39 (d, J = 12.5, PhCH); 4.35 (d, J = 12.1, PhCH);
3.95 (ddd, J = 8.4, 7.2, 4.1, H–C(1)); 3.84 (d, J = 12.1, CH–C(2)); 3.76 (d, J = 12.5,
CH–C(2)); 2.41 (s, Me); 2.50–2.29 (m, CH2(6)). ESI-MS (the sample was contaminated with

Under Ar, neat 801 (11.4 mg, 27 µmol) was heated at 160° for 3 d. After cooling to r.t. FC (2
g of silica gel, cyclohexane/AcOEt 3:1) gave 807 (5.9 mg, 52%) as a colourless oil. Rf
cyclohexane/AcOEt 1:1) 0.64. FT-IR (0.5%, CHCl3): 3021 w, 1725 s (C=O), 1593 w, 1494 w,
1455 w, 1399 m, 1383 m, 1362 m, 1265 s, 1131 s, 1089 s, 1063 w, 909 w, 893 w. 1H-NMR (300
MHz, CDC13): 7.85 (br. d, J = 8.4, 2 arom. H); 7.41–7.29 (5 arom. H); 7.26 (d, J = 8.4, 2
arom. H); 6.07–6.04 (m, H–C(7), H–C(8)); 4.95–4.91 (m, H–C(5)); 4.65–4.61 (m (not a
dd), J = 3.7, 1.9, H–C(1)); 4.49, 4.43 (2d, J = 11.8, PhCH2); 3.46 (dd, J = 9.7, 6.5, CH–C(9)); 3.29
(dd, J = 9.3, 8.4, CH–C(9)); 2.91 (br. dt, J = 18.7, 2.5, H–C(6)); 2.58 (br. dd, J = 19.0, 4.0,
H–C(6)); 2.42 (s, Me); 2.39 (ddt, J = 8.4, 6.5, 2.0, H–C(9)). 13C-NMR (75 MHz, CDC13):
144.71; 137.3; 135.5; 130.19, 125.20 (C(7), C(8)); 129.14 (2C); 128.67 (2C); 128.46 (2C);
127.87; 127.46 (2C); 73.54 (PhCH2); 70.12 (CH2–C(9)); 67.76 (C(1)); 52.45 (C(5)); 36.73.
383.26 (C(6), C(9)); 21.76 (Me). ESI-MS: 452 (27, [M + K]+); 436 (86, [M + Na]+); 431 (87, [M + NH4]+); 414 (100, [M + 1]+).

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A solution of 828 (30 mg, 95 µmol) in AcOH (3 ml) was treated with NIS (65 mg, 287 µmol), stirred at r.t. for 45 min., and evaporated. FC (2 g of silica gel, hexane/AcOEt 8:1) gave 828 (36 mg, 86%) as a yellow oil. 

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R_f (\text{cyclohexane/AcOEt 3:1}) 0.65. \]

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1H-NMR (300 MHz, CDCl_3): 7.38–7.25 (5 \text{ arom. H}) \quad 4.76–4.72 (m, H–C(1)) \quad 4.68–4.64 (m, H–C(8)) \quad 4.57, 4.49 (2d, J = 11.8, PhCH_2) \quad 4.00–3.96 (m, H–C(5)) \quad 3.58 (dd, J = 9.0, 7.5, CH–C(6)) \quad 3.30 (dd, J = 9.0, 6.9, CH′–C(6)) \quad 2.68 (dt, J = 14.3, 1.6, H_{ax}–C(9)) \quad 2.65–2.54 (m, H–C(6)) \quad 2.11–2.03 (m, H_{eq}–C(7)) \quad 1.88 (dd, J = 14.3, 3.9, 1.9, H_{eq}'–C(9)) \quad 1.48 \quad \text{(signals of } C(3) \text{ and CF}_3 \text{ and of one aromatic CH hidden by noise)}.
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13C-NMR (75 MHz, CDCl_3): 138.00 (s); 128.26 (2d); 127.52 (3d); 124.45 (C(8)); 73.65; 71.22; 48.04 (d, C(5)); 38.51 (d, C(6)); 30.28 (d, C(7)) \quad 26.66 (d, C(8)); 24.28 (d, C(9)).
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A solution of 828 (36 mg, 82 µmol) in THF (4 ml) was treated with DBU (0.015 ml, 98 µmol), heated under reflux for 24 h, cooled to r.t., and evaporated. FC (2 g of silica gel, hexane/AcOEt 5:1) gave 827 (22 mg, 86%) as a colourless oil. 

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R_f (\text{cyclohexane/AcOEt 3:1}) 0.46. \]

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1H-NMR (300 MHz, CDCl_3): 7.38–7.24 (5 \text{ arom. H}) \quad 6.07 (dd, J = 10.0, 1.6, H–C(7)) \quad 5.98 (dddd, J = 10.0, 5.3, 2.5, 1.3, H–C(8)) \quad 4.94–4.89 (m, H–C(1)) \quad 4.60, 4.55 (2d, J = 11.8, PhCH_2) \quad 4.11–4.06 (m, H–C(5)) \quad 3.74 (dd, J = 9.0, 6.9, CH–C(6)) \quad 3.42 (t, J = 9.0, CH′–C(6)) \quad 2.92–2.84 (m, H–C(6)) \quad 2.07 (dddd, J = 13.4, 4.4, 3.4, 1.6, H_{eq}–C(9)) \quad 1.92 (dd, J = 13.4, 2.2, 1.2, H_{ax}′–C(9)). \]

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13C-NMR (75 MHz, CDCl_3): 133.84 (C(7)); 128.61 (2C); 127.90 (2C); 127.85; 124.45 (C(8)); 73.61; 71.58; 68.18; 47.66; 45.42; 27.45; \quad \text{(signals of } C(3) \text{ and CF}_3 \text{ and of one aromatic CH hidden by noise)}.
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19F-NMR (282 MHz, CDCl_3): –73.53. \]

Part 4.

Methyl 1-(Hydroxymethyl)cyclohex-3-enecarboxylate (830).

A soln of iPr₂NH (1.58 ml, 11.3 mmol) in THF (40 ml) was cooled to −20°, treated dropwise 1.5 M BuLi in hexane (5.6 ml, 8.45 mmol), stirred for 20 min, cooled to −78°, treated dropwise with a soln. of 829 (0.79 g, 5.6 mmol) in THF (25 ml), stirred for 1 h, warmed to −50°, treated with a ca. 0.4 M soln. of formaldehyde in THF (50 ml, ca. 16 mmol; [1037]), stirred for 3 h while slowly warming to r.t., and treated with sat. aq. NH₄Cl soln. (60 ml). The mixture was extracted with Et₂O (3 x 100 ml). The combined organic phases were dried (Na₂SO₄) and evaporated. Two FC’s (45 g of silica gel, cyclohexane/AcOEt 3:1) of the orange-brown oil (1.43 g) gave 829 (503 mg, 53%) as a red oil and 830 (452 mg, 47%) as a yellow oil. R_f (cyclohexane/AcOEt 3:1) 0.20. FT-IR (1.5%, CHCl₃): 3620 w (OH), 3008 m, 2953 m, 2928 m, 2847 w, 1725 s (C=O), 1655 w, 1437 m, 1390 w, 1343 w, 1390 w, 1343 w, 1298 m, 1272 m, 1172 m, 1079 m, 1038 s, 968 w, 891 w, 872 w. ¹H-NMR (300 MHz, CDCl₃): 5.71–5.59 (m, H–C(3), H–C(4)); 3.72 (s, MeO); 3.67 (d, J = 6.5, CH₂–C(1)); 2.50 (dm, J = 17.7, 1 H); 2.28–2.01 (m, 4 H); 1.94 (dt, J = 13.2, 6.7, 1 H); 1.77 (br. dt, J = 12.2, 6.0, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 176.99 (s, C=O); 125.99, 123.98 (2d, C(3), C(4)); 66.34 (t, CH₂–C(1)); 52.11 (q, MeO); 46.66 (s, C(1)); 29.39, 26.31, 21.93 (3t, C(2), C(5), C(6)). EI-MS: 182 (15), 170 (1, [M]+), 152 (61, [M − 18]+), 124 (10), 120 (22), 111 (17), 104 (9), 92 (100).

Methy 1-(Benzyloxymethyl)cyclohex-3-enecarboxylate (831) and Benzyl 1-(Hydroxymethyl)cyclohex-3-enecarboxylate (832).

A suspension of NaH (127 mg of a 60% suspension in oil, 3.17 mmol) in THF (5 ml) was cooled to 0°, treated dropwise with a soln. of 830 (450 mg, 2.64 mmol) in THF (2 ml), stirred for 1 h, treated with Bu₄NI (195 mg, 0.53 mmol) and 18-crown-6 (1 mg) and dropwise with BnBr (0.47 ml, 3.97 mmol), stirred for 1 d at r.t., treated with 0.1 N HCl (1 ml) and poured into H₂O (30 ml). The mixture was extracted with Et₂O (3 x 30 ml). The combined organic phases were washed with sat. aq. NaHCO₃ soln. and brine (75 ml of each), dried (Na₂SO₄), and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 20:1) of the red oil (960 mg) gave 831 (217 mg, 31%) as a yellow oil, 832 (82 mg, 12%) as a yellow oil and an unidentified byproduct (41 mg) as a yellow oil.

Data of 831:
Rf (cyclohexane/AcOEt 3:1) 0.66. FT-IR (1.5%, CHCl3): 3066 w, 3008 m, 2952 m, 2846 m, 1729 s (C=O), 1496 w, 1454 m, 1437 m, 1363 w, 1283 m, 1170 w, 1098 s, 1048 w, 1028 w, 988 w, 932 w, 909 w. 1H-NMR (300 MHz, CDCl3): 7.37–7.24 (5 arom. H); 5.65–5.62 (m, H–C(3), H–C(4)); 4.50 (s, PhCH2); 3.69 (s, MeO); 3.56, 3.49 (2d, J = 8.7, CH2–C(1)); 2.54 (dm, J = 17, 1 H); 2.09–1.91 (m, 4 H); 1.75 (br. quint., J = 6.4, 1 H). 13C-NMR (75 MHz, CDCl3): 175.82 (s, C=O); 138.19 (s); 128.14 (2d), 127.34 (d), 127.22 (2d), 126.02 (d), 124.51 (d) (Ph, C(3), C(4)); 74.88, 73.16 (2t, PhC=CH2); 46.23 (s, C(1)); 36.98, 35.38, 29.31, 26.82, 22.91 (3t, C(2), C(5), C(6)). EI-MS: 260 (1, M+), 242 (3), 230 (2), 210 (1), 200 (1, [M–C2H4O2]+), 183 (2, [M–Ph]+), 169 (4, [M–Bn]+), 151 (17), 139 (21), 118 (5), 107 (9), 91 (100).

Data of 832:

Rf (cyclohexane/AcOEt 3:1) 0.24. FT-IR (1.5%, CHCl3): 3508 w (OH), 3068 w, 3008 m, 2926 m, 2845 w, 1726 s (C=O), 1654 w, 1603 w, 1498 w, 1455 m, 1439 m, 1377 w, 1343 m, 1268 s, 1170 s, 1078 s, 1040 s, 966 m, 907 w, 824 w. 1H-NMR (300 MHz, CDCl3): 7.40–7.28 (5 arom. H); 5.71–5.61 (m, H–C(3), H–C(4)); 5.16 (s, PhCH2); 3.69 (br. s, CH2–C(1)); 2.55 (dm, J = 17.1, 1 H); 2.35 (br. s, OH); 2.09–1.93 (m, 4 H); 1.79 (br. quint., J = 6.4, 1 H). 13C-NMR (75 MHz, CDCl3): 176.15 (C=O); 135.69; 128.34 (2C), 127.97, 127.61 (2C), 125.91, 123.93 (Ph, C(3), C(4)); 66.36, 66.34 (CH2–C(1), PhCH2); 46.71 (C(1)); 29.31, 26.20, 21.85 (C(2), C(5), C(6)). EI-MS: 246 (< 1, M+), 228 (4), 216 (2), 200 (2), 183 (1), 155 (4, [M–Bn]+), 137 (19), 125 (18), 107 (9), 91 (100).

1-(Benzyloxymethyl)cyclohex-3-enecarboxylic Acid (833).

A soln. of 831 (214 mg, 0.82 mmol) in THF (8 ml) and H2O (5 ml) was treated with LiOH·H2O (207 mg, 4.93 mmol), and stirred at r.t. for 17 h and at 50° for 3.5 h, but TLC indicated no consumption of the starting material. The mixture was concentrated to 4 ml, diluted with MeOH (5 ml), and stirred at r.t. for 18 h, when TLC indicated complete conversion of 831. After evaporation of MeOH, the aq. layer was acidified with 1 M HCl to pH ≈ 1 and extracted with AcOEt (5 x 20 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 3:1 —→ AcOEt/HOAc 5:1) gave 833 (181 mg, 89%) as a yellow oil. Rf (cyclohexane/AcOEt 3:1) 0.17. FT-IR (1.5%, CHCl3): 3515 w, 3400–2500 m (br.), 3066 m, 3008 m, 2922 m, 2864 m, 1747 m, 1705 s (C=O), 1654 w, 1602 w, 1496 w, 1454 m, 1440 m, 1411 w, 1384 m, 1306 w, 1098 m, 1048 w, 1028 w, 937 w, 909 w. 1H-NMR (300 MHz, CDCl3): 7.36–7.14 (5 arom. H); 5.69–5.59 (m, H–C(3), H–C(4)); 4.54 (s, PhCH2); 3.59 (d, J = 9.0, CH–C(1)); 3.53 (d, J = 8.7, CH–C(1)); 2.55 (br. d, J = 17.1, 1 H); 2.36 (s, OH); 2.18–1.92 (m, 4 H); 1.80 (br. dd, J = 14.6, 7.8, 1 H). 13C-NMR (75 MHz, CDCl3): 137.73, 128.26 (2C), 127.53, 127.40 (2C), 126.03, 124.23 (Ph, C(3), C(4)); 74.08,
tert-Butyl N-[1-(Benzyloxymethyl)cyclohex-3-enyl]carbamate (834).

A soln. of 833 (152 mg, 0.62 mmol) in toluene (7 ml) was treated with Et3N (0.095 ml, 0.68 mmol) and diphenylphosphoryl azide (0.14 ml, 0.65 mmol), warmed slowly to 100°, refluxed for 3 h, cooled to r.t., treated with tBuOH (0.3 ml, 3.1 mmol) and CuCl (10 mg, 0.1 mmol), stirred at 80° for 6 d, cooled to r.t., treated with sat. aq. NaHCO3 soln. (10 ml), and extracted with Et2O (3 x 20 ml). The combined organic phases were dried (Na2SO4) and evaporated. FC (15 g of silica gel, cyclohexane/AcOEt 12:1) of the brown oil (198 mg) gave 834 (56 mg, 28%) as a colourless oil. Elution with MeOH gave a byproduct (122 mg) presumably the corresponding amine. Rf (cyclohexane/AcOEt 3:1) 0.68. FT-IR (0.5%, CHCl3): 3426 w (NH), 3020 w, 3011 w, 1711 s (C=O), 1498 w, 1455 w, 1426 w, 1393 w, 1114 w, 1091 w, 1059 w, 912 w, 843 m. 1H-NMR (300 MHz, CDCl3): 7.37–7.24 (5 arom. H); 5.67 (dddd, J = 10.0, 5.3, 3.4, 1.9), 5.55 (dddd, J = 10.0, 5.6, 3.7, 1.9) (H–C(3), H–C(4)); 4.58 (br. s, NH); 4.54 (s, PhCHO); 3.67, 3.58 (2d, J = 9.3, CH2–C(1)); 2.31–2.26 (m, 2 H); 2.08–1.99 (m, 2 H); 2.16 (br. dd, J = 12.0, 6.1, 1 H); 1.65 (ddd, J = 13.1, 7.2, 5.9, 1 H); 1.43 (s, Me3C). 13C-NMR (75 MHz, CDCl3): 154.80 (s, C=O); 138.47 (s); 128.24 (2d), 127.41 (3d), 126.63 (d), 123.70 (d) (Ph, C(3), C(4)); 78.85 (s, Me3C); 73.39, 73.19 (2t, PhCHOCH2); 53.77 (s, C(1)); 33.55 (t); 28.55 (q, Me3C); 27.44 (t); 22.72 (t). ESI-MS: 356 (4, [M + K]+), 340 (39, [M + Na]+), 318 (17, [M + 1]+), 280 (6, [M + 1 – CO]+), 262 (82, [M + 1 – C4H8]+), 236 (93), 218 (100, [M + 1 – C4H8 – CO2]+).
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