Master Thesis

Studies Towards the Synthesis of 2,5-Dideoxy-2,5-imino-D-hexitol Derivatives

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Abstract

Iminoalditols, which are sugar analogues with a basic trivalent nitrogen instead of the oxygen in the ring, are well known as powerful glycosidase inhibitors. Therefore, such compounds are used as analytical tools for the investigation of carbohydrate processing enzymes as well as their application as pharmaceuticals against diseases involving this enzyme class.

In line with the research towards applications of *N*-modified iminoalditols as pharmacological chaperones we have become interested in the synthesis of α-galactosidase inhibitors in context with Fabry´s disease. To this end, 2,5-dideoxy-2,5-imino-D-altritol, originally isolated form *Adenophora triphylla*, is known to have respective biological properties for this application.

The aim of this work was to find a short synthetic route towards 1-amino-1,2,5-trideoxy-2,5-imino-D-talitol. However, a final product, in this class of iminosugars, could not be synthesised, but important results towards the desired product were made.

In a second part of this master thesis, two iminosugars in the 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol series were successfully synthesised. These two molecules will be further investigated for their biological activity towards glycosyl hydrolases.

Kurzfassung

Iminoaldite sind Kohlenhydrat-Analoga mit einem basischen, trivalenten Stickstoff an Stelle des Sauerstoffs im Ring und sind bekannt als starke Glycosidaseninhibitoren. Solche Verbindungen werden als analytische Werkzeuge zur Untersuchung von kohlenhydratverarbeitenden Enzymen verwendet. Weiters finden sie Anwendung als Arzneimittel gegen Krankheiten dieser Enzymklassen.

Im Einklang mit der Forschung zur Anwendung von *N*-modifizierten Iminoalditen als pharmakologische Chaperone sind wir an der Synthese von α-Galactosidaseinhibitoren, im Zusammenhang mit Morbus Fabry, interessiert. Es ist bekannt, dass für diesen Zweck, 2,5-Didesoxy-2,5-imino-D-altrit, ursprünglich isoliert aus *Adenophora triphylla*, geeignete biologische Eigenschaften aufweist.

Das Ziel dieser Arbeit war es einen kurzen Syntheseweg für 1-Amino-1,2,5-tridesoxy-2,5-imino-D-talit zu finden. Obwohl kein Endprodukt in dieser Klasse von Iminozuckern synthetisiert werden konnte, wurden wichtige Ergebnisse auf dem Syntheseweg zum gewünschten Produkt erzielt.

In einem zweiten Teil dieser Master Thesis wurden zwei Iminozucker der 1-Amino-1,2,5-trideoxy-2,5-imino-D-mannit Serie erfolgreich synthetisiert. Diese beiden Moleküle werden auf ihre biologische Aktivität hinsichtlich Glykosylhydrolasen untersucht.

Statutory Declaration

I declare that I have authored this thesis independently, that I have not used other than the declared sources / resources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Date Signature

Abbreviations

Ac	acetyl
Bn	benzyl
Cbz	carboxybenzyl
Trit	triphenylmethyl
Ph	phenyl
C	cyclohexane
DIBALH	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimetyhl formamide
EA	ethyl acetate
HCCA	α-cyano-4-hydroxycinnamic acid
THF	tetrahydrofuran
pTSA	*p*-toluenesulfonic acid
PpTS	pyridinium *p*-toluenesulfonate
aq.	aqueous
eq	equivalent
CC	column chromatography
CC-S	column chromatography solvent
conc.	concentrated
MALDI	matrix-assisted laser desorption/ionisation
MW	molecular weight
M	molar
NMR	nuclear magnetic resonance
R_f	retention factor
RT	room temperature
sat.	saturated
TLC	thin layer chromatography
TLC-S	thin layer chromatography solvent

Contents

1 Introduction

1.1 Carbohydrates

The name "*carbohydrate*" is a historical designation, this term was used for monosaccharides with a corresponding molecular formula $C_xH_{2x}O_x$. Molecules with that formula were regarded as the hydrate of the carbon atom. Furthermore, the word saccharide comes from the greek word *sakcharon* and means sugar. [1, 2] The main elements of carbohydrates are carbon, hydrogen and oxygen. It is known, that carbohydrates can also include other important elements such as nitrogen, sulphur, selen. For example, carbohydrates with a nitrogen in the ring instead of an oxygen are called iminosugars. For that reason the historical definition is not very strict any more. [3]

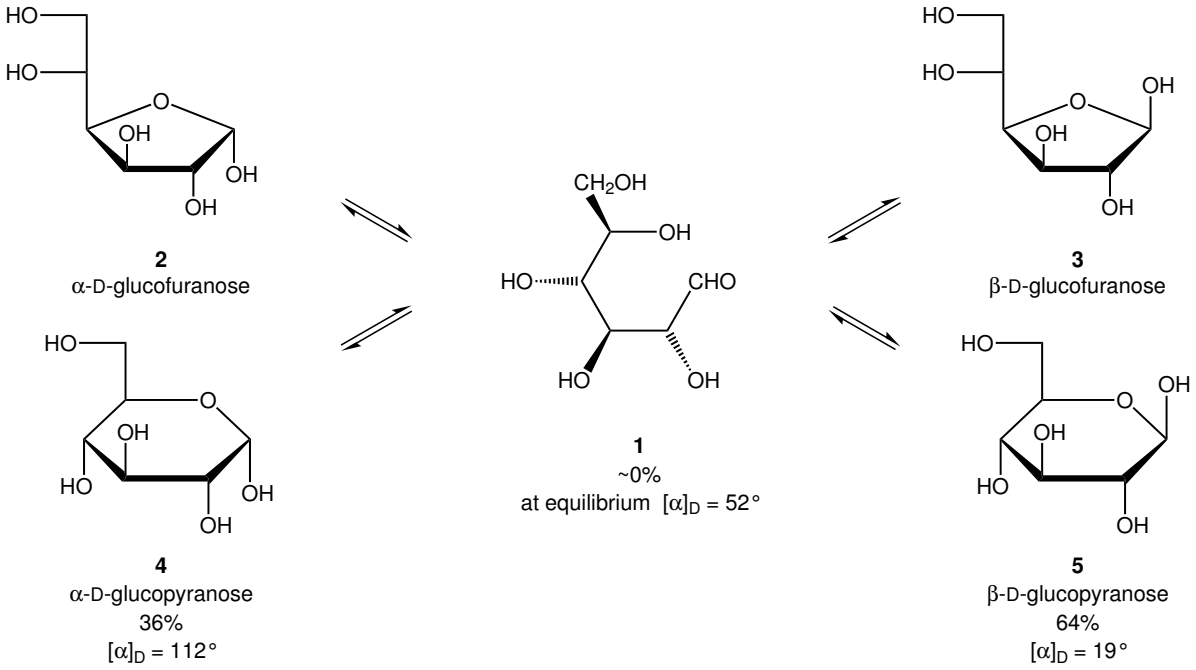


Figure 1.1: α, β-D-Glucose in open chain, pyranose and furanose form.

Carbohydrates are distinguished in mono-, oligo- or polysaccharides, depending on the number of monomeric units. Monosaccharides, the smallest subunit, are subdivided by the number of carbon atoms in their main chain, into trioses (C_3), tetroses (C_4),

pentoses (C_5), hexoses(C_6) and so on. In nature, the most common carbohydrates are pentoses ($C_5H_{10}O_5$) and hexoses ($C_6H_{12}O_6$). Chemically they are polyhydroxy aldehydes or ketones and they are termed as aldoses and ketoses, respectively. In water as solvent monosaccharides are in an equilibrium with their open chain **1** and their ring forms. In the ring forms they can form furanoses or pyranoses in the α- or β-anomeric configuration. But, for example, D-glucose was never isolated in the furanose **2**, **3** form. In water α-D-glucose (**4**) changes from the pure anomeric form to a α/β equilibrium mixture of 36/64 % by a phenomenon called *mutarotation*. To observe this phenomenon, the optical rotation has to be measured. For example, the pure α-D-glucose (**4**) with the specific rotation at +112°, shows in solution within some time a final value of +52°. Conversely, the pure β-D-glucose (**5**) rises the value from +19° to +52° (Figure: 1.1). [4]

There are millions of possible ways to link single building blocks to form oligo- or polysaccharides with different physical and chemical properties. Oligosaccharides contain two to ten monosaccharide units linked via a glycosidic bond. This bond can be formed between both hydroxyl groups at the anomeric center or between one hydroxyl group of the anomeric center and another alcoholic group somewhere along the sugar unit. If both hydroxyl groups of the anomeric center are linked together they are called *none reducing sugars* like sucrose (**6**) and in the later case they are called *reducing sugars* like lactose (**7**) (Figure: 1.2). [4, 5]

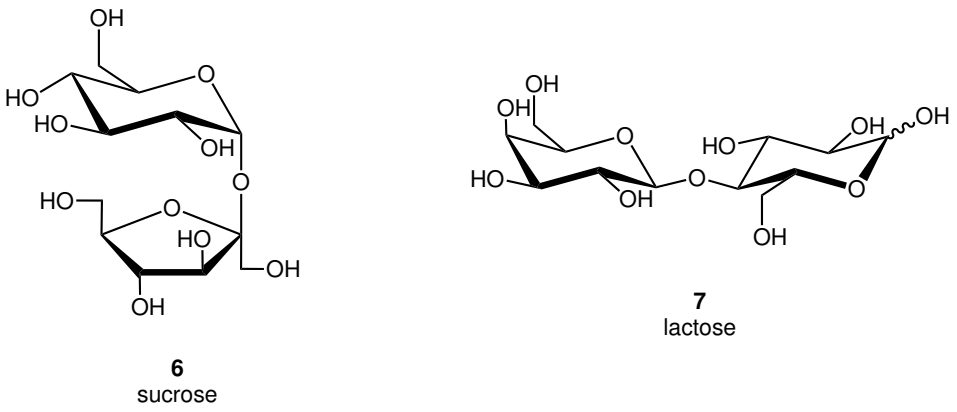


Figure 1.2: Structure of sucrose and lactose.

Carbohydrates consisting of more then ten units are called polysaccharides, they are very important building blocks for plants, starch (**8**) is responsible for energy storage and for example cellulose (**9**) as structural compound. The difference between starch (**8**) and cellulose (**9**) is that starch (**8**) is an α-1,4-linked (amylose) D-glucose with an α-1,6-crosslinked (amylopectin) D-glucose polymer, versus, cellulose (**9**) is a β-1,4-linked D-glucose linear polymer (Figure: 1.3). A representative of polysaccharides including nitrogen is chitin, the major structural compound of the exoskeletons of insects or

crustaceans. Chitin is a β-1,4 linked *N*-acetyl-D-glucosamine. [4]

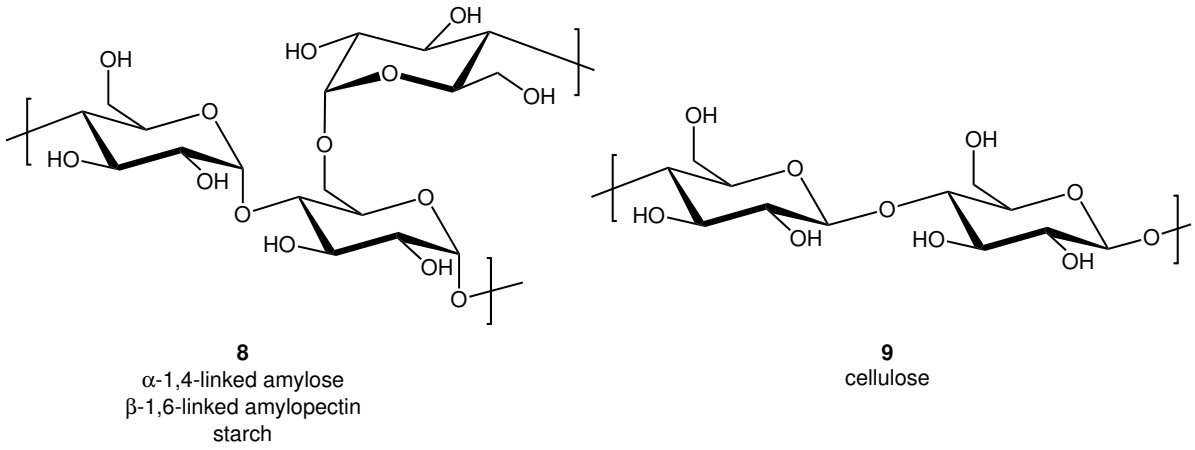


Figure 1.3: Structure of starch and cellulose.

Carbohydrates appear as single molecule or as conjugates of natural products, they play important roles in conferring certain physical, chemical, and biological properties to their carrier molecules. For example they occur in all cells in some or another form, as peptido- and proteoglycans, glycoproteins, nucleic acids, lipopolysaccharides or glycolipids. In the cells they are implicated in many processes, including cell/cell recognition, cellular transport and adhesion. Due to their importance as building blocks, synthetic targets, biological tools and their potential as drug candidates, investigations of carbohydrate structure, their functions in biomolecules and conjugates offer a large field of research possibilities. [6]

1.2 Glycosphingolipids

Sphingolipids and glycosphingolipids are essential structural components of mammalian cell membranes and are found basically on all cell surfaces. Glycosphingolipids consist of a ceramide part linked through a β-glycosidic linkage from glucose or galactose to the primary hydroxyl group of the *N*-acylated sphingosine component. A very simple glycosphingolipid, galactosylceramide (**10**) is shown in figure 1.4. A broad range of complex glycosphingolipids is given by addition of oligosaccharides and sulfate groups, for example like *N*-acetylneuraminic acid, *N*-acetylgalactosamine, galactose and glucose. [7]

The breakdown of glycosphingolipids is a stepwise process and takes place in the lysosomes. Different exoglycosidases are cleaving sequentially carbohydrates from the non reducing end of glycosphingolipids. Finally, the ceramide is cleaved to a fatty acid and a sphingosin. (Figure: 1.5) [7]

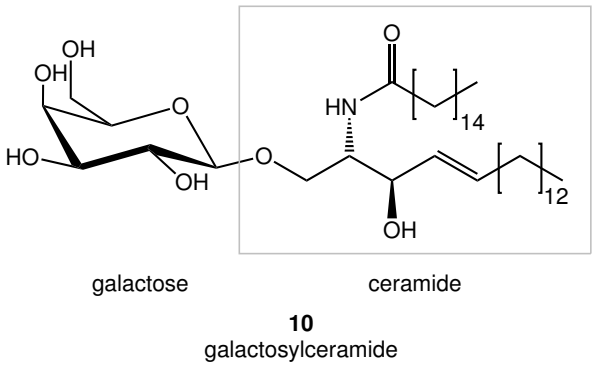


Figure 1.4: Structure of galactosylceramide.

1.3 Lysosomal storage diseases (LSD)

Lysosomal storage diseases are incurable and count to the orphan diseases. Today over 70 different types are known. Gene mutants of the enzymes, being responsible for the breakdown of certain macromolecules, causes the storage of incompletely degenerated molecules in the lysosome. In table 1.1 representatives of lysosomal storage diseases are shown, they occur with incomplete degeneration of glycosphingolipids. [8, 9]

Table 1.1: Lysosomal storage diseases.

Disease	Defect enzyme	stored molecule
Pompe disease	α-Glucosidase	Glycogen
G_{M1}-Gangliosidosis	β-Galactosidase	Ganglioside G_{M1}
Tay-Sachs disease	β-Hexosamidase A	Ganglioside G_{M2}
Sialidose	Neuraminidase	Ganglioside G_{M3}
Gaucher disease	Glucocerebrosidase	Glucosylceramide
Fabry diseasee	α-Galactosidase A	Globotriaosylceramide
Sandhoff disease	β-Hexosaminidase B	Globoside

The most common lysosomal storage disease is the Gaucher-syndrome. Gaucher disease affects an estimated 1 in 50,000 to 1 in 100,000 people in the general population. It is an autosomal recessive disease. This means that the mother and father must both pass one abnormal copy of the gene to the child for the disease to develop. The Gaucher disease effects the liver, spleen, bones and bone marrow. The stored molecules prevent cells and organs from working properly. There are three different types of Gaucher disease, type 1 disease is most common. It involves bone disease, anemia, an enlarged spleen and thrombocytopenia. Type I affects both children and adults. Type 2 disease usually

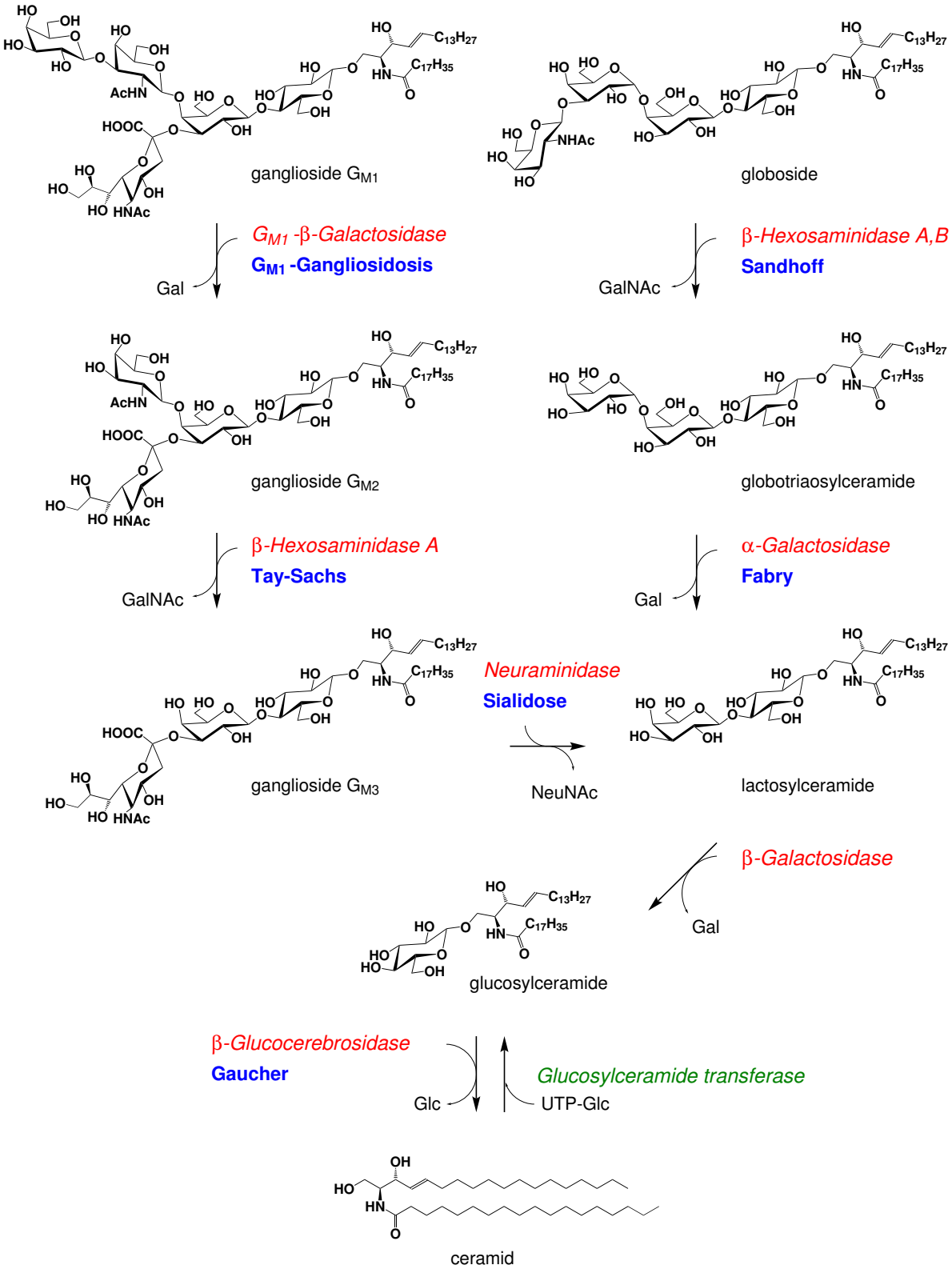


Figure 1.5: Lysosomal degradation cascade of glycosphingolipids.

begins in infancy with severe neurology involvement. This form can lead to rapid and very often early death. Type 3 disease may cause liver, spleen, and brain problems. Patients may live into their adulthood. How well a person does depends on the subtype of the disease. The infantile form of Gaucher disease may lead to early death. Most affected children die before the age of five. Adults suffering from Gaucher disease type 1 can expect "normal" life expectancy with enzyme replacement therapy. For prevention a genetic counselling is recommended for prospective parents with a family history of Gaucher disease. Testing can determine if parents carry the gene that could pass on the Gaucher disease to their children. A prenatal test can also tell if the fetus has Gaucher syndrome. Lysosomal storage diseases are incurable just their symptoms are treatable. [8–10]

1.3.1 Therapy of lysosomal storage diseases

Today different treatment strategies are available. Every treatment is selectively, depending on the form of the disease. To raise life quality of the patient an early diagnosis and treatment is very important. The lifelong treatment is very expensive, depending on the strategy the costs can be up to 700,000 euro per year and person. Enzyme replacement therapy (ERT), substrate reduction therapy (SRT), gene therapy (GT) and chaperone mediated therapy (CMT) are four possible therapies for lysosomal storage diseases. [11]

Chaperon mediated therapy

In the lumen of the endoplasmatic reticulum (ER) proteins are generally folded by the principle of self-assembly. Depending on their amino acid sequences in a thermodynamic fashion and support of molecular chaperones the new synthesised proteins fold into their biological active forms. If the proteins are not folded into their active form, they are degraded by the quality control mechanism, namely ER-associated degradation (ERAD). Shown in figure: 1.7, pathway **a** and **b**. [8]

11
1-deoxygalactonojirimycin

12
2,5-dideoxy-2,5-imino-D-altritol

Figure 1.6: Structure of 1-deoxygalactonojirimycin and 2,5-dideoxy-2,5-imino-D-altritol.

Small active side specific chaperones (ASSC) regaining the biological activity by

acting as a folding template to the proteins to fold and assembly right. The protein-chaperon complex is further transported to the lysosome. They are commonly called pharmacological chaperones and they are highly selectively in contrast to chemical chaperones which also effects proper folded proteins. Shown in figure: 1.7, pathway **c**. For Fabrys disease the best potential ASSC so far is 1-deoxygalactonojirimycin (**11**) [12], also the five membered ring 2,5-dideoxy-2,5-imino-D-altritol (**12**) was found as a good pharmacological chaperone. [13] (Figure: 1.6). In some disease forms, also the nerve system is effected. Pharmaceuticals, like small active side specific chaperones, are able to pass the blood-brain barrier to act as active substance. Furthermore, the ASSC can be applied orally which raises the life quality for patients compared to other therapies. Moreover, the cost of such a therapy are lower in comparison to others. [8, 9, 13]

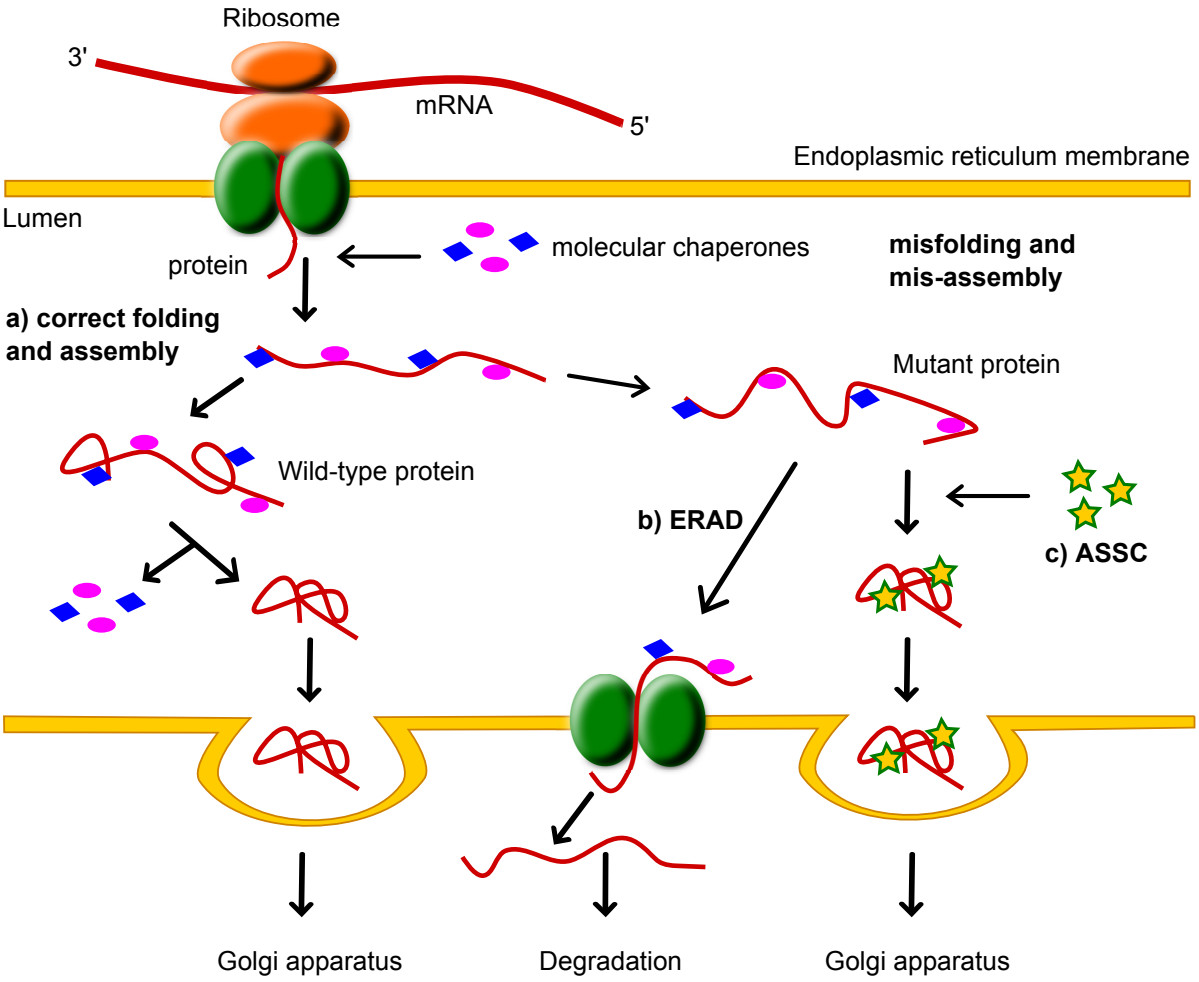


Figure 1.7: Proposed mechanism of enzyme stabilisation by chaperones. (adapted from [14])

Enzyme replacement therapy

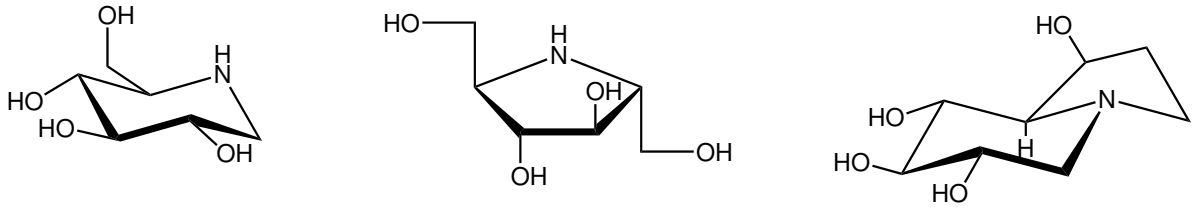
The principal behind this treatment strategy is that recombinant enzymes are replacing the mutant proteins in the lysosomes. A big disadvantage is that this enzymes are not able to pass the blood-brain barrier which makes them unavailable for diseases affecting the nerve system. Also the high costs and the weekly intravenous infusions are disadvantages. But this kind of therapy works well on Gaucher's type I patients, adults with this form and therapy can expect "normal" life expectancy. [9, 10]

Substrate reduction therapy

This kind of therapy inhibits the building of lysosomal proteins to achieve a lower level of catabolic products. Big disadvantages of this therapy are that a high concentration is needed and the lack of specificity towards the respective synthase. Furthermore, this therapy is afflicted with side effects such as gastrointestinal complaints, transitory diarrhoea, flatulence and bloating. [9]

1.4 Iminosugars

Everything started in 1966 as H. Paulsen and his co-worker I. Sangster published the synthesis of 1-deoxynojirimycin [15]. The biological activity was not investigated at that time. Ten years later the study of iminosugars changed dramatically, as the Research Center of Bayer AG was studying the treatment against diabetes and found 1-deoxynojirimycin as a good inhibitor of α-glucosidase. This important result started the iminosugars era, from then on iminosugars became very important in the study of enzymes. [16]



14
1-deoxynojirimycin

15
2,5-dideoxy-2,5-imino-D-mannitol

13
castanospermine

Figure 1.8: Structure of common iminosugars.

Iminosugars, whether of natural or synthetic origin, are small basic sugar analogues containing a nitrogen atom instead of oxygen in the ring system. Carbohydrate linkages are generally cleaved by glycosidases in biochemical reactions, iminosugars are well known

as powerful glycosidase inhibitors. Therefore, iminosugars are used as analytical tools for the investigation of carbohydrate processing enzymes as well as their application as pharmaceuticals against diseases involving this enzyme class. Today, there are up to 1000 derivatives of iminosugars known. In figure 1.8 some iminosugars are shown as for example the bicyclo-iminosugar castanospermin (**13**) a natural iminosugar from the seeds of *Castanospermum australe*. Castanospermin (**13**) reduces the growth of HI-virus or tumours. 1-Deoxynojirimycin (**14**) for example can be extracted from mulberry leaves (*Morus alba* and *Morus bombysis*). [16–22]

1.5 Amadori rearrangement

The Amadori rearrangement is named after Mario Amadori who reported the first products between 1925 and 1931. [23–26] The Amadori rearrangement is a key step in the Maillard reaction cascade, the non enzymatic browning of food. This reaction cascade is very important for the taste, aroma and color of food during cooking, baking or preservation process of food.

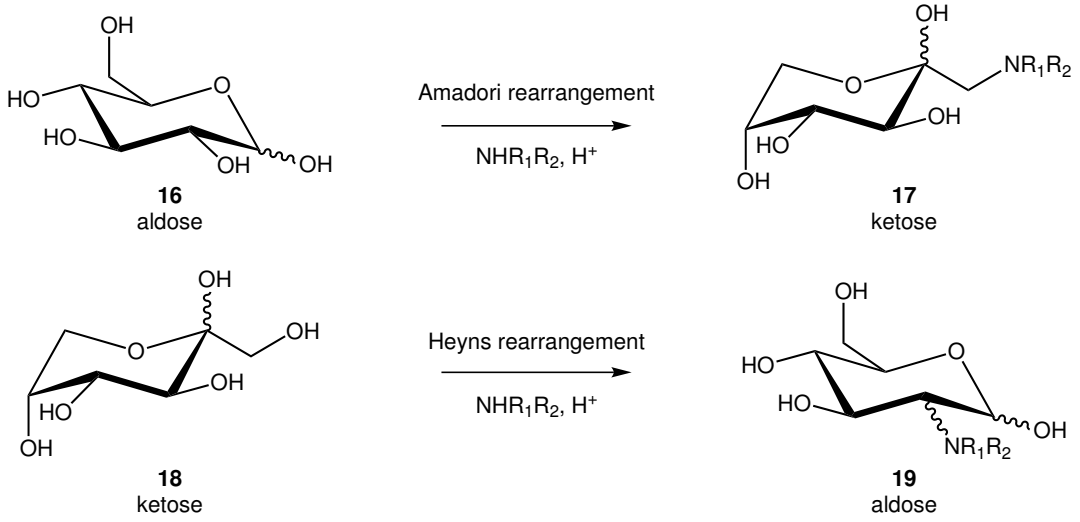


Figure 1.9: Amadori and Heyns rearrangement products.

The Amadori rearrangement is a reaction between a hydroxy aldehyde (**16**) and a primary or secondary amine. The product of the Amadori rearrangement is an 1-amino-1-deoxyketose (**17**). The Heyns rearrangement, as equivalent to the Amadori rearrangement, starts from a hydroxy ketose (**18**) and the product is an 2-amino-2-deoxyaldose (**19**). One of the big advantages of the Amadori rearrangement is, that no protecting groups are needed. Furthermore, a bright variety of reducing sugars and amines or amino acids can be used for the Amadori rearrangement. The Amadori rearrangement reaction has

also some disadvantages, in some cases a mixture of the desired rearrangement product and the isomeric glycosly amine precursors are obtained. It can be difficult to separate these two compounds. Furthermore, the product can easily enter the Maillard reaction cascade leading towards unwanted side products. To keep side products to a minimum, moderate temperatures and short reaction times are preferable. [27–29]

Kuhn and Weygand proposed the still widley accepted mechanism of the Amadori rearrangement. [30] In the first step of the rearrangement mechanism a glycoslyamine **20** is formed between glucose (**16**) and a primary amine **21**. Protonation of the nitrogen in the glycosylamine **22** and ring opening leads to an cationic imine **23** which is in equilibrium with the enol **24**. The enol **24** is stabalized by the formation of 1-amino-1-deoxyketose (**17**).

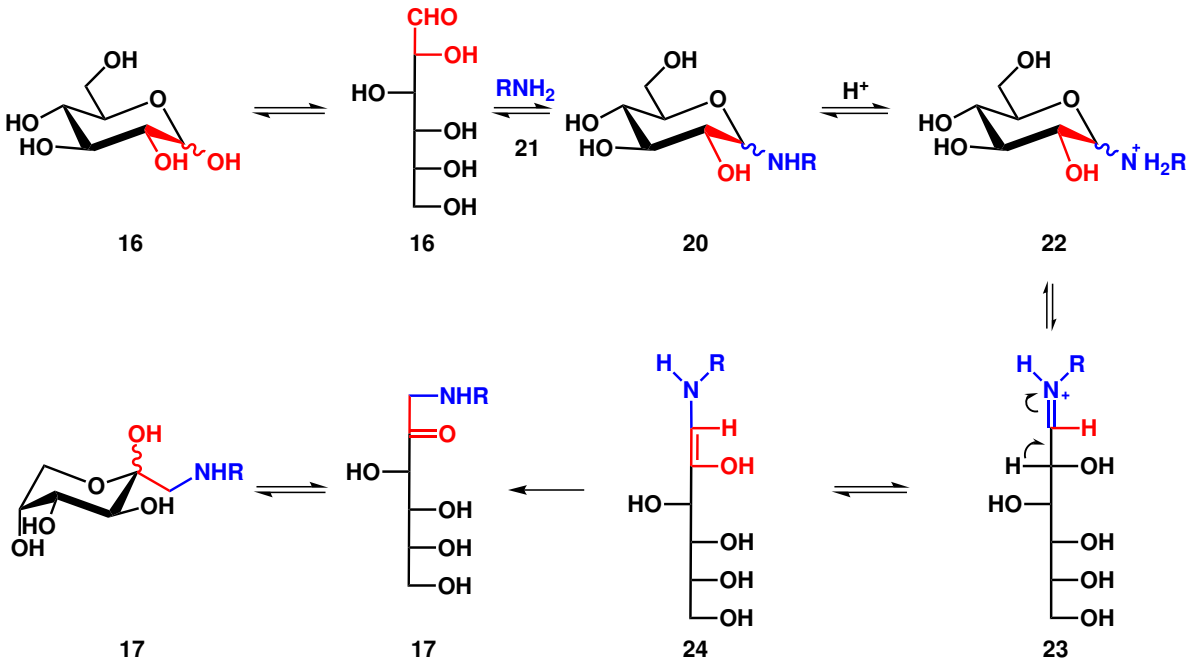


Figure 1.10: Amadori rearrangement mechanism.

One of the first applications for the Amadori rearrangement was an alternative approach to lactulose (**25**) (Figure: 1.11). [31] Starting from lactose (**7**) and *p*-toluidene in pyridine with acatic acid as acidic catalyst gave the corresponding Amadori product (**26**). Lactulose (**25**) was obtained after catalytic hydrogenolysis (**27**) and subsequent deamination of the rearrangement product. [28]

Furthermore, for example, an intramolecular Amadori rearrangement can directly lead towards iminosugars. Therefore, an intramolecular Amadori rearrangement was described by Paulsen (Figure: 1.12). [32] This type of rearrangement led from 5-amino-5-deoxy-D-xylose (**28**) to 1,5-dideoxy-1,5-imino-D-*threo*-pentulose (**31**), a direct precursor

of 1,5-dideoxy-1,5-iminoxylitol (**32**). [28]

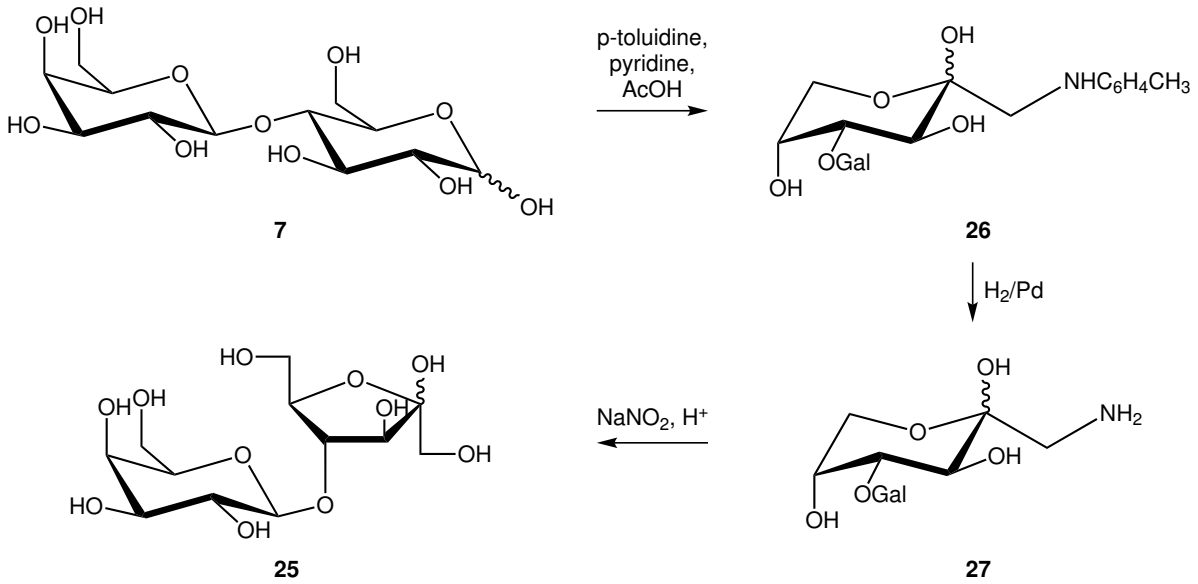


Figure 1.11: Synthesis from lactose (**7**) to lactulose (**27**) via the Amadori rearrangement.

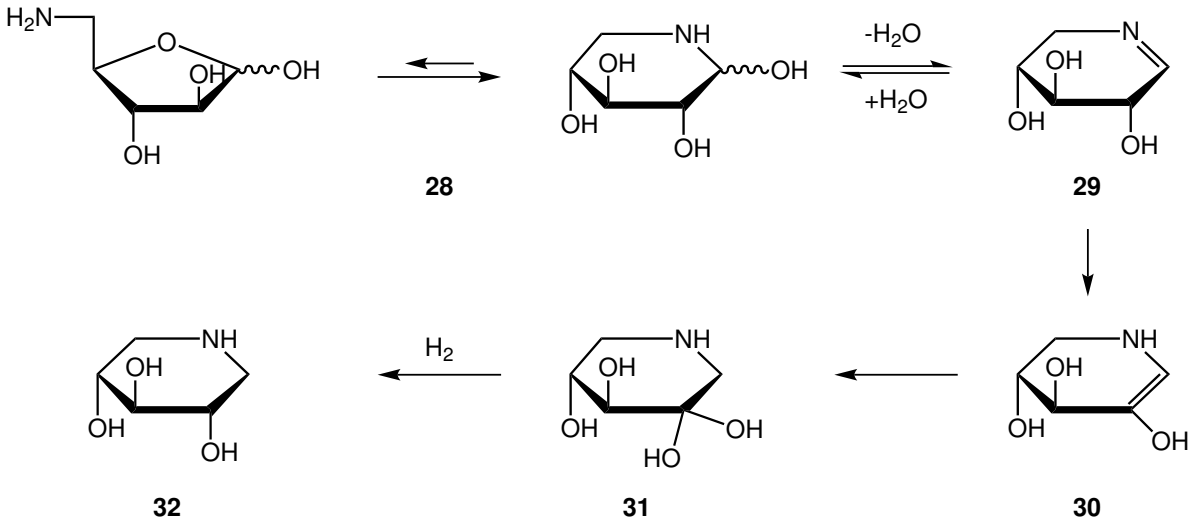


Figure 1.12: Intramolecular Amadori rearrangement.

2 NMR spectroscopy in carbohydrate chemistry

2.1 Introduction

Nuclear magnetic resonance (NMR) spectroscopy is arguably one of the most powerful tools available for chemists for the structural analysis, dynamics and chemical kinetics of molecules and biological systems. [33, 34] There are also other powerful methods like mass spectroscopy, but especially in carbohydrate chemistry NMR spectroscopy has become a very important tool. Mass spectroscopy would not lead to satisfying results because the determination of an exact structure is not possible. Often carbohydrates are different only in their stereochemistry from each other, which makes them indistinguishable for any mass spectroscopy detector. In NMR spectroscopy it is possible to differentiate carbohydrates even if the NMR spectroscopy data are very similar. There are several ways to perform a structural analysis of a saccharide by NMR spectroscopy, each research groups perform carbohydrate structural determination by their own approaches. In the description of classical NMR methods, the experiments are generally either direct observeable 1D or 2D homo- or heteronuclear experiments, such as COSY and HSQC. [35] To analyse more complex molecules, like polysaccharides or proteins, a lot of NMR methods are described in the literature. [34, 35]

In this chapter methods and approaches mainly used in this masters thesis are shown. To get good NMR data, it is of advantage to purify product mixtures to obtain a single product. It is also possible to analyse product mixtures but then it is quite a challenge to analyse every single signal. A complete structural analysis can never be achieved by a single method, it is always necessary to have a multiple data set available, obtained by different experiments.

2.2 ^{1}H and NOESY

There are several ways to perform a first structural analysis, the shortest possible way is to record the ^{1}H spectra to obtain a fast result. In 1983 Vliegenthart *et al.* [36] introduced the *structural reporter group concept*. This concept is based on signals outside of the bulk region (3-4 ppm) in the ^{1}H spectra of carbohydrates.

In figure 2.2 a time dependent NMR study of an Amadori rearrangement is shown. The reactions starts from a D-glucofuranose (**33**), the product is the corresponding D-fructopyranose (**34**) (Figure: 2.1).

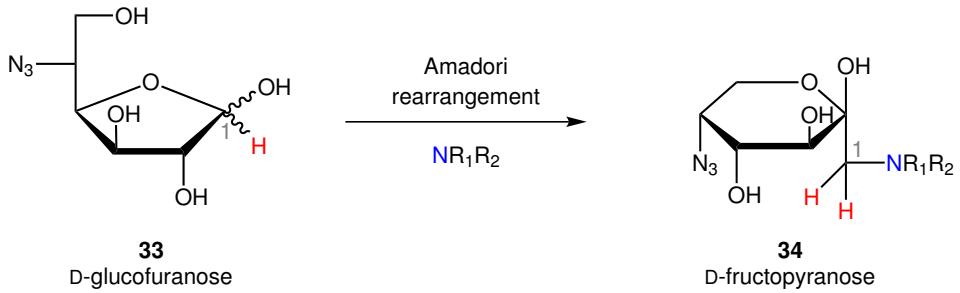


Figure 2.1: Amadori rearrangement from D-glucofuranose (**33**) to D-fructopyranose (**34**).

The kinetic recording shows the consumption of the starting material and the formation of the desired product, clearly visible at the α/β anomeric protons, as reporter groups. With this kind of data it is also possible to follow a reaction mechanism. In this case of the Amadori rearrangement mechanism, no formation of the glycosyl amine or any other intermediate product formation could be observed within the time domain of the NMR experiment.

From the ^{1}H data the second results, the coupling constants can be obtained. With this data it is easy to get important information about the configuration or a change in configuration. In figure 2.3 the vicinal coupling constants for α-D-glucose (**4**) and β-D-glucose (**5**) are shown. In a solution with water as solvent, two doublets δ=5.22 and δ=4.63 can be found for the protons at position C-1. The α-proton can be found more down field, compared to the β-proton, with a smaller coupling constant towards the proton at position C-2. [37]

In this work an inversion of a hydroxyl function at position C-4 from the D-*fructo* configuration **65** to D-*tagato* configuration **66** was a key step (Figure: 2.4). By comparison of the two ^{1}H spectra and the respective coupling constants of H-3, it was quite clear that the inversion worked well. The coupling constant for H-3 and H-4 in the D-*fructo* configuration was found as expected with $J_{3,4}$=9.6 Hz (δ=3.69 H-3$_\beta$). After the inversion to the D-*tagato* configuration the coupling constant was found to be $J_{3,4}$=3.5 Hz (δ=3.60

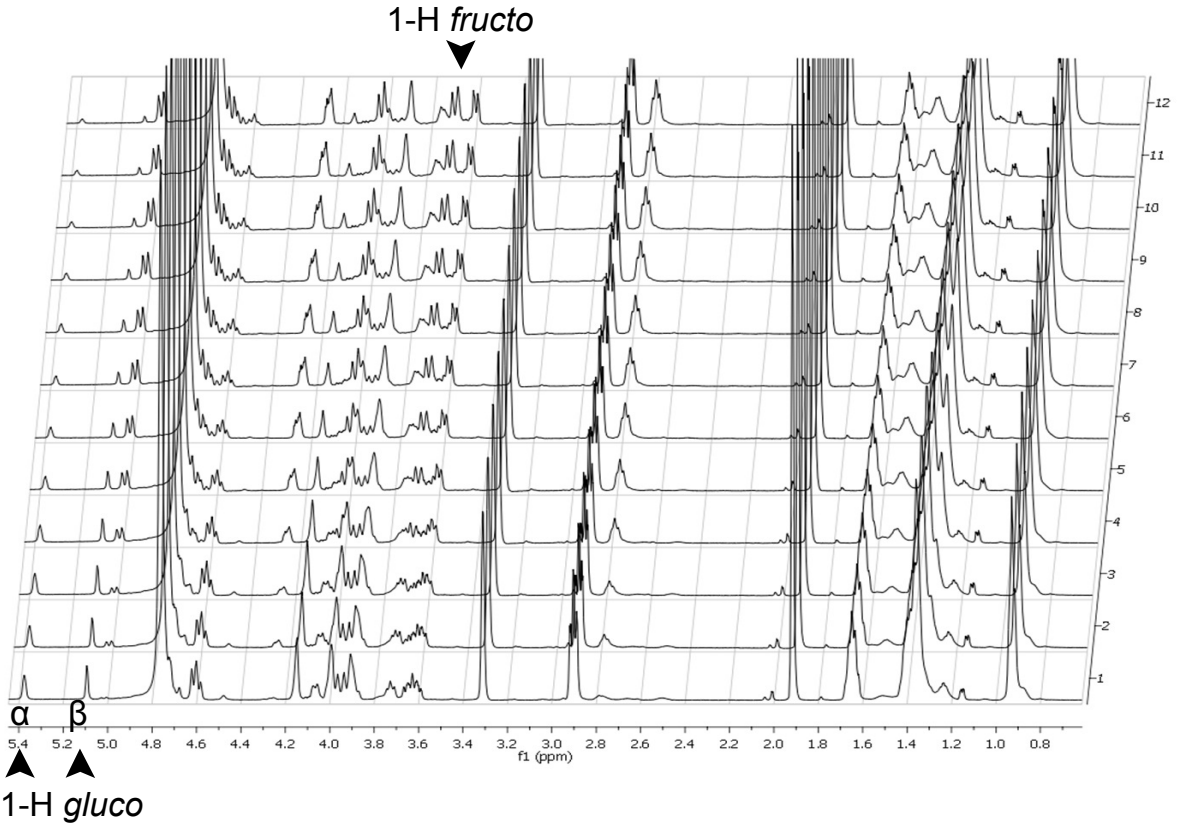


Figure 2.2: Time dependent NMR study of an Amadori rearrangement: D-*gluco* to D-*fructo*.

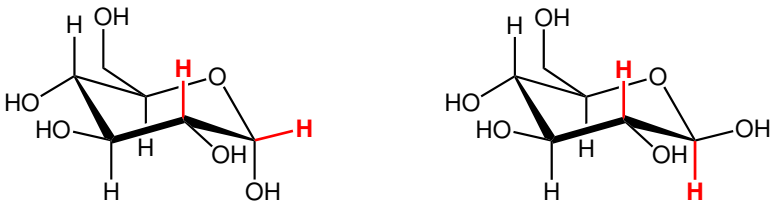


Figure 2.3: Coupling constants of α- and β-D-glucose.

H-3). Furthermore, compound **65** was a α/β-D-*fructo* mixture. It was necessary to find some reporter groups where the chemical shift is separated in the ^{1}H spectrum, in this case luckily the CH_2-Ph protons were better resolved. Calculation of the integrals gave the ratio between the α- and β-compound. The next question to answer was which one is the main component. By taking a closer look, there are just two possibilities how the actual structure can look like, the β-compound **65** (**50**) must appear in a $^2C_5$ and the α-compound in a $^5C_2$ chair formation.

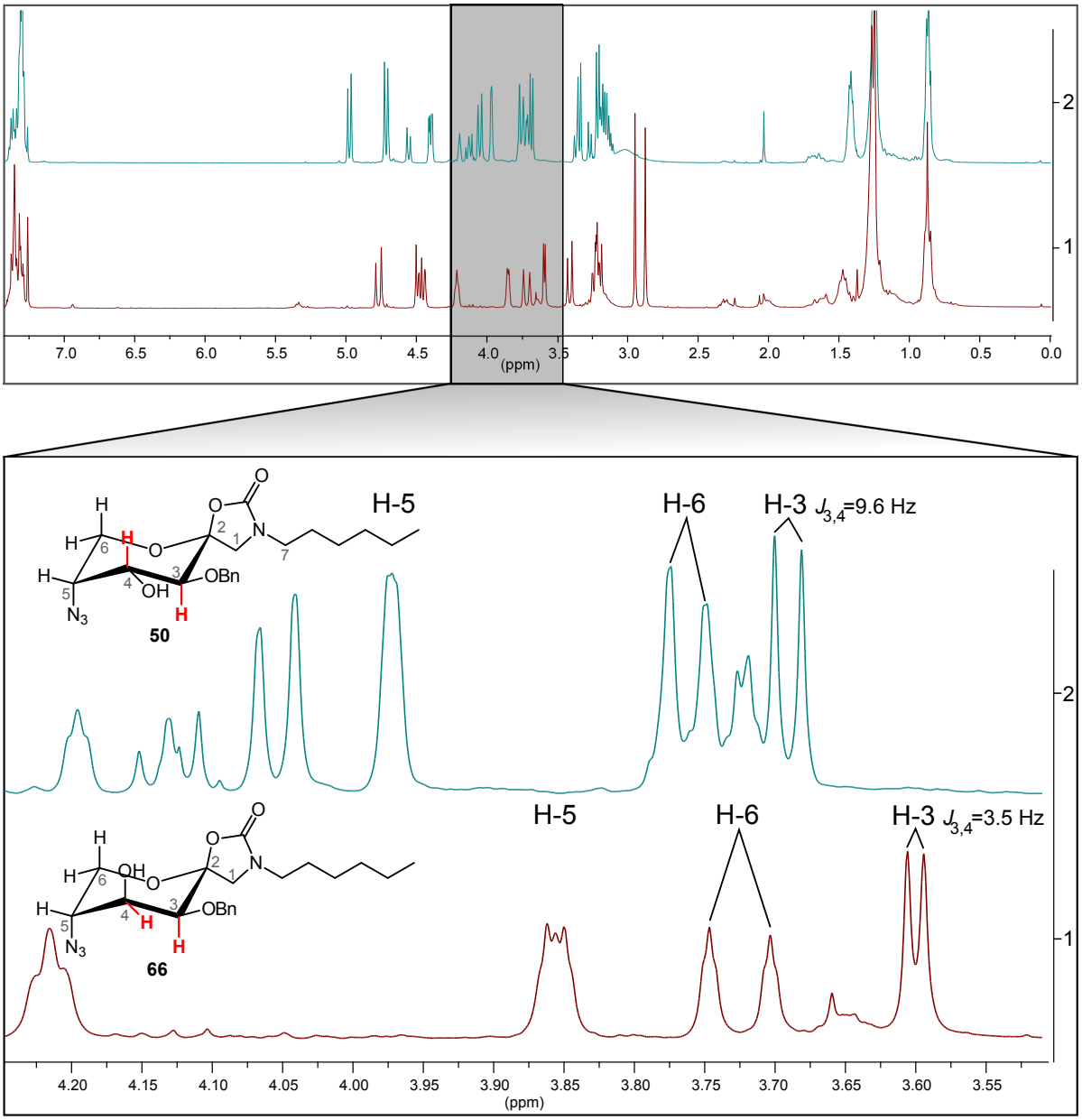


Figure 2.4: ^{1}H spectra of the inversion from D-*fructo* to D-*tagato*.

To answer that question, NOESY spectra were recorded, because if the β-product is the main component a NOE must be observable between one of the protons at position

C-1 and the proton at position C-3. (Figure: 2.4 and figure: 4.9, page: 31) To prove this hypothesis, the proton at position C-3 was stimulated and a signal response in the expected area was found. A double check was possible, by stimulation of the area of position C-1 which showed the same response vice versa. With the NOESY spectra it was possible to identify the β-D-*fructo* compound **65** as the main product.

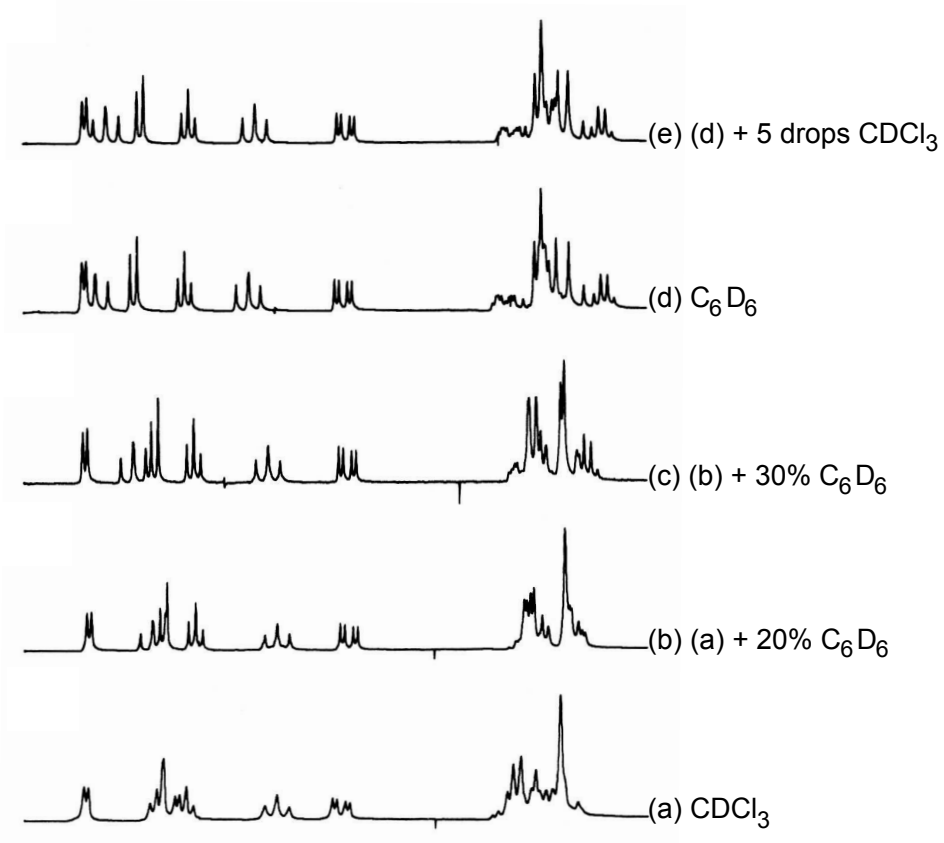


Figure 2.5: ^{1}H spectra of suchrose octa-acetat in different solvent systems.

Very often the signals in a ^{1}H spectrum are overlapping and it is difficult to identify each signal for each proton. Furthermore, it would be difficult to obtain good NOE results if a bulky area is stimulated. It is possible to resolve signal overlapping by using NMR solvent systems. Sanders *et al.* [38] described this possibility of high-field spreading based on sucrose octa-acetat. In figure 2.5 a 250MHz ^{1}H spectrum of sucrose octa-acetat in pure $CDCl_3$ (**a**) is shown, the addition of 20 % C_6D_6 (**b**) produces a dramatic change in the spectrum. In every region of the spectrum a peak shift can be observed, the addition of further 30 % C_6D_6 (**c**) shows even better results. In a second series the sucrose octa-acetat was dissolved in pure C_6D_6 (**d**) but there was some overlapping observed. To get a better result, to the 0.5 mL C_6D_6 solution five drops of $CDCl_3$ (**e**) were added and then eight resolved multiplets and six proton signals overlapped were exhibited.

2.3 ^{13}C and APT

Most of the time ^{1}H spectra give not enough information to characterise a product. The second fastest method to obtain information is a ^{13}C or an APT (Attached Proton Test) spectrum. The APT is a simple experiment for assigning multiplicities in ^{13}C NMR spectroscopy. With that method it is possible to differ between C_q, CH_2 and CH, CH_3 signals. Compared to the DEPT (Distortionless Enhancement by Polarization Transfer) experiment all carbon nuclei are visible in one spectra. [39] In figure 2.6 the difference between a ^{13}C and an APT spectrum can be shown on the example of 1-(*N,N*-dibenzyl)amino-5-azido-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (**68**). In the ^{13}C spectrum it can be difficult to identify all carbon atoms right, here the APT spectrum can be useful.

A very conspicuous reporter signal in a ^{13}C and APT spectrum is the anomeric carbon, the signal can be found typically between 90-110 ppm, mostly in this region no other carbon signals are found. Following a reaction cascade by NMR spectroscopy it is always good to know which signals are reporter signals. For example, inventing a benzyl-protecting group, aromatic signals around 130 ppm are expected or an isopropylidene protection group, two CH_3 signals are expected at approximately 25 ppm and a signal for the acetal at approximately 110 ppm have to show up.

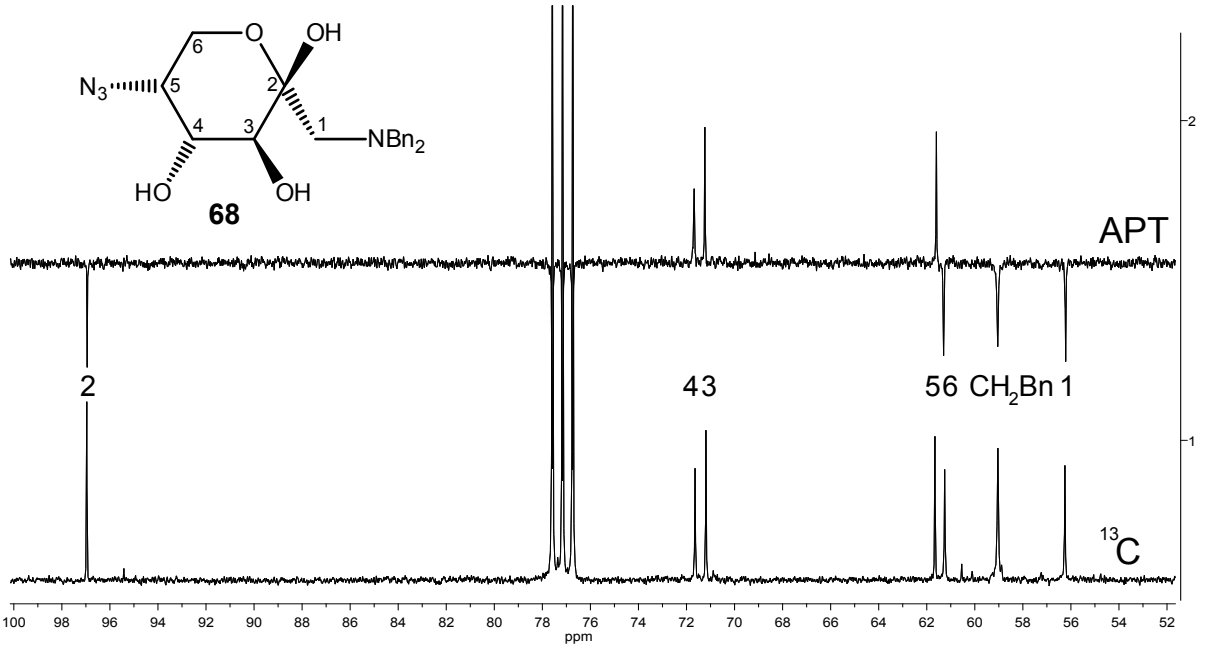


Figure 2.6: ^{13}C and APT data for 1-(*N,N*-Dibenzyl)amino-5-azido-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (**68**).

In this work, in one reaction, compound **42** was expected as the main product, but

there was a signal at 211 ppm and a signal missing in the anomeric region (Page: 66). A ^{13}C spectrum gave the information to recognise that the product was not the desired one.

2.4 COSY and HSQC

COSY (H-correlation spectroscopy) and HSQC (heteronuclear single quantum coherence) are two methods to obtain 2D NMR spectra which provide more information about a molecule and are useful to determine the structure of molecules like carbohydrates. The obtained information from a COSY spectra are couplings between protons with a maximum distance over three bindings. With that information in hand it becomes an easy way to tell which ^{1}H signal belongs to which proton in the molecule. In combination with a HSQC spectrum, were the affiliation between protons and carbons is shown, it is possible to identify every signal. In figure: 2.7 a detail from a HSQC spetctrum of compound 66 is shown.

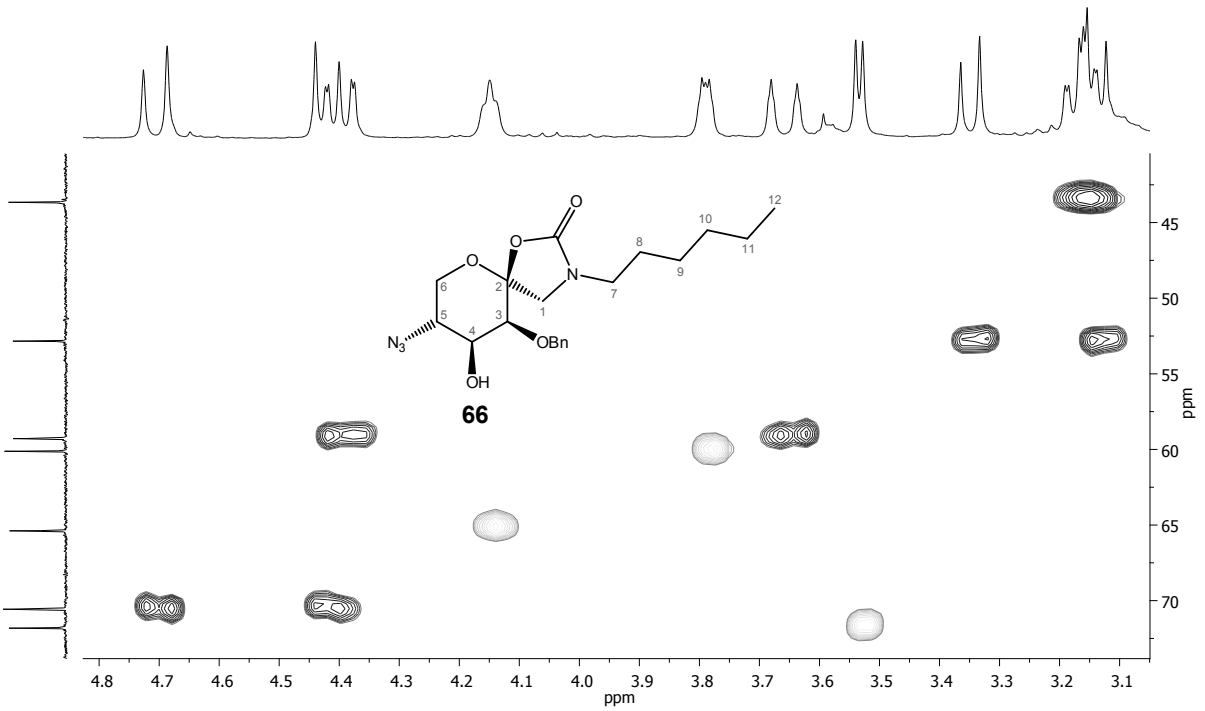


Figure 2.7: Details from a HSQC spectrum of compound **66**.

For analysing complex molecules like carbohydrates excellent results can be obtained by NMR spectroscopy within one hour measuring time. A combination of standard ^{1}H, ^{13}C, COSY and HSQC experiments leads to good analytical results within a short time.

3 Objectives

Iminoalditols, which are sugar analogues with a basic trivalent nitrogen instead of the oxygen in the ring, are well known as powerful glycosidase inhibitors. Therefore, such compounds are used as analytical tools for the investigation of carbohydrate processing enzymes as well as their application as pharmaceuticals against diseases involving this enzyme class.

In the research towards applications of *N*-modified iminoalditols as pharmacological chaperones the interest was paid to the synthesis of glycosidase inhibitors in context with lysosomal storage diseases.

Studies towards the D-altritol series

The main objective of this master thesis was to find a synthesis towards 1-amino-1,2,5-trideoxy-2,5-imino-D-talitol (**35**) derivates, starting from α,β-D-glucufuranorono-6,3-lactone (**36**) as commercially available compound. A key step to introduce an amino group at position C-1, was the Amadori rearrangement, resulting in compound **37**. Furthermore, an important step was the inversion of the configuration at position C-4 starting from compound **37** (D-*fructo*) to compound **38** (D-*tagato*). In the end the desired iminosugar **35** could be synthesised via reductive amination.

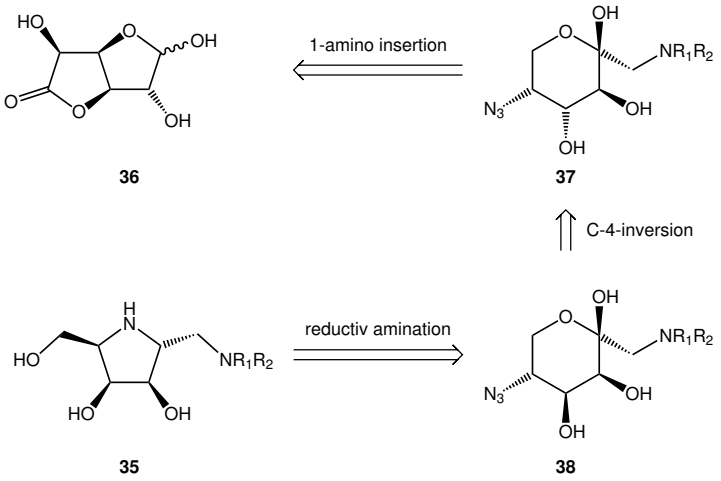


Figure 3.1: Retro-synthetic pathway of 1-amino-1,2,5-trideoxy-2,5-imino-D-talitol.

Studies towards the D-mannitol series

In a second part of this master thesis, two iminosugars in the 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol series, compound **75** and **77**, should be synthesised, starting from 5-azido-5-deoxy-α, β-D-*gluco*-furanose (**67**).

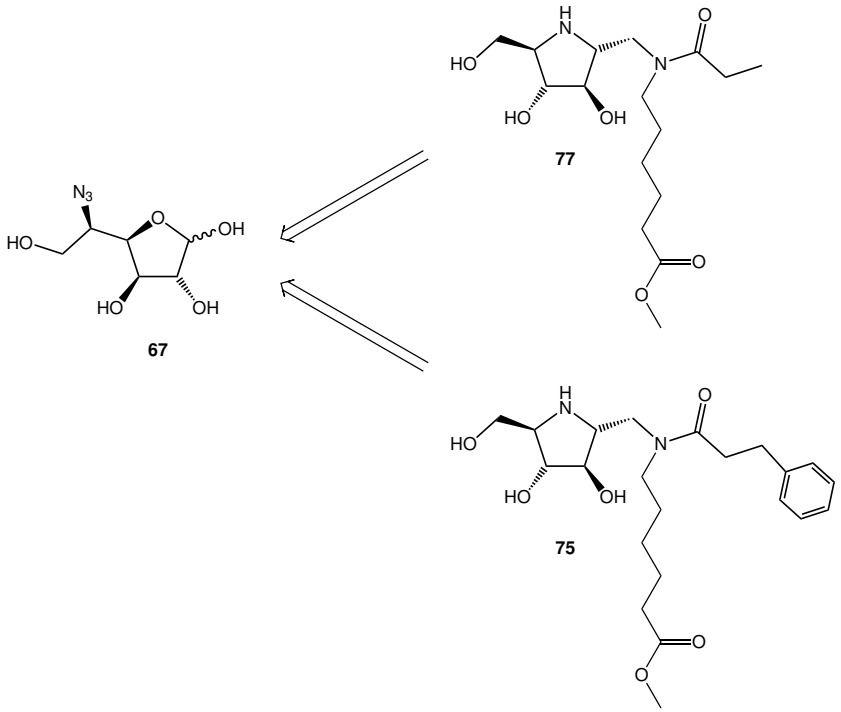


Figure 3.2: Retro-synthetic pathway towards the 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol series.

4 Results and Discussion

4.1 Studies towards the D-altritol series via 2,3-*O*-isoproyplidene protection

The first synthetic aim of this master thesis was to synthesise 1-amino-1,2,5-trideoxy-2,5-imino-D-talitol (**35**) via well known chemical reactions using a 2,3-*O*-isoproyplidene protection as the key step.

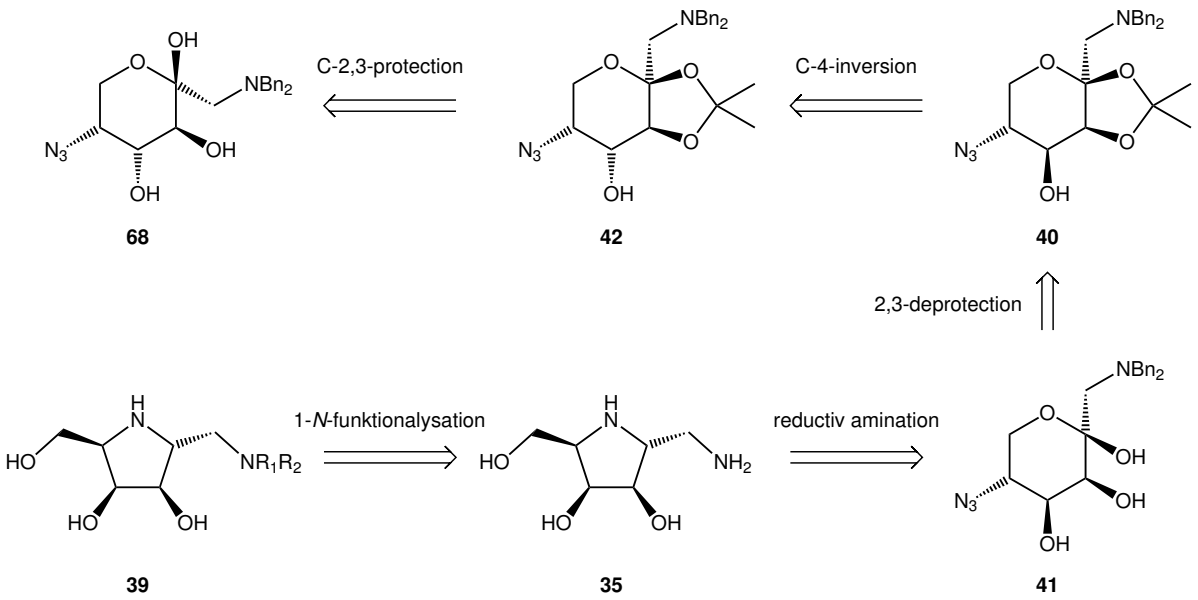


Figure 4.1: Retro-synthetic pathway of 1-amino-1,2,5-trideoxy-2,5-imino-D-talitol (**35**) via 2,3-*O*-isoproyplidene protection.

In order to get a single unprotected hydroxyl function at position C-4 allowing for an inversion of configuration at this stereocenter thereby changing from the D-*fructo* to the D-*tagato* configuration and from there on to the desired iminosugar **35**, 2,3-*O*-isoproyplidene protection of compound **68** was the main objective. Compound **68** was synthesised starting from α,β-D-glucufuranorono-6,3-lactone (**36**), a reasonable prized commercially available compound. The seven steps (Figure: 4.2) towards compound **68** are well known. [40]

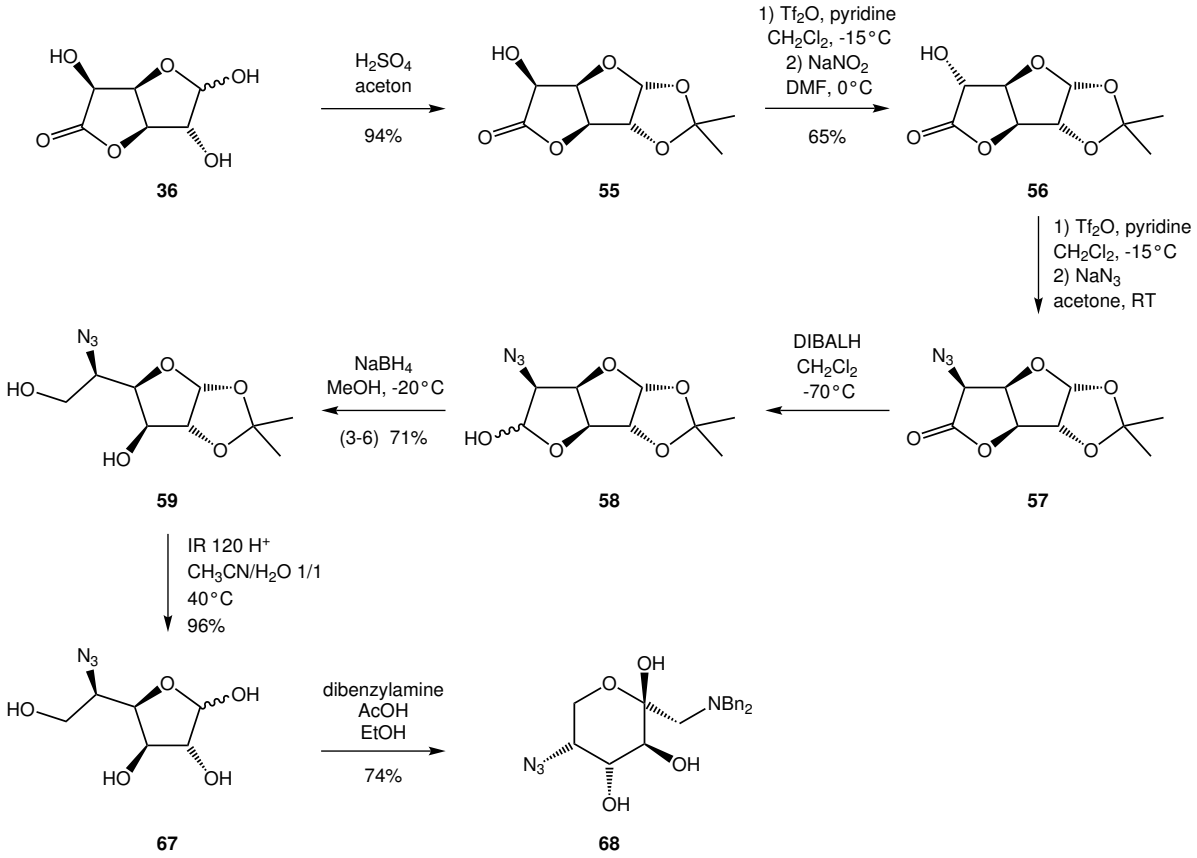


Figure 4.2: Synthesis of 1-(*N,N*-dibenzyl)amino-5-azido-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose **68**.

Starting from compound **36**, an isoproyplidene protecting group was introduced at positions *O*-1 and *O*-2 under acid catalysis in aceton, to obtain compound **55**. In order to remain in the *gluco* configuration, first a S_N2 reaction at position C-5 of compound **56** was performed leading to the L-*ido* configuration in compound **56** followed by a second S_N2 reaction to insert the azido group at the same position was performed to obtain 5-azido-5-deoxy-1,2-*O*-isoproyplidene-α-D-*gluco*-furanurono-6,3-lactone (**67**). The reduction from compound **57** to compound **59** was performed in a two step strategy described by Fleet *et al.* [41]. First the lacton **57** was reduced with DIBALH to the respective lactol **58**, in the second step the lactol **58** was reduced with $NaBH_4$ to 5-azido-5-deoxy-1,2-*O*-isoproyplidene-α-D-*gluco*-furanose (**59**). In principal, it would be possible to reduce the lacton **57** to compound **59** directly with $NaBH_4$ under pH control, but the two step procedure gave a much better yield. In the next step the 1,2-*O*-isoproyplidene protection group in component **59** was hydrolysed under acidic conditions employing acid ion exchange resin in a solvent system containing water and acetonitrile in an excellent yield of 96 %. To obtain compound **68** with unprotected hydroxyl groups at position C-2,3,4 a disubstituted amine was used to introduce the 1-amino function at position C-1

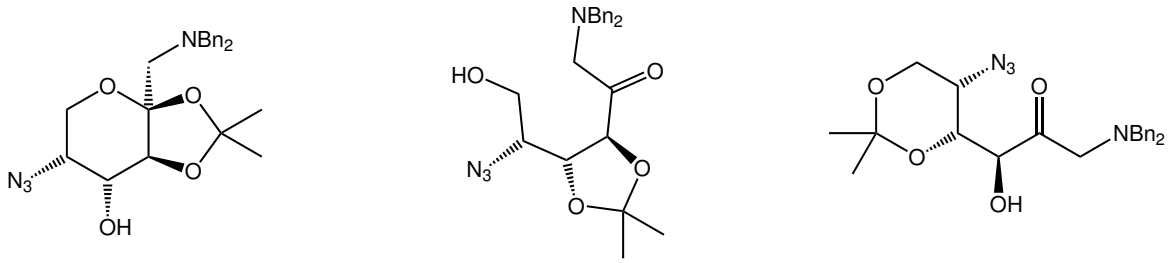
and protect it at the same time. Dibenzylamine was used for the Amadori rearrangement reaction to get 1-(*N,N*-dibenzyl)amino-5-azido-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (**68**). Furthermore, in a later reductive amination step the two benzyl protecting groups of the dibenzylamino compound will be hydrolytically cleaved to obtain an unprotected amine group.

To protect the hydroxyl functions at position C-2 and C-3 in compound **68**, the main idea was to use the same technique as in the first step of this reaction cascade. In preliminary test, compound **68** was dissolved in aceton (2 mL) and in one case two drops and in a second case ten drops of H_2SO_4 were added. TLC showed full conversion of the starting material after one hour reaction time. After treatment with $NaHCO_{3\ aq.\ sat.}$, TLC showed again starting material in the reaction with two drops H_2SO_4, the reaction with ten drops showed no starting material but also no possible product formation. Because of these results, obviously a change to more moderate reaction conditions was the logical consequence. As acid catalysts pTSA and PpTS, aceton as solvent and dimethoxypropane was used in test reactions. After a reaction time of 24 hours the reaction catalysed with pTSA exhibit two possible product spots on the TLC.

After these first positive results, an upscaling of the reaction with compound **68** (100 mg, 0.28 mmol, 1 eq) as starting material was performed. In the first reaction, aceton (20 mL), dimethoxypropane (2 mL, 16.1 mmol, 58 eq) and pTSA (100 mg, 0.53 mmol, 1.9 eq) were stirred for one hour until TLC showed full conversion of the starting material. There was again some salt formation observed, which was confirmed after the reaction mixture was washed with CH_2Cl_2 and $NaHCO_{3\ aq.\ sat.}$. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography. A first NMR analysis of one of the main product spots showed promising results, the compound could be the desired 1-(*N,N*-dibenzyl)amino-5-azido-1,5-dideoxy-2,3-*O*-isoproyplidene-β-D-*fructo*-hex-2-ulopyranose (**42**) (40 mg, yield 30 %). But NMR analysis showed ambiguous results, in fact there was just a very small amount of the product. To get better analytical information a mass spectrum was recorded and showed an expected mass of 424g·mol^{-1}.

To optimise the yield of the products, slightly different reaction conditions were used in the following reactions. In particular, the dimethoxypropane volume and the reaction time were changed. The highest yield (67 %) was achieved by using compound **68** (100 mg, 0.28 mmol, 1 eq), aceton (20 mL) and dimethoxypropane (1 mL, 8.0 mmol, 29 eq) at room temperature for four days. Then a NMR analysis with higher concentration showed that the formed product was not the expected 2,3-*O*-isoproyplidene sugar **42**. The analysed product turned out to be the open chain reductive alditol **69**, namely 1-(*N,N*-dibenzyl)amino-5-azido-1,5-dideoxy-3,4-*O*-isoproyplidene-D-*arabino*-hex-2-ulose **69**

(Figure: 4.3).



42
Chemical Formula: $C_{23}H_{28}N_4O_4$
Exact Mass: 424,21

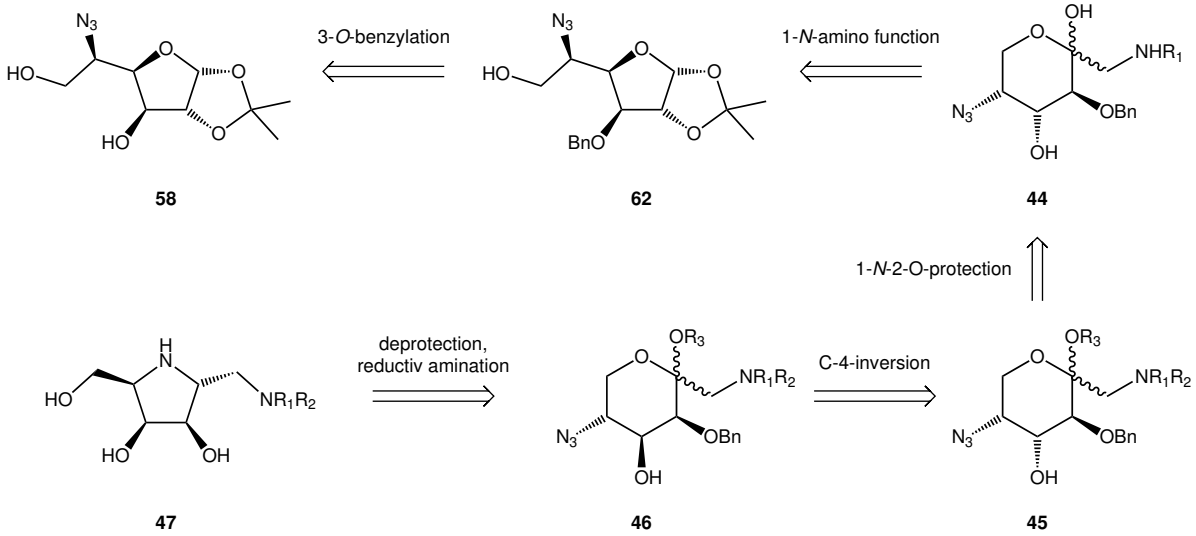
69
Chemical Formula: $C_{23}H_{28}N_4O_4$
Exact Mass: 424,21

43
Chemical Formula: $C_{23}H_{28}N_4O_4$
Exact Mass: 424,21

Figure 4.3: Possible product isomers by isoproyplidene protection.

With none of these reaction conditions, desired compound **42** could be isolated. In another series different acid catalysts were tried. In small volume reactions, AcOH, sulfamic acid, trichloroacetic acid and dimethoxypropane with aceton as solvent were used, but no conversion of the starting material could be observed. Therefore, we changed our synthetic strategy for the preparation of the desired 1-amino-1,2,5-trideoxy-2,5-imino-D-talitol (**35**).

4.2 Studies towards the D-altritol series via 3-*O*-benzyl protection



58 **62** **44**

47 **46** **45**

Figure 4.4: Retro-synthetic pathway of towards 1-amino-1,2,5-trideoxy-2,5-imino-D-talitol (**35**) via 3-*O*-benzyl protection.

Because the first attempt of a synthetic path to 1-amino-1,2,5-trideoxy-2,5-imino-D-talitol (**35**) failed, a slightly longer route was designed. The main idea of the second way was to start from 5-azido-5-deoxy-1,2-*O*-isoproyplidene-α-D-*gluco*-furanose (**59**) and to protect the hydroxyl function at position C-3 with a benzyl group which is hydrogenolytically cleaveable in the reductive amination step. After the hydroxyl group at position C-3 was protected to give compound **62**, an amino function at position C-1 should be introduced to give compound **44** followed by protection of the amine and the hydroxyl group at position C-2 as cyclic carbamate, to give compound **45** in order gain the hydroxyl function at position C-4 available for the inversion step to obtain compound **46**. To complete the synthesis the cyclic carbamate **45** could be cleaved and finally an intramolecular reductive amination with concomitant debenzylation would give desired 1-amino-1,2,5-trideoxy-2,5-imino-D-talitol derivative (**47**).

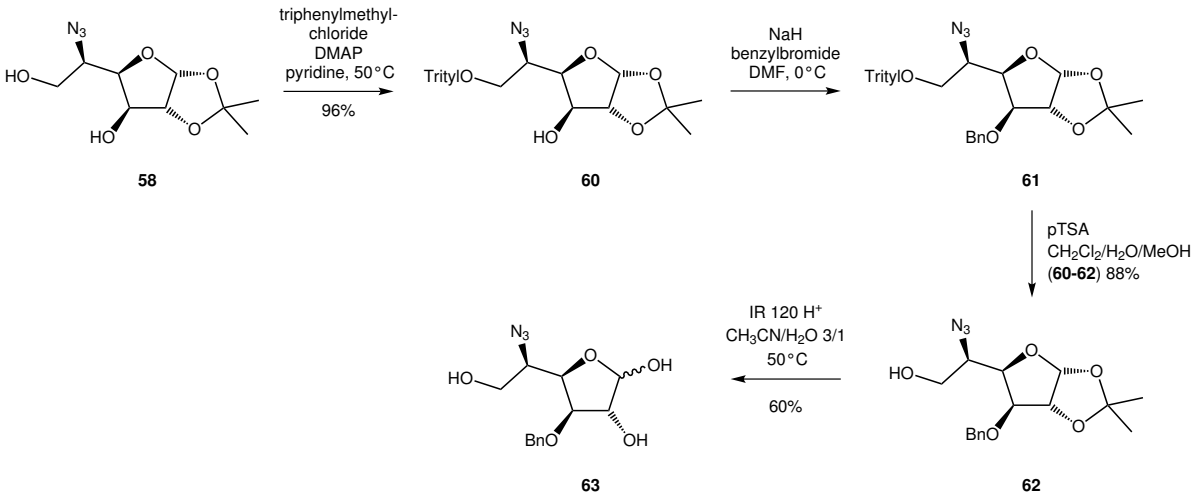


Figure 4.5: Synthesis towards 5-azido-3-*O*-benzyl-5-deoxy-α,β-D-*gluco*-furanose (**63**).

For the protection of the hydroxyl group at position C-3 of compound **59**, first the hydroxyl group at position C-6 was blocked by a trityl group. A trityl-protecting group can be installed regio-selectively at primary hydroxyl groups and in this case with very good yields (96 %) to obtain compound **60**. The free hydroxyl group on compound **60** was benzylated under standard conditions to obtain compound **61**. The trityl- and 1,2-*O*-isoproyplidene protection groups are both acid labile. Hydroxyl groups at positions C-1, C-2 and C-6 could be deprotected within one step, because both, the trityl group as well as the isopropylidene group can be split off under acid conditions. Acid ion exchange resin (IR 120 H^+) in H_2O/CH_3CN (v/v, 1/1) was used. Unfortunately, compound **61** could not be dissolved in the solvent system, therefore, a two step deprotection cascade had to be performed. In the first step the hydroxyl group at position C-6 was deprotected with pTSA in a CH_2Cl_2/H_2O/MeOH solvent system, and in the second step the 1,2-*O*-

isoproyplidene protection group was deprotected with acid ion exchange resin (IR 120 H^+) in H_2O/CH_3CN (v/v, 1/1). Overall the complete deprotection took eleven days and compound **63** was obtained in acceptable yields.

4.2.1 6-Aminohexanol as amino component in the Amadori rearrangement

The reason why 6-aminohexanol was used in the Amadori rearrangement was the terminal hydroxyl group on the spacer for further functionalization. The amine was used under standard Amadori rearrangement conditions to obtain 1-(*N*-hydroxyhexyl)amino-5-azido-3-*O*-benzyl-1,5-dideoxy-α,β-D-*fructo*-hex-2-ulopyranose (**70**). To protect the secondary amine at position C-1 and the alcohol at position C-2 at the same time a cyclic carbamate, compound **71**, was formed, however only a yield of 22 % was obtained. Nevertheless, remaining compound **71** was used for further studies. The primary alcohol was protected using the trityl group to give compound **72**, also in this protection step the yield was not satisfying (30 %).

To oxidise the hydroxyl function at position C-4, a small amount of compound **72** was treated with Dess Martin reagent in CH_2Cl_2 at room temperature for 16 hours. No significant product **48** was observed on TLC. Again the strategy had to be changed, a shorter pathway by excluding the terminal hydroxyl group on the spacer was planned.

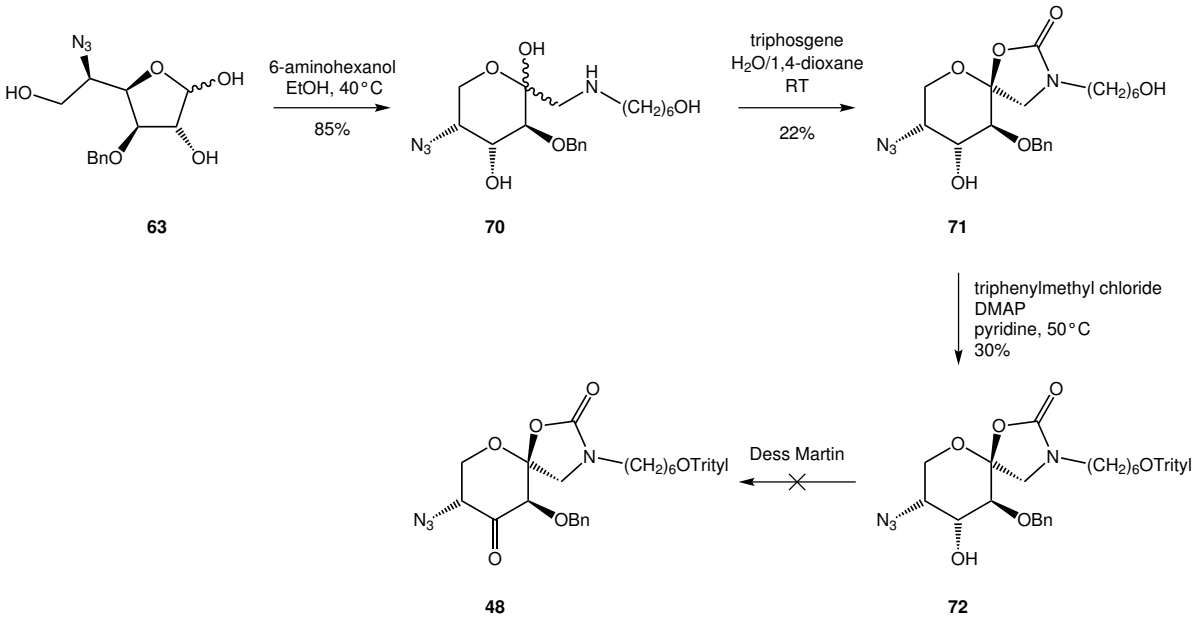


Figure 4.6: Synthesis towards 1-(*N*-trityloxyhexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2,4-*O*-dicarbonyl-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (**72**).

4.2.2 Hexylamine as amino component in the Amadori rearrangement

Starting with compound **63**, hexylamine was used under standard Amadori rearrangement reaction conditions to obtain 1-(*N*-hexyl)amino-5-azido-3-*O*-benzyl-1,5-dideoxy-α,β-D-*fructo*-hex-2-ulopyranose (**64**) in a good yield (81 %). To optimise the reaction conditions some changes in the reaction temperature and reaction time were made. Room temperature and shortest possible reaction time gave the best yield (Table: 4.1). With higher temperatures (>40 °C), even for a short period, TLC showed very fast conversion of the starting material. In every case the yield was not good, properly the obtained product steps forward in the Maillard reaction cascade at higher temperatures. The solvent was removed under reduced pressure at 40 °C for about 15 minutes. Therefore, perhaps the yield will be higher if room temperature is used to remove the solvent.

Table 4.1: Reaction conditions for Amadori rearrangement with hexylamine.

Time	Temperature	Yield
20 h	44 °C	42 %
1 h/0.5 h	RT/40 °C	50 %
66 h	RT	76 %
18 h	RT	81 %

To protect the amine at position C-1 and the hydroxyl group at position C-2, a cyclic carbamate was introduced, in an acceptable yield (67 %) compound **65** in an α/β ratio of 2/5 was obtained. The hydroxyl function at position C-4 remained as the only unprotected group. For the inversion of the alcohol at position C-4, an oxidation-reduction sequence was conceived. The oxidation was performed employing Dess Martin reagent in CH_2Cl_2 at room temperature, but TLC showed no product formation or consumption of the starting material.

There exists the posibillity that the starting material **65** and product **49** could have the same R_f-value on TLC. After a reaction time of five hours the reaction mixture was washed with CH_2Cl_2 and $NaHCO_{3\ aq.\ sat.}$, the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. It was tried to purify the residue by column chromatography but no product could be isolated. Maybe the desired product was formed, but was degraded in work up process.

Another oxidation method for the secondary alcohol at position C-4 to a carbonyl is to use pyridiniumdichromat (PDC), related to the work of Fechter *et. al.* [42] Compound **65** was dissolved in CH_2Cl_2 and PDC was added, the reaction was stirred at room temperature for 20 hours. Again TLC showed no product formation. Because of the

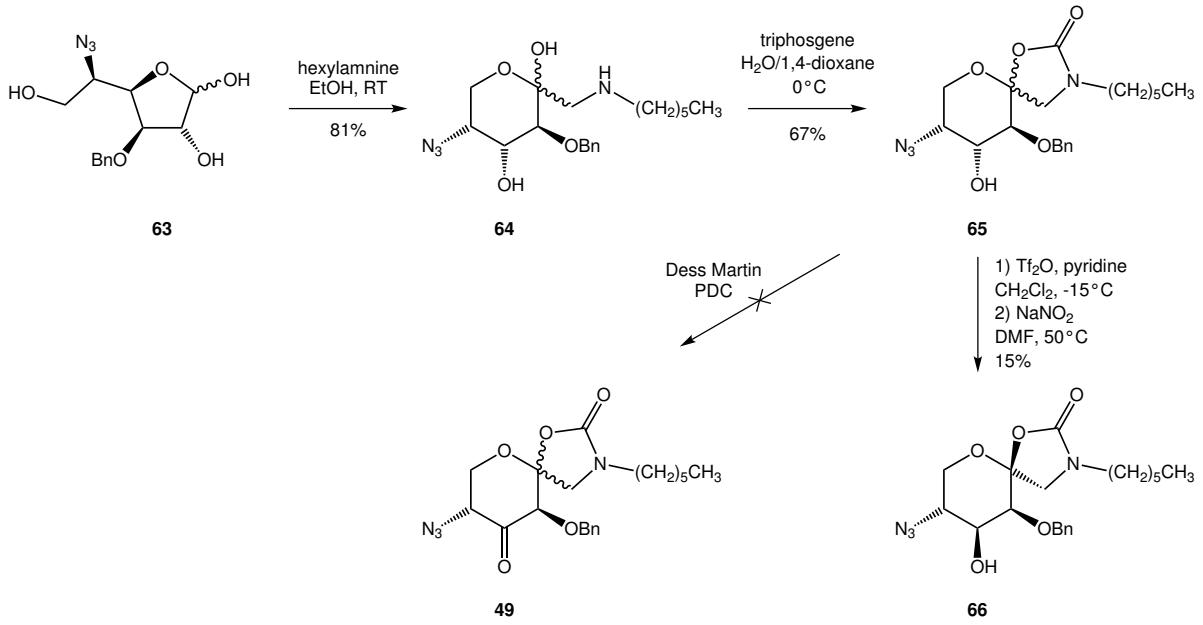


Figure 4.7: Synthesis towards 1-(*N*-hexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-β-D-*tagato*-hex-2-ulopyranose.

possibility that starting material and product may have the same R_f-value the reaction mixture was worked up and purified by column chromatography. Again NMR analysis showed no conversion of the starting material.

To invert the hydroxyl function at position C-4 from D-*fructo* to D-*tagato* a S_N2 reaction was the next option. Compound **65** was treated in the same way as in case of the inversion from compound **55** to **56** (Section: 4.1) by a two step procedure. Compound **65** was dissolved in CH_2Cl_2, cooled to 0 °C and triflic anhydride was added. After TLC showed two more polar spots (A,B in Figure: 4.8), which confirmed the assumption that there an α/β mixture was formed.

In the second step, two different progressions were observed. After 16 hours stirring at room temperature a conversion from compound **B** to **C** was observed, but there was still no conversion from compound **A** to **66**. Compound **C** was a red spot on the TLC which indicates a possible elimination product (Figure: 4.8). Afterwards the reaction was heated up to 50 °C for six days, the formation of product **66** was slowly observed during that time. A full conversion of compound **A** has never been observed. There is the possibility that the activated hydroxyl group at position C-4 is very stable under that reaction conditions applied. After work up the residue was purified by column chromatography. 1-(*N*-hexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-β-D-*tagato*-hex-2-ulopyranose (**66**) was clearly identified by NMR analysis. It was not possible to separate compound **A** and **C** by column chromatography, therefore, no further

analytical experiment were made.

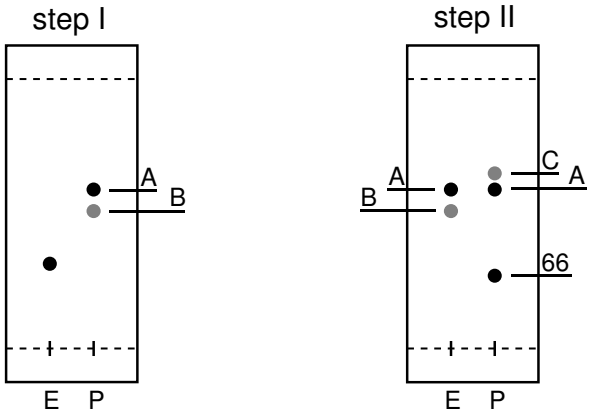


Figure 4.8: TLC-progress towards 1-(*N*-hexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-β-D-*tagato*-hex-2-ulopyranose (**66**).

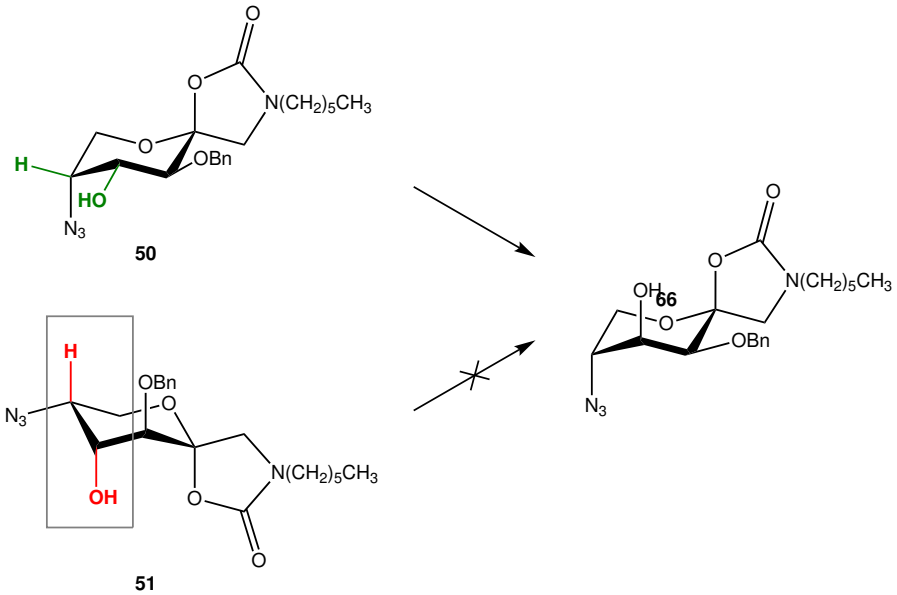


Figure 4.9: Chair conformations of compound **65** and compound **66**.

With this method in hands it was possible to invert the hydroxyl function at position C-4, but a maximum yield of 30 % and a quite long reaction time were not satisfying. The α/β mixture was one of the reasons, that there was such a bad yield, because just the β-product **50** can be converted to compound **66**. The α-product **51** forms an elimination product, because the hydroxyl group at position C-4 and the hydrogen at position C-5 are in a trans-diaxial position (Figure 4.9). For that reason a change in protecting group strategy for the amine and the alcohol at position C-2 was made. The idea was to protect the amine selectively with a Cbz protecting group (Figure: 4.10).

In the first reaction compound **64** (300 mg, 0.79 mmol, 1 eq) was dissolved in CH_2Cl_2, Et_3N (0.22 mL, 1.59 mmol, 2 eq) and benzyl chloroformate (0.14 mL, 0.79 mmol, 1 eq) were added. TLC showed full conversion of the starting material after 15 minutes. The reaction was diluted with CH_2Cl_2 washed with $HCl_{aq.}$ (6 %) and $NaHCO_{3\ aq.\ sat.}$, the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue, was purified by column chromatography to obtain (170 mg, 24 %) the possible 1-(*N*-carboxybenzyl-*N*-hexyl)amino-5-azido-3-*O*-benzyl-1,5-dideoxy-α,β-D-*fructo*-hex-2-ulopyranose (**52**). NMR analysis showed no clear result. Possibly the free hydroxyl group at position C-4 was also protected with the Cbz group under the reaction conditions employed. In a very small experiment under slightly different reaction conditions, MeOH as solvent and without Et_3N, the same product spot was observed by TLC analysis.

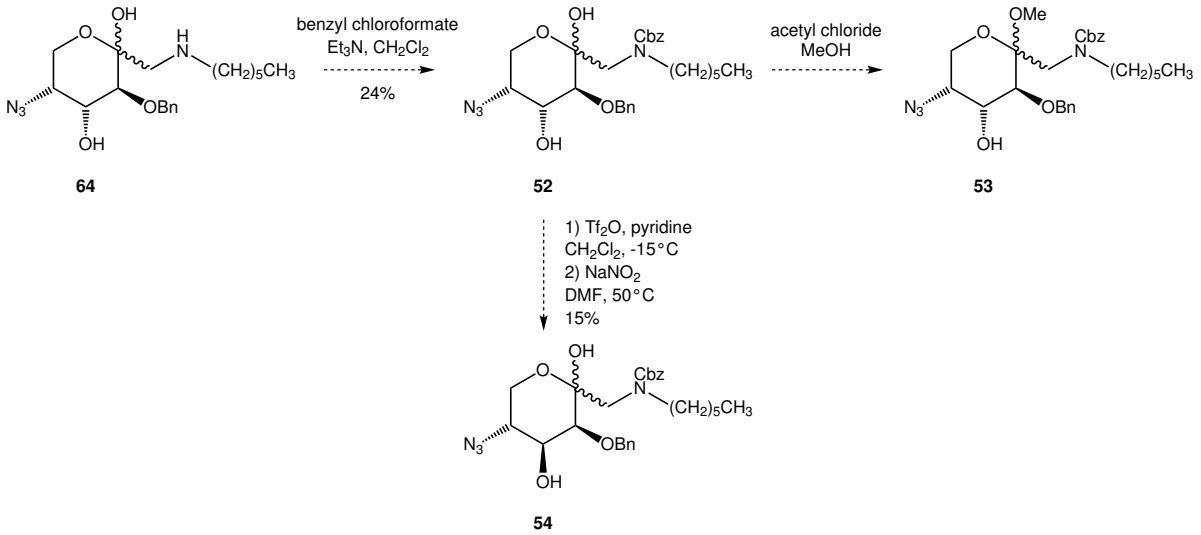


Figure 4.10: Synthesis towards the Cbz-protected amine.

To clarify the situation, the anomeric hydroxyl group was tried to be converted to a methyl glycoside (**53**). To form the methyl glycoside, a very small amount of possible compound **52** was dissolved in MeOH and acetyl chloride was added. After 20 hours, TLC showed full conversion of the starting material. The solvent was removed under reduced pressure and a crude NMR was recorded, but the product amount was to small to get any result. Because TLC showed conversion of the starting material a fully protection of compound **52** could be excluded. Any attempt to clear the situation was unsuccessful, desired compound **53** could not be identified.

In the assumption that compound **52** is the expected one, an inversion of the hydroxyl group at position C-4 was tried, to obtain compound **54**. The reaction conditions applied were the same which were employed for compound **66**. After the first step, TLC showed

four possible product spots. In the second step just one of the spots turned into another product spot but the desired product could not be isolated. By running out of starting material this reaction sequence was not further investigated.

4.3 Studies towards the D-mannitol series

In the end of this master thesis a reaction pathway towards 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol derivatives, compound **75** and **76**. , was investigated. The aim was to synthesise two iminosugars for investigation of their biological activity towards glycosyl hydrolases.

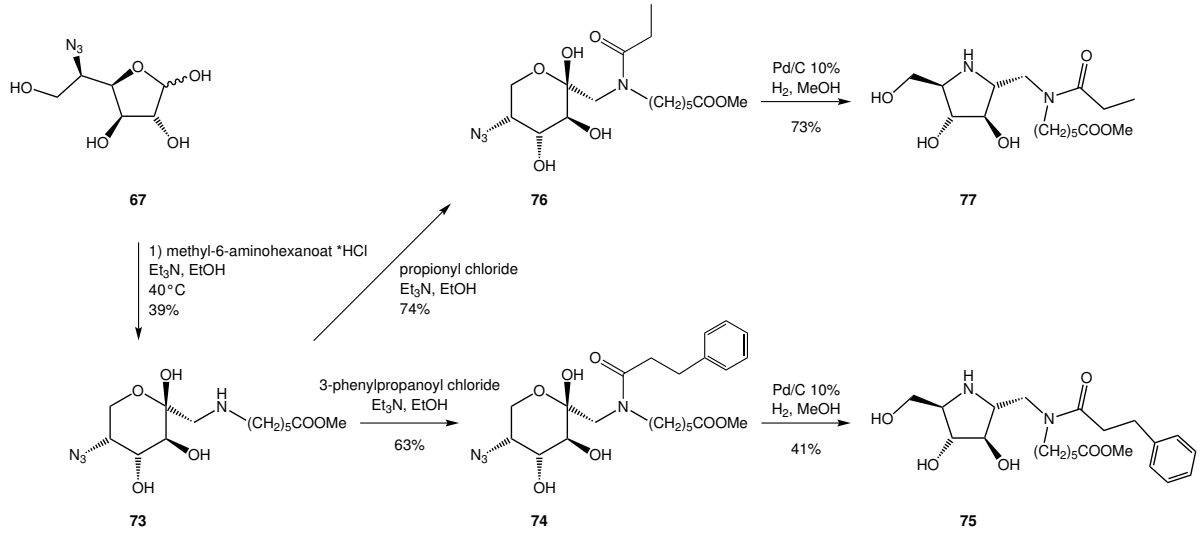


Figure 4.11: Synthesis of 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol derivatives, compound **75** and **76**.

Starting from compound **67** and methyl 6-aminohexanoat hydrochlorid an Amadori rearrangement gave compound **73** in moderate yields (39 %). In that case, the reaction was always stirred at 40 °C or even higher temperature. Maybe a higher yield can be achieved, if the reaction would have been stirred at room temperature, like in section 4.2.2 described. Subsequently, the amine of the Amadori rearrangement product was transformed to an amide. In the first case, the amide formation worked with a yield of 63 %, to obtain compound **74**. The second compound **76** was obtained in a good yield of 74 %.

The last and final step of this master thesis was the reductive amination of compound **74** and **76**. Both reactions were performed as described in section 6.3.2. Compound **75** was obtained in a yield of 41 % and compound **77** in a good yield of 73 %. The reaction towards 1-(*N*-ethylcarbonyl-*N*-methoxycarbonylpentyl)amino-1,2,5-trideoxy-2,5-imino-

D-mannitol (**76**) was also performed on a H-Cube [43]. In this case Pd/C as catalyst was used, but a small loading of starting material inactivated the catalyst. Toward the formation of an iminosugar, the H-Cube is not the method of choice.

The NMR analysis of both products showed a double set of signals. This could be explained, because the electron pair and the three substituents hindered a inversion of the nitrogen which was observable in the NMR time domain. Another possibility was the formation of C-2 diastereomers. A drop of hydrochloric acid was added to the NMR-sample to form a hydrochloride, followed NMR results showed just one set of signals, confirming no C-2 diastereomer formation. In figure 4.12, part of the NMR data, before and after the addition of hydrochloric acid to compound **77**, are shown.

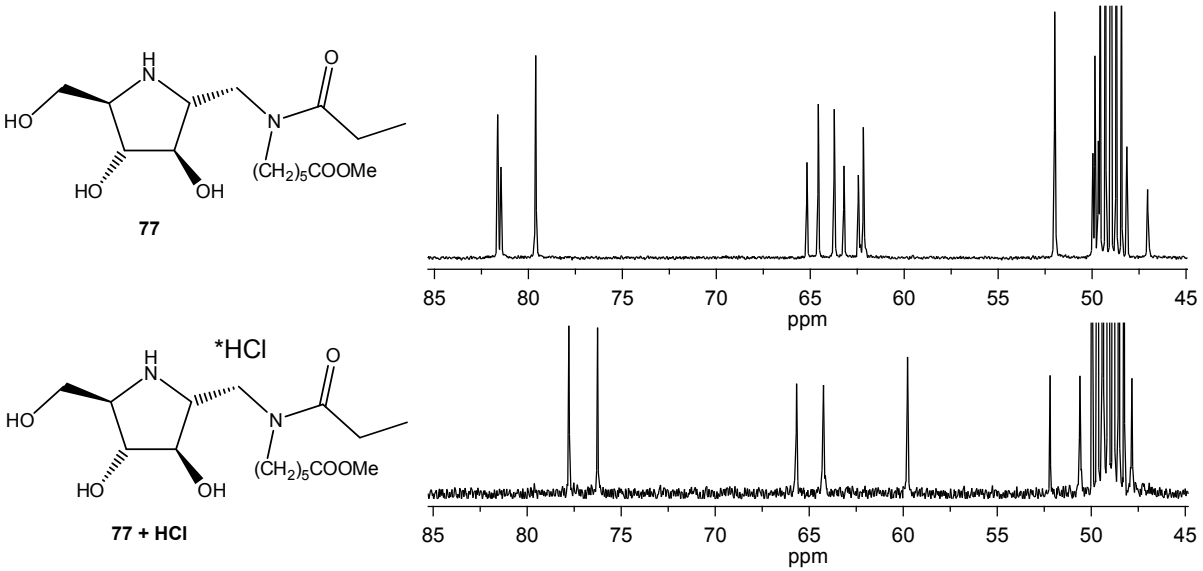


Figure 4.12: NMR data, before and after the addition of HCl to compound **77**.

5 Conclusion

In conclusion, the synthesis towards 1-amino-1,2,5-trideoxy-2,5-imino-D-talitol (**35**) was investigated, to get potential α-galactosidase inhibitors. In this case the Amadori rearrangement was used as a key step which opens the possibility for introduction of different amino substituents at position C-1. Follow up chemistry at the C-1 amino terminus allows for further decoration with reporter groups such as fluorescent dyes, biotin or fluoroalkyl substituents.

The first synthetic attempt of this master thesis was a pathway with well known chemical reactions using a 2,3-*O*-isoproyplidene protection. Herein, the protection strategy did not work as expected and gave, as a main product, the open chain reductive alditol **69**. This molecule may be used for other synthetic aims in carbohydrate chemistry, but a further investigation was to extensive.

Therefore, the strategy was changed into a slightly longer route and a different amine for the Amadori rearrangement was used. The major reason for the change of the Amadori product and following protection group strategy was, to gain the hydroxyl group at position C-4 available for inversion. This was realized by protection of the hydroxyl group at position C-3 with a benzyl group and both the amine at position C-1 as well as the hydroxyl group at position C-2 were protected by a cyclic carbamate.

The use of 6-aminohexanol as amine, the above described protection strategy followed by inversion of the hydroxyl group at position C-4, failed by using an oxidation-reduction sequence. The same attempt, using hexylamine as amine for the Amadori rearrangement, also failed.

The inversion could sucessfully be acheived by a S_N2 reaction. However, the yield was rather low because the carbamate protected compound **65** was an α/β mixture were just the β-compound give the desired product. To complete the synthesis the cyclic carbamate **66** has to be cleaved and finally an intramolecular reductive amination with concomitant debenzylation would give desired *N*-hexyl-1-amino-1,2,5-trideoxy-2,5-imino-D-talitol (**35**). Because of the low yield this reaction cascade was not further investigated at this time.

One major reason because the protection group strategy had to be changed a third time, was the rather low yield of compound **66**. Instead of the cyclic carbamate, a protection of the amine at position C-1 by a Cbz group **52** and a conversion of the

hydroxyl group at position C-2 to a methyl glycoside **53** was tried. The ambiguously results obtained from NMR studies were never clarified.

In the end of this master thesis a reaction pathway towards 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol derivatives, compound **75** and **77** was investigated and worked quite well. These two compounds will be investigated for their biological activity towards glycosyl hydrolases.

6 Experimental

6.1 Analytics

Thin layer chromatography

Analytical TLC was performed on silica gel coated aluminium plates. (Merck, TLC Silica gel 60 F_{254}). Spot detection by UV-light (254 nm) and visualization reagent by subsequent heating.

Visualization reagent

- **vanilline/sulfuric acid:** 0,3 g Vanillin in: 30 mL H_2O, 25 mL EtOH and 4 mL H_2SO_4 $_{conc.}$
- **ammoniummolybdate/ceric sulfate:** solution I: Ammonium molybdate (100 g in 1000 mL H_2SO_4 (10 %)), solution II: Ceric(IV)sulfat (8 g in 80 mL H_2SO_4 (10 %)); Both solutions were prepared separately and were combined afterwards.

Optical rotations

Optical rotation was measured on a Perkin Elmer 341 polarimeter at the wavelength of 589 nm, a cell path length of 10 cm and at 20 °C.

NMR

For ^{1}H and ^{13}C spectra a Bruker Ultrashield 300MHz (^{1}H 300.36MHz and ^{13}C 75.53MHz) and a Varian Inova 500MHz (^{1}H 499.98MHz and ^{13}C 125.69MHz) spectrometer were used. For ^{1}H spectra the chemical shifts are reported in δ (ppm) with the solvent signal as internal standard. All spectra were recorded at room temperature.

The NMR data is reported as follows: chemical shift (^{13}C carbon; ^{1}H multiplicity, quantity, coupling constant and assignment).

Table 6.1: Abbreviations used for reporting NMR multiplicity.

s	singlet	bs	broad singlet
d	doublet	dd	doublet of doublets
t	triplet	ddd	doublet of doublet of doublets
q	quadruplet	m	multiplet

Mass spectroscopy

MALDI-TOF Mass Spectrometry was performed on a Micromass TofSpec 2E Time-of-Flight Mass Spectrometer. The instrument is equipped with a nitrogen laser (337 nm wavelength, operated at a frequency of 5 Hz), and a time lag focusing unit. Ions were generated by irradiation slightly above the threshold laser power. Positive ion spectra were recorded in reflectron mode applying an accelerating voltage of 20 kV and externally calibrated with a suitable mixture of poly(ethyleneglycol)s (PEG). The spectra of 100-150 shots were averaged to improve the signal-to-noise ratio. Analysis of data was done with MassLynx-Software V3.5 (Micromass/Waters, Manchester, UK). Sample were typically prepared by mixing a solution of HCCA ($c = 10\,\mathrm{mg/mL}$ in $CH_3CN/H_2O/TFA$=70/30/1) and a solution of the analyte ($c = 0.1\,\mathrm{mg/mL}$ in CH_3CN) in a ratio of 20/1 (v/v). 0.5 μL of the resulting mixture were deposited on the sample plate (stainless steel) and allowed to dry under air. [44]

6.2 Materials

Unless otherwise stated, all chemicals were obtained commercially and used without further purification.

6.3 General procedures

6.3.1 Amadori rearrangement (AR)

The respective aldose was dissolved in ethanol, for a better solubility a small amount of water can be added. To this solution, the respective amine and acetic acid, one equivalent each, were added. The reaction mixture was stirred at temperature indicated further down in the experimental part, until TLC showed full conversion of the starting material. The solvent was removed under reduced pressure and the crude product mixture was purified by column chromatography.

6.3.2 Reductive amination (RA)

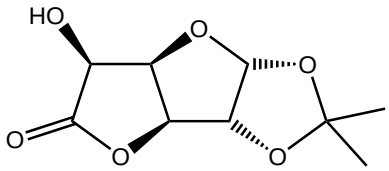
The respective 5-azido-sugar was dissolved in methanol, as a catalyst palladium on charcoal (10 %) was added. The reaction mixture was stirred under hydrogen atmosphere (balloon) at room temperature until TLC showed full conversion of the starting material. The catalyst was filtered off, the solvent was removed under reduced pressure and the obtained product was purified by column chromatography.

6.4 Experimental procedures

6.4.1 2,5-Dideoxy-2,5-imino-D-altritol series

1,2-*O*-Isopropylidene-α-D-*gluco*-furanurono-6,3-lactone (55)

α,β-D-Glucufuranorono-6,3-lactone **36** (25 g, 141.94 mmol, 1 eq) was dissolved in aceton (450 mL), concentrated H_2SO_4 (15 mL) was added and the reaction mixture was stirred at room temperature for 20 hours. The reaction was neutralized by addition of solid Na_2CO_3, filtered and concentrated under reduced pressure. The obtained crude product was purified by crystallizing from CH_2Cl_2 and cyclohexane to afford compound **55** as white solid (28.76 g, 94 %).



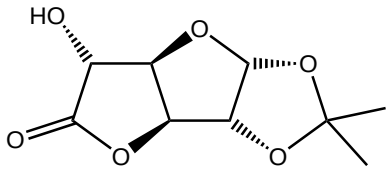
MW	216.19g·mol^{-1}
TLC-S	C/EA 1/1
R_f	0.38
yield	94 %

1,2-*O*-Isopropylidene-*β*-L-*ido*-furanurono-6,3-lactone (56)

Compound **56** was synthesised in two steps starting from compound **55**.

Step I: Compound **55** (10 g, 46.3 mmol, 1 eq) was dissolved in CH_2Cl_2 (260 mL), pyridine (7.4 mL, 92.6 mmol, 2 eq) was added and the reaction mixture cooled to -15 °C ($MeOH/N_{2\,l}$). Triflic anhydride (8.2 mL, 48.6 mmol, 1.05 eq in 10 mL CH_2Cl_2) was added drop wise at this temperature. When TLC analysis showed full conversion of the starting material, the reaction mixture was washed with cold $HCl_{aq.}$ (6 %) and $NaHCO_{3\ aq.\ sat.}$, the organic layer was dried over Na_2SO_4, filtered and the solvent was almost removed under reduced pressure at room temperature until a wet slurry was obtained. The obtained orange suspension was immediately used in step II.

Step II: The suspension of step I was diluted with DMF (260 mL), cooled to 0 °C (H_2O/ice) and $NaNO_2$ (6.4 g, 92.5 mmol, 4 eq) was added. After 30 minutes TLC showed full conversion of the starting material, CH_2Cl_2 (260 mL) was added and the reaction mixture was stirred at room temperature for 30 minutes. The solids were filtered off, the filtrate concentrated under reduced pressure, diluted with CH_2Cl_2 (400 mL) and washed with H_2O. The organic layer was dried over Na_2SO_4, filtered and the solution was concentrated under reduced pressure. The obtained crude product was purified by crystallizing from CH_2Cl_2 and cyclohexane to obtain compound **56** as white solid (6.5 g, 65 %).



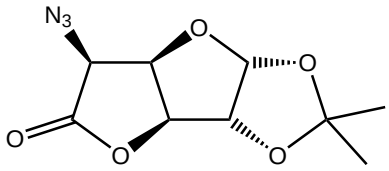
MW	216.19g·mol^{-1}
TLC-S	C/EA 1/1
R_f	0.70
yield	65 %

5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-furanurono-6,3-lactone (57)

Compound **57** was synthesised in two steps starting from compound **56**.

Step I: Compound **56** (3 g, 13.9 mmol, 1 eq) was dissolved in CH_2Cl_2 (90 mL), pyridine (2.3 mL, 27.8 mmol, 2 eq) was added and the reaction mixture was cooled to -15 °C ($MeOH/N_{2\,l}$). Triflic anhydride (2.5 mL, 14.6 mmol, 1.05 eq in 10 mL CH_2Cl_2) was added drop wise at this temperature. When TLC analysis showed full conversion of the starting material, the reaction mixture was washed with cold $HCl_{aq.}$ (6 %) and $NaHCO_{3\ aq.\ sat.}$, the organic layer was dried over Na_2SO_4, filtered and the solvent was almost removed under reduced pressure at room temperature until a wet slurry was obtained. The obtained orange suspension was immediately used in step II.

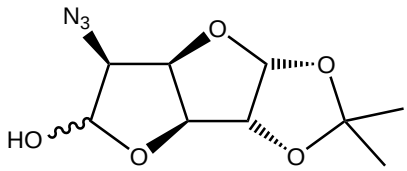
Step II: The suspension of step I was diluted with aceton (80 mL) and NaN_3 (4.1 g, 62.5 mmol, 4.5 eq) was added at room temperature. After three hours reaction time TLC showed full conversion of the the starting material, CH_2Cl_2 (100 mL) was added and the reaction mixture was stirred at room temperature for 30 minutes. The solids were filtered off, the filtrate concentrated under reduced pressure, diluted with CH_2Cl_2 (100 mL) and washed with H_2O. The organic layer was dried over Na_2SO_4, filtered and the solution was concentrated under reduced pressure. The obtained orange oil was not further purified (3.18 g, 95 %).



MW	241.20g·mol^{-1}
TLC-S	C/EA 2/1
R_f	0.44
$yield_{crude}$	95 %

5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-furanurono-6,3-lactol (58) [41]

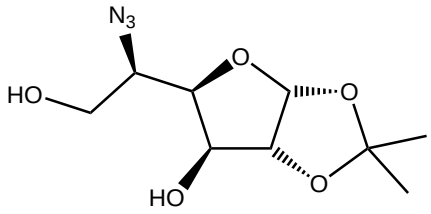
To a solution of compound **57** (3.18 g, 13.2 mmol, 1 eq) in CH_2Cl_2 (20 mL) which was cooled to -70 °C ($MeOH/N_{2\,l}$), DIBALH (25.8 mL, 1M in hexane, 2 eq in 20 mL CH_2Cl_2) was added drop wise. After 30 minutes at -70 °C TLC showed full conversion of the starting material, CH_2Cl_2 (120 mL) and NaK-tartrate solution$_{aq.\ sat.}$ (130 mL) were added and the reaction mixture was stirred at room temperature for 24 hours. The layers were separated and the aqueous layer was extracted six times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The obtained dark yellow oil was not further purified (2.58 g, 76 %).



MW	243.22g·mol^{-1}
TLC-S	C/EA 2/1
R_f	0.30
yield$_{crude}$	76 %

5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-furanose (59) [41]

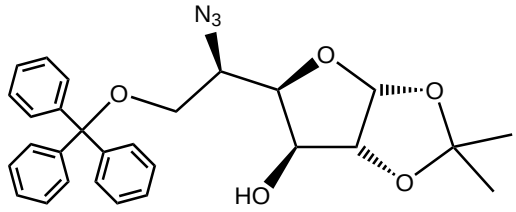
To a solution of compound **58** (3.38 g, 13.9 mmol, 1 eq) in MeOH (50 mL), which was cooled to -20 °C ($MeOH/N_{2\,l}$), $NaBH_4$ (0.13 g, 3.5 mmol, 0.25 eq) was added. The reaction mixture was stirred at -20 °C for one hour. When TLC showed full conversion of the starting material, the pH-value was adjusted to pH 6 by adding AcOH. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography to obtain compound **59** as colorless oil. The overall yield after three steps was 71 %.



MW	243.22g·mol^{-1}
TLC-S	C/EA 1/1
CC-S	C/EA 3/1→1/1
R_f	0.45
yield	71 % compounds **56-59**

5-Azido-5-deoxy-1,2-*O*-isopropylidene-6-*O*-trityl-α-D-*gluco*-furanose (60)

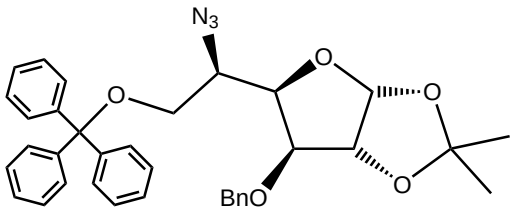
Compound **59** (2 g, 8.2 mmol, 1 eq) was dissolved in pyridine (20 mL), triphenylmethyl chloride (4.4 g, 15.8 mmol, 1.94 eq) and a catalytic amount DMAP were added. The reaction mixture was stirred at 50 °C for 24 hours until TLC showed full conversion of the starting material. The reaction was quenched by adding MeOH (40 mL), stirred for 30 minutes and solvents were removed under reduced pressure. The dark brown oil was diluted with CH_2Cl_2, washed with $HCl_{aq.}$ (6 %) and $NaHCO_{3\ aq.\ sat.}$, the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography to obtain compound **60** (3.8 g, 96 %).



MW	487.55g·mol^{-1}
TLC-S	C/EA 2/1
R_f	0.52
CC-S	C→C/EA 20/1→EA
yield	96 %

5-Azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-6-*O*-trityl-α-D-*gluco*-furanose (61)

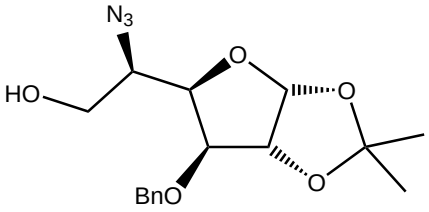
To a cooled solution (0 °C, H_2O/ice) of compound **60** (3.8 g, 7.8 mmol, 1 eq) in DMF (50 mL) NaH (washed with cyclohexane, 0.8 g, 33.3 mmol, 4.3 eq) was added. After a immediate color change to green and to orange, benzyl bromide (1.3 mL, 11.1 mmol, 1.4 eq in 5 mL DMF) was added dropwise and the reaction mixture was stirred at room temperature. When TLC showed full conversion of the starting material, the reaction was quenched by adding MeOH (10 mL), stirred for 30 minutes, washed with CH_2Cl_2, $HCl_{aq.}$ (6 %) and $NaHCO_{3\ aq.\ sat.}$, the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The obtained yellow oil was not further purified (5.6 g, >100 %).



MW	577.67g·mol^{-1}
TLC-S	C/EA 2/1
R_f	0.74
$yield_{crude}$	>100 %

5-Azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-furanose (62)

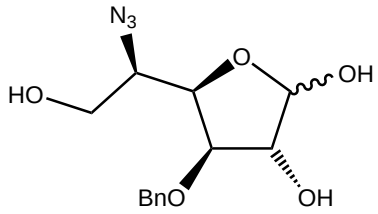
Compound **61** (6.0 g, 10.4 mmol, 1 eq) was dissolved in CH_2Cl_2 (65 mL), H_2O (5 mL) and an adequate amount of MeOH was added. To start the reaction pTSA (2.0 g, 11.6 mmol, 1.1 eq) was added, the reaction mixture was stirred at room temperature for four days. When TLC showed full consumption of the starting material the reaction mixture was washed with $HCl_{aq.}$ (6 %) and $NaHCO_{3\ aq.\ sat.}$, the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography to obtain compound **59** as colorless oil. (2.6 g, 88 % two steps from compound **60** to **62**).



MW	335.36g·mol^{-1}
TLC-S	C/EA 3/1
R_f	0.39
CC-S	C/EA 50/1→10/1→EA
yield	88 % compounds **60-62**

5-Azido-3-*O*-benzyl-5-deoxy-α,β-D-*gluco*-furanose (63)

Compound **62** (2.6 g, 7.8 mmol) was dissolved in H_2O/CH_3CN (v/v, 3/1, 160 mL), ion exchange resin (IR 120 H^+washed with H_2O) was added and stirred at 50 °C for seven days until TLC showed full conversion of the starting material. The ion exchange resin was filtered off and the solvent was removed under reduced pressure. The residue was purified by column chromatography to obtain compound **63** as colorless oil (1.37 g, 60 %).



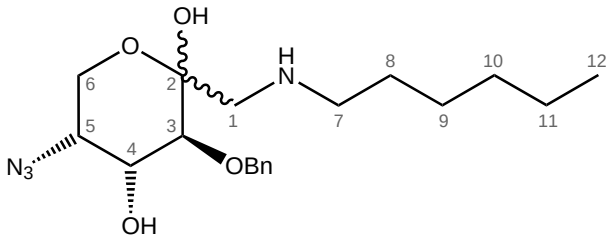
MW	225.29g·mol^{-1}
TLC-S	C/EA 1/1
R_f	0.23
CC-S	C/EA 2/1→2/3→EA
yield	60 %
α/β	2/1

^{13}C (75.53MHz, $CDCl_3$): δ=137.5, 137.3, 136.6, 128.8, 128.6, 128.5, 128.44, 128.1, 128.07 ($Ph_{\alpha,\beta}$), 103.5, 97.55 (2C, C-$1_{\alpha,\beta}$), 83.3, 82.3 (2C, C-$2_{\alpha,\beta}$), 97.7, 77.0 (2C, C-$4_{\alpha,\beta}$), 73.9 (C-3), 72.7, 72.0 (2C, $CH_2Ph_{\alpha,\beta}$), 62.9, 62.6 (2C, C-$6_{\alpha,\beta}$), 61.6, 60.8 (2C, C-$5_{\alpha,\beta}$).

^{1}H (300.36MHz, $CDCl_3$): δ=7.38–7.27 (m, 5H, Ph), 5.47 (d, 1H, $J_{1,2}$=1.5 Hz, H-1_α), 5.19 (s, 1H, H-1_β), 4.69–4.52 (m, 4H, $CH_2Ph_{\alpha,\beta}$), 4.40–4.15 (m, 4H, C-$3_{\alpha,\beta}$, C-$4_{\alpha,\beta}$), 4.07–4.00 (m, 2H, C-$2_{\alpha,\beta}$), 3.95–3.75 (m, 6H, C-$5_{\alpha,\beta}$, C-$6_{\alpha,\beta,a,b}$).

1-(*N*-Hexyl)amino-5-azido-3-*O*-benzyl-1,5-dideoxy-α,β-D-*fructo*-hex-2-ulopyranose (64)

Applying general procedure for AR (Section: 6.3.1) to compound **63** (1.36 g, 4.61 mmol, 1 eq), EtOH (70 mL), hexylamine (0.67 mL, 5.07 mmol, 1.1 eq) and AcOH (0.28 mL, 4.61 mmol, 1 eq) at room temperature gave compound **64** as yellow oil (1.4 g, 81 %).



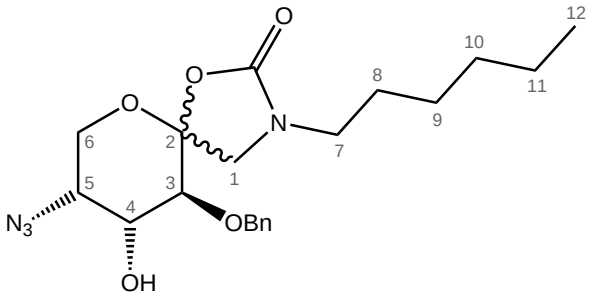
MW	378.47g·mol^{-1}
TLC-S	C/EA 1/2
R_f	0.13
CC-S	C/EA 4/1→EA
yield	81 %
α/β	2/3

^{13}C (75.53MHz, $CDCl_3$): δ=137.9, 128.8, 128.3 (Ph), 95.9 (C-2), 79.7 (C-3), 75.2 (CH_2Ph), 70.5 (C-4), 63.3 (C-5), 61.4 (C-6), 53.7 (C-1), 49.0 (C-7), 31.4, 23.5, 22.5 (3C, C-9, C-10, C-11), 27.2 (C-8), 14.0 (C-12).

^{1}H (300.36MHz, $CDCl_3$): δ=7.39–7.27 (m, 5H, Ph), 4.97 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.5 Hz, CH_2Ph_β), 4.65 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.5 Hz, CH_2Ph_β), 4.64 (d, 1H, J_{CH_2Ph,CH_2Ph}= 11.4 Hz, CH_2Ph_α), 4.65 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.4 Hz, CH_2Ph_α), 4.36 (dd, 1H, $J_{3,4}$=9.5 Hz, $J_{4,5}$=3.5 Hz, H-4$_\beta$), 4.13–4.00 (m, 2H, H-6$_{\alpha,\beta}$), 3.86-3.81 (m, 1H, H-5), 3.63–3.51 (m, 4H, H-6$_{\alpha,\beta}$, H-3$_{\alpha,\beta}$), 3.05 (d, 1H, $J_{1,1}$=9.5 Hz, H-1$_\alpha$) 2.86 (d, 1H, $J_{1,1}$=12.5 Hz, H-1$_\beta$), 2.67 (d, 1H, $J_{1,1}$=12.5 Hz, H-1$_\beta$), 2.64–2.44 (m, 2H, H-7), 1.56–1.47 (m, 2H, H-8), 1.34-1.13 (m, 6H, H-9, H-10, H-11), 0.86 (t, 3H, H-12).

1-(*N*-Hexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-α,β-D-*fructo*-hex-2-ulopyranose (65)

A solution of compound **64** (434 mg, 1.15 mmol, 1 eq) and Na_2CO_3 (1 g, 9.66 mmol, 8.4 eq) in H_2O/1,4-Dioxane (v/v, 1/1, 40 mL) was stirred at 0 °C (H_2O/ice) for 15 minutes. Triphosgene (477 mg, 1.61 mmol, 1.4 eq) was added to the reaction mixture. When TLC showed full conversion of the starting material, the solution was extracted with H_2O and CH_2Cl_2, the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography to obtain compound **65** as yellow oil (309 mg, 67 %).



MW	404.46g·mol^{-1}
TLC-S	C/EA 1/2
R_f	0.52
CC-S	C/EA 8/1→2/1
yield	67 %
α/β	2/5

^{13}C (75.53MHz, $CDCl_3$): δ=156.2 (C=O), 137.9, 128.7, 128.2, 128.1 (Ph), 102.3 (C-2), 75.3 (CH_2Ph), 72.3 (C-4), 63.4 (C-6), 62.5 (C-5), 52.5 (C-1), 43.8 (C-7), 31.5, 26.2, 22.6 (3C, C-9, C-10, C-11), 27.3 (C-8), 14.1 (C-12).

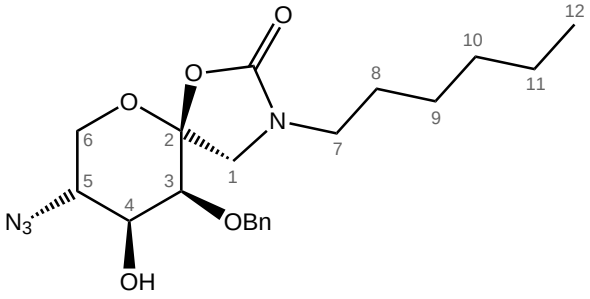
^{1}H (499.98MHz, $CDCl_3$): δ=7.39–7.27 (m, 5H, Ph), 4.98 (d, 1H, J_{CH_2Ph,CH_2Ph}=12.0 Hz, CH_2Ph_β), 4.71 (d, 1H, J_{CH_2Ph,CH_2Ph}=12.0 Hz, CH_2Ph_β), 4.55 (d, 1H, J_{CH_2Ph,CH_2Ph}= 11.6 Hz, CH_2Ph_α), 4.40 (dd, 1H, $J_{3,4}$=9.6 Hz, $J_{4,5}$=3.7 Hz, H-4$_\beta$), 4.16–4.08 (m, 1H, H-6$_\alpha$), 4.07-4.02 (m, 1H, H-6$_\beta$), 3.98-3.95 (m, 1H, H-5), 3.76 (dd, 1H, $J_{6e,6a}$=12.8 Hz, $J_{5,6e}$=1.0 Hz, H-6$_\beta$), 3.73–3.70 (m, 1H, H-6$_\alpha$), 3.69 (d, 1H, $J_{3,4}$=9.6 Hz, H-3$_\beta$), 3.37 (d, 1H, $J_{1,1}$=10.3 Hz, H-1$_\alpha$), 3.34 (d, 1H, $J_{1,1}$=9.6 Hz, H-1$_\beta$), 3.27 (d, 1H, $J_{1,1}$=10.3 Hz, H-1$_\alpha$), 3.21 (d, 1H, $J_{1,1}$=9.6 Hz, H-1$_\beta$), 3.20-3.10 (m, 2H, H-7), 1.45–1.38 (m, 2H, H-8), 1.32–1.19 (m, 6H, H-9, H-10, H-11), 0.91-0.83 (m, 3H, H-12).

1-(*N*-Hexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-*β*-D-*tagato*-hex-2-ulopyranose (66)

Compound **66** was synthesised in two steps starting from compound **65**.

Step I: Compound **65** (200 mg, 0.49 mmol, 1 eq) was dissolved in CH_2Cl_2 (10 mL), pyridine (1 mL, 12.6 mmol, 25.7 eq) was added and the reaction mixture was cooled to 0 °C (H_2O/ice). Triflic anhydride (0.2 mL, 0.74 mmol, 1.5 eq) was added at this temperature. When TLC analysis showed full conversion of the starting material, the product mixture was washed with cold $HCl_{aq.}$ (6 %) and $NaHCO_{3\ aq.\ sat.}$. The organic layer was dried over Na_2SO_4, filtered and the solvent was almost removed under reduced pressure at room temperature until a wet slurry was obtained. The obtained orange suspension was immediately used in step II.

Step II: The suspension of step I was diluted with DMF (4 mL), cooled to 0 °C (H_2O/ice) and $NaNO_2$ (274 mg, 3.96 mmol, 8 eq) was added. The reaction mixture was stirred at 50 °C for seven days until TLC showed full conversion of the starting material. The reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2 (400 mL) and washed with H_2O. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography to obtain compound **66** as yellow oil (30 mg, 15 %).



MW	404.46g·mol^{-1}
TLC-S	C/EA 2/1
R_f	0.25
CC-S	C/EA 12/1→EA
yield	15 %

^{13}C (75.53MHz, $CDCl_3$): δ=155.7 (C=O), 136.5, 128.9, 128.7, 128.4 (Ph), 100.6 (C-2), 71.9 (C-3), 70.7 (CH_2Ph), 65.5 (C-4), 60.2 (C-5), 59.4 (C-6), 52.9 (C-1), 43.8 (C-7), 31.5, 26.2, 22.6 (3C, C-9, C-10, C-11), 27.3 (C-8), 14.1 (C-12).

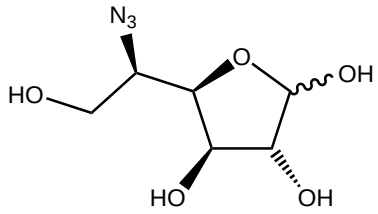
^{1}H (300.36MHz, $CDCl_3$): δ=7.40–7.28 (m, 5H, Ph), 4.77 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.8 Hz, CH_2Ph), 4.48 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.8 Hz, CH_2Ph), 4.46 (dd, 1H, $J_{6a,6e}$=9.6 Hz, $J_{5,6e}$=1.5 Hz, H-6$_e$), 4.23-4.19 (m, 1H, H-4), 3.87–3.83 (m, 1H, H-5), 3.76-3.68 (m, 1H,

H-6_a), 3.60 (d, 1H, $J_{3,4}$=3.5 Hz, H-3), 3.41 (d, 1H, $J_{1,1}$=9.5 Hz, H-1), 3.20 (d, 1H, $J_{1,1}$=9.5 Hz, H-1), 3.26-3.19 (m, 2H, H-7), 1.50–1.44 (m, 2H, H-8), 1.33-1.19 (m, 6H, H-9, H-10, H-11), 0.87 (t, 3H, H-12).

m/z: 427.2 $[MNa]^+$, ionisation: MALDI, matrix: HCCA

5-Azido-5-deoxy-α, β-D-*gluco*-furanose (67)

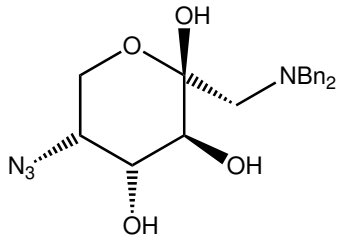
Compound **59** (2 g, 8.15 mmol, 1 eq) was dissolved in H_2O/CH_3CN (v/v, 1/1, 50 mL), ion exchange resin (IR 120 H^+ washed with H_2O) was added and the reaction mixture was stirred at 40 °C for two days until TLC showed full conversion of the starting material. The ion exchange resin was filtered off and the solvent was removed under reduced pressure. The residue was purified by column chromatography to obtain compound **67** as white powder (1.61 g, 96 %).



MW	205.17g·mol^{-1}
TLC-S	EA/MeOH 10/1
R_f	0.60
CC-S	C/EA 20/1
yield	96 %

1-(*N,N*-Dibenzyl)amino-5-azido-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (68) [40]

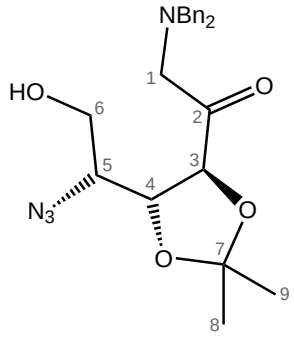
Applying general procedure for AR (Section: 6.3.1) to compound **67** (0.8 g, 3.9 mmol, 1 eq), EtOH (70 mL), dibenzylamine (0.75 mL, 3.9 mmol, 1 eq) and AcOH (0.23 mL, 3.9 mmol. 1 eq) at 45 °C compound **68** was obtained as yellow oil (1.11 g, 74 %).



MW	384.43g·mol^{-1}
TLC-S	EA
R_f	0.83
CC-S	C/EA 5/1→1/1
yield	74 %

1-(*N,N*-Dibenzyl)amino-5-azido-1,5-dideoxy-3,4-*O*-isopropylidene-D-*arabino*-hex-2-ulose (69)

Compound **68** (100 mg, 0.28 mmol, 1 eq) was dissolved in aceton (20 mL) and dimethoxypropane (1 mL, 8.0 mmol, 29 eq) was added. The pH-value was adjusted to pH 3 by adding pTSA. The reaction mixture was stirred at room temperature for three days until TLC showed full conversion of the starting material. The reaction mixture was diluted with CH_2Cl_2 and washed with $NaHCO_{3\ aq.\ sat.}$, the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography to obtain compound **69** as yellow oil (76 mg, 69 %).



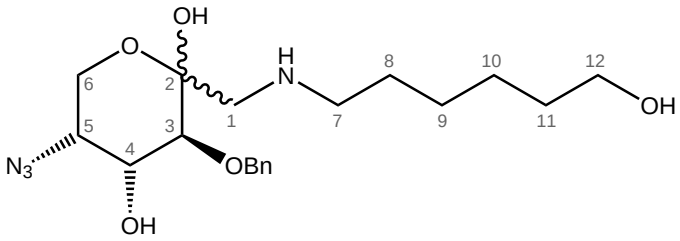
MW	424.49g·mol^{-1}
TLC-S	C/EA 3/1
R_f	0.27
CC-S	C/EA 10/1
yield	69 %

^{13}C (75.53MHz, $CDCl_3$): δ=211.2 (C-2), 138.8, 129.2, 129.1, 128.5, 127.4 (2x Ph), 110.8 (C-7), 79.6, 78.0 (2C, C-3, C-4), 63.4 (C-5), 61.9 (C-6), 59.2 (C-1), 58.4 (2C, CH_2Ph), 26.3, 25.2 (2C, C-8, C-9).

^{1}H (300.36MHz, $CDCl_3$): δ=7.41–7.22 (m, 10H, Ph), 4.39–4.32 (m, 2H, H-3, H-4), 3.92-3.86 (m, 1H, H-5), 3.84-3.67 (m, 4H, CH_2Ph), 3.66-3.50 (m, 4H, H-1, H-6), 1.44 (s, 3H, H-8, H-9), 1.44 (s, 3H, H-8, H-9).

1-(*N*-Hydroxyhexyl)amino-5-azido-3-*O*-benzyl-1,5-dideoxy-α, β-D-*fructo*-hex-2-ulopyranose (70)

Applying general procedure for AR (Section: 6.3.1) to compound **63** (430 mg, 1.46 mmol, 1 eq), 30 mL EtOH, 6-aminohexanol (1.71 mg, 1.61 mmol, 1.1 eq) and AcOH (87 μL, 1.46 mmol, 1 eq) at 40 °C compound **70** was obtained as yellow oil (499 mg, 85 %).



MW	394.47g·mol^{-1}
TLC-S	EA/MeOH 4/1
	+ 1 d. NH_4OH
R_f	0.43
CC-S	EA/MeOH/NH_4OH
	14/1/0.5 %
yield	85 %
α/β	1/2

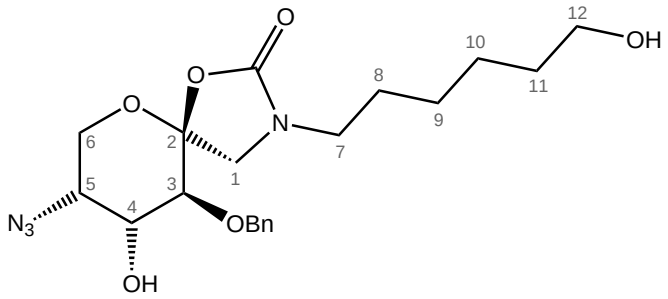
NMR signals for β anomer, for α anomer not listed.

^{13}C (75.53MHz, $CDCl_3$): δ=138.0, 128.8, 128.7, 128.3 (Ph), 96.4 (C-2), 79.5 (C-3), 75.3 (CH_2Ph), 70.6 (C-4), 63.2 (C-5), 62.5 (C-6), 60.5 (C-12), 53.8 (C-1), 49.1 (C-7), 32.4 (C-8), 28.03, 25.4 (2C, C-9, C-10), 26.5 (C-11).

^{1}H (300.36MHz, $CDCl_3$): δ=7.38–7.27 (m, 5H, Ph), 4.92 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.7 Hz, CH_2Ph_β), 4.67 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.7 Hz, CH_2Ph_β), 4.65 (d, 1H, J_{CH_2Ph,CH_2Ph}= 11.7 Hz, CH_2Ph_α), 4.50 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.7 Hz, CH_2Ph_α), 4.32 (dd, 1H, $J_{3,4}$=9.5 Hz, $J_{4,5}$=3.7 Hz, H-4), 4.07-4.00 (m, 1H, H-6), 3.87-3.82 (m, 1H, H-5), 3.64-3.55 (m, 3H, H-6, H-12), 3.53 (d, 1H, $J_{3,4}$=9.6 Hz, H-3), 2.79 (d, 1H, $J_{1,1}$=12.4 Hz, H-1), 2.67 (d, 1H, $J_{1,1}$=12.4 Hz, H-1), 2.72–2.43 (m, 2H, H-7), 1.57-1.45 (m, 2H, H-8), 1.38–1.27 (m, 6H, H-9, H-10, H11).

1-(*N*-Hydroxyhexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-*β*-D-*fructo*-hex-2-ulopyranose (71)

A solution of compound **70** (220 mg, 0.53 mmol, 1 eq) and Na_2CO_3 (500 mg, 4.69 mmol, 9.4 eq) in H_2O/1,4-Dioxane (v/v, 4/1, 12.5 mL) was stirred at 0 °C (H_2O/ice) for 15 minutes. Triphosgene (232 mg, 0.78 mmol, 1.4 eq) was added and stirring was continued at room temperature for 20 hours until TLC showed full conversion of the starting material. The solvent was removed under reduced pressure, the residue was extracted with H_2O and CH_2Cl_2, the organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography to obtain compound **71** as yellow oil (234 mg, 22 %).



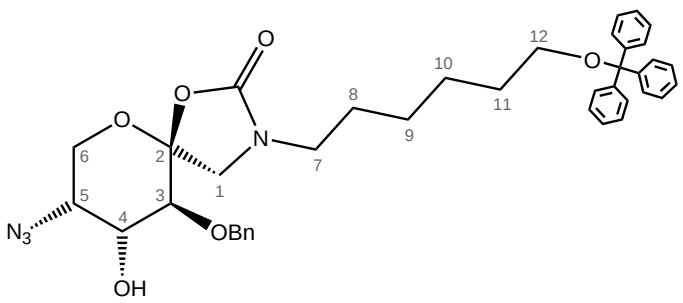
MW	394.47g·mol^{-1}
TLC-S	EA + 1 d. NH_4OH
R_f	0.44
CC-S	C/EA/NH_4OH/MeOH
	1/1/0.5 %/0.1 %
yield	22 %

^{13}C (75.53MHz, $CDCl_3$): δ=156.4 (C=O), 137.9, 128.7, 128.2, 128.1 (Ph), 102.4 (C-2), 77.3 (C-3), 75.3 (CH_2Ph), 71.2 (C-4), 63.5 (C-6), 62.6 (2C, C-5, C-12), 52.5 (C-1), 43.4 (C-7), 32.5 (C-8), 27.1, 26.0, 25.1 (2C, C-9, C-10, C-11).

^{1}H (300.36MHz, $CDCl_3$): δ=7.30 (s, 5H, Ph), 4.99 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.9 Hz, CH_2Ph), 4.71 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.9 Hz, CH_2Ph), 4.37 (dd, 1H, $J_{3,4}$=9.3 Hz, $J_{4,5}$=2.7 Hz, H-4), 4.09-3.99 (m, 1H, H-6), 3.99-3.94 (m, 1H, H-5), 3.80-3.72 (m, 1H, H-6), 3.69 (d, 1H,$J_{3,4}$=9.5 Hz, H-3), 3.56 (t, 2H, H-12), 3.33 (d, 1H,$J_{1,1}$=9.5 Hz, H-1), 3.23-3.13 (m, 3H, H-1, H-7), 1.54–1.37 (m, 2H, H-8), 1.36–1.10 (m, 6H, H-9, H-10, H-11).

1-(*N*-Trityloxyhexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (72)

Compound **71** (51 mg, 0.12 mmol, 1 eq) was dissolved in pyridine (5 mL), triphenylmethyl chloride (136 mg, 0.48 mmol, 2 eq) and a catalytic amount of DMAP were added. The reaction mixture was stirred at 50 °C for six days until TLC showed full conversion of the starting material. The reaction mixture was quenched by adding MeOH (20 mL), stirred for 20 minutes and the solvent was removed under reduced pressure. The dark brown oil was diluted with CH_2Cl_2, washed with $HCl_{aq.}$ (6 %) and $NaHCO_{3\ aq.\ sat.}$. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification was performed by column chromatography to obtain compound **72** as yellow oil (22 mg, 30 %).



MW	662,77g·mol^{-1}
TLC-S	C/EA 1/1
	+ 1 d. NH_4OH
R_f	0.55
CC-S	C→C/EA 10/1→EA
yield	30 %

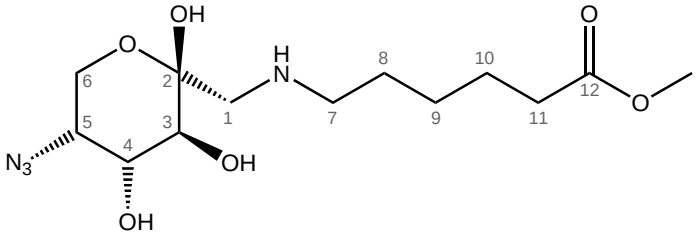
^{13}C (75.53MHz, $CDCl_3$): δ=156.0 (C=O), 144.6, 137.8, 128.8, 128.3, 128.1, 128.0, 127.8, 127.4, 127.0 (4x Ph), 102.1 (C-2), 86.5 (C-Ph_3), 77.4 (C-3), 75.4 (CH_2Ph), 71.2 (C-4), 63.5 (C-12), 63.3 (C-6), 62.4 (C-5), 52.5 (C-1), 43.8 (C-7), 30.0, 29.8, 27.0, 26.5 (4C, C-8, C-9, C-10, C-11).

^{1}H (300.36MHz, $CDCl_3$): δ=7.54–7.27 (m, 20H, 4x Ph), 5.02 (d, 1H, J_{CH_2Ph,CH_2Ph}= 11.9 Hz, CH_2Ph), 4.78 (d, 1H, J_{CH_2Ph,CH_2Ph}=11.9 Hz, CH_2Ph), 4.43 (dd, 1H, $J_{3,4}$=9.5 Hz, $J_{4,5}$=3.6 Hz, H-4), 4.40 (dd, $J_{6,6}$=12.8 Hz, $J_{5,6}$=1.4 Hz, H-6), 4.07–4.02 (m, 1H, H-5), 3.83 (dd, 1H, $J_{6,6}$=12.8 Hz, $J_{5,6}$=1.4 Hz, H-6), 3.66 (d, 1H, $J_{3,4}$=9.4 Hz, H-3), 3.40 (d, 1H, $J_{1,1}$=9.5 Hz, H-1), 3.27 (d, 1H, $J_{1,1}$=9.5 Hz, H-1), 3.31–3.14 (m, 2H, H-7), 3.09 (t, 2H, H-12), 1.71–1.57 (m, 2H, H-11), 1.51–1.20 (m, 6H, H-8, H-9, H-10).

6.4.2 2,5-Dideoxy-2,5-imino-D-mannitol series

1-(*N*-Methoxycarbonylpentyl)amino-5-azido-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (73)

A solution of methyl 6-aminohexanoat hydrochlorid (2.52 g, 13.89 mmol, 1.5 eq) and triethylamine (1.95 mL, 13.89 mmol, 1.5 eq) in EtOH (50 mL) was stirred at room temperature for 30 minutes. Compound **67** (1.9 g, 9.26 mmol, 1 eq) was dissolved in EtOH (30 mL) and added to the first solution. The reaction mixture was stirred at 40 °C for 24 hours until TLC showed full conversion of the respective sugar. The solvent was removed under reduced pressure, the dark orange oil was purified by column chromatography to obtain compound **73** as yellow oil (1.22 g, 39 %).



MW	332,35g·mol^{-1}
TLC-S	EA/MeOH 4/1
R_f	0.18
CC-S	EA/MeOH/NH_4OH 20/1/0.5 %
yield	39 %

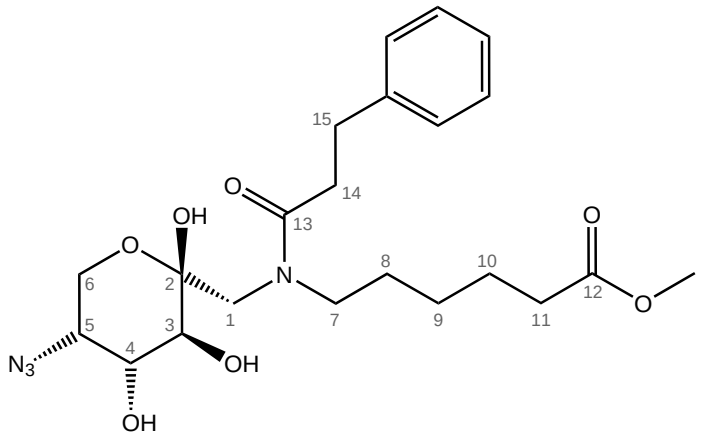
^{13}C (75.53MHz, MeOD): δ=175.9 (C-12), 98.5 (C-2), 71.8, 71.7 (2C, C-3, C-4), 64.4 (C-5), 62.0 (C-6), 52.0 (OMe), 50.7 (2C, C-1, C-7), 34.7 (C-11), 30.2 (C-8), 27.7 (C-9), 25.8 (C-10).

^{1}H (300.36MHz, MeOD): δ=4.07–3.98 (m, 2H, H-4, H-6), 3.86–3.82 (m, 1H, H-5), 3.65 (s, H, OMe) 3.66–3.58 (m, 2H, H-3, H-6), 2.78 (d, 1H, $J_{1,1}$=15.1 Hz, H-1), 2.72–2.56 (m, 3H, H-1, H-7), 2.34 (t, 2H, H-11), 1.69-1.57 (m, 2H, H-10), 1.57-1.46 (m, 2H, H-8), 1.42-1.27 (m, 2H, H-9).

$[\alpha]_D^{20}$: -43.00 (c = 3.20, MeOH)

1-(*N*-Methoxycarbonylpentyl-*N*-phenylethylcarbonyl)amino-5-azido-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (74)

Compound **73** (100 mg, 0.30 mmol, 1 eq) was dissolved in MeOH (10 mL), triethylamine (60 μL, 0.60 mmol, 2 eq) and 3-phenylpropanoyl chloride (90 μL, 0.45 mmol, 1.5 eq) were added. The reaction mixture was stirred at room temperature for two hours until TLC showed full conversion of the starting material. The solvent was removed under reduced pressure, purification was performed by column chromatography to obtain compound **74** as yellow oil (88 mg, 63 %).



MW	464,51g·mol^{-1}
TLC-S	EA/MeOH 4/1
	+ 1 d. NH_4OH
R_f	0.72
CC-S	C/EA/MeOH 2/1/5 %
yield	63 %

Two signals each carbon due two nitrogen rotamers.

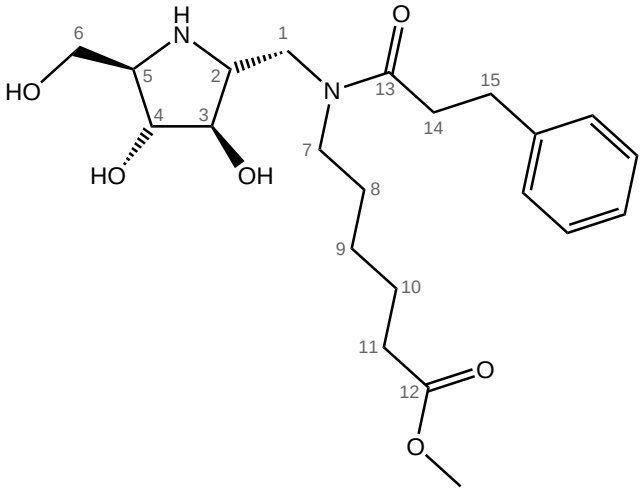
^{13}C (75.53MHz, MeOD): δ=177.1, 176.4, 175.8, 175.7 (2C, C-12, C-13), 142.5, 142.3, 129.6, 129.5, 129.5, 129.4, 127.2, 127.0 (Ph), 100.0, 99.9 (C-2), 71.7, 70.8, 70.8 (2C, C-3, C-4), 64.3, 64.1 (C-5), 62.3, 62.1 (C-6), 53.6, 53.3 (C-1), 52.0 (OMe), 51.0, 48.6 (C-7), 36.0, 35.8, (C-14), 34.6, 34.5 (C-11), 32.9, 32.6 (C-15), 28.9, 27.5, 27.4, 27.1 (2C, C-8, C-9), 25.7, 25.6 (C-10).

^{1}H (300.36MHz, MeOD): δ=Signals for protons were found in the expected region and verified by COSY and HSQC data.

m/z: 487.2 $[MNa]^+$ ionisation: MALDI, matrix: HCCA

1-(*N*-Methoxycarbonylpentyl-*N*-phenylethylcarbonyl)amino-1,2,5-trideoxy-2,5-imino-D-mannitol (75)

Applying general procedure for RA (Section: 6.3.2) to compound **74** (97 mg, 0.21 mmol) in MeOH (10 mL) compound **75** was obtained as yellow oil after two hours (36 mg, 41 %).



MW	422,52g·mol^{-1}
TLC-S	$CHCl_3$/MeOH/NH_4OH 6/1/1 %
R_f	0.26
CC-S	$CHCl_3$/MeOH/NH_4OH 6/1/1 %
yield	41 %

APT (75.53MHz, MeOD + HCl): δ=177.4, 175.8 (C-12, C-13), 142.4, 129.6, 129.5, 127.3 (Ph), 77.7, 76.2 (2C, C-3, C-4), 65.7, 64.4 (2C, C-2, C-5), 59.7 (C-6), 52.0 (OMe), 50.6, 47.8 (2C, C-1, C-7), 35.8 (C-14), 34.5 (C-11), 32.2, (C-15), 29.2 (C-8), 27.1 (C-9), 25.6 (C-10).

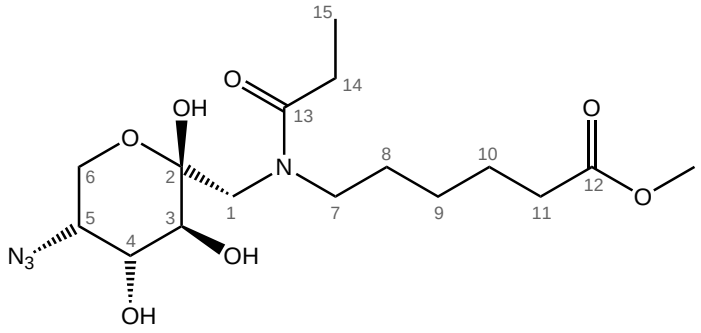
^{1}H (499.98MHz, MeOD + HCl): δ=7.21–7.06 (m, 5H, Ph), 3.92–3.67 (m, 4H, H-1, H-3, H-4, H-6), 3.71 (dd, 1H, $J_{6,6}$=11.5 Hz, $J_{5,6}$=6.5 Hz, H-6), 3.57–3.38 (m, 3H, H-1, H-2, H-5), 3.26 (s, 3H, OMe), 3.24–3.20 (m, 2H, H-7), 2.86 (t, 2H, H-14), 2.68-2.62 (m, 2H, H-15), 2.22 (t, 2H, H-11), 1.55-1.47 (m, 2H H-10), 1.45-1.37 (m, 2H, H-8), 1.23–1.15 (m, 2H, H-9).

m/z: 423.2 $[MH]^+$ ionisation: MALDI, matrix: HCCA

$[\alpha]_D^{20}$: +15.75 (c = 1.25, MeOH)

1-(*N*-Ethylcarbonyl-*N*-methoxycarbonylpentyl)amino-5-azido-1,5-dideoxy-*β*-D-*fructo*-hex-2-ulopyranose (76)

Compound **73** (896 mg, 2.69 mmol, 1 eq) was dissolved in MeOH (80 mL) and cooled to 0 °C (H_2O/ice), triethylamine (1.51 mL, 10.8 mmol, 4 eq) and propionyl chloride (0.43 mL, 5.39 mmol, 2 eq) were added. The reaction mixture was stirred at room temperature for 30 minutes until TLC showed full conversion of the starting material. The reaction mixture was quenched by adding H_2O (10 mL), the solvent was removed under reduced pressure, purification was performed by column chromatography to obtain compound **76** (778 mg, 74 %).



MW	388,42g·mol^{-1}
TLC-S	EA/MeOH 4/1
	+ 1 d. NH_4OH
R_f	0.66
CC-S	$CHCl_3$/MeOH/NH_4OH
	30/1/0.5 %
yield	74 %

Two signals each carbon due two nitrogen rotamers.

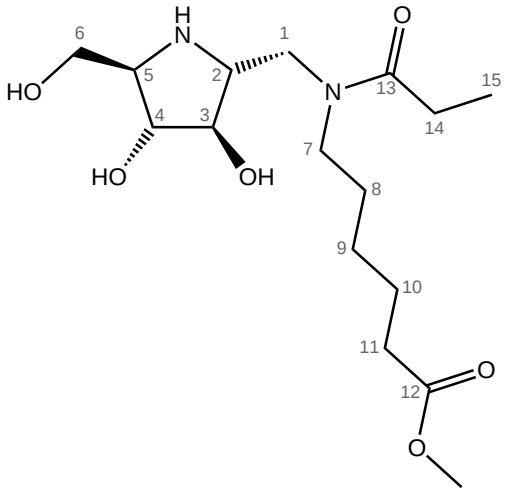
^{13}C (75.53MHz, MeOD): δ=178.7, 178.0, 175.9, 175.8 (C-12, C-12), 100.1, 99.9 (C-2), 71.8, 70.8 (2C, C-3, C-4), 64.3, 64.1 (C-5), 62.3, 62.1 (C-6), 53.4, 52.9 (C-1, C-7), 52.0 (OMe), 50.8 (C-1, C-7), 34.6, 34.5 (C-11), 28.9, 27.5, 27.4, 27.3, 27.1 25.7, 25.6 (4C, C-8, C-9, C-10, C-14), 10.1, 10.0 (C-15).

^{1}H (300.36MHz, MeOD): δ=4.08-3.98 (m, 2H, H-4, H-6), 3.87 (d, 1H, $J_{1,1}$=14.7 Hz, H-1), 3.82-3.78 (m, 1H, H-5), 3.66 (s, 3H, OMe), 3.64-3.61 (m, 1H, H-6), 3.46 (d, 1H, $J_{1,1}$=10.0 Hz, H-3), 3.54-3.36 (m, 2H, H-7) 3.26 (d, 1H, $J_{1,1}$=14.7 Hz, H-1), 2.58-2.40 (m, 2H, H-14), 2.40-2.29 (m, 2H, H-11), 1.71–1.50 (m, 4H, H-8, H-10), 1.3-1.24 (m, 2H, H-9), 1.18–1.03 (m, 3H, H-15).

m/z: 411.2 $[MNa]^+$ ionisation: MALDI, matrix: HCCA

1-(*N*-Ethylcarbonyl-*N*-methoxycarbonylpentyl)amino-1,2,5-trideoxy-2,5-imino-D-mannitol (77)

Applying general procedure for RA (Section: 6.3.2) to compound **76** (778 mg, 2.00 mmol) and MeOH (60 mL) compound **77** was obtained as yellow oil after for 26 hours (508 mg, 73 %).



MW	346,42g·mol^{-1}
TLC-S	$CHCl_3$/MeOH/NH_4OH 6/1/1 %
R_f	0.23
CC-S	$CHCl_3$/MeOH/NH_4OH 30/1/0.5 %
yield	73 %

^{13}C (75.53MHz, MeOD + HCl): δ=179.0, 175.9 (C-12, C-13), 77.7 (C-3), 76.2 (C-4), 65.6 (C-5), 64.1 (C-2), 59.7 (C-6), 52.1 (OMe), 50.5 (C-7), 47.7 (C-1), 34.6 (C-11), 29.2, 25.6 (2C, C-8, C-10), 27.10 (2C, C-9, C-14), 9.7 (C-15).

^{1}H (300.36MHz, MeOD + HCl): δ=4.04-3.93 (m, 3H, H-1, H-3, H-4), 3.89 (dd, 1H, $J_{6a,6b}$=12.1 Hz, $J_{5,6a}$=3.9 Hz, H-6_a), 3.81 (dd, 1H, $J_{6a,6b}$=12.1 Hz, $J_{5,6b}$=6.4 Hz, H-6_b), 3.65 (s, 3H, OMe), 3.63-3.51 (m, 3H, H-1, H-2, H-5), 3.46-3.38 (m, 2H, H-7), 2.47 (q, 2H, H-14), 2.36 (t, 2H, H-11), 1.72-1.57 (m, 4H, H-8, H-10), 1.42-1.27 (m, 2H, H-9), 1.12 (t, 3H, C-15).

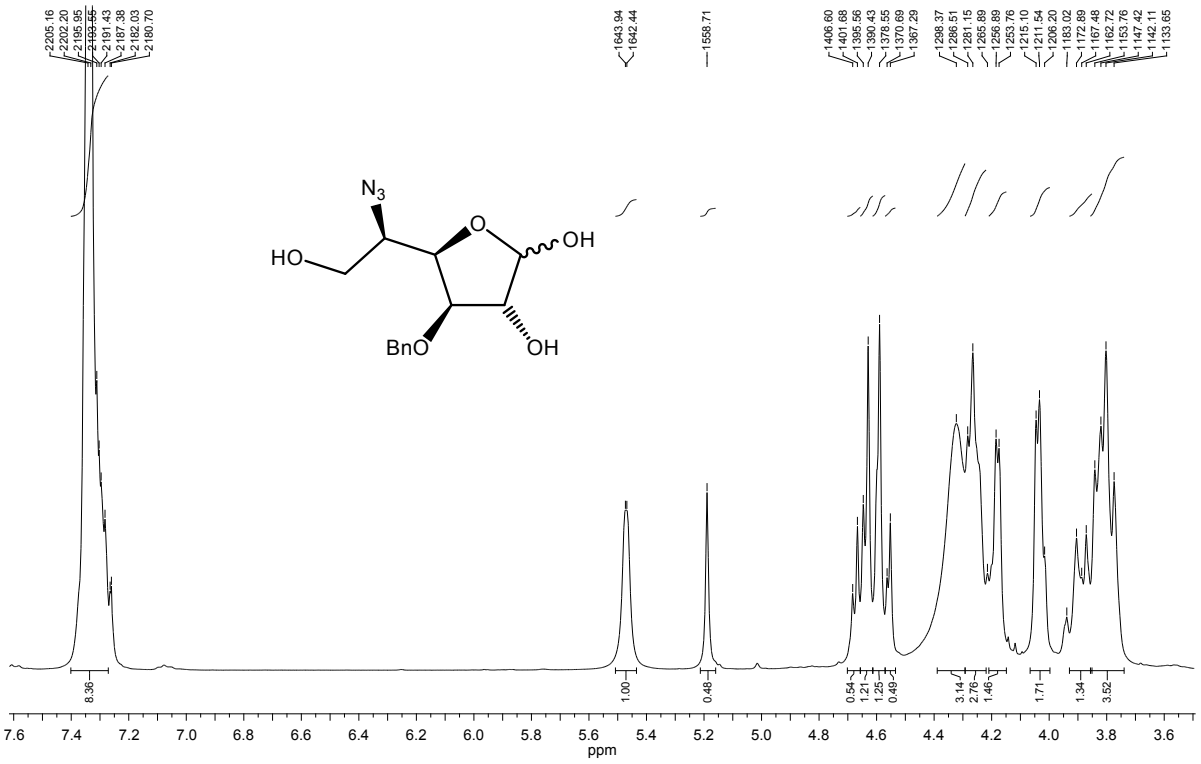
m/z: 347.2 $[MH]^+$ ionisation: MALDI, matrix: HCCA

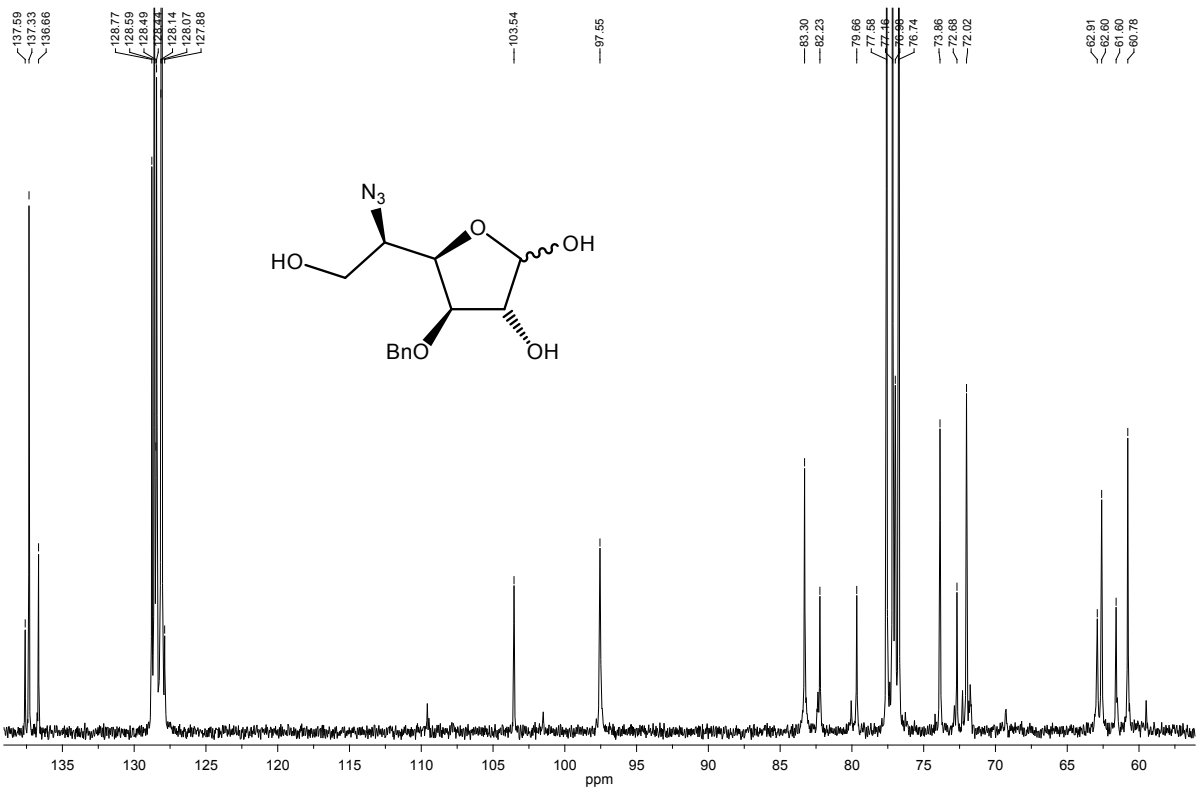
$[\alpha]_D^{20}$: +22.64 (c = 4.75, MeOH)

7 Appendix

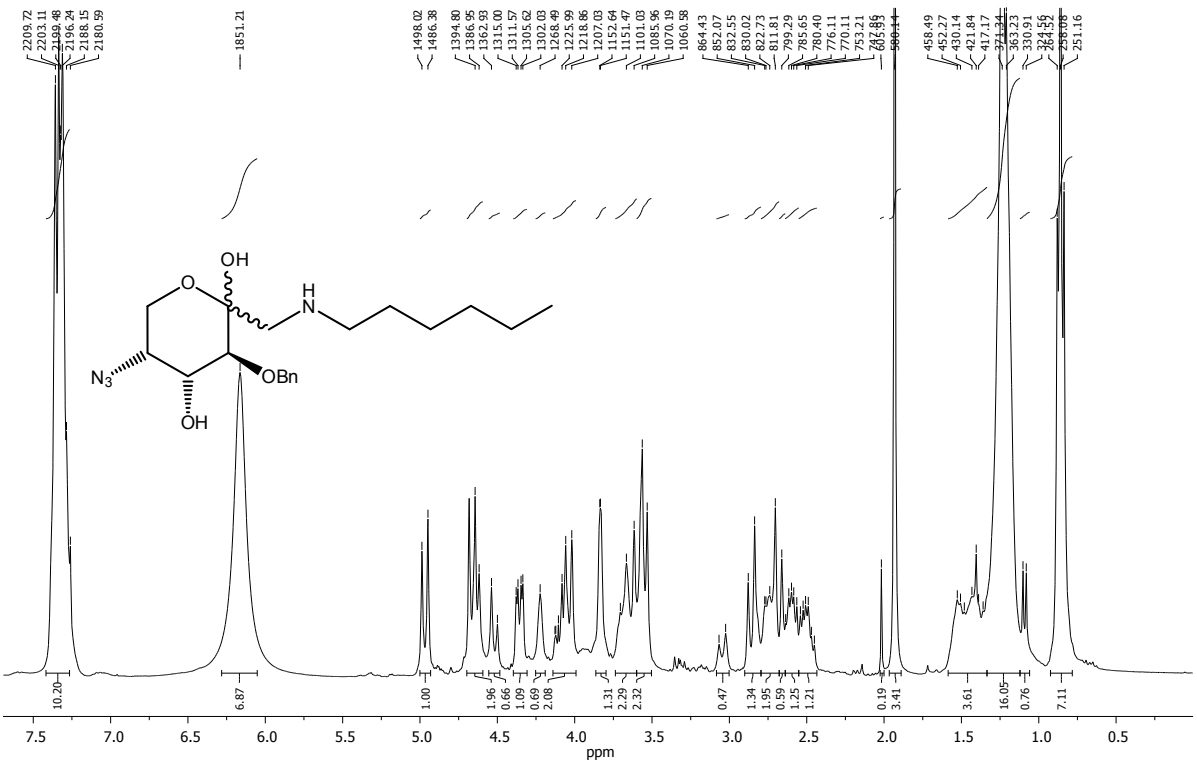
NMR-spectra

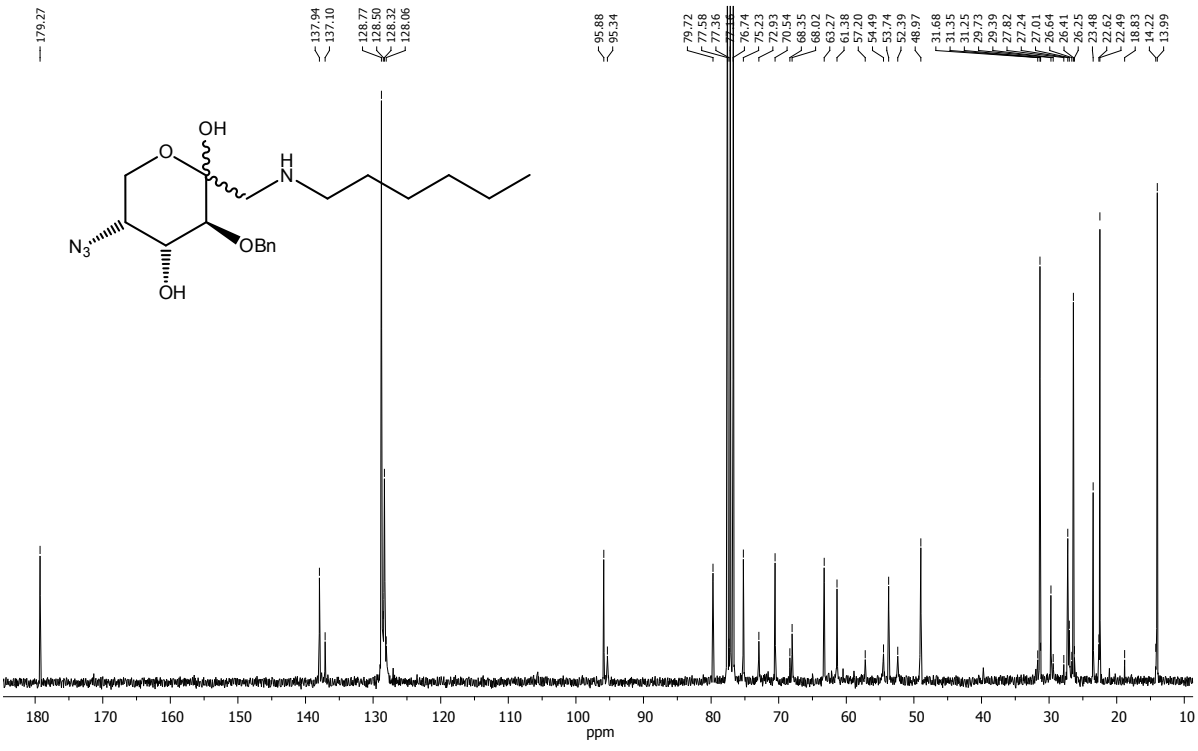
5-Azido-3-*O*-benzyl-5-deoxy-α, β-D-*gluco*-furanose (63)



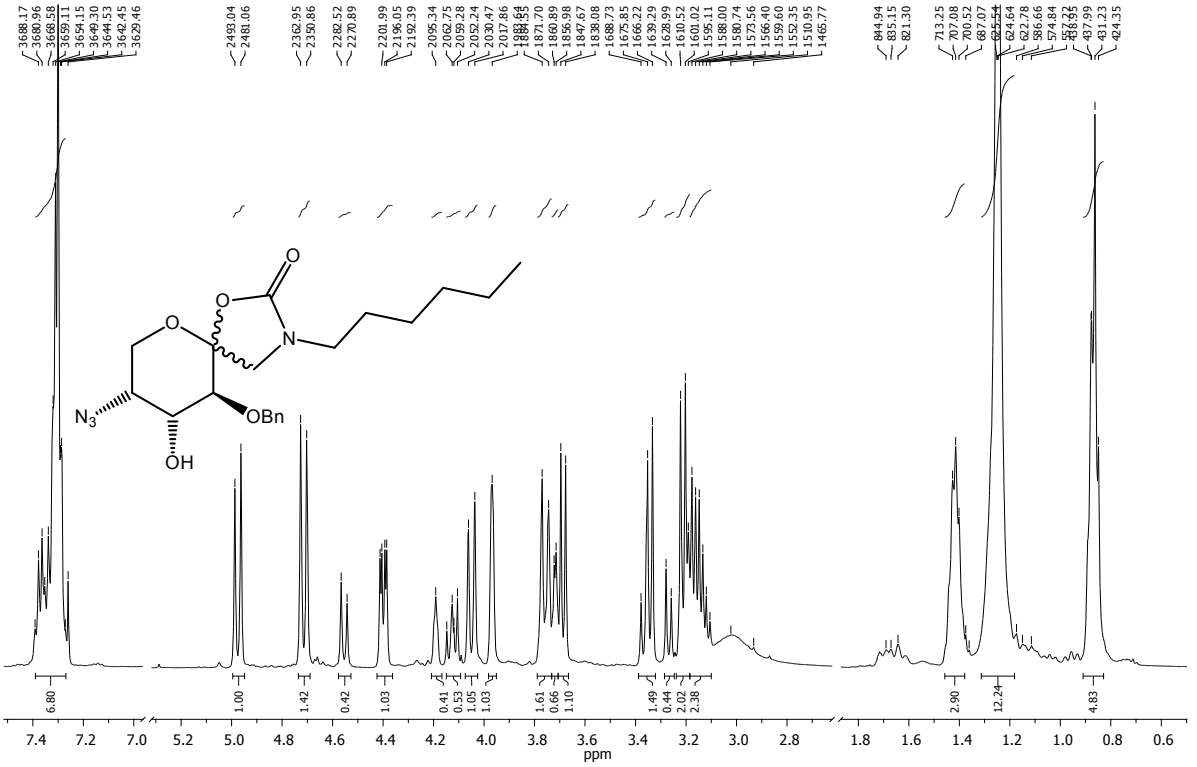


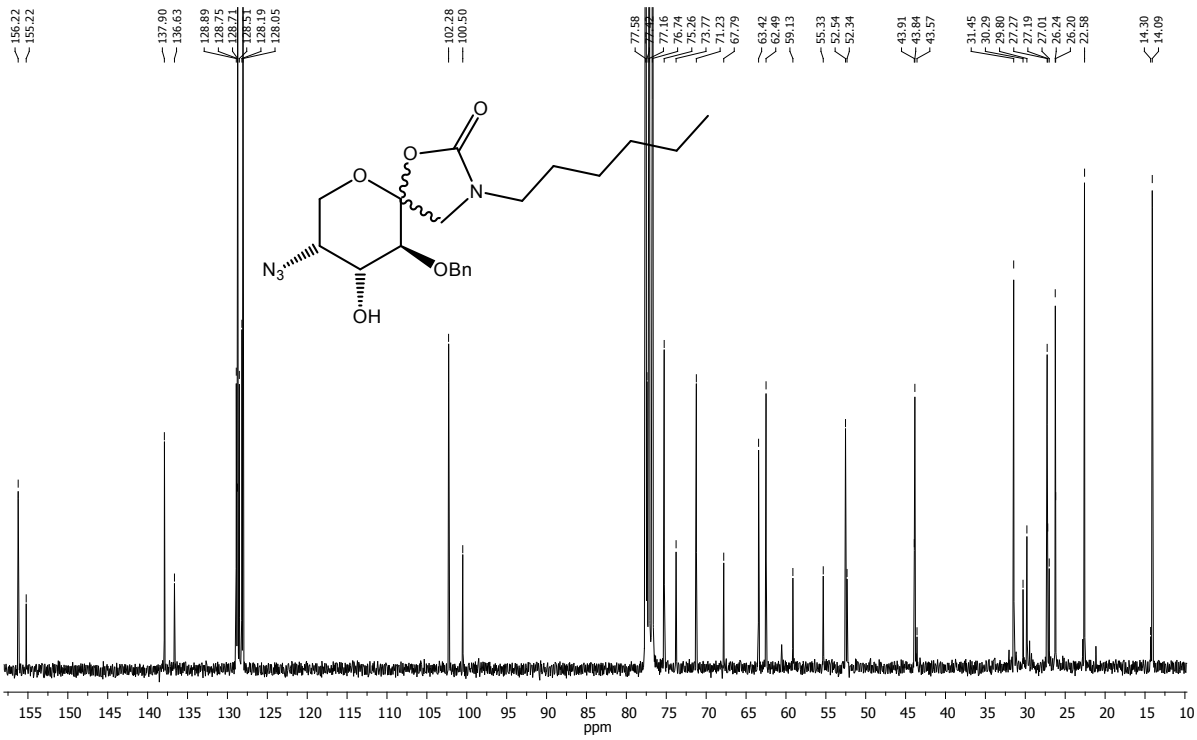
1-(*N*-Hexyl)amino-5-azido-3-*O*-benzyl-1,5-dideoxy-α, β-D-*fructo*-hex-2-ulopyranose (64)



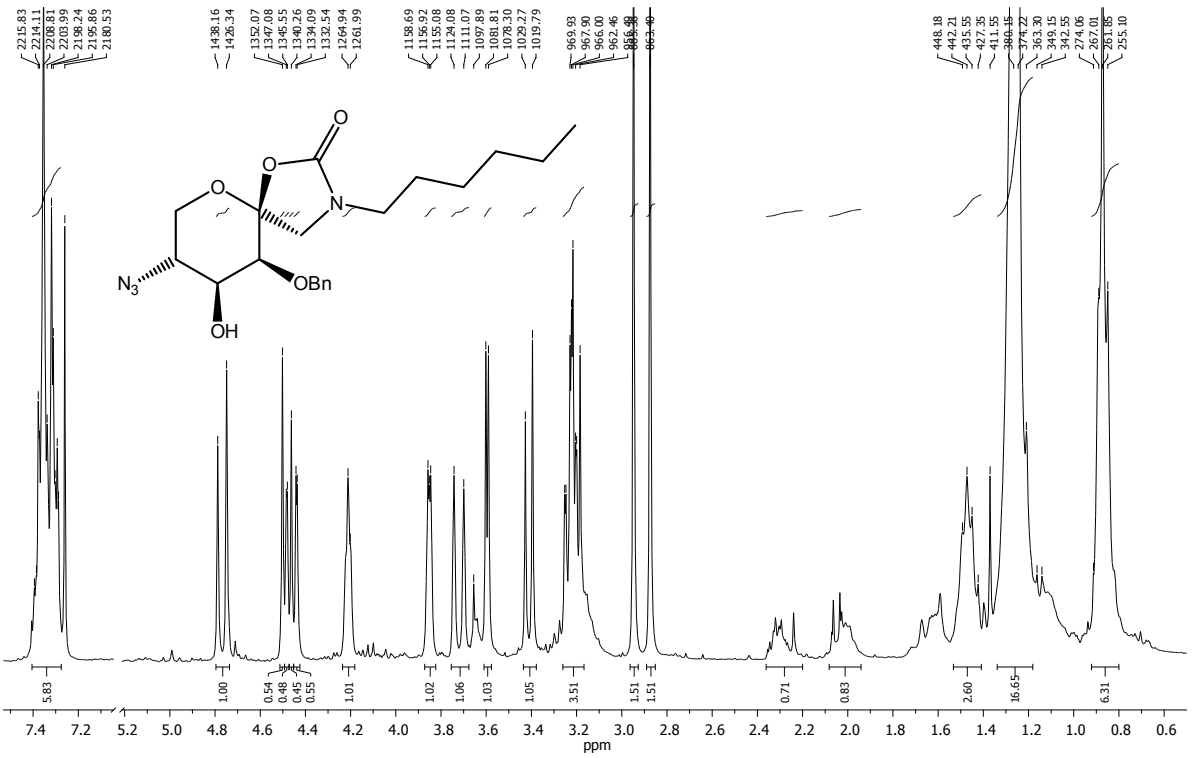


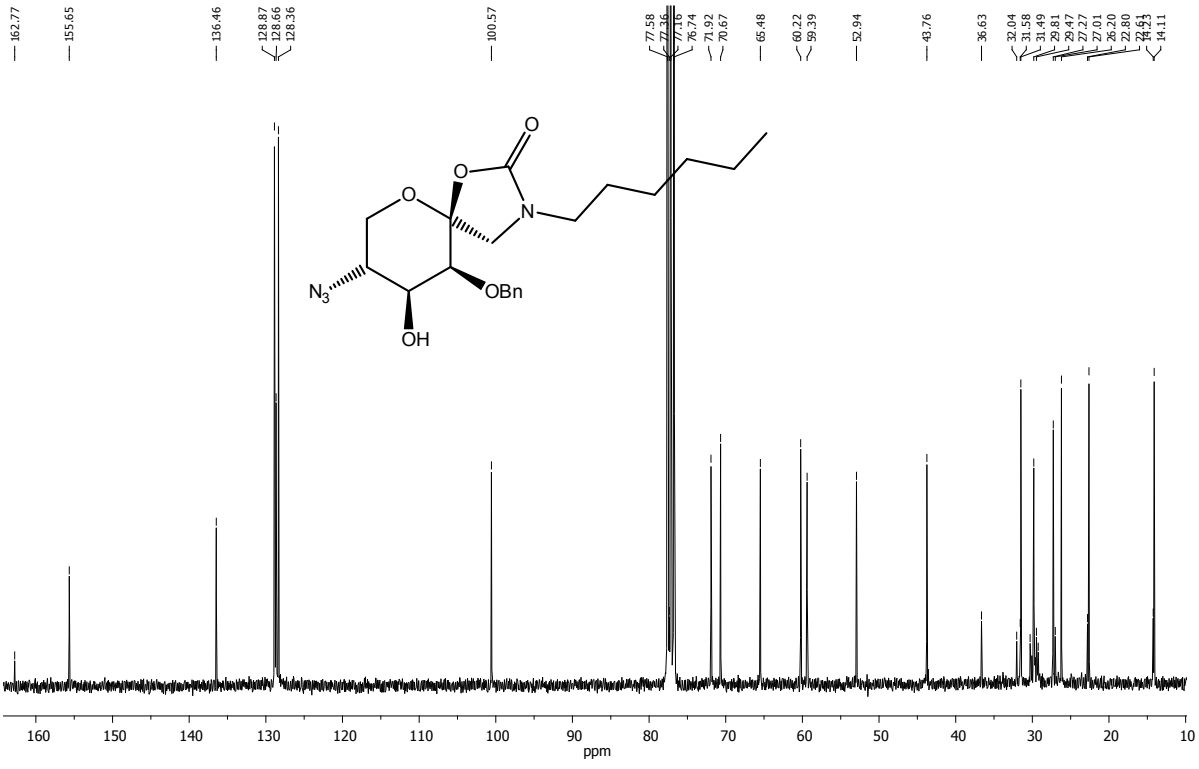
1-(*N*-Hexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-α,β-D-*fructo*-hex-2-ulopyranose (65)



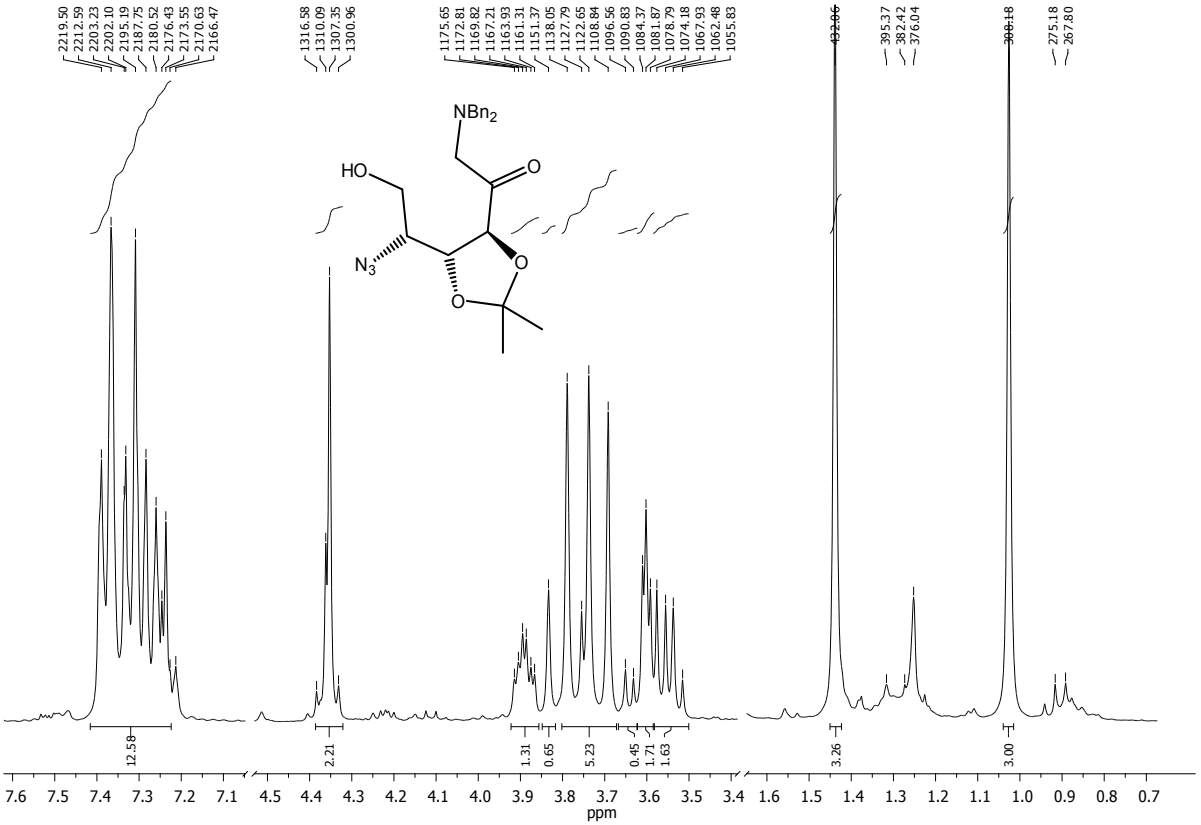


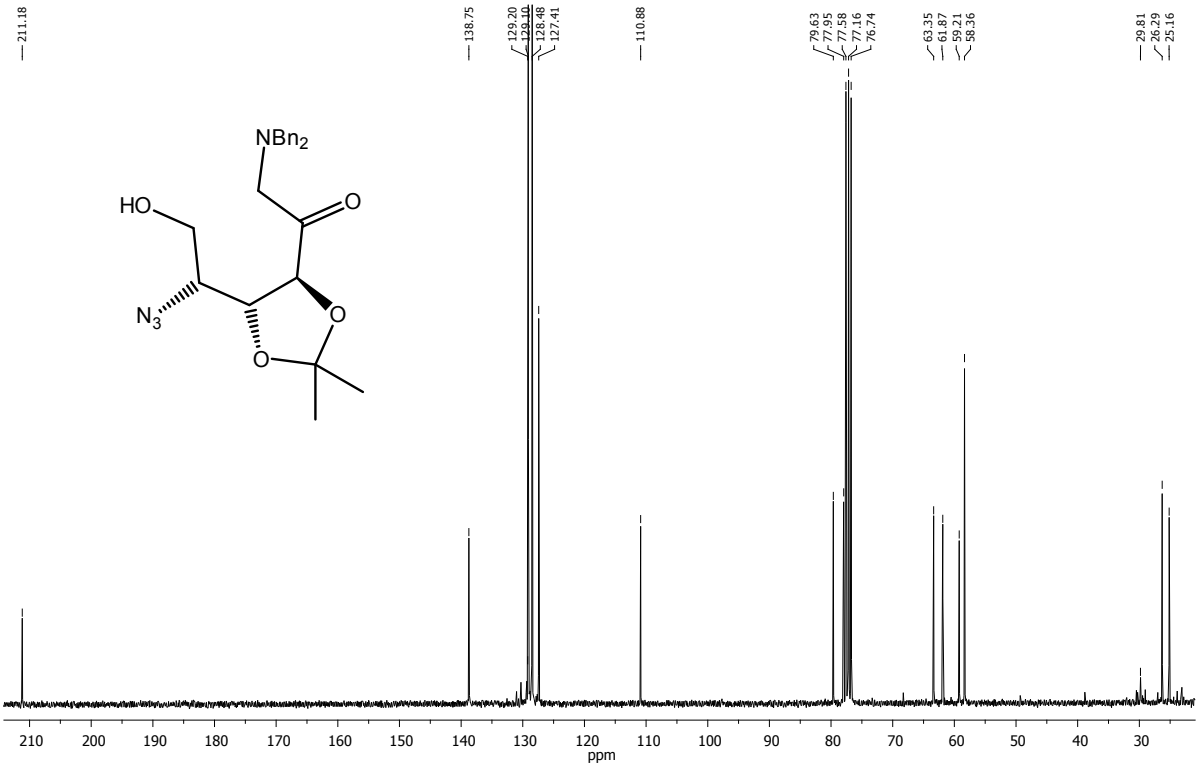
1-(*N*-Hexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-*β*-D-*tagato*-hex-2-ulopyranose (66)



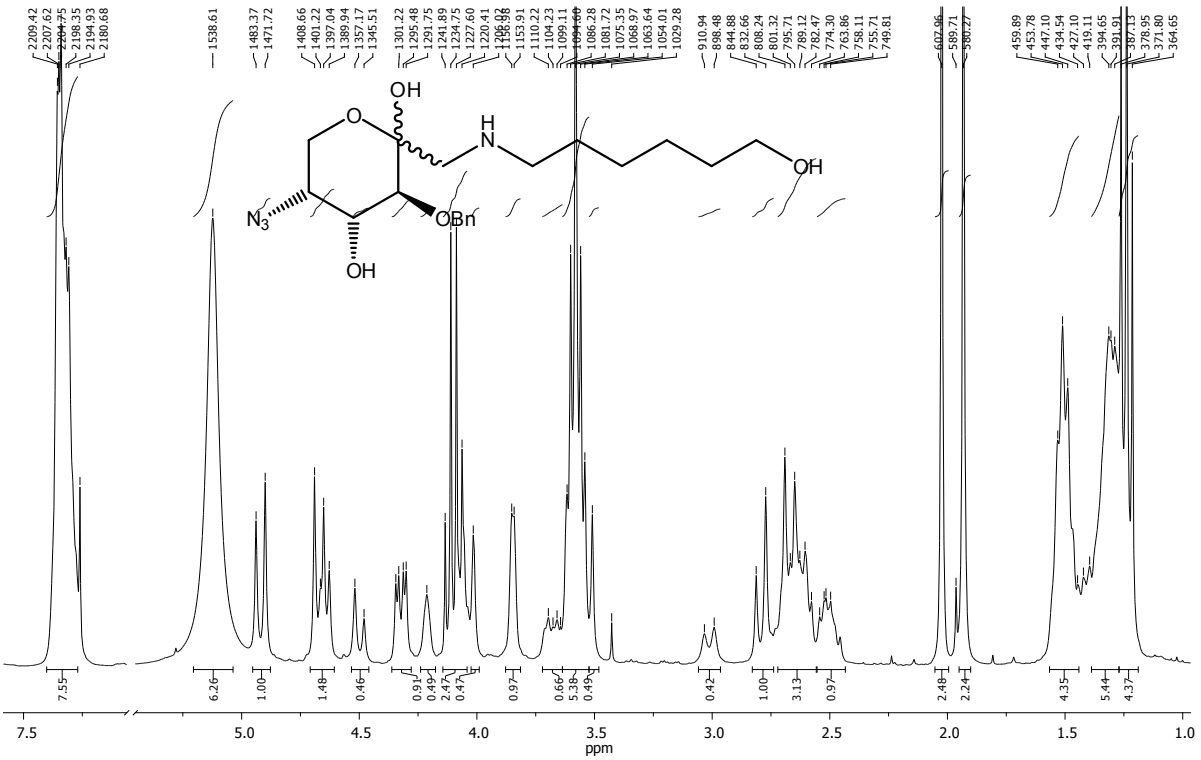


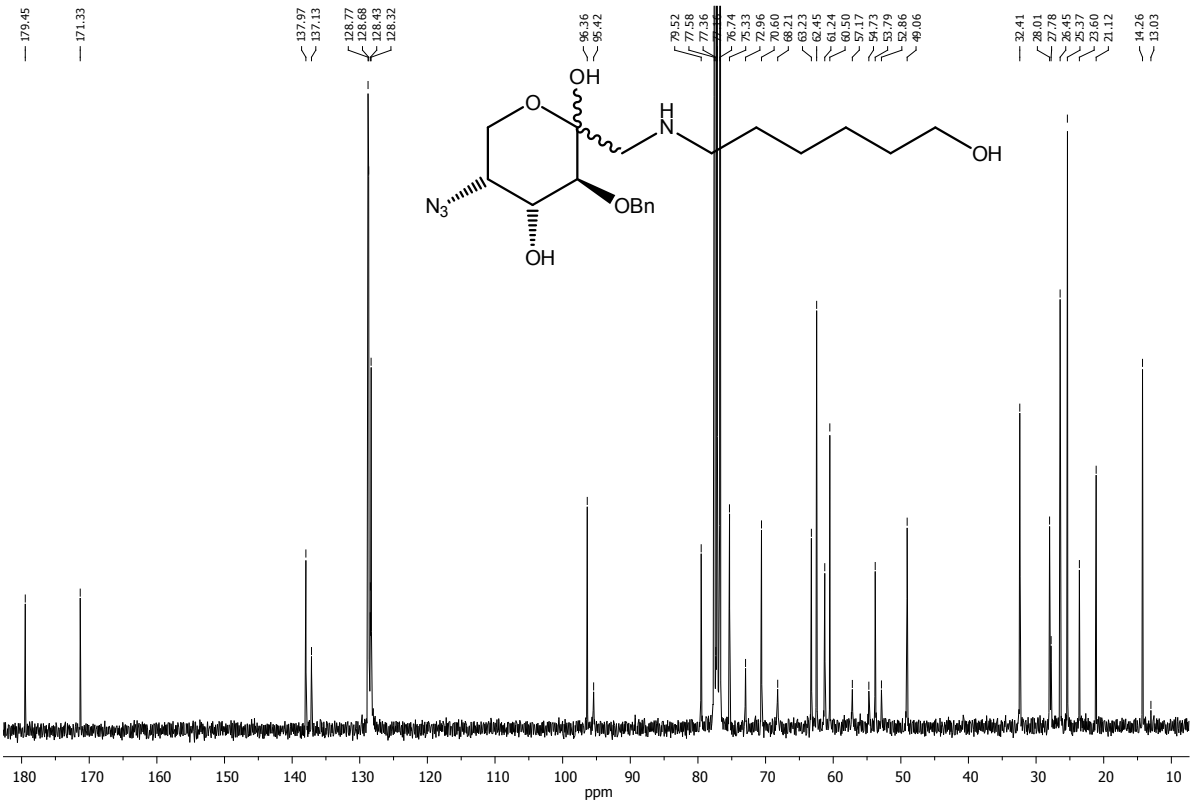
1-(*N*,*N*-Dibenzyl)amino-5-azido-1,5-dideoxy-3,4-*O*-isopropylidene-D-*arabino*-hex-2-ulose (69)



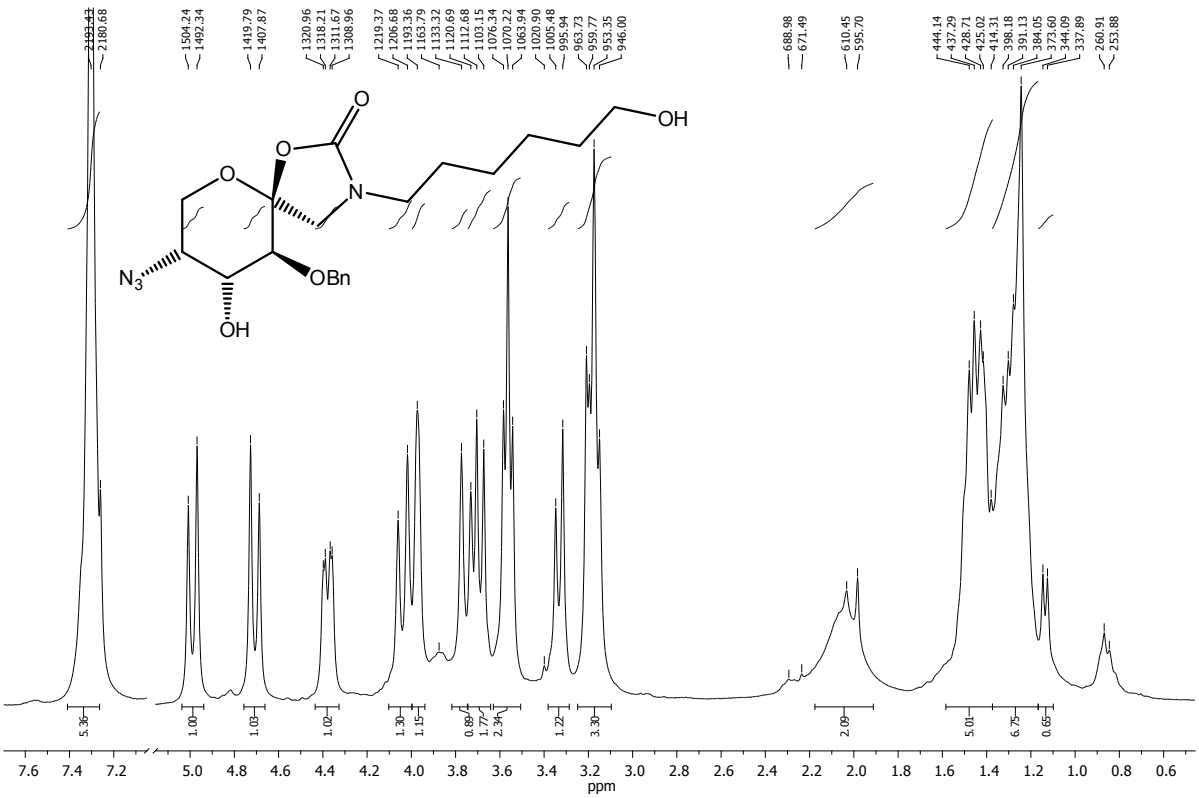


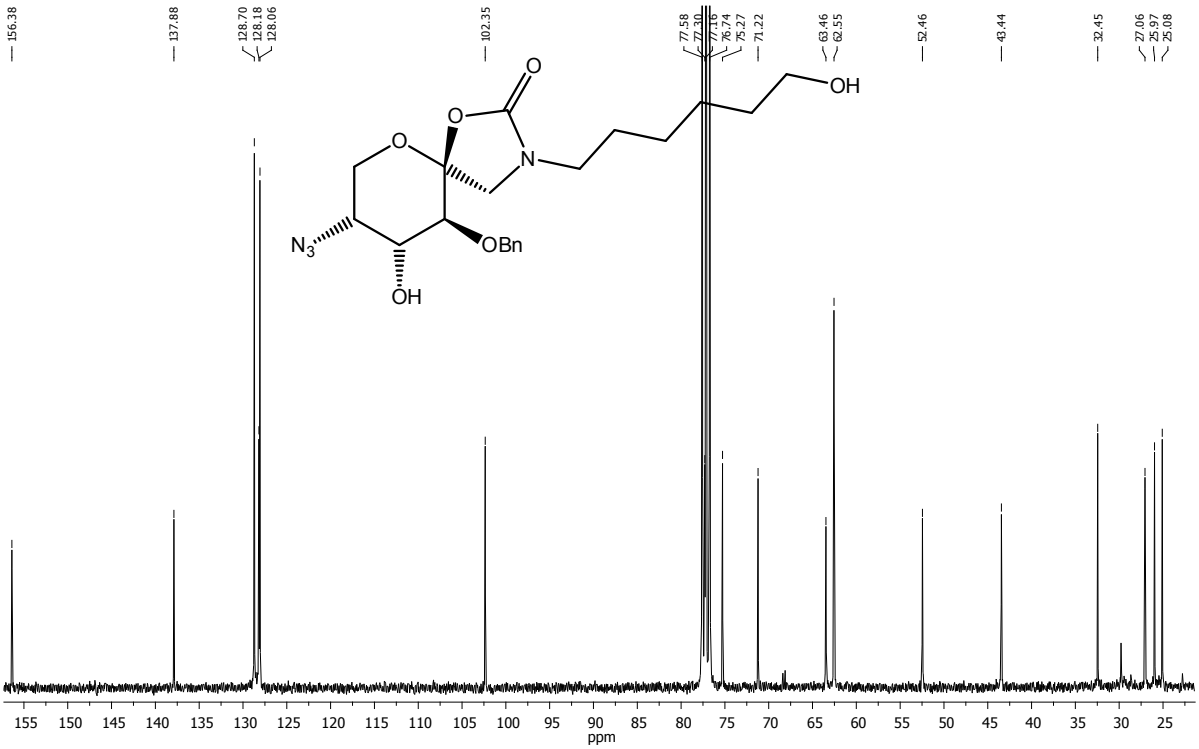
1-(*N*-Hydroxyhexyl)amino-5-azido-3-*O*-benzyl-1,5-dideoxy-α, β-D-*fructo*-hex-2-ulopyranose (70)



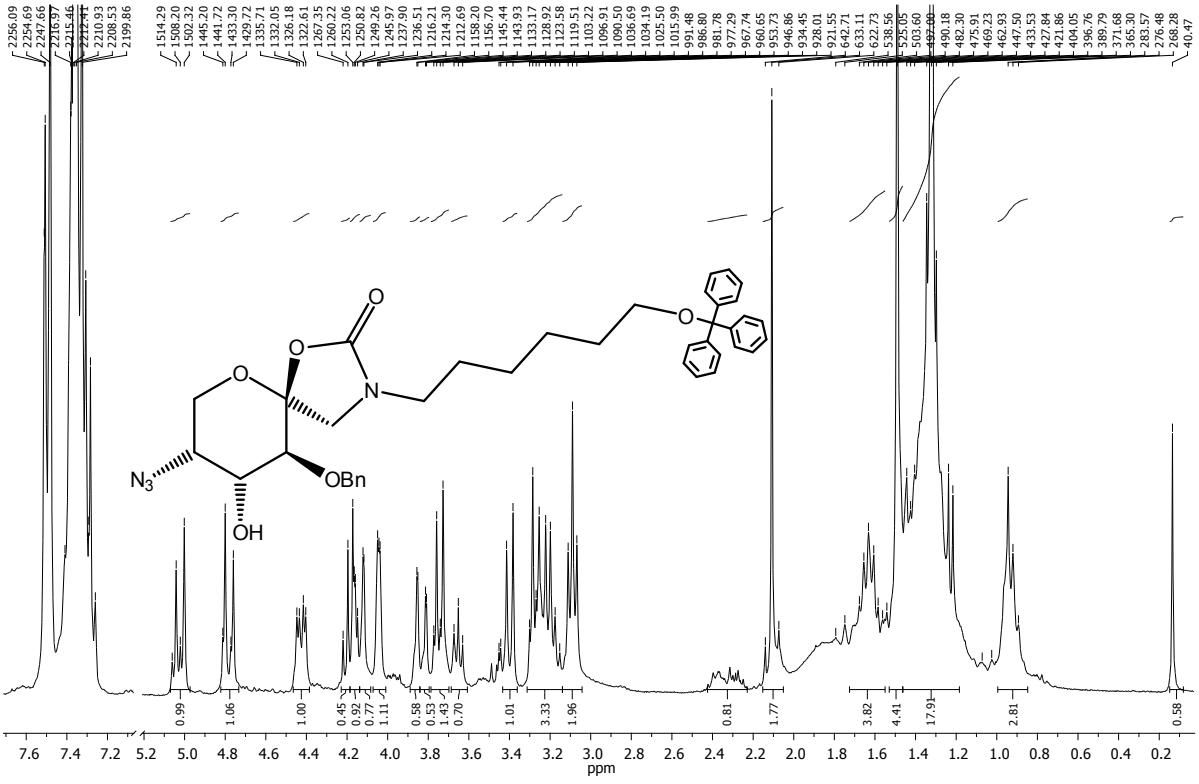


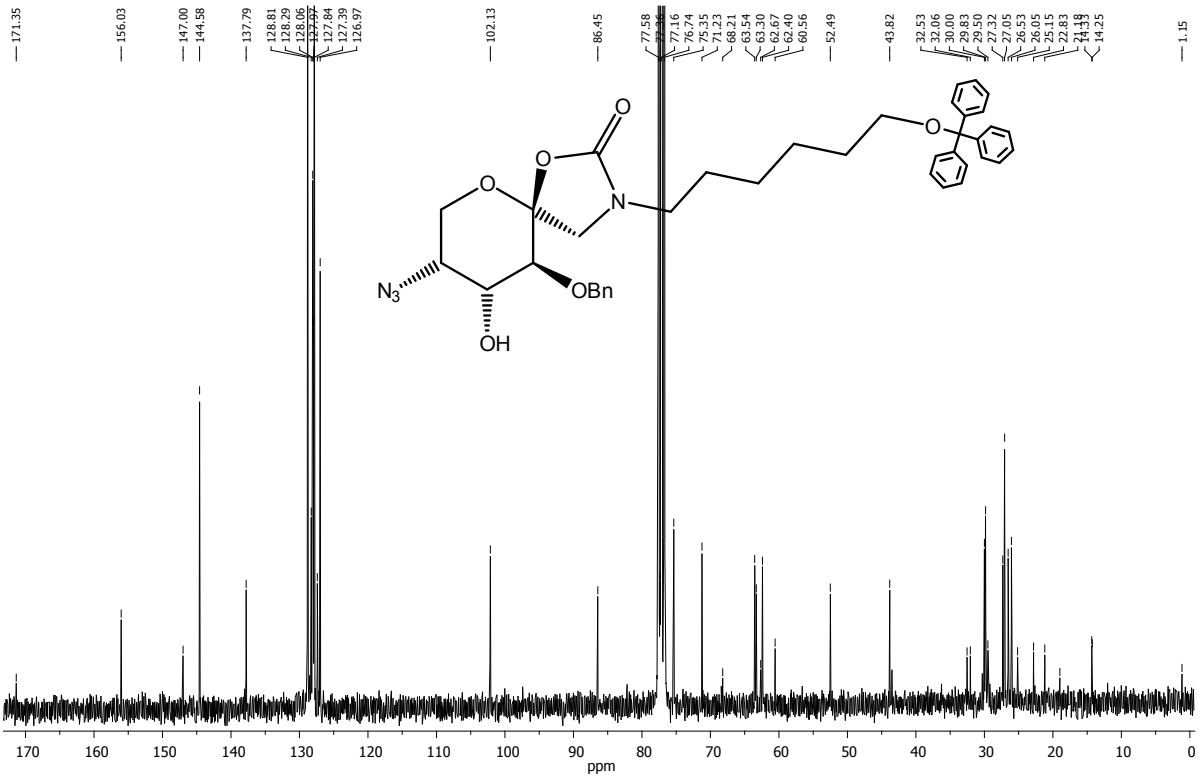
1-(*N*-Hydroxyhexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (71)



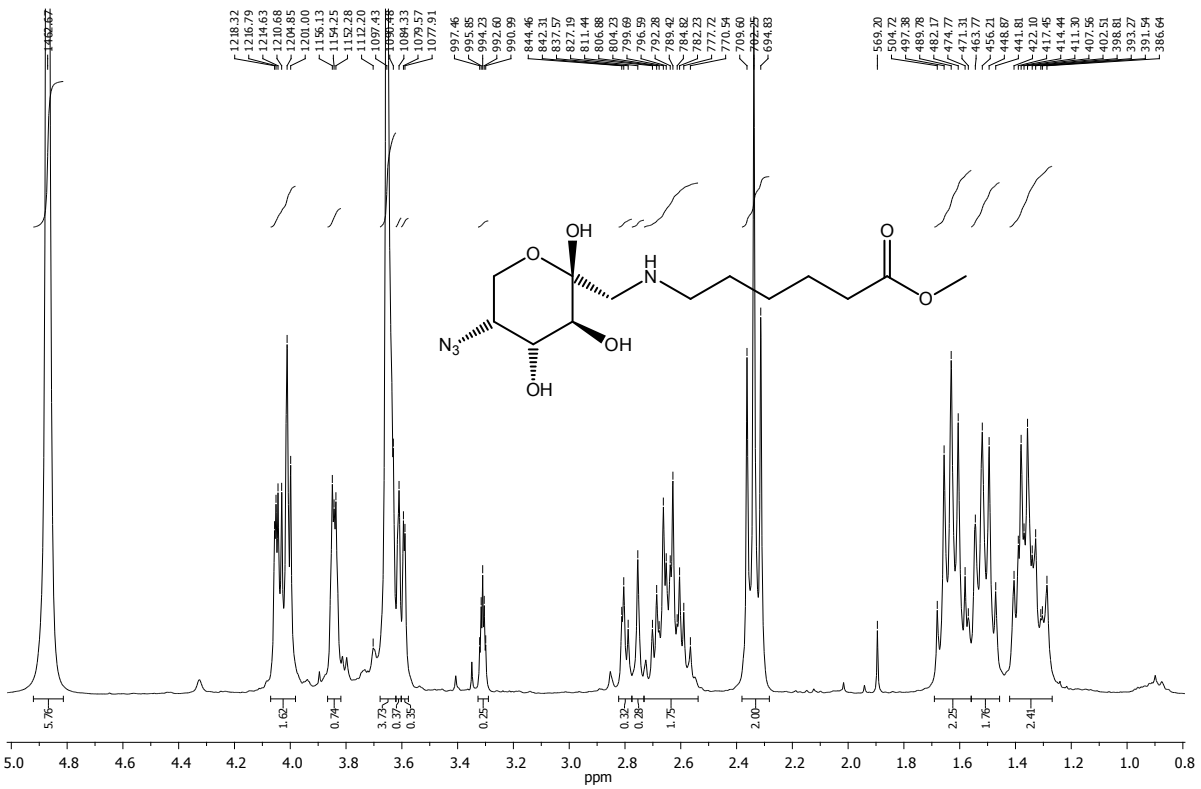


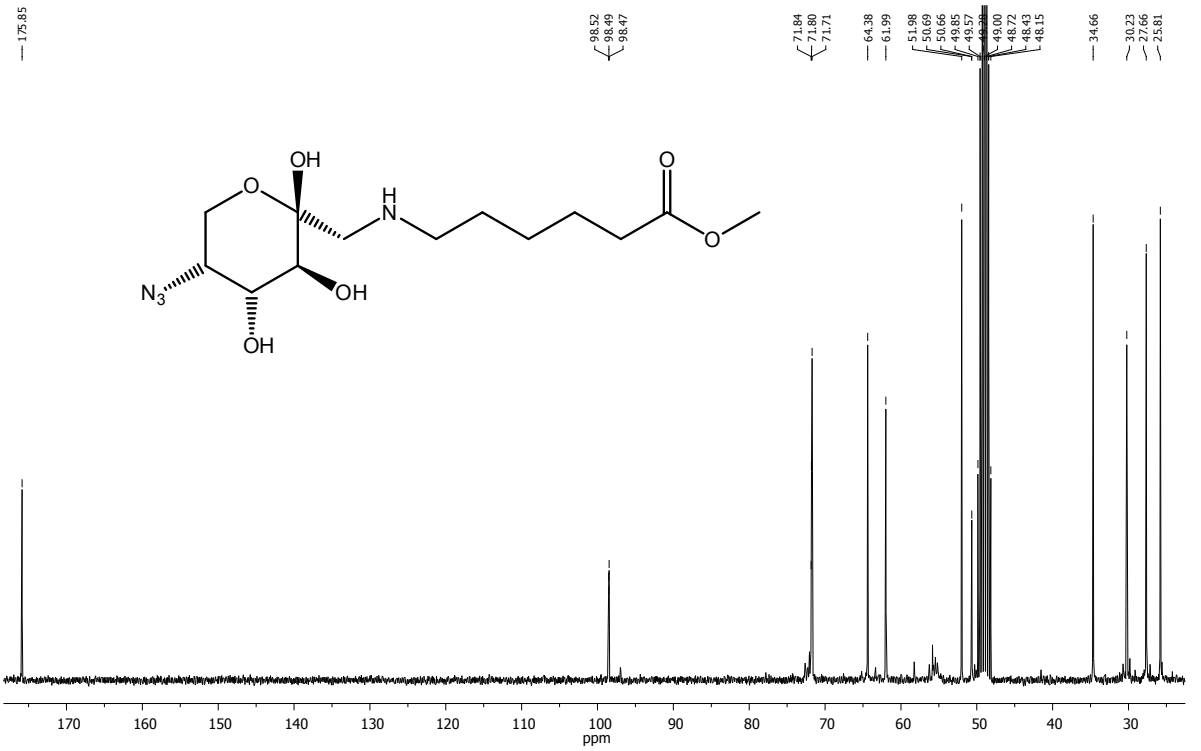
1-(*N*-Trityloxyhexyl)amino-5-azido-3-*O*-benzyl-1-*N*,2-*O*-carbonyl-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (72)



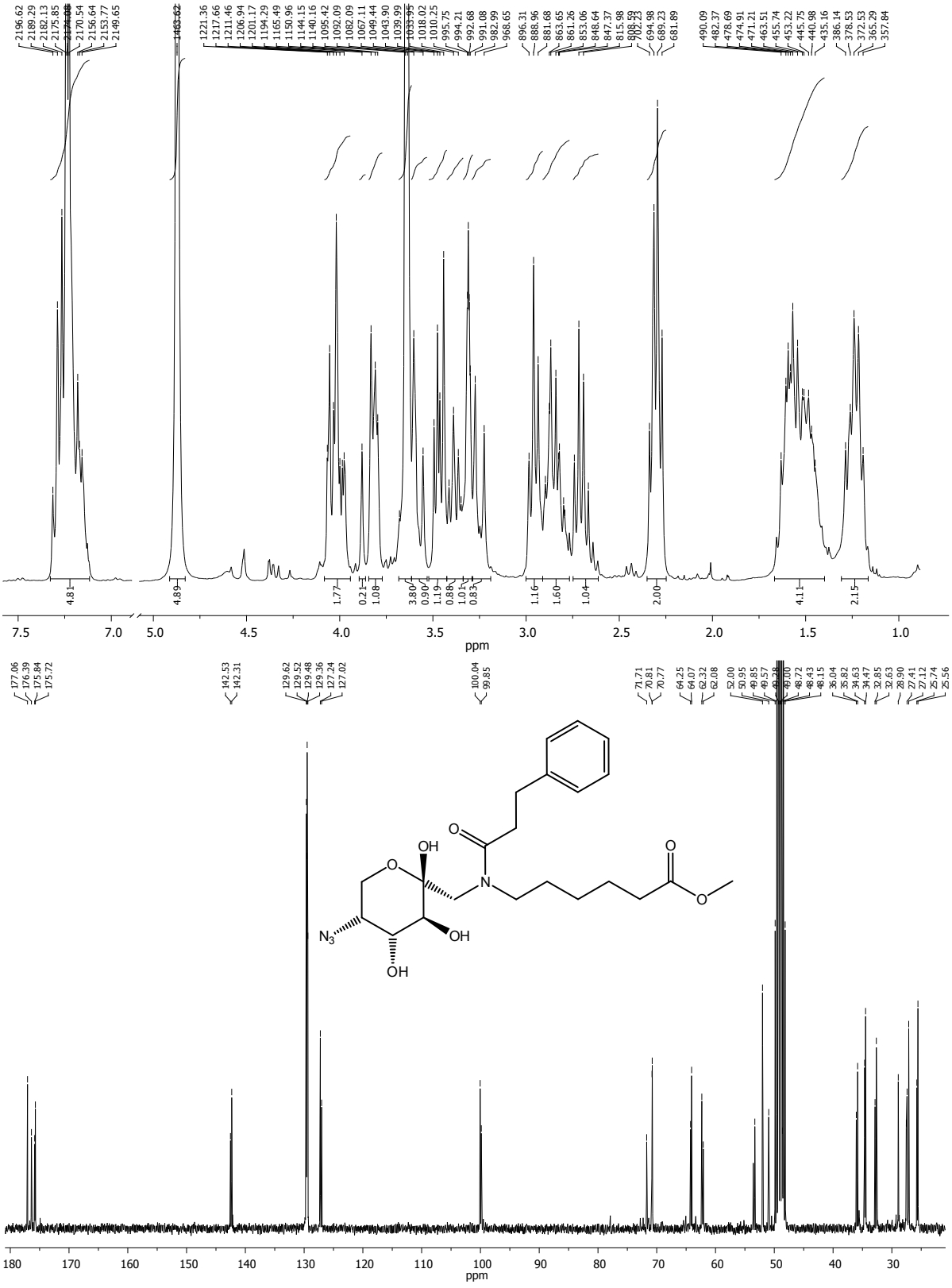


1-(*N*-Methoxycarbonylpentyl)amino-5-azido-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (73)

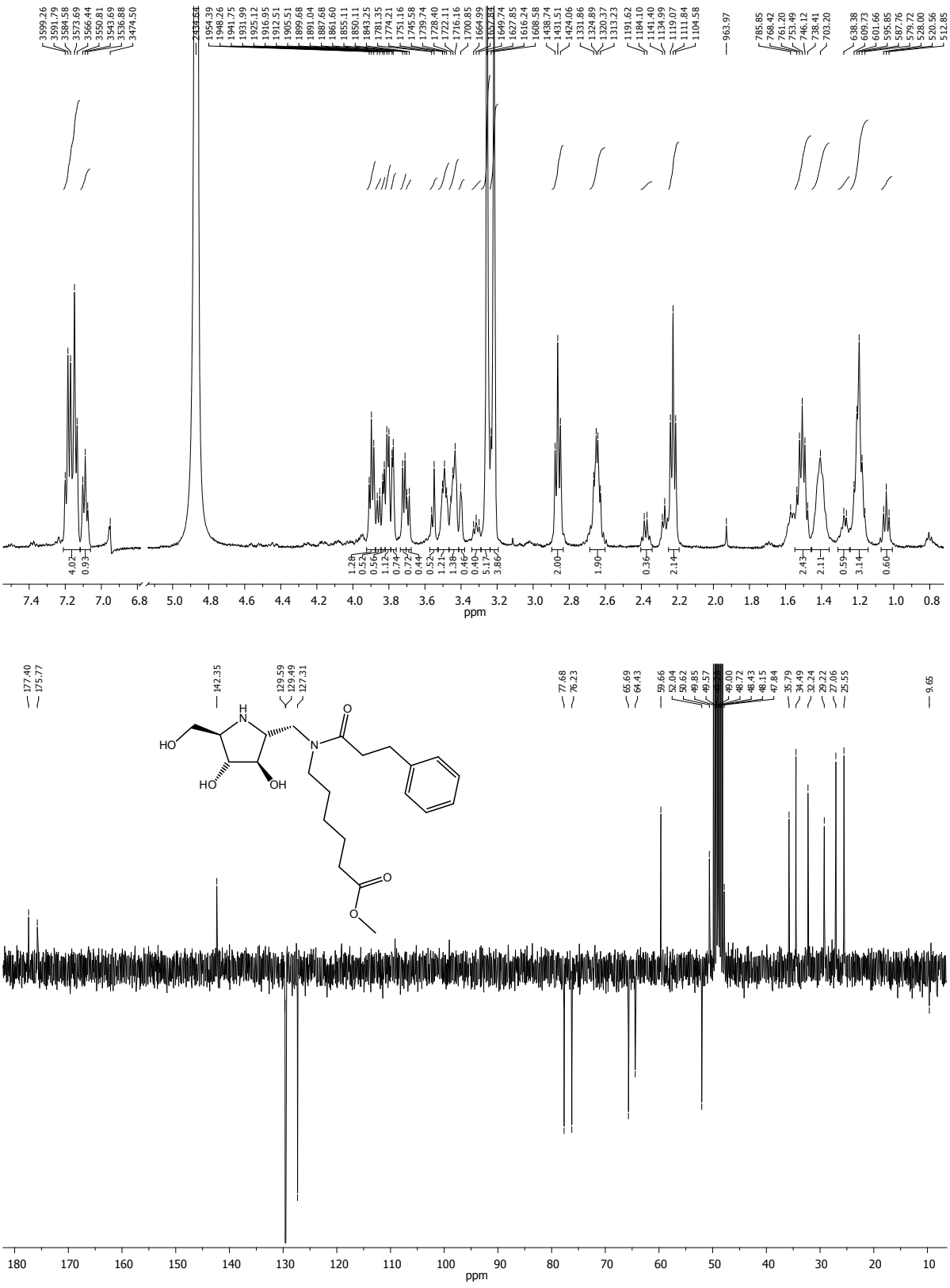




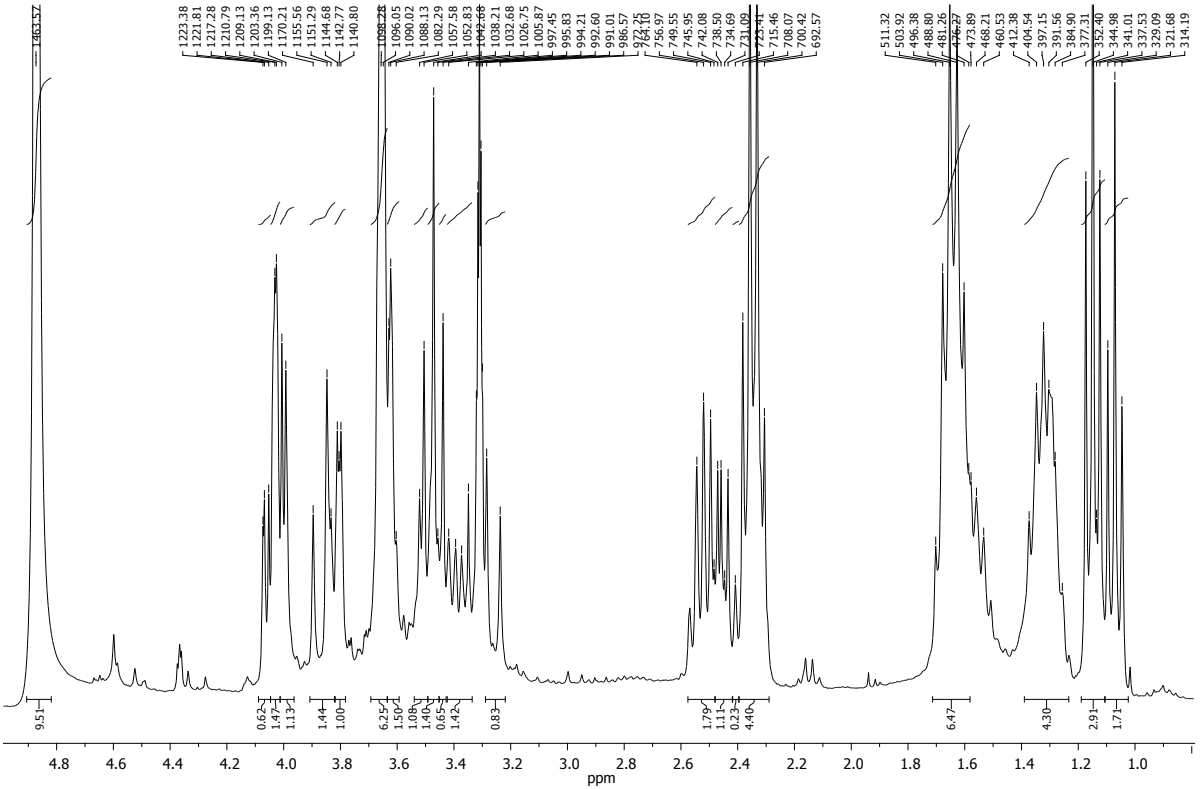
1-(*N*-Methoxycarbonylpentyl-*N*-phenylethylcarbonyl)amino-5-azido-1,5-dideoxy-β-D-*fructo*-hex-2-ulopyranose (74)

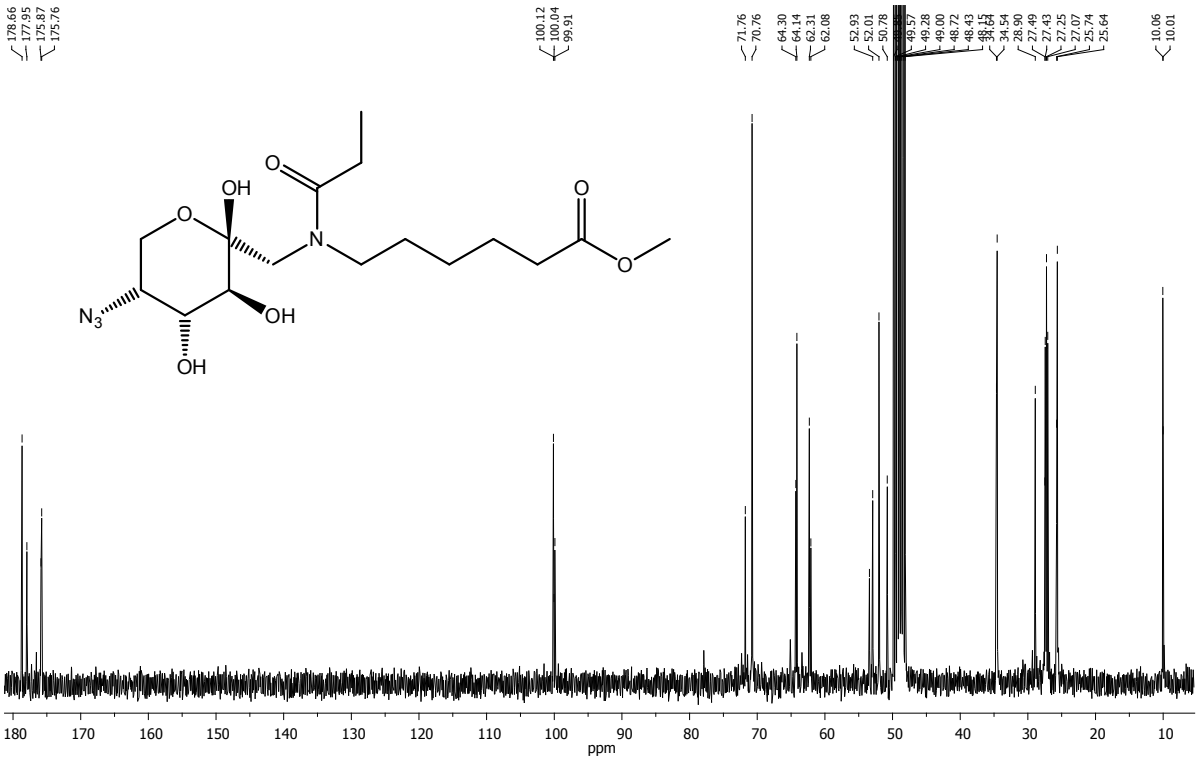


1-(*N*-Methoxycarbonylpentyl-*N*-phenylethylcarbonyl)amino-1,2,5-trideoxy-2,5-imino-D-mannitol (75)

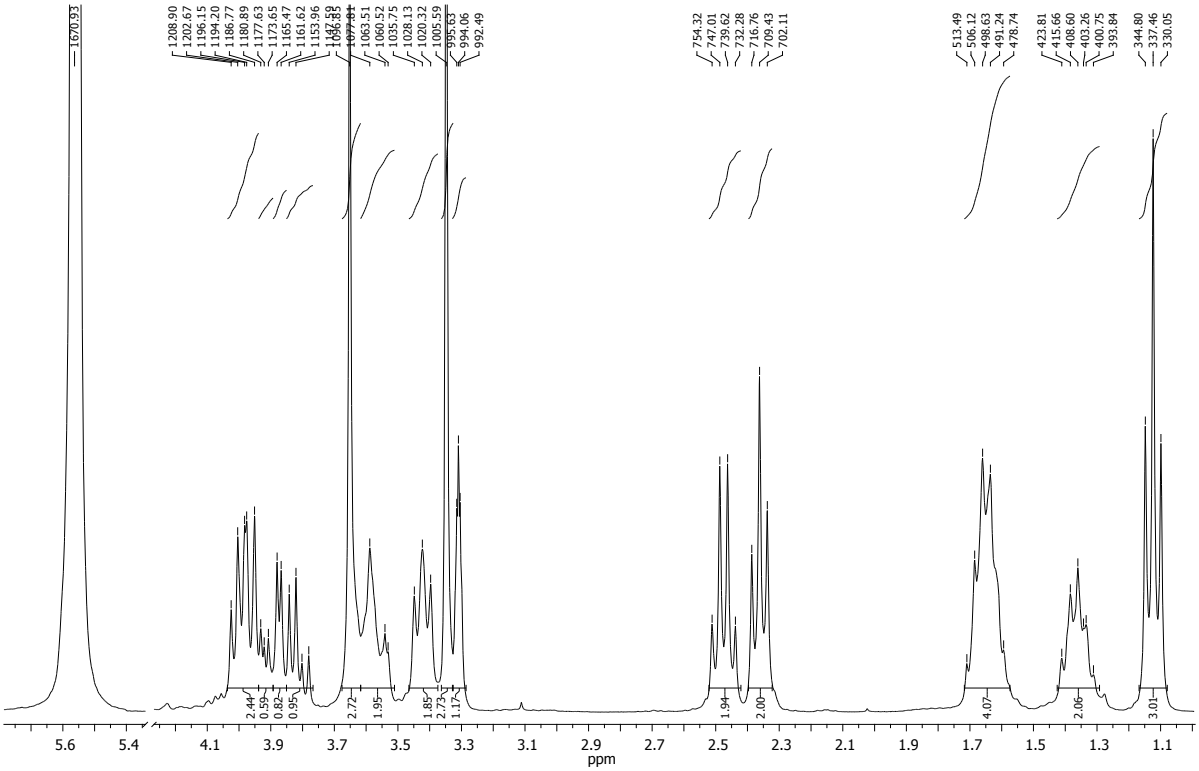


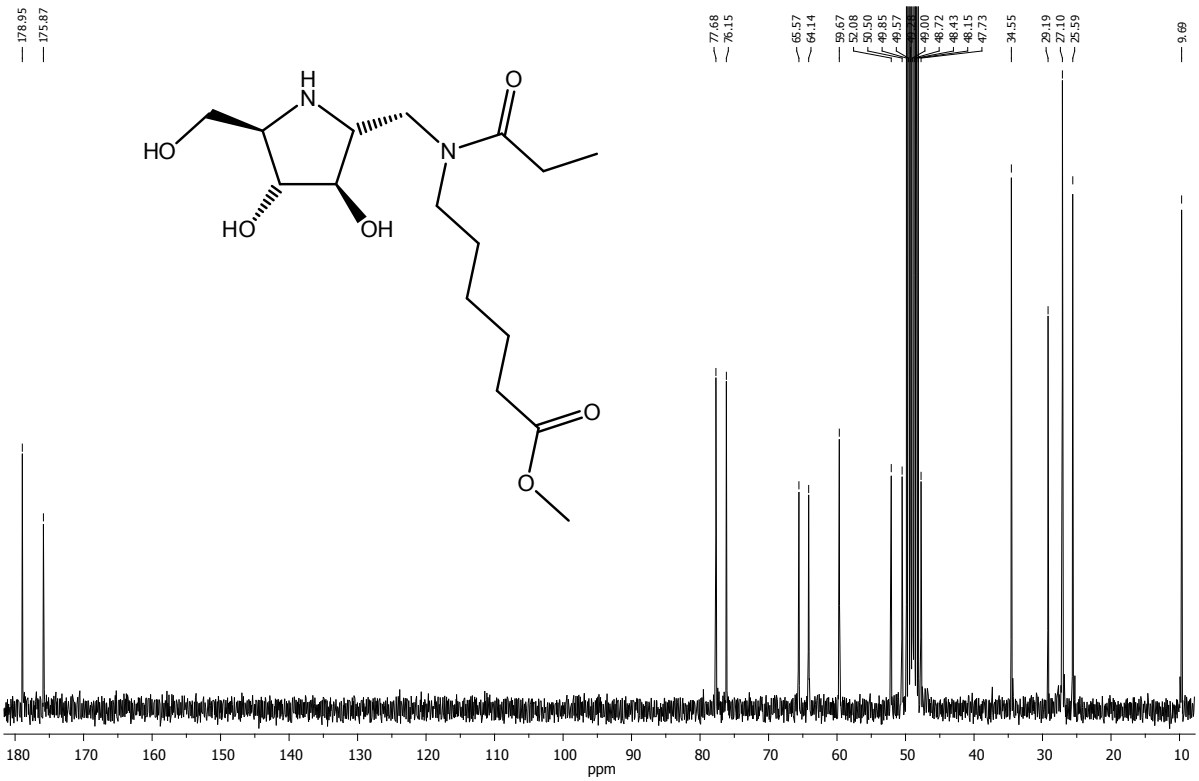
1-(*N*-Ethylcarbonyl-*N*-methoxycarbonylpentyl)amino-5-azido-1,5-dideoxy-*β*-D-*fructo*-hex-2-ulopyranose (76)





1-(*N*-Ethylcarbonyl-*N*-methoxycarbonylpentyl)amino-1,2,5-trideoxy-2,5-imino-D-mannitol (77)





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9 Curriculum vitae

Patrick Kosmus

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Education

1989 - 1993	Elementary school: Volksschule Puntigam/Graz
1993 - 1997	Primary school: Sporthauptschule St. Peter/Graz - Athletics
1997 - 2002	HTBLA Ortwein/Graz - Building construction
Jun 2002	University Entrance Certficate
2002 - 2003	Military service
2003 - 2010	Undergraduate studies, Technical Chemistry,
	Graz University of Technology
Mar 2010	1. Diploma exam
Mar 2010 - present	Masters degree programme: Technical Chemistry, NAWI Graz
Mar 2011 - present	Masters thesis: **Studies towards the synthesis of 2,5-dideoxy-2,5-imino-D-hexitol derivatives.**

10 Publications

Posters

- "Synthesis of 2,5-dideoxy-2,5-imino-D-hexitol derivatives: Potential inhibitors of lysosomal α- Galactosidase?"

  Patrick Kosmus, Martin Thonhofer, Arnold E. Stütz, Tanja M. Wrodnigg, Hansjörg Weber;
  14. Österreichische Chemietage, Linz, Austria, September 26-29, ***2011***

- "C-5 modifications in the hexose series"

  Martin Thonhofer, Patrick Kosmus, Tanja M. Wrodnigg, Arnold E. Stütz;
  14. Österreichische Chemietage, Linz, Austria, September 26-29, ***2011***

- "Synthesis of 2,5-dideoxy-2,5-imino-D-hexitol derivatives: Potential inhibitors of lysosomal α- Galactosidase?"

  Tanja M. Wrodnigg, Patrick Kosmus, Martin Thonhofer, Arnold E. Stütz;
  16. European Carbohydrate Symposium, Sorrento – Naples, Italy, July 3-7, ***2011***

- "C-5 modifications in the hexose series"

  Arnold E. Stütz , Martin Thonhofer, Patrick Kosmus, Tanja M. Wrodnigg;
  16. European Carbohydrate Symposium, Sorrento – Naples, Italy, July 3-7, ***2011***

- "Synthesis of Photolabelled Carbohydrate Building Blocks for Glycoclusters and Dendrimers via the Amadori Rearrangement"

  Patrick Kosmus, Tanja M. Wrodnigg, Thisbe Lindhorst, Bianca Kunz;
  13. Österreichische Chemietage, Vienna, Austria, August 24-27, ***2009***

Oral presentations

- "Studien zur Synthese von 2,5-Didesoxy-2,5-imino-D-hexitderivaten"

  Patrick Kosmus;
  16. Österreichischer Kohlenhydrat-Workshop, BOKU-Vienna, Vienna, Austria, February 16, ***2012***