Doctoral Thesis ETH No. 16026

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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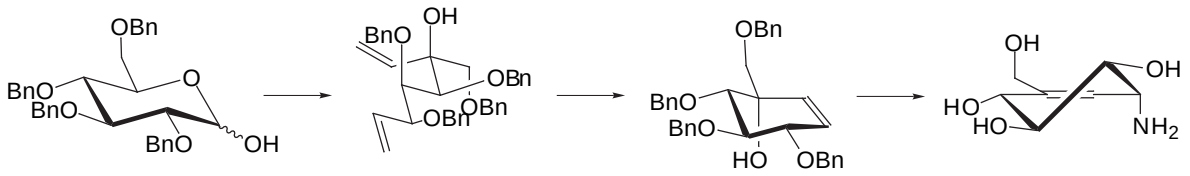
Abbreviations

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
*m*CPBA	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.

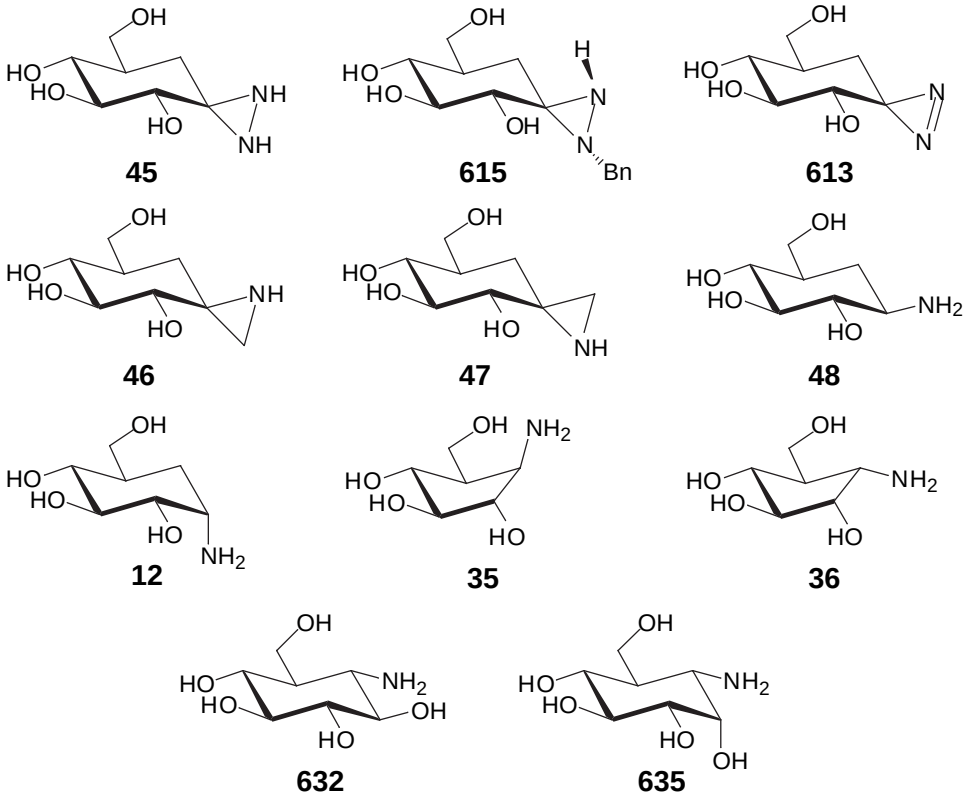


39 **441** **40** **22**

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** (pK_{HA} = 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, $LiAlH_4$ 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** (pK_{HA} = 6.8) is a weak irreversible inhibitor of the β-glucosidase from *Caldocellum saccharolyticum* (K_i = 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.



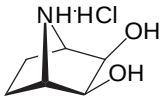
In view of the synthesis of bicyclic amines that are of interest as building blocks and potential glycosidase inhibitors I studied the intramolecular bromoamidation and the dibromination-cyclisation of the *N*-acylcyclohex-3-en-1-amines **712**, **71**, **714**, **716**, **72**, **718**, and **655**. 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. Br_2 in CH_2Cl_2 transformed the alkenes **712** and **71** predominantly into the expected diaxial *trans*-

trans-dibromides **728** and **730**. The reaction of **71** in CH_2Cl_2 with $PhMe_3NBr_3$ or with Br_2 in the presence of Et_4NBr gave predominantly the diequatorial *trans-cis* **729** besides some **730**, denoting a neighbouring group participation of $NHCOCF_3$. Bromination of the C(5) substituted *N*-acyl-4-aminocyclohexenes **714**, **716**, **72**, and **718** in CH_2Cl_2 was accompanied by intramolecular side-reactions that were suppressed by the addition of excess Et_4NBr to $PhMe_3NBr_3$. Under these conditions, **714** reacted to the dibromides **737** (84%) and **738** (6%), while the reaction with Br_2 afforded **737** (28%) and **738** (30%) along with the dihydrooxazinone **739** (36%). Similarly, **716** reacted with $PhMe_3NBr_3/Et_4NBr$ to the dibromide **731** (82%), while bromination with Br_2 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 $PhMe_3NBr_3/Et_4NBr$ to the dibromide **735** (89%), and with Br_2 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 $PhMe_3NBr_3/Et_4NBr$ to the dihydrooxazinone **740**, and with Br_2 to the dihydrooxazinone **740** (32%) and the bicyclic ether **741** (26%). The high stereoselectivity of the bromination with $PhMe_3NBr_3/Et_4NBr$ 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]non-7-en-2-ones **798** and **801** gave the *N*-tosyl cyclohexadienylamines **803**, **805**, and **806** rather than *N*-tosyl-6-azabicyclo[3.1.1]hept-2-enes. At 160°, neat **801** underwent a [3.3]sigmatropic rearrangement to the isomeric *N*-tosyl-2-oxa-4-azabicyclo[3.3.1]non-7-en-2-one **807** (52%). This result encouraged me to explore a synthesis of *N*-acyl-6-azabicyclo[3.1.1]hept-2-enes by a ring-contractive [3.3]sigmatropic rearrangement of 2-oxa-4-azabicyclo[3.3.1]nona-2,7-dienes. However, several 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 $^{1,4}B$ conformation, are

only weak inhibitors of the β-mannosidase from snail, the α-mannosidase from jack bean, the β-glucosidases from sweet almonds, the β-glucosidase from *Caldocellum saccharolyticum*, and the α-glucosidase from brewer's yeast. The weak inhibition by **58** and **59** suggests that these enzymes do not stabilise $^{1,4}B$ reactive conformers.



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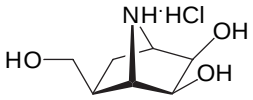

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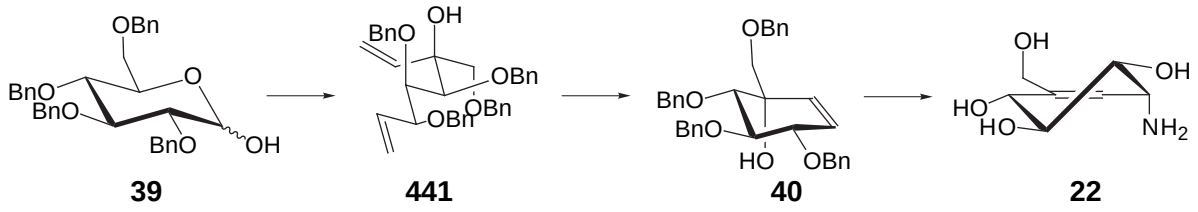
Zusammenfassung

(+)-Valienamin (**22**) wurde in sieben Schritten und in einer Gesamtausbeute von 27% aus 2,3,4,6-Tetra-*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-*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-*O*-benzyl-D-arabinofuranose hergestellt.

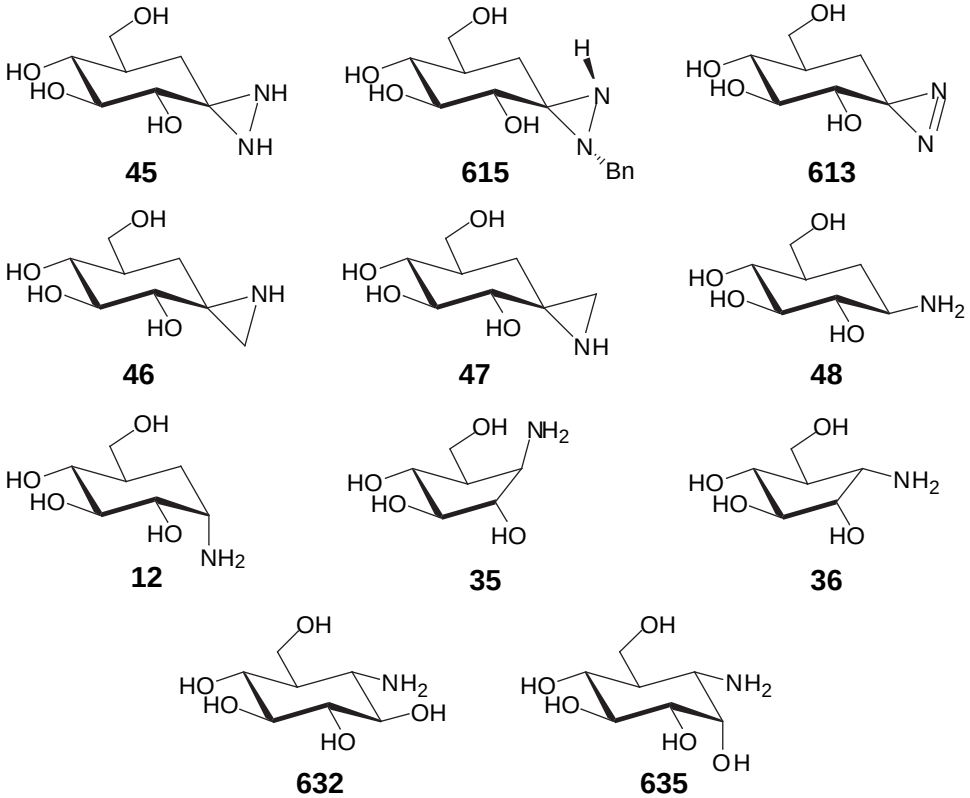


39 **441** **40** **22**

Die *spiro*-Diaziridine **45** und **615** sind Carbazucker-Derivate und potentielle Hemmer von α- und β-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** essentiell. Die Oxidation von **45** führte zum *spiro*-Diazirin **613**. Die Diaziridine **45** (pK_{HA} = 2.6) und das Diazirin **613** hemmten weder die β-Glucosidasen aus Süssmandeln, noch die β-Glucosidase aus *Caldocellum saccharolyticum*, noch die α-Glucosidase aus Bierhefe. Das *N*-Benzyldiaziridin **615** erwies sich als ein sehr schwacher Hemmer der α-Glucosidase, war jedoch inaktiv gegen die β-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_{HA} = 6.8) ist ein schwacher irreversibler Hemmer der β-Glucosidase aus *Caldocellum saccharolyticum* (K_i = 3 mM) und ein schwacher reversibler Hemmer der α-Glucosidase aus Bierhefe. Es hemmte aber nicht die β-Glucosidasen aus Süssmandeln. Das wenig stabile Aziridin **47** hemmte diese drei Glucosidasen schwach. Ebenso erwies sich das 1-*epi*-Validamin (**48**, pK_{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-*epi*-Validamins eher auf strukturellen Faktoren als auf der Basizität beruht. Dies wird untermauert durch die starke Hemmwirkung der Cyclopentylamine **35** (pK_{HA} = 7.9) und **36**, welche mikromolare Hemmer der untersuchten Glucosidasen sind. Der geringe pK_{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 β-Glucosidasen aus Mandeln und der α-Glucosidase aus Bierhefe, was darauf hindeutet, dass die starke Hemmwirkung der Cyclopentylamine auf dem Cyclopentangerüst basiert.



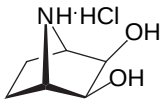
Im Hinblick auf die Synthese von bicyclischen Aminen, welche als Synthese-Bausteine und als potentielle Glycosidase-Hemmer von Interesse sind, habe ich die intramolekulare Bromoamidierung und die Dibromierung-Zyklisierung der *N*-Acylcyclohex-3-en-1-amine

712, **71**, **714**, **716**, **72**, **718** und **655** untersucht. 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 Br_2 in CH_2Cl_2 wurden die Alkene **712** und **71** vorwiegend in die erwarteten diaxialen *trans-trans*-Dibromide **728** und **730** umgewandelt. Die Reaktion von in CH_2Cl_2 gelöstem **71** mit $PhMe_3NBr_3$ oder mit Br_2 in Gegenwart von Et_4NBr führte überwiegend zum diequatorialen *trans-cis* **729** neben etwas **730**, was auf eine Nachbargruppenbeteiligung von $NHCOCF_3$ hinweist. Die Bromierung der C(5)-substitutierten *N*-Acyl-4-aminocyclohexene **714**, **716**, **72** und **718** in CH_2Cl_2 wurde von intramolekularen Nebenreaktionen begleitet. Diese Nebenreaktionen wurden bei der Bromierung mit $PhMe_3NBr_3$ durch einen Überschuss Et_4NBr unterdrückt. Unter diesen Bedingungen reagierte **714** zu den Dibromiden **737** (84%) und **738** (6%), während die Reaktion mit Br_2 neben **737** (28%) und **738** (30%) auch das Dihydrooxazinon **739** (36%) lieferte. Ähnlich reagierte **716** mit $PhMe_3NBr_3$/Et_4NBr zum Dibromid **731** (82%) und mit Br_2 zu den Dibromiden **731** (18%) und **732** (6%), dem Dihydrooxazinon **733** (43%) und dem bicyclischen Ether **734** (32%). Das *N*-trifluoracetamid **72** reagierte mit $PhMe_3NBr_3$/Et_4NBr zum Dibromid **735** (89%) und mit Br_2 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 $PhMe_3NBr_3$/Et_4NBr zum Dihydrooxazinon **740** und mit Br_2 zum Dihydrooxazinon **740** (32%) und dem bicyclischen Ether **741** (26%). Als Erklärung für die hohe Stereoselektivität der Bromierung mit $PhMe_3NBr_3$/Et_4NBr wurde eine Nachbargruppenbeteiligung durch den NHR Substituenten postuliert, welche zu einer bevorzugten diaxialen Bromierung der pseudoaxialen *N*-Acylcyclohex-3-enyl-1-amine führt.

Durch entfernen der Schutzgruppen, Cyclisierung und Carbamoylierung wurden die Dibromide **729**, **737** und **731** in die 7-Azanorbornane **744** (93%), **761** (62%) und **754** (84%) umgewandelt. Eine entsprechende Umwandlung der Dibromide **728** und **738** in bicyclische Azetidine (6-Azabicyclo[3.1.1]heptane) misslang. Nach längerem Erhitzen der ungeschützten Amine **747** und **759** bei über 120°C in 1,3-Dichlorbenzol und Carbamoylierung wurden die 7-Azanorbornane **744** und **761** isoliert. Dies legt nahe, dass die Dibromide **747** und **759** unter diesen Bedingungen epimerisierten. Weitere Versuche zur Herstellung von 6-Azabicyclo[3.1.1]heptanen waren nicht erfolgreich. Eine Pd(0)-katalysierte decarboxylierende Umlagerung der *N*-Tosyl-2-oxa-4-azabicyco[3.3.1]non-7-en-2-one **798** und **801** führte zu den *N*-Tosylcyclohexadienylaminen **803**, **805** und **806** statt zu den gewünschten *N*-Tosyl-6-azabicyclo[3.1.1]hept-2-enen. Bei 160°C lagerte reines **801** [3.3]sigmatrop zum isomeren *N*-Tosyl-2-oxa-4-azabicyco[3.3.1]non-7-en-2-on **807** (52%) um. Durch dieses Ergebnis ermutigt untersuchte ich eine ringverengende [3.3]sigmatrope Umlagerung von 2-Oxa-4-azabicyclo[3.3.1]nona-2,7-dienen zu *N*-Acyl-6-aza-bicyclo-

[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-Eliminerung 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 β-Mannosidase aus Schnecken, der α-Mannosidase aus der Jackbohne, der β-Glucosidasen aus Süssmandeln, der β-Glucosidase aus *Caldocellum saccharolyticum* und der α-Glucosidase aus Bierhefe. Die schwache Hemmwirkung von **58** und **59** bedeutet, dass diese Enzyme allfällige reaktive $^{1,4}B$ Konformere nicht stabilisieren.



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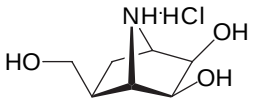

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Prologue

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, respectively[1]), 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 10^7 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

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[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-NH_2 group are acylated by amino acids [3]. Crosslinking of collagen strands and of elastin strands occurs by branching [10].

- the anomeric configuration of the glycosyl donor as α– and β-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—>e (cleaving equatorial glycosides) and a—>a (cleaving axial glycosides) and inverting pyranosidases as e—>a (cleaving equatorial glycosides) and a—>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 α/β-nomenclature of glycosides [4] (which may be confusing [14], as α-D-pyranosides are axial and α-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.* α-D-altropyranosides, α-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.* β-*O*-glucosidases as EC 3.2.1.21, α-*O*-glucosidases as EC 3.2.1.20, β-*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 β-*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 β-*O*-glucosidases, β-glucuronidases, β-mannosidases, β-*O*-galactosidases,

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[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 β-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 β-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

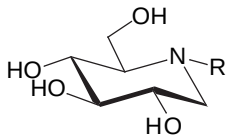
Glycosidases are indispensable in the normal functioning of most organisms. They are involved in the breakdown of food carbohydrates [4], in malignant transformation and metastasis [19] [20], viral and bacterial infection [5] [6], the processing of eukaryotic glycoproteins [8] [9], and the catabolism 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 β-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 β-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, *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. *N*-butyldeoxynojirimycin (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, *N*-nonyldeoxynojirimycin (**1b**) leads to a twofold increase of mutant (N370S) β-glucocerebrosidase activity in cultured fibroblasts.

Scheme 1.2.1



1a R = $(CH_2)_3CH_3$
1b R = $(CH_2)_8CH_3$

Influenza is a serious respiratory viral infection causing substantial morbidity and mortality. Influenza virus replication and infectivity is dependent on neuraminidase (sialidase), a retaining α-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

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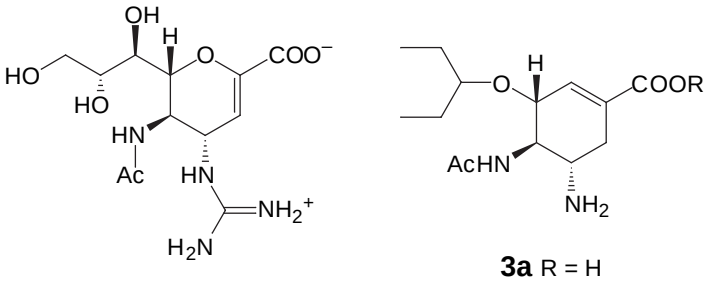
[3]) See the website of the *National Gaucher Foundation* of the USA at www.gaucherdisease.org and the website of *Genzyme Co.* at www.genzyme.com for comprehensive information about *Gaucher* disease and its treatment.

administered orally and is hydrolysed by liver esterases to the active drug oseltamivir carboxylate.

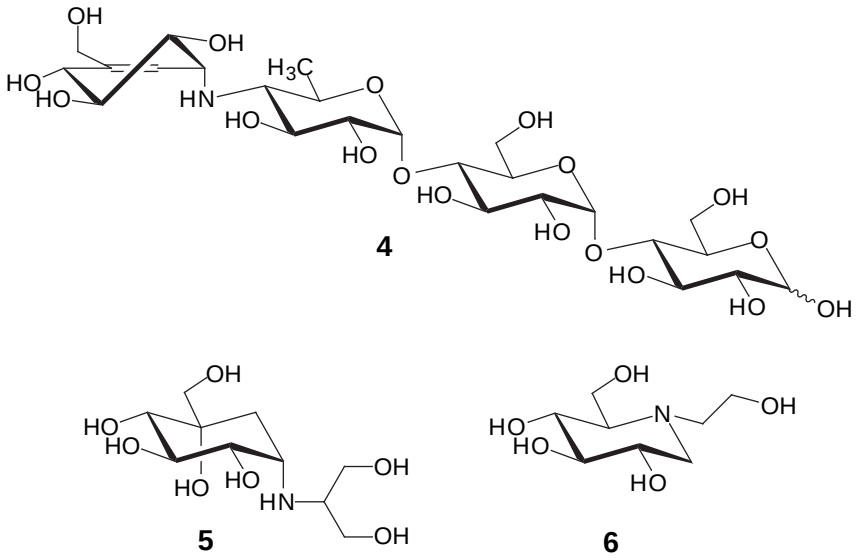
Scheme 1.2.2



The blood glucose level in healthy humans is maintained at a concentration of *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 α-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 α-glucosidase inhibitors acarbose (**4**, *Glucobay*, Scheme 1.2.3) [28] [29], voglibose (**5**, *Basen*) [30] (a derivative of valiolamine [31]), and miglitol (**6**, *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.

Scheme 1.2.3



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 β-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

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

[6]) *N*-butyldeoxynojirimycin (**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 β-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 β-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 anomeric 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 anomeric carbon. The second step is characterised by hydrolysis of the glycosylenzyme ester. In this step the free carboxylate group acts as general base catalyst, activating the water molecule that attacks the anomeric carbon and displaces the catalytic nucleophile *via* a similar transition state as in the first step.

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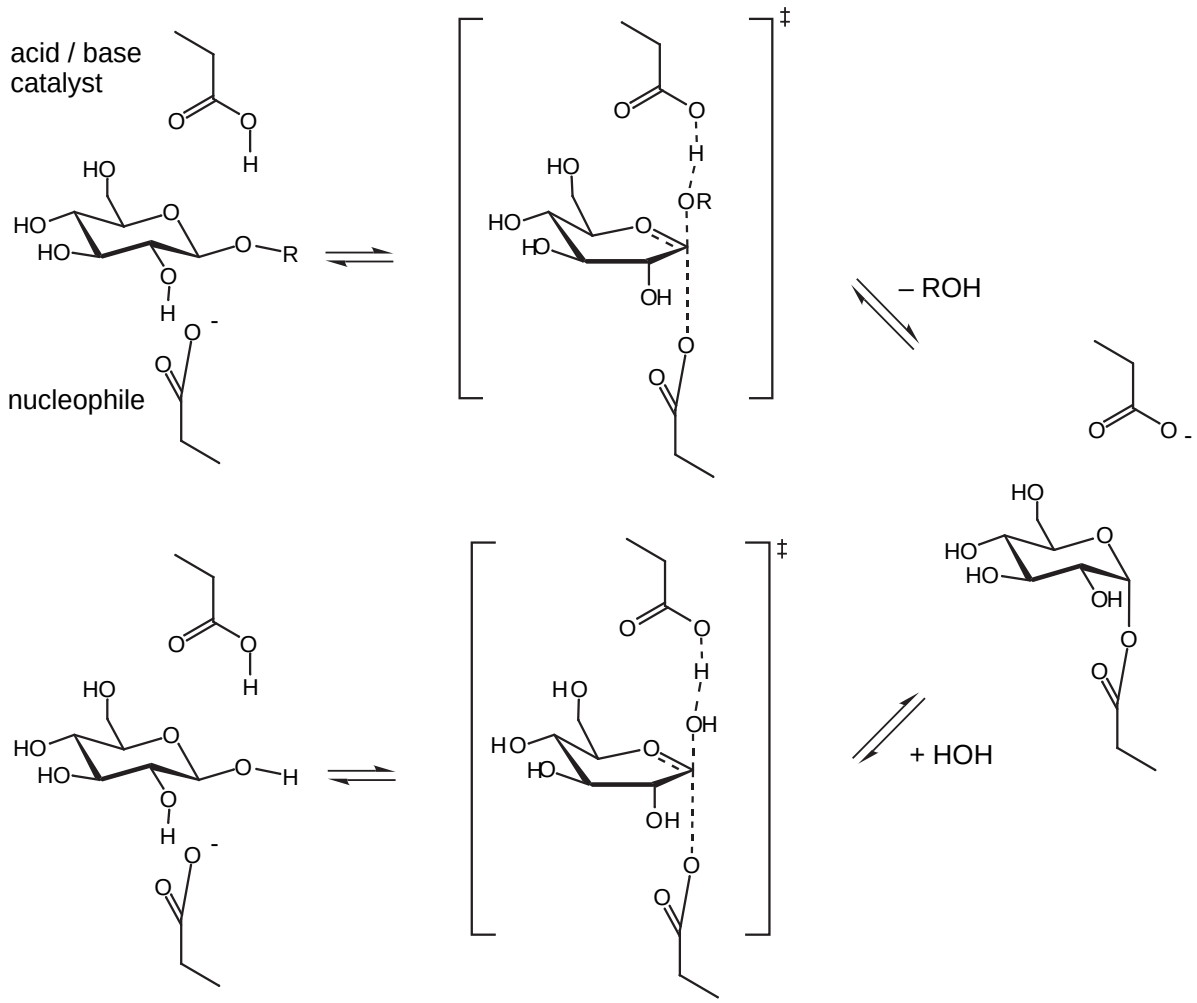
[8]) This proposal was supported by the experimental finding that hexa-*N*-acetylchitohexaose is hydrolyzed by lysozyme to a tetramer and a dimer, the cleavage separating two residues from the reducing end.

Scheme 1.3.1



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 x 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 S_N2-like mechanism with an "exploded" transition state characterised by a highly cationic character (*i.e.* according to a mechanism that is between the paradigmatic S_N1 and S_N2 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 S_N2-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 ${}^{4}H_{3}$, ${}^{3}H_{4}$, ${}^{2,5}B$, $B_{2,5}$, ${}^{4}E$, E_{4}, ${}^{3}E$, 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 σ-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 α-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 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"[11]) [79]. As it was deduced from fundamental stereoelectronic principles, *Deslongchamps's* hypothesis that β-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 β-pyranoside **7**, which cannot adopt a ${}^{1,4}B$ conformation, than that of the α-pyranoside **8** (Scheme 1.5.1) [80]. However, the *trans*-fused rings of the β-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 β-anomer requires a reactive conformation with a pseudoaxial

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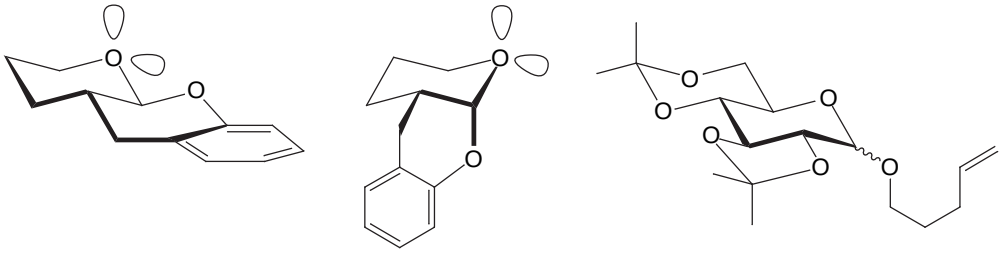
[9]) The “helping electron pair” corresponds to the axial non-binding, doubly occupied sp^3-orbital of the ring oxygen.

[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[12]). Hydrolysis of the conformationally restrained *n*-pentenyl *β*-glucoside **9a** with electrophilic reagents (*e.g.* NBS) "was not dramatically slower" than that of the *α*-anomer **9b** [81] [82], "raising doubts that *β*-anomers react *via* boat conformations" [83][13]).

Scheme 1.5.1



7 **8** **9a** β
9b α

An ab initio study of 2-oxanol (a simple pyranose) by *Smith* showed that protonation of the chair conformer with an equatorial OH group yields an oxonium ion (*i.e.* 2-oxanol protonated at the exocyclic oxygen) in the chair conformation ($^2C_5$) which reacts *via* a transition state with a slightly flattened chair conformation to an oxycarbenium ion-water complex with a $^5H_4$ 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 $^5H_4$ conformation [84]. These calculations support *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][14]) which may restrict the validity to *Smith's* conclusion that protonation of axial pyranosides leads directly to cleavage of the glycosidic bond to processes in the condensed phase.

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[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.

[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.

[14]) These protonated species fragment to $[M - (\text{aglycon–OH})]^+$ 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 *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" (ω) was derived from the observed kinetic isotope effect (KIE_{obs}) by solving the equation

$$KIE_{obs} = \cos^2(\omega) \times KIE_{max}$$

for ω, setting an empirical upper limit KIE_{max} for the kinetic isotope effect for ω = 0° [67] [71].

From kinetic isotope effects on the specific acid catalysed hydrolysis of methyl α- and β-glucosides, *Bennet* and *Sinnott* deduced that the transition state for the glycoside cleavage of the α anomer adopts a flattened $^1S_3$ conformation (ω ≈ 54 – 66°) and that for the glycoside cleavage of the β anomer a $^4C_1$ conformation flattened somewhat towards a $^4H_3$ half chair (ω ≈ 52°) [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 β anomer and $^1S_3$ for the α anomer[15])). From kinetic isotope effects on the hydrolysis of α- and β-glucopyranosyl fluorides (not subject to the "inverse anomeric effect") at near neutral pH, *Zhang et al.* deduced that the transition state of the α-anomer adopts a $^4C_1$ conformation flattened towards $^4H_3$ (ω ≈ 32°) and that of the β-anomer a flattened $^4C_1$ conformation (ω ≈ 41°) [71]. A ^4S transition state conformation (ω ≈ 12°) was deduced for the hydrolysis of α-glucosyl fluoride by comparing KIE_{obs} with calculated (ab initio) kinetic isotope effects [71].

The rather large discrepancy between this value and that derived "empirically " (ω ≈ 32°) shows that the error of the estimated ω values (and thus of the transition state conformations) is quite large. Another weakness of *Sinnott's* work is that ω 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 ω 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

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[15]) *Bennett* and *Sinnott* say that the $^1S_3$ ground state conformation of protonated α-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 *β*-glucoside and the *β*-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 *α*-glucosidase catalysed cleavage of aryl *α*-glucosides and *α*-glucosyl pyridinium ions [89]. There was no ^{18}O (glycosidic oxygen) kinetic isotope effect on V_{max} for the hydrolysis of *α*-*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_{max} for the hydrolysis of the *α*-glucosyl pyridinium 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-rebybridised (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 $^{2,5}B$ conformation and that the non-covalent event preceding cleavage of *p*-nitrophenyl *α*-D-glucoside is a conjoint change in the conformation of the substrate (from $^4C_1$ to $^{2,5}B$). As *α*-glucosyl pyridinium ions adopt a $^1S_3$ conformation (*vide supra*), a conformational change to the similar $^{2,5}B$ conformation should be faster than for *p*-nitrophenyl *α*-D-glucoside ($^4C_1$). The $^{2,5}B$ 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 *α*-glucosidase by castanospermine which cannot adopt a $^{2,5}B$ conformation [89] and also the strong binding of *α*-glucosyl pyridinium ions (which adopt a $^1S_3$ conformation similar to the $^{2,5}B$ 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 *α*-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 *α*-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 *β*-glucosides **9a** and **b** [81] [82], *vide supra*) and ab initio calculations of glycoside cleavage (*e.g.* [93]) *Fraser-Reid et al.* concluded that *α*-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 *β*-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 $^4C_1$ 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 sp^3 to sp^2, placing a p orbital in a *syn*-periplanar arrangement with the scissile glycosidic bond. Even in the proposed reactive $^{2,5}B$ 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 sp^3 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 $B_{2,5}$ configuration hydrolyse at similar rates as non-constrained glucopyranosides [94][16]).

Deslongchamps's hypothesis – requiring an antiperiplanar arrangement of the scissile glycosidic bond and an sp^3 lone pair of the ring oxygen in the reactive substrate conformation – is a restricted formulation of the principle of stereoelectronic control, considering only sp^3 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 $^4C_1$ or $^{1,4}B$ conformer this requires an *anti*-periplanar orientation of the scissile bond and a lone pair of O–C(5).

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[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 β-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, *i.e.* more S_N1-like) than the glycosylation step [101] [102], indicating that the principle of microscopic reversibility does *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 *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 [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 (*e.g.* low pH) and therefore might not represent the structures involved in catalysis.

Davies et al. gained insight into the conformational itinerary of the retaining *endo*-glucosidase Cel5A (family 5) from *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 [72]. In a complex with 2,4-dinitrophenyl 2-deoxy-2-fluoro-β-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-β-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 (*β*-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-cellopentoside [104] and a "mixed-linkage cellotetrasaccharide" (possessing an *α*-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 $^{1}S_{3}$ 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 $^{4}C_{1}$ 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 $^{4}C_{1}$ conformation. However, in a complex with the retaining *exo*-*β*-(1,3)-glucanase from *Candida albicans* (another family 5 glucosidase) this inhibitor was found in a twisted $^{1,4}B$ 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 $^{1,4}B$ 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 $^{1,4}B$ 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 *β*-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 ($^{1,4}B$) 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 ^{4}S (or flattened $^{1,4}B$) 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 ($^{1,4}B$) 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 ^{4}S or flattened $^{4}C_1$ conformation and the transition state conformation must lie between one of these conformations and $^{1,4}B$. 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 Φ(C(5)–O–C(1)–C(2)) ≈ 0° 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 β-1,4-xylanase from *Bacillus circulans*, the 2-fluoro-xylose residue covalently bound in subsite -1 was found in a $^{2,5}B$ 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 β-1,4-xylanase both the α-configured covalent glycosyl-enzyme intermediate and an enzyme-product complex displayed a $^{2,5}B$ 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 α-glycosides must hydrolyse *via* their ground state conformation" [79], which should also apply to α-configured glycosyl enzyme esters of β-D-glycosidases. However, the $^{2,5}B$ 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 $^{2,5}B$ conformation (a $^{2,5}B$ transition state conformation was proposed by *Sinnott* for the hydrolysis of α-glucosides [95] (*vide supra*)). *Withers et al.* suggested that the conformational itinerary from the $^4C_1$ ground state conformation to the $^{2,5}B$ conformation is $^4C_1$—>$^2H_3$—>^2S_O—>$^{2,5}B$ [73], but it remains elusive whether this distortion precedes bond cleavage or occurs concomitantly with it.

The retaining *endo-β*-(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 $^{1,4}B$). 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 cellobiohydrolase Cel6A from *Trichoderma reesei* (family 6) displayed a $^{2}S_{O}$ 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 cellobio-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][17]) 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° to –44°) 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 (Φ(C(5)–O–C(1)–C(2)) ≈ 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 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" [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 ΦC(5)–O–C(1)–C(2)) ≈ 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 ${}^{2,5}B$ 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.

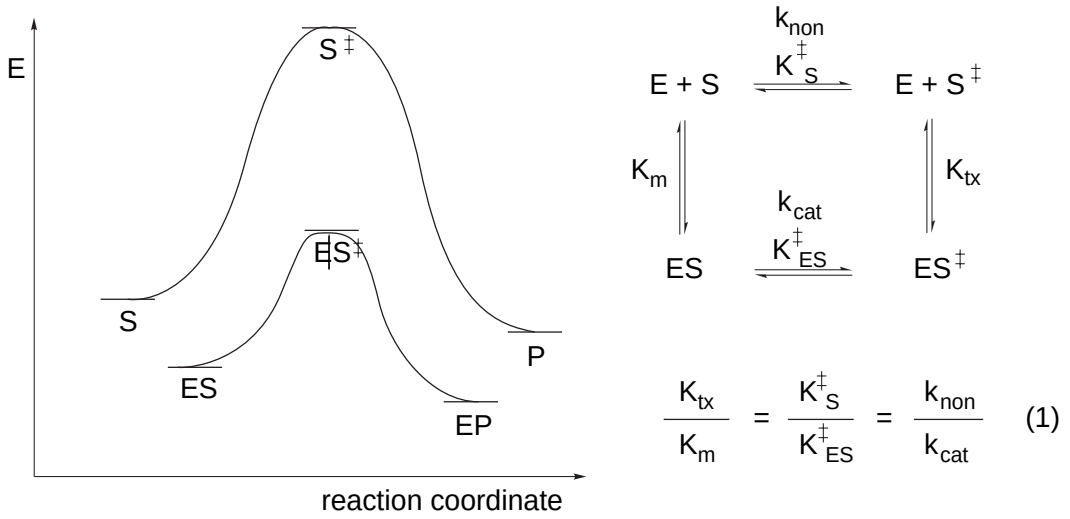
Glycosidase inhibitors are classified as irreversible and reversible inhibitors, and the reversible inhibitors may be further classified as analogues of the substrate (in the ground state or in a reactive conformation), as analogues of the transition state, or as product analogues.

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-α-D-glucan maltohydrolase from sweet potato ($k_{cat}/k_{non} > 10^{17}$), *Wolfenden et al.* estimated an upper limit of K_i of an ideal transition state analogue at 10^{-22}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-β-D-*arabino*-pyranoside (K_m = 0.7 mM) binds more strongly to the β-glucosidase A from bitter almonds than the corresponding β-D-glucopyranoside (K_m = 1.7 mM), but is hydrolysed by this enzyme much more slowly (k_{cat} = 12 min^{-1} *vs.* 26400 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 NH_2 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 CO_2^- 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 CO_2^- 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

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[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 $O^{\varepsilon 2}$ 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 $O^{\varepsilon 2}$ of the catalytic nucleophile will affect the proposed H bond between C(2)–OH and $O^{\varepsilon 1}$ of the catalytic nucleophile[20]).

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 $Å^{-2}mol^{-1}$ (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 of the

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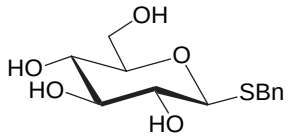
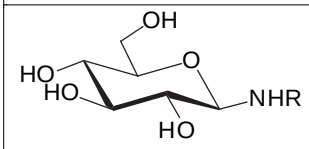
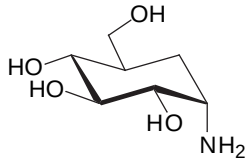
[20]) By trapping the covalent sialyl-enzyme intermediate and LC-MS/MS analysis of peptic digests, Tyr342 of the trans-sialidase from *Trypanosoma cruzi* (family 33) was identified as the catalytic nucleophile of this enzyme [131]. See [132] for a possible explanation why sialidases may use tyrosine as the catalytic nucleophile.

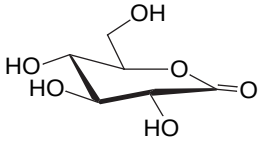
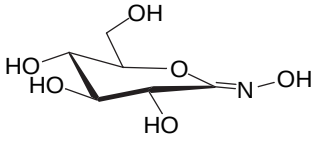
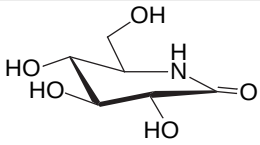
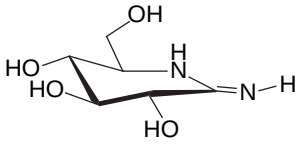
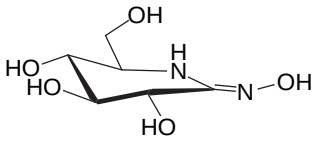
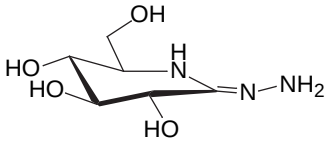
β-glucosidase from sweet almonds than *β*-glucosylbenzene, it was assumed that glucosylamines bind to this enzyme in their unprotonated form [135] (For a few other examples of substrate analogues see [135 – 141]).

Table 1.7.1: Glycosidase Inhibitors, Substrate Analogues.

Inhibitor	**Enzyme inhibited (pH of assay), inhibition constant (inhibition type)**	**Reference**
 **10**	*β*-glucosidase from almonds (6.0): K_i = 1.4 mM (comp.)	[135]
 **11a** R = H **11b** R = Bn	**11a** (pK_{HA} = 5.6): *β*-glucosidase from almonds (6.0): K_i = 0.3 mM (comp.) **11b** (pK_{HA} = 5.3): *β*-glucosidase from almonds (6.0): K_i = 0.3 μM (comp.)	[135]
 **12**	*α*-glucosidase from brewer's yeast (6.8): IC_{50} = 0.58 mM *β*-glucosidase from almonds (6.8): IC_{50} = 1.5 mM	[31]

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.

Inhibitor	**Enzyme inhibited (pH of assay), inhibition constant (inhibition type)**	**Reference**
 **13**	β-glucosidase from almonds (6.2): K_i = 0.2 mM (comp.) β-glucosidase from almonds (4.5): K_i = 37 μM (comp.)	[57] [117] [155]
 **14**	β-glucosidase from almonds (6.8): K_i = 4.3 mM (comp.) β-glucosidase from almonds (4.5): K_i = 0.1 mM (comp.)	[155]
 **15**	($pK_{HA} \approx 0.6$): β-glucosidase from almonds (6.8): K_i = 0.13 mM (comp.)	[57]
 **16**	(pK_{HA} = 10.6): β-glucosidase from almonds (6.8): K_i = 10 μM (comp.)	[156]
 **17**	(pK_{HA} = 5.6): β-glucosidase from almonds (6.8): K_i = 16 μM (comp.)	[157]
 **18**	(pK_{HA} = 8.7): β-glucosidase from almonds (6.8): K_i = 8.4 μM (comp.)	[156]

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 nagstatin, 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].

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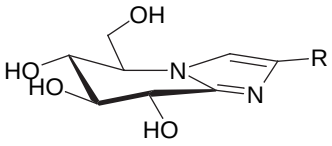
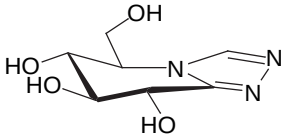
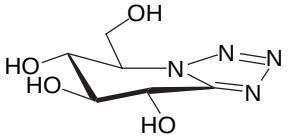
[21]) Crystal structure analysis of Cel5A in complex with a cellobiose-derived imidazole or with a distorted substrate ($^1S_3$ conformation) revealed that the catalytic acid is able to bind to the axial glycosidic O atom (1.4 Å above the ring plane) of the substrate complex as well as to the "glycosidic" 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.

Inhibitor	**Enzyme inhibited (pH of assay), inhibition constant (inhibition type)**	**Reference**
 **19a** R = H **19b** R = CH_2CH_2Ph	**19a** (pK_{HA} = 6.1): *β*-glucosidase from almonds (6.8): K_i = 0.1 μM (comp.) *β*-glucosidase from *Caldocellum s.* (6.8): K_i = 20 nM (mixed, α = 3.2) **19b** (pK_{HA} = 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, α = 15)	[163] [169] [169]
 **20**	(pK_{HA} = 2.4): *β*-glucosidase from almonds (6.8): K_i = 19 μM (comp.) *β*-glucosidase from *Caldocellum s.* (6.8): K_i = 0.17 μM (comp.)	[163]
 **21**	(pK_{HA} = – 4.0): *β*-glucosidase from almonds (6.8): K_i = 0.15 mM *β*-glucosidase from *Caldocellum s.* (6.8): K_i = 5 μM (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-isofagomine 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 isofagomine[22]). 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 (**4** *vide supra*) [28] [29], a strong inhibitor of intestinal sucrase (K_i = 2.6 x 10^{-7} 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)).

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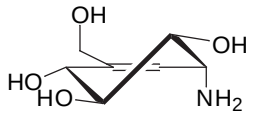
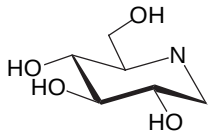
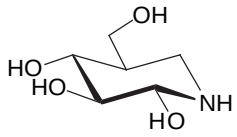
[22]) An earlier attempt to dissect the thermodynamics of binding of **23** and **24** to the *β*-glucosidase from sweet almonds by simple van't Hoff analysis [173] gave wrong results, as the assumption that ΔH is temperature independent is not correct [171].

Table 1.7.4: Glycosidase Inhibitors, Amines.

Inhibitor	**Enzyme inhibited (pH of assay), inhibition constant (inhibition type)**	**Reference**
 **22**	β-glucosidase from almonds (6.8): IC_{50} = 8.8 mM α-glucosidase from yeast (6.8): IC_{50} = 18 μM	[31]
 **23**	(pK_{HA} = 6.7): β-glucosidase from almonds (6.8): K_i = 26.3 μM (comp.) α-glucosidase from yeast (6.8): K_i = 15 μM (comp.)	[173] [174] [194]
 **24**	(pK_{HA} = 8.6): β-glucosidase from almonds (6.8): K_i = 0.11 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 ϕ(C(5)–O–C(1)–C(2)) ≈ 0°). 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 $^{2,5}B$ 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 $^{2,5}B$ 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 mM [174]).

The isofagomine disaccharide analogue **26a**, designed to mimic the pseudoaxial orientation of the aglycon in a $^{1,4}B$ distorted β-glucopyranoside, is only a weak inhibitor of the retaining endoglucanase Cel7B from *Fusarium oxysporum* (family 7) [195], for which distortion of a substrate analogue to a boat conformation was observed in the crystal structure (*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].

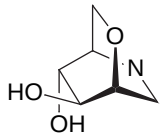
In our group, the isoquinuclidines **27**, **28**, **29**, **30**, **31**, and **32**, mimicking $^{1,4}B$ conformers of manno-pyranose, gluco-pyranose, and GlcNAc, respectively, were first prepared as racemates by *Lorthiois* and *Meyyappan* and then as pure enantiomers by *Boehm via* an elegant enantioselective formal [4+2] cycloaddition [196 – 199]. The mannose-analogue **27** is only a weak inhibitor of the β-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 β-glucosidases (*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 β-mannosidase towards higher pH values (α also increases, the inhibition becomes almost fully competitive at pH 5.5), *Boehm et al.* concluded that the unprotonated forms of **27** and **28** bind to the enzyme and derived K_i values of 2.2 μM 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 μM 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 μM 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 β-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 β-glucosidase may be that hydrolysis by this enzyme proceeds *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

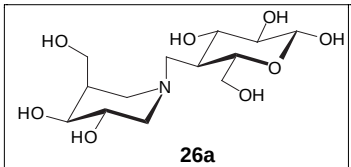
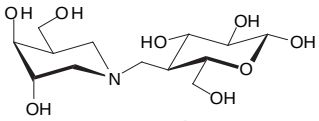
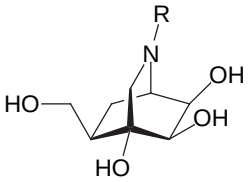
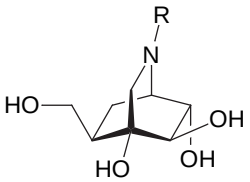
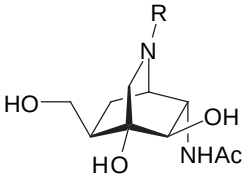
distortion of the substrate to a reactive conformation and glycosylation are concerted. From the inhibition data for the *manno* and *gluco* isoquinuclidines *Boehm et al.* conclude that "the glycosidase induced lengthening of the scissile bond and rehybridisation of the anomeric centre are more strongly 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 kidney[23]) [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 $^{1,4}B$ 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.

Inhibitor	**Enzyme inhibited (pH of assay), inhibition constant (inhibition type)**	**Reference**
 **25**	β-glucosidase from almonds (6.8): K_i = 1 mM (comp.) α-glucosidase from yeast (6.8): K_i = 7 mM (comp.) α-mannosidase from almonds (5.0): K_i = 15 mM (comp.)	[194]

[23]) The amino-acid sequence and the 3D structure of this enzyme are not known.

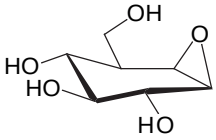
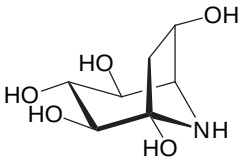
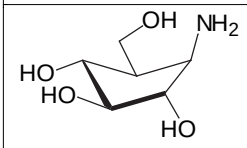
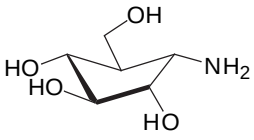
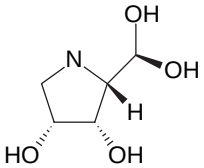
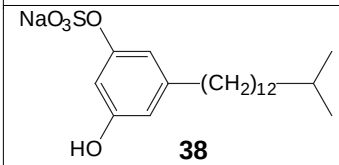
 **26a**  **26b**	Cel7B from *Humicola insolens* (8.5): K_i = 0.2 mM (comp.)	[195]
 **27** R = H **28** R = Bn	**27** (pK_{HA} = 8.4) β-mannosidase from snails (4.5): K_i = 1.2 mM (mixed, α = 1.1) α-mannosidase from Jack beans (4.5): IC_{50} = 2 mM **28** (pK_{HA} = 7.5) β-mannosidase from snails (4.5): K_i = 1.0 μM (mixed, α = 1.9) α-mannosidase from Jack beans (4.5): IC_{50} > 5 mM	[197]
 **29** R = H **30** R = Bn	**29** (pK_{HA} = 7.8) β-glucosidase from almonds (6.8): IC_{50} = 2.7 mM β-glucosidase from *Caldocellum s.* (6.8): K_i = 1.3 mM (mixed, α = 9.0) **30** (pK_{HA} = 6.6) β-glucosidase from almonds (6.8): IC_{50} = 3.3 mM β-glucosidase from *Caldocellum s.* (6.8): IC_{50} = 3.3 mM	[198]
 **31** R = H **32** R = Bn	**31** (pK_{HA} = 7.7) *N*-Acetyl-β-hexosaminidase from Jack beans (5.0): K_i = 14 nM (comp.) *N*-Acetyl-β-hexosaminidase from bovine kidney (4.1): K_i = 67 nM (comp.) **32** (pK_{HA} = 5.9) *N*-Acetyl-β-hexosaminidase from Jack beans (5.0): K_i = 81 nM (comp.) *N*-Acetyl-β-hexosaminidase from bovine kidney (4.1): K_i = 300 nM (comp.)	[199]

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 β-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)-cyclopentane 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 (Φ(C(5)–O–C(1)–C(2)) = 0°). 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 α-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.

Inhibitor	**Enzyme inhibited (pH of assay), inhibition constant (inhibition type)**	**Reference**
 **33**	β-glucosidase from almonds (6.8): K_i = 0.34 mM (irreversible, k_i = 2.38 min^{-1})	[217]
 **34**	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]
 **35**	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]
 **36**	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]
 **37**	α-mannosidase from Jack beans (4.5): K_i = 0.76 μM (comp.)	[218]
 **38**	β-glucosidase from almonds (6.8): IC_{50} = 0.24 μM	[216]

1.8. Aims and Questions

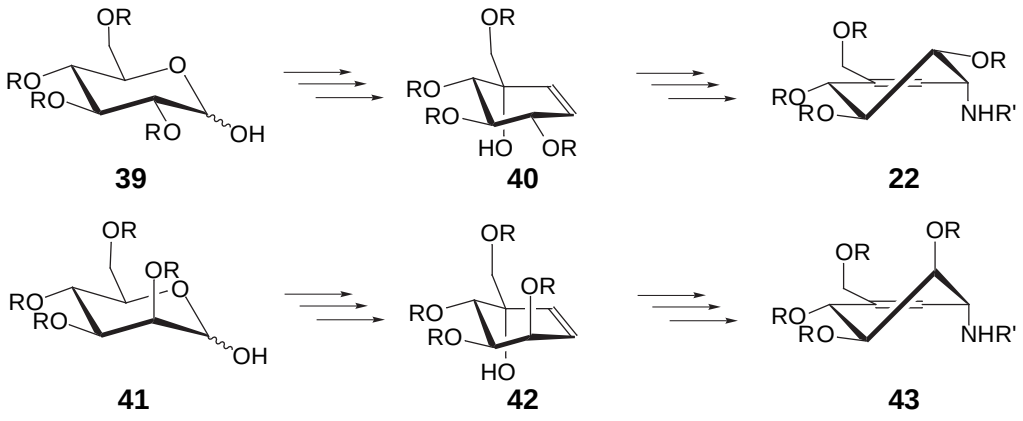
Although glycosidases have been studied extensively and a plethora of kinetic and structural data has been collected, important details of the mechanism of action remain unclear and are the subject of controversy. As outlined in chapter 1.4, it remains elusive if glycosylation proceeds *via* a short-lived oxycarbenium ion rather than by an S_N2-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 carbocyclic 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 = Bn, R' = 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



[24]) *Prof. Francisco Sarabia*, University of Malaga, Spain, post-doctoral fellow from June 1998 to October 1998.

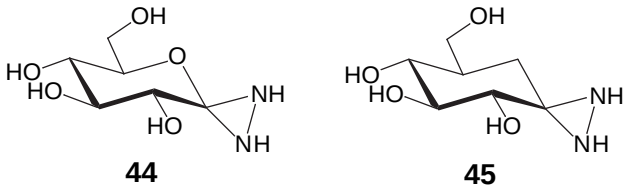
Sarabia used benzyl protecting groups (R = Bn) in his carbasugar syntheses. In order to study the influence of the nature of the protecting group on the ring-closing alkene metathesis, we also studied the synthesis of the methoxymethyl derivative of **40** (R = MOM) from 2,3,4,6-tetra-*O*-methoxymethyl-D-glucopyranose. 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[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** (*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 *manno*-pyranose with orthogonal protection of C(2)–OH, in analogy to the synthesis of **42** from mannose.

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

Scheme 1.8.2



44 **45**

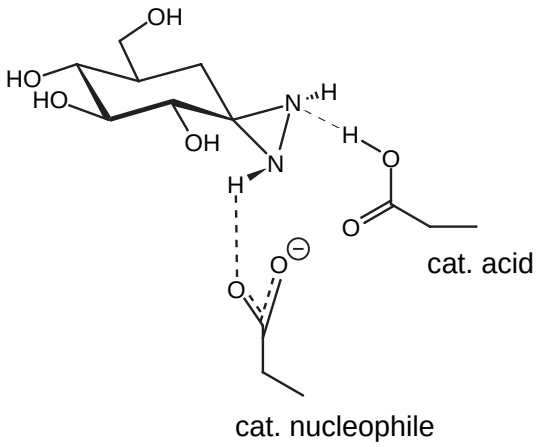
[25]) *Dr. Lubos Remen*, post-doctoral fellow from March 1999 to December 2001.

[26]) *Dr. Halasyam Mohan*, post-doctoral fellow from May 1997 to February 2002.

[27]) *Nathalie Leclerc*, diploma student (under my supervision) from the E.N.S.C.M., France, from October 1998 to June 1999.

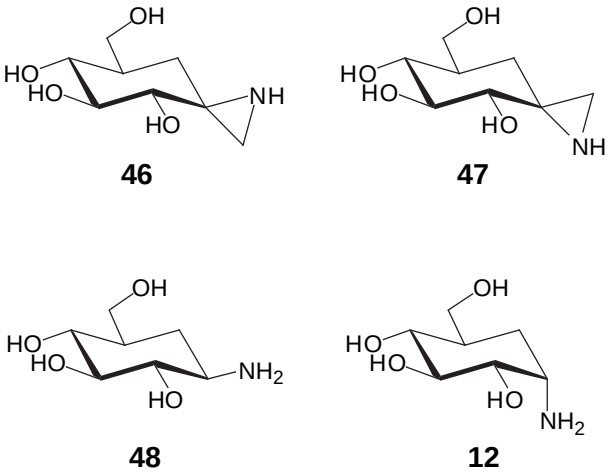
In complex with a β-glucosidase, the "β"-N of **45** may accept a H-bond from the catalytic acid, while the "α"-N may donate a H-bond to the catalytic nucleophile, or, in its protonated state, form a salt bridge with the catalytic nucleophile (Figure 1.8.1). An inverse situation should be present in 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.



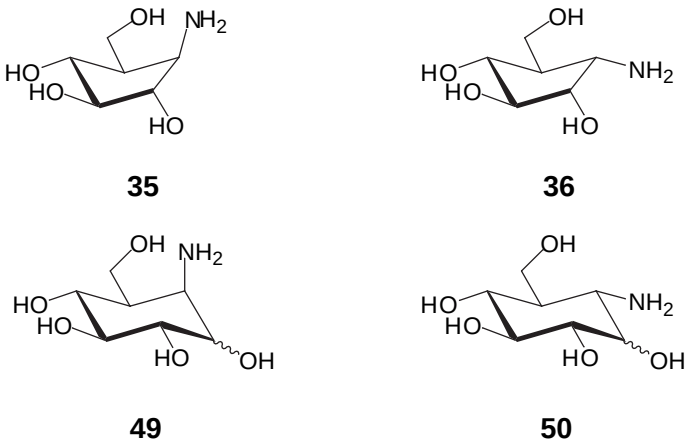
To differentiate between the effects of shape and charge on the inhibition by the diaziridines **45**, I also required the related *spiro*-aziridines **46** and **47**, and 1-*epi*-validamine (**48**, Scheme 1.8.3) [224]. I also included the known inhibition data for validamine (**12**) [31] in the comparison. The basicity of these potential inhibitors is expected to increase in the order **45** < **46**, **47** < **48**, **12**.

Scheme 1.8.3



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**.

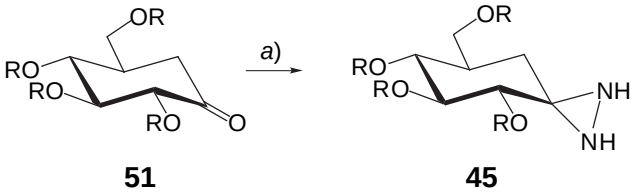
Scheme 1.8.4



Validone (**51**, Scheme 1.8.5), which is available by NBS-cleavage of validoxylamine A)

[225] [226][28]), 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

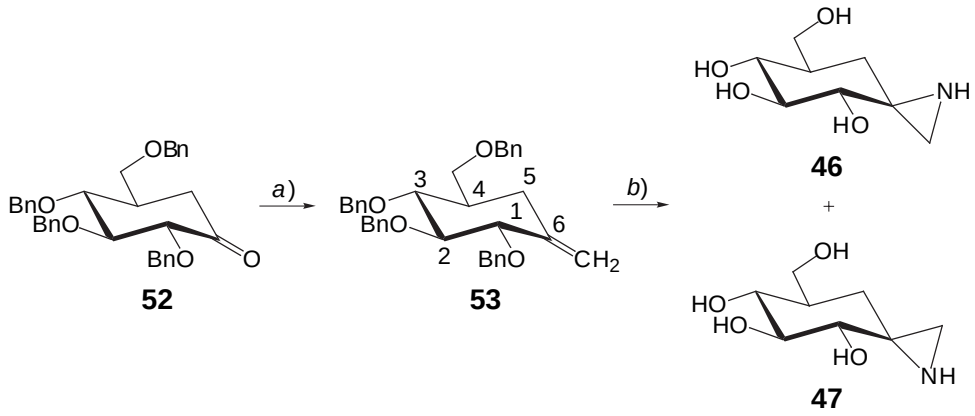


51 **45**

Proposal for the synthesis of **45**. *a*) i. NH_3, MeOH, then NH_2OSO_3H; 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-*O*-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



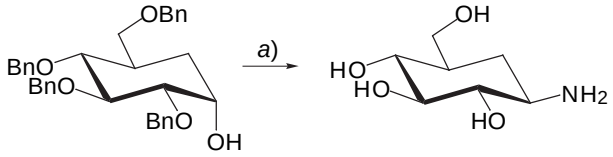
Proposal for the synthesis of **46** and **47**. *a*) $Ph_3P{=}CH_2$, THF. *b*) Aziridination (*e.g.* chloramine T, $PhMe_3NBr_3$, MeCN [229], TsN_3, toluene, 110° [230] [231], or TfN_3, CH_2Cl_2 [232]), deprotection; or i. mCPBA, CH_2Cl_2; ii. NaN_3, DMF; iii. Sulfonylation with TsCl or MsCl; iv. Reductive cyclisation with $LiAlH_4$ [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

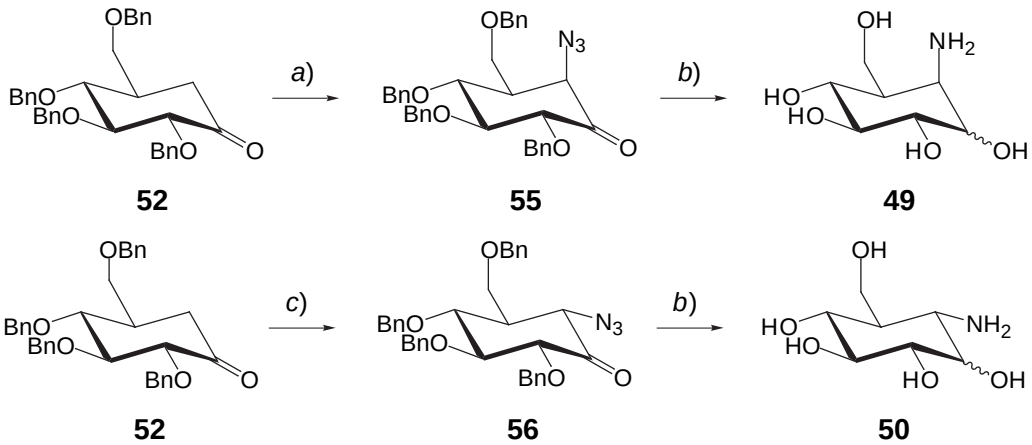


54 **48**

Proposal for the synthesis of **48**. *a*) i. Sulfonylation; 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



52 **55** **49**

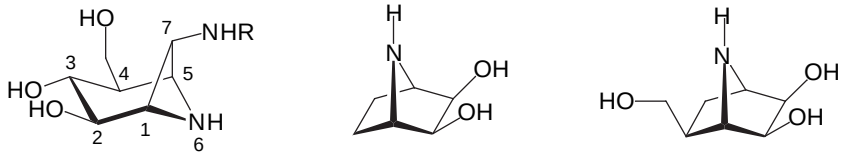
52 **56** **50**

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 ($LiAlH_4$, DIBAHL, or $NaBH_4$); ii. Hydrogenation. *c*) i. $PhMe_3NBr_3$, 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.

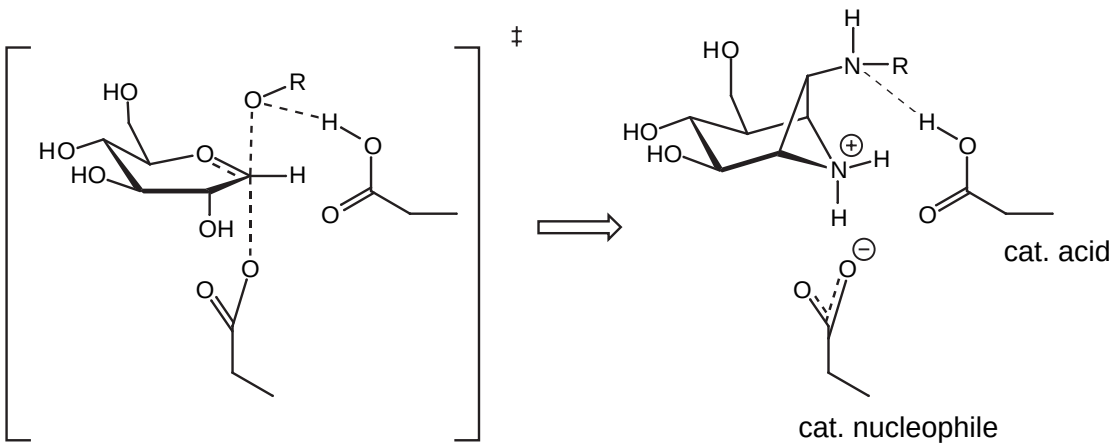
Scheme 1.8.9



57 **58** **59**

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]).

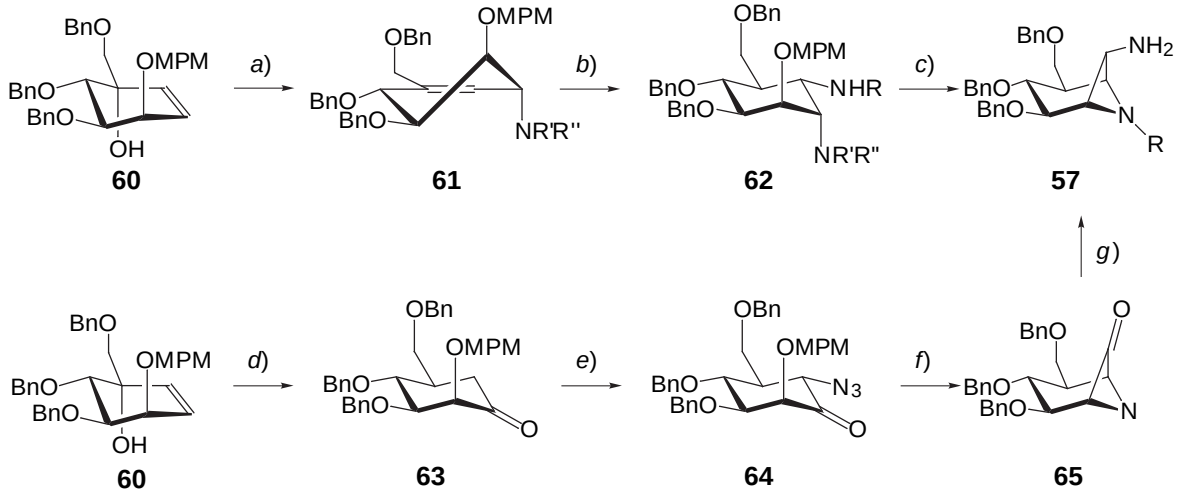
Figure 1.8.2: Proposed Interaction of **57** with a retaining β-Glycosidase.



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 $^{1,4}B$ 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 Ph_3P. 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 Ph_3P; 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.* $NaBH_4$), 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:

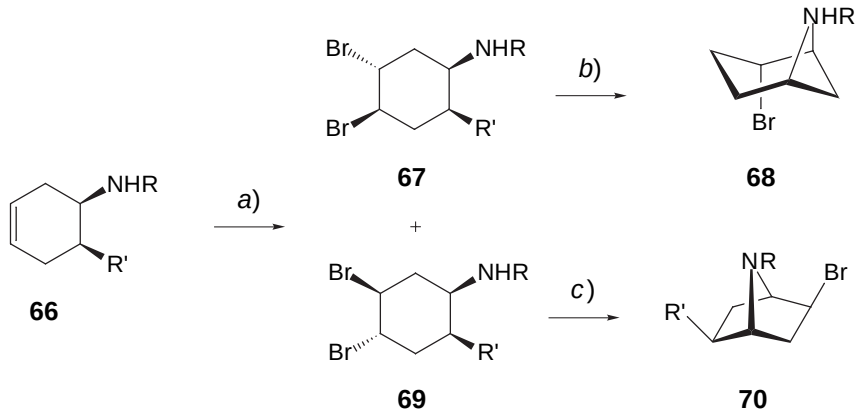
- The synthesis of **60** was low yielding and would require extensive optimisation.
- There were serious doubts if **62** or **64** would cyclise to the azetidines **57** or **65**. This cyclisation presumably requires an axial orientation of N and an equatorial orientation of the leaving group. However, **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-aminocyclohenes **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**.

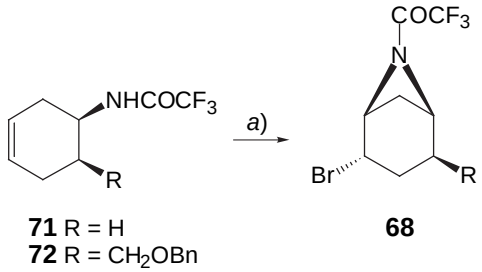
Scheme 1.8.11



Proposal for the synthesis of azetidines **68** and 7-azanorbornanes **70**. *a*) Bromination (*e.g.* Br_2). *b*,*c*) Base-catalysed cyclisation.

- 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

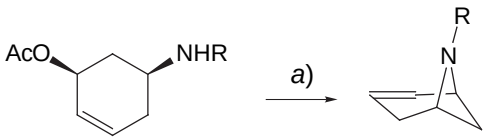


71 R = H
72 R = CH_2OBn

Proposed synthesis of azetidines **68**. *a*) NBS, AcOH.

- 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

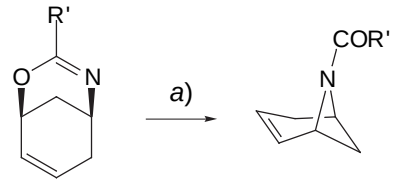


73 **74**

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

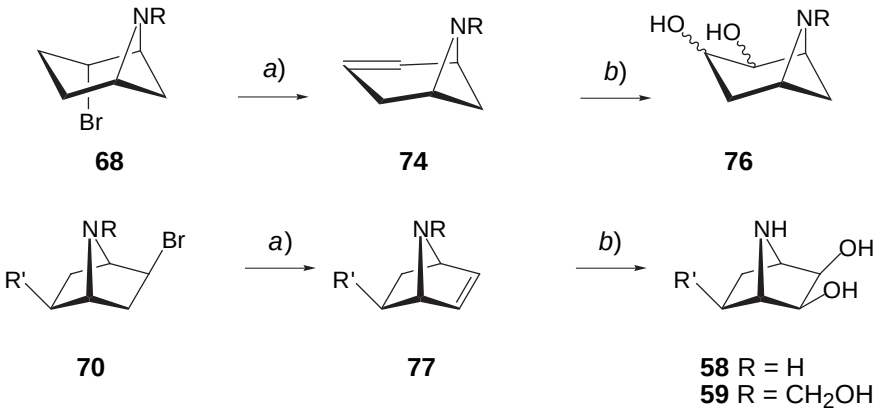


75 **74**

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.

Scheme 1.8.15



Proposal for the synthesis of the potential glycosidase inhibitors **76**, **58**, and **59**. *a*) DBU. *b*) OsO_4, NMO; then deprotection.

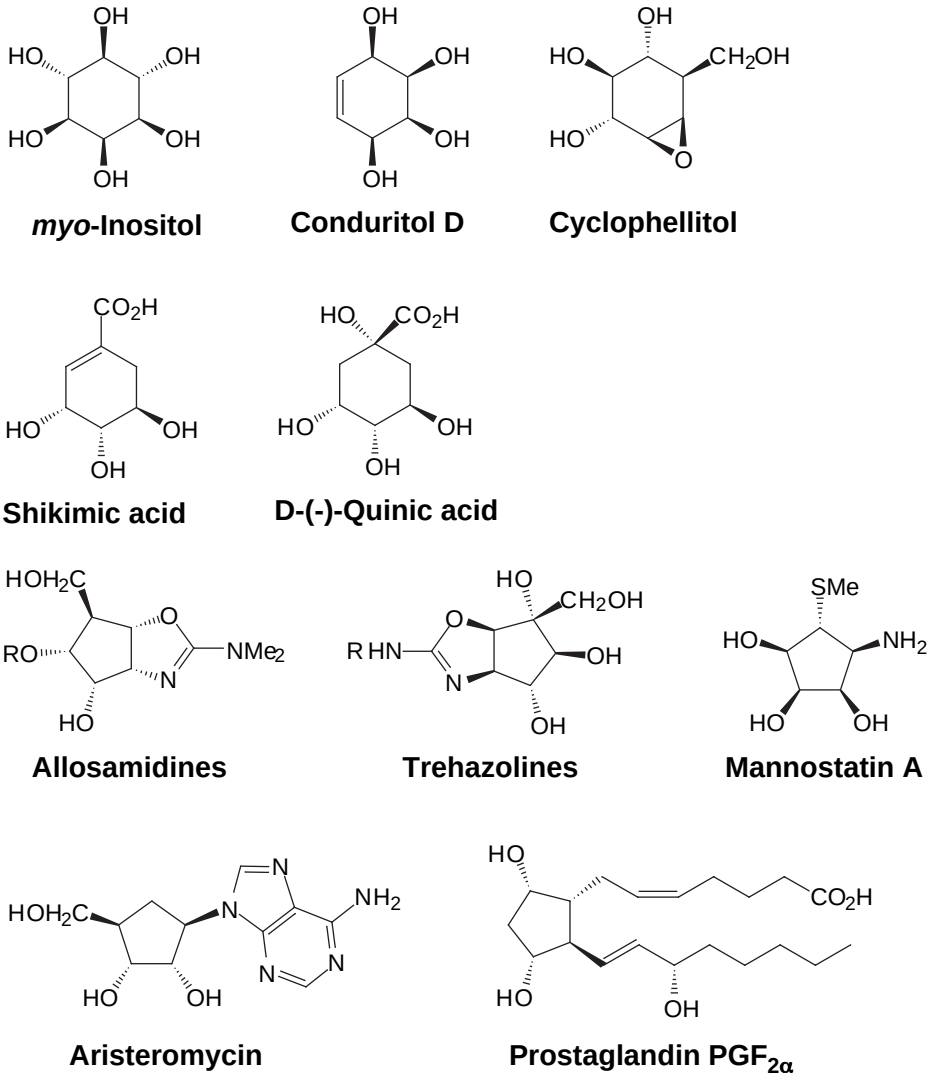
2. Part 1: Carbasugars from Sugars *via* Ring-Closing Alkene Metathesis

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 $F_{2\alpha}$) are cyclopentanepolyols.

Figure 2.1.1: Naturally Occurring Carbasugars.



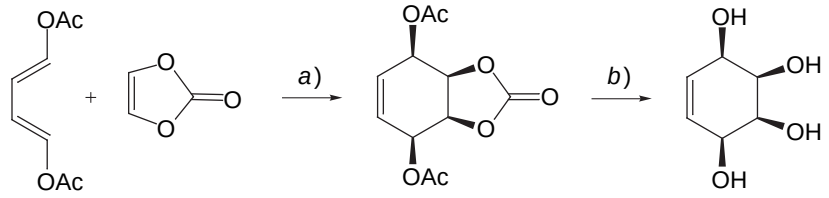
Owing to their biological activity, naturally occurring carbasugars and their analogues have received extensive synthetic interest, which has been reviewed comprehensively [119] [120] [124] [258 – 271]. In principle, carbasugars can be prepared *de novo*, from other carbasugars, or from sugars. In the 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-cyclohexadienecarboxylic 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

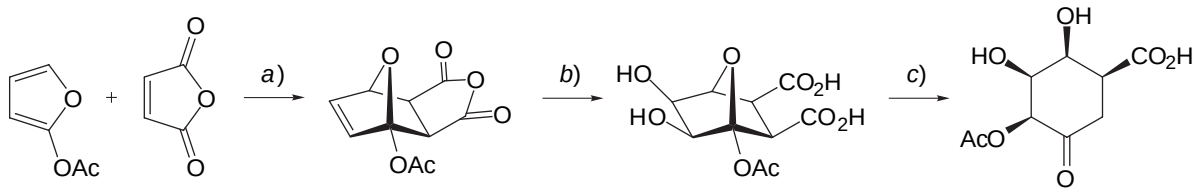


79 **80** **81** **82**

a) 205°C, autoclave; 30% [272]. *b*) $Ba(OH)_2$, H_2O; 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

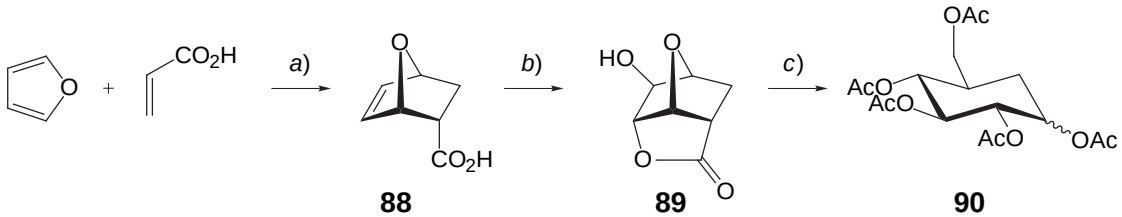


83 **84** **85** **86** **87**

a) Conditions not given; 67 – 90% [245]. *b*) Hydroxylation, hydrolysis; 50 – 69% [245]. *c*) H_2O, r.t.; 58 – 88% [245].

The oxanorbornene **88** (Scheme 2.1.3), available by *Diels-Alder* cycloaddition of furan and acrylic acid was used in the synthesis of various racemic carbasugars [261]. Resolution of **88** allowed the synthesis of pure enantiomers [282]. Hydroxylation of **88** with hydrogen peroxide and formic acid provided the lactone **89**, which was converted to α- and β-5a-carbaglucopyranose by reductive opening of the lactone and acid-catalysed hydrolysis of the 1,4-ether linkage. *Cis*-hydroxylation of the oxanorbornene **88** allowed the synthesis of *gulo*- and *allo*-5a-carbapyranose.

Scheme 2.1.3

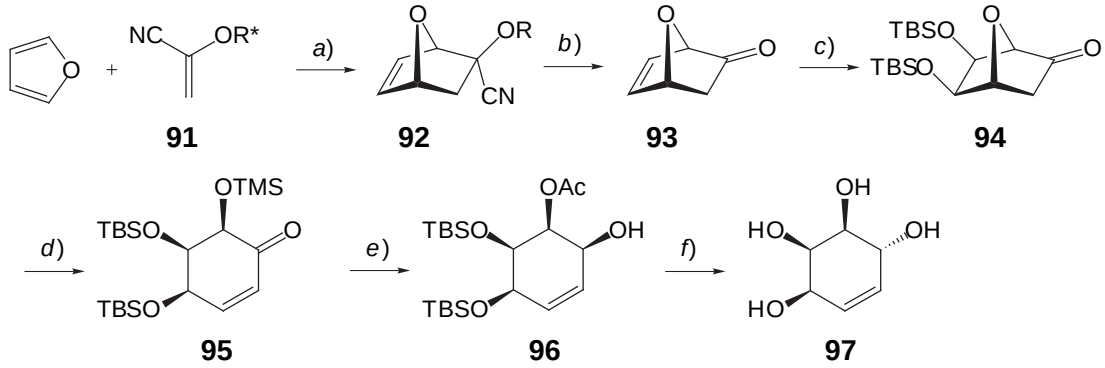


88 **89** **90**

a) Neat, 45%; [261]. H_2O_2, HCO_2H, H_2O; 66% [261]. *c*) i. $LiAlH_4$, THF, then Ac_2O, pyridine;76% ii. AcOH, Ac_2O, H_2SO_4; 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 carbafuranoses, furanoses, and pyranoses; they were regio- and stereoselectively functionalised at C(3), C(5), and C(6) [264] [283] [284].

Scheme 2.1.4

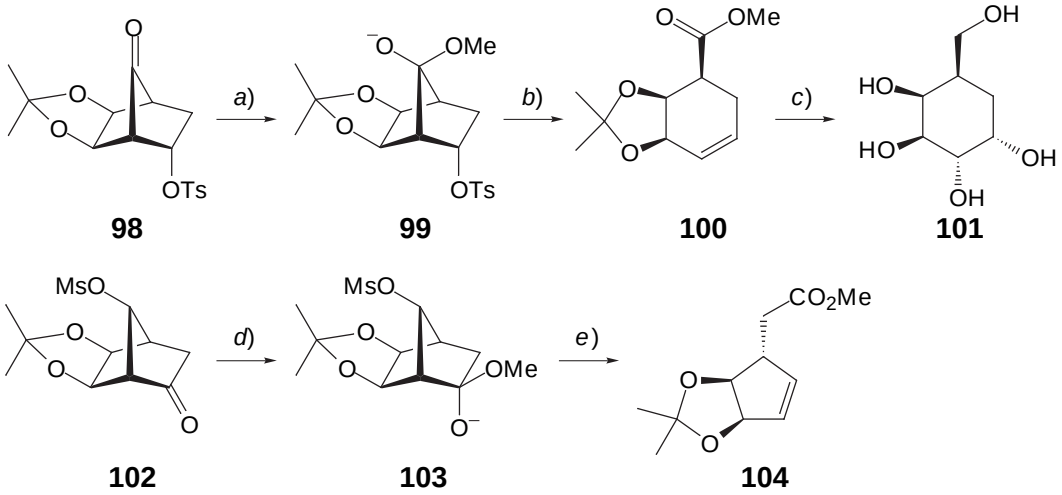


R* = (1*S*)-camphanoyl. *a*) ZnI_2; 92% [283]. *b*) NaOMe, MeOH; [283]. *c*) i. OsO_4, NMO, acetone; [283]. *d*) TMSOTf, Et_3N; [283]. *e*) i. HF, MeOH, H_2O; ii. Ac_2O, DMAP, pyridine; iii. $NaBH_4$, $CeCl_3$, MeOH; [283]. *f*) i. DEAD, PPh_3, BzOH, THF; ii. MeOH, KOH; iii. HF, MeCN; 49% from **94** [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

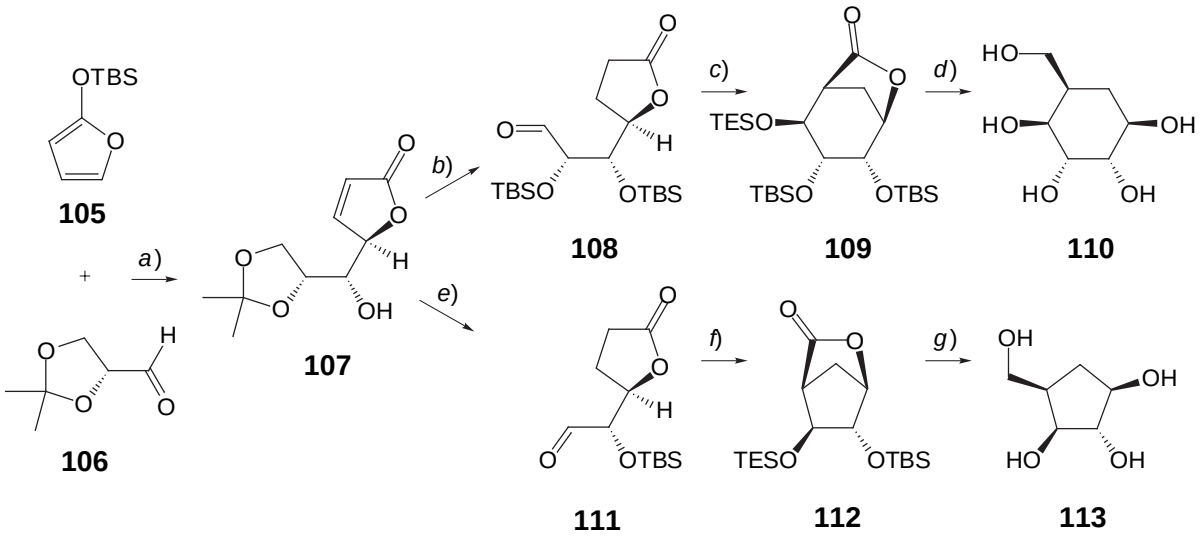


a, *b*) NaOMe, MeOH; 70%; [293]. *c*) i. OsO_4, NMO; 95%; ii. $LiAlH_4$, THF; 88%; iii. Amberlyst 15, aq. MeOH; 74% [293]. *d*, *e*) NaOMe, MeOH; 40% [297].

Ozonolysis of norbornenes led to carbafuranoses [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-silyloxypyrrole provided aminocyclohexitols and aminocyclopentitols [305].

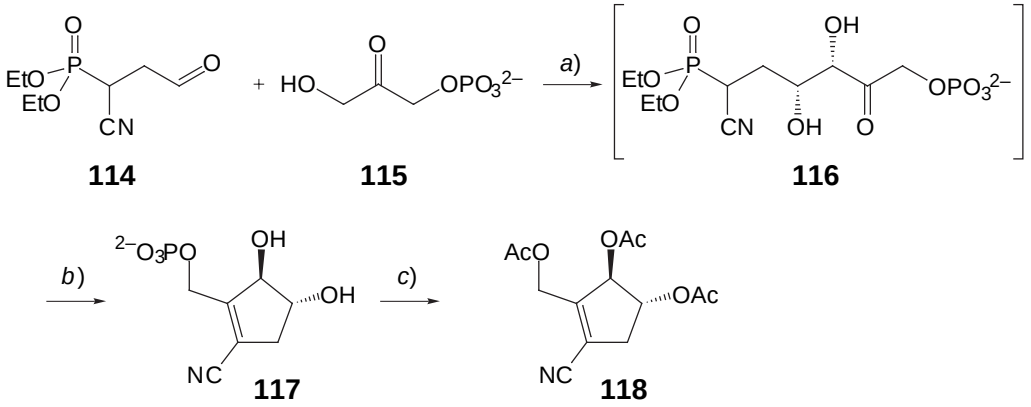
Scheme 2.1.6



a) $BF_3{\cdot}OEt_2$, CH_2Cl_2; 75% [301]. *b*) Six steps, 43%; [301]. *c*) i. LDA, THF; 51%; ii. TESOTf, DMAP, pyridine; 95% [301]. *d*) i. $LiAlH_4$, 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. $LiAlH_4$, 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



114 **115** **116** **117** **118**

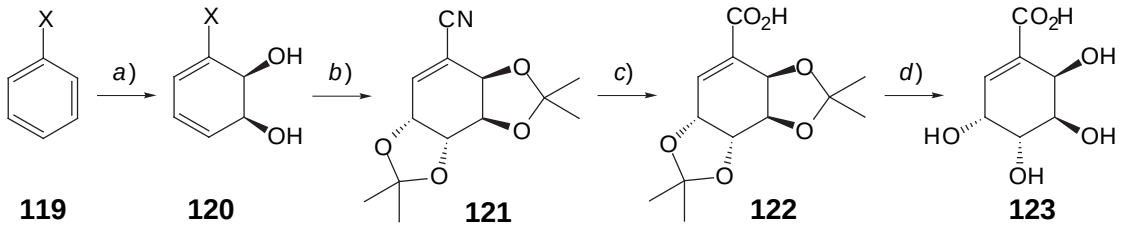
a, *b*) FDP aldolase, H_2O, pH 6.8 – 6.1; [306]. *c*) i. Phosphatase, H_2O; pH 4.8; ii. Ac_2O, pyridine; 71% overall [306].

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], 5a-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%).

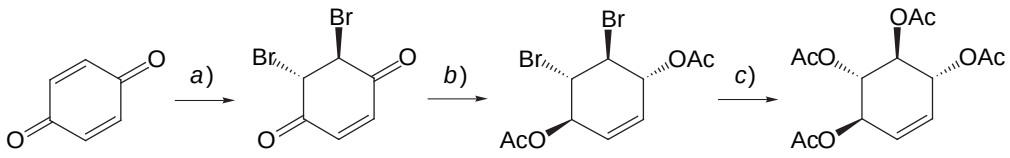
Scheme 2.1.8



a) X = CN, toluene dioxygenase from *Pseudomonas putida* F1; 94% [318]. *b*) i. 2,2-dimethoxypropane, TsOH, DMF; 94%; ii. OsO_4, NMO, *t*BuOH, THF, H_2O; 72%; iii. 2,2-dimethoxypropane, TsOH, DMF; 94% [318]. *c*) i. DIBAL, THF; 38.7%; ii. $NaClO_2$, MeCN, H_2O; 72% [318]. *d*) HCl, MeOH, H_2O; quant. [318].

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].

Scheme 2.1.9

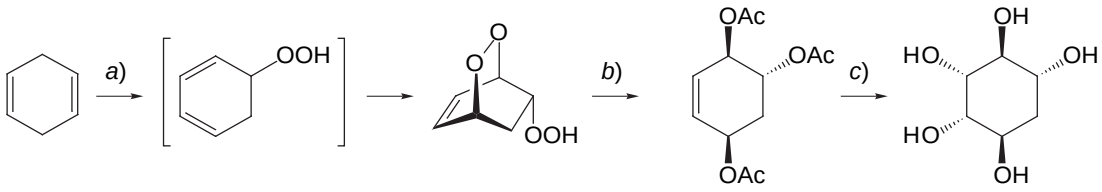


124 **125** **126** **127**

a) Br_2, CCl_4; [321]. *b*) i. $NaBH_4$, Et_2O, H_2O; ii. Ac_2O, pyridine; 70% from **124** [321]. *c*) KOAc, Ac_2O, HOAc; 72% [321].

Various cyclohexitols were prepared from 1,4-cyclohexadiene by *cis*-dihydroxylation, epoxidation, and singulet oxygen ene reaction [326 – 330]. A concise synthesis of DL-*proto*-quercitol (**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].

Scheme 2.1.10



128 **129** **130** **131**

a) O_2, tetraphenylporphyrin, CH_2Cl_2, *hν*; 63% of **129** and 7% of the *exo*-isomer of **129** [331]. *b*) i. Thiourea, MeOH; 70% [331]; ii. Ac_2O, pyridine; 67% [331]. *c*) i. $KMnO_4$, $MgSO_4$, H_2O; 66% [331]; ii. Ac_2O, pyridine; 73% [331]; iii. NH_3, MeOH; quant. [331].

Cyclohexene was transformed into cyclohexitols and aminocyclohexitols by allylic halogenation, alkene halogenation, elimination, S_N2' substitution, hydroxylation, epoxidation, oxyselenylation, and selenoxide elimination [333 – 337].

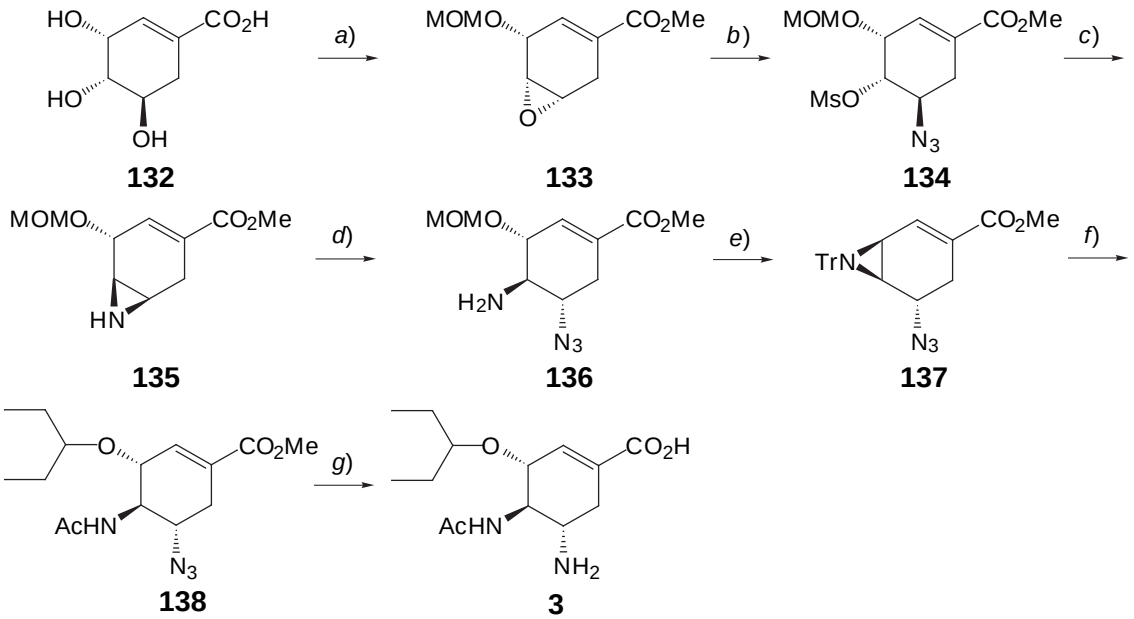
Annulated bicyclic cyclitols were prepared from naphthalene [338] and from cyclooctatetraene [339]. Cyclooctitols were prepared from cyclooctatetraene [340]. Carbafuranoses were prepared from 2-cyclopentenone [341], from cyclopentadiene [342], and from both enantiomers of 4-hydroxy-2-cyclopentenone [343]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

synthesis of carbafuranoses, 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



a) i. Esterification; ii. Ph_3P, DEAD, THF; 77% [346]; iii. MOMCl, DIPEA, CH_2Cl_2; 97% [25]. *b*) i. NaN_3, NH_4Cl, MeOH, H_2O; 86%; ii. MsCl, Et_3N, CH_2Cl_2; 99% [25]. *c*) Ph_3P, THF, then Et_3N, H_2O; 78% [25]. *d*) NaN_3, NH_4Cl, DMF; 76% [25]. *e*) i. HCl, MeOH; 99%; ii. TrCl, Et_3N, CH_2Cl_2; iii. MsCl, Et_3N, CH_2Cl_2; 86% from **136** [25]. *f*) i. 3-Pentanol, $BF_3{\cdot}OEt_2$; ii. Ac_2O, DMAP, pyridine; 69% from **137** [25]. *g*) i. Ph_3P, THF, then Et_3N, H_2O; ii. KOH, THF, H_2O; 75% from **138** [25].

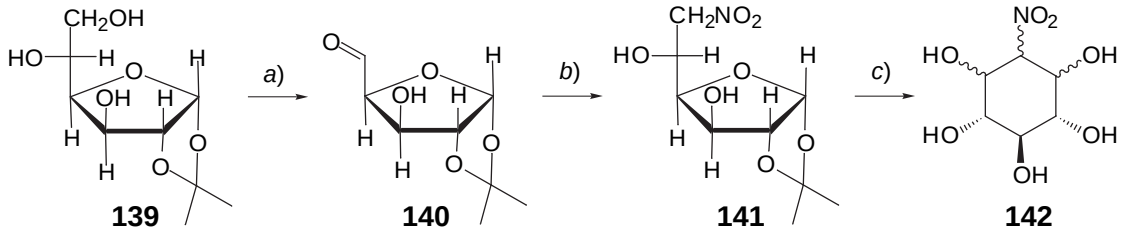
2.1.3. Carbasugars From Sugars

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



139 **140** **141** **142**

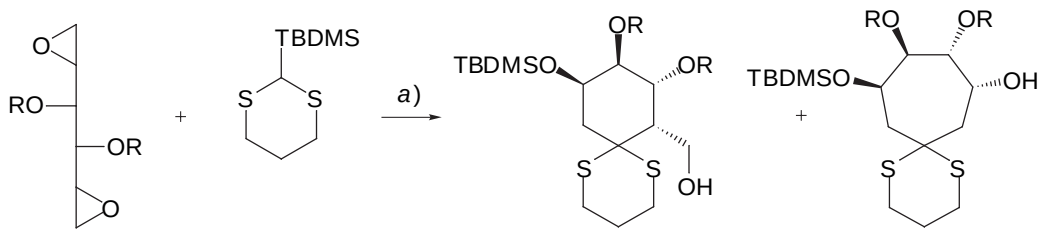
a) i. $Pb(OAc)_4$, benzene; 80% [347]. *b*) CH_3NO_2, EtOH, NaOMe; 50% of a mixture of **141** and the *ido*-isomer [347]. *c*) i. H_2SO_4, H_2O; yield not given; ii. $Ba(OH)_2$, H_2O; 90% of a mixture of 6 isomers [348].

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

[352], or by the reaction of C_2-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

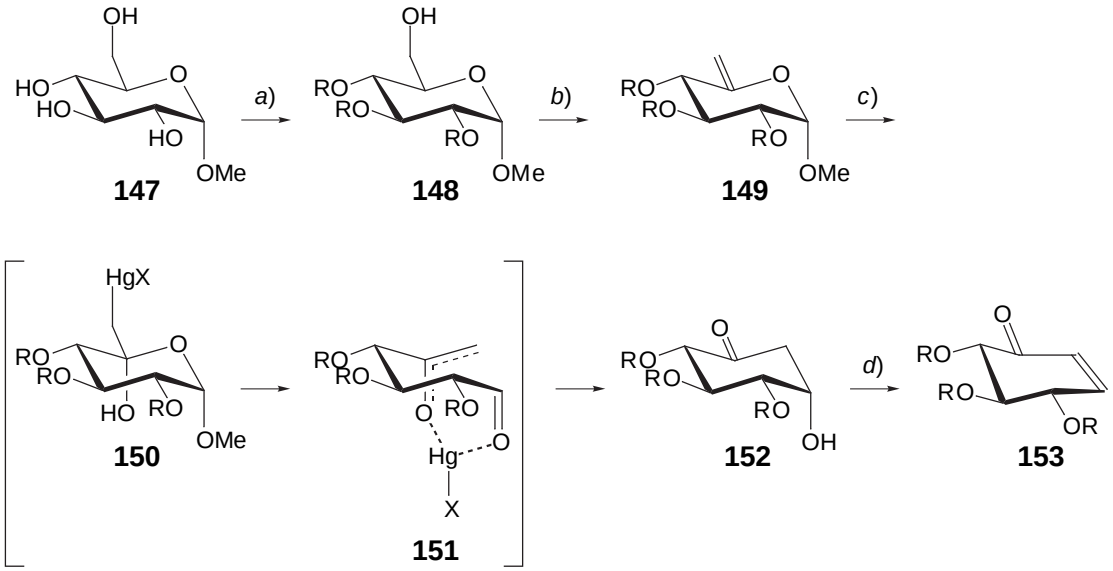


143 **144** **145** **146**

a) Five eq. of **144**, BuLi, Bu_2Mg, THF, HMPA; for R = isopropylidene: 67% of **145**, 24% of **146**; for R = Bn: 10% of **145**, 82% of **146** [354].

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 (*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).

Scheme 2.1.14[29])

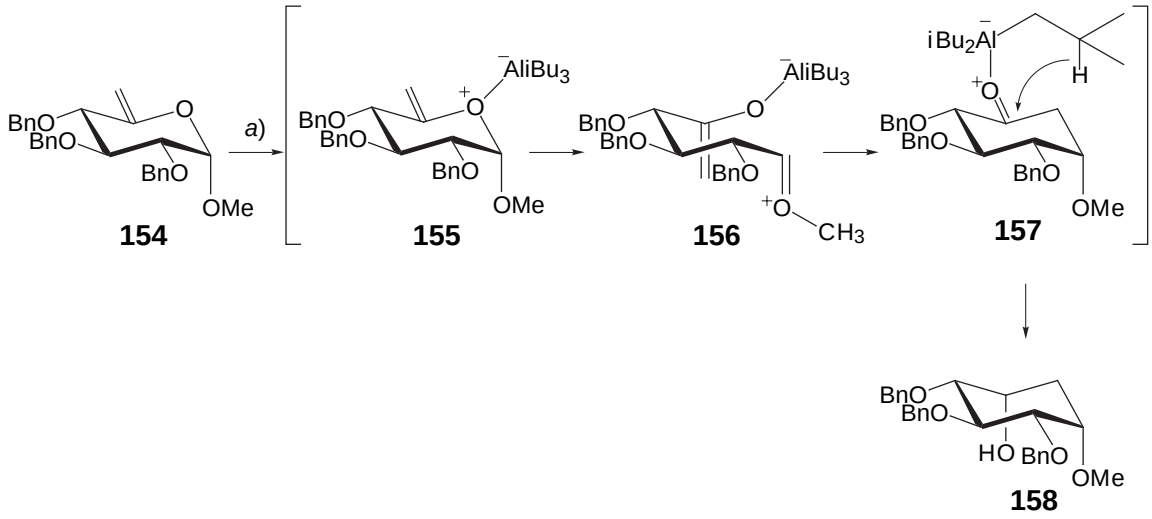


R = Bn *a*) See [358]. *b*) Three steps, 79% [359]. *c*) $HgCl_2$, acetone, H_2O; 84% [359]. *d*) MsCl, pyridine; 91% [359].

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 $Ti(O\textit{i}Pr)Cl_3$ 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.

Scheme 2.1.15

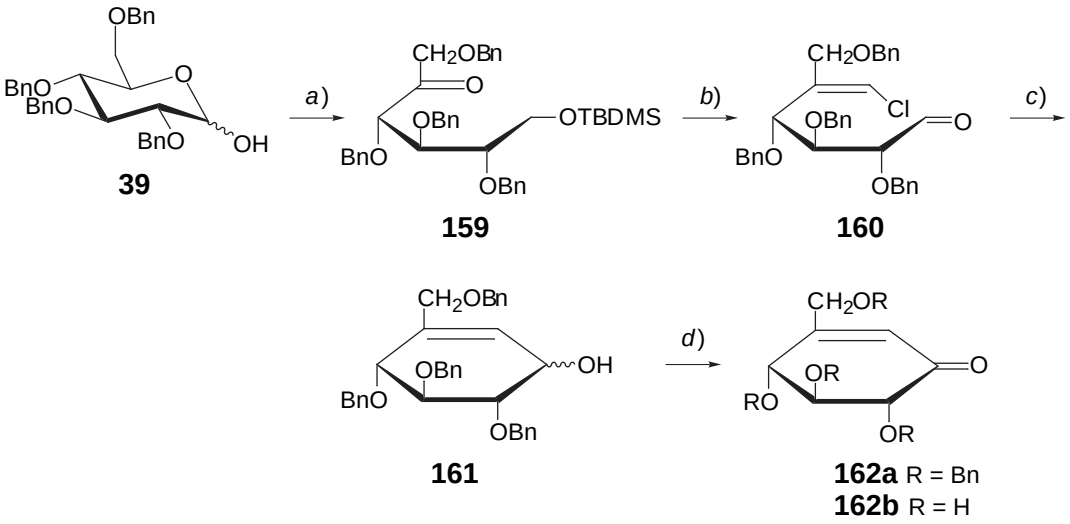


a) *i*Bu3Al, toluene; 79% [360].

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].

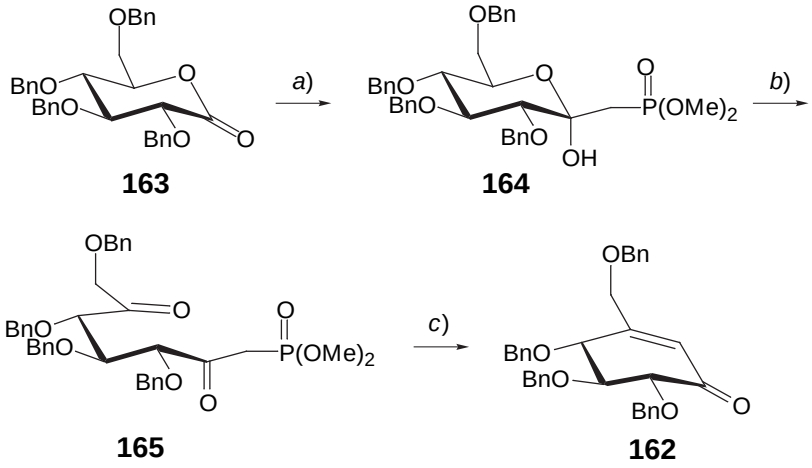
Scheme 2.1.16



a) i. $NaBH_4$, THF, H_2O; 98%; ii. TBDMSCl, pyridine; 97%; iii. PCC, AcONa, MS 4Å, CH_2Cl_2; 90% [364]. *b*) i. $Ph_3P{=}CHCl$, THF; 92%; ii. Bu_4NF, THF; 90%; iii. *Dess-Martin* periodinane, CH_2Cl_2; 70% [364]. *c*) $CrCl_2$, $NiCl_2$, DMF; 61% (1:1 mixture of diastereoisomers) [364]. *d*) i. PCC, AcONa, MS 4Å, CH_2Cl_2; 76%; BCl_3, CH_2Cl_2; 74% of **162b** [364].

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-*O*-benzylgabosine I (**162**, Scheme 2.1.17) was prepared from tetra-*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 (*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

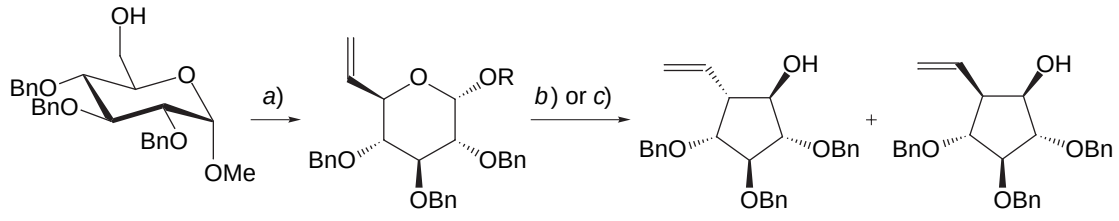


163 **164** **165** **162**

a) BuLi, dimethyl methylphosphonate, THF; 95%. [367] *b*) i. $NaBH_4$, THF; 94%; ii. $(CF_3CO)_2O$, DMSO, Et_3N, CH_2Cl_2; 94% [367]. *c*) K_2CO_3, 18-K-6, toluene; 76% [367].

The reaction of 6-enopyranosides with $Pd(Ph_3)_4$ and SmI_2 [369] or with Cp_2Zr and $BF_3{\cdot}OEt_2$ [370] [371] leads to vinylcyclopentanols (Scheme 2.1.18). The cascade reaction with Cp_2Zr and $BF_3{\cdot}OEt_2$ 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 $Pd(Ph_3)_4$ and SmI_2 proceeds *via* an allyl Sm complex [369]. The vinylcyclopentanols are obtained in moderate yield. The reaction with Pd(0)/SmI_2 gives *cis/trans* mixtures with moderate to poor diastereoselectivity, the reaction with $Cp_2Zr/BF_3{\cdot}OEt_2$ provides the *cis*-products with high diastereoselectivity and therefore is preparatively more useful.

Scheme 2.1.18



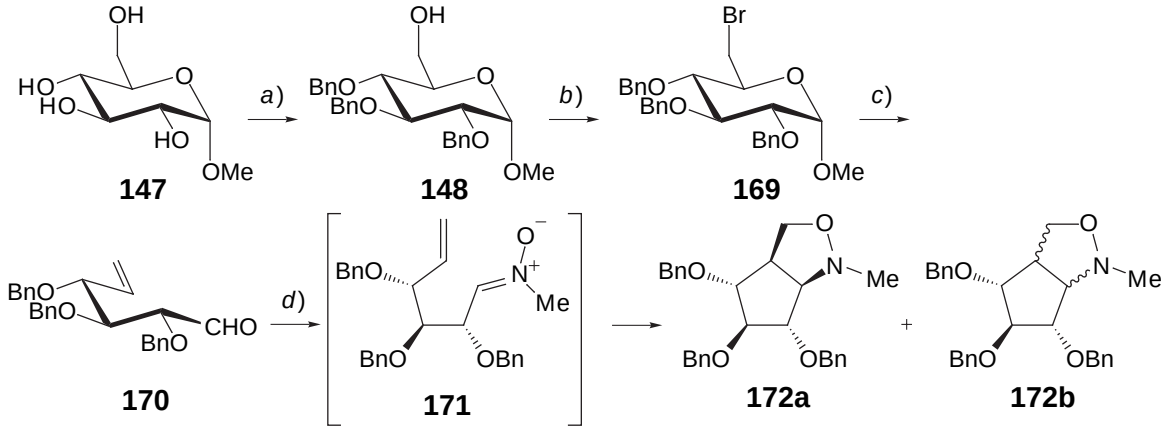
148 **166a** R = Me **166b** R = Ac **167** **168**

a) i. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; ii. $Ph_3P{=}CH_2$, THF; 76% of **166a** from **148**; iii. Ac_2O, H_2SO_4; 56–90% of **166b** [369]. *b*) From **166a** Cp_2ZrCl_2, BuLi, $BF_3{\cdot}OEt_2$, THF; 65% of **168** (>98% d.e.) [370]. *c*) From **166b** $Pd(Ph_3P)_4$, three eq. of SmI_2, THF; 58% of **167**, 13% of **168** [369].

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.

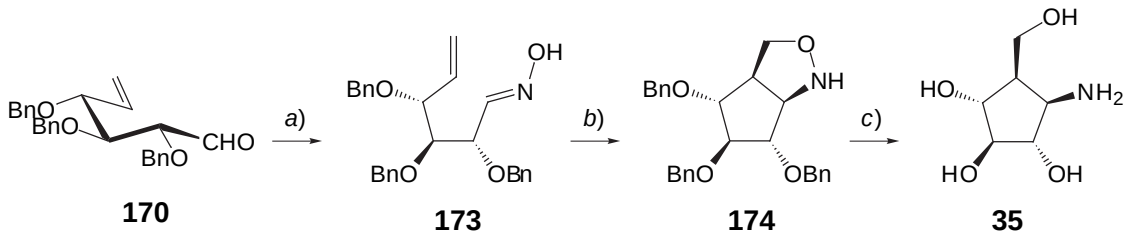
Scheme 2.1.19



a) i. TrCl, pyridine; 81%; ii. NaH, BnCl, DMF; 77%; iii. H_2SO_4, MeOH; 85% [372]. *b*) i. MsCl, Et_3N, CH_2Cl_2; ii. LiBr, butanone; 95% (two steps) [372]. *c*) Zn, aq. EtOH [372]. *d*) MeNHOH·HCl, NaOMe, $NaHCO_3$, 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

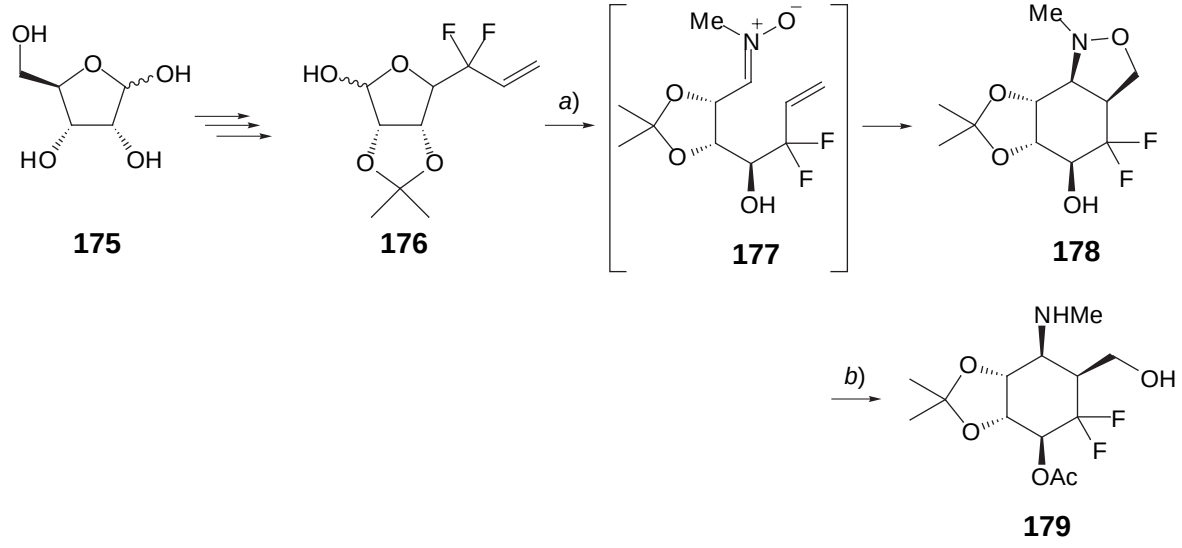


170 **173** **174** **35**

a) $NH_2OH \cdot HCl$, 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



175 **176** **177** **178** **179**

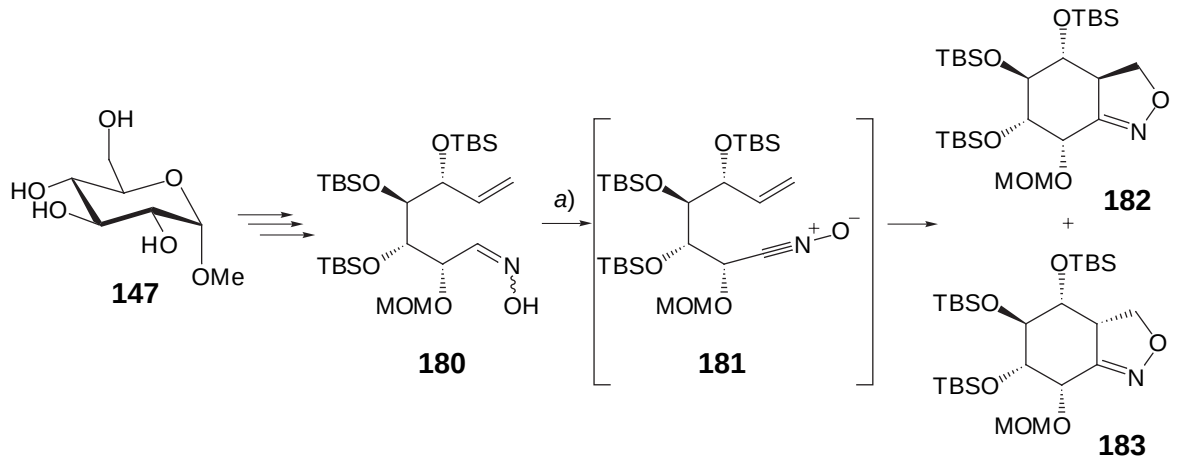
a) $MeNHOH \cdot HCl$, pyridine; 85% [377]. *b*) i. Ac_2O, DMAP, pyridine; quant.; ii. H_2, $Pd(OH)_2$/C, EtOH; 92% [377].

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.

Scheme 2.1.22



a) NCS, basic alumina, pyridine, $CHCl_3$; 95%, **182**/**183** = 1:2 [226].

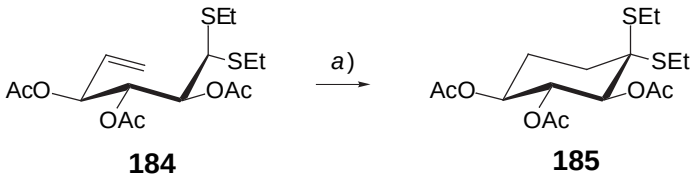
A range of cycloheptenitols were prepared by intramolecular 1,3-dipolar nitrone additions [270] [378]. An α,β-unsaturated ester has also been used as the dipolarophile [379]. Intramolecular dimerisiation of carbohydrate-derived bis-nitrile oxides led to [3.3.0]- and [4.3.0]-bicyclic furoxanes [380].

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

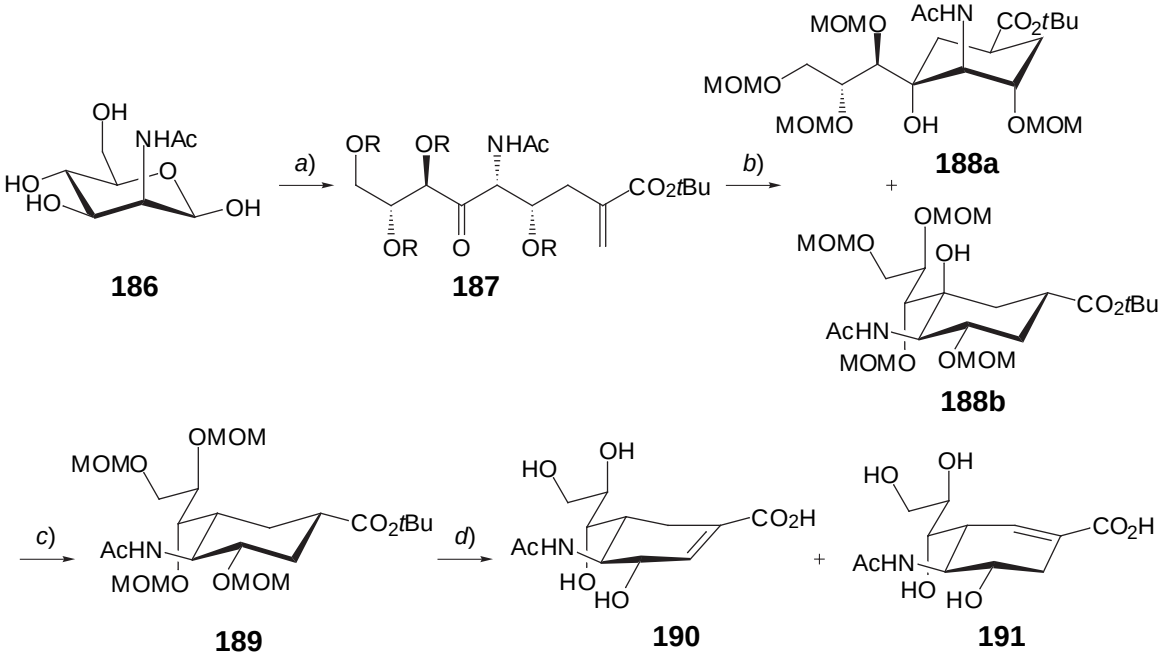


184 **185**

a) Acetone, H_2O, irradiation under sunlight; 40% of **184**, 36% of **185** [384].

Vorwerk applied a SmI_2-mediated radical 6-*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 **187** gave in high yield a 2:3 mixture of the diastereoisomers **188a** and **b**, both of which were transformed into the target compounds **190** and **191** *via* the common intermediate **189**.

Scheme 2.1.24



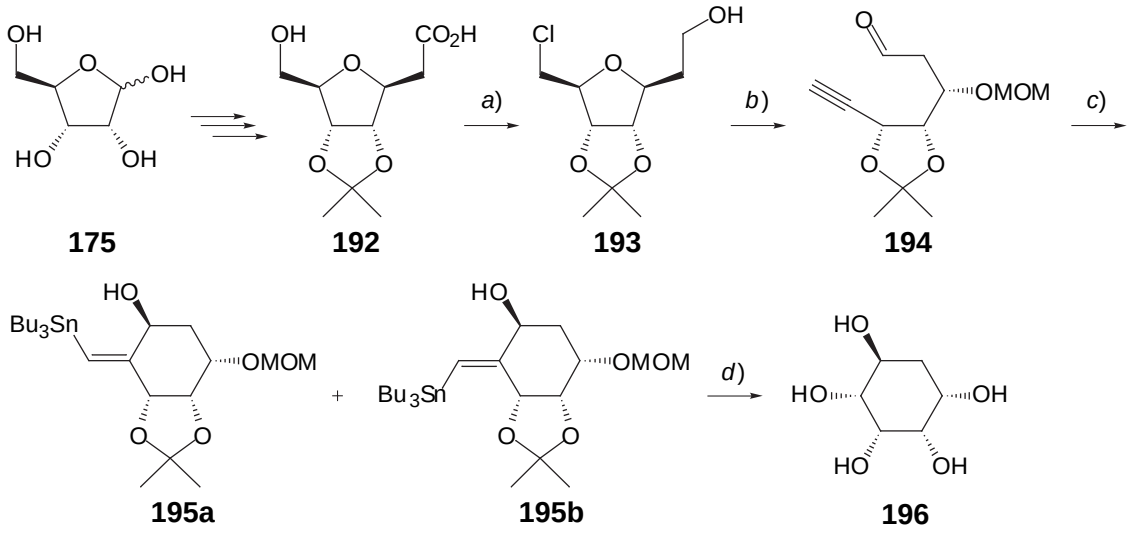
186 **187** **189** **190** **191**

a) 9 steps, 24% [138]. *b*) SmI_2, THF, HMPA, *t*BuOH; 93% (**188a**/**188b** = 2:3) [138]. *c*) Three steps from **188a**, 55%; two steps from **188b**, 78% [138]. *d*) Six steps; 21% of **190**, 11% of **191** [138].

Several cyclopentitols and cyclohexitols were prepared by the *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 [383] [385 – 391], thiocarbonates [392] [393], dithiocarbonates [383], or alkenes [394] [395]. *Barton* and coworkers generated the radical from a carbohydrate derived aryl telluride [396].

Allo-quercitol (**196**) was prepared from D-ribose using a radical 6-*exo*-trig-cyclisation of the heptinal **194** with Bu_3SnH and AIBN as the key step (Scheme 2.1.25, 14 steps from **192**, 15%) [397]. It was presumed that the reaction proceeds by the addition of a vinyl radical to the carbonyl group [397].

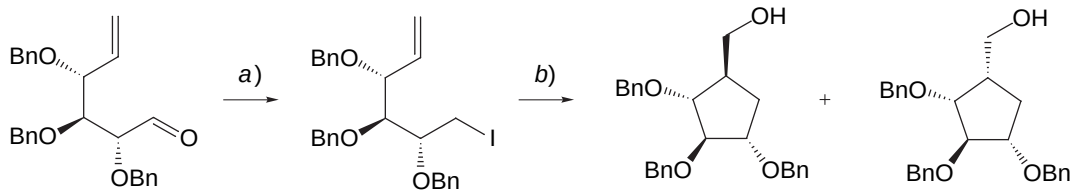
Scheme 2.1.25



a) i. Ph_3P, CCl_4; 88%; ii. $LiAlH_4$, Et_2O; 90% [397]. *b*) i. $LiNH_2$, NH_3; 91%; ii. TBDMSCl, imidazole, CH_2Cl_2; 80%; iii. MOMCl, *i*Pr_2EtN, CH_2Cl_2; 75%; iv. Bu_4NF, THF; 95%; v. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; 90% [397]. *c*) Bu_3SnH, AIBN, benzene; 56% of **195a**, 10% of **195b** [397]. *d*) i. Silica gel, CH_2Cl_2; 95%; ii. TBDMSCl, imidazole, CH_2Cl_2; 82%; iii. OsO_4, NMO, acetone, H_2O; 85%; iv. $NaIO_4$, THF, H_2O; 80%; v. $NaBH_4$, MeOH; 94%; vi. HCl, MeOH, H_2O; 95% [397].

A cobalt-catalysed radical-cyclisation/oxygenation of the iodide **198** (Scheme 2.1.26) with $NaBH_4$ under air gave the carba-pentofuranosides **199a** and **199b** in 69% yield and a ratio of 12:1 [387].

Scheme 2.1.26



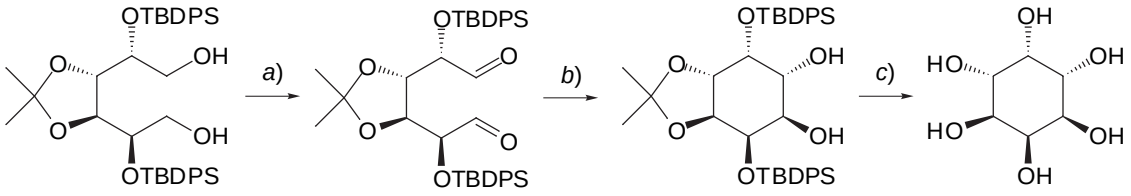
197 **198** **199a** **199b**

a) i.$NaBH_4$. ii. TsCl, pyridine. iii. NaI, HMPA; (yields not given) [387]. *b*) $NaBH_4$, Co(salen), NaOH, EtOH, under air; 64% of **199a**, 5% of **199b** [387].

The pinacol-type cyclisation of carbohydrate-derived α,ω-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_3SnH-initiated radical cyclisation of carbohydrate-derived ω-halo-oxime ethers, carbonyl-tethered oxime ethers, and of oxime ethers bearing an α,β-unsaturated ester in δ-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

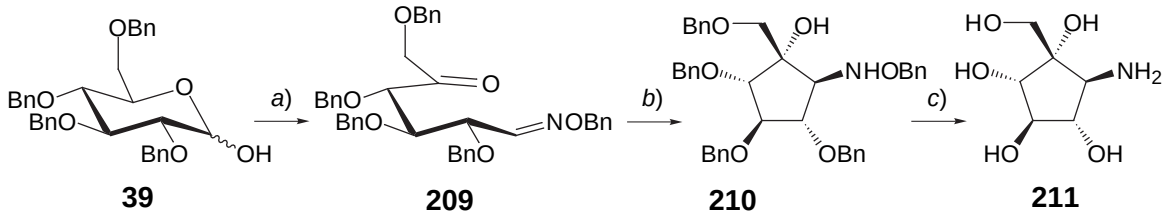


205 **206** **207** **208**

a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 [398]. *b*) SmI_2, *t*BuOH, THF; 79% (two steps) [398]. *c*) i. CF_3CO_2H, MeOH; ii. Bu_4NF, THF; 41% [398].

The trehazolamine 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

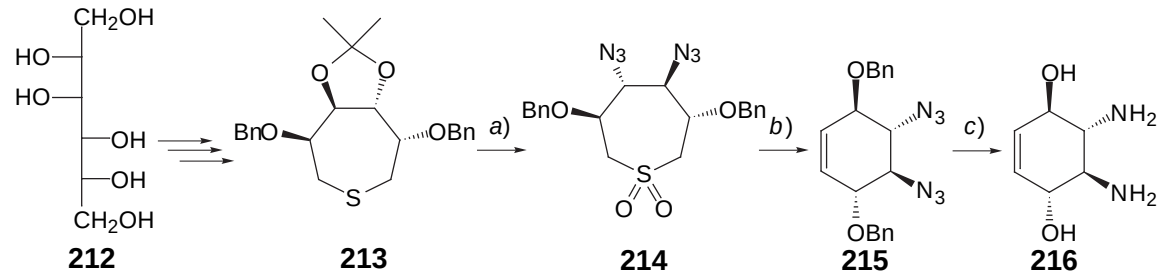


a) i. $BnONH_2 \cdot HCl$, pyridine, MeOH; ii. PCC, MS 3Å, NaOAc, CH_2Cl_2; 81% (two steps) [401]. *b*) SmI_2, THF, *t*BuOH; 80% [401]. *c*) H_2, $Pd(OH)_2/C$, EtOH, THF, CF_3CO_2H; 80% [400].

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].

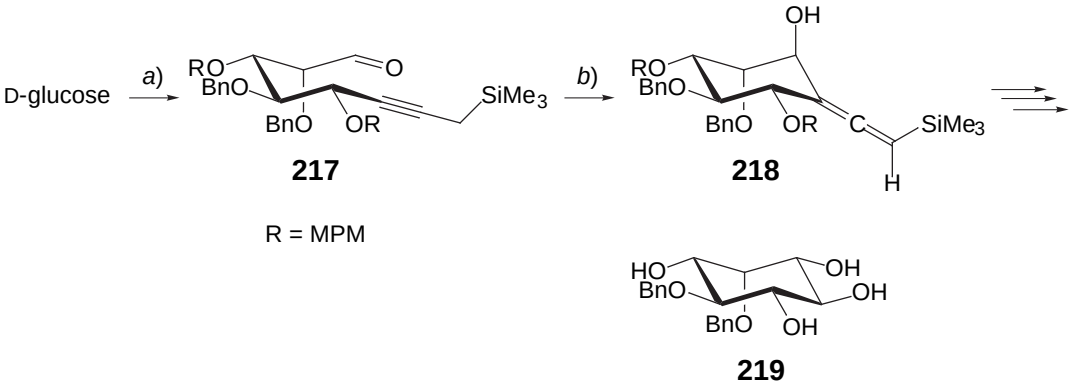
Scheme 2.1.29



a) i. CF_3CO_2H, H_2O, MeCN; 95%; ii. MsCl, pyridine; 92%; NaN_3, DMSO; 85%; iv. mCPBA, CH_2Cl_2; 98% [403]. *b*) KOH, CCl_4, *t*BuOH, H_2O; 61% [403]. *c*) i. Et_3N, 1,3-propanediol, MeOH; 68%; ii. BCl_3, CH_2Cl_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].

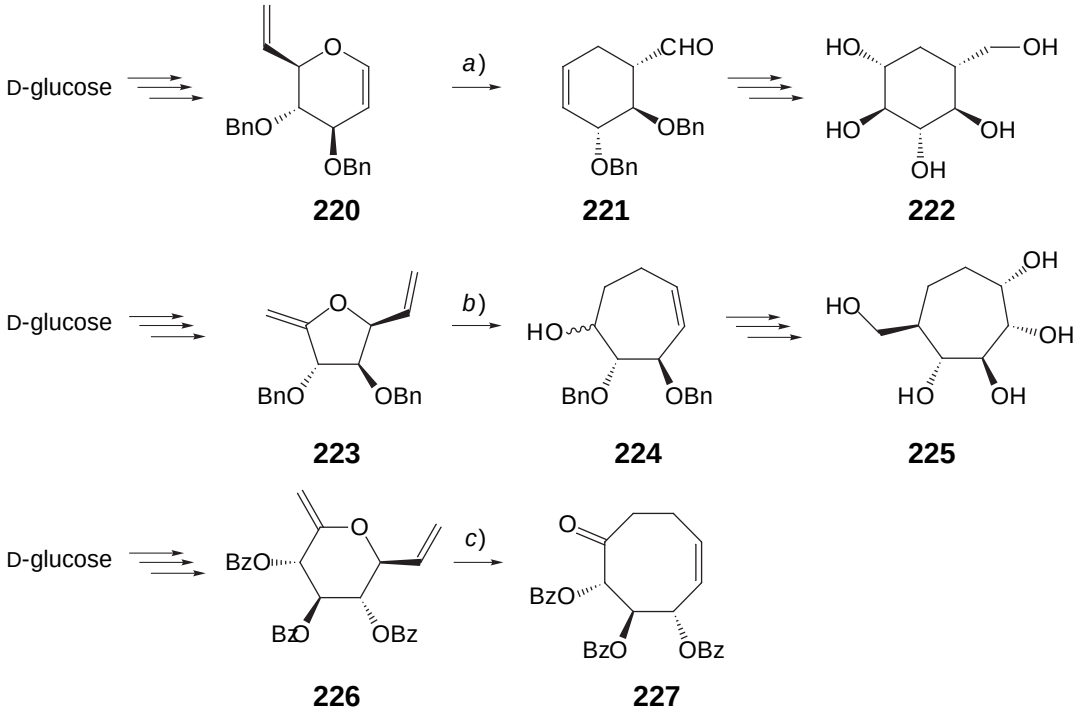
Scheme 2.1.30



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].

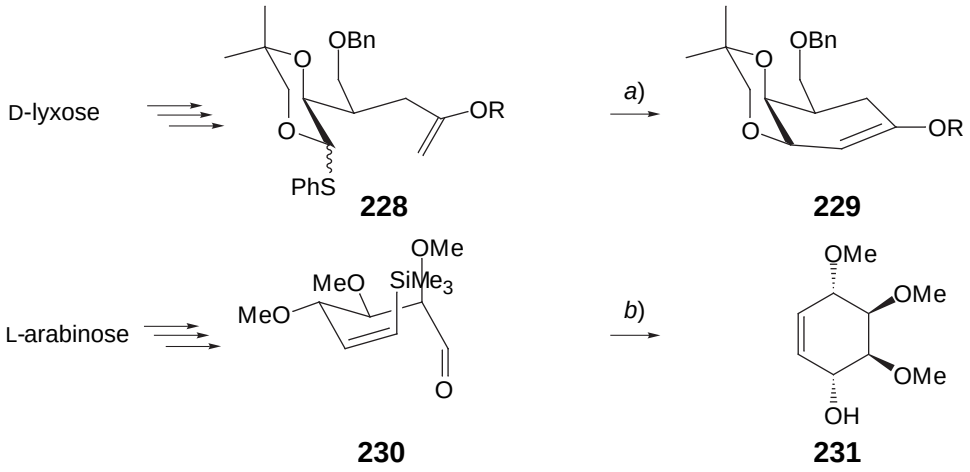
Scheme 2.1.31



a) *o*-Dichlorobenzene, 240°C; 84% [406]. *b*) *i*Bu3Al, 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]. $BF_3{\cdot}OEt_2$-activation of the aldehyde **230** gave the conduritol derivative **231** in 86% yield [410].

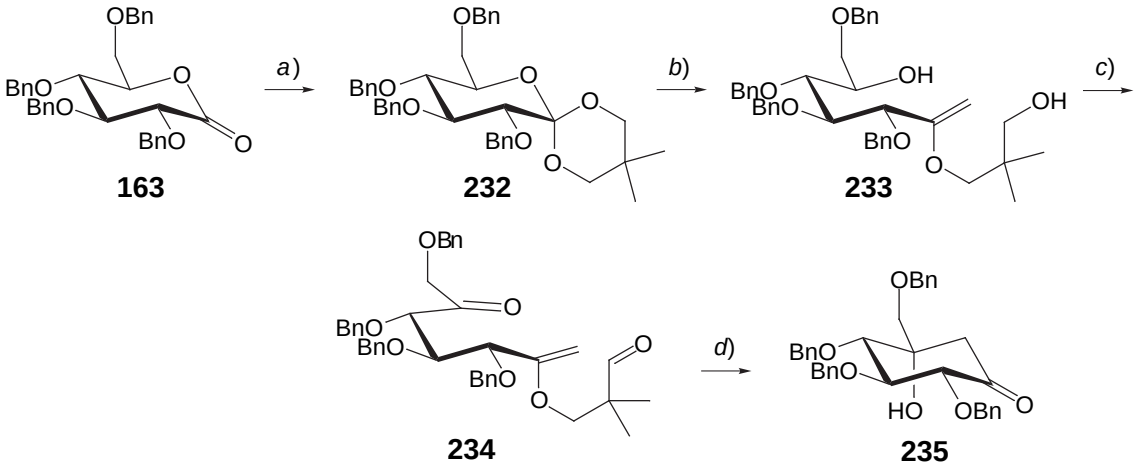
Scheme 2.1.32



a) MeOTf, 2,6-di-*tert*butyl-4-methylpyridine, CH_2Cl_2; 64 – 75% [409]. *b*) $BF_3{\cdot}OEt_2$, CH_2Cl_2; 86% [410].

Ohtake et al. reported a $ZnCl_2$-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



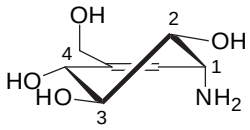
a) 2,2-Dimethyl-3,3-propanediol, TMSOMe, TMSOTf, toluene; 94% [411]. *b*) $AlMe_3$, CH_2Cl_2; 93% [411]. *c*) DMSO, Ac_2O [411]. *d*) $ZnCl_2$, THF, H_2O; 73% from **233** [411].

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.

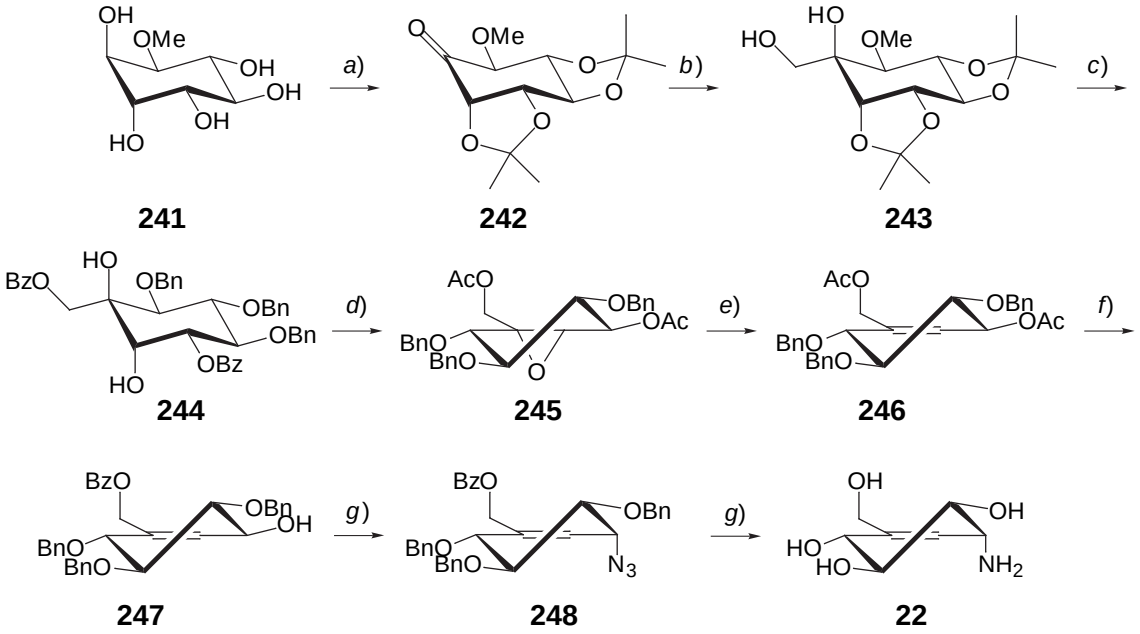
Figure 2.1.2: (+)-Valienamine.



22

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*, starting from L-quebrachitol (**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 HN_3/Ph_3P, followed by deprotection gave (+)-valienamine in an overall yield of 1% (21 steps).

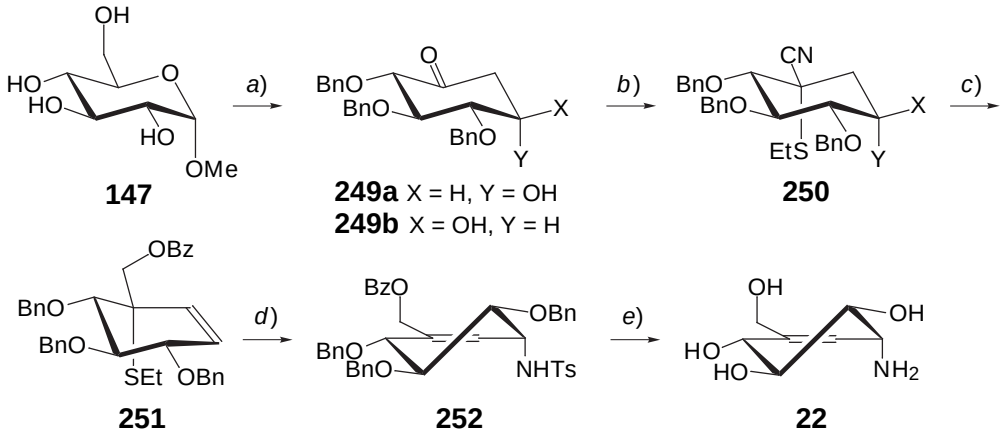
Scheme 2.1.34



a) i. 2,2-Dimethoxypropane, TsOH, DMF; 85%; ii. RuO_2, $NaIO_4$, K_2CO_3, CH_2Cl_2; 81% [415]. *b*) i. $Me_3SO^+I^-$, NaH, THF, DMSO; 57%; ii. KOH, dioxane, H_2O; 89% [415]. *c*) Six steps, 40% [415]. *d*) i. MsCl, pyridine; ii. NaOMe, MeOH; iii. Ac_2O, pyridine [415]. *e*) i. NaI, NaOAc, acetone, AcOH; ii. $POCl_3$, pyridine; 69% from **244** [415]. *f*) i. NaOMe, MeOH; 93%; ii. BzCN, Et_3N, MeCN; 54% [415]. *g*) HN_3, Ph_3P, toluene; 70% [415]. *g*) i. NaOMe, MeOH; 92%; ii. Ph_3P, NH_3, MeOH; 61%; iii. Na, NH_3, 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 thioketals and substitution of an ethylthiogroup with a CN group. Transformation of the CN substituent into a benzoyloxymethyl group and elimination of H_2O 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.

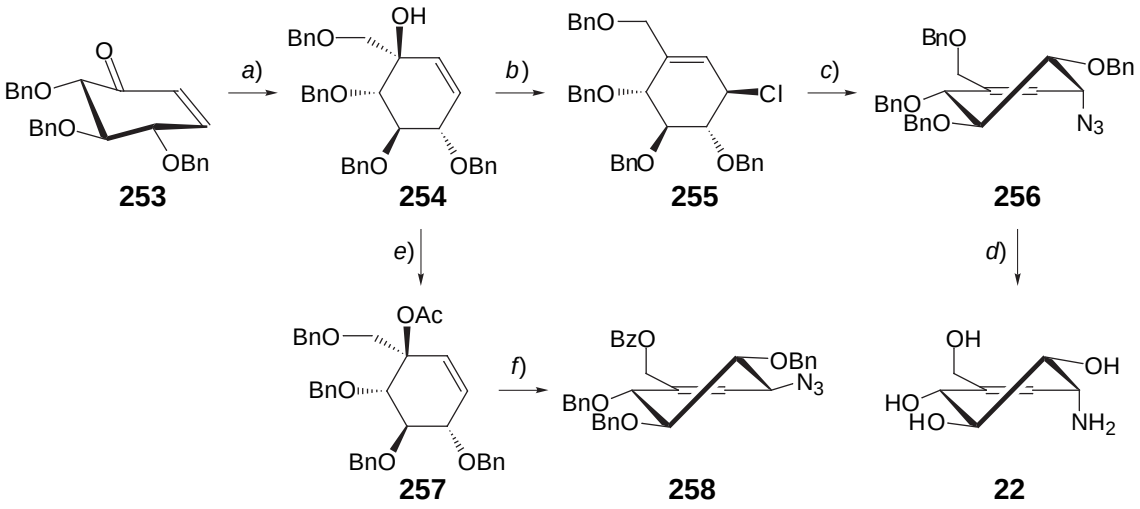
Scheme 2.1.35



a) Six steps (*Ferrier* cyclisation), 40%, **249a**/**249b** = 4:1 [416]. *b*) i. EtSH, HCl, MeOH; ii. Ac_2O, pyridine; 86% (two steps); iii. Me_3SiCN, $SnCl_4$, CH_2Cl_2; 85% [416]. *c*) i. DIBAH, CH_2Cl_2, petroleum ether; then H_2O 78%; ii. $LiAlH_4$, THF; 85%; iii. BzCN, Et_3N, MeCN; 73%; iv. Ph_3P, DEAD, toluene; 79% [416]. *d*) Chloroamine T, $BnEt_3NCl$, CH_2Cl_2; 78% [416]. *e*) Na, NH_3; 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 benzyloxymethylmagnesium chloride, providing the allylic alcohol **254**. A (formal) S_N2' reaction of **254** with $SOCl_2$ 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.

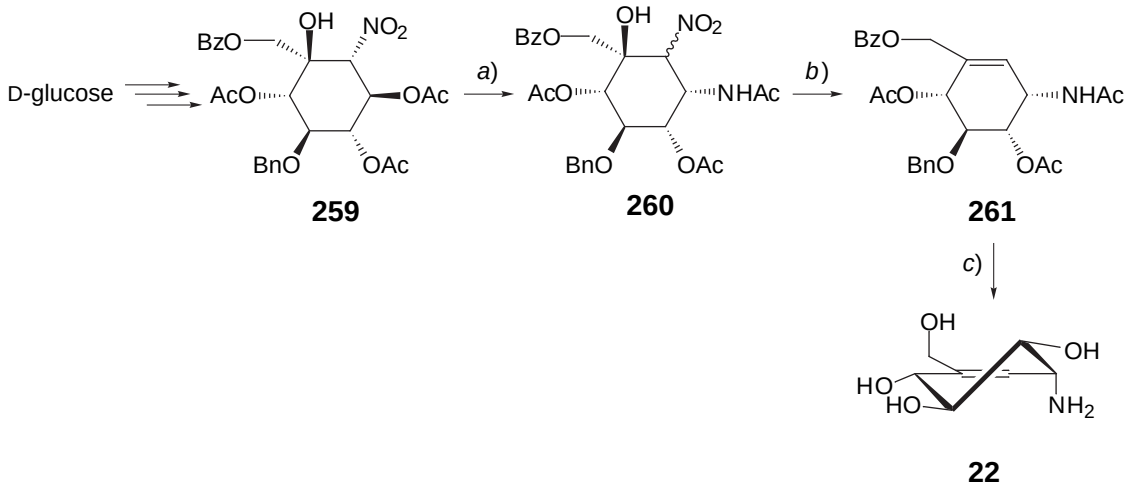
Scheme 2.1.36



a) $BnOCH_2MgCl$, THF; 75% [417]. *b*) $SOCl_2$, Et_2O; 81% [417]. *c*) NaN_3, DMF; 83% [417]. *d*) Na, NH_3, THF; 56% [417]. *e*) From **253**: $BnOCH_2MgCl$, THF, then Ac_2O; 73% [417]. *f*) NaN_3, $Pd(PPh_3)_4$, THF, H_2O; 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 NH_3, followed by acetylation gave the amide **260**. Removal of the nitro group and elimination of H_2O provided the valienamine derivative **261**, which was deprotected to give valienamine in 29% yield from **259**.

Scheme 2.1.37

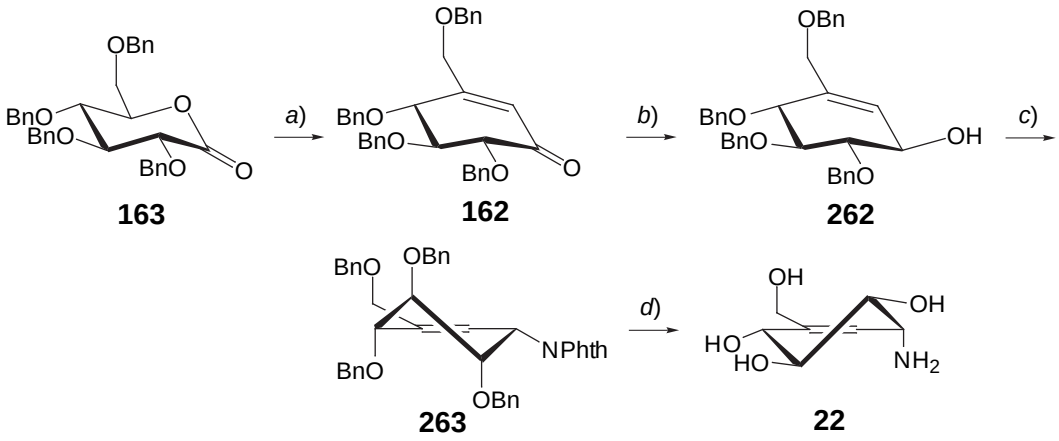


259 **260** **261** **22**

a) i. NH_3, THF; ii. Ac_2O, $TsOH \cdot H_2O$; 60% [418]. *b*) i. Bu_3SnH, AIBN, benzene; 60%; ii. $SOCl_2$, pyridine; 89% [418]. *c*) i. NaOMe, MeOH; ii. Na, NH_3; iii. Ac_2O, 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-gluconolactone 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-gluconolactone (8 steps). This was the most efficient synthesis of (+)-valienamine when we started our work.

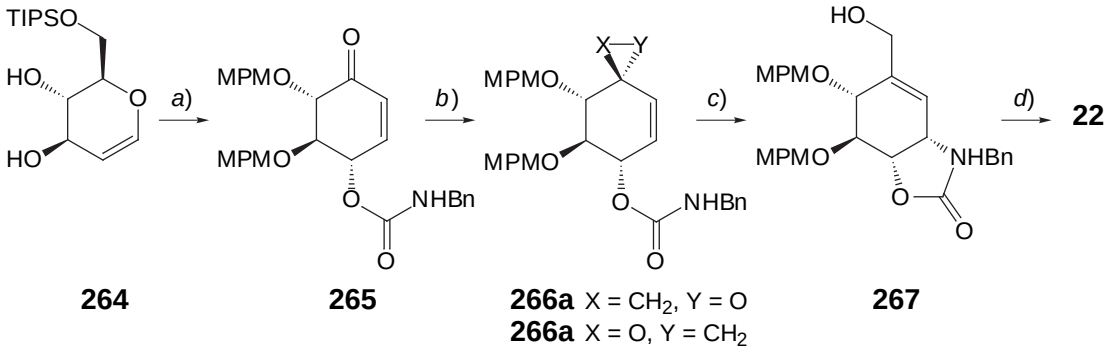
Scheme 2.1.38



a) Four steps, 64% [367] (see chapter 2.1.3.1). *b*) $NaBH_4$, $CeCl_3$, EtOH, THF; 75% [367]. *c*) Ph_3P, DEAD, phthalimide, THF; 52% [367]. *d*) i. $N_2H_4{\cdot}H_2O$, MeOH, THF; 74%; ii. Na, NH_3, 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 S_N2'-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).

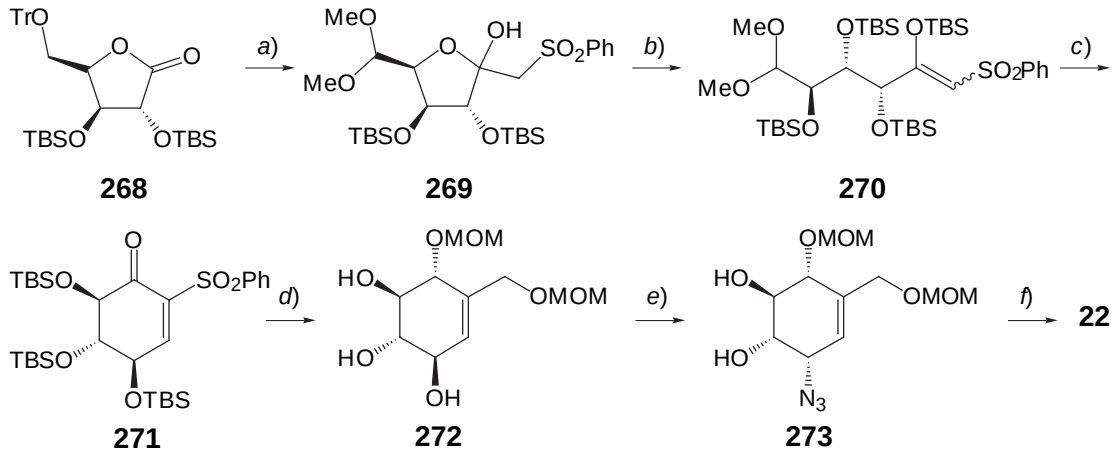
Scheme 2.1.39



a) 13 steps, 23% [420]. *b*) i. CH_2I_2, Zn, $TiCl_4$, THF, 46%; ii. mCPBA, $NaHCO_3$, CH_2Cl_2; 57% of **266a**, 28% of **266a** [420]. *c*) KHMDS, 18-K-6, THF; 75% [420]. *d*) i. Na, NH_3, THF; iii. LiOH, EtOH, H_2O; 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 $SnCl_4$ as the key steps [421]. The hydroxymethyl side chain was introduced by treatment of **271** with Bu_3SnLi and formaldehyde; the reaction was thought to proceed by a conjugated addition of Bu_3Sn^- to **271**, trapping of the resulting anion with formaldehyde, and elimination of Bu_3Sn and SO_2Ph [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).

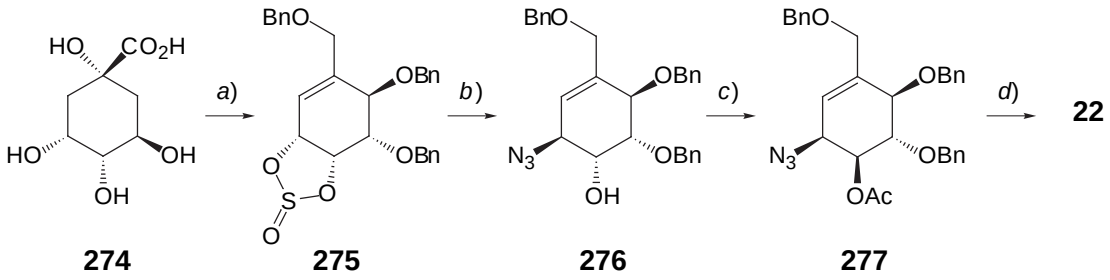
Scheme 2.1.40



a) Four steps, 54% [421]. *b*) TBSOTf, 2,5-lutidine, CH_2Cl_2; 92% [421]. *c*) $SnCl_4$, CH_2Cl_2; 70% [421]. *d*) i. Bu_3SnLi, H_2CO, THF; 84%; ii. $Zn(BH_4)_2$, Et_2O; 80%; iii. MOMCl, Bu_4NI, *i*Pr_2EtN, dichloroethane; 85%; iv. H_2, Raney-Ni, H_2O, dioxane; 97% [421]. *e*) HN_3, Ph_3P, DEAD, THF; 81% [421]. *f*) i. H_2, Raney-Ni, H_2O, 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).

Scheme 2.1.41

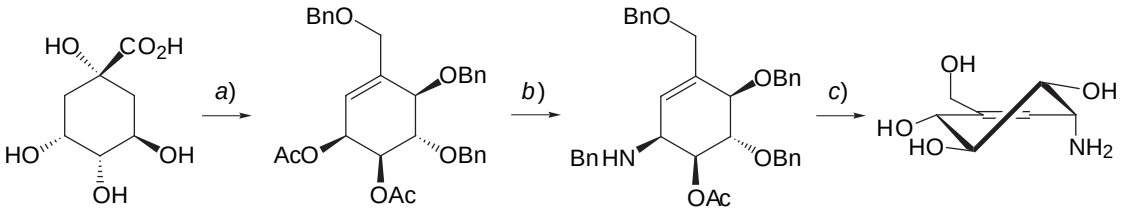


274 **275** **276** **277**

a) 11 steps, 16% [422]. *b*) LiN_3, DMF; 80% [422]. *c*) i. MsCl, Et_3N, CH_2Cl_2; 98%; ii. Bu_4NOAc, DMF; 81% [422]. *d*) i. MeOH, K_2CO_3; 100%; ii. Ph_3P, pyridine, NH_4OH; 97%; iii. Na, NH_3; 68% [422].

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).

Scheme 2.1.42



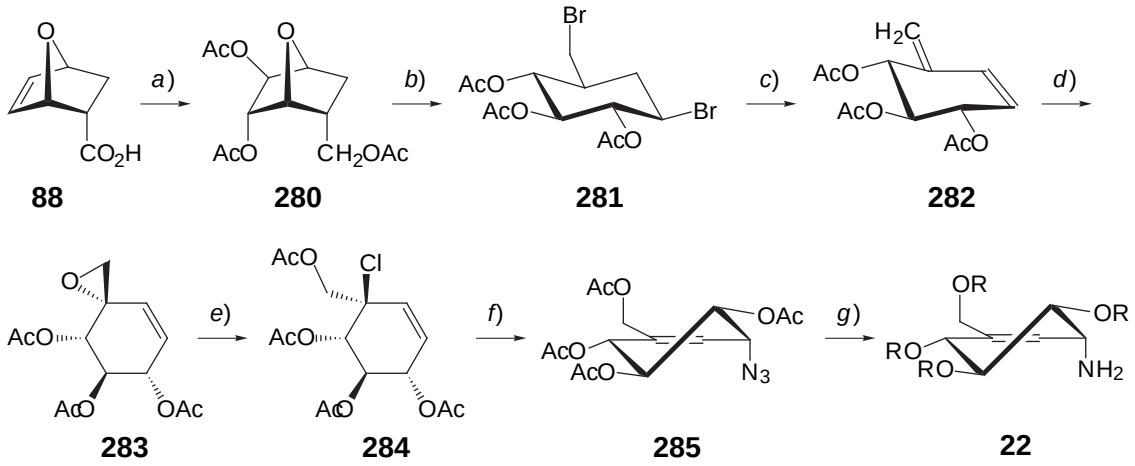
274 **278** **279** **22**

a) 16 steps, 26% [423]. *b*) $Pd(PPh_3)_4$, Ph_3P, $BnNH_2$, MeCN; 65% [423]. *c*) i. NaOMe, MeOH; 92%; ii. Na, NH_3, THF; 69% [423].

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 S_N2' 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].

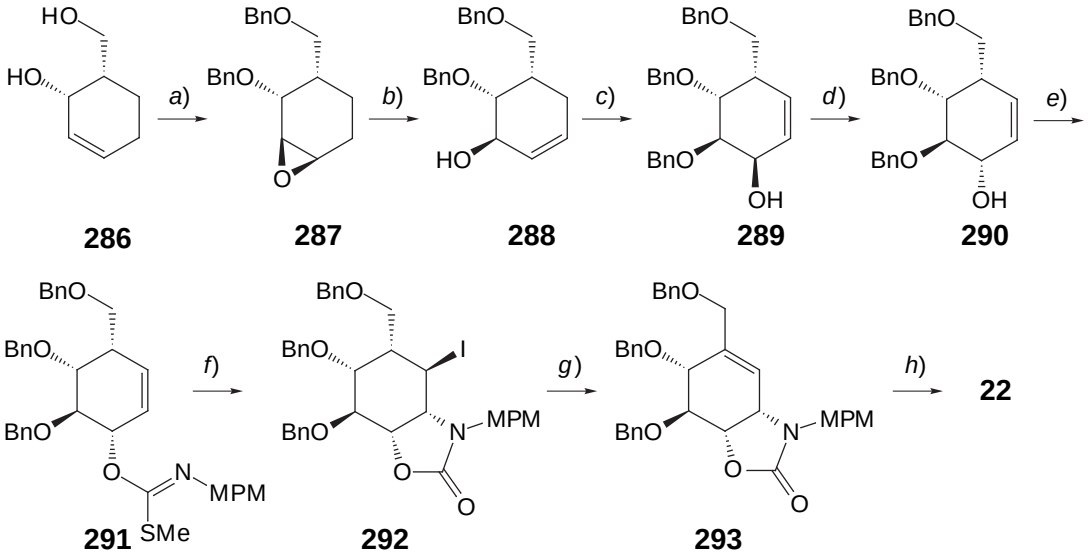
Scheme 2.1.43



a) i. H_2O_2, HCO_2H, H_2O; 66%; ii. $LiAlH_4$, THF; iii. Ac_2O, pyridine; 76% (two steps) [282]. *b*) HBr, AcOH; 53% [282]. *c*) DBU, toluene; [427]. *d*) mCPBA, CH_2Cl_2; 27% of **283** from **281** (plus 12% of its diastereoisomer) [427]. *e*) i. HCl, THF, H_2O; ii. Ac_2O, pyridine; 92% [427]. *f*) NaN_3, DMF; 99% [427]. *g*) i. H_2S, pyridine, H_2O; ii. Ac_2O, 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

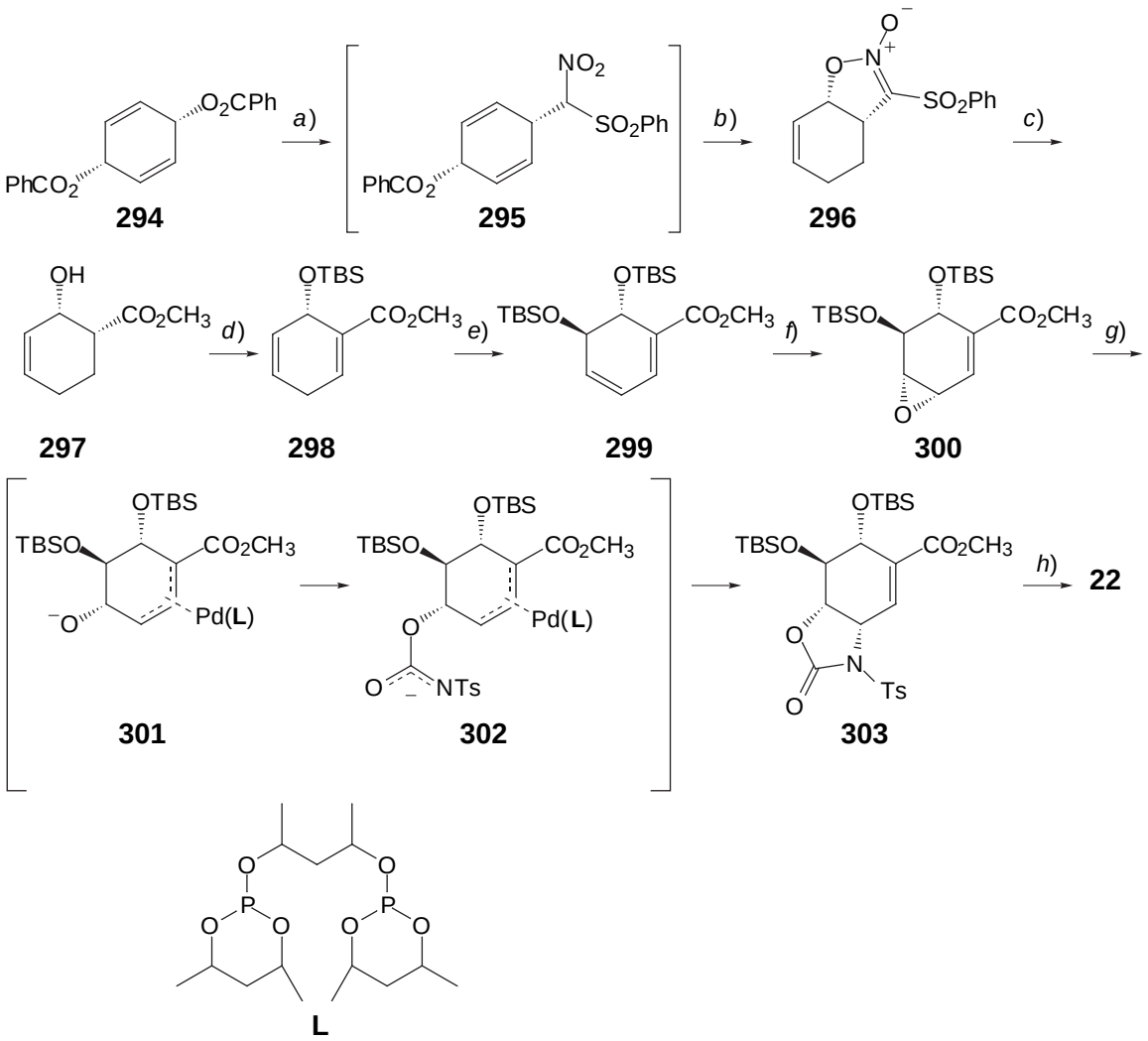


a) i. NaH, BnBr, THF, HMPA; ii. mCPBA, CH_2Cl_2; 83% (two steps) [428]. *b*) i. PhSeNa, EtOH, THF; ii. mCPBA, CH_2Cl_2; iii. *i*Pr_2EtN, toluene, 45°; 86% (three steps) [428]. *c*) i. mCPBA, CH_2Cl_2; ii. NaH, BnBr, THF, HMPA; 82% (two steps); iii. PhSeNa, EtOH, THF; iv. mCPBA, CH_2Cl_2; v. *i*Pr_2EtN, toluene, 70°, 74% (three steps) [428]. *d*) i. $PhCO_2H$, DEAD, Ph_3P; ii. KOH, THF, EtOH, H_2O; 84% (two steps) [428]. *e*) KH, 4-methoxybenzylisothiocyanate, THF, then MeI [428]. *f*) I_2, THF, molecular sieves, then aq. Na_2SO_3; 65% from **290** [428]. *g*) mCPBA, CH_2Cl_2; 71% [428]. *h*) i. CAN, SiO_2, aq. MeCN; ii. KOH, MeOH, H_2O; iii. Na, NH_3, 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



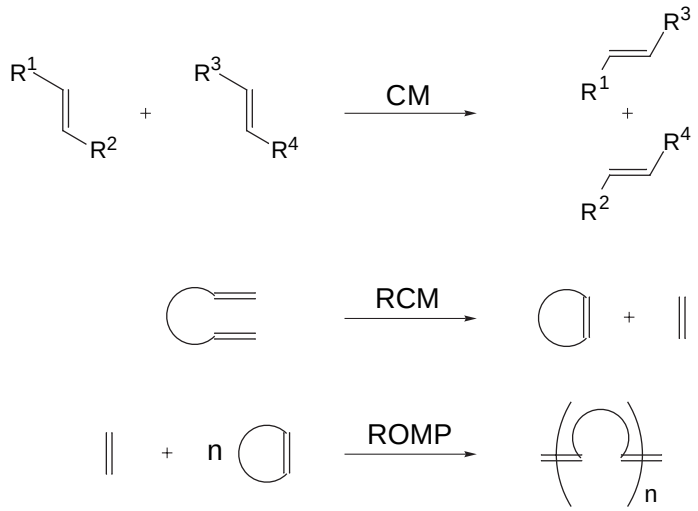
a) $PhSO_2CH_2NO_2$, $(Pd(all)Cl)_2$, (1*S*,2*S*)-bis[(diphenylphosphino)benzamido]cyclohexane, $NaHCO_3$, THF, H_2O [429]. *b*) $Pd_2(dba)_3{\cdot}CHCl_3$, Ph_3P, THF; 87% (two steps) [429]. *c*) i. $SnCl_2{\cdot}H_2O$, MeCN, then KF, Et_2O; 88%; ii. K_2CO_3, MeOH; 57% from **296**; iii. $Mo(CO)_6$, $B(OH)_3$, MeCN, MeOH, H_2O; 61% [429]. *d*) i. LDA, THF, then PhSeSePh; 54%; ii. TBDMSCl, imidazole, DMAP, CH_2Cl_2; 86.5%; iii. mCPBA, $CaCO_3$, CH_2Cl_2; 92% [429]. *e*) i. mCPBA, $NaHCO_3$, CH_2Cl_2; 48% from **297**; ii. TBDMSCl, DBU, DMAP, CH_2Cl_2; 90% [429]. *f*) mCPBA, $NaHCO_3$, CH_2Cl_2; 88% [429]. *g*) $Pd(OAc)_2$, **L** (configuration of the ligand not given), BuLi, TsNCO, Me_3SnOAc, THF; 54% [429]. *h*) i. DIBAL-H, CH_2Cl_2, then NaOMe, MeOH; ii. HF, H_2O, MeCN; Na, NH_3; 31% from **303** [429].

Of these syntheses, the one by *Fukase* and *Horii* appears to be the most efficient, providing (+)-valienamine in 12% overall yield and 8 steps from tetra-*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 $TiCl_4$ 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. WCl_6/Et_3Al) [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 WCl_6/Et_3Al 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].

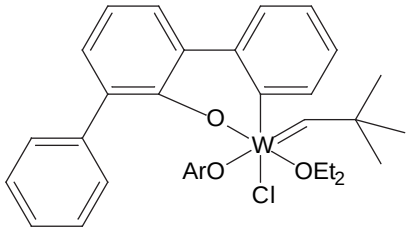
Since the 1960's, alkene metathesis has been successfully applied in the chemical industry to the production of bulk and fine chemicals (reviewed in [437] [448], novel industrial applications of alkene metathesis using homogeneous catalysts were recently reviewed [449]). Application of the *Philips* 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 WCl_6 and Me_4Sn [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].

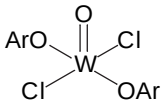
2.2.1. Ring-Closing Alkene Metathesis

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 [$(Ph_3P)_2Cl_2(NO)_2Mo$] and $Me_3Al_2Cl_3$ 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 $Bu_4N[Mo(CO)_5COPh]$ 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 WCl_6/Me_4Sn catalyst [451]. An RCM of diallyl ether to 2,5-dihydrofuran and of allyl 3-butenyl ether to 2,3-dihydro-α-pyrane 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 WCl_6 and Cp_2TiMe_2 in benzene [450]. RCM of di(8-heptadecenyl)ketone failed both with this catalyst and with the WCl_6/Me_4Sn 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 $WCl_6/SnCl_4$ 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 $Re_2O_7/SiO_2{\cdot}Al_2O_3$ and Bu_4Sn [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 $MeReO_3$ on silica gel/aluminium oxide [464], a synthesis of 3-cyclopentenecarboxylic esters from diallyl acetic acid esters using a homogeneous WCl_6/1,1,3,3-tetramethyl-1,3-disilacyclobutane catalyst [465], and the syntheses of 3-methylcyclopentene from citronellene and of 3-cyclopentenecarboxylic esters from diallyl acetic acid esters by RCM in the presence of the oxo-tungsten complex **309** and Et_4Pb [466].

Scheme 2.2.2



308 Ar = 2,6-diphenyl-phenyl



309 Ar = 2,6-Br_2-C_6H_3

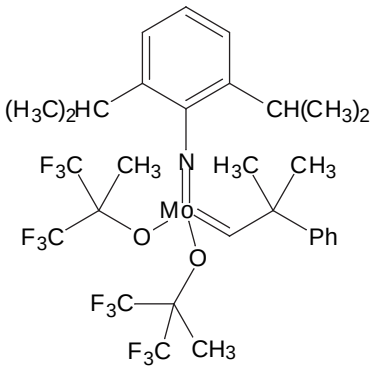
The modern use of ring-closing alkene metathesis can be traced back to a series of papers by *Grubbs* and coworkers who demonstrated the selective, high-yielding ring-closing alkene metathesis of functionalised dienes to unsaturated (double bond substituted) 5-, 6-, and 7-membered oxygen heterocycles (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.

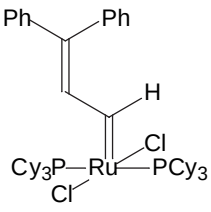
Consequently, less sensitive catalysts were searched for, and *Grubbs* and coworkers developed the ruthenium alkylidene-complexes **311** [476] and **312**, known as the *Grubbs's* catalysts [477 – 479]. These complexes are moderately stable to air and moisture and therefore more easy to handle than 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.

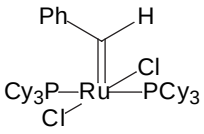
Scheme 2.2.3



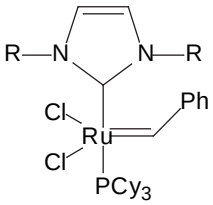
310

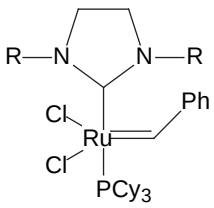


311



312





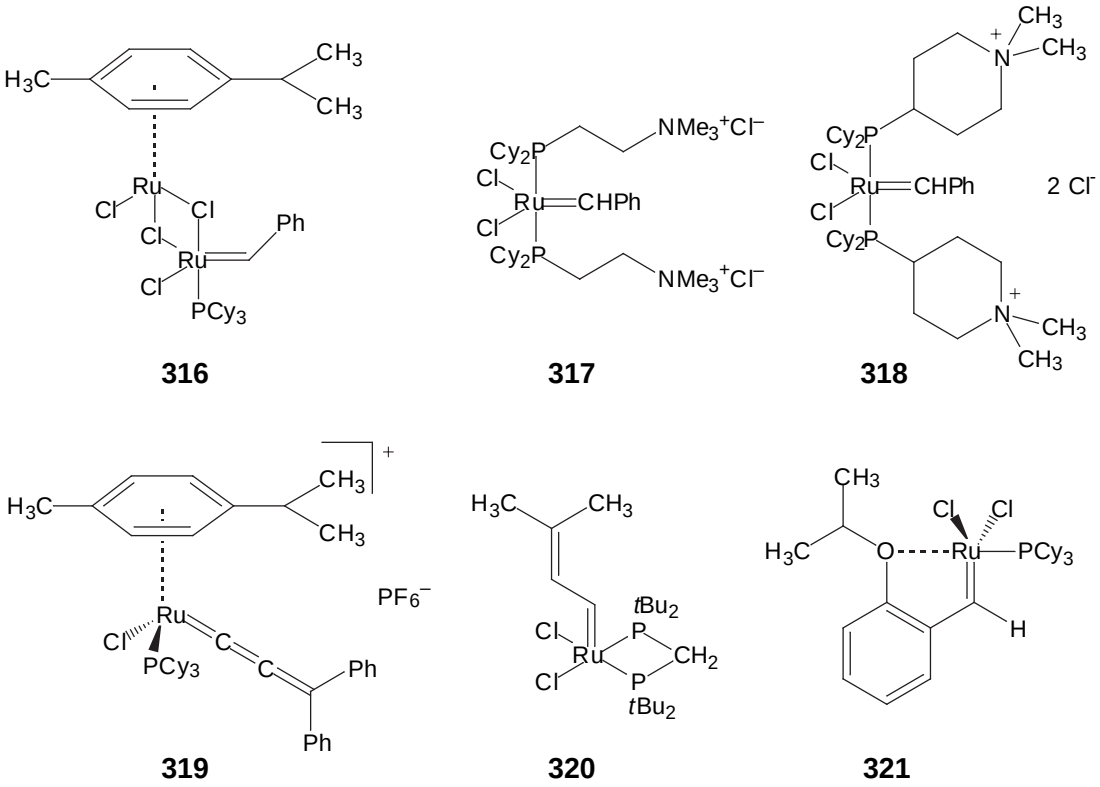
313 R = 2,4,6-$(CH_3)_3$-C_6H_2 **315** R = 2,4,6-$(CH_3)_3$-C_6H_2

314 R = (*R*,*R*)-1-Phenylethyl

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*-cymene)$RuCl_2]_2$ and PCy_3 under neon light [497].

Scheme 2.2.4



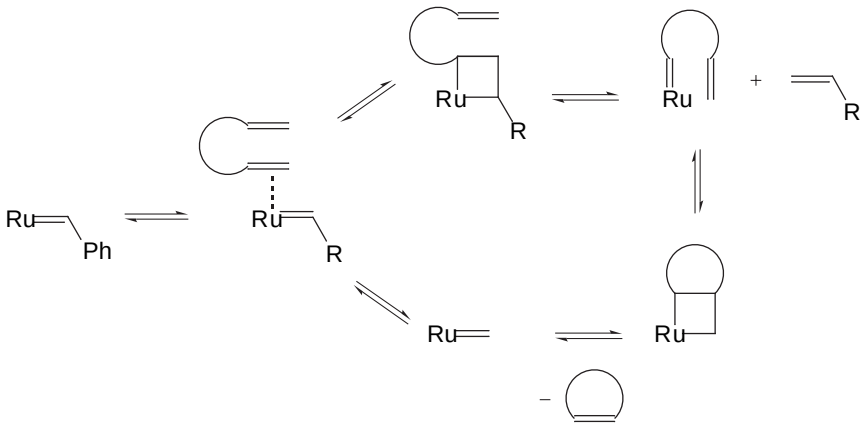
316 **317** **318**

319 **320** **321**

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].

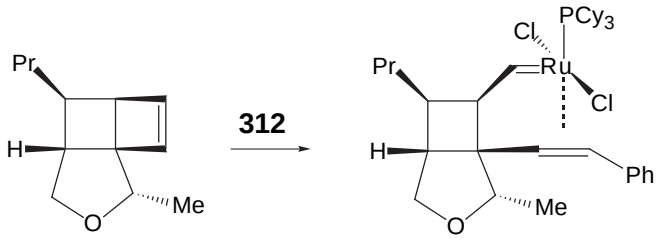
Scheme 2.2.5



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].

Scheme 2.2.6

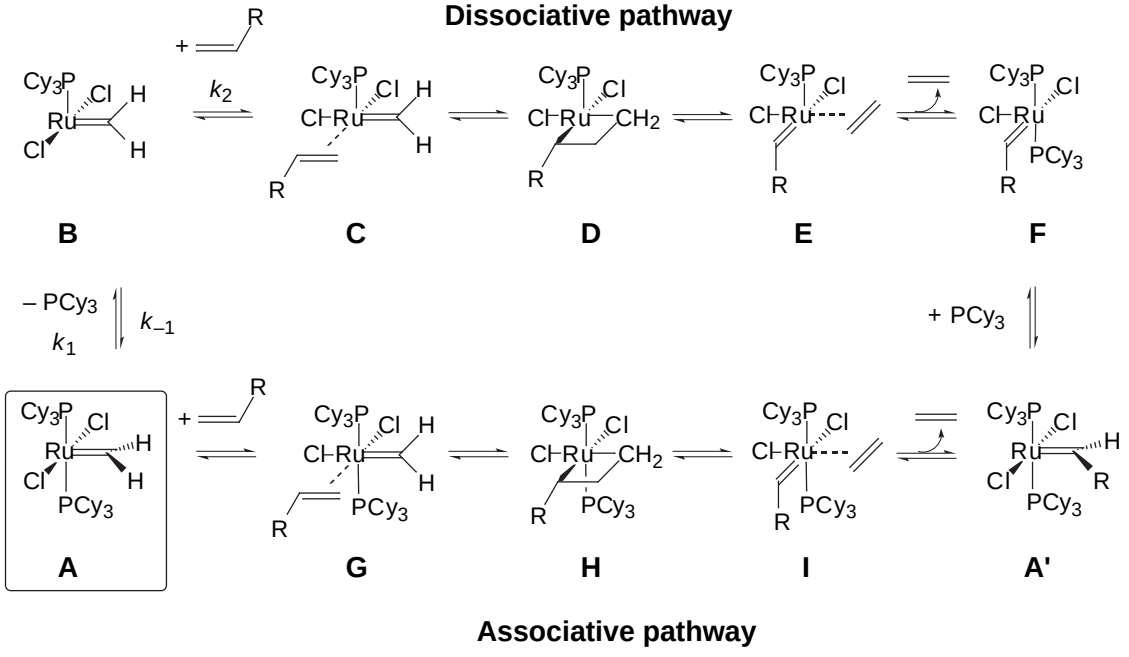


322 **323**

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.

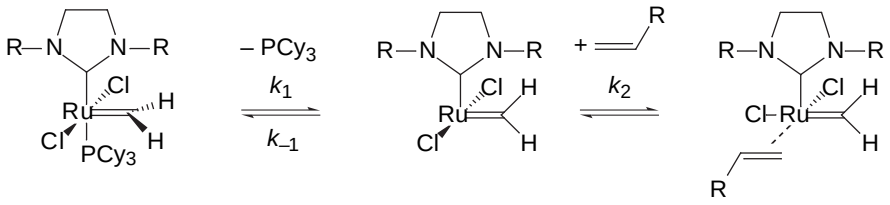
Scheme 2.2.7



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 *Adlhart* 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

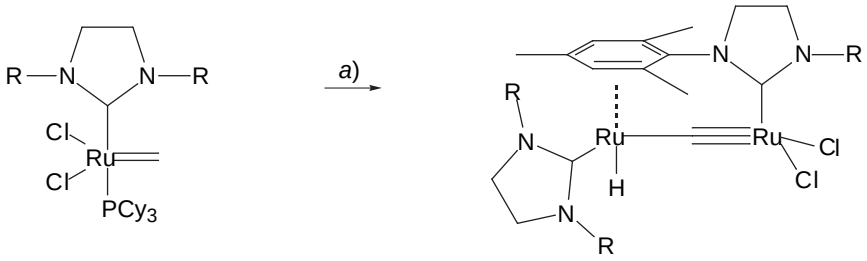


J **K** **L**

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 **313** denatures more rapidly during RCM than **312**. Recently, the dinuclear ruthenium complex **M** (Scheme 2.2.9) and methyl tricyclohexyl phosphonium chloride were identified as products of the decomposition of the methylidene complex **315a**, and a mechanism of catalyst decomposition was postulated [507].

Scheme 2.2.9



315a R = 2,4,6-$(CH_3)_3$-C_6H_2 **M** R = 2,4,6-$(CH_3)_3$-C_6H_2

a) Benzene, 55°C; 46% [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].

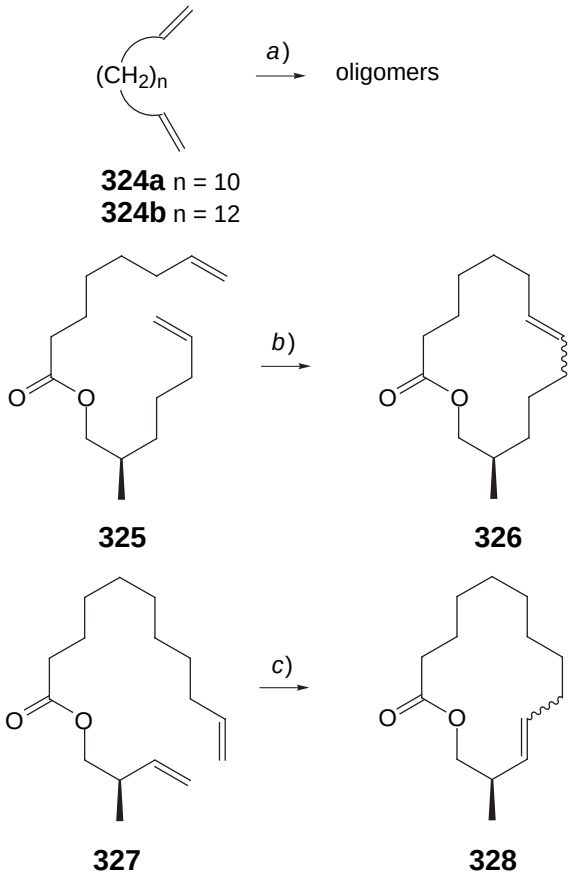
Grubbs's catalyst **312** also catalyses the *Kharasch* addition of $CHCl_3$ and CCl_4 to alkenes [514 – 516] and atom transfer radical polymerisations, both radical processes, as corroborated by the effect of radical reaction inhibitors. *Amir-Ebrahimi et al.* demonstrated the formation of radicals 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



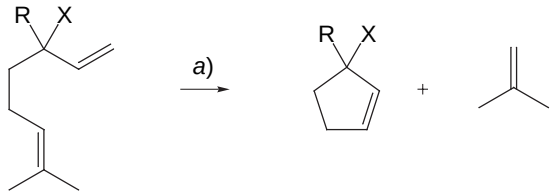
a) **311**, CH_2Cl_2 [520]. *b*) **311**, CH_2Cl_2; 72% [520]. *c*) **311**, CH_2Cl_2; 10% [520].

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



329 **330**

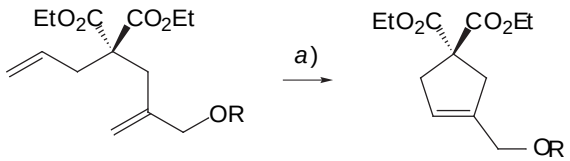
a) **312**, $CDCl_3$; see Table 2.2.1 [522].

Table 2.2.1: RCM of **329.**

R	X	rel. reaction rate
H	OH	60
Me	OH	12
Me	H	8
H	OMe	1
Me	OMe	≈ 0

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



331a R = H
331b R = Ac

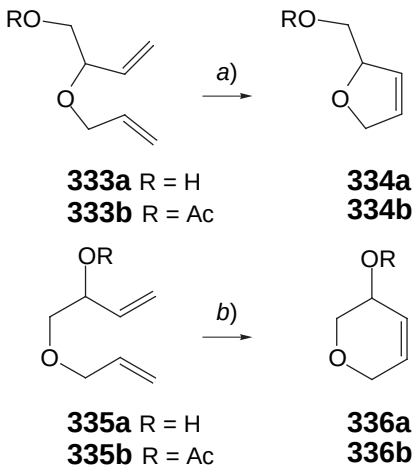
332a
332b

a) **312**, CH_2Cl_2; 98% of **332a**, 97% of **332b** [523].

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].

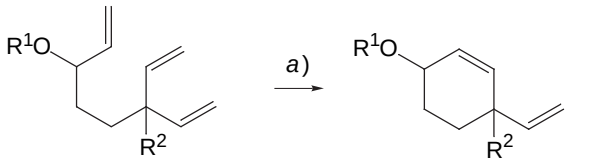
Scheme 2.2.13



a) **312**, CH_2Cl_2; 79% of **334a**, 98% of **334b** [524]. *b*) **312**, CH_2Cl_2; 87% of **336a**, 96% of **336b** [524].

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



337 R^2 = Me
338 R^2 = Et
339 R^2 = Ph

340 R^2 = Me
341 R^2 = Et
342 R^2 = Ph

R^1, see Table 2.2.2. *a*) **312**; see Table 2.2.2 [526].

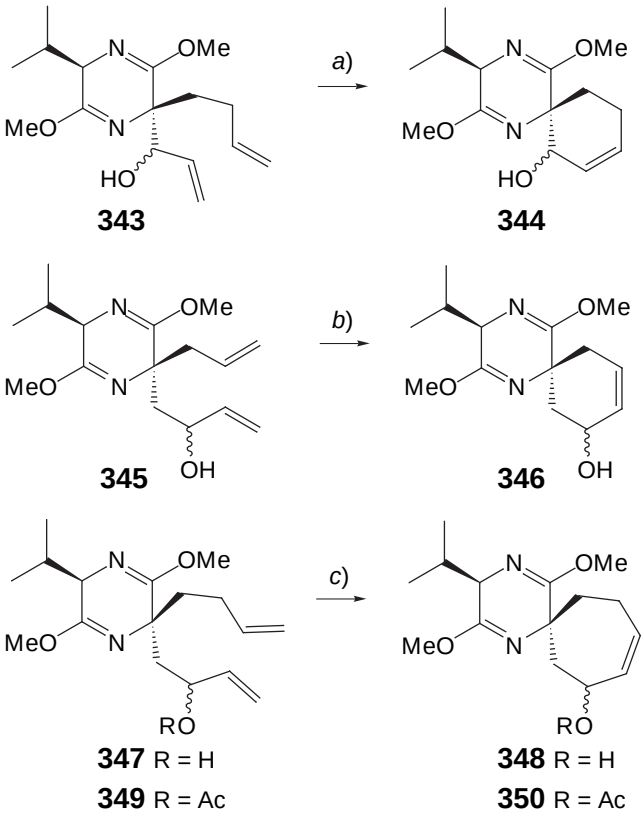
Table 2.2.2: RCM of the Dienes **337b-e**, **338b-e**, and **339b-e**.

Substrate	R^1	R^2	Yield (%)[a])	dr (1*RS*,4*SR*)
337b	Bn	Me	78	71:29
337c	TMS	Me	69	74:26
337d	MOM	Me	61	64:36
337e	Bz	Me	90	64:36
338b	Bn	Et	80	85:15
338c	TMS	Et	84	86:14
338d	MOM	Et	69	77:23
338e	Bz	Et	85	71:29
339b	Bn	Ph	87	56:44
339c	TMS	Ph	55	61:39
339d	MOM	Ph	88	62:38
339e	Bz	Ph	85	62:38

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



343 **344**

345 **346**

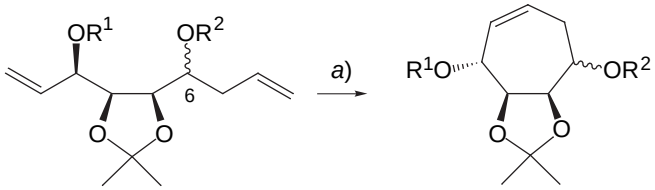
347 R = H **348** R = H

349 R = Ac **350** R = Ac

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 (6*S*)-diol (R^1 = R^2 = H) cyclised in good yield (85% after 6 h), RCM of the (6*R*)-diastereoisomer was sluggish (45% yield after 7 days). In contrast, the diacetate (R^1 = R^2 = Ac), the dibenzylether (R^1 = R^2 = Bn), and the 3-*O*-TBS-6-acetoxy derivative (R^1 = TBS, R^2 = Ac) of the 6*R*-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



351 **352**

R^1, R^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.

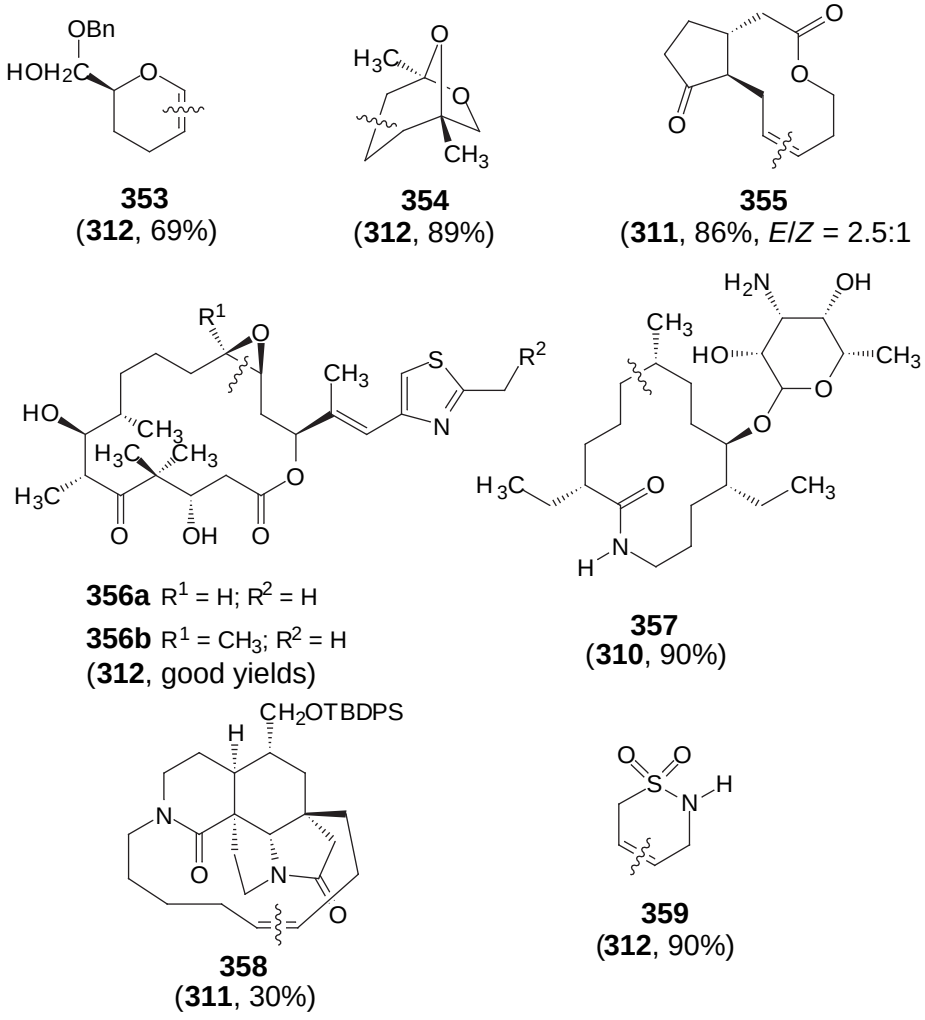
The starting dienes for RCM are readily available by *Wittig* alkenylation or alkenyl addition to carbonyl compounds, by elimination, or by rearrangement from other alkenes. The resulting cycloalkenes are much less readily available and yet very valuable and versatile intermediates, allowing electrophilic 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 B_1, **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].

Scheme 2.2.17



353
(**312**, 69%)

354
(**312**, 89%)

355
(**311**, 86%, *E*/*Z* = 2.5:1

356a R^1 = H; R^2 = H
356b R^1 = CH_3; R^2 = H
(**312**, good yields)

357
(**310**, 90%)

358
(**311**, 30%)

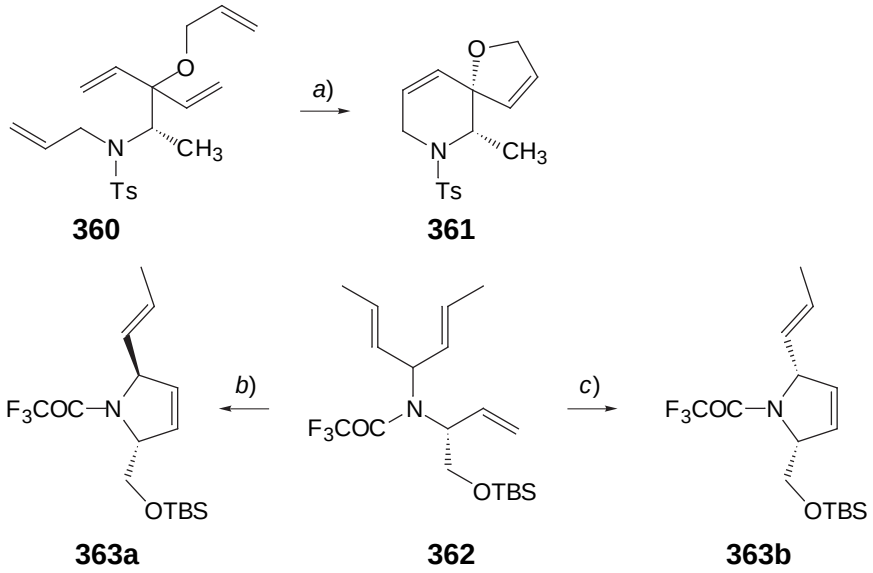
359
(**312**, 90%)

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[31]).

[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.

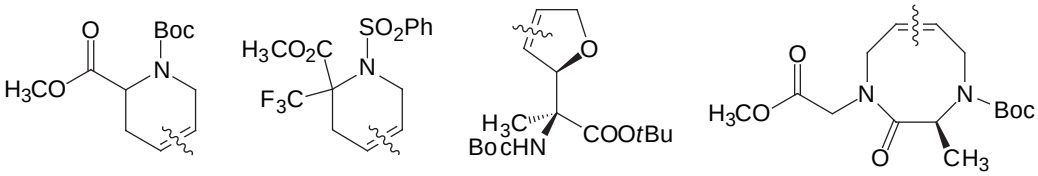
Scheme 2.2.18



a) **312**, $CHCl_3$, 74%, 92% d.e. [548]. *b*) **312**, benzene; 88%, 92% d.e. [525]. *c*) **310**, benzene; 97%, 72% d.e. [525].

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-^{Me}N-Ala-L-(3-butenyl)gly-D-^{Me}N-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 WCl_6-$EtAlCl_2$-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].

Scheme 2.2.19

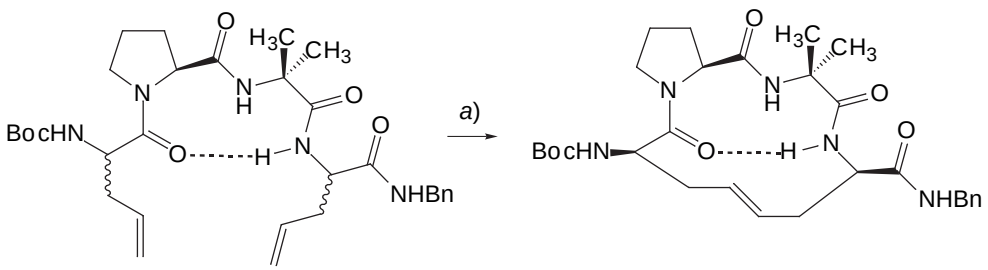


364 (**311**, 90%) **365** (**312**, 93%) **366** (**312**, 98%) **367** (**311**, 51%)

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.

Scheme 2.2.20



368 **369**

a) **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].

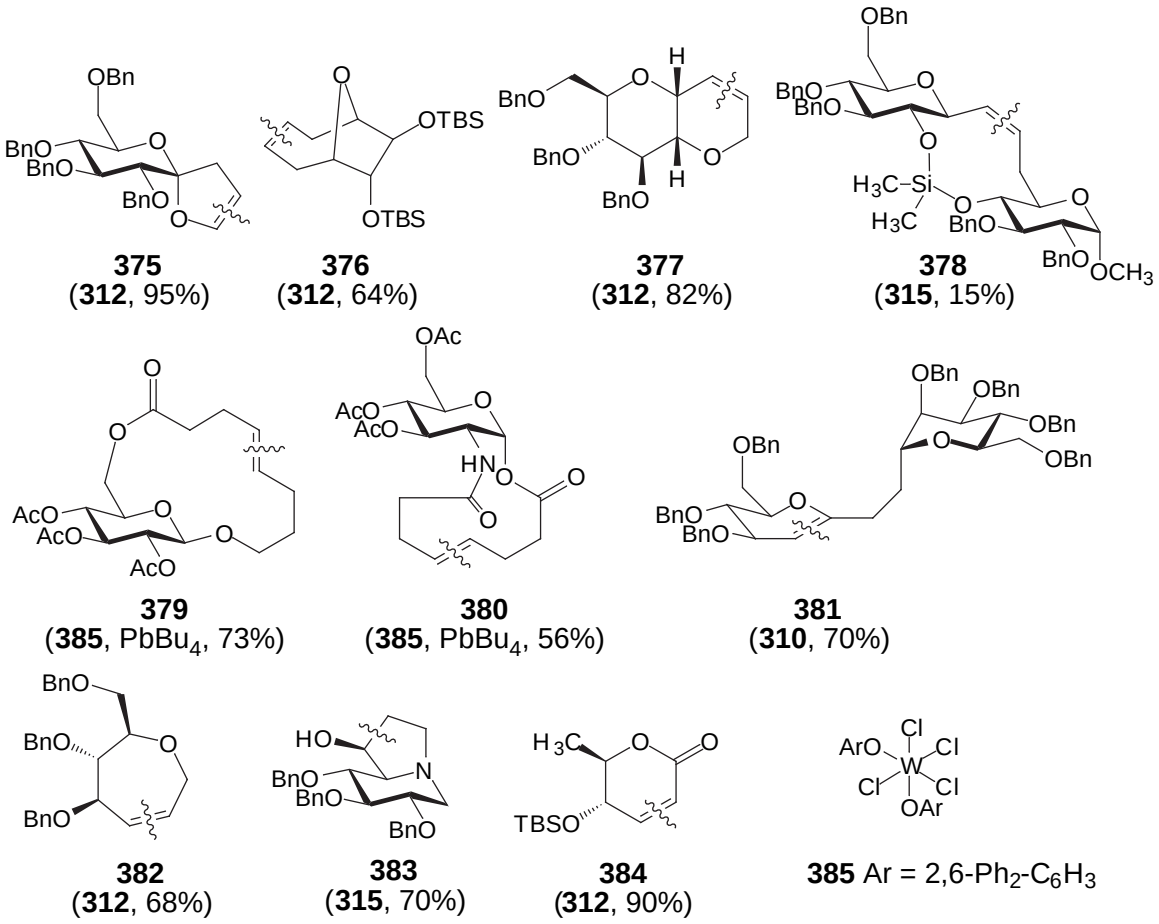
- The synthesis of a phosphonosugar [591].

- The synthesis of indolizidines, pyrrolizidines, quinolizidines [546] [592 – 594] (*e.g.* castanospermine (**383**) [595]), calystegin B_2 [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].

Scheme 2.2.21



375 (**312**, 95%) **376** (**312**, 64%) **377** (**312**, 82%) **378** (**315**, 15%)

379 (**385**, $PbBu_4$, 73%) **380** (**385**, $PbBu_4$, 56%) **381** (**310**, 70%)

382 (**312**, 68%) **383** (**315**, 70%) **384** (**312**, 90%) **385** Ar = 2,6-Ph_2-C_6H_3

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.

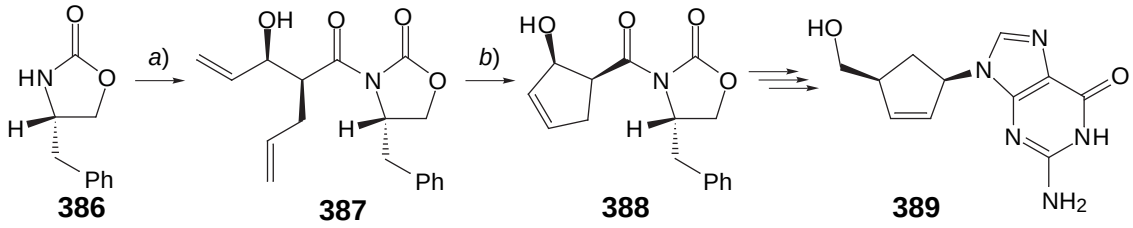
Several syntheses formed the aglycon or peripheral substituents of glycosides by RCM [614] [615]; carbohydrates also served as starting materials for syntheses involving an RCM [616 – 622].

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].

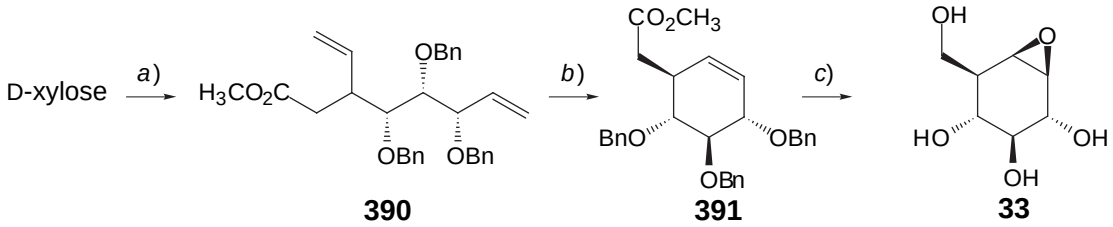
Scheme 2.2.22



a) i. BuLi, 4-pentenoic pivaloic mixed anhydride, THF; 99%; ii. Bu_2BOTf, Et_3N, acroleine, CH_2Cl_2; 82% [634]. *b*) 0.01 eq. of **312**, CH_2Cl_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

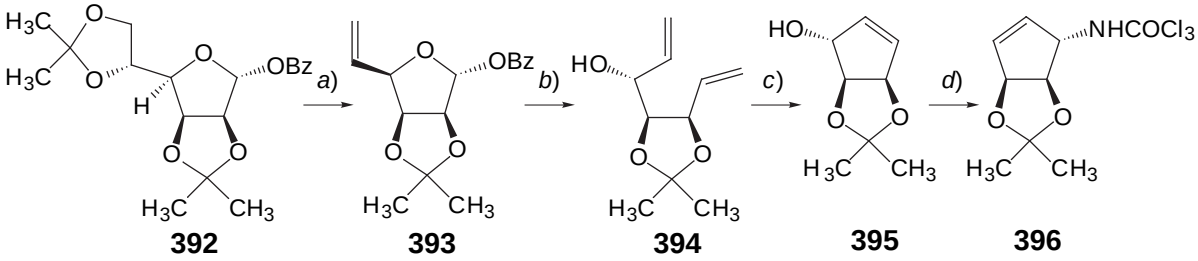


a) 9 steps, 32%; [220]. *b*) 0.14 eq. of **312**, CH_2Cl_2; 92% [220]. *c*) Seven steps, 31% [220].

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.

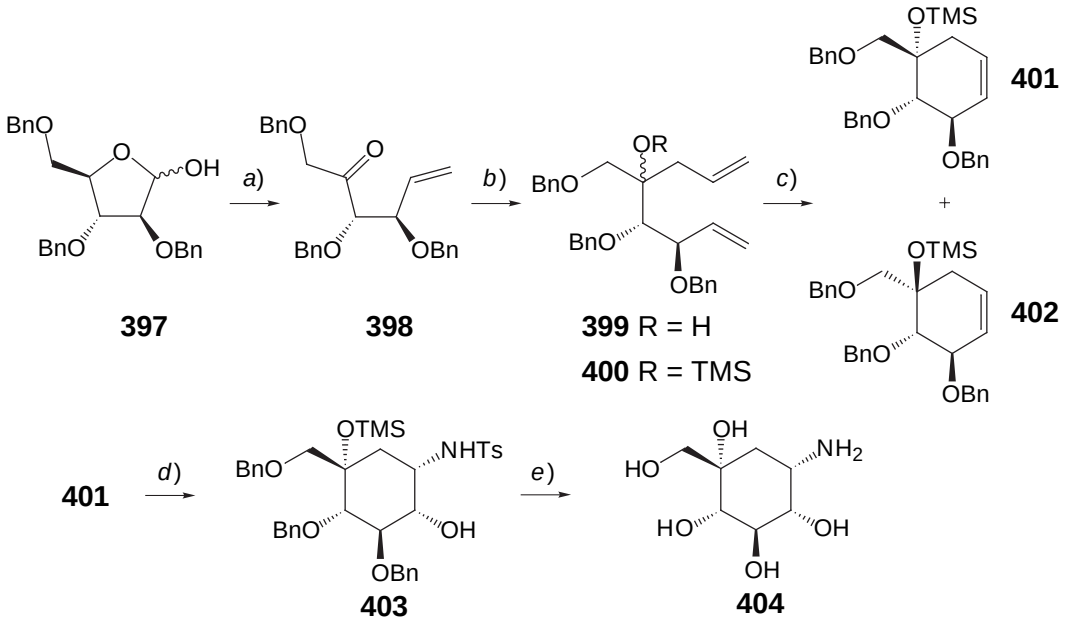
Scheme 2.2.24



a) i. aq. AcOH; ii. $HC(OEt)_3$, AcOH; iii. Ph_3CO_2H; 93% (three steps) [221]. *b*) i. KO*t*Bu, MeOH; 96%; ii. $Ph_3P{=}CH_2$, THF; 98% [221]. *c*) 0.005 eq. of **312**, CH_2Cl_2; 92% [221]. *d*) i. Cl_3CCN, DBU, CH_2Cl_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_2Cl_2 gave the hexenulose **398**. Addition of allylmagnesium bromide to **398** afforded in 97% yield a 7:3 mixture of the (5*S*) and (5*R*) 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.

Scheme 2.2.25



a) i. $Ph_3P{=}CH_2$, THF; 92%; ii. CrO_3, pyridine, CH_2Cl_2; 87% [639]. *b*) i. AllMgBr, THF; 97%; ii. TMSOTf, 2,6-lutidine; 82% of **400** [639]. *c*) 0.08 eq. of **310**, benzene; 42% of **401**, 19% of **402** [639]. *d*) i. Bu_4NF, THF; 92%; ii. OsO_4, chloramine T, Et_3BnNCl, $CHCl_3$, H_2O; 55% [639]. *e*) Na, NH_3; 50% [639].

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 carbafuranose from diallyl malonic acid diethyl ester [640] and to a carbafuranose and a carbapyranose from ω-unsaturated acyl sultams by analogy to the synthesis by *Crimmins* and *King* (*vide supra*) [641].

- Carbafuranoses 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* alkenlyation of

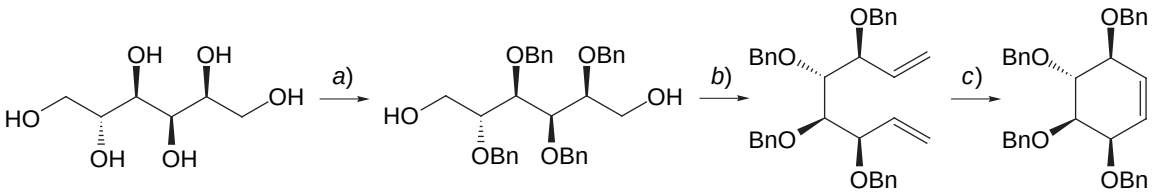
pyranoses or furanoses, followed by oxidation, or *Bernet-Vasella* fragmentation of 6-iodopyranosides or 5-iodofuranosides lead to enuloses whose carbonyl groups allowed the introduction of a second alkene group by *Wittig* alkenylation or addition of alkenyl *Grignard* reagents. Alternatively, oxidation 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

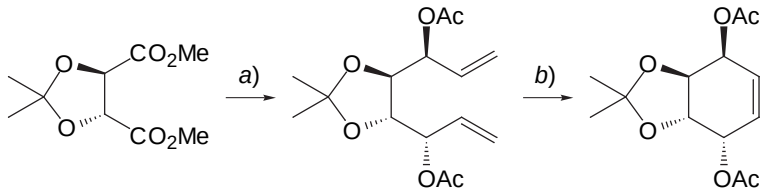


405 **406** **407** **408**

a) i. Monomethoxytrityl chloride, DMAP, pyridine; 85%; ii. BnBr, NaH, THF; 96%; iii. H_2SO_4, MeOH, CH_2Cl_2; 87% [509]. *b*) i. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; quant.; ii. $Cp_2Ti(Cl)(CH_2)AlMe_3$, THF, pyridine; 42% [509]. *c*) i. 0.05 eq. of **312**, CH_2Cl_2; 32%; ii. 0.05 eq. of **310**, CH_2Cl_2; 92%; iii. 0.05 eq. of **313**, CH_2Cl_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

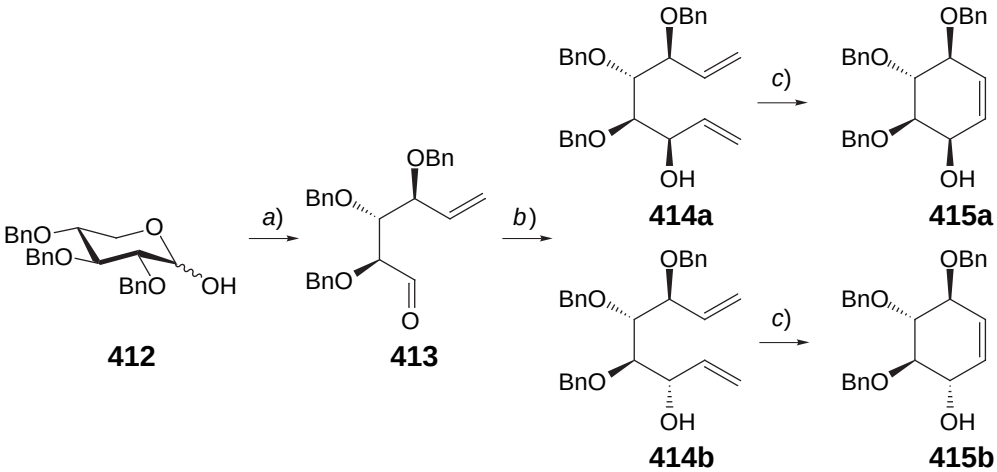


409 **410** **411**

a) i. DIBALH, toluene, then vinylmagnesium bromide; 42%; ii. Ac_2O, pyridine, CH_2Cl_2; 83% [509]. *b*) i. 0.2 eq. of **312**, CH_2Cl_2; 77%; ii. 0.01 eq. of **313**, CH_2Cl_2; 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* methylenation, 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

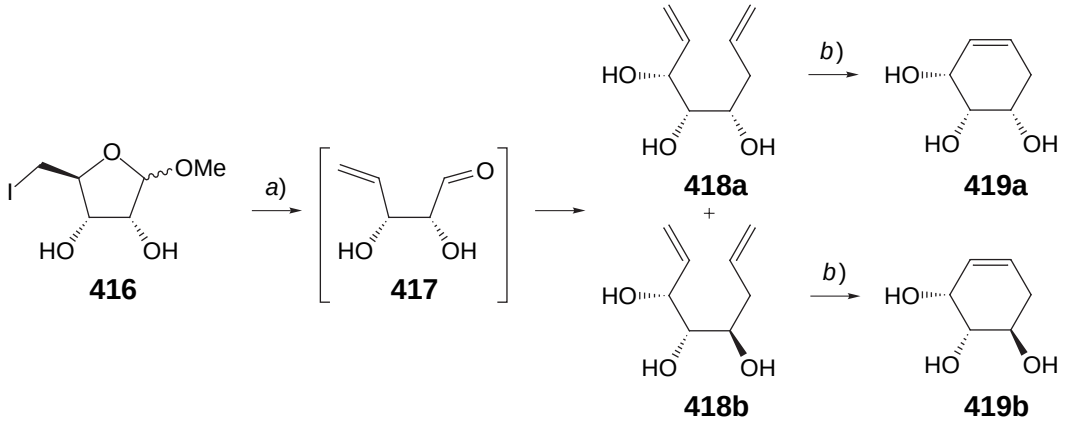


412 **413** **414a** **415a** **414b** **415b**

a) i. $Ph_3P{=}CH_2$, THF; ii. DMSO, $(COCl)_2$, CH_2Cl_2; yield not given [657]. *b*) vinylmagnesium bromide, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2; yield not given, **414a**:**414b** = 8:1 [657]. *c*) 0.1 eq. of **312**, CH_2Cl_2; 99% of **415a**, 95% of **415b** [657].

Hyldtoft et al. prepared cyclohexenes from methyl 5-deoxy-5-iodoribofuranosides (**416**)[32]) [655] (Scheme 2.2.29). A domino reaction comprised of a *Bernet-Vasella* fragmentation and a *Barbier* alkylation afforded the dienes **418a**,**b**. RCM of these dienes in the presence of 0.1 eq. of *Grubbs's* catalyst **312** gave the cyclohexenes **419a**,**b** in high yield.

Scheme 2.2.29

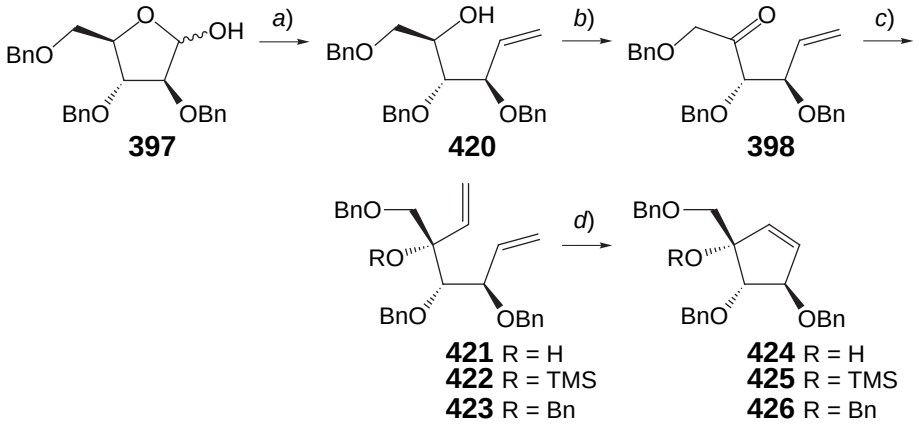


a) Zn, allBr, THF, H_2O; 30% of **418a**, 70% of **418b** [655]. *b*) 0.1 eq. of **312**, CH_2Cl_2; 96% of **419a**, 95% of **419b** [655].

After *Leclerc*[27]) had finished her diploma work on the synthesis of carbafuranoses, *Seepersaud et al.* [642] and *Sellier et al.* [643] independently reported an almost identical synthesis of carbafuranoses 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.

[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.

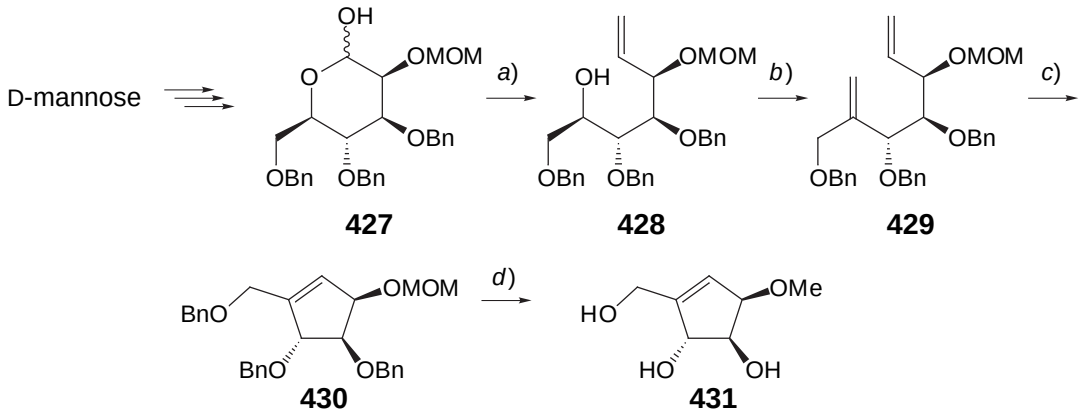
Scheme 2.2.30



a) BuLi, $Ph_3P{=}CH_2$, THF; 87% [642]. *b*) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; 90% [642]. *c*) i. Vinylmagnesium bromide, THF; 92% of **421** [642]; ii. 1. BnBr, NaH, Bu_4NI, DMF; 98% of **423** [642]; 2. TMSOTf, 2,6-lutidine; 94% of **422** [643]. *d*) 0.1 eq. of **310**, CH_2Cl_2; 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.

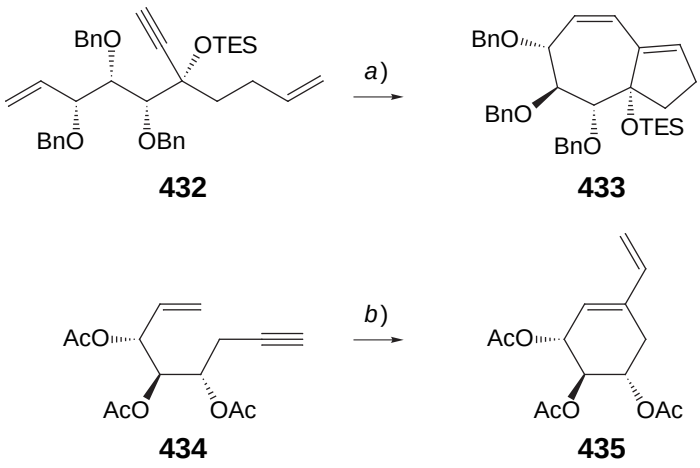
Scheme 2.2.31



a) BuLi, $Ph_3P{=}CH_2$, THF; 72% [648]. *b*) i. PCC, NaOAc, MS4Å, CH_2Cl_2; 85%; ii. $Ph_3P{=}CH_2$, THF; 76% [648]. *c*) 0.2 eq. of **310**, toluene; 74% [648]. *d*) i. $(Ph_3P)_3RhCl$, H_2, toluene; 83%; ii. HCl, MeOH; 90%; iii. MeI, NaH, THF; iv. H_2, Pd/C, MeOH, AcOH; 94% (two steps) [648].

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].

Scheme 2.2.32



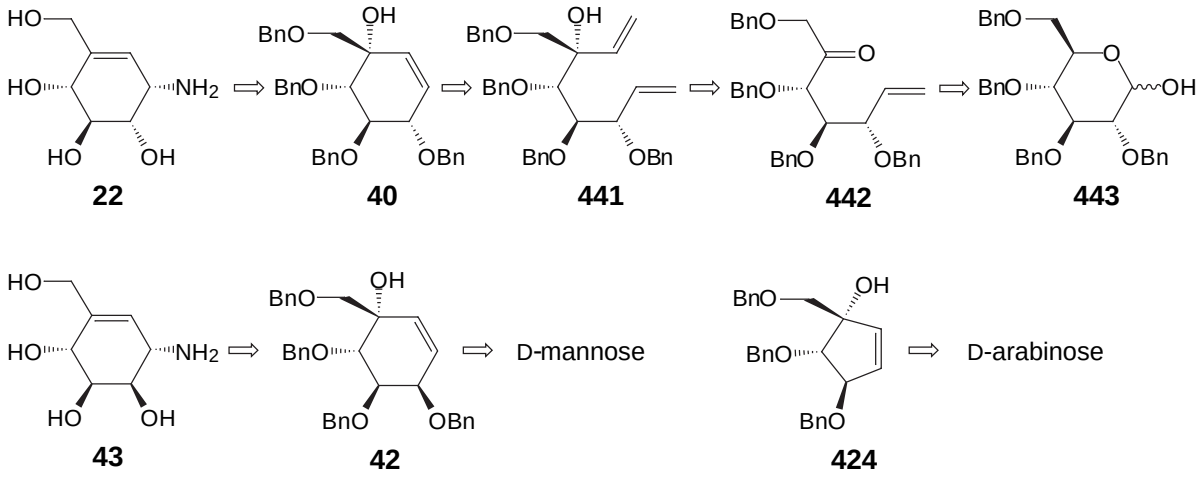
a) 0.1 eq. of **315**, CH_2Cl_2; 96% [668]. *b*) 0.08 eq. of **315**, CH_2Cl_2; 58% [667].

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 ($NaBH_4/CeCl_3$) 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.

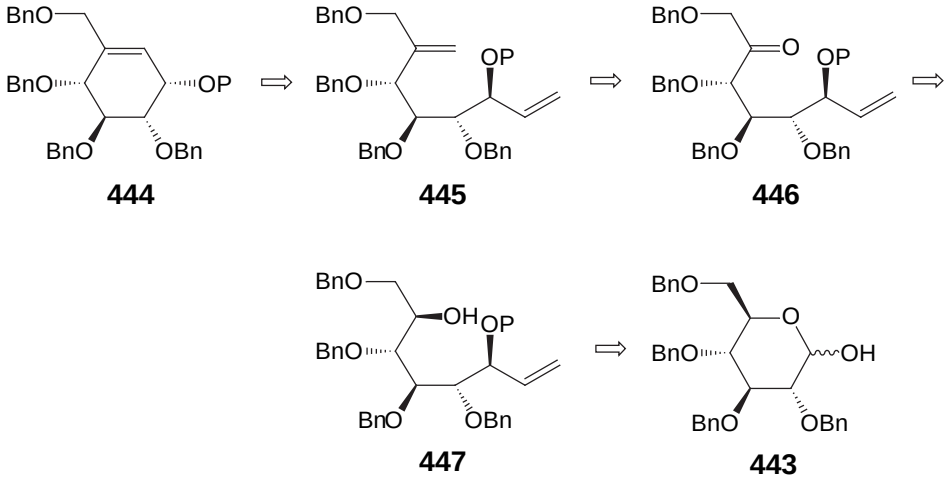
Scheme 2.3.1



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) methylidene 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

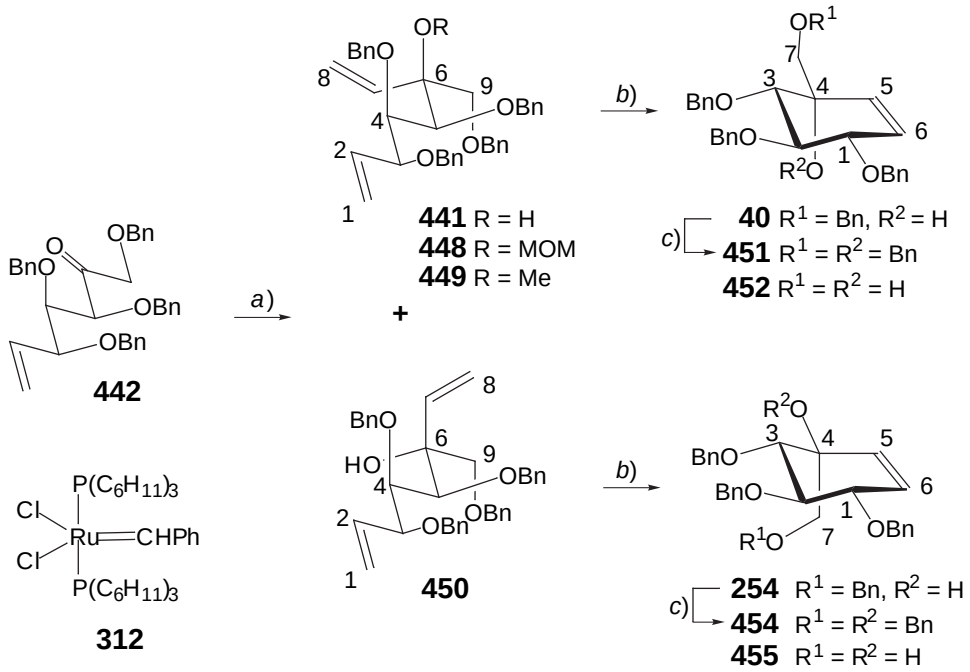


2.3.1. Synthesis of (+)-Valienamine from D-Glucose *via* RCM

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 ^{1}H- and ^{13}C-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 CH_2Cl_2 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.

Scheme 2.3.3



a) H_2C=CHMgBr, THF; 86% of **441**, 1% of **450**. *b*) i. **312**, CH_2Cl_2; 58% of **40**; 66% of **254**; ii. **315**, CH_2Cl_2; 89% of **40**. *c*) NaH, DMF, then BnBr; 88% of **451**; 49% of **454**.

Using the second-generation *Grubbs's* catalyst **315** (0.1 eq.) in CH_2Cl_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_2Cl_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_2Cl_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 Cy_3P to Cy_3PO). *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 reactions[34]), 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. Ruda*[35]) 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 ^{1}H-NMR spectrum of **454** matched the data reported by *Nicotra et al.* [417], thus establishing the (4*R*)-configuration of **254** and the (6*R*)-configuration of **450**, and, indirectly, the (4*S*)-configuration of **40** and the (6*S*)-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 (3*S*,4*R*,5*S*)-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 unclear[36]).

The vicinal coupling constants for the ring H of **40**, **451**, **254**, and **454** indicate a $^3H_2$

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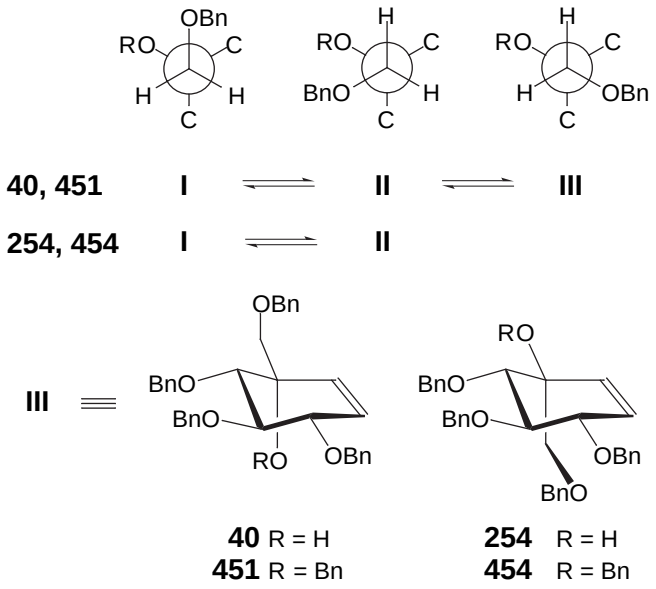
[34]) As suggested by *Prof. P. Hofmann*, Universität Heidelberg, in a personal discussion.

[35]) *Dr. Katinka Ruda*, post-doctoral fellow from September 1998 to November 1999.

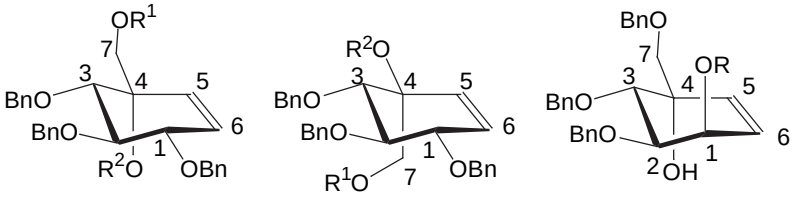
[36]) Original samples and spectra were no longer available in *Paulsen's* group. We thank *Prof. Dr. H. Paulsen* for pertinent discussions.

conformation[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) (ΔJ = 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:



[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).



40 R^1 = Bn, R^2 = H **254** R^1 = Bn, R^2 = H **42** R = Bn
451 R^1 = R^2 = Bn **454** R^1 = R^2 = Bn **60** R = MPM

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**.

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

[a]) In C_6D_6

[b]) Not assigned

[c]) At 20°

The transformation of **40** into (+)-valienamine is formally an S_N2' 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^{2+}, Pd^{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°). The versatile isocyanate products can be converted into various amine derivatives *in situ*.

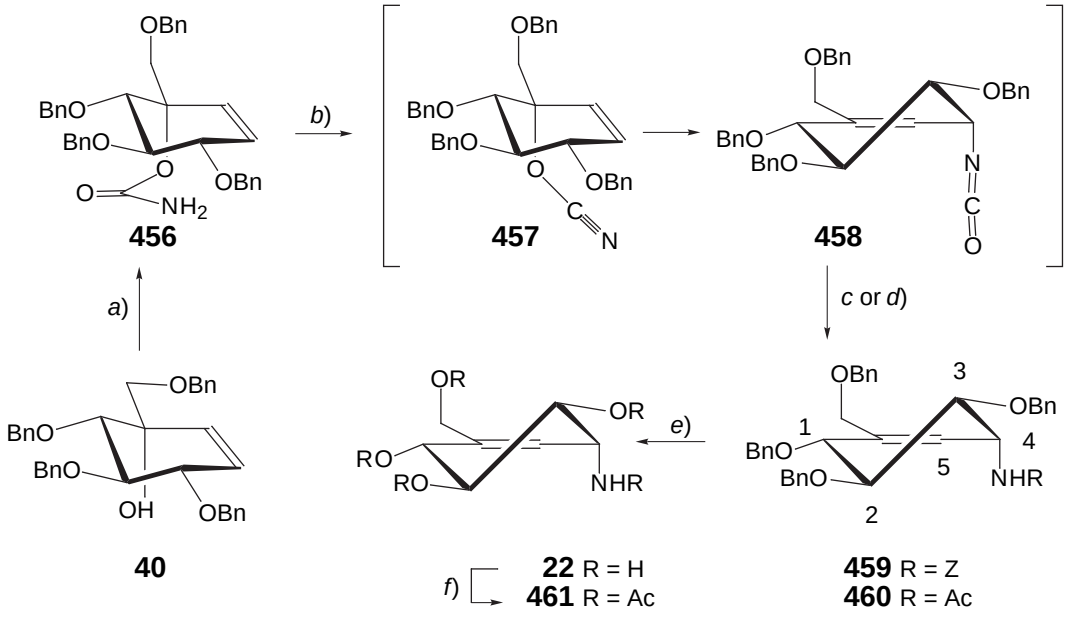
Sarabia[24]) had attempted the *Overman* rearrangement [695 – 698] of the trichloroacetimidate derived from **40**, but obtained the desired trichloroacetamide derivative of (+)-valienamine in low yields only. The low yields were probably due to the reversibility of the trichloroacetimidation of the 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_2Cl_2 at 0˚, followed by hydrolysis with K_2CO_3 in aqueous MeOH gave 86% of the carbamate **456** (Scheme 2.3.4). Dehydration of **456** with triphenylphosphine, Et_3N, and tetrabromomethane in CH_2Cl_2 at –20˚ 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_3Al yielded 77% of *N*-acetyl-tetra-*O*-benzylvalienamine (**460**) [225]. Its ^1H- and ^{13}C-NMR spectra were

identical to those of an authentic sample[38]), confirming the (4*S*)-configuration of **40** and the (6*S*)-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].

Scheme 2.3.4



a) CCl_3CO-NCO, CH_2Cl_2, then K_2CO_3, MeOH/H_2O; 86%. *b*) PPh_3, Et_3N, CBr_4, CH_2Cl_2. *c*) BnOH; 70% of **459** (from **456**). *d*) Me_3Al; 77% of **460** (from **456**). *e*) **459**, Na, NH_3/THF; 78%. *f*) Ac_2O, pyridine; 86%.

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[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 468

We next examined the synthesis of the MOM-protected cyclohexene **468** from 2,3,4,6-tetra-*O*-methoxymethyl-D-gluco-pyranose (**464**) (Scheme 2.3.5)[39]). 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 $Pd(CF_3COO)_2$ 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 $Ph_3P{=}CH_2$ (prepared from Ph_3PCH_3Br 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 CH_2Cl_2 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.

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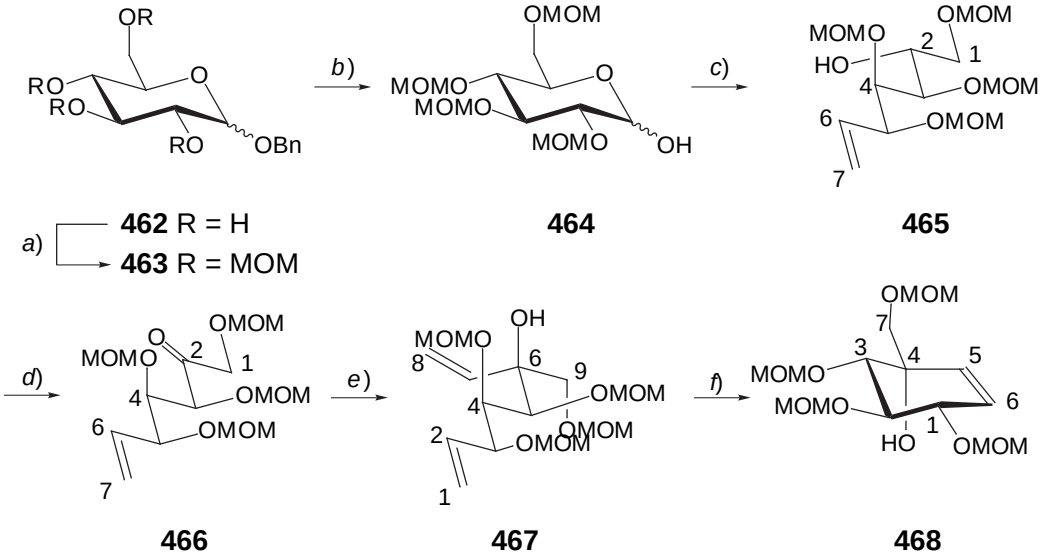
[39]) This work was largely done by *N. Leclerc*, see[27]).

Scheme 2.3.5



a) NaH, DMF, then MOMCl; 56%. *b*) Na, NH_3, THF; 91%. *c*) BuLi, $Ph_3P{=}CH_2$, THF; 63%. *d*) PCC, CH_2Cl_2; 89%. *e*) CH_2=CHMgBr, THF; 90%. *f*) **312**, CH_2Cl_2; 54%.

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_2C(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).

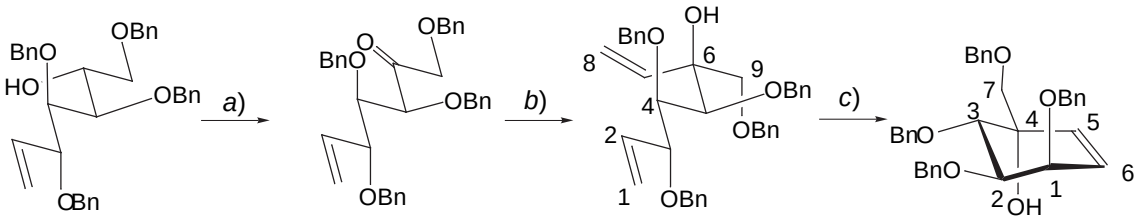
Chromatographic purification of the polar MOM-derivatives **463** – **468** was difficult, as the R_f values of main products and by-products were similar for several eluent mixtures tested. The ^{1}H-NMR spectra of these compounds were complex, so that information on the constitution was deduced mostly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

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

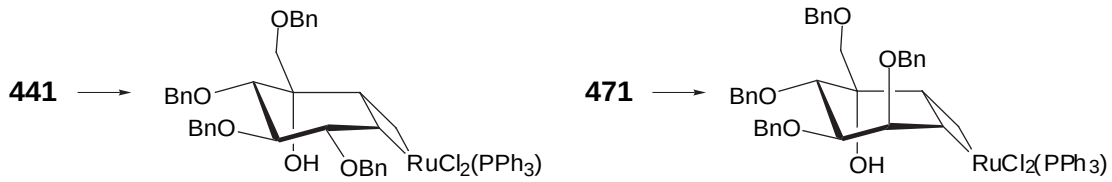


469 **470** **471** **42**

a) DMSO, DCC, pyridine, CF_3CO_2H, toluene; 87%. *b*) H_2C=CHMgBr, THF; 95%. *c*) **312**, CH_2Cl_2, r.t.; 89%.

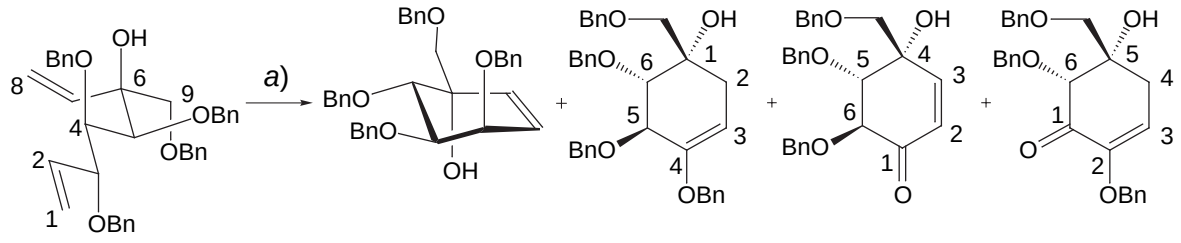
RCM of **471** in CH_2Cl_2 in the presence of 0.15 eq. of **312** gave the cyclohexene **42** in 89% yield as a green oil. The higher yield for the RCM of **471** as compared to the one of **441** is presumably due to the different conformational strain of the bicyclic metallacyclobutane intermediates 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 *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 *trans* to the RuL_n moiety.

Figure 2.3.2: Postulated Bicyclic Ruthenacyclobutane Intermediates in RCM of the Dienes **441** and **471**.



Remen[40]) 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 α,β-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



471 **42** **472** **473** **474**

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**.

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[40]) *Dr. Lubos Remen*, see[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 $CHCl_3$): 3468, **471** (1.5% in $CHCl_3$): 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 $H_2C(9)$ 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** ($\Delta[\alpha]_D^{25}$ = 40.7) is very similar to that between **441** and **442** ($\Delta[\alpha]_D^{25}$ = 34.5).

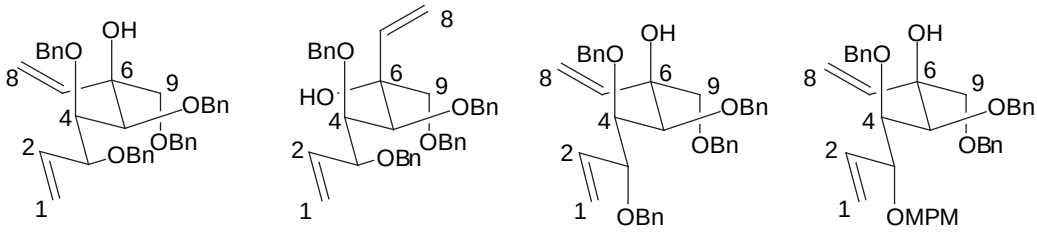


Table 2.3.2: Selected ^{1}H- and ^{13}C-NMR ($CDCl_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] and Optical rotations ($CHCl_3$) of **441**, **450**, **471**, and **486**.

	441	**450**	**471**	**486**
H–C(1)	5.30	5.26	5.47–5.42	5.44
H'–C(1)	5.20	5.25	5.47–5.42	5.43
H–C(2)	5.83	5.94	6.02–5.91	5.95
H–C(3)	4.07	4.09	4.05	4.04
H–C(4)	3.88–3.84	3.74–3.68	3.90	3.86
H–C(5)	3.88–3.84	3.99	4.07	4.05
CH–C(6)	3.63	3.74–3.68	3.73	3.72
CH'–C(6)	3.29	3.28	3.28	3.27
HO–C(6)	3.74	3.09	3.75	3.79
J(1,2)	10.3	17.1	[a])	17.7
J(1',2)	17.4	10.6	[a])	10.0
J(2,3)	7.8	7.5	7.5	7.8
J(3,4)	6.5	4.4	7.2	7.5
J(4,5)	3.5	5.9	2.5	2.5
J(CH,CH')	8.7	9.3	8.7	8.4
$[\alpha]_D^{25}$	35.2	[a])	–4.5	[a])

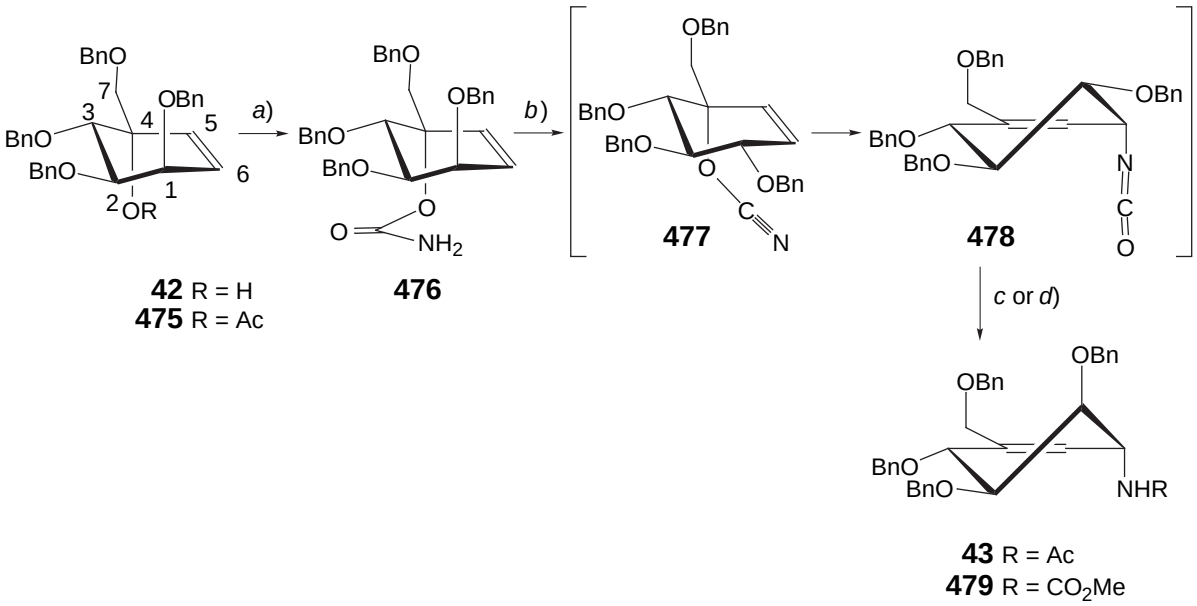
[a]) Not determined

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 $H_2C(2)$ (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. $H_2C(4)$ 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_2Cl_2, followed by hydrolysis (K_2CO_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_3Al (95%) or into the methylcarbamate **479** by treatment with MeOH (91%).

Scheme 2.3.8



42 R = H
475 R = Ac

476

477

478

43 R = Ac
479 R = CO_2Me

a) CCl_3CO-NCO, CH_2Cl_2, then K_2CO_3, MeOH/H_2O; 93%. *b*) PPh_3, Et_3N, CBr_4, CH_2Cl_2. *c*) Me_3Al, heptane; 95% of **43** from **476**. *d*) MeOH; 91% of **479** from **476**.

The Pd(0)-catalysed allylic azidation of the acetate **475** (obtained from **42** in 73% yield) under the conditions reported by *Nicotra* ($Pd(Ph_3P)_4$, 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 $PdCl_2$ in MeOH (85%) [720] [721].

Treatment of the pyranose **483** with four eq. of $Ph_3P{=}CH_2$ 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 $Ph_3P{=}CH_2$ 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 $Ph_3P{=}CH_2$ 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 $Ph_3P{=}CH_2$ in THF at –78° to r.t. did not improve the result; according to TLC it led to the formation of several by-products.

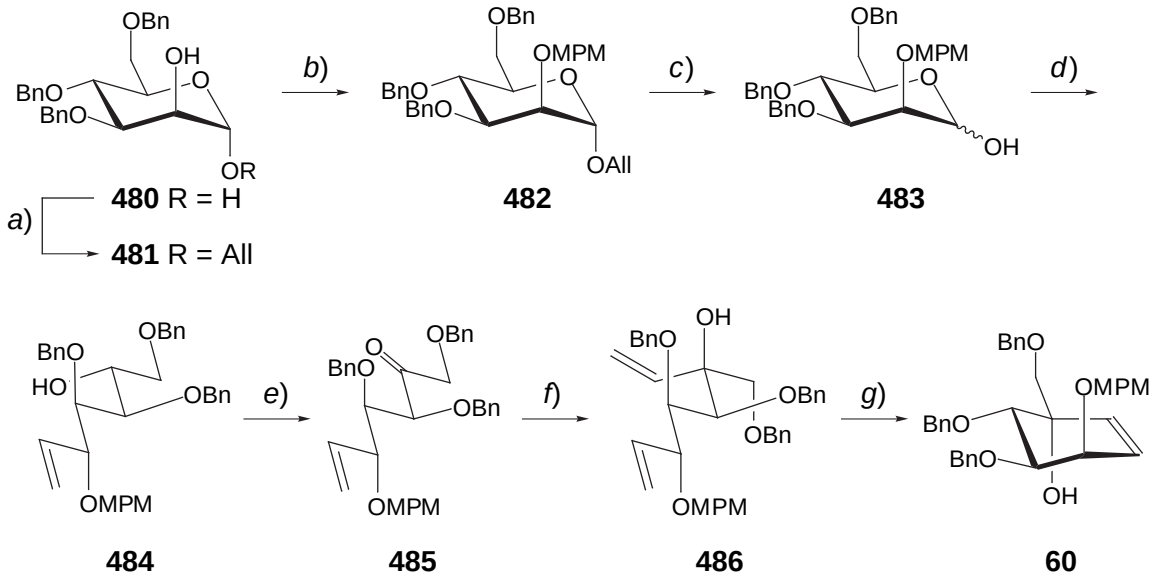
- Dropwise addition of a soln. of the pyranose **483** in THF to a boiling soln. of $Ph_3P{=}CH_2$ in THF gave the alkene **484** in 38% yield.

- The reaction of **483** with $Ph_3P{=}CH_2$ in toluene at –78° to 90° or at 0° to 60° was sluggish, and led to complex mixtures.

- Treatment of **483** with $Ph_3P{=}CH_2$ in THF and in the presence of 0.5 eq. of Bu_3SnCl (*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_2Cl_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).

Scheme 2.3.9



a) AllOH, CSA; 100%. *b*) NaH, DMF, then MPMCl; 98%. *c*) $PdCl_2$, MeOH; 85%. *d*) $Ph_3P{=}CH_2$ (prepared in THF from Ph_3PMeBr and 1.6M BuLi in Hexane), THF, –78° to reflux; 44%. *e*) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; 100%. *f*) $CH_2{=}CHMgBr$, THF; 96%. *g*) **312**, CH_2Cl_2; 49% of **60**, 45% of **486**.

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).

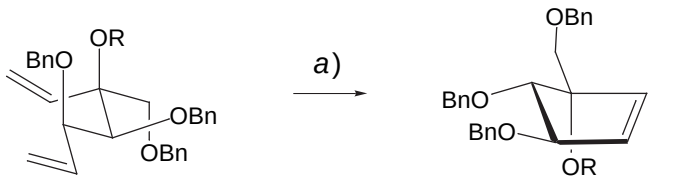
In conclusion, the orthogonally protected mannose-derived cyclohexene **60** was prepared in six steps and an overall yield of 16%. The low overall yield is due to the low yield of the *Wittig* methylenation and to the sluggish RCM. The RCM might be improved by using the second-generation *Grubbs's*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



421 R = H
422 R = TMS
423 R = Bn

424 R = H
425 R = TMS
426 R = Bn

a) See Table 2.3.3.

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

Entry	Diene	Catalyst	Conditions	Yield	Reference
1	**421**	0.15 eq. of **312**	CH_2Cl_2, r.t.	63%	[222]
2	**421**	0.2 eq. of **312**	CH_2Cl_2, reflux	29%	[643]
3	**422**	0.2 eq. of **312**	CH_2Cl_2, reflux	0%	[643]
4	**422**	0.1 eq. of **310**	benzene, r.t.	90%	[643]
5	**423**	0.1 eq. of **312**	CH_2Cl_2, r.t.	35%	[642]
6	**423**	0.2 eq. of **310**	CH_2Cl_2, r.t.	87%	[642]

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]. *Remen*[25]) 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]

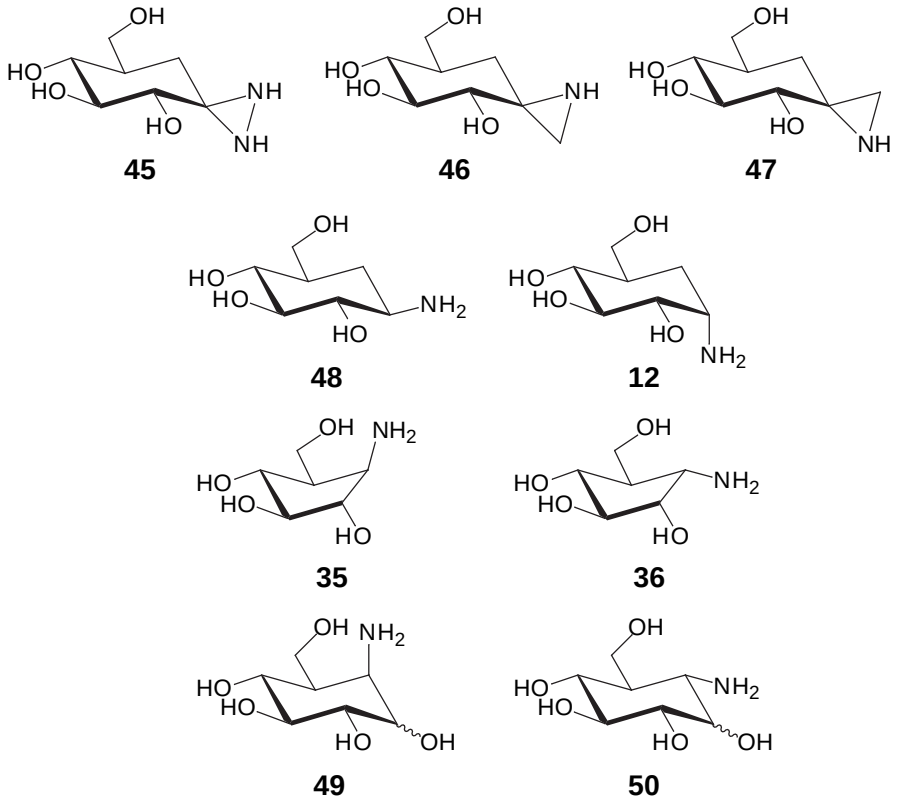
will be more efficient. For the synthesis of unbranched aminocyclitols**,** the *Ferrier* rearrangement provides the appropriate intermediates and will remain the method of choice. For the synthesis of multi-kilogram quantities of some carbasugars, *Diels-Alder* and biocatalytic approaches appear attractive. 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 *spiro*-Diaziridines and *spiro*-Aziridines, of 1-*epi*-*V*alidamine, and of 5a-Amino-5a-carba-pyranoses

3.1. Introduction

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

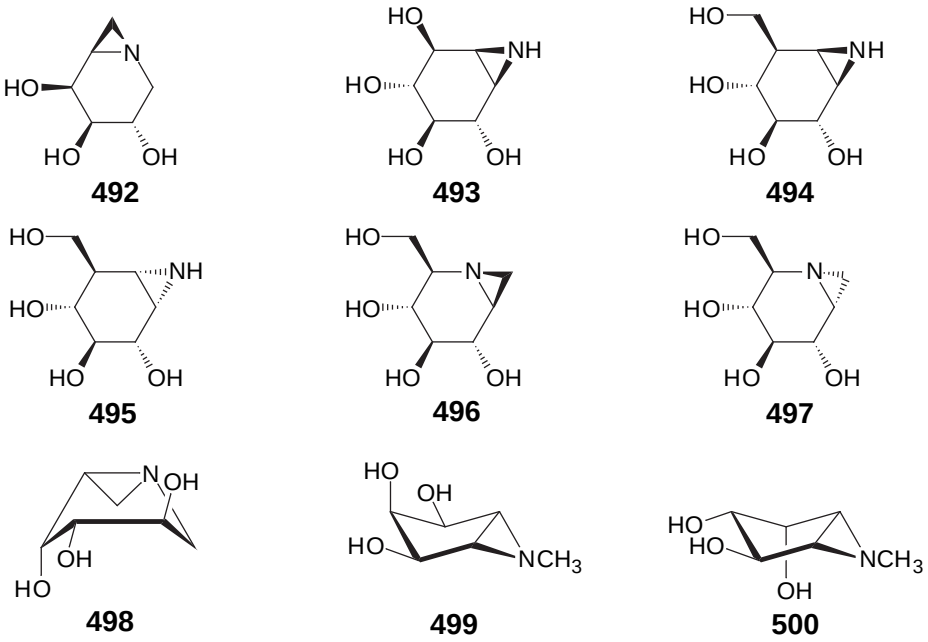
Scheme 3.1.1



At the beginning of this project, there were no known diaziridine glycosidase inhibitors. Some aziridine (but no spiro-aziridine) glycosidase inhibitors are known [59]. The aziridine **492** (Figure 3.1.1) inhibits the α-galactosidase from coffee beans irreversibly (K_i = 7 μM) [724]. Conduritol aziridine **493** is a weak irreversible inhibitor of the β-glucosidase from *Alcaligenes faecalis* (K_i = 3.0 mM) and the α-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 (IC_{50} = 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 (K_i = 8.0 μM), whereas (±)-**499** does not inhibit several *α*- and *β*-glycosidases.

Figure 3.1.1: Aziridine Glycosidase Inhibitors.



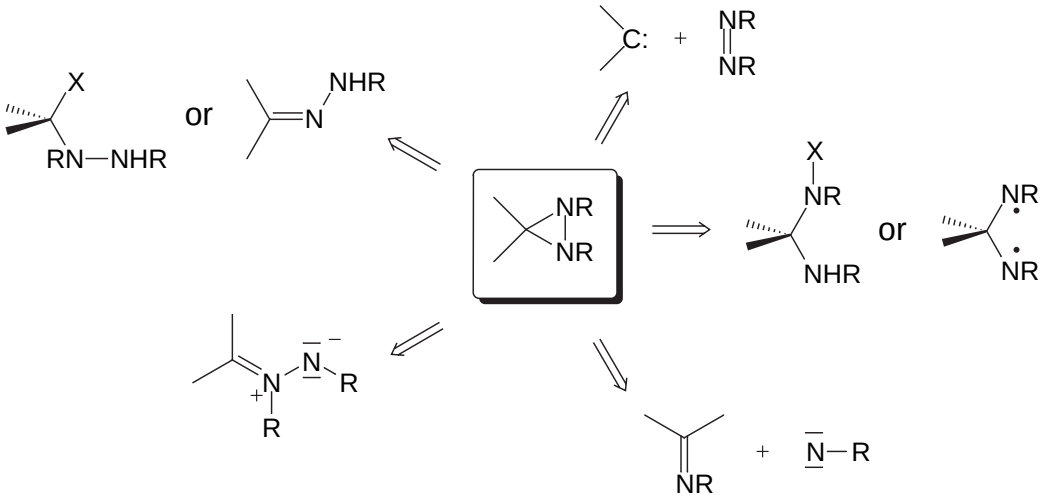
1-*Epi*-validamine (**48**, Scheme 3.1.1) is a competitive inhibitor of pig kidney trehalase (K_i = 1.2 μM) [224]. In a comprehensive literature search, no inhibition data for this compound against the enzymes studied here were found. Likewise, no inhibition data for 5a-aminocyclohexitols like **49** 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 N_2 from Δ^2-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

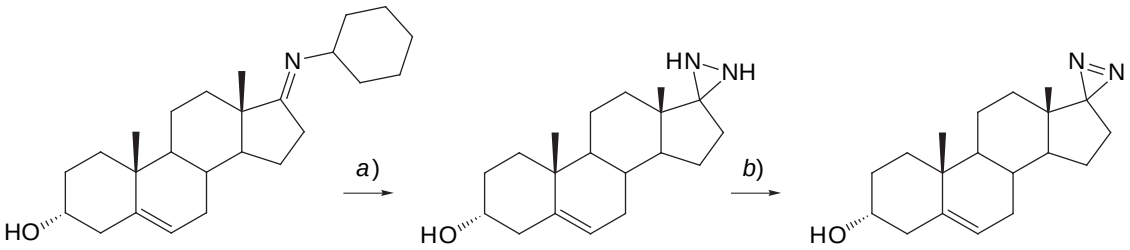


Most diaziridines were prepared by N–N bond formation by intramolecular substitution of an N,N-acetal bearing a leaving group on one of the N. Such N,N-acetals are generated from a carbonyl compound, an amine, and a nitrenoid (for reviews, see [729] [731] [732] and the PhD thesis of *Briner* [734]). 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 Cl_2 or *t*BuOCl (*in situ* formation of $ClNH_2$ 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

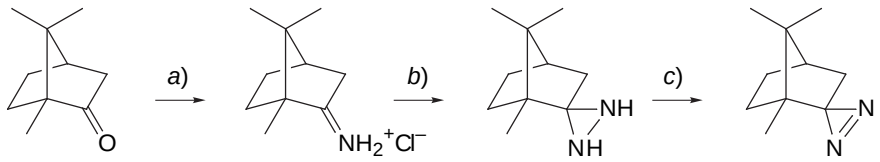


501 **502** **503**

a) NH_3, MeOH, then NH_2OSO_3H; 58% [741]. *b*) Br_2, Et_3N, $CHCl_3$, 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



504 **505** **506** **507**

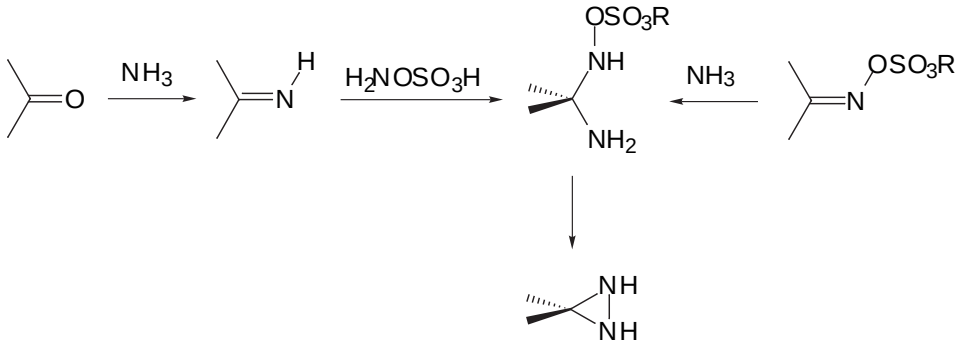
a) i. NH_2OH; 90%; ii. $NaNO_2$, H_2SO_4; iii. NH_3, then HCl; 60% (two steps) [743]. *b*) NH_2OSO_3H, NH_3, MeOH, H_2O [743]. *c*) I_2, Et_3N, MeOH; 48% (two steps) [743].

A complementary diaziridine synthesis is based on the addition of ammonia or primary

amines to *N*-chloroimines or ketoxime-*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 α-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

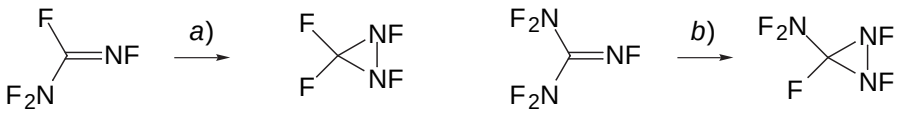


3,3-Disubstituted diazirines are generally prepared by oxidation of diaziridines with I_2 in the presence of Et_3N or Me_3N [752] [753], or Ag_2O [227]. In earlier examples, HgO, $KMnO_4$, dichromate, cupric salts, Br_2, *t*BuOCl, or chloramine were used as oxidant [729] [731]. 3-Halo-3-alkyl- and 3-halo-3-aryl-diazirines 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 diazo-acetamides 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

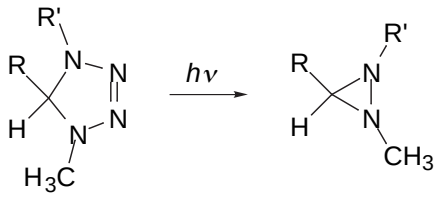


508 **509** **510** **511**

a) KF, $CF_2(NF_2)_2$; not isolated [757]. *b*) RbF; 25% [757].

Photolysis of the Δ^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 Δ^2-tetrazolines were prepared from 1-methyl-5-phenyl- or 1,5-diphenyl-5-tetrazole by methylation at N(4) and $NaBH_4$ reduction.

Scheme 3.1.7

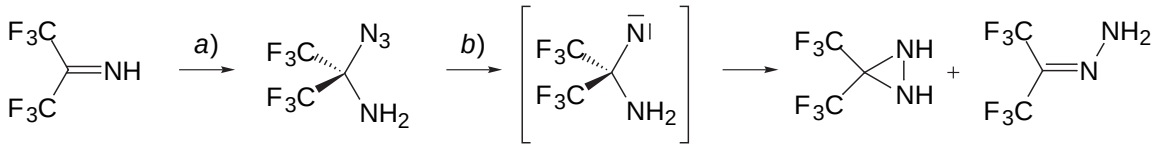


512 **513**

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 α-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

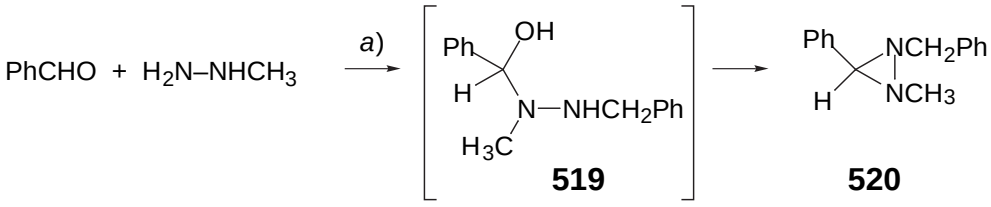


514 **515** **516** **517** **518**

a) HN_3, CH_2Cl_2; 52% [759]. *b*) $h\upsilon$ 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



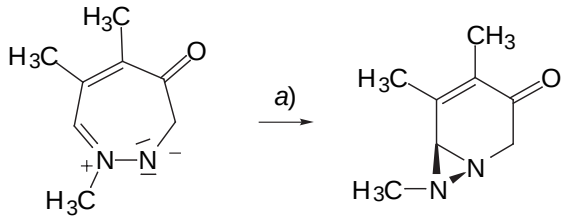
519 **520**

a) BH_3, 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

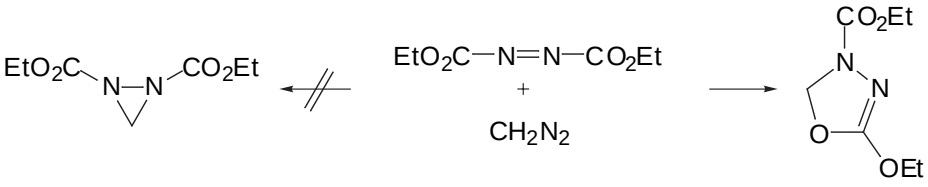


521 **522**

a) *hυ*, $CHCl_3$, MeOH; 70% [761].

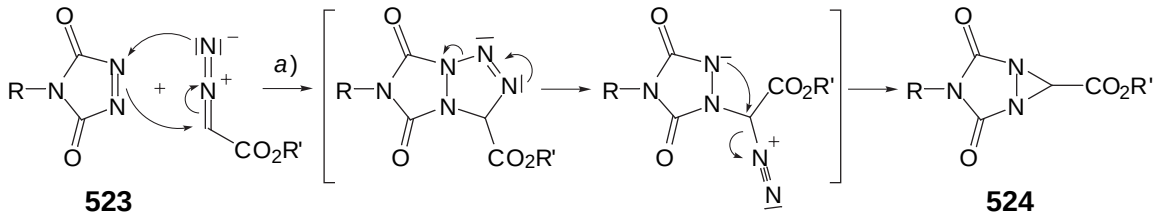
The reaction of diazomethane with diethyl azodicarboxylate leads to oxadiazolines (1,4-addition), and not to diaziridines (Scheme 3.1.11) [731] [763] [764].

Scheme 3.1.11



In contrast, the addition of ethyl diazoacetate to 4-phenyl-1,2,4-triazolin-2,4-dione (**523**, R = Ph) provided the diaziridine **524** (R = 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 N_2-elimination, rather than by addition of a free carbene (its formation generally requiring temperatures above 100°).

Scheme 3.1.12



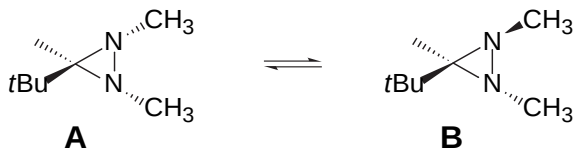
a) Benzene, 0°C; see text [765].

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-*tert*butyldiaziridine, 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 $CHCl_3$ the ratio is 1:2) [768]. Steric interactions between the methyl groups and the *tert*butyl 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].

Scheme 3.1.13



Inversion of the configuration at the N atoms of diaziridines is slow and proceeds stepwise,

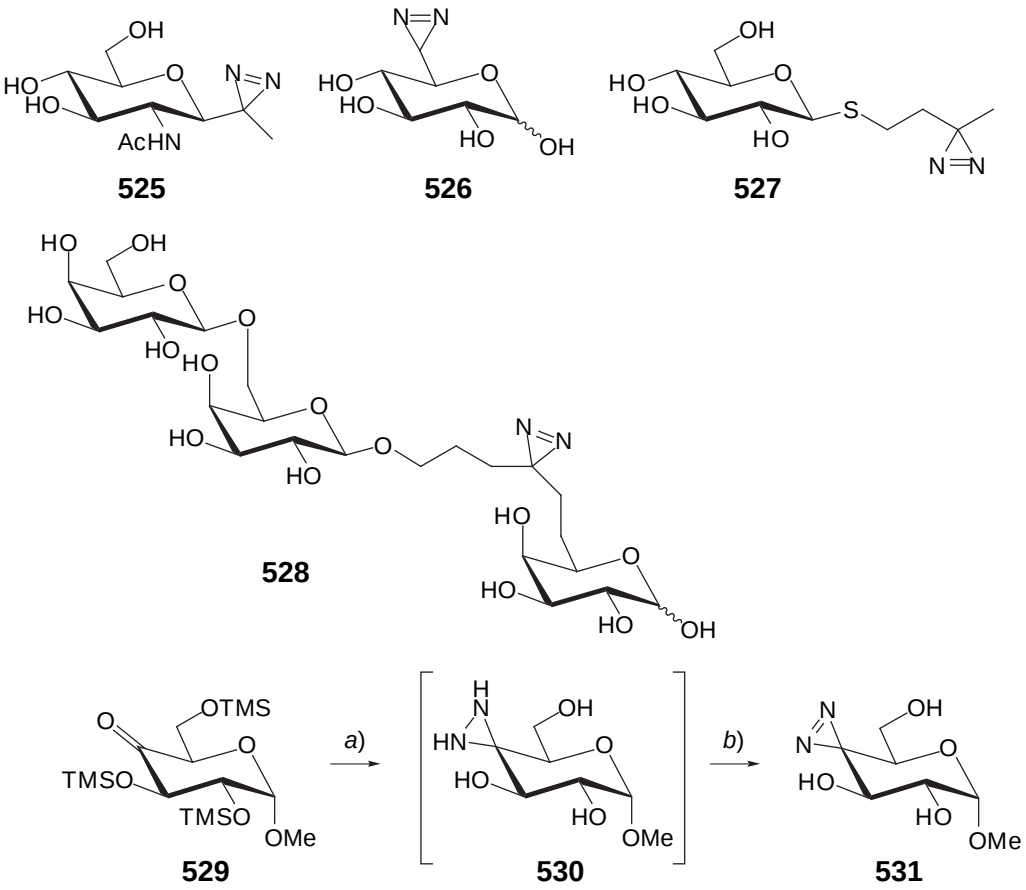
ergo via the *cis* diaziridine [767]. The inversion barrier $\Delta G^{\neq}$ is larger than 23 kcal/mol (as a rule, 22– 28 kcal/mol) [769] [770]. This has allowed the isolation of pure diastereoisomers of diaziridines [771], and of the pure enantiomers of C_2-symmetric diaziridines with only the N atoms 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 σ^* 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_3N. 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].

Scheme 3.1.14

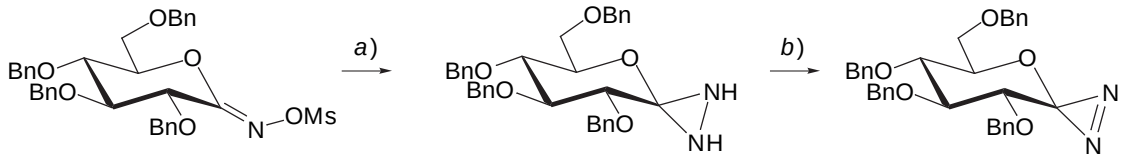


a) NH_3, MeOH, – 20°, then NH_2OSO_3H, –20° to r.t. [782]. *b*) I_2, Et_3N, MeOH; 13% from **529** [782].

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*-benzylgluconolactone 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_3N (or the more volatile Me_3N) 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

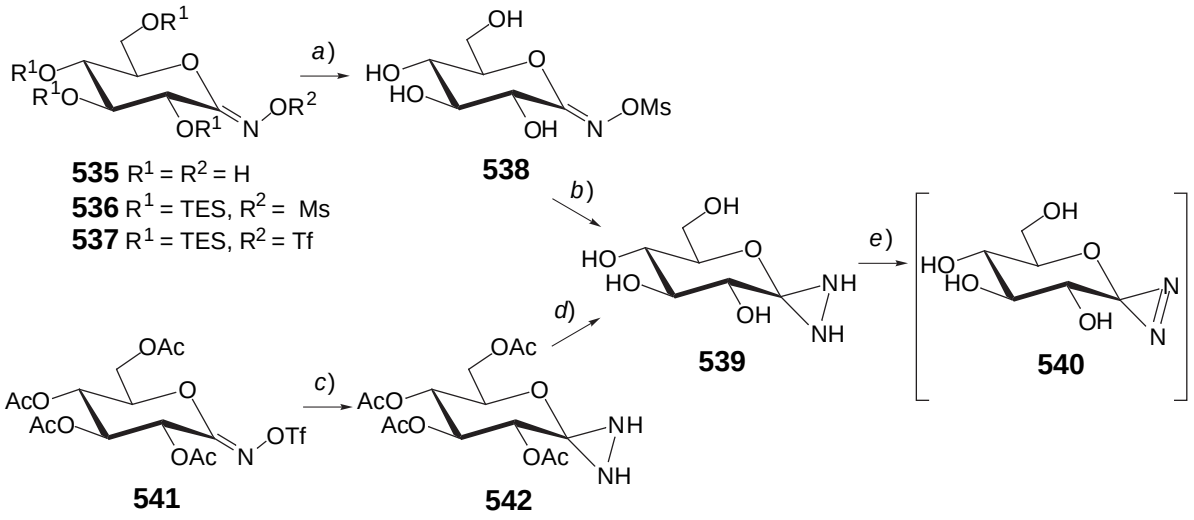


532 **533** **534**

a) NH_3, MeOH, r.t.; 82% [784]. *b*) I_2, Et_3N, 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_2Cl_2/MeOH gave the acetyl protected diaziridine **542** in 71% yield. Hydrolysis of **542** (NH_3, MeOH, H_2O) 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 α- and β-D-glucosides, most probably *via* the diazirine **540**.

Scheme 3.1.16



a) HF, pyridine, THF; 76% from **536** [223]. *b*) NH_3, MeOH, 25°; 31% of crude **539** [223]. *c*) NH_3, MeOH, CH_2Cl_2, –20°; 71% [223]. *d*) NH_3, MeOH, H_2O, 25°; 72% [223]. *e*) I_2, Et_3N, H_2O, MeOH; mixture of D-glucose and methyl α- and β-D-glucopyranoside formed *via bona fide* **540** (yield not given) [223].

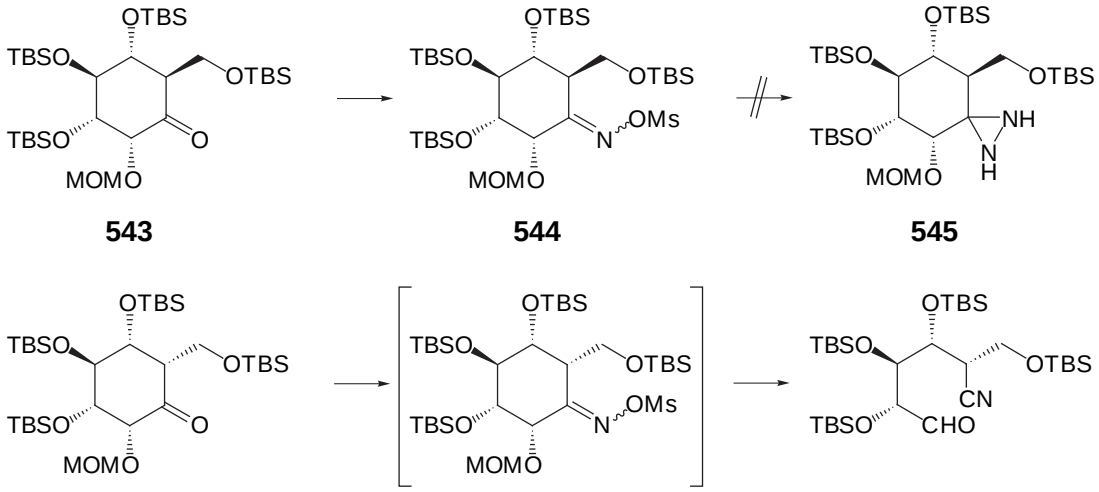
3.1.4. Previous Work Directed at the Synthesis of Carbasugar-Derived *spiro*-Diaziridines

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.

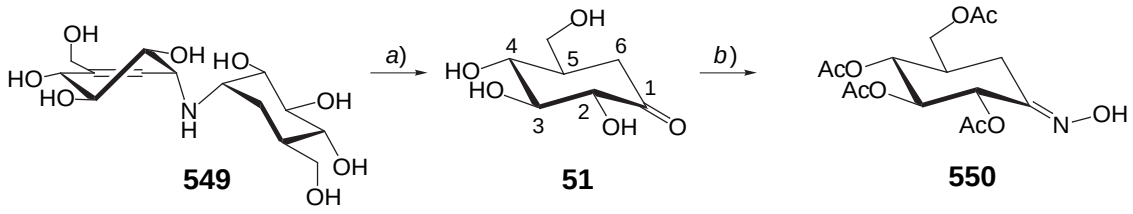
Scheme 3.1.17



See text.

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*[30]) prepared validone (**51**) by NBS-cleavage of validoxylamine A (**549**)[28]) [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

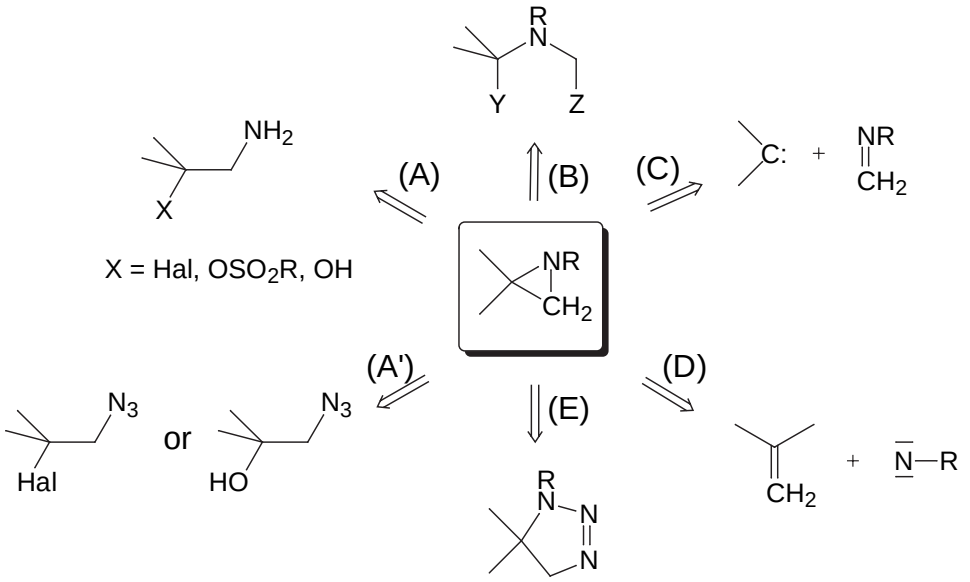


a) NBS, MeCN, H_2O; 50% [226]. *b*) i. NH_2OH, MeOH; 97%; ii. Acetylation [226].

3.1.5. Synthesis of Aziridines

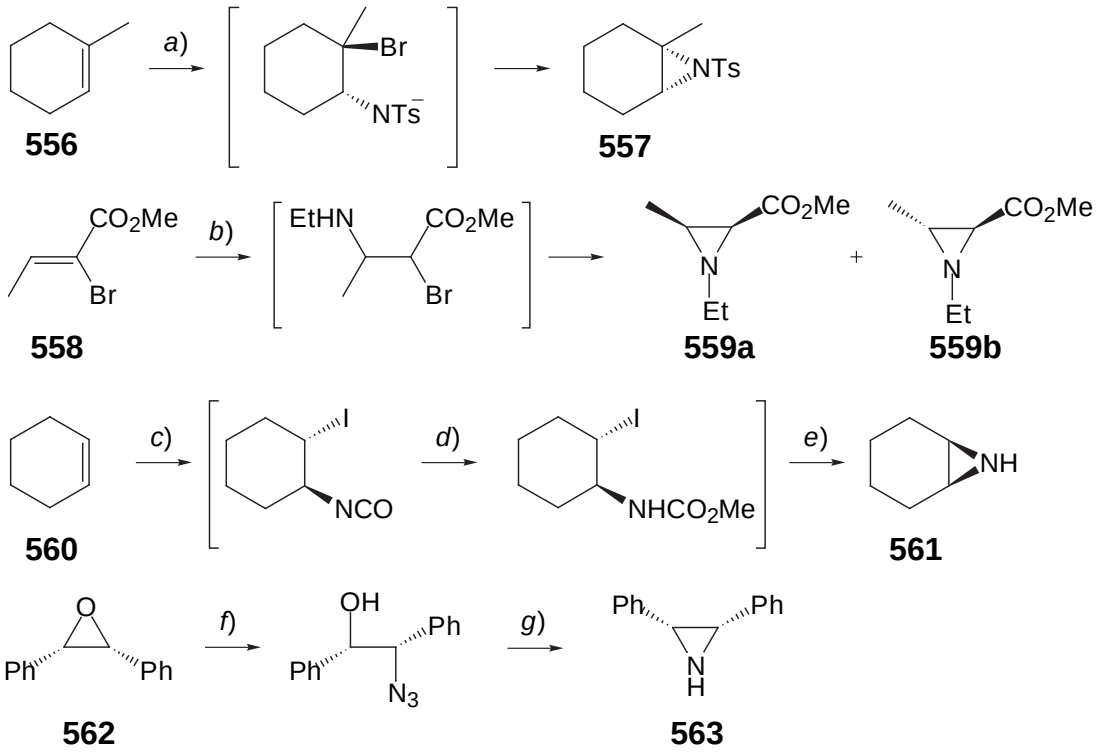
Aziridines are made by C–N-bond formation, C–C-bond formation, addition of nitrenes to alkenes, addition of carbenes to imines, and ring contraction of 1,2,3-triazolines (Scheme 3.1.19) [816 – 820].

Scheme 3.1.19



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 $PhMe_3NBr_3$ [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].

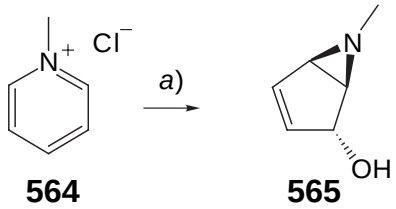
Scheme 3.1.20



a) Chloramine T, $PhMe_3NBr_3$, MeCN; 51% [229]. *b*) $EtNH_2$, MeOH; 84% of **559a**, 16% of **559b** [821]. *c*) I–NCO, Et_2O; [823]. *d*) LiOH, MeOH; [823]. *e*) KOH, MeOH; 60% from **560** [823]. *f*) NaN_3, acetone; 77% [824]. *g*) Ph_3P, Et_2O; 77% [824].

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].

Scheme 3.1.21

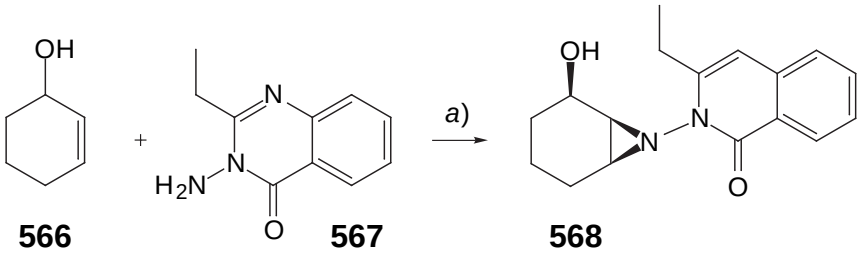


564 **565**

a) KOH, *hυ*, H_2O; yield not given [828].

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).

Scheme 3.1.22



566 **567** **568**

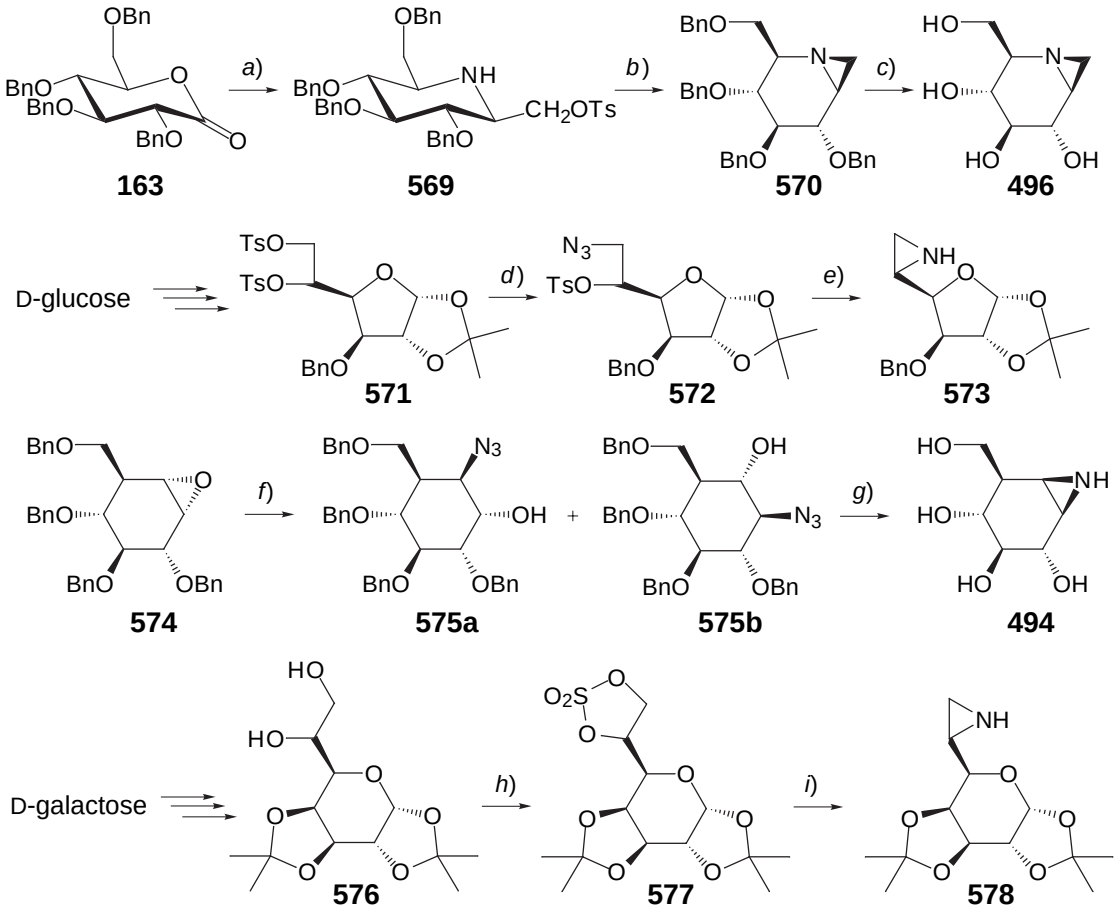
a) $Pb(OAc)_4$, CH_2Cl_2; 70%, 90% d.e. [836].

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 N_2 (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]).

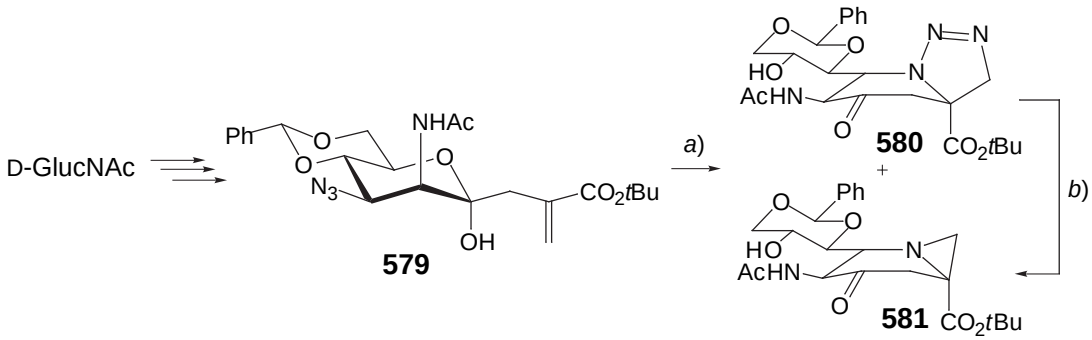
Scheme 3.1.23



a) Six steps; 25% [726]. *b*) DBU, THF; 45% [726]. *c*) Ca, NH_3; 75% [726]. *d*) NaN_3, DMF; 87% [847]. *e*) $LiAlH_4$, THF; 95% of crude **573** [847]. *f*) NaN_3, DMF; 50% of **575a**, 25% of **575b** [850]. *g*) i. PPh_3, toluene, 110°; 60%; ii. Li, NH_3, Et_2O; 60% [850]. *h*) i. $SOCl_2$, CH_2Cl_2; quant. ii. $NaIO_4$, $RuCl_3$, CH_2Cl_2, MeCN, H_2O; 78% [853]. *i*) LiN_3, THF, then $LiAlH_4$; quant. yield of crude **578** [853].

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].

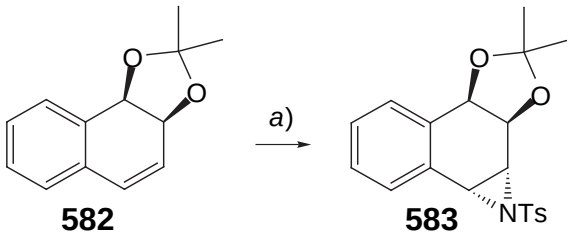
Scheme 3.1.24



a) Benzene, reflux; 58% of **580**, 16% of **581** [857]. *b*) AcOH, H_2O, THF; 88% of **581** from a 3.6:1 mixture of **580** and **581** [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].

Scheme 3.1.25

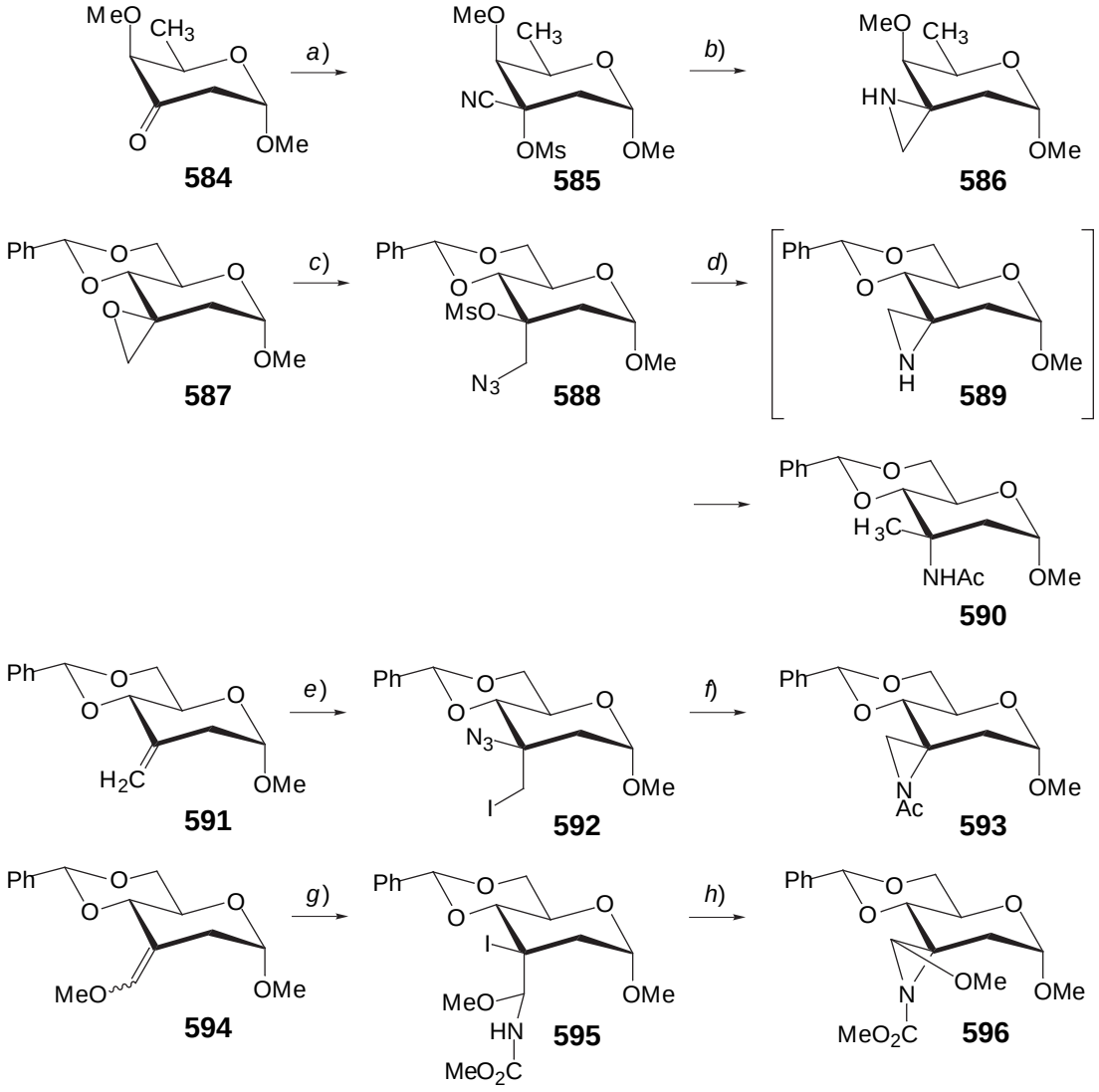


a) PhI=NTs, $Cu(acac)_2$, MeCN; 30% [858].

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 $LiAlH_4$ [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 $LiAlH_4$ 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



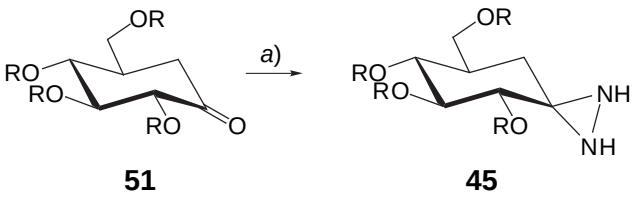
a) KCN, $NaHCO_3$, CH_2Cl_2/H_2O, then MsCl, Et_3N, DMAP; 87% [866]. *b*) $LiAlH_4$, Et_2O; 50% [866]. *c*) NaN_3, DMF, then MsCl, pyridine; 46% [868]. *d*) H_2/Pd, MeOH, then Ac_2O, pyridine; 55% [868]. *e*) IN_3, MeCN; 24% [870]. *f*) $LiAlH_4$, Et_2O, then Ac_2O, pyridine; 52% [870]. *g*) I-NCO, THF, then MeOH; 12%, along with 36% of the diastereoisomer [871]. *h*) KOH, H_2O, 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



51 **45**

Proposal for the synthesis of **45**. *a*) i. NH_3, MeOH, then NH_2OSO_3H; 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.

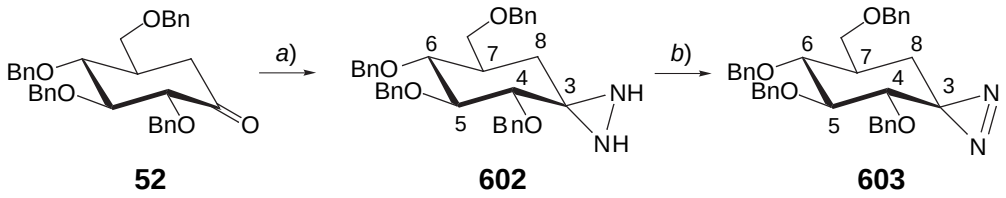
The cyclohexanone **52** (Scheme 3.2.2) was obtained from octa-*O*-benzyl validoxylamine A[28]) in two steps (benzylation followed by NBS cleavage) and in a yield of 50%, following a known procedure [225].

Saturation of a solution of **52** in MeOH at –20° with NH_3, 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 I_2 in the presence of Et_3N [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} ($CHCl_3$) is characteristic for diaziridines [731] [872] (3,3-pentamethylenediaziridine [872] shows a band at 3266 cm^{-1}). The ^{1}H-NMR spectrum ($CDCl_3$) (see Table 3.2.3) shows that **602** is a *ca*. 4:1 mixture of diastereoisomers. The NH signals exchanged with D_2O; 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 ^{13}C-NMR C(3) resonates as a *s* at 57.06 ppm (*cf*. [873]).

The UV spectrum of the diazirine **603** in CH_2Cl_2 shows a typical maximum at 340 nm (ε = 92) [731] [754]. The IR N=N band ($CHCl_3$) at 1590 cm^{-1} is characteristic for diazirines [731] [754]. A large chemical shift difference was observed for the two H–C(8) ($\Delta\delta$ = 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 $^6C_3$ conformation.

Scheme 3.2.2



52 **602** **603**

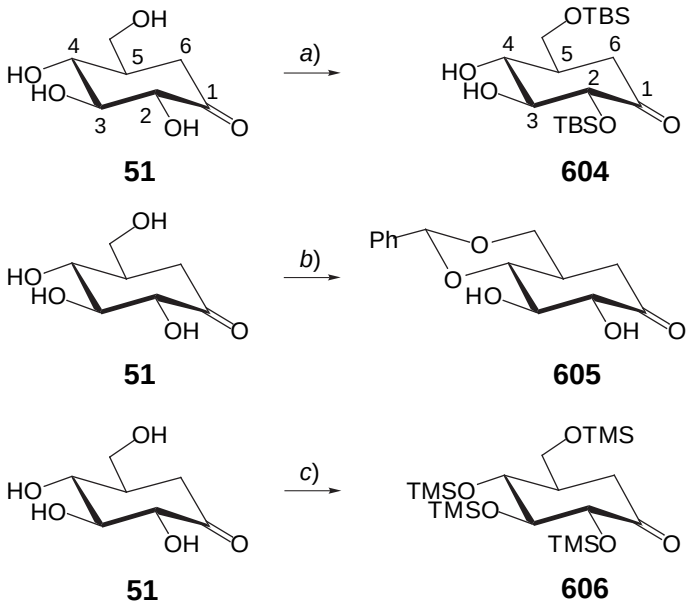
a) NH_3, MeOH, then NH_2OSO_3OH; 35%. *b*) I_2, Et_3N, MeOH, CH_2Cl_2; 85%.

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 Li_2S in MeCN [875] led to decomposition of the starting material. The reaction with

TBSCl 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° (*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



a) TBSCl, DMF, imidazole; 9%. *b*) $PhCH(OMe)_2$, *p*$TsOH \cdot H_2O$, DMF; 8%. *c*) 2-Trimethylsilyloxy-propene, HCl, MeCN; 33%.

Sarabia[24]) 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].

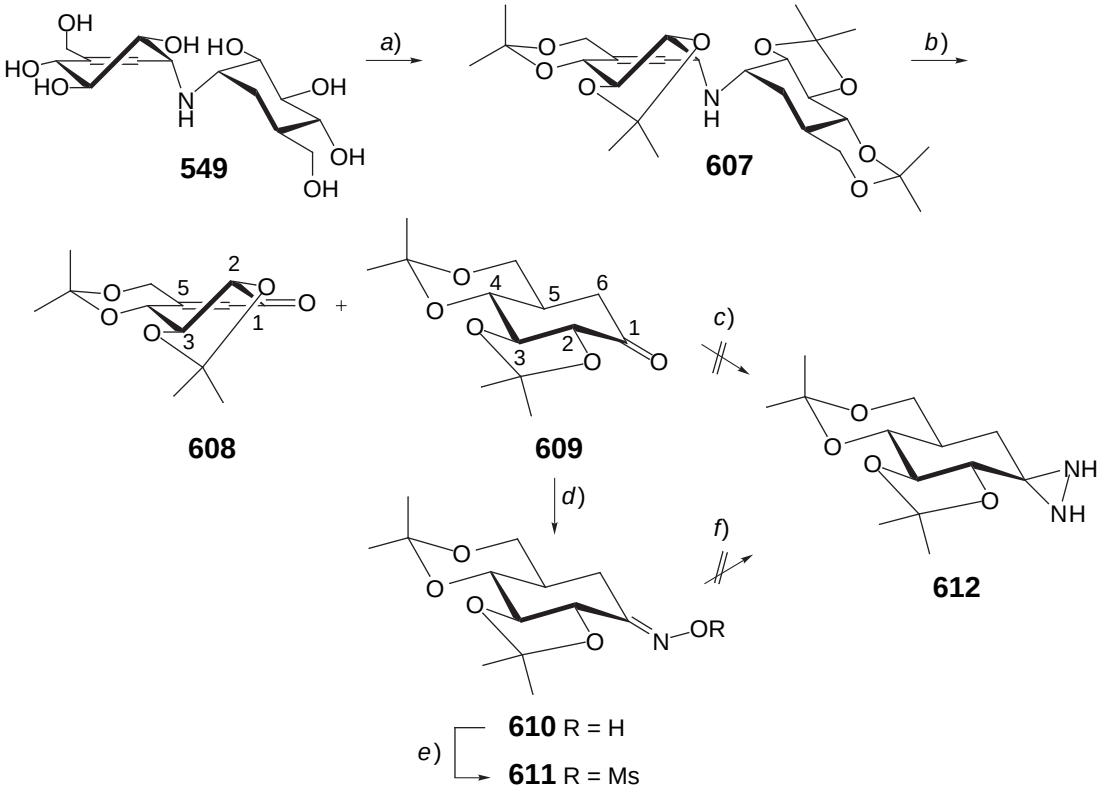
The synthesis of di-*O*-isopropylidene validone by NBS-cleavage of tetra-*O*-isopropylidene validoxylamine A (**607**) was examined next. Racemic **609** had been prepared by *Ogawa et al.* by oxidation of the corresponding equatorial alcohol, which in turn was prepared in a *de novo* carbasugar synthesis [883]. Treatment of validoxylamine A[28]) 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 NH_3 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 ^{1}H-NMR spectrum, however, this fraction was a complex mixture.

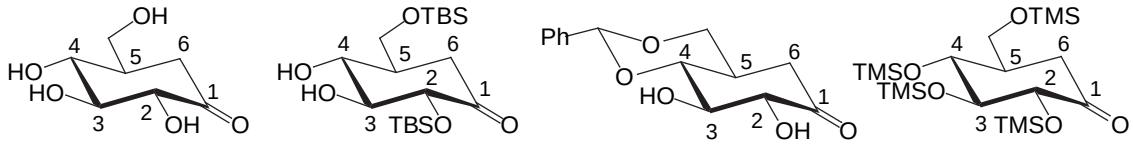
Therefore the diaziridine synthesis *via* the oxime methanesulfonylate of **609** was studied. Condensation of **609** with hydroxylamine in MeOH gave the oxime **610** (66%). Treatment of **610** with Et_3N and MsCl in CH_2Cl_2 at 0° afforded in quantitative yield the crude *bona fide* oxime methanesulfonylate **611**, which decomposed rapidly, and, therefore, was immediately used in the subsequent step. The reaction of crude **611** with a solution of NH_3 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 ^{1}H-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

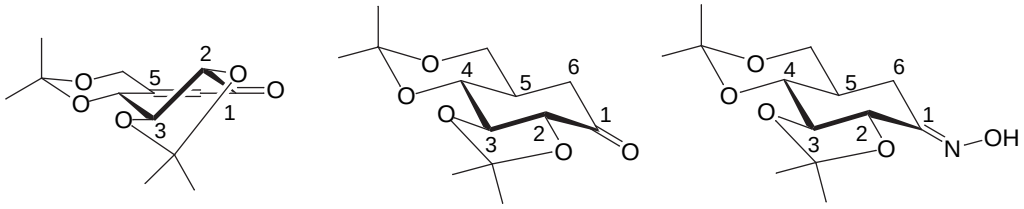


a) 2-Methoxypropene, *p*TsOH, DMF; 55%. *b*) NBS, MeCN, H_2O; 23% of **608**, 58% of **609**. *c*) NH_3, MeOH, then NH_2OSO_3H; see text. *d*) NH_2OH, MeOH; 66%. *e*) MsCl, Et_3N, CH_2Cl_2; quant. crude. *f*) NH_3, MeOH; see text.

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 Ph*H*. 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.



51 **604** **605** **606**



608 **609** **610**

The structure of tetra-*O*-isopropylidene validoxylamine A **607** is evidenced by its MS and ^{13}C-NMR spectrum. The *C*Me$_2$ *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 $^2H_3$ 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 *C*Me$_2$ 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**.

	51[a]	**604**	**605**[b]	**606**	**608**	**609**	**610**
H–C(2)	4.25	4.10	4.17	4.03	4.15	4.61–4.53	4.68
H–C(3)	3.50–3.30	3.54	3.76	3.46	3.96	4.61–4.53	4.15
H–C(4)	3.84–3.60	3.88	3.88	3.76	4.78	3.70	3.76
H–C(5)	2.00–1.44	1.94–1.78	2.12–1.94	1.70–1.56	–	2.33–2.15	1.71–1.58
H–C(6)	2.63–2.41	2.49–2.31	2.47 (eq)	2.40 (ax)	5.80	2.50 (eq)	2.94 (eq)
H'–C(6)	2.63–2.41	2.49–2.31	2.19 (ax)	2.30 (eq)	–	1.99 (ax)	1.85 (ax)
H–C(7)	3.84–3.60	3.95	4.25	3.76	4.56	3.89	3.86
H'–C(7)	3.84–3.60	3.65	3.71	3.47	4.43	3.62	3.66
J(2,3)	10	10.0	9.3	9.5	10.6	[c]	6.2
J(3,4)	[c]	10.0	9.5	9.0	8.4	11.8	7.8
J(4,5)	[c]	10.0	9.4	9.8	–	6.2	11.5
J(5,6)	[c]	[c]	3.7	14.0	–	6.9	4.4
J(5,6')	[c]	[c]	13.7	4.7	–	11.2	13.4
J(5,7)	[c]	4.2	4.3	3.1	–	5.6	5.0
J(5,7')	[c]	4.6	10.7	2.5	–	11.2	11.2
J(6,6')	[c]	[c]	13.7	14.0	–	17.7	16.4
J(7.7')	[c]	10.0	11.2	10.0	16.2	11.8	11.5
C(1)	212.9	203.05	[c]	207.24	[c]	220.88	154.0
C(2)-C(4)	81.1	77.38	[c]	80.20	[c]	79.39	79.07
	80.8	76.53	[c]	79.76	[c]	78.09	75.02
	74.4	69.61	[c]	73.50	[c]	73.36	74.42
C(5)	43.6	36.47[d]	[c]	39.45	[c]	30.09	32.44
C(6)	41.7	38.25[d]	[c]	41.57	[c]	36.38	21.81
C(7)	64.3	60.88	[c]	61.76	[c]	63.58	64.17

[a]) In D_2O.

b) In $CDCl_3$ + D_2O.

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 NH_3, 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, H_2O), 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 1M HCl to a methanol solution of **45** (to pH 1) led to rapid decomposition to a complex mixture[41]). Pure **45** hydrolysed partially to validone (according to TLC), when it was submitted to *Sephadex G-10* chromatography (eluent water)[42]).

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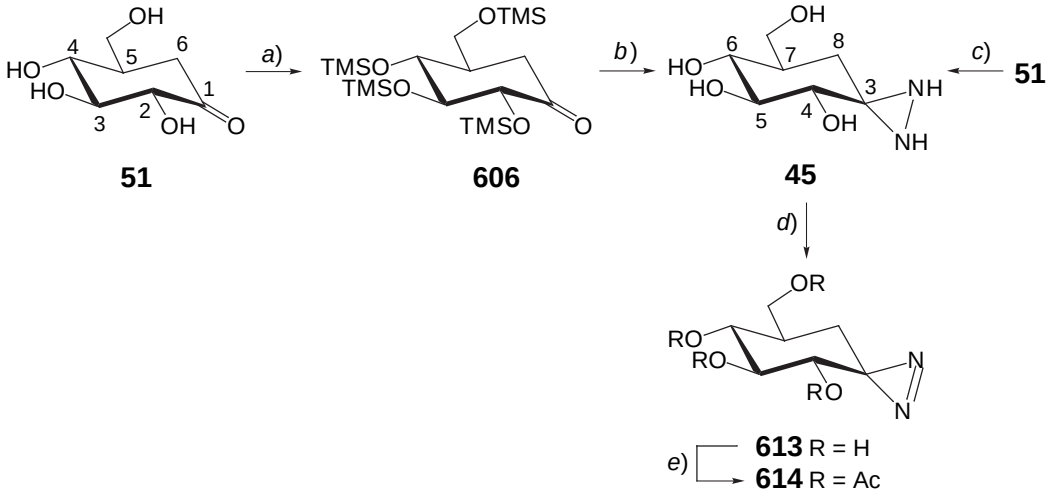
[41]) The higher sensitivity to HCl than to the strong ion exchanger ($R–SO_3H$) may be due to the higher nucleophilicity of Cl^- as compared to that of $R–SO_3^-$.

[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.

Scheme 3.2.5



a) TMSCl, HMDS, pyridine; 27% (chrom., 94% crude). *b*) NH_3, MeOH, then NH_2OSO_3H; 50%. *c*) See text. *d*) I_2, Et_3N, MeOH; 89%. *e*) Ac_2O, pyridine; 84% from **45**.

The diaziridine **45** was also obtained by treating validone (**51**) with NH_3 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 H_2O formed in the condensation of NH_3 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 NH_3/hydroxylamine-*O*-sulfonic acid (*Entry 1*, 28%). Using hexamethyldisilazane and NH_3 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 NH_3/hydroxylamine-*O*-sulfonic acid

provided **602** in 29% yield (*Entry 6*). Treating **52** with excess chlorotrimethylsilane and NH_3/hydroxylamine-*O*-sulfonic acid resulted in a significantly higher yield (*Entry 7*, 50%), suggesting that the trimethylsilyl ether **606** acts as a H_2O scavenger.

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

Entry	Starting material	Reagents	Product (yield)
1	**51**	NH_3, then NH_2OSO_3H	**45** (28%[b])
2	**51**	$HN(SiMe_3)_2$ (four eq.), then NH_2OSO_3H	**45** (20%[b])
3	**51**	$HN(SiMe_3)_2$ (two eq.), NH_3, then NH_2OSO_3H	**45** (38%[b])
4	**606**	NH_3, then NH_2OSO_3H	**45** (69%[b])
5	**52**	NH_3, then NH_2OSO_3H	**602** (35%)
6	**52**	$HN(SiMe_3)_2$ (two eq.), NH_3, then NH_2OSO_3H	**602** (29%)
7	**52**	Me_3SiCl (four eq.), NH_3, then NH_2OSO_3H	**602** (52%)

[a]) Conditions: A soln. of the starting material in MeOH was treated with $HN(SiMe_3)_2$ at r.t. (*entries 2*, *3*, and *6*) or with Me_3SiCl at –20° (*entry 7*), saturated with NH_3 at –20° (except for *entry 2*), treated dropwise with NH_2OSO_3H (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 I_2 in MeOH in the presence of Et_3N gave a mixture of the diazirine **613** and Et_3N (2.5:1) (Scheme 3.2.5), which could not be separated even by repeated FC. Replacing Et_3N with the more volatile Me_3N, 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 Et_3N gave the tetraacetate **614**[43]) (84% from **45**). Pure diazirine **613** (89%) was obtained from **613**·Et_3N 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].

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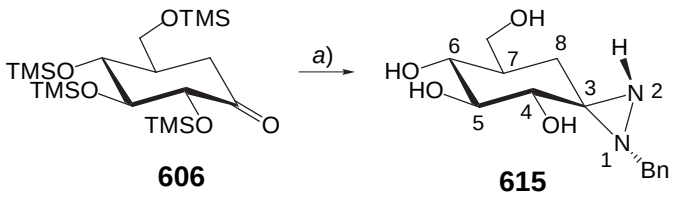
[43]) This acetate of **613** was only prepared for analytical reasons. Deacetylation of **614** was not attempted.

Treatment of the silylated validone **606** with $BnNH_2$ 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 $BnNH_2$, 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 NH_3 or H_2NMe to glyconolactone oxime mesylates in the formation of alkoxydiaziridines, see [813].

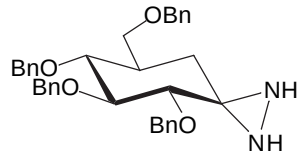
Scheme 3.2.6



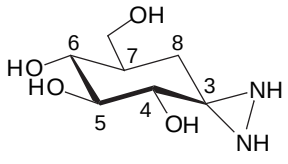
606 **615**

a) $BnNH_2$, MeOH, then NH_2OSO_3H; 27%.

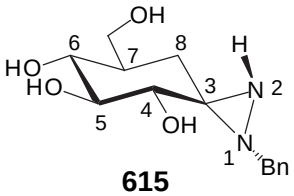
The diaziridines **45** and **615** oxidise iodide to iodine in acidic medium. According to its ^{1}H-NMR spectrum in (D_6)DMSO (Table 3.2.3), **45** is a *ca*. 3:2 mixture of two diastereoisomers. The NH signals of the major isomer appear as two *d* at 2.30 and 2.13 ppm (J = 8.1 Hz) and the NH signals 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]).



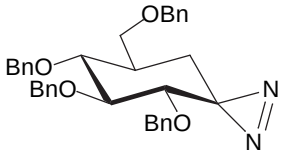
602



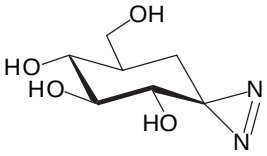
45



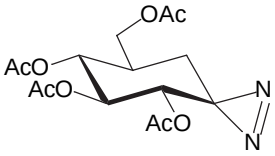
615



603



613



614

According to its ^{1}H-NMR spectrum (D_2O), 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 Ph*C*H_2 as a *t* at 57.27 ppm (compare [772]).

The UV spectrum of **613** (H_2O) shows a typical maximum at 340 nm (ε = 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 $^6C_3$ 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**.

Compounds	**602**	**45**	**615**	**603**	**613**	**614**
Solvent	$CDCl_3$	a)	b)	$CDCl_3$	D_2O	$CDCl_3$
$[\alpha]_D^{25}$	29.4	22.2	59.7	49.7	37.2	47.4
H–C(4)	3.90	3.70	3.62	3.70	3.86	5.15
H–C(5)	3.56	3.06	3.36	3.82	3.54	5.33
H–C(6)	3.69	3.16	3.43	3.65–3.57	3.48	5.13
H–C(7)	2.19–2.06	1.52–1.47	1.53–1.40	2.13–2.05	2.00–1.85	2.40–2.29
H–C(8)	2.26 (ax)	1.95 (ax)	2.04 (eq)	2.05 (ax)	2.00–1.85 (ax)	2.02 (ax)
H´–C(8)	1.35 (eq)	1.52–1.47 (eq)	1.93 (ax)	0.67 (eq)	0.72 (eq)	0.79 (eq)
CH–C(7)	3.77	3.56	3.75	3.63	3.77	4.07
CH´–C(7)	3.48	3.38	3.64	3.42	3.66	3.90
N–H	2.64	2.30/2.24	–	–	–	–
N'–H	1.57	2.13/2.07	–	–	–	–
J(4,5)	9.6	9.0	9.3	9.2	9.3	9.7
J(5,6)	9.6	9.0	9.0	9.2	9.3	9.7
J(6,7)	10.0	9.0	9.0	c)	9.3	10.6
J(7,8)	12.9	14.9	4.1	12.8	c)	9.0
J(7,8´)	2.9	c)	14.0	*ca*. 1	2.8	4.4
J(8,8´)	12.9	14.9	14.3	12.8	13.1	15.1
J(7,CH)	3.7	3.1	3.4	4.4	3.1	5.6
J(7,CH´)	2.5	6.2	5.9	3.4	c)	3.1
J(CH,CH`)	9.1	10.6	11.5	9.0	11.2	11.5
J(NH,N'H)	7.9	8.1/8.1	–	–	–	–
C(3)	57.06	60.02	62.90	28.82	32.34	26.75
C(7)	39.96	43.50	43.05	39.66	43.46	37.28
C(8)	34.80	34.91	27.55	30.21	31.76	29.67
CH_2–C(7)	c)	c)	64.02	c)	c)	c)

a) ^{1}H-NMR spectrum in D_6-DMSO/TFA (NH signals from D_6-DMSO spectrum). ^{13}C-NMR spectrum in D_2O.

b) ^{1}H-NMR spectrum in D_2O. ^{13}C-NMR spectrum in CD_3OD. PhC*H*: 3.92, PhC*H*': 3.81; *J* (PhC*H*,PhC*H*') = 14.5.

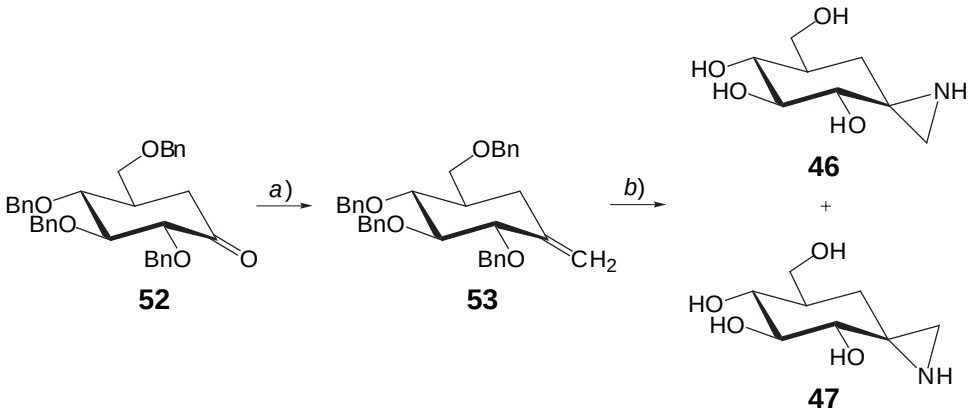
c) Not determined.

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**).

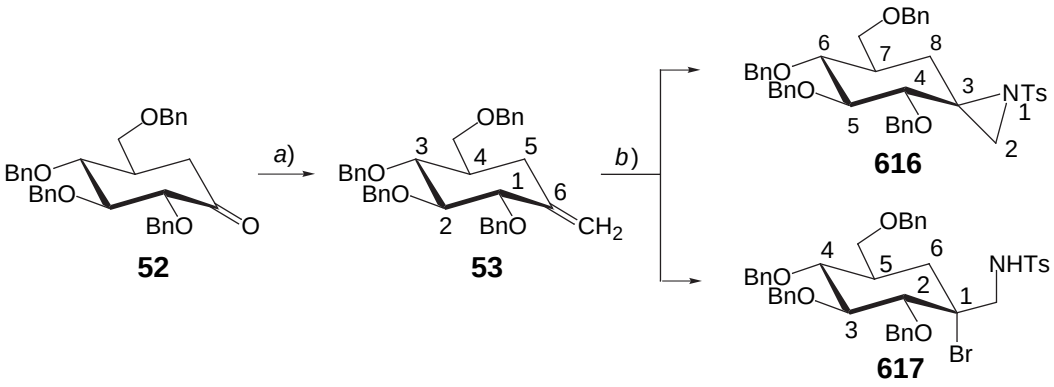
Scheme 3.2.7



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



a) $Ph_3P{=}CH_2$, THF; 77%. *b*) Chloramine T, $PhMe_3NBr_3$, MeCN; 18% of **616**, 2% of **617**.

The alkene **53** did not react with TsN_3 in toluene at 110° ([230] [231]), with TfN_3 in CH_2Cl_2 ([232]), with diphenylphosphoryl azide in toluene at 70°, with NBS and NaN_3 in DME/H_2O (or DMF) ([827]), nor with I-NCO in Et_2O, 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 NaN_3 in MeCN ([825] [869] [870] [889]) gave 34% of a mixture of IN_3 addition products which on treatment with $LiAlH_4$ gave **53** (43%, see exp. part). Such an elimination of a *β*-iodoazide by $LiAlH_4$ 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 *m*CPBA/$NaHCO_3$ 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 NaN_3 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 $LiAlH_4$ 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

acid ion exchanger (elution with 2% aq. NH_3) and then on a CN phase silica gel (elution with MeOH). The CN phase chromatography was only successful if the column had been used in a previous chromatography of **46**. Chromatography of **46** on a new CN phase led to demodification[44]). A ^{1}H-NMR spectrum of the eluate showed 4 multiplets with relative intensities of 2:2:2:3 resonating at 2.56–2.40, 1.85–1.65, 0.86–0.66, and 0.28–0.06 ppm, consistent with the structure $R^1R^2Si(CH_3)–(CH_2)_3–CN$. According to the manufacturer the cyanopropyl group is attached to the silica gel *via* a –X–Si(Y)(CH_3)– linker, where X and Y remain a trade secret. The CN phase is demodified by anhydrous MeOH, but not by MeOH containing traces of water (1 drop of water per one litre of MeOH)[45]).

Birch debenzylation 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*).

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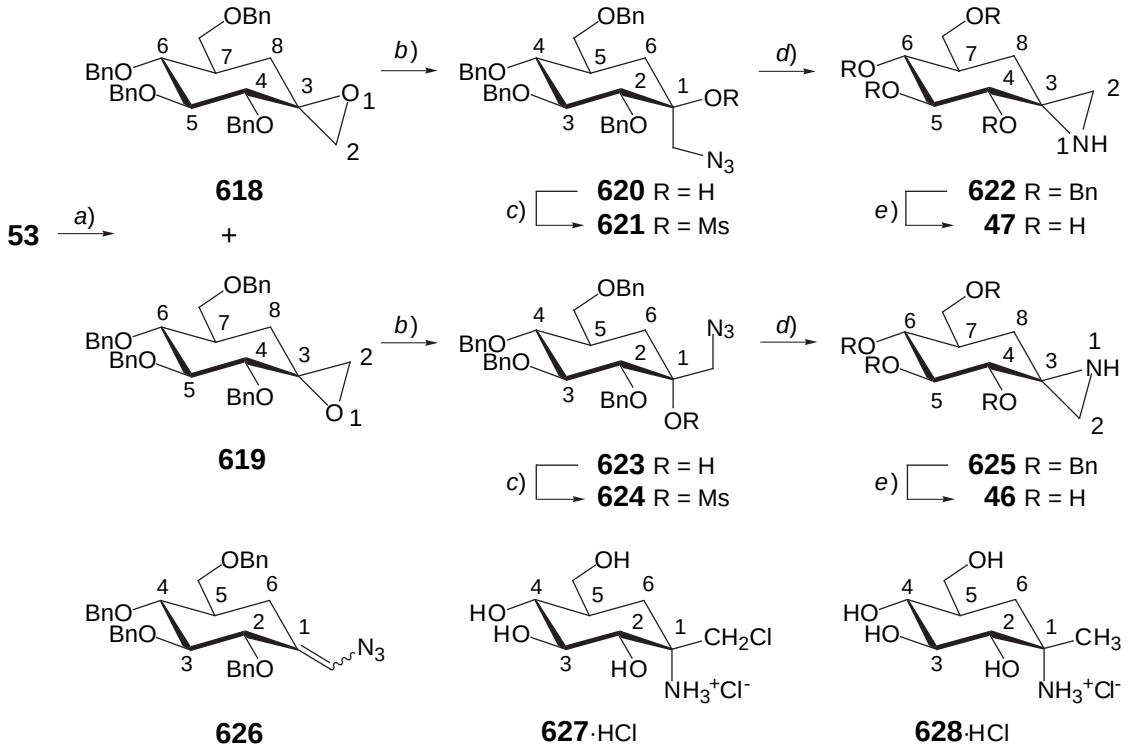
[44]) The CN phase is a "reversed phase" silica gel prepared by derivatising Si–OH groups at the surface of the silica with a cyanopropyl group attached to a linker, a process called modification. Demodification involves cleavage of the cyanopropyl group (along with the spacer?) from the silica gel. 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].

[47]) *Dr. J. F. Poisson*, post-doctoral fellow from November 2000 to October 2001.

Scheme 3.2.9



a) *m*CPBA, $NaHCO_3$, CH_2Cl_2; 25% of **618**, 61% of **619**. *b*) NaN_3, DMF; 91% of **620**; 88% of **623**. *c*) MsCl, DMAP, 2,5-lutidine; 95% of **621**, 4% of **626**; 99% of **624**. *d*) $LiAlH_4$, THF; 83% of **622**; 74% of **625**. *e*) Na, NH_3, THF; 45% of **46**; (yield of **47**: see text).

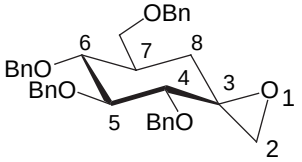
Poisson[47]), convinced that **47** should be stable, re-examined its synthesis. His attempts to improve the synthesis of the protected derivative **622** from **52** were not fruitful. He then attempted to prepare **47** *via* the trifluoroacetamide of **622**, but was unable to obtain the pure amide. 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 ^{1}H-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) ($\Delta\delta$ = 0.29 ppm) and H–C(7) ($\Delta\delta \approx$ 0.2 ppm), as compared to **618**. This shift confirms the assignment of the configuration of **618** and **619**.

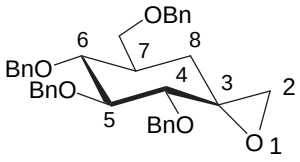
The ^{1}H-NMR spectrum of the *N*-tosyl aziridine **616** shows two br. *s* at 2.63 and 2.59 ppm (H_2–C(2)) (Table 3.2.4). Their small coupling constants are typical for aziridines [715]. C(3) appears as a *s* at 51.73 ppm and C(2) as a *t* at 28.77 ppm. The configuration of **616** was determined by 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.

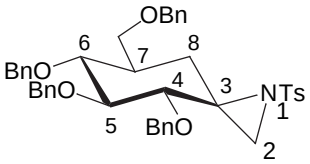
H_2–C(2) of the crude aziridine **47** resonate as two br. *s* at 1.96 and 1.53 ppm, respectively. The coupling constants evidence a $^6C_3$ conformation. In the HR-MS, the $[M + 1]^+$-peak appears at 190.1076 (calc. 190.1079).



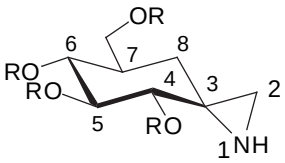
618



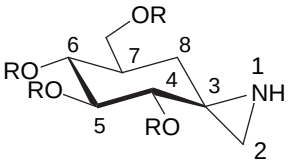
619



616



622 R = Bn
47 R = H



625 R = Bn
46 R = H

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**.

	618	**619**	**616**	**622**	**625**	**47**	**46**
Solvent	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	D_2O	CD_3OD
$[\alpha]_D^{25}$	36.0	16.5	–9.2	32.1	8.8	a)	6.0
H–C(2)	3.18	2.98	2.63	1.87	1.98	1.96	2.02
H´–C(2)	2.56	2.59	2.59	1.40	1.29	1.53	1.34
H–C(4)	3.73	3.69	3.78	3.78	3.65–3.57	3.80	3.48
H–C(5)	3.54	3.83	3.39	3.60	3.65–3.57	3.36	3.22
H–C(6)	3.61–3.54	3.66	3.63	3.68	3.65–3.57	3.45	3.30
H–C(7)	1.93–1.81	2.09–2.00	1.88–1.78	2.15–2.06	1.93-1.81	1.87–1.78	1.68–1.57
H–C(8)	2.09	2.09–2.00	2.42–2.35	2.01	2.00	1.87–1.78	1.73
H´–C(8)	1.46	1.36	2.42–2.35	1.29–1.21	1.31–1.25	1.26	1.29
CH–C(7)	3.61–3.54	3.75	3.70	3.79	3.65–3.57	3.78	3.75
CH´–C(7)	3.50	3.41	3.51	3.45	3.49	3.70	3.58
N–H	–	–	–	1.17–0.85	1.18–0.85	–	–
OH	–	–	–	–	–	–	–
J(2,2')	5.3	5.0	0	0	0	ca. 0.5	ca. 0.5
J(4,5)	9.3	9.6	9.3	9.0	a)	9.3	9.0
J(5,6)	a)	9.3	9.2	9.2	a)	9.2	9.0
J(6,7)	a)	9.6	10.6	9.5	a)	9.5	9.2
J(7,8)	13.1	a)	a)	12.9	a)	a)	12.5
J(7,8´)	3.4	*ca.* 1	a)	a)	a)	a)	2.8
J(8,8´)	13.4	10.0	a)	12.9	12.5	10.6	12.5
J(7,7^1)	a)	3.4	4.4	3.7	a)	3.1	3.7
J(7,7$^{1'}$)	2.8	1.9	2.5	2.2	2.8	5.0	5.9
J(7^1,7$^{1'}$)	8.7	9.0	9.0	9.0	9.0	11.3	10.9
C(2)	49.61	49.70	28.77	27.17	26.97	a)	27.36
C(3)	59.77	58.76	51.73	37.42	37.86	a)	39.90
C(7)	40.06	39.80	41.58	40.29	40.92	a)	43.77
C(8)	32.64	32.17	35.28	33.62	34.32	a)	34.27

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. CH_2–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 CH_2–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 N_3 and OH groups. C*H*$_2$–N_3 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** ($\Delta\delta \approx 0.3$ ppm for H–C(3) and $\Delta\delta \approx 0.4$ ppm for H–C(5)) and **621** ($\Delta\delta = 0.37$ ppm for H–C(3) and $\Delta\delta \approx 0.4$ ppm for H–C(5)). H–C(2) ($\Delta\delta \approx 0.8$ ppm) and H_{ax}–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 CH_2–N_3 substituent of **620** and **621** are larger than those of the equatorial CH_2–N_3 of **623** and **624** (ΔJ = 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 N_3 group, by a br. *t* at 6.36 ppm (*J* = 1.2 Hz) for C*H*–N_3, and by the MS spectrum (*m/z* 570 corresponding to $[M + Na - N_2]^+$). 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 $^4C_1$[48]). 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.

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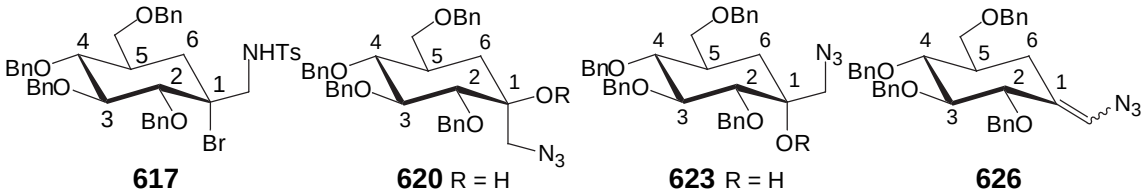
[48]) Generic locants are used in the *Scheme* and *Table* to describe **626**. IUPAC nomenclature is used in the experimental part.



617 **620** R = H **621** R = Ms **623** R = H **624** R = Ms **626**

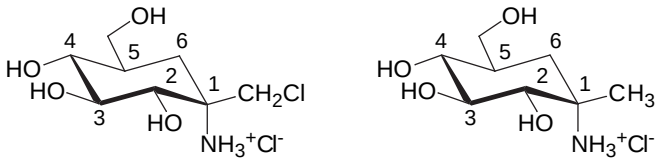
Table 3.2.5: Optical Rotation and Selected ^{1}H- and ^{13}C-NMR Chemical Shifts [ppm] and Coupling Constants [Hz] for **617**, **620**, **623**, **621**, **624**, and **626**.

	617	**620**	**623**	**621**	**624**	**626**
Solvent	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
$[\alpha]_D^{25}$	a)	16.2	9.1	a)	a)	a)
CH–C(1)	3.18	3.74	3.29	4.10	4.17	6.36
CH´–C(1)	3.04	3.34	3.22	3.45	3.90	-
H–C(2)	3.13	3.62–3.49	3.46	4.38	3.54	3.92
H–C(3)	4.03	3.62–3.49	3.87	3.53	3.90	3.45
H–C(4)	3.57	3.62–3.49	3.54	3.66	3.62	3.58
H–C(5)	2.29–2.15	1.75–1.62	2.21–2.09	1.79–1.66	2.25-2.13	1.72–1.60
H–C(6)	2.09–1.91	2.06	1.80	2.66	2.40	2.73
H´–C(6)	2.09–1.91	1.58	1.67	2.52	1.89	1.80
CH-C(5)	3.70	3.66	3.76	3.67	3.79	3.65
CH´–C(5)	3.40	3.45	3.43	3.51	3.43	3.52-3.47
N–H	3.62	–	–	–	–	–
OH	–	2.13	2.41	–	–	–
$J(1^1,1^{1'})$	13.4	12.8	11.8	14.0	12.1	(1.2)
J(2,3)	9.0	a)	9.3	9.3	9.7	7.5
J(3,4)	9.2	a)	9.3	9.3	9.3	8.7
J(4,5)	10.9	a)	10.9	9.3	10.9	9.5
J(5,6)	a)	2.5	4.1	3.7	3.4	3.7?
J(5,6´)	a)	13.1	14.3	13.1	13.4	13.4
J(6,6´)	a)	12.8	14.3	13.4	14.8	13.7
$J(5,5^1)$	4.1	4.1	4.1	4.7	3.7	4.7
$J(5,5^{1'})$	2.2	2.5	2.5	2.5	2.5	2.5
$J(5^1,5^{1'})$	9.0	9.0	9.0	9.0	9.3	9.0
CH_2–C(1)	a)	54.49	57.89	52.94	53.46	–
C(1)	a)	75.68	74.67	95.31	94.00	a)
C(5)	a)	38.64	37.39	38.64	37.83	42.24
C(6)	a)	33.80	33.02	30.94	32.67	30.39

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 ^{1}H-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



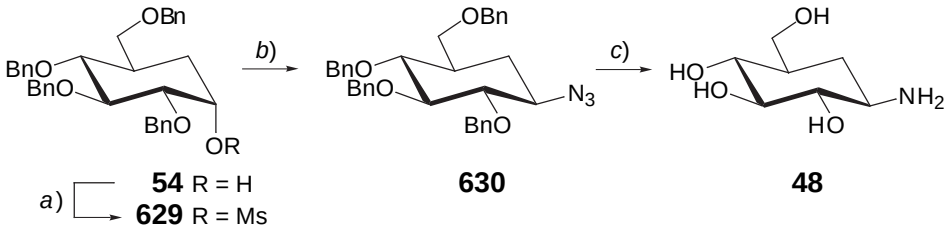
627·HCl **628**·HCl

In the ^{1}H-NMR spectrum of the mixture **627**·HCl/**628**·HCl, C*H*$_3$ of **628**·HCl resonates as a *s* at 1.43 ppm. C*H*$_2$–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 NH$_3^+$ is bound to CH$_2$–C(1) (*cf.* the C*H*$_2$–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-bromocyclohexane 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 NaN_3 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.

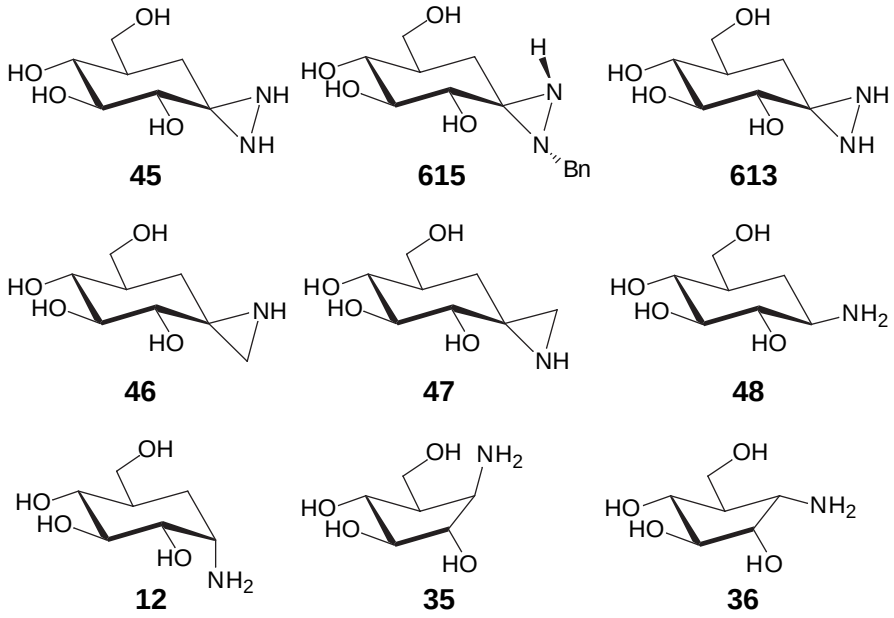
Scheme 3.2.11



a) MsCl, pyridine; 93%. *b*) NaN_3, DMF; 94%. *c*) H_2 (6 bar), 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 (IC_{50} = 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 ([IC_{50}] 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].

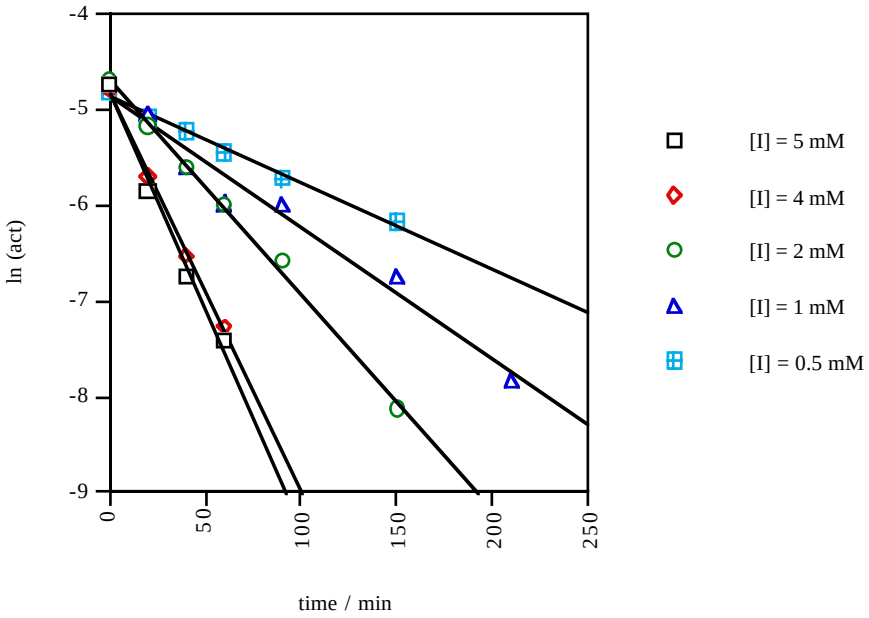
Inhibitor (pK_{HA})	β-Glucosidase (Sweet Almonds)	β-Glucosidase (*C. saccharolyticum*)	α–Glucosidase (Brewer's Yeast)
45 (2.6)[j])	no inh. at 8.8mM	no inh. at 2.2mM[a])	no inh. at 8.8mM
615	no inh. at 3.7mM	[b])	≈ 1.7
613	no inh. at 5.8mM	[b])	no inh. at 11.6mM
47[c])	ca. 30% inh.	ca. 10% inh.	ca. 50% inh.[d])
46 (6.8)	no inh. at 1.3mM	3[e]) (irreversible)	≈ 1[f])
48 (8.4)	1.7	1.0	0.7
12[g])	1.5	–	0.58
35[h]) (7.9)	0.0034[e])	0.00018[e])	0.013[e])
36[i])	0.0065[e])	0.0015[e])	0.0006[e])

[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]) K_i 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 acyloxylating 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 *β*-Glucosidase from *Caldocellum saccharolyticum* by **46**. Plot of the ln of the residual activity *vs.* time.

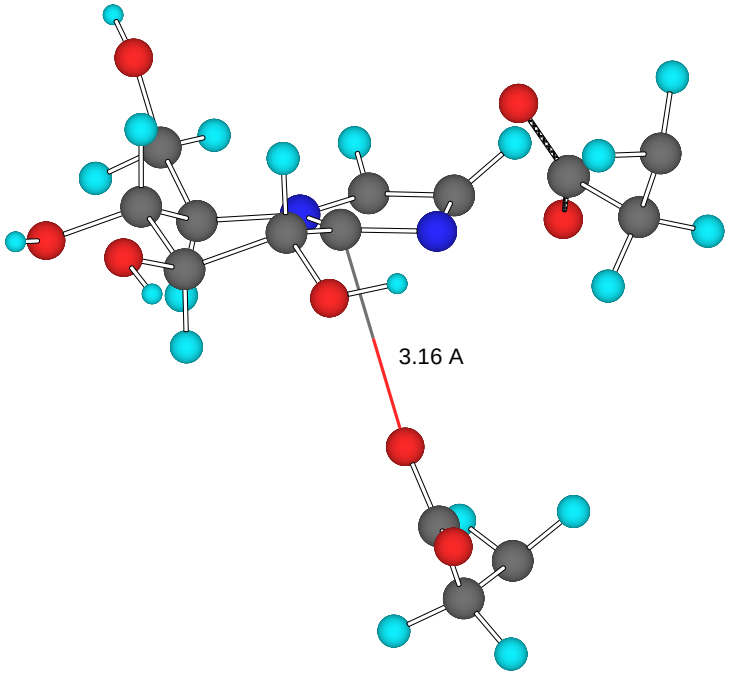


Also 1-*epi*-validamine (**48**) proved a weak inhibitor of all three enzymes, with IC_{50} values in the millimolar range, similar as its epimer validamine (**12**) [31].

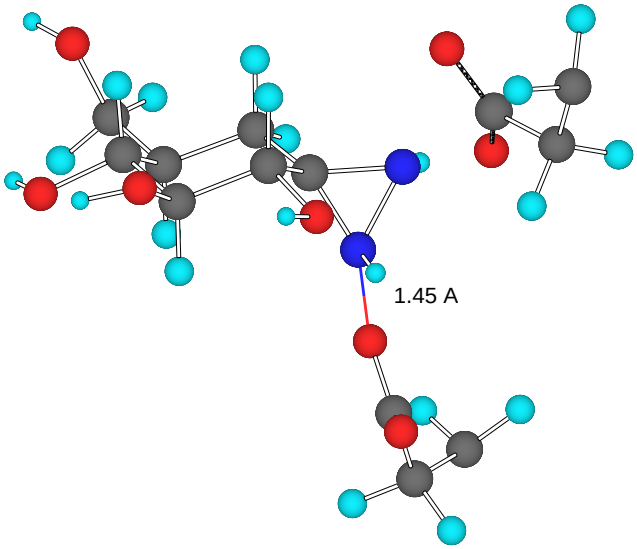
The very low inhibition by the diaziridines, aziridines, and *epi*-validamine suggests that structural factors rather than basicity are at the root of the weak interaction of the glycosidases tested. Basicity does have some effect and the lower basicity of the diaziridine **45** as compared to the one 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 *β*-glucosidase by **45** and **46** is probably due to steric crowding due to the relatively bulky (as compared to H) NH or CH_2 "*α*-anomeric" substituent and the catalytic nucleophile. Superimposing the diaziridine **45** over the imidazole **19** in complex with the *β*-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)



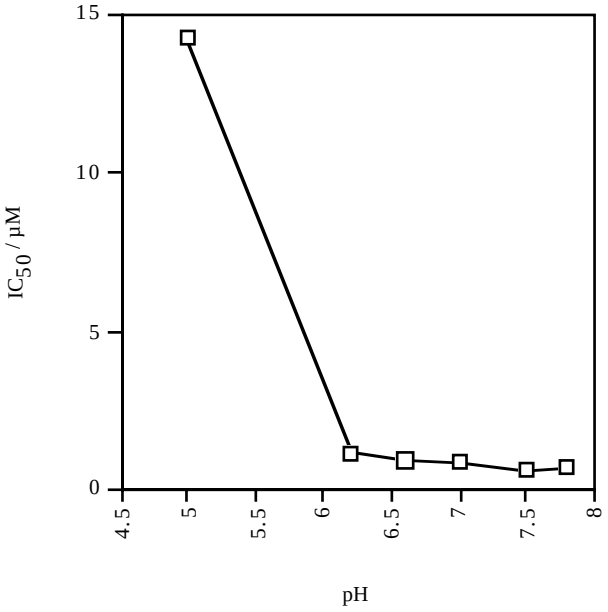
b)



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 between 0.2 and 13 μM [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 *β*-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 *β*-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 *β*-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

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[50]) I thank *Dr. B. Bernet* for generously providing a sample of **35**.

$^{1,4}B$ or flattened conformation requires too much energy.

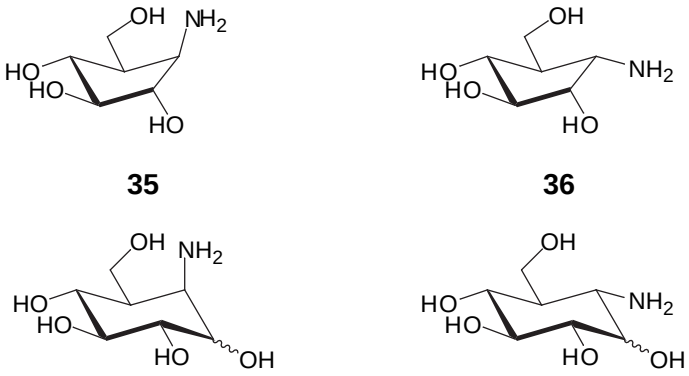
For some endo-glycosidases from families 5 and 7 it was proposed that the substrate first binds in a $^{4}C_{1}$ conformation, bypassing the active site, and then is pulled into the active site and simultaneously distorted to a boat-like reactive conformation (see Chapter 1.6). There is no evidence for 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 β-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-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 embarked upon the synthesis of 5a-aminocarbapyranoses like **49** and **50**. In the literature, no inhibition data for such aminocyclohexitols was found. Some 5a-amino-1-deoxycarbapyranoses were prepared as aminocyclitol analogues, but no inhibition data were given [235].

Scheme 3.3.1

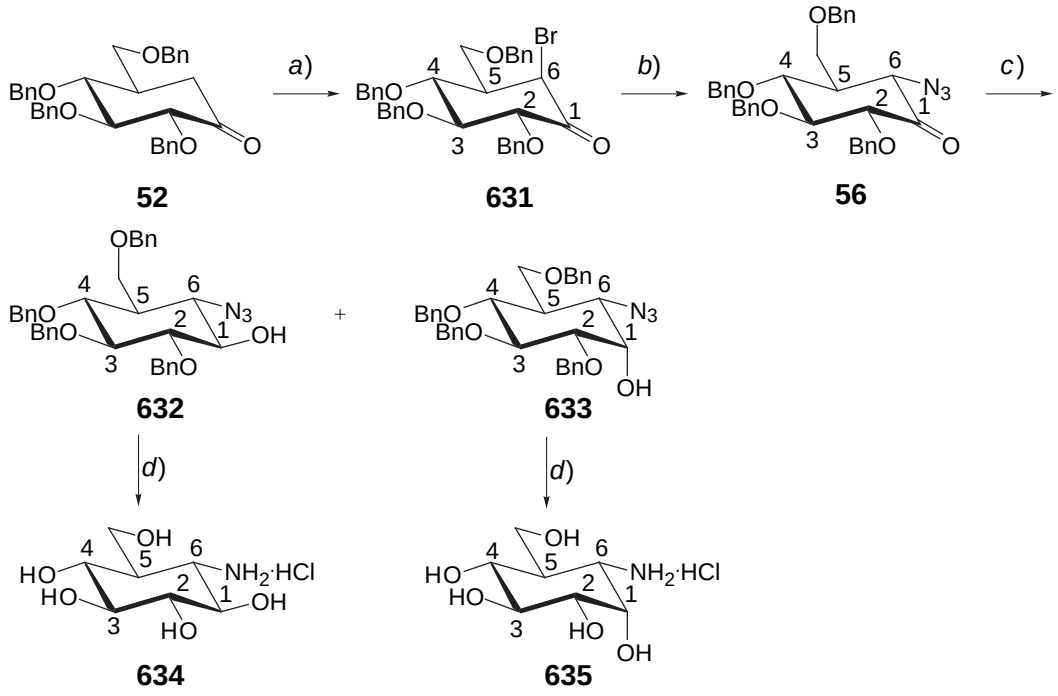


3.3.2. Results and Discussion

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 $PhMe_3NBr_3$ 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



a) $PhMe_3NBr_3$, camphorsulfonic acid, THF; 58%. *b*) NaN_3, DMF; 91%. *c*) i. *i*Bu_2AlH, CH_2Cl_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_2O·MeOH; 100% of **635**·HCl·H_2O.

The 5a-aminocarbapyranoses **634** and **635** are only weak inhibitors of the β-glucosidases of sweet almonds and the α-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 α-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 α-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 (*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_2. Why **36** with an "α"-NH_2 substituent is such a good inhibitor of the β-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 β-glycosidase. 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°).

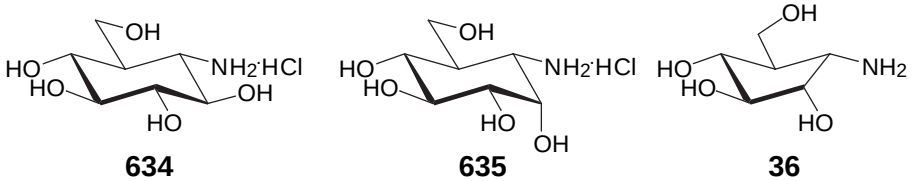


Table 3.3.1: Inhibition of the β-Glucosidases from Sweet Almonds and of the α-Glucosidase from Brewer's Yeast by the 5a-Aminocarbapyranoses **634** and **635** (IC_{50} Values in mM) and by the Aminocyclopentitol **36** (K_i Values in mM [213]).

	634	**635**	**36**
β-Glucosidase (Almonds)	*ca.* 1	> 1	0.0065
α-Glucosidase (Yeast)	*ca.* 0.4 [a])	> 1	0.0006

[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 ($CHCl_3$) band at 2110 cm^{-1}. In the ^{1}H-NMR spectrum, H–C(6) resonates as a *dd* at 4.24 ppm. *J*(5,6) = 12.5 Hz evidences that N_3 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 ($CHCl_3$) OH bands at 3588 and 3579 cm^{-1}, respectively, and N_3 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 N_3 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 N_3 is equatorial. Weak w coupling is observed between *H*O–C(1) and H–C(6) (1.3 Hz).

The ^{1}H-NMR spectrum (CD_3OD) 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 CH_2–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 benzyloxymethyl 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 N_3 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 benzyloxymethyl 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–CH_2–C(5) moiety could also be induced by the conformational changes resulting from the rehybridisation of C(1) from sp^2 to sp^3.

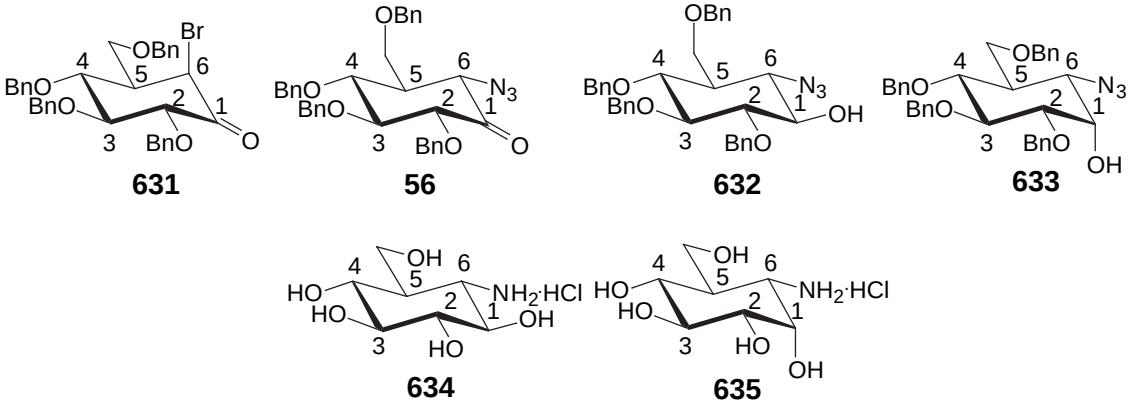


Table 3.3.2: Selected ^{1}H and ^{13}C NMR Shifts [ppm] and Coupling Constants [Hz] for **631**, **56**, **632**, **633**, **634**·HCl, and **635**·HCl.

	631	**56**	**632**	**634**	**633**	**635**
H–C(1)	–	–	3.51	3.37–3.13	4.29–4.20	4.02
H–C(2)	5.08	4.16	3.38	3.37–3.13	3.41	3.36–3.28
H–C(3)	3.76	3.70	3.53	3.37–3.13	3.90	3.61
H–C(4)	3.48	4.00	3.72	3.37–3.13	3.61	3.20
H–C(5)	2.17	1.73	1.50	1.70	2.24	2.04
H–C(6)	4.67	4.24	3.59	3.05	3.46	3.36–3.28
CH–C(5)	3.92	3.87	3.80	4.02	3.89	3.93
CH'–C(5)	3.90	3.62	3.67	3.79	3.62	3.82
OH	–	–	2.53	4.88	2.46	4.88
J(1,2)	–	–	9.2	[a])	2.6	2.6
J(2,3)	10.0	10.0	9.3	[a])	9.5	9.3
J(3,4)	9.3	9.3	9.2	10.9	9.5	9.3
J(4,5)	9.3	10.7	10.7	10.9	8.9	10.6
J(5,6)	3.4	12.5	10.9	10.9	11.8	10.9
J(6,1)	–	–	10.0	[a])	2.5	2.6
J(2,6)	0	1.5	0	[a])	0	0
J(5,7)	2.2	1.7	2.0	3.4	1.6	3.4
J(5,7')	4.0	2.3	2.5	6.8	5.0	6.2
J(7,7')	8.7	9.5	9.3	10.9	9.6	11.2
J(1,OH)	–	–	2.2	[a])	1.3	[a])
J(6,OH)	–	–	0	[a])	1.3	[a])
C(1)	199.83	201.68	[a])	[a])	[a])	[a])
C(5)	42.59	44.85	44.80	43.55	41.42	42.34
C(6)	51.41	63.05	61.49[b])	54.58	58.69	52.80

[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 H_2O.

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]. Carbafuranose-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.

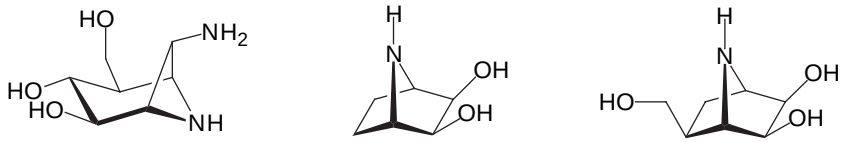
To obtain deeper insight into the strong inhibition by the cyclopentylamine **36**, I prepared the related 5a-amino-5a-carbapyranoses **634** and **635**. The weak inhibition by **634** and **635** suggested that the strong inhibition by **36** depends on the cyclopentane scaffold. The cyclopentanes ("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. Part 3: Bridged Bicyclic Amines as Glycosidase Inhibitors Mimicking Distorted Reactive Substrate Conformers. The Synthesis of 7-Azabicyclo[2.2.1]heptanes and Approaches to the Synthesis of 6-Azabicyclo[3.1.1]heptanes

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.

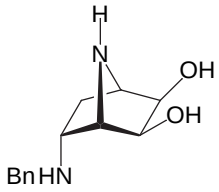
Figure 4.1.1: Potential Glycosidase Inhibitors.



57 **58** **59**

6-Azabicyclo]3.1.1]heptanes have never been examined as glycosidase inhibitors. The only 7-azanorbonanes 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 μM, respectively), the β-galactosidase from bovine liver (65% and 90% inhibition at 1 mM, respectively) and the α-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.



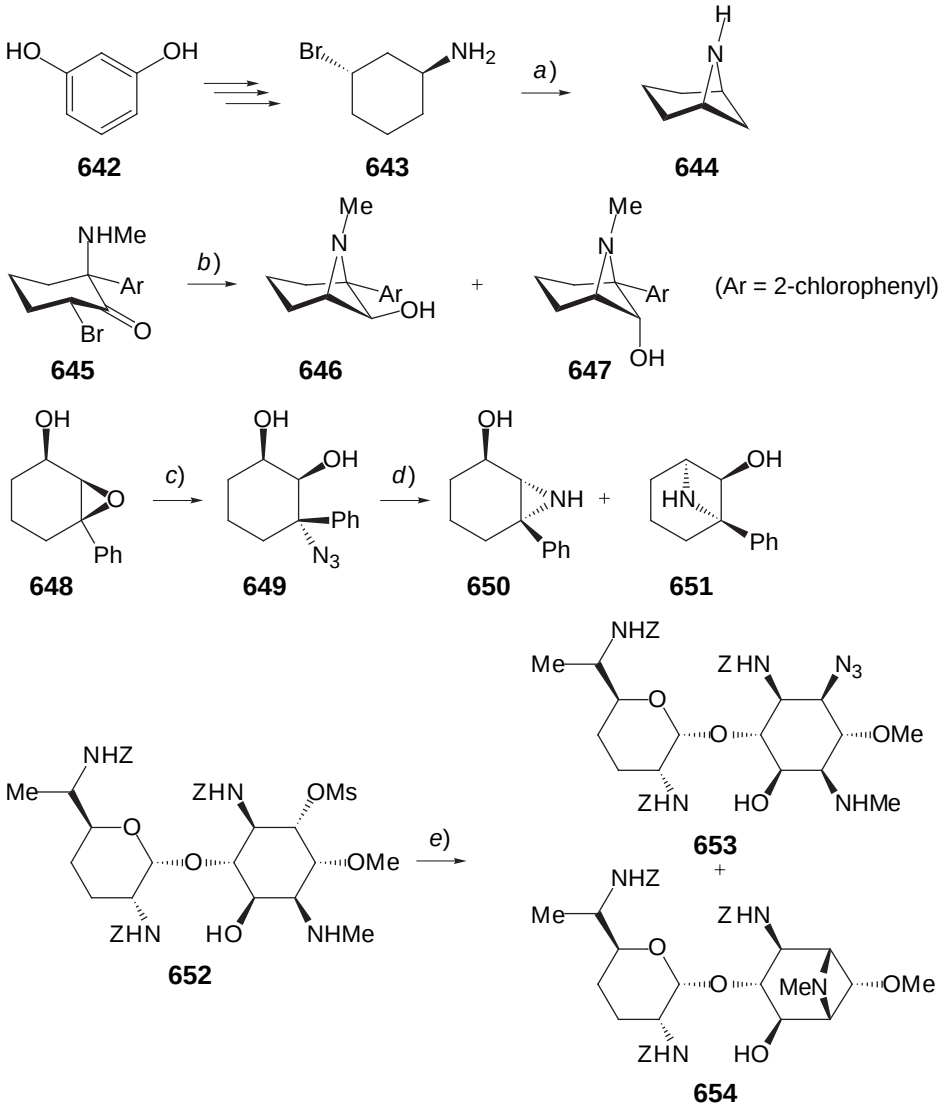
641

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, H_2O) 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 $NaBH_4$ 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 Ph_3P 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 NaN_3 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].

Scheme 4.1.1

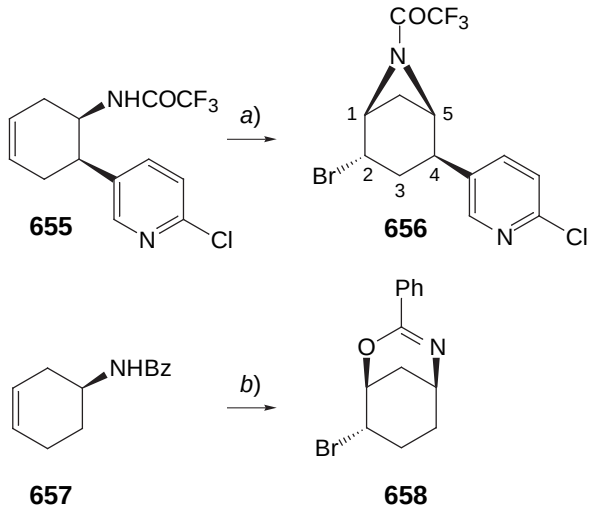


a) NaOH, H_2O; low yield [243]. *b*) $NaBH_4$, EtOH, THF, r.t. to reflux; 55% of **646**, 28% of **647** [244]. *c*) NaN_3, NH_4Cl, MeOH, H_2O; 94% [902]. *d*) Ph_3P, r.t. to reflux, solvent not given; 40% of **650**, 24% of **651** [902]. *e*) NaN_3, DMF; 12% of **653**, 22% of **654** [903].

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].

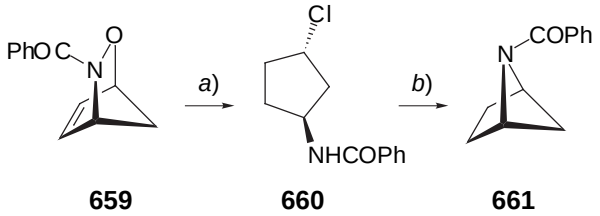
Scheme 4.1.2



a) NBS, AcOH, 0° to 23°; 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 (KO*t*Bu, 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



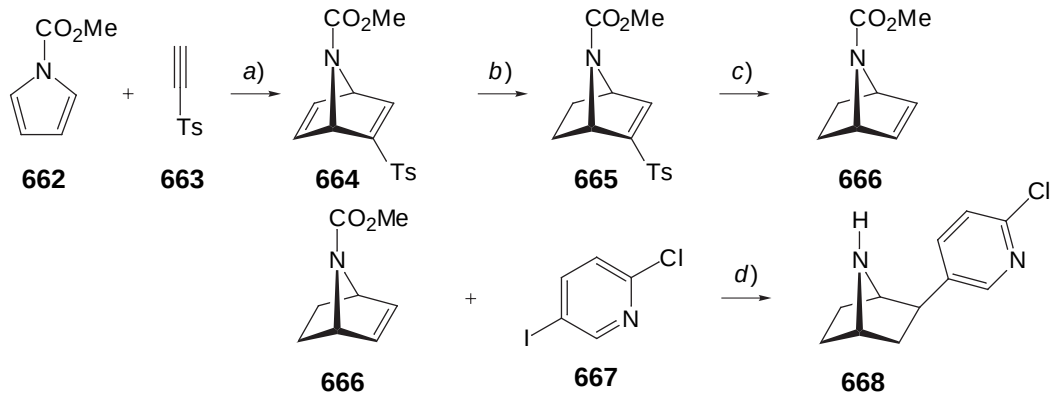
a) i. H_2, Pd/C, EtOH; 95%; ii. Al(Hg), THF, H_2O; 95%; iii. $SOCl_2$, Et_3N, $CHCl_3$; 65% [908]. *b*) KO*t*Bu, DMF, benzene; 83% [908].

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]).

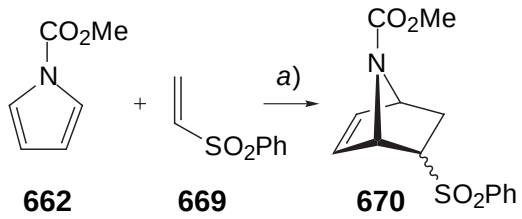
Scheme 4.1.4



a) Neat, 80 – 85°; 36% [925] or CH_2Cl_2, 12 kbar, 85 – 87°; 81% [927]. *b*) H_2, Pd/C, MeCN; 99% [925]. *c*) Na-Hg, Na_2HPO_4, NaH_2PO_4, MeOH, THF; 39% [925]. *d*) i. $(Ph_3P)_2Pd(OAc)_2$, DMF, piperidine, HCO_2H; 35%; 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].

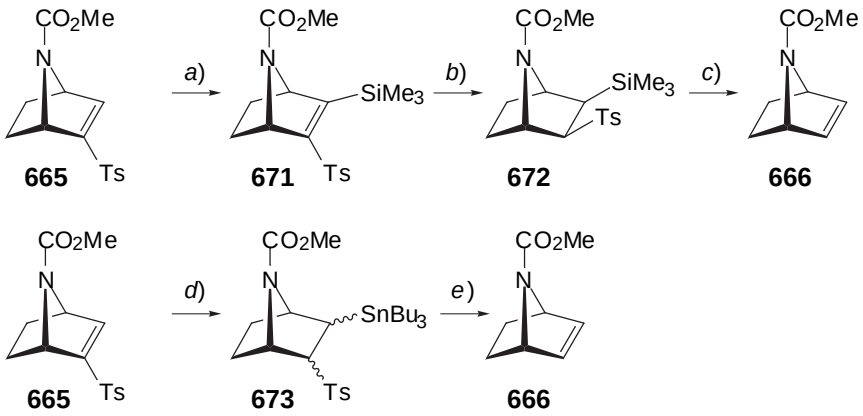
Scheme 4.1.5



a) 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.

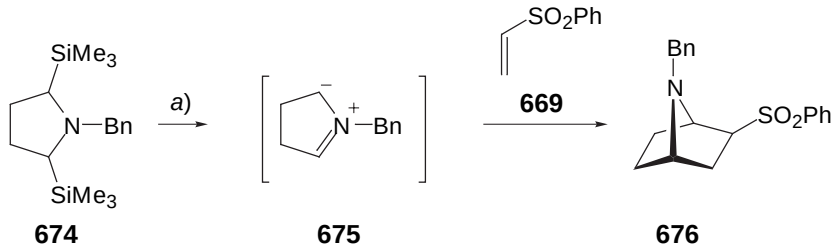
Scheme 4.1.6



a) LDA, THF, then Me_3SiCl; 97% [927]. *b*) $KO_2CN{=}NCO_2K$, AcOH, MeOH; 99% [927]. *c*) Bu_4NF, THF; 86% [927]. *d*) Bu_3SnH, AIBN, benzene; 78 – 91% depending on the scale [928]. *e*) Bu_4NF, 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



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 debocylation afforded the *t*-4-bromocyclohexylamine **682** which cyclised to epibatidine in boiling $CHCl_3$.

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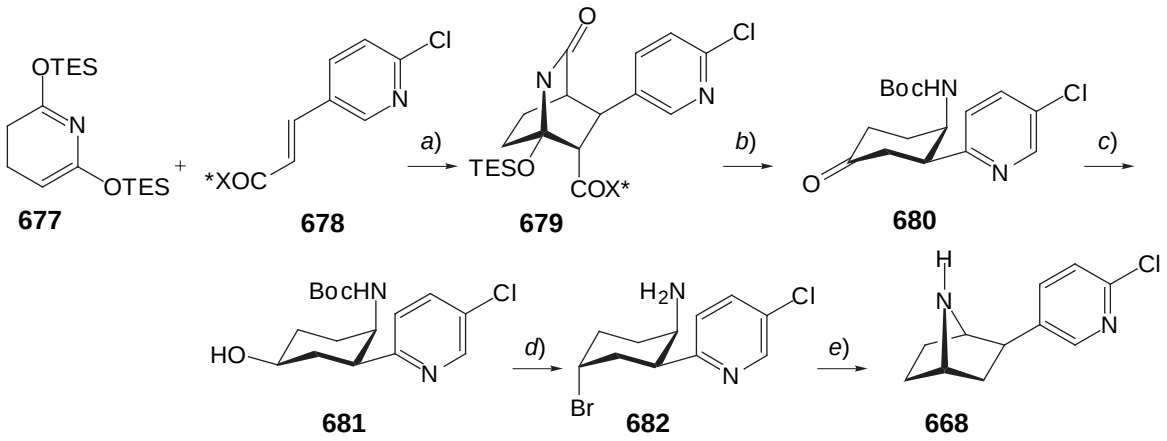
[51]) *t*-4-aminocyclohexanol hydrochloride is commercially available and has been transformed into 7-azanorbornane [908].

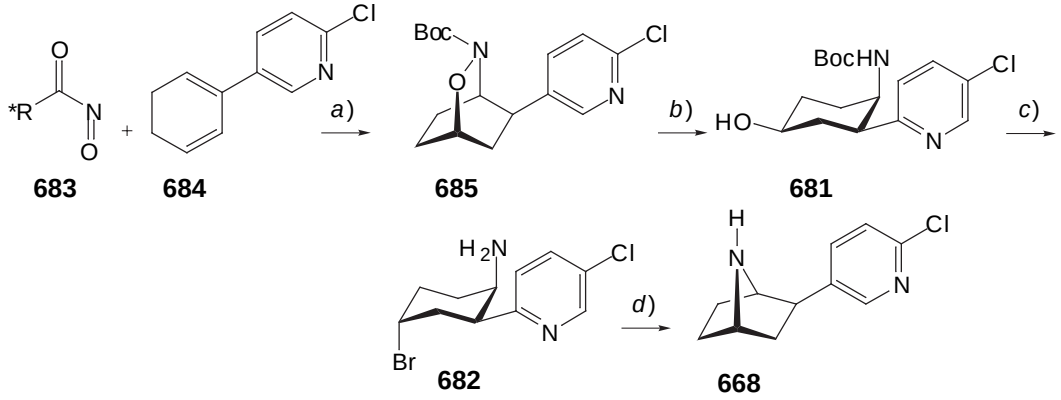
Scheme 4.1.8



a) (X* = (*S*)-4-benzyl-oxazolidinone) Me_2AlCl, CH_2Cl_2; 79% [937]. *b*) Six steps, 33% [937]. *c*) $NaBH_4$, MeOH; 82% of **681**, besides 7% of its diastereoisomer [937]. *d*) i. MsCl, Et_3N, CH_2Cl_2; 92%; ii. LiBr, THF; 84%; iii. CF_3CO_2H, CH_2Cl_2; 91% [937]. *e*) $CHCl_3$, reflux; 95%.

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].

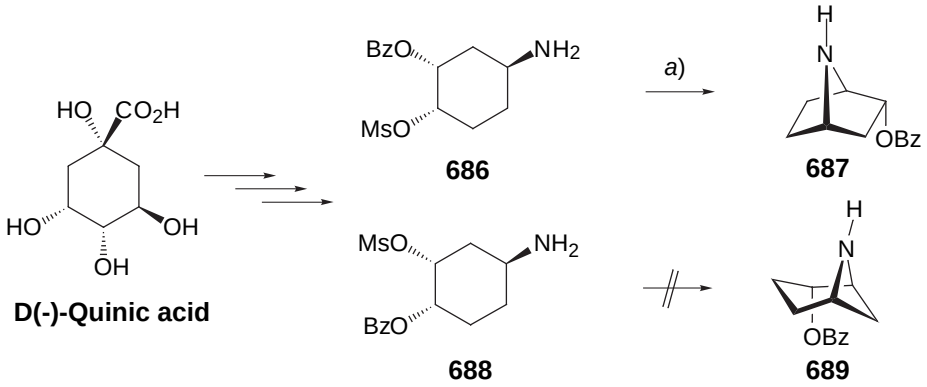
Scheme 4.1.9



a) (R* = 8-(2-naphthyl)menthol) four steps; 20% [939]. *b*) $Mo(CO)_6$, MeCN, H_2O; 85% [939]. *c*) i. Ph_3P, CBr_4, MeCN; 42%; ii. CF_3CO_3H, CH_2Cl_2, then K_2CO_3; 96% [939]. *d*) $CHCl_3$, reflux, then K_2CO_3; 97% [939].

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.

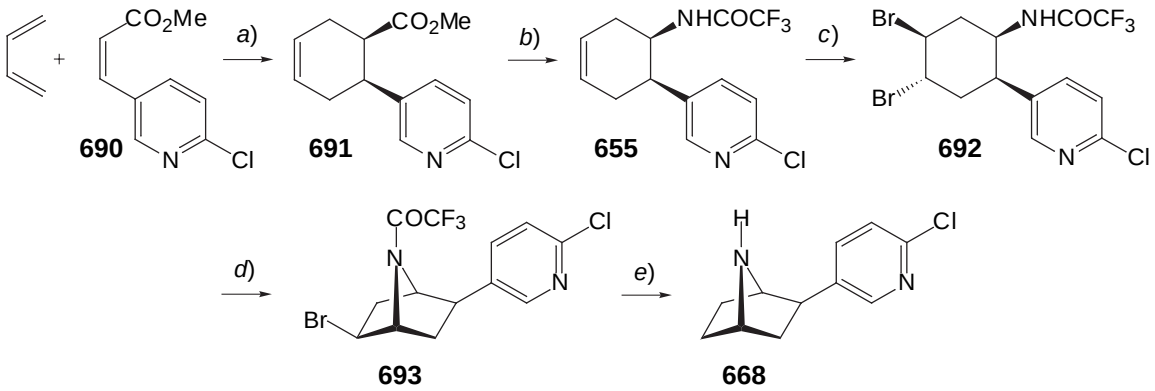
Scheme 4.1.10



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 (Br_2 in the presence of 10 eq. of Bu_4NBr) 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.

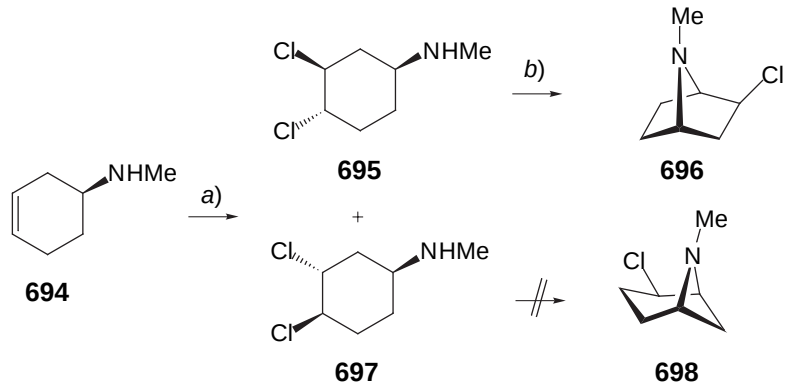
Scheme 4.1.11



a) i. Toluene, 190°; 95%. *b*) i. LiOH, THF; 100%; ii. Et_3N, DPPA, toluene, then $TMSCH_2CH_2OH$; 95%; iii. Bu_4NF, THF; iv. $(CF_3CO)_2O$, Et_3N, CH_2Cl_2; 80% (two steps) [241]. *c*) 10 eq. of Et_4NBr, Br_2, CH_2Cl_2, –78°; 96% [241]. *d*) KO*t*Bu, THF; 75% [241]. *e*) i. Bu_3SnH, 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 (Cl_2) 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].

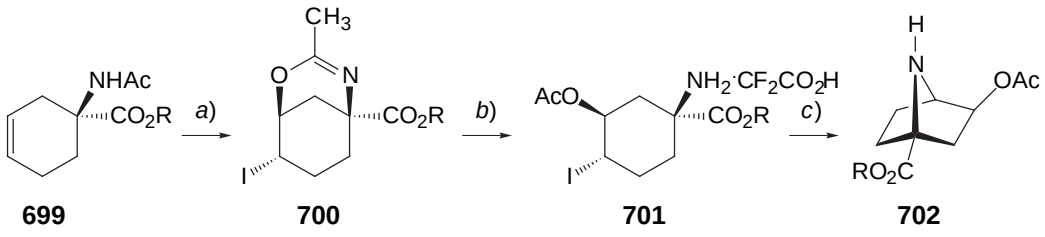
Scheme 4.1.12



a) **694**·HCl, Cl_2, CH_2Cl_2, 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-aminocyclohexenes, establishing the 1,4-*trans* relation between the amino substituent and a leaving group by iodocyclisation. Thus, treatment of **699** with NIS in CH_2Cl_2 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].

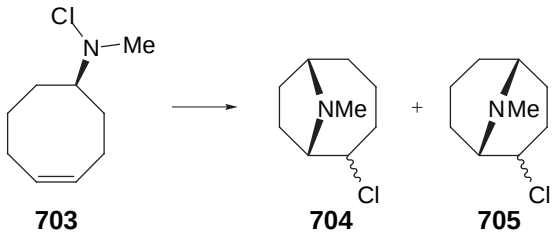
Scheme 4.1.13



(R = (–)-8-phenylmenthyl) *a*) NIS, CH_2Cl_2; 100% [949]. *b*) CF_3CO_2H, THF, H_2O; 99% [947]. *c*) Na_2CO_3, 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



703 **704** **705**

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]).

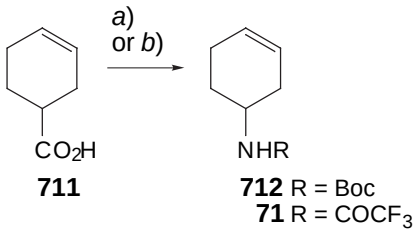
Therefore, I decided to study the effect of the nature of the *N*-acyl goup, of a substitutent at C(6), and of the brominating agent on the bromocyclisation and dibromination-cyclisation of *N*-acylaminocyclohex-3-enes.

The starting cyclohexenes **712** [955] [956] and **71** [957] were prepared in one pot by *Curtius* rearrangement (Et_3N, DPPA) of commercial cyclohex-3-enecarboxylic acid (**711**)[52]),

[52]) 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 *t*BuOH 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-enecarbonyl chloride. The *Curtius* rearrangement of cyclohex-3-enecarbonyl chloride with NaN_3 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

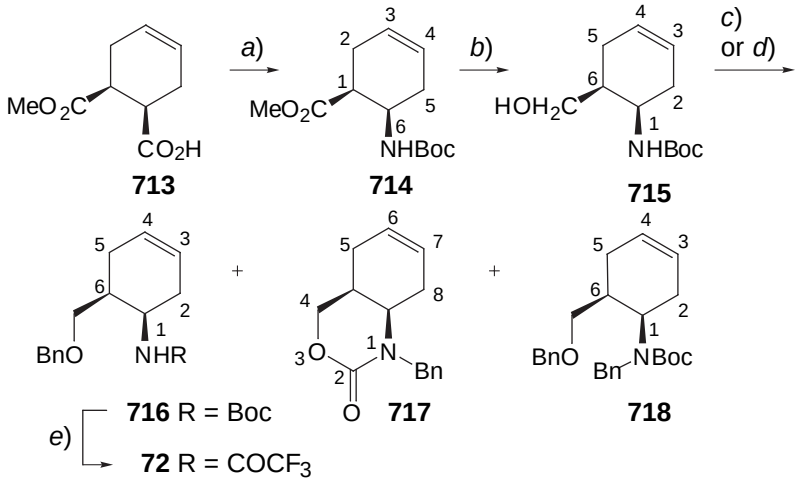


a) DPPA, Et_3N, toluene, then *t*BuOH, CuCl; 92% of **712**. *b*) DPPA, Et_3N, toluene, then CF_3COOH; 84% of **71**.

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 *t*BuOH/CuCl [958] gave the *β*-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

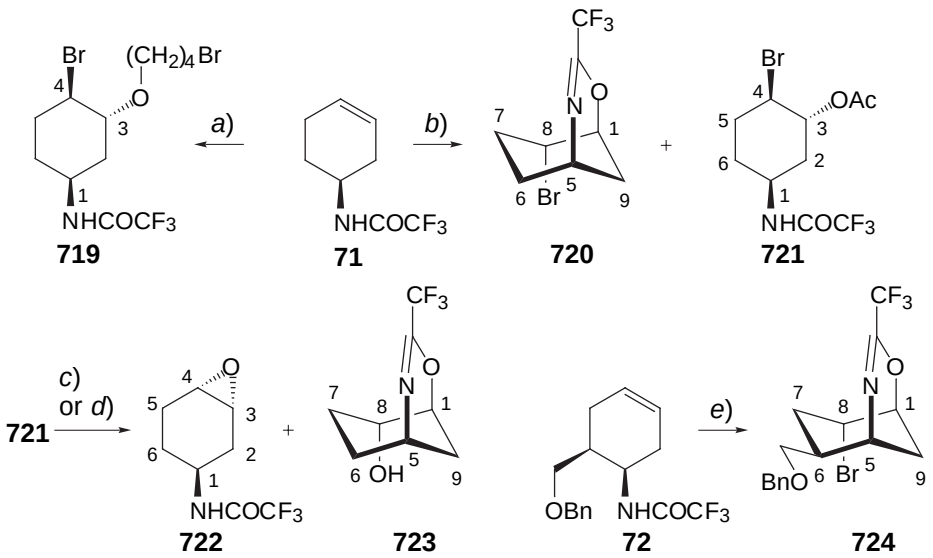


a) DPPA, Et_3N, toluene, then *t*BuOH, CuCl; 90%. *b*) $LiBH_4$, THF; 74%. *c*) Addition to NaH, DMF, then BnBr; 95% of **716**, 5% of **717**. *d*) NaH, DMF, then BnBr; 12% of **718**, 55% of **716**, 33% of **717**. *e*) i: CF_3COOH, CH_2Cl_2; ii: $(CF_3CO)_2O$, Et_3N, CH_2Cl_2; 84%.

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 $^1H_6$, $^6H_1$, $^{2,5}B$, and $B_{2,5}$ conformers (calculated coupling constants (*Macromodel version 6.0, MM3* force field* [707]) for $^1H_6$: $J(1,2) = 5.2$ Hz, $J(1,2') = 1.7$ Hz, $J(1,6) = 2.6$ Hz; for $^6H_1$: $J(1,2) = 4.7$ Hz, $J(1,2') = 11.9$ Hz, $J(1,6) = 2.1$ Hz; for $^{2,5}B$: $J(1,2) = 3.9$ Hz, $J(1,2') = 12.3$ Hz, $J(1,6) = 9.2$ Hz); for $B_{2,5}$: $J(1,2) = 4.2$ 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**. CH_2(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 $^{4a}H_{8a}$ 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 K_2CO_3 in MeOH/H_2O. 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%.

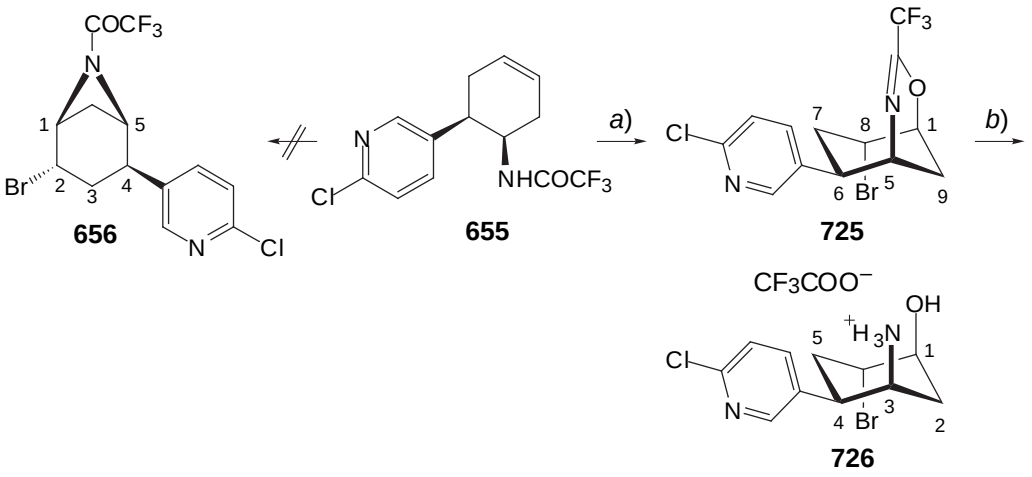
Scheme 4.2.3



a) NBS, THF; 31%. *b*) NBS, AcOH; 31% of **720**, 24% of **721**. *c*) **721**, NaH, THF; 28% of **722**, 33% of **723**. *d*) **721**, K_2CO_3, MeOH, H_2O; 89% of **723**. *e*) NBS, AcOH; 79%.

In view of these results I decided to re-examine the reaction of the trifluoroacetamide **655** with NBS in AcOH which according to *Corey et al.* yielded the bicyclic azetidine **656** [241]. Treatment of **655** (prepared as described in [241]) with NBS in AcOH yielded 81% of a single product **725** (Scheme 4.2.4). Its ^{13}C-NMR data could not be distinguished from those reported by *Corey et al.* for their main product to which they assigned structure **656**. Also the chemical shift values for the ^{1}H signals of **725** (NMR spectrum registered at 300 MHz) were indistinguishable from those reported by *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 **725** rather than **656**, I hydrolysed the cyclisation product with aqueous CF_3COOH in THF, and obtained the trifluoroacetate **726**·CF_3COOH in a nearly quantitative yield.

Scheme 4.2.4



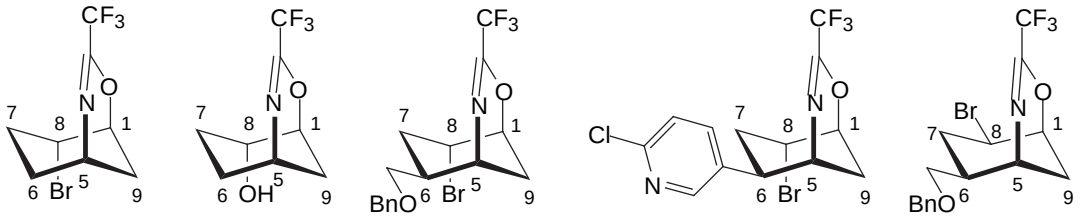
a) NBS, AcOH; 81%. *b*) CF_3COOH, THF, H_2O; quant.

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 $NHCOCF_3$ 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) *d* 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) *d* 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) *d* 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. ^{13}C chemical shift values for similar azetidine trifluoroacetamides have not been reported. The *C*–N *d* of the azetidine moiety of a tricyclic azetidine acetamide resonate at 62.8 and 60.6 ppm [967]. Similarly, the *C*–N *d* 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 $J(7_{ax},8)$ = 3.4 Hz evidences the axial orientation of HO–C(8). The large $J(6,7_{ax})$ for **724** and **725** (12.1 and 10.3 Hz, respectively) evidences that the benzyloxymethyl and the pyridyl groups are equatorial.



720 **723** **724** **725** **762**

The δ value for the C(1) *d* (68.14 ppm) of the salt **726**·CF_3COOOH is typical for a secondary alcohol. The δ values for the C(3) and C(6) *d* 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 $^1C_4$ 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 $J(1,2_{ax})=J(2_{ax},3)$ = 3.4 Hz evidence the *syn* configuration at C(1) and C(3). The large $J(4,5_{ax})$ = 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**.

	720	**723**	**724**	**725**	**762**
υ(C=N)	1686	1689	1688	1688	1689
H–C(1)	4.75–4.70	4.59–4.55	4.74–4.69	4.79	4.79–4.75
H–C(5)	3.93–3.88	3.90–3.84	4.04–3.99	4.02–3.97	4.06–4.02
H–C(6)	2.18–2.01	2.02	2.65–2.54	3.52	2.28–2.16
H'–C(6)	1.99–1.83	1.88–1.78	–	–	–
H–C(7)	1.99–1.83	1.73–1.62	2.12	2.21–2.08	2.36
H'–C(7)	1.99–1.83	1.53	1.57	2.21–2.08	1.52
H–C(8)	4.50–4.45	4.18–4.13	4.51–4.47	4.62–4.57	4.16
H–C(9)	2.59	2.26	2.54	2.74	2.11
H'–C(9)	1.77	1.73–1.62	1.83	1.95	1.86
CH–C(6)	–	–	3.56	–	3.55
CH'–C(6)	–	–	3.29	–	3.27
J (1,5)	[a]	[a]	[a]	2.2	[a]
J (1,8)	[a]	[a]	[a]	3.5	2.2
J (1,9)	1.6	1.5	1.6	1.6	4.1
J (1,9')	3.7	[a]	3.9	4.0	1.6
J (5,6)	[a]	3.1	[a]	2.2	[a]
J (5,6')	[a]	[a]	–	–	–
J (5,9)	1.6	1.5	1.6	1.6	4.1
J (5,9')	3.7	[a]	3.9	4.0	1.6
J (6,7)	[a]	4.7	ca. 3.6	6.5	4.7
J (6,7')	[a]	13.4	12.1	10.3	12.5
J (6',7)	[a]	[a]	–	–	–
J (6',7')	[a]	5.3	–	–	–
J (6,6')	[a]	13.6	–	–	–
J (6,10)	–	–	7.5	–	7.2
J (6,10')	–	–	6.5	–	6.9
J (7,8)	[a]	[a]	[a]	[a]	5.3
J (7',8)	[a]	3.4	4.0	[a]	12.5
J (7,7')	[a]	15.3	15.9	[a]	14.0
J (8,9')	1.9	[a]	1.6	1.6	0
J (9,9')	14.0	14.0	14.3	14.3	14.0
J (10,10')	–	–	9.0	–	9,0
C(1)	74.47	74.26	74.33	73.82	74.99
C(3)	[a]	[a]	147.62	[a]	
C(5)	46.73[b]	46.94	47.80[b]	51.26[b]	46.50[b]
C(8)	48.17[b]	67.39	47.68[b]	47.62[b]	44.26[b]
C*F*$_3$	[a]	–73.43	–73.10	–73.54	–73.69

[a]) Not determined.

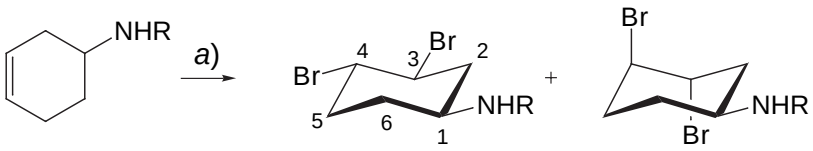
[b]) Assignment may be interchanged.

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 Br_2 in the presence of 10 eq. of Et_4NBr (*cf.* [241]), bromination with two eq. of $PhMe_3NBr_3$, and bromination with excess Br_2.

I first examined the bromination of the carbamate **712** and the amide **71**. The crude products were analysed by ^{1}H-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 $PhMe_3NBr_3$ in CH_2Cl_2 (6:1, *Entry 14*) or with Br_2/Et_4NBr in CH_2Cl_2 (5.5:1, *Entry 11*). On a 10 g scale, bromination of **71** with $PhMe_3NBr_3$ in CH_2Cl_2 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** (1:1.3, *Entry 5*, 1.3:1, *Entry* 1) also resulted from bromination under these conditions. Conversely, the highest ratio in favour of the *t*-3,*c*-4 diastereoisomer resulted from treating **712** with Br_2 in Et_2O at –78° (< 1:10, *Entry 3*). Among the conditions that were used for the bromination of both **712** and **71**, Br_2 in CH_2Cl_2 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 $PhMe_3NBr_3$ in Et_2O, cyclohexane, and toluene (*Entries 7 – 9*) led to a higher proportion of the diaxial dibromide **728** than the reaction in CH_2Cl_2, $CHCl_3$, or MeCN (*Entries 5*, *6*, and *10*). This probably reflects the lower solubility of $PhMe_3NBr$ in Et_2O, cyclohexane, and toluene, and the bromination by $PhMe_3NBr_3$ in these solvents may be mostly due to free Br_2. This hypothesis is corroborated by the similar selectivity of the bromination of **712** with $PhMe_3NBr_3$ in Et_2O and with Br_2 in Et_2O (compare *Entries 4* and *7*).

Scheme 4.2.5



712 R = Boc
71 R = $COCF_3$

727 R = Boc
729 R = $COCF_3$

728 R = Boc
730 R = $COCF_3$

a) Et_4NBr, then Br_2, or Br_2, or $PhMe_3NBr_3$; see Table 4.2.2.

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

Entry	Starting material	Reagents	Solvent	T	**727** / **728** or **729** / **730**
1	**712**	Et_4NBr, Br_2	CH_2Cl_2	–78°	1.3:1
2	**712**	Br_2	CH_2Cl_2	–78°	1:5
3	**712**	Br_2	Et_2O	–78°	< 1:10
4	**712**	Br_2	Et_2O	0°	1:6
5	**712**	$PhMe_3NBr_3$	CH_2Cl_2	0°	1:1.3
6	**712**	$PhMe_3NBr_3$	$CHCl_3$	0°	1:1.7
7	**712**	$PhMe_3NBr_3$	Et_2O	0°	1:6
8	**712**	$PhMe_3NBr_3$	cyclohexane	r.t.	1:5
9	**712**	$PhMe_3NBr_3$	toluene	r.t.	1:3
10	**712**	$PhMe_3NBr_3$	MeCN	0°	*ca*. 1:1.5
11	**71**	Et_4NBr, Br_2	CH_2Cl_2	–78°	5.5:1
12	**71**	Br_2	CH_2Cl_2	–78°	1:3.3
13	**71**	$PhMe_3NBr_3$	CH_2Cl_2	0°	6:1
14	**71**	$PhMe_3NBr_3$	MeCN	0°	3.5:1

Conditions: Two eq. of Br_2. For Et_4NBr, Br_2 see method A in the exp. part. For $PhMe_3NBr_3$ 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 $PhMe_3NBr_3$ in CH_2Cl_2 gave the dibromide **731** (46%) and the dihydrooxazin-2-one **733** (49%)[53]). A yield of 82% of **731** was realised by treating a more highly concentrated solution of **716** in CH_2Cl_2 with two eq. of $PhMe_3NBr_3$ in the presence of 10 eq. of Et_4NBr. Bromination of **716** with Br_2 in CH_2Cl_2 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 $PhMe_3NBr_3$ and 10 eq. of Et_4NBr in CH_2Cl_2 gave the dibromide **735** as the only product in a yield of 89%, while bromination of **72** with Br_2 in CH_2Cl_2 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 $PhMe_3NBr_3$ and 10 eq. of Et_4NBr in CH_2Cl_2 gave the dibromides **737** (84%) and **738** (6%). Bromination with Br_2 in CH_2Cl_2 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 Br_2 in CH_2Cl_2 gave the bicyclic ether **741** (26%) and the oxazin-2-one **740** (32%). According to TLC, bromination of **718** with two eq. of $PhMe_3NBr_3$ and 10 eq. of Et_4NBr in CH_2Cl_2 gave the oxazin-2-one **740** as the main product; **741** was not detected.

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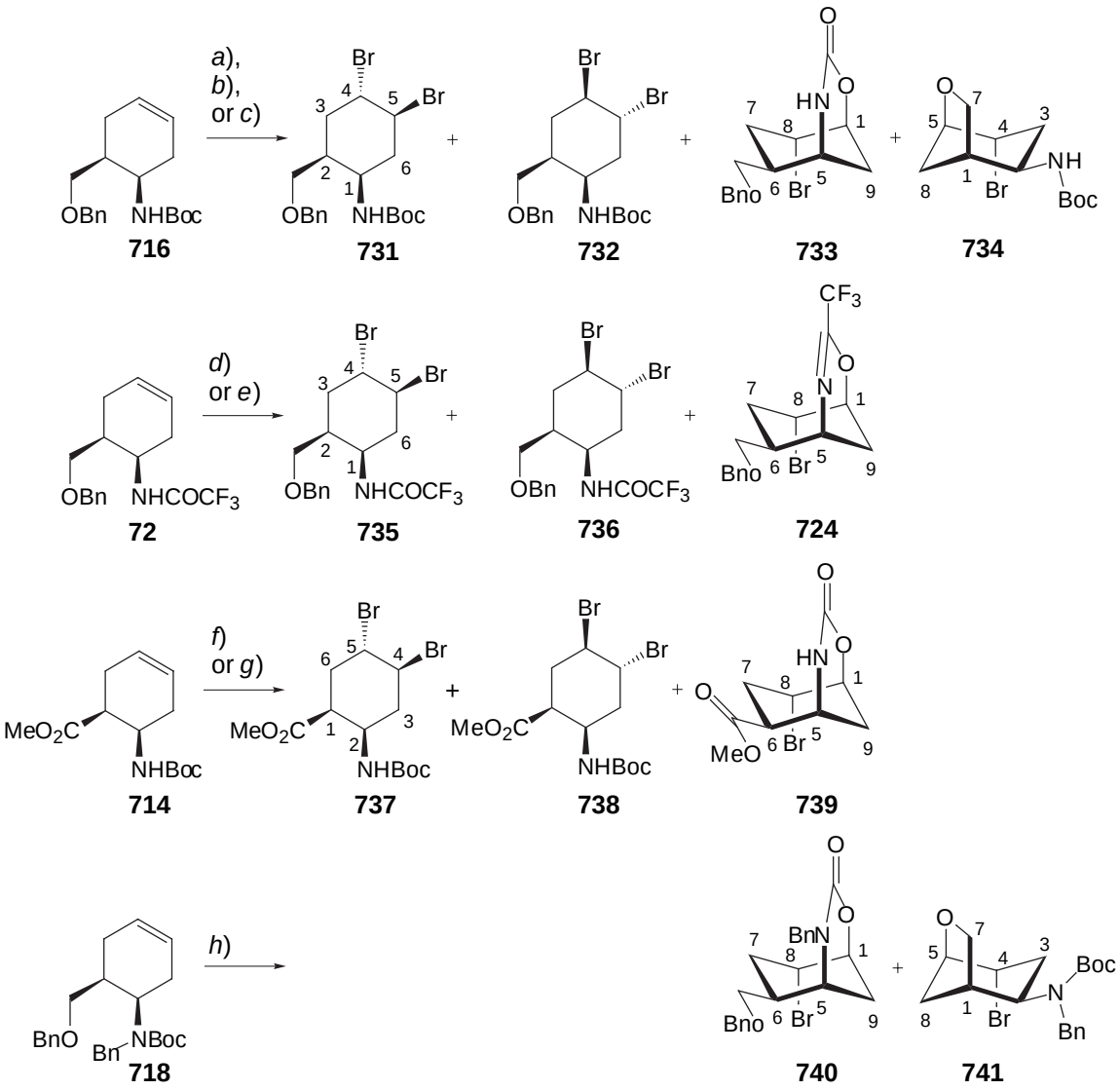
[53]) For a related bromo-carbamoylation, see [955].

Scheme 4.2.6



a) $PhMe_3NBr_3$, CH_2Cl_2; 46% of **731**, 49% of **733**. *b*) Br_2, CH_2Cl_2; 18% of **731**, 6% of **732**, 32% of **734**, 43% of **733**. *c*) Et_4NBr, $PhMe_3NBr_3$, CH_2Cl_2; 82% of **731**. *d*) Et_4NBr, $PhMe_3NBr_3$, CH_2Cl_2; 89% of **735**. *e*) Br_2, CH_2Cl_2; 19% of **724**, 42% of **735**, 32% of **736**. *f*) Et_4NBr, $PhMe_3NBr_3$; 84% of **737**, 6% of **738**. *g*) Br_2, CH_2Cl_2; 28% of **737**, 30% of **738**, 36% of **739**. *h*) Br_2, CH_2Cl_2; 26% of **741**, 32% of **740**.

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

71. 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 $PhMe_3NBr_3/Et_4NBr$ as the brominating agent. Substituting the benzyloxymethyl by the methoxycarbonyl group such as in **714** led to a slightly decreased diastereoselectivity of the brominations with $PhMe_3NBr_r/Et_4NBr$ and with Br_2.

In addition to dibromides, bromination of **714**, **716**, and **72** led also to bicyclic dihydrooxazin-2-ones and bicyclic oxolanes[54]). 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 Br_2 and with $PhMe_3NBr_3$. The oxolanes **734** and **741** and the dihydro-1,3-oxazine **724** were only formed in the reaction with Br_2. Preparatively significant is the addition of excess Br^- in the $PhMe_3NBr_3$ 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 suggests a different reaction mechanism for the brominations by $PhMe_3NBr_3/Et_4NBr$ and by Br_2 in CH_2Cl_2, as it is known from kinetic studies of brominations with Br_2 and with Br_3^- (see [969 – 972] and references cited there). With Br_2, the rate-limiting ionisation of a 2:1 π-complex between Br_2 and the alkene leads to an epibromonium tribromide ion pair which collapses rapidly to the dibromide and Br_2. Bromination with tribromides[55]) is characterised by a rate-limiting nucleophilic attack of Br^- on a 1:1 π-complex between Br_2 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 Br_2 but not by Br_3^- correlates with the higher reactivity of an epibromonium ion as compared to a Br_2-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 Br_2, ionisation of a $(Br_2)_2$: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

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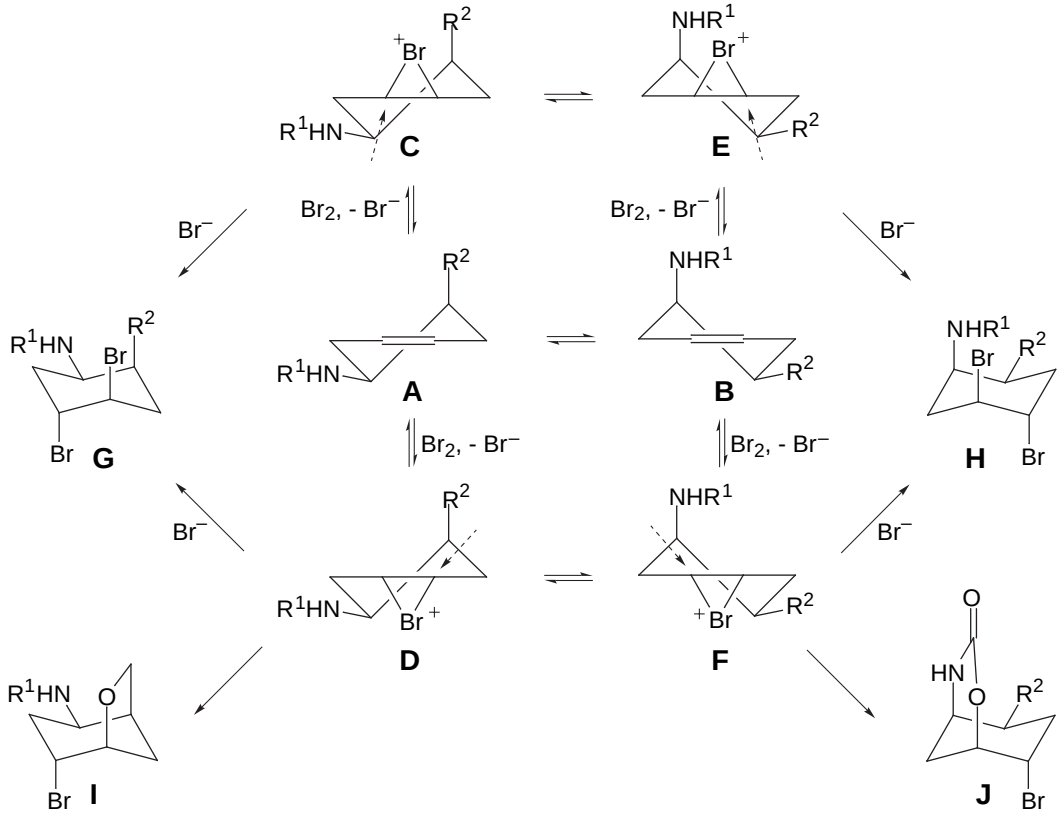
[54]) A similar formation of bicyclic products in the bromination of **712** and **71** by Br_2 cannot be excluded; side products were observed, but not isolated.

[55]) Br_2 and Br^- are in equilibrium with Br_3^-; Br_3^- predominates: $K \geq 2 \times 10^7$ l/mol (dichloroethane); $K = 1.2 \times 10^5$ 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.

Scheme 4.2.7

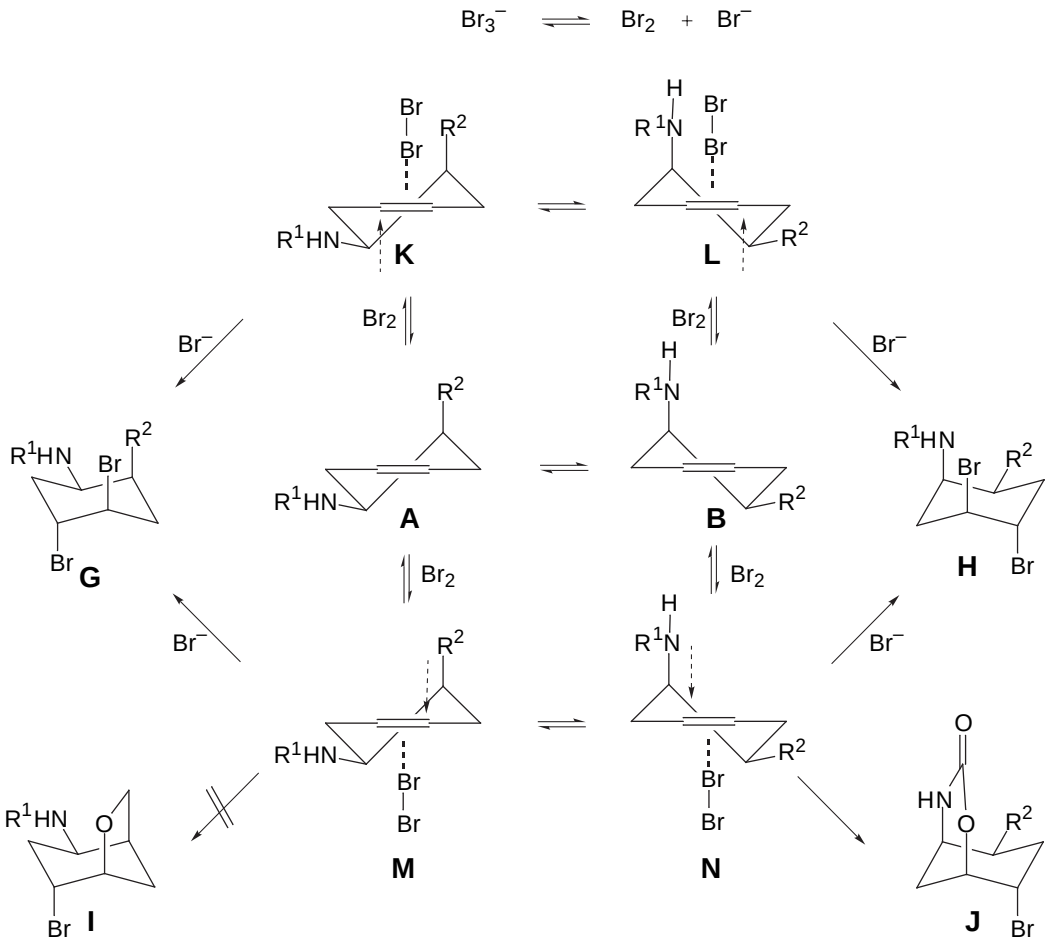


Proposed conformational itinerary for the bromination by Br_2 in CH_2Cl_2. The dashed arrows indicate the trajectories for nucleophilic attack on the epibromonium ions according to the *Fürst-Plattner* rule.

Similarly, bromination by Br_3^- will proceed *via* the 1:1 Br_2 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 Br_3^- indicate that under these conditions bromination *via* the pseudoaxial conformers **L** and **N** is favoured, suggesting a neighbouring group

participation by the NHR group[56]). Both NHBoc and $NHCOCF_3$ can act as hydrogen bond donor to Br^- acting as nucleophile (in the reaction *via* **N**) (*cf.* [975]) or as leaving group (in the reaction *via* **L**) (*cf.* [969] [971] [976 – 978]). Alternatively, a H-bonded complex of Br_3^- (*cf.* [979] [980]) with the pseudoaxial conformer **B** may promote the liberation of Br_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_3^- but not in the bromination by Br_2. This may correlate with the higher reactivity of Br_2 as compared to Br_3^-.

Scheme 4.2.8



Proposed conformational itinerary for the bromination by Br_3^- in CH_2Cl_2. The dashed arrows indicate the trajectories for nucleophilic attack on the π complexes according to the *Fürst-Plattner* rule.

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[56]) Similarly, the *syn*-selectivity of the *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 $NHCO_2R$ 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**).

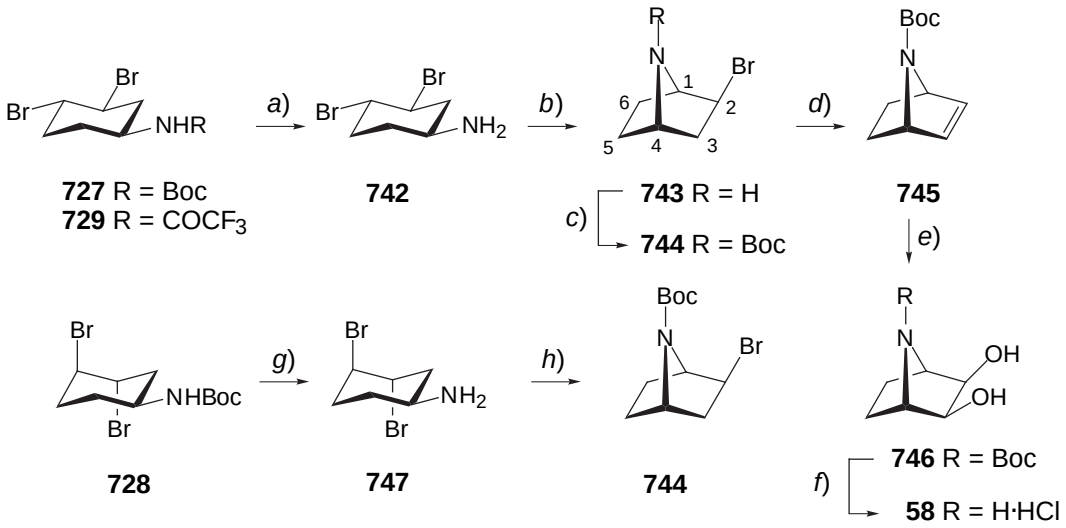
4.2.2. Cyclisation of 3,4-Dibromocyclohexylamines

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.

Debocylation of the carbamates **727** and **728** (CF_3CO_2H) 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_2CO_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_2CO_3, MeOH, H_2O) 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_2O, *cf*. [982]) of **745** provided the diol **746** that was isolated in 56% yield by chromatography (82%), followed by crystallisation. Debocylation (CF_3COOH, CH_2Cl_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_2CO_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**.

Scheme 4.2.9

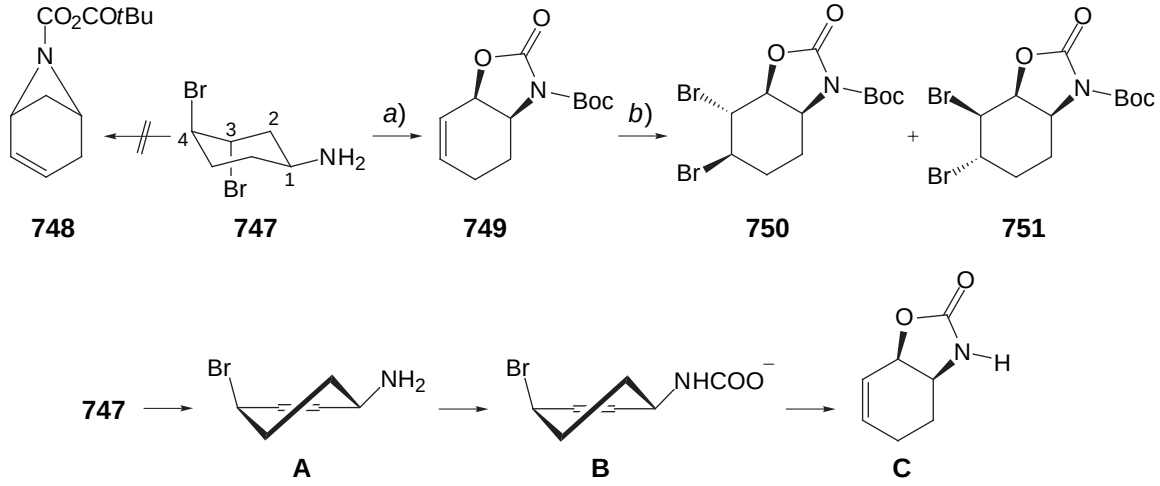


a) From **727**: CF_3COOH, CH_2Cl_2; quant.; from **729**: K_2CO_3, MeOH, H_2O; 99%. *b*) K_2CO_3, $CHCl_3$; quant. *c*) Boc_2O, K_2CO_3, $CHCl_3$; 83% from **727**, 93% from **729**. *d*) KO*t*Bu, THF; 87%. *e*) OsO_4, NMO, acetone, H_2O; 56% (cryst.). *f*) 0.1N HCl, quant. *g*) CF_3COOH, CH_2Cl_2; 100%. *h*) K_2CO_3, 1,3-dichlorobenzene, then Boc_2O, 1,3-dichlorobenzene; 62%.

Treating **747** with K_2CO_3 in DMF at 80° led to the formation of a new compound which was carbamoylated *in situ* (Boc_2O) 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 CH_2Cl_2 / 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 S_N2' like reaction.

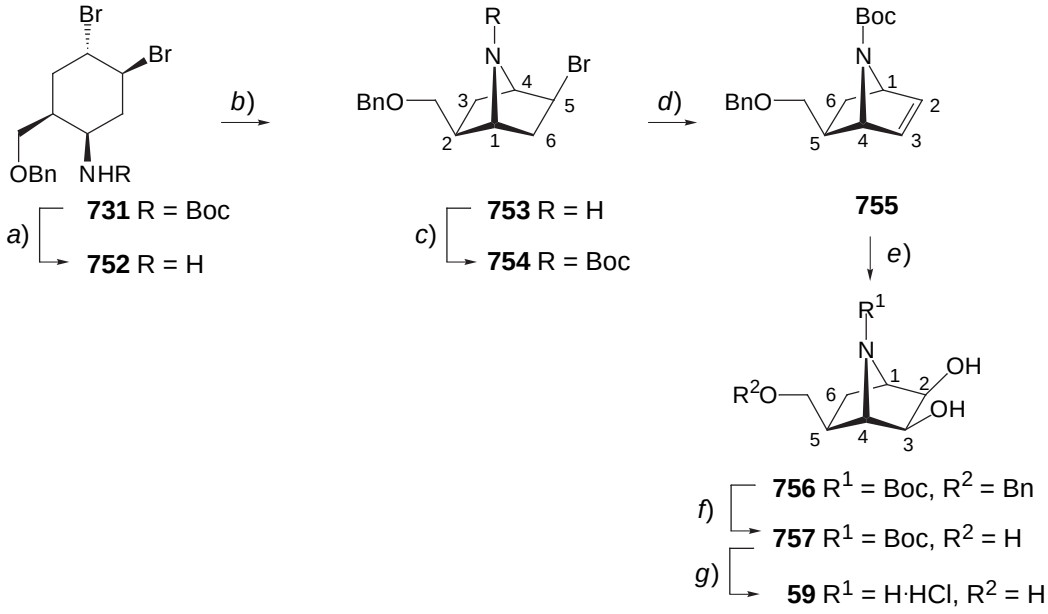
Scheme 4.2.10



a) K_2CO_3, DMF, then Boc_2O; 28%. *b*) $PhMe_3NBr_3$, CH_2Cl_2; 38% of **750**, 30% of **751**.

Debocylation (CF_3COOH, CH_2Cl_2) of the carbamate **731** gave the amine **752** in quantitative yield (Scheme 4.2.11). According to its ^{1}H-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 $CHCl_3$ in the presence of K_2CO_3 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 (OsO_4, NMO, acetone/H_2O, *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

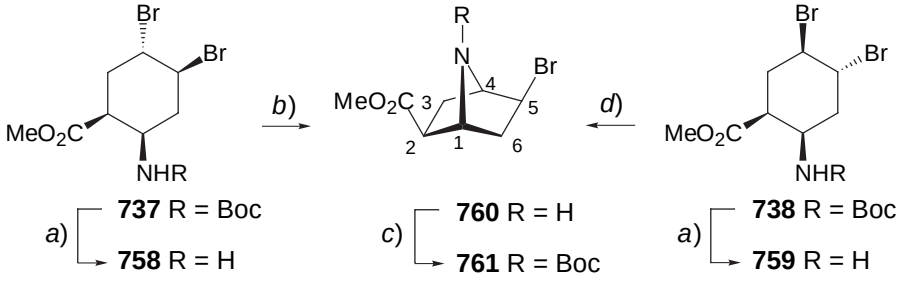


a) CF_3COOH, CH_2Cl_2; quant. *b*) K_2CO_3, $CHCl_3$; quant. *c*) Boc_2O, K_2CO_3, $CHCl_3$; 84% from **731**. *d*) KO*t*Bu, THF; 92%. *e*) OsO_4, NMO, acetone, H_2O; 81%. *f*) H_2-Pd/C, MeOH; 90% crude, 60% after repeated chrom. *g*) 0.1N HCl; 100%.

Debocylation of the carbamates **737** and **738** gave the amines **758** and **759**, respectively, in quantitative yield (Scheme 4.2.12). Boiling **758** in $CHCl_3$ in the presence of K_2CO_3 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 K_2CO_3 in boiling $CHCl_3$ and in 1,3-dichlorobenzene up to 100°. At 120°, a slow conversion to a new compound was observed by TLC. Carbamoylation (Boc_2O, K_2CO_3) of the new product afforded the 7-azanorbornane **761** (21%), *i.e.* **759** behaved similarly as **747**.

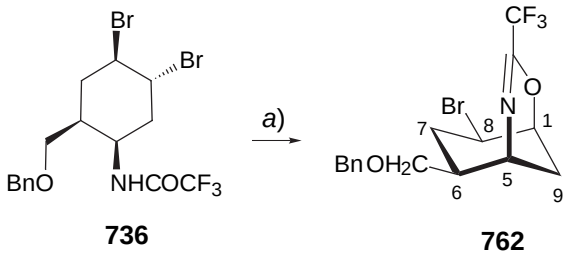
Scheme 4.2.12



a) CF_3COOH, CH_2Cl_2; quant. **758**; quant. **759**. *b*) K_2CO_3, $CHCl_3$. *c*) Boc_2O, K_2CO_3, $CHCl_3$; 62% from **737**. *d*) K_2CO_3, 1,3-dichlorobenzene, then Boc_2O, K_2CO_3; 21%.

An attempt to hydrolyse the amide **736** (K_2CO_3, MeOH/H_2O) 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].

Scheme 4.2.13

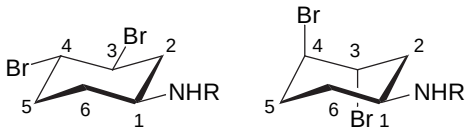


736 **762**

a) K_2CO_3, MeOH, H_2O; quant.

In contrast to *t*-3-bromocyclohexylamine [243], the dibromo amines **747** and **759** did not cyclise to azetidines. This different behaviour might be due to the dipole-dipole repulsion between the two equatorial Br substituents of **747** and **759** [985 – 987]. Towards the transition state of cyclisation this dipole repulsion increases (and finally becomes a charge dipole repulsion), and concomitantly the radius of the leaving Br and thus the steric repulsion between the two Br substituents increases.

The configuration and conformation of the dibromides **727**, **728**, **729**, **730**, **742**, and **747** were deduced from their proton NMR spectra.



727 R = Boc
729 R = $COCF_3$
742 R = H

728 R = Boc
730 R = $COCF_3$
747 R = H

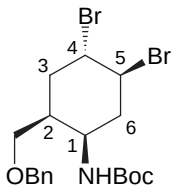
In these bromides, the N substituent is equatorial, as evidenced by the large $J(1,2_{ax})$ and $J(1,6_{ax})$ values (Table 4.2.3) for **742**, **728**, **729**, **730**, and **747** and by the large $\tau_{1/2}$ of *ca*. 20 Hz for the H–C(1) *m* of **727**. The small $\tau_{1/2}$ values for the H–C(3) 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 (≈ 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 4.2.3: Selected ^{1}H- and ^{13}C-NMR ($CDCl_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] of **727**, **728**, **729**, **730**, **742**, and **747**.

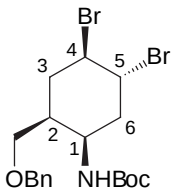
	727	**728**	**729**	**730**	**742**	**747**
H–C(1)	3.66–3.53	4.07–3.92	4.08	4.40	2.84	3.33
H–C(2)	*2.79–2.69*	*2.33–2.18*	2.80 (eq)	2.46 (ax)	2.59 (eq)[b]	2.33 (ax)
H'–C(2)	*2.06–1.73*	*2.33–2.18*	2.16–1.91	2.25 (eq)	*1.98–1.72*	2.17 (eq)
H–C(3)	4.10[b]	4.64–4.60 [b]	4.33–4.19	4.69–4.64	4.06[c]	4.70–4.65
H–C(4)	4.02[b]	4.60–4.55 [b]	4.33–4.19	4.64–4.59	3.98[c]	4.60–4.56
H–C(5)	*2.52–2.43*	2.55 (ax)	2.51 (eq)	2.61 (ax)	2.47 (eq)[b]	2.51 (ax)
H'–C(5)	*2.06–1.73*	*2.04–1.94*	2.16–1.91	2.05 (eq)	*1.98–1.72*	2.04 (eq)
H–C(6)	*2.06–1.73*	*1.93–1.83*	2.16–1.91	1.98 (eq)	*1.98–1.72*	1.88–1.69
H'–C(6)	*1.38–1.21*	1.71 (ax)	1.65–1.53	1.86 (ax)	*1.32–1.18*	1.88–1.69
NH	4.67–4.57	4.53–4.43	7.13–7.00	6.41–6.29	[a]	[a]
J (1,2)	[a]	[a]	4.1	11.7	3.7	10.9
J (1,2')	[a]	[a]	8.1	4.1	11.1	4.4
J (2,2')	[a]	[a]	14.0	14.2	13.1	14.3
J (2,3)	4.1	[a]	4.1	3.4	4.4	3.4
J (2',3)	9.3	[a]	[a]	[a]	10.6	[a]
J (3,4)	9.3	[a]	[a]	[a]	10.6	[a]
J (4,5)	4.1	3.4	3.4	4.1 or 3.1	4.4	4.4 or 3.1
J (4,5')	9.3	[a]	[a]	[a]	10.6	[a]
J (5,5')	[a]	15.6	14.6	15.3	14.0	15.3
J (5,6)	[a]	[a]	7.2	4.1 or 3.1	7.8	4.4 or 3.1
J (5,6')	[a]	12.1	3.4	12.5	[a]	12.1
J (5',6)	[a]	[a]	[a]	[a]	[a]	[a]
J (5',6')	[a]	3.4	[a]	3.7	[a]	[a]
J (6,6')	[a]	12.3	[a]	12.1	[a]	[a]
J (6,1)	[a]	[a]	4.1	4.1	3.7	4.4
J (6',1)	[a]	12.3	8.1	12.1	11.2	10.6
C(1)	48.18	44.95	46.61	44.83	50.03	45.33
C(3)	55.33[b]	52.36[c]	53.54[b]	51.30[b]	56.29[b]	52.78[b]
C(4)	53.44[b]	51.79[c]	51.66[b]	50.58[b]	54.57[b]	52.71[b]

[a]) Not determined. [b]), [c]) Assignment may be interchanged.
Values in *italics*: assignment by comparison, not proven.

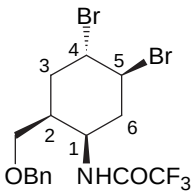
The identical $J(1,6) = J(5,6) = 4.4$ Hz and $J(1,6') = J(5,6') = 7.1 – 7.3$ Hz) of the dibromides **731** and **735** (Table 4.2.4) evidence the 1,5-*cis* configuration. The identical coupling pattern for the H–C(3) and H'–C(3) *ddd* resonating at 2.34 (J = 14.6, 7.6, 3.6 Hz) and 2.08 ppm (J = 14.6, 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-*trans* configuration and an equilibrium of the $^4C_1$ and $^1C_4$ conformers.



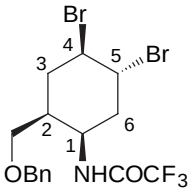
731



732



735



736

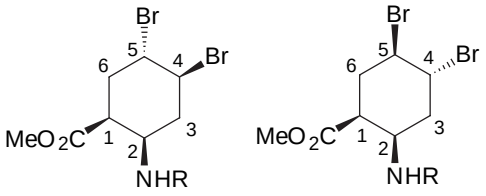
The large $J(2,3_{ax} = J(3_{ax},4) = 9.7$ Hz and $J(5,6_{ax}) = 10$ Hz of the dibromide **736** evidence an equatorial orientation of the benzyloxymethyl and Br substituents and a $^1C_4$ conformation. The small $J(1,6_{ax}) = 3.6$ Hz evidences the axial orientation of $NHCOCF_3$–C(1).The structure of **732** was tentatively assigned as the diastereoisomer of **731**, assuming that only *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**.

	731	**732**	**735**	**736**
H–C(1)	4.03–3.93	*4.00–3.94*	4.48–4.24	4.27–4.16
H–C(2)	2.49–2.40	?	2.53	2.21–2.11
H–C(3)	2.34	?	2.46	2.57
H'–C(3)	2.08	?	2.06	2.27
H–C(4)	4.50–4.41	*4.26–4.05*	4.48–4.24	4.27–4.16
H–C(5)	4.37–4.29	*4.26–4.05*	4.48–4.24	4.27–4.16
H–C(6)	2.66	?	2.74	2.91
H'–C(6)	2.22	?	2.30	2.14
CH–C(2))	3.67	3.54	3.73	3.83
CH'–C(2)	3.47	3.41	3.54	3.58
NH	5.60	5.21	8.01–7.91	7.90–7.81
J (1,2)	[a])	[a])	4.0	[a])
J (1,6)	4.4	[a])	4.4	4 or 5
J (1,6')	7.3	[a])	7.1	3.6
J (2,3)	7.6	[a])	8.3	3.9
J (2,3')	4.0	[a])	2.8	9.7
J (3,3')	14.6	[a])	14.0	14.5
J (3,4)	3.6	[a])	3.6	3.9
J (3',4)	7.6	[a])	7.8	9.7
J (4,5)	[a])	[a])	[a])	[a])
J (5,6)	4.4	[a])	4.4	4 or 5
J (5,6')	7.3	[a])	7.1	10.0
J (6,6')	14.6	[a])	14.9	14.6
J (2,7)	7.2	5,1	8.6	6.2
J (2,7')	5.3	4.4	3.6	2.3
J (7,7')	9.7	9.3	9.7	9.6
C(1)	48.33	48.54	52.18	51.30
C(2)	36.43	40.62	35.58	38.61
C(4)	52.06[b])	49.67[b])	48.55[b])	50.65[b])
C(5)	53.06[b])	52.78[b])	50.7[b])	53.00[b])
C*F*$_3$			–76.68	–75.80

[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 $^1C_4$ 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 $^1C_4$ and $^4C_1$ conformers.



737 R = Boc
758 R = H

738 R = Boc
759 R = H

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_2N–C(2) and a $^4C_1$ conformation.

Table 4.2.5: Selected ^{1}H- and ^{13}C-NMR ($CDCl_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] of **737**, **738**, **758**, and **759**.

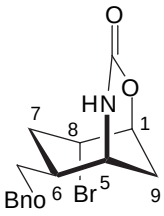
	737	**738**	**758**	**759**
H–C(1)	3.01	*2.87–2.75*	3.02–2.98	2.68–2.56
H–C(2)	4.10–3.94	*4.40–4.28*	3.42–3.31	2.68–2.58
H–C(3)	2.58 (eq)	*2.61–2.50*	2.62	2.52 (eq)
H'–C(3)	2.28 (ax)	*2.04*	2.34	2.08 (ax)
H–C(4)	4.34–4.10	*4.63–4.53*	4.35–4.26[b])	4.50
H–C(5)	4.34–4.10	*4.40–4.28*	4.61–4.52[b])	4.12–4.03
H–C(6)	2.78 (eq)	*2.87–2.75*	2.77	2.68–2.56
H'–C(6)	2.09 (ax)	*2.87–2.75*	2.13	2.68–2.56
NH	5.50	5.62–5.45	[a])	[a])
J (1,2)	5.0 or 4.4	[a])	[a])	[a])
J (1,6)	5.6 or 3.4	[a])	7.6	[a])
J (1,6')	4.7	[a])	4.4	[a])
J (2,3)	[a])	[a])	[a])	4.4
J (2,3')	9.0	*4.7*	7.4	3.1
J (3,3')	14.0	*14.6*	14.2	14.3
J (3,4)	[a])	[a])	[a])	4.4
J (3',4)	9.0	*4.7*	7.4	11.2
J (4,5)	[a])	[a])	[a])	9.8
J (5,6)	5.6 or 3.4	[a])	3.7	[a])
J (5,6')	9.3	[a])	8.0	[a])
J (6,6')	14.5	[a])	14.8	[a])
C(1)	38	*42.20*	[a])	[a])
C(2)	52.02	*45.49*	[a])	[a])
C(4)	47.84[b])	*52.13*	[a])	[a])
C(5)	43.37[b])	*50.39*	[a])	[a])

[a]) Not determined.

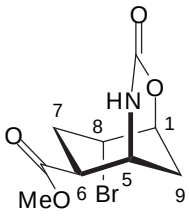
[b]) Assignment may be interchanged.

Values in *italics*: assignment by comparison; not proven.

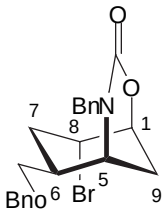
The MS of the dihydrooxazin-2-ones **733**, **739**, and **740** show the presence of only one Br substituent. Strong IR bands at 1715, 1715, and 1687 cm^{-1}, respectively, evidence the carbonyl group. No signals for a *tert*-butyl group were observed in the NMR spectra (Table 4.2.6). The chemical shift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



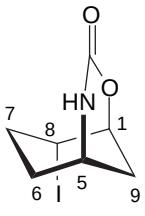
733



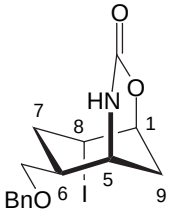
739



740



795



799

The similar $J(1,9_{ax})$ = 1.6 Hz and $J(5,9_{ax})$ = 2.2 Hz are in agreement with the bicyclic structure. A w coupling (1.6 Hz) was observed between NH and the axial H–C(9) of **733** and **739**. A w 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 $J(6,7_{ax})$ (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 benzyloxymethyl substituents.

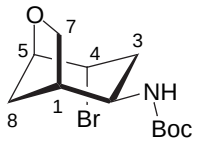
Table 4.2.6 Selected IR Bands [cm^{-1}], ^1H- and ^{13}C-NMR ($CDCl_3$) Chemical Shifts [ppm], and Coupling Constants [Hz] of **733**, **739**, **740**, **795**, and **799**.

	733	**739**	**740**	**795**	**799**
υ(C=O)	1715	1715	1687	1721	1713
H–C(1)	4.68–4.64	4.67–4.63[a])	4.64	4.72–4.68[a])	4.72–4.68[a])
H–C(5)	3.78–3.73	4.06–4.01	3.80–3.76	3.65	3.74–3.69
H–C(6)	2.41–2.30	3.00	2.50–2.42	?	2.35
H'–C(6)	–	–	–	?	–
H–C(7)	1.97–1.90	2.43–2.37	1.98	?	1.86
H'–C(7)	1.97–1.90	2.43–2.37	1.88	?	1.89–1.83
H–C(8)	4.50–4.46	4.56–4.51[a])	4.51–4.47	4.66–4.61[a])	4.66–4.61[a])
H–C(9)	2.53	2.56	2.43	2.69	2.66
H'–C(9)	2.04	2.10	1.74	?	2.08
CH–C(6)	3.37	–	3.42–3.37	–	3.39–3.30
CH'–C(6)	3.31	–	3.42–3.37	–	3.39–3.30
NH	5.33–5.28	5.76–5.68	–	6.31–6.23	6.00–5.75
J (1,8)	[b])	[b])	3.4	[b])	[b])
J (1,9)	1.6	1.6	1.6	1.6	0
J (1,9')	4.0	4.1	4.0	[b])	[b])
J (5,6)	[b])	1.6	[b])	0	[b])
J (5,6')	–	–	–	0	–
J (5,9)	2.2	2.2	2.2	2.3	0
J (5,9')	4.0	4.1	4.0	0	[b])
J (6,6')	–	–	–	[b])	–
J (6,7)	[b])	10.9	12.1	[b])	3.6 or 0
J (6,7')	[b])	5.9	[b])	[b])	[b])
J (6'7)	–	–	–	[b])	–
J (6',7')	–	–	–	[b])	–
J (6,10)	5,1	–	[b])	–	[b])
J (6,10')	9.2	–	[b])	–	[b])
J (7,7')	[b])	[b])	15.8	[b])	9.2
J (7,8)	[b])	[b])	4.0	[b])	3.6 or 0
J (7',8)	[b])	[b])	[b])	[b])	[b])
I (8,9')	1.6	1.6	1.6	[b])	[b])
J (9,9')	14.0	14.2	14.0	13.9	14.0
J (9,NH)	1.6	1.6	–	1.6	[b])
J (10,10')	9.4	–	[b])	–	[b])
C(1)	75.49	[b])	76.03	76.64	76.81
C(3)	153.72	[b])	[b])	154.02	[b])
C(5)	47.68[a])	[b])	49.26[a])	45.24	46.20
C(8)	46.00[a])	[b])	47.73[a])	27.73	26.74

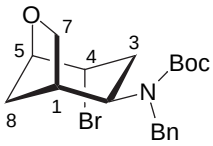
[a]) Assignment may be interchanged.

[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.



734



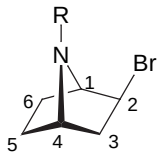
741

The chemical shift values for the C(5) *d* 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).

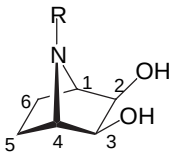
Table 4.2.7: Selected ^{1}H- and ^{13}C-NMR ($CDCl_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] of **734** and **741**.

	734	**741**
H–C(1)	2.59–2.54	2.54–2.48
H–C(2)	4.05–3.93	4.57–4.49
H–C(3)	2.20 (eq)	2.43 (ax)
H'–C(3)	1.97 (ax)	1.99 (eq)
H–C(4)	4.14	4.16–4.12
H–C(5)	4.29	4.24
H–C(7)	3.86	3.86
H'–C(7)	3.79	3.64
H–C(8)	2.52 (ax)	2.55 (ax)
H'–C(8)	1.87 (eq)	1.84 (eq)
NH	4.51	–
J (1,2)	[a])	[a])
J (1,7)	0	0
J (1,7')	4.0	4.1
J (1,8)	0	0
J (1,8')	5.6	5.4
J (2,3)	5.5	13.2
J (2,3')	12.1	4.8
J (2,NH)	6.9	–
J (3,4)	0	5.1
J (3',4)	5.3	0
J (3,3')	15.0	14.5
J (4,5)	4.4	4.4
J (4,8')	1.2	1.6
J (5,8)	0	0
J (5,8')	5.6	5.6
J (7,7')	8.7	8.9
J (8,8')	12.7	12.5
C(1)	40.37	40.63
C(2)	47.80[b])	53.04
C(4)	47.47[b])	48.58
C(5)	77.11	77.23
C(7)	68.52	69.61

[a]) Not determined. [b]) Assignment may be interchanged.



743 R = H
744 R = Boc



746 R = Boc
58 R = H·HCl

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).

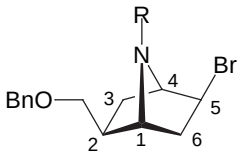
Table 4.2.8: Selected ^{1}H- and ^{13}C-NMR ($CDCl_3$) Chemical Shifts [ppm] and Coupling Constants [Hz] of **743**, **744**, **746**, and **58**.

	743	**744**	**746**	**58**
H–C(1)	3.73–3.67[a])	4.41–4.36[a])	4.11	4.06
H–C(2)	4.08	3.99	3.79	4.16
H–C(3)	*2.18 (endo)*	2.33–2.23 (exo)	3.79	4.16
H'–C(3)	*2.00*	2,17 (endo)	–	–
H–C(4)	3.64–3.56[a])	4.34–4.27[a])	4.11	4.06
H–C(5)	*1.64–1.52*	1.78–1.63	1.73–1.65	1.95–1.88
H'–C(5)	1.28–1.09	1.43–1.25	1.81	1.69
H–C(6)	*1.73*	1.94–1.82	1.73–1.65	1.95–1.88
H'–C(6)	1.28–1.09	1.43–1.25	1.81	1.69
CH–C(5)	–	–	–	–
CH'–C(5))	–	–	–	–
NH	[b])	–	–	4.80
J (1,2)	0	0	0	0
J (2,3)	*6.9*	3.4	–	–
J (2,3')	*2.8*	7.2	–	–
J (3,3')	*14.3*	13.7	–	–
J (3,4)	*0*	[b])	0	0
J (3',4)	*2.5*	0	–	–
J (4,5)	[b])	[b])	[b])	?
J (4,5')	[b])	[b])	[b])	?
J (5,5')	[b])	[b])	8.1?	8.1
J (5,6)	[b])	[b])	–	–
J (5,6')	*5.3*	[b])	8.1?	8.1
J (5',6)	[b])	[b])	8.1?	8.1
J (5',6')	*11.8*	[b])	–	–
J (6,6')	*11.8*	[b])	8.1?	8.1
J (6,1)	[b])	[b])	[b])	?
J (6',1)	*3.7*	[b])	[b])	?
J (5,7)	–	–	–	–
J (5,7')	–	–	–	–
J (7,7')	–	–	–	–
C(1)	64.97	63.89	62.26	64.32
C(2)	53.84	49.71	74.24	71.47
C(4)	56.74	55.61	62.26	64.32
C(6)				

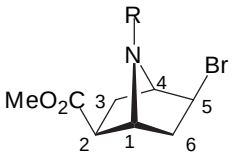
[a]) Assignment maybe interchanged.

[b]) Not determined.

Values in *italics*: assignment by comparison; not proven.



753 R = H
754 R = Boc



760 R = H
761 R = Boc

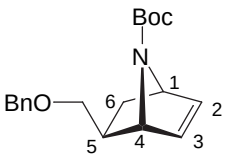
Similarly, the *exo*-orientation of the C(2) and C(5) substituents of the azanorbornanes **753**, **754**, **760**, and **761** (Table 4.2.9) is evidenced by the absence of coupling between the corresponding H and the bridgehead H.

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**.

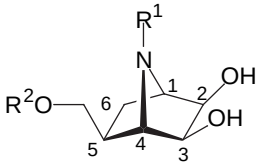
	753	**754**	**760**	**761**
H–C(1)	3.84[a])	4.37	3.92	4.60–4.43
H–C(2)	1.84	1.98–1.85	2.36	1.82
H–C(3)	1.55 (endo)	1.55 (endo)	2.05 (exo)	2.24 (exo)
H'–C(3)	1.45	1.47–1.35 (exo)	1.58 (endo)	0.87 (endo)
H–C(4)	3.88[a])	4.50	3.80	4.38–4.25
H–C(5)	4.07	4.00	4.00	3.29
H–C(6)	2.31–2.17	2.31 (exo)	2.17 (endo)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

[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 azanorbornene **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).



755



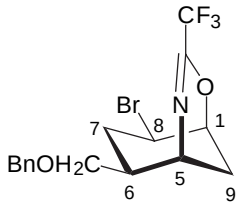
756 R^1 = Boc, R^2 = Bn
757 R^1 = Boc, R^2 = H
59 R^1 = H·HCl, R^2 = H

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_3OD. 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**.

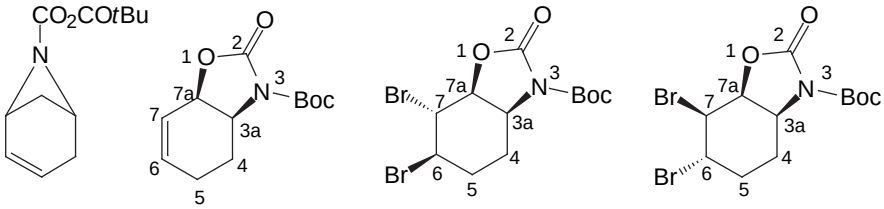
	755	**756**	**757**	**59**
H–C(1)	4.70–4.51	4.02–3.97[a])	3.99	3.93
H–C(2)	6.29	3.46–3.41[b])	3.80[a])	4.10–4.06
H–C(3)	6.29	3.39–3.33[b])	3.77[a])	4.10–4.06
H'–C(3)	–	–	–	–
H–C(4)	4.70–4.51	4.25–4.17[a])	4.02	3.91
H–C(5)	1.90–1.79	1.46	1.82	2.09
H–C(6)	1.38–1.28	0.83–0.76	1.48 (endo)	1.86 (endo)
H'–C(6)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

[a]), [b]) Assignment may be interchanged.
[c]) Not determined.
Values in *italics*: assignment by comparison; not proven.



762

The IR ($CHCl_3$) 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 $J(7_{ax},8) = J(6,7_{ax})$ = 12.5 Hz evidence the equatorial orientation of Br–C(8) and of the C(6) benzyloxymethyl substituent. Due to a γ-effect, H_{ax}–C(9) of the dihydro-1,3-oxazines **720**, **724**, and **725** ($\delta(H_{ax}–C(9))$ = 2.26–2.74 ppm) with axial Br is shifted downfield as compared to **762** (Br equatorial, $\delta(H_{ax}–C(9))$= 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]).



748 **749** **750** **751**

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 $^{4}H_{3a}$ 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**.

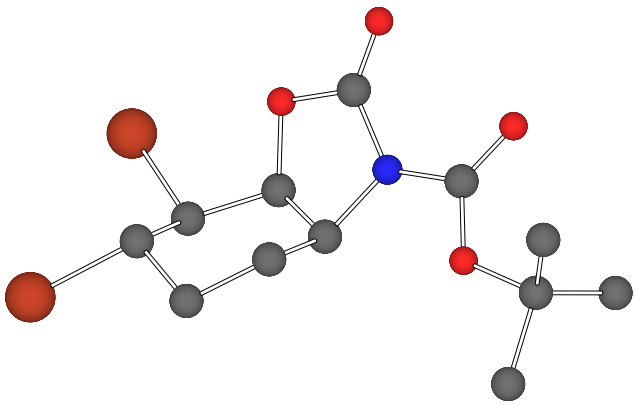


Table 4.2.11: Selected Bond Lengths [Å], Bond Angles, and Torsional Angles [°] of **751**.

C(6)–Br(6)	1.963(6)	O(1)–C(7a)–C(3a)	102.4(4)
C(7)–Br(7)	1.947(7)	O(1)–C(7a)–C(7)	111.5(5)
C(7a)–O(1)	1.461(7)	C(3a)–C(7a)–C(7)	116.7(5)
C(3a)–C(7a)	1.514(8)	N(3)–C(3a)–C(4)	111.7(5)
C(3a)–N(3)	1.475(7)	N(3)–C(3a)–C(7a)	98.5(4)
C(2)–N(3)	1.385(7)	C(4)–C(3a)–C(7a)	114.1(4)
N(3)–C(7')	1.395(7)	C(2)–N(3)–C(3^{1})	123.0(5)
C(2)–O(C(2))	1.199(7)	C(2)–N(3)–C(3a)	110.0(4)
C(2)–O(1)	1.357(7)	C(3^{1})–N(3)–C(3a)	125.8(5)
C(3^{1})–O(C(3^{1}))	1.201(7)	O(C(2))–C(2)–O(1)	123.1(5)
		O(C(2))–C(2)–N(3)	129.0(6)
		O(1)–C(2)–N(3)	107.8(5)
		C(2)–O(1)–C(7a)	108.4(4)

Table 4.2.12: Selected Torsional Angels [°] of **751**

O(1)–C(7a)–C(7)–C(6)	–78.8(7)
O(1)–C(7a)–C(3a)–C(4)	84.2(5)
N(3)–C(3a)–C(4)–C(5)	158.5(5)
N(3)–C(3a)–C(7a)–C(7)	–156.3(4)
O(1)–C(7a)–C(3a)–N(3)	–34.2(4)
C(7a)–C(3a)–N(3)–C(2)	28.5(5)
C(3a)–N(3)–C(2)–O(1)	–10.7(6)
N(3)–C(2)–O(1)–C(7a)	–13.3(6)
C(2)–O(1)–C(7a)–C(3a)	31.0(5)
C(4)–C(3a)–C(7a)–C(7)	–37.9
C(3a)–C(7a)–C(7)–C(6)	38.5(7)
C(5)–C(4)–C(3a)–C(7a)	47.9(7)
Br(7)–C(7)–C(6)–C(5)	–175.1(4)
Br(7)–C(7)–C(6)–Br(6)	65.3(5)
Br(6)–C(6)–C(5)–C(4)	–178.9(4)
C(3^1)–N(3)–C(2)–O(C(2))	–1.5(9)
C(3a)–N(3)–C(2)–O(C(2))	166.5(6)
C(3^1)–N(3)–C(2)–O(1)	–178.8(4)
C(2)–N(3)–C(3^1)–O(C(3^1))	–19.4(8)

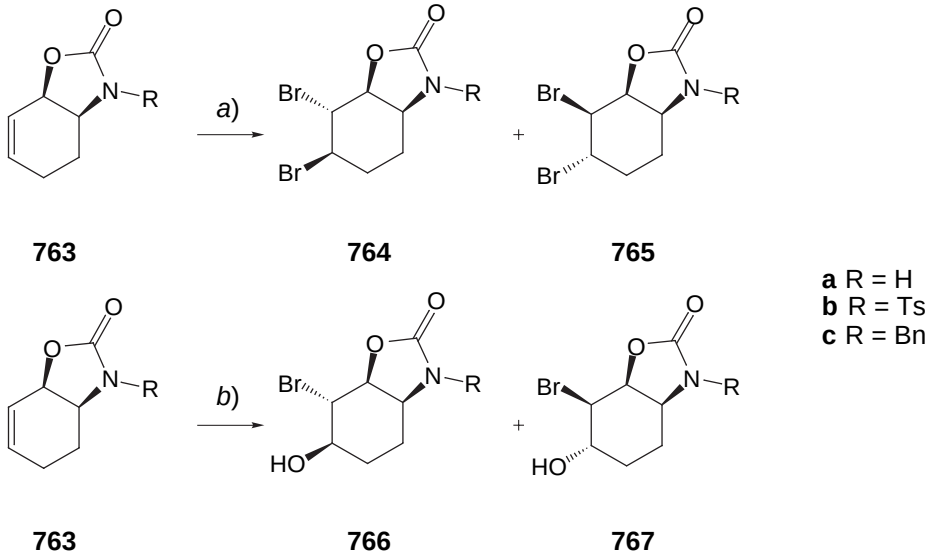
The crystal structure of **751** revealed a ${}^{7a}C_5$ conformation of the cyclohexane with equatorial Br substituents, a pseudoaxial orientation of C(7a)–O, and a pseudoequatorial orientation of C(3a)–N. The conformation of the dihydrooxazol-2-one is somewhere between E_{7a} and ${}^{3a}E$.

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 Br_2 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].

Scheme 4.2.14



a, *b*) [948] (see text and Table 4.2.13).

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

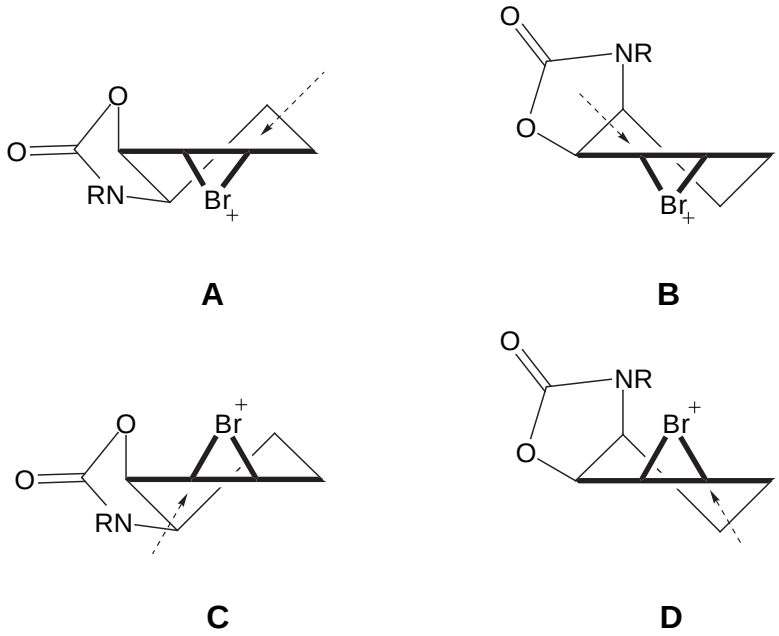
Starting material	Conditions	Combined yield	**764** / **765** or **766** / **767**
763a	Br_2, CH_2Cl_2, r.t.	95%	[a])
763b	Br_2, CH_2Cl_2, r.t.	96%	<5:95
763c	Br_2, CH_2Cl_2, r.t.	90%	50:50
763a	two eq. of NBS, DMSO / H_2O (1:1), r.t.	50%	>95:5
763c	two eq. of NBS, DMSO / H_2O (1:1), r.t.	72%	80:20
763a	two eq. of Br_2, DME / H_2O, r.t.	70%	65:35
763b	two eq. of Br_2, DME / H_2O, r.t.	75%	20:80

[a]) 30% d.e., the structure of the major product was not determined.

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

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



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_2O 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 diaxial opening of **A** is the one which is kinetically most favourable. Diaxial 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 α-position of the positively polarised C–O atom). The build-up of 1,3-diaxial 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 Br_2 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 Br_2 bromohydroxylation of **763a** must result from a selective formation of the epibromonium ion on the less hindered *trans* face of the alkene. Diaxial 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*).

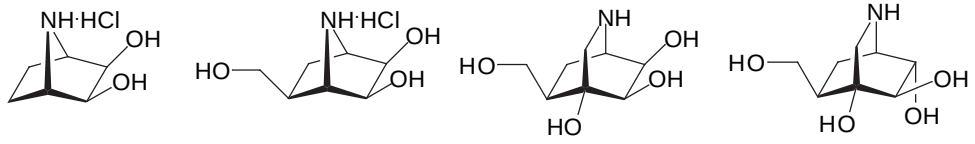
The inverse selectivity in the Br_2 bromohydroxylation of **763b** (yielding **767b** as the major product) must in turn result from a selective formation of the *cis*-epibromonium ion and the exclusive diaxial opening of the conformer **D**. The selective formation of the *cis* epibromonium ion means that the *endo* attack of Br_2 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 Br_2 [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 $PhMe_3NBr_3$ dibromination of **749** must take account of the different reaction mechanism: The rate-limiting step is the attack of Br^- on a 1:1 Br_2-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 Br_2. 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.



58 **59** **27** **29**

Table 4.2.14: Inhibition of Several Glycosidases by the 7-Azanorbornanes **58** and **59** (IC_{50} Values in mM).

	(±)-**58**	(±)-**59**	(±)-**27** [197]	**29** [198]
β-mannosidase (snail)	no inh. at 2 mM	ca. 25% inh. at 2.5 mM	2.7	2.0
α-mannosidase (Jack beans)	no inh. at 2 mM	0.55	3.9	[a])
β-glucosidases (almonds)	1.74	2.05	[a])	2.7
β-glucosidase (*C. sacch.*)	2.2	1.95	4.3	1.9
α-glucosidase (brewer's yeast)	ca. 10% inh. at 1.6 mM	no inh. at 2 mM	[a])	[a])

[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 IC_{50} 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 ϕ(C(5)–O–C(1)–C(2)) ≈ 0°. Inhibition of the *β*-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 *β*-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 anomeric 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 anomeric 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 ϕ(C(5)–O–C(1)–C(2)) ≈ 0° 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.

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[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

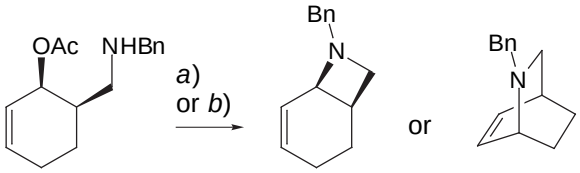
4.3.1. By Pd-Catalysed Intramolecular Allylic Amination

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

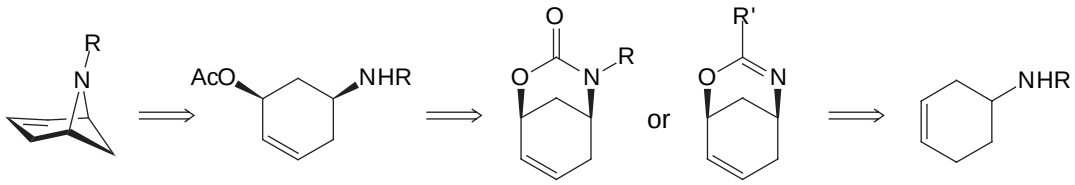


773 **774** **775**

a) Formation of **774** under conditions of kinetic control; conditions and yield not given [687]. *b*) ($Ph_3P)_4Pd$, Et_3N, 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

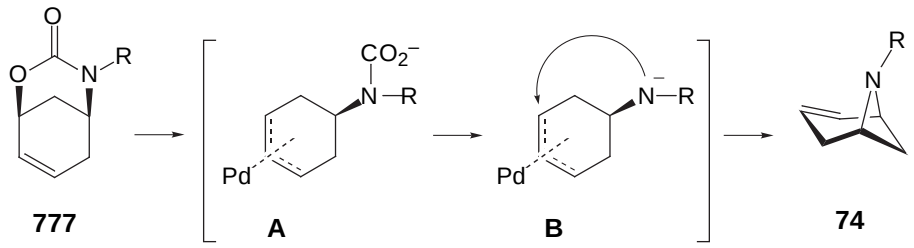


74 **73** **777** **75**

Retrosynthetic analysis of the azetidine **74**.

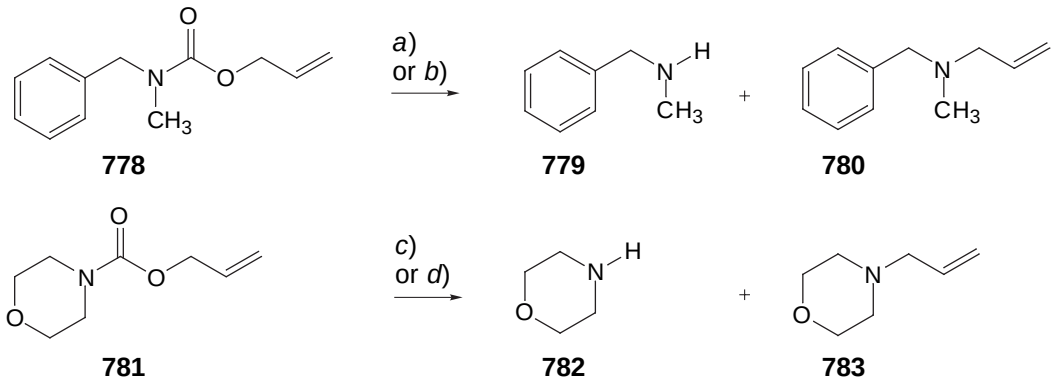
It was most intriguing that the dihydrooxazin-2-ones **777** themselves might serve as substrates for the Pd-catalysed intramolecular amination, as allylic carbamates are suitable substrates for Pd-catalysed allylations (*vide supra*). Oxidative addition of **777** to Pd(0) should lead to a carbamate **A** (Scheme 4.3.3) which might lose CO_2, 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**.

Scheme 4.3.3



In the literature, there are only few examples for a related Pd(0)-catalysed conversion of allyl-carbamates to allylamines by extrusion of CO_2. *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 Et_2NH. 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 ($Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, THF) of methyl 2-methyl-3-oxopentanoate [1019]. For additional examples of such decarboxylative allylic carbamate to allylic amine conversions, see [1020 – 1022].

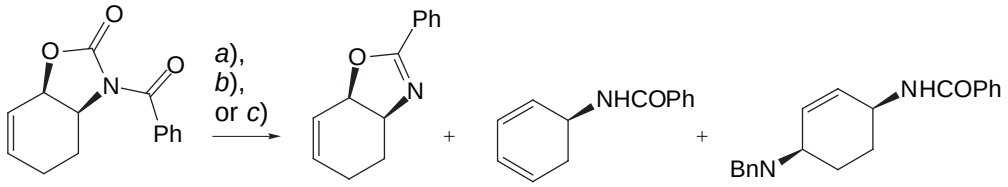
Scheme 4.3.4



a) $Pd(OAc)_2$, TPPTS, two eq. of Et_2NH, MeCN, H_2O; 30% of **779**, 70% of **780** [1006]. *b*) $Pd(OAc)_2$, TPPTS, 40 eq. of Et_2NH, MeCN, H_2O; 97% of **779**, 3% of **780** [1006]. *c*) $Pd(OAc)_2$, TPPTS, two eq. of Et_2NH, MeCN, H_2O; 98% of **782**, 2% of **783** [1006]. *d*) Methyl 2-methyl-3-oxopentanoate, $Pd_2(dba)_3{\cdot}CHCl_3$, Ph_3P, THF; 60% of **783**, 40% of methyl 2-allyl-2-methyl-3-oxopentanoate [1019].

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 $Pd_2(dba)_3{\cdot}CHCl_3/Ph_3P$ in CH_2Cl_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 $Pd_2(dba)_3{\cdot}CHCl_3$/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

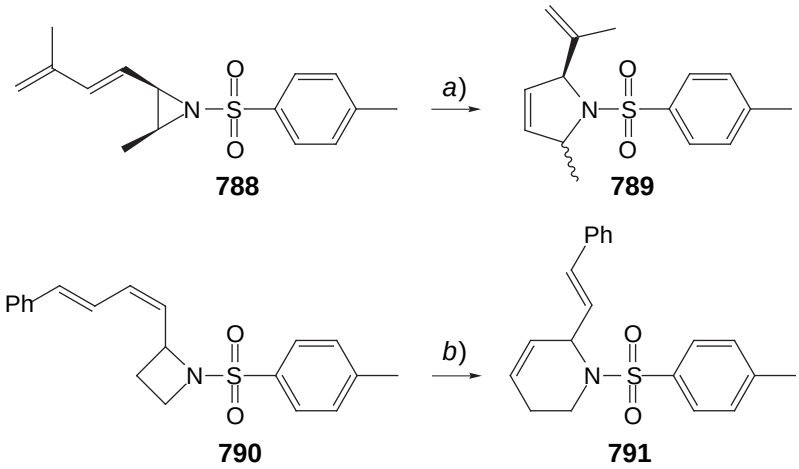


784 **785** **786** **787**

a) Diethyl malonate, $Pd_2(dba)_3{\cdot}CHCl_3$, Ph_3P, CH_2Cl_2; **785** (quant.) [1007]. *b*) $BnNH_2$, $Pd_2(dba)_3{\cdot}CHCl_3$, Ph_3P, CH_2Cl_2; 10% of **785**, 90% of **786** [1007]. *c*) $BnNH_2$, $Pd_2(dba)_3{\cdot}CHCl_3$, 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].

Scheme 4.3.6

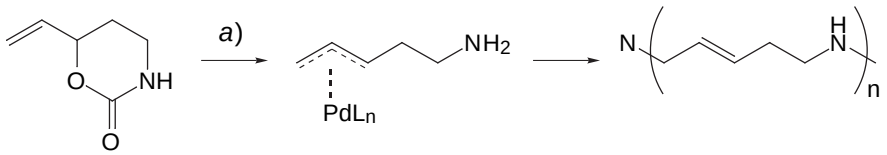


788 **789** **790** **791**

a) $(Ph_3P)_4Pd$, DMSO; 98% (d.e. = 90%) [1009]. *b*) $(Ph_3P)_4Pd$, DMSO; 80% [1009]

Suzuki et al. reported a Pd(0)-catalysed decarboxylative ring-opening polymerisation of 4-vinyl-1,3-oxazin-2-ones **792** [1008] (Scheme 4.3.7). Allylic substitution of the carbamate by $Pd_2(dba)_3{\cdot}CHCl_3$/8 Ph_3P in CH_2Cl_2 and decarboxylation of the carbamoyl leaving group generated the allyl-π-complex **793**, the propagating species of the polymerisation to **794**.

Scheme 4.3.7



792 **793** **794**

a) $Pd_2(dba)_3{\cdot}CHCl_3/Ph_3P$, CH_2Cl_2; *ca*. 70% yield [1008].

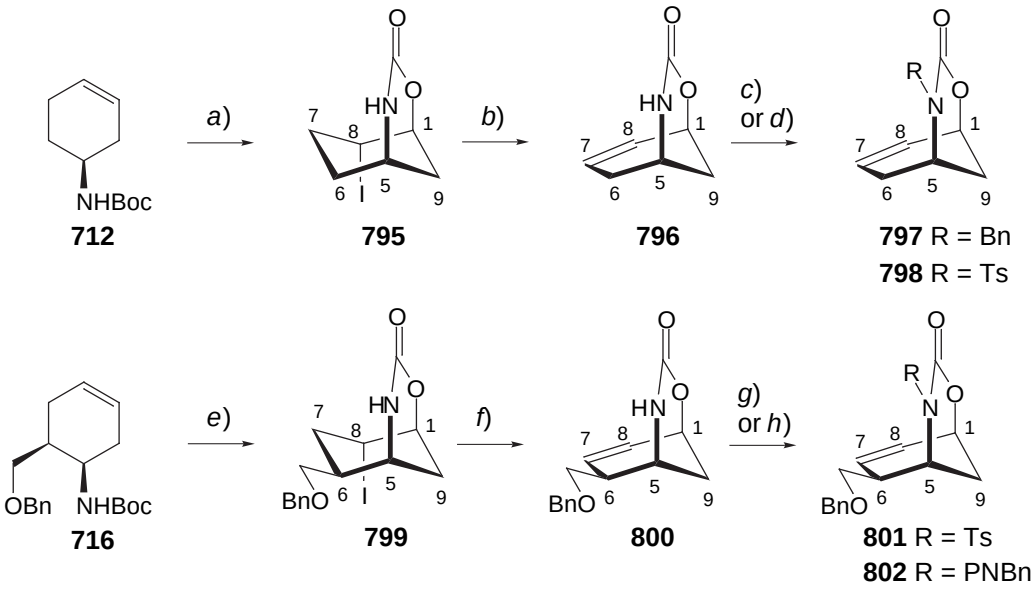
Another example is the transformation of **300** to **303** applied in *Trost's* synthesis of (+)-valienamine (see Scheme 2.1.45 in chapter 2.1.4).

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%), or tosylated (NaH, THF, then TsCl [1024]) to give **798** (89%).

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

Scheme 4.3.8



a) I_2, K_2CO_3, Et_2O; quant. *b*) DBU, THF; 75%. *c*) BuLi, THF, then BnBr; 92% of **797**. *d*) NaH, THF, then TsCl; 89% of **798**. *e*) I_2, K_2CO_3, Et_2O; quant. *f*) DBU, THF; 78%. *g*) NaH, THF, then TsCl; 86% of **801**. *h*) NaH, DMF, then 4-nitrobenzylbromide; 58% of **802**.

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 $(Ph_3P)_4Pd$, $Pd(OAc)_2(PPh_3)_2$, and $Pd_2(dba)_3$·benzene/Ph_3P [1005]. Even when the carbamate **797** was

activated with $In(OTf)_3$[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 **798** was readily transformed into a new compound, the diene **803** (*Entry 6*) (this volatile compound was isolated in 15% yield after FC and evaporation) (Scheme 4.3.9). Treatment of **798** with $Pd(PPh_3)_4$ in EtOH at r.t. gave the diene **803** (22%) besides the ethyl allyl-ether **804** (28%) (*Entry 7*), whereas the analogous reaction in MeCN afforded only the diene according to TLC (*Entry 8*). At r.t., **798** did not react with $Pd(PPh_3)_4$ in THF in the presence of LiCl (*cf.* [1007]) (*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 **798** with $Pd(PPh_3)_4$ in the presence of LiCl at r.t. gave the diene **803** and the ethyl allyl ether **804** (TLC) (*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 **801** to an azetidine has a higher chance of succeeding, as the benzyloxymethyl substituent should favour a conformation with an axial sulfonylamino group. However, the reaction of **801** with $Pd(PPh_3)_4$ in THF at r.t. gave the diene **805** (70%) (*Entry 11*). In the presence of LiCl, **801** did not react with $Pd(PPh_3)_4$ in THF at r.t., while in boiling THF it was transformed into the diene **806** (39%) (*Entry 12*).

The *N*-*p*-nitrobenzyl carbamate **802** was inert to Pd(0) in THF at r.t. and under reflux (*Entry 14*). The reactivity of the carbamates **796**, **797**, **798**, **801**, and **802** towards Pd(0) correlates with their IR C=O bands. For the reactive carbamates **798** and **801**, bearing the strongly electron withdrawing tosyl group, the IR C=O band is observed at 1721 cm^{-1}. For the inert carbamates **796**, **797**, and **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 σ-acceptor properties of the benzyl groups.

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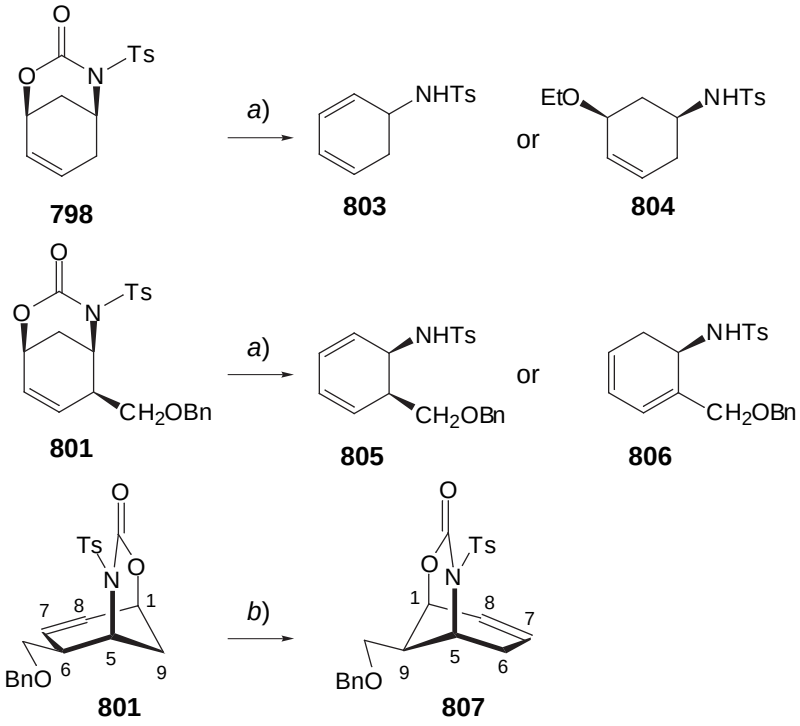
[58]) As suggested by *Professor B. Trost* (personal communication). I thank *Professor B. Trost* for a discussion of the Pd chemistry.

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 CO_2. 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



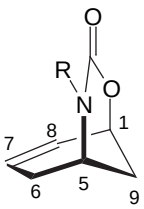
a) See text and Table 4.3.1; *b*) 160°, neat; 52%.

Table 4.3.1: Pd-Catalysed and Thermal Reactions of the Carbamates **796**, **797**, **798**, **801**, and **802**.

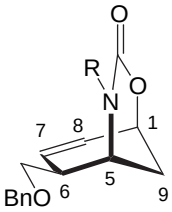
Entry	Starting material	R	Catalyst/additive	Conditions	Result
1	**796**	H	10% $Pd(PPh_3)_4$	THF, r.t.	no reaction
2	**797**	Bn	10% $Pd(PPh_3)_4$	THF, r.t.–>reflux	no reaction
3	**797**	Bn	10% $Pd(PPh_3)_4$	MeCN, r.t.–>80°	no reaction
4	**797**	Bn	25% $Pd(acac)_2$, 25% PBu_3	THF, r.t.–>reflux	no reaction
5	**797**	Bn	10% $Pd(PPh_3)_4$, 10% $In(OTf)_3$	THF, r.t. –>reflux	no reaction; mixture (TLC)
6	**798**	Ts	10% $Pd(PPh_3)_4$	THF, r.t.	15% of **803**
7	**798**	Ts	10% $Pd(PPh_3)_4$	EtOH, r.t.	22% of **803**, 28% of **804**
8	**798**	Ts	10% $Pd(PPh_3)_4$	MeCN, r.t.	**803** (TLC)
9	**798**	Ts	10% $Pd(PPh_3)_4$, 20% LiCl	THF, r.t.–>reflux	see text
10	**798**	Ts	10% $Pd(PPh_3)_4$, 20% LiCl	EtOH, r.t.	**803**, **804** (TLC)
11	**801**	Ts	10% $Pd(PPh_3)_4$	THF, r.t.	70% of **805**
12	**801**	Ts	10% $Pd(PPh_3)_4$, 15% LiCl	THF, r.t. –>reflux	no reaction; 39% of **806**
13	**801**	Ts	none	160°, neat	52% of **807**
14	**802**	pNBn	10% $Pd(PPh_3)_4$	THF, r.t.–>reflux	no reaction

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).

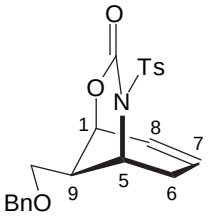
Conversion to the unsaturated carbamates **796** and **800** is evidenced by typical olefinic signals in the ^{1}H- and ^{13}C-NMR spectra (Table 4.3.2). The H–C(8) *dddd* resonate at 5.94 and 6.06 ppm, respectively. H–C(7) resonates as a *m* at 6.09–6.02 ppm for **796** and as a *dt* at 5.54 ppm for **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 H–C(9) and H–C(8) (1.3 Hz) and between the axial H'–C(9) and NH (1.9 Hz).



796 R = H
797 R = Bn
798 R = Ts



800 R = H
801 R = Ts
802 R = PNBn



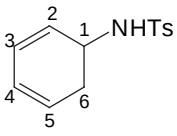
807

The constitution of the rearranged carbamate **807** is evidenced by the different coupling pattern for the axial H–C(9) as compared to **801**. The H–C(9) *ddt* resonating at 2.39 ppm couples with H–C(1) and H–C(5) (2.0 Hz), and with CH–C(9) (6.5 Hz) and CH'–C(9) (8.4 Hz). H–C(5) couples with H–C(6) (2.5 Hz) and with H'–C(6) (4.0 Hz).

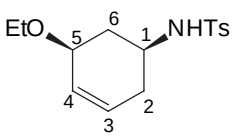
Table 4.3.2: Selected IR Bands [cm^{-1}], ^{1}H- and ^{13}C-NMR ($CDCl_3$) Chemical Shifts [ppm], and Coupling Constants [Hz] of **796**, **797**, **798**, **800**, **801**, **802**, and **807**.

	796	**797**	**798**	**800**	**801**	**802**	**807**
υ(C=O)	1701	1680	1721	1705	1721	1680	1725
H–C(1)	4.77–4.73	4.75–4.71	4.76–4.71	4.78–4.74	4.75–4.69	4.81–4.76	4.65–4.61
H–C(5)	3.88–3.82	3.67–3.62	4.93–4.88	3.94–3.89	5.10–5.05	3.85–3.80	4.95–4.91
H–C(6)	2.41–2.25	2.42	2.89	–	–	–	2.91
H'–C(6)	2.41–2.25	2.24–2.13	2.53	2.73–2.6	2.91–2.81	2.87–2.79	2.58
H–C(7)	5.94	5.91	6.05–6.02	5.54	6.16	5.63	6.07–6.04
H–C(8)	6.09–6.02	6.11–6.04	6.05–6.02	6.06	6.05	6.12	6.07–6.04
H–C(9)	2.21(eq)	2.24–2.13 (eq)	2.25(eq)	2.25	2.23–2.11	2.11	–
H'–C(9)	1.90(ax)	1.91(ax)	2.10(ax)	1.90	2.23–2.11	1.95	2.39
CH–C(6)	–	–	–	3.58	4.11	3.63	3.46 (9)
CH'–C(6)	–	–	–	3.45	3.62	3.54	3.29 (9)
NH	5.99–5.84	–	–	5.42–5.30	–	–	–
J (1,8)	[a])	5.9	[a])	5.6	5.4	5.9	[a])
J (1,9)	3.3	[a])	[a])	3.3	3.1	3.8	–
J (1,9')	2.3	2.2	2.3	2.2	[a])	≈2	2.0
J (5,6)	[a])	2.0	[a])	–	–	–	2.5
J (5,6')	[a])	[a])	3.6	[a])	[a])	[a])	4.0
J (5,7)	1.3	1.3	[a])	1.6	≈1	[a])	[a])
J (5,9)	4.5	[a])	[a])	3.3	3.1	3.8	–
J (5,9')	1.9	1.9	1.9	1.9	[a])	≈2	2.0
J (6,6')	[a])	18.7	19.2	–	–	–	18.9
J (6,7)	4.0	4.7	[a])	–	–	–	2.5
J (6',7)	2.8	2.2	≈0	1.6	1.9	[a])	≈0
J (6,8)	[a])	1.6	[a])	2.5	2.7	3.3	[a])
J (6,10)	–	–	–	6.2	5.9	5.3	6.5
J (6,10')	–	–	–	9.3	9.2	10.4	8.4
J (7,8)	10.0	9.7	[a])	10.0	10.0	9.6	[a])
J (8,9)	≈1.2	[a])	[a])	1.3	0	≈1	–
J (9,9')	13.3	13.1	13.7	13.4	0	13.5	–
J (9',NH)	1.9	–	–	1.9	–	–	–
J (10,10')	–	–	–	9.8	9.1	9.7	9.5
C(1)	67.99	67.69	68.61	68.05	69.16	68.17	67.76
C(3)	154.99	153.67	156.83	153.52	148.59	153.77	144.71
C(5)	44.27	48.30	50.74	45.41	52.82	49.67	52.45

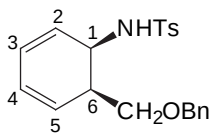
[a]) Not determined.



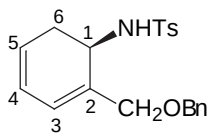
803



804



805



806

The structure of the diene **803** is evidenced by signals for 4 olefinic H. H–C(1) resonates as a *ddd* at 3.93 ppm and CH_2(6) as a *ddd* at 2.38 ppm.

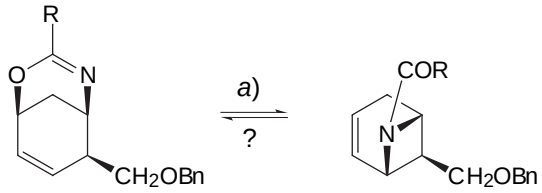
The ethoxy group of the ether **804** is evidenced by 2 *dq* at 3.51 and 3.46 ppm and a *t* at 1.21 ppm. The constitution of **804** is evidenced by coupling of CH_2(2) with the olefinic protons, coupling of CH_2(6) with H–C(1) and H–C(5), and coupling of H–C(1) with both CH_2(2) and CH_2(6). The configuration is evidenced by the large $J(1,2_{ax}) = J(1,6_{ax})$ = 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 *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 *ddd* at 3.95 ppm. The CH_2–C(2) resonate as *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 *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

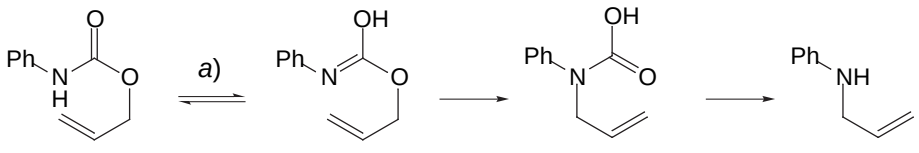


808 **776**

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 CO_2 provides the driving force for this rearrangement.

Scheme 4.3.11

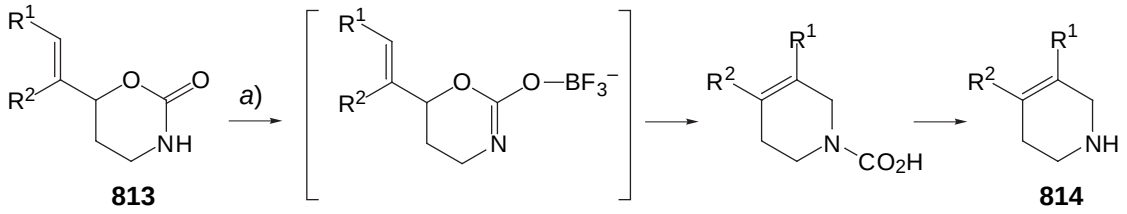


809 **810** **811** **812**

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 $BF_3{\cdot}OEt$ in CH_2Cl_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

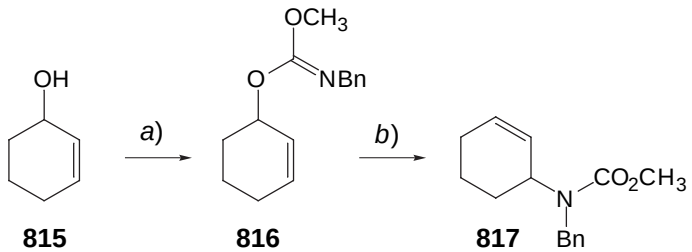


813 **814**

a) $BF_3{\cdot}OEt_2$, CH_2Cl_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



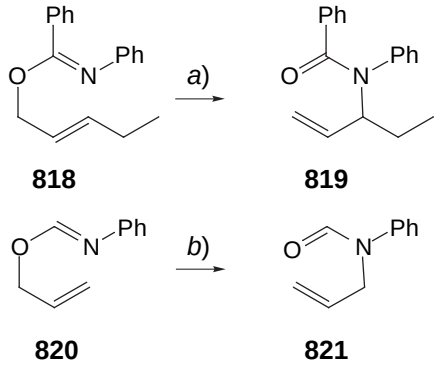
815 **816** **817**

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*.

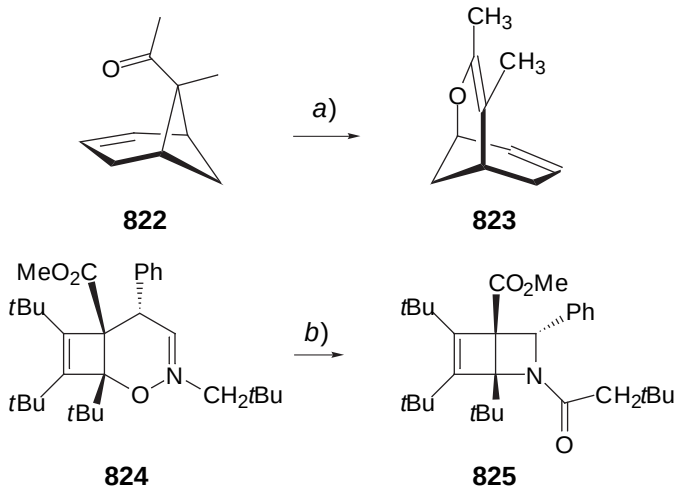
Scheme 4.3.14



a) 250°; 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 = $OSiR_3$, 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**.

Scheme 4.3.15



a) 180°, neat, 3 h; 85% [1034]. *b*) $CHCl_3$, CF_3CO_2H; 84% [1035].

I first tried a $BF_3{\cdot}OEt_2$ catalysed rearrangement of the carbamate **800** (Scheme 4.3.16). In CH_2Cl_2 no reaction was observed in the presence of one equivalent of $BF_3{\cdot}OEt_2$ at r.t. or under reflux. In boiling THF, **800** did not react with two equivalents $BF_3{\cdot}OEt_2$. When **800** was treated with two equivalents $BF_3{\cdot}OEt_2$ in diglyme at 150°, NMR and TLC[59]) indicated consumption of the starting material. However, after carbamoylation (Boc_2O, K_2CO_3) 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 (Et_3N, Me_3SiCl) [1036] of **800** was incomplete after 1 d, according to a ^{1}H-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 Et_3N in CH_2Cl_2 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 ^{1}H-NMR spectrum, a complex mixture was obtained. The reaction in diglyme at 150°, followed by trifluoroacetylation ($(CF_3CO)_2O$, Et_3N) and FC, did not afford any isolated product.

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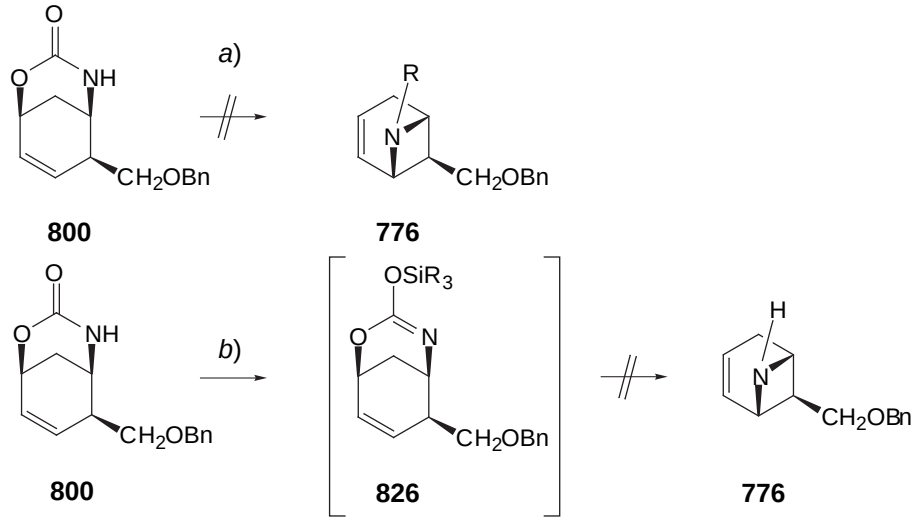
[59]) A smear was observed on TLC.

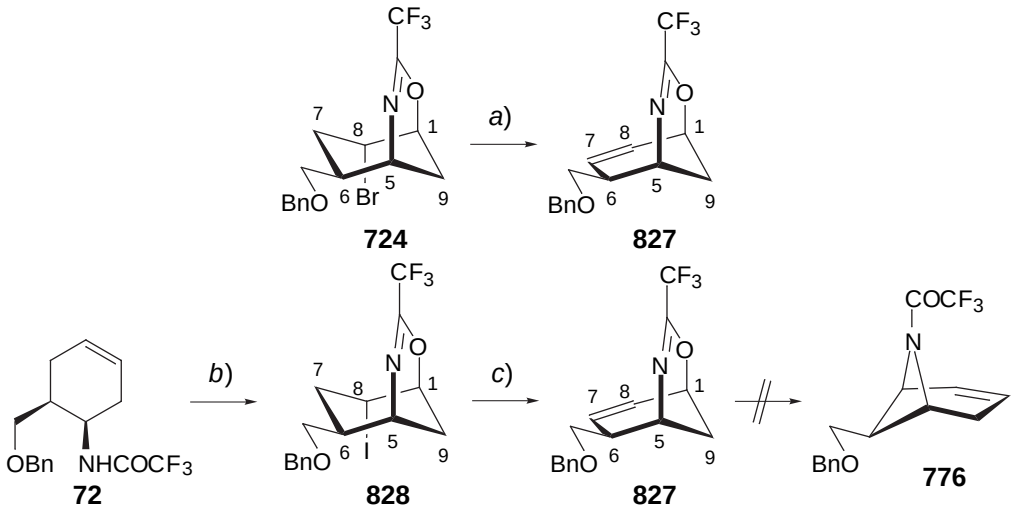
Scheme 4.3.16



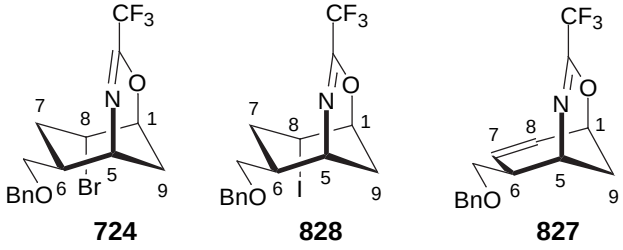
a) $BF_3 \cdot OEt_2$, see text. *b*) Me_3SiCl, Et_3N or TBSOTf, Et_3N, see text.

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 = alkyl, 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; KO*t*Bu, 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.

Scheme 4.3.17



a) DBU, THF; 0% or KO*t*Bu, THF; 19%. *b*) NIS, AcOH; 86%. *c*) DBU, THF; 86%.



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**.

	724	**828**	**827**
H–C(1)	4.74–4.69	4.76–4.72	4.94–4.89
H–C(5)	4.04–3.99	4.00–3.96	4.11–4.06
H–C(6)	2.65–2.54	2.65–2.54	2.92–2.84
H'–C(6)	–	–	–
H–C(7)	2.12	2.11–2.03	6.07
H'–C(7)	1.57	1.48	–
H–C(8)	4.51–4.47	4.68–4.64	5.98
H–C(9)	2.54	2.68	2.07
H'–C(9)	1.83	1.88	1.86
CH–C(6)	3.56	3.58	3.74
CH'–C(6)	3.29	3.30	3.42
J (1,5)	[a]	[a]	2.2
J (1,8)	[a]	[a]	5.3
J (1,9)	1.6	1.6	3.4
J (1,9')	3.9	3.9	1.2
J (5,6)	[a]	[a]	[a]
J (5,6')	–	–	–
J (5,9)	1.6	1.6	3.4
J (5,9')	3.9	3.9	1.2
J (6,7)	ca. 3.6	[a]	1.6
J (6,7')	12.1	12.5	–
J (6',7)	–	–	–
J (6',7')	–	–	–
J (6,6')	–	–	–
J (6,10)	7.5	7.5	6.9
J (6,10')	6.5	6.9	9.0
J (7,8)	[a]	[a]	10.0
J (7',8)	4.0	4.7	–
J (7,7')	15.9	16.2	–
J (8,9')	1.6	1.9	1.2, *J*(8,9)
J (9,9')	14.3	14.3	13.4
J (10,10')	9.0	9.0	9.0
C(1)	74.33	73.65	73.61
C(3)	147.62	[a]	[a]
C(5)	47.80[b]	48.04	47.66
C(8)	47.68[b]	26.66	[a]
C*F*$_3$	–73.10	[a]	[a]

[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-azanorbornenes **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.

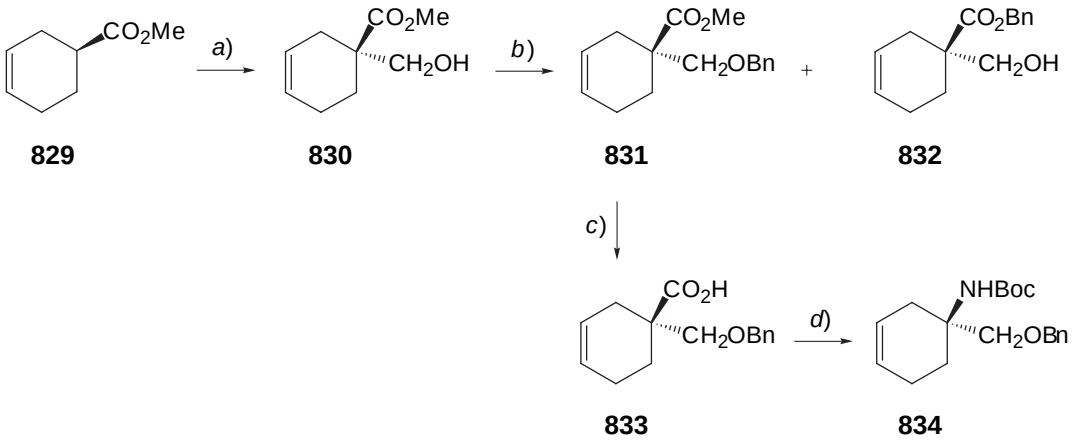
The 7-azanorbornanes **58** and **59** are only weak inhibitors of the β-mannosidase from snail and of the β-glucosidases from sweet almonds and from *Caldocellum saccharolyticum*, suggesting that these enzymes do not stabilise ^{14}B conformers in their active site. The 7-azanorbornanes are lower homologues 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*-(Benzyloxymethyl)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 α-acetamido acrylates or 2-alkylidene-5(4H)-oxazolones to butadiene [931] [938].

Scheme 5.1.1



a) LDA, THF, then CH_2O; 53%. *b*) NaH, THF, then Bu_4NI, BnBr; 31% of **831**, 12% of **832**. *c*) LiOH, H_2O; 89%. *d*) Et_3N, DPPA, toluene, then *t*BuOH, 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_{tx}, which is estimated at 10^{-14} to 10^{-18} M for a retaining β-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 β-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.

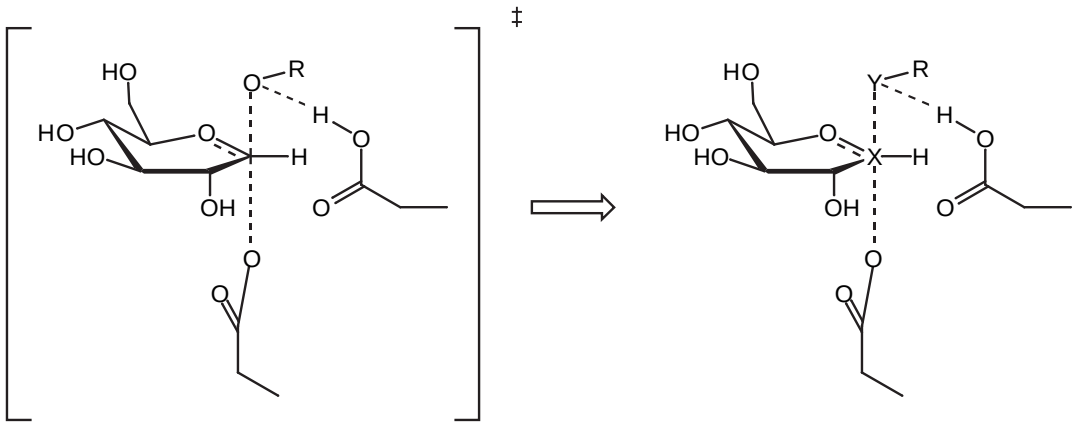
The ideal transition state analogue must perfectly mimic the shape and charge of the transition state, *i.e.* the bond and torsional angles and the bond length and strength. Such a perfect mimicry, however, is only possible for the transition state itself, as any substitution of an element by another 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 5^{th} 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.



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 CaH_2 (CH_2Cl_2, MeOH, DMF, Et_3N) or Na/benzophenone (THF, toluene), Na ($BnNH_2$), 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 $CHCl_3$ was dried by filtration through Al_2O_3.

Camphorsulphonic acid was recrystallised from AcOEt.

NH_4OH = 25% aq. NH_3 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% $(NH_4)_6Mo_7O_{26} \cdot 4\ H_2O$, 0.1% $Ce(SO_4)_2 \cdot H_2O$, in 10% H_2SO_4 soln. or by treatment with a 1% soln. of $KMnO_4$ in a 6% aq. K_2CO_3 soln. or with a soln. of vanillin in ethanol.

Flash chromatography (FC): silica gel 60 (40–63 μm); 0.05 – 0.5 bar N_2.

M.p.: open capillary, uncorrected.

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

FT-IR spectra: absorption in cm^{-1}.

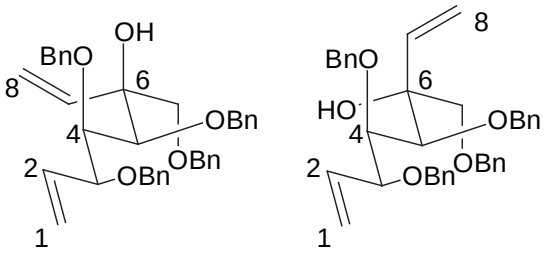
NMR spectra: recorded at 23 – 26°, unless stated otherwise. Chemical shifts in ppm relative to TMS (^1H, ^{13}C); coupling constants in Hz. Multiplicities of ^{13}C signals were determined by DEPT. NOE experiments allowed unambiguous assignments of all ^1H-NMR signals of **40** and **42**, and HSQC.GRASP spectra unambiguous assignments of the ^{13}C-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_2O. The pK_{HA} of **45** was estimated as the pH, at which c(**45**) = c(**45**·HCl) as described in [135].

I gratefully acknowledge the help of the analytical staff of the Laboratory for Organic Chemistry, ETH Zurich. *Mrs. B Brandenberg* and *Mr. P. Zumbrunnen* are thanked for recording NOE difference and 2D NMR spectra. *Mr. R.. Häfliger, Mr. O. Greter*, and *Mr. O. Scheidegger* are thanked for recording all MS spectra reported in this thesis. *Mr. M. Manser and Mr. B. Schneider* are thanked for determining elemental analyses and pK_{HA} values. *Dr. B. Schweizer* is thanked for crystal structure analysis.

Part 1.



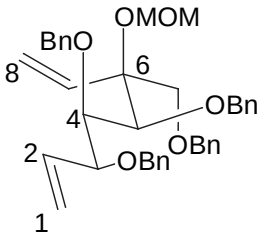
3,4,5-Tri-O-*benzyl-6*-C-*(benzyloxymethyl)-1,2,7,8-tetradeoxy*-D-gluco-*octa-1,7-dienitol* (**441**) and *3,4,5-Tri*-O-*benzyl-6*-C-*(benzyloxymethyl)-1,2,7,8-tetradeoxy*-L-ido-*octa-1,7-dienitol* (**450**).

A cooled (–78°) 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°, and treated with Et_2O (80 ml) and sat. aq. NH_4Cl soln. (80 ml). The organic phase was separated, washed with brine (50 ml), dried ($MgSO_4$), 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. R_f (hexane/AcOEt 3:1) 0.57. $[\alpha]_D^{25}$ = 35.2 (*c* = 3.3, $CHCl_3$). FT-IR (3%, $CHCl_3$): 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*, 1093*s*, 1028*m*, 996*m*, 934*m*, 822*w*, 606*w*, 515*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.23 (*m*, 20 arom. H); 5.97 (*dd*, *J* = 17.1, 10.6, H–C(7)); 5.83 (*ddd*, *J* = 17.4, 10.3, 7.8, H–C(2)); 5.47 (*dd*, *J* = 17.1, 1.9, H–C(8)); 5.30 (br. *dd*, *J* = 10.3, 1.9, H–C(1)); 5.20 (br. *dd*, *J* = 17.4, 1.9, H'–C(1)); 5.19 (*dd*, *J* = 10.6, 1.9, H'–C(8)); 4.84 (*d*, *J* = 11.2, PhC*H*); 4.78 (*d*, *J* = 11.5, PhC*H*); 4.65–4.61 (*m*, 3 PhC*H*); 4.48 (*d*, *J* = 12.1, PhC*H*); 4.43 (*d*, *J* = 11.8, PhC*H*); 4.35 (*d*, *J* = 11.8, PhC*H*); 4.07 (br. *dd*, *J* = 7.8, 6.5, H–C(3)); 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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*); 74.54 (*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 $C_{37}H_{40}O_5$ (564.72): C 78.70, H 7.14; found: C 78.87, H 7.35.

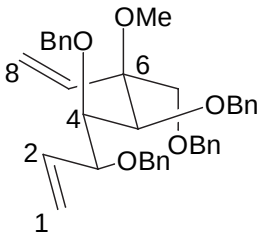
Data of **450**: colourless oil. R_f (hexane/AcOEt 3:1) 0.62. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.21 (*m*, 20 arom. H); 6.07 (*dd*, *J* = 17.4, 10.9, H–C(7)); 5.94 (*ddd*, *J* = 17.1, 10.6, 7.5, H–C(2)); 5.45 (*dd*, *J* = 17.4, 2.2, H–C(8)); 5.26 (br. *dd*, *J* = 17.1, 1.0, H–C(1)); 5.25 (br. *dd*, *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, PhC*H*); 4.68 (*d*, *J* =

11.5, PhC*H*); 4.64 (*d*, *J* = 11.8, PhC*H*); 4.62–4.43 (*m*, 4 PhC*H*); 4.35 (*d*, *J* = 11.8, PhC*H*); 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). ^{13}C-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**):

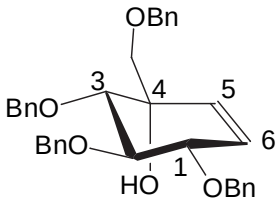
A suspension of NaH (17 mg, 0.708 mmol, washed with hexane) in DMF (5 ml) was treated at 0° with a soln. of **441** (200 mg, 0.354 mmol) in DMF (5 ml), stirred at 0° for 30 min., treated with MOMCl (57 mg, 0.708 mmol), and stirred for 20 h while warming to r.t.. The mixture was treated with MeOH (0.5 ml) and 10% aq. NaCl soln. (20 ml) and extracted with AcOEt (3 x 30 ml). The combined organic phases were dried (Na_2SO_4) 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. R_f (cyclohexane/AcOEt 3:1) 0.75. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, CH_2(1), CH_2(8)); 4.84–4.79 (*m*, PhC*H*, OC*H*O); 4.82 (*d*, *J* = 11.5, PhC*H*); 4.68–4.64 (*m*, PhC*H*, OC*H*O); 4.68 (*d*, *J* = 11.8, PhC*H*); 4.62 (*d*, *J* = 11.8, PhC*H*); 4.47 (*d*, *J* = 11.5, PhC*H*); 4.42 (*d*, *J* = 12.1, PhC*H*); 4.32 (*d*, *J* = 11.8, PhC*H*); 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)

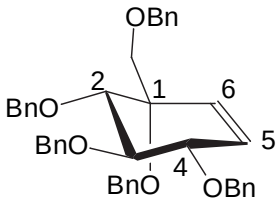
and diluted with AcOEt (40 ml). The resulting solution was washed with brine (2 x 15 ml), dried (Na_2SO_4), and evaporated. FC (30 g of silica gel, cyclohexane/AcOEt 50:1) of the residue (290 mg, yellow oil) gave **449** (125 mg, 55%) as a colourless oil and **449** contaminated with **441** (58.7 mg, 26%). R_f (cyclohexane/AcOEt 9:1) 0.29. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.19 (20 arom. H); 5.83 (*ddd*, *J* = 17.3, 10.4, 8.0, H–C(2)); 5.72 (*dd*, *J* = 17.3, 11.7, H–C(7)); 5.27–5.11 (*m*, CH_2(1), CH_2(8)); 4.75 (*d*, *J* = 11.8, PhC*H*); 4.70 (*d*, *J* =11.8, PhC*H*); 4.68 (*d*, *J* = 11.5, PhC*H*); 4.62 (*d*, *J* = 11.5, PhC*H*); 4.60 (*d*, *J* = 11.5, PhC*H*); 4.48 (*d*, *J* 10.9, PhC*H*); 4.44 (*d*, *J* = 12.1, PhC*H*); 4.32 (*d*, *J* = 11.8, PhC*H*); 4.04 (br. *dd*, *J* = 7.6, 4.7, H–C(3)); 3.84–3.81 (*m*, H–C(5)); 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).



*(1*D*)-(1,3,4/2)-1,2,3-Tri*-O-*benzyl-4*-C-*(benzyloxymethyl)cyclohex-5-ene-1,2,3,4-tetrol* (**40**).

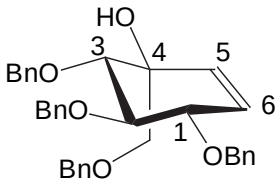
A soln. of **441** (2.20 g, 3.89 mmol) in CH_2Cl_2 (200 ml) was degassed by purging with N_2, treated with **312** (0.48 g, 0.54 mmol), stirred at r.t. for 7 d, and evaporated. FC (300 g of silica gel, hexane/AcOEt 3:1) of the residual oil gave **441** (0.5 g, 23%) as a dark green oil and **40** (1.25 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%). Green oil. R_f (hexane/AcOEt 3:1) 0.33. $[\alpha]_D^{25}$ = 70.8 (*c* = 1.51, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3538*m*, 3089*m*, 3066*m*, 3008*m*, 2863*m*, 1951*w*, 1875*w*, 1811*w*, 1731*w*, 1604*w*, 1496*m*, 1454*m*, 1393*w*, 1361*m*, 1294*w*, 1136*m*, 1064*s*, 1028*m*, 929*w*, 912*w*, 857*w*, 628*w*, 609*w*, 548*w*, 537*w*, 525*w*, 518*w*, 511*w*, 503*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.16 (*m*, 20 arom. H); 5.92 (*dd*, *J* = 10.3, 1.9, H–C(6)); 5.69 (*dd*, *J* = 10.3, 2.2, H–C(5)); 4.95 (*d*, *J* = 10.9, PhC*H*); 4.93 (*d*, *J* = 10.9, PhC*H*); 4.86 (*d*, *J* = 11.2, PhC*H*); 4.72 (*s*, PhCH_2); 4.48 (*d*, *J* = 12.5, PhC*H*); 4.46 (*d*, *J* = 10.9, PhC*H*); 4.38 (*d*, *J* = 12.1, PhC*H*); 4.20 (*dt*, *J* = 8.1, 2.1, irrad. at 5.92 —> NOE of 6%, H–C(1)); 4.02 (*dd*, *J* = 10.3, 8.1, H–C(2)); 3.76 (*d* , *J* = 10.3, H–C(3)); 3.38 (*d*, *J* = 8.7, CH–C(4)); 3.30 (*d*, *J* = 8.7, irrad. at 5.69 —> NOE of 3%, CH'–C(4)); 2.80 (*s*, OH). ^{13}C-NMR (75 MHz, $CDCl_3$, 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*, *C*H_2–C(4)); 73.47 (*t*); 72.97 (*s*, C(4)); 72.01 (*t*). FAB-MS (NOBA): 559 (6, $[M + Na]^+$), 535 (15, $[M - 1]^+$), 519 (36, $[M - OH]^+$), 429 (5, $[M - BnO]^+$), 412 (15, $[M - OH - BnO]^+$), 411 (17, $[M - H_2O - BnO]^+$), 321 (26), 297 (17), 291 (11), 271 (15), 213 (17),

197 (12), 181 (100). Anal. calc. for $C_{35}H_{36}O_5$ (536.67): C 78.33, H 6.76; found: C 78.42, H 6.91.



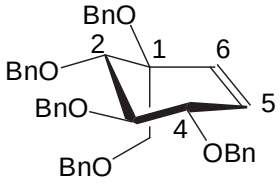
*(1*L*)-(1,2,4/3)-1,2,3,4-Tetra*-O-*benzyl-1*-C-*(benzyloxymethyl)-cyclohex-5-ene-1,2,3,4-tetrol* (**451**).

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 H_2O (3 6 10 ml), dried (Na_2SO_4), and evaporated. FC (40 g of silica gel, hexane/AcOEt 10:1) of the oily residue gave **451** (264 mg, 88%). Colourless oil. R_f (hexane/AcOEt 9:1) 0.20. $[\alpha]_D^{20}$ = 20.1 (*c* = 0.50, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, C_6D_6): 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, PhC*H*); 4.96 (*d*, *J* = 11.5, PhC*H*); 4.89 (*d*, *J* = 11.5, PhC*H*); 4.76–4.64 (*m*, 3 PhC*H*); 4.61 (*d*, *J* = 12.1, PhC*H*); 4.55 (*d*, *J* = 12.1, PhC*H*); 4.49 (*dd*, *J* = 10.6, 7.5, H–C(3)); 4.23 (*d*, *J* = 12.1, PhC*H*); 4.19 (*dt*, *J* = 7.5, 2.2, H–C(4)); 4.18 (*d*, *J* = 12.1, PhC*H*); 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 $C_{42}H_{42}O_5$ (626.79): C 80.48, H 6.75; found: C 80.35, H 6.61.



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

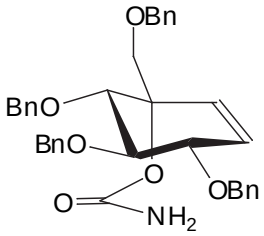
A soln. of **450** (22 mg, 0.04 mmol) in CH_2Cl_2 (5 ml) was degassed by purging with N_2, treated with **312** (10 mg, 0.012 mmol), stirred at r.t. for 5 d, and evaporated. FC (5 g of silica gel, hexane/AcOEt 4:1) of the residual oil gave 18 mg of a green oil, which was subjected to an additional FC (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 (*t*); 75.14 (*t*); 73.99 (*t*); 73.78 (*t*); 73.13 (*t*). 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).



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

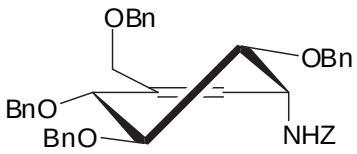
A cooled (0°) solution of **254** (7.5 mg, 14 µmol) in DMF (1.5 ml) was treated with NaH (60% suspension in oil, 5 mg, 125 µmol), stirred for 30 min, treated with BnBr (30 µl, 250 µmol), allowed to warm to r.t., and stirred for 4 h. The mixture was treated with MeOH (0.1 ml), diluted with EtOAc (20 ml), washed with H_2O (2 6 5 ml), brine (5 ml), dried (Na_2SO_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_6D_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, PhC*H*); 4.91 (*d*, *J* = 11.5, PhC*H*); 4.86 (*s*, PhCH_2); 4.65 (*d*, *J* = 12.1, PhC*H*); 4.59 (*d*, *J* = 12.1, PhC*H*); 4.47-4.38 (*m*, 2 PhC*H*, H-C(3)); 4.36 (*d*, *J* =11.8, PhC*H*); 4.27 (*d*, *J* = 11.8, PhC*H*); 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)).



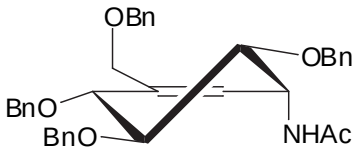
*(1*D*)-(1,3,4/2)-1,2,3-Tri*-O-*benzyl-4*-C-*(benzyloxymethyl)-4*-O-*carbamoylcyclohex-5-ene-1,2,3,4-tetrol* (**456**).

A cooled (0°) soln. of **40** (300 mg, 0.56 mmol) in CH_2Cl_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_2O (1 ml), was cooled to 0°, treated with K_2CO_3 (0.24 g, 1.72 mmol), and stirred for 100 min at 0° and 100 min at r.t.. After evaporation of MeOH, the aqueous soln. was diluted with H_2O (10 ml) and extracted with CH_2Cl_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. $[\alpha]_D^{25}$ = 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*w*, 1810*w*, 1729*s*, 1582*s*, 1497*m*, 1454*m*, 1357*s*, 1281*w*, 1175*w*, 1143*m*, 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, PhC*H*); 4.70 (*s*, PhCH_2); 4.58 (*d*, *J* = 10.9, PhC*H*); 4.51 (*d*, *J* = 12.1, PhC*H*); 4.40 (*d*, *J* = 12.1, PhC*H*); 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, $[M – NH_2CO_2]^+$), 472 (95, $[M – BnO]^+$), 411 (66, $[M – BnOH – NH_2CO_2]^+$), 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.



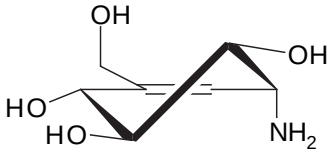
*(1*L*)-(1,3,4/2)-1,2,3-Tri*-O-*benzyl-4-(benzyloxycarbonylamino)-6-(benzyloxymethyl)cyclohex-5-ene-1,2,3-triol* (**459**).

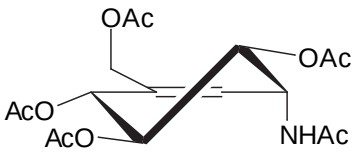
A cooled (–20°) soln. of **456** (228 mg, 0.39 mmol), PPh_3 (258 mg, 0.98 mmol) and Et_3N (110 µl, 0.79 mmol) in CH_2Cl_2 (4.5 ml) was treated dropwise with a soln. of CBr_4 (365 mg, 1.10 mmol) in CH_2Cl_2 (2.1 ml), stirred for 1 h at –20°, treated dropwise with BnOH (326 µl, 3.15 mmol), and allowed to warm to r.t. overnight. The mixture was poured into H_2O (10 ml). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (4 6 10 ml). The combined organic phases were washed with brine (10 ml), dried (Na_2SO_4), 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. R_f (hexane/AcOEt 3:1) 0.43. $[\alpha]_D^{25}$ = 30.9 (*c* = 1.51, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CHCl_3$): 7.38–7.23 (*m*, 25 arom. H); 5.81 (br. *d* , *J* = 3.1, H–C(5)); 5.11 (*s*, PhC*H*$_2$OC=O); 5.07 (*d*, *J* = 9.7, NH); 4.77–4.63 (*m*, 2 PhC*H*, H–C(4)); 4.60 (*s*, PhC*H*$_2$); 4.59 (*d J* = 11.2, PhC*H*); 4.57 (*d*, *J* = 11.5, PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.40 (*d*, *J* = 11.8, PhC*H*); 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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*, CH_2–C(6)); 66.92 (*t*, COO*C*H$_2$Ph); 47.20 (*d*, C(4)). FAB-MS (NOBA): 670 (9, $[M + 1]^+$), 562 (100, $[M – BnO]^+$), 534 (6), 518 (7, $[M – BnOCO_2]^+$), 472 (9), 429 (12), 181 (33). Anal. calc. for $C_{43}H_{43}NO_6$ (669.82): C 77.11, H 6.47, N 2.09; found: C 77.10, H 6.25, N 2.09.



*(1*L*)-(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°) soln. of **456** (260 mg, 0.45 mmol), PPh_3 (296 mg, 1.13 mmol) and Et_3N (126 µl, 0.90 mmol) in CH_2Cl_2 (5 ml) was treated dropwise with a soln. of CBr_4 (420 mg, 1.27 mmol) in CH_2Cl_2 (2.4 ml), stirred for 1 h at this temperature, and treated dropwise with 2.0M Me_3Al in heptane (1.8 ml, 3.62 mmol). After stirring for 1 h at –20°, the mixture was treated carefully with MeOH (2 ml), CH_2Cl_2 (5 ml), and 0.2M HCl (10 ml) and allowed to warm to 0°. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (6 6 10 ml). The combined organic phases were washed with brine (10 ml), dried ($MgSO_4$), 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. R_f (hexane/AcOEt 1:1) 0.21. $[\alpha]_D^{23}$ = 23.4 (*c* = 1.01, $CHCl_3$; [225]: $[\alpha]_D^{23}$ = 22 (*c* = 1, $CHCl_3$)). FT-IR (0.6%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.70 (*d*, *J* = 10.3, PhC*H*); 4.62 (*d*, *J* = 11.2, PhC*H*); 4.60 (*d*, *J* = 12.1, PhC*H*); 4.58 (*d*, *J* = 11.5, PhC*H*); 4.54 (*d*, *J* = 11.5, PhC*H*); 4.49 (*d*, *J* = 12.1, PhC*H*); 4.40 (*d*, *J* = 11.8, PhC*H*); 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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*, *C*H_2–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).



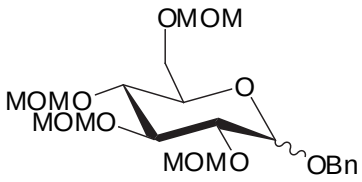


*(1*L*)-(1,3,4/2)-4-Amino-6-(hydroxymethyl)cyclohex-5-ene-1,2,3-triol ((+)-valienamine*, **22**) [367] [415] [708] and *(1*L*)-(1,3,4/2)-4-Acetamido-1,2,3-tri*-O-*acetyl-6-(acetyloxymethyl)cyclohex-5-ene-1,2,3-triol* (**461**) [417] [427] [429].

At –78°, NH_3 (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 NH_4Cl (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 H_2O). After washing with water (30 ml), elution with 2% aq. NH_3 gave **22**(30 mg, 78%). Slightly yellow solid. $[\alpha]_D^{25}$ = 79.3 (*c* = 1.5, H_2O; [708]: $[\alpha]_D^{25}$ = 81.6 (H_2O)). ^{1}H-NMR (300 MHz, D_2O): see [367]. ^{13}C-NMR (75 MHz, D_2O): see [708]. Conventional acetylation of **22** gave, after FC **461** (55 mg, 86%). Colourless crystals (Et_2O). R_f (toluene/acetone 7:2) 0.08. M.p. 94–95° ([427]: 92.5-95° (EtOH/toluene)). $[\alpha]_D^{25}$ = 26.3 (*c* = 1.02, $CHCl_3$; [417]: $[\alpha]_D$ = 24 (*c* = 1, $CHCl_3$)). ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$): see [429]. FAB-MS (NOBA): 771 (21, $[2M + 1]^+$), 386 (41, $[M + 1]^+$), 326 (100, $[M – AcO]^+$), 284 (7), 206 (7), 164 (12), 122 (12).

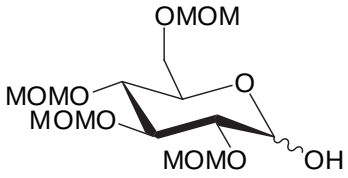
Oxidative rearrangement of **40** to **162**.

A soln. of **40** (100 mg, 0.186 mmol) in CH_2Cl_2 (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 Et_2O (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.



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

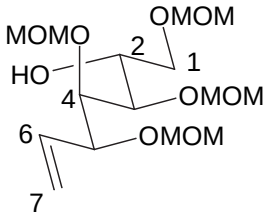
A cooled (0°) suspension of oil-free NaH (0.62 g, 25.9 mmol, washed with hexane) was treated dropwise with a solution of Benzyl-*D*-glucopyranoside (1.69 g, 6.25 mmol) in DMF (40 ml) over 30 min, then treated dropwise with methylchloromethyl ether (2.9 ml, 37.2 mmol), stirred at 23° for 65 h, treated 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 (Na_2SO_4) 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. R_f (hexane/acetone 3:2) 0.58. ^{1}H-NMR ($CDCl_3$): 7.40–7.28 (*m*, 5 *arom.* H); 4.98 (*m*, H–C(1)); 4.90–4.54 (*m*, 12 H, (O-C*H*$_2$-O-CH$_3$, PhC*H*$_2$); 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-CH$_2$-O-C*H*$_3$). ^{13}C-NMR ($CDCl_3$): 137.39 (*s*); 127.84–128.6 (several *d*); 98.74 (*t*, (O-*C*H$_2$-O-CH$_3$)); 98.66 (*t*, (O-*C*H$_2$-O-CH$_3$)); 98.58 (*t*, (O-*C*H$_2$-O-CH$_3$)); 97.59 (*t*, (O-*C*H$_2$-O-CH$_3$)); 97.07 (*d*); 96.73 (*d*, C(1)); 78.89 (*d*); 78.81 (*d*); 78.76 (*d*); 78.75 (*d*); 69.65 (*t*, (PhCH$_2$); 66.37 (*t*, C(6)); 56.53 (*q*, (O-CH$_2$-O-*C*H$_3$)); 56.32 (*q*, (O-CH$_2$-O-*C*H$_3$); 55.74 (*q*, (O-CH$_2$-O-*C*H$_3$)); 55.49 (*q*, (O-CH$_2$-O-*C*H$_3$)). CI-MS (NH_4-DCI.): 464 (16, [*M* + NH_4]$^+$), 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**).

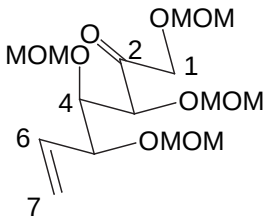
Na (200 mg, 8.7 mmol) was dissolved in NH_3 (25 ml) at -78°. The blue solution was treated dropwise with a solution of **463** (1.75 g, 3.92 mmol) in THF (25 ml), stirred for 15 min at -78°, treated with NH_4Cl (2g), stirred for 2 h at r.t., and treated with Et_2O (70 ml) and saturated NH_4Cl soln. (30 ml). The org. phase was separated, the aq. phase was extracted with Et_2O (3∗40 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, 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. R_f (hexane/acetone 3:2) 0.39. ^{1}H-NMR ($CDCl_3$): 5.35 (*s*, 1

H, OH); 4.97 (*m*, 1 H, H–*C*(1)); 4.89–4.68 (*m*, 8 H, (O-C*H*$_2$-O-CH$_3$)); 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-CH$_2$-O-C*H*$_3$)). ^{13}C-NMR ($CDCl_3$): 98.64 (*t*, (O-*C*H$_2$-O-CH$_3$)); 98.51 (*t*, (O-*C*H$_2$-O-CH$_3$)); 97.59 (*t*, (O-*C*H$_2$-O-CH$_3$)); 96.94 (*t*, (O-*C*H$_2$-O-CH$_3$)); 96.82 (*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-CH$_2$-O-*C*H$_3$)); 56.30 (*q*, (O-CH$_2$-O-*C*H$_3$)); 55.79 (*q*, (O-CH$_2$-O-*C*H$_3$)); 55.45 (*q*, (O-CH$_2$-O-*C*H$_3$)). FAB-MS (NOBA.): 355 (10, [*M* + 1]$^+$), 291 (41), 247 (51), 215 (100, [*M* – 2 OMOM – OH]$^+$), 185 (84), 155 (40).



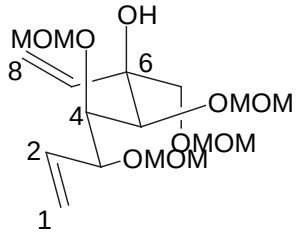
1,3,4,5-Tetra-O-*methoxymethyl-6,7-dideoxy*-L-gulo-*hept-6-enitol* (**465**).

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 $PH_3P{=}CH_2$ (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. $NaHCO_3$ 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 ($MgSO_4$), and evaporated. FC of the oily residue (hexane/acetone 3:1) afforded **465** (0.682 g, 1.92 mmol, 63%) as a colourless oil. R_f (hexane/acetone 3:2) 0.52. IR (CH_2Cl_2): 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*. ^{1}H-NMR ($CDCl_3$): 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-C*H*$_2$-O-CH$_3$)); 4.38–4.31 (*m*, 1 H); 3.92–3.61 (*m*, 6 H); 3.41–3.33 (*m*, 12 H, (O-CH$_2$-O-C*H*$_3$)). ^{13}C-NMR ($CDCl_3$): 134.75 (*d*, C(6)); 120.01 (*t*, C(7)); 99.17 (*t*, (O-*C*H$_2$-O-CH$_3$)); 98.93 (*t*, (O-*C*H$_2$-O-CH$_3$)); 97.14 (*t*, (O-*C*H$_2$-O-CH$_3$)); 94.18 (*t*, (O-*C*H$_2$-O-CH$_3$)); 80.68 (*d*); 79.97 (*d*); 77.50 (*d*); 69.81 (*d*, C(2)); 69.05 (*t*, C(1)); 56.50 (*q*, (O-CH$_2$-O-*C*H$_3$)); 56.34 (*q*, (O-CH$_2$-O-*C*H$_3$)); 55.92 (*q*, (O-CH$_2$-O-CH$_3$)); 55.48 (*q*, (O-CH$_2$-O-*C*H$_3$)). 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**).

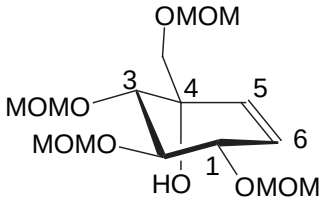
A suspension of molecular sieves (3 Å, 0.5 g) and pyridinium chlorochromate (PCC) (0.334 g, 1.56 mmol, 2.2 eq) in CH_2Cl_2 (15 ml) at 22° was treated with a soln. of **465** (0.251 g, 0.711 mmol) in CH_2Cl_2 (5 ml), stirred for 2 h, filtered through celite, and evaporated. FC of the crude product (cyclohexane/acetone 3:1) afforded **466** (0.223 g, 0.632 mmol, 89%) as a colourless oil. R_f (cyclohexane/acetone 3:2) 0.53. ^{1}H-NMR ($CDCl_3$): 5.84 (*ddd*, *J* = 17.43, 9.96, 7.78, H–C(6)); 5.41–5.33 (*m*, H_2–C(7)); 4.77–4.50 (*m*, 8 H, (O-C*H*$_2$-O-CH_3)); 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-CH_2-O-C*H*$_3$)). ^{13}C-NMR ($CDCl_3$): 206 (*s*, (C(2)); 134.35 (*d*, (C(6)); 120.01 (*t*, (C(7)); 98.45 (*t*, (O-*C*H_2-O-CH_3)); 98.03 (*t*, (O-*C*H_2-O-CH_3)); 96.70 (*t*, (O-*C*H_2-O-CH_3)); 93.76 (*t*, (O-*C*H_2-O-CH_3)); 80.88 (*d*); 79.44 (*d*); 77.16 (*d*); 71.46 (*t*, C(1)); 56.72 (*q*, (O-CH_2-O-C*H*$_3$)); 56.48 (*q*, (O-CH_2-O-*C*H_3); 55.93 (*q*, (O-CH_2-O-*C*H_3)); 55.77 (*q*, (O-CH_2-O-*C*H_3)). 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**).

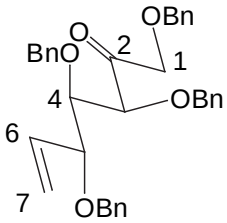
A cooled (-78°) soln. of **466** (0.159 g, 0.45 mmol) in THF (10 ml) was treated dropwise with 1M vinylmagnesium bromide in THF (0.68 ml, 0.68 mmol), stirred for 60 min, treated with Et_2O (20 ml), warmed to 0°, and treated with sat. aq. NH_4Cl soln. (10 ml). The org. phase was separated and the aq. phase extracted with Et_2O (2∗20ml). The combined org. phases were washed with brine (10 ml), dried ($MgSO_4$), and evaporated. FC of the oily residue (cyclohexane/acetone 10:1) afforded **467** (0.155 g, 0.41 mol, 90 %) as a colourless oil. R_f (cyclohexane/acetone 3:2) 0.54. ^{1}H-NMR ($CDCl_3$): 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*, H_2–C(1),

H'–C(8)); 4.86–4.55 (*m*, 8 H, (O-C*H*$_2$-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-C*H*$_3$), 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-*C*H$_2$-O-CH$_3$)); 98.77 (*t*, (O-*C*H$_2$-O-CH$_3$)); 97.38 (*t*, (O-*C*H$_2$-O-CH$_3$)); 94.37 (*t*, (O-*C*H$_2$-O-CH$_3$)); 78.66 (*d*); 77.90 (*d*); 77.16 (*d*); 72.58 (*t*, *C*H$_2$–C(6)); 56.72 (*q*, (O-CH$_2$-O-*C*H$_3$)); 56.48 (*q*, (O-CH$_2$-O-*C*H$_3$)); 55.93 (*q*, (O-CH$_2$-O-*C*H$_3$)); 55.77 (*q*, (O-CH$_2$-O-*C*H$_3$)); 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).



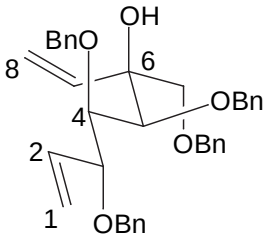
*(1*D*)-(1,3,4/2)-1,2,3-tri*-O-*methoxymethyl-4*-C-[*methoxymethyloxymethyl] cyclohex-5-ene-1,2,3,4-tetrol* (**468**).

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*H*–O–CH$_3$); 4.97 (*d*, *J* = 6.5, O–C*H*'–O–CH$_3$); 4.84–4.62 (*m*, 6 H, (O-C*H*$_2$-O-CH$_3$)); 4.59 (*m*, 2 H, C*H*$_2$–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-C*H*$_3$), OH). ^{13}C-NMR (CDCl$_3$): 131.38 (*d)* ; 129.61(*d*); 98.90 (*t*, (O-*C*H$_2$-O-CH$_3$)); 98.27 (*t*, (O-*C*H$_2$-O-CH$_3$)); 97.10 (*t*, (O-*C*H$_2$-O-CH$_3$)); 97.05 (*t*, (O-*C*H$_2$-O-CH$_3$)); 78.50 (*d*); 78.34 (*d*); 77.05 (*d*); 72.55 (*s*); 71.53 (*t*, *C*H$_2$–C(4)); 56.27 (*q*, (O-CH$_2$-O-*C*H$_3$)); 56.64 (*q*, (O-CH$_2$-O-*C*H$_3$)); 55.66 (*q*, (O-CH$_2$-O-*C*H$_3$)); 55.49 (*q*, (O-CH$_2$-O-*C*H$_3$).



1,3,4,5-Tetra-O-*benzyl-6,7-dideoxy*-D-arabino-*hept-6-en-2-ulose* (**470**).

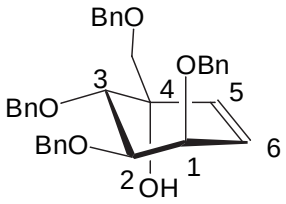
A solution of **469** [712] (1.86 g, 3.45 mmol) in toluene (6.7 ml) was treated with dicyclohexyl carbodiimide (1.67 g, 8.09 mmol), DMSO (0.93 ml, 17.60 mmol), and pyridine (0.37 ml, 4.58 mmol), and then dropwise with trifluoroacetic acid (0.37 ml, 3.32 mmol), and stirred for 4 h. The mixture was treated with H_2O (2 ml), Et_2O (9.5 ml), and filtered through *Celite*. The filter residue was washed with Et_2O (25 ml). The filtrate was washed with 1M HCl (2 6 10 ml), sat. aq. $NaHCO_3$ soln. (20 ml), and brine (20 ml), dried (Na_2SO_4), 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. R_f (hexane/AcOEt 3:1) 0.59. $[\alpha]_D^{25}$ = –39.8 (*c* = 1.52, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 (36, $[M]^+$), 536 (26, $[M – 1]^+$), 429 (96, $[M – BnO]^+$), 271 (31), 181 (100). Anal. calc. for $C_{35}H_{36}O_5$ (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-tetradeoxy*-d-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 Et_2O (40 ml), warmed to 0°, and treated with sat. aq. NH_4Cl soln. (40 ml). The organic phase was separated and the aqueous phase extracted with Et_2O (2 6 20 ml). The combined organic phases were washed with brine (30 ml), dried (Na_2SO_4), 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. R_f (hexane/AcOEt 3:1) 0.64. $[\alpha]_D^{25}$ = –4.5 (*c* = 1.5, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3462*m*, 3089*m*, 3066*m*, 3008*m*, 2909*m*, 1951*w*, 1870*w*, 1810*w*, 1749*w*, 1700*w*, 1637*w*, 1605*w*, 1558*w*, 1497*m*, 1454*m*, 1420*w*, 1397*m*, 1348*m*, 1307*w*, 1091*s*, 1028*s*, 1000*m*, 934*m*, 634*w*, 602*w*, 580*w*, 564*w*, 550*w*, 544*w*, 534*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.22 (20 arom. H); 6.18 (*dd*, *J* = 17.4, 10.9, H–C(7)); 6.02–5.91 (*m*, H–C(2)); 5.56 (*dd*, *J* = 17.4, 1.9, H–C(8)); 5.47–5.42 (*m*, 2 H–C(1)); 5.26 (*dd*, *J* = 10.9, 1.9, H'–C(8)); 4.71 (*d*, *J* = 10.6, PhC*H*); 4.72–4.52 (*m*, 4 PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.43 (*d*, *J* = 12.1, PhC*H*); 4.24 (*d*, *J* = 11.8, PhC*H*); 4.07 (*d*, *J* = 2.5, H–C(5)); 4.05 (br. *t*, *J* = 7.5, H–C(3)); 3.90 (*dd*, *J* = 7.2, 2.5, H–C(4)); 3.75 (*s*, OH); 3.73 (*d*, *J* = 8.7, CH–C(6)); 3.28 (*d*, *J* = 8.7, CH'–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 140.72 (*d*, C(7)); 138.97 (*s*); 138.55 (*s*); 138.49 (*s*); 138.34 (*s*); 136.35 (*d*, C(2)); 128.63–127.63 (several *d*); 120.22 (*t*, C(1)); 114.87 (*t*, C(8)); 81.46 (*d*); 81.04 (*d*); 78.56 (*d*); 78.05 (*s*, C(6)); 75.09 (*t*); 74.97 (*t*); 73.61 (*t*); 73.37 (*t*); 70.05 (*t*). FAB-MS (NOBA): 1129 (3, $[2M + 1]^+$), 587 (8, $[M + Na]^+$), 565 (100, $[M + 1]^+$), 457 (27, $[M – BnO]^+$), 181 (15). Anal. calc. for $C_{37}H_{40}O_5$ (564.72): C 78.70, H 7.14; found: C 78.60, H 7.12.



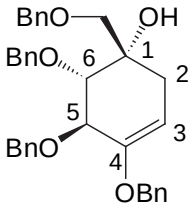
*(1*D*)-(1,2/3,4)-1,2,3-Tri*-O-*benzyl-4*-C-*(benzyloxymethyl)cyclohex-5-en-1,2,3,4-tetrol* (**42**).

A solution of **471** (2.20 g, 3.89 mmol) in CH_2Cl_2 (200 ml, degassed by purging with N_2) was treated with **312** (480 mg, 0.58 mmol), stirred for 4 d under N_2, and concentrated. FC (250 g of silica gel, hexane/AcOEt 4:1) of the oily residue gave **42** (1.85 g, 89%). Green oil. R_f (cyclohexane/AcOEt 3:1) 0.44. $[\alpha]_D^{25}$ = –35.2 (*c* = 1.5, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 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*m*, 1098*s*, 1028*m*, 913*w*, 855*w*, 636*w*, 601*w*, 563*w*, 536*w*, 524*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.41–7.22 (20 arom. H); 5.95 (*dd*, *J* = 10.0, 5.0, H–C(6)); 5.79 (*d*, *J* = 10.0, irrad. at 3.45 —> NOE of 5%, H–C(5)); 4.97 (*d*, *J* = 10.9, PhC*H*); 4.77 (*d*, *J* = 12.1, PhC*H*); 4.75-4.67 (*m*, 3 PhC*H*); 4.59 (*d*, *J* = 10.9, PhC*H*); 4.57 (*d*, *J* = 12.1, PhC*H*); 4.46 (*d*, *J* = 12.1, PhC*H*); 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,

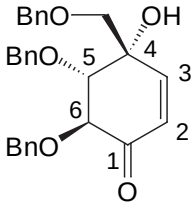
CH–C(4)); 3.43 (*d*, *J* = 9.3, CH'–C(4)); 3.10 (*s*, OH). ^{13}C-NMR (75 MHz, $CDCl_3$): 139.10 (*s*); 138.88 (*s*); 138.52 (*s*); 138.39 (*s*); 132.84 (br. *d*, C(5)); 128.59-127.81 (several *d*, incl. C(6)); 78.16 (*d*, C(2)); 75.98 (*d*, C(3)); 75.57 (*t*); 74.55 (*t*, *C*H_2–C(4)); 73.58 (*t*); 73.08 (*s*, C(4)); 72.87 (*t*); 71.88 (*t*); 71.69 (*d*, C(1)). Anal. calc. for $C_{35}H_{36}O_5$ (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 N_2 at 80° 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%), **42** (18 mg, 9%), **473** (2.6 mg, 2%), and **474** (3.0 mg, 2%).

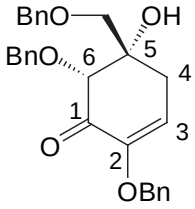


Data of *(1*S,*5*S,*6*S*)-4,5,6-Tris-benzyloxy-1-(benzyloxymethyl)cyclohex-3-enol* (**472**): Colourless oil. *R*f (cyclohexane/AcOEt 3:1) 0.48. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.24 (20 arom. H); 4.86 (*d*, *J* = 11.2, PhC*H*); 4.81 (*d*, *J* = 11.2, PhC*H*); 4.78 (*s*, PhCH_2); 4.72 (br. *t*, *J* = 4.0, H–C(3)); 4.65 (*d*, *J* = 11.5, PhC*H*); 4.62 (*d*, *J* = 11.5, PhC*H*); 4.54 (*d*, *J* = 12.1, PhC*H*); 4.48 (*d*, *J* = 12.1, PhC*H*); 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, $C_{35}H_{36}NaO_5^+$, $[M + Na]^+$; calc. 559.2460).

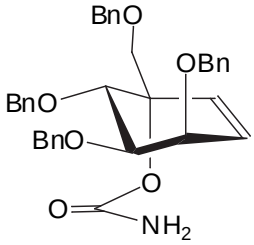


Data of *(4*S,*5*S,*6*S*)-5,6-Bis-benzyloxy-4-(benzyloxymethyl)-4-hydroxycyclohex-2-enone* (**473**): *R*f (cyclohexane/AcOEt 3:1) 0.30. FT-IR (0.5%, $CHCl_3$): 1700*s* (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.45–7.19 (15 arom. H); 6.71 (*d*, *J* = 10.3, H–C(3)); 6.13 (*d*, *J* = 10.3, H–C(2)); 5.08

(*d*, *J* = 11.2, PhC*H*); 4.94 (*d*, *J* = 10.9, PhC*H*); 4.70 (*d*, *J* = 11.5, PhC*H*); 4.49 (*d*, *J* = 11.2, PhC*H*); 4.46 (*d*, *J* = 11.2, PhC*H*); 4.42 (*d*, *J* = 9.7, H–C(6)); 4.36 (*d*, *J* = 11.8, PhC*H*); 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??, $C_{28}H_{28}NaO_5^+$, [*M* + Na]$^+$; calc. 467.1834).



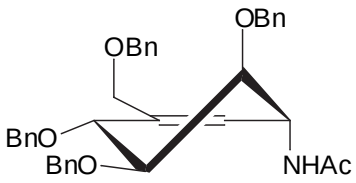
Data of *(5*S,*6*R*)-2,6-Bis-benzyloxy-5-(benzyloxymethyl)-5-hydroxy-cyclohex-2-enone* (**474**): *R*f (cyclohexane/AcOEt 3:1) 0.23. FT-IR (0.5%, $CHCl_3$): 1703*s* (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.21 (15 arom. H); 5.73–5.69 (*m*, H–C(3)); 5.09 (*d*, *J* = 10.9, PhC*H*); 4.91 (*d*, *J* = 12.5, PhC*H*); 4.82 (*d*, *J* = 12.1, PhC*H*); 4.69 (*d*, *J* = 10.9, PhC*H*); 4.47 (*s*, PhCH_2); 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??, $C_{28}H_{28}NaO_5^+$, [*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**).

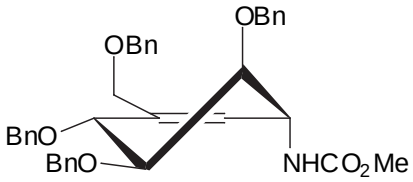
A solution of **42** (140 mg, 0.26 mmol) in CH_2Cl_2 (2.5 ml) was cooled to 0°, treated dropwise with CCl_3CONCO (62 μl, 0.52 mmol), stirred for 30 min, and evaporated. A solution of the residue in MeOH (3.5 ml) and H_2O (0.5 ml) was cooled to 0º, treated with K_2CO_3 (120 mg, 0.86 mmol), and stirred at 0º for 100 min and at r.t. for 14 h. After evaporation of MeOH, the residue was diluted with H_2O (20 ml) and extracted with CH_2Cl_2 (3 x 30 ml). The combined organic phases were washed with brine ((20 ml) and dried (Na_2SO_4). Evaporation and FC (30 g of silica gel, cyclohexane/AcOEt 5:2) gave **476** (141 mg, 93%). Colourless oil. *R*f (cyclohexane/AcOEt 3:1) 0.07. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.72 (*d*,

J = 12.1, PhC*H*); 4.70–4.63 (*m*, 4 PhC*H*); 4.56–4.43 (br. *s*, NH_2); 4.54 (*d*, *J* = 12.1, PhC*H*); 4.44 (*d*, *J* = 12.1, PhC*H*); 4.37 (*d*, *J* = 9.0, H–C(3)); 4.22 (br. *t*, *J* = 4.1, H–C(1)); 4.13 (*d*, *J* = 9.0, CH–C(4)); 4.02 (*dd*, *J* = 9.0, 4.0, H–C(2)); 3.84 (*d*, *J* = 9.0, CH'–C(4)).



(1L)-(1,4/2,3)-4-Acetamido-1,2,3-tri-O-*benzyl-6-[(benzyloxy)methyl]cyclohex-5-ene-1,2,3-triol* (**43**).

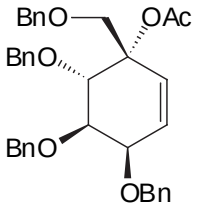
A solution of **476** (139 mg, 0.24 mmol), Ph_3P (157 mg, 0.60 mmol), and Et_3N (66 μl, 0.48 mmol) in CH_2Cl_2 (2.5 ml) was cooled to –20°, treated dropwise with a solution of CBr_4 (223 mg, 0.67 mmol) in CH_2Cl_2 (1.2 ml), stirred for 1 h, treated dropwise with 2.0M Me_3Al in heptane (0.96 ml, 1.92 mmol), stirred for 1 h, treated carefully with MeOH (1 ml), CH_2Cl_2 (2.5 ml), and 0.1M HCl (10 ml), and allowed to warm to 0º. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (6 x 15 ml). The combined organic phases were washed with brine (30 ml) and dried (Na_2SO_4). Evaporation and FC (30 g of silica gel, cyclohexane/AcOEt 1:1) gave **43** (132 mg, 95%). R_f (cyclohexane/AcOEt 1:1) 0.24. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.22 (20 arom. H); 5.69 (*d*, *J* = 3.1, H–C(5)); 5.08 (br. *d*, *J* = 8.4, AcN*H*); 4.88–4.79 (*m*, H–C(4)); 4.67 (*d*, *J* = 11.5, 2 PhC*H*); 4.62 (*d*, *J* = 11.5, PhC*H*); 4.55 (*d*, *J* = 12.1, 2 PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.48 (*d*, *J* = 12.5, PhC*H*); 4.36 (*d*, *J* = 11.8, PhC*H*); 4.16 (br. *d*, *J* = 4.7, H–C(1)); 4.15 (br. *d*, *J* ≈ 11, CH–C(6)); 3.87 (br. *d*, *J* ≈ 12.8, CH'–C(6)); 3.83 (*dd*, *J* = 5.0, 2.2, H–C(2)); 3.70 (*dd*, *J* = 6.9, 2.2, H–C(3); 1.89 (*s*, Ac). MALDI-MS: 600 (100, $[M + Na]^+$).



(1L)-(1,4/2,3) -1,2,3-Tri-O-*benzyl-6-[(benzyloxy)methyl]-4-[(methoxycarbonyl)amino]cyclohex-5-ene-1,2,3-triol* (**479**).

A solution of **476** (144 mg, 0.25 mmol), Ph_3P (163 mg, 0.62 mmol), and Et_3N (70 μl, 0.50 mmol) in CH_2Cl_2 (3 ml) was cooled to –20°, treated dropwise with a solution of CBr_4 (231 mg, 0.70 mmol) in CH_2Cl_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 CH_2Cl_2 (4 x 20 ml), and the combined organic phases were washed with brine (30 ml) and dried (Na_2SO_4). 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. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.20 (20 arom. H); 5.74–5.70 (*m*, H–C(5)); 4.69 (*d*, *J* = 12.1, PhC*H*); 4.67–4.54 (*m*, 2 PhC*H*, H–C(4), NH); 4.62 (*d*, *J* = 11.8, PhC*H*); 4.58 (*d*, *J* = 12.1, PhC*H*); 4.53 (*d*, *J* = 12.1, PhC*H*); 4.49 (*d*, *J* = 11.8, PhC*H*); 4.36 (*d*, *J* = 11.8, PhC*H*); 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.01 (*s*, C=O); 138.68, 138.52, 136.11 (3*s*); 128.72–127.49 (several *d*); 77.46 (*d*); 75.22 (2*d*); 74.16, 72.61, 71.83, 70.48 (4*t*, 1*t* hidden); 52.34 (*q*, MeO); 49.83 (*d*, C(4)). HR-MS (MALDI): 616.2667 (100??, $C_{37}H_{39}NaNO_6^+$, $[M + Na]^+$; calc. 616.2675).

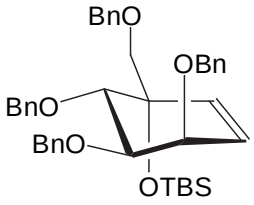


*1*L*-(1,2/3,4)-1*-O*-Acetyl-2,3,4-tri*-O*-benzyl-1*-C*-(benzyloxymethyl)-cyclohex-5-ene-1,2,3,4-tetrol* **475**.

A soln. of **42** (280 mg, 0.52 mmol) in pyridine (2.5 ml) was treated with Ac_2O (2.5 ml, 26.4 mmol) and DMAP (5 mg), stirred at r.t. for 12 h, and coevaporated repeatedly with toluene. FC (30 g of silica gel, hexane/AcOEt 6:1) of the residue (brown oil) gave **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. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.73 (*d*, *J* = 12.1, PhC*H*); 4.72–4.65 (*m*, 3 PhC*H*); 4.64 (*d*, *J* = 11.8, PhC*H*); 4.51 (*d*, *J* = 11.8, PhC*H*); 4.44 (*d*, *J* = 12.1, PhC*H*); 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).

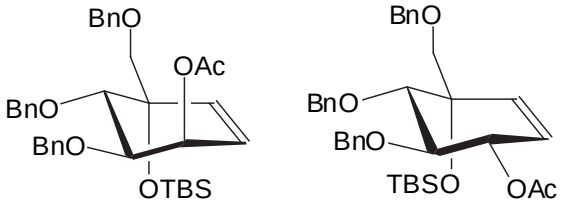
Reaction of **475** *with Pd(PPh3)4 and NaN3 (cf.* [417]*).*

A soln. of **475** (80 mg, 0.138 mmol) in THF (2.5 ml) was treated with $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) and 1M aq. NaN_3 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).



*(1*L*)-(1,2/3,4)-1,2,3-Tri*-O-*benzyl-4-tert-butyl-dimethyl-silyl-4*-C-*[(benzyloxy)metyl] cyclohex-5-ene-1,2,3,4-tetrol* (**836**).

A cooled (0°) solution of **42** (0.623 g, 1.16 mmol) in CH_2Cl_2 (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. NH_4Cl soln. (20 ml). The org. phase was separated and the aq. phase was extracted with CH_2Cl_2 (3∗30 ml). The combined organic phases were washed with brine (20 ml), dried ($MgSO_4$), 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 (Cyclohexane/AcOEt 10:1) 0.72. ^{1}H-NMR ($CDCl_3$): 7.43–7.25 (*m*, 20 arom. H); 5.86 (*d*, *J* = 9.96, H–C(5)); 5.80 (*dd*, *J* = 9.96, 4.67, H–C(6)); 5.09 (*d*, *J* = 11.83 Hz, PhC*H*); 4.87 (*d*, *J* = 12.45Hz, PhC*H*)); 4.81 (*d*, *J* = 12.45, PhC*H*); 4.75 (*s*, PhCH_2) ; 4.61 (*d*, *J* = 11.83, PhC*H*)); 4.51 (*d*, *J* = 12.13Hz, PhC*H*); 4.39 (*d*, *J* = 12.13, PhC*H*); 4.17 (*d*, *J* = 10.27, H–C(3)); 4.11 (*dd*, *J* = 4.67, 4.05, H–C(1)); 4.01 (*dd*, *J* = 10.27, 4.05, H–C(2)); 3.48 (*dd*, *J* = 8.72 Hz, *C*H_2–C(4)); 0.89 (*s*, 9 H, C(CH_3)$_3$); 0.04 (*s*, 3H, Si-CH_3); – 0.08 (*s*, 3H, Si-CH_3). ^{13}C-NMR ($CDCl_3$) 139.91 (*s*); 139.47 (*s*); 139.26 (*s*); 138.53 (*s*); 134.49 (*d*, (C(5)); 128.52-127.89 (several *d*, Ph); 127.66 (*d*, (C(6)); 77.85 (*d*, (C(2)); 76.77 (*d*, (C(2)); 74.97 (*t*, *C*H_2–C(4)); 74.02 (*t*, PhCH_2); 73.39 (*t*, PhCH_2); 73.19 (*t*, PhCH_2); 72.69 (*t*, PhCH_2); 25.91 (*q*); 18.54 (*s*); – 2.21 (*q*); – 2.47 (*q*). FAB-MS (NOBA) 650 (6, [*M*]$^+$), 181 (17), 91 (100), 73 (15).



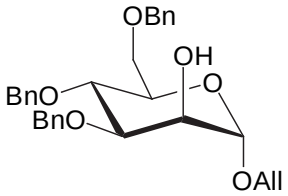
*(1*L*)-(1,2/3,4)-2,3-Di*-O-*benzyl-1*-O-*acetyl-4-tert-butyl-dimethyl-silyl-4*-C-*[(benzyloxy)metyl] cyclohex-5-ene-1,2,3,4-tetrol* (**837**) and *(1*D*)-(1,3,4/2)-2,3-Di*-O-*benzyl-1*-O-*acetyl-4-tert-butyl-dimethyl-silyl-4*-C-*[(benzyloxy)metyl] cyclohex-5-ene-1,2,3,4-tetrol* (**838**).

A solution of **836** (30.05 mg, 0.046 mmol) was treated with $Zn(OTf)_2$ (51.4 mg, 0.141 mmol), Ac_2O (1 ml), stirred at 24° for 2 h, treated with CH_2Cl_2 (10 ml), and sat. aq. NH_4Cl soln. (20

ml). Theorg. phase was separated and the aq. phase was extracted with CH_2Cl_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.

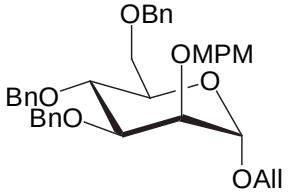
Data of **837** (57%): ^{1}H-NMR ($CDCl_3$): 7.34–7.25 (*m*, 15 arom. H); 5.92 (*d*, *J* = 9.65, H–C(5)); 5.76–5.74 (*dd*, *J* = 9.65, 4.05, H–C(6)); 5.67 (*d*, *J* = 4.05 Hz, 4.04 Hz H–C(1)); 5.00 (*d*, *J* = 11.51, PhC*H*); 4.83–4.33 (*m*, 5 PhC*H*)); 4.03 (*dd*, *J* = 10.58, 4.04, H–C(2)); 3.96 (*d*, *J* = 10.58, H–C(3)); 3.58 (*d*, *J* = 8.41, C*H*–C(4)); 3.33 (*d*, *J* = 8.41 Hz, C*H*'–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, PhC*H*)); 4.83–4.33 (*m*, 5 PhC*H*); 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**).

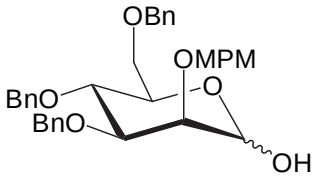
A solution of **480** (2.0 g, 4.44 mmol) in allylic alcohol (15 ml) was treated with camphorsulfonic acid (0.5 g) and stirred at 90° for 2 d. Evaporation and FC (20 g of silica gel, cyclohexane/AcOEt 3:1) gave **481** (2.29 g, 100%). Colourless oil. R_f (cyclohexane/AcOEt 1:1) 0.73. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.74 (*d*, *J* = 11.5, PhC*H*); 4.69 (*d*, *J* = 11.5, PhC*H*); 4.68 (*d*, *J* = 12.1, PhC*H*); 4.55 (*d*, *J* = 12.1, PhC*H*); 4.53 (*d*, *J* = 10.6, PhC*H*); 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.57 (2*s*); 138.24 (1*s*); 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, $C_{30}H_{34}NaO_6^+$, $[M + Na]^+$; calc. 513.2253), 471 (20, $[M + Na - C_3H_6]^+$).



Allyl 3,4,6-Tri-O-*benzyl-2*-O-*(4-methoxybenzyl)-α*-D-*mannopyranoside* (**482**).

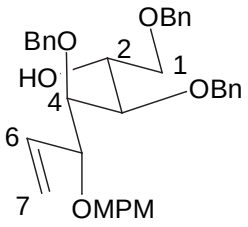
A solution of **481** (2.03 g, 4.14 mmol) in DMF (50 ml) was cooled to 0°, treated with NaH (0.36 g, 55% in oil, 8.28 mmol), stirred for 40 min, treated with 4-methoxybenzyl chloride (1.12 ml, 8.28 mmol), warmed to r.t., stirred for 15 h, cooled to 0°, treated with MeOH (1 ml), stirred for 20 min, and diluted with AcOEt (100 ml). The organic phase was separated, washed with H_2O (70 ml) and brine (70 ml), and dried (Na_2SO_4). Evaporation and FC (100g of silica gel, cyclohexane/AcOEt 6:1) gave **482** (2.49 g, 98%). Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.63. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.70 (*d*, *J* = 12.1, PhC*H*); 4.69 (*s*, PhCH_2); 4.63 (*s*, PhCH_2); 4.61 (*d*, J = 11.5,

PhC*H*); 4.53 (*d*, *J* = 10.6, PhC*H*); 4.19 (*ddt*, *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 (3*s*); 134.14 (*d*, C(2´)); 130.69–127.71 (several *d*); 117.42 (*t*, C(3´)); 113.96 (2*d*); 97.30 (*d*, C(1)); 80.39 (*d*); 75.31 (*t*, Ph*C*H$_2$); 75.17 (*d*); 74.29 (*d*); 73.52, 72.30, 72.22 (3*t*, 2 Ph*C*H$_2$, MeOC$_6$H$_4$*C*H$_2$); 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_3H_6]$^+$).



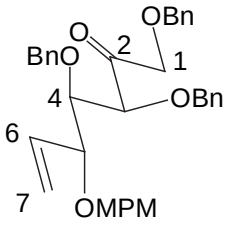
3,4,6-Tri-O-*benzyl-2*-O-*(4-methoxybenzyl)*-D-*mannopyranose* (**483**).

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_3N (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 diestereoisomers, >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, PhC*H*); 4.67 (*s*, PhC*H*$_2$); 4.61 (*s*, PhC*H*$_2$); 4.59 (*d*, *J* = 10.0, PhC*H*); 4.53 (*d*, *J* = 12.1, PhC*H*); 4.51 (*d*, *J* = 10.9, PhC*H*); 4.05 (*ddd*, *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 (2*s*), 138.71 (1*s*); 130.67–127.79 (several *d*); 113.98 (2*d*); 92.96 (*d*, C(1)); 79.89 (*d*); 75.41 (*d*); 75.18 (*t*, 2 Ph*C*H$_2$); 74.42 (*d*); 73.44, 72.38, 72.24 (3*t*, 2 Ph*C*H$_2$, MeOC$_6$H$_4$*C*H$_2$); 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**).

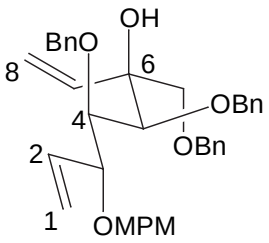
A solution of **483** (115 mg, 0.20 mmol) in THF (5 ml) was cooled to –78°, treated dropwise with a solution of $Ph_3P{=}CH_2$ (prepared at 0° from Ph_3PMeBr (287 mg, 0.80 mmol) and 1.6M BuLi in hexane (0.5 ml) in THF (5 ml)), heated under reflux for 12 min, cooled to 0°, and poured into sat. aqueous $NaHCO_3$ solution (50 ml). The mixture was extracted with AcOEt (60 ml). The organic phase was washed with brine (2 ×50 ml) and dried (Na_2SO_4). 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. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.63 (*d*, *J* = 11.2, PhC*H*); 4.55 (*d*, *J* = 11.2, PhC*H*); 4.54 (*dd*, *J* = 11.8, PhC*H*); 4.50 (*s*, PhCH_2); 4.47 (*d*, *J* = 10.6, PhC*H*); 4. 20 (*d*, *J* = 11.5, PhC*H*); 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, $CDCl_3$): 159.44 (*s*); 138.68 (2*s*); 138.34 (1*s*); 136.68 (*d*, C(6)); 130.69–127.75 (several *d*); 119.87 (*t*, C(7)); 113.98 (2*d*); 81.04, 80.04, 78.74 (3*d*); 74.44, 74.07, 73.47, 71.43 (4*t*, 3 Ph*C*H$_2$, MeOC_6H_4*C*H$_2$); 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 CH_2Cl_2 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 CH_2Cl_2 (1 ml), stirred for 30 min, allowed to warm to –25°, treated with Et_3N (70 µl, 500 µmol), warmed to 0°, stirred for 90 min, and poured into ice-cold sat. aqueous $NaHCO_3$

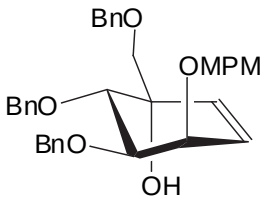
solution (20 ml). The mixture was extracted with Et_2O (2 × 20 ml). The organic phase was washed with brine (20 ml) and dried (Na_2SO_4). Evaporation and FC (6 g of silica gel, cyclohexane/AcOEt 6:1) gave **485** (20 mg, 100%). Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.53. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.50 (*d*, *J* = 11.2, PhC*H*); 4.46 (*d*, *J* = 10.0, PhC*H*); 4.43 (*s*, PhCH_2); 4.38 (*d*, *J* = 10.9, PhC*H*); 4.36 (*d*, *J* = 11.8, PhC*H*); 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, PhC*H*); 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 (3*d*, C(3), C(4), C(5)); 75.09, 74.68, 74.52, 73.35 (4*t*, 3 Ph*C*H_2, MeOC_6H_4*C*H_2); 69.81 (*t*, C(1)); 55.37 (*q*, MeO). HR-MS (MALDI): 589.2560. (100, $C_{36}H_{38}NaO_6^+$, $[M + Na]^+$; calc. 589.2561), 453 (21), 347 (10).



4,5-Di-O-*benzyl-6*-C-*[(benzyloxy)methyl]-1,2,7,8-tetradeoxy-3-(4-methoxybenzyl)*-D-*manno-octa-1,7-dienitol* (**486**).

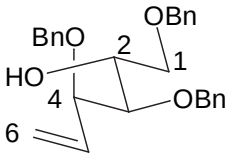
A solution of **485** (19 mg, 33 μmol) in THF (2 ml) was cooled to –78°, treated dropwise with a solution of 1M vinylmagnesium bromide in THF (50 μl), stirred for 45 min, allowed to warm to 0°, diluted with Et_2O (20 ml), and treated with sat. aqueous NH_4Cl solution (20 ml). The organic phase was separated, washed with brine (20 ml), and dried (Na_2SO_4). Evaporation and FC (10 g of silica gel, cyclohexane/AcOEt 6:1) gave **486** (19 mg, 96%). Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.64. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.59–4.51 (*m*, 4 PhC*H*); 4.48 (*d*, *J* = 11.8, PhC*H*); 4.42 (*d*, *J* = 12.1, PhC*H*); 4.18 (*d*, *J* = 11.51, PhC*H*); 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 140.49 (*d*, C(7)); 138.73 (2*s*); 138.24 (1*s*); 136.24 (*d*, C(2)); 130.27–127.36 (several *d*); 119.98 (*t*, C(1)); 114.61 (*t*, C(8)); 113.78 (2*d*); 81.32,

80.35, 78.28 (3*d*, C(3), C(4), C(5)); 77.94 (*s*, C(6)); 74.91, 74.85, 73.42, 73.20 (4*t*, 3 Ph*C*H_2, MeOC_6H_4*C*H_2); 69.51 (*t*, *C*H_2–C(6)); 55.27 (*q*, MeO). HR-MS (MALDI): 617.2856 (100, $C_{38}H_{42}NaO_6^+$, [*M* + Na]$^+$; calc. 617.2874), 481 (40), 376 (32).



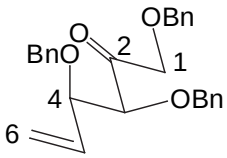
*(1*L*)-(1,2/3,4)-2,3-Tri*-O-*benzyl-4*-C-*[(benzyloxy)methyl]-1*-O-*(4-methoxybenzyl)cyclohex-5-ene-1,2,3,4-tetrol* (**60**).

A soln. of **486** (19 mg, 32 μmol) in CH_2Cl_2 (5 ml) was degassed by purging with N_2 and added via cannula to **312** (8 mg, 10 μmol). The mixture was stirred under N_2 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. R_f (cyclohexane/AcOEt 3:1) 0.58. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.70–4.63 (*m*, 4 PhC*H*); 4.58 (*d*, *J* = 11.2, PhC*H*); 4.55 (*d*, *J* = 12.1, PhC*H*); 4.45 (*d*, *J* = 12.1, PhC*H*); 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.39 (3*s*); 132.65–127.79 (several *d*, including C(5) and C(6)); 113.95 (2*d*); 78.13 (*d*, C(2)); 76.04 (*d*, C(3)); 75.52 (*t*); 74.60 (*t*, *C*H_2–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, $C_{36}H_{38}NaO_6^+$, [*M* + Na]$^+$; calc. 589.2561).



1,3,4-Tri-O-*benzyl-5,6 dideoxy*-D-lyxo-*hex-5-enitol* (**420**).

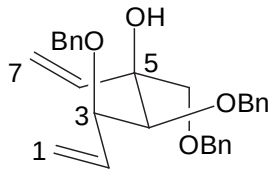
A soln. of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (commercially available, 5 g, 11.89 mmol) in THF (70 ml) was cooled to –78°, treated with $PH_3P{=}CH_2$ (prepared from a solution of Ph_3PMeBr (8.50 g, 23.8 mmol) in THF (80 ml) by dropwise addition of 1.6M butyllithium in hexane (15 ml, 24 mmol)), refluxed for 3 h, cooled to r.t., treated with acetone (50 ml) and with sat. aq. NH_4Cl soln. (50 ml), and diluted with Et_2O (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 ($MgSO_4$), 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. $[\alpha]_D^{25}$ = –8.4 (*c* = 1.48, $CHCl_3$). IR ($CHCl_3$): 3570–3480*m*, 3090*m*, 3070*m*, 3000*m*, 2920*s*, 2870*s*, 1500*s*, 1450*s*, 1400*m*, 1350*m*, 1250*m*, 1090*s*, 930*s*. ^{1}H-NMR ($CDCl_3$): 7.23–7.37 (*m*, 15 arom. H); 5.96 (*ddd*, *J* = 16.5, 11.2, 7.5, H–C(5)); 5.34 (*dm*, *J* ≈ 11.2, H–C(6)); 5.32 (*dm*, *J* ≈ 16.5, H'–C(6)); 4.64 (*d*, *J* = 12.1, 2 PhC*H*); 4.56 (*d*, *J* = 11.51, PhC*H*)); 4.51 (*s*, PhCH_2)); 4.37 (*d*, *J* = 12.1, PhC*H*)); 4.11 (br. *dd*, *J* = 7.5, 4.1, H–C(4)); 4.01 (*dt*, *J* = 7.2, 4.4, H–C(2)); 3.63 (*dd*, *J* = 7.2, 4.1, H–C(3)); 3.61–3.56 (*m*, CH_2(1)). ^{13}C-NMR ($CDCl_3$): 138.45; 138.21; 137.81; 135.46 (C(5)); 128.57–127.87 (several *d*); 118.98 (C(6)); 80.88, 80.49 (C(3), 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 $C_{27}H_{30}O_4$ (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**).

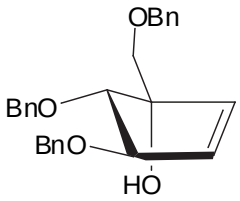
A soln. of **420** (3.71 g, 8.85 mmol) in CH_2Cl_2 (50 ml) was treated with a solution of *Dess Martin*'s periodinane (4.5 g, 10.58 mmol) in CH_2Cl_2 (50 ml), stirred at 24° for 30 min, diluted with Et_2O (150 ml), treated with 1.3M NaOH (50 ml), stirred for 15 min, and treated with sat. aq. NH_4Cl soln. (40 ml). The org. phase was separated, washed with H_2O (40 ml), dried ($MgSO_4$), 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. $[\alpha]_D^{25}$ = –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, PhC*H*); 4.58 (*d*, *J* = 11.8, PhC*H*); 4.51 (*d*, *J* = 11.8, PhC*H*); 4.50 (*d*, *J* = 11.8, PhC*H*); 4.43 (*d*, *J* = 11.8, PhC*H*); 4.33 (br. *s*, CH_2(1)); 4.29 (*d*, *J* = 11.8, PhC*H*); 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 Ph*C*H_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**).

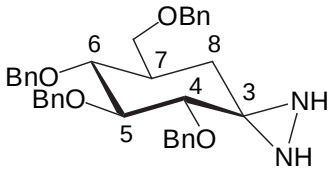
A soln. of **398** (3.858 g, 9.24 mmol) in THF (80 ml) was cooled to –78°, treated dropwise with 1M vinylmagnesium bromide in THF (13.9 ml, 13.9 mmol), stirred for 60 min, treated with Et_2O (100 ml), warmed to 0°, and treated with sat. aq. NH_4Cl soln. (40 ml). The org. phase was separated and the aq. phase extracted with Et_2O (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. $[\alpha]_D^{25}$ = –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*, 1028s, 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, PhC*H*); 4.63 (*d*, *J* = 11.2, PhC*H*); 4.56 (*d*, *J* = 11.2, PhC*H*); 4.46, 4.42 (2*d*, *J* = 11.8, Ph*CH*$_2$); 4.23 (d, *J* = 11.5, PhC*H*); 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 Ph*C*H_2); 70.67 (*C*H_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.



*(1*L*)-(1,2/3)-1,2-Di*-O-*benzyl-3*-C-*[(benzyloxy)methyl]-cyclopent-4-ene-1,2,3-triol* (**424**).

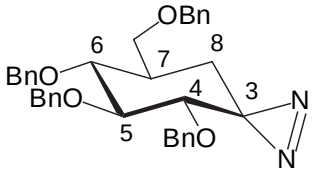
A soln. of **421** (109 mg, 0.245 mmol) in CH_2Cl_2 (15ml) was degassed by 3 cycles of freeze pump thaw, treated with *Grubbs's* catalyst **312** (30 mg, 0.037 mmol), refluxed for 4 days under N_2, and evaporated. Two FC's (cyclohexane/AcOEt 7:1) of the dark-green oily residue afforded **424** (64.7 mg, 63%) as a green oil. R_f (cyclohexane/AcOEt 3:1) 0.70. $[\alpha]_D^{25}$ = –46.4 (*c* = 0.44, $CHCl_3$). IR ($CHCl_3$): 3528*m*, 3066*m*, 3008*s*, 2663*m*, 1711*s*, 1496*m***,** 1454*m*, 1362s, 1093*s*, 1028*m*. ^{1}H-NMR ($CDCl_3$):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, PhC*H*); 4.66 (*d*, *J* = 11.5, PhC*H*); 4.66–4.64 (*m*, H–C(1)); 4.57 (*s*, PhCH_2); 4.55 (*d*, *J* = 11.8, PhC*H*); 4.51 (*d*, *J* = 11.8, PhC*H*); 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). ^{13}C-NMR ($CDCl_3$): 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 Ph*C*H_2); 71.79 (*C*H_2–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.



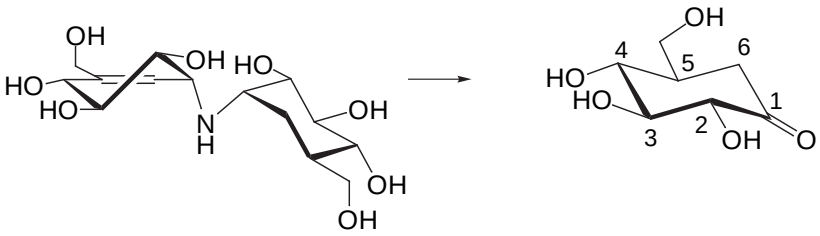
*(4*S*,5*S*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-1,2-diazaspiro[2.5]octane* (**602**).

At –20°, a suspension of **52** [225] (115 mg, 0.21 mmol) in MeOH (5 ml) was saturated with 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°. $[\alpha]_D^{25}$ = 29.4 (*c* = 0.98, $CHCl_3$). 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, PhC*H*); 4.91 (*d*, *J* = 10.8, PhC*H*); 4.89 (*d*, *J* = 11.6, PhC*H*); 4.82 (*d*, *J* = 10.8, PhC*H*); 4.70 (*d*, *J* = 10.4, PhC*H*); 4.59 (*d*, *J* = 11.2, PhC*H*); 4.47 (*s*, PhCH_2); 3.90 (*d*, *J* = 9.6, H–C(4)); 3.77 (*dd*, *J* = 9.1, 3.7, CH–C(7)); 3.69 (*t*, *J* = 10.0, H–C(6)); 3.56 (*t*, *J* = 9.6, H–C(5)); 3.48 (*dd*, *J* = 9.1, 2.5, CH´–C(7)); 2.64 (br. *d*, *J* = 7.9, 0.8 H, exchange with D_2O, NH); 2.26–2.06 (0.2 H, exchange with D_2O, NH); 2.26 (br. *t*, *J* = 12.9, H_{ax}–C(8)); 2.19–2.06 (*m*, H–C(7)); 1.57 (*d*, *J* = 7.9, 0.8 H, exchange with D_2O, NH); 1.44 (*d*, *J* = 8, 0.2 H, exchange with D_2O, NH); 1.35 (*dd*, *J* = 12.9, 2.9, H_{eq}–C(8)). ^{13}C-NMR (75 MHz, $CDCl_3$, one set of signals): 139.00, 138.88, 138.62, 138.50 (4*s*); 128.62–127.79 (several *d*); 88.20, 80.33, 79.49 (3*d*, C(4), C(5), C(6)); 76.38, 76.01, 75.51, 73.21 (4*t*, 4 PhCH_2); 69.42 (*t*, CH_2–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, $[M – NH_2]^+$), 531 (10), 461 (18), 459 (22, $[M – Bn]^+$), 443 (96, $[M – BnO]^+$), 428 (27). Anal. calc. for $C_{35}H_{38}N_2O_4$ (550.70): C 76.34, H 6.95, N 5.09; found: C 76.04, H 6.66, N 4.98.



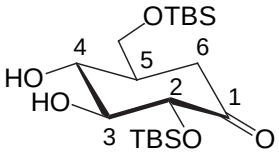
*(4*S*,5*S*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-1,2-diazaspiro[2.5]oct-1-ene* (**603**).

At 0°, a soln. of **602** (61 mg, 0.11 mmol) in MeOH (10 ml) and CH_2Cl_2 (10 ml) was treated with Et_3N (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. R_f (hexane/AcOEt 3:1) 0.73. M.p. 59–61°. $[\alpha]_D^{25}$ = 49.7 (*c* = 1.03, $CHCl_3$). UV (CH_2Cl_2): 232 (846), 252 (846), 258 (906), 340 (92). FT-IR (1%, $CHCl_3$): 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, $CDCl_3$): 7.37–7.19 (*m*, 20 arom. H); 4.93 (*d*, *J* = 10.9, PhC*H*); 4.88 (*d*, *J* = 10.9, PhC*H*); 4.82 (*d*, *J* = 10.9, PhC*H*); 4.57 (*d*, *J* = 10.9, PhC*H*); 4.42 (*s*, PhCH_2); 4.26 (*d*, *J* = 11.2, PhC*H*); 4.21 (*d*, *J* = 11.2, PhC*H*); 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, H_{ax}–C(8); 0.67 (br. *d*, *J* = 10.6, H_{eq}–C(8)). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.94, 138.79, 138.49, 137.39 (4 *s*); 128.67–127.75 (several *d*); 86.39, 80.55, 78.10 (3*d*, C(4), C(5), C(6)); 75.86, 75.57, 73.23, 73.19 (4*t*, 4 Ph*C*H_2); 69.46 (*t*, *C*H_2–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, $[M - BnO - N_2]^+$), 307 (33). Anal. calc. for $C_{35}H_{36}N_2O_4$ (548.68): C 76.62, H 6.61, N 5.11; found: C 76.75, H 6.73, N 4.88.



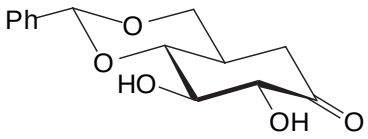
*(2*R*,3*S*,4*R*,5*R*)-2,3,4-Trihydroxy-5-(hydroxymethyl)-cyclohexanone* (**51**).

A suspension of **549** (2.0 g, 5.96 mmol) in MeCN (30 ml) and H_2O (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/H_2O 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 (H_2O) and lyophilisation. R_f (nPrOH/AcOH/H_2O 4:1:1) 0.53. ^{1}H-NMR (200 MHz, D_2O): 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)). ^{13}C-NMR (50 MHz, D_2O): 212.9 (*s*, C(1)); 81.1, 80.8, 74.4 (3*d*, C(2), C(3), C(4)), 64.3 (*t*, *C*H_2–C(5)); 43.6 (*d*, C(5)); 41.7 (*t*, C(6)). CI-MS (NH_3): 194 (77, $[M + NH_4]^+$), 176 (7, $[M]^+$), 141 (26, $[M +1 – 2\ H_2O]^+$), 123 (100, $[M + 1 – 3\ H_2O]^+$), 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 (Na_2SO_4). Evaporation and FC (6 g of silica gel, hexane/AcOEt 6:1) gave **604** (9.7 mg, 9%). Colourless amorphous solid. R_f (hexane/AcOEt 3:1) 0.32. ^{1}H-NMR (200 MHz, $CDCl_3$): 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 D_2O -> *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 D_2O -> *t*, *J* = 10.0, H–C(3)); 3.19 (*d*, *J* = 1.2, exchanged with D_2O, HO–C(4)); 2.73 (*d*, *J* = 2.1, exchanged with D_2O, HO–C(3)); 2.49–2.31 (*m*, CH_2(6)); 1.94–1.78 (*m*, H–C(5)); 0.96, 0.92 (2*s*, 2 Me_3C); 0.19, 0.10, 0.09, 0.07 (4*s*, 2 Me_2Si). ^{13}H-NMR (50 MHz, $CDCl_3$): 203.05 (C(1)); 77.38, 76.53, 69.61 (C(2), C(3), C(4)); 60.88 (*C*H_2–C(5)); 38.25, 36.47 (C(5), C(6); 23.39 (2 *Me*$_3$CSi); 16.06, 15.77 (2 Me_3*C*Si); –6.89, –7.9 (2 Me_2Si).

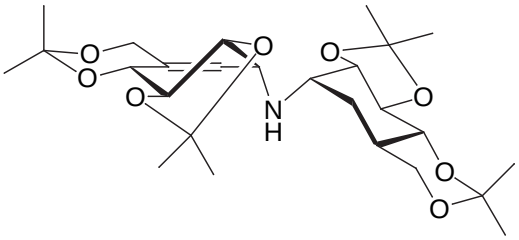


Benzylidenation of **51**.

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 $TsOH \cdot H_2O$ (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 (Na_2SO_4), 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. R_f (AcOEt(*i*PrOH/H_2O 8:2:1) 0.58. ^{1}H-NMR (300 MHz, $CDCl_3/D_2O$): 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, CH_{eq}–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, CH_{ax}–C(5)); 2.47 (*dd*, *J* = 13.7, 3.7, H_{eq}–C(6)); 2.19 (*td*, *J* = 13.7, 1.3, H_{ax}–C(6)); 2.12–1.94 (*m*, H–C(5)).

Isopropylidenation 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 (Na_2SO_4) 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. R_f (hexane/AcOEt 9:1) 0.63. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, H_{ax}–C(6)); 2.30 (*dd*, *J* = 14.0, 4.7, H_{eq}–C(6)); 1.70–1.56 (*m*, H–C(5)); 0.19, 0.15, 0.14, 0.09 (4*s*, 4 Me_3Si). ^{13}C-NMR (75 MHz, $CDCl_3$): 207.24 (*s*, C=O); 80.20, 79.76, 73.50 (3*d*, C(2), C(3), C(4)); 61.76 (*t*, CH_2–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, $[M - TMS–O_2]^+$), 331 (32), 305 (13).



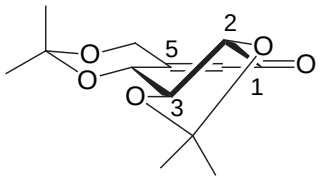
2,3:4,6:2',3':4',6'-Tetra-Oisopropylidenevalidoxylamine A (**607**).

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_2CO_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°. $[\alpha]_D^{25}$ = 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*, 1269*m*, 1171*s*, 1095*s*, 1039*s*, 1012*m*, 990*w*, 981*w*, 966*w*, 908*w*, 867*m*, 851s, 835*m*. ^{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´)); 111.47, 110.61 (2*s*, *C*Me_2 in dioxolane rings); 99.17, 99.00 (2*s*, *C*Me_2 in dioxane rings); 80.63 (*d*); 77.69 (*d*); 75.33 (*d*); 75.20 (*d*); 74.47 (*d*); 71.69 (*d*); 64.42, 62.97 (2*t*, *C*H_2-O); 54.62, 54.31 (2*d*, *C*H–N); 33.69 (*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*); 1 *q* 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-isoproylidenegabosine 1 and 2,3:4,6-Di-O-isopropylidenevalidone (**609**).

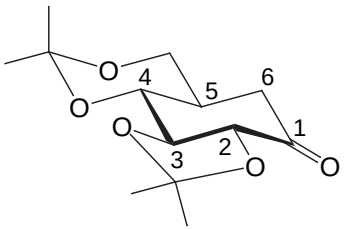
A solution of **607** (1.72 g, 3.47 mmol) in MeCN (50 ml) and H_2O (12 ml) was treated with NBS (0.93 g, 5.21 mmol), stirred for 2 h at r.t., poured on saturated aq. $NaHCO_3$ solution/ ice (100 ml), and extracted with AcOEt (4 x 100 ml). The combined organic phases were washed with brine (100 ml), dried (Na_2SO_4), treated with Et_3N (1 ml), and evaporated. FC (80 g of silica gel, cyclohexane/AcOEt/Et_3N 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 (*ddd*, *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* = 10.6, 8.4, H–C(3)); 1.56 (*s*, Me), 1.48 (*s*, 2 Me), 1.43 (*s*, Me).

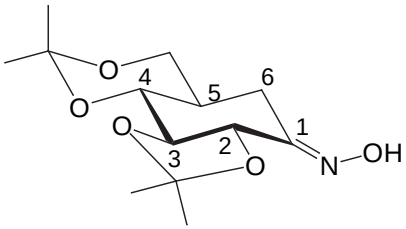


Data of **609**:

Colourless foam. R_f (cylcohexane/AcOEt 3:1) 0.13. $[\alpha]_D^{25}$ = 39.4 (*c* = 1.6, $CHCl_3$). FT-IR (1.6%, $CHCl_3$): 2996*s*, 2941*m*, 2908*m*, 2868*m*, 1735*s* (C=O), 1457*m*, 1411*w*, 1385*s*, 1376*s*, 1161*m*, 1104*s*, 1091*s*, 1050*m*, 1018*m*, 999*m*, 966*w*, 948*w*, 932*w*, 886*m*, 856*m*. ^{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, H_{eq}–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 (2*d*, 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.

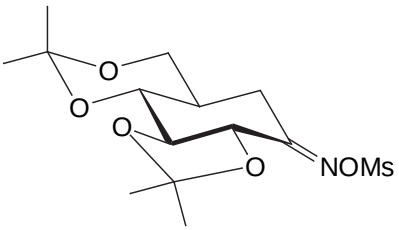
Reaction of **609** *with* NH_3/NH_2OSO_3H.

A soln. of **609**(100 mg, 0.39 mmol) in MeOH (5 ml) was saturated at –20° with gaseous NH_3, treated dropwise with a soln. of hydroxylamin-*O*-sulfonic acid (44 mg, 0.39 mmol) in MeOH (5 ml), stirred for 3 h at –20°, 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 vanilline. This component was purified by FC (15 g of silica gel, cyclohexane/AcOEt 3:1 –> 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-isopropylidenevalidoneoxime (**610**).

The ketone **609** (259 mg, 1.01 mmol) was treated with a *ca*. 0.2M solution of NH_2OH in MeOH (40 ml, 8 mmol) , stirred for 3 d, and evaporated. FC (25 g of silica gel, cyclohexane/AcOEt/Et_3N 6:2:0.01) gave **610** (133 mg, 48%) and a mixture of **610** and **609** (62 mg). Treatment of the latter with NH_2OH for 10 d gave more **610** (47 mg, 18%). Colourless foam. R_f (cyclohexane/AcOEt 1:1) 0.54. $[\alpha]_D^{25}$ = 13.0 (*c* = 1.49, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 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*m*, 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, CH_{eq}-C(5)); 3.76 (*dd*, *J* = 11.5, 8.1, H–C(4)); 3.66 (*t*, *J* ≈ 11.2, CH_{ax}–C(5)); 2.94 (*dd*, *J* = 16.5, 4.4, H_{eq}–C(6)); 1.85 (*ddd*, *J* = 16.2, 13.4, 0.9, H_{ax}–C(6)); 1.71–1.58 (*m*, H–C(5)); 1.55, 1.50, 1.45, 1.40 (4 *s*, 2 Me_2C); OH hidden. ^{13}C-NMR (75 MHz, $CDCl_3$): 154.0 (*s*, C=N); 110.61 (*s*, Me_2C of the dioxolane ring); 99.35 (*s*, Me_2C of the diolane ring); 79.07 (*d*, C(3)); 75.02, 74.42 (2*d*, C(2), C(4)); 64.17 (*t*, CH_2–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 $C_{13}H_{21}NO_5$ (271.31): C 57.55, H 7.80, N 5.16; found: C 57.59, H 7.84, N 5.05.

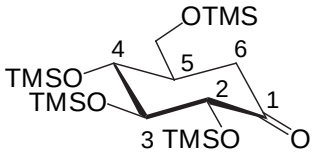


2,3:4,6-Di-O-isopropylidenvalidonoxim-mesylate (**611**).

A soln. of **610** (59 mg, 0.217 mmol) in CH_2Cl_2 (5 ml) was cooled to 0°, treated with Et_3N (80 µl, 0.543 mmol) and MsCl (22 µl, 0.282 mmol), and stirred for 45 min. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with 1M aq. $NaHCO_3$ soln. (12 ml) and H_2O (10 ml). Drying (Na_2SO_4) and evaporation gave crude **611** (144 mg, quant.) as a yellow oil, which rapidly became brown and therefore was immidiately used in the subsequent step. R_f (cyclohexane/AcOEt 1:1) 0.47.

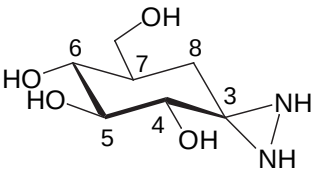
Reaction of **611** *with* NH_3.

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 NH_3 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/Et_3N 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 ^{1}H-NMR spectrum. R_f (cyclohexane/AcOEt 1:1) 0.16.



*(2*R*,3*S*,4*R*,5*R*)-2,3,4-Tris(trimethylsilyloxy)-5-(trimethylsilyloxymethyl)cyclohexanone* (**606**).

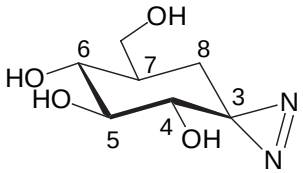
At 25°, a soln. of **51** (630 mg, 3.59 mmol) was treated with hexamethyldisilazane (HMDS, 10 ml, 48.0 mmol) and Me_3SiCl (5 ml, 39.5 mmol), stirred for 6.5 h, evaporated, and dried in h.v. The residue was digested with CH_2Cl_2 (3 x 50 ml) and filtered. The organic phase was washed with ice-cold H_2O (75 ml), dried ($MgSO_4$), and evaporated. FC (30 g of silica gel, hexane/AcOEt/Et_3N 400:10:0.4) of the residue (1.28 g, brown oil) gave **606** (448 mg, 27%). Colourless oil. R_f (hexane/AcOEt 9:1) 0.63. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, H_{ax}–C(6)); 2.30 (*dd*, *J* = 14.0, 4.7, H_{eq}–C(6)); 1.70–1.56 (*m*, H–C(5)); 0.19, 0.15, 0.14, 0.09 (4*s*, 4 Me_3Si). ^{13}C-NMR (75 MHz, $CDCl_3$): 207.24 (*s*, C=O); 80.20, 79.76, 73.50 (3*d*, C(2), C(3), C(4)); 61.76 (*t*, *C*H_2–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, $[M – TMS–O_2]^+$), 331 (32), 305 (13).



*(4*S*,5*S*,6*R*,7*R*)-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 NH_3, 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/H_2O 4:2:1) gave a colourless soln. of

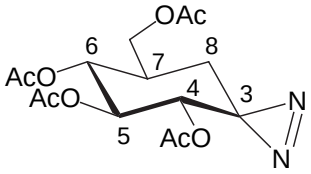
45. After removal of most of the AcOEt *in vacuo* below 30°, this soln. was applied to an ion exchange column (5 ml of *Dowex 50-WX-8*, H^+-form, washed with MeOH (50 ml) and H_2O to pH 7). After washing with H_2O (200 ml), elution with 2% aq. NH_3 and lyophilisation gave colourless, amorphous **45** (53 mg, 50%). R_f (AcOEt/iPrOH/H_2O 4:2:1) 0.13. R_f (acetone/H_2O 2:1) 0.72. R_f (iPrOH/H_2O 4:1) 0.43. M.p. 68–76°. $[\alpha]_D^{25}$ = 22.2 (*c* = 1.50, H_2O). p*K*(HA) = 2.6. ^{1}H-NMR (300 MHz, (D_6)-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), CH_2–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 H_{ax}–C(8)); 1.60 (*t*, *J* = 13.0, 0.6 H_{ax}–C(8)); 1.57–1.37 (*m*, H–C(7)); 1.27–1.15 (*m*, H_{eq}–C(8)). ^{1}H-NMR (300 MHz, (D_6)DMSO/CF_3COOH): 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, H_{ax}–C(8)); 1.52–1.47 (*m*, H–C(7), H_{eq}–C(8)). ^{1}H-NMR (500 MHz, CD_3OD, 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)). ^{13}C-NMR (75 MHz, D_2O, *ca*. 1:1 mixture of diastereoisomers): 80.37, 79.87 (2*d*); 75.50, 75.21 (2*d*); 72.19 (*d*); 64.70 (*t*, CH_2–C(7)); 60.02 (*s*, C(3)); 43.78, 43.50 (2*d*, 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 ($C_7H_{14}N_2NaO_4^+$, $[M + Na]^+$; calc. 213.0851); 191.1026 ($C_7H_{15}N_2O_4^+$, $[M + H]^+$; calc. 191.1027).



*(4*S*,5*S*,6*R*,7*R*)-7-(Hydroxymethyl)-1,2-diazaspiro[2.5]oct-1-ene-4,5,6-triol* (**613**).

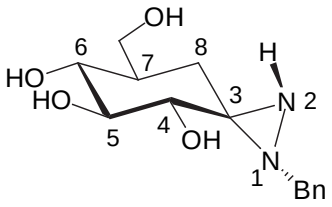
A soln. of I_2 (*ca*. 30 mg) in MeOH (1 ml) was added dropwise at 25° to a soln. of **45** (55 mg, 0.29 mmol) in MeOH (8 ml) and Et_3N (0.1 ml, 0.72 mmol) until the brown colour persisted. Evaporation and FC (20 g of silica gel, CH_2Cl_2/MeOH 9:1) gave a mixture of **613** and Et_3N (2.5:1, 60 mg). This mixture was applied to an ion exchange column (7 ml of *Dowex-CCR-2*, H^+-form, washed with MeOH (100 ml) and H_2O to pH 7). Elution with H_2O and lyophilisation gave **613** (48.8 mg, 89%). Colourless syrup. R_f (AcOEt/iPrOH/H_2O 4:2:1) 0.75. $[\alpha]_D^{25}$ = 37.2 (*c* = 1.03, H_2O). UV (H_2O): 340 (68). ^{1}H-NMR (300 MHz, D_2O): 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), H_{ax}–C(8)); 0.72 (*dd*, *J* = 13.1, 2.8, H_{eq}–C(8)). ^{13}C-NMR (75 MHz, D_2O): 80.60, 75.38, 71.93 (3*d*, C(4), C(5), C(6)); 64.68 (*t*, *C*H_2–C(7)); 43.46 (*d*, C(7)); 32.34 (*s*, C(3)); 31.76 (*t*, C(8)). HR-ESI-MS (MeOH): 211.069 ($C_7H_{12}NaN_2O_4$, $[M + Na]^+$; calc. 211.0695).



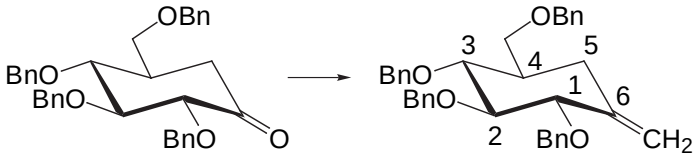
*(4*S*,5*S*,6*R*,7*R*)-4,5,6-Tris(acetyloxy)-7-(acetyloxymethyl)-1,2-diazaspiro[2.5]oct-1-ene* (**614**).

At 0°, a soln. of a mixture of **613** and Et_3N (84 mg, prepared as described above from **45** (79 mg, 0.42 mmol)) in pyridine (10 ml) was treated with Ac_2O (1 ml), allowed to warm to r.t. overnight, and poured into ice-water (50 ml). The aq. phase was extracted with CH_2Cl_2 (4 x 50 ml). Drying (Na_2SO_4), evaporation, and FC (30 g of silica gel, hexane/AcOEt 3:1) gave **614** (124 mg, 84%). Colourless oil. R_f (hexane/AcOEt 3:1) 0.15. $[\alpha]_D^{25}$ = 47.4 (*c* = 1.54, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3038*w*, 2954*w*, 1751*s* , 1594*w* , 1443*w*, 1377*m*, 1248*s*, 1131*w*, 1064*m*, 1033*m*, 978*w*, 932*w*, 896*w*, 846*w*. UV (CH_2Cl_2): 229 (130), 334 (83). ^{1}H-NMR (300 MHz, $CDCl_3$): 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 (4*s*, 4 AcO); 2.02 (*dd*, *J* = 15.1, 9.0, H_{ax}–C(8)); 0.79 (*dd*, *J* = 15.1, 4.4, H_{eq}–C(8)). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.86, 170.11, 170.00, 169.03 (4*s*, 4 C=O); 73.69, 71.07, 68.26 (3*d*, C(4), C(5), C(6)); 62.66 (*t*. *C*H_2–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 (4*q*, 4 Me). FAB-MS (NOBA): 379 (11, $[M + Na]^+$), 357 (24, $[M + 1]^+$), 297 (9, $[M – AcO]^+$), 269 (100, $[M – AcO – N_2]^+$), 227 (21), 208 (11), 167 (93). Anal. calc. for $C_{15}H_{20}N_2O_8$ (356.33): C 50.56, H 5.66, N 7.86; found: C 50.80, H 5.58, N 7.64.



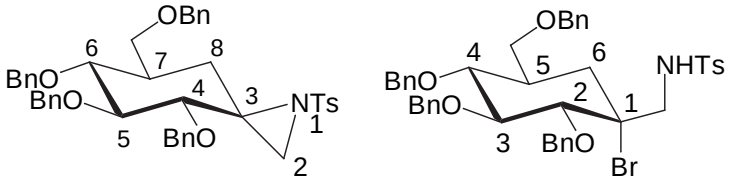
*(1*R,*2*R,*3*S,*4*S,*5*S,*6*R,*7*R*)-1-Benzyl-7-(hydroxymethyl)-1,2-diazaspiro[2.5]octane-4,5,6-triol* (**615**).

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_2O, applied on an ion exchange column (15 g of *Dowex-CCR-2*, H^+-form, washed with MeOH (100 ml) and H_2O to pH = 7), and eluted with H_2O. Lyophilisation gave colourless, amorphous **615** (76 mg, 27%). R_f (AcOEt/iPrOH/H_2O 4:2:1) 0.51. M.p. 52–58°. $[\alpha]_D^{25}$ = 59.7 (*c* = 1.53, H_2O). ^{1}H-NMR (300 MHz, D_2O): 7.49–7.38 (*m*, 5 arom. H); 3.92 (*d*, *J* = 14.0, irrad. at 2.04 -> NOE of 4%, PhC*H*); 3.81 (*d*, *J* = 14.0, irrad. at 2.04 -> NOE of 6 %, PhC*H*); 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, irrad. 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, irrad. at 3.92 and 3.81 -> NOE of 6%, H_{eq}–C(8)); 1.93 (br. *t*, *J* = 14.0, irrad. at 3.62 -> NOE of 4%, H_{ax}–C(8)); 1.53–1.40 (*m*, irrad. at 3.81 and 3.75 -> NOE of 8%, H–C(7)). ^{13}C-NMR (75 MHz, CD_3OD): 140.07 (*s*); 129.83 (*d*, 2 C); 129.65 (*d*, 2 C); 128.52 (*d*); 79.66, 74.45, 73.10 (3*d*, C(4), C(5), C(6)); 63.96 (*t*, *C*H_2–C(7)); 62.87 (*s*, C(3)); 57.19 (*t*, Ph*C*H_2); 43.02 (*d*, C(7)); 27.44 (*t*, C(8)). HR-MALDI-MS (DHB): 303.1310 ($C_{14}H_{20}NaN_2O_4^+$, $[M + Na]^+$; calc. 303.1316); calc. for ; found: 281.1492 ($C_{14}H_{21}N_2O_4^+$, $[M + H]^+$; calc. 281.1496). Anal. calc. for $C_{14}H_{20}N_2O_4 \cdot 0.25\ H_2O$: C 59.04 , H 7.26, N 9.84; found: C 58.79, H 7.31, N 10.00.



*(1*S*,2*S*,3*R*,4*R*)-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 $Ph_3P{=}CH_2$ (prepared at 0° from Ph_3PMeBr (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. NH_4Cl soln. (150 ml). The aq. phase was extracted with CH_2Cl_2 (3 x 100 ml), and the extract dried (Na_2SO_4), and evaporated. FC (150 g of silica gel, cyclohexane/AcOEt 20:1) gave **53** (0.90 g, 71%). Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.75. $[\alpha]_D^{25}$ = 56.7 (*c* = 1.53, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3089*w*, 3066*m*, 3008*m*, 2908*m*, 2862*m*, 2789*w*, 1951*w*, 1876*w*, 1811*w*, 1657*w*, 1605*w*, 1496*m*, 1454*s*, 1400*w*, 1356*m*, 1309*w*, 1149*m*, 1100*s*, 1028*s*, 912*m*, 865*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.45–7.24 (20 arom. H); 5.22 (br. *d*, *J* = 0.9, CH=C(6)); 5.05 (*d*, *J* = 10.9, PhC*H*); 4.99 (*d*, *J* = 1.6, CH´=C(6)); 4.96 (*d*, *J* = 10.9, PhC*H*); 4.86 (*d*, *J* = 10.9, PhC*H*); 4.81 (*d*, *J* = 11.5, PhC*H*); 4.73 (*d*, *J* = 11.2, PhC*H*); 4.58 (*d*, *J* = 10.9, PhC*H*); 4.50 (*s*, PhCH_2); 3.96 (br. *d*, *J* = 9.3, H–C(1)); 3.66 (*dd*, *J* = 9.0, 1.9, CH–C(4)); 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, H_{eq}–C(5)); 2.16 (br. *t*, *J* = 13.4, H_{ax}–C(5)); 1.84–1.75 (*m*, H–C(4)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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*, *C*H_2=C(6)); 88.37, 83.82, 81.23 (3*d*, C(1), C(2), C(3)); 75.81, 75.44, 73.68, 73.26 (4*t*. 4 PhCH_2); 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 $C_{36}H_{38}O_4$ (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-aza-spiro[2.5]octane (**616**) and *4-Methyl-N-[(1*S*,2*R*,3*S*,4*R*,5*R*)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 $PhMe_3N{\cdot}Br_3$ (123 mg, 0.33 mmol). The mixture was stirred for 4.5 h, diluted

with AcOEt (250 ml), washed with H_2O (150 ml) and brine (150 ml), dried (Na_2SO_4), 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%).

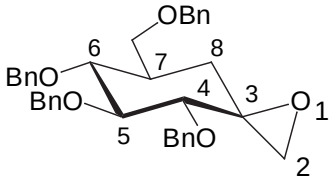
Data of **616**: Colourless oil. R_f (toluene/AcOEt 10:1) 0.47. Prep. HPLC t_R (toluene/AcOEt 40:1) 22.8 min. $[\alpha]_D^{25}$ = –9.2 (*c* = 1.56, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3064*w*, 3008*m*, 2866*m*, 1952*w*, 1810*w*, 1599*w*, 1496*w*, 1454*m*, 1357*m*, 1321*s*, 1158*s*, 1099*s*, 995*s*, 910*w*, 859*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.84 (*d*, *J* = 8.4, 2 arom. H); 7.40–7.08 (22 arom. H); 4.87 (*d*, *J* = 10.6, PhC*H*); 4.84 (*d*, *J* = 10.0, PhC*H*); 4.74 (*d*, *J* = 10.6, PhC*H*); 4.73 (*d*, *J* = 10.3, PhC*H*); 4.59 (*d*, *J* = 10.3, PhC*H*); 4.53 (*d*, *J* = 10.9, PhC*H*); 4.51 (*d*, *J* = 11.8, PhC*H*); 4.44 (*d*, *J* = 12.1, PhC*H*); 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, irrad. 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, irrad. at 2.63 -> NOE of 2%, H–C(5)); 2.63 (br. *s*, irrad. at 3.39 -> NOE of 1.5%, H–C(2)); 2.59 (br. *s*, irrad. at 2.63 -> NOE of 19%, H'–C(2)); 2.45 (*s*, Me); 2.42–2.35 (*m*, irrad. at 3.78 -> NOE of 1%, irrad. at 2.59 -> NOE of 1%, 2 H–C(8)); 1.88–1.78 (*m*, irrad. at 3.39 -> NOE of 9%, irrad. at 2.59 -> NOE of 1%, H–C(7)). ^{13}C-NMR (75 MHz, $CDCl_3$): 144.25 (*s*); 138.83, 138.55, 138.16 (3*s*, 1*s* hidden by noise or other signals); 129.82–127.58 (several *d*); 86.49, 80.96, 80.18 (3*d*, C(4), C(5), C(6)); 76.11, 75.93, 75.54, 73.35 (4*t*, 4 Ph*C*H_2); 69.50 (*t*, *C*H_2–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 $C_{43}H_{45}NO_6S$ (703.90): C 73.37, H 6.44, N 1.99; found: C 73.36, H 6.44, N 1.96.

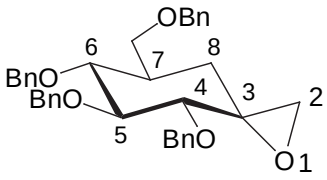
Data of **617**: Colourless oil. R_f (toluene/AcOEt 10:1) 0.45. Prep. HPLC: t_R (toluene/AcOEt 40:1) 27.2 min. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.56 (*d*, *J* = 8.4, 2 arom. H); 7.40–7.18 (22 arom. H); 4.94 (*d*, *J* = 10.9, PhC*H*); 4.92 (*d*, *J* = 11.8, PhC*H*); 4.89 (*d*, *J* = 11.2, PhC*H*); 4.87 (*d*, *J* = 10.9, PhC*H*); 4.73 (*d*, *J* = 12.1, PhC*H*); 4.55 (*d*, *J* = 10.9, PhC*H*); 4.44 (*s*, PhCH_2); 4.03 (*t*, *J* = 9.2, H–C(3)); 3.70 (*dd*, *J* = 9.0, 4.1, CH–C(5)); 3.62 (*dd*, *J* = 7.8, 6.2, irrad. 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, irrad. 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, $[M(^{81}Br) + Na]^+$), 806 (8, $[M(^{79}Br) + Na]^+$), 786 (59, $[M(^{81}Br) + H]^+$), 784 (100, $[M(^{81}Br) – H]^+$), $[M(^{79}Br) + H]^+$), 782 (51, $[M(^{79}Br) – H]^+$), 695 (14), 694 (33), 693 (12), 692 (29), 614 (11), 613 (23), 461 (15), 460 (54).

Iodoazidation and reduction of **53**.

A soln. of NaN_3 (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 H_2O (20 ml). The aq. phase was extracted with AcOEt (2 × 20 ml), and the combined organic phases were washed with 5% $Na_2S_2O_3$ (20 ml) and H_2O (2 × 20 ml), and dried (Na_2SO_4). Evaporation and FC (20 g of silica gel, cyclohexane/AcOEt 20:1) gave a mixture (^{1}H-NMR) of iodo-azides (9 mg, 34%). Colourless oil. R_f (toluene/AcOEt 10:1) 0.69. FT-IR (1%, $CHCl_3$): 2106*s* (N_3). HR-MS (MALDI): Calc. for, found: 726.1802 ($C_{36}H_{38}IN_3NaO_4^+$, $[M+Na]^+$; calc 726.1805).

A soln. of this mixture (9 mg, 13 μmol) in THF (2 ml) was treated at 0° with $LiAlH_4$ (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%).





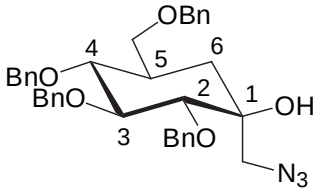
*(3*S*,4*R*,5*S*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-1-oxaspiro[2.5]octane* (**618**) and *(3*R*,4*R*,5*S*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-1-oxaspiro[2.5]octane* (**619**).

A soln. of **53** (20 mg, 37.4 mmol) in CH_2Cl_2 (1 ml) was treated with $NaHCO_3$ (7 mg, 84.2 mmol) and mCPBA (23 mg, 93.5 mmol), and stirred for 220 min.. The mixture was diluted with CH_2Cl_2 (25 ml), washed with sat. aq. $NaHCO_3$ soln. (3 x 20 ml) and brine (20 ml), dried (Na_2SO_4), 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. R_f (cyclohexane/AcOEt 3:1) 0.66. $[\alpha]_D^{25}$ = 36.0 (*c* = 1.32, $CHCl_3$). FT-IR (1.3%, $CHCl_3$): 3065*w*, 3008*m*, 2922*m*, 2863*m*, 1953*w*, 1877*w*, 1811*w*, 1726*w*, 1603*w*, 1496*w*, 1454*m*, 1358*m*, 1099*s*, 841*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.19 (20 arom. H); 4.91 (*d*, *J* = 10.9, 2 PhC*H*); 4.78 (*d*, *J* = 10.9, PhC*H*); 4.77 (*d*, *J* = 10.9, PhC*H*); 4.62 (*d*, *J* = 10.9, PhC*H*); 4.54 (*d*, *J* = 10.9, PhC*H*); 4.45 (*s*, PhCH_2); 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

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, H_{ax}–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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.81 (br. *s*); 128.62–127.79 (several *d*); 86.83, 80.75, 80.26 (3*d*, C(4), C(5), C(6)); 75.93, 75.56, 75.51, 73.23 (4*t*, 4 Ph*C*H_2), 69.89 (*t*, *C*H_2–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).

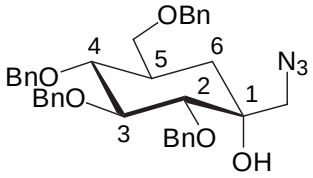
Data of **619**: Colourless, amorphous. R_f (cyclohexane/AcOEt 3:1) 0.55. $[\alpha]_D^{25}$ = 16.5 (*c* = 1.47, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): identical to that of **618**. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.22 (20 arom. H); 4.94 (*d*, *J* = 10.9, PhC*H*); 4.92 (*d*, *J* = 10.9, PhC*H*); 4.88 (*d*, *J* = 10.9, PhC*H*); 4.86 (*d*, *J* = 11.5, PhC*H*); 4.61 (*d*, *J* = 11.5, PhC*H*); 4.58 (*d*, *J* = 10.9, PhC*H*); 4.43 (*s*, PhCH_2); 3.83 (*t*, *J* = 9.3, H–C(5)); 3.75 (*dd*, *J* = 9.0, 3.4, CH–C(7)); 3.69 (*d*, *J* = 9.6, irrad. at 2.98 -> NOE of 1%, H–C(4)); 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), H_{ax}–C(8)); 1.36 (br. *d*, *J* = 10.0, irrad. at 2.59 -> NOE of 4%, H_{eq}–C(8)). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.94, 138.70, 138.07 (3*s*, 1 *s* hidden by other signal or noise); 128.68–127.79 (several *d*); 86.75, 80.81, 78.55 (3*d*, C(4), C(5), C(6)); 75.93, 75.47, 75.38, 73.18 (4*t*, 4 Ph*C*H_2); 69.54 (*t*, *C*H_2–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 $C_{36}H_{38}O_5$ (550.69): C 78.52, H 6.95; found: C 78.67, H 6.99.



*(1*S*,2*R*,3*S*,4*R*,5*R*)-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 NaN_3 (255 mg, 3.93 mmol), stirred at 100° for 20 h, cooled, diluted with AcOEt (200 ml), washed with H_2O (100

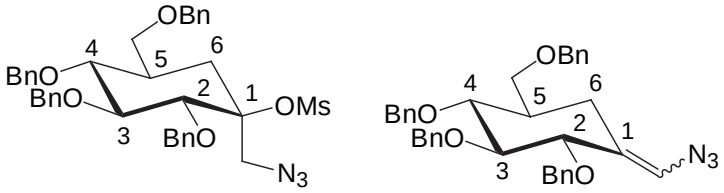
ml) and brine (100 ml), dried (Na_2SO_4), and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 9:1) gave colourless, amorphous **620** (170 mg, 91%). R_f (cyclohexane/AcOEt 3:1) 0.52. M.p. 79–80°. $[\alpha]_D^{25}$ = 16.2 (*c* = 1.50, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3555*w* , 3066*w*, 3008*m*, 2867*m*, 2107*s* , 1954*w*, 1812*w*, 1589*w*, 1496*w*, 1453*m*, 1359*m*, 1282*m*, 1065*s*, 912*w*, 871*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.19 (20 arom. H); 4.91 (*d*, *J* = 11.5, PhC*H*); 4.87 (*d*, *J* = 10.9, PhC*H*); 4.85 (*s*, PhCH_2); 4.79 (*d*, *J* = 10.6, PhC*H*); 4.54 (*d*, *J* = 10.6, PhC*H*); 4.46 (*s*, PhCH_2); 3.74 (br. *d*, *J* = 12.8, CHN_3); 3.66 (*dd*, *J* = 9.0, 4.1, CH–C(5)); 3.62–3.49 (*m*, H–C(2), H–C(3), H–C(4)); 3.45 (*dd*, *J* = 9.0, 2.5, CH´–C(5)); 3.34 (*d*, *J* = 12.8, CH´N_3); 2.13 (*s*, OH); 2.06 (*dd*, *J* = 12.8, 2.5, H_{eq}–C(6)); 1.75–1.62 (*m*, H–C(5)); 1.58 (br. *t*, *J* = 13.1, H_{ax}–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.76, 138.60 (2 br. *s*); 128.88–127.86 (several *d*); 86.81, 85.41, 81.06 (3*d*, C(2), C(3), C(4)); 76.06, 75.78 (2*t*, 2 Ph*C*H_2); 75.68 (*s*, C(1)); 75.54, 73.26 (2*t*, 2 Ph*C*H_2); 69.62 (*t*, *C*H_2–C(5)); 54.49 (*t*, *C*H_2N_3); 38.64 (*d*, C(5)); 33.80 (*t*, C(6)). MALDI-MS (DHB): 616 (68, $[M + Na]^+$), 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 $C_{36}H_{39}N_3O_5$ (593.72): C 72.83, H 6.62, N 7.08; found: C 72.65, H 6.62, N 6.91.



*(1*R,*2*R,*3*S,*4*R,*5*R*)-1-(Azidomethyl)-2,3,4-tris(benzyloxy)-5-(benzyloxymethyl)-cyclohexan-1-ol* (**623**).

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. $[\alpha]_D^{25}$ = 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**. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.61–7.20 (20 arom. H); 4.98 (*d*, *J* = 10.9, PhC*H*); 4.95 (*d*, *J* = 11.2, PhC*H*); 4.85 (*d*, *J* = 11.1, 2 PhC*H*); 4.62 (*d*, *J* = 11.2, PhC*H*); 4.57 (*d*, *J* = 10.9, PhC*H*); 4.48 (*d*, *J* = 12.1, PhC*H*); 4.44 (*d*, *J* = 12.1, PhC*H*); 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, CHN_3); 3.22 (*d*, *J* = 11.8, CH´N_3); 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 139.02, 138.73, 138.13 (3*s*, 1 *s* hidden by noise or other signals); 128.76–127.81 (several *d*); 85.67, 81.54, 81.01 (3*d*, C(2), C(3), C(4)); 75.78 (2 *t*), 75.31 (*t*, 3Ph*C*H_2); 74.67 (*s*, C(1)); 73.27 (*t*, Ph*C*H_2); 69.71 (*t*, *C*H_2–C(5)); 57.89 (*t*, *C*H_2N_3); 37.39 (*d*, C(5)); 33.02 (*t*, C(6)). MALDI-MS (DHB): 616 (47,

[*M* + 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 $C_{36}H_{39}N_3O_5$ (593.72): C 72.83, H 6.62, N 7.08; found: C 72.81, H 6.66, N 6.99.



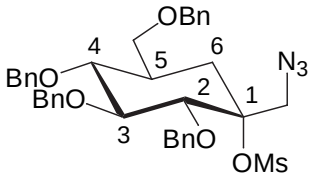
*(1*S*,2*R*,3*S*,4*R*,5*R*)-1-(Azidomethyl)-2,3,4-tris(benzyloxy)-5-(benzyloxymethyl)-cyclohex-1-yl methanesulfonate* (**621**) and *(1*S*,2*S*,3*R*,4*R*)-6-(Azidomethylen)-1,2,3-tris(benzyloxy)-4-(benzyloxymethyl)-cyclohexane* (**626**).

A soln. of **620** (165 mg, 0.28 mmol) in 2,6-lutidine (2.2 ml) was treated at 0°with MsCl (0.1 ml, 1.25 mmol) and DMAP (2 mg), stirred for 7.5 h, diluted with Et_2O (120 ml), washed with cold brine (2 x 60 ml), dried (Na_2SO_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, PhC*H*); 4.92 (*d*, *J* = 10.9, PhC*H*); 4.88 (*d*, *J* = 10.3, PhC*H*); 4.87 (*d*, *J* = 10.9, PhC*H*); 4.84 (*d*, *J* = 11.2, PhC*H*); 4.55 (*d*, *J* = 10.9, PhC*H*); 4.54 (*d*, *J* = 12.5, PhC*H*); 4.49 (*d*, *J* = 12.1, PhC*H*); 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´N_3); 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 Ph*C*H_2); 69.18 (*t*, *C*H_2–C(5)); 52.94 (*t*, *C*H_2N_3); 41.14 (*q*, MsO); 38.64 (*d*, C(5)); 30.94 (*t*, C(6)). MALDI-MS (DHB): 570 (100, [*M* + Na – HOMs – N_2]$^+$).

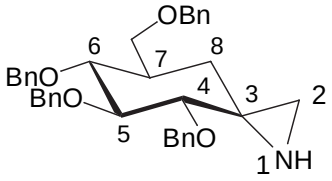
Data of **626**: Colourless oil. R_f (toluene/AcOEt 10:1) 0.67. FT-IR (1.5%, $CHCl_3$): 3089*w*, 3067*w*, 3008*m*, 2914*w*, 2862*m*, 2109*s* , 1950*w*, 1732*w*, 1668*w*, 1604*w*, 1496*w*, 1454*m*, 1358*m*, 1327*w*, 1275*w*, 1151*m*, 1130*m*, 1095*m*, 1028*m*, 909*w*, 843w. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.18 (20 arom. H); 6.36 (br. *t*, *J* = 1.2, C*H*N_3); 4.93 (*d*, *J* = 10.9, PhC*H*); 4.87 (*d*, *J* = 10.9, PhC*H*); 4.81 (*d*, *J* = 10.9, PhC*H*); 4.75 (*d*, *J* = 11.5, PhC*H*); 4.69 (*d*, *J* = 11.5, PhC*H*); 4.53 (*d*, *J* = 10.9, PhC*H*); 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, $[M + 1 - N_2]^+$).



*(1*R*,2*R*,3*S*,4*R*,5*R*)-1-(Azidomethyl)-2,3,4-tris(benzyloxy)-5-(benzyloxymethyl)cyclohex-1-yl methanesulfonate* (**624**).

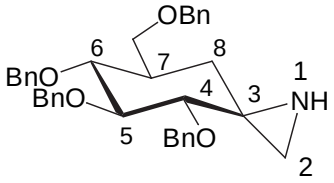
Similarly as described above, treatment of **623** (103 mg, 0.17 mmol) with MsCl (0.06 ml, 0.77 mmol) and DMAP (1 mg) in 2,6-lutidine (3 ml) at 0° gave **624** (116 mg, 99%). Colourless oil. R_f (toluene/AcOEt 10:1) 0.38. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.42–7.19 (20 arom. H); 4.96 (*d*, *J* = 11.2, PhC*H*); 4.91 (*d*, *J* = 10.9, PhC*H*); 4.89 (*d*, *J* = 10.6, PhC*H*); 4.85 (*d*, *J* = 10.9, PhC*H*); 4.69 (*d*, *J* = 11.2, PhC*H*); 4.56 (*d*, *J* = 10.9, PhC*H*); 4.48 (*d*, *J* = 11.8, PhC*H*); 4.43 (*d*, *J* = 12.1, PhC*H*); 4.17 (*d*, *J* = 11.8, CHN_3); 3.90 (*t*, *J* = 9.3, H–C(3)); 3.90 (*d*, *J* = 12.1, $CH'N_3$); 3.79 (*dd*, *J* = 9.3, 3.7, CH–C(5)); 3.62 (*dd*, *J* = 10.9, 9.3, H–C(4)); 3.54 (*d*, *J* = 9.7, H–C(2)); 3.43 (*dd*, *J* = 9.3, 2.5, CH'–C(5)); 3.07 (*s*, MsO); 2.40 (*dd*, *J* = 14.9, 3.4, H_{eq}–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 (4*s*); 128.70–127.87 (several *d*); 94.00 (*s* (C(1)); 84.66, 81.06, 80.54 (3*d*, C(2), C(3), C(4)); 76.04, 75.77, 75.62, 73.34 (4*t*, 4 Ph*C*H_2); 69.00 (*t*, *C*H_2–C(5)); 53.46 (*t*, *C*H_2N_3); 40.71 (*q*, MsO); 37.83 (*d*, C(5)); 32.67 (*t*, C(6)). MALDI-MS (DHB): 570 (100, $[M + Na - HOMs - N_2]^+$).



*(3*R*,4*S*,5*S*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-1-aza-spiro[2.5]octane* (**622**).

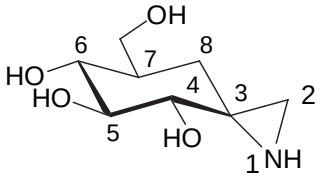
A soln. of **621** (165 mg, 0.25 mmol) in THF (15 ml) was treated at 0° with $LiAlH_4$ (49 mg, 1.2 mmol), stirred for 3.5 h, treated with MeOH (14 ml) and 1M NaOH, filtered through *Celite*, and evaporated. FC (20 g of silica gel, cyclohexane/AcOEt 1:1) gave **622** (112 mg, 83%). Colourless oil. R_f (cyclohexane/AcOEt 1:1) 0.14. $[\alpha]_D^{25}$ = 32.1 (*c* = 1.50, $CHCl_3$). FT-

IR (1.5%, $CHCl_3$): 3296*w* , 3066*m*, 3007*s*, 2911*m*, 2863*m*, 1952*w*, 1877*w*, 1811*w*, 1725*w*, 1585*w*, 1497*m*, 1453*m*, 1359*m*, 1152*s*, 1095*s*, 909*m*, 869*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.24 (20 arom. H); 4.94 (*d*, *J* = 10.9, PhC*H*); 4.92 (br. *d*, *J* = 12.1, 2 PhC*H*); 4.86 (*d*, *J* = 10.9, PhC*H*); 4.62 (*d*, *J* = 10.9, PhC*H*); 4.57 (*d*, *J* = 11.2, PhC*H*); 4.48 (*d*, *J* = 12.1, PhC*H*); 4.44 (*d*, *J* = 12.1, PhC*H*); 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, H_{ax}–C(8)); 1.87 (br. *s*, H–C(2)); 1.40 (br. *s*, H´–C(2)); 1.29–1.21 (*m*, H_{eq}–C(8)); 1.17–0.87 (br. *s*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 (3*d*, C(4), C(5), C(6)); 75.96, 75.88, 75.44, 73.19 (4*t*, 4 Ph*C*H_2); 69.84 (*t*, *C*H_2–C(7)); 40.29 (*d*, C(7)); 37.42 (*s*, C(3)); 33.62 (*t*, C(8)); 27.17 (*t*, C(2)). MALDI-MS (DHB): 588 (2, $[M + K]^+$), 572 (100, $[M + Na]^+$), 550 (4, $[M + 1]^+$). Anal. calc. for $C_{36}H_{39}NO_4$ (549.71): C 78.66, H 7.15, N 2.55; found: C 78.57, H 7.12, N 2.48.



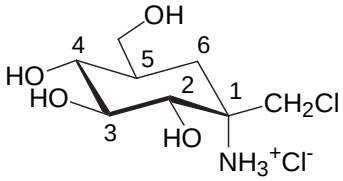
*(3*S*,4*S*,5*S*,6*R*,7*R*)-4,5,6-Tris(benzyloxy)-7-(benzyloxymethyl)-1-azaspiro[2.5]octane* (**625**).

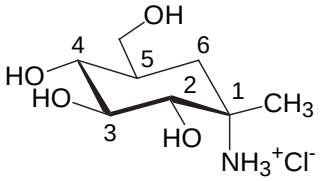
Similarly as described above, a soln. of **624** (116 mg, 0.17 mmol) in THF (11 ml), was treated with $LiAlH_4$ (35 mg, 0.86 mmol) at 0° for 9 h to yield **625** (70 mg, 74%). Colourless oil. R_f (cyclohexane/AcOEt 1:1) 0.22. $[\alpha]_D^{25}$ = 8.8 (*c* = 1.42, $CHCl_3$). FT- IR (1.4%, $CHCl_3$): identical to that of **622**. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.23 (20 arom. H); 4.93 (*d*, *J* = 10.9, PhC*H*); 4.92 (*d*, *J* = 11.8, PhC*H*); 4.91 (*d*, *J* = 10.9, PhC*H*); 4.86 (*d*, *J* = 10.9, PhC*H*); 4.59 (*d*, *J* = 10.9, PhC*H*); 4.58 (*d*, *J* = 11.5, PhC*H*); 4.46 (*s*, PhCH_2); 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. *t* , *J* ≈ 12.5, H_{ax}–C(8)); 1.98 (br. *s*, H–C(2)); 1.93–1.81 (*m*, H–C(7)); 1.31–1.25 (*m*, H_{eq}–C(8)); 1.29 (br. *s*, H'–C(2)); 1.18–0.85 (br. *s*, NH). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.89, 138.71, 138.45 (3*s*, 1 *s* hidden); 128.85–127.78 (several *d*); 88.61, 81.54, 79.60 (3*d*, C(4), C(5), C(6)); 75.75, 75.64, 75.51, 73.21 (4*t*, 4 Ph*C*H_2); 70.02 (*t*, *C*H_2–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 $C_{36}H_{39}NO_4$ (549.71): C 78.66, H 7.15, N 2.55; found: C 78.86, H 7.32, N 2.60.



*(3*R*,4*S*,5*S*,6*R*,7*R*)-7-(Hydroxymethyl)-1-azaspiro[2.5]octane-4,5,6-triol* (**47**).

A soln. of **622** (10 mg, 18 mmol) in NH_3 (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 NH_4Cl (*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 H_2O), and lyophilisation gave a mixture of **47**, an unidentified byproduct, and inorganic material (13 mg, colourless powder). R_f (nPrOH/AcOH/H_2O 4:1:1) 0.31. ^{1}H-NMR (300 MHz, D_2O): 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), H_{ax}–C(8)); 1.53 (br. *s*, H'–C(2)); 1.35 (*d*, *J* = 6.9, ?); 1.26 (br. *d*, *J* = 10.6, H_{eq}–C(8)). HR-MALDI-MS (DHB): Calc. for , found: 190.1076 ($C_8H_{16}NO_4^+$, $[M + H]^+$; calc. 190.1079).





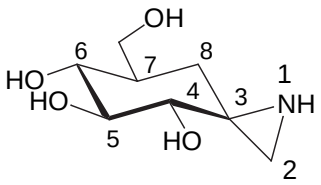
*(1*S*,2*S*,3*S*,4*R*,5*R*)-1-Amino-1-(chloromethyl)-5-(hydroxymethyl)-cyclohexane-2,3,4-triol Hydrochloride* (**627**·HCl) and *(1*S*,2*S*,3*S*,4*R*,5*R*)-1-Amino-1-methyl-5-hydroxymethyl-cyclohexane-2,3,4-triol Hydrochloride* (**628**·HCl).

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 H_2 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). R_f (*n*PrOH/AcOH/H_2O 4:1:1) 0.35. ^{1}H-NMR (300 MHz, D_2O, **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, $[M(^{37}Cl) + Na]^+$), 248 (11, $[M(^{35}Cl) + Na]^+$), 228 (14, $[M(^{37}Cl) + 1]^+$), 226 (34,

[*M*(*^{35}Cl)* + 1]$^+$), 222 (34, [*M* – Cl + MeOH]$^+$), 190 (100, [*M* – Cl]$^+$). Data for **628**: 224 (8, [*M* + MeOH + 1]$^+$), 192 (94, [*M* + 1]$^+$).

*(1*S*,2*S*,3*S*,4*R*,5*R*)-1-Amino-1-(chloromethyl)-5-(hydroxymethyl)-cyclohexane-2,3,4-triol Hydrochloride* (**627**·HCl) (This experiment was done by *Dr. Poisson*).

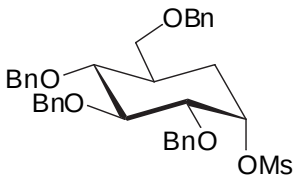
At –60°, Na (70 mg, 2 mmol) was dissolved in NH_3 (3 ml) and THF (5 ml), stirred for 15 min., treated dropwise with a soln. of **622** (31 mg, 0.05 mmol) in THF (1 ml), and stirred for 30 min. at –50°. The blue mixture was treated with NH_4Cl in small portions, until it became colourless, and NH_3 was 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 NH_4Cl (64 mg). ^{1}H-NMR (300 MHz, D_2O): 4.11 (*d*, *J* = 12.3, C*H*–C(1)); 3.85 (*d*, *J* = 12.3, C*H*'–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)).



*(3*S*,4*S*,5*S*,6*R*,7*R*)-7-(Hydroxymethyl)-1-azaspiro[2.5]octane-4,5,6-triol* (**46**).

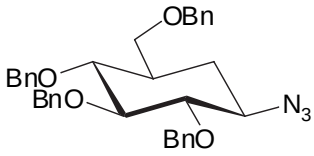
A soln. of **625** (33 mg, 60 mmol) in NH_3 (10 ml) and THF (2.5 ml) was treated at –78° with Na in small pieces (*ca*. 30 mg), until the blue colour persisted for 1 h, treated with NH_4Cl (*ca*. 50 mg), until the blue colour disappeared, and allowed to warm to r.t. overnight. The solvent was evaporated, 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 H_2O). After washing with H_2O (50 ml), elution with 2% aq. NH_3 gave crude **46** (6 mg). Chromatography (25 g of Nucleoprep 20 CN, MeOH) gave colourless, amorphous **46** (5.2 mg, 45%). R_f (nPrOH/AcOH/H_2O 4:1:1) 0.26. $[\alpha]_D^{25}$ = 6.0 (*c* = 0.31, H_2O). pK_{HA} = 6.78. ^{1}H-NMR (300 MHz, CD_3OD): 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, H_{ax}–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, H_{eq}–C(8)). ^{13}C-NMR (75 MHz, CD_3OD): 80.44, 75.30,

72.11 (3*d*, C(4), C(5), C(6)); 64.25 (*t*, *C*H_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, $[2\,M + Na]^+$), 379 (71, $[2\,M + 1]^+$), 212.0891 (19, $C_8H_{15}NO_4Na^+$, $[M + Na]^+$; calc. 212.0899), 207.1337 (23, $C_8H_{19}N_2O_4^+$, $[M + NH_4]^+$; calc. 207.1345), 190.1074 (100, $C_8H_{16}NO_4$’ $[M + H]^+$; calc. 190.1079).



*(1*S*,2*S*,3*S*,4*R*,5*R*)-2,3,4-Tris(benzyloxy)-5-(benzyloxymethyl)-1-cyclohex-1-yl methanesulfonate* (**629**).

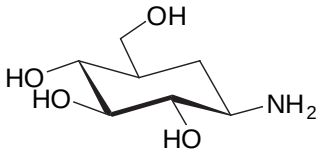
A soln. of **54** [234] (200 mg, 0.37 mmol) in pyridine (6 ml) at 0° was treated with MsCl (0.12 ml, 1.49 mmol), stirred for 45 min at 0° and for 90 min at r.t., diluted with AcOEt (100 ml), washed with H_2O (100 ml) and brine (100 ml), dried (Na_2SO_4), and evaporated. FC (20 g of silica gel, cyclohexane/AcOEt 9:1) gave colourless, amorphous **629** (212 mg, 93%). R_f (cyclohexane/AcOEt 3:1) 0.40. M.p. 137–138°. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.21 (20 arom. H); 5.22–5.18 (*m*, H–C(1)); 4.94 (*d*, *J* = 10.9, PhC*H*); 4.90 (*d*, *J* = 9.7, PhC*H*); 4.84 (*d*, *J* = 10.6, PhC*H*); 4.78 (*d*, *J* = 11.2, PhC*H*); 4.69 (*d*, *J* = 10.9, PhC*H*); 4.55 (*d*, *J* = 10.9, PhC*H*); 4.43 (*s*, PhCH_2); 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), H_{eq}–C(6)); 1.77 (br. *t*, *J* = 13.7, H_{ax}–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.9, 138.55, 137.78 (3*s*, 1 *s* hidden by other signals); 128.76–127.84 (several *d*); 83.39, 81.20, 80.34, 79.07 (4*d*, C(1), C(2), C(3), C(4)); 75.89, 75.54, 73.40, 73.21 (4*t*, 4 PhCH_2); 69.08 (*t*, CH_2–C(5)); 39.03 (*d*, C(5)); 37.42 (*q*, MsO); 30.32 (*t*, C(6)). FAB-MS (NOBA): 639 (25, $[M + Na]^+$), 615 (100, $[M - 1]^+$), 525 (48), 435 (6), 391 (7). Anal. calc. for $C_{36}H_{40}O_7S$ (616.77): C 70.11, H 6.54; found: C 69.88, H 6.47.



*(1*R*,2*S*,3*S*,4*R*,5*R*)-1-Azido-2,3,4-tris(benzyloxy)-5-(benzyloxymethyl)cyclohexane* (**630**).

A soln. of **629** (210 mg, 0.34 mmol) in DMF (15 ml) was treated with NaN_3 (221 mg, 3.4 mmol), stirred at 120° for 3 h, cooled to r.t., diluted with AcOEt (60 ml), washed with H_2O (50 ml) and brine (50 ml), dried (Na_2SO_4), and evaporated. FC (30 g of silica gel, cyclohexane/AcOEt 20 :1) gave colourless, amorphous **630** (181 mg, 94%). R_f (cyclohexane/AcOEt 9:1) 0.36. M.p. 69–70°. $[\alpha]_D^{25}$ = 49.5 (*c* = 1.49, $CHCl_3$). FT-IR (1.5%, $CHCl_3$): 3066*w*, 3006*w*, 2865*w*, 2103*s*, 1497*w*, 1454*m*, 1359*m*, 1260*w*, 1089*m*, 1028*m*, 910*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.18 (20 arom. H); 4.93–4.83 (*m*, 5 PhC*H*); 4.53 (*d*, *J* = 10.9, PhC*H*); 4.46 (*s*, PhCH_2); 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, H_{eq}–C(6)); 1.82–1.69 (*m*, H–C(5)); 1.48 (*q*, *J* = 13.0, H_{ax}–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.84, 138.63, 138.50, 138.24 (4*s*); 128.67–127.86 (several *d*); 86.91, 85.05, 80.62 (3*d*, C(2), C(3), C(4)); 75.91 (*t*, 2 Ph*C*H_2); 75.52, 73.34 (2*t*, 2 Ph*C*H_2); 69.71 (*t*, *C*H_2–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), 537 (20), 510 (18), 496 (12), 461 (100), 452 (13), 444 (20), 429 (19), 422 (17), 408 (14), 392 (10), 339 (29), 329 (12). Anal. calc. for $C_{35}H_{37}N_3O_4$ (563.70): C 74.58, H 6.62, N 7.45; found: C 74.61, H 6.71, N 7.23.



*(1*R*,2*S*,3*S*,4*R*,6*R*)-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 H_2-atmosphere (6 bar) for 15 h, filtered through *Celite*, and evaporated. The residue was adsorbed on neutral *Dowex 50 WX8* (3 ml, washed with H_2O). After washing with H_2O (70 ml), elution with 2% aq. NH_3 gave **48** (16 mg, 100%). R_f (nPrOH/AcOH/H_2O 4:1:1) 0.31. $[\alpha]_D^{25}$ = 17 (*c* = 0.42, H_2O; [224]: 17.2 (*c* = 0.57, H_2O)). ^{1}H-NMR (300 MHz, D_2O): 3.77 (*dd*, *J* = 11.2, 3.4, CH–C(6)); 3.62 (*dd*, *J* = 11.2, 6.2, CH´–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, H–C(4)); 1.92 (*dt*, *J* = 13.1, 4.0, H_{eq}–C(5)); 1.75–1.60 (*m*, H–C(6)); 1.15 (br. *q*, *J* = 12.6, H_{ax}–C(5)). ^{13}C-NMR (75 MHz, D_2O): 80.26, 80.10, 75.68 (3*d*, C(1), C(2), C(3)); 65.09 (*t*, *C*H_2–C(6)); 54.81 (*d*, C(4)); 44.05 (*d*, C(6)); 33.77 (*t*, C(5)).

Inhibition Studies. The IC_{50} values were determined based on a range of inhibitor concentrations (typically 4–8 concentrations) which bracket the IC_{50} value.

a) Inhibition of the β-Glucosidase from almonds in the pH range of 6.2–7.8. IC_{50} values were determined at 37° in 0.08M KH_2PO_4/K_2HPO_4 or NaH_2PO_4/Na_2HPO_4 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). IC_{50} 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 IC_{50} value. To

check for slow inhibition, the dependence of the inhibition on the incubation time was determined.

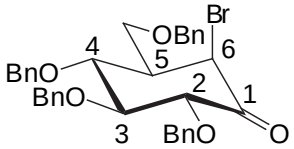
b) Inhibition of the β-Glucosidase from almonds at pH 4.2. See *a). I*C_{50} values were determined at 37° in 0.08M citric acid/Na_2HPO_4 buffer (pH 4.2). The enzymatic reaction was started after incubation of the enzyme for 15 min in the presence of the inhibitor by the addition of substrate. The mixture 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°.

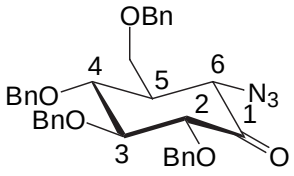
d) Inhibition of the α-Glucosidase from brewer's yeast at pH 6.8. As described in *a)* . All measurements were performed at 37°, using 4-nitrophenyl α-D-glucopyranoside as substrate.

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 K_i *and* k_i *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 KH_2PO_4/K_2HPO_4 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 K_i and k_i were determined.

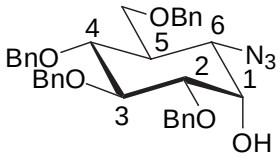


*(2*R*,3*S*,4*R*,5*R*,6*R*)-2,3,4-Tris-(benzyloxy)-5-(benzyloxymethyl)-6-bromocyclohexanone* (**631**). A soln. of **52** (228 mg, 0.425 mmol) in THF (50 ml) was cooled to 0°, treated with $PhMe_3NBr_3$ (176 mg, 0.467 mmol) and CSA (10 mg, 43 μmol), stirred at 0° for 5 min, and for 7 h while warming to r.t., and treated with sat. aq. $Na_2S_2O_5$ soln. (50 ml). The mixture was extracted with Et_2O (2 x 60 ml). The combined organic phases were dried (Na_2SO_4) 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. R_f (cyclohexane/AcOEt 3:1) 0.66. M.p.: 83.4–89.5°. FT-IR (0.5%, $CHCl_3$): 3038*w*, 2868*w*, 1731*m* (C=O), 1496*w*, 1451*m*, 1359*w*, 1146*w*, 1094*s*, 1046*m*, 993*w*, 911*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.48–7.12 (20 arom. H); 5.08 (*d*, *J* = 10.0, H–C(2)); 5.00 (*d*, *H* = 10.6, PhC*H*); 4.97 (*d*, *J* = 11.2, PhC*H*); 4.94 (*d*, *J* = 10.9, PhC*H*); 4.79 (*d*, *J* = 10.6, PhC*H*); 4.67 (*d*, *J* = 3.4, H–C(6)); 4.63 (*d*, *J* = 11.2, PhC*H*); 4.55 (*d*, *J* = 10.9, PhC*H*); 4.52 (*s*, PhCH_2); 3.92 (*dd*, *J* = 8.7, 2.2, CH–C(5)); 3.90 (*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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 (4*t*, 4 Ph*C*H_2); 67.70 (*t*, *C*H_2–C(5)); 51.41 (*d*, C(6)); 42.59 (*d*, C(5)). HR-MS (MALDI): 639 (100), 637.1567 (95, $C_{35}H_{35}BrNaO_5^+$, [*M* + Na]$^+$; calc. 637.1566); 559 (47, [*M* + Na + H – Br]$^+$).



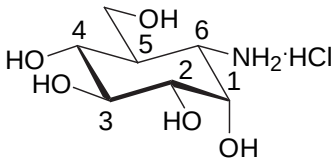
*(2*S*,3*R*,4*R*,5*S*,6*R*)-2-Azido-4,5,6-tris-(benzyloxy)-3-(benzyloxymethyl)cyclohexanone* (**56**). A soln. of **631** (133 mg, 216 μmol) in DMF (13 ml) was cooled to 0°, treated with NaN_3 (140 mg, 2.16 mmol), stirred for 65 min, and poured into ice-water (150 ml). The mixture was extracted with AcOEt (2 x 150 ml). The combined organic phases were dried (Na_2SO_4) 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%). R_f (toluene/AcOEt 10:1) 0.71. FT-IR (0.5%, $CDCl_3$): 3067*w*, 3033*w*, 3013*w*, 2925*w*, 2873*w*, 2110*s* (N_3), 1742*m* (C=O), 1497*s*, 1454*w*, 1359*w*, 1146*m*, 1090*s*, 1072*m*, 1055*m*, 1028*m*, 1005*w*, 909*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.42–7.15 (20 arom. H); 5.01 (*d*, *J* = 10.9, PhC*H*); 4.98 (*d*, *J* = 10.6, PhC*H*); 4.98 (*d*, *J* = 11.5, PhC*H*); 4-81 (*d*, *J* = 10.6, PhC*H*); 4.60 (*d*, *J* = 11.5, PhC*H*); 4.59 (*d*, *J* = 10.9, PhC*H*); 4.54 (*d*, *J* = 11.5, PhC*H*); 4.46 (*d*, *J* = 11.8, PhC*H*); 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 201.68 (*s*, C=O); 138.36, 138.27, 138.02, 137.48 (4*s*); 128.73–128.05 (several *d*); 85.77, 84.48, 76.80 (3*d*, C(4), C(5), C(6)); 76.20, 76.07, 73.78, 73.52 4*t*, Ph*C*H_2); 64.80 (*t*, *C*H_2–C(3)); 63.05 (*d*, C(2)); 44.85 (*d*, C(3)). HR-MS (MALDI): 600.2475 (55, $C_{35}H_{35}N_3NaO_5^+$, [*M* + Na]$^+$; calc. 600.2474) ; 572 (100, [*M* + Na – N_2]$^+$).



*(1*S*,2*S*,3*R*,4*R*,5*S*,6*S*)-2-Azido-4,5,6-(benzyloxy)-3-(benzyloxymethyl)cyclohexanol* (**633**).

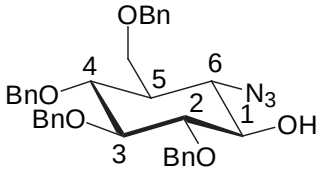
A soln. of **56** (49 mg, 84.8 μmol) in MeOH (12 ml) was cooled to 0°, treated with $NaBH_4$ (19.3 mg, 509 μmol), stirred for 55 min, and evaporated. A soln. of the residue in AcOEt (50 ml) was washed with sat. aq. NH_4Cl soln. and brine (40 ml of each). The aq. phases were extracted with AcOEt (50 ml). The combined organic phases were dried (Na_2SO_4) 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). R_f (cyclohexane/AcOEt 3:1) 0.51. FT-IR (1%, $CHCl_3$): 3579*w* (OH), 3034*w*, 3011*w*, 2873*w*, 2105*s* (N_3), 1496*w*, 1454*w*, 1360*w*, 1126*w*, 1093*m*, 1066*m*, 1028*m*, 909*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.44–7.15 (20 arom. H); 4.91 (*d*, *J* = 10.9, PhC*H*); 4.88 (*d*, *J* = 10.9, PhC*H*); 4.83 (*d*, *J* = 10.6, PhC*H*); 4.73 (*d*, *J* = 11.5, PhC*H*); 4.69 (*d*, *J* = 11.5, PhC*H*); 4.51 (*d*, *J* = 11.5, PhC*H*); 4.50 (*d*, *J* = 9.3, PhC*H*); 4.39 (*d*, *J* = 11.8, PhC*H*); 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, CH'–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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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, $C_{35}H_{37}N_3NaO_5^+$, [*M* + Na]$^+$; calc. 602.2631), 574 (100, [*M* + Na – N_2]$^+$), 554 (48).



*(1*R*,2*S*,3*S*,4*S*,5*S*,6*R*)-5-Amino-6-(hydroxymethyl)cyclohexane-1,2,3,4-tetrol Hydrochloride Monohydrate* (**635**·HCl·H_2O).

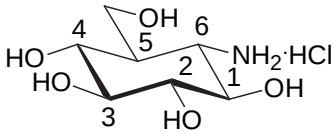
A suspension of 10% Pd/C (25 mg) in MeOH (2 ml) was treated with 3 drops of conc. HCl and with a soln. of **633** (36 mg, 62 μmol) in MeOH (10 ml), and stirred under H_2 at r.t. for 14 h. Filtration and evaporation gave colourless glassy **635**·HCl·H_2O (15.4 mg, 100%). R_f

(*n*PrOH/AcOH/H_2O 4:1:1) 0.31. ^{1}H-NMR (300 MHz, CD_3OD): 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 (*tdd*, *J* = 10.9, 6.2, 3.4, H–C(6)). ^{13}C-NMR (75 MHz, CD_3OD): 74.68; 73.07; 71.37; 70.88 (C(1), C(2), C(3), C(4)); 60.82 (*C*H_2–C(6)); 52.80 (C(5)); 42.34 (C(6)). ESI-MS: 409 (56 [2 *M* + Na]$^+$), 360 (21), 338 (30), 248 (14, [*M* + Na + MeOH]$^+$), 216 (22, [*M* + Na]$^+$), 194 (100, [*M* + 1]$^+$).



*(1*R,*2*S,*3*R,*4*R,*5*S,*6*S*)-2-Azido-4,5,6-tris-(benzyloxy)-3-(benzyloxymethyl)cyclohexanol* (**632**).

A soln. of **56** (38 mg, 65 μmol) in CH_2Cl_2 (5 ml) was cooled to –78°, treated with 1.5M 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. Na_2SO_4 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%). R_f (cyclohexane/AcOEt 3:1) 0.54. FT-IR (0.5%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39–7.18 (20 arom. H); 4.97 (*d*, *J* = 11.2, PhC*H*); 4.90 (*s*, PhCH_2); 4.88 (*d*, *J* = 9.3, PhC*H*); 4.73 (*d*, *J* = 11.2, PhC*H*); 4.55 (*d*, *J* = 11.2, PhC*H*); 4.51 (*d*, *J* = 12.1, PhC*H*); 4.44 (*d*, *J* = 11.8, PhC*H*); 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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, $C_{35}H_{37}N_3NaO_5^+$, [*M* + Na]$^+$; calc. 602.2631), 574 (100, [*M* + Na – N_2]$^+$), 554 (57).

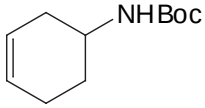


*(1*R,*2*S,*3*S,*4*R,*5*S,*6*R*)-5-Amino-6-(hydroxymethyl)cyclohexane-1,2,3,4-tetrol Hydrochloride Monohydrate* (**634**·HCl·H_2O).

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 H_2 at r.t. for 29 h, and filtered. Evaporation gave colourless glassy **634**·HCl·H_2O·MeOH (9.3 mg, quant.). R_f (*n*PrOH/AcOH/H_2O 4:1:1) 0.32. ^{1}H-NMR (300 MHz, CD_3OD): 4.02 (*dd*, *J* = 10.9, 3.4,

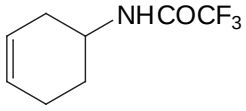
CH–C(6)); 3.79 (*dd*, *J* = 10.9, 6.8, CH'–C(6)); 3.37 (*dd*, *J* = 10.3, 8.4, 1 H); 3.24–3.13 (*m*, 3 H); 3.05 (*t*, *J* = 10.9, H–C(5)); 1.70 (*tdd*, *J* = 10.9, 7.3, 3.6, H–C(6)). ^{13}C-NMR (75 MHz, CD_3OD): 76.56; 74.74; 72.91; 70.18 (C(1), C(2), C(3), C(4)); 60.45 (CH_2–C(6)); 54.58 (C(5)); 43.55 (C(6)). ESI-MS: 409 (35 $[2M + Na]^+$), 360 (57), 338 (84), 248 (10, $[M + Na + MeOH]^+$), 216 (16, $[M + Na]^+$), 194 (42, $[M + 1]^+$).

Part 3.



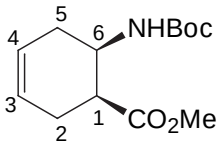
O-*tertButyl* N-*(cyclohex-3-enyl)carbamate* (**712**) [955] [956].

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 Et_3N (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 *t*BuOH (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. $NaHCO_3$ soln. (100 ml) and extracted with Et_2O (3 x 100 ml). The organic phases were dried (Na_2SO_4) and evaporated. FC (50 g of silica gel, cyclohexane/AcOEt 12;1) gave **712** (2.88 g, 92%) as colourless crystals. R_f (cyclohexane/AcOEt 3:1) 0.71. M.p. 52–54°. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.71–5.63, 5.63–5.55 (2*m*, 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*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 127.21, 124.75 (2*d*, C(3), C(4)); 79.21 (*s*,Me_3*C*); 45.77 (*d*, C(1)); 32.15 (*t*); 28.49 (*q*, *Me*$_3$C): 23.67 (*t*, 2 C).



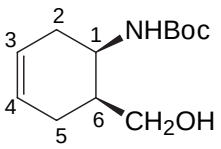
N-*(Cyclohex-3-enyl)-2,2,2-trifluoroacetamide* (**71**) [957].

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 Et_3N (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. $NaHCO_3$ soln. (2 x 400 ml), dried (Na_2SO_4), and evaporated. FC (60 g of silica gel, cyclohexane/AcOEt 12:1) gave **71** (12.91 g, 84%) as colourless crystals. R_f (cyclohexane/AcOEt 3:1) 0.70. M.p. 59–60° ([957]: 62–63°). FT-IR (1.5%, $CHCl_3$): 3428*m* (NH), 3008*w*, 2926*w*, 2845*w*, 1723*s* (C=O), 1532*m*, 1439*w*, 1372*w*, 1337*w*, 1290*m*, 1171*s*, 1045*w*, 940*w*, 865*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.28–6.14 (*m*, NH, exch. with D_2O); 5.79–5.71, 5.67–5.59 (2*m*, H–C(3), H–C(4)); 4.25–4.13 (*m*, H–C(1)); 2.52–2.40 (*dm*, $J \approx 17.7$, 1 H); 2.27–2.07 (*m*, 2 H); 2.04–1.86 (*m*, 2 H); 1.77–1.64 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 127.49, 123.73 (2*d*, C(3), C(4)); 45.55 (*d*, C(1)); 30.95, 27.17, 22.93 (3*t*, C(2), C(5), C(6)). ^{19}F-NMR (282 MHz, $CDCl_3$): –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 Et_3N (22.7 ml, 163 mmol) and diphenylphosphoryl azide (30.7 ml, 143 mmol), heated slowly to 80°, kept at this temperature until N_2 evolution ceased, and refluxed for 200 min. After cooling to r.t., the mixture was treated with *t*BuOH (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. $NaHCO_3$ soln. (2 x 400 ml). The aq. phases were extracted with Et_2O (2 x 400 ml). The combined organic phases were dried (Na_2SO_4) 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°. R_f (cyclohexane/AcOEt 3:1) 0.52. M.p. 51.8–55.5°. FT-IR (1%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.78 (*s*, *C*O_2Me); 155.17 (*s*, *C*O_2CMe_3); 124.85, 124.68 (2*d*, C(3), C(4)); 79.30 (*s*, Me_3*C*); 51.92 (*q*, MeO); 46.21 (*d*, C(1)); 42.18 (*d*, C(6)); 30.81 (*t*); 28.46 (*q*, *Me*$_3$C); 25.45 (*t*). EI-MS: 255 (1, M^+), 201 (7, [*M* – C_4H_6]$^+$), 199 (9, [*M* – C_4H_8]$^+$), 182 (13), 168 (14), 155 (18, [*M* – C_4H_8 – CO_2]$^+$), 150 (16), 145 (14, [*M* – C_4H_8 – C_4H_6]$^+$), 142 (8), 138 (61), 101 (87, [*M* – C_4H_8 – C_4H_6 – CO_2]$^+$). Anal. calc. for $C_{13}H_{21}NO_4$ (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**).

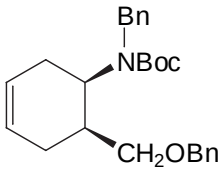
A cold (0°) soln. of **714** (27.6 g, 108 mmol) in THF (350 ml) was treated with $LiBH_4$ (3.5 g, 162 mmol), stirred at r.t. for 19 h. After cooling to 0°, the mixture was treated with sat. aq. NH_4Cl soln. (40 ml) and diluted with AcOEt (400 ml). The organic phase was separated, washed with sat. aq. $NaHCO_3$ soln. (2 x 400 ml), dried (Na_2SO_4), and evaporated. FC (125 g of silica gel, cyclohexane/AcOEt 3:1) gave colourless crystalline **715** (18.3 g, 74%). R_f (cyclohexane/AcOEt 3:1) 0.26. M.p. 105.0–105.9°. FT-IR (0.5%, $CHCl_3$): 3611*w*, 3435*w*, 2983*w*, 1684*m* (C=O), 1502*s*, 1368*m*, 1062*w*, 921*w*, 843*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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) (C*H*$_2$–OH);

2.44 (*dm*, $J \approx 18.0$, H–C(2)); 2.09 (*dm*, $J \approx 18$, 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*, Me_3C). ^{13}C-NMR (75 MHZ, $CDCl_3$): 157.26 (*s*, C=O); 126.45, 123.49 (2*d*, C(3), C(4)); 79.89 (*s*, Me_3C); 63.57 (*t*, CH_2OH); 43.26 (*d*, C(1)); 38.90 (*d*, (C(6)); 31.16 (*t*, C(5)); 28.39 (*q*, Me_3C); 23.40 (*t*, C(2)). EI-MS: 227 (0.1, M^+), 197 (1, [M – **H_2C=O]**$^+$), 173 (20, [M – C_4H_6]$^+$), 171 (20, [M – C_4H_8]$^+$), 154 (16), 153 (13, [M – C_4H_8 – H_2O]$^+$), 141 (6), 127 (7, [M – C_4H_8 – CO_2]$^+$), 117 (56, [M – C_4H_8 – C_4H_6]$^+$), 110 (26), 99 (27, [M – C_4H_8 – C_4H_6 – H_2O]$^+$), 93 (25), 92 (75), 73 (68, [M – C_4H_8 – C_4H_6 – CO_2]$^+$). Anal. calc. for $C_{12}H_{21}NO_3$ (227.30): C 63.41, H 9.31, N 6.16; found: C 63.60, H 9.16, N 6.11.

O-*tertButyl*-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 H_2O (2 x 500 ml), dried (Na_2SO_4), 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.

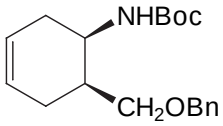
b) A cold (0°) soln. of **715** (380 mg, 1.67 mmol) in DMF (5 ml) was treated with NaH (88 mg of a 55% suspension in oil, 2.00 mmol), stirred for 30 min. at 0°, treated dropwise with BnBr (0.30 ml, 2.51 mmol), stirred for 5 min, allowed to warm to r.t., and stirred for 19 h. The mixture was cooled to 0°, treated with MeOH (0.15 ml), stirred at 0° for 30 min, diluted with AcOEt (50 ml), and washed with H_2O (2 x 30 ml). The organic phase was dried (Na_2SO_4) 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**:

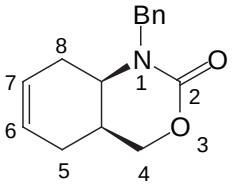
Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.74. FT-IR (3%, $CHCl_3$): 3089*w*, 3067*w*, 3030*m*, 3013*s*, 2980*m*, 2931*m*, 2862*m*, 1681*s*, 1496*m*, 1477*m*, 1454*s*, 1405*m*, 1392*m*, 1367*s*, 1351*m*, 1339*m*, 1272*m*, 1123*m*, 1076*m*, 1028*w*, 1012*w*, 971*w*, 904*w*, 884*w*, 857*w*, 853*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*N); 4.54–4.45 (*m*, H–C(1)); 4.51 (*d*, *J* = 11.8), 4.45 (*d*, *J* =11.8) (PhC*H*$_2$O); 4.29 (*d*, *J* = 16.8, PhC*H*'N); 3.64 (*dd*, *J* = 9.2, 4.8, C*H*–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*, Me$_3$C). ^{13}C-NMR (75 MHz, CDCl$_3$): 155.90 (*s*, C=O); 140.53, 138.42 (2*s*); 128.87–125.90 (several *d*); 125.77, 125.11 (2*d*, C(3), C(4)); 79.67 (*s*, Me$_3$*C*); 73.07, 70.26 (2*t*, Ph*C*H$_2$O, *C*H$_2$–C(6)); 52.54 (*d*, C(1)); 48.22 (*t*, Ph*C*H$_2$N); 37.77 (*d*, C(6)); 28.35 (*q*, *Me*$_3$C); 27.55 and 27.26 (2*t*, C(2), C(5)). ESI-MS: 837 (9, [2 *M* + Na]$^+$), 467 (25), 446 (7, [*M* + K]$^+$), 430 (46, [*M* + Na]$^+$), 408 (16, [*M* + 1]$^+$), 318 (26), 308 (14, [*M* + 1 – C$_4$H$_8$ – CO$_2$]$^+$).



Data of **716**:

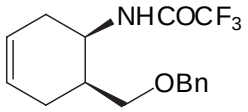
R$_f$ (cyclohexane/AcOEt 3:1) 0.66. M.p. 62.8–65.8. FT-IR (3%, CHCl$_3$): 3438*m* (NH), 3090*w*, 3067*w*, 3020*m*, 2981*m*, 2922*m*, 2866*m*, 1706*s* (C=O), 1501*s*, 1455*m*, 1392*m*, 1367*s*, 1337*w*, 1303*w*, 1118*m*, 1075*m*, 1029*w*, 1001*w*, 968*w*, 941*w*, 909*w*, 875*w*, 844*w*. ^{1}H-NMR (300 MHz, CDCl$_3$): 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 (2*d*, *J* = 11.8, PhC*H*$_2$); 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*, Me$_3$C). ^{13}C-NMR (75 MHz, CDCl$_3$): 155.56 (*s*, C=O); 138.23 (*s*);128.28 (*d*, 2 C);, 127.52 (*d*, 2 C), 127.47 (*d*); 125.55, 124.59 (2*d*, C(3), C(4)); 78.84 (*s*, Me$_3$*C*); 73.36, 72.05 (2*t*, Ph*C*H$_2$, *C*H$_2$–C(6)); 46.41 (*d*, C(1)); 36.48 (*d*, C(6)); 30.97 (*t*, C(5)); 28.55 (*q*, *Me*$_3$C); 26.33 (*t*, C(2)). ESI-MS: 657 (14, [2 *M* + Na]$^+$), 377 (6), 356 (4, [*M* + K]$^+$), 340 (36, [*M* + Na]$^+$), 318 (60, [*M* + 1]$^+$), 262 (13, [*M* + 1 – C$_4$H$_8$]$^+$), 218 (4, [*M* + 1 – C$_4$H$_8$ – CO$_2$]$^+$). Anal. calc. for C$_{19}$H$_{27}$NO$_3$ (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. *R*$_f$ (cyclohexane/AcOEt 3:1) 0.12. M.p. 79.8–81.6°. FT-IR (1.5%, CDCl$_3$): 3028*w*, 3015*m*, 2912*w*, 2851*w*, 1682*s* (C=O), 1604*w*, 1486*w*, 1451*m*, 1361*w*, 1129*m*, 1075*w*, 1035*w*, 963*w*. ^{1}H-NMR (300 MHz, CDCl$_3$): 7.38–7.24 (5 arom. H); 5.60–5.49 (*m*, H–C(6), H–C(7)); 5.03 (*d*, *J* = 15.3, PhC*H*); 4.27 (*t*, *J* = 11.4, H–C(4)); 4.19 (*d*, *J* = 15.3, PhC*H*'); 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)). ^{13}C-NMR (75 MHz, CDCl$_3$): 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 (2*d*, C(6), C(7)); 67.77 (*t*, C(4)); 50.87 (*t*, Ph*C*H$_2$); 50.80 (*d*, C(8a)); 29.90

(*d*, C(4a)); 27.31, 25.46 (2*t*, C(5), C(8)). EI-MS: 243 (23, M^+), 189 (17, $[M - C_4H_6]^+$), 150 (4), 144 (20), 128 (9), 91 (100, $[Bn]^+$).



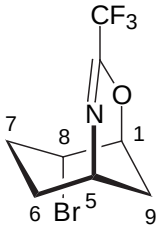
N-*(*cis-*6-[Benzyloxymethyl)-cyclohex-3-enyl]-2,2,2-trifluoroacetamide* (**72**).

A soln. of **716** (1 g, 3.15 mmol) in CH_2Cl_2 (25 ml) was treated with CF_3CO_2H (4 ml, 52 mmol), stirred at r.t. for 1.5 h, and evaporated. The soln. of the residue (milky oil) in CH_2Cl_2 (10 ml) was treated with Et_3N (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 (cyclohexane/AcOEt 3:1) 0.66. FT-IR (1%, $CHCl_3$): 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*, 849*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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 (2*d*, *J* = 11.5, PhC*H*$_2$); 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.10 (*s*); 128.41 (*d*, 2 C); 127.94 (*d*); 127.73 (*d*, 2 C); 124.91, 123.98 (2*d*, C(3), C(4)); 73.85, 71.51 (2*t*, Ph*C*H$_2$,*C*H$_2$–C(6)); 47.76 (*d*, C(1)); 34.94 (*d*, C(6)); 28.16, 27.37 (2*t*, C(2), C(5)); signals for $COCF_3$ hidden by noise. ^{19}F-NMR (282 MHz, $CDCl_3$): –76.14 (*s*). ESI-MS: 368 (7, $[M + Na + MeOH]^+$), 352 (18, $[M + K]^+$), 336 (100, $[M + Na]^+$), 314 (60, $[M + 1]^+$).

*(±)-(*1*R**,5*R**,8*R**)-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**).

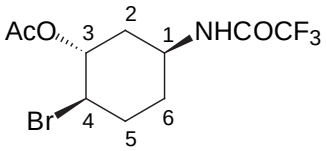
a) A soln. of **71** (210 mg, 1.09 mmol) in AcOH (10 ml) was treated with NBS (580 mg, 3.26 mmol), stirred at r.t. for 85 min., and evaporated. The residue, suspended in AcOEt (25 ml) was washed with sat. aq. $NaHCO_3$ soln. (20 ml) and brine (20 ml). The aq. phases were extracted with AcOEt (25 ml), and the combined organic phases were dried (Na_2SO_4) and evaporated. FC (15 g of silica gel, 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. $NaHCO_3$ soln. (20 ml) and brine (20 ml), dried (Na_2SO_4), 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**:

*R*f (cyclohexane/AcOEt 3:1) 0.68. FT-IR (1.5%, $CHCl_3$): 2953*w*, 1788*w*, 1686*m*, 1443*w*, 1391*w*, 1369*w*, 1349*m*, 1332*w*, 1288*m*, 1159*s*, 1124*s*, 1114*m*, 1090*w*, 1051*m*, 1021*m*, 981*w*, 903*w*, 851*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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), CH_2(7)); 1.77 (*dtt*, *J* = 14.0, 3.7, 1.9, H'–C(9)). ^{13}C-NMR (75 MHz, $CDCl_3$): 74.47 (*d*, C(1)); 48.17, 46.73 (2*d*, C(5), C(8)); 25.02, 24.90, 22.85 (3*t*, C(6), C(7), C(9)); *q* for CF_3CO hidden by noise. ESI-MS: 196 (10), 194 (10, $[M - CCF_3 + 4\ H]^+$); 87 (100).



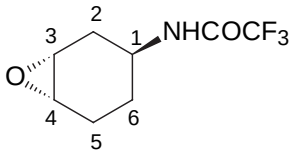
Data of **721**:

*R*f (cyclohexane/AcOEt 3:1) 0.49. FT-IR (1.5%, $CHCl_3$): 3426*w* (NH), 3034*w*, 3008*w*, 2959*w*, 1727*s* (C=O), 1537*m*, 1457*w*, 1436*w*, 1374*m*, 1260*m*, 1095*w*, 1063*w*, 1036*m*, 1018*m*, 983*w*, 909*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.89 (*s*, *C*OMe); 156.85 (*q*, *J* = 37.6, *C*OCF_3); 115.91 (*q*, *J* = 289.3, CF_3); 71.96 (*d*, C(3)); 47.53, 44.75 (2*d*, C(1), C(4)); 30.81, 28.43, 26.55 (3*t*, C(2), C(5), C(6)); 21.07 (*q*, Me). ^{19}F-NMR (282 MHz, $CDCl_3$): –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 (±)-(*1*R**,5*R**,8*R**)-*3-Trifluoromethyl-2-oxa-4-azabicyclo[3.3.1]non-3-en-8-ol* (**723**).

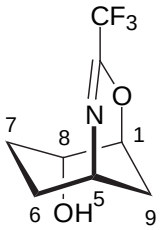
a) A cold (0°) soln. of **721** (17 mg, 51 μmol) in THF (1.5 ml) was treated with NaH (3.7 mg of a 50% suspension in oil, 77 μmol), stirred at 0° for 1 h, stirred for 20 h while warming to r.t., and poured into H_2O (10 ml). The mixture was extracted with CH_2Cl_2 (4 x 15 ml). The combined organic phases were dried (Na_2SO_4), 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 H_2O (0.2 ml) with K_2CO_3 (30 mg, 217 μmol).



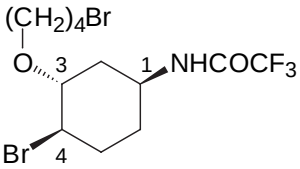
Data of **722**:

*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, –> *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 (*ddd*, *J* = 14.6, 8.6, 2.7, H'–C(2)); 1.38 (*dtd*, *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_3CO 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**:

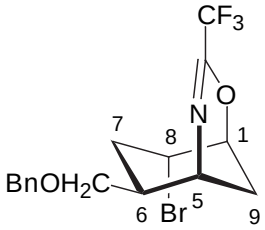
*R*f (cyclohexane/AcOEt 1:1) 0.47. FT-IR (0.5%, $CHCl_3$): 3618*w* (OH), 2998*w*, 2948*w*, 1689*m*, 1446*w*, 1393*w*, 1322*w*, 1290*m*, 1262*w*, 1153*s*, 1100*s*, 1080*m*, 1023*m*, 1004*m*, 970*w*, 936*w*, 851*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.59–4.55 (*m*, H–C(1)); 4.18–4.13 (*m*, H–C(8)); 3.90–3.84 (*m*, H–C(5)); 2.26 (*dt*, *J* = 14.0, 1.5, H–C(9)); 2.02 (*tdd*, *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 (3*t*, C(6), C(7), C(9)). ^{19}F-NMR (282 MHz, $CDCl_3$): –73.43 (*s*). EI-MS: 209 (24, $[M]^+$); 153 (99, $[M - 56]^+$).



N-*[*c-*4-Bromo*-t-*3-(4-bromobutoxy)-cyclohexyl]-2,2,2-trifluoroacetamide* (**719**).

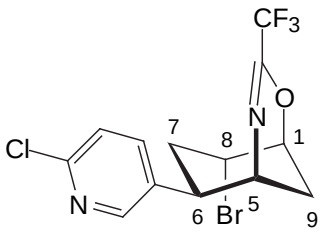
A cold (0°) soln. of **71** (59 mg, 0.33 mmol) in THF (2 ml) was treated with NBS (29 mg, 0.16 mmol) and stirred for 25 h while allowed to warm to r.t. The mixture was diluted with Et_2O (10 ml), washed with sat. aq. $Na_2S_2O_5$ soln. (3 x 10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated. 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_f (toluene/AcOEt 10:1) 0.58. FT-IR (1.5%, $CHCl_3$): 3428*w* (NH), 2953*w*, 1725*s* (C=O), 1536*m*, 1435*w*, 1384*w*, 1357*w*, 1097*m*, 968*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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) (CH_2(1'), CH_2(4')); 2.30 (*ddt*, *J* = 15.4, 12.1, 3.5, H–C(5)); 2.10–1.65 (*m*, CH_2(2), H'–C(5), CH_2(6), CH_2(2'), CH_2(3')). ^{13}C-NMR (75 MHz, $CDCl_3$): 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')). ^{19}F-NMR (282 MHz, $CDCl_3$): –75.74 (*s*). ESI-MS: 482 (7), 480 (13), 478 (7, $[M + Na + MeOH]^+$); 466 (20), 464 (37), 462 (18, $[M + K]^+$); 450 (50), 448 (100), 446 (51, $[M + Na]^+$).



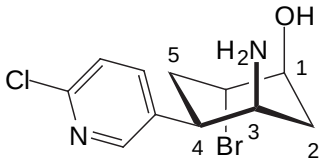
*(±)-(1*R*,5*S*,6*R*,8*R*)-6-(Benzyloxymethyl)-8-bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene* (**724**).

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. $NaHCO_3$ soln. (20 ml) and brine (20 ml). The aq. phases were extracted with AcOEt (20 ml). The combined organic phases were dried (Na_2SO_4), 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_f (cyclohexane/AcOEt 3:1) 0.68. FT-IR (0.5%, $CHCl_3$: 3008*w*, 2927*m*, 2857*w*, 1728*w*, 1688*m*, 1602*w*, 1454*w*, 1442*w*, 1390*w*, 1362*w*, 1166*s*, 1130*s*, 1110*m*, 1076*m*, 1040*w*, 914*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.26 (5 arom. H); 4.74–4.69 (*m*, H–C(1)); 4.57 (*d*, *J* = 11.8, PhC*H*); 4.51–4.47 (*m*, H–C(8)); 4.49 (*d*, *J* = 11.8, PhC*H*); 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, H_{ax}–C(9)); 2.12 (br. *dd*, *J* = 15.9, 2.5, H_{eq}–C(7)); 1.83 (*dtd*, *J* = 14.3, 3.9, 1.6, H_{eq}–C(9)); 1.57 (*ddd*, *J* = 15.9, 12.1, 4.0, H_{ax}–C(7)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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, CF_3); 74.33 (*d*, C(1)); 73.28 (*t*, Ph*C*H_2); 71.34 (*t*, *C*H_2–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)). ^{19}F-NMR (282 MHz, $CDCl_3$): –73.10 (*s*). HR-MS (MALDI): 412 (86), 410.0578 (100) ($C_{16}H_{20}BrF_3NO_3^+$ [*M* + H_3O]$^+$; calc. 410.0579); 394 (1); 392.0475 (1) ($C_{16}H_{18}BrF_3NO_2^+$, $[M + 1]^+$; calc. 392.0473); 316 (16), 314 (16, $[M + 4 – CF_3C]^+$); 312 (14), 310 (14); 298 (6), 296 (6, $[M + 2 – COCF_3]^+$).



*(±)-(*1R*,5S*,6S*,*8*R**)-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. $NaHCO_3$ soln. (20 ml) and brine (20 ml), dried (Na_2SO_4), 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. R_f (toluene/AcOEt 10:1) 0.42. FT-IR(1%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, CH_2(7)); 1.95 (*dtd*, *J* = 14.3, 4.0, 1.6, H'–C(9)). ^{13}C-NMR (75 MHz, $CDCl_3$): 150.54 (*s*); 149.54 (*d*); 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 (2*t*, C(7), C(9)); 2 *q* for CF_3CO hidden by noise. ^{19}F-NMR (282 MHz, $CDCl_3$): –73.54 (*s*).



Hydrolysis of **725** to c-*3-Ammonia*-t-*6-bromo*-c-*3-(6-chloro-3-pyridinium)-cyclohexane trifluoroacetamide* **726**·CF_3COOH.

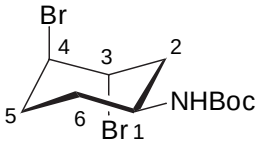
A soln. of **725** (5.6 mg, 14.6 μmol) in THF (1 ml) and H_2O (0.33 ml) was treated with CF_3COOH (1 drop), stirred at r.t. for 50 min, and evaporated. The residue was coevaporated with MeOH to yield crude **726**·CF_3COOH (7.8 mg, quant.) as a colourless oil. R_f (CH_2Cl_2/MeOH 9:1) 0.40. ^{1}H-NMR (300 MHz, D_2O): 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 –> *t*, *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)). ^{13}C-NMR (75 MHz, D_2O): 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)). ^{19}F-NMR (282 MHz, D_2O): –76.08 (*s*). HR-MS (MALDI): 425 (24), 423

(23); 402 (22); 380 (28); 307 (38), 305.0044 (33) ($C_{11}H_{15}BrClN_2O^+$, $[M + 1]^+$; calc. 305.0056).

O-*tertButyl* N-*(*t-*3*,c-*4-dibromocyclohexyl)carbamate* (**728**) *and* O-*tertButyl* N-*(*c-*3*,t-*4-dibromocyclohexyl)carbamate* (**727**).

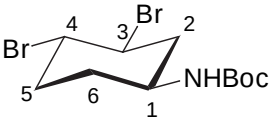
Method A)

A solution of **712** (849 mg, 4.3 mmol) in CH_2Cl_2 (50 ml) was treated with Et_4NBr (9.0 g, 43 mmol) at r.t., cooled to –78°, treated with Br_2 (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. $Na_2S_2O_5$ soln. (50 ml). The mixture was extracted with AcOEt (4 x 50 ml), and the combined organic phases dried (Na_2SO_4) 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. R_f (cyclohexane/AcOEt 3:1) 0.67. M.p. 105–106°. FT-IR (1.5%, $CHCl_3$): 3442*m* (NH), 3008*m*, 2980*m*, 1709*s* (C=O), 1503*s*, 1454*w*, 1435*w*, 1392*w*, 1368*m*, 1323*w*, 1310*w*, 1280*w*, 1166*s*, 1045*m*, 1031*w*, 1018*m*, 958*w*, 906*w*, 867*w*. 4.64–4.60, 4.60–4.55 (2*m*, H–C(3), H–C(4)); 4.53–4.43 (br. *s*, NH); 4.07–3.92 (br. *s*, H–C(1)); 2.55 (*ddt*, *J* = 15.6, 12.1, 3.4, H–C(5)); 2.33–2.18 (*m*, 2 H); 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*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.30 (*s*, C=O); 79.66 (*s*, Me_3C); 52.36, 51.79 (2*d*, C(3), C(4)); 44.95 (*d*, C(1)); 35.24 (*t*, C(2)); 28.45 (*q*, *Me*$_3$C); 28.38, 27.59 (2*t*, 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. R_f (cyclohexane/AcOEt 3:1) 0.60. M.p. 128–129°. FT-IR (1.5%, $CHCl_3$): 3441*w* (NH), 3008*m*, 2980*m*, 1708*s* (C=O), 1501*s*, 1449*w*, 1392*w*, 1368*m*, 1337*w*, 1313*m*, 1274*m*, 1164*s*, 1076*w*, 1045*m*, 1012*w*, 949*w*, 917*w*, 860*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, HW_{50} ≈ 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*, Me_3C); 1.38–1.21 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.13 (*s*, C=O); 79.91 (*s*, *Me*$_3$*C*); 55.33, 53.44 (2*d*, C(3), C(4)); 48.18 (*d*, C(1)); 42.99 (*t*, C(2)); 34.33, 32.12 (2*t*, C(5), C(6)); 28.43 (*q*, *Me*$_3$C). ESI-MS: 414

(53), 412 (100), 410 (56, [*M* + Na + MeOH]$^+$); 336 (37), 334 (78), 332 (36). Anal. calc. for $C_{11}H_{19}Br_2NO_2$ (357.08): C 37.00, H 5.36, N 3.92; found: C 37.25, H 5.31, N 3.85.

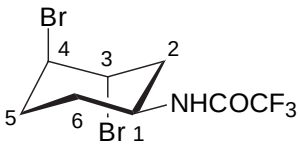
N-*(*t-*3*,c-*4-Dibromocyclohexyl)-2,2,2-trifluoroacetamide* (**730**) *and* N-*(*c-*3*,t-*4-Dibromocyclohexyl)-2,2,2-trifluoroacetamide* (**729**).

Method B)

At 0°, a solution of **71** (11.61 g, 60.1 mmol) in CH_2Cl_2 (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. $Na_2S_2O_5$ soln. (600 ml). The aqueous phase was extracted with AcOEt (2 x 500 ml), and the combined organic phases were dried (Na_2SO_4) and evaporated. FC (200 g of silica gel, cyclohexane/AcOEt 12:1) gave **730** (3.27 g, 15%) and **729** (16.79 g, 79%).

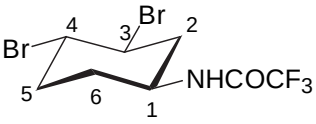
Method A)

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. R_f (cyclohexane/AcOEt 3:1) 0.59. M.p. 114–115°. FT-IR (1.5%, $CHCl_3$): 3426*m* (NH), 3011*w*, 2957*w*, 1728*s* (C=O), 1536*m*, 1454*w*, 1436*w*, 1385*w*, 1339*w*, 1298*w*, 1278*w*, 1259*m*, 1171*s*, 1027*w*, 962*w*, 899*w*, 849*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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 (*dddd*, *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 (d*m*, *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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 51.30, 50.58 (2*d*, C(3), C(4)); 44.83 (*d*, C(1)); 33.82 (*t*, C(2)), 27.81, 26.49 (2*t*, 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 $C_8H_{10}Br_2NOF_3$ (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. R_f (cyclohexane/AcOEt 3:1) 0.48. M.p. 99–100°. FT-IR (1.5%, $CHCl_3$): 3426*w* (NH), 3400*w*, 3008*w*, 2957*w*, 2862*w*, 1727*s* (C=O), 1535*m*, 1448*w*, 1438*w*, 1424*w*, 1381*w*, 1344*w*, 1293*w*, 1263*m*, 1170*s*, 1082*w*, 997*w*, 950*w*, 928*w*, 878*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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,

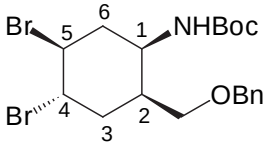
H–C(1)); 2.80 (*dtd*, *J* = 14.0, 4.1, 1.6, H–C(2)); 2.51 (*ddt*, *J* = 14.6, 7.2, 3.4, H–C(5)); 2.16–1.91 (*m*, H–C(6), H'–C(2), H'–C(5)); 1.65–1.53 (*m*, H'–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.77 (*q*, *J* = 37, C=O); 115.89 (*q*, *J* = 288, *C*F_3); 53.54, 51.66 (2*d*, C(3), C(4)); 46.61 (*d*, C(1)); 38.20 (*t*, C(2)), 30.84, 28.85 (2*t*, 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 $C_8H_{10}Br_2NOF_3$ (352.98): C 27.22, H 2.86, N 3.97; found: C 27.34, H 2.50, N 3.91.

O-*tertButyl*-N-*[*c-*2-(benzyloxymethyl)*-t-*4*,c-*5-dibromo-cyclohexyl]carbamate* (**731**), O-*tertButyl*-N-*[*c-*2-(benzyloxymethyl)*-c-*4*,t-*5-dibromo-cyclohexyl]carbamate* (**732**), *(±)-(1*R*,*2*S*,*4*S*,*5*S**)-4-Bromo-2-[(*tert-*butyloxy)carbonylamino]-6-oxabicyclo[3.2.1]octane* (**734**), and *(±)-(1*R*,*5*S*,*6*R*,*8*R**)-6-(Benzyloxymethyl)-8-bromo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one* (**733**)

a) At 0°, soln. of **716** (130 mg, 0.41 mmol) in CH_2Cl_2 (10 ml) was treated with $PhMe_3NBr_3$ (310 mg, 0.82 mmol), stirred for 160 min., treated with sat. aq. $Na_2S_2O_5$ soln. (20 ml), and extracted with Et_2O (2 x 20 ml). The combined organic phases were dried (Na_2SO_4) 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 CH_2Cl_2 (10 ml) was treated with Br_2 (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%).

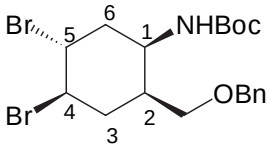
c) At –78°, a suspension of **716** (2.0 g, 6.5 mmol) and Et_4NBr (13.2 g, 63 mmol) in CH_2Cl_2 (20 ml) was treated with $PhMe_3NBr_3$ (4.79 g, 12.6 mmol), and allowed to warm to r.t. within 20 h. Workup as described in a) and FC (100 g of silica gel, cyclohexane/AcOEt 10:1) gave **731** (2.48 g, 82%) as colourless crystals.



Data of **731**:

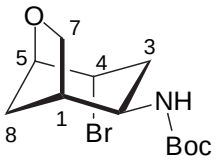
Colourless crystals. R_f (toluene/AcOEt 10:1) 0.58. M.p.: 117° (decomp.). FT-IR (2%, $CHCl_3$): 3433*w* (NH), 3020*m*, 2981*m*, 2932*w*, 2868*w*, 1707*s* (C=O), 1502*s*, 1455*m*, 1393*m*, 1377*m*, 1323*w*, 1280*w*, 1090*m*, 1040*w*, 1028*w*, 981*w*, 857*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39–7.26 (5 arom. H); 5.60 (br. *d*, *J* = 8.1, NH); 4.54, 4.46 (2*d*, *J* = 11.8, PhC*H*$_2$); 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*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.07 (*s*, C=O);

137.65 (*s*); 128.41 (*d*, 2 C); 127.34 (*d*); 127.58 (*d*, 2 C); 79.35 (*s*, Me_3C); 73.46 (*t*, PhCH_2); 70.69 (*t*, CH_2–C(2)); 53.06, 52.06, 48.33 (3*d*, C(1), C(4), C(5)); 36.43 (*d*, C(2)); 28.54 (*q*, Me_3C); 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, $[M + Na - C_4H_8]^+$); 380 (5), 378 (10), and 376 (7, $[M + 1 - C_4H_8 - CO_2]^+$). Anal. calc. for $C_{19}H_{27}Br_2NO_3$ (477.24): C 47.82, H 5.70, N 2.93; found: C 47.94, H 5.76, N 2.86.



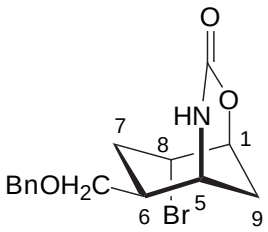
Data of **732**:

Colourless oil. R_f (toluene/AcOEt 10:1) 0.56. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.12 (5 arom. H); 5.21 (br. *s*, NH); 4.49 (*d*, *J* = 12.1), 4.44 (*d*, *J* = 11.8) (PhCH_2); 4.26–4.05 (*m*, 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)); 2.79 (br. *d*, *J* = 14.0, 1 H); 2.58–2.39 (*m*, 2 H); 2.09–1.96 (*m*, 2 H); 1.46 (*s*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 155.32 (C=O); 137.48; 128.35 (2 C); 127.73; 127.61 (2 C); 80.35 (Me_3C); 73.59 (PhCH_2); 71.56 (CH_2–C(2)); 52.78, 49.67, 48.54 (C(1, C(4), C(5)); 40.62 (C(2); 35.86; 28.47 (Me_3C); 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. R_f (toluene/AcOEt 10:1) 0.25. M.p.: 153.3–155.0. FT-IR (1%, $CHCl_3$): 3445*w* (NH), 3031*w*, 3011*m*, 2981*m*, 2885*w*, 1711*s* (C=O), 1501*s*, 1454*w*, 1393*w*, 1368*m*, 1326*w*, 1278*m*, 1087*w*, 1053*m*, 1030*m*, 1000*w*, 971*w*, 945*w*, 923*w*, 883*w*, 859*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, $HW_{50} \approx 20$ Hz, H–C(2)); 3.86 (*d*, *J* = 8.7, H_{endo}–C(7)); 3.79 (*dd*, *J* = 8.7, 4.0, H_{exo}–C(7)); 2.59–2.54 (*m*, H–C(1)); 2.52 (*d*, *J* = 12.8, H_{ax}–C(8)); 2.20 (*dd*, *J* = 15.1, 5.5, irr. at 3.99 –> *d*, *J* = 15.1, H_{eq}–C(3)); 1.97 (*ddd*, *J* = 14.9, 12.1, 5.3, irr. at 3.99 –> *dd*, *J* = 14.9, 5.3, H_{ax}–C(3)); 1.87 (*dtd*, *J* = 12.5, 5.6, 1.2, H_{eq}–C(8)); 1.43 (*s*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 154.70 (*s*, C=O); 79.71 (*s*, Me_3C); 77.11 (*d*, C(5)); 68.52 (*t*, C(7)); 47.80, 47.47 (2*d*, C(2), C(4)); 40.37 (*d*, C(1)); 34.54, 31.94 (2*t*, C(3), C(8)); 28.43 (*q*, Me_3C).ESI-MS: 356 (100); 346 (12), 344 (12, $[M + K]^+$); 330 (37), 328 (29, $[M + Na]^+$).



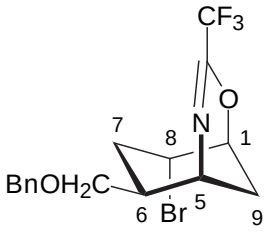
Data of **733**:

Yellow amorphous. R_f (toluene/AcOEt 10:1) 0.02. M.p.: 136–141°. 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*. ^{1}H-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, PhC*H*); 4.50–4.46 (*m*, H–C(8)); 4.45 (*d*, *J* = 12.1, PhC*H*'); 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'–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 (*dtd*, *J* = 14.0, 4.0, 1.6, irr. at 4.48 –> *dt*, H_{eq}–C(9)); 1.97–1.90 (*m*, CH_2(7)). ^{13}C-NMR (75 MHz, $CDCl_3$): 153.72 (*s*, C=O); 137.80 (*s*); 128.45 (*d*, 2 C); 127.82 (*d*); 127.34 (*d*, 2 C); 75.49 (*d*, C(1)); 73.30 (*t*, Ph*C*H_2); 70.35 (*t*, *C*H_2–C(6)); 47.68, 46.00 (2*d*, C(5), C(8)); 36.92 (*d*, C(6)); 28.19, 24.30 (2*t*, 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, $[M + 1 - CO_2]^+$).

*(±)-(1*R*,*5*S*,*6*R*,*8*R*)*-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**).

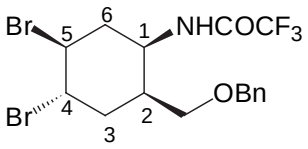
a) A cold (0°) soln. of **72** (31 mg, 98.9 μmol) in CH_2Cl_2 (1 ml) was treated with Et_4NBr (208 mg, 989 μmol) and $PhMe_3NBr_3$ (75 mg, 198 μmol), stirred for 1 h, and treated with sat. aq. $Na_2S_2O_5$ soln. (2 ml). The mixture was extracted with Et_2O (2 x 20 ml), and the combined organic phases were dried (Na_2SO_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°, a solution of **72** (52.5 mg, 167 μmol) in CH_2Cl_2 (2 ml) was treated with Br_2 (25 μl, 502 μmol), stirred for 1 h, and treated with sat. aq. $Na_2S_2O_5$ soln. (15 ml). The mixture was extracted with Et_2O (2 x 20 ml), and the combined organic phases were dried (Na_2SO_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.



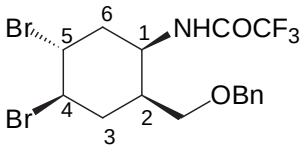
Data of **724**:

*R*f (cyclohexane/AcOEt 3:1) 0.68. FT-IR (0.5%, $CHCl_3$: 3008*w*, 2927*m*, 2857*w*, 1728*w*, 1688*m*, 1602*w*, 1454*w*, 1442*w*, 1390*w*, 1362*w*, 1166*s*, 1130*s*, 1110*m*, 1076*m*, 1040*w*, 914*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.26 (5 arom. H); 4.74–4.69 (*m*, H–C(1)); 4.57 (*d*, *J* = 11.8, PhC*H*); 4.51–4.47 (*m*, H–C(8)); 4.49 (*d*, *J* = 11.8, PhC*H*); 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, H_{ax}–C(9)); 2.12 (br. *dd*, *J* = 15.9, 2.5, H_{eq}–C(7)); 1.83 (*dtd*, *J* = 14.3, 3.9, 1.6, H_{eq}–C(9)); 1.57 (*ddd*, *J* = 15.9, 12.1, 4.0, H_{ax}–C(7)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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, CF_3); 74.33 (*d*, C(1)); 73.28 (*t*, Ph*C*H_2); 71.34 (*t*, *C*H_2–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)). ^{19}F-NMR (282 MHz, $CDCl_3$): –73.10 (*s*). HR-MS (MALDI): 412 (86), 410.0578 (100) ($C_{16}H_{20}BrF_3NO_3^+$ [*M* + H_3O]$^+$; calc. 410.0579); 394 (1); 392.0475 (1) ($C_{16}H_{18}BrF_3NO_2^+$, [*M* + 1]$^+$; calc. 392.0473); 316 (16), 314 (16, [*M* + 4 – CF_3C]$^+$); 312 (14), 310 (14); 298 (6), 296 (6, [*M* + 2 – $COCF_3$]$^+$).



Data of **735**:

*R*f (toluene/AcOEt 10:1) 0.62. FT-IR (0.5%, $CHCl_3$): 3389*w* (NH), 3339*w* (NH), 2928*w*, 2857*w*, 1722*s*, 1603*w*, 1541*m*, 1452*w*, 1427*w*, 1369*w*, 1292*w*, 1278*w*, 1102*w*, 1091*w*, 1027*w*, 987*w*, 929*w*, 906*w*, 856*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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) (PhCH_2); 4.48–4.41, 4.41–4.33, 4.33–4.24 (3*m*, 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 (*ddd*, *J* = 14.3, 8.3, 3.6, H–C(3)); 2.30 (*dt*, *J* = 14.9, 7.1, H'–C(6)); 2.06 (*ddd*, *J* = 13.7, 7.8, 2.8, H'–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.85 (*q*, *J* = 36.6, C=O); 137.07; 128.83 (2 C); 128.43; 128.16 (2 C); CF_3 hidden by noise; 74.10 (Ph*C*H_2); 70.88 (*C*H_2–C(2)); 52.18 (C(1)); 50.71, 48.55 (C(4), C(5)); 35.58 (C(2)); 27.13 (C(3), C(6)). ^{19}F-NMR (282 MHz, $CDCl_3$): –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]$^+$).



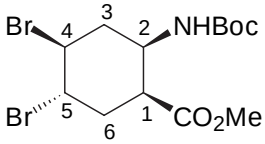
Data of **736** :

*R*f (cyclohexane/AcOEt 3:1) 0.51. FT-IR (1%, $CHCl_3$): 3331*w* (NH), 3033*w*, 3013*w*, 2868*w*, 1725*s* (C=O), 1539*m*, 1455*w*, 1366*w*, 1283*w*, 1102*m*, 1072*w*, 1028*w*, 895*w*. ^{1}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_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. *ddd*, *J* ≈ 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 (*ddd*, *J* = 14.6, 10.0, 3.6, H'–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 136.39; 128.54 (2 C); 128.23; 127.95 (2 C); 74.02 (Ph*C*H_2); 71.86 (*C*H_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)); $COCF_3$ signals hidden by noise. ^{19}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, $[M + Na]^+$).

Methyl-c-*4*,t-*5-dibromo*-c-*2-(tertbutoxycarbonylamino)-cyclohexanecarboxylate* (**737**), *Methyl*-t-*4*,c-*5-dibromo*-c-*2-(tertbutoxycarbonylamino)-cyclohexanecarboxylate* (**738**), and *Methyl (±)-(1*R**,5*S**,6*R**,8*R**)-8-Bromo-3-oxo-2-oxa-4-aza-bicyclo[3.3.1]nonane-6-carboxylate* (**739**)

a) At 0°, a suspension of **714** (110 mg, 0.43 mmol) and Et_4NBr (905 mg, 4.3 mmol) in CH_2Cl_2 (1 ml) was treated with $PhMe_3NBr_3$ (323 mg, 0.86 mmol), stirred for 2 h, treated with sat. aq. $Na_2S_2O_5$ soln. (10 ml), and extracted with Et_2O (2 x 10 ml). The combined organic phases were dried (Na_2SO_4) and evaporated. FC (12 g of silica gel, cyclohexane/AcOEt 9:1) gave **737** (151 mg, 84%) and **738** (11 mg, 6%).

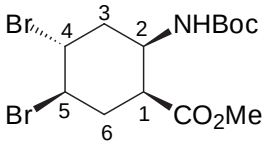
b) At –78°, a solution of **714** (210 mg, 0.795 mmol) in CH_2Cl_2 (2 ml) was treated with Br_2 (0.2 ml, 3.9 mmol), stirred for 75 min, treated with sat. aq. $Na_2S_2O_5$ soln. (10 ml), and warmed to 0°. Workup as described in a) and FC (50 g of silica gel, cyclohexane/AcOEt 9:1) of the residue (293 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**:

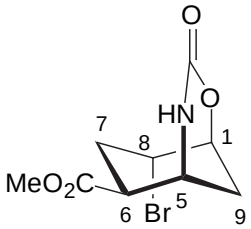
Colourless crystals. *R*f (toluene/AcOEt 10:1) 0.47. M.p.: 148.8–150.0°. FT-IR (0.5%, $CHCl_3$): 3437*w* (NH), 3019*s*, 2980*w*, 2952*w*, 1728*s* (C=O), 1709*s* (C=O), 1602*w*, 1499*s*, 1446*w*, 1367*m*, 1309*m*, 1065*w*, 1012*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.50 (br. *d*, *J* = 9.3,

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 (*ddd*, *J* = 14.3, 9.3, 4.7, H'–C(6)); 1.40 (*s*, $C(CH_3)_3$). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.30 (*s*, CO_2Me); 154.70 (*s*, CO_2CMe_3); 79.77 (*s*, Me_3C); 52.27 (*q*, OCH_3); 52.02 (*d*, C(2)); 47.84, 43.37 (2*d*, C(4), C(5)); 38 (br. *d*, C(1)); 28.39 (*q*, Me_3C) (the C(3) and C(6) *t* are hidden, presumably under the Me_3C *q*). ESI-MS: 418 (45), 416 (100), 414 (52, $[M + 1]^+$); 362 (14), 360 (32), 358 (15, $[M + 1 - C_4H_8]^+$).



Data of **738**:

Colourless crystals. R_f (toluene/AcOEt 10:1) 0.43. M.p.: 101.5–109.0. FT-IR (0.5%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$):155.20 (CO_2CMe_3) (one signal hidden by noise); 79.94 (Me_3C); 52.46 (MeO); 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 (Me_3C). 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, $[M + 1 - C_4H_8]^+$); 318 (5), 316 (9), 314 (5, $[M + 1 - C_4H_8 - CO_2]^+$).

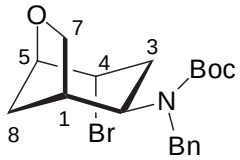


Data of **739**:

Yellowish, amorphous. R_f (cyclohexane/AcOEt 3:1) 0.0. mp.: 190–197° (dec.). FT-IR (1.5%, $CHCl_3$): 3438*w* (NH), 3025*w*, 3011*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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, H_{ax}–C(9)); 2.43–2.37 (*m*, CH_2(7)); 2.10 (*dtd*, *J* = 14.3, 4.1, 1.6, H_{eq}–C(9)). ESI-MS$^+$: 329 (33), 327 (34, $[M + MeOH + NH_4]^+$); 312 (19), 310 (18, $[M + MeOH + 1]^+$); 280 (100), 278 (80, $[M + 1]^+$).

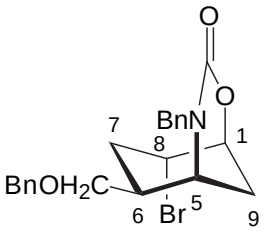
*(±)-(1*R*,2*S*,4*S*,5*S*)-2-{*N*-[(tert-Butyloxy)carbonyl]benzylamino}-4-bromo-6-oxabicyclo[3.2.1]octane* (**741**) *and (±)-(1*R*,5*S*,6*R*,8*R*)-4-Benzyl-6-(benzyloxymethyl)-8-bromo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one* (**740**).

At –78°, a soln. of **718** (30 mg, 73 μmol) in CH_2Cl_2 (3 ml) was treated with Br_2 (7.5 μl, 146 μmol), stirred for 3 h, and treated with sat. aq. $Na_2S_2O_5$ soln. The mixture was extracted with Et_2O (2 x 20 ml). The combined organic phases were dried (Na_2SO_4) 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**:

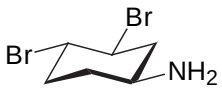
R_f (cyclohexane/AcOEt 3:1) 0.49. FT-IR (1.5%, $CHCl_3$): 3027*w*, 3013*m*, 2979*m*, 2887*w*, 1683*s* (C=O), 1604*w*, 1496*w*, 1478*w*, 1454*m*, 1392*m*, 1381*m*, 1367*m*, 1353*m*, 1330*w*, 1313*w*, 1120*w*, 1082*w*, 1055*m*, 1035*m*, 1019*w*, 974*w*, 955*w*, 929*w*, 882*w*, 864*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.34–7.11 (5 arom H); 4.57 (*d*, *J* = 17.1, PhC*H*); 4.57–4.49 (*m*, H–C(2)); 4.49 (*d*, *J* = 16.8, PhC*H*'); 4.24 (*t*, *J* = 5.0, H–C(5)); 4.16–4.12 (*m*, H–C(4)); 3.86 (*d*, *J* = 8.7, H_{endo}–C(7)); 3.64 (*dd*, *J* = 9.0, 4.1, H_{exo}–C(7)); 2.55 (*d*, *J* = 12.5, H_{ax}–C(8)); 2.54–2.48 (*m*, H–C(1)); 2.43 (br. *td*, *J* = 13.2, 5.1, H_{ax}–C(3)); 1.99 (br. *dd*, *J* = 14.5, 4.8, H_{eq}–C(3)); 1.84 (*dtd*, *J* = 12.5, 5.4, 1.6, H_{eq}–C(8)); 1.45 (*s*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 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*, Me_3C); 77.23 (*d*, C(5)); 69.61 (*t*, C(7)); 53.04 (*d*, C(2); 48.58 (*d*, C(4)); 47.12 (*t*, Ph*C*H_2); 40.63 (*d*, C(1)); 34.00, 32.66 (2*t*, C(3), C(8)); 28.46 (*q*, *Me*$_3$C). ESI-MS: 817 (10), 815 (15), 813 (9, [2 *M* + 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 – C_4H_8]$^+$).



Data of **740**:

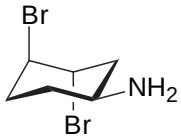
R_f (cyclohexane/AcOEt 3:1) 0.21. FT-IR (0.5%, $CHCl_3$): 3014*w*, 2952*w*, 2862*w*, 1687*s* (C=O), 1604*w*, 1496*w*, 1450*m*, 1362*w*, 1309*w*, 1123*m*, 1106*m*, 1074*w*, 1046*w*, 1001*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.42–7.19 (10 arom. H); 5.27 (*d*, *J* = 14.9, PhC*H*N); 4.64 (br. *t*, *J* = 3.4, H–C(1)); 4.67 (*s*, PhCH_2O); 4.51–4.47 (*m*, H–C(8)); 3.80–3.76 (*m*, H–C(5)); 3.76 (*d*, *J* =

14.9, PhC*H*'N); 3.42–3.37 (*m*, CH_2–C(6)); 2.50–2.42 (*m*, H–C(6)); 2.43 (*ddd*, *J* = 14.0, 2.2, 1.6 H_{ax}–C(9)); 1.98 (*ddd*, *J* = 15.6, 12.1, 4.0, H_{ax}–C(7)); 1.88 (*dm*, *J* = 15.9, H_{eq}–C(7)); 1.74 (*dtd*, *J* = 14.0, 4.0, 1.6, H_{eq}–C(9)). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.61, 137.24 (2*s*); 128.84, 128.40, 128.30, 128.22, 127.94 (5*d*); 76.03 (*d*, C(1)); 73.61 (*t*, Ph*C*H_2O); 70.49 (*t*, *C*H_2–C(6)); 52.92 (*t*, Ph*C*H_2N); 49.26, 47.73 (2*d*, C(5), C(8)); 37.19 (*d*, C(6)); 28.39, 25.73 (2 *t*, C(7), C(9)). ESI-MS: 901 (4), 899 (8), 897 (3, $[2\,M + K]^+$); 885 (59), 883 (100), 881 (49, $[2\,M + Na]^+$); 486 (10), 484 (9, $[M + Na + MeOH]^+$); 470 (27), 468 (23, $[M + K]^+$); 454 (92), 452 (95, $[M + Na]^+$); 432 (7), 430 (6, $[M + 1]^+$).



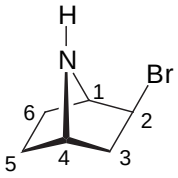
c-*3*,t-*4*-*Dibromocyclohexylamine* (**742**).

At r.t, a solution of **727** (350 mg, 0.98 mmol) in CH_2Cl_2 (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. K_2CO_3 soln. (15 ml), was extracted with $CHCl_3$ (4 x 40 ml), and the combined organic phases were dried (K_2CO_3), and evaporated to yield crude **742** (266 mg, 100%). Colourless oil. R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.49. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.06, 3.98 (2*td*, *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). ^{13}C-NMR (75 MHz, $CDCl_3$): 56.29, 54.57 (2*d*, C(3), C(4)); 50.03 (*d*, C(1)); 47.75 (*t*, C(2)), 35.97, 35.89 (2*t*, C(5), C(6)). ESI-MS: 260 (46), 258 (100), 256 (51, $[M + 1]^+$); 178 (50), 176 (53, $[M - Br]^+$).



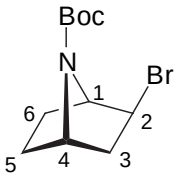
t-*3*,c-*4*-*Dibromocyclohexylamine* (**747**).

According to the preparation of **742**, **728** (295 mg, 0.826 mmol) yielded **747** (226 mg, quant.) as a colourless oil. R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.47. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, H_{ax}–C(5)); 2.33 (*ddd*, *J* = 14.3, 10.9, 3.4, H_{ax}–C(2)); 2.17 (*dm*, *J* = 14.3, H_{eq}–C(2)); 2.04 (*dm*, *J* = 15.3, H_{eq}–C(5)); 1.88–1.69 (*m*, CH_2(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 52.78, 52.71 (2*d*, C(3), C(4)); 45.33 (*d*, C(1)); 38.65 (*t*, C(2)); 30.98, 28.48 (2*t*, 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, $[M + 1]^+$).



*(±)-(1*R**,2*S**,4*S**)-2-Bromo-7-aza-bicyclo[2.2.1]heptane* (**743**).

A solution of **742** (266 mg, 0.98 mmol) in $CHCl_3$ (20 ml) was treated with K_2CO_3 (140 mg, 0.98 mmol), stirred under reflux for 12 d, cooled to r.t., and treated with 10% aq. K_2CO_3 soln. (10 ml). The organic phase was separated, and the aqueous phase extracted with $CHCl_3$ (4 x 20 ml). The combined organic phases were dried (K_2CO_3), and evaporated to give crude **743** (200 mg, 100%). Brown oil. R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.56. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.08 (*dd*, *J* = 7.2, 2.8, H–C(2)); 3.73–3.67, 3.64–3.56 (2*m*, 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 64.97 (*d*, C(1)); 56.74 (*d*, C(4)); 53.84 (*d*, C(2)); 44.83 (*t*, C(3)); 28.56, 27.04 (2 *t*).



*(±)-(1*R**,2*S**,4*S**)-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 $CHCl_3$ (10 ml) was treated with K_2CO_3 (140 mg, 0.98 mmol) and Boc_2O (855 mg, 3.92 mmol), and stirred for 19 h. The mixture was washed with water, and the aqueous phase extracted with $CHCl_3$ (2 x 25 ml). The combined organic phases were dried (Na_2SO_4) and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 12:1) gave **744** (224 mg, 83% from **727**). Colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.61. FT-IR (0.7%, $CHCl_3$): 3008*m*, 2980*m*, 2879*w*, 1694*s* (C=O), 1477*w*, 1454*w*, 1392*s*, 1368*s*, 1321*m*, 1177*m*, 1153*s*, 1134*m*, 1101*m*, 1048*w*, 983*w*, 907*m*, 886*w*, 872*w*, 849*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.41–4.36, 4.34–4.27 (2*m*, 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, H_{exo}–C(3)); 2.17 (*dd*, *J* = 13.7, 7.5, H_{endo}–C(3)); 1.94–1.82 (*m*, H–C(6)); 1.78–1.63 (*m*, H–C(5)); 1.46 (*s*, Me_3C); 1.43–1.25 (*m*, H'–C(6), H'–C(5)). ^{13}C-NMR (75 MHz, $CDCl_3$); 155.00 (*s*, C=O); 79.93 (*s*, Me_3C); 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 (2*t*, C(5), C(6)); 28.27 (*q*, *Me*$_3$C). ESI-MS: 332 (97), 330 (100, $[M + Na + MeOH]^+$); 316 (50), 314 (45, $[M + K]^+$); 300 (45), 298 (46, $[M + Na]^+$). Anal. calc. for $C_{11}H_{18}BrNO_2$ (276.17): C 47.84, H 6.57, N 5.07; found: C 47.78, H 6.47, N 5.16.

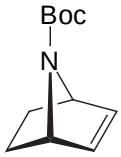
Transformation of **729** into **744**.

At r.t., a solution of **729** (15.28 g, 43.3 mmol) in MeOH (500 ml) and H_2O (200 ml) was treated with K_2CO_3 (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. K_2CO_3 soln. (100 ml) and extracted with $CHCl_3$ (5 x 300 ml). The combined organic phases were dried (K_2CO_3) and evaporated. The residue (crude **742** (11.1 g, 43.2 mmol) was dissolved in $CHCl_3$ (1 l), treated with K_2CO_3 (5.97 g, 43.2 mmol), heated under reflux for 13 d, cooled to r.t., treated with Boc_2O (60 ml, 0.26 mol) and K_2CO_3 (5.97 g, 43.2 mmol), and stirred at r.t. for 3 d. The mixture was washed with H_2O (500 ml), and the aqueous phase extracted with $CHCl_3$ (500 ml). The combined organic phases were dried (Na_2SO_4) and evaporated. FC (300 g of silica gel, toluene/AcOEt 40:1) gave **744** (11.27 g, 93% from **729**).

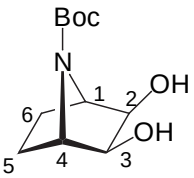
Attempted cyclisation of **747**

A solution of **747** (49 mg, 0.19 mmol) in 1,3-dichlorobenzene (10 ml) was treated with K_2CO_3 (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 (R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.56). The mixture was cooled to r.t., treated with Boc_2O (0.21 ml, 0.95 mmol), stirred for 3 d, and washed with sat. aq. K_2CO_3 soln. (25 ml). The aqueous phase was extracted with $CHCl_3$ (3 x 25 ml) and the combined organic phases were dried (Na_2SO_4) 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]).

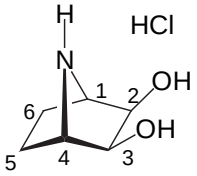
A soln. of **744** (1.058 g, 3.83 mmol) in THF (50 ml) was treated with KO*t*Bu (473 mg, 4.21 mmol), heated under reflux for 3 h, cooled, and poured into brine (50 ml). The resulting mixture was extracted with Et_2O (3 x 100 ml). The combined organic phases were dried (Na_2SO_4) and evaporated. FC (35 g of silica gel, cyclohexane/AcOEt 12:1) gave **745** (652 mg, 87%) as a colourless oil. Data see [981].



*(±)-(1*R*,2*R*,3*S*,4*S*)-7-[(*tert-*Butyloxy)carbonyl]-7-azabicyclo[2.2.1]heptane-2,3-diol* (**746**).

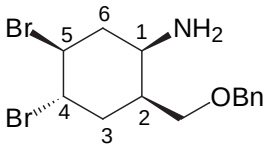
A soln. of **745** (98 mg, 0.50 mmol) in acetone (23 ml) and water (2.5 ml) was treated with N-methylmorpholineoxide monohydrate (102 mg, 0.75 mmol) and 2.5% OsO_4 in *t*BuOH (0.5 ml, 40 μmol), stirred at r.t. for 22 h, diluted with sat. aq. $Na_2S_2O_5$ soln. (50 ml), and

extracted with $CHCl_3$ (4 x 100 ml). The combined organic phases were dried (Na_2SO_4) 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/CH_2Cl_2 gave colourless needles of **746** (64 mg, 56%). R_f (cyclohexane/AcOEt 1:1) 0.19. M.p. 82°. FT-IR (0.5%, $CHCl_3$): 3502*w* (OH), 3004*m*, 2988*m*, 2884*w*, 1697*s* (C=O), 1466*m*, 1368*s*, 1318*m*, 1170*s*, 1141*s*, 1111*m*, 1056*s*, 1010*w*, 972*w*, 931*w*, 803*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, Me_3C); 1.81 (*d J* = 8.1, H'–C(5), H'–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.22 (*s*, C=O); 80.25 (*s*, Me_3C); 74.24 (*d*, C(2), C(3)); 62.26 (*d*, C(1), C(4)); 28.26 (*q*, Me_3C); 24.27 (*t*, C(5), C(6)). ESI-MS: 498 (4, $[2M + K]^+$), 481 (45, $[2M + Na]^+$), 476 (8, $[2M + NH_4]^+$), 459 (3, $[2M + 1]^+$), 262 (13, $[M + MeOH + 1]^+$), 247 (95, $[M + NH_4]^+$), 230 (96, $[M + 1]^+$), 206 (2), 174 (7). Anal. calc. for $C_{11}H_{19}NO_4$ (229.28): C 57.63, H 8.35, N 6.11; found C 57.78, H 8.25, N 6.10.



*(±)-(1*R*,2*R*,3*S*,4*S*)-2,3-Dihydroxy-7-azoniabicyclo[2.2.1]heptane Chloride* (**58**·HCl).

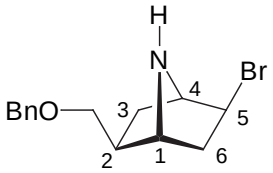
A soln. of **746** (19.9 mg, 86 µmol) in 0.1N HCl (5 ml, 500 µmol) was stirred at 30° for 20 h and lyophilised to give colourless amorphous **58**·HCl (14.0 mg, 97%). R_f (*n*PrOH/AcOH/H_2O 4:1:1) 0.25. M.p.: 205–215°(dec.). ^{1}H-NMR (300 MHz, D_2O): 4.80 (*d*, *J* = 1.2, OH, NH); 4.16 (*d*, *J* = 1.2, H–C(2), H–C(3)); 4.06 (*ddd*, *J* = 3.7, 2.3, 1.5, H–C(1), H–C(4)); 1.95–1.88 (*m*, H–C(5), H–C(6)); 1.69 (*dm*, *J* = 8.1, H'–C(5), H'–C(6)). ^{13}C-NMR (75 MHz, D_2O): 71.47 (*d*, C(2), C(3)); 64.32 (*d*, C(1), C(4)); 21.18 (*t*, C(5), C(6)), ESI-MS: 152 (7, $[M + Na]^+$), 130 (100, $[M + 1]^+$), 87 (24). HR-ESI-MS: 130.08620 (100) ($C_6H_{12}NO_2^+$, $[M + 1]^+$; calc.130.08626).



r-*1-Amino*-c-*2-(benzyloxymethyl)*-t-*4*,c-*5-dibromocyclohexane (***752**).

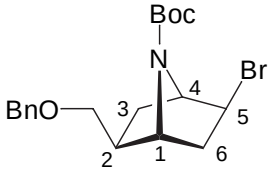
A soln. of **731** (290 mg, 0.607 mmol) in CH_2Cl_2 (15 ml) was treated with CF_3CO_2H (0.93 ml, 12.1 mmol), stirred at r.t. for 3 h, and evaporated. The residue was taken up in sat. aq. K_2CO_3 soln. (20 ml) and extracted with $CHCl_3$ (3 x 25 ml). The combined organic phases were dried (K_2CO_3) and evaporated to give crude **752** as a colourless oil (250 mg, quant.).

R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.61. ESI-MS: 380 (1), 378 (2), 376 (1, $[M + 1]^+$); 298 (96), 296 (100, $[M – Br]^+$).



*(±)-(1*R*,2*S*,4*R*,5*S*)-2-(Benzyloxymethyl)-5-bromo-7-azabicyclo[2.2.1]heptane* (**753**).

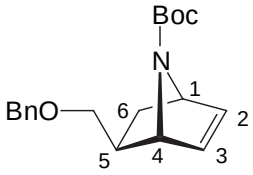
A solution of crude **752** (250 mg) in $CHCl_3$ (20 ml) was treated with K_2CO_3 (83 mg, 0.607 mmol), heated under reflux for 40 h, cooled to r.t., treated with K_2CO_3 (*ca*. 100 mg), and filtered. Evaporation of the filtrate gave crude **753** (268 mg, quant.) as a slightly yellow oil. R_f (CH_2Cl_2/MeOH/NH_4OH 9:1:0.1) 0.88. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.25 (5 arom. H); 4.54 (*d*, *J* = 12.1), 4.48 (*d*, *J* = 11.8) (PhCH_2); 4.20–3.90 (br. *s*, NH); 4.07 (*dd*, *J* = 6.1, 4.5, H–C(5)); 3.88 (*d*, *J* = 5.0), 3.84 (*d*, *J* = 3.4) (H–C(1), H–C(4)); 3.46 (*t*, *J* ≈ 8.9, CH–C(2)); 3.31 (*dd*, *J* = 9.3, 5.3, CH'–C(2)); 2.31–2.17 (*m*, CH_2C(6)); 1.84 (*tt*, *J* = 8.4, 5.1, H–C(2)); 1.55 (*dd*, *J* = 13.1, 8.4, H_{endo}–C(3)); 1.45 (*dt*, *J* =13.1, 5.0, H_{exo}–C(3)). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.00 (*s*); 128.35 (*d*, 2 C); 127.72 (*d*, 2 C); 127.63 (*d*); 73.29 (*t*, Ph*C*H_2); 72.45 (*t*, *C*H_2–C(2)); 65.26, 59.42 (2*d*, C(1), C(4)); 50.68 (*d*, C(5)); 43.87 (*t*); 40.95 (*d*, C(2)); 31.30 (*t*). ESI-MS: 298 (10), 296 (6, $[M + 1]^+$); 97 (100).



*(±)-(1*R*,2*S*,4*R*,5*S*)-2-(Benzyloxymethyl)-7-[(*tert*-buyloxy)carbonyl]-5-bromo-7-azabicyclo[2.2.1]heptane* (**754**).

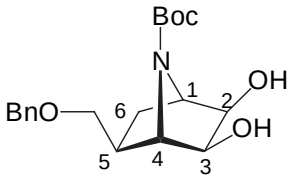
A solution of **753** (268 mg) in $CHCl_3$ (25 ml) was treated with K_2CO_3 (84 mg, 0.607 mmol) and Boc_2O (0.55 ml, 2.4 mmol) and stirred at r.t. for 6 d. The mixture was washed with H_2O (25 ml) and the aqueous phase extracted with $CHCl_3$. The combined organic phases were dried (Na_2SO_4) and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 10:1) gave colourless crystalline **754** (194 mg, 84% from **731**). R_f (cyclohexane/AcOEt 3:1) 0.59. M.p. 112.2–113.6°. FT-IR (1%, $CHCl_3$): 3027*w*, 3015*m*, 2977*w*, 2932*w*, 2864*w*, 1693*s* (C=O), 1477*w*, 1455*w*, 1393*m*, 1368*m*, 1322*m*, 1111*m*, 910*w*. ^{1}H-NMR (300 MHz, $CDCl_3$) (*ca*. 2:1 mixture of diastereoisomers): signals for the major diastereoisomer: 7.38–7.24 (5 arom. H); 4.54 (*d*, *J* = 12.1, PhC*H*); 4.50 (br. *s*, H–C(4)); 4.45 (*d*, *J* = 11.8, PhC*H*'); 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)); 3.17 (*dd*, *J* = 9.2, 6.4, CH'–C(2)); 2.31 (br. *dt*, *J* = 14.0, 4.4, H–C(6)); 2.21 (*dd*, *J* = 13.9, 7.3, H'–C(6)); 1.98–1.85 (*m*, H–C(2)); 1.55 (*dd*, *J* = 12.9, 8.3, H–C(3)); 1.48 (*s*, C(CH_3)$_3$); 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. ^{13}C-NMR (75 MHz, $CDCl_3$) (*ca*. 2:1 mixture of diastereoisomers): signals of the major diastereoisomer: 138.01 (*s*);128.35, 128.27, 127.61, 127.49 (4*d*); 80.05 (*d*, Me$_3$*C*); 73.25 (*t*, Ph*C*H_2); 72.42 (*t*,

CH_2–C(2)); 63.79, 57.18 (2*d*, 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 (4*d*); 79.92 (*d*, Me$_3$*C*); 73.34 (*t*, Ph*C*H_2); 72.30 (*t*, *C*H_2–C(2)); 62.91, 57.65 (2*d*, 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, $[M + Na - C_4H_8]^+$); 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.



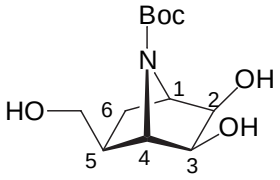
*(±)-(1*R*,4*R*,5*S*)-5-(Benzyloxymethyl)-7-[(*tert*-Butyloxy)carbonyl]-7-azabicyclo[2.2.1]hept-2-ene* (**755**).

A soln. of **754** (167 mg, 0.42 mmol) in THF (12 ml) was treated with KO*t*Bu (71 mg, 0.63 mmol), heated under reflux for 25 h, cooled to 0°, diluted with Et_2O (20 ml), and washed with brine (25 ml). The aqueous phase was extracted with Et_2O (25 ml). The combined organic phases were dried (Na_2SO_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*, Ph*C*H_2, *C*H_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, $[M + 1 - C_4H_8]^+$) 216 (8, $[M + 1 - C_4H_8 - CO_2]^+$). 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.



*(±)-(1*R*,2*R*,3*S*,4*S*,5*S*)-5-(Benzyloxymethyl)-7-[(*tert*-butoxy)carbonyl]-7-azabicyclo[2.2.1]heptane-2,3-diol* (**756**).

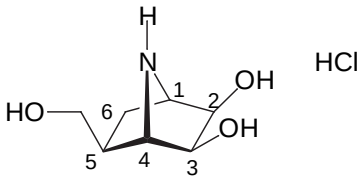
A soln. of **755** (114 mg, 0.36 mmol) in acetone (23 ml) and water (2.5 ml) was treated with *N*-methylmorpholineoxide monohydrate (73 mg, 0.54 mmol) and 2.5% OsO_4 in *t*BuOH (0.5 ml), stirred at r.t. for 13 h, diluted with sat. aq. $Na_2S_2O_5$ soln. (50 ml), and extracted with $CHCl_3$ (2 x 100 ml). The combined organic phases were dried (Na_2SO_4) and evaporated. FC (12 g of silica gel, cyclohexane/AcOEt 1:1) gave **756** (102 mg, 81%) as a yellow oil. R_f (cyclohexane/AcOEt 1:1) 0.19. FT-IR (1%, $CHCl_3$): 3488*w* (br., OH), 3028*w*, 3013*m*, 2981*m*, 2932*w*, 2864*w*, 1727*w*, 1692*s*, 1670*s*, 1500*w*, 1478*w*, 1455*m*, 1386*s*, 1368*s*, 1318*m*, 1112*m*, 1091*m*, 1051*m*, 909*w*, 870*w*. ^{1}H-NMR (300 MHz, C_6D_6, 50°): 7.24–7.02 (5 arom. H); 4.26 (*d*, *J* = 12.1, PhC*H*); 4.20 (*d*, *J* = 11.2, PhC*H*'); 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*, Me_3C); 0.83–0.76 (*m*, CH_2(6)). ^{13}C-NMR (75 MHz, $CDCl_3$, *ca*. 1:1 mixture of diastereoisomers, most signals isochronic for both diastereoisomers): 155.76 (*s*, C=O); 137.91 (*s*); 128.31, 127.58 (2*d*) (1 *d* hidden by noise or other signal); 80.30 (*s*, Me_3C); 74.62, 74.01 (2*d*, C(2), C(3)); 73.25 (*t*, Ph*C*H_2); 72.17 (*t*, *C*H_2–C(5)); 64.64 (*d*, *ca*.0.47 C), 62.99(*d*), 60.89 (*d*, *ca*. 0.53 C) (C(1), C(4)); 38.44 (*d*, C(5)); 28.77 (*t*, C(6)); 28.34 (*q*, *Me*$_3$C). HR-MALDI-MS (DHB): 372.1783 (80) ($C_{19}H_{27}NNaO_5^+$, [*M* + Na]$^+$; calc. 372.1787), 316 (66, [*M* + Na –C_4H_8]$^+$), 272 (28, [*M* + Na –C_4H_8 – CO_2]$^+$), 250 (100, [*M* + 1 –C_4H_8 – CO_2]$^+$).



*(±)-(1*R*,2*R*,3*S*,4*S*,5*S*)-7-(*tert*-Butyloxycarbonyl)-5-(hydroxymethyl)-7-azabicyclo[2.2.1]heptane-2,3-diol* (**757**).

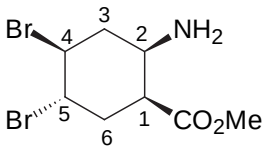
A suspension of 10% Pd/C (30 mg) in MeOH (5 ml) was treated with a solution of **756** (91 mg, 0.26 mmol) in MeOH (5 ml), put under a H_2 atmosphere (balloon), and stirred at r.t. for 19 h. Filtration through a membrane filter and evaporation gave crude **757** as a yellow oil (61 mg, 90%). Repeated FC (12 g of silica gel, CH_2Cl_2/MeOH 12:1) gave **757** as a colourless oil (41 mg, 60%). R_f (CH_2Cl_2/MeOH 9:1) 0.46. FT-IR (1%, $CHCl_3$): 3693*w*, 3623*w*, 3489*w* (br., OH), 3028*w*, 3011*m*, 2972*s*, 2875*w*, 1674*s* (C=O), 1603*w*, 1475*m*, 1456*m*, 1393*s*, 1369*s*, 1318*m*, 1115*m*, 1050*m*, 911*w*, 872*w*. ^{1}H-NMR (300 MHz, CD_3OD, *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*, CH_2–C(5)); 1.82 (*dtd*, *J* = 8.1, 7.9, 4.7, H–C(5)); 1.48 (*dd*, *J* =12.8, 8.4, H–C(6)); 1.45 (*s*, $C(CH_3)_3$); 1.10, 1.09 (2 *dt*, *J* = 12.5, 5.3, H'–C(6)). ^{13}C-NMR (75 MHz, CD_3OD, *ca.* 1:1 mixture of diastereoisomers): 156.61 (C=O); 79.92, 79.80 (Me_3C); 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), CH_2–C(5)); 40.99 (2 C, C(5)); 28.25, 27.94 (C(6); 27.43 (Me_3C). HR-MALDI-MS (DHB): 314.1745 (49) ($C_{13}H_{25}NNaO_6^+$, [*M* + Na + MeOH]$^+$; calc. 314.1580), 224 (11).



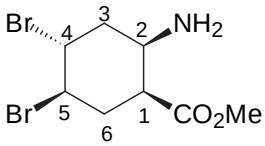
*(±)-(1*R*,2*R*,3*S*,4*S*,5*S*)-2,3-Dihydroxy-5-(hydroxymethyl)-7-azoniabicyclo[2.2.1]heptane Chloride* (**59**·HCl)

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·H_2O (33.2 mg, 100%). R_f (*n*PrOH/AcOH/H_2O 4:1:1) 0.52. ^{1}H-NMR (300 MHz, CD_3OD): 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)). ^{13}C-NMR (75 MHz, CD_3OD): 72.11 (C(2), C(3));, 68.48 (CH_2–C(5)); 66.03 C(4); 63.21 (C(1)); 37.46 (C(5)); 26.74 (C(6)). HR-ESI-MS: 160.09655 ($C_7H_{14}NO_3^+$, [*M* + 1]$^+$; calc. 160.09682).



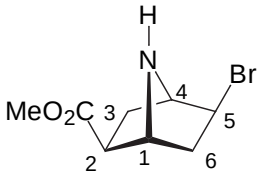
Methyl-c-*2-amino*-c-*4*,t-*5-dibromocyclohexanecarboxylate* (**758**).

A solution of **737** (147 mg, 0.356 mmol) in CH_2Cl_2 (7.5 ml) was treated with CF_3CO_2H (0.5 ml), stirred at r.t. for 13 h, and evaporated. The residue was suspended in sat. aq. K_2CO_3 soln. (15 ml) and extracted with $CHCl_3$ (3 x 20 ml). The combined organic phases were dried (K_2CO_3) and evaporated to give **758** (140 mg, quant.) as a slightly yellow oil. R_f (CH_2Cl_2/MeOH 9:1) 0.72. ^{1}H-NMR (300 MHz, $CDCl_3$): 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]$^+$).



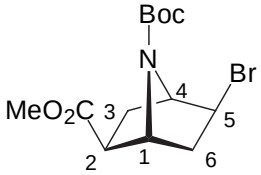
Methyl-c-*2-amino*-t-*4,*c-*5-dibromocyclohexanecarboxylate* (**759**).

According to the preparation of **758**, **738** (84 mg, 0.20 mmol) was transformed into **759** (93 mg, quant.). Slightly yellow oil. R_f (CH_2Cl_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 (±)-(1*R*,*2*S*,*4*R*,*5*S**)-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_2CO_3 (0.35 mmol), heated under reflux for 30 d, allowed to cool to r.t., and washed with sat. aq. K_2CO_3 soln. (15 ml). The aqueous phase was extracted with $CHCl_3$ (2 x 25 ml). The combined organic phases were dried (K_2CO_3) and evaporated to give crude **760** (122 mg) as a yellow oil. R_f (CH_2Cl_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 (2*d*, C(1), C(4)); 52.18 (*q*, MeO); 50.95 (*d*, C(5)); 45.95 (*d*, C(2)); 43.53, 32.45 (2*t*, C(3), C(6)).



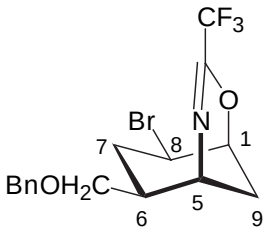
*Methyl (±)-(1*R*,*2*S*,*4*R*,*5*S**)-5-Bromo-7-[(*tert-*butyloxy)carbonyl]-7-azabicyclo[2.2.1]heptane-2-carboxylate* (**761**).

A soln. of **760** (122 mg, ca. 0.35 mmol) in $CHCl_3$ (15 ml) was treated with K_2CO_3 (48 mg, 0.35 mmol) and Boc_2O (0.32 ml, 1.4 mmol), stirred at r.t. for 16 d, and washed with H_2O (20 ml). The aqueous phase was extracted with $CHCl_3$ (2 x 20 ml). The combined organic phases were dried (K_2CO_3) and evaporated. FC (15 g of silica gel, cyclohexane/AcOEt 6:1) gave colourless crystalline **761** (74 mg, 62% from **737**). R_f (cyclohexane/AcOEt 3:1) 0.35. M.p.: 56.7–58.6°. FT-IR (1.5%, $CHCl_3$): 3027*w*, 3012*w*, 2982*w*, 2954*w*, 1737*s* (COOMe), 1697*s* (COO*t*Bu), 1477*w*, 1437*m*, 1392*m*, 1368*s*, 1323*m*, 1303*w*, 1145*s*, 1104*w*, 1039*w*, 979*w*, 916*w*, 883*w*. ^{1}H-NMR (300 MHz, C_6D_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 (*ddd*, *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*, Me_3C); 0.87 (*dd*, *J* = 13.1, 8.7, H'–C(3)). ^{13}C-NMR (75 MHz, C_6D_6, 50°): 172.23 (*s*, CO_2Me); 153.99 (*s*, CO_2CMe_3); 79.83 (*s*, Me_3C); 64.18, 59.51 (2*d*, C(1), C(4)); 51.63 (*q*, MeO); 48.36, 46.15 (2*d*, C(2), C(5)); 43.25 (*t*), 31.67 (2*t*, C(3), C(6)); 28.29 (*q*,Me_3 C). 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, $[M + 1 - C_4H_8]^+$); 236 (16), 234 (18, $[M + 1 - C_4H_8 - CO_2]^+$).

Attempted Cyclisation of **759**.

A soln. of **759** (93 mg, ca. 0.20 mmol) in 1,3-dichlorobenzene (15 ml) was treated with K_2CO_3 (27.6 mg, 0.20 mmol), stirred for 28 d at 120°, allowed to cool to r.t., treated with K_2CO_3 (27.6 mg, 0.20 mmol) and Boc_2O (0.3 ml, 1.3 mmol), stirred at r.t. for 10 d, and washed with H_2O (30 ml). The aqueous phase was extracted with $CHCl_3$ (2 x 20 ml). The combined organic phases were dried (Na_2SO_4) 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.



*(±)-(1*R*,5*S*,6*R*,8*S*)-6-(Benzyloxymethyl)-8-bromo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene* (**762**).

A soln. of **736** (9.3 mg, 19.7 μmol) in MeOH (1.5 ml) and H_2O (0.6 ml) was treated with K_2CO_3 (13.5 mg, 98 μmol), stirred at r.t. for 26 h, and evaporated. The residue was suspended in sat. aq. K_2CO_3-soln. (10 ml), and extracted with $CHCl_3$ (3 x 10 ml) The combined organic phases were dried (K_2CO_3) and evaporated to yield crude **762** (1.6 mg, quant.) as a colourless oil. R_f (toluene/AcOEt 10:1) 0.36. FT-IR (1%, $CHCl_3$): 3008*m*, 2871*m*, 1689*m*, 1455*w*, 1393*w*, 1373*w*, 1319*w*, 1300*w*, 1128*s*, 1107*s*, 1090*s*, 909*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.27 (5 arom. H); 4.79–4.75 (*m*, H–C(1)); 4.54, 4.48 (2*d*, *J* = 11.8, PhCH_2); 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, H_{eq}–C(7)); 2.28–2.16 (*m*, H–C(6)); 2.11 (*dt*, *J* = 14.0, 4.1, H_{eq}–C(9)); 1.86 (*dt*, *J* = 14.0, 1.6, Hax–C(9)); 1.52 (*dt*, *J* = 14.0, 12.5, H_{ax}–C(7)). ^{13}C-NMR (75 MHz, $CDCl_3$); 137.88 (*s*); 128.33, 127.60 (2*d*); 75.65 (*d*, C(1)); 73.41 (*t*, PhCH_2)); 71.38 (*t*, CH_2–C(6)); 50.15, 46.50 (2*d*, C(5), C(8)); 44.27 (*d*, C(6)); 31.65 (*t*, C(9)); 28.82 (*t*, C(7)); ^{19}F-NMR (282 MHz, $CDCl_3$): –73.69 (*s*). ESI-MS: 448 (1), 446 (1, $[M + Na + MeOH]^+$); 432 (16), 430 (15, $[M + K]^+$); 416 (97), 414 (100, $[M +$

Na]$^+$); 394 (23), 392 (22, [*M* + 1]$^+$); 380 (42), 378 (81), 376 (40, [*M* – CF_3CN + HBr]$^+$); 298 (11), 296 (16, [*M* – CF_3CN]$^+$).

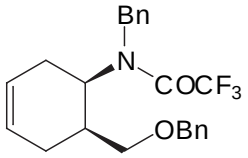
Inhibition studies

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] ≈ K_M.

β-Glucosidase from almonds (pH 6.8, 37°), *β-Glucosidase from* Caldocellum saccharolyticum (pH 6.8, 55°), and *α-Glucosidase from brewer's yeast* (ph 6.8, 37°) as described previously [1043].

β-Mannosidase from snail acetone powder (pH 4.5, 27°) using 4-nitrophenyl-β-D-mannopyranoside as substrate [197].

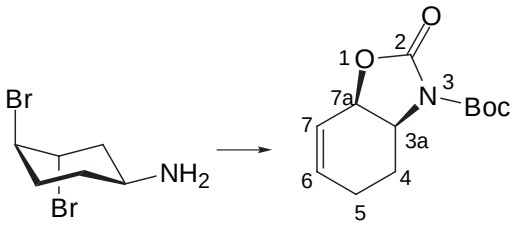
α-Mannosidase from jack bean (pH 4.5, 25°) using 4-nitrophenyl-α-D-mannopyranoside as substrate [197].



N-*Benzyl*-N-*[c-6-(benzyloxymethyl)cyclohex-3-enyl]-2,2,2-trifluoroacetamide* (**839**).

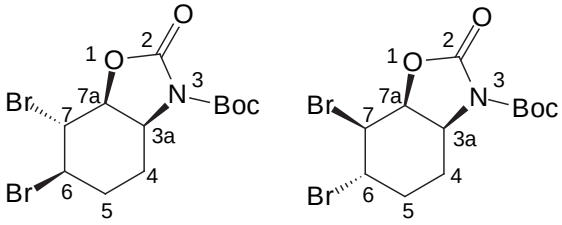
A soln. of **718** (1.248 g, 3.06 mmol) in CH_2Cl_2 (25 ml) was treated with CF_3CO_2H (4 ml, 52 mmol), stirred at r.t. for 95 min, and evaporated. A soln. of the residue in CH_2Cl_2 (20 ml) was treated with Et_3N (4.6 ml, 33 mmol) and $(CF_3CO)_2O$ (1.7 ml, 12.2 mmol), stirred at r.t. for 20 h, and 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 (2*m*, 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 (Ph*C*H_2O); 69.85 (*C*H_2–C(6)); 55.67, 49.39 (C(1), Ph*C*H_2N); 35.55 (C(6); 28.47, 25.33 (C(2), C(5)); signals for CF_3CO hidden by noise. ^{19}F-NMR (282 MHz, $CDCl_3$, 7:3 mixture

of diastereoisomers): –67.81 (0.3); –68.49 (0.7). ESI-MS: 442 (11, $[M + K]^+$), 426 (29, $[M + Na]^+$), 404 (65, $[M + 1]^+$).



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 K_2CO_3 (172 mg, 1.25 mmol) and stirred at 80° for 4 d. The mixture was cooled to r.t., treated with Boc_2O (1.6 ml, 7.18 mmol), stirred for 3 d, diluted with AcOEt (250 ml), and washed with H_2O (150 ml) and brine (150 ml). The aqueous phases were extracted with AcOEt (200 ml). The combined organic phases were dried (Na_2SO_4) and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 5:1) of the organge oil gave colourless crystalline **749** (86 mg, 28%). R_f (cyclohexane/AcOEt 3:1) 0.28. M.p.: 116.0–118.5°. FT-IR (1%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): CO signals hidden by noise; 135.19 (*d*, C(7)); 121.37 (*d*, C(6)); 83.72 (*s*, Me_3C); 69.27 (*d*, C(7a)); 54.51 (*d*, C(3a)); 28.15 (*q*, Me_3C); 24.07, 22.20 (2*t*, 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 CH_2Cl_2 (7 ml) was cooled to 0°, treated with $PhMe_3NBr_3$ (470 mg, 1.26 mmol), stirred for 18 h while slowly warming to r.t., and poured into ice-cold sat. aq. $Na_2S_2O_5$ soln. (20 ml). The mixture was extracted with AcOEt (3 x 25 ml). The combined organic phases were dried (Na_2SO_4) 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. R_f (cyclhexane/AcOEt 3:1) 0.46. FT-IR (1.5%, $CHCl_3$): 3030*w*, 2984*w*, 1819*s* (C=O), 1721*m*, 1477*w*, 1456*w*, 1437*w*, 1370*s*, 1358*s*, 1346*m*, 1330*m*, 1301*m*, 1283*w*, 1158*m*, 1075*s*, 1035*w*, 984*w*, 909*w*, 846*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, Me_3C). ^{13}C-NMR (300 MHz, $CDCl_3$): 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 (Me_3C); 25.25, 22.73 (C(4), C(5)). ESI-MS: 841 (1), 839 (2), 837 (4), 835 (2), 833 (1, $[2\,M + K^+]$); 825 (17), 823 (65), 821 (100), 819 (64), 817 (14, $[2\,M + Na]^+$]); 456 (11), 454 (24), 452 (12, $[M + Na + MeOH]^+$); 440 (28), 438 (53), 436 (24, $[M + K]^+$); 424 (32), 422 (71), 420 (36, $[M + Na]^+$); 400 (3), 398 (6), 396 (2, $[M + Na + MeOH - C_4H_8]^+$); 368 (4) 366 (9), 364 (4, $[M + Na - C_4H_8]^+$).

Data of **751**:

Colourless needles. R_f (cyclohexane/AcOEt 3:1) 0.39. M.p.: 168°. FT-IR (1%, $CHCl_3$): 3031*w*, 2984*w*, 2933*w*, 1819*s* (C=O), 1722*m*, 1477*w*, 1455*w*, 1449*w*, 1383*m*, 1371*m*, 1353*s*, 1321*m*, 1287*w*, 1159*m*, 1139*m*, 1077*s*, 1062*m*, 1046*w*, 1006*w*, 952*w*, 915*w*, 843*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.75 (*dd*, *J* = 6.2, 3.1, H–C(7a)); 4.33 (*dt*, *J* = 8.1, 6.1, H–C(3a)); 4.25 (*ddd*, *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, H_{eq}–C(5)); 2.32 (*dtd*, *J* = 14.6, 6.2, 3.1, H_{eq}–C(4)); 1.98 (*dddd*, *J* = 14.6, 11.5, 8.4, 3.1, H_{ax}–C(5)); 1.69 (*dddd*, *J* = 14.6, 11.5, 8.1, 3.4, H_{ax}–C(4)); 1.53 (*s*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 150.00, 148.62 (2 C=O); 84.55 (Me_3C); 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 (Me_3C). 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, $[M + Na - C_4H_8]^+$). Anal. calc. for $C_{12}H_{17}Br_2NO_4$ (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 recrystallisded from hexane/CH_2Cl_2.

Table 1. Selected crystal structure data for **751**.

Crystal	colourless needle	0.12 x 0.10 x 0.10 mm
Crystal system	monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 10.678(2) Å	α = 90°
	b = 10.685(2) Å	β = 93.36(2)°
	c = 14.084(2) Å	γ = 90°
Z	4	
Calculated density	1.652 g/cm^3	
F(000)	792	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3).

	x	y	z	U(eq)
Br(6)	7373(1)	4020(1)	6148(1)	87(1)
Br(7)	8886(1)	1798(1)	4765(1)	97(1)
C(7a)	6559(5)	1789(5)	3682(4)	54(1)
C(7)	7252(6)	2551(6)	4456(4)	61(2)
C(6)	6504(6)	2770(6)	5327(4)	58(2)
C(5)	5220(6)	3245(6)	5036(5)	68(2)
C(4)	4500(6)	2291(6)	4412(4)	59(2)
C(3a)	5168(5)	2041(5)	3514(4)	50(1)
N(3)	4793(4)	829(4)	3083(3)	47(1)
C(2)	5601(6)	-104(6)	3423(4)	55(1)
O(1)	6588(4)	454(4)	3904(3)	60(1)
O(8)	5484(4)	-1217(4)	3362(3)	67(1)
C(7')	3665(5)	582(6)	2569(4)	52(1)
O(7')	3440(4)	-396(4)	2174(3)	71(1)
O(1')	2938(3)	1581(4)	2593(3)	56(1)
C(1')	1671(5)	1608(6)	2094(5)	64(2)
C(2')	1191(7)	2900(8)	2357(6)	89(2)
C(2")	875(7)	578(8)	2479(8)	106(3)
C(2"')	1831(8)	1529(9)	1032(5)	91(3)

Table 3. Bond lengths [Å].

Br(6)-C(6)	1.963(6)
Br(7)-C(7)	1.947(7)
C(7a)-O(1)	1.461(7)
C(7a)-C(3a)	1.514(8)
C(7a)-C(7)	1.518(8)
C(7)-C(6)	1.521(8)
C(6)-C(5)	1.497(9)
C(5)-C(4)	1.525(8)
C(4)-C(3a)	1.511(7)
C(3a)-N(3)	1.475(7)
N(3)-C(2)	1.385(7)
N(3)-C(7')	1.395(7)
C(2)-O(8)	1.199(7)
C(2)-O(1)	1.357(7)
C(7')-O(11)	1.201(7)
C(7')-O(14)	1.322(7)
O(14)-C(1')	1.488(7)
C(1')-C(2''')	1.518(9)
C(1')-C(2'')	1.511(10)
C(1')-C(2')	1.526(9)

Table 4. Bond angles [°].

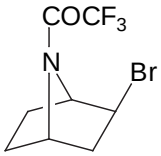
O(1)-C(7a)-C(3a)	102.4(4)
O(1)-C(7a)-C(7)	111.5(5)
C(3a)-C(7a)-C(7)	116.7(5)
C(7a)-C(7)-C(6)	113.9(5)
C(7a)-C(7)-Br(2)	109.4(4)
C(6)-C(7)-Br(2)	112.9(4)
C(5)-C(6)-C(7)	110.3(5)
C(5)-C(6)-Br(3)	108.9(4)
C(7)-C(6)-Br(3)	109.1(4)
C(6)-C(5)-C(4)	110.7(5)
C(3a)-C(4)-C(5)	110.7(5)
N(3)-C(3a)-C(4)	111.7(5)
N(3)-C(3a)-C(7a)	98.5(4)
C(4)-C(3a)-C(7a)	114.1(4)
C(2)-N(3)-C(7')	123.0(5)
C(2)-N(3)-C(3a)	110.0(4)
C(7')-N(3)-C(3a)	125.8(5)
O(8)-C(2)-O(1)	123.1(5)
O(8)-C(2)-N(3)	129.0(6)
O(1)-C(2)-N(3)	107.8(5)

C(2)-O(1)-C(7a)	108.4(4)
O(11)-C(7')-O(14)	127.8(5)
O(11)-C(7')-N(3)	123.3(5)
O(14)-C(7')-N(3)	108.9(5)
C(7')-O(14)-C(1')	121.5(4)
O(14)-C(1')-C(2''')	108.2(5)
O(14)-C(1')-C(2'')	109.4(6)
C(£17)-C(1')-C(2'')	114.3(7)
O(14)-C(1')-C(2')	102.3(5)
C(£17)-C(1')-C(2')	110.4(6)
C(£16)-C(1')-C(2')	111.5(6)

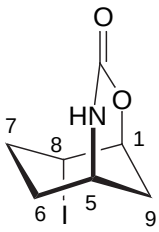
Table 5. Torsion angles [°].

O(1)-C(7a)-C(7)-C(6)	-78.8(7)
C(3a)-C(7a)-C(7)-C(6)	38.5(7)
O(1)-C(7a)-C(7)-Br(2)	48.5(5)
C(3a)-C(7a)-C(7)-Br(2)	165.8(4)
C(7a)-C(7)-C(6)-C(5)	-49.6(7)
Br(2)-C(7)-C(6)-C(5)	-175.1(4)
C(7a)-C(7)-C(6)-Br(3)	-169.2(4)
Br(2)-C(7)-C(6)-Br(3)	65.3(5)
C(7)-C(6)-C(5)-C(4)	61.4(7)
Br(3)-C(6)-C(5)-C(4)	-178.9(4)
C(6)-C(5)-C(4)-C(3a)	-60.9(7)
C(5)-C(4)-C(3a)-N(3)	158.5(5)
C(5)-C(4)-C(3a)-C(7a)	47.9(7)
O(1)-C(7a)-C(3a)-N(3)	-34.2(4)
C(7)-C(7a)-C(3a)-N(3)	-156.3(4)
O(1)-C(7a)-C(3a)-C(4)	84.2(5)
C(7)-C(7a)-C(3a)-C(4)	-37.8(7)
C(4)-C(3a)-N(3)-C(2)	-91.8(6)
C(7a)-C(3a)-N(3)-C(2)	28.5(5)
C(4)-C(3a)-N(3)-C(7')	75.9(6)
C(7a)-C(3a)-N(3)-C(7')	-163.9(5)
C(7')-N(3)-C(2)-O(8)	-1.5(9)
C(3a)-N(3)-C(2)-O(8)	166.5(6)
C(7')-N(3)-C(2)-O(1)	-178.8(4)
C(3a)-N(3)-C(2)-O(1)	-10.7(6)
O(8)-C(2)-O(1)-C(7a)	169.2(5)
N(3)-C(2)-O(1)-C(7a)	-13.3(6)
C(3a)-C(7a)-O(1)-C(2)	31.0(5)
C(7)-C(7a)-O(1)-C(2)	156.6(5)
C(2)-N(3)-C(7')-O(11)	-19.4(8)

C(3a)-N(3)-C(7')-O(11)	174.5(5)
C(2)-N(3)-C(7')-O(14)	161.2(5)
C(3a)-N(3)-C(7')-O(14)	-5.0(7)
O(11)-C(7')-O(14)-C(1')	-0.2(9)
N(3)-C(7')-O(14)-C(1')	179.2(4)
C(7')-O(14)-C(1')-C(2''')	-65.7(7)
C(7')-O(14)-C(1')-C(2'')	59.4(8)
C(7')-O(14)-C(1')-C(2')	177.8(6)

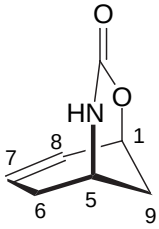


*(±)-(1*R*,2*S*,4*S*)-1-(2-Bromo-7-azabicyclo[2.2.1]hept-7-yl)-2,2,2-trifluoroethanone* (**840**). A soln. of **729** (51 mg, 144 μmol) in THF (2.5 ml) was cooled to 0°, treated with NaH (9.5 mg of a 55% suspension in oil, 217 μmol), allowed to warm to r.t., stirred at 50° for 21 h and under reflux for 22 h, cooeld to r.t., and poured into H_2O (10 ml). The mixture was extracted with CH_2Cl_2 (4 x 15 ml). The combined organic phases were washed with brine (10 ml), and the aq. phase was extracted with CH_2Cl_2 (10 ml). The combined organic phases were dried (Na_2SO_4) and evaporated. FC (10 g of silica gel, cyclohexane/AcOEt 9:1) of the colourless oil (43.6 mg) gave **840** (10 mg, 25%) as a colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.37. ^{1}H-NMR (300 MHz, $CDCl_3$, *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). ^{13}C-NMR (75 MHz, $CDCl_3$, *ca*. 3:2 mixture of diastereoisomers, minor diastereoisomer in *italics*): *64.94*, 63.02 (2*d*, C(1)); *57.2*, 55.35 (2*d*, C(4)); 47.83, *46.39* (2*d*, C(2)); 44.22, *42.36* (2*t*, C(3)); *29.43*, 28.72, 27.25, *26.50* (4*t*, C(5), C(6)). ^{19}F-NMR (282 MHz, $CDCl_3$, *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, $[M + Na]^+$).



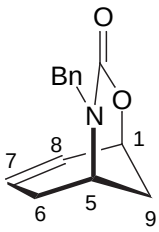
(±)-(1R,5R*,8R*)-8-Iodo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one* (**795**).

A soln. of **712** (1 g, 5.06 mmol) in Et_2O (50 ml) was treated with K_2CO_3 (1.4 g, 10.14 mmol) and I_2 (2.58 g, 10.14 mmol), stirred at r.t. for 24 h, diluted with AcOEt (150 ml), and washed with sat. aq. $Na_2S_2O_5$ soln. The aq. phase was extracted with AcOEt (2 x 150 ml). Drying (Na_2SO_4) and evaporation of the combined organic phases gave brown amorphous **795** (1.42 g, quant.). R_f (cyclohexane/AcOEt 3:1) 0.03. FT-IR (1%, $CDCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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, $[M - I - CO_2]^+$).



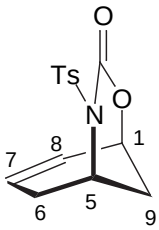
2-Oxa-4-azabicyclo[3.3.1]non-7-en-3-one (**796**).

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, CH_2Cl_2/acetone 5:2) of the residue gave colourless crystalline **796** (533 mg, 75%). R_f (CH_2Cl_2/MeOH 9:1) 0.53. M.p.: 202.9–204.5°. FT-IR (0.5%, $CHCl_3$): 3442*w*, 3008*w*, 1701*s* (C=O), 1452*w*, 1450*m*, 1420*m*, 1412*m*, 1350*w*, 1329*w*, 1296*w*, 1259*w*, 1107*m*, 1058*m*, 1019*w*, 976*w*, 966*w*, 913*w*, 849*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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*, CH_2C(6)); 2.21 (*dddt*, *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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 154.99 (*s*, C=O); 129.96, 125.59 (2*d*, C(7), C(8)); 67.99 (*d*, C(1)); 44.27 (*d*, C(5)); 34.87, 26.85 (2*t*, 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**).

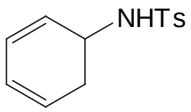
A suspension of **796** (115 mg, 0.83 mmol) in THF (10 ml) was cooled to –78°, treated dropwise with 1.5M BuLi in hexane(0.6 ml, 0.91 mmol), stirred for 15 min, treated with BnBr (0.29 ml, 2.47 mmol), stirred for 22 h while warming to r.t., and poured into sat. aq. NH_4Cl soln. The mixture was extracted with AcOEt (3 x 50 ml. The combined organic phases were dried (Na_2SO_4) 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%). R_f (cyclohexane/AcOEt 1:1) 0.27. M.p.: 93.5–94.0°. FT-IR (1.5%, $CHCl_3$): 3008*w*, 2944*w*, 1680*s* (C=O), 1496*w*, 1448*m*, 1422*w*, 1393*w*, 1358*w*, 1330*w*, 1291*w*, 1144*w*, 1126*m*, 1067*w*, 1039*w*, 977*w*, 942*w*, 847*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.75-4.71 (*m*, H–C(1)); 4.07 (*d*, *J* = 15.6, PhC*H*'); 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 153.67 (*s*, C=O); 137.24 (*s*); 129.25 (*d*), 128.58 (2*d*), 127.56 (2*d*), 127.44 (*d*), 125.69 (*d*) (arom. C, C(7), C(8)); 67.69 (*d*, C(1)); 50.97 (*t*, Ph*C*H_2); 48.30 (*d*, C(5)); 31.18, 28.10 (2*t*, C(6), C(9)). ESI-MS: 481 (100, [2 *M* + 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**).

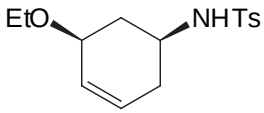
A suspension of **796** (100 mg, 0.72 mmol) in THF (8 ml) was cooled to 0°, treated with NaH (78 mg, of a 55% suspension in oil, 1.79 mmol), stirred for 0.5 h, treated with TsCl (164 mg, 0.86 mmol), and stirred for 2.5 h while warming to r.t. The mixture was acidified with 1M HCl to pH 4.5, diluted with H_2O (20 ml), and extracted with Et_2O (3 x 25 ml) and CH_2Cl_2 (3 x 30 ml). The combined organic phases were dried (Na_2SO_4) 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%). R_f (cyclohexane/AcOEt 1:1) 0.49. M.p.: 174.0–174.7°. FT-IR (1%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.87 (*d*, *J* = 8.4, 2 arom. H); 7.30 (*d*, *J* =

8.1, 2 arom. H); 6.05–6.02 (*m*, H–C(7), H–C(8)); 4.93–4.88 (*m*, H–C(5)); 4.76–4.71 (*m*, H–C(1)); 2.89 (*dm*, *J* = 19.3, H–C(6)); 2.53 (br. *dd*, *J* = 19.0, 3.6, H'–C(6)); 2.43 (*s*, Me); 2.25 (*dm*, *J* = 13.4, H–C(9)); 2.10 (*dt*, *J* = 13.7, 2.3, H'–C(9)). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.83 (*s*, C=O); 148.67, 144.70 (2*s*); 129.93, 124.78 (2*d*, C(7), C(8)); 129.20 (2*d*), 128.68 (2*d*) (4 arom. C); 68.61 (*d*, C(1)); 50.74 (*d*, C(5)); 34.08 (*q*, Me); 28.12, 21,76 (2*t*, C(6), C(9)). ESI-MS: 625 (1, $[2\,M + K]^+$), 609 (47, $[2\,M + Na]^+$), 348 (17, $[M + Na + MeOH]^+$), 332 (21, $[M + K]^+$), 316 (100, $[M + Na]^+$), 294 (8, $[M + 1]^+$). Anal. calc. for $C_{14}H_{15}NO_4S$ (293.34): C 57.32, H 5.15, N 4.77; found: C 57.13, H 5.16, N 4.62.



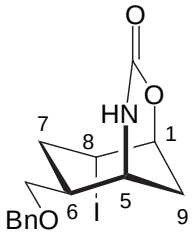
N-*(Cyclohexa-2,4-dienyl)-(4-methylbenzene)sulfonamide* (**803**).

A soln. of **798** (10.9 mg, 37 μmol) in THF (5 ml) was purged with Ar, treated with $Pd(PPh_3)_4$ (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. R_f (cyclohexane/AcOEt 9:1) 0.90. FT-IR (0.5%, $CHCl_3$): 3379*w* (NH), 3009*w*, 2927*w*, 1599*w*, 1403*m*, 1334*m*, 1305*w*, 1158*s*, 1094*m*, 1034*m*, 909*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, CH_2(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, $[M + 18]^+$).



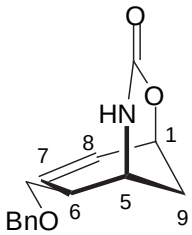
N-*(*c-*5-Ethoxycyclohex-3-enyl)-(4-methylbenzene)sulfonamide* (**804**).

A soln. of **798** (9.7 mg, 33 μmol) in EtOH (6 ml) was purged with Ar, treated with $Pd(PPh_3)_4$ (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. R_f (cyclohexane/AcOEt 1:1) 0.66. FT-IR (1%, $CHCl_3$): 3312*w*, 3008*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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, MeC*H*$_2$O); 2.43 (*s*, Ph*Me*); 2.18–2.14 (*m*, CH_2(2)); 1.74 (*t*, *J* = 4.5, CH_2(6)); 1.21 (*t*, *J* = 7.0, *Me*CH_2O). ESI-MS: 629 (3, $[2\,M + K]^+$), 613 (30, $[2\,M + Na]^+$), 313 (5, $[M + NH_4]^+$), 296 (35, $[M + 1]^+$).



*(±)-(1*R*,5*S*,6*R*,8*R*)-6-(Benzyloxymethyl)-8-iodo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one* (**799**).

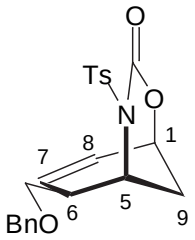
A soln.of **716** (1.0 g, 3.15 mmol) in Et_2O (50 ml) was treated with K_2CO_3 (0.87 g, 6.30 mmol) and I_2 (1.6 g, 6.3 mmol), stirred at r.t. for 42 h, diluted with AcOEt ((150 ml), and washed with sat. aq. $Na_2S_2O_5$ soln. (150 ml). The aq. phase was extracted with AcOEt (2 x 150 ml). Drying (Na_2SO_4) and evaporation of the combined organic phases gave orange amorphous **799** (1.48 g, quant.). R_f (CH_2Cl_2/MeOH 9:1) 0.71. M.p.: 134–136°. FT-IR (1.5%, $CHCl_3$): 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*, 1053*m*, 1036*w*, 903*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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) (PhC*H*$_2$); 3.74–3.69 (*m*, H–C(5)); 3.39–3.30 (*m*, CH_2–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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 128.46 (2*d*), 127.88 (*d*), 127.68 (2*d*); 76.81 (*d*, C(1)); 73.28 (*t*, Ph*C*H$_2$); 70.08 (*t*, *C*H$_2$–C(6)); 46.20 (*d*, C(5)); 37.52 (*d*, C(6)); 29.58 (*t*, C(9)); 26.74 (*d*, C(8)); 25.91 (*t*, C(7)). ESI-MS: 797 (13, [2 *M* + Na]$^+$), 426 (10, [*M* + K]$^+$), 410 (100, [*M* + Na]$^+$).



*(±)-(1*R*,5*S*,6*R*)-6-(Benzyloxymethyl)-2-oxa-4-azabicyclo[3.3.1]non-7-en-3-one* (**800**).

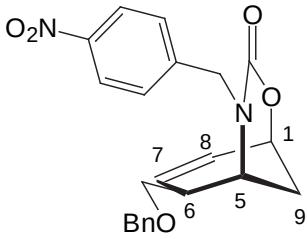
A soln. of **799** (1.48 g, *ca*. 3.15 mmol) in THF (50 ml) was treated with DBU (0.56 ml, 3.78 mmol), refluxed for 50 h, and evaporated. FC (40 g of silica gel, cyclohexane/AcOEt 2:5) of the brown residue gave yellow amorphous **800** (640 mg, 78%). R_f (CH_2Cl_2/MeOH 9:1) 0.62. M.p.: 164.0–165.0°. FT-IR (1%, $CHCl_3$): 3442*w* (NH), 3015*m*, 2866*w*, 1705*s* (C=O), 1439*m*, 1412*w*, 1357*w*, 1291*w*, 1191*m*, 1090*w*, 1060*m*, 1028*w*, 980*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.41–7.29 (5 arom. H); 6.06 (*dddd*, *J* = 10.0, 5.6, 2.5, 1.3, H–C(8)); 5.54 (*dt*, *J* = 10.0, 1.6, H–C(7)); 5.42–5.30 (br. *s*, NH); 4.78–4.74 (*m*, H–C(1)); 4.55, 4.51 (2*d*, *J* = 12.1, PhC*H*$_2$); 3.94–3.89 (*m*, H–C(5)); 3.58 (*dd*, *J* = 9.3, 6.2, CH–C(6)); 3.45 (*dd*, *J* = 10.3, 9.3, CH'–C(6)); 2.73–2.64 (*m*, H–C(6)); 2.25 (br. *dt*, *J* = 13.4, 3.3, H–C(9)); 1.90 (*ddt*, *J* = 13.4, 2.2, 1.9, H'–C(9)). ^{13}C-NMR (75 MHz, $CDCl_3$): 153.52 (*s*, C=O); 137.56 (*s*); 129.84, 126.67 (2*d*, C(7), C(8));128.49 (2*d*), 127.93 (*d*), 127.65 (2*d*); 73.29 (*t*, Ph*C*H$_2$); 69.37 (*t*, *C*H$_2$–C(6));

68.05 (*d*, C(1)); 45.41, 43.24 (2*d*, 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 $C_{15}H_{17}NO_3$ (259.30): C 69.48, H 6.61, N 5.40; found: C 69.45, H 6.42, N 5.36.



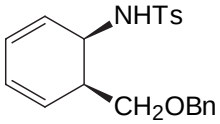
*(±)-(1*R*,*5*S*,*6*R**)-6-(Benzyloxymethyl)-4-(toluene-4-sulfonyl)-2-oxa-4-azabicyclo[3.3.1]non-7-en-3-one* (**801**).

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 H_2O (25 ml) and CH_2Cl_2 (25 ml). The organic phase was separated and the aq. phase was extracted with CH_2Cl_2 (25 ml). The combined organic phases were dried (Na_2SO_4) 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%). R_f (cyclohexane/AcOEt 1:1) 0.50. M.p.: 175.6–177.1°. FT-IR (0.5%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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 (2*d*, *J* = 11.5, PhC*H*$_2$); 4.11 (*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, CH_2(9)). ^{13}C-NMR (75 MHz, $CDCl_3$): 148.59 (*s*, C=O); 144.71, 138.00, 135.89 (3*s*); 132.07, 124.69 (2*d*, C(7), C(8)), 129.17 (2*d*), 128.71 (2*d*), 128.30 (2*d*), 127.82 (2*d*), 127.60 (*d*) (Ph, Ts); 73.50 (*t*, Ph*C*H$_2$); 70.67 (*t*, *C*H$_2$–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, $[M + 1]^+$).



*(±)-(1*R**,5*S**,6*R**)-6-(Benzyloxymethyl)-4-(4-nitrobenzyl)-2-oxa-4-azabicyclo[3.3.1]non-7-en-3-one* (**802**).

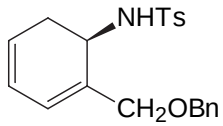
A soln. of **800** (45 mg, 173 μmol) in DMF (2 ml) was cooled to 0°, treated with NaH (9.1 mg of a 55% suspension in oil, 208 μmol), stirred at 0° for 30 min, treated with 4-nitrobenzyl bromide (75 mg, 347 μmol), stirred for 23 h while warming to r.t., and poured into sat. aq. NH_4Cl soln. The mixture was extracted with AcOEt (3 x 10 ml). The combined organic phases were dried (Na_2SO_4) 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%, $CHCl_3$): 3023*w*, 3011*w*, 2970*w*, 2864*w*, 1680*s* (C=O), 1606*w*, 1523*m*, 1491*w*, 1454*m*, 1415*w*, 1347*s*, 1134*w*, 1122*w*, 1110*w*, 1086*w*, 1005*w*, 956*w*, 909*w*, 857*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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. *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, ArC*H*); 4.81–4.76 (*m*, H–C(1)); 4.61, 4.55 (2*d*, *J* = 11.5, PhCH_2O); 4.13 (*d*, *J* = 15.6, ArC*H*'); 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, $CDCl_3$): 153.77 (*s*, C=O); 147.11, 145.12, 136.97 (3*s*, Ph); 129.42, 126.76 (2*d*, C(7), C(8)); 128.53 (2*d*), 128.49 (2*d*), 128.16 (*d*), 127.91 (2*d*), 123.60 (2*d*) (Ar, Ph); 73.34 (*t*, Ph*C*H_2O); 69.66 (*t*, *C*H_2–C(6)); 68.17 (*d* (C(1)); 51.35 (*t*, Ph*C*H_2N); 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]$^+$).



N-*[*c*-6-(Benzyloxymethyl)cyclohexa-2,4-dienyl]-(4-methylbenzene)sulfonamide* (**805**).

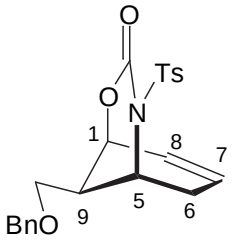
A degassed (purged with Ar) soln. of **801** (10 mg, 24 μmol) in THF (5 ml) was treated with $Pd(PPh_3)_4$ (3 mg, 2.4 μmol), degassed, stirred at r.t. for 21 h, and evaporated. FC (2 g of silica gel, cyclohexane/AcOEt 4.5:1) of the brown oil gave **805** (6.2 mg, 70%) as a colourless oil. R_f (cyclohexane/AcOEt 1:1) 0.81. FT-IR (0.5%, $CHCl_3$): 3367*m* (NH), 3032*s*, 3013*s*, 2927*s*, 2864*m*, 1694*s*, 1599*m*, 1496*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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 (*ddt*, *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, PhC*H*); 4.41 (*d*, *J* =11.8, PhC*H*');

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-(Benzyloxymethyl)cyclohexa-2,4-dienyl]-(4-methylbenzene)sulfonamide* (**806**).

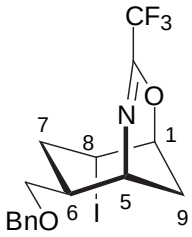
A degassed (purged with Ar) soln. of **801** (10 mg, 24 μmol) in THF (5 ml) was treated with LiCl (1 mg, 23 μmol) and $Pd(PPh_3)_4$ (3 mg, 2.4 μmol), degassed, stirred at r.t. for 1 h, refluxed for 22 h, cooled to r.t., and evaporated. FC (2 g of silica gel, cyclohexane/AcOEt 9:2) of the yellow oil gave **806** (3.5 mg, 39%) as a colourless oil. R_f (cyclohexane/AcOEt 1:1) 0.78. FT-IR (0.5%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 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, PhC*H*); 4.35 (*d*, *J* = 12.1, PhC*H*'); 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*, CH_2(6)). ESI-MS (the sample was contaminated with HCl): 462 (16), 460 (35, [*M* + HCl + MeOH + Na]$^+$); 446 (25), 444 (53, [*M* + HCl + K]$^+$).



*(±)-(1*R*,5*S*,9*S*)-9-(Benzyloxymethyl)-4-(toluene-4-sulfonyl)-2-oxa-4-azabicyclo[3.3.1]non-7-en-3-one* (**807**).

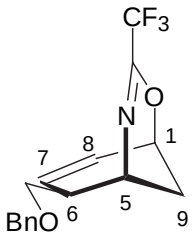
Under Ar, neat **801** (11.4 mg, 27 μmol) was heated at 160° for 3 d. After cooling to r.t. FC (2 g of silica gel, cyclohexane/AcOEt 3:1) gave **807** (5.9 mg, 52%) as a colourless oil. R_f (cyclohexane/AcOEt 1:1) 0.64. FT-IR (0.5%, $CHCl_3$): 3021*w*, 1725*s* (C=O), 1593*w*, 1494*w*, 1455*w*, 1399*m*, 1383*m*, 1362*m*, 1265*s*, 1131*s*, 1089*s*, 1063*w*, 909*w*, 893*w*. ^{1}H-NMR (3000 MHz, $CDCl_3$): 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 (2*d*, *J* = 11.8, PhC*H*$_2$); 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)). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 (Ph*C*H$_2$); 70.12 (*C*H$_2$–C(9)); 67.76 (C(1)); 52.45 (C(5)); 36.73,

35.26 (C(6), C(9)); 21.76 (Me). ESI-MS: 452 (27, $[M + K]^+$); 436 (86, $[M + Na]^+$); 431 (87, $[M + NH_4]^+$); 414 (100, $[M + 1]^+$).



*(±)-(1*R*,5*S*,6*R*,8*R*)-6-(Benzyloxymethyl)-8-iodo-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]non-3-ene* **828**.

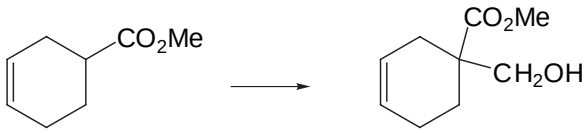
A solution of **828** (30 mg, 95 μmol) in AcOH (3 ml) was treated with NIS (65 mg, 287 μmol), stirred at r.t. for 45 min., and evaporated. FC (2 g of silica gel, hexane/AcOEt 8:1) gave **828** (36 mg, 86%) as a yellow oil. R_f (cyclohexane/AcOEt 3:1) 0.65. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.25 (5 arom. H); 4.76–4.72 (*m*, H–C(1)); 4.68–4.64 (*m*, H–C(8)); 4.57, 4.49 (2*d*, *J* = 11.8, PhCH_2); 4.00–3.96 (*m*, H–C(5)); 3.58 (*dd*, *J* = 9.0, 7.5, CH–C(6)); 3.30 (*dd*, *J* = 9.0, 6.9, CH'–C(6)); 2.68 (*dt*, *J* = 14.3, 1.6, H_{ax}–C(9)); 2.65–2.54 (*m*, H–C(6)); 2.11–2.03 (*m*, H_{eq}–C(7)); 1.88 (*dtd*, *J* = 14.3, 3.9, 1.9, H_{eq}'–C(9)); 1.48 (*ddd*, *J* = 16.2, 12.5, 4.7, H_{ax}'–C(7)). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.00 (*s*); 128.26 (2*d*), 127.52 (3*d*); 73.65 (*d*, C(1)); 73.25 (*t*, Ph*C*H$_2$*);* 71.22 (*t*, *C*H$_2$–C(6)); 48.04 (*d*, C(5)); 38.51 (*d*, C(6)); 30.28 (*t*, C(7)); 26.66 (*d*, C(8)); 24.28 (*t*, C(9)); signals of C(3) and CF_3 hidden by noise..



*(±)-(1*R*,5*S*,6*R**)-6-(Benzyloxymethyl)-3-(trifluoromethyl)-2-oxa-4-azabicyclo[3.3.1]nona-3,7-diene* **827**.

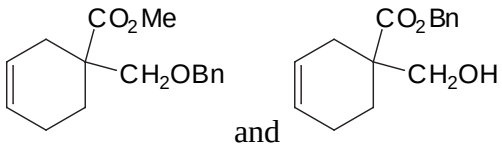
A solution of **828** (36 mg, 82 μmol) in THF (4 ml) was treated with DBU (0.015 ml, 98 μmol), heated under reflux for 24 h, cooled to r.t., and evaporated. FC (2 g of silica gel, hexane/AcOEt 5:1) gave **827** (22 mg, 86%) as a colourless oil. R_f (cyclohexane/AcOEt 3:1) 0.46. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.38–7.24 (5 arom. H); 6.07 (*dd*, *J* = 10.0, 1.6, H–C(7)); 5.98 (*dddd*, *J* = 10.0, 5.3, 2.5, 1.3, H–C(8)); 4.94–4.89 (*m*, H–C(1)); 4.60, 4.55 (2*d*, *J* = 11.8, PhCH_2); 4.11–4.06 (*m*, H–C(5)); 3.74 (*dd*, *J* = 9.0, 6.9, CH–C(6)); 3.42 (*t*, *J* = 9.0, CH'–C(6)); 2.92–2.84 (*m*, H–C(6)); 2.07 (*dddd*, *J* = 13.4, 4.4, 3.4, 1.6, H_{eq}–C(9)); 1.86 (*ddd*, *J* = 13.4, 2.2, 1.2, H_{ax}'–C(9)). ^{13}C-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; signals of C(3) and CF_3 and of one aromatic CH hidden by noise. ^{19}F-NMR (282 MHz, $CDCl_3$): –73.53. ESI-MS: 350 (16, $[M + K]^+$), 334 (100, $[M + Na]^+$), 312 (89, $[M + 1]^+$).

Part 4.



Methyl 1-(Hydroxymethyl)cyclohex-3-enecarboxylate (**830**).

A soln of *i*Pr$_2$NH (1.58 ml, 11.3 mmol) in THF (40 ml) was cooled to –20°, treated dropwise 1.5M 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.* 0.4M 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. NH_4Cl soln. (60 ml). The mixture was extracted with Et_2O (3 x 100 ml). The combined organic phases were dried (Na_2SO_4) 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%, $CHCl_3$): 3620*w* (OH), 3008*m*, 2953*m*, 2928*m*, 2847*w*, 1725*s* (C=O), 1655*w*, 1437*m*, 1390*w*, 1343*w*, 1298*m*, 1272*m*, 1172*m*, 1079*m*, 1038*s*, 968*w*, 891*w*, 872*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.71–5.59 (*m*, H–C(3), H–C(4)); 3.72 (*s*, MeO); 3.67 (*d*, *J* = 6.5, CH_2–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). ^{13}C-NMR (75 MHz, $CDCl_3$): 176.99 (*s*, C=O); 125.99, 123.98 (2*d*, C(3), C(4)); 66.34 (*t*, *C*H_2–C(1)); 52.11 (*q*, MeO); 46.66 (*s*, C(1)); 29.39, 26.31, 21.93 (3*t*, 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**).

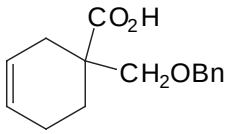
A suspension of NaH (127 mg of a 60% suspension in oil, 3.17 mmol) in THF (5 ml) was cooled to 0°, treated dropwise with a soln. of **830** (450 mg, 2.64 mmol) in THF (2 ml), stirred for 1 h, treated with Bu_4NI (195 mg, 0.53 mmol) and 18-crown-6 (1 mg) and dropwise with BnBr (0.47 ml, 3.97 mmol), stirred for 1 d at r.t., treated with 0.1N HCl (1 ml) and poured into H_2O (30 ml). The mixture was extracted with Et_2O (3 x 30 ml). The combined organic phases were washed with sat. aq. $NaHCO_3$ soln. and brine (75 ml of each), dried (Na_2SO_4), 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**:

R_f (cyclohexae/AcOEt 3:1) 0.66. FT-IR (1.5%, $CHCl_3$): 3066*w*, 3008*w*, 2952*m*, 2922*m*, 2846*m*, 1729*s* (C=O), 1496*w*, 1454*m*, 1437*m*, 1363*w*, 1283*w*, 1170*w*, 1098*s*, 1048*w*, 1028*w*, 988*w*, 932*w*, 909*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.37–7.24 (5 arom. H); 5.65–5.62 (*m*, H–C(3), H–C(4)); 4.50 (*s*, PhCH_2); 3.69 (*s*, MeO); 3.56, 3.49 (2*d*, *J* = 8.7, CH_2–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). ^{13}C-NMR (75 MHz, $CDCl_3$): 175.82 (*s*, C=O); 138.19 (*s*); 128.14 (2*d*), 127.34 (*d*), 127.22 (2*d*), 126,02 (*d*), 124.51 (*d*) (Ph, C(3), C(4)); 74.88, 73.16 (2*t*, Ph*C*H_2O*C*H_2); 51.88 (*q*, MeO); 46.23 (*s*, C(1)); 30.31, 26.82, 22.91 (3*t*, C(2), C(5), C(6)). EI-MS: 260 (1, M^+), 242 (3), 230 (2), 210 (1), 200 (1, [*M* – $C_2H_4O_2$]$^+$), 183 (2, [*M* – Ph]$^+$),169 (4, [*M* – Bn]$^+$), 151 (17), 139 (21), 118 (5), 107 (9), 91 (100).

Data of **832**:

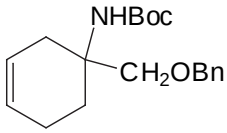
R_f (cyclohexane/AcOEt 3:1) 0.24. FT-IR (1.5%, $CHCl_3$): 3508*w* (OH), 3068*w*, 3008*m*, 2926*m*, 2845*w*, 1726*s* (C=O), 1654*w*, 1603*w*, 1498*w*, 1455*m*, 1439*m*, 1377*w*, 1343*w*, 1296*m*, 1268*s*, 1170*s*, 1078*m*, 1040*s*, 966*m*, 907*w*, 824*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.28 (5 arom. H); 5.71–5.61 (*m*, H–C(3), H–C(4)); 5.16 (*s*, PhCH_2); 3.69 (br. *s*, CH_2–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). ^{13}C-NMR (75 MHz. $CDCl_3$): 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 (*C*H_2–C(1), Ph*C*H_2); 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 H_2O (5 ml) was treated with LiOH·H_2O (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 1M HCl to pH ≈ 1 and extracted with AcOEt (5 x 20 ml). The combined organic phases were dried (Na_2SO_4) 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. R_f (cyclohexane/AcOEt 3:1) 0.17. FT-IR (1.5%, $CHCl_3$): 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*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.14 (5 arom. H); 5.69–5.59 (*m*, H–C(3), H–C(4)); 4.54 (*s*, PhCH_2); 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.73; 128.26 (2C), 127.53, 127.40 (2C), 126.03, 124.23 (Ph, C(3), C(4)); 74.08,

73.42 (Ph*C*H$_2$O*C*H$_2$); 45.83 (C(1)); 29.97, 26.61, 22.09 (C(2), C(5), C(6)); C=O signal hidden by noise. EI-MS: 246 (1, M^+) 228 (2), 216 (1), 200 (2), 183 (1), 155 (2, [M – Bn]$^+$), 137 (12), 125 (14), 107 (12), 91 (100).



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 Et$_3$N (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 *t*BuOH (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. NaHCO$_3$ soln. (10 ml), and extracted with Et$_2$O (3 x 20 ml). The combined organic phases were dried (Na$_2$SO$_4$) and evaporated. FC (15 g of silica gel, cyclohexane/AcOEt 12:1) of the brown oil (198 mg) gave **834** (56 mg, 28%) al a colourless oil. Elution with MeOH gave a byproduct (122 mg) presumably the corresponding amine. R_f (cyclohexane/AcOEt 3:1) 0.68. FT-IR (0.5%, CHCl$_3$): 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*. ^{1}H-NMR (300 MHz, CDCl$_3$): 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*, PhC*H*$_2$); 3.67, 3.58 (2*d*, *J* = 9.3, CH$_2$–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*, Me$_3$C). ^{13}C-NMR (75 MHz, CDCl$_3$): 154.80 (*s*, C=O); 138.47 (*s*); 128.24 (2*d*), 127.41 (3*d*), 126.63 (*d*), 123.70 (*d*) (Ph, C(3), C(4)); 78.85 (*s*, Me$_3$*C*); 73.39, 73.19 (2*t*, Ph*C*H$_2$O*C*H$_2$); 53.77 (*s*, C(1)); 33.55 (*t*); 28.55 (*q*, *Me*$_3$C); 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 – C$_4$H$_8$]$^+$), 236 (93), 218 (100, [M + 1 – C$_4$H$_8$ – CO$_2$]$^+$).

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Curriculum Vitae

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