Michael Schalli, Dipl.-Ing., BSc

Carbasugars for β-Galactosidase Related Lysosomal Diseases and for Investigation of G_{M1}-Ganglioside Metabolism

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Ao.Univ.-Prof. Dipl.-Ing. Dr.techn. Arnold E. Stütz

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Meinen Eltern

Monika und Ernst Schalli

Zwei Dinge sind zu unserer Arbeit nötig:

Unermüdliche Ausdauer und die Bereitschaft,

etwas, in das man viel Zeit und Arbeit gesteckt hat,

wieder wegzuwerfen.

Albert Einstein

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EIDESSTATTLICHE ERKLÄRUNG

Ich erkläre an Eides statt, dass ich die vorliegende Arbeit selbstständig verfasst, andere als die angegebenen Quellen/Hilfsmittel nicht benutzt, und die den benutzten Quellen wörtlich und inhaltlich entnommenen Stellen als solche kenntlich gemacht habe. Das in TUGRAZonline hochgeladene Textdokument ist mit der vorliegenden Dissertation identisch.

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Abstract

G_{M1}-Gangliosidosis belongs to the group of lysosomal storage deseases which are caused by single mutations in genes which encode the lysosomal enzymes for the metabolism of carbohydrates in living organisms. A promising approach to enhance lysosomal enzyme activity is the so called “chaperon mediated therapy”. In this study, carbacyclic carbohydrate analouges were prepared to test them as glycosidase inhibitors and potential chemical chaperones for this type of desease. Starting from commercial available monosaccharides highly functionalized five and six membered “carbasugars” were synthesized and compared to the benchmarkmolecule *N*-octyl-4-epi-β-valienamine (NOEV).

Kurzfassung

G_{M1}-Gangliosidose gehört zur Gruppe der lysosomalen Speicherkrankheiten die durch Punktmutationen in Genen, die für die Codierung der lysosomalen Enzyme des Kohlenhydrat-Stoffwechsels zuständig sind, hervorgerufen wird. Ein vielversprechender Ansatz um die Aktivität der lysosomalen Enzyme zu steigern, ist die „Chaperon-Therapie”. In dieser Arbeit wurden carbazyklische Kohlenhydrat Analoga synthetisiert und auf ihre Aktivität als Glycosidasen-Inhibitoren und chemische Chaperone getestet. Ausgehend von kommerziell erhältlichen Monosacchariden wurden hoch funktionalisierte Fünf- und Sechsringe synthetisiert und mit dem Benchmark-Molekül *N*-octyl-4-epi-β-valienamin (NOEV) verglichen.

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1 Introduction

1.1 Carbohydrates

Carbohydrates are widespread in nature. Their functions reach from simple energy storage to recognition of cell-cell interactions. The term carbohydrate was initially exclusively used for molecules which contain oxygen, hydrogen and carbon with the formula $C_nH_{2n}O_n$. Due to the fact, that there are many different types of sugars, containing heteroatoms such as sulfur, nitrogen, selenium or deoxygenated sugars such as rhamnose or fucose, this traditional definition is not true anymore. Nowadays, the definition of carbohydrates has changed to polyhydroxyaldehydes and polyhydroxyketones and their derivatives. As shown in figure **1**, monosaccharides can have different numbers of carbon atoms, different configurations, constitutions, etc. There are also many reactions types know which can derivatize monosaccharide units. (figure **2**).

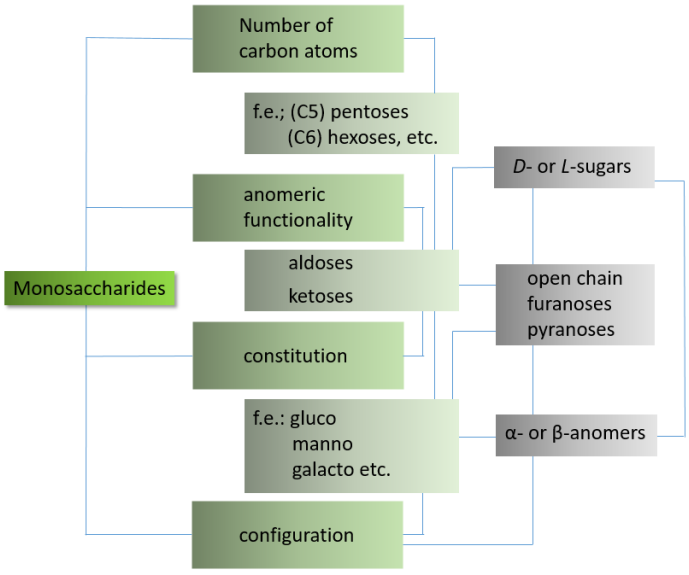


Figure 1: Carbohydrate classification.

The terminus “oligosaccharide” means, that 2 up to 10 monosaccharide units are linked together via glycosidic bonds. Polysaccharides have more than 10 such units linked together. There are homooligo- and homopolysaccharides where the entire molecule

consists of only one repeating monosaccharide as well as heterooligo- and heteropolysaccharides with different types of repeating units that are linked together. Two of the widely known macromolecules that contain monosaccharide units are starch and cellulose, where the glycosidic linkage of the glucose units distinguishes the properties of the macromolecules.

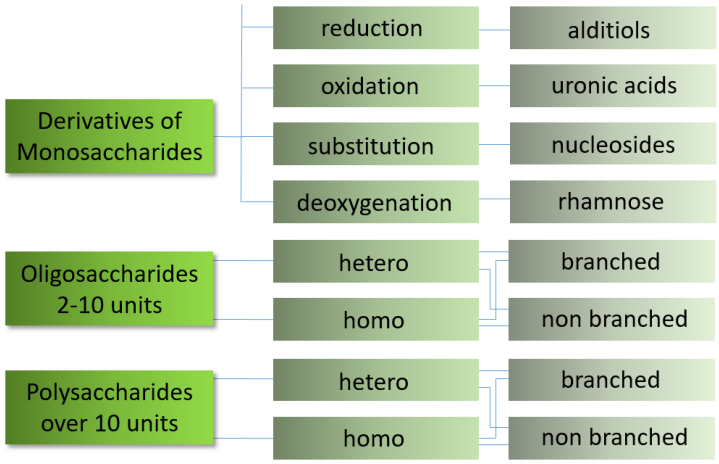


Figure 2: Different classes of modified saccharides.

Carbohydrates may also be linked to other biomolecules, for example, lipids, amino acids or proteins to create so called glycoconjugates. In recent decades, the pronounced importance of carbohydrate containing structures in biology was discovered, such as in transmission of chemical signals, for example, through carbohydrate- protein interactions. Carbohydrate mediated cell-cell recognition, cell development, cell growth and cell-cell adhesion are also important metabolic roles.[1]

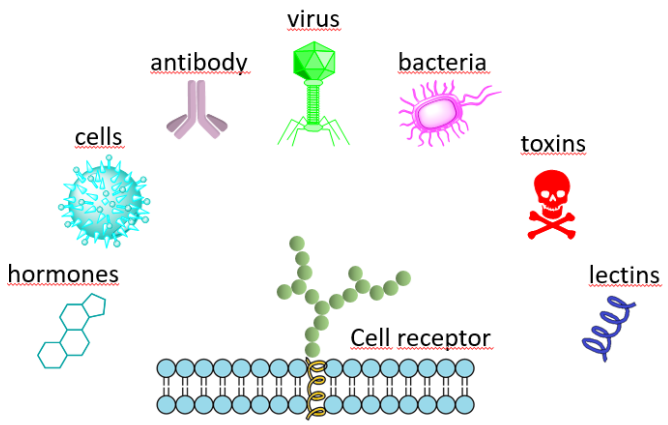


Figure 3: Carbohydrate recognising biological systems docking onto the cell surface.[2]

The improved understanding of biological processes and the development of new analytical devices have changed the classic picture of the carbohydrate as a simple energy source. The often highly functionalized carbohydrate derivatives as well as simple carbohydrate units serve as building blocks in DNA or RNA, as well as core molecules in various coenzymes.

Due to the fact, that carbohydrates are highly functionalized molecules, with plenty of stereochemical information, their application in medicinical chemistry was clear. Big challenges for these carbohydrate based pharmaceuticals are the challenging syntheses, as well as their physiochemical behaviours. (The glycosidic bond could be hydrolysed, substances are highly polar, etc.) Thus, carbohydrate mimicking substances should be developed to circumvent such disadvantages.

1.2 Carbohydrate processing enzymes

Because carbohydrates are essential for life, there are many enzymes found that build up or degrade carbohydrates in different metabolic pathways. The high variety of these enzymes has made it necessary to divide them into different groups, regarding the specific chemical reaction they catalyse. (Enzyme commission number EC)[3] Glycosyltransferases (EC 2.4) and glycolsylhydrolases (EC 3.2) are the most common families. For glycosidic bond formation catalysed by glycosyltransferases, sugar donors containing a lipid phosphate or nucleosidic phosphate leaving group are used (figure **4**). Glycosylation of lipids, proteins or construction of oligosaccharide chains is feasible.

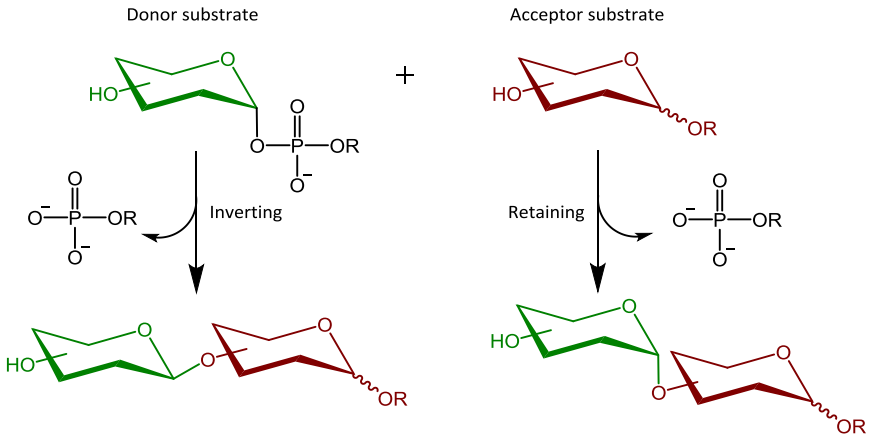


Figure 4: Glycosyltransferases.[4]

Glycosyltransferases play a key role in many biological processes including cellular adhesion, cell wall biosynthesis or cell signalling. They are present in prokaryotes as well as in eukaryotes. In eukaryotic cells, most glycosyltransferases exist as membrane proteins of the Golgi apparatus.[5] They are mainly classified according to the types of sugars they built up and are divided into different subfamilies based on structural similarities (Carbohydrate Active EnZyme [CAZy] database).[6] The catalytical cleavage of glycosidic bonds refers to glycosyl hydrolases which play an important role in the energy management of living organisms.

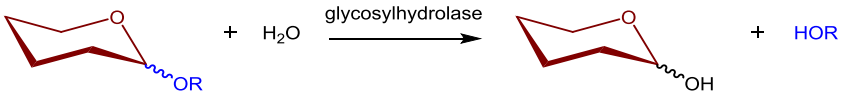


Figure 5: Glycosyl hydrolases can catalyse the hydrolysis of O-, N- and S-linked glycosides.

Glycoside hydrolases (glycosidases) can be classified in different ways:

Exo/endo glycosidases

The definition as *exo/endo* glycosidases is referring to the ability of the enzyme cleaving the glycosidic bond of the substrate at the non reducing end which classifies this particular enzyme as an *exo*-glycosidase or cleaving in the middle of the substrate (*endo*-glycosidase). A large number of *exo*-glycosidases act at the non-reducing end, but a few examples for reducing end *exo*-acting glycosidases are known in literature.[7,8]

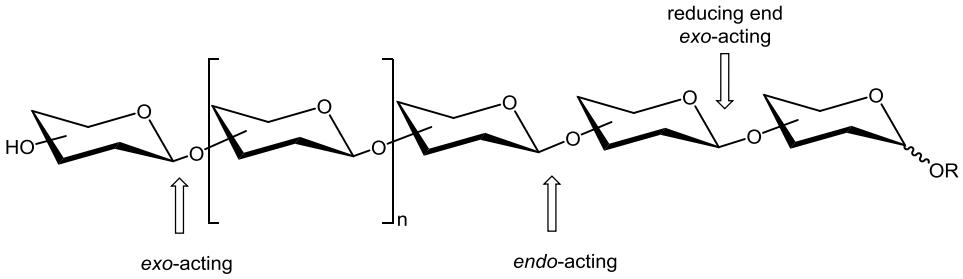


Figure 6.

Enzyme commission number (EC)[9]

The Enzyme commission number is a code for numerical classification schemes of enzymes which is based on the chemical reactions that are catalysed. Different enzymes, that catalyse the same reaction receive the same EC number. If the function of an enzyme is biochemically

identified, the EC commission classifies the enzyme with a code, which could have more than on number if the enzyme catalyses more than one reaction.

Sequence based classification

Glycoside hydrolases have been classified into more than 100 families through algorithmic methods. Parts of the amino acid or nucleotide sequence must be known for a sequence based classification. Separation into larger groups, so called “clans” was suggested by Henrissat and coworkers.[10] The definition of a “clan” is the significant similarity of their catalytic residues, reaction mechanisms and tertiary structures.[6,8]

Reaction mechanism based classification

Two major reaction mechanisms, an “inverting” mechanism and a “retaining” mechanism, were found for glycosyl hydrolases.

Inverting glycosyl hydrolases:

An acid base catalysed reaction mechanism with an oxocarbeniumion transition state leads to the inversion of configuration at the anomeric carbon in one step.[11]

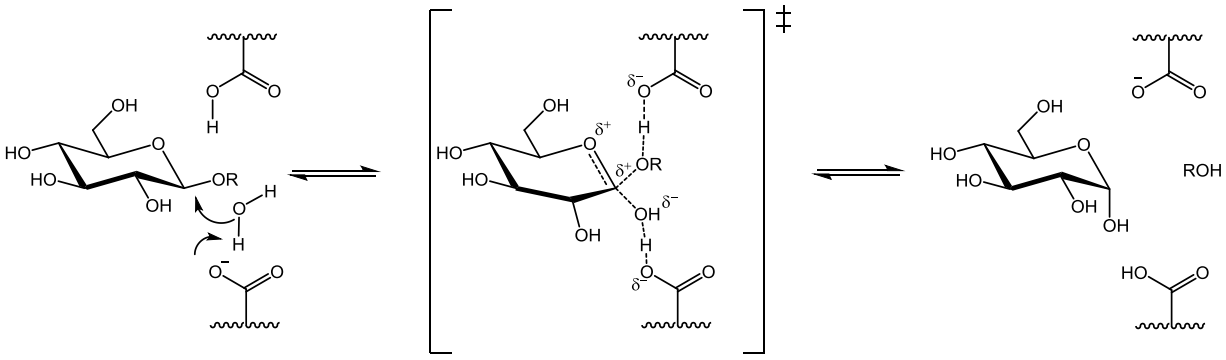


Figure 7: Mechanism for inverting glycosyl hydrolases.

The carboxylate is deprotonating a water molecule, which could attack the anomeric carbon leading to the transition state shown in figure **7**.[11]

Retaining glycosyl hydrolases:

In the first step, the carboxylate directly attacks the anomeric carbon forming the oxocarbenium transition state which gives, under liberation of the aglycon, a covalent linkage with the carbohydrate. In the next step a water molecule is deprotonated and attacks the anomeric center. After the second transition state, a hydrolysed carbohydrate with inverted configuration on C-1 is released (figure **8**).

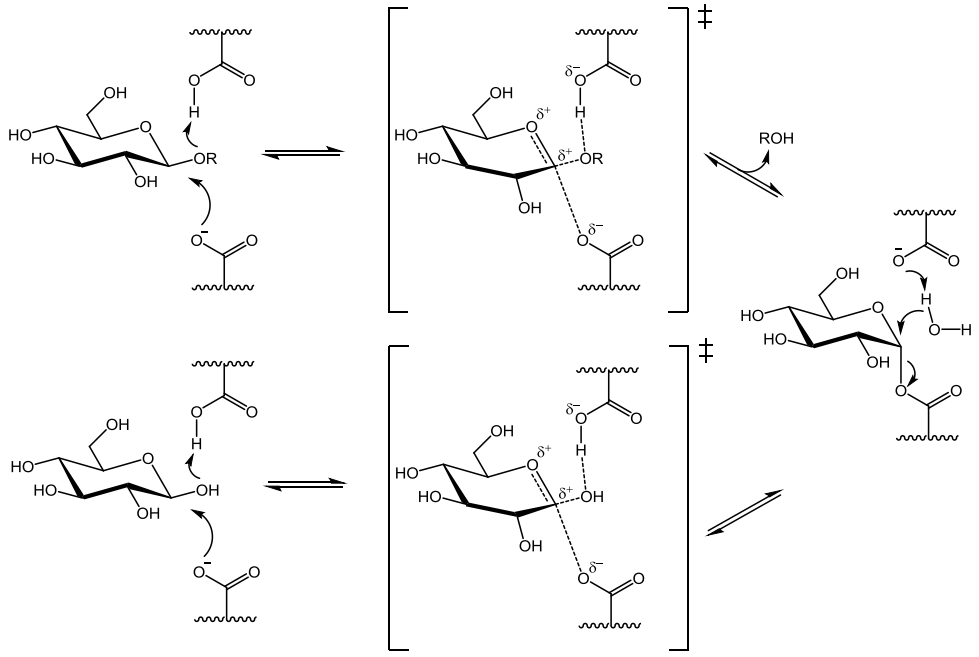


Figure 8: Retaining glycosyl hydrolase mechanism.[11]

1.3 Glycosidase inhibitors

The presence of glycosidases and their vital roles in many different metabolic pathways of living organisms has made it interesting to investigate small molecules which can interact with this type of enzymes. Compounds that are able to decrease the activity of glycosidases are called glycosidase inhibitors. Applications for characterisation and investigation of enzymes and their reaction mechanisms as well as treatment of different metabolic diseases were investigated over the last decades.

Naturally occurring glycosidase inhibitors discovered in organisms such as microbes or plants are known and are, for example, are used for treatment of diseases such as diabetes.[12] The large number of metabolic disorders and the lack of agents for treatment makes it necessary

to find synthetic pathways for glycomimetics that can be used as inhibitors. The structural similarity of sugar based glycosidase inhibitors to the natural substrate of the enzyme can enhance recognition in the active side and makes it feasible to create different types of inhibitors for a wide range of glycosidases. The so called competitive or reversible inhibitors compete with the natural substrate of the enzyme. Higher affinity of the inhibitor to the active side often results in complete inactivation of the enzyme which can be reversed by an increase of the substrate concentration.

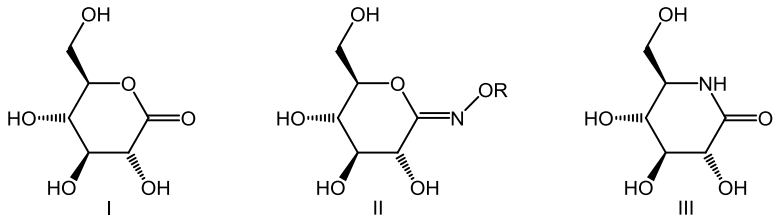


Figure 9: Sugar based reversible inhibitors.[13]

The class of irreversible inhibitors binds covalently to the active side which results in inactivation of the enzyme. These molecules are mostly used for mechanistically studies and not for enzyme modulation. Examples of such inhibitors are shown in figure **10**.

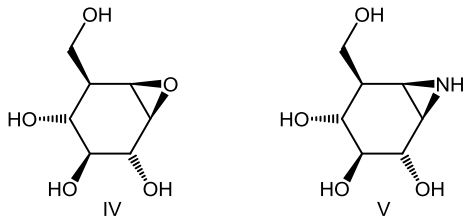


Figure 10: Irreversible glycosidase inhibitors.[14]

1.4 Carbohydrate mimetics with a basic nitrogen

The largest group of biologically active sugar analogues, acting as reversible inhibitors and bearing a trivalent nitrogen, are the imino and isoiminosugars. Their ring-nitrogen can form ionic bonds with the active site of the enzyme influencing the activity. [15]

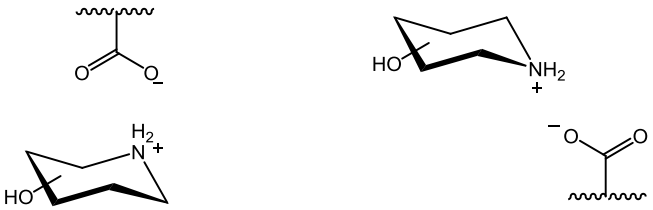


Figure 11: Ionic character of imino and isoiminosugars.[15]

1.4.1 Iminosugars

Iminosugars such as nojirimycins (**VI**)[12], 1-deoxynojirimycins (**VII**)[16] and 1-*C*-alkyliminoalditols[17] (**VIII**) shown in figure **12**, are representatives for six-membered glycomimetics bearing a basic nitrogen which is replacing the ring oxygen of the sugar backbone. Isofagomines (**IX**)[18] have a methylene group instead of the ring oxygen and a nitrogen at the position of the anomeric carbon. This iminosugars resemble the positively charged half chair conformation of the transition state of glycosidases which makes them reversible competitive inhibitors for this type of enzymes.

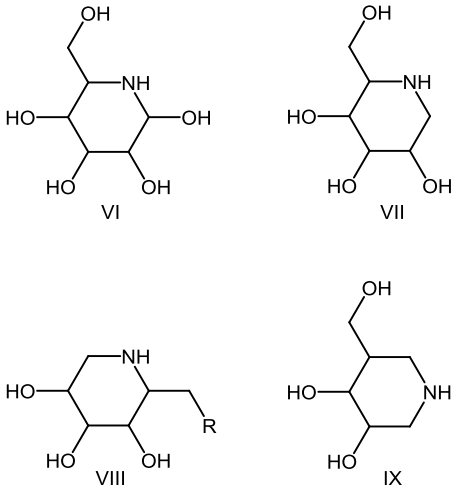


Figure 12: Piperidine derivatives.

The first iminosugar isolated from nature was 5-amino-5deoxy-D-glucopyransose which was originally isolated from *Streptomyces roseochromogenes* but was named nojirimycin after its isolation from *Streptomyces nojiriensis*. [19,20,21] Soon after the discovery of nojirimycins and their inhibitory effect on glycosidases, many naturally occurring iminosugars were isolated

from plants. 1-Deoxynojirimycin (DNJ) was synthesized before its discovery in nature and also showed good inhibitory characteristics.[22]

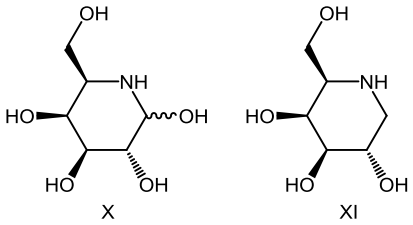


Figure 13: 5-Amino-5-deoxy-D-galactose (**X**) and 1,5-dideoxy-1,5-imio-D-galactitol (**XI**).

The K_i-value of 5-Amino-5-deoxy-D-galactose (**X**) for β-galactosidase (*e. coli*) is 0.045 µM in comparison to 1,5-dideoxy-1,5-imio-D-galactitol (**XI**) with a K_i-value of 12.5 µM.[23] For the inhibition of α-galactosidases (*e. coli*), K_i-values for these compounds were 0.17 µM for **X** and 0.24 µM for compound **XI**.[23] Small structural differences can obviously affect the inhibitory effect of molecules directing them for inhibition of different glycosidases.

Potent inhibitors can also be found in the five-membered series as shown for the pyrrolidine derivatives in figure **13**. For example, 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP) was isolated from species of the legume genus *Lonchocarpus*.[24,25] The structural similarities to 2-deoxy-β-D-fructofuranose and its activity as glucosidase[26] inhibitor with a K_i-value of 0.2 µM for β-D-glucosidase (*Agrobacterium faecalis*) made this furanoide type of molecule interesting for further investigations and modifications in the past.[27]

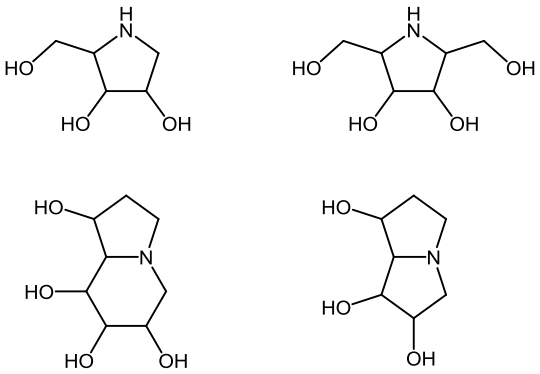


Figure 14: Pyrrolidine derivatives and bicyclic iminosugars.

The castanospermines (**XII**) and pyrrolizidines such as australine (**XIII**) are representatives of bicyclic inhibitors. In nature, castanospermine, a polyhydroxylated alkaloid was found in *Castanospermum australe*.[28] The K_i-value of **XII** for α-glucosidase (rice) is 0.015 µM[29] and for β-glucosidase (*aspergillus wenti*) 0.9 µM[29] which indicates that castanospermine is a potent glucosidase inhibitor in the low micromolar range. Australine (**XIII**) has an IC_{50} value of 35 µM[30] for α-glucosidase (maltase, *rat white, small intestine*) and an IC_{50} value of 330 µM[31] for β-glucosidase (*mouse gut digestive*).

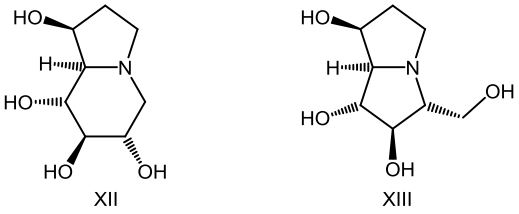


Figure 15: Castanospermine (**XII**) and Australine (**XIII**).

Isofagomine, structurally related to 1-deoxynojirimycin was first reported by Bols and collaborators with a K_i-value of 0.11 µM for β-glucosidase (almonds).[18] 4-epi-Isofagomine which is the C-4 epimere of isofagomine is a strong β-galactosidase inhibitor. The structural modification of the position C-5a (position of the ring oxygen in conventional monosaccharides) increased the inhibition of β-galactosidases.[108,110]

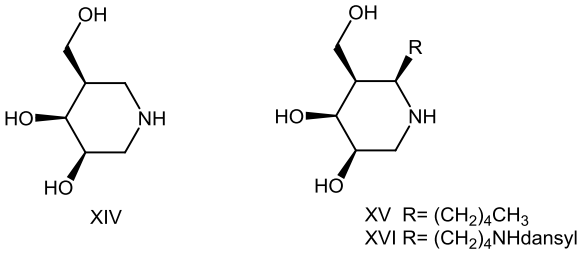


Figure 16: 4-epi-isofagomine (**XIV**) and derivatives **XV** and **XVI**.

1.4.2 Carbasugars

The first synthesis of former so called "pseudosugars", a class of molecules in which the ring oxygen of a monosaccharide is replaced by a methylene group was reported by McCasland and coworkers in 1966.[32,33,34] The cyclohexane backbone with a substitution pattern similar

to common monosaccharides, was predicted to be recognised by carbohydrate processing enzymes but was predicted to have higher stability because of the lack of the ring oxygen. Now these molecules are known as carbasugars.[35] A couple of years after the first carbasugar (5a-carba-α-DL-talopyranose) was synthesized, 5a-carba-α-D-galactopyranose (**XVIII**) was isolated from *Streptomyces sp*.(figure **17**).[36]

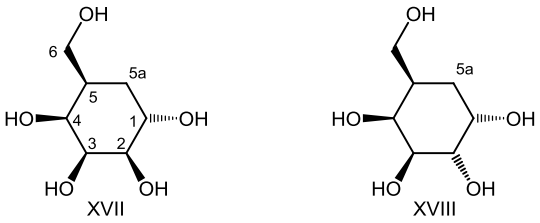


Figure 17: 5a-carba-α-D-talopyranose (**XVII**) and 5a-carba-α-D-galactopyranose (**XVIII**).

In the past decades, cyclohexane and cyclohexene dervivatives related to carbasugars, as well as nitrogen containing analogues were intensively investigated.[37,38] In nature, different substances were found, such as cyclophellitol[39,40] (**IV**) which was isolated from *Phellinus sp*. or streptol[41], isolated from *Streptomyces sp*.. Other natural products containing a cyclohexane or cyclohexene backbone are: Pericosines A-E (*Periconia byssoides* a marine fungus)[42,43]; MK7607 (*Curvularia eragrostidis*); valienone (*Streptomyces lincolnensis*)[44]; gabosines (different *Streptomyces* strains)[45,46] and COTC (*Streptomyces griseosporeus*)[47].

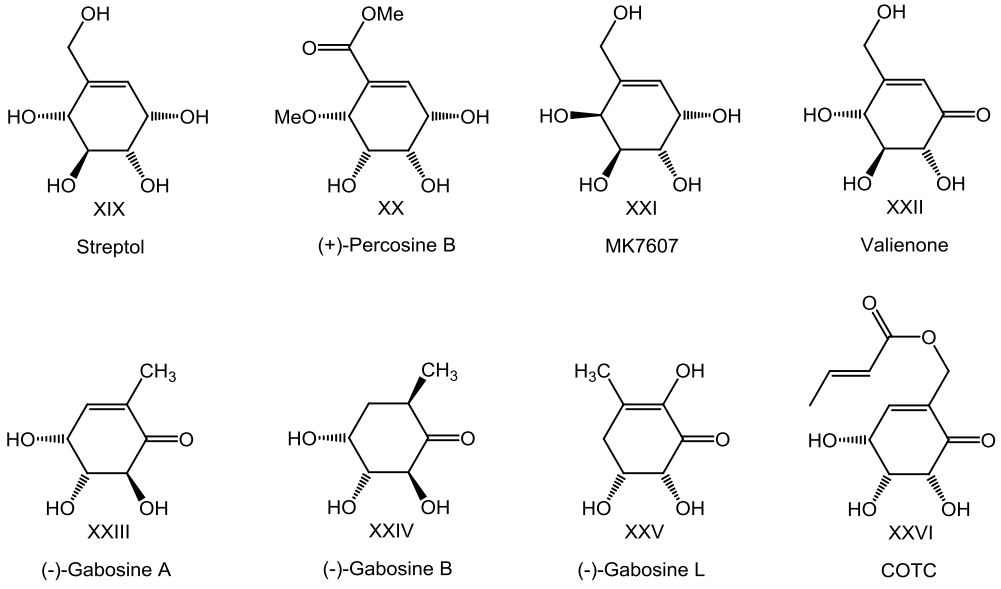


Figure 18: Different natural occuring cyclohexane and cyclohexene derivatives.

The class of amino-carbasugars such as validamines, hydroxyvalidamines, valienamines or valiolamine are mainly found in nature as parts of more complex molecules such as acarbose (**XXXI**),[48,49,50] validamycins or carbaoligosaccharides and are secondary metabolites which are exclusively produced by microorganisms. Validamycins are antibiotics, which were isolated by fermentation cultures of *Streptomyces hygroscopicus*.[51,52]

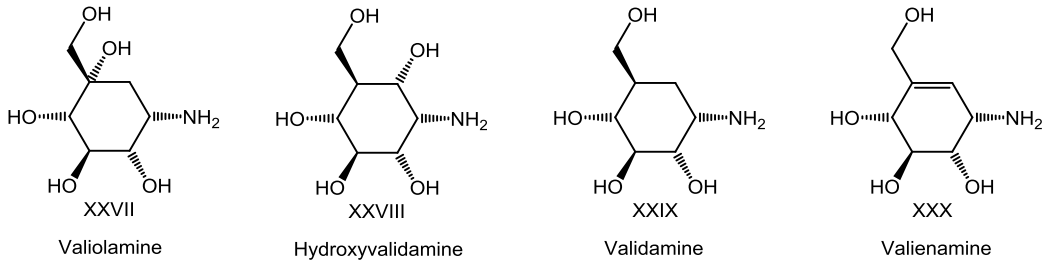


Figure 19: Aminocarbasugars.

Acarbose (**XXXI**) which contains a valienamine moiety, is a very powerful α-glucosidase inhibitor and is used for treatment of type II diabetes. Other structurally related compounds in this context are voglibose[53] and the iminosugar derivative miglitol[54]. (figure **21**)

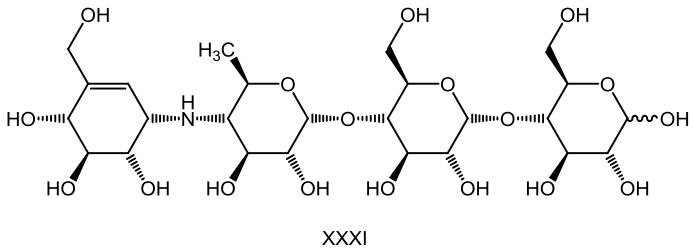


Figure 20: Acarbose (**XXXI**).

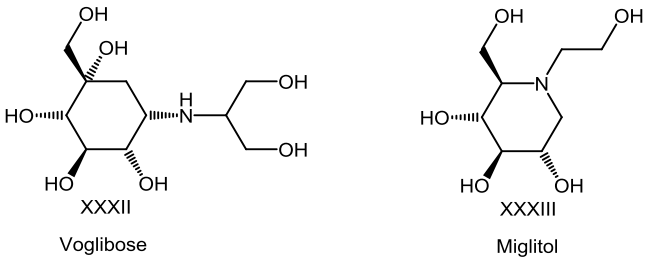


Figure 21.

Carbafuranoses are mainly found in nature as subunits of larger molecules like carbanucleosides[55], but there are 2 examples in literature, caryose (from *Pseudomonas*

caryophylli)[56] and calditol (from *Caldariella*)[57] that were isolated as polyhydroxylated cyclopentane units.

Synthetic strategies to carbapyranoses as well as carbafuranose derivatives starting from simple monosaccharides as well as *de novo* syntheses starting from non-carbohydrate material are frequent in the literature. Intramolecular cyclisation reactions employing SmX_2 complexes, intramolecular nucleophilic aldolreactions, ringclosing metathesis reactions and radical cyclisation reactions were described.

In recent years, Ogawa and coworkers showed, that 1,4-di-epi-D-valienamine derivatives and 1,4-di-epi-D-validamine derivatives are potent inhibitors for β-galactosidases. They created a set of molecules with different *N*-substituents for inhibition screenings.

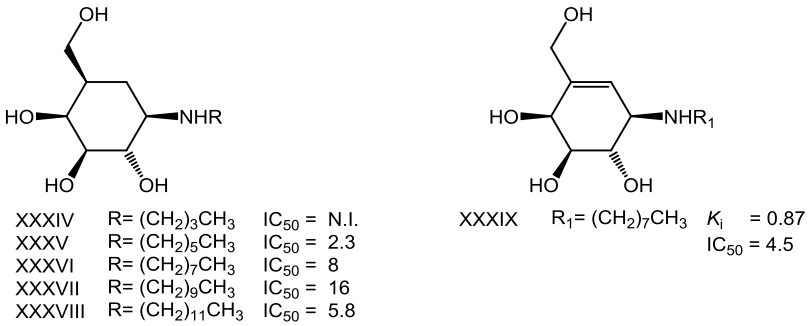


Figure 22: Different 1,4-di-epi-D-validamine derivatives and NOEV (**XXXIX**) tested against β-galactosidase (*bovine liver*)[58,100,102] (μM).

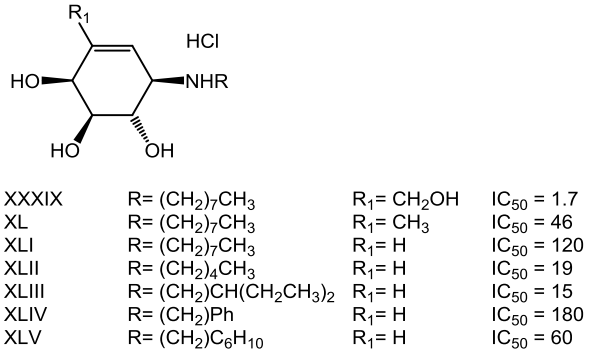
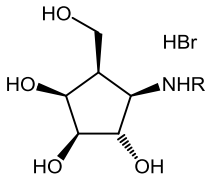


Figure 23: NOEV, 6-deoxy-NOEV and *N*-substituted conduramine derivatives tested against human β-galactosidase (μM).[59]

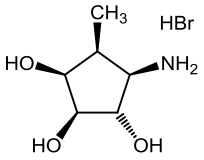
The *N*-octyl derivative **XXXIX** with an K_i value of 0.87 μM against β-galactosidase (bovine liver) was one of the best inhibitors compared to the *N*-alkylated validamine derivatives (figure **22**) reported in literature.[58,100,102] Compound **XXXIX** with the endocyclic double bond

seems to be in the half-chair conformation which enhances inhibition of the tested β-galactosidase. Nevertheless, *N*-alkylated validamines **XXXV**, **XXXVI** and **XXXVIII** are inhibitors in low µM range. The hydroxymethyl function seems to be necessary for potent inhibition because if NOEV (**XXXIX**), 6-deoxy-NOEV (**XL**) and *N*-octyl-conduramine (**XLI**) are compared in terms of inhibition against human β-galactosidase, the interaction gets weaker when the hydroxyl group is removed and weakens the inhibition 70-fold if the hydroxymethyl group is missing.

5-Membered *N*-alkyl analogues which were tested against β-galactosidases activity were found very active maybe due to the envelope form of the cyclopentane backbone with a protonated nitrogen mimicking the transition state of the acting enzyme. A series of derivatives shown in figure **24** were prepared by Jäger and coworkers indicating that aromatic moietys like benzyl or para-halogenated benzyl groups rise the activity significantly.[60,61,116]



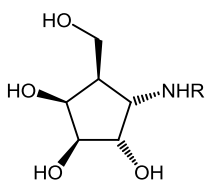
XLVI	R= H	Ki = 3.3
XLVII	R= CH_3	Ki = 0.09
XLVIII	R= $(CH_2)_2OH$	Ki = 0.48
XLIX	R= C_6H_{10}	Ki = 3
L	R= $CH_2(C_6H_{10})$	Ki = 0.004
LI	R= $(CH_2)Ph$	Ki = 0.006
LII	R= $CH_2(4\text{-}C_6H_4Br)$	Ki = 0.0007



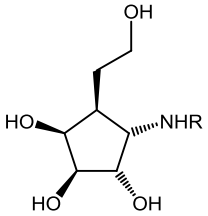
LII Ki = 4

Figure 24: Polyhydroxylated cyclopentane derivatives. (µM) β-galactosidase (*bovine liver*).[116]

The removal of the primary hydroxyl group lowered the activity from 3.3 µM to 4 µM for β-galactosidase (*bovine liver*) but the effect is more significant for other β-galactosidases (*E. coli* **XLVI** 4.5 µM; **LII** 8 µM) (*Aspergillus niger* **XLVI** 0.85 µM; **LII** ca. 1000 µM).[116]



LIII	R= H	Ki = 5.31
LIV	R= $(CH_2)Ph$	Ki = 1.01



LV	R= H	Ki = 31.6
LVI	R= $(CH_2)Ph$	Ki = 20.7

Figure 25: (µM) β-galactosidase (*bovine liver*).[62]

If the amino function of the cyclopentane ring is inverted showing α-configuration on the anomeric carbon in terms of carbohydrate nomenclature, Lundt and collaborators[62] showed, that this type of molecule is also active against β-galactosidases. The interaction is weaker if the derivatives are compared to their epimeric counterparts but the K_i values are in the low micromolar range. Maybe this could be described by conformational changes because the N-alkyl residue wants to be equatorial and directing into a similar position as for the β-amino derivatives. Chain extension of the hydroxymethyl group to a hydroxyethyl group lowered the activity significantly but increased selectivity for β-galactosidases. It was reported, that compounds **LV** and **LVI** showed no inhibition against α-galactosidases (green coffee beans)[62].

1.5 Fluorine in carbohydrate chemistry

Fluorine is one of the most common halogens on earth although biological systems that use molecules containing fluorine atoms are mostly found in plants or microorganisms. Fluoroacetate (**LVII**) is the most common organic molecule in this context which is produced by different plants in Australia, Brazil and Africa to defend themselves against herbivores.[63]

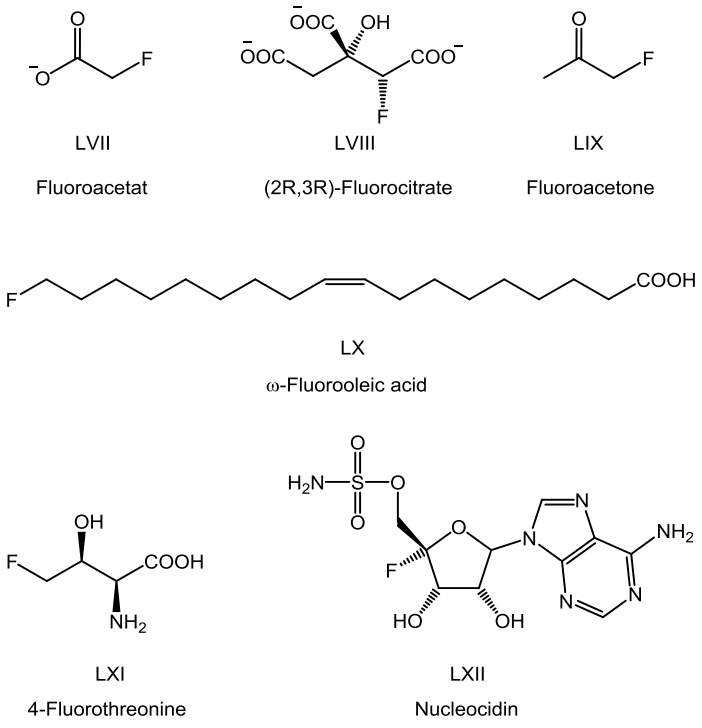
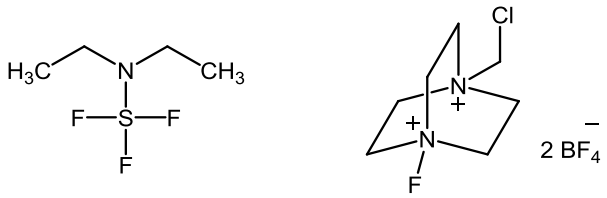


Figure 26: Fluorine containing natural products.[64]

Some of the plants that produce fluoroacetate (**LVII**) also produce fluorocitrate (**LVIII**) at low nontoxic concentrations. From the seeds of the West African shrub *D. toxicarium* fluorine containing fatty acid (**LX**) was isolated besides small amounts of other fluorine fatty acids. Nucleocidin (**LXII**), an antibiotic was isolated from the bacterium *S. calvus*, but high toxicity prevented it from further applications. [64]

Due to the high electronegativity, fluorine atoms show a strong electronic withdrawing effect and are able to influence neighbouring functional groups. The acidity of hydroxyl groups in the neighbourhood is increased and amino groups show reduced basicity. This makes fluorine an interesting "modifier" for small molecules which could be used as inhibitors for various enzymes. A great challenge during the decades since fluorination of organic molecules was first investigated has been the introduction of the fluorine atom. The first attempts for the introduction were nuclephilic fluorine reagents like Olah's reagent (HF.pyridine) or HF.Et_3N, which work under harsh conditions.[65,66,67] Many reviews containing alternative fluorination methods are published.[68,69] Among those reagents, diethylamino-sulfur trifluoride (DAST) compared all advantages of nucleophilic fluorination reagents acting as a leaving group and fluorine donor at the same time. The invention of electrophilic fluorination agents beside the nucleophilic reagent described before, enabled a wide range of applications for fluorine chemistry.[70] One of the most potent electrophilic fluorination reagents nowadays is Selectfluor® (**LXIV**) which enables fluorination of enol-ether systems under mild conditions with easy handling in terms of toxicity, oxidation potential as well as state of matter.[71,72,73]



LXIII LXIV

Figure 27: Diethylaminosulfur trifluoride (**LXIII**) and Selectfluor®(**LXIV**).

The described features of fluorine containing molecules made it interesting to introduce fluorine moieties into enzyme inhibitors to change selectivity and activity. In the 1990's the first fluorine containing iminosugars were developed by Stütz[74] and coworkers (**LXV**) bearing

a primary fluorine substituent, as well as Vogel[75] and collaborators (**LXVI**) featuring a secondary fluorine functional group. Examples for carbohydrate analogues featuring a tertiary fluorine substituent are the potent purine nucleoside phosphorylase inhibitor (F-DADMe-immucillin-H (**LXVI**))[76] and the anti-hepatitis C drug sofosbuvir[77] (**LXVIII**) which has been introduced several years ago.

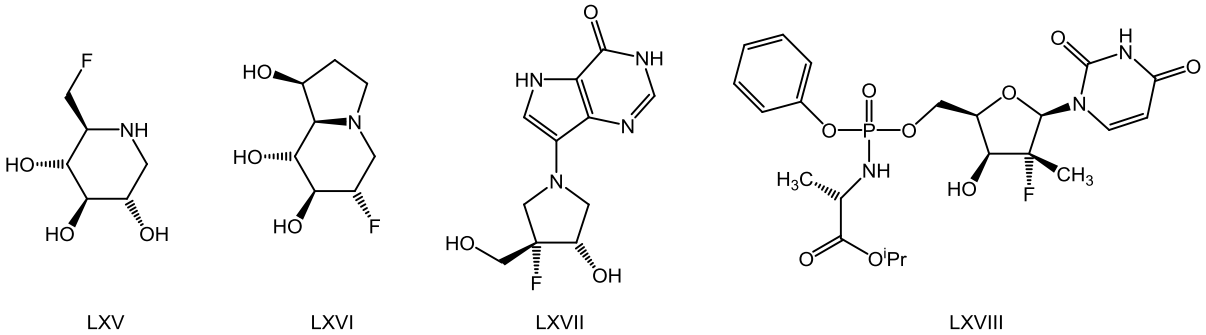


Figure 28: Fluorine containing carbohydrate derivatives.

1.6 Glycolipids

Glycolipids occur in all living organisms, for example bacteria, plants, animals and humans, and are components of the cell membrane. Glycosphingolipids (GSLs) contain a mono- or polysaccharide unit which is *O*-glycosilated with a non-polar sphingolipid or ceramide moiety.

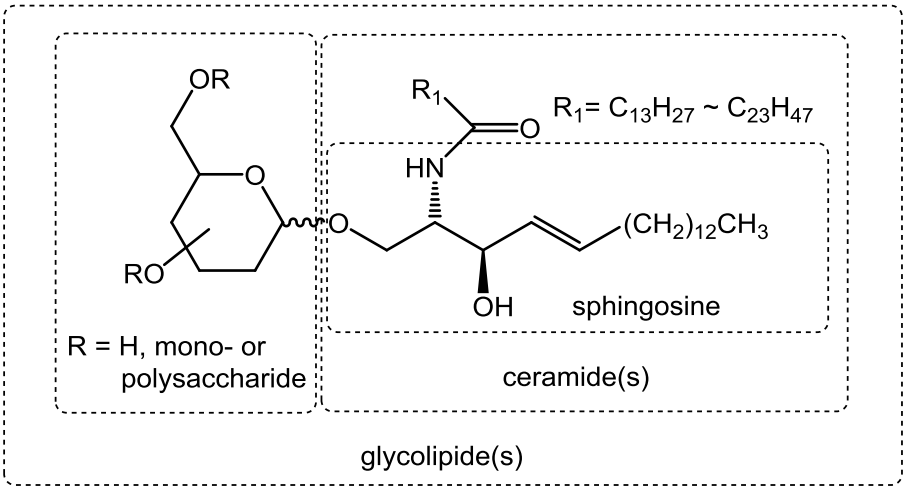


Figure 29: General structure of glycosphingolipids.[78]

Glycosphingolipids are mainly catabolized in the lysosomes and in the late endosomes, which are the acidic parts of the cell.[79] Lysosomal *exo*-glycosyl hydrolases are responsible for the degradation of GLS's cleaving sugar moieties starting from the non-reducing end. A short schematic overview of this degradation is shown in figure **30**. They play a vital role in cell-cell recognition, receptor modulation and signal transduction and are involved in cell- adhesion processes.

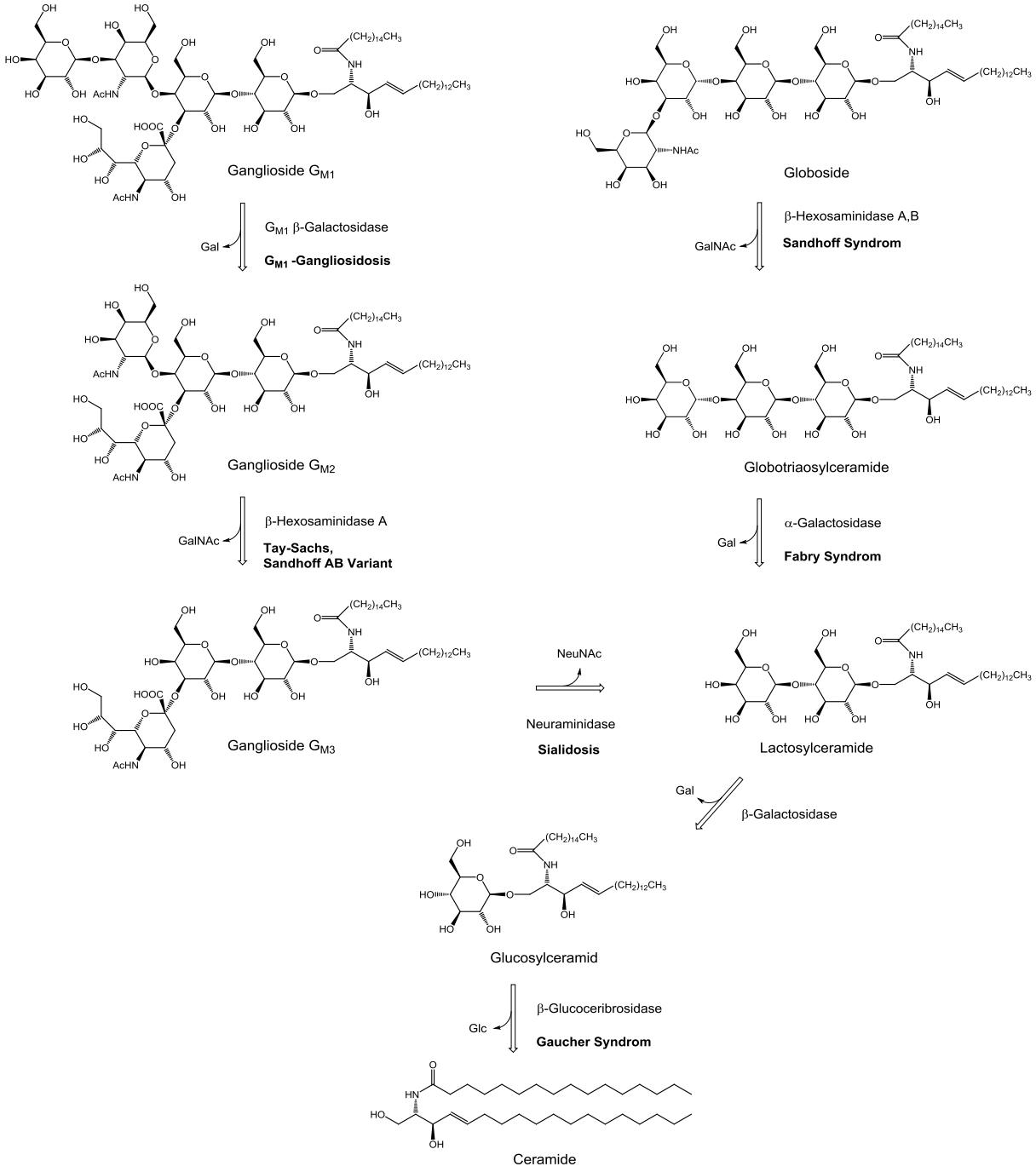


Figure 30: Degradation pathway of GLS's. [80,81]

1.7 Lysosomal storage diseases

Lysosomal storage diseases (LSD) are a group of approximately 50 different[82] disorders which are caused by single mutations in specific genes which are responsible for the biosynthesis of lysosomal enzymes. The lack of correctly working enzymes leads to an accumulation of unprocessed substrate molecules inside the living cell.[83] A selection of different disorders concerning malfunctioning lysosomal enzymes is shown in figure 32.[86]

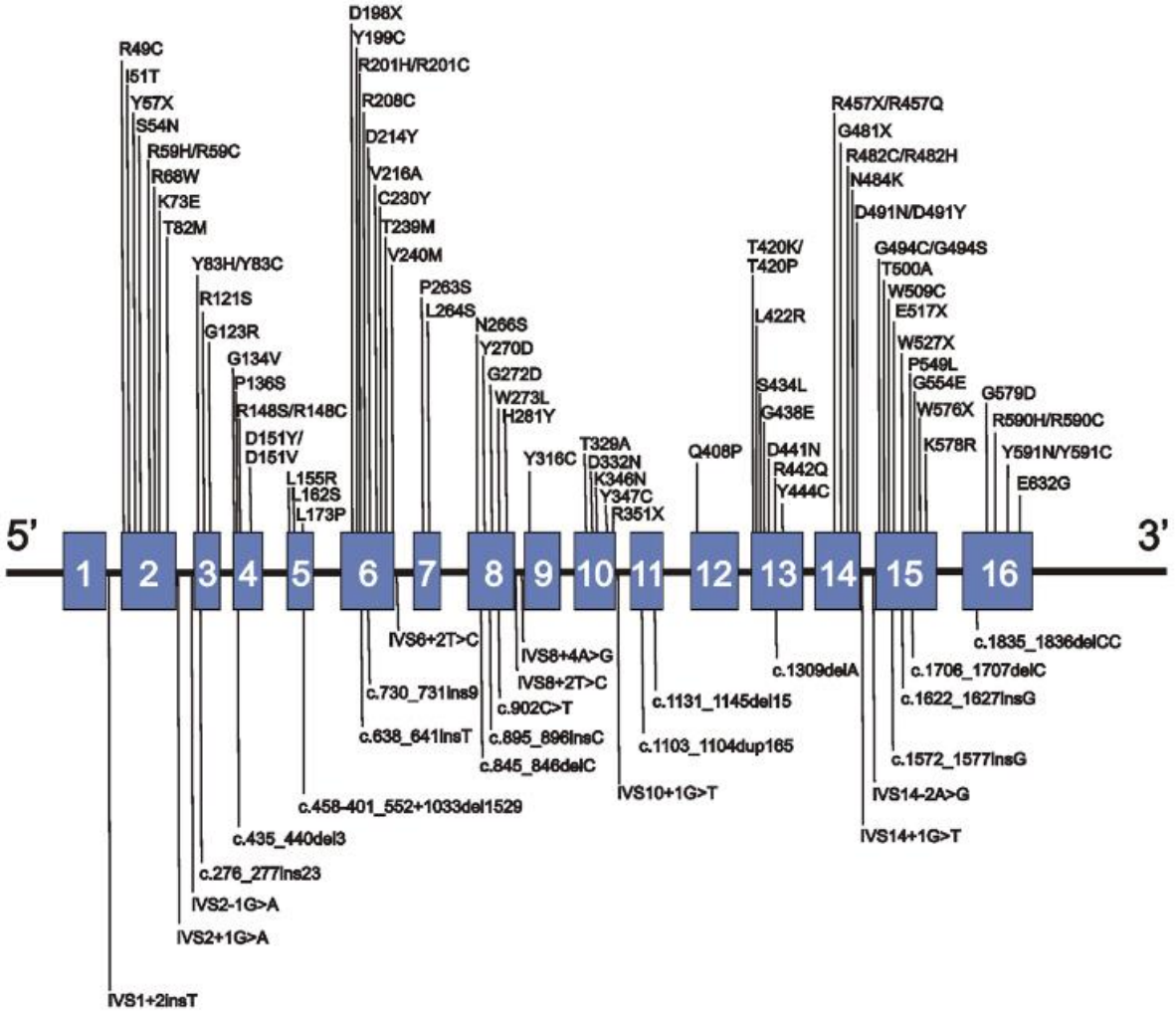


Figure 31: *GLB1*-mutations causing G_{M1}-gangliosidosis or Morqiuo B [84]

Approximately 1 of 100 000 births is affected of LSD's which indicates this class of diseases to be rare, but the occurrence of glycosphingolipid related disorders (1:8000 births) makes these types to the most frequent cause of pediatric neurodegenerative diseases worldwide.[85]

	Disorder	Defective enzyme	Storage material
Mucopolysaccharidoses (MPS)	MPS I (M. Hurler, M. Scheie, M. Hurler/Scheie)	α-Iduronidase	DS, HS, G_{M2}, G_{M3}, SCMAS
	MPS II (Hunter)	Iduronate-2-sulfatase	DS, HS, G_{M2}, G_{M3}, SCMAS
	MPS III A (M. Sanfilippo A)	Heparan *N*-sulfatase (sulfamidase)	HS, G_{M2}, G_{M3}, G_{D2}, SCMAS, ubiquitin
	MPS III B (M. Sanfilippo B)	*N*-Acetyl-α-glucosaminidase	HS, G_{M2}, G_{M3}, G_{D2}, SCMAS, unesterified cholesterol
	MPS IV A (M. Morquio A)	*N*-Acetylgalactosamine-6-sulfatesulfatase	KS, chondroitine-6-sulfate
	MPS IV B (M. Morquio B)	β-Galactosidase	KS, oligosaccarides
Mucolipidoses (ML)	ML II (I-cell disease)	N-Acetylglucosamine-1-phosphotransferase	various lipids, mucopolysaccharides, oligosaccharides
	ML III (Pseudo-Hurler-Polydystrophy)	N-Acetylglucosamine-1-phosphotransferase	various lipids, mucopolysaccharides, oligosaccharides
Gangliosidoses	G_{M1} Gangliosidosis	β-Galactosidase	G_{M1}, G_{A1}, G_{M2}, G_{M3}, G_{D1a}, lyso-G_{M1}, glucosylceramide, lactosylceramide, oligosaccharides, keratan sulfatase
	G_{M2} Gangliosidosis (M. Tay-Sachs)	β-hexosaminidase A	G_{M2}, G_{D1a}, GalNAc, G_{A2}, lysoG$_{M2}$
	G_{M2} Gangliosidosis (M. Sandhoff)	β-hexosaminidase A and B	G_{M2}, G_{D1a}, GalNAc, globoside, oligosaccharides, lyso-G_{M2}
Lipidoses	M. Gaucher I (chronic), II (neuropathic), III (subacute)	β-Glucosidase	G_{M1}, G_{M2}, G_{M3}, G_{D3}, glucosyl-ceramide, glucosylsphingosine
	Globoid cell leukodystrophy (M. Krabbe)	Galactocerebroside β-galactosidase	Galactosylceramide, psychosine, lactosylceramide, globotriaosylceramide, globotetraosylceramide, fucosylneolactotetraosylceramide
	M. Niemann-Pick I and II	Sphingomyelinase	Sphingomyelin, cholesterol, bismonoacylglycerophosphate, G_{M2}, G_{M3}, glucosylceramide, lactosylceramide, globotriaosylceramide, globotetraosylceramide
	M. Fabry	α-Galactosidase A	Globotriaosylceramide, glabiosylceramide, globotriaosylsphingosine, blood-group-B glycolipids
	Metachromatic leukodystrophy	Arylsulfatase A	Sulfatide, 3-*O*-sulfolactosylceramide, lysosulfatide, seminolipid, gangliotetraosylceramide-bis-sulfate, G_{M2}

Figure 32: DS = dermatan sulfate; HS = heparan sulfate; G_{M1}, G_{A1}, G_{A2}, G_{M2}, G_{M3}, G_{D2}, G_{D3}, G_{D1a}, lyso-G_{M1}, lyso-G_{M2}, G_{D1a}GalNac = subtypes of gangliosides; SCMAS =subunit c of mitochondrial ATP synthase.[86]

1.7.1 G_{M1}-Gangliosidosis and Morquio B

Two diseases caused by a malfunction of lysosomal β-galactosidase (EC 3.2.1.23) are G_{M1}-gangliosidosis and Morquio B. (figure 30 and 32) Different mutations in the human galactosidase beta 1 gene (GLB1, Gene ID 2720)[87] which encodes the human lysosomal acid β-galactosidase cause the malfunction of the enzyme. Currently 102 mutations in GLB1, which contains 16 exons and is located at chromosome 3p21.33, were reported. (figure 31)[84] G_{M1}-gangliosidosis is mainly characterized by the accumulation of neuronal ganglioside G_{M1}. Patients with Morquio B, suffer from an accumulation of oligosaccharides in inner organs and bones.

1.7.2 Therapies

Different approaches for treatment of Lysosomal storage diseases were developed in the past. They could be divided in two major groups: -treatment of the symptoms and -treatment of the cause of the disease.

Gene therapy:

For the treatment of the disease a viral vector containing DNA for the missing enzyme is transported into the cell. The gene is then expressed by the cellular machinery which allows the cell to produce functional enzymes that can be secreted and reach neighbouring cells by receptor mediated endocytosis.

Substrate reduction therapy:

The main target is the reduction of the synthesized storage material by inhibiting the substrate biosynthesis. The balance between biosynthesis and impaired degradation can be improved with this method.[88]

Stem-cell therapy:

Missing enzymes are donated via enzyme secretion and receptor mediated uptake by healthy donor cells which can migrate to the affected tissue.

Enzyme replacement therapy:

Recombinant enzymes are administered to the patient and enter the cell by receptor mediated endocytosis and are directed to the lysosomes, where they can act instead of the misfolded enzymes.

Chaperone therapy:

The chaperone therapy for lysosomal storage diseases is a concept which aims at the proper folding of misfolded enzymes via stabilization. Therapeutic options are shown in several reviews.[89,90,91,92,93]

1.7.3 Chaperone mediated therapy (CMT):

Generally, single mutations in genes result in the biosynthesis of misfolded or unfolded enzymes or proteins in the ribosomes. They are transported into the endoplasmatic reticulum in a highly unfolded state, are detected by the quality control and degraded, which leads to a shortage of acting enzymes. With the help of small molecules called “active site specific chaperones” (ASSC) or “pharmacological chaperones” (PC), the proteins can be folded properly and are transported to the lysosomes. There, the pharmacological chaperone can be replaced by the natural substrate or dissociate from the active site of the enzyme.

Since 1999 when Fan and collaborators[94] reported the first example of PC stabilized lysosomal glycosidases, the general concept of CMT was demonstrated for several other lysosomal storage diseases. An overview of protein folding in the endoplasmatic reticulum is shown in figure 33.[95]

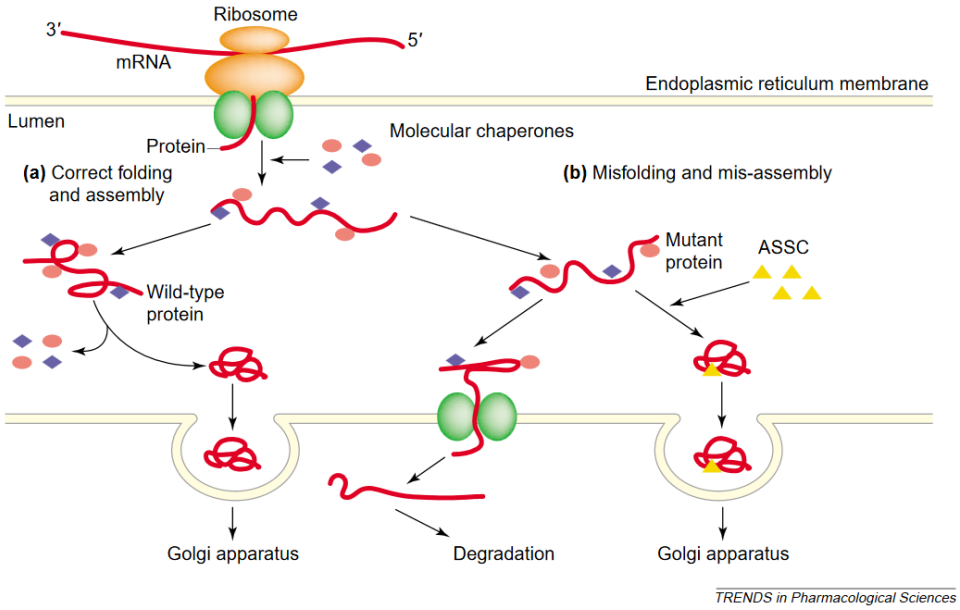


Figure 33: Schematic overview of PC supported protein folding in the ER.[95]

In literature, two major subtypes of PC's were investigated for lysosomal β-galactosidase concerning G_{M1}-gangliosidosis and Morquio B. The carbasugar derivative NOEV (**XXXIX**) is a glycosidase inhibitor which was intensively tested for its activity as pharmacological chaperone in sub-micromolar range and is the benchmark molecule for comparison with other small molecules.[96,97,104] Derivatives lacking the hydroxymethyl sidechain (e.g.: **XLI**-**XLV**) have been tested in the past and their activities with skin fibroblasts carrying β-galactosidase mutations (R201C) were reported.[59]

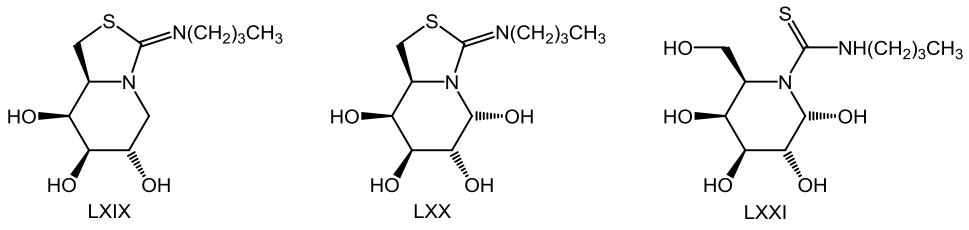
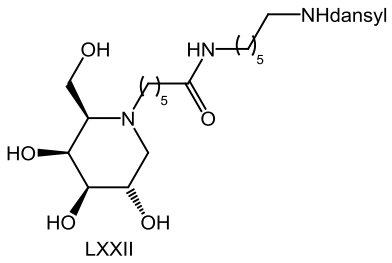


Figure 34: Examples of iminosugar derivatives tested for their chaperon activity.[98]

The second large group of PC's is based on iminosugar derivatives such as DGJ (**XI**). Compounds shown in figure 34 are potent iminosugar based pharmacological chaperones bearing substituents on the ring nitrogen. These compounds were introduced by Garcia-

Fernandez and collaborators and are examples of bicyclic so called sp^2-iminosugars (**LXIX** and **LXX**).[98]



LXXII

Figure 35: *N*-(Dansylamino)hexylaminocarbonylpentyl-1,5-dideoxy-1,5-imino-D-galacitol (**LXXII**).[99]

Compounds **LXXI**[98] and **LXXII**[99] are representatives for N-substituted DGJ derivatives which show interesting properties as PC's for G_{M1}-gangliosidosis. All of the reported small molecules tested as pharmacological chaperones are inhibitors of their respective glycosidases, where inhibition potency is essential but not crucial for their chaperone activity.

2 General Aims and synthetic targets

In the literature, synthetic D-*galacto* related derivatives of validamines[100], valienamines[101,102] and five membered analogues were reported to be potent glycosidase inhibitors. Examples such as NOEV (*N*-octyl-*epi*-valienamine) (**15**) which is still one of the benchmark molecules in this context, turned out to be potent chaperones for GM1 gangliosidosis[103,104,105] For five membered carbasugars chaperone activity has not been tested, but structural similarities and reported inhibitor activities suggested to have a look at the chaperone effect of this type of molecules.

In this work, a set of different glycosidase inhibitors was targeted exploiting various ring sizes as well as substitution patterns. Unsaturated as well as saturated structures were poised to be probed for their inhibitory effects as well as for screening of their chaperone activities. In figure 36, 4 general structures are presented which show the main targets for molecule design.

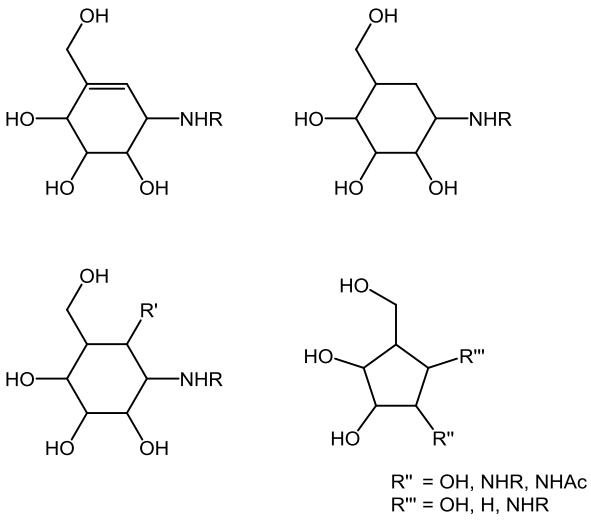


Figure 36: General structures of target glycosidase inhibitors.

NOEV (**15**) and *N*-octyl-*epi*-validamine should be prepared as internal standards for inhibitory and chaperone activity. The introduction of functionalities and lipophilic spacer arms at C-5a of the respective validamines should be realized. In the latter case, variation of lipophilic chain lengths on the nitrogen moiety as well as a set of different spacers should be combined and evaluated.

One of the major difficulties in carbohydrate chemistry is the construction of the carbacylic backbone via intramolecular C-C bond formation. Different approaches to easily get access to the target backbones were planned to be investigated. Introduction of the amine functionality was also deemed to be challenging as one of the major tasks to achieve.

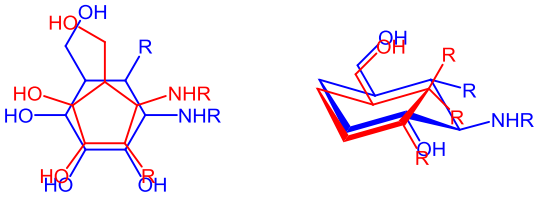


Figure 37: Structure overlays.

In case of the five membered carbasugars, addressed in this study, a set of N-alkylated inhibitors should be prepared. Variation of the lipophilic spacer on the nitrogen as well as the position of the nitrogen should be made available and screened for their inhibitory and chaperone activities. The introduction of a fluorine moiety at the tertiary position of sugars and carbasugars should be investigated to create a new type of precursor molecules for downstream chemistry.

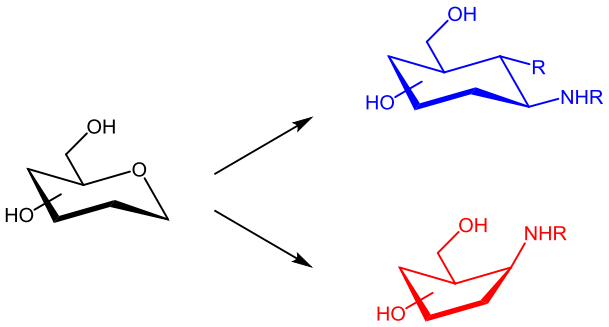


Figure 38: Highly functionalized carbasugar derivatives from simple monosaccharides.

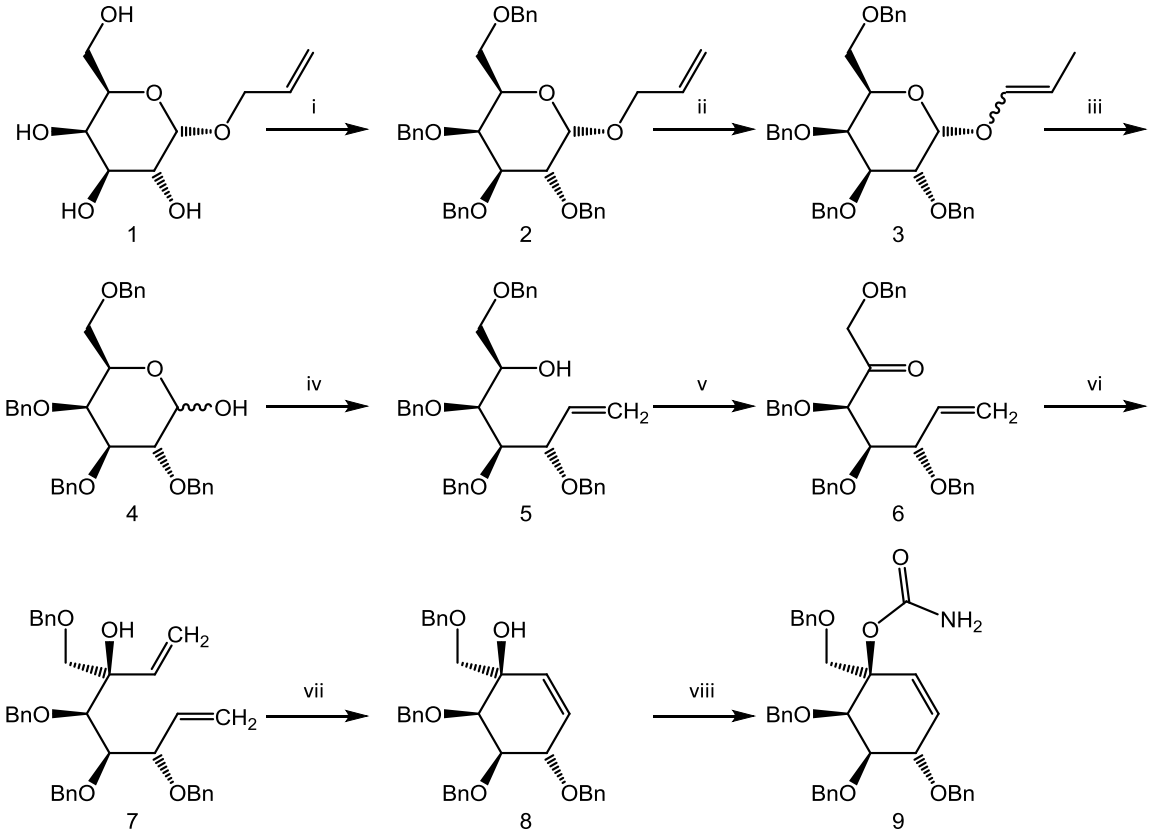
Synthetic strategies needed to be robust, final products had to be available from cheap commercially available monosaccharides in a straight forward manner.

3 Results and discussion

3.1 Carbahexoses

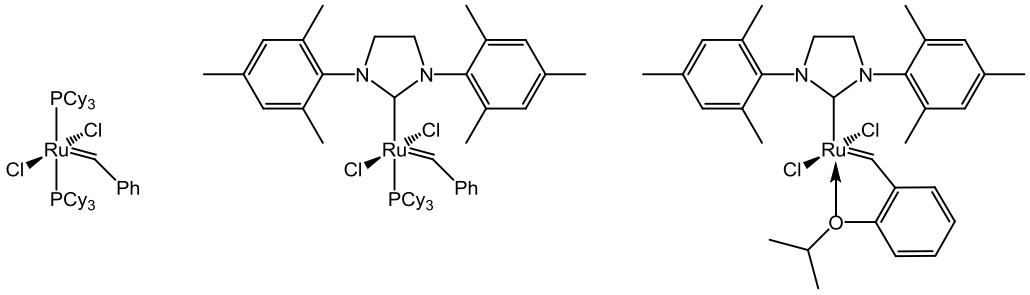
3.1.1 Synthesis of NOEV (*N*-octyl-epi-valienamine) (15) and *N*-octyl-epi-validamin (17):

A new synthetic route to obtain enantiomerically pure *N*-octyl-*epi*-valienamine (NOEV) (**15**) was investigated starting from allyl-α-D-galactopyranoside **1** employing a 3-steps sequence via benzylation of the free hydroxyl groups to provide compound **2**, basic isomerisation of the allyl system with *t*-BuOK in DMSO at 120°C to an *E/Z* mixture of vinylacetal **3** and subsequent hydrolysis with pTSA in CH_2Cl_2/MeOH/H_2O to obtain the per-*O*-benzylated galactopyranose **4**.



Scheme 1: i) BnBr, NaH, DMF/THF (3:1); ii) t-BuOK, DMSO, 120°C; iii) pTSA, CH_2Cl_2/MeOH/H_2O; iv) PPh_3CH_3Br, n-BuLi, THF; v) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2; vi) $CH_2CHMgBr$, THF; vii) Grubbs II, CH_2Cl_2; viii) 1) $Cl_3CCONCO$, CH_2Cl_2; 2) K_2CO_3, MeOH/H_2O.

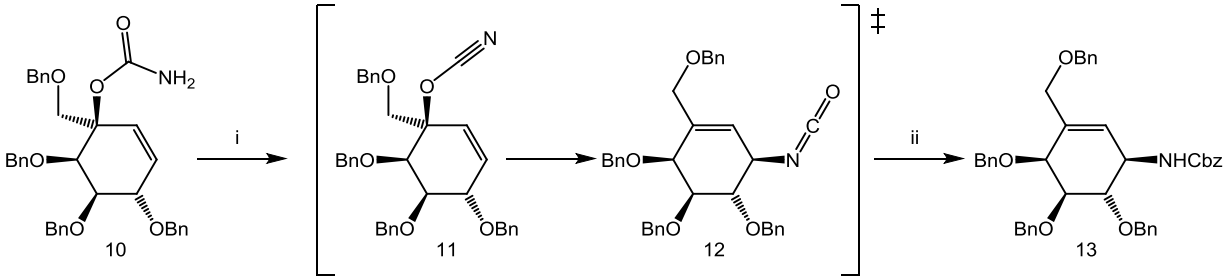
A simple Wittig reaction led to open chain derivative **5** which was easily transformed to ulose **6** via a Swern oxidation step. To obtain the branched diene system **7**, a Grignard reaction with vinylmagnesiumbromide was performed, in which only one of the two possible diastereomeres was formed highly selectively. After ring closing with Grubbs 2nd generation catalyst in CH_2Cl_2 at room temperature, cyclohexene derivative **8** was obtained. Toluene as solvent, higher temperatures as well as using Hoveyda-Grubbs 2nd generation catalyst were found to lower the yields significantly. Employing Grubbs 1st generation catalyst under inert conditions in CH_2Cl_2 showed no conversion at all over a period of several days.



Grubbs 1 Grubbs 2 Hoveyda-Grubbs 2

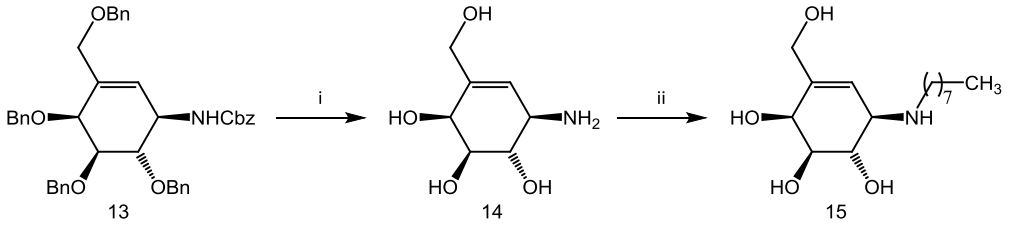
Figure 39: Different catalysts used for ringclosing reaction.[106]

The conversion of the tertiary allylic alcohol with trichloroacetyl isocyanate in CH_2Cl_2 at 0°C with subsequent saponification using K_2CO_3 in MeOH/H_2O 10:1 led to carbamate **9**. If the saponification reaction was allowed to run further, the urethane moiety was also cleaved slowly, yielding the starting material **8**. Following Vasella's[107] procedure, compound **9** was treated with PPh_3, CBr_4, Et_3N in CH_2Cl_2 at -20°C to obtain the isocyanate **12** which was converted by addition of benzyl alcohol to Cbz-protected 4-*epi*-β-valienamine **13** (scheme 2). It was necessary to perform this reaction sequence between -20 to -10°C because at higher temperatures no conversion of the starting material could be observed.



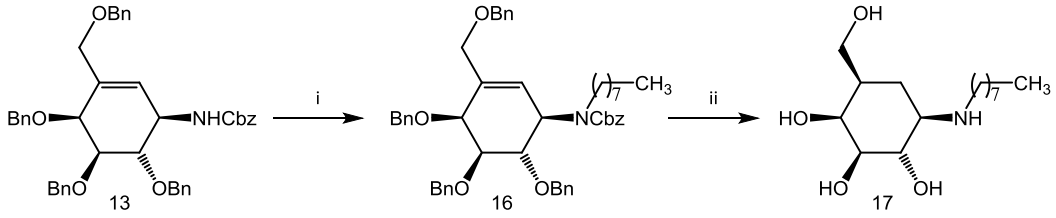
Scheme 2: Allylic rearrangement sequence; i) PPh_3, CBr_4, CH_2Cl_2, Et_3N; ii) BnOH, Et_3N.

The removal of the benzyl groups from compound **13** led to free 4-epi-β-valienamine **14** which was subsequently *N*-alkylated in DMF employing octyl bromide and $NaHCO_3$ as base at 60°C to obtain desired NOEV (**15**) in good yields. The ^{1}H and ^{13}C spectra were identical with those reported in the literature.[101]



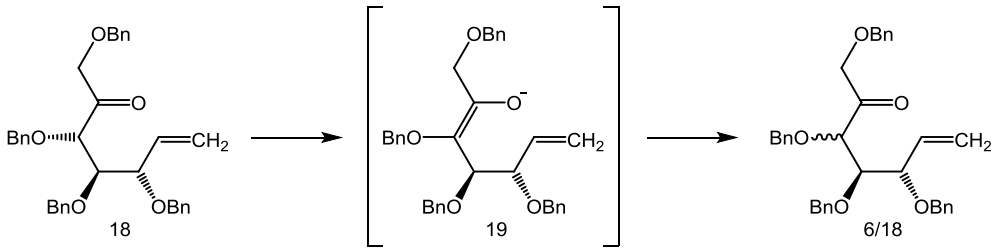
Scheme 3: Synthesis of NOEV; i) Na, NH_3/THF; ii) $CH_3(CH_2)_7Br$, $NaHCO_3$, DMF, 60°C.

Starting from compound **13** it was also possible to synthesise 4-epi-*N*-octyl-β-validamine **17** via N-alkylation in DMF with octyl bromide and NaH as the base, followed by hydrogenolytic removal of the protecting groups and concomitant reduction of the C-5-C-5a double bond (scheme 4). In this reaction sequence, formation of *galacto* configurated aminosugar was exclusively observed due to the attack of hydrogen from the sterically less crowded face.



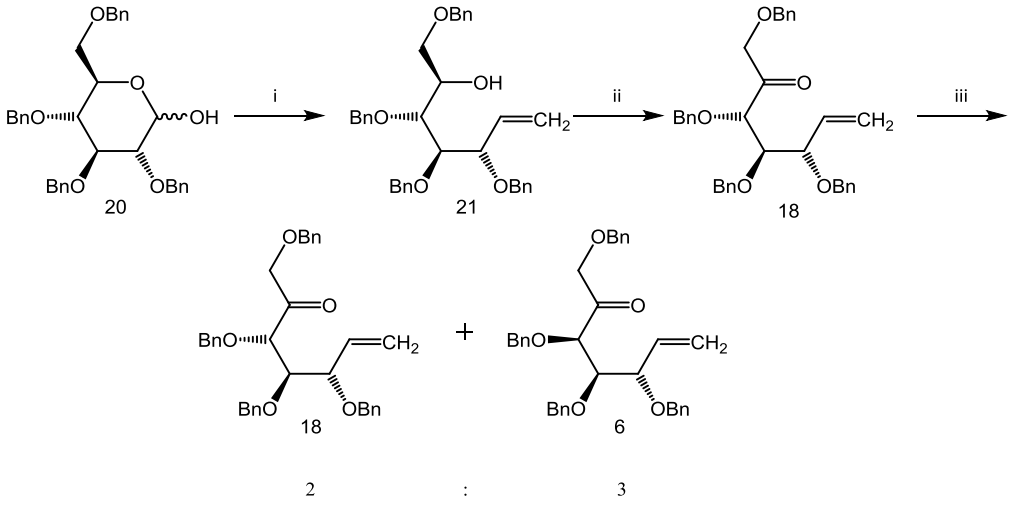
Scheme 4: Synthesis of N-octyl validamine; i) $CH_3(CH_2)_7Br$, NaH, DMF; ii) $Pd(OH)_2/C$, MeOH.

Due to the fact that allyl-α-*D*-galactopyranoside is not a cheap starting material, we investigated an alternative route to create the open chain ulose compound **6**. As starting material, we chose 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside, which was converted via a 2-steps reaction sequence into known compound **18**.[107]



Scheme 5: Isomerization from D-*xylo* to a D-*xylo*/L-*arabino* mixture.

In the presence of the carbonyl function, it was possible to isomerize open-chain compound **18** from D-*xylo*-configuration into the desired L-*arabino*-configuration. The basic conditions in this reaction step allowed only isomerization at the neighboring stereocenter and no β-elimination was observed. The resulting mixture of diastereomers (scheme 6) was easily separated by column chromatography, yielding D-*xylo* and L-*arabino* derivatives **18** and **6** in a ratio of 2:3. The more polar product (D-*xylo* configuration) was recycled and treated again with DABCO. ^{1}H and ^{13}C spectra of the galacto-uloside showed an identical pattern to those from the previous described synthesis. The reduction from a 5-step to a 3-step sequence exploiting cheap 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside with better overall yields and simple reaction conditions, made it easy to prepare multigram quantities of intermediates.

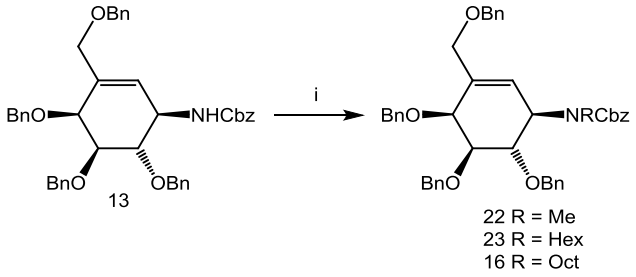


Scheme 6: i) PPh_3CH_3Br, n-BuLi, THF; ii) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2; DABCO, $MeCN/H_2O$, ultrasound.

3.1.2 Synthesis of C-5a-modified validamine derivatives

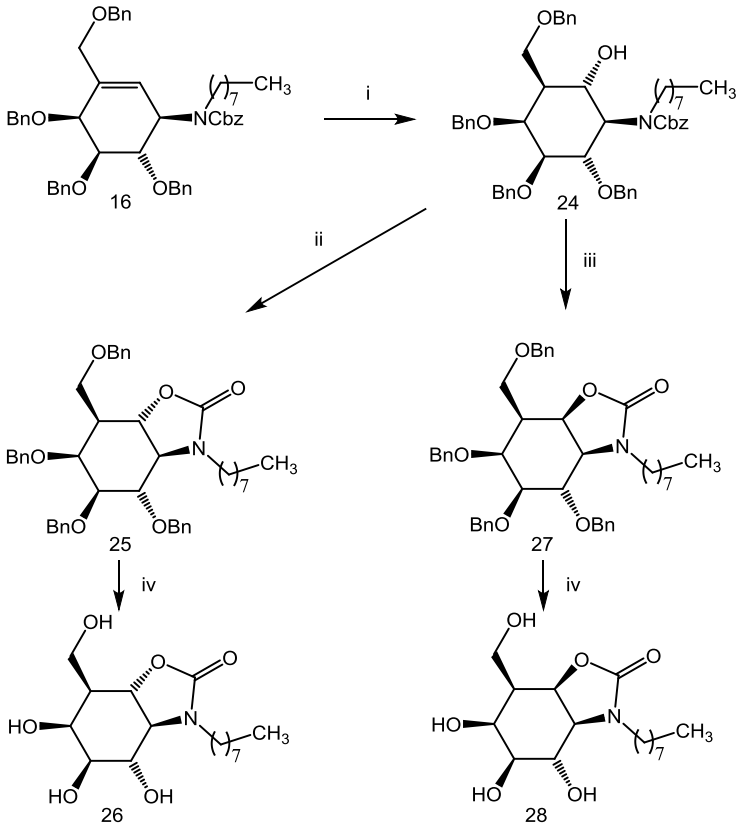
Due to the synthetic challenge of introducing functional groups at position C-5a of a sugar mimicking cyclohexane derivative and the interesting results recently found with C-5a elongated 4-*epi* isofagomines[108,109,110], it was decided to investigate the effects of different C-5a substituents in the D-*galacto*-validamine series.

Starting from protected 4-*epi*-β-*galacto*-valienamine **13**, 3 different alkyl substituents were introduced by *N*-alkylation to form compounds **16**, **22** and **23**. Sodium hydride turned out to be a suitable base to support a fast and clean alkylation of the Cbz-protected allylamine.



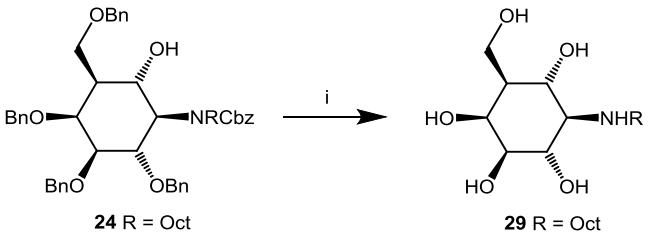
Scheme 7: *N*-alkylation of protected compound **13**; i) RX, NaH, DMF, RT.

Hydroboration of compound **16** with BH_3.THF led to partially protected branched inositol **24**. As expected, hydroboration of derivatives **16**, **22** and **23** occurred at the less substituted position C-5a. Treatment of **24** with base, led to bicyclic compound **25.** Basic conditions cause the attack of the generated alkoxide at the Cbz group, liberating benzyl alcohol and resulting in stable cyclic carbamate **25**. Hydrogenolytic removal of the benzyl groups with Pd/C (10%) led to free inhibitor compound **26** in good yields. Treatment of **24** with Tf_2O, pyridine in CH_2Cl_2 at -20°C led to a mixture (1:1) of compounds **25** and **27** either the secondary alcohol did not react with the anhydride but formed the bicyclic carbamate **25**, or the triflate was formed but was attacked by the carbonyl oxygen of the Cbz group to furnish compound **27**.



Scheme 8: Synthesis of bicyclic carbamates **26** and **28**; i) BH_3*THF, NaOH, H_2O_2; ii) KO*t*Bu/DMF or NaH/DMF; iii) DAST/CH_2Cl_2; iv) H_2, $Pd(OH)_2$/C, MeOH, HCl.

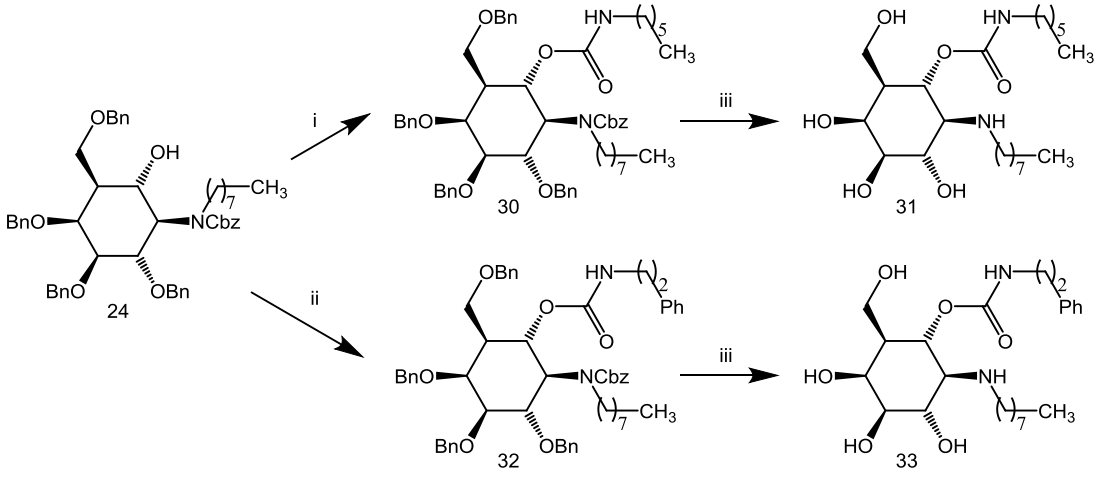
Conversion of compound **24** with DAST reagent led to a single product, by nucleophilic displacement of the sulfinic-acid type leaving group at C-5a by the carbonyl oxygen forming stable compound **27**. Removal of the benzyl groups with Pd/C (10%) gave compound **28**. (scheme 8)



Scheme 9: Deprotection of compound **24** gave polyol **29**; i) Pd/C (10%), H_2, MeOH.

To avoid undesired basic conditions for the introduction of a side chain at position C-5a, various isocyanates were investigated for the carbamate formation. Reaction of partially protected compound **24** with hexyl isocyanate or phenetyl isocyanate in toluene in the

presence $BF_3.Et_2O$ led to compounds **30** and **32**, which were deprotected by hydrogenolytic removal of the benzyl groups to give free inhibitors **31** and **33**.



Scheme 10: Carbamate formation under acidic conditions; i) Hexyl isocyanate, BF_3*Et_2O, toluene; ii) Phenethyl isocyanate, BF_3*Et_2O, toluene; iii) $Pd(OH)_2/C$, H_2, $MeOH/H_2O$, HCl.

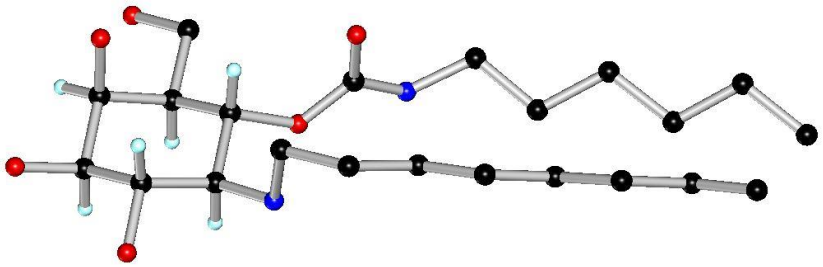
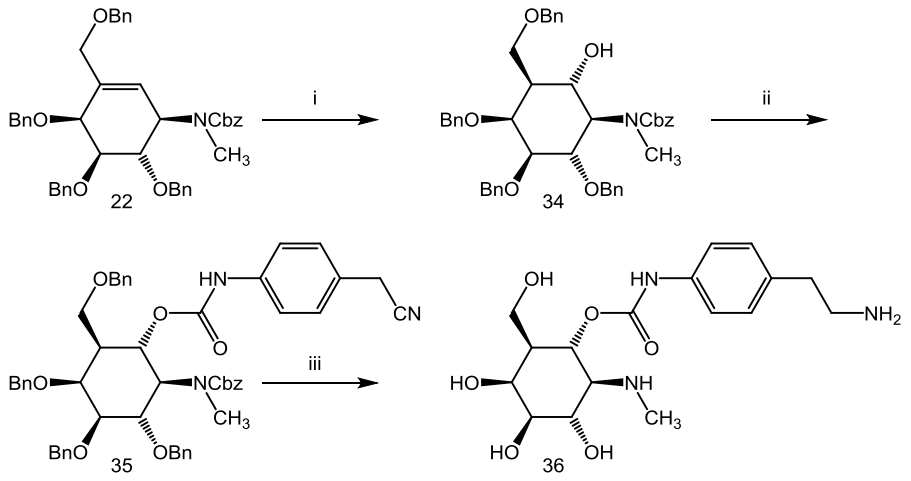
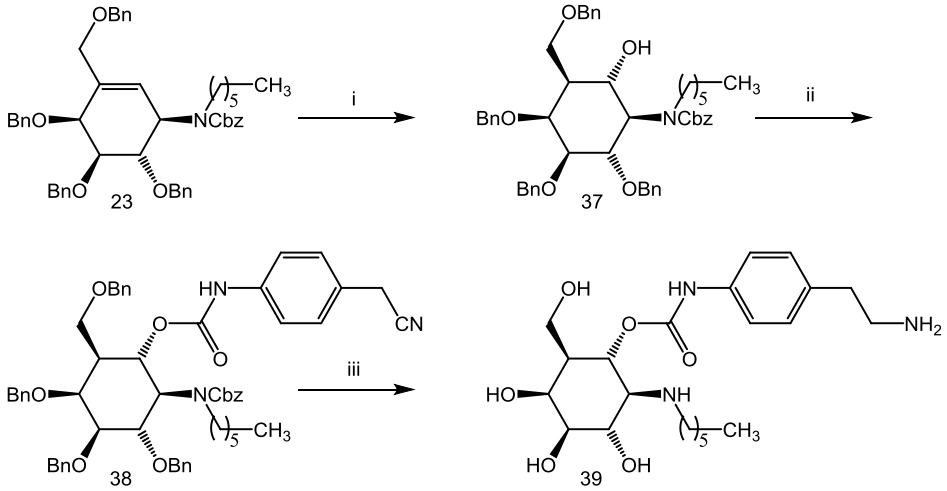


Figure 40: XRD of compound **31**. (CCDC 1513378)

The investigation of different *N*-alkyl chain lenghts at position C-1 as well as different spacer-molecules at position C-5a made it necessary to create a set of derivatives for biological evaluation. Therefore, compound **22** with the *N*-methyl group as well as **23** with the *N*-hexyl group were hydroborated with BH_3.THF to give the respecting secondary alcohols. NMR spectra of these protected aminosugars were poorly resolved due to the presence of stable rotameric populations which caused multiple or split signals in the ^{1}H as well as in the ^{13}C NMR spectra. Carbamate formation with subsequent deprotection of the different aminosugar derivatives led to single products (schemes **8-10**) with well-resolved NMR spectra.

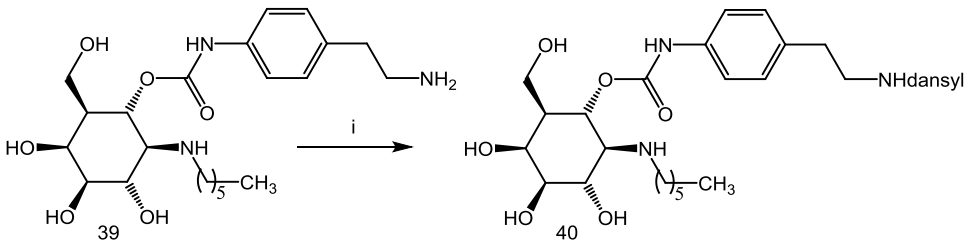


Scheme 11: Reaction sequence to the deprotected inhibitor **36**; i) BH_3*THF, NaOH, H_2O_2; ii) 4-isocyanato-benzyl cyanide, $BF_3.Et_2O$, toluene; iii) $Pd(OH)_2/C$, H_2, MeOH/H_2O, HCl.



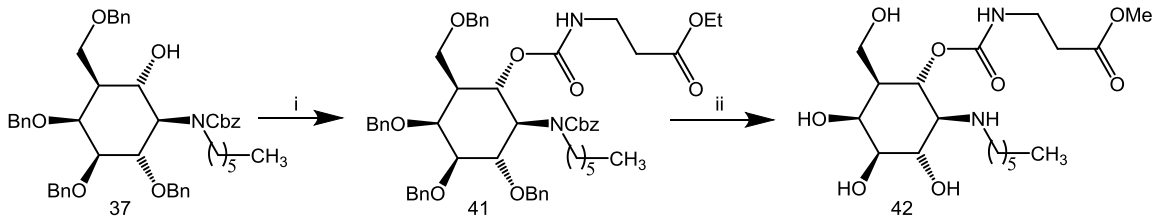
Scheme 12: Reaction sequence to free inhibitor **39**; i) BH_3*THF, NaOH, H_2O_2; ii) 4-isocyanato-benzyl cyanide, $BF_3.Et_2O$, toluene; iii) $Pd(OH)_2/C$, H_2, MeOH/H_2O, HCl.

Compound **39** featuring a terminal primary amino group at the spacer arm was reacted with dansyl chloride and Na_2CO_3 in methanol to obtain inhibitor **40** for biological evaluation.



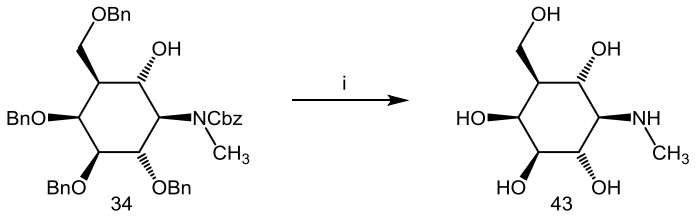
Scheme 13: Selective sulfonylation of the primary amine; i) dansyl chloride, Na_2CO_3, MeOH.

The synthesis starting from compound **37** via carbamate formation and subsequent hydrogenolytic removal of the benzyl groups led to compound **42** bearing a methyl ester at the end of the spacer-arm. Under hydrogenolytic conditions the ethyl ester is quantitatively transesterified to the methyl ester, due to excess of methanol which is used as solvent and the acidic conditions in this reaction. (scheme 14)



Scheme 14: Synthesis of inhibitor **42**; i) Ethyl 3-isocyanato propionate, BF_3*Et_2O, toluene; ii) $Pd(OH)_2/C$, H_2, $MeOH/H_2O$, HCl.

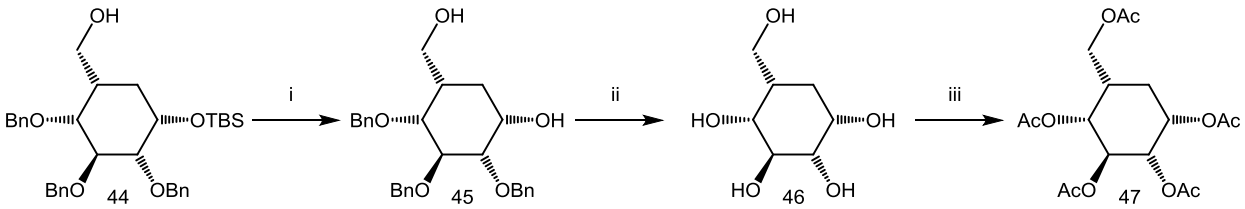
To obtain free inhibitor **43**, compound **34** was treated with H_2, $Pd(OH)_2/C$ and catalytic amounts of HCl conc. in $MeOH/H_2O$. (scheme **15**)



Scheme 15: Deprotection of compound **34**; i) $Pd(OH)_2/C$, H_2, $MeOH/H_2O$, HCl.

3.1.3 Synthesis of L-*ido*-validamine derivatives

For the synthesis of glucosidase inhibitors, α-L-*ido* configured validamine derivatives were investigated. Starting from compound **44** which was prepared employing a previously reported strategy[111], cleavage of the TBS group with TBAF gave compound **45** which was easily deprotected and peracetylated to obtain compound **47** as colourless crystals. (scheme 16) XRD measurements confirmed the β-L-ido configuration of **47** which contrasts with previously reported data.[111] (figure 41)



Scheme 16: Reaction sequence to peracetylated compound **47**; i) TBAF, THF/H_2O; ii) H_2, $Pd(OH)_2/C$, MeOH; iii) Ac_2O, DMAP, pyridine.

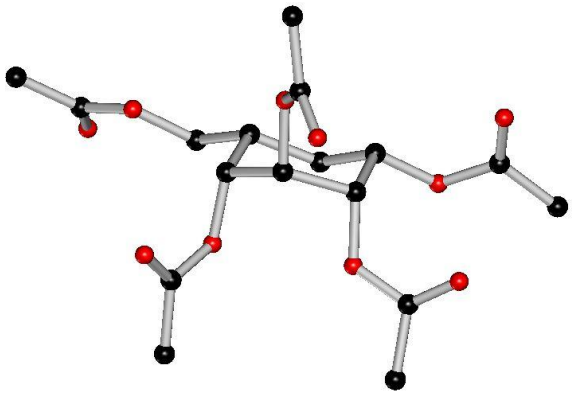
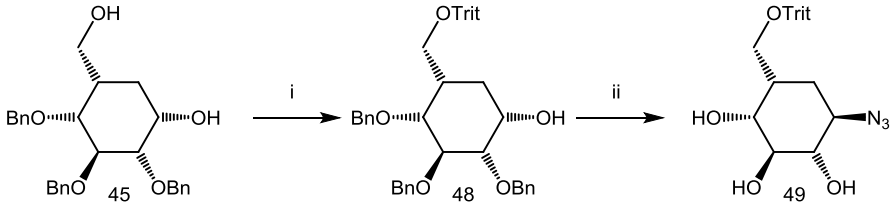
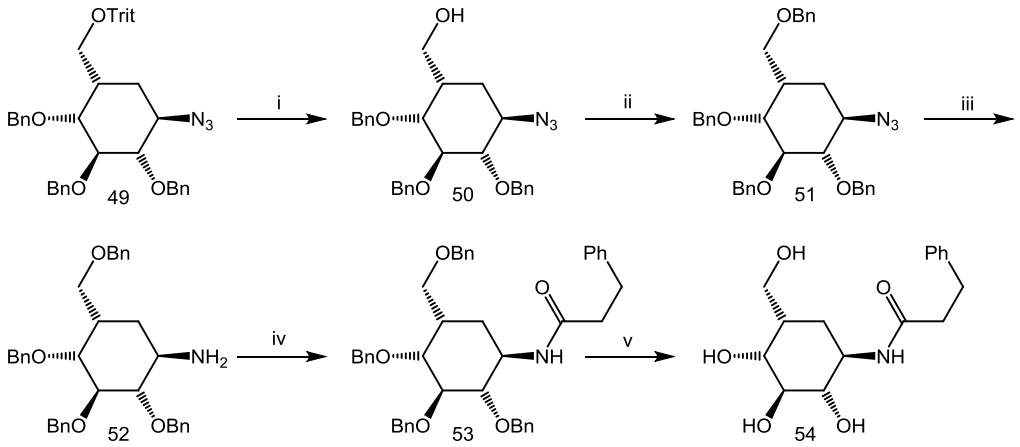


Figure 41: XRD of compound **47**.



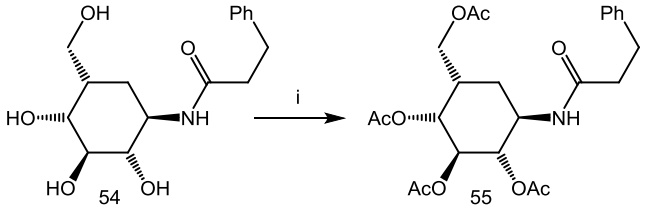
Scheme 17: i) Ph_3CCl, DMAP, pyridine, CH_2Cl_2; ii) 1) Tf_2O, pyridine, CH_2Cl_2; 2) NaN_3, DMF.

Selective *O*-tritylation of compound **45** at the primary hydroxyl group gave compound **48** which was converted via O-triflation and subsequent S_N2-reaction with NaN_3 to obtain **49**. Compound **49** was found to be highly water-sensitive so this temporary protecting group had to be removed before Staudinger reaction (scheme 18).



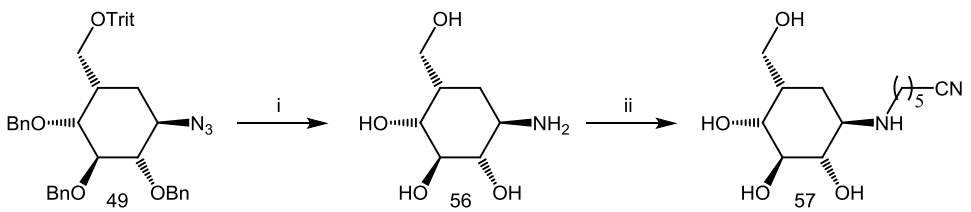
Scheme 18: Synthesis to free inhibitor **54**; i) pTSA, CH_2Cl_2/MeOH/H_2O; ii) BnBr, NaH, DMF/THF; iii) PPh_3, THF, then H_2O; iv) 3-Phenylpropionylchloride, Et_3N, CH_2Cl_2; v) H_2, Pd/C (5%), MeOH.

Acidic removal of the trityl group in CH_2Cl_2/MeOH/H_2O with pTSA led to compound **50** which was *O*-benzylated to give fully protected compound **51**. A Staudinger reaction was performed to obtain the free amine **52**. *N*-acylation with 3-Phenylpropionyl chloride furnished compound **53** in good yields. Hydrogenolytic removal of the benzyl groups led to free inhibitor **54**.



Scheme 19: Per-*O*-acetylation of compound **54**; i) Ac_2O, DMAP, pyridine.

O-Acetylation of compound **54** with acetic anhydride in pyridine gave compound **55**. Unfortunately all attempts to obtain crystals of **55** for XRD analysis failed.

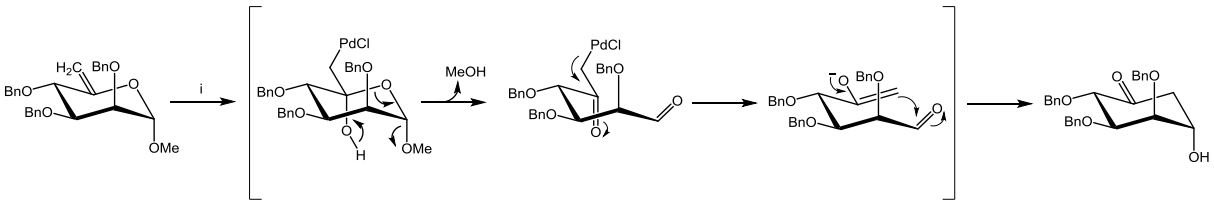


Scheme 20: Synthesis of free inhibitor **56** and **57**; i) H_2, $Pd(OH)_2$/C, MeOH/H_2O, HCl; ii) $CH_3(CH_2)_5CN$, $NaHCO_3$, DMF, 60°C.

For comparison with the neutral inhibitor **54** it was also interesting to design a representative related molecule of basic glycosidase inhibitors. The synthetic strategy was nearly the same but with a smaller number of synthetic steps. For the reduction of the azido group to an amine functionality simple stirring of compound **49** in a mixture of MeOH and water with catalytic amounts of HCl under an atmosphere of hydrogen with $Pd(OH)_2/C$ (20%) as catalyst gave deprotected inhibitor **56** in one step. To provide an example with an aliphatic spacer moiety, the nitrogen was alkylated in DMF at 60°C using 6-bromohexanoic-nitrile and $NaHCO_3$.

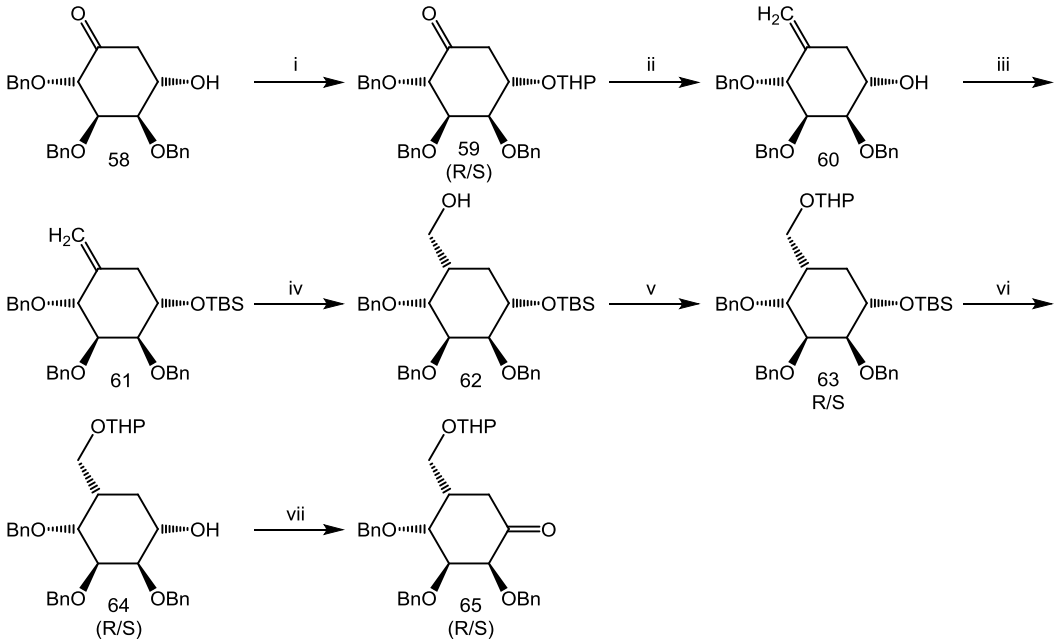
3.1.4 Synthesis of L-*gulo*-validamine derivatives

For the synthesis of novel D-mannosidase inhibitors, α-L-*gulo* configurated validamine derivatives were synthesised via the Ferrier II reaction as the key step in the synthesis. (scheme 21)



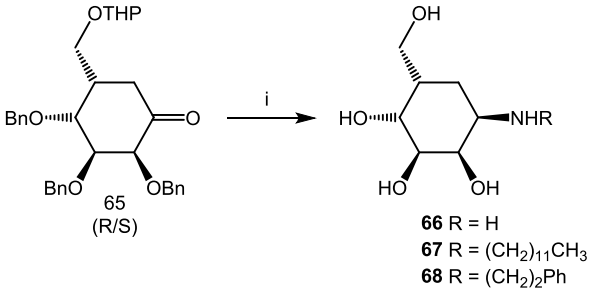
Scheme 21: Mechanism of the Ferrier II reaction.[112] i) $PdCl_2$, acetone, H_2O.

Known cyclohexanone **58** was prepared following a reported procedure exploring a different solvent system (acetone/H_2O) in the cyclisation step.[113] Protection of the free hydroxyl group with 3,4-dihydro-*2H*-pyran followed by a 2-step sequence employing a Grignard reaction followed by Peterson olefination yielded compound **60** which was subsequently protected with a TBS group. Hydroboration with BH_3.THF gave carbasugar **62** which underwent a protection and deprotection sequence to provide compound **64(R/S)** featuring a free secondary alcohol at position C-1. Oxidation of the hydroxyl group with Dess-Martin reagent gave cyclohexanone derivative **65(R/S)**. (scheme 22)



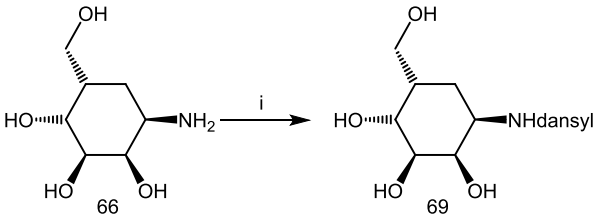
Scheme 22: Synthesis of cyclohexanone **65(R/S)**; i) DHP, pPTS, CH_2Cl_2; ii) 1) $TMSCH_2MgCl$, Et_2O; pTSA, CH_2Cl_2/MeOH/H_2O; iii) TBSCl, imidazole, DMF; iv) BH_3*THF, NaOH, H_2O_2; v) DHP, pPTS, CH_2Cl_2; vi) TBAF, THF/H_2O; vii) DMP, CH_2Cl_2.

Attempts to introduce an azido group via *O*-triflation and S_N2 reaction with NaN_3 equally to the L-*ido* synthesis, failed under various conditions which made it necessary to search for an alternative route for amine introduction. Formation of the amino function was then performed via reductive amination of the respective amines shown in scheme 23, using H_2, Pd/C (10%) in MeOH, followed by acidic cleavage of the THP group. Three amines, benzylamine, dodecylamine as well as phenethylamine were exploited as examples for this amination reaction, yielding three inhibitors. Due to the sterically demanding benzyl groups, only α-L-*gulo* configured validamines **66**-**68** were formed.



Scheme 23: Reductive amination reaction; i) RNH_2, H_2, Pd/C (10%), MeOH, then HCl, MeOH/H_2O.

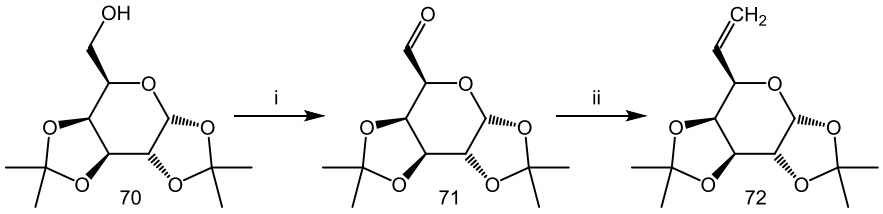
Sulfonylation of the free amine function of compound **66** with dansyl chloride gave inhibitor **69** in excellent yields. (scheme 24)



Scheme 24: i) dansyl chloride, Na_2CO_3, MeOH.

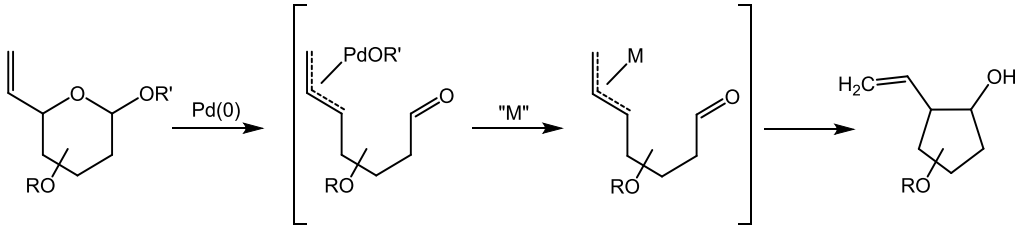
3.1.5 Synthesis of cyclopentane derivatives

Starting from commercially available galactose derivative (**72**) C-6 was oxidized by Swern oxidation, followed by a Wittig reaction to introduce a double bond which is essential for the cyclisation step. (scheme 25) The synthetic sequence was performed as previously reported.[114]



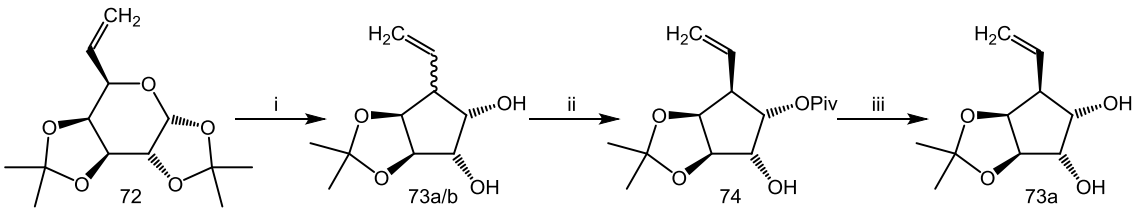
Scheme 25: Synthesis of compound **72**. i) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2; ii) PPh_3CH_3Br, n-BuLi, THF.

The key step of this reaction sequence is the cyclisation of the carbohydrate derivative **72** with $Et_2Zn/Pd(Ph_3)_4$ and $ZnCl_2$ in dry THF at room temperature[115] to a cyclopentane derivative. A 3:1 mixture of epimeres **73a** and **73b** was formed.



Scheme 26: Described reaction mechanism for the cyclisation with $Et_2Zn/Pd(Ph_3)_4$.[115]

The generally predicted reaction scheme for intramolecular allylation of the aldehyde moiety using $Et_2Zn/Pd(Ph_3)_4$ is shown in scheme 26. During selective protection of the homoallylic hydroxyl group with PivCl under basic conditions, the vinyl group isomerized to the more favoured trans position. Cleavage of the pivaloyl ester employing Zemplen saponification gave compound **73a**, which crystallized from CH_2Cl_2/benzene and allowed to obtain an X-ray structure. (figure 42.)



Scheme 27: Cyclisation reaction to cyclopentane derivative **73a**; i) Et_2Zn, $Pd(Ph_3)_4$, $ZnCl_2$, THF_{abs}, ii) PivCl, DMAP, pyridine, CH_2Cl_2, iii) NaOMe, MeOH.

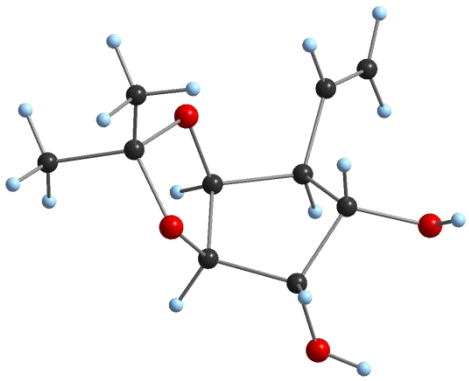
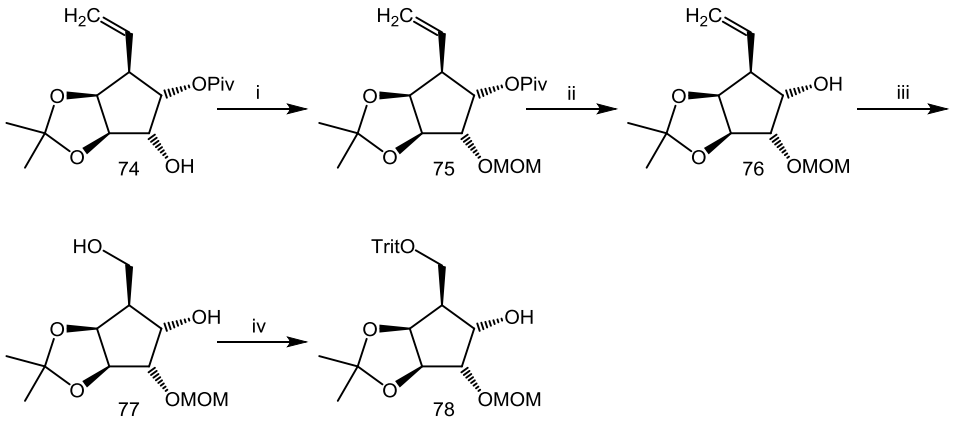


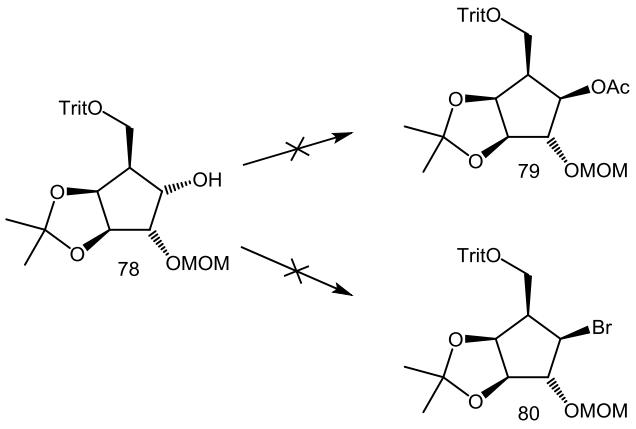
Figure 42: X-ray structure of compound **73a**.

As shown in scheme 28, the secondary hydroxyl group of compound **74** was protected with a MOM group followed by cleavage of the pivaloyl ester. All attempts to invert the deprotected hydroxyl group using an oxidation/reduction sequence as well as an Appel reaction or by S_N2 reaction yielded the product of β elimination. An approach to circumvent this problem was to treat the vinyl group with O_3 in methanol with reductive workup using $NaBH_4$ to form **77** to prevent the system from β-elimination. Discrimination of the two free hydroxyl groups was observed during *O*-tritylation, which is selective to primary alcohols yielding compound **78**.



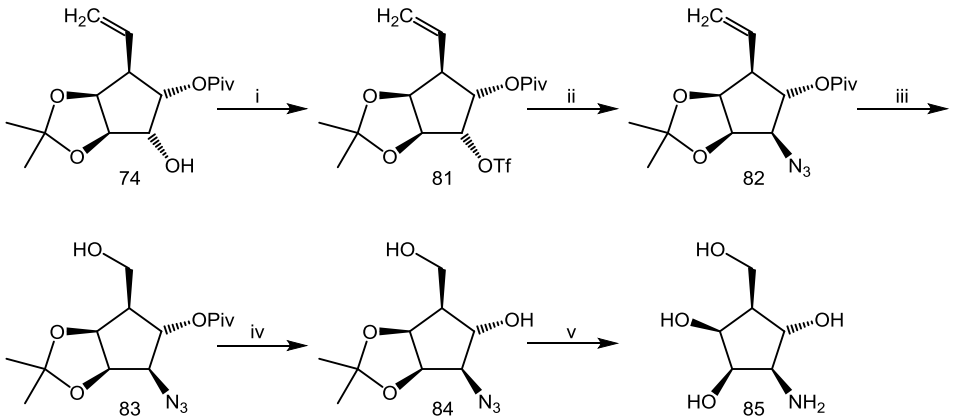
Scheme 28: Synthesis of compound **78**; i) MOMCl or MOMBr, Hünigs base, CH_2Cl_2; ii) NaOMe, MeOH; iii) O_3, MeOH, then $NaBH_4$; iv) TritCl, DMAP, pyridine, CH_2Cl_2.

With molecule **78** which had no exocyclic vinyl group, it was neither possible to invert the stereocenter under Mitsunobu conditions nor by S_N2 reaction using triflate and NaOAc. Under Appel conditions the starting material was consumed but gave no desired product. Probably this is caused by the formation of the product followed by elimination of the acetate or bromine functionality which is trans-diaxial to the hydrogen on the tertiary position.



Scheme 29: Approaches to invert the desired stereocenter failed.

Nonetheless, I could develop a short synthesis with good yields to create cyclopentane derivatives with different positions available for further chemistry with limitations described above.



Scheme 30: Synthesis of free inhibitor 85; i) Tf_2O, pyridine, CH_2Cl_2; ii) NaN_3, DMF; iii) O_3, MeOH, then $NaBH_4$; iv) NaOMe, MeOH; v) H_2, $Pd(OH)_2/C$, acidic MeOH.

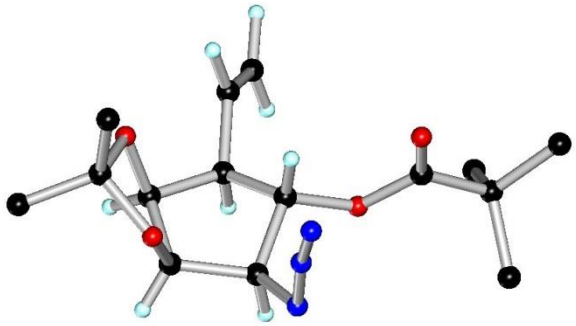
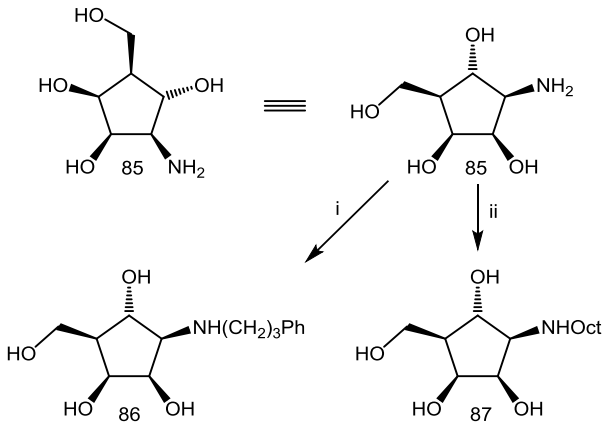


Figure 43: XRD of compound **82.**

As described in scheme 30, it was possible to convert the secondary alcohol of compound **74** into the respective triflate **81**, which is stable to column-chromatography and could be reacted with NaN_3 to give compound **82,** via inversion of configuration, in good yields. It could be recrystallized from cyclohexane/ethylacetate to give colorless crystals for XRD analysis (figure 43). After ozonolysis with subsequent reduction of the aldehyde, the pivaloyl group was cleaved off employing sodium methanolate to get compound **84**. Treatment of **84** with $Pd(OH)_2/C$ under an atmosphere of hydrogen in acidic methanol gave compound **85**.



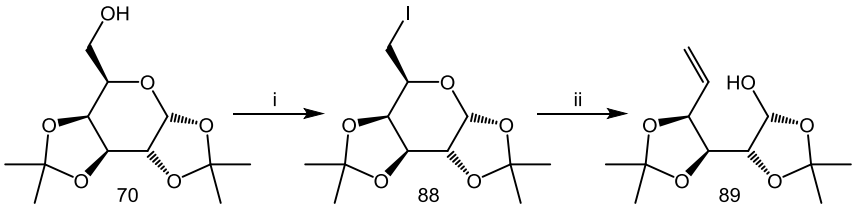
Scheme 31: Alkylation of 85; i) Phenylpropyl bromide, $NaHCO_3$, DMF, 60°C; ii) Octyl bromide, $NaHCO_3$, DMF, 60°C.

To provide one inhibitor of this class with an aromatic moiety, compound **85** was converted into **86** via an alkylation step employing phenylpropyl bromide. The second inhibitor was alkylated with bromooctane to give a comparable molecule to the six-membered carbasugars.

3.2 Carbapentoses

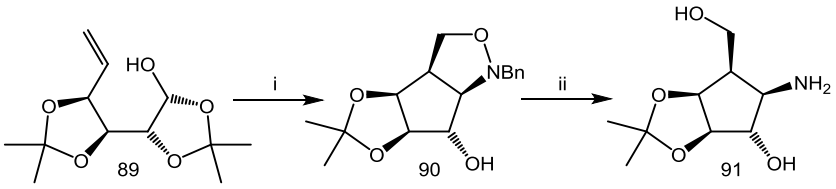
3.2.1 Synthesis of 5-membered D-galacto configured aminocyclopentanetriols

For the synthesis of five-membered carbacycles with a nitrogen at C-1 in "beta"-position, a strategy of Jäger and coworkers[116] was adopted. Starting from 1,2;3,4-di-*O*-isopropyliden-α-D-galactose, a Garegg reaction was performed to introduce an iodine at position C-6. Previously, the reductive ring opening step was performed exploiting vitamin B_{12} as a catalyst. This was found not to be necessary when a system of Zn dust and NH_4Cl was allowed to stir for twenty minutes in methanol before adding compound **88**.[117] After five minutes, completed conversion of **88** to open chain compound **89** was achieved. Filtration of the solids over a plug of silica gel followed by extraction with EA/H_2O, gave pure **89** as a pale-yellow oil.



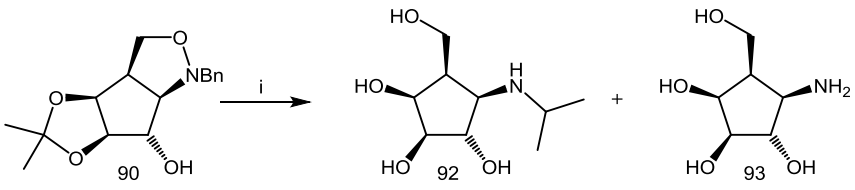
Scheme 32: Reaction sequence to key compound **89**; i) PPh_3, imidazole, I_2, toluene; ii) Zn dust, NH_4Cl, MeOH.

The cyclisation step to tricyclic compound **90** was performed in methanol using *N*-benzylhydroxylamine hydrochlorid and $NaHCO_3$. With this solvent, I only obtained compound **90** with no formation of other products. After crystallization from EA/cyclohexane it was possible to get an X-ray structure of compound **90** for unambiguous determination of configuration. (figure 44)



Scheme 33: i) BnNHOH HCl, $NaHCO_3$, NaOMe, MeOH; ii) H_2, Pd/C (10%), MeOH.

Reaction of **90** under hydrogenolytic conditions using H_2, Pd/C (10%) in methanol gave compound **91** in good yields. Direct deprotection of **90** under acidic conditions with H_2, $Pd(OH)_2/C$ and HCl conc. in methanol furnished a mixture of **92** and **93**, because of imine formation of the sugar part with the liberated acetone and subsequent reduction to the isopropylamine functionality. (scheme 34)



Scheme 34: i) $Pd(OH)_2/C$, H_2, $MeOH/H_2O$, HCl.

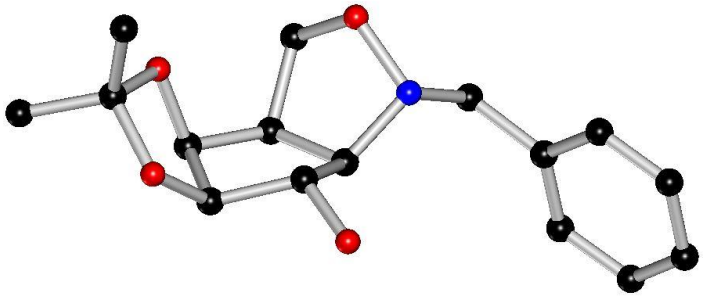
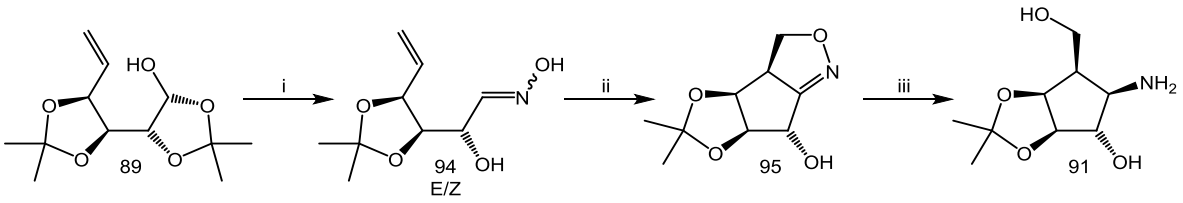


Figure 44: X-ray structure of compound **90** (CCDC 1530133).

Investigation of another reaction sequence to form compound **91** using aqueous hydroxylamine is shown in scheme 35. In the first step, starting from **89**, aqueous hydroxylamine (50 % wt) was added to a stirred solution of compound **89** in methanol. Completed conversion to an inseperable *E/Z* mixture of oxime **94** was reached after addition of the reagent, which was then evaporated to dryness. For the cyclisation step, the *E/Z* mixture was dissolved in isopropanol, silica gel was added and the mixture was stirred while adding aqueous NaOCl (10-15%). After full conversion of the starting material, CH_2Cl_2 was added and the organic layer was extracted with HCl (2N) and saturated $NaHCO_3$ to give compound **95** as a colorless oil. Recrystallization from CH_2Cl_2/cyclohexane gave colourless crystals for X-ray analysis. (figure 45)



Scheme 35: Cyclisation reaction to compound 95; i) H_2NOH (50 %wt), MeOH; ii) $NaOCl_{aq}$, silica gel, isopropanol; iii) LAH, THF.

Oxidation of open chain oxime **94** employing a Chloramin T/silica gel system[118] in MeOH turned out to be very fast, but gave a challenging mixture of product **95** and Chloramine T artefacts which could not be separated by chromatography.

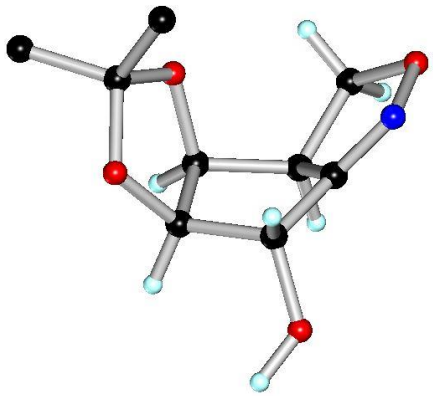
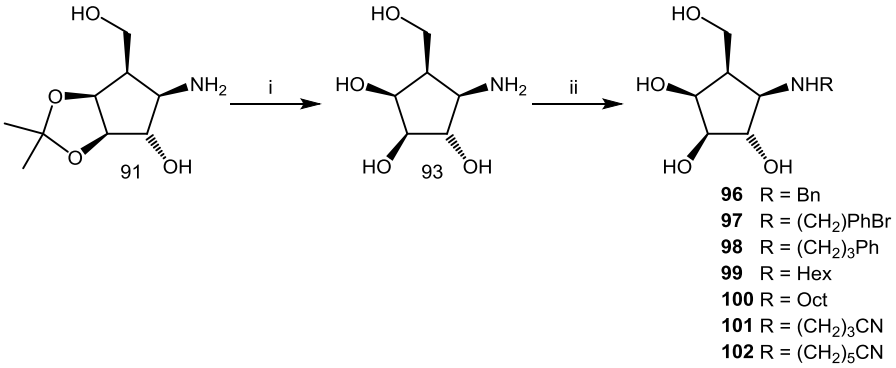


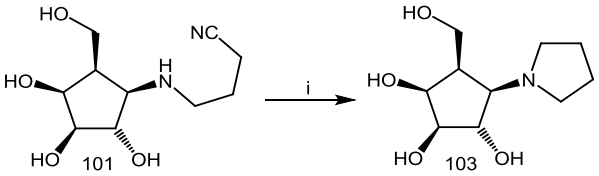
Figure 45: X-ray structure of compound **95** (CCDC 1530134).

Reduction of the isoxazolidine **95** with $LiAlH_4$ in THF gave partially protected compound **91** in good yields. Cleavage of the isopropylidene group was performed with HCl conc. in $MeOH/H_2O$ at 40°C to give free carbapentose derivative **93**.



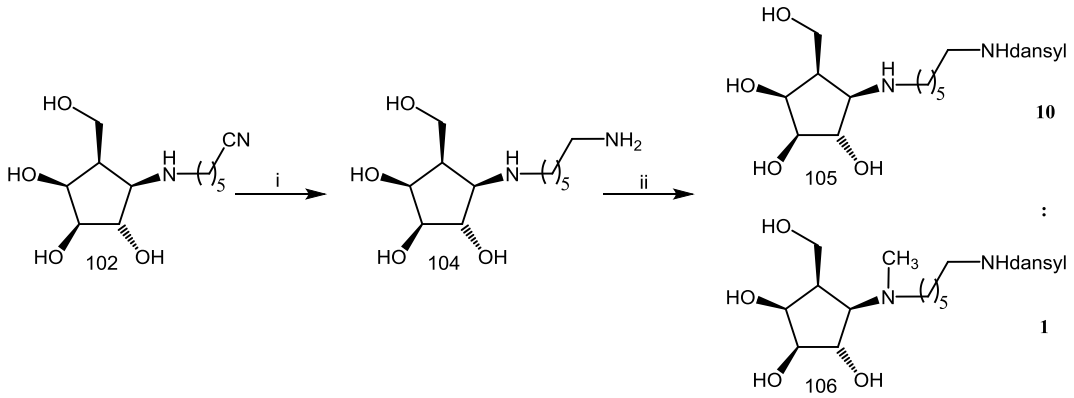
Scheme 36: Synthesis of different inhibitors; i) HCl, $MeOH/H_2O$; ii) RBr, $NaHCO_3$, DMF, 60°C.

To create a set of different inhibitors, free compound **93** was treated with a selection of alkyl bromides in DMF with $NaHCO_3$ as base to monoalkylate the nitrogen on the ring. (scheme 36) Three aromatic as well as two aliphatic spacers were investigated. In addition, two systems with terminal nitrile functionalities were probed.



Scheme 37: Cyclisation reaction to compound 103; i) H_2, $Pd(OH)_2/C$, $MeOH/H_2O$, HCl at pH=2.

Bicyclic compound **103** was synthesized by an intramolecular reductive amination reaction in which nitrile **101** was reduced to the aldimine compound which hydrolysed to the aldehyde and was intramolecularily attacked by the secondary amine forming a cyclic imine which was subsequently reduced under H_2 atmosphere using $Pd(OH)_2/C$ at pH 2 (HCl conc.) in a $MeOH/H_2O$ solvent system to give **103** in good yields.



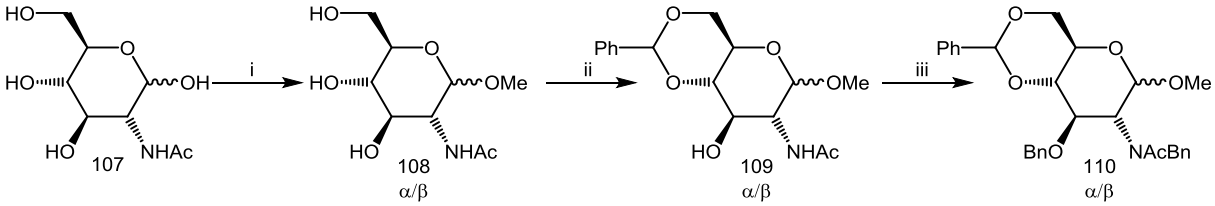
Scheme 38: Nitrile reduction and sulfonylation of the primary amine; i) H_2, $Pd(OH)_2/C$, MeOH; ii) dansyl chloride, $NaHCO_3$, MeOH.

Reduction of the nitrile in compound **102** to primary amine **104** was performed with H_2 and $Pd(OH)_2/C$ in methanol with quantitative yields. After purification on silica gel, the primary amine was sulfonylated with dansyl chloride Na_2CO_3 in MeOH which gave a mixture of two products (**105** and **106**) in a ratio of 10:1. (scheme 38) The additional methyl group of compound **106** was introduced under workup conditions. The evaporation of the solvent without quenching the excess of dansyl chloride may cause sulfonylation of solvent molecules where the dansyl leaving group could be attacked by the basic nitrogen at position C-1 forming the *N*-methylated inhibitor **106** as a side product. Dansylation of the secondary amine was not observed under the described conditions.

3.2.2 Synthesis of 5-membered carba-N-acetyl-galactosamine derivatives

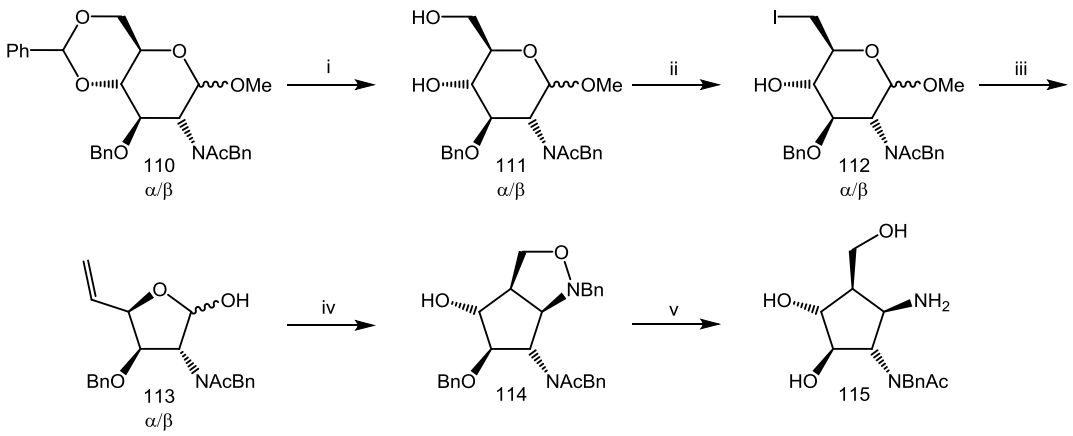
The synthesis of five membered carbacycles with an *N*-acetyl group starting from commercial available *N*-acetyl-D-glucosamine (**107**) was another task of this thesis. In this work, a simple protecting group strategy was developed to gain access to a molecule with a

free hydroxyl group on position C-4 of the hexose which could be converted to the respective D-*galacto* configurated carbasugar by inversion of configuration of this center.



Scheme 39: Synthesis to protected *N*-acetyl-glucosamine derivative 110; i) IR-120, MeOH, reflux; ii) benzaldehyde dimethylacetal, pTSA, DMF; iii) BnBr, NaH, DMF.

Fischer glycosylation of compound **107** employing IR-120 ion exchange resin in methanol gave an inseparable 1:1 mixture of α/β-pyranosides **108** which was converted to compound **109** via transacetalisation with benzaldehyde dimethylacetal. Benzylation of **109** with BnBr and NaH in DMF gave known compounds **110** in good yields. (scheme 39)



Scheme 40: i) IR-120, MeOH/H_2O; ii) PPh_3, imidazole, I_2; iii) Zn dust, NH_4Cl, MeOH; iv) $BnNH_2OHCl$, $NaHCO_3$, MeOH; v) H_2, $Pd(OH)_2/C$, MeOH.

Cleavage of the benzylidene group with IR-120 in methanol, followed by deoxyiodination of the primary hydroxyl group, led to compound **112**, which underwent a reductive ring opening step employing the Zn/NH_4Cl system described before. α/β-Mixtures of the described compounds were inseparable by column chromatography and were co-spotting on TLC. The cyclisation reaction with benzylhydroxylamine hydrochloride in methanol gave

compound **114** which was hydrogenolytically deprotected. Compound **115** was recrystallized in toluene/MeOH to give colorless crystals for X-ray analysis. (figure 46) The *N*-benzyl group on the amide turned out very stable under deprotection conditions. To circumvent this problem, it will be necessary to change the conditions to higher pressure and longer reaction times.

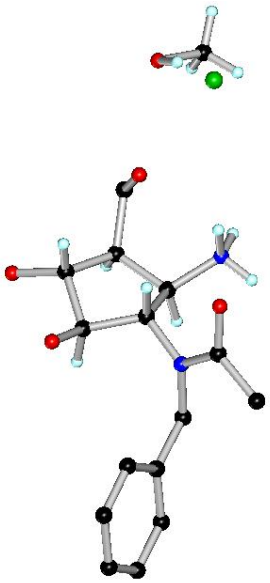
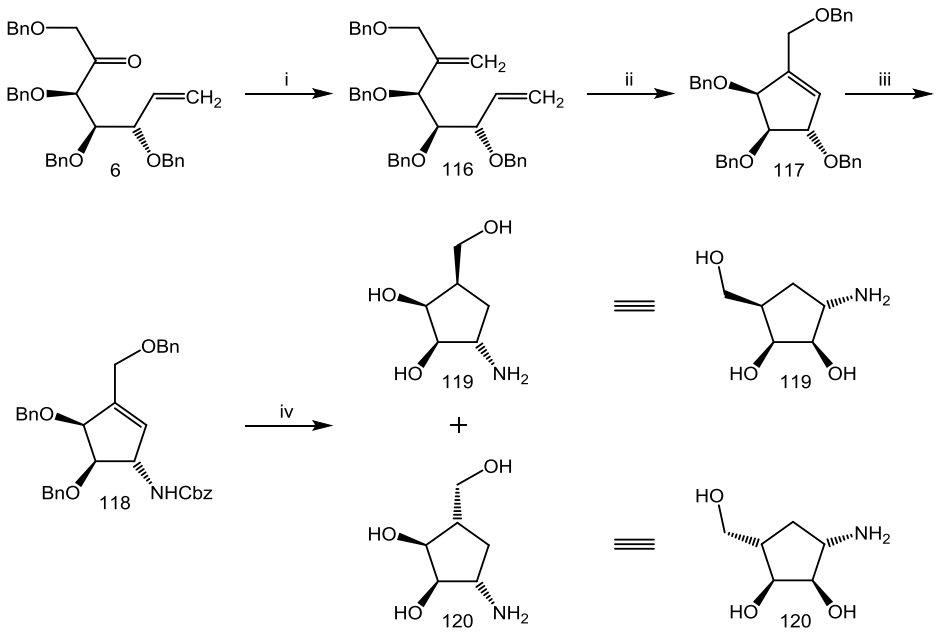


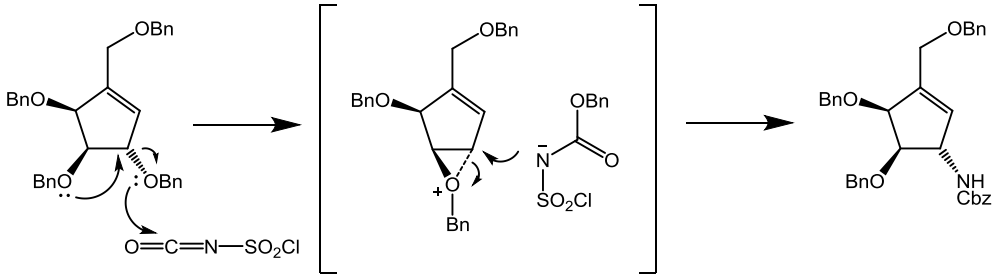
Figure 46: Crystal structure of compound **115.**

3.2.3 Synthesis of carbapentose derivatives

Starting from ulose **6,** a Wittig reaction followed by ring closing metathesis was conducted to create cyclopentene system **117**.[119] The introduction of the nitrogen was performed by a procedure reported by a Korean group[120,121] providing compound **118** in good yields. Hydrogenolytic removal of the benzyl groups and reduction of the double bond was performed using H_2, $Pd(OH)_2/C$ in methanol furnishing an inseperable mixture of epimers **119**/**120** at the branching point. Separation will be achieved by further derivatisation of the nitrogen.



Scheme 41: Synthesis to compounds 119 and 120; i) PPh_3CH_3Br, n-BuLi, THF; ii) Grubbs II, CH_2Cl_2, reflux; iii) CSI, Na_2CO_3, CH_2Cl_2, 0°C, then Na_2SO_3; iv) H_2, $Pd(OH)_2/C$, MeOH.

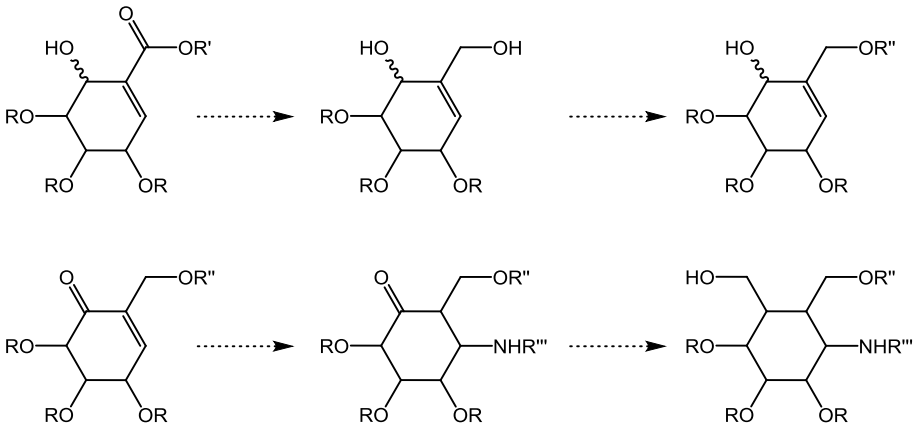


Scheme 42: Adopted proposed reaction mechanism for the reaction of **117** with CSI followed by Na_2SO_3.[122]

3.3 Other synthetic studies

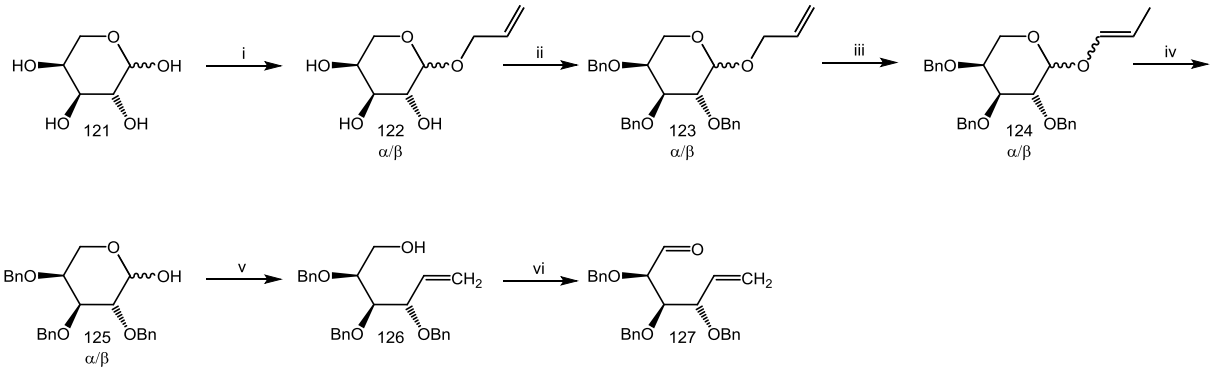
3.3.1 Morita-Baylis-Hillman (MBH) reaction and preliminary results.

As shown before, C-5a elongated validamine derivatives are potent inhibitors for β-galactosidases as well as of β-glucosidases. To avoid the urethane linker between the sugar moiety and the lipophilic spacer part, different reaction types were investigated. Promising results were obtained with the Morita-Baylis-Hillman reaction sequence.



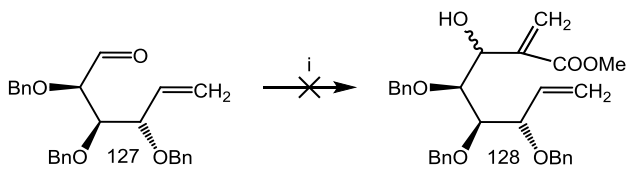
Scheme 43: Synthesis strategy towards C5a-C elongated Validamine derivatives.

The first approach to build up the starting material for the MBH started with L-arabinose which was glycosylated via a Fischer glycosylation in allyl alcohol[123] and subsequently *O*-benzylated. Cleavage of the allyl group was performed in the same way as described before for D-galactose derivatives. Wittig reaction followed by Swern oxidation gave compound **127** in good yields.



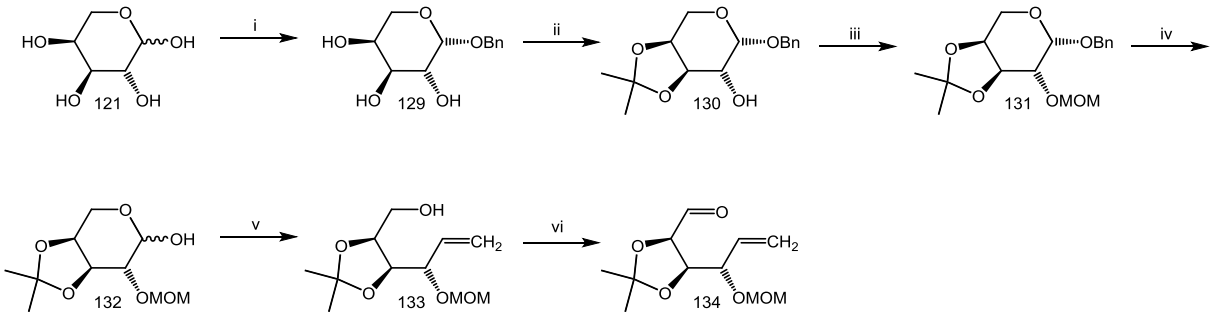
Scheme 44: i) Allyl alcohol, H_2SO_4, 40°C; ii) BnBr, NaH, DMF/THF (3:1); iii) t-BuOK, DMSO, 120°C; iv) pTSA, CH_2Cl_2/MeOH/H_2O; v) PPh_3CH_3Br, n-BuLi, THF; vi) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2.

The MBH reaction was carried out in 1,4-dioxane/H_2O with methyl acrylate using DABCO as a base. All attempts to form the desired product under investigated conditions failed.



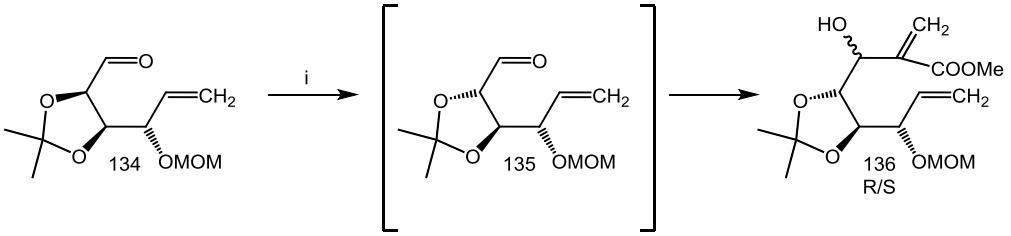
Scheme 45: Morita-Baylis-Hillman reaction with **127**; i) Methyl acrylate, DABCO, 1,4-dioxane/H_2O.

To create a similar type of molecule for the C-elongation, another reaction sequence was investigated. Starting from L-arabinose (**121**), a glycosylation reaction employing benzyl alcohol was performed followed by trans-acetalisation to compound **130** with subsequent MOM protection of the remaining hydroxyl group. Hydrogenolytic removal of the benzyl group followed by a Wittig reaction and Swern oxidation provided compound **134** in good yields.



Scheme 46: Synthesis of compound **134**; i) Acetyl chloride, benzyl alcohol; ii) Acetone dimethylacetal, pTSA, acetone; iii) MOMCl, Hünig's base, CH_2Cl_2; iv) Pd/C (10%), H_2, MeOH; v) PPh_3CH_3Br, n-BuLi, THF; vi) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2.

As shown in scheme 47, the aldehyde is isomerized to the D-*xylo* configuration under the basic reaction conditions faster than the C-C bond formation which turned out to be a quantitative conversion to the *R/S* mixture of **136.** Similar molecules were synthesized previously starting from D-ribose[124] or tartaric acid.[125]



Scheme 47: Morita-Baylis-Hillman reaction with **134**; i) Methyl acrylate, DABCO, 1,4-Dioxane/H_2O.

Compound **136** should be easily cyclized by ring closing metathesis to give access to C-5a elongated validamine derivatives.

3.3.2 Fluorinated carbasugars.

The introduction of a fluorine into the tertiary position C-5 of the cyclohexane ring was carried out with Selectfluor® which is a suitable electrophilic fluorination reagent. To prove the applicability of this reagent, different sugar derivatives with a wide range of protecting groups were tested.[126]

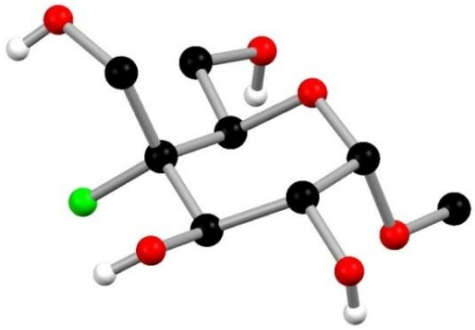
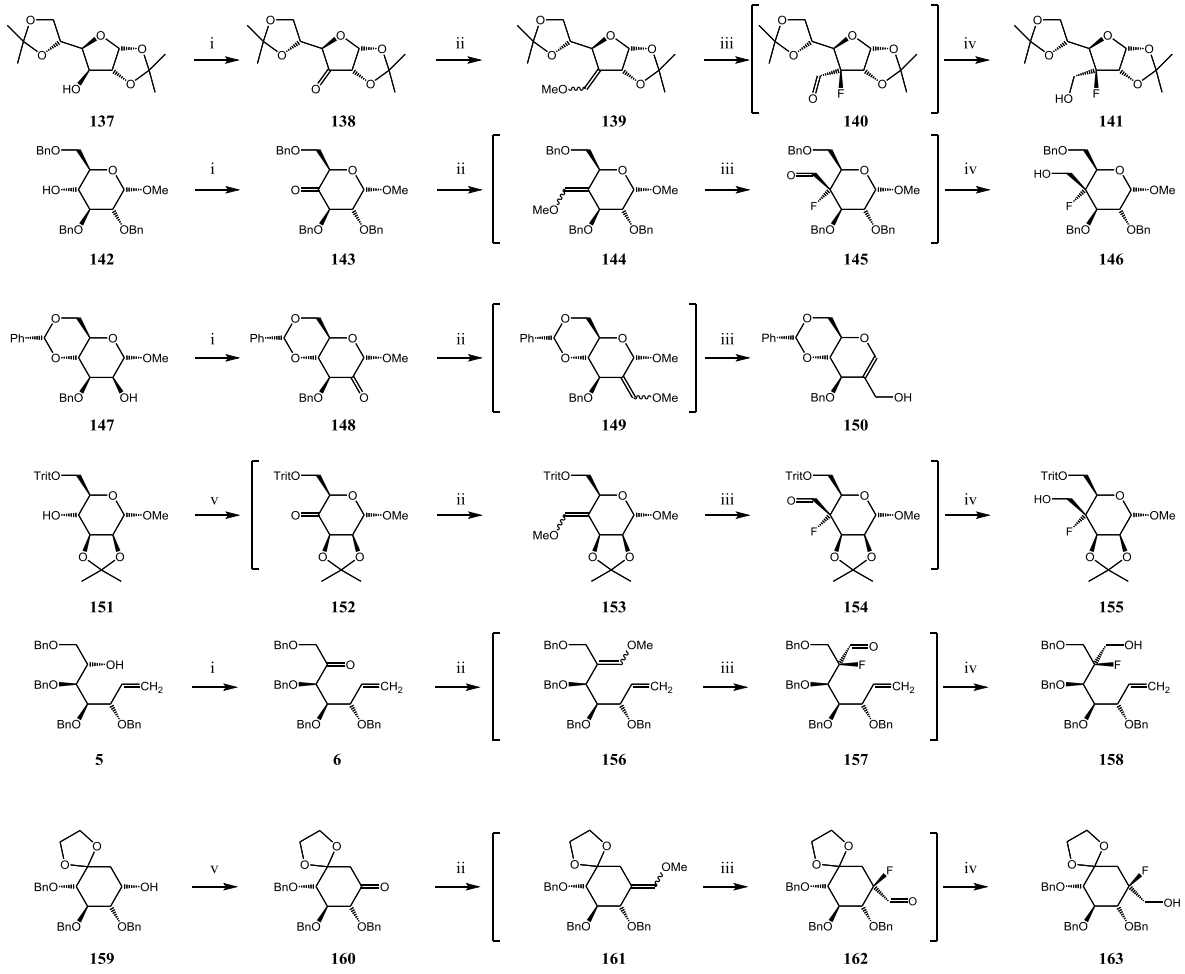


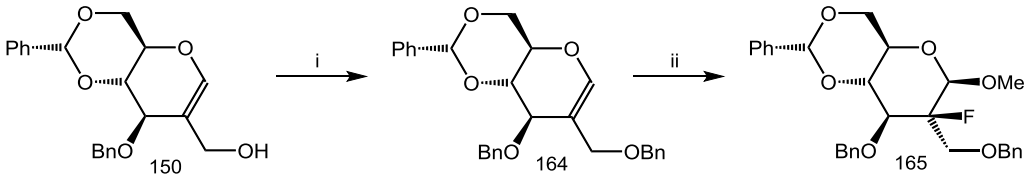
Figure 47: XRD of compound **146a**. (CCDC 1508806).[126]



Scheme 48: i) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2; ii) $MeOCHP(Ph)_3$ THF; iii) Selectfluor, $MeCN/H_2O$, iv) $NaBH_4$, MeOH; v) Dess-Martin periodinane, CH_2Cl_2.[126]

The simple strategy of oxidising a secondary alcohol to the corresponding ulose which undergoes a Wittig reaction followed by treatment with Selectfuor® reagent leading, after reduction of the α-fluoro aldehyde, to the fluorinated sugar derivatives, was investigated. Only in the case of compound **149** fluorination of the desired center was not observed due to β elimination followed by reduction of the α/β unsaturated aldehyde with $NaBH_4$. (scheme 48).

Stereochemical outcomes were determined by XRD measurements for **146** and **158**. (figure 47 and 48) Benzylation of compound **150** with subsequent fluorination gave a mixture of 2 substances which was seperable by column chromatography but only the minor product could be identified. (figure 49)



Scheme 49: Reaction sequence to compound 165; i) BnBr, NaH, DMF/THF; ii) Selectfluor, $MeOH/H_2O$.

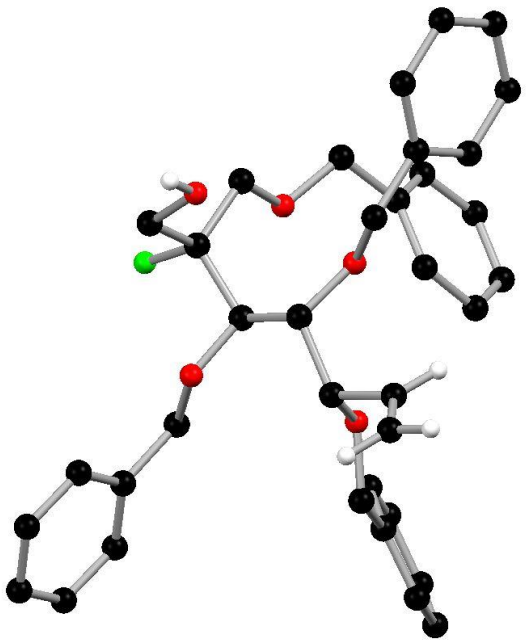


Figure 48: XRD of compound **158**. (CCDC 1508808).[126]

Compound **163**, which was synthesized from cyclohexane derivative **159** showed, after fluorination, D-*ido* configuration as single stereoisomer. The synthesis of D-gluco and L-ido configurated carbasugar derivatives bearing a tertiary fluorine, which could be compared with the validamine derivatives described before, started eith compound **165**[130] which was protected with a TBS group to give **166**. Wittig reaction and subsequent fluorination with Selectfluor gave a mixture of C-5 epimers which was reduced to the fluorine containing carbasugars **170** and **171**. The introduction of the amino function should be similar to the synthesis described in scheme 48. Long reaction times during the fluorination step as well as harsh conditions during the reduction of the aldehyde cleaved the TBS group and provided a 1,6-free carbasugar for further chemistry.

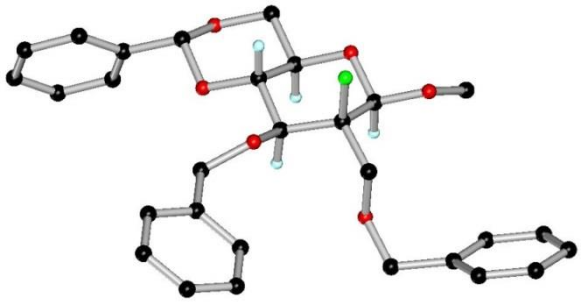
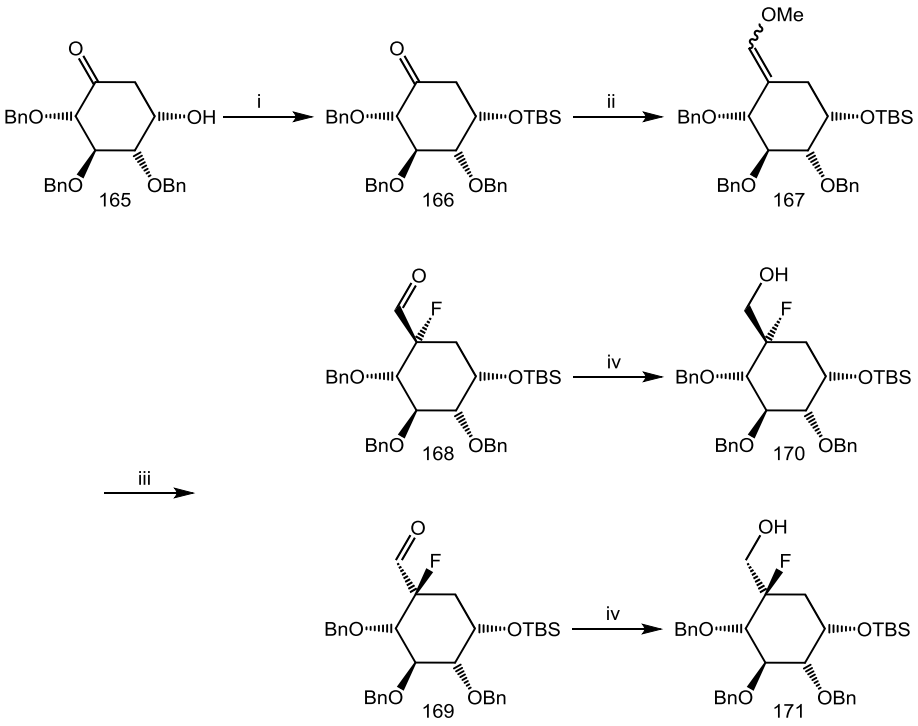


Figure 49: X-ray structure of product **165**.



Scheme 50: i) TBSCl, imidazole, DMF; ii) $MeOCHP(Ph)_3$ THF; iii) Selectfluor, $MeCN/H_2O$, iv) $NaBH_4$, MeOH.

3.3.3 Synthesis of substituted inososes and their enantiomers.

Following a synthesis of compound **177** that was published several years ago,[130] it was possible to synthesise enough material to get suitable crystals for XRD measurements. The crystal structures of compound **165** and its enantiomer **177** are shown in figure 50. A great advantage of the synthesis is the fact, that all the steps in the sequence are clean and proceeding very fast. The precursor molecule **177** is the entrance to the D-*ido*-validamine series as well as gabosines[127,128] and other related molecules.[129] Following the same synthetic strategy it was also possible to convert a D-*manno* configurated cyclohexanone (**58**) into the L-*galacto* configuration (**183**/**184**). (scheme 52)

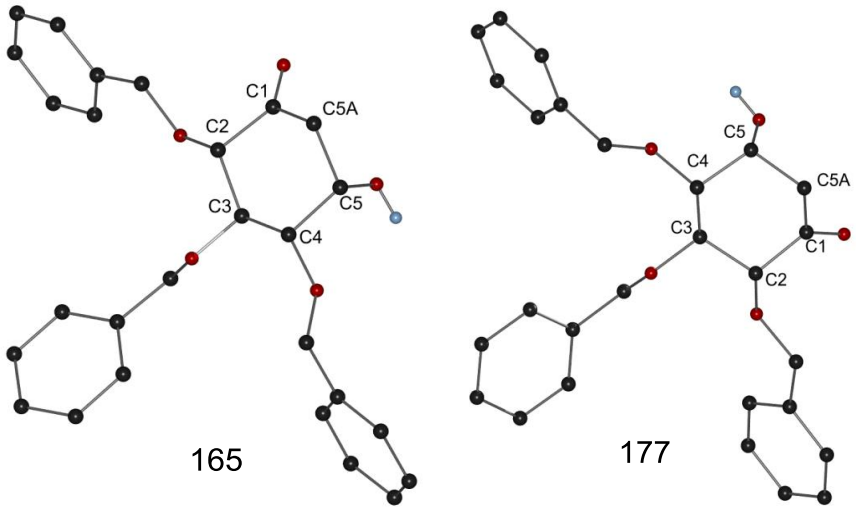
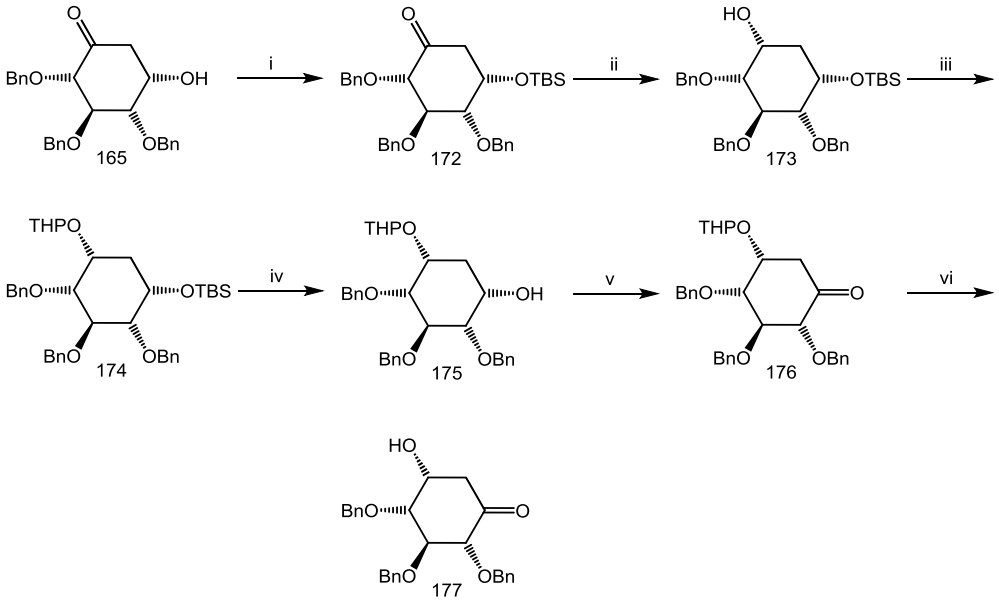
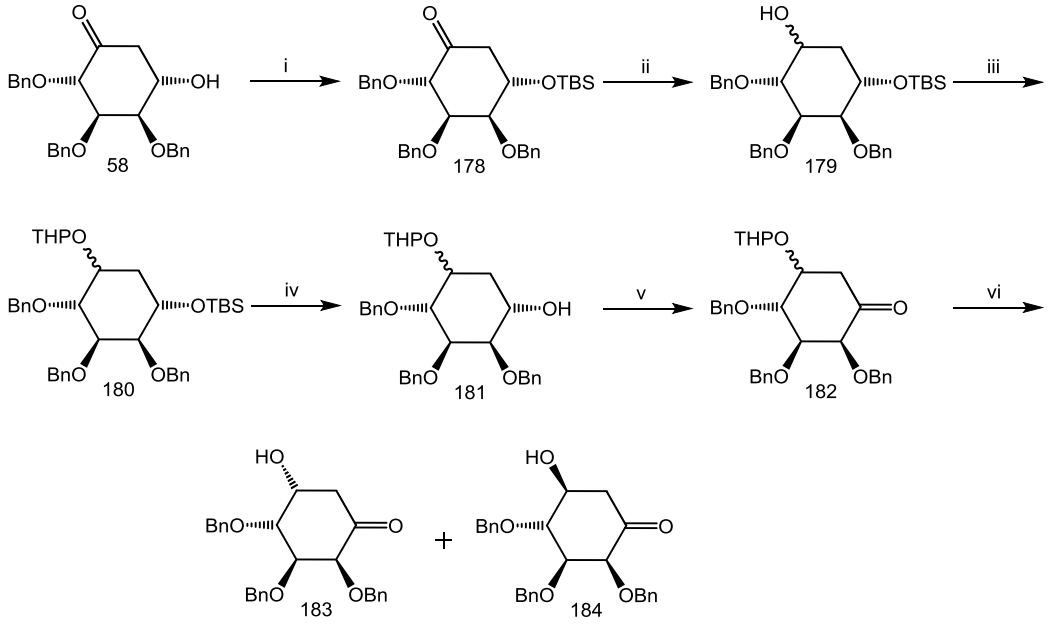


Figure 50: X-ray structures of compound **165** and **177**.

This easy synthetic strategy exploiting symmetry in the starting material makes it possible to have access to various products in the L-series. Also, starting from D-*galacto* configured cyclohexanones the entrance to L-*manno* derivatives should be possible. The reduction of compound **178** to the secondary alcohol gave a mixture of epimeres, which could not be separated. After cleavage of the THP group of **182** separation was achieved with a very unpolar column solvent system.



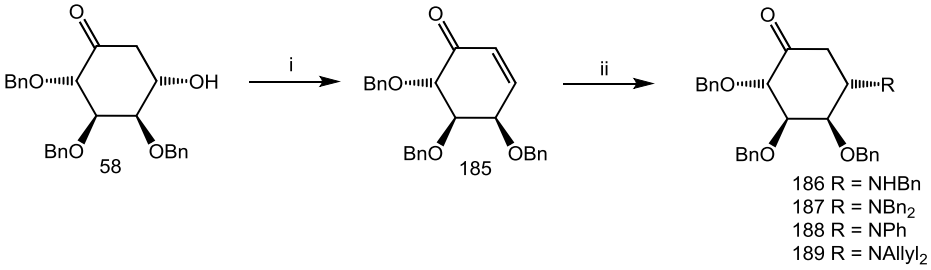
Scheme 51: Synthesis of the enantiomer of **177**.[130] i) TBSCl, imidazole, DMF; ii) $NaBH_4$, THF; iii) DHP, pPTS, CH_2Cl_2; iv) TBAF, THF/H_2O; v) Dess-Martin periodinane, CH_2Cl_2; vi) pTSA, CH_2Cl_2/H_2O.



Scheme 52: Synthesis of **183** and **184**; i) TBSCl, imidazole, DMF; ii) $NaBH_4$, THF; iii) DHP, pPTS, CH_2Cl_2; iv) TBAF, THF/H_2O; v) Dess-Martin periodinane, CH_2Cl_2; vi) pTSA, CH_2Cl_2/H_2O.

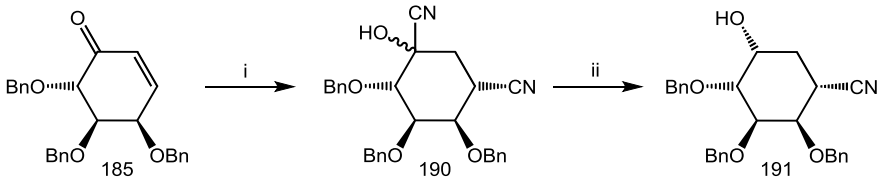
For the introduction of amino functions to obtain validamine precursors the aza-Michael addition was investigated. Cyclohexanone **58** which was prepared via Ferrier II reaction and was easily converted into the cyclohexenone derivative by acetylation of the secondary alcohol with subsequent beta elimination to compound **185**. The use of tosyl chloride to

form a leaving group for β-elimination was found to be ineffective because of slow reaction rates, even at higher temperatures.



Scheme 53: i) Ac_2O, DMAP, pyridine; ii) RH, t-BuOH, MeCN.

The yields of the aza-Michael addition were ranging between 10% conversion for diallylamine up to 80% for benzylamine, giving products **186**-**189**. The introduction of the side chain should be possible via methoxymethyl-Wittig reaction followed by acidic enolether opening and reduction of the aldehyde. The introduction of a fluorine atom should be possible as described before, in addition giving the opportunity for a second pathway to 5-fluoro validamines.



Scheme 54: i) Acetonecyanohydrine, Na_2CO_3, t-BuOH, MeCN; ii) $NaBH_4$, THF, 0°C.

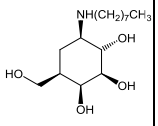
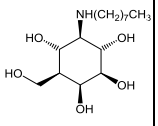
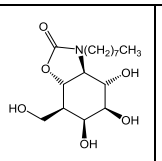
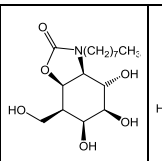
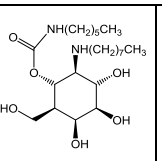
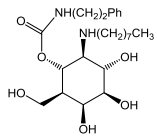
Furthermore C-elongation via nitrile 1,4-addition was investigated employing acetone cyanhydrine. In the first, step addition of the nitrile occurred with subsequent formation of the cyanohydrine on the carbonyl function of the cyclohexanone. The stable mixture of epimers was then reduced with $NaBH_4$ to give compound **191** which can be regarded as a masked carbasugar derivative. Reduction of the nitrile as well as saponification and reduction are means to gain access to the D-*altro* series.

3.4 Biological evaluation

Synthesized compounds presented in this thesis were tested against several glycosidases. Promising activities for different products concerning inhibition of β-galactosidases made it interesting to test them for chaperone activity with lysosomal human β-galactosidase.

Biological evaluation was carried out at the laboratory of Stephen G. Withers at UBC, Canada and Prof. Windischhofer and co-workers at the Medical University of Graz.

Table 1: K_i-Values for validamine derivatives

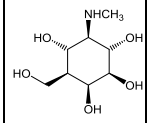
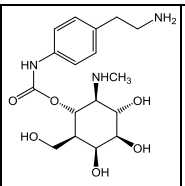
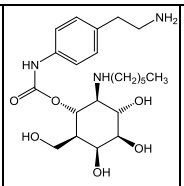
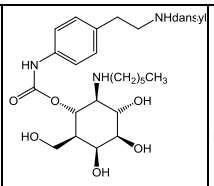
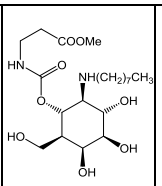
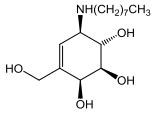
	 **17**	 **29**	 **26**	 **28**	 **31**	 **33**
Abg	12.4	N.I.	47.4	462	6.6	9.8
β-Gal (E.coli)	0.081	235	202	21.1	0.5	3.1
β-Gal (bovine liver)	n.d.	n.d.	n.d.	n.d.	1.5	4.2
Fabrazyme	9.3	49.3	N.I.	N.I.	N.I.	N.I.
α-Gal (*S. cer*)	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
GCase	129	290	756	200	N.I.	33.2

K_i-values [μM] of compounds with Abg = β-glucosidase/β-galactosidase from *Agrobacterium* sp.; *E. coli* = *lac Z* β-galactosidase from *E. coli*; bovine liver = β-galactosidase from bovine liver; Fabrazyme = commercial recombinant lysosomal α-galactosidase; GCase = β-glucocerebrosidase; N.I. = no inhibition, with Ki > 2 mM; n.d., not determined.

In case of synthesized C-5a elongated validamine derivatives, compound **31** (table 1) turned out to be the best inhibitor in low micromolar range for β-galactosidases bearing two aliphatic chains on the carbasugar core structure. All of the compounds are quite selective except activity for glucocerebrosidase and activity of unsubstituated validamine derivative **17** and hydroxyvalidamine derivative **29** which show some activity against α-galactosidase (fabrazyme). Neutral compounds **26** and **28** are week inhibitors as expected but showed increase of β-galactosidase inhibition if the center of C-5a is inverted to give the "cis" configuration related to the hydroxymethyl sidechain and the nitrogen on C-1. Dansylated

compound **40** was the best inhibitor for Abg in nanomolar range with weeker inhibition against β-galactosidases (*bovine liver*; *E.coli*).

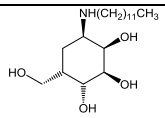
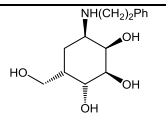
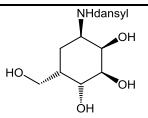
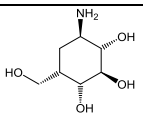
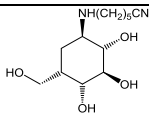
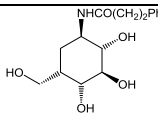
Table 2: K_i-Values for synthesized validamine derivatives and NOEV.

	 **43**	 **36**	 **39**	 **40**	 **42**	 **15**
Abg	1.1	36	0.4895	0.0019	3.1	7.7
β-Gal (E.coli)	N.I.	31	N.I.	74.6	10.2	2.8
β-Gal (bovine liver)	N.I.	n.d.	N.I.	107.7	14.5	0.87 lit
Fabrazyme	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
α-Gal (*S. cer*)	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
GCase	N.I.	N.I.	N.I.	22.5	N.I.	83

K_i-values [μM] of compounds with Abg = β-glucosidase/β-galactosidase from *Agrobacterium* sp.; *E. coli* = *lac Z* β-galactosidase from *E. coli*; bovine liver = β-galactosidase from bovine liver; Fabrazyme = commercial recombinant lysosomal α-galactosidase; GCase = β-glucocerebrosidase; N.I. = no inhibition, with Ki > 2 mM; n.d., not determined.

L-Idose- and L-gulose-validamine derivatives shown in table 3 were no or week inhibitors tested for β-galactosidases. Unsubstituted compound **56** was a quite selective inhibitor for GCase and Abg which is related to the L-ido configuration. Substitution with an alkylchain (compound 57) decreases the activity massively. Products **67**, **68** and **69** which show α-L-gulo configuration are not active against α-mannosidase which can be explained via configuration of the nitrogen functionality which is cis to the hydroxylgroup on C-2 showing the β-mannose configuration except the hydroxymethyl group which is inverted. It could be shown that α-L-ido and α-L-gulo configurated validamine derivatives which were isolated for comparison are not inhibitors (except two week inhibitors e.g. **67**; **54**) for β-galactosidases.

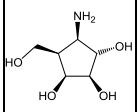
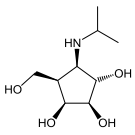
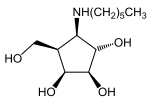
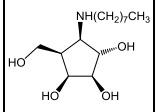
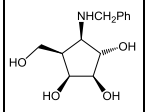
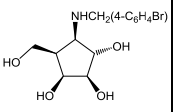
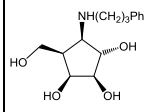
Table 3: K_i-Values for synthesized α-L-ido and α-L-gulo derivatives.

	 **67**	 **68**	 **69**	 **56**	 **57**	 **54**
Abg	216	930	66.4	0,0878	157	N.I.
β-Gal (E.coli)	123	N.I.	N.I.	N.I.	N.I.	34.5
β-Gal (bovine liver)	n.d.	n.d.	N.I.	N.I.	n.d.	n.d.
Fabrazyme	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
α-Gal (*S. cer*)	n.d.	n.d.	N.I.	N.I.	N.I.	n.d.
GCase	1.2	216	203.3	4.7	147	N.I.
α-Man (*jack beans*)	N.I.	N.I.	n.d.	n.d.	n.d.	N.I.

K_i-values [μM] of compounds with Abg = β-glucosidase/β-galactosidase from *Agrobacterium* sp.; *E. coli* = *lac Z* β-galactosidase from *E. coli*; bovine liver = β-galactosidase from bovine liver; Fabrazyme = commercial recombinant lysosomal α-galactosidase; GCase = β-glucocerebrosidase; N.I. = no inhibition, with Ki > 2 mM; n.d., not determined.

Carbapentosamines turned out to be the most potent β-galactosidases synthesized and described in this thesis. Compounds **93**, **96** and **97** were described before and showed high potential in β-galactosidase inhibition.

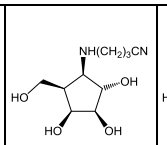
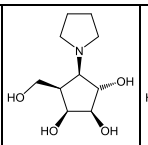
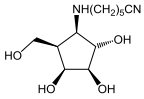
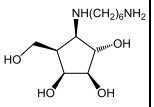
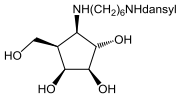
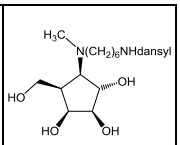
Table 4: K_i-Values for furanoid carbasugar amines.

	 **93**	 **92**	 **99**	 **100**	 **96**	 **97**	 **98**
Abg	0.0947	3.8	0.0046	0.0010	0.0131	0.0010	0.0062
β-Gal (E.coli)	33.3	5.0	0.1015	0.0132	0.0653	0.0039	0.0609
β-Gal (bovine liver)	54.3	13.0	0.0489	0.1167	0.1398	0.0030	0.0849
Fabrazyme	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
α-Gal (*S. cer*)	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
GCase	78.1	N.I.	0.2311	0.0639	0.3755	0.0668	0.2058

K_i-values [μM] of compounds with Abg = β-glucosidase/β-galactosidase from *Agrobacterium* sp.; *E. coli* = *lac Z* β-galactosidase from *E. coli*; bovine liver = β-galactosidase from bovine liver; Fabrazyme = commercial recombinant lysosomal α-galactosidase; GCase = β-glucocerebrosidase; N.I. = no inhibition, with Ki > 2 mM; n.d., not determined.

Promising results were obtained with compounds **105** and **106** bearing an aliphatic chain on the nitrogen with a dansylamide reporter group on the end. K_i- values were in nanomolar range for β-galactosidases and both compounds turned out to be quite selective. Products shown in table 4 and 5 are not active against α-galactosidases tested, with exception of compound **105** which is a week inhibitor for fabrazyme α-galactosidase.

Table 5: K_i-Values for furanoid carbasugar amines.

	 **101**	 **103**	 **102**	 **104**	 **105**	 **106**
Abg	0.0024	1.8	0.0060	0.0963	0.0012	0.0028
β-Gal (E.coli)	0.0675	33	0.1342	16.2	0.0101	0.016
β-Gal (bovine liver)	0.1257	n.d.	0.1056	31.2	0.0053	n.d.
Fabrazyme	N.I.	N.I.	N.I.	N.I.	238.1	N.I.
α-Gal (*S. cer*)	N.I.	N.I.	N.I.	N.I.	N.I.	N.I.
GCase	10.3	123	10.7	54.2	0.0193	0.001

K_i-values [μM] of compounds with Abg = β-glucosidase/β-galactosidase from *Agrobacterium* sp.; *E. coli* = *lac Z* β-galactosidase from *E. coli*; bovine liver = β-galactosidase from bovine liver; Fabrazyme = commercial recombinant lysosomal α-galactosidase; GCase = β-glucocerebrosidase; N.I. = no inhibition, with Ki > 2 mM; n.d., not determined.

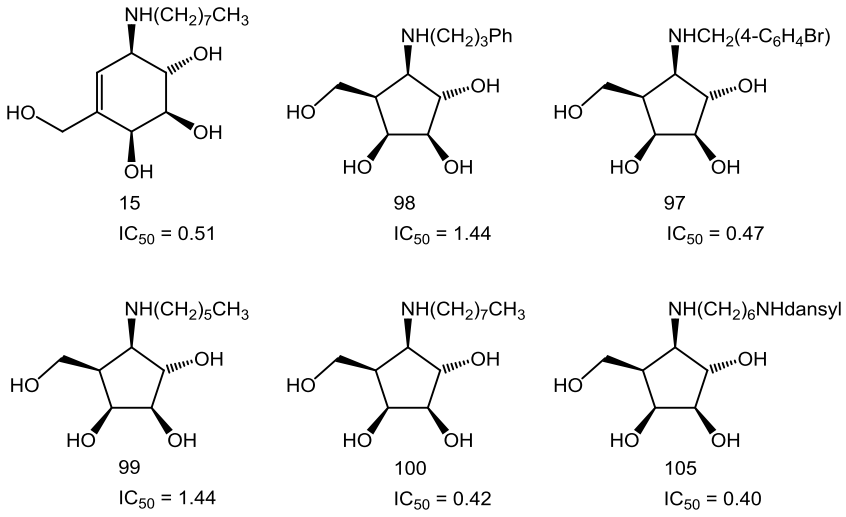


Figure 51: IC_{50}-values for human lysosomal β-galactosidase (wilde type) were determined in confluent fibroblasts from healthy patients.

Selected compounds were tested against lysosomal β-galactosidase from patients healthy fibroblasts shown in figure 51. Compared to benchmark molecule (NOEV) with an IC_{50} value of 0.51 (in literature: 0.125[96]) all of the five compounds tested were in the low micromolar range. The N-dansylated inhibitor **105** was the best of the whole bunch with an IC_{50} value of 0.40 micromolar. This promising results for inhibition of human lysosomal β-galactosidase made this type of carbasugars interesting to test them for their effect as pharmacological chaperones.

Inhibitors shown in figure 51 were tested for their activities against the R201C mutant enzyme employing patients´ skin fibroblasts. The increase of activity at different concentrations is shown in figure 52. Best results were observed with compound **105** (red squares) which showed an enhancement of nearly 7-fold at a concentration of 1µM. Compound **100** (green circles) with the N-alkylated octyl chain showed a similar profile as the benchmark NOEV (**15**). Surprisingly product **97** (purple squares) which is one of the best inhibitors for β-galactosidases (0.7 nM; *bovine liver*)[116] reported by Jäger and his group showed considerably less enhancement at the same concentrations.

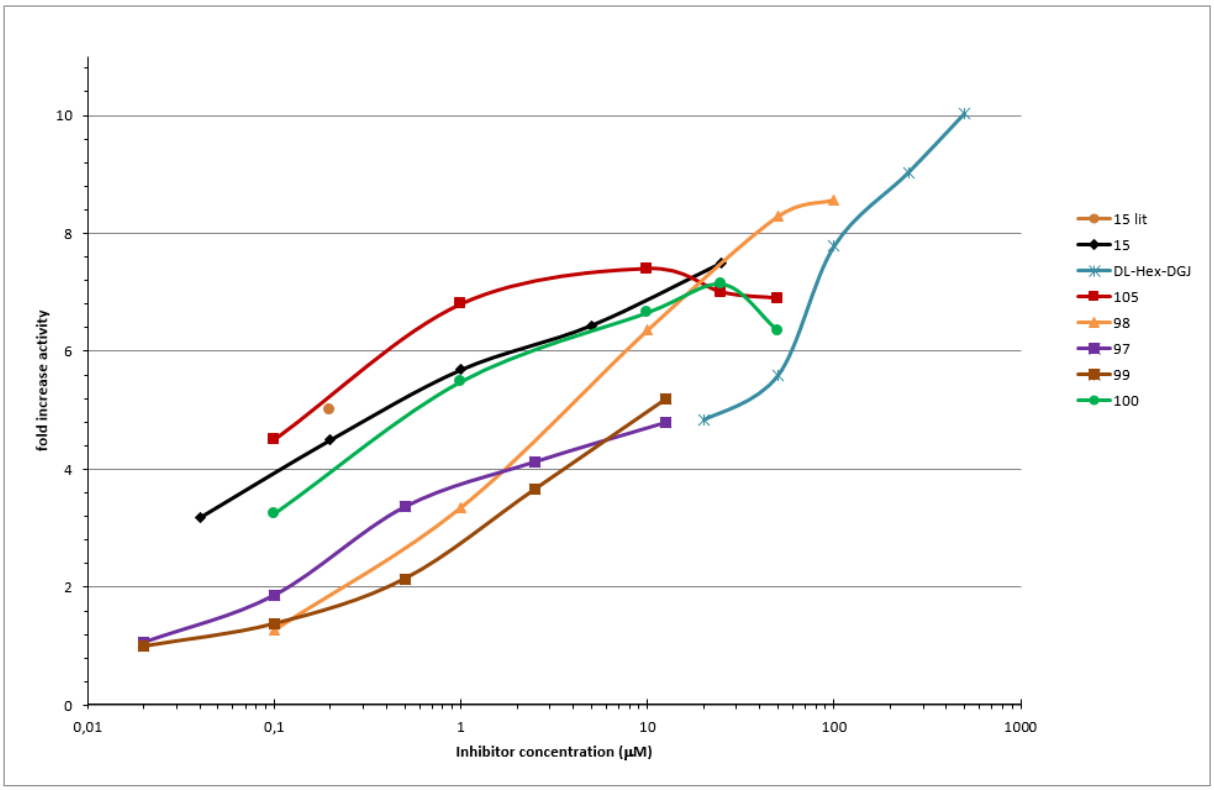
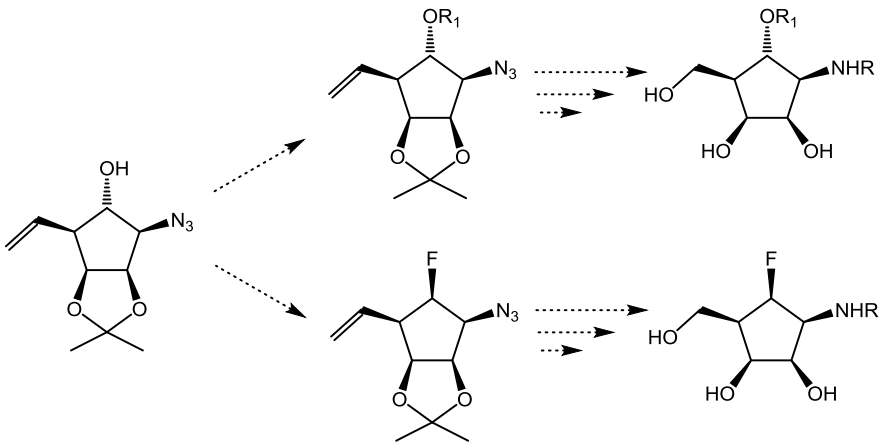


Figure 52: Chaperone activities of selected compounds with R201C mutant human lysosomal β-galactosidase. (**15** lit)[100]; DL-Hex-DGJ (**LXXII**)[99]

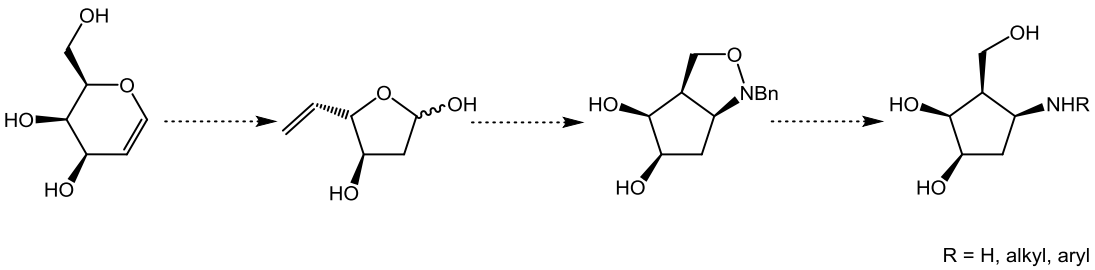
3.5 Conclusion and Outlook

In this thesis new glycosidase inhibitors were prepared and tested against several glycosylhydrolases. It could be shown that six membered carbacycles with a side chain on position C-5a are inhibitors (low micromolar range) for β-galactosidases and were compared to benchmark NOEV (**15**) and *N*-octyl-1,4-epi-validamine (**17**). New validamine derivatives in the L-ido and L-gulo series were prepared and tested, showing week to no inhibition against galactosidases and are week inhibitors for glucocerebrosidase with high selectivity. Cyclopentane derivatives prepared via a 2+3 cycloaddition were N-alkylated with different substituents and tested as glycosidase inhibitors and pharmacological chaperones. Compound **105** was the best product concerning chaperone activity and β-galactosidase inhibition which was also compared to NOEV which is still a benchmark compound in this field.

A possible synthetic route to fluorinated cyclopentane derivatives as well as alkylethers is shown in figure 53. Synthetic proof of concept as well as biological evaluation of these compounds can be achieved exploiting the synthetic route described in scheme 23 starting from simple D-galactose.



Scheme 55: Fluorinated carbapentoseamines and *O*-alkylated derivatives.



Scheme 56: Synthetic strategy to 2-deoxy carbapentoseamines.

The synthesis of 2-deoxy derivatives of the powerful cyclopentane derivatives described in this thesis should be possible starting from galactal following the described procedures with selective iodination, zinc mediated ring opening and 2+3 cyclisation to the desired cyclopentane derivatives. The influence of the hydroxyl group on position C-2 of the carbasugar backbone in terms of glycosidase recognition and inhibition as well as the influence of the pKa of the amino functionality should be investigated.

4 Experimental

Abbreviations:

$[a]_D^{20}$	specific optical rotation
R_f	retardation factor
TLC	thin-layer chromatography
MW	molecular weight

Organic residues

Cbz	carboxybenzyl-
CN	nitrile-
Et	ethyl-
Hex	hexyl-
Me	methyl-
MOM	methoxymethyl-
Oct	octyl-
Ph	phenyl-
Piv	pivaloyl-
TBS	tert-butyl dimethylsilyl-
THP	tetrahydropyranyl-
Trit	trityl-

Reagents and Solvents

Ac_2O	acetic anhydride
$BF_3.Et_2O$	boron trifluride diethyl etherate
BH_3.THF	borane tetrahydrofuran complex
BnBr	benzyl bromide
BnNHOH.HCl	N-benzylhydroxylamine hydrochloride
CH_2Cl_2	dichloromethane
ClCOCOCl	oxalyl chloride
CSI	chlorosulfonyl isocyanate
DMAP	4-dimethylamino pyridine
DMF	dimethyl formamide
DMSO	dimethyl sulfonamide
Et_3N	triethyl amine
H_2NOH	hydroxylamine
H_2O_2	hydrogen peroxide
H_2SO_4	sulfuric acid
HCl	hydrochloric acid

IR-120	Amberlite IR-120 strongly acidic ion exchange resin
K_2CO_3	potassium carbonate
$LiAlH_4$	lithium aluminium hydride
MeOH	methanol
MOMBr	bromomethyl methylether
MOMCl	chloromethyl methylether
Na_2CO_3	sodium carbonate
Na_2SO_3	sodium sulfite
$NaBH_4$	sodium borohydride
NaH	sodium hydride
$NaHCO_3$	sodium hydrogencarbonate
NaN_3	sodium azide
NaOAc	sodium acetate
NaOCl	sodium hypochlorite
NaOH	sodium hydroxide
NaOMe	sodium methoxide
n-Buli	n-butyllithium
NH_3	ammonia
$Pd(OH)_2/C$	palladium hydroxide on activated charcoal
Pd/C	palladium on activated charcoal
PivCl	pivaloyl chloride
PPh_3CH_3Br	methyltriphenylphosphoniumbromide
pTSA	p-toluenesulfonic acid monohydrate
TBAF	tetrabutylammonium fluoride
t-BuOH	tert-butanol
t-BuOK	potassium tert-butoxide
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofurane
TritCl	trityl chloride
$ZnCl_2$	zinc chloride

4.1 General methods

Optical rotations were measured at 20° C on a Perkin Elmer 341 polarimeter at a wavelength of 589 nm and a path length of 10 cm. NMR spectra were recorded on a Bruker Ultrashield spectrometer at 300.36 and 75.53 MHz, respectively. $CDCl_3$ was employed for protected compounds and methanol-d4 or D_2O for unprotected compounds. Chemical shifts are listed in delta employing residual, non-deuterated solvent as the internal standard. Signals were assigned unambiguously by COSY, HSQC as well as APT analysis. The signals of the protecting groups as well as of the N-substituents were found in the expected regions and are only listed explicitly when overlapping with important spectral features of the respective compound. For crucial intermediates, structures were confirmed by XRD structural analysis. MALDI-TOF Mass Spectrometry was performed on a Micromass TofSpec 2E Time-of-Flight Mass Spectrometer. Analytical TLC was performed on precoated aluminum plates silica gel 60 F254 (E. Merck 5554) and detected with UV light (254 nm). For staining, a solution of vanillin (9 g) in a mixture of H_2O (950 mL)/ EtOH (750 mL)/ H_2SO_4 (120 mL) or ceric ammonium molybdate (100 g ammonium molybdate/8 g ceric sulfate in 1 L 10% H_2SO_4) were employed followed by heating on a hotplate. For column chromatography, silica gel 60 (Acros Organics, AC 24036) were used.

4.2 General procedures

4.2.1 General procedure A: N- alkylation (NaH):

To a cooled (0°C) 10 % solution of respective amine in dry DMF was added NaH and alkylbromide and stirred at RT. After quenching of the remaining reagent with MeOH, the solution was diluted with CH_2Cl_2 and washed with HCl (2N) and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered off and evaporated to provide crude product.

4.2.2 General procedure B: N- alkylation ($NaHCO_3$):

To a 10 % solution of respective amine in dry DMF was added $NaHCO_3$, alkylbromide and heated up to 60°C. After complete conversion of the starting material, the remaining reagent was quenched with MeOH and concentrated under reduced pressure to provide the crude product.

4.2.3 General procedure C: Hydroboration (BH_3):

A cooled (0°C) 10 % solution of respective Alkene in dry THF was treated with BH_3*THF (1M in THF) under an atmosphere of nitrogen and stirred for 12 hours at ambient temperature. After cooling the reaction mixture to 0°C H_2O, NaOH (3N) and H_2O_2 (33 %) were added and stirred for additional 10 hours. CH_2Cl_2 was added and washed with HCl (2N) and saturated $NaHCO_3$, dried over Na_2SO_4 filtered off and concentrated under reduced pressure.

4.2.4 General procedure D: Hydrogenolytic deprotection:

To a 10 % solution of the starting material, $Pd(OH)_2/C$ was added and stirred under an atmosphere of H_2 at ambient pressure at RT. After full conversion of the starting material the catalyst was filtered off and the solution was concentrated under reduced pressure.

4.2.5 General procedure E: Carbamate formation:

To a 10 % solution of starting material in Toluene was added BF_3*Et_2O and respective isocyanate. After stirring for 20 minutes at ambient temperature the reaction mixture was diluted with CH_2Cl_2 and subsequently washed with HCl (2N) and saturated Na_2CO_3, dried over Na_2SO_4 filtered off and concentrated under reduced pressure, to give crude product.

4.2.6 General procedure F: N-Dansylation:

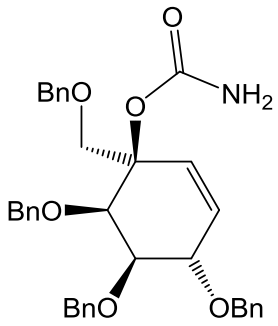
To a suspension of the respective amine and Na_2CO_3 in MeOH, dansyl chloride was added at ambient temperature. After completed conversion of the starting material, the reaction mixture was evaporated to dryness.

4.2.7 General procedure G: Swern oxidation:

To a 10 % solution of oxalyl chloride (2 equiv) and DMSO (2.5 equiv) in CH_2Cl_2 the respective alcohol (5% in CH_2Cl_2) was added dropwise at – 78°C. The resulting reaction mixture was stirred for 30 minutes at -60°C and Et_3N (5 equiv) was added. After formation of the corresponding carbonyl compound (indicated by TLC) the solution was diluted with CH_2Cl_2 and successively washed with HCl (2 N) and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4 filtered off and evaporated to dryness to obtain the crude corresponding products.

N-Benzyloxycarbonyl-2,3,4,6-tetra-O-benzyl-1,4-di-*epi-*valienamine (13)

To a cooled (0°C) solution of compound **8** (2.1 g, 3,9 mmol) in CH_2Cl_2 (100 ml) was added CCl_3CONCO (0.839 ml, 7.0 mmol) and stirred for 30 minutes at this temperature. After evaporation of the solvent, the residue was dissolved in 165 ml MeOH/H_2O 10:1 and treated with K_2CO_3 (1.3 g, 9.4 mmol) at 0°C and stirred for 20 hours at this temperature. After evaporation of the solvent, the residue was extracted with CH_2Cl_2/H_2O, dried with Na_2SO_4 and evaporated. Purification on silica gel afforded **9** (2.2 g, 3.8 mmol, 97.0 %) as a colourless syrup.



$C_{36}H_{37}NO_6$

MW: 579.69 g/mol

TLC: UV, VAN

R_f: 0.17 (C/EA 3:1 v/v)

SCG: (C/EA 6:1 v/v)

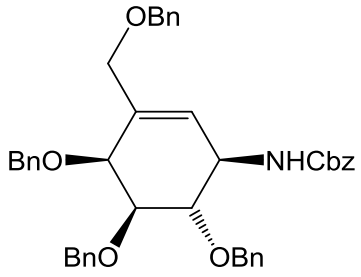
$[a]_D^{20}$ = +51.3 (c 1.116, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.96 (m, 2H, H-1, H-5a), 5.16 (s, NH_2), 5.10-4.69 (m, 6H, 3x C$\underline{H}_2$Ar), 4.68 (bs, 1H, H-2), 4.64-4.52 (m, 3H, H-4, 1x C$\underline{H}_2$Ar), 4.04 (d, 1H, $J_{6A,6B}$ 10.3 Hz, H-6A), 3.95-3.88 (m, 2H, H-3, H-6B);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 155.8 (C=O), 139.0, 138.7, 138.5, 138.0 (4x ipso Ar), 130.2 (C-5a), 128.5-127.5 (Ar), 126.8 (C-1), 82.8 (C-5), 81.1 (C-3), 78.3 (C-2), 76.5 (C-4), 75.4, 73.5, 72.4, 72.2 (4x $\underline{C}H_2$Ar), 72.2 (C-6).

MS: Calcd for [$C_{36}H_{37}NO_6Na$]: *m/z* 602.2518 $[M+Na]^+$; Found $[M+Na]^+$ 602.3037.

To a cooled (-20°C) solution of compound **9** (478.5 mg, 0.83 mmol), Et_3N (229 µl, 1.65 mmol) and PPh_3 (541 mg, 2.06 mmol) in 9.5 ml CH_2Cl_2 was added CBr_4 (766 mg, 2.30 mmol) dissolved in 3 ml CH_2Cl_2 and stirred for 30 minutes at this temperature. After full conversion of the starting material, BnOH (687 µl, 6.60 mmol) and additional Et_3N (458 µl, 3.30 mmol) were added and stirred at RT for 20 hours. The reaction mixture was washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. The remaining residue was dissolved in 15 ml pyridine and catalytic amounts of DMAP were added before addition of Ac_2O (1.0 ml, 10.8 mmol) at 0°C. After 20 minutes at this temperature all of the remaining benzylalcohol was consumed. The reaction mixture was diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **13** (512.0 mg, 0.76 mmol, 92.6%) as a colourless syrup.



$C_{43}H_{43}NO_6$

MW: 669.82 g/mol

TLC: UV, VAN

R_f: 0.30 (C/EA 3:1 v/v)

SCG: (C/EA 20:1 v/v)

$[\alpha]_D^{20}$ = -26.1 (c 1.138, $CHCl_3$)

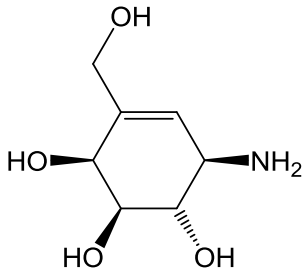
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.57 (bs, 1H, H-5a), 5.10-4.96 (m, 2H, C$\underline{H}_2$Ar), 4.83 (bd, 1H, NH), 4.75-4.42 (m, 6H, 3x C$\underline{H}_2$Ar), 4.40-4.26 (m, 3H, H-1, C$\underline{H}_2$Ar), 4.19 (bs, 1H, H-4), 4.04 (d, 1H, $J_{6A,6B}$ 12.4 Hz, H-6A), 3.80 (d, 1H, H-6B), 3.72 (dd, 1H, $J_{1,2}$ 5.8 Hz, $J_{2,3}$ 7.8 Hz, H-2), 3.65 (dd, 1H, $J_{3,4}$ 3.3 Hz, H-3);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 156.0 (C=O), 138.7, 138.4, 138.4, 138.3 (4x ipso Ar), 136.7 (C-5), 136.2 (ipso Cbz), 128.6-127.8 (Ar), 125.8 (C-5a), 78.3 (C-3), 77.8 (C-2), 74.0 ($\underline{C}H_2$Ar), 73.6 (C-4), 73.4, 73.4, 72.4, 72.4 (4x $\underline{C}H_2$Ar), 70.6 (C-6), 66.8 ($\underline{C}H_2$Ar), 51.2 (C-1).

MS: Calcd for [$C_{43}H_{43}NO_6Na$]: *m/z* 692.2988 $[M+Na]^+$; Found $[M+Na]^+$ 692.2930.

1,4-di*-epi *Valienamine (14)

NH_3 was condensed into a solution of **13** (135.0 mg, 0.20 mmol) in 15ml dry THF at -78°C. The solution was then treated with pieces of Na (35mg), stirred for 3 hours, then treated with NH_4Cl 302mg and stirred at ambient temperature overnight. Purification on silica gel afforded compound **14** which was directly used in the next step.



$C_7H_{13}NO_4$

MW: 175.18 g/mol

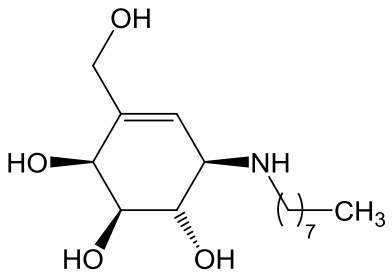
TLC: UV, CAM

R_f: 0.30 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:4:1 v/v/v)

N*-Octyl-*1,4-di*-epi *Valienamine (15)

Following general procedure B compound **14** (28.9 mg, 0.17 mmol) was treated with $NaHCO_3$ (55 mg) octyl bromide (31.6 µl, 0.18 mmol). Purification on silica gel afforded **15** (36.2 mg, 0.13 mmol, 62.5% over 2 steps) as a pale yellow syrup.



$C_{15}H_{29}NO_4$

MW: 287.40 g/mol

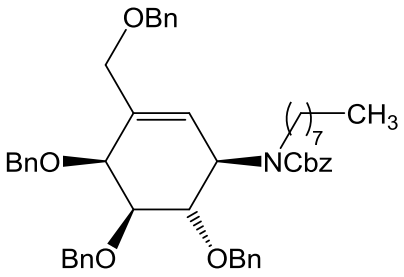
TLC: UV, CAM

R_f: 0.75 ($CHCl_3$/MeOH/NH_4OH 8:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

N-Benzyloxycarbonyl-2,3,4,6-tetra-O-benzyl-N-octyl-1,4-di-*epi*-valienamine (16)

Following general procedure A compound **13** (529.5 mg, 0,79 mmol) was treated with NaH (30.4 mg, 1.26 mmol) and octylbromide (192.6 µl, 1,11 mmol) and stirred for 6 hours. Purification on silica gel afforded **16** (543.6 mg, 0.70 mmol, 87.9%) as a pale yellow syrup.



$C_{51}H_{59}NO_6$

MW: 782.03 g/mol

TLC: UV, VAN

R_f: 0.45 (C/EA 3:1 v/v)

SCG: (C/EA 10:1 v/v)

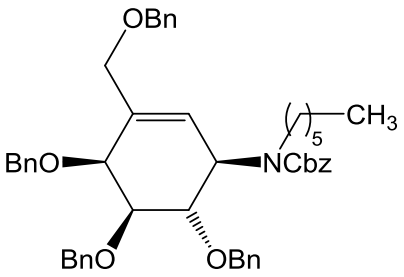
$[a]_D^{20}$ = -24.5 (c 1.078, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ =5.59 (m, 1H, H-5a), 5.33-4.38 (m, 10H, 5x C$\underline{H}_2$Ar), 4.87 (dd, 1H, $J_{1,2}$ 12.5 Hz, H-1), 4.28 (m, 2H, H-2, H-4), 4.12-3.85 (m, 2H, H-6A, H-6B), 3.70 (m, 1H, H-3), 3.21-2.82 (m, 2H, H-1'), 1.71-1.08 (m, 12H, H-2', H-3', H-4', H-5', H-6', H-7'), 0.95 (t, 3H, H-8'); **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 156.7, 156.1 (C=O), 139.3-136.7 (ipso Ar), 128.8-127.5 (H-5a, Ar), 82.3 (C-3), 76.4, 74.4 (C-2, C-4), 74.9-72.3 (4x $\underline{C}H_2$Ar), 70.9 (C-6), 67.1 ($\underline{C}H_2$Ar), 59.6 (C-1), 44.4 (C-1'), 31.9, 30.3, 29.3, 29.2, 27.1, 22.7 (C-2', C-3', C-4', C-5', C-6', C-7'), 14.2 (C-8').

MS: Calcd for [$C_{51}H_{59}NO_6Na$]: *m/z* 804.4240 $[M+Na]^+$; Found $[M+Na]^+$ 804.4302.

N-Benzyloxycarbonyl-2,3,4,6-tetra-O-benzyl-N-hexyl-1,4-di-*epi*-valienamine (23)

Following general procedure A compound **13** (649.7 mg, 0.97 mmol) was treated with NaH (93 mg, 3.80 mmol) and hexylbromide (271 µl, 1.90 mmol) and stirred for 22 hours. Purification on silica gel afforded **23** (507.1 mg, 0.67 mmol, 69.3%) as a pale yellow syrup.



$C_{49}H_{55}NO_6$

MW: 753.98 g/mol

TLC: UV, VAN

R_f: 0.47 (C/EA 3:1 v/v)

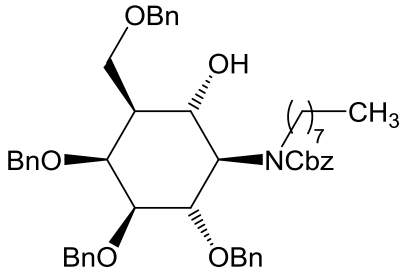
SCG: (C/EA 15:1 v/v)

$[a]_D^{20}$ = -23.7 (c 0.700, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.41 (m, 1H, H-5a), 5.15-4.21 (m, 10H, 5x C$\underline{H}_2$Ar), 4.70 (dd, 1H, $J_{1,2}$ 11.4 Hz, H-1), 4.08 (m, 2H, H-2, H-4), 3.94-3.67 (m, 2H, H-6A, H-6B), 3.53 (m, 1H, H-3), 3.02-2.65 (m, 2H, H-1'), 1.54-0.90 (m, 8H, H-2', H-3', H-4', H-5'), 0.73 (t, 3H, H-6');
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 156.7, 156.1 (C=O), 139.3-137.0 (ipso Ar), 128.7-127.6 (Ar), 82.3 (C-3), 76.5, 73.3 (C-2, C-4), 74.6-72.3 (4x $\underline{C}H_2$Ar), 70.9 (C-6), 67.1 ($\underline{C}H_2$Ar), 59.5 (C-1), 44.1 (C-1'), 31.4, 30.2, 26.8, 22.7 (C-2', C-3', C-4', C-5'), 14.1 (C-6').
MS: Calcd for [$C_{49}H_{55}NO_6Na$]: *m/z* 776.3927 $[M+Na]^+$; Found $[M+Na]^+$ 776.3927.

(5aS)-2,3,4,6-Tetra-O-benzyl-N,5a-O-carbonyl-5a-hydroxy-N-octyl-1,4-di-*epi-*validamine (25)

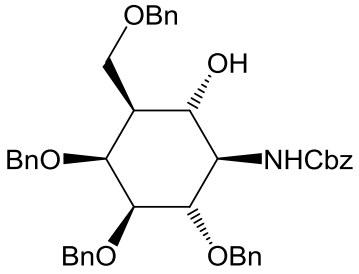
Following general procedure C compound **16** (866.5 mg, 1.11 mmol) was treated with BH_3*THF (4.4 ml, 4.4 mmol). Purification on silica gel afforded **24** (729.5 mg, 0.91 mmol, 82.3%) as a colourless syrup. Due to the presence of stable rotameric populations in comparable concentrations, spectra were too poorly resolved to allow for meaningful interpretation and listing.



$C_{51}H_{61}NO_7$
MW: 800.05 g/mol
TLC: UV, VAN
R_f: 0.30 (C/EA 3:1 v/v)
SCG: (C/EA 10:1 v/v)
$[a]_D^{20}$ = -10.2 (c 0.984, $CHCl_3$)

MS: Calcd for [$C_{51}H_{61}NO_7Na$]: *m/z* 822.4346 $[M+Na]^+$; Found $[M+Na]^+$ 822.4670.

Following general procedure C compound **13** (185.0 mg, 0.28 mmol) was treated with BH_3*THF (0.5 ml, 0,50 mmol). Purification on silica gel afforded **192** (62.0 mg, 0.09 mmol, 32.6%) as a pale yellow syrup.



$C_{43}H_{45}NO_7$

MW: 687.83 g/mol

TLC: UV, VAN

R_f: 0.30 (C/EA 2:1 v/v)

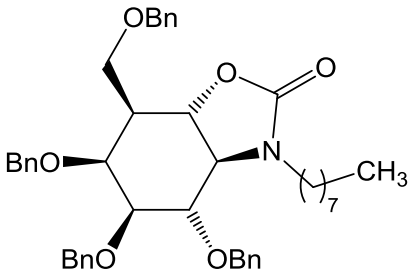
SCG: (C/EA 20:1 v/v)

Condition A:

To a solution of **192** (43.0 mg, 0.06 mmol) in 1.5 ml DMF was added NaH (3.3 mg, 0.14 mmol) and octylbromide (13 µl, 0,08 mmol) and stirred for 120 minutes. The reaction mixture was quenched with 0.2 ml MeOH stirred for additional 20 minutes, diluted with CH_2Cl_2 washed with HCl (2N) and saturated Na_2CO_3, the combined organic layers were dried over Na_2SO_4, filtered off and concentrated under reduced pressure. Purification on silica gel provided **25** (27.0 mg, 0.04 mmol, 62.4%) as a colourless syrup.

Condition B:

To a solution of **24** (11.1 mg, 0.01 mmol) in 1.5 ml THF/DMF 3:1 was added KOt-Bu (3.0 mg, 0.27 mmol) at ambient temperature. After 5 minutes the reaction was diluted with CH_2Cl_2 washed with HCl (2N) and saturated Na_2CO_3, the combined organic layers were dried over Na_2SO_4, filtered off and concentrated under reduced pressure. Purification on silica gel provided **25** (9.0 mg, 0.01 mmol, 93.8%) as a colourless syrup.



$C_{44}H_{53}NO_6$

MW: 691.91 g/mol

TLC: UV, VAN

R_f: 0.60 (C/EA 2:1 v/v)

SCG: (C/EA 8:1 v/v)

$[a]_D^{20}$ = +3.4 (c 1.435, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02 (d, 1H, C$\underline{H}_2$Ar), 4.86 (d, 1H, C$\underline{H}_2$Ar), 4.70 (d, 1H, C$\underline{H}_2$Ar), 4.56 (m, 2H, C$\underline{H}_2$Ar), 4.45 (d, 1H, C$\underline{H}_2$Ar), 4.39 (m, 2H, C$\underline{H}_2$Ar), 4.25 (bs, 1H, H-4), 3.99 (dd, 1H, $J_{1,5a}$ 12.0 Hz, H-5a), 3.93 (m, 1H, H-2), 3.62 (m, 2H, H-6A, H-6B), 3.48 (dd, 1H, $J_{3,4}$ 2.6 Hz, $J_{2,3}$

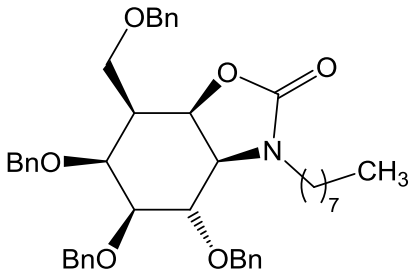
8.7 Hz, H-3), 3.25 (m, 1H, H-1'A), 3.23 (dd, 1H, $J_{1,2}$ 10.1 Hz, $J_{1,5a}$ 12.0 Hz, H-1), 3.05 (m, 1H, H-1'B), 2.14 (m, 1H, H-5), 1.52-0.90 (m, 12H, H-2', H-3', H-4', H-5', H-6', H-7'), 0.79 (t, 3H, H-8');

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.8 (C=O), 138.7,138.1, 137.9, 137.9 (4x ipso Ar), 128.6-127.6 (Ar), 86.7 (C-3), 79.7 (C-2), 75.9, 75.0 (2x $\underline{C}H_2Ar$), 74.5, 74.5 (C-4, C-5a), 73.7, 72.3 (2x $\underline{C}H_2Ar$), 66.4 (C-6), 63.4 (C-1), 44.6 (C-1'), 43.3 (C-5), 34.9, 31.9, 29.5, 29.4, 27,6, 22.8 (C-2', C-3', C-4', C-5', C-6', C-7`), 14.2 (C-8').

MS: Calcd for $[C_{44}H_{53}NO_6Na]$: *m/z* 714.3771 $[M+Na]^+$; Found $[M+Na]^+$ 714.3730.

*(5aR)-2,3,4,6-Tetra-O-benzyl-N,5a-O-carbonyl-5a-hydroxy-N-octyl-1,4-di-*epi-*validamine (27)*

To cooled (-20°C) solution of **24** (176.6 mg, 0.22 mmol) and pyridine (178 µl, 2.20 mmol) in 2 ml CH_2Cl_2 was added dropwise DAST (146 µl, 1.10 mmol) and stirred at this temperature for 18 hours. The reaction mixture was washed with HCl (2N) and saturated $NaHCO_3$, dried over Na_2SO_4 filtered off and concentrated under reduced pressure. Purification on silica gel gave compound **27** (113.7 mg, 0.16 mmol, 74.4%) as a colourless oil.



$C_{44}H_{53}NO_6$

MW: 691.91 g/mol

TLC: UV, VAN

R_f: 0.50 (C/EA 3:1 v/v)

SCG: (C/EA 10:1 v/v)

$[a]_D^{20}$ = +23.1 (c 1.156, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.14 (d, 1H, C$\underline{H}$Ar), 4.99 (d, 1H, C$\underline{H}$Ar), 4.80 (d, 1H, C$\underline{H}$Ar), 4.63 (m, 4H, H-5a, 3x C$\underline{H}$Ar), 4.48 (m, 2H, $C\underline{H}_2Ar$), 4.22 (bs, 1H, H-4), 4.19 (dd, 1H, $J_{1,2}$ 7.7 Hz, $J_{2,3}$ 9.8 Hz, H-2), 3.86-3.76 (m, 2H, H-6A, H-6B), 3.71 (dd, 1H, H-1), 3.65 (m, 1H, H-1'A), 3.50 (dd, $J_{3,4}$ 1.4 Hz, H-3), 3.15 (m, 1H, H-1'B), 2.08 (m, 1H, H-5), 1.72-1.09 (m, 12H, H-2', H-3', H-4', H-5', H-6', H-7'), 0.92 (t, 3H, H-8');

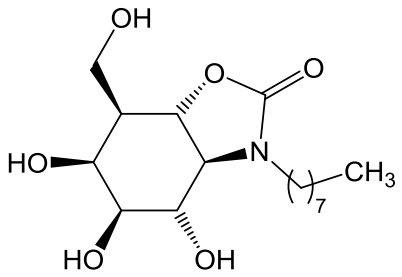
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.6 (C=O), 138.9, 138.4, 138.0 (4x ipso Ar), 128.6-127.4 (Ar), 84.4 (C-3), 80.8 (C-2), 75.1, 74.4 (2x $\underline{C}H_2Ar$), 74.2 (C-5a), 73.7 ($\underline{C}H_2Ar$), 73.6 (C-4), 72.4

($\underline{C}H_2Ar$), 67.7 (C-6), 59.9 (C-1), 42.9 (C-1'), 41.4 (C-5), 31.9, 29.3, 27.6, 26.7, 22.7 (C-2', C-3', C-4', C-5', C-6', C-7'), 14.2 (C-8').

MS: Calcd for $[C_{44}H_{53}NO_6Na]$: *m/z* 714.3771 $[M+Na]^+$; Found $[M+Na]^+$ 714.3777.

(5aS)-N,5a-O-Carbonyl-5a-hydroxy-N-octyl-1,4-di-*epi-*validamine (26)

Following general procedure D compound **25** (27.0 mg, 0.04 mmol) was treated with $Pd(OH)_2/C$ (20%) (25 mg) and stirred for 16 hours. Purification on silica gel afforded **26** (11.2 mg, 0.03 mmol, 86.6%) as a white powder.



$C_{16}H_{29}NO_6$

MW: 331.41 g/mol

TLC: UV, CAM

R_f: 0.50 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[a]_D^{20}$ = -14.9 (c 0.705, MeOH)

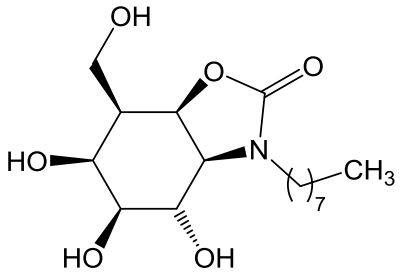
^{1}H NMR (300 MHz, MeOH-d_4): δ = 4.22 (bs, 1H, H-4), 4.07 (dd, 1H, $J_{5,5a}$ 11.8 Hz, H-5a), 3.84 (m, 2H, H-6A, H-6B), 3.82 (dd, 1H, $J_{1,2}$ 10.0 Hz, H-2), 3.46-3.27 (m, 4H, H-1, H-3, H-1'), 2.10 (m, 1H, H-5), 1.66 (m, 2H, H-2'), 1.42-1.24 (m, 10H, H-3', H-4', H-5', H-6', H-7'), 0.93 (t, 3H, H-8');

^{13}C NMR (75.5 MHz, MeOH-d_4): δ = 162.3 (C=O), 77.9 (C-3), 76.6 (C-4), 73.2 (C-2), 71.0 (C-5a), 65.9 (C-1), 60.0 (C-6), 45.8 (C-5), 45.2 (C-1'), 33.0, 30.4, 30.4, 28.8, 27.9, 23.7 (C-2', C-3', C-4', C-5', C-6', C-7'), 14.4 (C-8').

MS: Calcd for $[C_{16}H_{29}NO_6Na]$: *m/z* 354.1893 $[M+Na]^+$; Found $[M+Na]^+$ 354.1898.

(5aR)-N,5a-O-Carbonyl-5a-hydroxy-N-octyl-1,4-di-*epi-*validamine (28)

Following general procedure D compound **27** (59.0 mg, 0.09 mmol) was treated with $Pd(OH)_2/C$ (20%) (30 mg) and stirred for 15 hours. Purification on silica gel afforded **28** (22.4 mg, 0.07 mmol, 79.3%) as a colourless syrup.



$C_{16}H_{29}NO_6$

MW: 331.41 g/mol

TLC: UV, CAM

R_f: 0.40 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[a]_D^{20}$ = +33.3 (c 1.145, MeOH)

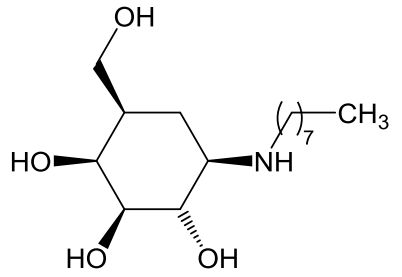
^{1}H NMR (300 MHz, MeOH-*d_4*): δ = 4.68 (dd, 1H, $J_{1,2}$ 5.7 Hz, $J_{5,5a}$ 7.0 Hz, H-5a), 4.07 (bs, 1H, H-4), 3.98-3.84 (m, 3H, H-2, H-6A, H-6B), 3.68 (dd, 1H, $J_{1,2}$ 5.7 Hz, H-1), 3.61-3.39 (bm, 2H, H-1'), 3.36 (dd, 1H, $J_{2,3}$ 10.7 Hz, $J_{3,4}$ 2.7 Hz, H-3), 2.03 (m, 1H, H-5), 1.79-1.24 (m, 12H, H-2', H-3', H-4', H-5', H-6', H-7') 0.93 (t, 3H, H-8');

^{13}C NMR (75.5 MHz, MeOH-*d_4*): δ = 160.2 (C=O), 76.4 (C-5a), 75.2 (C-3), 74.1 (C-2), 70.4 (C-4), 62.1 (C-1), 60.7 (C-6), 44.1 (C-1'), 43.7 (C-5), 33.0, 30.4, 30.3, 28.4, 27.7, 23.7 (C-2', C-3', C-4', C-5', C-6', C-7'), 14.4 (C-8').

MS: Calcd for [$C_{16}H_{29}NO_6Na$]: *m/z* 354.1893 $[M+Na]^+$; Found $[M+Na]^+$ 354.1897.

4-epi-N-octyl-β-validamine (17)

Following general procedure D compound **16** (88.8 mg, 0.11 mmol) was treated with $Pd(OH)_2$/C (20%) (35 mg) and stirred for 25 hours. Purification on silica gel afforded **17** (24.4 mg, 0.08 mmol, 74.2 %) as a colourless syrup.



$C_{15}H_{31}NO_4$

MW: 289.42 g/mol

TLC: UV, CAM

R_f: 0.40 ($CHCl_3$/MeOH/NH_4OH 8:4:1 v/v/v)

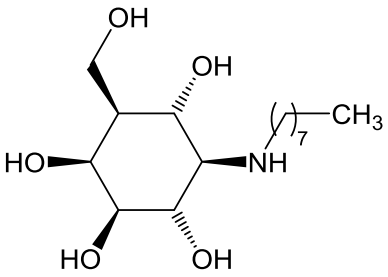
SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[a]_D^{20}$ = -9.5 (c 1.180, MeOH)

MS: Calcd for [$C_{15}H_{31}NO_4Na$]: *m/z* 312.2151 $[M+Na]^+$; Found $[M+Na]^+$ 312.2133.

(5aS)-5a-Hydroxy-N-octyl-1,4-di*-epi-*validamine (29)

Following general procedure D compound **24** (78.0 mg, 0.10 mmol) was treated with $Pd(OH)_2/C$ (20%) (50 mg) and stirred for 32 hours. Purification on silica gel afforded **29** (19.9 mg, 0.07 mmol, 66.8 %) as a colourless syrup.



$C_{15}H_{31}NO_5$

MW: 305.41 g/mol

TLC: UV, CAM

R_f: 0.30 ($CHCl_3$/MeOH/NH_4OH 8:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[a]_D^{20}$ = -6.9 (c 0.53, MeOH)

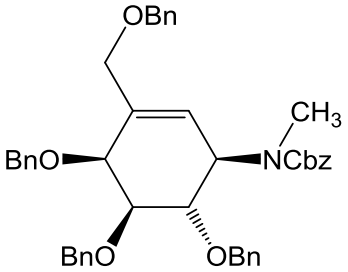
^{1}H NMR (300 MHz, MeOH-d_4): δ = 3.99 (bs, 1H, H-4), 3.81 (dd, 1H, $J_{5,6A}$ =4.8 Hz, $J_{6A,6B}$ 10.7 Hz, H-6A), 3.75 (m, 3H, H-2, H-5a, H-6B), 3.31 (dd, 1H, $J_{3,4}$ 2.9 Hz, $J_{2,3}$ 9.2 Hz, H-3), 3.06 (m, 2H, H-1'), 2.85 (dd, 1H, $J_{1,2} = J_{1,5a}$ 10.3 Hz, H-1), 1.71-1.52 (m, 3H, H-5, H-2'), 1.38-1.13 (m, 10H, H-3', H-4', H-5', H-6', H-7'), 0.81 (t, 3H, H-8');

^{13}C NMR (75.5 MHz, MeOH-d_4): δ = 76.4 (C-3), 70.6 (C-4), 69.0 (C-2), 67.0 (C-1), 66.2 (C-5a), 61.2 (C-6), 48.3 (C-5), 46.6 (C-1'), 32.9, 30.2, 30.2, 27.6, 23.7 (C-2', C-3', C-4', C-5', C-6', C-7'), 14.4 (C-8').

MS: Calcd for [$C_{15}H_{31}NO_5$H]: *m/z* 306.2281 $[M+H]^+$; Found $[M+H]^+$ 306.2278.

(5aS)-5a-Hydroxy-N-methyl-1,4-di*-epi-*validamine (43)

Following general procedure A compound **13** (227.4 mg, 0.34 mmol) was treated with NaH (15.9 mg, 0.66 mmol) and MeI (45 µl, 0.73 mmol) and stirred for 72 hours. Purification on silica gel afforded **22** (220.3 mg, 0.32 mmol, 94.9%) as a yellow syrup.



$C_{44}H_{45}NO_6$

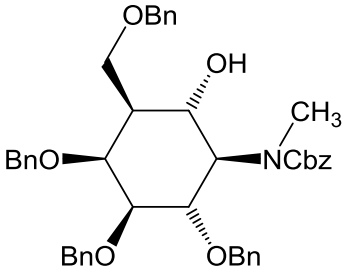
MW: 683.847 g/mol

TLC: UV, VAN

R_f: 0.40 (C/EA 3:1 v/v)

SCG: (C/EA 10:1 v/v)

Following general procedure C compound **22** (171.3 mg, 0.25 mmol) was treated with BH_3*THF (1.25 ml, 1.25 mmol). Purification on silica gel afforded **34** (61.8 mg, 0,09 mmol, 35.2%) as a colourless syrup.



$C_{44}H_{47}NO_7$

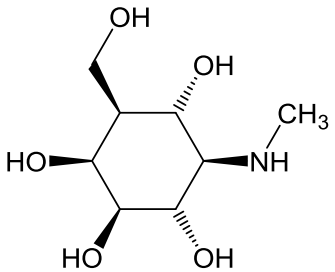
MW: 701.86 g/mol

TLC: UV, CAM

R_f: 0.20 (C/EA 2:1 v/v)

SCG: (C/EA 4:1 v/v)

Following general procedure D compound **34** (58.2 mg, 0.08 mmol) was treated with $Pd(OH)_2$/C (20%) (55 mg) and stirred for 31 hours. Purification on silica gel afforded **43** (14.6 mg, 0.07 mmol, 85.0%) as a white solid.



$C_8H_{17}NO_5$

MW: 207.23 g/mol

TLC: UV, CAM

R_f: 0.15 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:4:1 v/v/v)

$[a]_D^{20}$ = -3.9 (c 0.730, H_2O)

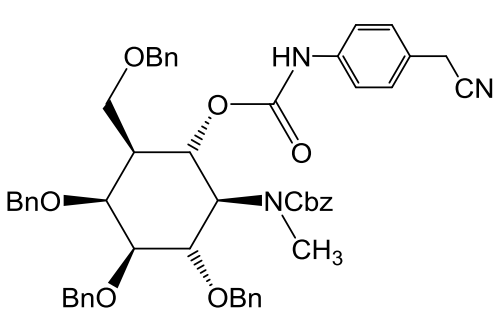
^{1}H NMR (300 MHz, D_2O): δ = 4.01 (bs, 1H, H-4), 3.85-3.68 (m, 4H, H-2, H-5a, H-6A, H-6B), 3.32 (dd, 1H, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 3.0 Hz, H-3), 2.85 (dd, 1H, $J_{1,5a}$ = $J_{1,2}$ 10.7 Hz, H-1), 2.67 (s, 3H, N-Me), 1.59 (m, 1H, H-5);

^{13}C NMR (75.5 MHz, D_2O): δ = 76.4 (C-3), 70.6 (C-4), 68.4 (C-2), 67.5 (C-1), 65.6 (C-5a), 61.1 (C-6), 48.3 (C-5), 30.4 (N-Me).

MS: Calcd for $[C_8H_{17}NO_5H]$: *m/z* 208.1185 $[M+H]^+$; Found $[M+H]^+$ 208.1149.

(5aS)-5a-(4-aminoethyl)phenylaminocarbonyloxy-N-methyl-1,4-di*-epi-*validamine (36)

Following general procedure E compound **34** (32.1 mg, 0.05 mmol) was treated with BF_3*Et_2O (12.8 µl, 0,10 mmol) and 4-isocyanatobenzylcyanide (36.0 mg, 0.20 mmol) and stirred for 30 minutes. Purification on silica gel afforded **35** (20.6 mg, 0.02 mmol, 52.4%) as a syrup.



$C_{53}H_{53}N_3O_8$

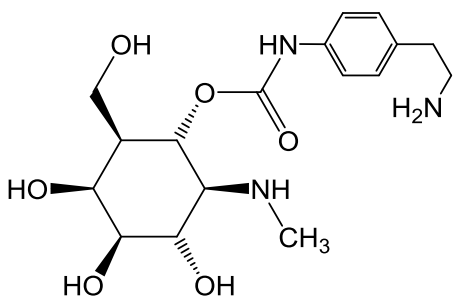
MW: 860.02 g/mol

TLC: UV, VAN

R_f: 0.30 (C/EA 2:1 v/v)

SCG: (C/EA 6:1 v/v)

Following general procedure D compound **35** (47.0 mg, 0.06 mmol) was treated with $Pd(OH)_2$/C (20%) (70 mg) and catalytic amounts of HCl conc. and stirred for 20 hours. Purification on silica gel afforded **36** (15.6 mg, 0.04 mmol, 77.3%) as a colourless syrup.



$C_{17}H_{27}N_3O_6$

MW: 369.42 g/mol

TLC: UV, CAM

R_f: 0.45 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:4:1 v/v/v)

$[\alpha]_D^{20}$ = -34.5 (c 0.460, MeOH)

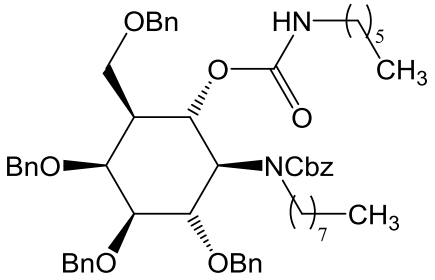
^{1}H NMR (300 MHz, MeOH-d_4): δ = 5.24 (dd, 1H, $J_{1,5a}$ 10.6 Hz, $J_{5,5a}$ 10.9 Hz, H-5a), 4.18 (bs, 1H, H-4), 4.00 (dd, 1H, $J_{2,3}$ 9.4 Hz, $J_{1,2}$ 10.6 Hz, H-2), 3.78 (dd, 1H, $J_{5,6A}$ 10.9 Hz, $J_{6A,6B}$ 10.6 Hz, H-6_A), 3.66 (dd, 1H, $J_{6A,6B}$ 10.6 Hz, $J_{5,6B}$ 3.7 Hz, H-6B), 3.50 (dd, 1H, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 2.6 Hz, H-3), 3.37 (dd, $J_{1,5a}$ 10.6 Hz, H-1), 3.15 (m, 2H, H-2''), 2.93 (m, 2H, H-1''), 2.77 (s, 3H, N-Me), 1.97 (m, 1H, H-5);

^{13}C NMR (75.5 MHz, MeOH-d_4): δ = 154.9 (C=O), 138.9, 132.9, (2x ipso Ar), 130.3, 120.5 (Ar), 75.9 (C-3), 70.0 (C-4), 68.2 (C-5a), 67.9 (C-2), 64.6 (C-1), 60.1 (C-6), 47.4 (C-5), 42.0 (C-2''), 33.9 (C-1''), 29.4 (N-Me).

MS: Calcd for $[C_{17}H_{27}N_3O_6H]$: *m/z* 370.1978 $[M+H]^+$; Found $[M+H]^+$ 370.2000.

(5aS)-5a-hexylaminocarbonyloxy-N-octyl-1,4-di-*epi*-validamine (31)

Following general procedure E compound **24** (67.5 mg, 0.08 mmol) was treated with BF_3*Et_2O (23.5 µl, 0.19 mmol) and hexylisocyanide (61.5 µl, 0.42 mmol) and stirred for 2 hours. Purification on silica gel afforded **30** (64.9 mg, 0.07 mmol, 83.0%) as a colourless syrup. Due to the presence of stable rotameric populations in comparable concentrations, spectra were too poorly resolved to allow for meaningful interpretation and listing.



$C_{58}H_{74}N_2O_8$

MW: 927.24 g/mol

TLC: UV, VAN

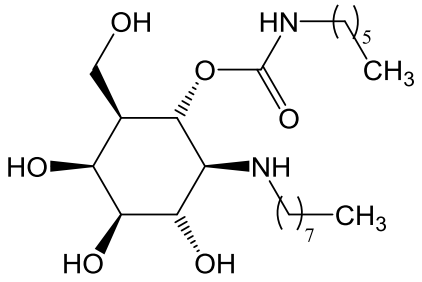
R_f: 0.50 (C/EA 3:1 v/v)

SCG: (C/EA 20:1 v/v)

$[\alpha]_D^{20}$ = -18.1 (c 1.160, $CHCl_3$)

MS: Calcd for $[C_{58}H_{74}N_2O_8Na]$: *m/z* 949.5343 $[M+Na]^+$; Found $[M+Na]^+$ 949.5483.

Following general procedure D compound **30** (111.1 mg, 0.12 mmol) was treated with $Pd(OH)_2$/C (20%) (80 mg) and stirred for 24 hours. Purification on silica gel afforded **31** (37.3 mg, 0.09 mmol, 72.0%) as a colourless solid.



$C_{22}H_{44}N_2O_6$

MW: 432.60 g/mol

TLC: UV, CAM

R_f: 0.40 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

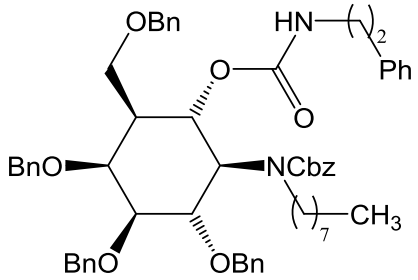
SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = -27.1 (c 0.720, MeOH)

^{1}H NMR (300 MHz, MeOH-d4): δ = 5.08 (dd, 1H, $J_{1,5a}$ 10.6 Hz, H-5a), 4.15 (bs, 1H, H-4), 3.93 (dd, 1H, $J_{2,3}$ 9.3 Hz, H-2), 3.75 (dd, 1H, $J_{5,6A}$ 8.7 Hz, $J_{6A,6B}$ 10.6 Hz, H-6A), 3.62 (dd, 1H, $J_{6A,6B}$ 10.6 Hz, $J_{5,6B}$ 3.9 Hz, H-6B), 3.44 (dd, 1H, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 2.9 Hz, H-3), 3.25 (dd, 1H, $J_{1,5a}$ 10.6 Hz, $J_{1,2}$ 10.9 Hz, H-1), 3.20-3.02 (m, 4H, H-1', H-1''), 2.14 (bm, 1H, H-5), 1.75-1.24 (m, 20H, H-2', H-3', H-4', H-5', H-6', H-7', H-2'', H-3'', H-4'', H-5''), 0.91 (2t, 6H, H-8', H-6'');
^{13}C NMR (75.5 MHz, MeOH-d4): δ = 158.2 (C=O), 75.9 (C-3), 70.0 (C-4), 69.1 (C-5a), 68.6 (C-2), 64.8 (C-1), 60.0 (C-6), 47.3 (C-5), 45.8, 42.1, 32.9, 32.7, 30.8, 30.2, 30.2, 27.6, 27.4, 23.7 (C-1', C-2', C-3', C-4', C-5', C-6', C-7', C-1'', C-2'', C-3'', C-4'', C-5''), 14.4 (C-8', C-6'').
MS: Calcd for [$C_{22}H_{44}N_2O_6H$]: *m/z* 433.3278 $[M+H]^+$; Found $[M+H]^+$ 433.3284.

(5aS)-5a-(2-phenyl)ethylaminocarbonyloxy-N-octyl-1,4-di*-epi-*validamine (33)

Following general procedure E compound **24** (105.6 mg, 0.13 mmol) was treated with BF_3*Et_2O (37.0 µl, 0.30 mmol) and phenethylisocyanide (111.0 µl, 0.66 mmol) and stirred for 90 minutes. Purification on silica gel afforded **32** (49.3 mg, 0.05 mmol, 39.4%) as a white powder.



$C_{60}H_{70}N_2O_8$

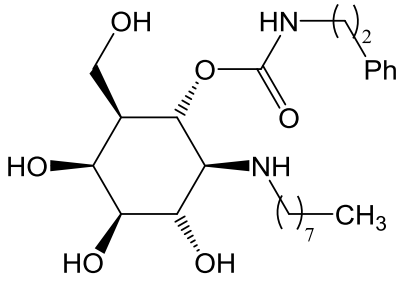
MW: 947.23 g/mol

TLC: UV, CAM

R_f: 0.30 (C/EA 3:1 v/v)

SCG: (C/EA 16:1 v/v)

Following general procedure D compound **32** (49.3 mg, 0.05 mmol) was treated with $Pd(OH)_2/C$ (20%) (40 mg) and stirred for 23 hours. Purification on silica gel afforded **33** (12.6 mg, 0.03 mmol, 53.5%) as a colourless solid.



$C_{24}H_{40}N_2O_6$

MW: 452.59 g/mol

TLC: UV, CAM

R_f: 0.70 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = -12.2 (c 0.370, MeOH)

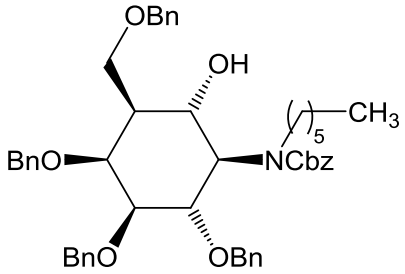
^{1}H NMR (300 MHz, MeOH-d_4): δ = 5.06 (dd, 1H, $J_{5,5a}$ 10.7 Hz, H-5a), 4.14 (bs, 1H, H-4), 3.92 (dd, 1H, $J_{1,2}$ 9.7 Hz, H-2), 3.71 (dd, $J_{6A,6B}$ 10.0 Hz, H-6A), 3.58 (dd, $J_{6A,6B}$ 10.0 Hz, $J_{5,6B}$ 2.9 Hz, H-6B), 3.42 (dd, $J_{2,3}$ 7.8 Hz, H-3), 3.23 (dd, 1H, $J_{1,5a}$ 11.3 Hz, H-1), 3.19-2.75 (m, 4H, H-1', H-1''), 2.14 (NH), 1.86 (bm, 1H, H-5), 1.79-1.18 (m, 14H, H-2', H-3', H-4', H-5', H-6', H-7', H-2''), 0.88 (t, 3H, H-8');

^{13}C NMR (75.5 MHz, MeOH-d_4): δ = 158.1 (C=O), 140.2 (ipso Ar), 129.8, 129.5, 127.4 (Ar), 75.8 (C-3), 69.9 (C-4), 69.1 (C-5a), 68.5 (C-2), 64.7 (C-1), 60.0 (C-6), 47.2 (C-5), 45.8, 43.6, 36.9, 32.8, 30.1, 30.1, 27.5, 27.4, 23.6 (C-1', C-2', C-3', C-4', C-5', C-6', C-7', C-1'', C-2''), 14.4 (C-8').

MS: Calcd for [$C_{24}H_{40}N_2O_6$H]: *m/z* 453.2964 $[M+H]^+$; Found $[M+H]^+$ 453.2968.

(5aS)-5a-(4-aminoethyl)phenylaminocarbonyloxy-N-hexyl-1,4-di-*epi*-validamine (39)

Following general procedure C compound **23** (470.4 mg, 0.62 mmol) was treated with BH_3*THF (1.9 ml, 1.90 mmol). Purification on silica gel afforded **37** (230.1 mg, 0.30 mmol, 47.8%) as a colourless syrup.



$C_{49}H_{57}NO_7$

MW: 772.00 g/mol

TLC: UV, VAN

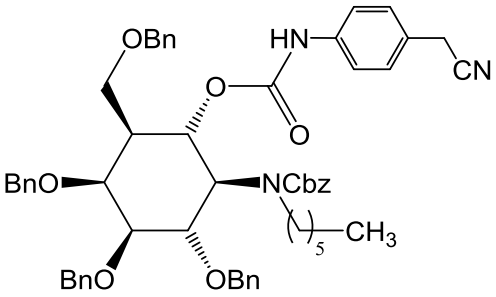
R_f: 0.35 (C/EA 3:1 v/v)

SCG: (C/EA 16:1 v/v)

$[a]_D^{20}$ = -9.5 (c 1.606, $CHCl_3$)

MS: Calcd for [$C_{49}H_{57}NO_7Na$]: *m/z* 794.4033 $[M+Na]^+$; Found $[M+Na]^+$ 794.4030.

Following general procedure E compound **37** (156.3 mg, 0.20 mmol) was treated with BF_3*Et_2O (38.5 µl, 0.30 mmol) and 4-isocyanatobenzylcyanide (96.0 mg, 0.61 mmol) and stirred for 22 hours. Purification on silica gel afforded **38** (149.8 mg, 0.16 mmol, 79.5%) as a colourless oil.



$C_{58}H_{63}N_3O_8$

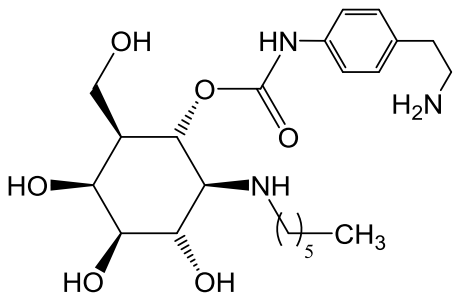
MW: 930.15 g/mol

TLC: UV, VAN

R_f: 0.70 (C/EA 1:1 v/v)

SCG: (C/EA 8:1 v/v)

Following general procedure D compound **38** (95.1 mg, 0.10 mmol) was treated with $Pd(OH)_2$/C (20%) (110 mg) with catalytic amounts of HCl conc. and stirred for 24 hours. Purification on silica gel afforded **39** (39.5 mg, 0.09 mmol, 87.9%) as a colourless syrup.



$C_{22}H_{37}N_3O_6$

MW: 439.55 g/mol

TLC: UV, CAM

R_f: 0.60 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[a]_D^{20}$ = -27.7 (c 1.215, MeOH)

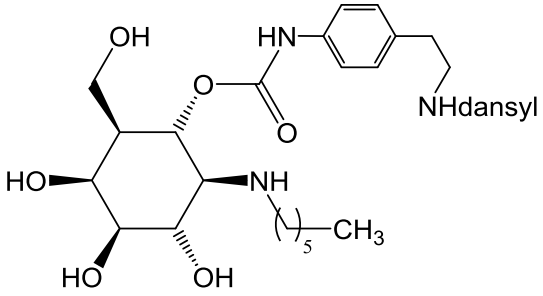
^{1}H NMR (300 MHz, MeOH-d_4): δ = 7.49 (d, 2H, Ar), 7.25 (d, 2H, Ar), 5.22 (dd, 1H, $J_{1,5a}$ 10.4 Hz, H-5a), 4.19 (bs, 1H, H-4), 3.97 (dd, 1H, $J_{1,2}$ 9.9 Hz, $J_{2,3}$ 9.4 Hz, H-2), 3.80 (dd, 1H, $J_{5,6A}$ 9.2 Hz, $J_{6A,6B}$ 10.4 Hz, H-6A), 3.69 (dd, 1H, $J_{6A,6B}$ 10.4 Hz, $J_{5,6B}$ 3.8 Hz, H-6B), 3.51 (dd, 1H, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 2.8 Hz, H-3), 3.35 (m, 1H, H-1), 3.27-2.89 (m, 6H, H-1', H-1'', H-2''), 1.99 (m 1H, H-5), 1.75-1.22 (m, 8H, H-2', H-3', H-4', H-5'), 0.86 (t, 3H, H-6');

^{13}C NMR (75.5 MHz, MeOH-d_4): δ = 155.1 (C=O), 138.8, 133.0 (2x ipso Ar), 130.3, 120.5 (2x Ar), 75.8 (C-3), 70.1 (C-4), 69.1 (C-5a), 68.5 (C-2), 64.6 (C-1), 60.2 (C-6), 47.2 (C-5), 45.5, 42.0, 33.9, 32.3, 27.5, 27.3, 23.4 (C-1', C-2', C-3', C-4', C-5', C-1'', C-2''), 14.3 (C-6').

MS: Calcd for $[C_{22}H_{37}N_3O_6H]$: *m/z* 440.2761 $[M+H]^+$; Found $[M+H]^+$ 440.2758.

(5aS)-5a-(4-dansylaminoethyl)phenylaminocarbonyloxy-N-hexyl-1,4-di-*epi*-validamine (40)

Following general procedure F compound **39** (21.0 mg, 0.05 mmol) was treated with Na_2CO_3 (11.1 mg, 0.11 mmol) and dansylchloride (14.2 mg, 0.05 mmol) and stirred for 15 minutes. Purification on silica gel afforded **40** (24.1 mg, 0.04 mmol, 75.0%) as a pale yellow solid.



$C_{34}H_{48}N_4O_8S$

MW: 672.32 g/mol

TLC: UV, CAM

R_f: 0.70 ($CHCl_3$/MeOH/NH_4OH 8:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = -10.8 (c 0.715, MeOH)

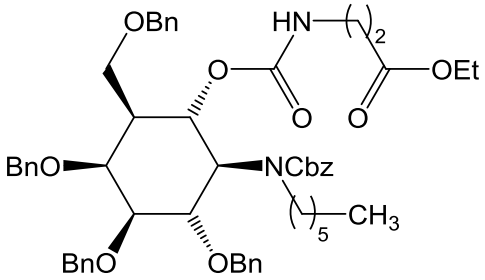
^{1}H NMR (300 MHz, MeOH-d_4): δ = 8.61-6.87 (10H, Ar), 5.21 (dd, 1H, $J_{1,5a}$ 10.8 Hz, H-5a), 4.21 (bs, 1H, H-4), 3.96 (dd, 1H, $J_{1,2}$ 10.5 Hz, H-2), 3.83 (dd, 1H, $J_{5,6A}$ 8.4 Hz, $J_{6A,6B}$ 10.1 Hz, H-6A), 3.72 (dd, 1H, $J_{5,6B}$ 3.7 Hz, $J_{6A,6B}$ 10.1 Hz, H-6B), 3.51 (dd, 1H, $J_{3,4}$ 2.7 Hz, $J_{2,3}$ 9.5 Hz, H-3), 3.33 (m, 1H, H-1), 3.07 (m, 2H, H-1'), 2.90 (s, 6H, $N(CH_3)_2$), 2.58 (m, 2H, H-1''), 1.98 (m, 1H, H-5), 1.66 (m, 2H, H-2'), 1.42-1.18 (m, 8H, H-3', H-4', H-5', H-2''), 0.83 (t, 3H, H-6');

^{13}C NMR (75.5 MHz, MeOH-d_4): δ = 153.2 (C=O), 137.2-116.5 (Ar), 75.8 (C-3), 70.2 (C-4), 69.3 (C-5a), 68.8 (C-2), 64.8 (C-1), 60.2 (C-6), 47.1 (C-5), 45.8 [$N(Me)_2$], 45.5 (C-1'), 36.4, 32.3, 27.8, 27.3, 23.4 (C-2'), C-3', C-4', C-5', C-1'', C-2''), 14.2 (C-6').

MS: Calcd for $[C_{34}H_{48}N_4O_8SH]$: *m/z* 673.3271 $[M+H]^+$; Found $[M+H]^+$ 673.3267.

(5aS)-5a-(2-methoxycarbonyl)ethylamino-carbonyloxy-N-octyl-1,4-di-*epi*-validamine (42)

Following general procedure E compound **37** (62.0 mg, 0.08 mmol) was treated with BF_3*Et_2O (15.3 µl, 0.12 mmol) and Ethyl 3-isocyanatopropionate (31.7 µl, 0.24 mmol) and stirred for 15 minutes. The remaining residue was used in the next step without purification.



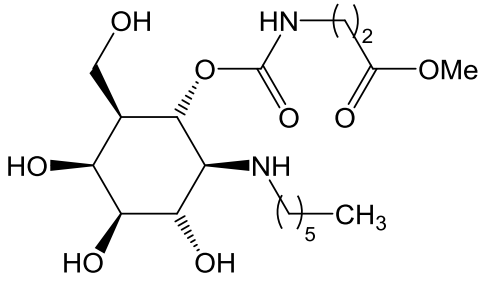
$C_{55}H_{66}N_2O_{10}$

MW: 915.14 g/mol

TLC: UV, VAN

R_f: 0.20 (C/EA 3:1 v/v)

Following general procedure D compound **41** was treated with $Pd(OH)_2$/C (20%) (60mg) with catalytic amounts of HCl conc. and stirred for 21 hours. Purification on silica gel afforded **42** (19.5 mg, 0.05 mmol, 59.7% over 2 steps) as a colourless wax.



$C_{18}H_{34}N_2O_8$

MW: 406.48 g/mol

TLC: UV, CAM

R_f: 0.60 ($CHCl_3$/MeOH/NH_4OH 8:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[a]_D^{20}$ = -19.8 (c 0.665, MeOH)

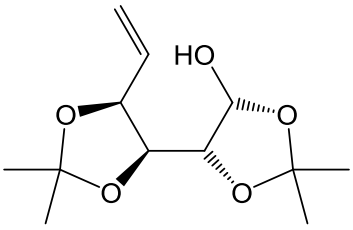
^{1}H NMR (300 MHz, MeOH-d_4): δ = 4.95 (dd, 1H, $J_{1,5a}$ = $J_{5,5a}$ 10.7 Hz, H-5a), 4.13 (bs, 1H, H-4), 3.78-3.69 (m, 2H, H-2, H-6A), 3.68 (s, 3H, OMe), 3.57 (dd, $J_{6A,6B}$ 10.4 Hz, $J_{5,6B}$ 3.6 Hz, H-6B), 3.43-3.33 (m, 2H, H-1''), 3.31 (m, 1H, H-3), 2.75 (m, 2H, H-2''), 2.69 (dd, 1H, $J_{1,2}$ 10.1 Hz, H-1), 2.54 (m, 2H, H-1'), 1.77 (m, 1H, H-5), 1.56-1.27 (m, 8H, H-2', H-3', H-4', H-5'), 0,91 (t, 3H, H-6');

^{13}C NMR (75.5 MHz, MeOH-d_4): δ = 173.8 (COOMe), 158.5 (C=O), 76.4 (C-3), 72.2 (C-5a), 71.3 (C-2), 70.2 (C-4), 65.6 (C-1), 60.3 (C-6), 52.2 (OMe), 47.8 (C-2''), 47.4 (C-5); 37.8, 35.2, 32.8, 30.5, 27.9, 23.6 (C-1', C-2', C-3', C-4', C-5', C-1''), 14.4 (C-6').

MS: Calcd for $[C_{18}H_{34}N_2O_8H]$: *m/z* 407.2393 $[M+H]^+$; Found $[M+H]^+$ 407.2394.

(3aR,3bS,6aR,7S,7aR)-Hexahydro-5,5-dimethyl-1-(phenylmethyl)-1H-[1,3]Dioxolo[3,4]cyclopent[1,2-c]isoxazol-7-ol (90)

A suspension of Zn dust (1.4 g, 21.88 mmol) and NH_4Cl (1.2 g, 21.88 mmol) in 15mL MeOH is stirred for 30 minutes at ambient temperature. A solution of **88** (0.54 g, 1.46 mmol) in 6mL MeOH is added, stirred for additional 60 minutes filtrated over silica gel concentrated under reduced pressure diluted with EA and washed with H_2O. The combined organic layers were dried over Na_2SO_4 and evaporated providing compound **89** (0.29 g, 1.19 mmol, 81.4%) as a pale yellow oil.



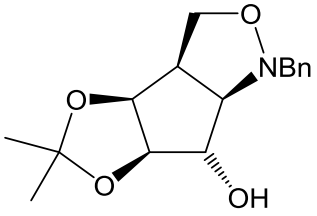
$C_{12}H_{20}O_5$

MW: 244.29 g/mol

TLC: UV, VAN

R_f: 0.75 (C/EA 1:1 v/v)

To a stirred solution of *N*-Benzylhydroxylamine hydrochloride (279 mg, 1.75 mmol) in 6 mL MeOH was added dropwise 6 mL NaOMe (1 M) and $NaHCO_3$ (490 mg, 5.83 mmol). After 15 minutes **89** (285 mg, 1.17 mmol) in 6 mL MeOH was added, stirred at 50°C for 6 hours, diluted with ethyl acetat and washed with H_2O 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified on silica gel to provide **90** (140.7 mg 0.48 mmol, 41.4 %). Recrystallization with MeOH/EA afforded pale yellow crystals for XRD analysis.



$C_{16}H_{21}NO_4$

MW: 291.35 g/mol

TLC: UV, CAM

R_f: 0.3 (C/EA 1:1 v/v)

SCG: (C/EA 5:1 v/v)

$[\alpha]_D^{20}$ = +62.9 (c 1.690, $CHCl_3$)

m.p.: 108-110°C

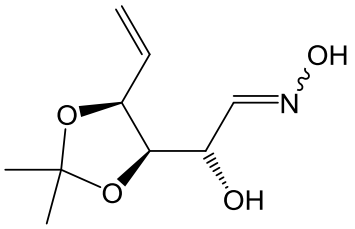
^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.51 (dd, 1H, $J_{4,5}$ 7.1 Hz, H-4), 4.30 (dd, 1H, $J_{3,4}$ 6.3 Hz, H-3), 4.16 (dd, 1H, $J_{5,6a}$ 4.2 Hz, $J_{6a,6b}$ 8.8 Hz, H-6a), 3.98-3.82 (m, 3H, H-2, H-6b, C$\underline{H}_2$Ar), 3.62 (d, 1H, C$\underline{H}_2$Ar), 3.48 (dd, 1H, $J_{1,2}$ 8.0 Hz, $J_{1,5}$ 7.1 Hz, H-1), 3.18 (m, 1H, H-5), 1.42, 1.22 (2s, 3H each, C(C$\underline{H}_3$)$_2$);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 136.7 (ipso Ar), 129.1, 128.5, 127.5 (Ar), 112.7 (*C*$(CH_3)_2$), 86.4 (C-3), 79.7 (C-2), 77.5 (C-1), 77.1 (C-4), 64.9 (C-6), 59.7 (*C*H_2Ar), 45.6 (C-5), 27.3, 25.5 (C(*C*$H_3)_2$);

MS: Calcd for [$C_{16}H_{21}NO_4$H]: *m/z* 292.1549 $[M+H]^+$; Found $[M+H]^+$ 292.1613.

(E/Z)-5,6-Dideoxy-5-eno-3,4-O-isopropylidene-L-arabinohexose oxime (94)

A suspension of Zn dust (3.7 g, 55.9 mmol) and NH_4Cl (3.0 g, 55.9 mmol) in 40mL MeOH is stirred for 30 minutes at ambient temperature. A solution of **88** (1.38 g, 3.73 mmol) in 5mL MeOH is added, stirred for additional 60 minutes filtrated over silica gel concentrated under reduced pressure diluted with EA and washed with H_2O. The combined organic layers were dried over Na_2SO_4 and evaporated. The resulting residue was diluted in 20ml MeOH and H_2NOH (50 %wt in H_2O, 685 µl, 11.2 mmol) was added and stirred for additional 60 minutes at ambient temperature. After full conversion of the starting material the reaction was evaporated to dryness. **94** (680.1 mg, 3.38 mmol, 90.7 %) was observed as a mixture of E/Z as a colourless syrup.



$C_9H_{15}NO_4$

MW: 201.22 g/mol

TLC: UV, VAN

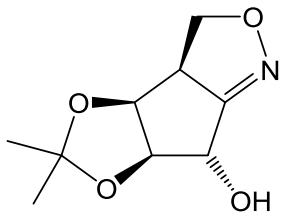
R_f: 0.4 (C/EA 1:1 v/v)

^{13}C NMR major isomer (75.5 MHz $CDCl_3$) δ = 150.1 (C-1), 133.5 (C-5), 119.9 (C-6), 109.3 (*C*$(CH_3)_2$), 79.1 (C-3), 78.9 (C-4), 68.2 (C-2), 27.2, 25.0 (C(*C*$H_3)_2$);

^{13}C NMR minor isomer (75.5 MHz $CDCl_3$) δ =152.5 (C-1), 133.5 (C-5), 120.1 (C-6), 109.2 (*C*$(CH_3)_2$), 79.1 (C-3), 78.2 (C-4), 64.5 (C-2), 26.8, 24.7 (C(*C*$H_3)_2$);

(3aS,4S,5S,6S)-6-Hydroxy-4,5-isopropylidenedioxy-3a,4,5,6-tetrahydro-3H-cyclopent[c]isoxazole (95)

To a stirred solution of **94** (590.7 mg, 2.94 mmol) in 20 ml 2-propanol was added silica gel (8 g) and 4.5 ml NaOCl (10-15% active chlorine) and stirred for 60 minutes at ambient temperature. After full conversion of the starting material, the reaction mixture was filtered and diluted with CH_2Cl_2 and consecutively washed with H_2O, HCl (2*N*) and saturated $NaHCO_3$. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification on silica gel afforded **95** (473.3 mg, 2.38 mmol, 80.9%) as a colourless syrup. Recrystallisation with EA/C gave colourless crystals for XRD analysis.



$C_9H_{13}NO_4$

MW: 199.21 g/mol

TLC: UV, VAN

R_f: 0.3 (C/EA 1:1 v/v)

SCG: (C/EA 6:1 v/v)

$[a]_D^{20}$ = -140,2 (c 1.620, $CHCl_3$)

m.p.: 113-116°C

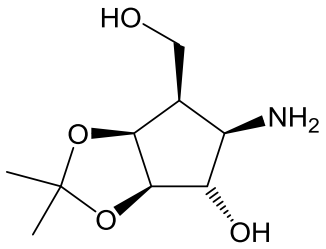
^{1}H NMR (300 MHz) $CDCl_3$) δ = 4.70 (dd, 1H, $J_{3,4}$ 5.2 Hz, H-3), 4.61 (dd, 1H, $J_{4,5}$ 5.6 Hz, H-4), 4.47 (s, 1H, H-2), 4.41 (dd, 1H, $J_{5,6a}$ 8.2 Hz, $J_{6a,6b}$ 11.7 Hz, H-6a), 4.31 (dd,1H, $J_{5,6b}$ 8.4 Hz, H-6b), 4.04 (m, 1H, H-5), 3.39 (bs, 1H, 2-OH), 1.34, 1.24 (2s, 3H each, C($C\underline{H_3}$)$_2$);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 165.3 (C-1), 111.6 (C(CH_3)$_2$), 90.1 (C-3), 75.1 (C-4), 70.0 (C-6), 68.9 (C-2), 54.4 (C-5), 26.4, 24.7 (C(CH$_3$)$_2$);

MS: Calcd for [$C_9H_{13}NO_4H$]: *m/z* 200.0923 $[M+H]^+$; Found $[M+H]^+$ 200.0936.

(1S,2S,3S,4R,5R)-1,2-O-Isopropylidene-4-amino-5-hydroxymethyl-1,2,3-cyclopentanetriol (91)

To a stirred suspension of LAH (902 mg 24 mmol) in THF (40 ml) was added dropwise a solution of compound **95** (470.2 mg, 2.4 mmol) in 15ml THF at 0°C. After full conversion of the starting material, H_2O and NaOH (3M) was added dropwise until the reaction mixture turned milky- white. The resulting suspension was filtered and evaporated to dryness. Purification on silica gel gave **91** (374.0 mg, 1.84 mmol; 78.0%) as a colourless oil.



$C_9H_{17}NO_4$

MW: 203.24 g/mol

TLC: UV, CAM

R_f: 0.3 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = +1.2 (c 1.350, MeOH)

^{1}H NMR (300 MHz, MeOH-d_4) δ = 4.80 (dd, 1H, $J_{4,5}$ 5.2 Hz, H-4), 4.47 (d, 1H, $J_{3,4}$ 5.7 Hz, H-3), 4.13 (s, 1H, H-2), 3.94 (dd, 1H, $J_{5,6a}$ 7.2 Hz, $J_{6a,6b}$ 11.1 Hz, H-6a), 3.85 (dd, 1H, $J_{5,6b}$ 8.2 Hz, H-6b), 3.35 (m, 1H, H-1), 2.59 (m, 1H, H-5), 1.47, 1.31 (2s, 3H each, C($C\underline{H_3}$)$_2$);

^{13}C NMR (75.5 MHz, MeOH-d_4) δ= 112.1 (C(CH_3)$_2$) 87.4 (C-3), 81.7 (C-4), 79.9 (C-2), 60.7 (C-1), 58.2 (C-6), 47.0 (C-5), 26.2, 23.0 (C(CH$_3$)$_2$);

MS: Calcd for [$C_9H_{17}NO_4H$]: *m/z* 204.1236 $[M+H]^+$; Found $[M+H]^+$ 204.1221.

(1S,2S,3S,4R,5R)-4-Amino-5-hydroxymethyl-1,2,3-cyclopentanetriol (93)

Condition A:

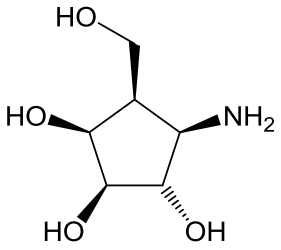
To a solution of **90** (140,0 mg, 0,48 mmol) in MeOH (5 mL) and 20 µL HCl conc., was added $Pd(OH)_2$ (20%, 60 mg) and the mixture was stirred under an atmosphere of hydrogen at ambient pressure for 24 hours. The catalyst was removed by filtration and washed with MeOH. The solvent was removed under reduced pressure and the remaining residue was chromatographed on silica gel ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v) to give compound **92** (34.8 mg, 0.17 mmol, 35.3%) and compound **93** (42,8 mg, 0,26 mmol, 54,6%).

Condition B:

To a solution of **90** (83,0 mg, 0,29 mmol) in MeOH (4 mL) and 100 µL HCl conc., was added $Pd(OH)_2$ (20%, 50 mg) and the mixture was stirred under an atmosphere of hydrogen at ambient pressure for 23 hours. The catalyst was removed by filtration and washed with MeOH. The solvent was removed under reduced pressure and the remaining residue was chromatographed on silica gel ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v) to give compound **93** (36.2 mg, 0.22 mmol, 77.9%) as a pale yellow syrup

Condition C:

To a solution of compound **91** (60.0 mg, 0.30 mmol) in 5 ml MeOH/H_2O 4:1 was added HCl conc.(50 µl) and stirred for 60 minutes. After complete conversion indicated by TLC, the reaction mixture was evaporated to dryness. Purification on silica gel gave **93** (41.7 mg, 0.26 mmol, 86.6%) as a pale yellow syrup.



$C_6H_{13}NO_4$

MW: 163.17 g/mol

TLC: UV, CAM

R_f: 0.3 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[a]_D^{20}$ = +24.6 (c 0.965, H_2O)

^{1}H NMR (300 MHz, D_2O) δ= 4.14 (dd, 1H, $J_{4,5}$ 3.5 Hz, H-4), 4.11 (dd, 1H, $J_{1,2}$ 4.7 Hz, $J_{2,3}$ 7.4 Hz, H-2), 3.89 (dd, 1H, $J_{5,6a}$ 4.0 Hz, $J_{6a,6b}$ 11.5 Hz, H-6a), 3.88 (m, 1H, H-3), 3.82 (dd, 1H, $J_{5,6b}$ 8.4 Hz, H-6b), 3.47 (dd, 1H, $J_{1,2}$ 4.7 Hz, $J_{1,5}$ 8.4 Hz, H-1);

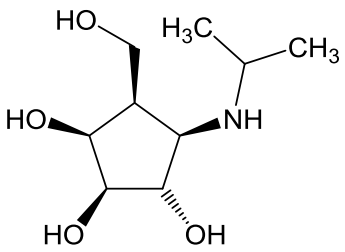
^{13}C NMR (75.5 MHz, D_2O) δ= 81.0 (C-2), 77.9 (C-3), 72.3 (C-4), 57.0 (C-6), 56.7 (C-1), 41.9 (C-5);

93.HCl: **^{13}C NMR** (75.5 MHz, D_2O) δ= 79.6 (C-2), 77.9 (C-3), 72.1 (C-4), 56.8 (C-6), 56.7 (C-1), 41.3 (C-5);

MS: Calcd for $[C_6H_{13}NO_4H]$: *m/z* 164.0923 $[M+H]^+$; Found $[M+H]^+$ 164.0929.

(1S,2S,3S,4R,5R)-N-isopropyl-4-amino-5-hydroxymethyl-1,2,3-cyclopentanetriol (92)

To a stirred solution of **93** (42.8 mg, 0.26 mmol) in MeOH (3 ml) and HCl conc. (10 µL) was added acetone (29 µl, 0.39 mmol) and stirred under an atmosphere of hydrogen at ambient pressure in prescence of $Pd(OH)_2/C$ (20 %; 40 mg) for 24 hours. The catalyst was removed by filtration and washed with MeOH. The solvent was removed under reduced pressure and the remaining residue was chromatographed on silica gel to give compound **92** (48.7 mg, 0.24 mmol, 90.0%) as a colourless wax.



$C_9H_{19}NO_4$

MW: 205.25 g/mol

TLC: UV, CAM

R_f: 0.6 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[a]_D^{20}$ = +19.8 (c 1.305, H_2O)

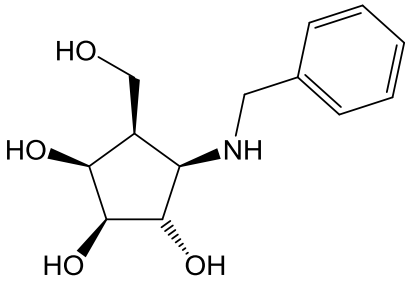
^{1}H NMR (300 MHz, D_2O) δ= 4.25 (dd, 1H, $J_{2,3}$ 6.9 Hz, H-2), 4.11 (dd, 1H, $J_{3,4}$ 4.1 Hz, H-4), 3.93-3.79 (m, 3H, H-3, H-6a, H-6b), 3.69 (dd, 1H, $J_{1,2}$ 6.0 Hz, $J_{1,5}$ 9.1 Hz, H-1), 3.63 (m, 1H, C<u>H</u>$(CH_3)_2$), 2.65 (m, 1H, H-5), 1.32 (m, 6H, CH(C<u>H</u>$_3$)$_2$);

^{13}C NMR (75.5 MHz, D_2O) δ= 78.6 (C-2), 77.4 (C-3), 71.4 (C-4),59.9 (C-1), 57.1 (C-6), 50.6 (*C*H$(CH_3)_2$), 41.5 (C-5), 19.1, 17.5 (CH(*C*H$_3$)$_2$);

MS: Calcd for $[C_9H_{19}NO_4H]$: *m/z* 206.1392 $[M+H]^+$; Found $[M+H]^+$ 206.1381.

(1S,2S,3S,4R,5R)-N-benzyl-4-amino-5-hydroxymethyl-1,2,3-cyclopentanetriol (96)

Following general procedure B compound **93** (19.8 mg, 0.12 mmol) was treated with $NaHCO_3$ (40 mg, 0.48 mmol) and benzylbromide (16.0 µl, 0.13 mmol) and stirred for 25 hours. Purification on silica gel afforded **96** (22.0 mg, 0.09 mmol, 71.6%) as a colourless wax.



$C_{13}H_{19}NO_4$

MW: 253.30 g/mol

TLC: UV, CAM

R_f: 0.8 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = +39.9 (c 1.350, MeOH)

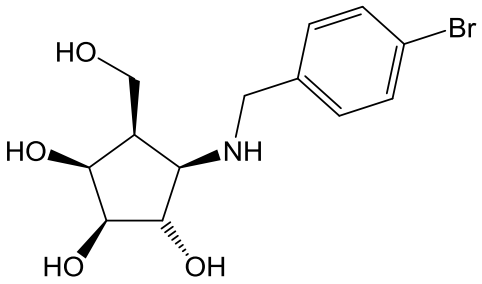
^{1}H NMR (300 MHz, D_2O) δ= 4.50 (d, 1H, C<u>H</u>$_2$Ar), 4.38 (dd, 1H, $J_{1,2}$ 5.8 Hz, $J_{2,3}$ 7.4 Hz, H-2), 4.27 (d, 1H, C<u>H</u>$_2$Ar), 4.06 (dd, 1H, $J_{3,4}$ 3.8 Hz, H-4), 3.94-3.74 (m, 3H, H-3, H-6a, H-6b), 3.51 (dd, 1H, $J_{1,5}$ 9.0 Hz, H-1), 2.61 (m, 1H, H-5);

^{13}C NMR (75.5 MHz, D_2O) δ= 130.1, 129.8, 129.8, 129.3 (Ar), 78.5 (C-2), 77.7 (C-3), 71.4 (C-4), 61.3 (C-1), 56.9 (C-6), 50.1 (*C*H_2Ar), 41.4 (C-5);

MS: Calcd for [$C_{13}H_{19}NO_4Na$]: *m/z* 276.1212 $[M+Na]^+$; Found $[M+Na]^+$ 276.1205.

(1S,2S,3S,4R,5R)-N-(4-bromo)benzyl-4-amino-5-hydroxymethyl-1,2,3-cyclopentanetriol (97)

Following general procedure B compound **93** (19.3 mg, 0.12 mmol) was treated with $NaHCO_3$ (40.0 mg, 0.48 mmol) and 4-bromo-benzylbromide (32.5 mg, 0.13 mmol) and stirred for 19 hours. Purification on silica gel afforded **97** (31.5 mg, 0.10 mmol, 80.2%) as a pale yellow syrup.



$C_{13}H_{18}BrNO_4$

MW: 332.19 g/mol

TLC: UV, CAM

R_f: 0.85 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

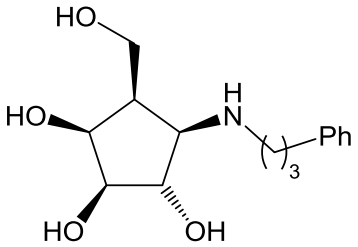
SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = +17.6 (c 0.48, H_2O)

^{1}H NMR (300 MHz, D_2O) δ= 4.16-4.06 (m, 2H, H-2, H-4), 3.98 (d, 1H, C$\underline{H}_2$Ar), 3.88-3.73 (m, 4H, H-3, H-6a, H-6b, C$\underline{H}_2$Ar), 3.11 (dd, 1H, $J_{1,2}$ 5.0 Hz, $J_{1,5}$ 8.8 Hz, H-1), 2.46 (m, 1H, H-5);
^{13}C NMR (75.5 MHz, D_2O) δ= 137.0 (ipso Ar), 131.6, 130.5 (Ar), 120.8 (ArBr), 82.1 (C-2), 78.3 (C-3), 72.0 (C-4), 61.7 (C-1), 57.4 (C-6), 50.1 (CH_2Ar), 43.1 (C-5);
MS: Calcd for [$C_{13}H_{18}BrNO_4H$]: *m/z* 332.0497 $[M+H]^+$; Found $[M+H]^+$ 332.0863.

(1S,2S,3S,4R,5R)-N-(3-Phenyl)propyl-4-amino-5-hydroxymethyl-1,2,3-cyclopentanetriol (98)

Following general procedure B compound **93** (19.5 mg, 0.12 mmol) was treated with $NaHCO_3$ (40.0 mg, 0.48 mmol) and phenylpropylbromide (20.5 µl, 0.13 mmol) and stirred for 96 hours. Purification on silica gel afforded **98** (29.4 mg, 0.10 mmol, 87.4%) as a colourless syrup.



$C_{15}H_{23}NO_4$

MW: 281.35 g/mol

TLC: UV, CAM

R_f: 0.75 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = +26.8 (c 1.135, MeOH)

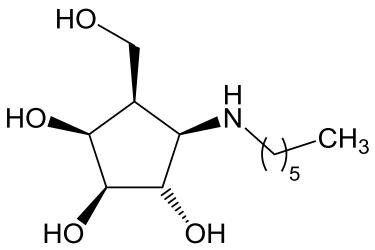
^{1}H NMR (300 MHz, MeOH-d_4) δ= 4.14 (dd, 1H, $J_{1,2}$ 5.4 Hz, H-2), 3.97 (dd, 1H, $J_{3,4}$ 4.2 Hz, H-4), 3.85 (m, 2H, H-6a, H-6b), 3.73 (dd, 1H, $J_{2,3}$ 6.7 Hz, H-3), 3.41 (dd, 1H, $J_{1,2}$ 5.4 Hz, $J_{1,5}$ 8.9 Hz, H-1), 3.23-2.99 (m, 2H, H-1'); 2.71-2.61 (t, 2H, H-3'), 2.53 (m, 1H, H-5), 2.13-1.91 (m, 2H, H-2');

^{13}C NMR (75.5 MHz, MeOH-d_4) δ=141.6 (ipso Ar), 129.6, 129.4, 127.4 (Ar), 80.2 (C-2), 79.8 (C-3), 73.3 (C-4), 65.0 (C-1), 58.6 (C-6), 43.7 (C-1'), 33.6 (C-3'), 28.5 (C-2');

MS: Calcd for $[C_{15}H_{23}NO_4H]$: *m/z* 282.1705 $[M+H]^+$; Found $[M+H]^+$ 282.1709.

(1S,2S,3S,4R,5R)-N-Hexyl-4-amino-5-hydroxymethyl-1,2,3-cyclopentanetriol (99)

Following general procedure B compound **93** (20.1 mg, 0,12 mmol) was treated with $NaHCO_3$ (40.0 mg, 0.48 mmol) and hexylbromide (19.0 µl, 0.14 mmol) and stirred for 90 hours. Purification on silica gel afforded **99** (25.4 mg, 0.10 mmol, 83.4%) as a white wax.



$C_{12}H_{25}NO_4$

MW: 247.34 g/mol

TLC: UV, CAM

R_f: 0.8 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = +24.0 (c 0.780, MeOH)

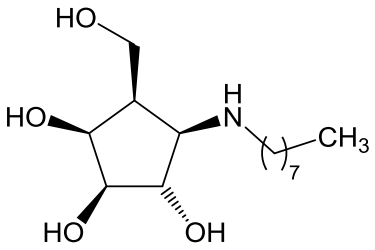
^{1}H NMR (300 MHz, MeOH-d_4) δ= 4.22 (dd, 1H, H-2), 4.04 (dd, 1H, $J_{3,4}$ 4.2 Hz, H-4), 3.92 (m, 2H, H-6a, H-6b), 3.80 (dd, 1H, $J_{2,3}$ 6.6 Hz, H-3), 3.48 (dd, 1H, $J_{1,2}$ 8.7 Hz, $J_{1,5}$ 8.7 Hz, H-1), 3.28-3.03 (m, 2H, H-1'), 2.60 (m, 1H, H-5), 1.86-1.64 (m, 2H, H-2'), 1.47-1.28 (m, 6H, H-3', H-4', H-5'), 0.93 (t, 3H, H-6');

^{13}C NMR (75.5 MHz, MeOH-d_4) δ= 80.2 (C-2), 79.8 (C-3), 73.3 (C-4), 64.9 (C-1), 58.6 (C-6), 48.5 (C-1') 43.7 (C-5), 32.4, 27.2, 26.7, 23.5 (C-2', C-3', C-4', C-5'), 14.3 (C-6');

MS: Calcd for $[C_{12}H_{25}NO_4H]$: *m/z* 248.1862 $[M+H]^+$; Found $[M+H]^+$ 248.1864.

(1S,2S,3S,4R,5R)-N-Octyl-4-amino-5-hydroxymethyl-1,2,3-cyclopentanetriol (100)

Following general procedure B compound **93** (20.3 mg, 0.12 mmol) was treated with $NaHCO_3$ (40.0 mg, 0.48 mmol) and octylbromide (23.5 µl, 0.14 mmol) and stirred for 90 hours. Purification on silica gel afforded **100** (31.2 mg, 0.11 mmol, 91.1%) as a colourless syrup.



$C_{14}H_{29}NO_4$

MW: 275.39 g/mol

TLC: UV, CAM

R_f: 0.8 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = +24.2 (c 1.325, MeOH)

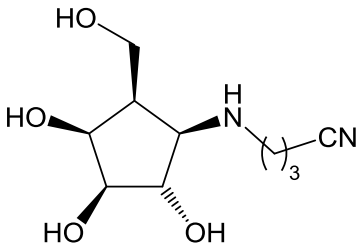
^{1}H NMR (300 MHz, MeOH-d_4) δ= 4.23 (dd, 1H, $J_{2,3}$ 6.5 Hz, H-2), 4.05 (dd, 1H, $J_{3,4}$ 4.2 Hz, H-4), 3.93 (m, 2H, H-6a, H-6b), 3.81 (dd, 1H, H-3), 3.49 (dd, 1H, $J_{1,2}$ 5.4 Hz, $J_{1,5}$ 8.7 Hz, H-1), 3.29-3.04 (m, 2H, H-1'), 2.61 (m, 1H, H-5), 1.85-1.67 (m, 2H, H-2'), 1.45-1.26 (m, 10H, H-3', H-4', H-5', H-6', H-7'), 0.91 (t, 3H, H-8');

^{13}C NMR (75.5 MHz, MeOH-d_4) δ= 80.2 (C-2), 79.7 (C-3), 73.3 (C-4), 64.9 (C-1), 58.6 (C-6), 48.5 (C-1'), 43.7 (C-5), 32.8, 30.1, 30.1, 27.6, 26.7, 23.6 (C-2', C-3', C-4', C-5', C-6', C-7'), 14.4 (C-8');

MS: Calcd for [$C_{14}H_{29}NO_4H$]: *m/z* 276.2175 $[M+H]^+$; Found $[M+H]^+$ 276.2355.

(1S,2S,3S,4R,5R) -4-pyrrolidinyl-5-hydroxymethyl-1,2,3-cyclopentanetriol (103)

Following general procedure B compound **93** (20.2 mg, 0.12 mmol) was treated with $NaHCO_3$ (40.0 mg, 0.48 mmol) and 4-bromobutyronitrile (13.5 µl, 0.14 mmol) and stirred for 72 hours. Purification on silica gel afforded **101** (25.2 mg, 0.11 mmol, 88.4%) as a colourless wax.



$C_{10}H_{18}N_2O_4$

MW: 230.26 g/mol

TLC: UV, CAM

R_f: 0.6 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

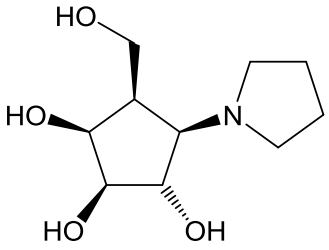
$[\alpha]_D^{20}$ = +27.6 (c 0.680, MeOH)

^{1}H NMR (300 MHz MeOH-d_4) δ= 4.23 (dd, 1H, $J_{2,3}$ 6.2 Hz, H-2), 4.05 (dd, 1H, $J_{3,4}$ 4.2 Hz, H-4), 3.93 (m, 2H, H-6a, H-6b), 3.80 (dd, 1H, H-3), 3.49 (dd, 1H, $J_{1,2}$ 5.5 Hz, $J_{1,5}$ 8.5 Hz, H-1), 3.37 (m, 1H, H-1'a), 3.22 (m, 1H, H-1'b), 2.68-2.55 (m, 3H, H-5, H-3'), 2.22-2.02 (m, 2H, H-2');

^{13}C NMR (75.5 MHz, MeOH-d_4) δ= 119.9 (C-6'), 80.2 (C-2), 79.7 (C-3), 73.3 (C-4), 65.2 (C-1), 58.6 (C-6), 47.1 (C-1'), 43.8 (C-5), 23.1 (C-2'), 15.0 (C-3');

MS: Calcd for [$C_{10}H_{18}N_2O_4$H]: *m/z* 231.1345 $[M+H]^+$; Found $[M+H]^+$ 231.1346.

Following general procedure D compound **101** (12.8 mg, 0.06 mmol) was treated with $Pd(OH)_2$/C (20%) (30mg) with catalytic amounts of HCl conc. and stirred for 23 hours. Purification on silica gel afforded **103** (9.1 mg, 0.04 mmol, 75.3%) as a colourless syrup.



$C_{10}H_{19}NO_4$

MW: 217.27 g/mol

TLC: UV, CAM

R_f: 0.5 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = -14.2 (c 0.450, MeOH)

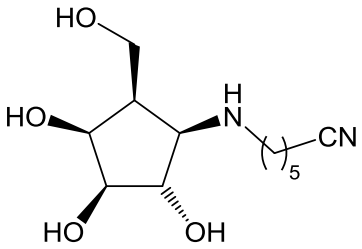
^{1}H NMR (300 MHz MeOH-d_4) δ= 4.14 (dd, 1H, $J_{3,4}$ 6.2 Hz, H-4), 4.05 (dd, 1H, $J_{2,3}$ 3.3 Hz, $J_{1,2}$ 7.6 Hz, H-2), 3.86 (m, 2H, H-6a, H-6b), 3.77 (dd, 1H, H-3), 2.94-2.71 (m, 4H, H-1', H-4'), 2.62 (dd, 1H, $J_{1,2}$ 7.6 Hz, H-1), 2.45 (m, 1H, H-5), 1.89-1.77 (m, 4H, H-2', H-3');

^{13}C NMR (75.5 MHz, MeOH-d_4) δ= 82.4 (C-2), 80.1 (C-3), 71.8 (C-4), 71.3 (C-1), 59.7 (C-6), 54.7 (C-1',C-4'), 47.5 (C-5), 24.1 (C-2', C-3');

MS: Calcd for [$C_{10}H_{19}NO_4$H]: *m/z* 218.1392 $[M+H]^+$; Found $[M+H]^+$ 218.1388.

(1S,2S,3S,4R,5R)-N-dansylaminohexyl-4-amino-5-hydroxymethyl-1,2,3-cyclopentanetriol (105)

Following general procedure B compound **93** (51.1 mg, 0.14 mmol) was treated with $NaHCO_3$ (51.6 mg, 0.61 mmol) and 6-bromohexanenitrile (24.0 µl, 0.18 mmol) and stirred for 60 hours. Purification on silica gel afforded **102** (24.5 mg, 0.10 mmol, 65.9%) as a colourless wax.



$C_{12}H_{22}N_2O_4$

MW: 258.32 g/mol

TLC: UV, CAM

R_f: 0.7 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

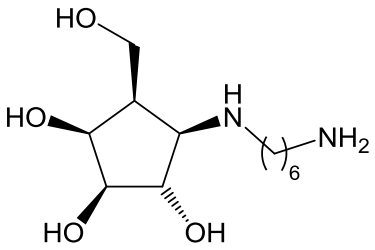
$[\alpha]_D^{20}$ = +29.8 (c 0.795, MeOH)

^{1}H NMR (300 MHz MeOH-d_4) δ= 4.09 (dd, 1H, $J_{2,3}$ 5.6 Hz, H-2), 4.03 (dd, 1H, $J_{3,4}$ 4.3 Hz, H-4), 3.88 (m, 2H, H-6a, H-6b), 3.77 (dd, 1H, H-3), 3.25 (dd, 1H, $J_{1,2}$ 5.0 Hz, $J_{1,5}$ 8.4 Hz, H-1), 3.06 (m, 1H, H-1'a), 2.90 (m, 1H, H-1'b), 2.54-2.43 (m, 3H, H-5, H-5'), 1.78-1,46 (m, 6H, H-2', H-3', H-4');

^{13}C NMR (75.5 MHz, MeOH-d_4) δ= 121.0 (C-6'), 82.0 (C-2), 80.2 (C-3), 73.6 (C-4), 65.3 (C-1), 58.8 (C-6), 44.6 (C-1'), 27.6, 27.0, 26.1 (C-2', C-3', C-4'), 17.2 (C-5');

MS: Calcd for [$C_{12}H_{22}N_2O_4Na$]: *m/z* 281.1477 $[M+Na]^+$; Found $[M+Na]^+$ 281.1436.

Following general procedure D compound **102** (12.0 mg, 0.05 mmol) was treated with $Pd(OH)_2$/C (20%) (25mg) with catalytic amounts of HCl conc. and stirred for 25 hours. Purification on silica gel afforded **104** (8.9 mg, 0.03 mmol, 73.0%) as a pale yellow syrup.



$C_{12}H_{26}N_2O_4$

MW: 262.35 g/mol

TLC: UV, CAM

R_f: 0.15 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:4:1 v/v/v)

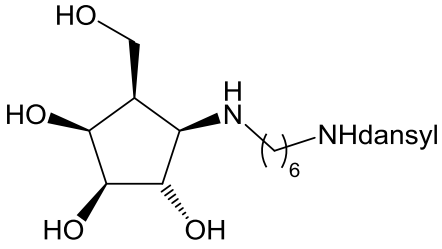
$[\alpha]_D^{20}$ = +16.1 (c 0.800, H_2O)

^{1}H NMR (300 MHz D_2O) δ= 4.31 (dd, 1H, $J_{1,2}$ 5.9 Hz, $J_{2,3}$ 7.5 Hz, H-2), 4.14 (dd, 1H, $J_{3,4}$ 3.9 Hz, H-4), 3.99-3.83 (m, 3H, H-3, H-6a, H-6b), 3.61 (dd, 1H, $J_{1,5}$ 9.1 Hz, H-1), 3.28 (m, 1H, H-1'a), 3.13 (m, 1H, H-1'b), 3.00 (m, 2H, H-6'), 2.70 (m, 1H, H-5), 1.82-1.38 (m, 8H, H-2', H-3', H-4', H-5');

^{13}C NMR (75.5 MHz, D_2O) δ= 78.3 (C-2), 77.6 (C-3), 71.6 (C-4), 62.3 (C-1), 57.0 (C-6), 46.9 (C-1'), 41.6 (C-5), 39.3 (C-6'), 26.5, 25.2, 25.1, 24.9 (C-2', C-3', C-4', C-5');

MS: Calcd for [$C_{12}H_{26}N_2O_4H$]: *m/z* 263.1971 $[M+H]^+$; Found $[M+H]^+$ 263.1974.

Following general procedure F compound **104** (12.5 mg, 0.05 mmol) was treated with Na_2CO_3 (25.5 mg, 0.24 mmol) and dansyl chloride (16.7 mg, 0.06 mmol) and stirred for 30 minutes. Purification on silica gel afforded **105** (15.3 mg, 0.03 mmol, 64.8%) as a pale yellow syrup and **106** (4.8 mg, 0.01 mmol, 19.8%) as a pale yellow syrup.



$C_{24}H_{37}N_3O_6S$

MW: 495.64 g/mol

TLC: UV, CAM

R_f: 0.2 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

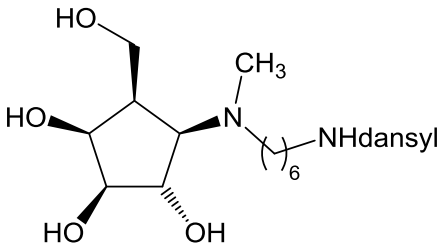
$[\alpha]_D^{20}$ = +10.6 (c 0.470, MeOH)

^{1}H NMR (300 MHz MeOH-d_4) δ= 4.01 (dd, 1H, $J_{4,5}$ 4.6 Hz, H-4), 3.91 (dd, 1H, $J_{2,3}$ 5.2 Hz, H-2), 3.88-3.76 (m, 2H, H-6a, H-6b), 3.72 (dd, 1H, $J_{3,4}$ 5.6 Hz, H-3), 2.95 (dd, 1H, $J_{1,2}$ 4.6 Hz, $J_{1,5}$ 8.1

Hz, H-1), 2.89 (s, 6H, N($C\underline{H_3}$)$_2$), 2.87-2.44 (m, 4H, H-1', H-6'), 1.38-1.06 (m, 8H, H-2', H-3', H-4', H-5');

^{13}C NMR (75.5 MHz, MeOH-*d_4*) δ= 153.2-116.4 (Ar), 83.8 (C-2), 80.7 (C-3), 73.8 (C-4), 65.7 (C-1), 59.1 (C-6), 48.7 (C-1'), 45.8 (2x NMe), 45.5 (C-5), 43.7 (C-6'), 30.4, 30.0, 27.6, 27.3 (C-2', C-3', C-4', C-5');

MS: Calcd for [$C_{24}H_{37}N_3O_6SNa$]: *m/z* 518.2301 [M+Na]$^+$; Found [M+Na]$^+$ 518.2307.



$C_{25}H_{39}N_3O_6S$

MW: 509.66 g/mol

TLC: UV, CAM

R_f: 0.5 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

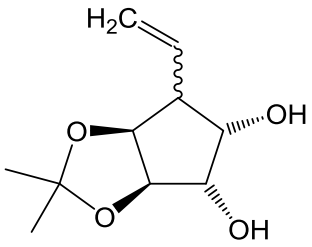
SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[a]_D^{20}$ = +2.0 (c 0.480, MeOH)

MS: Calcd for [$C_{25}H_{39}N_3O_6SNa$]: *m/z* 532.2457 [M+Na]$^+$; Found [M+Na]$^+$ 532.2276.

(1S,2R,3S,4S,5R)-5-C-ethylene-1,2-O-isopropylidene-4-O-pivalyl-cyclopentane-1,2,3,4-tetraol (74)

To a solution of compound **72** (3.5 g, 13.7 mmol) in 150 ml dry THF was added $Pd(PPh_3)_4$ (470 mg, 4.1 mmol), $ZnCl_2$ (2.2 g, 16.4 mmol) and Et_2Zn (1M in hexane) (34.1 ml, 34.1 mmol) under an atmosphere of N_2 and stirred for 24 hours at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded an inseparable 3:1 mixture of epimers **73a and 73b** (1.51 g, 7.5 mmol, 55.2%) as a colourless syrup.



$C_{10}H_{16}O_4$

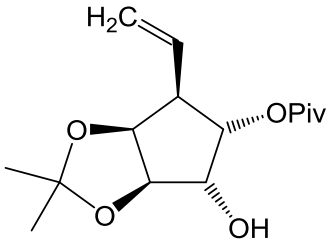
MW: 200.23 g/mol

TLC: UV, VAN

R_f: 0.3 (C/EA 1:1 v/v)

SCG: (C/EA 4:1 v/v)

To a solution of a 3:1 mixture of compounds **73a** and **73b** (1.25 g, 6.24 mmol) in 30 ml CH_2Cl_2 was added pyridine (2 ml, 25.0 mmol) and pivaloylchloride (1.5 ml, 12.5 mmol) and stirred for 30 hours at RT. The reaction mixture was washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **74** (1.43 g, 5.03 mmol, 80.6%) as a colourless syrup.



$C_{15}H_{24}O_5$

MW: 284.35 g/mol

TLC: UV, VAN

R_f: 0.8 (C/EA 1:1 v/v)

SCG: (C/EA 20:1 v/v)

$[\alpha]_D^{20}$ = -73.5 (c 1.158, $CHCl_3$)

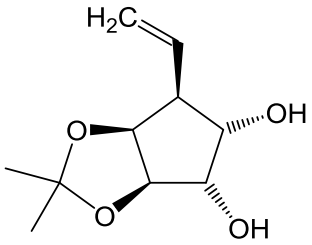
^{1}H NMR (300 MHz, $CDCl_3$) δ= 5.90 (m, 1H, H-6), 5.20-5.03 (m, 3H, H-7a, H-7b, H-1), 4.60 (dd, 1H, $J_{4,5}$ 5.5 Hz, H-4), 4.43 (dd, 1H, $J_{3,4}$ 5.7 Hz, H-3), 3.80 (dd, 1H, $J_{1,2}$ 3.9 Hz, H-2), 2.88 (m, 1H, H-5), 2.05 (bs, 1H, OH), 1.48-1.14 (m, 15H, $C(C\underline{H_3})_2$, $C(C\underline{H_3})_3$);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 177.7 (C=O), 133.9 (C-6), 118.4 (C-7), 110.6 ($C(CH_3)_2$), 82.7 (C-3), 79.0 (C-4), 75.9 (C-1), 73.9 (C-2), 48.6 (C-5), 39.0 ($C(CH_3)_3$), 27.3 ($C(CH_3)_3$), 26.0, 23.7 ($C(CH_3)_2$);

(1S,2R,3S,4S,5S)-5-C-ethylene-1,2-O-isopropylidene -cyclopentane-1,2,3,4-tetraol (73a)

To a solution of compound **74** (20.3 mg, 0.07 mmol) in 2 ml MeOH were added NaOMe (1M) (100 µl) and stirred for 35 hours at ambient temperature. The reaction mixture was diluted

with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **73a** (11.8 mg, 0.06 mmol, 82.5%) as a white solid. Recrystallisation from CH_2Cl_2/benzene gave white needles for XRD analysis.



$C_{10}H_{16}O_4$

MW: 200.23 g/mol

TLC: UV, VAN

R_f: 0.3 (C/EA 1:1 v/v)

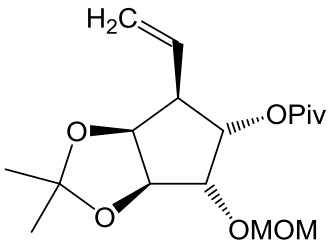
SCG: (C/EA 4:1 v/v)

$[\alpha]_D^{20}$ = -96.8 (c 0,910, $CHCl_3$)

^{1}H NMR (300 MHz $CDCl_3$) δ= 5.97 (m, 1H, H-6), 5.25 (m, 2H, H-7a, H-7b), 4.61 (dd, 1H, $J_{4,5}$ 5.5 Hz, H-4), 4.43 (dd, 1H, $J_{3,4}$ 6.1 Hz, H-3), 4.11 (dd, 1H, $J_{1,2}$ 4.3 Hz, $J_{1,5}$ 10.4 Hz, H-1), 4.02 (dd, 1H, $J_{1,2}$ 4.3 Hz, H-2), 2.62 (m, 1H, H-5), 2.15 (bs, 2H, 2xOH), 1.42, 1.28 (2t, 6H, 2x C($C\underline{H}_3$)$_2$);
^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 134.7 (C-6), 118.8 (C-7), 110.4 (C(CH_3)$_3$), 82.5 (C-3), 79.9 (C-4), 75.1 (C-2), 74.9 (C-1), 51.0 (C-5), 26.1, 23.7 (C(CH$_3$)$_2$);

(1S,2S,3S,4S,5R)-5-C-ethylene-1,2-O-isopropylidene-3-O-methoxylmethylene-4-O-pivalyl-cyclopentane-1,2,3,4-tetraol (75)

To a solution of **74** (143.0 mg, 0.50 mmol) in 6 ml CH_2Cl_2 were added Hünig's base (350 µl, 2.00 mmol) and bromomethyl-methylether (82.0 µl, 1.01 mmol) and stirred for 50 hours at ambient temperature. The reaction mixture was washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **75** (103.4 mg, 0.32 mmol, 62.6%) as a colourless syrup.



$C_{17}H_{28}O_6$

MW: 328.40 g/mol

TLC: UV, VAN

R_f: 0.6 (C/EA 3:1 v/v)

SCG: (C/EA 20:1 v/v)

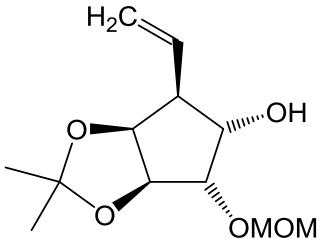
$[\alpha]_D^{20}$ = -65.2 (c 0.984, $CHCl_3$)

^{1}H NMR (300 MHz $CDCl_3$) δ= 5.86 (m, 1H, H-6), 5.13 (m, 2H, H-7a, H-7b), 5.02 (dd, 1H, $J_{1,2}$ 4.6 Hz, $J_{1,5}$ 11.4 Hz, H-1), 4.70-4.54 (m, 3H, H-4, O-C$\underline{H_2}$-O-CH_3), 4.44 (dd, 1H, $J_{3,4}$ 6.0 Hz, H-3), 4.13 (dd, 1H, $J_{1,2}$ 4.6 Hz, H-2), 3.33 (t, 3H, O-CH_2-O-C$\underline{H_3}$), 2.85 (m, 1H, H-5), 1.42, 1.25 (2t, 6H, C(C$\underline{H_3}$)$_2$), 1.15 (m, 9H, C(C$\underline{H_3}$)$_3$);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 178.0 (C=O), 134.0 (C-6), 118.4 (C-7), 110.7 (*C*$(CH_3)_3$), 96.5 (O-*C*H_2-O-CH_3), 81.9 (C-3), 78.7 (C-4), 78.4 (C-2), 75.0 (C-1), 55.7 (O-CH_2-O-*C*H_3), 49.1 (C-5), 38.8 (*C*$(CH_3)_3$), 27.2 (C(*C*$H_3)_3$), 26.0, 23.7 (C(*C*$H_3)_2$);

(1S,2S,3S,4S,5S)-5-C-ethylene-1,2-O-isopropylidene-3-O-methoxylmethylene--cyclopentane-1,2,3,4-tetraol (76)

To a solution of **75** (97.0 mg, 0.30 mmol) in 5 ml MeOH was added NaOMe (1M) (1.0 ml) and stirred for 24 hours at 60°C. The reaction mixture was diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **76** (58.9 mg, 0.26 mmol, 88.9%) as a colourless syrup.



$C_{12}H_{20}O_5$

MW: 244.29 g/mol

TLC: UV, VAN

R_f: 0.3 (C/EA 3:1 v/v)

SCG: (C/EA 16:1 v/v)

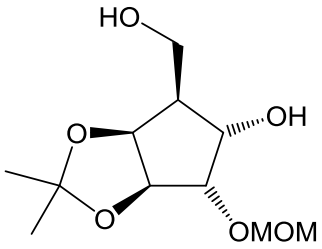
$[\alpha]_D^{20}$ = -118.8 (c 1.154, $CHCl_3$)

^{1}H NMR (300 MHz $CDCl_3$) δ= 5.93 (m, 1H, H-6), 5.24 (m, 2H, H-7a, H-7b), 4.73 (m, 2H, O-C$\underline{H_2}$-O-CH_3), 4.56 (dd, 1H, $J_{4,5}$ 5.7 Hz, H-4), 4.43 (dd, 1H, $J_{3,4}$ 5.9 Hz, H-3), 4.06 (dd, 1H, $J_{1,2}$ 4.4 Hz, $J_{1,5}$ 11.1 Hz, H-1), 3.92 (dd, 1H, $J_{1,2}$ 4.4 Hz, H-2), 3.39 (t, 3H, O-CH_2-O-C$\underline{H_3}$), 2.52 (m, 2H, H-5, OH), 1.40, 1.25 (2t, 6H, (C(C$\underline{H_3}$)$_2$);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 134.7 (C-6), 118.4 (C-7), 110.5 (*C*$(CH_3)_3$), 96.9 (O-*C*H_2-O-CH_3), 81.6 (C-2), 81.0 (C-3), 79.7 (C-4), 74.2 (C-1), 56.0 (O-CH_2-O-*C*H_3), 51.7 (C-5), 26.0, 23.7 (C(*C*H_3)$_2$);

(1S,2S,3S,4S,5S) -5-hydroxymethyl-1,2-O-isopropylidene-3-O-methoxylmethylene-cyclopentane-1,2,3,4-tetraol (77)

Through a stirred cooled (-20°C) solution of **76** (281.4 mg, 1.15 mmol) in 80 ml MeOH was bubbled O_3 for 180 minutes. After warming up to RT, N_2 was bubbled through the solution for 20 minutes before adding $NaBH_4$ (130.7 mg, 3.46 mmol) and stirred for additional 20 minutes. The reaction mixture was diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **77** (254.7 mg, 1.03 mmol, 89.1%) as a colourless oil.



$C_{11}H_{20}O_6$

MW: 248.27 g/mol

TLC: UV, VAN

R_f: 0.3 (C/EA 1:2 v/v)

SCG: (C/EA 2:1 v/v)

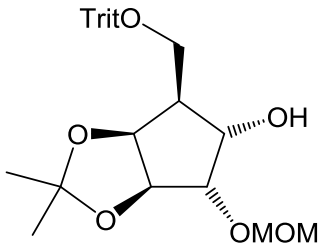
$[\alpha]_D^{20}$ = -61.9 (c 1,090, $CHCl_3$)

^{1}H NMR (300 MHz $CDCl_3$) δ= 4.79-4.66 (m, 3H, H-4, O-C$\underline{H_2}$-O-CH_3), 4.46 (dd, 1H, $J_{3,4}$ 6.4 Hz, H-3), 4.16 (dd, 1H, $J_{1,2}$ 4.5 Hz, $J_{1,5}$ 10.9 Hz, H-1), 4.04-3.86 (m, 3H, H-2, H-6a, H-6b), 3.40 (t, 3H, O-CH_2-O-C$\underline{H_3}$), 2.46 (bs, 2H, 2xOH), 2.09 (m, 1H, H-5), 1.41, 1.26 (2t, 6H, C(C$\underline{H_3}$)$_2$;

^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 110.8 (*C*$(CH_3)_3$), 97.0 (O-*C*H_2-O-CH_3), 81.8 (C-2), 81.2 (C-3), 78.7 (C-4), 72.6 (C-1), 61.0 (C-6), 56.0 (O-CH_2-O-*C*H_3), 48.0 C-5), 26.0, 23.7 (C(*C*$H_3)_2$);

(1S,2S,3S,4S,5S) -5-trityloxymethyl-1,2-O-isopropylidene-3-O-methoxylmethylene-cyclopentane-1,2,3,4-tetraol (78)

To a solution of **77** (41 mg, 0.17 mmol) in 10 ml CH2Cl2 was added pyridine (53 µl, 0.66 mmol), tritylchloride (60 mg, 0.21 mmol) and catalytic amounts of DMAP and stirred at RT for 48 hours. The reaction mixture was washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **78** (69.9 mg, 0.14 mmol, 86.3%) as a pale-yellow syrup.



$C_{30}H_{34}O_6$

MW: 490.60 g/mol

TLC: UV, VAN

R_f: 0.5 (C/EA 2:1 v/v)

SCG: (C/EA 10:1 v/v)

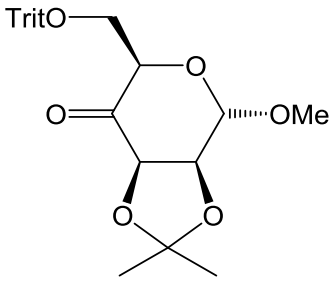
$[a]_D^{20}$ = -35.7 (c 1,205, $CHCl_3$)

^{1}H NMR (300 MHz $CDCl_3$) δ= 4.67 (m, 3H, H-2, O-C<u>H</u>$_2$-O-CH_3), 4.38 (dd, 1H, $J_{3,4}$ 6.0 Hz, H-3), 3.79 (m, 2H, H-1, H-4), 3.48 (dd, 1H, $J_{6a,6b}$ 8.6 Hz, H-6a), 3.32 (t, 3H, O-CH_2-O-C<u>H</u>$_3$), 3.25 (dd, 1H, $J_{6b,5}$ 6.4 Hz, $J_{6a,6b}$ 8.6 Hz, H-6b), 2.46 (bs, 1H, OH), 2.16 (m, 1H, H-5), 1.20, 1.19 (2t, 6H, C(C<u>H</u>$_3)_2$);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ= 144.3 (ipso Ar), 129.0, 127.8, 127.0 (Ar), 110.4 (*C*$(CH_3)_3$), 96.8 (O-*C*H_2-O-CH_3), 87.0 (*C*$(Ar)_3$), 81.4 (C-2), 81.3 (C-3), 77.7 (C-4), 73.7 (C-1), 62.0 (C-6), 55.9 (O-CH_2-O-*C*H_3), 47.2 (C-5), 26.1, 24.0 (C(*C*$H_3)_2$);

Methyl 4-deoxy-4-fluoro-4-C-(hydroxyl)methyl-2,3-O-isopropylidene-6-(triphenyl)methyl-α-D-mannopyranoside (155)

A solution of **151** (194 mg, 0.41 mmol) in CH_2Cl_2 (6 mL) was treated with Dess-Martin reagent (207 mg, 0.49 mmol) and stirred at ambient temperature for 2 hours. After completed conversion of the starting material, the reaction mixture was carefully quenched with saturated $NaHCO_3$. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain crude ulose **152** which had to be used without further purification in the next step



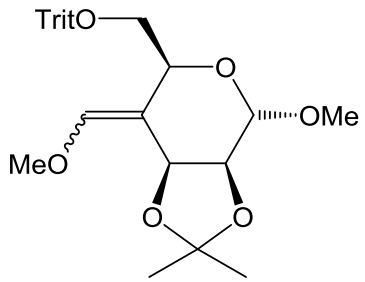
$C_{29}H_{30}O_6$

MW: 474.55 g/mol

TLC: UV, VAN

R_f: 0.5 (C/EA 3:1 v/v)

A solution of 2.5 M *n*-BuLi (0.54 mL, 1.34 mmol) in hexane was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (488.0 mg, 1.42 mmol) in dry THF (100 mL) under an atmosphere of nitrogen at -78°C. After stirring for 40 min at -20°C a solution of ulose **152** in dry THF (8 mL) was added dropwise, and the mixture was stirred for 18 h and allowed to reach ambient temperature. The reaction mixture was diluted with CH_2Cl_2 and consecutively washed with saturated NH_4Cl and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness to provide crude enolether **153** which was used in the next step without further purification.



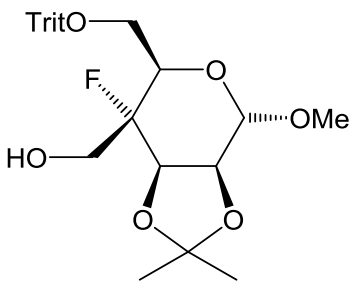
$C_{31}H_{34}O_6$

MW: 502.61 g/mol

TLC: UV, VAN

R_f: 0.7 (C/EA 3:1 v/v)

To a solution of crude compound **153** in MeCN/H_2O (6 mL, 5:1 v/v), Selectfluor® (216 mg, 0.61 mmol) was added and stirred at ambient temperature for 65 minutes. After completed conversion of the starting material (TLC) to highly unstable fluoro aldehyde **154**, the reaction mixture was neutralized with solid Na_2CO_3. The solvent was removed under reduced pressure and the remaining residue was diluted with MeOH (4 mL). The resulting suspension was sonicated and $NaBH_4$ (46.0 mg, 1.22 mmol,) was added carefully. After 2 h, the reaction mixture was diluted with CH_2Cl_2 and consecutively washed with HCl (2 *N*) and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The remaining residue was purified on silica gel (cyclohexane/ethyl acetate 8:1 v/v) to provide compound **155** (30.8 mg, 0.06 mmol, 14.9% from compound **151**) as pale yellow syrup.



$C_{30}H_{33}FO_6$

MW: 508.59 g/mol

TLC: UV, VAN

R_f: 0.3 (C/EA 3:1 v/v)

SCG: (C/EA 10:1 v/v)

$[a]_D^{20}$ = +15.1 (c 1.045, $CHCl_3$)

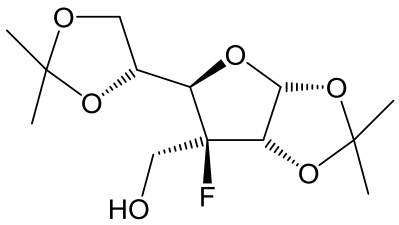
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.74 (s, 1H, H-1), 4.32 (dd, 1H, $J_{2,3}$ 7.2 Hz, $J_{3,F}$ 21.0 Hz, H-3), 4.17 (d, 1H, $J_{2,F}$ <1 Hz, H-2), 4.00 (m, 1H, H-5), 3.85-3.51 (m, 2H, H-1'a, H-1'b), 3.48 (s, 3H, OMe), 3.39 (m, 2H, H-6a, H-6b), 2.62 (bs, 1H, 1'OH);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ =143.8 (Ar), 128.8-127.3 (Ar), 109.7 ($C(CH_3)_2$), 99.1 (C-1), 92.9 ($J_{4,F}$ 179.7 Hz, C-4), 87.4 ($OC(Ph)_3$), 78.2 ($J_{3,F}$ 29.9 Hz, C-3), 76.5 ($J_{2,F}$ 8.0 Hz, C-2) 70.2 ($J_{5,F}$ 26.0 Hz, C-5), 62.1 ($J_{1',F}$ 22.0 Hz, C-1'), 61.6 (C-6), 55.7 (OMe), 26.1, 25.0 ($(CH_3)_2C$);

MS: Calcd for [$C_{30}H_{33}FO_6Na$]: *m/z* 531.2159 $[M+Na]^+$; found $[M+Na]^+$ 531.2635.

3-Deoxy-3-fluoro-3-C-hydroxymethyl-1,2; 5,6-di-Oisopropylidene-α-D-glucofuranose (141)

To a solution of **139** (183.9 mg, 0.64 mmol) in MeCN/H_2O (6 mL, 5:1 v/v), Selectfluor® (250 mg, 0.71 mmol) was added and stirred for 2 hours at ambient temperature. After completed conversion of the starting material (TLC) into highly unstable fluoroaldehyde **140**, the reaction mixture was neutralized with solid Na_2CO_3. The solvent was removed under reduced pressure and the remaining residue was diluted with MeOH (5 mL). The resulting suspension was sonicated and $NaBH_4$ (73.0 mg, 1.93 mmol) was added carefully. After 2 h, the reaction mixture was diluted with CH_2Cl_2 and consecutively washed with HCl (2 *N*) and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified on silica gel (cyclohexane/ethyl acetate 3:1 v/v) to obtain compound **141** (128.2 mg, 0.44 mmol, 68.3%) as a colourless syrup.



$C_{13}H_{21}FO_6$

MW: 292.30 g/mol

TLC: UV, VAN

R_f: 0.6 (C/EA 1:1 v/v)

SCG: (C/EA 3:1 v/v)

$[\alpha]_D^{20}$ = +27.5 (c 0.850, $CHCl_3$)

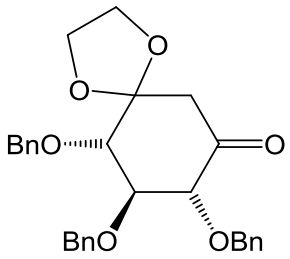
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.87 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.62 (dd, 1H, $J_{2,F}$ 11,2 Hz, H-2), 4.23 (m, 1H, H-5), 4.14-3.96 (m, 3H, H-6a, H-6b, H-1'a), 3.91 (dd, 1H, $J_{4,5}$ 2.2 Hz, $J_{4,F}$ 25.5 Hz, H-4), 3.88 (dd, 1H, $J_{1'a,1'b}$ 11.1 Hz, $J_{1'b,F}$ 25.2 Hz, H-1'b), 2.80 (bs, 1H, 1'OH)

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 113.2, 109.9 ($C(CH_3)_2$), 104.6 (C-1), 103.0 ($J_{3,F}$ 184.6 Hz, C-3), 83.7 ($J_{2,F}$ 37.0 Hz, C-2), 80.9 ($J_{4,F}$ 20.3 Hz, C-4), 71.7 ($J_{5,F}$ 6.6 Hz, C-5), 67.5 (C-6), 61.2 ($J_{1',F}$ 21.4 Hz, C-1'), 27.0, 26.8, 26.4, 25.2 ($CH_3)_2C$)

MS: Calcd (for molecular mass minus isopropylidene group which was invariantly lost) $[C_{10}H_{17}FO_6Na]$ *m/z* 275.0907 $[M+Na]^+$; found $[M+Na]^+$ 275.0877.

(2S)-(2,4/3)-2,3,4-tribenzyloxy-5-oxo-cyclohexanoneethylene acetal (160)

A solution of **159** (256.7 mg, 0.56 mmol) in CH_2Cl_2 (7 mL) was treated with Dess Martin reagent (260.1 mg, 0.61 mmol) and stirred at ambient temperature for 150 minutes. After completed conversion of the starting material, the reaction mixture was carefully quenched with saturated $NaHCO_3$. The organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification on silica gel (cyclohexane/ethyl acetate 6:1 v/v) gave compound **160** (250 mg, 0.53 mmol, 94.5%) as a pale yellow wax.



$C_{29}H_{30}O_6$

MW: 474.20 g/mol

TLC: UV, VAN

R_f: 0.8 (C/EA 1:1 v/v)

SCG: (C/EA 6:1 v/v)

$[\alpha]_D^{20}$ = -13.2 (c 0.990, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.00-4.54 (m, 6H, 3xCH_2Ph), 4.21-4.12 (m, 2H, H-2, O-C<u>H</u>H-CH_2-O), 4.09-3.96 (m, 3H, O-CH<u>H</u>-C<u>H</u>$_2$-O), 3.94 (d, 1H, $J_{3,4}$ 9.0 Hz, H-4) 3.85 (dd, 1H, $J_{2,3}$ 9.0 Hz, H-3), 2.76 (d, 1H, $J_{6a,6b}$ 13.9 Hz, H-6a), 2.57 (d, 1H, H6b);

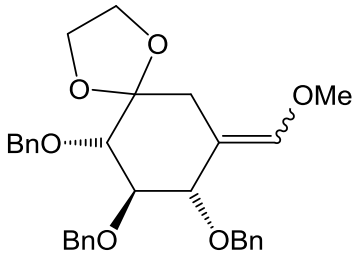
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 201.4 (C-5), 138.6, 138.4, 137.8 (Ar) 128.5-127.8 (Ar), 107.2 (C-1), 86.1 (C-2), 84.2 (C-4), 81.8 (C-3), 76.2, 76.1, 73.7 (*C*H_2Ph) 48.2 (C-6);

MS: Calcd for [$C_{29}H_{30}O_6Na$]: *m/z* 497.1940 $[M+Na]^+$; Found $[M+Na]^+$ 497.1974.

(2S,5S)-(2,4/3)-2,3,4-tribenzyloxy-5-fluoro-5-Chydroxymethyl-cyclohexanone ethylene acetal (163)

A solution of 2.5 M *n*-BuLi (633 µL, 1.58 mmol) in hexane was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (576 mg, 1.68 mmol) in dry THF (80 mL) under an atmosphere of nitrogen at -78°C. After stirring for 40 min at -20°C, a solution of carbonyl compound **160** (228.6 mg, 0,48 mmol) in dry THF (10 mL) was added dropwise, and the mixture was stirred for 18 h and allowed to reach ambient temperature.

The reaction mixture was diluted with CH_2Cl_2 and consecutively washed with saturated NH_4Cl and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude product was quickly passed through silica gel (cyclohexane/ethyl acetate 10:1 v/v) to provide unstable enol ether **161** (87.4 mg, 0.17 mmol, 36.1%, *E/Z* ca. 1:1) as a syrup.



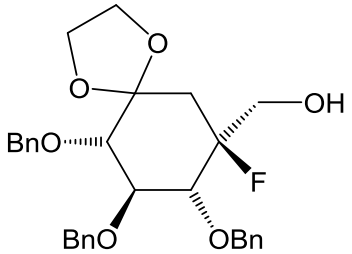
$C_{31}H_{34}O_6$

MW: 502.61 g/mol

TLC: UV, VAN

R_f: 0.5 (C/EA 3:1 v/v)

To a solution of intermediate **161** (68.3 mg, 0.14 mmol) in MeCN/H_2O (6 mL, 5:1 v/v), Selectfluor® (53 mg, 0.15 mmol,) was added and stirred for 30 minutes at ambient temperature. After complete conversion of the starting material (TLC) to highly unstable fluoro aldehyde **162**, the reaction was neutralized with solid Na_2CO_3. The solvent was removed under reduced pressure and the remaining residue was diluted with 5 ml MeOH. The resulting suspension was sonicated and $NaBH_4$ (10 mg, 0.27 mmol) was added carefully. After 2 h, the reaction mixture was diluted with CH_2Cl_2 and consecutively washed with HCl (2 *N*) and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification on silica gel (cyclohexane/ethyl acetate 5:1 v/v) gave compound **163** (15.1 mg, 0.03 mmol, 21.8%) as a colorless syrup.



$C_{30}H_{33}FO_6$

MW: 508.59 g/mol

TLC: UV, VAN

R_f: 0.6 (C/EA 1:1 v/v)

SCG: (C/EA 5:1 v/v)

$[a]_D^{20}$ = -17.7 (c 1.180, $CHCl_3$)

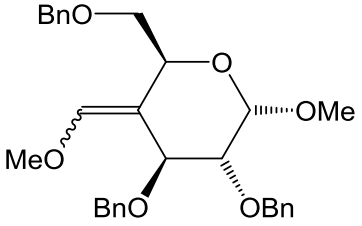
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.25-3.80 (m, 7H, O-CH2-CH2-O, H-1'a, H-1'b, H-4), 3.68 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ 9.6 Hz, H-3), 3.67-3.63 (m, 1H, H-2), 2.45, (dd, 1H, $J_{6a,6b}$ 13.7 Hz, $J_{6a,F}$ 1.5 Hz, H-6a) l.86 (dd, 1H, $J_{6b,F}$ 13.7 Hz, H-6b);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.6, 138.4, 138.2 (Ar), 128.5-127.7 (Ar) 107.3 ($J_{1,F}$ 17.7 Hz, C-1), 97.6 ($J_{5,F}$ 177.7 Hz, C-5), 85.8 ($J_{4,F}$ 19.0 Hz, C-4), 84.4 (C-2), 81.7 ($J_{3,F}$ 12.4 Hz, C-3), 76.3, 75.9, 75.8 (CH_2Ph) 64.1 ($J_{1',F}$ 24.8 Hz, C-1'), 38.1 ($J_{6,F}$ 21.7 Hz, C-6);

MS: Calcd for [$C_{30}H_{33}FO_6Na$]: *m/z* 531.2159 $[M+Na]^+$; Found $[M+Na]^+$ 531.2136.

Methyl 2,3,6-tri-O-benzyl-4-deoxy-4-fluoro-4-C-hydroxymethyl-α-D-glucopyranoside (146)

A solution of 2.5 M *n*-BuLi (0.79 mL, 1.96 mmol) in hexane was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (714 mg, 2.08 mmol,) in dry THF (80 mL) at -78°C under an atmosphere of nitrogen. After stirring for 40 min at -20°C a solution of carbonyl compound **143** (275.4 mg, 0.60 mmol) in dry THF (8 mL) was added dropwise, and the mixture was stirred for 18 h while warming to ambient temperature. The reaction was diluted with CH_2Cl_2 and consecutively washed with saturated NH_4Cl and saturated aqu. $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. Highly unstable product **144** had to be employed for the next step without further purification.



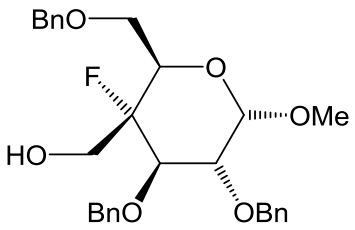
$C_{30}H_{34}O_6$

MW: 490.60 g/mol

TLC: UV, VAN

R_f: 0.4 (C/EA 3:1 v/v)

To a solution of **144** in MeCN/H_2O (6 mL, 5:1 v/v), Selectfluor® (316.4 mg, 0.89 mmol) was added at ambient temperature and stirred for 60 minutes. After completed conversion of the starting material (TLC) to highly unstable fluoroaldehyde **145**, the reaction mixture was neutralized with solid Na_2CO_3. The solvent was removed under reduced pressure and the remaining residue was diluted with MeOH (5 mL). The resulting suspension was sonicated and $NaBH_4$ (68 mg, 1.79 mmol) was added carefully. After 2 h, the reaction mixture was diluted with CH_2Cl_2 and consecutively washed with HCl (2 *N*) and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification on silica gel (cyclohexane/ethyl acetate 20:1 v/v) gave compound **146** (57.6 mg, 0.12 mmol, 19.5% from compound **143**) as a white wax.



$C_{29}H_{33}FO_6$

MW: 496.58 g/mol

TLC: UV, VAN

R_f: 0.4 (C/EA 2:1 v/v)

SCG: (C/EA 20:1 v/v)

$[\alpha]_D^{20}$ = +28.9 (c 1.028, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.61 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 4.12 (dd, 1H, $J_{2,3}$ 10.2 Hz, $J_{3,F}$ 15.8 Hz, H-3), 4.05 (m, 1H, H-1'a), 4.02-3.96 (m, 2H, H-5, H-1'b), 3.86-3.75 (m, 2H, H-6a, H-6b), 3.74 (dd, 1H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 10,2 Hz, H-2), 3.42 (s, 3H, OMe);

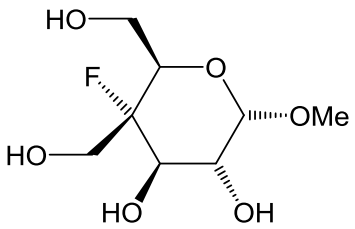
^{13}C NMR (75.5 MHz, $CDCl_3\delta$ = 138.2, 138.1, 137.3 (Ar), 128.6-127.8 (Ar), 98.2 (C-1), 94.7 ($J_{4,F}$ 186.0 Hz, C-4), 82.4 ($J_{3,F}$ 18.3 Hz, C-3), 77.8 ($J_{2,F}$ 9.8 Hz, C-2), 76.0, 74.0, 73.9 (CH_2Ph), 70.0 ($J_{5,F}$ 26.9 Hz, C-5), 67.3 (C-6), 60.2 ($J_{1',F}$ 28.1 Hz, C-1'), 55.5 (OMe);

MS: Calcd for [$C_{29}H_{33}FO_6$Na]: *m/z* 519.2159 $[M+Na]^+$; Found $[M+Na]^+$ 519.2117.

Methyl 4-deoxy-4-fluoro-4-C-hydroxymethyl-α-Dglucopyranoside (146a)

To a solution of compound **146** (57.6 mg, 0.12 mmol) in MeOH (3 mL), $Pd(OH)_2$/C (20%, 50 mg) was added and the mixture was stirred under an atmosphere of hydrogen at ambient pressure for 14 h. The catalyst was removed by filtration and washed with MeOH. The

solvent was removed under reduced pressure and the remaining residue was chromatographed on silica gel (ethyl acetate/MeOH 10:1 v/v) to give compound **146a** (23.1 mg, 0.10 mmol, 88.0%). Recrystallization from ethyl acetate/MeOH afforded hygroscopic colorless crystals.



$C_8H_{15}FO_6$

MW: 226.20 g/mol

TLC: UV, CAM

R_f: 0.3 (EA/MeOH 10:1 v/v)

SCG: (EA/MeOH 10:1 v/v)

$[\alpha]_D^{20}$ = +111.6 (c 1.350, H_2O)

m.p.: 86-88°C

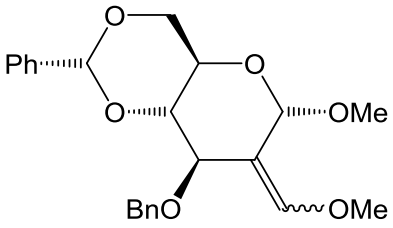
^{1}H NMR (300 MHz, D_2O): δ = 4.80 (d, 1H, $J_{1,2}$ 3.7 Hz, (H-1), 4.04-3.67 (m, 6H, H-3, H-5, H-6a, H-6b, H-1'a, H-1'b), 3.60 (dd, 1H, $J_{2,3}$ 10.2 Hz, H-2), 3.35 (s, 3H, OMe);

^{13}C NMR (75.5 MHz, D_2O): δ = 98.7 (C-1), 94.6 ($J_{4,F}$ 182.9 Hz, C-4), 73.6 ($J_{5,F}$ 19.3 Hz, C-5), 71.8 ($J_{3,F}$ 27.4 Hz, C-3), 69.8 ($J_{2,F}$ 8.1 Hz, C-2), 59.5 (C-6), 57.4 ($J_{1',F}$ 23.1 Hz, C-1'), 55.1 (OMe);

MS: Calcd for $[C_8H_{15}FO_6H]$: *m/z* 227.0931 $[M+H]^+$; found $[M+H]^+$ 227.0948.

1,5-Anhydro-3-O-benzyl-4,6-O-benzylidene-2-C-hydroxymethyl-D-arabino-hex-1-enitol (150)

A solution of 2.5 M *n*-BuLi (1.73 mL, 4.32 mmol) in hexane was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (1.57 g, 4.59 mmol) in dry THF (120 mL) at -78°C under an atmosphere of nitrogen. After stirring for 40 min at -20°C a solution of carbonyl compound **148** (485.4 mg, 1.31 mmol) in dry THF (12 mL) was added dropwise, and the mixture was stirred for 18 h and allowed to warm to ambient temperature. The reaction mixture was diluted with CH_2Cl_2 and consecutively washed with saturated NH_4Cl and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. Highly unstable product **149** had to be employed for the next step without further purification.



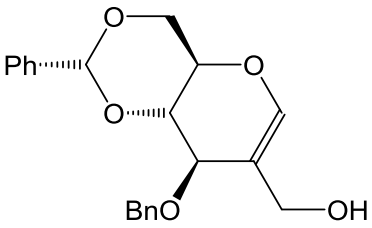
$C_{23}H_{26}O_6$

MW: 398.17 g/mol

TLC: UV, VAN

R_f: 0.5, (C/EA 2:1 v/v)

To a solution of intermediate **149** in MeCN/H_2O (12 mL, 5:1 v/v), Selectfluor® (580.3 mg, 1.64 mmol) was added and stirred at ambient temperature for 30 minutes. After completed conversion of the starting material (TLC) the reaction mixture was neutralized with solid Na_2CO_3. The solvent was removed under reduced pressure and the remaining residue was diluted with MeOH (6 ml). The resulting suspension was sonicated and $NaBH_4$ (100 mg, 2.62 mmol) was added carefully. After 2 h, the reaction mixture was diluted with CH_2Cl_2 and consecutively washed with HCl (2 *N*) and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification on silica gel (cyclohexane/ethyl acetate 6:1 v/v) gave compound **150** (250.3 mg, 0.70 mmol, 53.9% over 3 steps) as a white solid.



$C_{21}H_{22}O_5$

MW: 354.40 g/mol

TLC: UV, VAN

R_f: 0.3, (C/EA 2:1 v/v)

SCG: (C/EA 6:1 v/v)

$[\alpha]_D^{20}$ = +20.7 (c 1.440, $CHCl_3$)

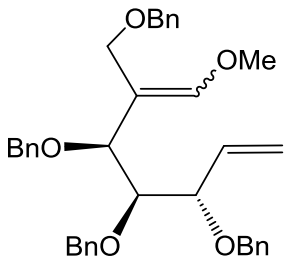
^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.46 (s, 1H, H-1), 4.54 (d, 1H, $J_{3,4}$ 7.0 Hz, H-3), 4.40 (dd, 1H, $J_{5,6a}$ 3.3 Hz, $J_{6a,6b}$ 8.9 Hz, H-6a), 4.13 (dd, 1H, $J_{4,5}$ 9.9 Hz, H-4), 4.09, (d, 1H, $J_{1'a,1'b}$ 12.2 Hz, H-1'a) 4.04 (d, 1H, H-1'b), 3.93 (ddd, 1H, $J_{5,6b}$ 10.2 Hz, H-5), 3.88 (d, 1H, H-6b), 2.44 (bs, 1H, 1'-OH);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.1, 137.3 (Ar), 129.2-126.1 (Ar), 143.8 (C-1), 113.5 (C-2), 101.2 (O_2*C*HPh), 80.9 (C-4), 75.1 (C-3), 74.0 (*C*H_2Ph), 68.8 (C-5), 68.4 (C-6), 61.2 (C-1');

MS: Calcd for [$C_{21}H_{22}O_5Na$]: *m/z* 377.1365 $[M+Na]^+$; Found $[M+Na]^+$ 377.1350.

3,4,5,7-Tetra-O-benzyl-1,2,6-trideoxy-6-fluoro-6-C-hydroxymethyl-D-galacto-hept-1-enitol (158)

A solution of 2.5 M *n*-BuLi (0.73 mL, 1.83 mmol) in hexane was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (660 mg, 1.93 mmol) in dry THF (80 mL) under an atmosphere of nitrogen at -78°C. After stirring for 40 min at -20°C, a solution of carbonyl compound **6** (295.2 mg, 0.55 mmol) in dry THF (8 mL) was added dropwise, and the mixture was stirred for 18 h and allowed to reach ambient temperature. The reaction mixture was diluted with CH_2Cl_2 and consecutively washed with saturated NH_4Cl and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. The resulting crude product was quickly passed through silica gel (cyclohexane/ethyl acetate 10:1 v/v) to provide unstable enol ether **156** (87.4 mg, 0.17 mmol, 36.1%, *E/Z* ca. 1:1) as a colorless syrup.



$C_{37}H_{40}O_5$

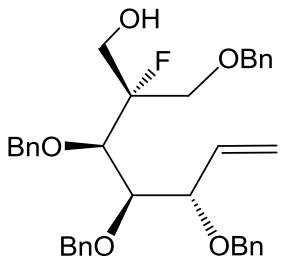
MW: 564.72 g/mol

TLC: UV, VAN

R_f: 0.7, (C/EA 3:1 v/v)

SCG: (C/EA 50:1 v/v)

To a solution of compound **156** (201 mg, 0.36 mmol) in MeCN/H_2O (6 mL, 5:1 v/v), Selectfluor® (151 mg, 0.43 mmol) was added at ambient temperature and stirred for 60 minutes. After completed conversion of the starting material (TLC) to highly unstable fluoroaldehyde **157**, the reaction was neutralized with solid Na_2CO_3. The solvent was removed under reduced pressure and the remaining residue was diluted with MeOH (4 ml). The resulting suspension was sonicated and $NaBH_4$ (40.4 mg, 1.07 mmol) was added carefully. After 2 h, the reaction mixture was diluted with CH_2Cl_2 and consecutively washed with HCl (2 *N*) and saturated $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification on silica gel (cyclohexane/ethyl acetate 10:1 v/v) gave compound **158** (120.5 mg, 0.22 mmol, 61.3%) as white crystals. Recrystallistation with cyclohexane/ethyl acetate afforded colorless crystals.



$C_{36}H_{39}FO_5$

MW: 570.70 g/mol

TLC: UV, VAN

R_f: 0.5, (C/EA 3:1 v/v)

SCG: (C/EA 10:1 v/v)

$[\alpha]_D^{20}$ = -15.8 (c 1.000, $CHCl_3$)

m.p.: 69-71°C

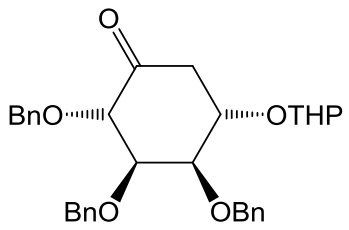
^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.87 (ddd, 1H, $J_{1,2E}$ 17.2 Hz, $J_{1,2Z}$ 10.2 Hz, $J_{2,3}$ 7.0 Hz, H-2), 5.45 (d, 1H, H-1*E*), 5.35 (d, 1H, H1*Z*), 4.31 (dd, 1H, $J_{3,F}$ <1 Hz, H-3), 4.19 (dd, 1H, $J_{4,5}$ 4.4 Hz, $J_{5,F}$ 7.0 Hz, H-5), 3.97 (ddd, 1H, $J_{1'a,1'b}$ 12.8 Hz, $J_{1'a,OH}$ 5.1 Hz, $J_{1'a,F}$ 22.8 Hz, H-1'a) 3.88 (m, 1H, H-4), 3.81-3.60 (m, 3H, H-7a, H-7b, H-1'b), 3.42 (dd, 1H, $J_{F,OH}$ 9.1 Hz, 1'-OH);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.7, 138.0 (Ar), 135.7 (C-2), 128.5-127.6 (Ar), 119.0 (C-1), 99.2 ($J_{6,F}$ 179.1 Hz, C-6), 82.8 (C-4), 81.4 ($J_{3,F}$ 5.4 Hz, C-3), 77.4 ($J_{5,F}$ 11.9 Hz, C-5), 76.3, 73.8, 73.4, (*C*H_2Ph), 71.0 ($J_{7,F}$ 23.3 Hz, C-7), 70.9 (*C*H_2Ph), 62.6 ($J_{1',F}$ 23.3 Hz, C-1');

MS: Calcd for [$C_{36}H_{39}FO_5Na$]: *m/z* 593.2679 $[M+Na]^+$; Found $[M+Na]^+$ 593.2667.

(2S,3R,4R,5S)-2,3,4-Tri-benzyloxy-5-tetrahydropyranyloxy-cyclohexanone (59)

To a solution of **58** (2.91 g, 6.73 mmol) in 30 ml CH_2Cl_2 was added DHP (0.74 ml, 8.07 mmol), pPTS (15 mg) and stirred for 19 hours at ambient temperature. The reaction mixture was washed with saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded an inseperable mixture of **59** (R/S) (3.16 g, 6.12 mmol, 90.9%) as a pale yellow syrup.



$C_{32}H_{36}O_6$

MW: 516.63 g/mol

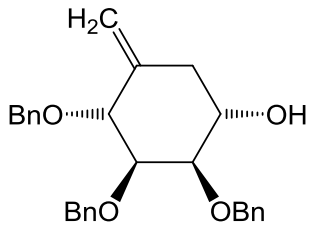
TLC: UV, VAN

R_f: 0.4, (C/EA 3:1 v/v)

SCG: (C/EA 10:1 v/v)

2,3,4-Tri-O-benzyl-6-deoxy-5a-carba-α-D-lyxo-hex-5-enopyranoside(60)

To a freshly prepared solution of (trimethylsilylmethyl)magnesiumchloride (4.5 g, 30.6 mmol) in 80 ml Et_2O was added **59** (3.16 g, 6.12 mmol) in 10 ml Et_2O at ambient temperature and stirred for 30 minutes. The reaction mixture was washed consecutively with saturated NH_4Cl and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. The resulting residue was dissolved in CH_2Cl_2/MeOH/H_2O 10:5:1 (112 ml), pTSA (250 mg) was added and stirred at ambient temperature for 21 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **60** (2.19 g, 5.09 mmol, 83.2%) as a colourless syrup.



$C_{28}H_{30}O_4$

MW: 430.54 g/mol

TLC: UV, VAN

R_f: 0.4, (C/EA 3:1 v/v)

SCG: (C/EA 10:1 v/v)

$[a]_D^{20}$ = +44.1 (c 1.120, $CHCl_3$)

^{1}H NMR (300 MHz $CDCl_3$): δ = 5.12 (s, 1H, H-6A), 4.98 (s, 1H, H-6B), 4.59-4.39 (m, 5H, C$\underline{H_2}$Ar), 4.21 (d, 1H, C$\underline{H_2}$Ar), 4.00-3.89 (m, 2H, H-1, H-4), 3.87 (dd, 1H, $J_{2,3}$ 3.0 Hz, H-2), 3.70 (dd, 1H, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 8.9 Hz, H-3), 2.52 (dd, 1H, $J_{5aA,5aB}$ 13.3 Hz, $J_{1,5aA}$ 5.2 Hz, H-5aA), 2.38 (d, 1H, $J_{1,OH}$ 1.5 Hz, OH), 2.26 (dd, 1H, H-5aB);

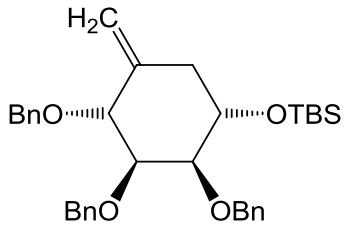
^{13}C NMR (75.5 MHz $CDCl_3$): δ = 141 (C-5), 138.6, 138.4, 138.3 (3x ipso Ar), 128.6-127.6 (Ar), 117.4 (C-6), 81.7 (C-3), 79.9 (C-4), 76.1 (C-2), 72.5, 72.1, 69.9 (3x CH_2Ar), 68.9 (C-1), 36.2 (C-5a).

MS: Calcd for [$C_{28}H_{30}O_4Na$]: *m/z* 453.2042 $[M+Na]^+$; Found $[M+Na]^+$ 453.2066.

tert-Butyldimethylsilyl-2,3,4-tri-O-benzyl-6-deoxy-5a-carba-α-D-lyxo-hex-5-enopyranosid (61)

To a solution of **60** (2.12 g, 4.92 mmol) in DMF (30 ml) was added imidazole (590 mg, 8.62 mmol) and TBSCl (1.11 g, 7.39 mmol) and stirred at ambient temperature for 14 hours. The

reaction mixture was diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **61** (2.64 g, 4.85 mmol, 98.4%) as a colourless syrup.



$C_{34}H_{44}O_4Si$

MW: 544.81 g/mol

TLC: UV, VAN

R_f: 0.8, (C/EA 3:1 v/v)

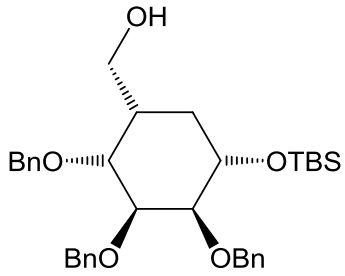
SCG: (C/EA 10:1 v/v)

$[\alpha]_D^{20}$ = +1.2 (c 0.770, $CHCl_3$)

^{1}H NMR (300 MHz $CDCl_3$): δ = 5.08 (s, 1H, H-6A), 4.96 (s, 1H, H-6B), 4.76-4.43 (m, 6H, C$\underline{H_2}$Ar), 4.06 (dd, 1H, $J_{3,4}$ 6.4 Hz, H-4), 3.92 (m, 1H, H-1), 3.76 (dd, 1H, $J_{2,3}$ 2.8 Hz, $J_{3,4}$ 6.4 Hz, H-3), 3.65 (dd, 1H, $J_{1,2}$ 6.6 Hz, $J_{2,3}$ 2.8 Hz, H-2), 2.48 (dd, 1H, $J_{1,5aA}$ 3.8 Hz, $J_{5aA,5aB}$ 13.7 Hz, H-5aA), 2.23 (dd, 1H, $J_{1,5aB}$ 7.0 Hz, H-5aB), 0.82 (m, 9H, $Si(CH_3)_2C(C\underline{H_3})_3$), 0.00, -0.07 (2t, $Si(C\underline{H_3})_2C(CH_3)_3$);
^{13}C NMR (75.5 MHz $CDCl_3$): δ = 142.1 (C-5), 139.2, 139.2, 138.8 (3x ipso Ar), 128.4-127.5 (Ar), 113.2 (C-6), 81.0 (C-2), 80.8 (C-4), 79.6 (C-3), 73.4, 73,4 (CH_2Ar), 71.7 (CH_2Ar), 70.0 (C-1), 38.2 (C-5a), 25.9 ($Si(CH_3)_2C(\mathit{C}H_3)_3$), 18.1 ($Si(CH_3)_2\mathit{C}(CH_3)_3$), -4.7, -4.7 ($Si(\mathit{C}H_3)_2C(CH_3)_3$);
MS: Calcd for [$C_{34}H_{44}O_4SiNa$]: *m/z* 567.2906 $[M+Na]^+$; Found $[M+Na]^+$ 567.2950.

tert-Butyldimethylsilyl-2,3,4-tri-O-benzyl-5a-carba-β-L-gulopyranosid (62)

Following general procedure C compound **61** (2.52 g, 4.63 mmol) was treated with BH_3*THF (9.25 ml, 9.25 mmol). Purification on silica gel afforded **62** (2.48 g, 4.41 mmol, 95.3%) as a colourless syrup.



$C_{34}H_{46}O_5Si$

MW: 562.82 g/mol

TLC: UV, VAN

R_f: 0.5, (C/EA 3:1 v/v)

SCG: (C/EA 10:1 v/v)

$[\alpha]_D^{20}$ = +7.1 (c 1.505, $CHCl_3$)

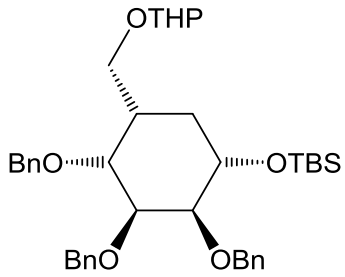
^{1}H NMR (300 MHz $CDCl_3$): δ = 4.75-4.42 (m, 4H, C$\underline{H}_2$Ar), 4.27-4.11 (m, 2H, C$\underline{H}_2$Ar), 3.97 (m, 1H, H-1), 3.69 (dd, 1H, $J_{2,3}$ 2.5 Hz, $J_{3,4}$ 4.2 Hz, H-3), 3.59 (dd, 1H, H-4), 3.55-3.46 (m, 2H, H-6A, H-6B), 3.43 (dd, 1H, $J_{1,2}$ 8.7 Hz, $J_{2,3}$ 2.5 Hz, H-2), 2.05-1.88 (m, 2H, H-5, OH), 1.63-1.47 (m, 9H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.00, -0.01 (2t, 6H, $Si(C\underline{H}_3)_2C(CH_3)_3$);

^{13}C NMR (75.5 MHz $CDCl_3$): δ = 139.4, 139.0, 138.1 (3x ipso Ar), 128.6-127.5 (Ar), 81.5 (C-2), 77.9 (C-4), 75.7 (C-3), 73.6, 73.4, 72.2 (CH_2Ar), 70.5 (C-1), 64.8 (C-6), 37.2 (C-5), 31.8 (C-5a), 26.0 ($Si(CH_3)_2C(\mathit{C}H_3)_3$), 18.2 ($Si(CH_3)_2\mathit{C}(CH_3)_3$), -4.4, -4.6 ($Si(\mathit{C}H_3)_2C(CH_3)_3$);

MS: Calcd for [$C_{34}H_{46}O_5SiNa$]: *m/z* 585.3012 $[M+Na]^+$; Found $[M+Na]^+$ 585.3037.

tert-Butyldimethylsilyl-2,3,4-tri-O-benzyl-5a-carba-6-O-tetrahydropyranyl-β-L-gulopyranosid (63)

To a solution of **62** (1.32 g, 2.35 mmol) in 10 ml CH_2Cl_2 was added DHP (150 µl, 1.61 mmol), pPTS (20mg) and stirred for 17 hours at ambient temperature. The reaction mixture was washed with saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded an inseperable mixture of **63** (R/S) (1.41 g, 2.18 mmol, 92.9%) as a pale yellow syrup.



$C_{34}H_{46}O_5Si$

MW: 646.94 g/mol

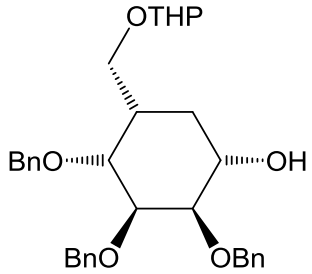
TLC: UV, VAN

R_f: 0.7, (C/EA 3:1 v/v)

SCG: (C/EA 16:1 v/v)

2,3,4-tri-O-benzyl-5a-carba-6-O-tertahydropyranyl-β-L-gulopyranosid (64)

To a solution of **63** (1.53 g, 2.37 mmol) in THF was added TBAF*$3H_2O$ and stirred for 17 hours at ambient temperature. After complete cleavage of the silyl ether, the reaction mixture was diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded an inseperable mixture of **65** (R/S) (1.13 g, 2.12 mmol, 89.7%) as a colourless syrup



$C_{33}H_{40}O_6$

MW: 532.68 g/mol

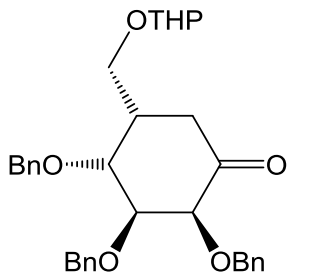
TLC: UV, VAN

R_f: 0.3, (C/EA 3:1 v/v)

SCG: (C/EA 10:1 v/v)

N-Dodecyl-α-L-gulo-validamine (67)

A solution of **64** (502.4 mg, 0.94 mmol) in 10 ml CH_2Cl_2 was treated with Dess Martin reagent (420.0 mg, 0.99 mmol) and stirred at ambient temperature for 80 minutes. After completed conversion of the starting material, the reaction mixture was carefully quenched with saturated $NaHCO_3$. The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification on silica gel afforded **65** (399.4 mg, 0.75 mmol, 79.8%) as a colourless syrup.



$C_{33}H_{38}O_6$

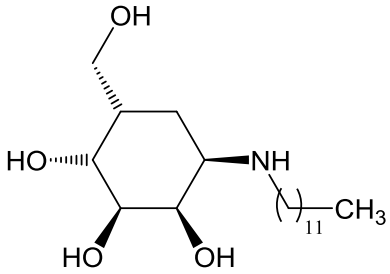
MW: 530.66 g/mol

TLC: UV, VAN

R_f: 0.4, (C/EA 3:1 v/v)

SCG: (C/EA 10:1 v/v)

To a solution of **65** (164,0 mg, 0.31 mmol) in 5 ml MeOH, dodecylamine (74.0 mg, 0.40 mmol) was added and stirred for 30 minutes at ambient temperature. Pd/C (5%) was added and stirred for 22 hours under an atmosphere of H_2 at ambient temperature. After filtration of the catalyst, 1 ml HCl (2N) was added and stirred for 21 hours at 40 °C. The reaction mixture was evaporated to dryness. Purification on silica gel gave **67** (46.7 mg, 0.14 mmol, 43.7%) as a colourless wax.



$C_{19}H_{39}NO_4$

MW: 345.52 g/mol

TLC: UV, CAM

R_f: 0.3 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[a]_D^{20}$ = -7.0 (c 0.775, MeOH)

^{1}H NMR (300 MHz MeOH-d_4) δ = 3.96 (dd, 1H, $J_{2,3}$ 2.6 Hz, H-2), 3.89 (dd, 1H, $J_{4,5}$ 3.1 Hz, $J_{3,4}$ 5.3 Hz, H-4), 3.75 (dd, 1H, $J_{2,3}$ 2.6 Hz, $J_{3,4}$ 5.3 Hz, H-3), 3.60 (dd, 1H, $J_{5,6A}$ 6.2 Hz, $J_{6A,6B}$ 10.7 Hz, H-6A), 3.44 (dd, 1H, $J_{5,6B}$ 7.0 Hz, H-6B), 3.40 (m, 1H, H-1), 2.98 (m, 2H, H-1'), 2.00 (m, 1H, H-5), 1.83-1.72 (m, 3H, H-2', H-5'A), 1.33-1.10 (m, 17H, H-3', H-4', H-5'B, H-6', H-7', H-8', H-9', H-10', H-11'), 0.78 (t, 3H, H-12');

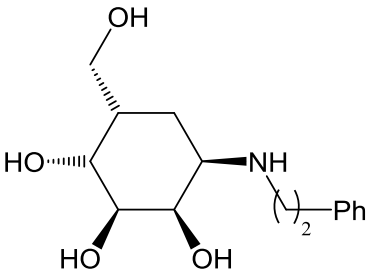
^{13}C NMR (75.5 MHz MeOH-d_4) δ = 74.1 (C-3), 70.9 (C-4), 66.9 (C-2), 63.0 (C-6), 59.3 (C-1), 47.9 (C-1'), 34.9 (C-5), 33.0, 30,7, 30.7, 30.6, 30.5, 30.4, 30.2, 27.6, 27.0 (C-2', C-3', C-4', C-5', C-6', C-7', C-8', C-9', C-10'), 24.1 (C-5a), 23.7 (C-11'), 14.4 (C-12');

MS: Calcd for [$C_{19}H_{39}NO_4$H]: *m/z* 346.2957 $[M+H]^+$; Found $[M+H]^+$ 346.2972.

N-Phenethyl-α-L-gulo-validamine (68)

To a solution of **65** (200.1 mg, 0.38 mmol) in 6 ml MeOH, phenethylamine (60.0 µl, 0.49 mmol) was added and stirred for 30 minutes at ambient temperature. Pd/C (5%) was added and stirred for 22 hours under an atmosphere of H_2 at ambient temperature. After filtration of the catalyst, 1 ml HCl (2N) was added and stirred for 21 hours at 40 °C. The reaction

mixture was evaporated to dryness. Purification on silica gel gave **68** (51.6 mg, 0.18 mmol, 48.6%) as a colourless syrup.



$C_{15}H_{23}NO_4$

MW: 281.35 g/mol

TLC: UV, CAM

R_f: 0.3 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

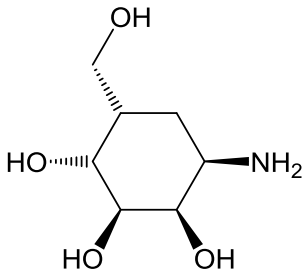
SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[a]_D^{20}$ = -8.1 (c 1,310, MeOH)

^{13}C NMR (75.5 MHz MeOH-d_4) δ = 137.7 (ipso Ar), 130.1, 129.8, 128.3 (Ar), 74.2 (C-3), 70.9 (C-4), 66.7 (C-2), 63.2 (C-6), 59.9 (C-1), 48.0 (C-1'), 34.3 (C-5), 33.1 (C-2'), 23.9 (C-5a);
MS: Calcd for [$C_{15}H_{23}NO_4$H]: *m/z* 282.1705 $[M+H]^+$; Found $[M+H]^+$ 282.1696.

N-Dansyl-α-L-gulo-validamine (69)

To a solution of **65** (303.1 mg, 0.57 mmol) in 30 ml MeOH, benzylamine (540 µl, 2.86 mmol) was added and stirred for 30 minutes at ambient temperature. $Pd(OH)_2$/C (20%) was added and stirred for 18 hours under an atmosphere of H_2 at ambient temperature. After filtration of the catalyst, 3 ml HCl (2N) were added. The reaction mixture was evaporated to dryness. Purification on silica gel gave **66** (72.8 mg, 0.41 mmol, 71.9%) as a colourless syrup.



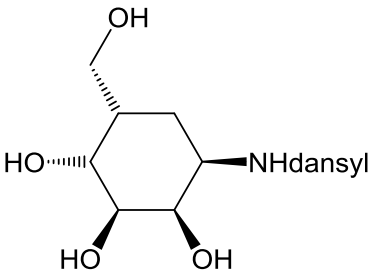
$C_7H_{15}NO_4$

MW: 177.20 g/mol

TLC: UV, CAM

R_f: 0.4 ($CHCl_3$/MeOH/NH_4OH 1:2:1 v/v/v)

Following general procedure F compound **66** (10.1 mg, 0.06 mmol) was treated with Na_2CO_3 (12.0 mg, 0.14 mmol) and dansyl chloride (18.0 mg, 0.07 mmol) and stirred for 23 hours. Purification on silica gel afforded **69** (15.0 mg, 0.04 mmol, 64.1%) as a pale yellow syrup.



$C_{19}H_{26}N_2O_6$

MW: 410.48 g/mol

TLC: UV, CAM

R_f: 0.7 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

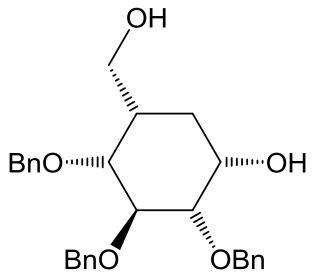
$[a]_D^{20}$ = +4.1 (c 0.950, MeOH)

^{13}C NMR (75.5 MHz MeOH-d_4) δ = 74.8 (c-3), 71.6 (C-3), 68.6 (C-2), 63.4 (C-6), 55.2 (C-1), 45.8 (NMe_2),34.8 (C-5), 27.9 (C-5a);

MS: Calcd for [$C_{19}H_{26}N_2O_6SNa$]: *m/z* 433.1409 $[M+Na]^+$; Found $[M+Na]^+$ 433.1413.

2,3,4-tri-O-benzyl-5a-carba-β-L-idopyranose (45)

To a solution of **44** (425.0 mg, 0.76 mmol) in 20 ml THF was added TBAF*3H_2O (477.0 mg, 1.51 mmol) and stirred for 40 hours at ambient temperature. After complete cleavage of the silyl ether, the reaction mixture was diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **45** (269.0 mg, 0.60 mmol, 79.4%) as a colourless syrup.



$C_{28}H_{32}O_5$

MW: 448.56 g/mol

TLC: UV, VAN

R_f: 0.3, (C/EA 1:1 v/v)

SCG: (C/EA 10:1 v/v)

$[a]_D^{20}$ = +7.4 (c 1.565, $CHCl_3$)

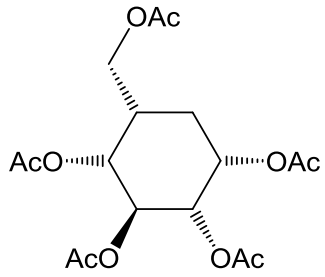
^{1}H NMR (300 MHz $CDCl_3$) δ = 4.72-4.45 (m, 6H, $C\underline{H_2}Ar$), 3.91 (m, 2H, H-1, H-3), 3.80-3.62 (m, 2H, H-6A, H-6B), 3.54 (dd, 1H, $J_{3,4}$ 7.5 Hz, $J_{4,5}$ 5.0 Hz, H-4), 3.41 (dd, 1H, $J_{1,2}$ 3.5 Hz, $J_{2,3}$ 7.4 Hz, H-2), 2.91 (bs, 1H, OH), 2.76 (bs, 1H, OH), 2.15 (m, 1H, H-5), 1.87 (m, 1H, H-5aA), 1.45 (m, 1H, H-5aB);

^{13}C NMR (75.5 MHz $CDCl_3$) δ = 138.7, 138.3, 138.2 (3x ipso Ar), 128.6-127.8 (Ar), 81.4 (C-2), 80.6 (C-4), 77.4 (C-3), 74.9, 73.0, 72.9 (3x CH_2Ar), 67.4 (C-1), 63.9 (C-6), 38.3 (C-5), 28.9 (C-5a);

MS: Calcd for $[C_{28}H_{32}O_5Na]$: *m/z* 471.2148 $[M+Na]^+$; Found $[M+Na]^+$ 471.2155.

1,2,3,4,6-penta-O-acetyl-5a-carba-β-L-idopyranose (47)

To a solution of **45** (130.0 mg, 0.29 mmol) in 5 ml MeOH was added $Pd(OH)_2/C$ (20%) (85 mg) and stirred at ambient temperature for 60 minutes under an atmosphere of H_2. After filtration of the catalyst, the reaction mixture was evaporated to dryness. The remaining residue was dissolved in pyridine (3 ml), catalytic amounts of DMAP and Ac_2O (376 µl, 3.97 mmol) were added at 0°C and stirred for 60 minutes at this temperature. The reaction mixture was quenched with 3 ml MeOH and evaporated to dryness. The resulting residue was diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **47** (69.5 mg, 0.18 mmol, 61.7%) as white crystals.



$C_{17}H_{24}O_{10}$

MW: 388.37 g/mol

TLC: UV, VAN

R_f: 0.5, (C/EA 1:1 v/v)

SCG: (C/EA 4:1 v/v)

$[a]_D^{20}$ = +10.4 (c 1.540, $CHCl_3$)

^{1}H NMR (300 MHz C_6D_6) δ = 5.57 (dd, 1H, $J_{2,3}$ 5.6 Hz, H-3), 5.36 (dd, 1H, $J_{1,2}$ 3.6 Hz, H-2), 5.26 (ddd, 1H, $J_{1,5aA}$ 7.0 Hz, $J_{1,5aB}$ 9.1 Hz, H-1), 5.14 (dd, 1H, $J_{3,4}$ 4.9 Hz, H-4), 4.22 (dd, 1H, $J_{5,6A}$ 7.9

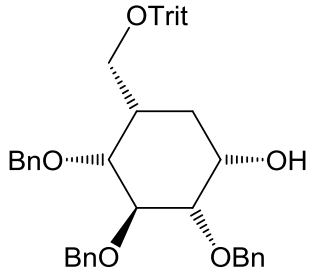
Hz, $J_{6A,6B}$ 11.1 Hz, H-6A), 3.98 (dd, 1H, $J_{5,6B}$ 6.6 Hz, $J_{6A,6B}$ 11.1 Hz, H-6B), 2.29 (m, 1H, H-5aA), 1.69, 1.65, 1.65, 1.65, 1.54 (5t, 15H, 5xCH_3), 1.25 (m, 1H, H-5B);

^{13}C NMR (75.5 MHz C_6D_6) δ = 169.4, 169.2, 169.2, 168.6 (4x C=O), 69.5 (C-2), 69.2 (C-4), 68.8 (C-1), 68.6 (C-3), 35.3 (C-5), 24.8 (C-5a), 20.5, 20.3, 20.3, 20.2, 20.1 (5x CH_3);

MS: Calcd for [$C_{17}H_{24}O_{10}Na$]: *m/z* 411.1267 $[M+Na]^+$; Found $[M+Na]^+$ 411.1280.

2,3,4-tri-O-benzyl-6-O-trityl-5a-carba-β-L-idopyranose (48)

To a solution of **45** (315.9 mg, 0.70 mmol) in pyridine (5 ml) was added TritCl (216.0 mg, 0.77 mmol and stirred for 27 hours at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **48** (343.5 mg, 0.50 mmol, 70.6%) as a colourless syrup.



$C_{47}H_{46}O_5$

MW: 690.88 g/mol

TLC: UV, VAN

R_f: 0.5, (C/EA 4:1 v/v)

SCG: (C/EA 20:1 v/v)

$[\alpha]_D^{20}$ = -11.8 (c 1.176, $CHCl_3$)

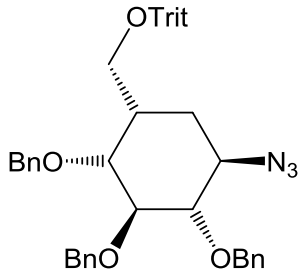
^{1}H NMR (300 MHz $CDCl_3$) δ = 4.53-4.18 (m, 6H, C$\underline{H_2}$Ar), 3.82 (ddd, 1H, $J_{1,2}$ 3.6 Hz, $J_{1,5aA}$ 8.2 Hz, H-1), 3.66 (m, 2H, H-3, H-4), 3.53 (dd, 1H, H-2), 3.14 (m, 2H, H-6A, H-6B) 2.28-2.11 (m, 2H, H-5, OH), 1.61 (m, 1H, H-5aA), 1.45 (m, 1H, H-5aB);

^{13}C NMR (75.5 MHz $CDCl_3$) δ = 144.4, 138.6, 138.3, 138.1 (4x ipso Ar), 128.8-127.0 (Ar), 86.6 (Ph_3CO), 79.1 (C-2), 75.9 (C-4), 74.6 (C-3), 73.1, 72.6, 72.5 (CH_2Ar), 67.9 (C-1), 63.9 (C-6), 36.9 (C-5), 28.3 (C-5a);

MS: Calcd for [$C_{47}H_{46}O_5Na$]: *m/z* 713.3243 $[M+Na]^+$; Found $[M+Na]^+$ 713.3542.

1-azido-2,3,4-tri-O-benzyl-6-O-trityl-5a-carba-α-L-idopyranose (49)

To solution of **48** (161.0 mg, 0.23 mmol) in 3 ml CH_2Cl_2 was added pyridine (41.0 µl, 0.51 mmol) and Tf_2O (43.0 µl, 0.25 mmol) and stirred at 0°C for 60 minutes. After full conversion of the starting material the reaction mixture was washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. The remaining residue was dissolved in 2 ml DMF and NaN_3 (150.0 mg, 2.3 mmol) was added and stirred at ambient temperature for 60 minutes. The reaction mixture was diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **49** (104.0 mg, 0.15 mmol, 62.3%) as a colourless syrup.



$C_{47}H_{45}N_3O_4$

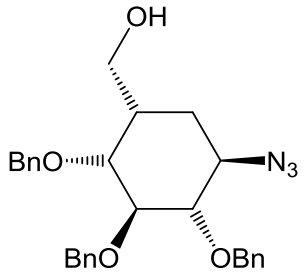
MW: 715.89 g/mol

TLC: UV, VAN

R_f: 0.8, (C/EA 3:1 v/v)

1-azido-2,3,4-tri-O-benzyl-5a-carba-α-L-idopyranose (50)

To a solution of **49** (98.2 mg, 0.14 mmol) in CH_2Cl_2/MeOH/H_2O 10:5:1 (16 ml) was added pTSA (30 mg) and stirred for 20 hours at ambient temperature. The reaction mixture was washed with saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **50** (58.9 mg, 0.12 mmol, 90.7%) as a colourless syrup.



$C_{28}H_{31}N_3O_4$

MW: 473.57 g/mol

TLC: UV, VAN

R_f: 0.3, (C/EA 3:1 v/v)

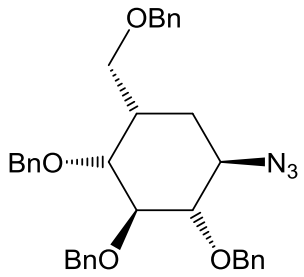
SCG: (C/EA 10:1 v/v)

$[\alpha]_D^{20}$ = +48.0 (c 0,960, $CHCl_3$)

^{1}H NMR (300 MHz $CDCl_3$) δ = 4.84-4.54 (m, 6H, C$\underline{H_2}$Ar), 3.86 (dd, 1H, $J_{5,6A}$ 7.6 Hz, $J_{6A,6B}$ 11.2 Hz, H-6A), 3.72 (dd, 1H, $J_{3,4}$ 9.1 Hz, H-3), 3.62-3.46 (m, 3H, H-1, H-4, H-6B), 3.25 (dd, 1H, $J_{2,3}$ 9.2 Hz, H-2), 2.52 (bs, 1H, OH), 2.29 (m, 1H, H-5), 1.91 (m, 1H, H-5aA), 1.27 (m, 1H, H-5aB); **^{13}C NMR** (75.5 MHz $CDCl_3$) δ = 138.6, 138.0, 137.9 (3x ipso Ar), 128.6-127.8 (Ar), 85.0 (C-2), 82.5, 82.5 (C-3, C-4), 75.8, 75.7, 73.5 (3x *C*H_2Ar), 62.7 (C-6), 60.6 (C-1), 37.4 (C-5), 29.4 (C-5a); **MS**: Calcd for [$C_{28}H_{31}N_3O_4$Na]: *m/z* 496.2212 $[M+Na]^+$; Found $[M+Na]^+$ 496.2223.

1-azido-2,3,4,6-tetra-O-benzyl-5a-carba-α-L-idopyranose (51)

To a solution of **50** (324.0 mg, 0.68 mmol) in 10 ml DMF was added NaH (26.3 mg, 1.10 mmol) and benzylbromide (114 µl, 0.96 mmol) and stirred for 5 hours at ambient temperature. After full conversion of the starting material, the reaction mixture was quenched with MeOH stirred for additional 20 minutes, diluted with CH_2Cl_2 and washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **51** (346.1 mg, 0.61 mmol, 89.7%) as a colourless syrup.



$C_{35}H_{37}N_3O_4$

MW: 563.70 g/mol

TLC: UV, VAN

R_f: 0.6, (C/EA 3:1 v/v)

SCG: (C/EA 16:1 v/v)

$[\alpha]_D^{20}$ = +7.3 (c 1.205, $CHCl_3$)

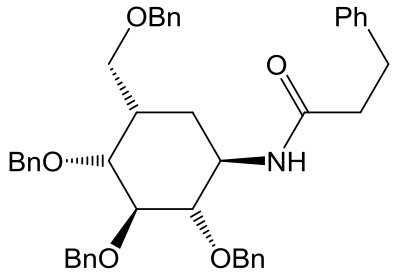
^{1}H NMR (300 MHz $CDCl_3$) δ = 4.82-4.37 (m, 8H, C$\underline{H_2}$Ar), 3.66-3.41 (m, 5H, H-1, H-3, H-4, H-6A, H-6B), 3.23 (dd, 1H, $J_{2,3}$ 9.3 Hz, H-2), 2.35 (m, 1H, H-5), 2.13 (m, 1H, H-5aA), 1.22 (m, 1H, H-5aB);

^{13}C NMR (75.5 MHz $CDCl_3$) δ = 138.8, 138.4, 138.3, 138.2 (4x ipso Ar), 128.6-127.7 (Ar), 85.0 (C-2), 82.9 (C-3), 81.5 (C-4), 75.7, 73.3, 72.5 (3x *C*H_2Ar), 67.5 (C-6), 60.7 (C-1), 35.7 (C-5), 29.0 (C-5a);

MS: Calcd for $[C_{35}H_{37}N_3O_4Na]$: *m/z* 586.2682 $[M+Na]^+$; Found $[M+Na]^+$ 586.2654.

1-(3-phenyl)-propylamido-2,3,4,6-tetra-O-benzyl-5a-carba-α-L-idopyranose (53)

To a solution of **51** (114.3 mg, 0.20 mmol) in THF (10 ml) was added PPh_3 (69 mg, 0.26 mmol) and stirred for 20 hours at ambient temperature. After addition of H_2O (7 ml) the reaction mixture was stirred for additional 6 hours at this temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. After drying with Na_2SO_4 the solvent was removed under reduced pressure. The remaining residue was diluted in CH_2Cl_2 (6 ml), Et_3N (62 µl, 0.44 mmol) and hydrocinnamoylchloride (60 µl, 0.4 mmol) were added and stirred at ambient temperature for 60 minutes. The reaction mixture was washed consecutively with HCl (2N) and saturated $NaHCO_3$. After drying with Na_2SO_4 the solvent was removed under reduced pressure. Purification on silica gel afforded **53** (104.3 mg, 0.16 mmol, 76.8%) as a pale yellow syrup.



$C_{44}H_{47}NO_5$

MW: 669.86 g/mol

TLC: UV, VAN

R_f: 0.7, (C/EA 1:1 v/v)

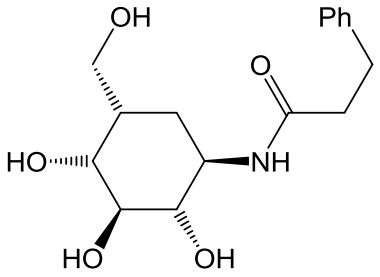
SCG: (C/EA 6:1 v/v)

$[a]_D^{20}$ = +2.4 (c 1.500, $CHCl_3$)

MS: Calcd for $[C_{44}H_{47}NO_5Na]$: *m/z* 692.3352 $[M+Na]^+$; Found $[M+Na]^+$ 692.3331.

1-(3-phenyl)-propylamido-5a-carba-α-L-idopyranose (54)

To a solution of **53** (56.9 mg, 0.09 mmol) in 10 ml MeOH was added Pd/C (5%) (45 mg) and stirred for 18 hours under an atmosphere of H_2 at ambient temperature, filtered and evaporated to dryness. Purification on silica gel gave **54** (25.8 mg, 0.83 mmol, 98.2%) as a colourless wax.



$C_{16}H_{23}NO_5$

MW: 309.36 g/mol

TLC: UV, CAM

R_f: 0.4 ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

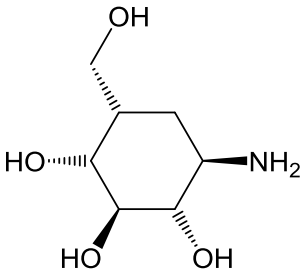
SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[a]_D^{20}$ = -9.7 (c 1.250, MeOH)

^{1}H NMR (300 MHz MeOH-d_4) δ = 3.83 (m, 1H, H-1), 3.76 (dd, 1H, $J_{5,6A}$ 5.5 Hz, $J_{6A,6B}$ 11.2 Hz, H-6A), 3.49 (m, 2H, H-4, H-6B), 3.35 (dd, 1H, $J_{3,4}$ 8.5 Hz, H-3), 3.11 (dd, 1H, $J_{1,2}$ 8.7 Hz, H-2), 2.81 (m, 2H, H-3'), 2.39 (m, 2H, H-2'), 2.00 (m, 1H, H-5), 1.82 (m, 1H, H-5aA), 1.18 (m, 1H, H-5aB);
^{13}C NMR (75.5 MHz MeOH-d_4) δ = 175.2 (C=O), 142.2 (ipso Ar), 129.5, 129.4, 127.2 (Ar), 76.6 (C-2), 75.4 (C-3), 74.4 (C-4), 60.9 (C-6), 50.1 (C-1), 41.1 (C-5), 39.2 (C-2'), 30.7 (C-3'), 29.1 (C-5a);
MS: Calcd for [$C_{16}H_{23}NO_5Na$]: *m/z* 332.1474 $[M+Na]^+$; Found $[M+Na]^+$ 332.1493.

α-L-ido-validamine (56)

Following general procedure D compound **49** (104.0 mg, 0.15 mmol) was dissolved in MeOH/H_2O 10/1, $Pd(OH)_2$/C (20%) (65 mg) was added and stirred under an atmosphere of H_2 for 22 hours at ambient temperature. After filtration, the reaction mixture was evaporated to dryness. Purification on silica gel afforded **56** (18.6 mg, 0.11 mmol, 72.3%) as a colourless syrup.



$C_7H_{15}NO_4$

MW: 177.20 g/mol

TLC: UV, CAM

R_f: 0.3 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 3:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = -33.6 (c 1.250, H_2O)

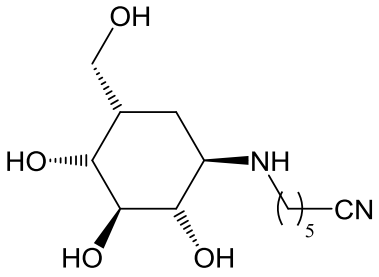
^{1}H NMR (300 MHz D_2O) δ = 3.81 (dd, 1H, $J_{5,6A}$ 4.5 Hz, $J_{6A,6B}$ 11.4 Hz, H-6A), 3.67 (dd, 1H, $J_{4,5}$ 5.8 Hz, $J_{3,4}$ 9.6 Hz, H-4), 3.53 (dd, 1H, $J_{5,6B}$ 9.6 Hz, $J_{6A,6B}$ 11.4 Hz, H-6B), 3.49-3.22 (m, 3H, H-1, H-2, H-3), 2.26 (m, 1H, H-5), 2.16 (m, H-5aA), 1.58 (m, 1H, H-5aB);

^{13}C NMR (75.5 MHz D_2O) δ = 73.9 (C-2), 73.5 (C-3), 72.4 (C-4), 58.4 (C-6), 50.2 (C-1), 39.5 (C-5), 25.9 (C-5a);

MS: Calcd for [$C_7H_{15}NO_4H$]: *m/z* 178.1079 $[M+H]^+$; Found $[M+H]^+$ 178.1078.

N-(5-cyano)pentyl-α-L-ido-validamine (56)

Following general procedure B compound **56** (10.0 mg, 0.06 mmol) was treated with $NaHCO_3$ (20 mg, 0.24 mmol) and 6-bromohexanenitrile (9.7 µl, 0.07 mmol) and stirred for 96 hours. Purification on silica gel afforded **57** (13.2 mg, 0.05 mmol, 85.8%) as a colourless syrup.



$C_{13}H_{24}N_2O_4$

MW: 272.35 g/mol

TLC: UV, CAM

R_f: 0.6 ($CHCl_3$/MeOH/NH_4OH 4:4:1 v/v/v)

SCG: ($CHCl_3$/MeOH/NH_4OH 8:1:0.01 v/v/v)

$[\alpha]_D^{20}$ = -43.1 (c 0.780, MeOH)

^{1}H NMR (300 MHz MeOH-d_4) δ = 3.77 (dd, 1H, $J_{5,6A}$ 4.5 Hz, $J_{6A,6B}$ 11.0 Hz, H-6A), 3.57-3.45 (m, 2H, H-4, H-6B), 3.39 (dd, 1H, $J_{3,4}$ 7.9 Hz, H-3), 3.28 (dd, 1H, $J_{1,2}$ 8.8 Hz, H-2), 3.09 (m, 1H, H-1), 2.90 (m, 2H, H-1'), 2.39 (m, 2H, H-5'), 2.22-2.10 (m, 2H, H-5, H-5aA), 1.68-1.34 (m, 7H, H-5aB, H-2', H-3', H-4');

^{13}C NMR (75.5 MHz MeOH-d_4) δ = 121.0 (CN), 75.4 (C-3), 74.9 (C-2), 74.1 (C-4), 60.5 (C-6), 57.9 (C-1), 46.3 (C-1'), 40.8 (C-5), 27.2, 26.9, 26.1 (C-2', C-3', C-4'), 25.7 (C-5a), 17.2 (C-5'); **MS**: Calcd for $[C_{13}H_{24}N_2O_4H]$: *m/z* 273.1814 $[M+H]^+$; Found $[M+H]^+$ 273.1817.

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„C-5a-Substituted Validamine Type Glycosidase Inhibitors"

Schalli, M.; Wolfsgruber, A.; Gonzalez Santana, A.; Tysoe, C.; Fischer, R.; Thonhofer, M.; Withers, S. G.; *Carb. Res.* **2017**, *440*; 1-9.

„From secondary alcohols to tertiary fluoro substituents: A simple route to hydroxymethyl branched sugars with a fluorine substituent at the branching point "

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„Synthesis of C-5a-substituted derivatives of 4-epi-isofagomine: notable β-galactosidase inhibitors and activity promotors of GM1-gangliosidosis related human lysosomal β-galactosidase mutant R201C."

Thonhofer, M.; Weber, P.; Gonzalez Santana, A.; Tysoe, C.; Fischer, R.; Pabst, B. M.; Paschke, E.; Schalli, M.; Stütz, A. E.; Tschernutter, M.; *Carb. Res*. **2016**; *429*; 71-80.

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„Synthesis of Carbasugar Pseudo-Disaccharides"

Schalli, M.; Stütz, A.

17. Österreichischer Kohlenhydratworkshop, TU-Graz, 14. February **2013**, Graz, Austria

„The Ferrier II reaction and selected examples of follow-up chemistry"

Schalli, M.; Thonhofer, M.; Zoidl, M.; Wrodnigg, T.; Fischer, R.; Torvisco Gomez, A.; Stütz, A.

18. Österreichischer Kohlenhydratworkshop. BOKU Wien, 13. February **2014**, Vienna, Austria

„Synthesis of functionalised iminoalditol building blocks for glycoprobes via a Staudinger/aza-Wittig/Strecker multi-component reaction“

Zoidl, M.; Schalli, M.; Thonhofer, M.; Torvisco Gomez, A.; Saf, R.; Stütz, A.; Siriwardena, A.; Wrodnigg, T.

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Zoidl, M.; Gonzalez Santana, A. .; Hojnik, C.; Saf, R.; Schalli, M.; Stütz, A.; Thonhofer, M.; Withers, S.; Wrodnigg, T.

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„A new approach to fluorinated 4-epi-isofagomine derivatives and their D-galactosidase inhibitory properties.”

Thonhofer, M.; Fischer, R.; Gonzalez-Santana, A.; Hojnik, C.; Saf, R.; Schalli, M.; Stütz, A.; Torvisco Gomez, A.; Withers, S. G.; Wrodnigg, T.; Zoidl, M.

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„Synthesis of substituted Inososes and their enantiomers.“

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„Glycolipid mimetics: Lipophilic carbasugars as inhibitors and chemical chaperones for GM1 gangliosidosis. “

Schalli, M.; Gonzales Santana, A.; Hojnik, C.; Paschke, E.; Stütz, A. E.; Thonhofer, M.; Withers, S. G.; Wrodnigg, T. M.; Zoidl, M.;

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„A powerful approach towards C-glycosyl type iminoalditol building blocks for biological applications.“

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23rd International Symposium on Glycoconjugates, 15.-20. September **2015**, Split, Croatia

Lebenslauf

Michael Schalli, geboren am 08. März 1985 in Graz als Sohn von Ernst Schalli und Monika Schalli, geborene Dirnberger.

1991-1995	Besuch der Volksschule St. Oswald bei Plankenwarth
1995-2003	Besuch des Bundesgymnasium Rein
07.10.2003	Absolvierung der Reifeprüfung
2004	Absolvierung des Grundwehrdienstes
WS 2004/05	Beginn des Studiums der Technischen Chemie an der Technischen Universität Graz
2009-2011	O&D Edelstahlanlagen
2012	Absolvierung der ersten Diplomprüfung (Abschluss des Bachelorstudiums Chemie NAWI Graz)
WS 2012/13	Beginn des Masterstudiums Technische Chemie NAWI Graz
2012-2013	Masterarbeit mit dem Thema: *„Carbazucker aus D-Glucose und D-Mannose: Bausteine für Enzymsonden“* am Institut für Organische Chemie der Technischen Universität Graz
26.09.2013	Absolvierung der Masterprüfung
Oktober 2013	Beginn der Disseration mit dem Thema: „Carbasugars for β-Galactosidase Related Lysosomal Diseases and for Investigation of G_{M1}-Ganglioside Metabolism” am Institut für Organische Chemie der Technischen Universität Graz