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DISSERTATION

„Synthesis of Rare 2,4-Diamino-2,4,6-trideoxy Hexoses
&
Allylation Strategies Towards the Nonulosonic Acids and 3-Deoxy-2-uloses“

Verfasser

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„Es ist keine Kunst,
etwas schwieriger zu klettern als es ist.“

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INTRODUCTION

1. Biological Background

Carbohydrates are among the most abundant molecules of life. They exceed the diversity of other common building blocks like amino acids due to multiple stereochemical patterns and different connectivities by far.[1] Additionally, substitution of hydroxyl functionalities increases the complexity of this class of compounds. But despite the numerous possibilities, only a small group of carbohydrates is predominantly found in nature, with D-glucose being the most frequent sugar molecule. D-Glucose is the most important energy storage compound and the major constituent of structural material in plants.[2] This are the fundamental roles of carbohydrates. However, in looking at biochemical pathways on molecular level, sugars are found to be involved in many other essential processes.[3] Examples include the regulation of activity of enzymes as well as recognition and communication processes.

The glycobiology of the cell membrane combines many aspects of carbohydrates. The membrane consists of and the surface is decorated with various different sugars responsible for mechanical strength, stability towards changing temperature and pressure as well as preventing invasion of undesired molecules.

1.1. The Bacterial Cell Wall

In general, bacteria can be divided into two major groups - the Gram-positive and the Gram-negative family.[4] A distinctive difference in their peptidoglycan (PG) layer determines their affiliation. Gram-positive bacteria consist of a thick PG and the dye used in the Gram-staining process is retained yielding in a purple color. In contrast, the Gram-negative cell envelope is not capable of keeping the dye and finally turns into a pink color due to counterstaining.[5]

1.1.1 Gram-negative Cell Envelope

The architecture of the cell envelope of Gram-negative bacteria consists of three major parts: the cytoplasmic membrane (CM), the periplasmic space and the outer membrane (Figure 1).[6] The cytoplasmic membrane is a typical phospholipid containing transmembrane and membrane anchored proteins that prevent hydrophilic molecules from leaving the cytoplasm.

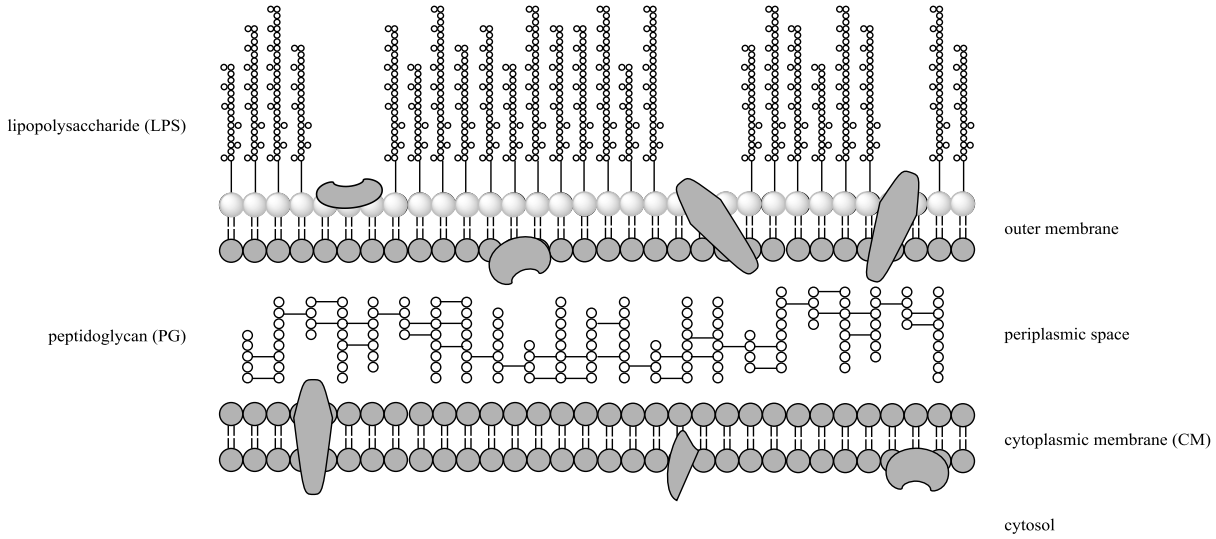


Figure 1. Organisation of the Gram-negative cell envelope.

The peptidoglycan is located in the periplasmic space and is responsible for the shape of the bacterium.[7] This rigid structure persists the turgor, nevertheless it is flexible enough and pores within the mesh-like peptidoglycan allow a controlled flow of molecules through the periplasmic space. It is built of a carbohydrate chain of alternating *N*-acetyl-D-glucosamine (GlcNAc) and *N*-acetyl-D-muramic acid (MurNAc) in a β–1,4 connectivity and is perpendicularly crosslinked with various amino acids *via* the lactyl residue.[8] The orientation of the sugar chain is supposed to be parallel to the cytoplasmic membrane, but more detailed investigations are necessary since there is no definite proof of this concept.

Figure 2 schematically shows the organization of the crosslinking. The length of the GlcNAc-MurNAc chain varies between strains as well as the connectivity (3-4, 3-3, 2-4, etc.) and the number of amino acids present in the bridge (0 to 7).[9] The carbohydrate moiety at the terminal end of the Gram-negative glycopeptide usually is 1,6-anhydro MurNAc.

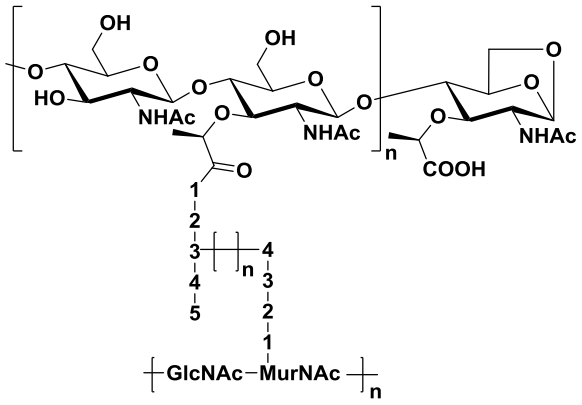


Figure 2. Crosslinking of the pepridoglycan chains.

In Gram-negative bacteria, the outer membrane is an unsymmetrical lipid bilayer composed of an inner phospholipid and the lipopolysaccharide (LPS) on the outer side (Figure 3). It was discovered by Richard Pfeiffer in 1892 and is referred to as endotoxin, since it is responsible for the pathogenicity of Gram-negative bacterial strains.[10] Furthermore, the LPS supports the ability of bacteria to adapt to extreme environmental conditions. The general structure of endotoxin is outlined in Figure 3.[11] The Lipid A is typically connected to the core region *via* 3-deoxy-D-*manno*-2-octulosonic acid (KDO) and the core region is linked to the O-specific polysaccharide (OPS).

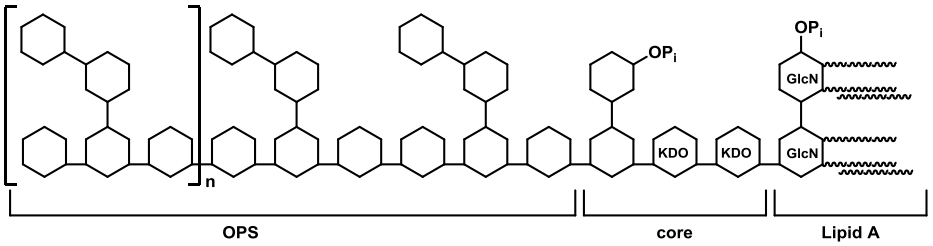


Figure 3.Schematic structure of the LPS of Gram-negative bacteria.

In contrast to the OPS, which shows structural diversity, the core region and Lipid A are far more conserved.[12] Lipid A is the major virulence factor of Gram-negative bacteria and anchors the LPS to the outer membrane of the cell. The carbon backbone generally consists of a repeating unit with two β−1,6 linked D-glucosamines (GlcN) that are substituted with fatty acids of different chain length varying between 10 and 18 C-atoms (Figure 4).[13] Phosphate groups are attached at the reducing as well as to the non-reducing sugar of the disaccharide. Although Lipid A is a rather conserved molecule, replacements of the phosphates with 4-amino-4-deoxy-L-arabinose (AraN), 2-amino-2-deoxy-D-galactose (GalN), D-galacturonic acid or D-mannose (Man) have been observed resulting in a fine tuning of the endotoxin structure.[11]

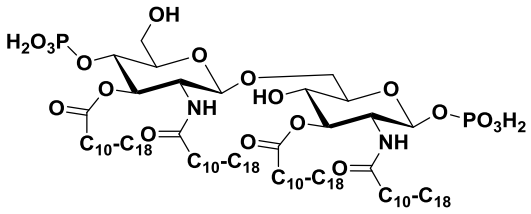


Figure 4. Conserved structur of Lipid A.

The core region contains, besides hexoses (mainly D-glucose (Glc), D-galactose (Gal)), higher carbohydrates throughout, such as the octulose KDO with varying linkages. Further modification of the sugars with acetates or substitution of hydroxyl groups with amino functionalities creates diversity among the strains.[14] Since phosphorylation is yet another frequent modification and KDO bears a carboxylic acid which is deprotonated under physiological conditions, negative charges are present, which support the rigidity of the cell wall due to incorporation of cations.

The O-polysaccharide of Gram-negative bacteria offers a variety of different carbohydrate patterns with D-glucose and D-galactose as the most prevalent sugars.[15] This part of the cell envelope represents the most extensive component and is built up by repeating units with two to eight residues. Besides hexoses, pentoses and heptoses are common constituents, whereas aldoses dominate compared to ketoses.

Deoxygenation offers a modification resulting in either deoxy or amino sugars. Considering the stereochemistry, D- as well as L-isomers have been identified obtaining different configurations.[16] Furthermore, 3-deoxy-2-ulosonic acids play an important role in the O-specific polysaccharide of bacteria. KDO[17] and neuraminic acid[18] have been isolated from cell wall material and additionally bacteria have evolved an exclusive set of nonulosonic acids (NulOs, Figure 5).[19] Pseudaminic acid (**1**, Pse) and legionaminic acid (**2**, Leg) were characterized and revealed an L-*glycero*-L-*manno* configuration for the former carbohydrate and a D-*glycero*-D-*galacto* configuration for the latter. Furthermore, the C4 (**3**, 4-*epi*-Leg) and C8 (**4**, 8-*epi*-Leg) epimer of Leg have been identified and their hydroxyl groups are frequently functionalized. For example, methylation, acetylation, phosphorylation and etherification with lactic acid can be found at various positions as well as amino acid conjugates.

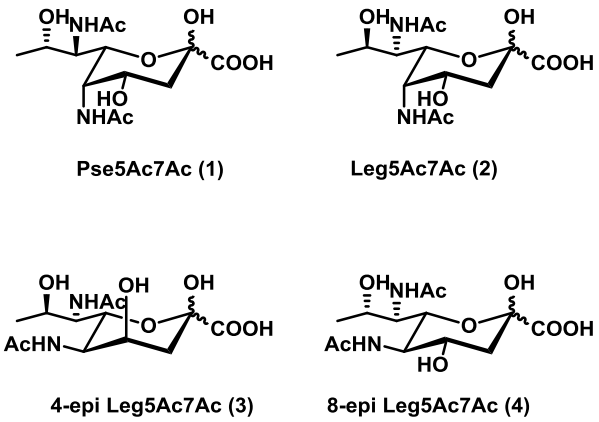


Figure 5. Bacterial nonulosonic acids.

1.1.2 Gram-positive Cell Envelope

The organization of the Gram-positive cell wall differs from that of the Gram-negative family (Figure 6).[6] They share a peptidoglycan covalently linked to the cytoplasmic membrane *via* MurNAc residues. However, this layer is up to ten times thicker in case of Gram-positive cells, which causes the retardation of the dying agent during the Gram-staining process. In contrast, the outer membrane found in Gram-negative bacteria is completely missing in the Gram-positive family. Instead of lipopolysaccharides this class uses covalently linked teichoic acids, CM anchored lipoteichoic acids and cell wall polysaccharides for their virulence factor.[20] These carbohydrate chains are responsible for adhesion as well as colonization and induce immune responses in the host.

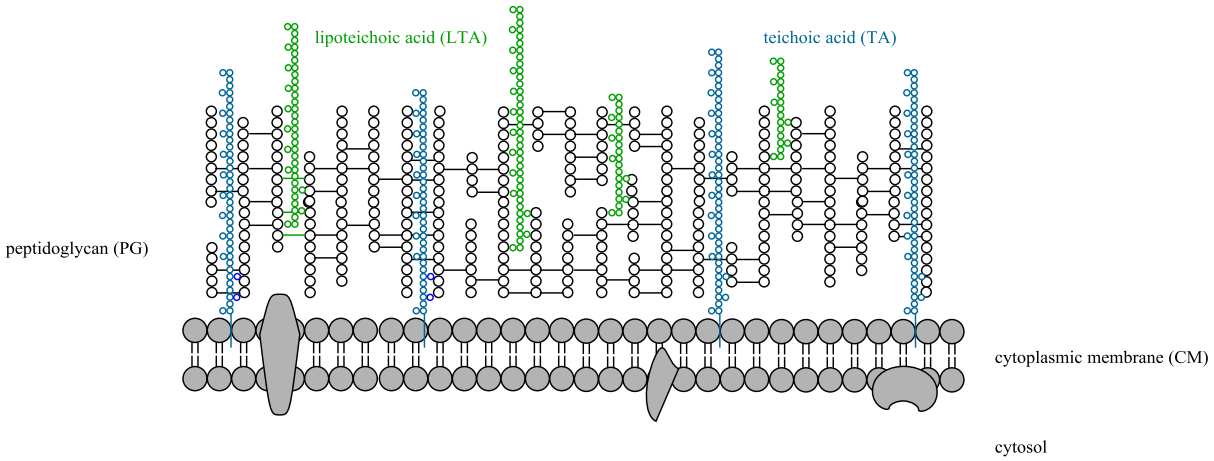


Figure 6. Schematic representation of the Gram-positive cell envelope.

The term teichoic acid refers to a group of cell wall glycopolymers that are linked to the peptidoglycan *via* a phosphate group.[21] Additionally, the linkage consists of GlcNAc and *N*-acetyl-D-mannosamine (ManNAc) residues attached to MurNAc. The architecture of teichoic acids is built of repeating units with reduced sugar phosphates such as glycerol and ribitol that can be further substituted with D-alanine. This substitution pattern adjusts the charge distribution on the cell surface, since positively charged free amines can balance the negative charges of the teichoic acids.[22]

The occurrence of negative charges on the cell surface proved to be indispensable for bacteria.[23] The incorporation of phosphates in teichoic acids accounts to this overall charge distribution and enables the essential interactions with cations. Gram-positive bacteria respond sensitively to the concentration of cations in their environment, especially to changes in Mg^{2+}-levels.[24] On the other hand, low concentration of phosphate results in an upregulation of teichuronic acid synthesis, which is another member of the cell wall polysaccharides with glucuronic acid incorporated that contributes to reestablish the negatively charged homeostasis.[25]

Lipoteichoic acids (LTA) are not covalently attached to the cell membrane, but possess a lipid anchor which reaches into the phospholipid membrane of the CM (Figure 7).[26] Two fatty acid residues are linked to the carbohydrate chain *via* glycerol. The most common sugars found in LTAs are D-glucose and D-galactose which can be directly connected or bridged with phosphates and glycerol units. However, amino sugars play an important role in these molecules with GlcNAc and *N*-acetyl-D-galactosamine (GalNAc) being the most widespread ones. The family of LTA is divided into 4 subclasses according to the distribution of carbohydrates.[27] Elucidation of the precise structure of the LTA type IV, with *S. pneumonia* as a prominent member, revealed a complex carbohydrate pattern. Besides Glc and GalNAc, a very rare 2,4-diamino-2,4,6-trideoxy-D-galactose is present.[28] Additionally, the amino functionalities can be found either acetylated or in its free, protonated form. Further substitutions of the hydroxyl groups with phosphates and D-alanyl residues diversify the architecture of these molecules. The extent of alanylation proved to be crucial for the biological activity of the bacteria, since cleavage of these labile substituents resulted in severe changes in their pathogenicity and in the immune responses of their hosts.

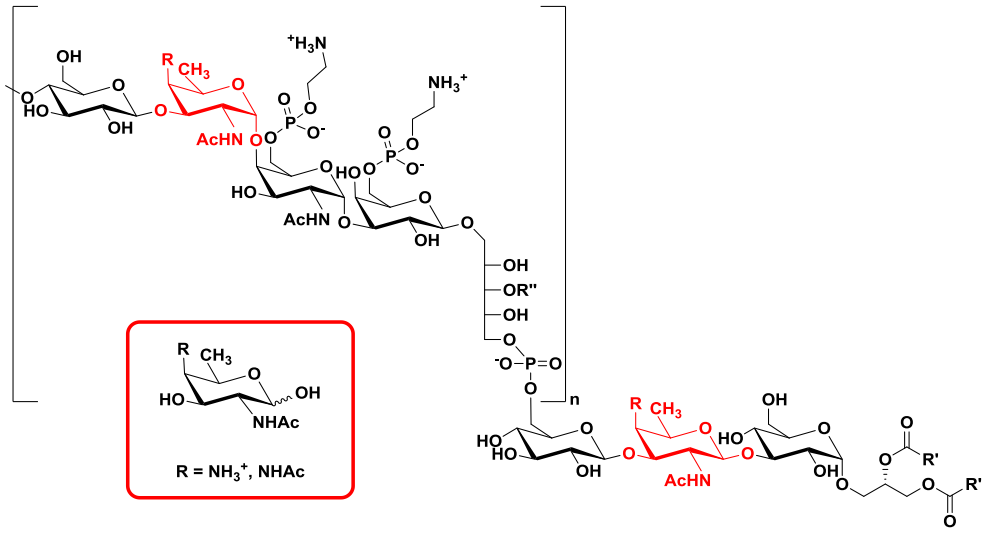


Figure 7. LTA of S. pneumonia.

1.1.3 Biosynthesis of Monosaccharide Building Blocks

Rare carbohydrates as constituents of the bacterial cell wall are of particular interest, since the enzymes involved in these processes present interesting targets for drug development.[29] The glycopolymer of bacteria consists of several unique polyamino-polydeoxy sugars. The following section gives an overview of the metabolism of these compounds.

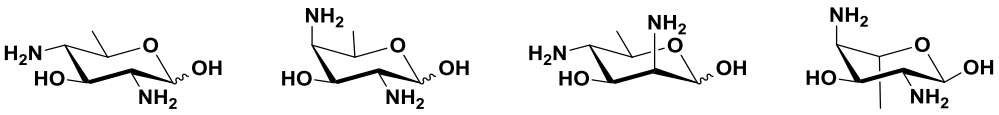
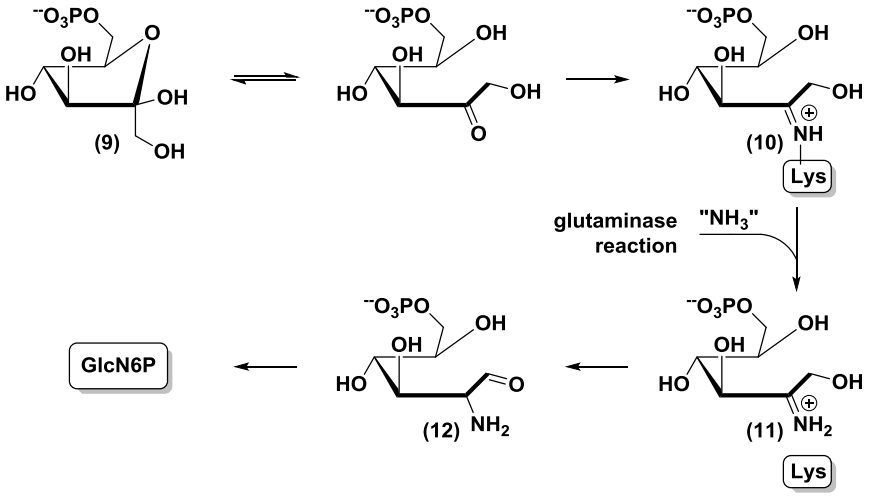


Figure 8. Frequent 2,4-diamino-2,4,6-trideoxy hexoses found in nature.

The biosynthesis of peptidoglycan can use external sources of amino sugars or D-fructose-6-phosphate (**9**, Fru6P) as starting molecules. In the latter case, the enzyme D-glucosamine-6-phosphat (GlcN6P) synthase is responsible for installing the amino functionality at C2 and utilizes glutamine as nitrogen source (Scheme 1).[30] The imine **10** of the carbonyl of the sugar with the ε–amino group of a lysine residue is transferred to 'free' ammonia arriving through a channel from the glutaminase active site. After isomerization of **11** to the *gluco*-configuration **12** and recyclisation, the product GlcN6P is released.

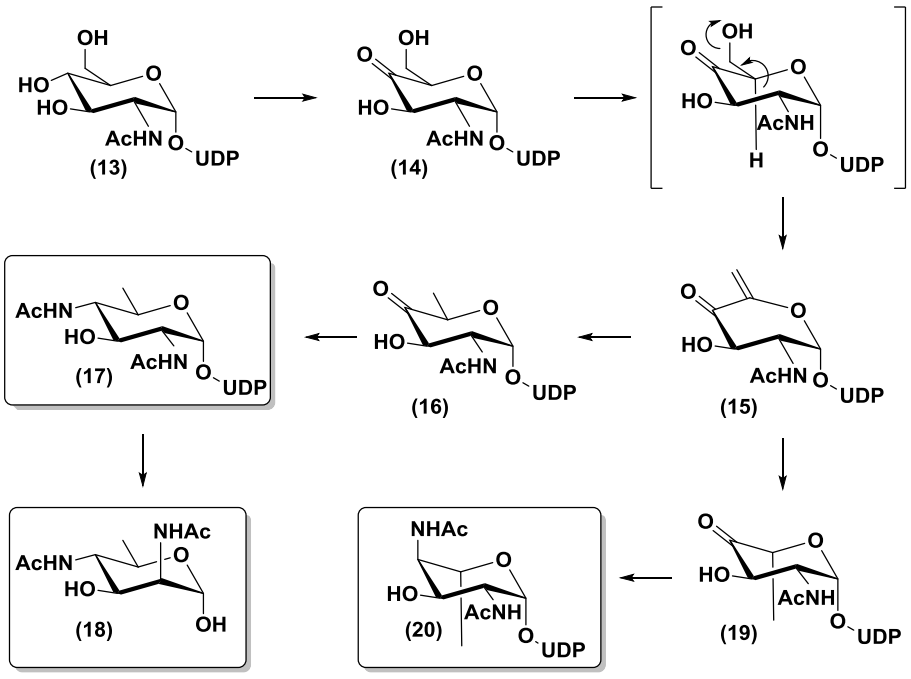


Scheme 1. Enzymatic conversion of Fru6P into GlcN6P.

In general, GlcN6P and *N*-actyl-D-glucosamine-6-phosphate (GlcNAc6P) are central metabolic intermediates in the biosynthesis of amino sugars **5**-**8**. Starting from these molecules, enzymatic conversions can lead to deoxygenated products with amino and hydroxyl substitutions at multiple positions.

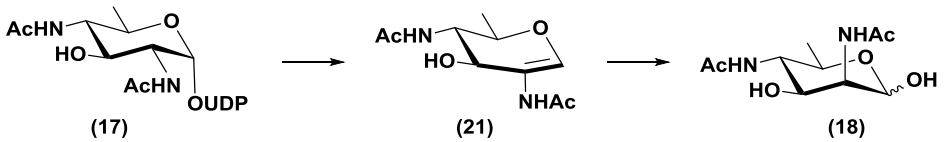
The deoxygenation at C6 requires an oxidation of the hydroxyl group at C4 leading to 4-keto-D-glucose (**14**, Scheme 2).[31] This additional step is essential, since the mechanism requires abstraction of hydrogen from C5 and formal elimination of a water molecule. The pK_a of H5 decreases from about 40 to 18-19 because of the adjacent carbonyl group allowing the reaction to work.[32] This concept is a general principle found in many enzymatic reactions. Enolization may facilitate α,β-eliminations even further as it enables additional acid/base catalysis. Nevertheless, it has been demonstrated that this concept is not applied in case of the 4,6-dehydratases.

The double bond between C5 and C6 of enone **15** is stereospecifically reduced yielding a D- or a L-sugar depending on the target molecule. The biosynthetic pathway of pseudaminic acid (**1**) demands a reduction from the 'top' of the molecule leading to the L-*altro* configuration (**20**).[33] The subsequent transamination uses glutamine as nitrogen source. In contrast, the synthesis of the D-series, requires the (*R)*-configuration at C5 and reductive amination of C4 leads to the *gluco* (**17**) or *manno (***18***)* configurated hexose, respectively.[34]



*Scheme 2. Biosynthetic pathways for D-gluco (**17**), D-manno (**18**) and L-altro (**20**) configurated 2,4-diacetamido-2,4,6-trideoxy hexoses.*

Interestingly, **17** is converted to the *manno* derivative **18** in the synthesis of Leg5Ac7Ac prior to the elongation comparable to the Neu5Ac pathway.[35] The responsible enzymes catalyze the *anti* elimination of UDP and H2 from the hexose resulting in glucal intermediate **21**, and the inversion at C2 is achieved *via syn* hydration of the double bond. The C2-isomerisation is redundant for Pse5Ac7Ac, since 6-deoxy-Alt2Ac4Ac requires no further epimerization.



Scheme 3. Inversion of the N-acetyl group at C2.

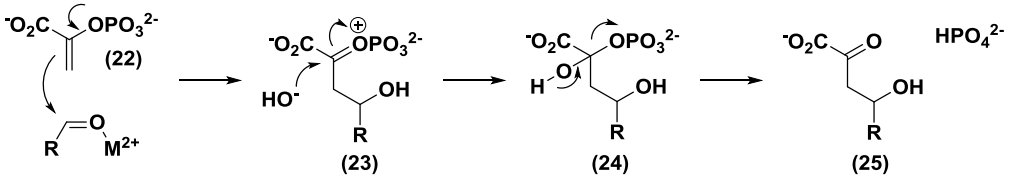
The enzymes involved in the conversion of GlcNAc6P to the precursors for pseudaminic (**1**) and legionaminic acid (**2**) are well described in literature and they demand di-phosphorylated pyrimidine nucleotides as substrates.[36] However, the biosynthetic equivalents for the synthesis of 2,4-diamino-2,4,6-trideoxy-D-galactose (**6**) have only been characterized scarcely. Investigation of the genomic sequence of *S. pneumoniae* and *B. fragilis*, two Gram-positive strains that incorporate this carbohydrate in their capsular polysaccharides, indicated the existence of complementary enzymes and their activity has been predicted using homology studies. Nevertheless, several enzymes of this biosynthetic pathway are not characterized so far.[37]

Muraminic acid biosynthesis requires the attachment of D-lactic acid to the hydroxyl group at C3 of the sugar moiety of UDP-GlcNAc (**13**).[38] The substitution is carried out by a transferase that forms the ether connection, which uses phosphoenolpyruvate (**22**, PEP) and eliminates inorganic phosphate from the tetrahedral ketal intermediate. In a second step, the double bond is reduced generating the correct stereochemistry of the lactic acid residue.

The last reaction depends on the initial reduction of enzyme bound flavine adenine dinucleotide (FAD^+) by nicotinamide adenine dinucleotide phosphate (NADPH).[39] The activated $FADH_2$ transfers a hydride to C3 of PEP creating a carbanion at C2. A closely located serine residue serves as a proton source to complete the reduction.

The application of phosphoenolpyruvat (**22**) as a C3 synthon is observed in the biosynthesis of nonulosonic acids as well. Hexose precursors undergo chain elongation to build the nine

carbon backbone. However, the mechanism proceeds differently. PEP is coupled with the aldehyde of the carbohydrate creating an oxocarbenium ion, which is trapped with an external hydroxyl group to generate tetrahedral intermediate **24**, and installs the 3-deoxy position simultaneously (Scheme 4). Subsequent elimination of phosphate with cleavage of the C-O bond forms the carbonyl functionality at C2, whereas the oxygen originates from the external hydroxyl group as proven with ^{18}O-labeling experiments. This mechanism is throughout conserved for sialic acid (Sia) synthases as well as for the homologs of pseudaminic (**1**)[40] and legionaminic acid (**2**).[35a] It leads to a *syn* relation between the newly formed stereocenter at C4 and the preexisting one at C5. Unfortunately, there are no detailed investigations dealing with the different stereochemical outcome of the synthesis of 4-*epi*-legionaminic acid (**3**) up to date.



Scheme 4. Mechanism for the elongation of hexoses to nonulosonic acids.

1.1.4 Cell Wall Assembly

1.1.4.1 Peptidoglycan

Peptidoglycan assembly can be divided into two major parts (Figure 9).[41] The monomers are synthesized at the cytoplasmic side of the cell and translocated to the outside where polymerization and cross-linking occurs.

MurNAc is used as a starting molecule and up to five amino acids are added stepwise to build a linear chain.[38,39,42] The resulting MurNAc-pentapeptide is transferred to undecaprenyl phosphate anchored in the phospholipid layer and the β−1,4 linkage between the MurNAc and an UDP-GlcNAc is installed.[43]

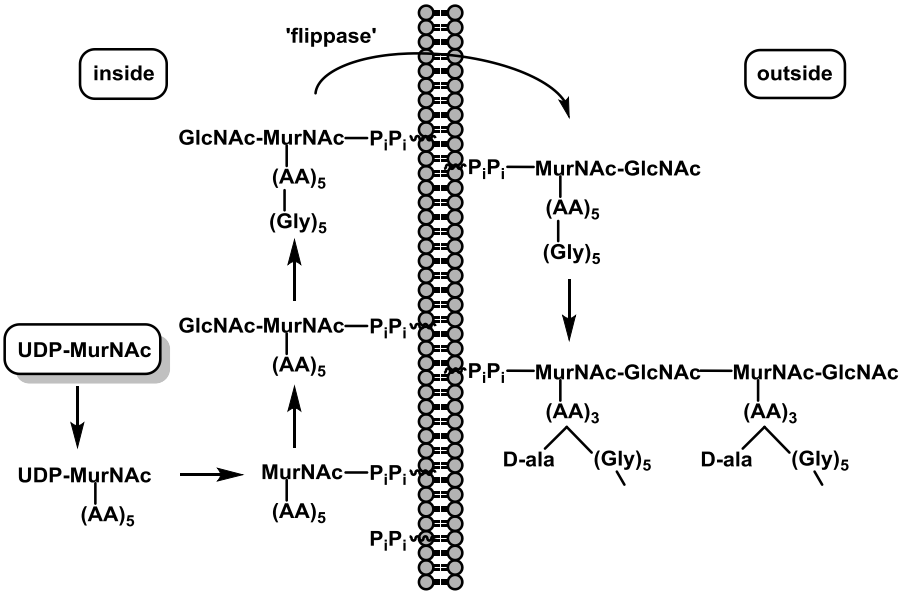


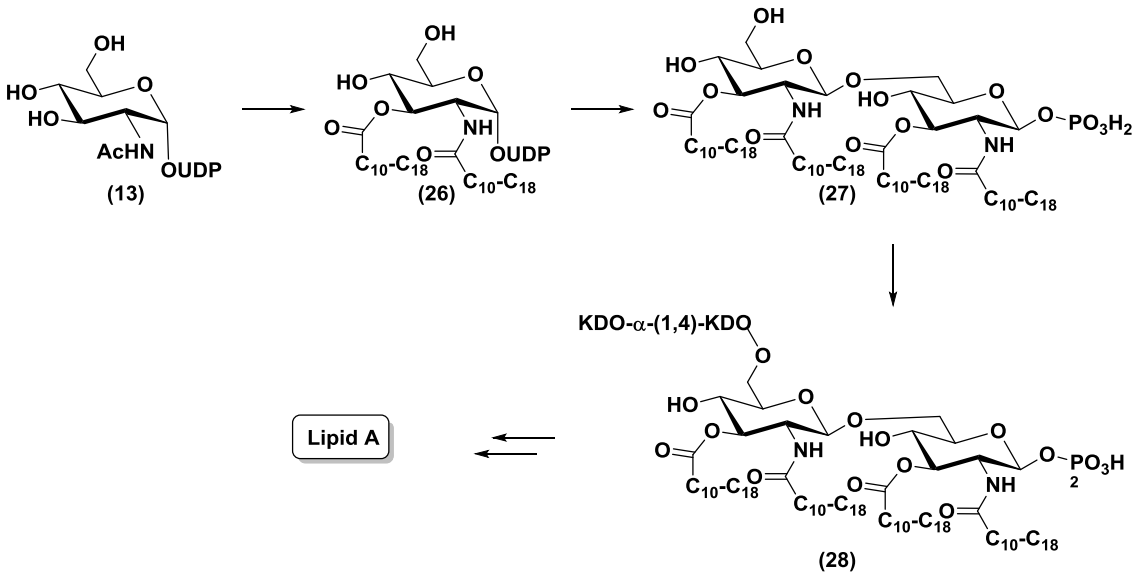
Figure 9. Peptidoglycan assembly of monomers (inside) and crosslinking (outside).

The next step in peptidoglycan synthesis has not been elucidated so far. It is still unknown, how exactly bacteria transport the peptidoglycan monomer units from the inside to the outside of the cell membrane. The involvement of a flippase has been postulated, but further investigations will have to confirm its existence to prove this hypothesis.[44]

At the outside of the cell, in the periplasmic space, the polymerization of the monomers takes place. A glycosyltransferase generates the β−1,4 linkage between the C4-hydroxyl group of the GlcNAc and the MurNAc of a growing unit. This coupling proceeds with cleavage of the undecaprenyl phosphate unit, which is recovered and used in a further peptidoglycan synthesis of the monomer unit inside the cell.[45] After polymerisation, the transpeptidation reaction installs crosslinkages between the amino acid chains as mentioned above.

1.1.4.2 LPS and Teichoic Acid

The biosynthetic assembly of Lipid A starts with UDP-GlcNAc (**13**), which is converted into a diacylated sugar (**26**) using two β−hydroxy fatty acids.[46] A 1,6-connected disaccharide **27** is glycosylated twice using CMP-KDO as donor substrate to give **28**. The specifity for cytidine mononucleotides in glycosylation reactions with 3-deoxy-2-ulosonic acids is a prevalent strategy in nearly all organisms from bacteria to mammals and the activated sugar appears consistently as a nucleotide monophosphate.[47]



Scheme 5. Initial steps of Lipid A biosynthsis.

The Lipid A is connected to the OPS *via* a core region and consists of a variation of different sugars and linkages. In general, three major pathways contribute to the biosynthesis.[48] The most common one for O-antigens is the Wzx/Wzy pathway.[49] Small oligosaccharides are synthesized within the cytoplasm and transported to the outside, where they are polymerized and further transmitted. The second one, the ABC transporter pathway, is generally processed for capsular polysaccharides.[50] In contrast, the whole carbohydrate chain is linked before the transport to the extracellular space takes place. The synthase pathway is less frequent compared to the two aforementioned routes and depends on only one responsible membrane protein.[50]

Although an emerging task in glycobiology, teichoic and teichuronic acid biosynthesis is less investigated than the LPS.[51] Membrane anchored undecaprenyl phosphate serves as starting molecule, which is linked to UDP-GlcNAc and the sugar chain is further elongated with a ManNAc residue. UDP-glycerol units are attached and after transportation to the outside of the cell membrane, a strain specific pattern of sugars and amino acids completes the LTA synthesis. Very little is known about the transfer of the teichoic acid to the peptidoglycan generating the family of wall anchored teichoic acids.

1.2 Bacterial Sialic Acids

In contrast to the long-standing opinion that sialic acids and their enzymes are an invention of higher members of the deuterostome only, phylogenetic analysis revealed conserved genes encoding for this machinery in various phyla.[52] Moreover, since the discovery that bacteria are capable of synthesizing Sias *de novo* themselves, a common ancestor model has been proposed.[53] Differences in expression levels of these carbohydrates and further modifications lead to the diversity that has been found on cell surfaces of various organisms.[54]

In many cases, the expression of Sias is not essential for bacteria, and their viability is not affected in their absence. Many bacteria do not have proteins necessary for *de novo* Sia synthesis, but can process them from the host either *via* transferases of the hosts' glycans or *via* uptake of free sugars located in the serum.[55] The differences in the responsible enzymatic machinery of various microorganisms are regarded as individual answer to environmental conditions. Nevertheless, evolutionary pressure directed bacteria towards decoration of their cell surface with NulOs. The advantages of this behavior are intensively discussed in literature. Masking the surface with host-like carbohydrates indisputably offers a possibility to evade the defensive system.[54] This well accepted protective mechanism is consistent with the fact that Sias are dispensable for the survival of certain bacterial strains.

A proposed protective role of these carbohydrates to prevent underlying patterns seems unlikely, since bacterial NulOs offer a very specific and unique target for the immune system.[54] In contrast, incorporation of NulOs can support the colonialization process in the host. A highly acetylated Leg derivative shows an increased hydrophobicity of the surface and therefore can facilitate the docking to epithelial cells.[56]

The aforementioned sialylation strategies are dramatically changed in the case of flagellates.[57] Their flagella are densely decorated with NulOs and in this case these molecules are essential for the motility and therefore for the survival of the whole organism. Especially Pse5Ac7Ac plays a vital role, whereas deletion of Leg5Ac7Ac proved to be less crucial.

It has been postulated that poly NulOs can prevent bacteria from dehydration.[55] Microorganisms with a distinctive capsule can survive significantly longer in a dry period because of conservation of water in the surrounding mucus.

1.3 Cell Surface Charge

The carboxylic acid of NulOs is deprotonated at physiological conditions and thus presents a negative charge at the surface, which effects electrostatic repulsion as well as cation homeostasis.[58] The precise distribution of the terminal sugars offers a pattern that is responsible for endogenous and exogenous recognition processes. For example, in the event of autolysis, negatively charged areas are predominantly targeted and enhancement of negative charges results in amplifications of autolysins and decomposition of the peptidoglycan.[59] Incorporation of alanyl residues with their protonated amino groups into the outer layer offers a possibility to balance this negative charge. It has been demonstrated that reducing the negative charge *via* substitution with alanine esters results in a greater resistance against cationic antimicrobial peptides and in increased capability of biofilm formation.[60] Further proof for the importance of the negative charges on the surface was shown by Brossmer e*t al*..[61] They gently reduced the carboxylic acid functionality with sodium borohydride and investigated the altered enzymatic activity of neuraminidases.

The global distribution of charges on the surface influences the biochemical and physicochemical properties of the cell.[62] Since the outermost layer controls the polarity of the surface, the incorporation of molecules with positive or negative charges plays a fundamental role. The stability and shape of the bacteria as well as resistance against environmental conditions depend on the correct functional interplay of the coating oligo- and polysaccharide chains. The ability to adhere to the host is a central and crucial point for the survival of many microorganisms. Therefore, the influence of terminal sugars is significant.[63]

Basically, there are two distinct mechanisms how microorganisms can attach to a surface. It is supposed that adhesion to artificial areas is achieved *via* nonspecific interactions like hydrophobicity and electrostatic attraction.[64] In contrast, target specific binding with lectins or adhesins dominate the interaction with living objects. In both cases terminal carbohydrates are responsible for the first contact with the surface. Thus, the ability to initiate the primary events of adhesion closely depends on the polarity introduced by those molecules.[65]

2. Chemical Background

2.1 Previous Synthesis

Chemical synthesis has emerged to be a powerful tool to meet biological questions. Especially the field of glycobiology often depends on synthetic or semisynthetic substrates for investigations of precise interactions between bacteria and host. Since purification of the intact and fully functional glycan chains of microorganisms is usually difficult and impurities can induce misleading results, organic synthesis has to supply the building blocks for pure and chemically appropriate biopolymers.[66]

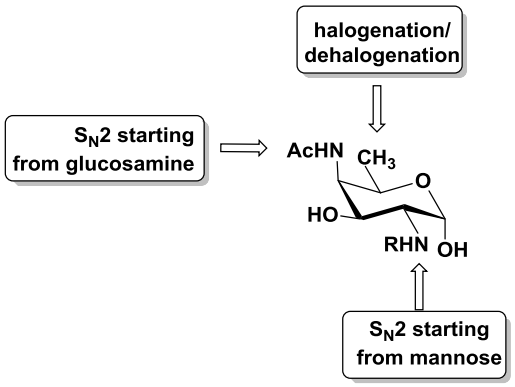


Figure 10. Overview of syntheses towards 2,4-diacetamido-2,4,6-trideoxy-D-galactose.

The class of 2,4-diamino-2,4,6-trideoxy hexoses has drawn a lot of attention. Starting in the mid-70s, a number of publications dealt with their syntheses using carbohydrates as starting materials (Table 1). In summary, the deoxygenation at position 6 was commonly achieved *via* selective halogenation-reduction protocols and several hydride sources or radical procedures have been applied (Figure 10). Introduction of amino functionalities into the sugars demanded selective protecting group strategies for non-participating hydroxyl groups in the reaction. Triflation and mesylation, respectively, followed by the attack of various nitrogen nucleophiles such as azide or phtalimide were applied.

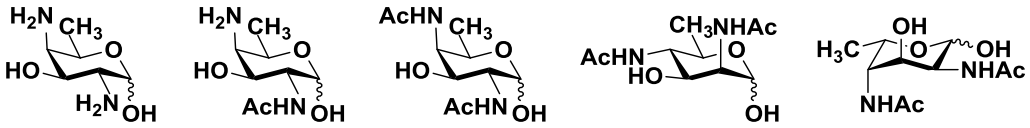
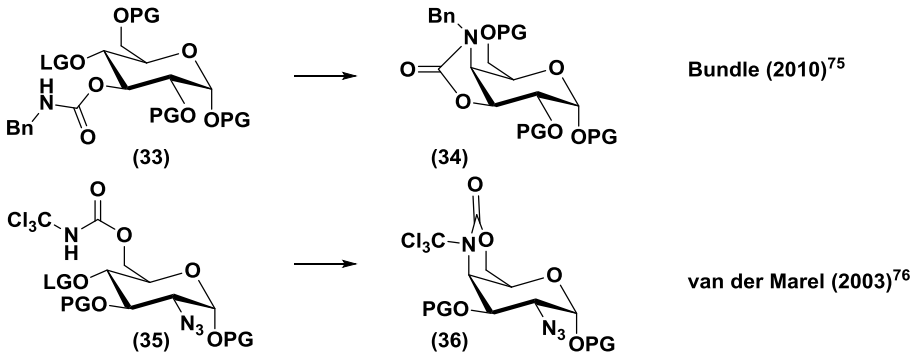


Figure 11. Various carbohydrates synthesized during the last decades.

entry	target	compound	deoxygenation	nucleophile	author
1	**6**	D-GlcN	iodination, hydrogenation	azide	Paulsen & Grage (1974), Sharon (1978)[67]
2	**31**	D-MAN	Barton-McCombie	azide	Van der Marel & van Boom (1987)[68]
3	**30**	D-GlcN	mesylation, NaBH4	azide	Lonngren (1984)[69]
4	**30**	D-GlcN	iodination, Zn (AcOH)	azide	Pozsgay (1997)[70]
5	**30**	D-GlcN	bromination, hydrogenation	azide	Grindley (2004)[71]
6	**30**	D-GlcN	mesylation, $NaBH_4$	azide	Bundle (2009)[72]
7	**30**	D-GlcN	iodination, $NaBH_3CN$	phtalimide	Schmidt (2010)[73]
8	**32**	L-rhamnose		azide	Zähringer (2001)[74]
9	**18**	D-fucose		azide	Zähringer (2001)[74]

Table 1. Selected procedures leading to the target compounds shown in Figure 11.

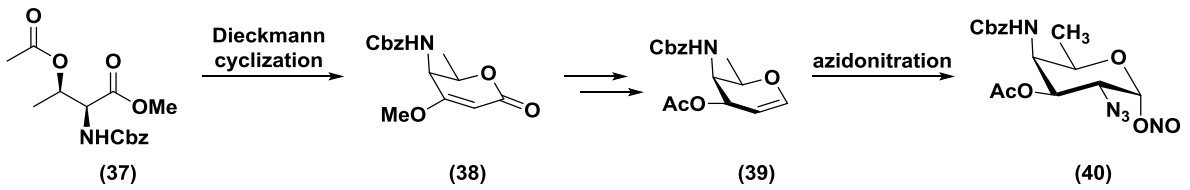
Intramolecular nucleophilic displacement reactions are reported in the literature (Scheme 6). As depicted in Scheme 6, the nitrogen of a carbamate group attacked the C4 hydroxyl group, which was primarily converted into a leaving group. The resulting heterocycle could be hydrolyzed to give the target *galacto* configurated derivative **34**[75] and **36**,[76] respectively.



Scheme 6. Intramolecular attack of carbamates to introduce the amino functionality.

The azido nitration, originally developed by Lemieux and Ratcliffe,[77] was used to functionalize the C1 and C2 of glycals to the corresponding 2-amino sugars. However, this method gave excellent regiochemistry but unfortunately mixtures of axial and equatorial azides. The mechanism is still not fully resolved, but it is proposed that an initial attack of an azide radical to the double bond takes place.

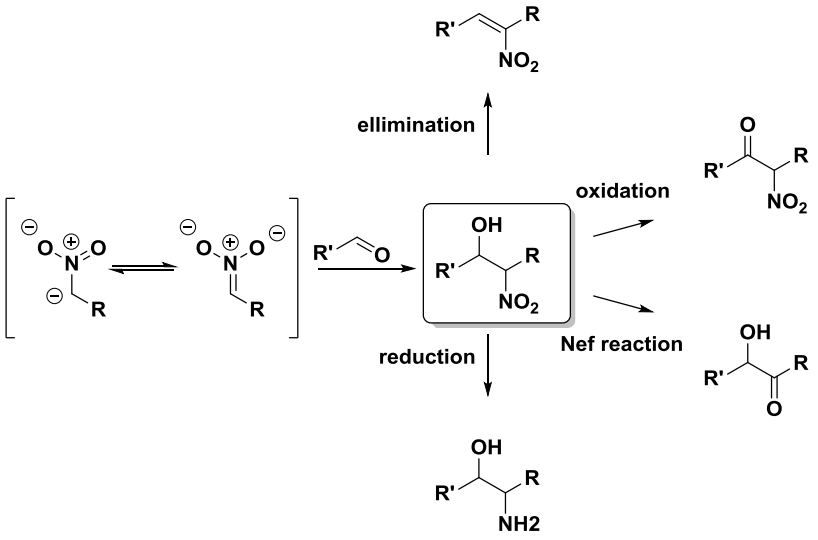
Seeberger *et al*. published a *de novo* synthesis of *galacto* configurated 2,4-diamino-2,4,6-trideoxy hexose derivative (**40**) starting from L-threonine. A Dieckmann cyclization of *O*-acetyl protected **37** generated the carbon backbone and after reduction the azido nitration converted the glycal **39** into the diamino hexose **40**.[78]



*Scheme 7. Seeberger's synthesis of compound **40**.*

2.2 Nitroaldol Reaction

The nitroaldol reaction is a powerful methodology to form carbon-carbon bonds. It depends on the formation of a nitronate species which is capable of a nucleophilic attack of carbonyl groups. The resulting nitroalcohol is a very versatile intermediate and can be transformed into different synthetically useful functional groups (Scheme 8).



Scheme 8. Nitroaldol and follow up reactions.

The reaction generates up to two chiral centers and many catalysts have been developed to control the enantioselectivity or diastereoselectivity, respectively. The most promising compounds are shown in Figure 12. The class of cinchona alkaloids (**42** & **43**) as well as thiourea/guanidine based reagents (**41**) has been extensively applied.[79]

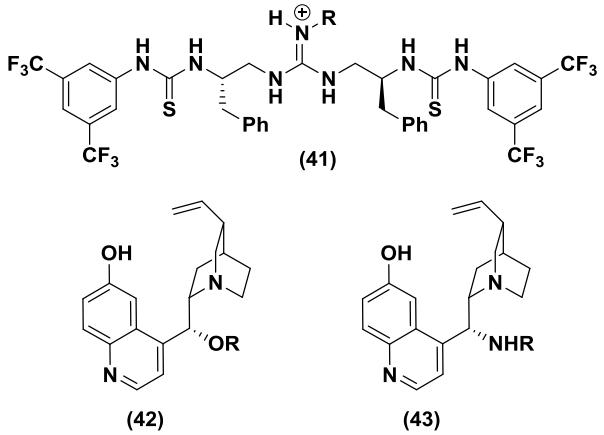


Figure 12. Catalysts applied to achieve stereoselectivity during nitroaldol reactions.

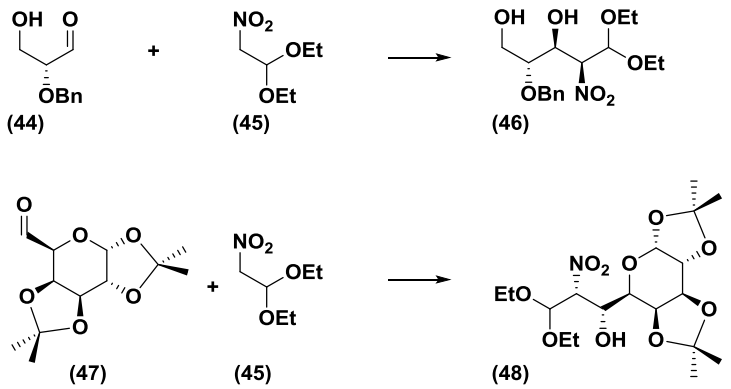
In many cases, the use of chiral catalysts can be avoided since the substrate controlled reaction provides excellent stereoselectivity. Especially, bulky substituents allow the generation of diastereoselectively enriched products. The reaction preferentially generates a *syn* relation between the new formed stereocenters of the β-nitroalcohol and *anti* to an adjacent functional group.

2.2.1 Application in Carbohydrate Chemistry

Many applications of nitroaldol reactions can be found in the literature. Scheme 9 and 10 show a selection of the various elegant synthetic procedures published.

Although nitroalkanes are the most reliable reaction partners in nitroaldol reactions, nitroacetaldehyde diethyl acetal (**45**) has been successfully applied in the synthesis of carbohydrates (Scheme 9). The advantage of the protected aldehyde functionality already present in the molecule was used to generate the carbon backbone of an *arabino* configurated glycosidase inhibitor by Jäger *et al*..[80] Catalytic amounts of tetrabutylammonium fluoride (TBAF) at low temperatures were used to achieve a selectivity of 9:1 in favor of the desired diastereomer **46**. The new stereocenters obtained showed a *syn* relation and *anti* to the existing bulky benzyl group. The minor diastereomer was found to have *anti-anti* configuration which refers to the inversed configuration of the nitro group.

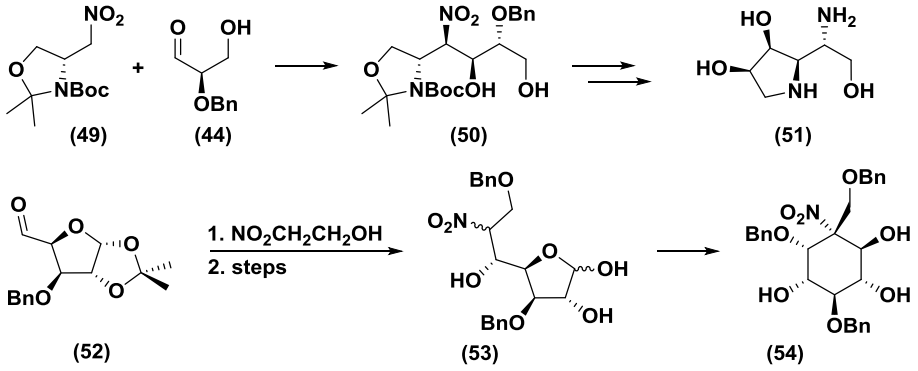
Compound **45** is suitable to construct more complex structures demonstrated in the synthesis of octodiose **48**.[81] Aldehyde **47** was subjected to the same reaction conditions as for **46** to yield a mixture of two diastereomers in a 4:1 ratio. Not surprisingly, the new chiral centers were in a *syn* correlation and *anti* to the adjacent stereocenter.



*Scheme 9. Application of 2-nitroacetaldehyde diethyl acetal (**45**).*

The synthesis of imino sugar **51** was realized using a nitroaldol reaction as key step.[82] The reaction between benzyl protected glyceraldehyde **44** and the D-serine derived nitro compound **49** was catalyzed by TBAF and provided depending on the stereochemistry of starting material *manno* or *gulo* configurated products, respectively. This stereochemical outcome is in turn consistent with published findings.

Another remarkable example of the scope of this reaction is demonstrated in the synthesis of inositol derivative **54**.[83] Starting from D-glucose derived compound **52**, a double nitroaldol reaction was applied. The first step used nitroethanol to elongate the carbon chain and the second intramolecular reaction generated the inositol backbone. Although starting from a diastereomeric mixture of **53**, the latter reaction yielded only a single isomer **54**, thus balancing the poor selectivity of 3:2 in the first step.

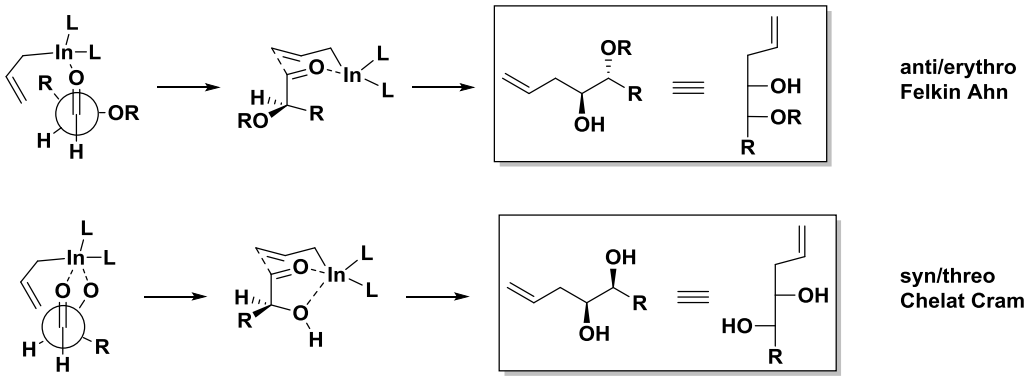


*Scheme 10. Syntheses towards imino sugar **51** and inositol **54**.*

2.3 Indium Mediated Barbier Reaction

Indium is located in the third main group of the periodic table of elements. However, its properties are often more comparable to elements of the first group.[84] For example, the first ionization potential of indium is in the range of the alkali metals. Nevertheless, indium mediated reactions can be performed in water or aqueous reaction media. Hence, it is a viable reagent for reactions with unprotected carbohydrates, which demand protic and polar solvents.

The Barbier type chain elongation of carbonyl compounds with indium is one of the frequent applications in the field of sugar chemistry.[85] It generates a new chiral center, which can either have *threo* or *erythro* configuration (Scheme 11). The stereochemical outcome depends on the nature of the functionality next to the carbonyl moiety. If chelation is possible, *syn* configurated compounds predominate according to the Chelat Cram model, whereas as non-chelating groups favor the Felkin Ahn model leading to *anti* diols.[86]



Scheme 11. Stereochemical course leading to threo or erythro relation.

This reaction tolerates many functional groups, such as esters, amides, (silyl)ethers and free hydroxyl groups. Mechanistically, an organoindium species is formed, which undergoes the nucleophilic attack. There is an actual discourse in literature, whether the indium is in its +1 or +3 oxidation state.[87] Originally, a sesquihalide structure (**57**) was proposed, but more detailed investigations revealed that in water the In(I) species (**55**) is predominant, but it is converted to the In(III) compound (**56**) after exposure to oxygen (Figure 13).

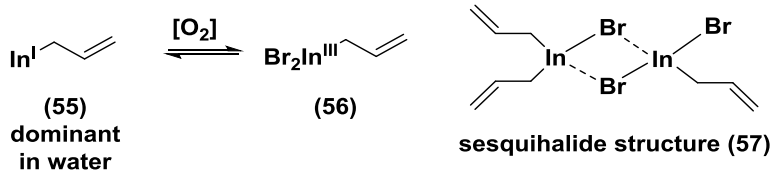
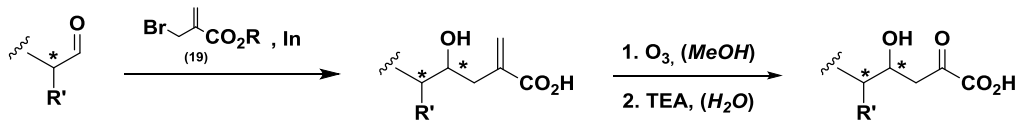


Figure 13. Possible organoindium intermediates.

The application of indium mediated chain elongations to obtain higher carbohydrates has established a powerful tool over the last decades. Especially, 2-(bromomethyl)acrylic acid ester is a useful synthon to introduce the C1 to C3 segment of 3-deoxy-2-ulosonic acids and related compounds (Scheme 12). The double bond provides the carbonyl functionality after ozonolysis and the 3-deoxy position is installed in the elongation step.



Scheme 12. Reaction sequence towards ulosonic acids.

The syntheses of many important, bioactive compounds have been achieved applying this methodology on different carbohydrates.[88] Figure 14 shows four prominent members of the 3-deoxy-2-ulosonic acid family frequently found in nature. The nine carbon sugars **58** and **59** were obtained using D-mannose[89] and *N*-acetyl-D-mannosamine[90], respectively, whereas D-arabinose[91] and D-erythrose[92] served as starting materials for compound **60** and **61**.

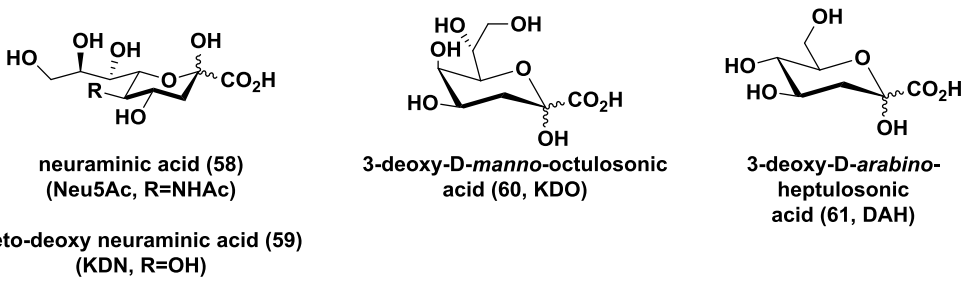


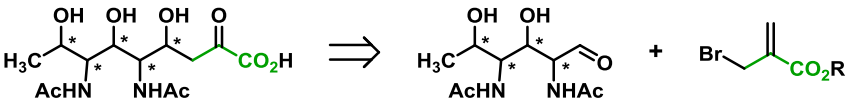
Figure 14. Prominent members of the 3-deoxy-2-ulosonic acid family.

SYNTHESIS

3. Synthesis of 2,4-Diamino-2,4,6-trideoxy Hexoses

3.1 Aim of the Project

The main focus was the syntheses of 2,4-diacetamido-2,4,6-trideoxy hexoses with various stereochemical patterns that can be converted into nonulosonic acids using the indium methodology described in section 2.3 (Scheme 13).



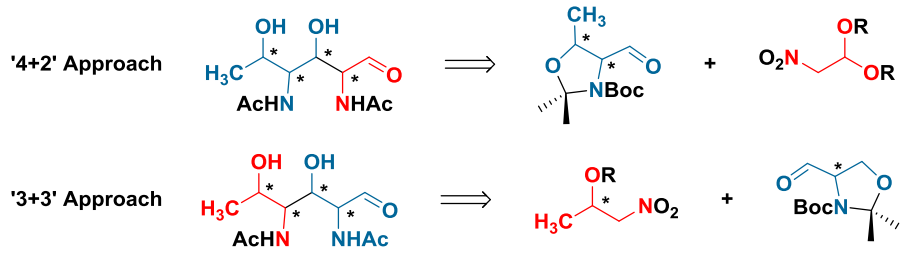
Scheme 13. Retrosynthetic analysis of the nonulosonic acid family.

As pointed out above (section 2.1), the majority of the published syntheses of these sugars used carbohydrates as starting material. Deoxygenation at C6 and nucleophilic displacement strategies often led to an increasing number of steps with moderate selectivities and yields. The aim was to develop a straightforward route that prevented delicate functional group transformations and offered stereochemical variability.

The nitroaldol reaction was a promising methodology to generate the carbon backbone of our target hexoses. The commercially available amino acids serine and threonine could be used as starting materials and stereochemical diversity was achieved by variation of their possible isomers.

Numerous chiral catalysts have been published that claim to efficiently control the outcome of this type of reaction.[79] Nevertheless, we intended to exploit substrate controlled induction to facilitate the sequence and avoid a (multi-step) synthesis of the catalyst.

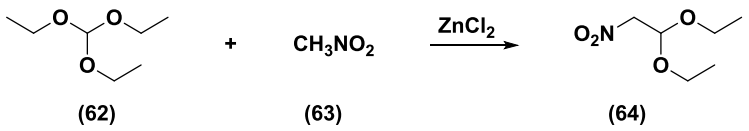
Basically, two disconnections were explored, both generating two out of four chiral centers of the sugar during the C-C bond forming step (Scheme 14). The first approach applied the achiral nucleophile **64** and threonine. Contrary, in approach 2 both synthons consisted of a chiral center.



Scheme 14. Retrosynthetic analysis of the target hexoses applying nitroaldol reactions.

3.2 The '4+2' Approach

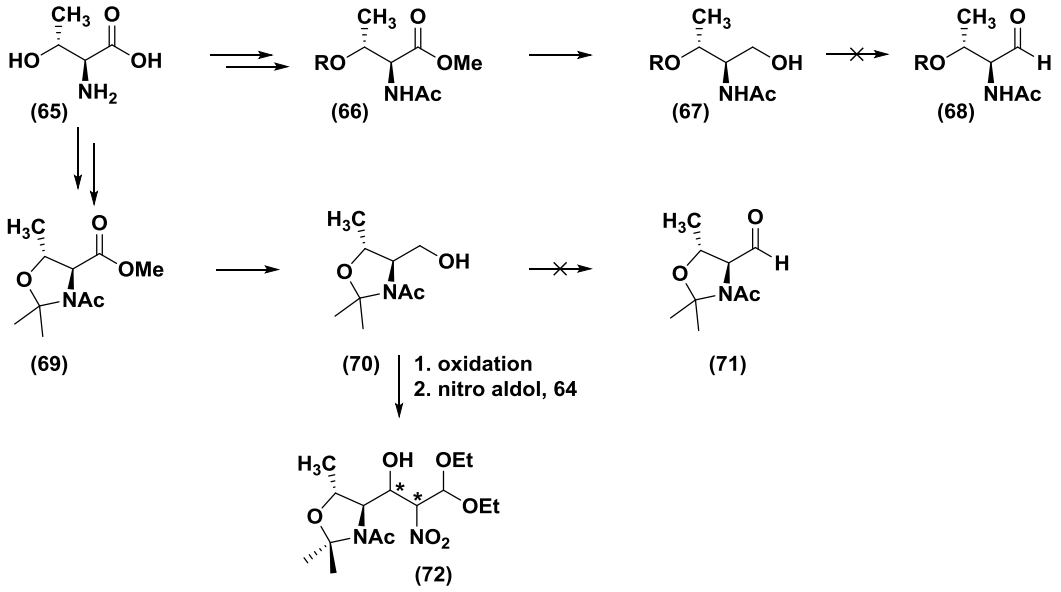
The nitroaldol reaction is a powerful C-C bond forming methodology. Nevertheless, some limitations reduce its applicability. Throughout the literature it is obvious that rather simple molecules most effectively serve as best nucleophiles, with nitromethane being the most commonly used reagent. Our first approach demanded a molecule with two carbon atoms and an oxygen functionality adjacent to the nitro group. Therefore, we initially focused on molecule **64**, which offered the advantage of the correct oxidation state of the final C1. Compound **64** was commercially not available and thus was synthesized from nitromethane (**63**) and triethyl orthoformiate (**62**) under Lewis acid catalysis with zinc chloride.[93]



*Scheme 15. Synthesis of 2-nitroacetaldehyde diethyl acetal **64**.*

The four carbon amino acid threonine was chosen because of its two chiral centers with the correct substitution pattern and the terminal methyl group. All possible configurations were commercially available although the *allo*-threonine series was far more expensive. The investigation started with the most abundant isomer L-threonine. The carboxylic acid had to be converted into an aldehyde in order to perform the elongation step.

Initially, we planned to introduce the *N*-acetate into aldehyde **68** or **71** to reduce the number of necessary steps. All our efforts to synthesize this compounds failed, since neither open chain derivatives **66**, nor cyclic ketals **70** could be converted into the aldehyde using reductions with diisobtutylaluminium hydride (DIBALH) or two step reduction-oxidation (sodium borohydride or DIBALH/Swern or TEMPO) sequences, respectively (Scheme 16). We supposed that aldehydes **68** and **71** decomposed rapidly and wanted to avoid a critical work up. Adding the nucleophile **64** to the oxidation procedure gave traces of our desired product **72**. However, the yield could not be improved and a different protecting group strategy was necessary.



Scheme 16. Reaction sequences towards the N-acetyl protected aldehyde.

The L-serine derived aldehyde **73** has been successfully applied in nitroaldol reactions (Figure 15).[80] Consequently, carbamates represented appropriate protecting groups for amines in course of the elongation step. Therefore, various derivatives (**74**-**76**) shown in Figure 15 as well as their influence on the reaction with 2-nitroacetaldehyde diethyl acetal (**64**) or nitroethanol, respectively, were investigated.

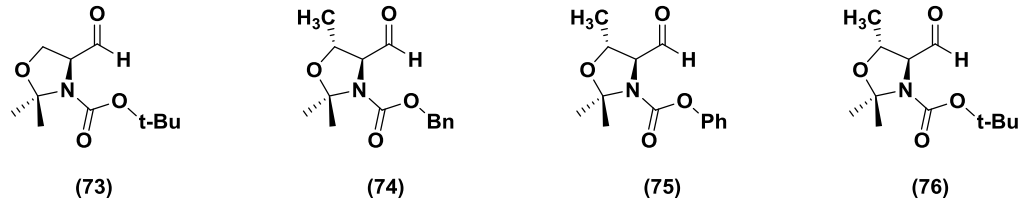
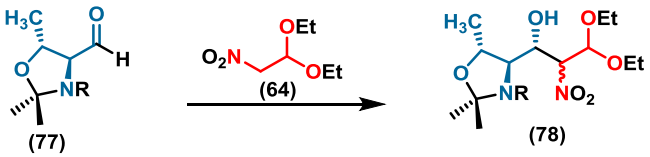


Figure 15. L-Serine and L-threonine derived aldehydes.

Nitroaldol reactions strongly depend on the nature of the applied base. The most common methodologies use tetrabutylammonium fluoride in anhydrous tetrahydrofurane (THF) as solvent. Despite the broad applicability in literature, we could not adopt these reaction conditions to our system. Decomposition was observed using different starting materials (**74**-**76**), equivalents of reaction components and variations in temperature (Table 2). Potassium fluoride failed as well as amine bases or lithiating bases such as butyl lithium. The latter tended to doubly deprotonate the nitro compound and therefore created a highly more reactive species that is unstable at temperatures above -90°C according to the literature.[94] The application of lithium hydroxide gave traces of aldol products using the phenyl protected derivative **75**. A major improvement in this approach was the application of *tert*-butyl carbamate (Boc) protected **76**. This derivative was the only L-threonine derived aldehyde performing the nitroaldol reaction and 43% of elongated product with a diastereomeric ratio of 2:1 could be isolated (Table 2, entry 4).

According to literature, quinine and its epimers (**42**, **42**) often give excellent selectivities in aldol reactions.[79] However, our system did not benefit from the catalytic activity and the reaction could not be improved applying various solvents or additional bases.

In general, the control of temperature is important in nitroaldol reactions. According to the literature, the diastereoselectivity is strongly influenced by changing this parameter.[95] Lowering the temperature to 0 °C led to significant improvements in the yield and increase of isolated product up to 77% was obtained. The diastereomeric ratio was not affected (Table 2, entry 6).



entry	R (77)	reaction conditions[b]	base[c]	yield 78 [%][d]
1	benzyl	THF (rt)	TBAF / NEt_3 / BuLi / LiOH	*nd*
2	phenyl	THF (rt)	TBAF / NEt_3 / BuLi / LiOH	*nd*
3	*tert*-butyl	THF (rt)	TBAF / CsF / KF + crown ether	traces
4	*tert*-butyl	THF (rt)	LiOH	43
5	*tert*-butyl	CH_2Cl_2 (0 °C)	LiOH	60
6	*tert*-butyl	THF (0 °C)	LiOH	77 (*gal*:*talo* 3:2)
7	*tert*-butyl	THF/H_2O 3:2 (0 °C)	LiOH	74 (*gal*:*talo* 5:1)
8	*tert*-butyl	THF/H_2O 1:4 (0 °C)	LiOH	41 (*gal*:*talo* 4:3)

*Table 2. Screening of reaction conditions for the reaction shown above. ([a] Reactions were performed on a 50 mg scale of **77** and 7 equivalents of **64** in 10 mL solvent for 16 h. [b] rt = room temperature. [c] when various bases are stated, they were used in different experiments. [d] isolated yields; nd = not detected; gal = galacto)*

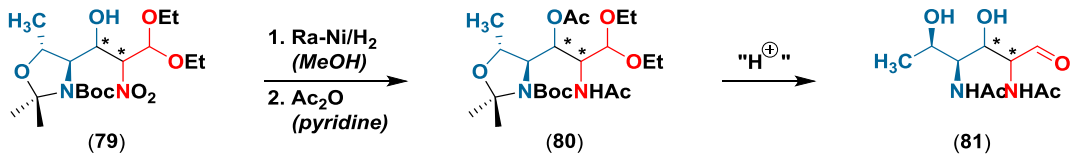
The solvent composition was crucial for this reaction. While dichloromethane as solvent at 0 °C gave decreasing yields (Table 2, entry 5), the application of aqueous tetrahydrofurane tremendously influenced the stereochemical outcome (Table 2, entry 7 & 8). A mixture of tetrahydrofurane with 40% water was found to be the optimum mixture. The yield changed slightly to 74%, whereas further increase of the aqueous component resulted in a significant drop to approximately 40%. An excess of 5:1 for the major diastereomer was achieved. The stereochemistry of the major and the minor isomer was determined using ^{1}H-NMR analysis of the free carbohydrates and is discussed below (section 3.2.1).

The diastereomers generated during the nitroaldol reaction were separated after the peracetylation step, since purification at an earlier stage resulted in a loss of yield. Nevertheless, an aliquot was taken to characterize the major isomer during these steps.

Despite the advantage to directly introduce a protected aldehyde moiety, the influence of other nucleophiles was investigated. In this type of reaction nitroethanol is a commonly used reagent and would require an oxidation step instead of acidic deprotection. Therefore it offered an alternative route towards the final carbohydrates. The reaction with Boc protected substrate **77** was performed with various bases (TBAF, LiOH, NaOH, LHMDS) in tetrahydrofurane but the yield could not be raised above 22% of a diastereomeric mixture.

In analogy to the diethyl compound, the dimethyl analog was synthesized to examine the potential for differences in the outcome of the reaction. The reduction of the steric demand resulted in a decrease in stereoselectivity to 3:1 with 49% yield. This finding supports the stereochemical model discussed in section 3.2.1.

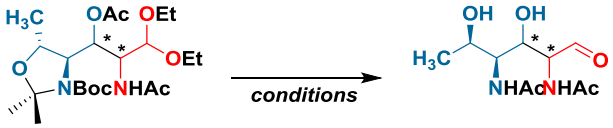
After the successful generation of the six carbon backbone the synthesis continued with the reduction of the nitro group using Raney-nickel in a hydrogenation flow reactor. Subsequent acetylation of the amine and the hydroxyl group afforded compound **80**, which contained the two acetates present in our target sugar as well as three acid labile protecting groups (Scheme 17).



Scheme 17. Consecutive steps and hypothetical deprotection.

We intended a global deprotection in a single step and expected to induce an acetyl migration from oxygen at C3 to the nitrogen at C4. However, the deprotection turned out to be more difficult (Table 3). In the first attempts, Brønsted acid catalysis was used (Table 3, entry 1-13 & 17-20). Hydrolysis in aqueous reaction media failed independent from proton concentration, whereas low pH values additionally caused decomposition of the molecule.

Since anhydrous methodologies such as gaseous hydrochloric acid, acetyl chloride/methanol and various water sensitive Lewis acids did not lead to any results, we focused on Lewis acid catalysis in aqueous media. The screening covered most of the common transition metals, rare earth compounds as well as the established main group elements (Table 3). Variation of the counteranion (Cl^-, ^-OTf) as well as different solvents were tested. To make a long story short, only tin and zinc chloride provided isolatable amounts of deprotected product **81** (Table 3, entry 24 & 52). Heating compound **80** in water with a catalytic amount of zinc chloride for 48 hours at 100 °C yielded a mixture of three different products including our desired sugar. Nevertheless, these results were not reproducible.



(**80**) (**81**)

entry	catalyyst	temperature	solvent	yield [%]
1	HCl (1N)	RT	THF/MeOH	nd
2	HCl (1N)	130	THF	nd
3	HCl (1N)	RT	MeOH	nd
4	HCl (0.1N)	RT	H_2O	nd
5	**HCl (0.01N)**	**130**	**H_2O**	**12**
6	HCl_{conc}	RT	H_2O	nd
7	HCl_{conc}	130	H_2O	nd
8	H_2SO_4	RT	AcCl	nd
9	HCl_{gas}	RT	DCM	nd
10	HCl_{gas}	RT	DCM/MeOH	nd
11	HCl_{gas}	RT	DCM/AcCl	nd
12	HCl_{gas}	RT	DCM/Ac_2O	nd
13	HCl_{gas}	RT	Et_2O	nd
14	BF_3.OEt	RT	Et_2O	nd
15	BF_3.OEt	RT	acetone/dimethoxypropane	nd
16	BF_3.OEt	RT	Et_2O	nd
17	TFA	RT	acetone	nd
18	TFA	RT	H_2O	nd
19	TFA	RT	neat	nd
20	TFA	RT	THF	nd
21	$Bi(NO_3)_3.5H_2O$	RT	DCM	nd
22	$CeCl_3.7H_2O$	RT	acetonitrile	nd
23	$SnCl_2.2H_2O$	RT	H_2O	nd
24	**$SnCl_2.2H_2O$**	**130**	**H_2O**	**10**
25	$SnCl_2.2H_2O$	80	H_2O	nd
26	$SnCl_2.2H_2O$	50	H_2O	nd
27	$SnCl_2.2H_2O$	RT	H_2O/DMSO	nd
28	$SnCl_2.2H_2O$	RT	H_2O/CH_3NO_2	nd
29	$ErOTf_3$	RT	H_2O/CH_3NO_3	nd
30	YCl_3	RT	H_2O	nd

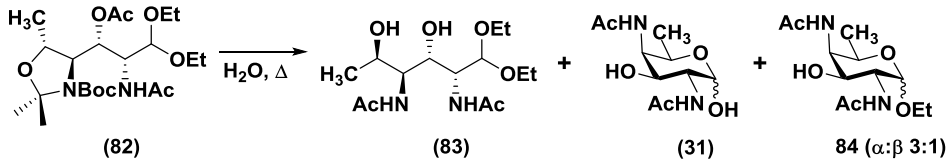
31	**YCl_3**	**130**	**H_2O**	**traces**
32	$YbOTf_3$	RT	H_2O	nd
33	**$YbOTf_3$**	**130**	**H_2O**	**traces**
34	$YbOTf_3$	RT	DCM	nd
35		RT	acetic acid (80%)	nd
36	$ZnCl_2$	RT	benzonitrile	nd
37	$ZnCl_2$	RT	acetonitrile	nd
38	$ZnCl_2$	RT	acetonitrile/H_2O	nd
39	$ZnCl_2$	RT	DCM/H_2O	nd
40	$ZnCl_2$	RT	EtSH	nd
41	$ZnCl_2$	RT	H_2O/CH_3NO_3	nd
42	AcCl	RT	DCM/MeOH	nd
43	TMSOTf	RT	DCM	nd
44	**I_2**	**RT**	**acetone**	**20**
45	Cs_2CO_3/imidazol	RT	acetonirile	nd
46	NaSEt	RT	DCM	nd
47	DOWEX H^+	RT	H_2O	nd
48	DOWEX H^+	RT	THF/H2O	nd
49	DOWEX H^+	RT	THF/MeOH	nd
50	DOWEX H^+	RT	MeOH	nd
51	DOWEX H^+	RT	$THF/CH(OMe)_1$	nd
52	**$ZnCl_2$**	**130**	**H_2O**	**40**

Table 3. Reaction conditions applied towards deprotection. (nd= no product detected).

It is known that pure deionized water at elevated temperature can perform acid-base catalyzed reactions. A detailed literature research revealed that the Boc protecting group[96] as well as acetals and ketals[97] can be cleaved under these reflux conditions. As a consequence, the metal salt was avoided and compound **80** was heated in deionized water over night (Scheme 18). We considered that the successful but non reproducible deprotection with zinc chloride (Table 3, entry 52) was rather an achievement of water catalysis than Lewis acid assisted cleavage. The addition of zinc chloride might have promoted decomposition rather than deprotection as observed under many other acidic reaction conditions probably explaining the poor reproducibility.

In order to avoid harsh reaction conditions, investigations were started at 80 °C for 12 hours (Table 4, entry 6). A concentration of 10 mg/mL afforded acetal **83** in 70% isolated yield. Prolonged reaction times did not improve the outcome but led to decomposition of our molecule. However, raising the temperature to 100 °C gave the diethyl acetal **83** and three other compounds, which were assigned as the two glycosides **84α** and **84β** and the free carbohydrate **31** (Table 4, entry7). Further analysis revealed that these products correspond to the mixture isolated from the zinc chloride methodology.

Moreover, the reaction strongly depended on the concentration of compound **82** suspended in water. Dilution of the reaction mixture increased the yield of the free sugar **31**. The optimal conditions are outlined in Table 4 (entry 2) using 1 mg/mL at 100 °C for 18 hours but formation of glycoside **84** as well as residual acetal **83** could not be prevented.



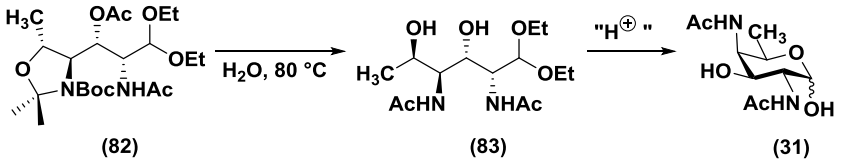
(82) (83) (31) 84 (α:β 3:1)

Scheme 18. Reaction products of the deprotection methodology.

entry	c [mg/mL]	time [h]	temperature [°C]	83 [%]	84 [%]	31 [%]
1	0,1	12	100	55	nd	22
2	**1**	**18**	**100**	**18**	**9**	**45**
3	1	12	100	21	12	21
4	2	18	100	nd	nd	32
5	4	48 (+ZnCl2)	100	7	10	40
6	10	12	80	68	nd	nd
7	10	12	100	47	5	10
8	10	8d	100	nd	nd	nd

Table 4. Concentration dependence of the deprotection.

The conversion of the acetal **83** to the free carbohydrate was investigated (Scheme 19). Interestingly, a two-step sequence with or without the assistance of acidic catalysis resulted in a significant loss in yield compared to the one step deprotection. In conclusion, the stability of the acetal **83** caused the moderate yield of the conversion of **82** to the free carbohydrate **31**. The precise mechanism of the deprotection is discussed in more detail in section 3.2.2.

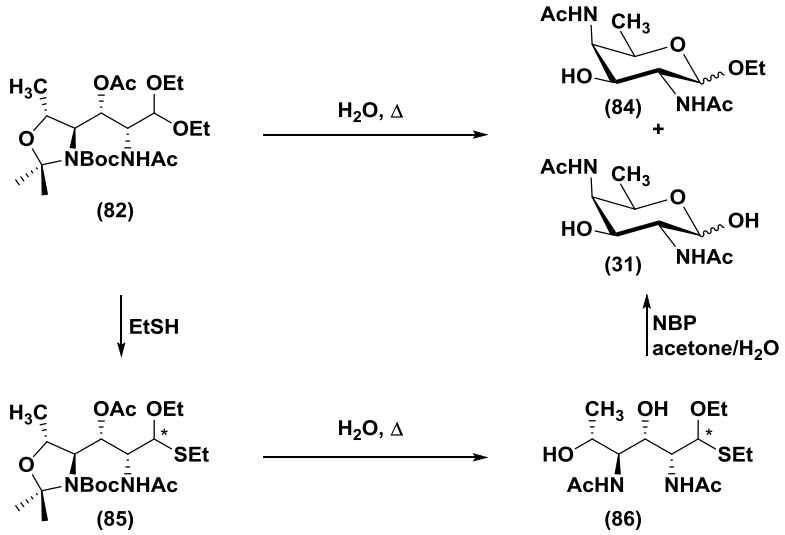


(82) (83) (31)

Scheme 19. Two step deprotection sequence.

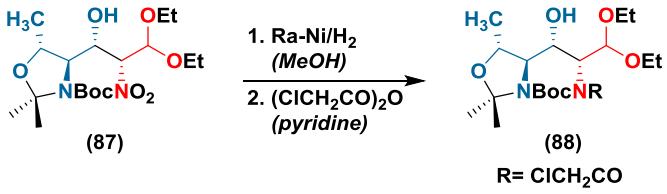
Microwave irradiation accelerates rates in many organic reaction.[98] Unfortunately, these conditions did not work for our system at all and conventional heating in an oil bath or using a heating mantle remained the methods of choice.

Simultaneously, an alternative route to obtain the unprotected carbohydrates was developed (Scheme 20). Since the stability of the aldehyde protecting group caused decreasing yields and byproduct formation, a derivatisation of the acetal was intended, which could be cleaved in a non-acidic way. The conversion into a thioacetal was advantageous since its cleavage could be performed with *N*-bromophtalimide. Therefore, acetal **82** was suspended in ethyl mercaptane and heated to reflux without any additional catalyst. Remarkably, freshly purchased ethyl mercaptane was not able to perform the transacetalisation and Lewis acid assistance was necessary, but led to decreasing yields of the mixed acetal **85**. We concluded that partial oxidation of the sulfur may have caused impurities that were fully capable of catalyzing this reaction. We were able to isolate the *S,O*-acetal **85** in 65% yield, whereas no full thioacetalisation was observed. Subsequent cleavage of the Boc and isopropylidene group yielded compound **86**, which was treated with *N*-bromophtalimide in aqueous acetone. Unfortunately, analysis of the reaction products showed a 1:1 mixture of glycoside **84** and unprotected carbohydrate **31**. Since Lewis acid catalyzed thioacetalisation resulted in poor yields and the final cleavage step did not improve the selectivity towards compound **31**, this approach was discarded.



Scheme 20. Thioacetalisation and subsequent deprotection procedure.

Additionally, X-ray crystallography should confirm the ^{1}H-NMR analysis. Substitution of the acetic acid anhydride with chloroacetic anhydride after the reduction step afforded crystalline compound **88** in 75% yield. Nevertheless, no suitable crystals to perform X-ray spectroscopy were obtained.



Scheme 21. Selective introduction of N-chloroacetate after the reduction step.

The complete reaction sequence from **76** to **31** was performed on a gram scale without any significant loss in yield. The nitroaldol reaction went smoothly and the subsequent reduction was performed in a flow reactor. Peracetylation provided compound **82** in nearly quantitative yield and the deprotection in deionized water gave compound **31** in 37% yield. The last step can still be optimized on this scale and an increase in yield in the range of the original outcome of 45% seems within reach.

3.2.1 Mechanism and Stereoselectivity

The stereochemistry was assigned *via* ^{1}H-NMR of the diastereomers generated during the nitroaldol reaction. The major isomer obtained a pyranosidic conformation with an α:β ratio of 0.9:1. Analysis of the coupling constants proved a *galacto* configuration with typical *J* values for the axial C4. Remarkably, the α-anomer showed an additional long range coupling of 0.5 Hz for the anomeric proton, which turned out to be present throughout in this type of carbohydrates. The interpretation of the ^{1}H-NMR spectrum of the minor isomer showed six different anomeric signals. The assignment of this carbohydrate has already been published and the chemical shifts as well as the percentages of the different conformations accurately agreed with our data and proved the *talo* configuration.[74]

The stereochemical outcome of nitroaldol reactions can either lead to *syn* or *anti* nitroalcohols (Figure 16). The transition state forms a cyclic six-membered ring in presence of a coordinating cation inducing a *syn* configuration of the nitroalcohol (Figure 17).

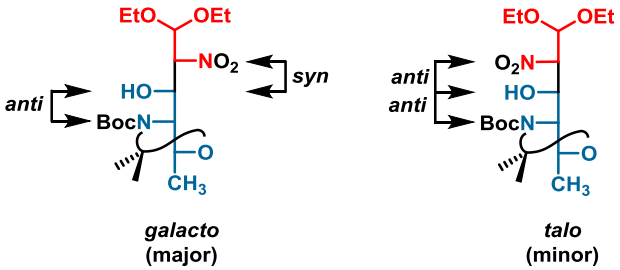


Figure 16. The major and minor isomer and their stereochemical relation of the chiral centers.

The catalytic effect of the lithium ion has been of considerable interest and *ab initio* calculations by Cossío *et al*. confirmed the prevailing *syn* relationship.[99] Solvation of the metal is crucial to increase the stereochemical influence through coordination. According to literature, the resulting enhanced nucleophilicity of the nitronate species explains the effect of water. This is fully consistent with our experimental findings that the increase of the aqueous percentage changed the diastereomeric ratio in favor of the *syn* nitroalcohol. The influence of steric interactions was also stressed with the dimethyl acetal analog. Applying identical reaction conditions led to a decrease in selectivity from 5:1 to 3:1.

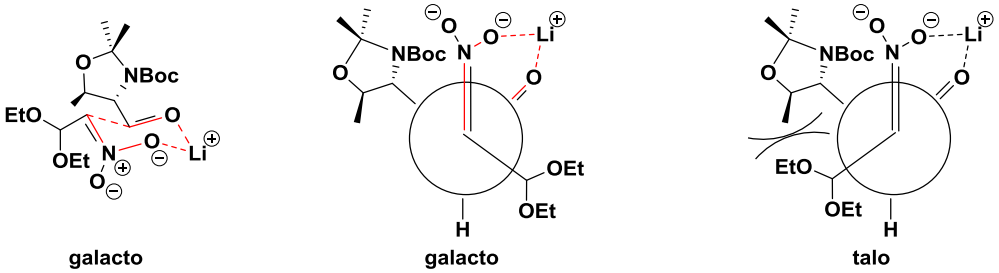


Figure 17. Proposed transition states.

The *anti* relationship between the newly formed chiral center and the existing one can be explained with steric interactions as well as the preference for equatorial positions of the substituents in the chair-like transition state.

3.2.2 Detailed Mechanism of the Deprotection Methodology

Since deprotection of derivative **82** removed three different protecting groups in a single step, the mechanism of this reaction and especially the order of cleavage were investigated in more detail. Therefore, aliquots were taken at an interval of one hour and the crude samples were studied with ^{1}H-NMR and mass spectroscopy (Figure 18 & 19). The results revealed that the diethyl acetal **83** was a central intermediate in the deprotection and the generation of this compound started early in this reaction. The acetyl signals of **83** clearly appeared in the ^{1}H-NMR after one hour and decreased in course of the reaction indicating its conversion to the products **31** and **84**.

Interpretation of the mass spectra suggested a sequential removal of the protecting groups. At the beginning of the reaction the appearance of a peak with *m/z* = 443.2363 indicated the primary cleavage of the isopropylidene group. This *m/z* value was consistent with a compound where the Boc group and the diethyl acetal were still attached, whereas the acetonide was already cleaved. Additionally, the peak with *m/z* = 343.1840 supported the formation of acetal **83** after one hour as observed in the ^{1}H-NMR spectrum. The driving force of this reaction appeared to be the thermodynamically favored acetyl migration towards the nitrogen. Subjecting the non-acetylated compound to our deprotection conditions resulted in no conversion and only a fraction of starting material could be reisolated.

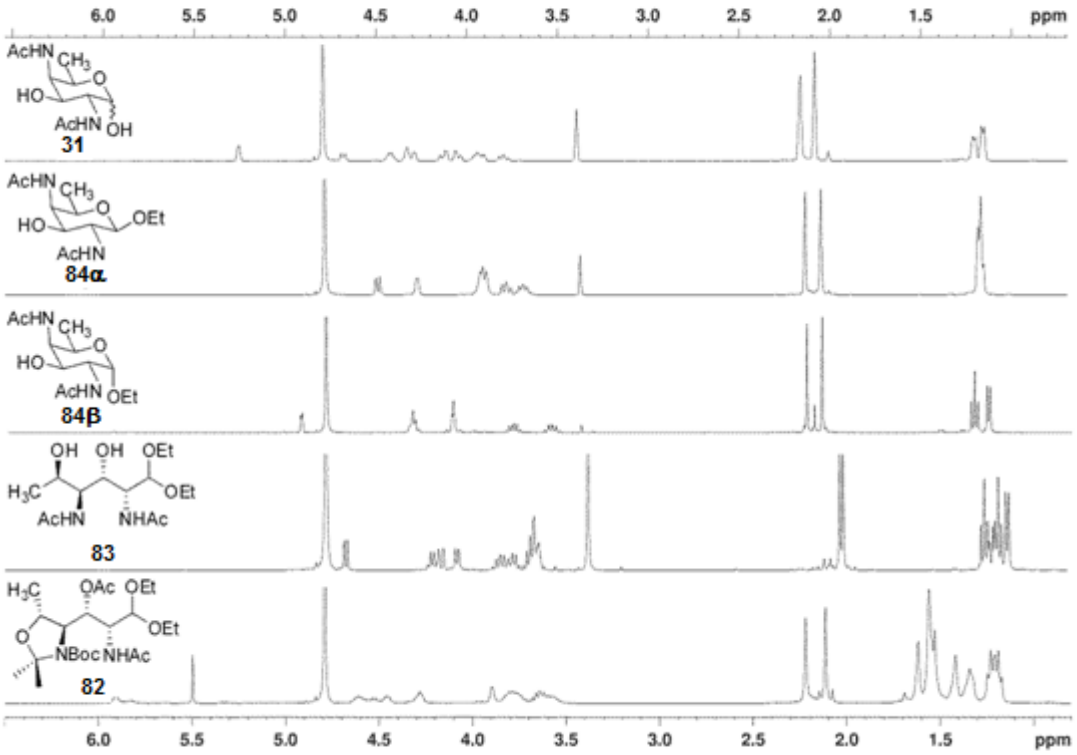


Figure 18. 400.13 MHz Spectra of purified compounds in D_2O.

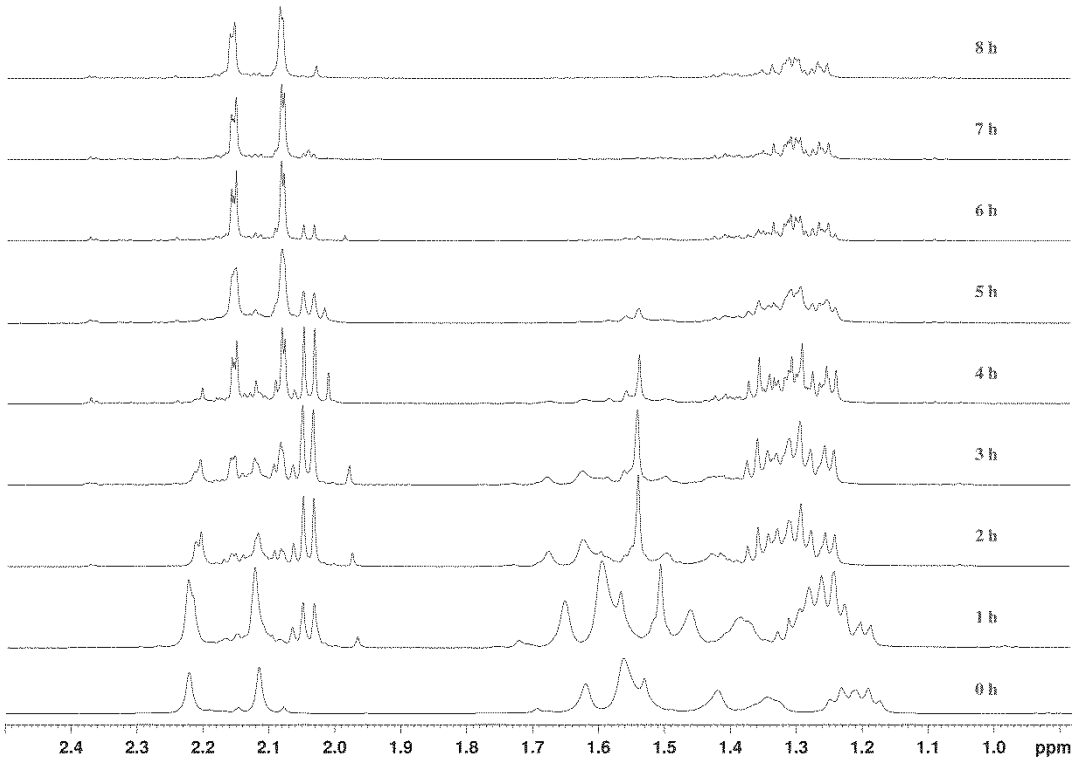


Figure 19. Reaction progress of the deprotection (^{1}H-NMR, 400.13 MHz).

3.2.3 Extension to the *allo*-Threonine Series

The successful application of the nitroaldol reaction to the L-threonine derived aldehyde **77** encouraged the extension to the *allo*-threonine series. As depicted in Figure 20, *allo*-threonine was an important starting material in order to achieve stereochemical patterns of the naturally abundant bacterial sialic acid. The D-*manno* configuration would offer access to legionaminic acid (**2**) and its C4-epimer **3**, respectively. In order to obtain the 8-*epi*-legionaminic acid (**4**) the L-*gulo* derivative was required and the pseudaminic acid (**1**) demanded the L-*altro* configurated hexose.

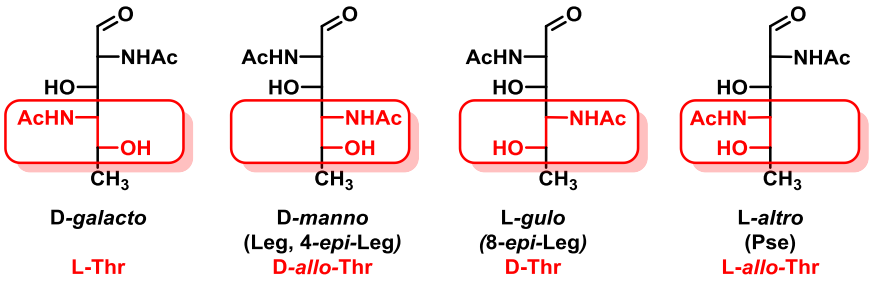
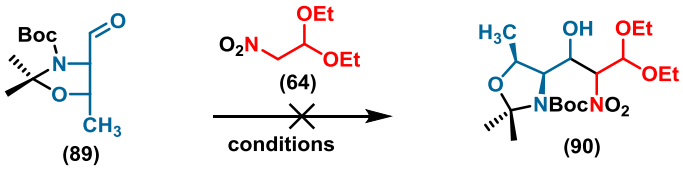


Figure 20. Required threonine isomer for the synthesis of important hexoses.

To our surprise, the nitroaldol reaction between aldehyde **90** and compound **64** gave very poor yields (22%) and nearly no selectivity (2:1:1). Variation of the temperature, different solvent mixtures (up to 50% water content) and various bases (LiOH, fluoride, amine bases, etc.) did not improve the outcome of this reaction (Scheme 22). Consequently, a different strategy had to be developed.

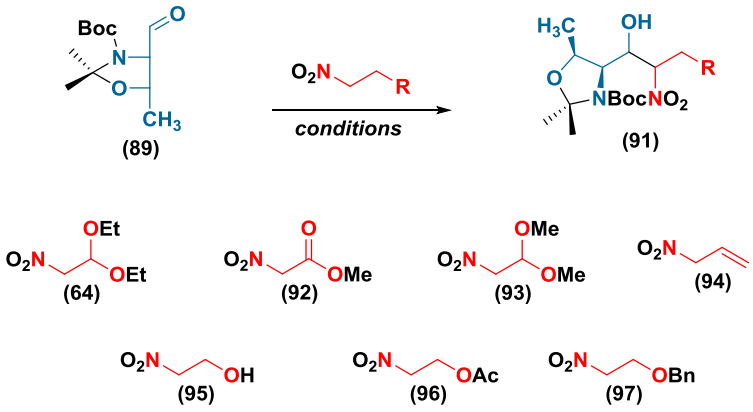


*Scheme 22. Unsuccessful application of nitroaldol reaction to D-allo-threonine derived **89**.*

3.2.3.1 Variation of the Nitro Compound

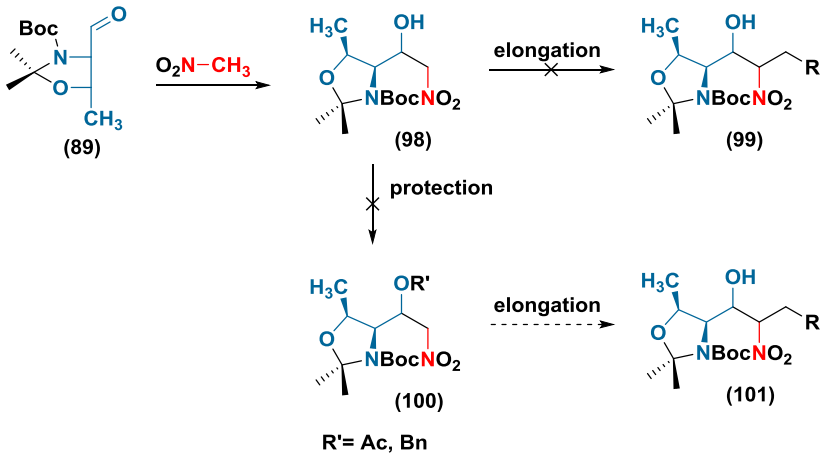
The poor reaction outcome of Scheme 22 may be caused by a conformational change in the molecule due to the inversed configuration of the terminal methyl group, thus reducing the accessibility of the aldehyde. Consequently, various nitro compounds were tested for their applicability.

The sterically less demanding dimethyl acetal **93** alongside with ester **92**, which is more reactive due to the enhanced acidity of the α-proton, resulted in even worse yields. 3-Nitro-1-propene (**94**), which was synthesized using allyl bromide and silver nitrite in a solvent free reaction, offered sterically and electronically quite different properties. Nevertheless, it did not lead to any product formation. The reaction with nitroethanol (**95**) as well as its acetyl (**96**) or benzyl (**97**) protected derivative gave no reasonable results.



Scheme 23. Various compounds tested in the reaction with D-allo-threonine.

Consequently, the reaction of **89** with nitromethane as the least demanding synthon was investigated. The reaction went smoothly within two hours using tetrahydrofurane as solvent and TBAF as base yielding 67% of a 1:1 diastereomeric mixture. However, this sequence required an additional C1-elongation step to generate the six carbon backbone. Different C1-equivalents (CH_2O, *p*-CH_2O, $CH(OEt)_3$) were applied under nitroaldol reaction conditions showing similar results (Scheme 24).



Scheme 24. Two step elongation sequence.

Analysis of the product mixtures revealed the retro reaction as predominant pathway. Therefore, the free hydroxyl group of **98** had to be protected avoiding the retro reaction. Neither acetylation nor benzylation resulted in a protected derivative but basic conditions during the protecting step always favored the retro reaction. Acidic protection methods such as the benzylimidate protocol turned out to be not successful as well and led to decomposition of our molecule. In conclusion, *allo*-threonine could not be applied as starting material in this reaction.

3.2.3.2 Preliminary Investigations Towards the Inversion of Stereocenters

Since the *allo*-threonine derived aldehyde **89** was not applicable in the nitroaldol addition, inversion of stereocenters should lead to variations in the stereochemistry of the sugar (Figure 21). In general, there were two hydroxyl groups present in the molecule that were targets for nucleophilic displacement. The C3-hydroxyl group of **87** was accessible after the elongation step as well as the reduction-acetylation sequence, respectively. Compound **101** could be obtained by selective *N*-acetylation with one equivalent of acetic anhydride, whereas careful deprotection of **82** at 80 °C gave rise to acetal **83** with two free hydroxyl groups - C3 and C5 - that could be addressed in a single reaction.

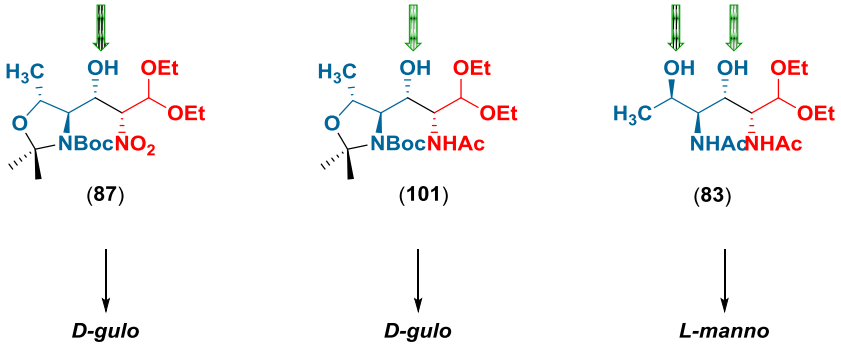


Figure 21. Overview of the addressable hydroxyl groups and resulting configurations.

The well-known Mitsunobu inversion has been used for decades to perform S_N2 reactions.[100] It depends on the crucial balance between basicity and nucleophilicity. The nucleophile has to be strong enough to deprotonate the alcohol but less nucleophilic than the resulting alcoholate. Figure 22 shows three different nucleophiles (**102**-**104**) that were investigated for our substrates **87**, **101** & **83**.

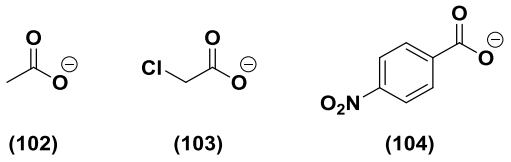


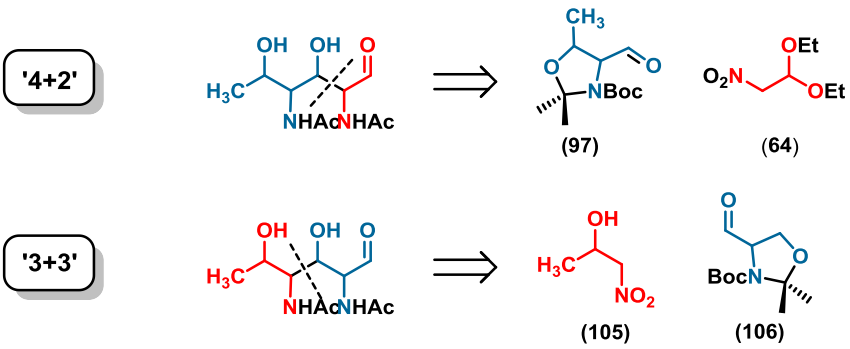
Figure 22. Nucleophiles for Mitsunobu inversion.

Acetate **102** prevented additional protecting group interconversions and was tested first. According to literature, this nucleophile is less favorable in Mitsunobu reactions and only a few successful examples are published.[100] For our desired reaction, acetate **102** did not succeed as well.

Within the narrow range of suitable reagents chloroacetate (**103**) and p-nitrobenzoate (**104**) are located. Unfortunately, both of them did not lead to inversions independent from starting material (**87**, **101** or **83**). Further investigations towards the application of nucleophilic displacement reactions to obtain various stereochemical patterns are currently under investigation in our lab.

3.3 The '3+3' Approach

Due to the limitations in the configuration of the starting aldehyde derived from threonine, a generally different strategy was developed.



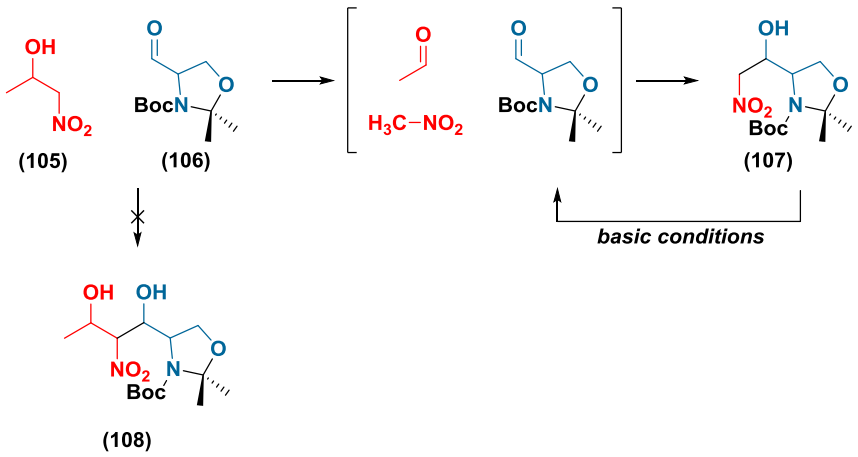
Scheme 25. '4+2' vs. '3+3' approach.

Analysis of the target hexoses revealed a second suitable disconnection for the nitroaldol reaction (Scheme 25). A serine derived aldehyde **106** and 1-nitro-2-propanol (**105**) were assigned in the '3+3' approach. Both isomers of serine are commercially available and the less frequent D-serine is much cheaper than *allo*-threonine.

A fundamental difference between these two approaches regarded the carbonyl functionality of the final sugar. In our first synthesis, the correct oxidation state of the final C1 was introduced directly *via* the nitro compound but in return caused a decrease in yield during the deprotection. In contrast, the '3+3' approach demanded a challenging oxidation of the primary hydroxyl group of the C3 of serine at the end of the sequence,

Commercially not available 1-nitro-2-propanol (**105**) was a key molecule. A number of procedures deal with the synthesis of this compound in an enantiomerically pure manner using chiral catalysts, acetic aldehyde and nitromethane as reaction partners.[101] Both enantiomers were required to increase the stereochemical diversity of the final hexoses, more precisely, to enter the D- and L-series of the sugars. Therefore we used a protocol without chiral induction to obtain nitroalcohol **105** in a racemic form.

The applicability of the reaction of compound **105** with aldehyde **106** was investigated using racemic **105** in the first attempts. However, no desired product **108** was observed but basic reaction conditions favored the retro reaction to give a four carbon skeleton **107** (Scheme 26).



Scheme 26. Preliminary test reactions in the '3+3' approach.

Neither variation of the base (TBAF, Cs_2CO_3, LiOH) nor different solvent mixtures prevented the favored retro reaction. Compound **107** was subjected to a second nitroaldol reaction with acetaldehyde again preferring the retro reaction. Only aldehyde **106** and aldol condensation products originating from the acetic aldehyde were isolated. Protection of the free hydroxyl group of **107** as acetyl or benzyl derivative to avoid undesirable side reactions in the second elongation was not successful. Since a two-step procedure towards the hexose skeleton was not feasible, functionalization of the hydroxyl group of 2-nitro-1-propanol prior to the reaction was expected to avoid side reactions.

In order to eliminate the possibility of retro aldol reactions, the free hydroxyl group of **105** had to be protected. Kinetic resolution using lipases addresses one single enantiomer and introduces an acetyl moiety into the molecule. Lipases from *Candida Rugosa* and from porcine pancreas are reported to show promising results and are well established in the resolution of nitroalcohols.[102] Both enzymes process vinyl acetate and can be applied in common organic solvents. In contrast to the lipase from *Candida Rugosa*, lipase from porcine pancreas did not convert any of our substrate. However, the enantiomeric excess of acetylated **109** from the *Canida Rugosa* esterification achieved less than 50%.

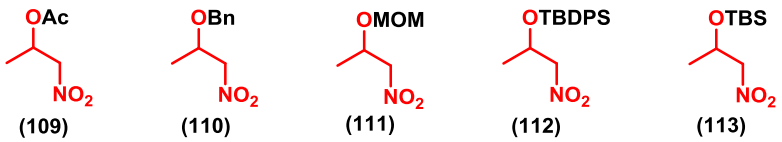
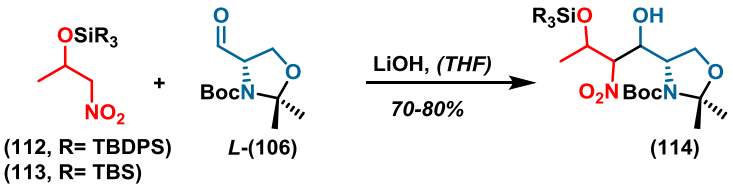


Figure 23. Various protected 1-nitro-2-propanols tested for applicability.

Consequently, chemical modification of the molecule was performed (Figure 23). Standard acetylation procedures of compound **105** gave poor yields due to the basic conditions in our experience.[103] However, reaction of **109** with aldehyde **106** under basic conditions did not lead to conversion. Changing to a benzyl protecting group was not successful either, as well as the reaction with a methoxymethyl (MOM) ether **111**.



Scheme 27. Test reaction for application of silyl protected 1-nitro-2-propanol.

It has been published that 1-nitro-2-propanol can be converted to a silyl protected derivative with excellent yields.[104] Applying this derivative, over 95% of compound **113** and 64% of **112** were isolated. In addition, the nitroaldol reaction with the racemic compound gave very promising results (Scheme 27). Thus the separation of the enantiomers using chiral HPLC was investigated. A Chiracel® OD-H column with hexanes/2-propanol mixtures as eluents was tested. The *tert*-butyldiphenylsilyl (TBDPS) protected compound **112** was not separable whereas the enantiomers of the *tert*-butyldimethylsilyl (TBS) derivative **113** eluted as two discrete peaks with a difference in retention time of three minutes (hexanes/2-propanol= 98:2, Figure 24).

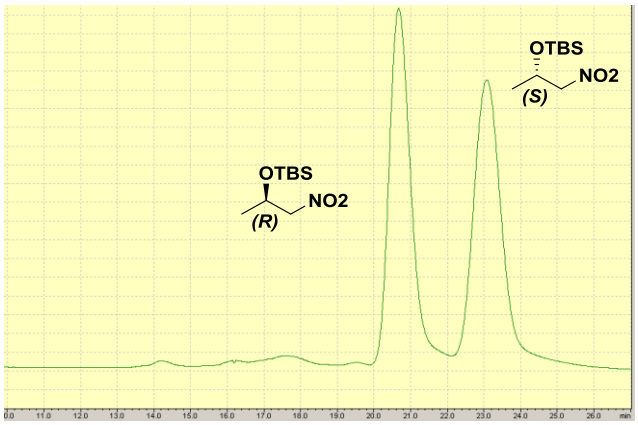
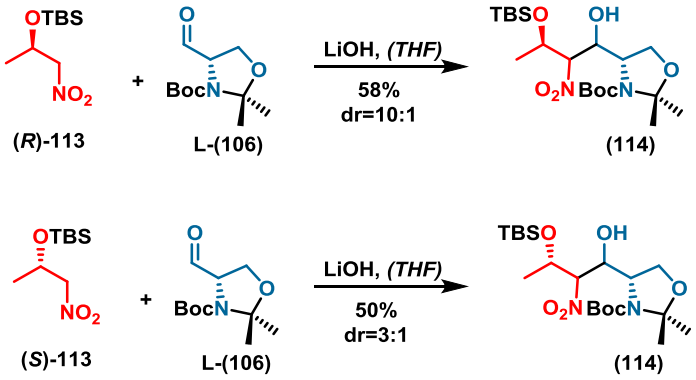


*Figure 24. Chromatogram for the separation of (R)-**113** and (S)-**113**.*

With the two TBS protected enantiomers in hand, optimization of the nitroaldol reaction was performed (Scheme 28). Lithium hydroxide in anhydrous tetrahydrofurane gave over 80% product with the racemic compound **113** but the yield dropped down to 58% for (*R*)-**113** and 50% for (*S*)-**113**. The addition of water and lowering the temperature did not improve the reaction in this case. In contrast, the diastereoselectivities were increased under anhydrous conditions (10:1 for (*R*)-**113**, 3:1 for (*S*)-**113**).

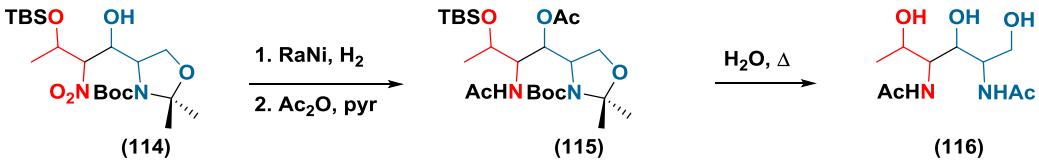


Scheme 28. Enantiomerically pure conducted nitroaldol reaction.

Caesium ions show unique properties and selectivities in many cases.[105] Nevertheless, the yield of the nitroaldol reaction decreased significantly applying caesium carbonate as base. However, caesium hydroxide was too basic and caused cleavage of the silyl protecting groups rendering the unprotected **108**, which underwent a retro reaction and the nitromethane adduct **107** as pointed out above (Scheme 26).

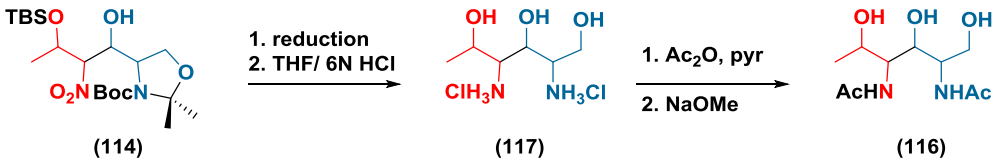
The most commonly used base in nitroaldol reactions is TBAF. However, the affinity of fluoride ions towards silyl groups is indisputable and this reagent represents a popular methodology to cleave these protecting groups. Generally, deprotection reactions are carried out at room temperature and careful adjustment of this parameter might increase the half-life of the TBS group in favor of the nitroaldol addition. The reaction was performed with 10 mol% of TBAF between -50 and -30 °C and provided excellent yields for both enantiomers. Starting from (*R)*-**113**, 82% of a single diastereomer was obtained, whereas (*S)*-**113** resulted in a 2:1 mixture with 80% yield. Impressively, the equivalents of protected 1-nitro-2-propanol **113** could be reduced from 7 to 4 equivalents without affecting the yield, which is quite unusual for nitroaldol reactions.

Initially, an analogous sequence compared to the '4+2' approach was intended (Scheme 29). Reduction with Raney-nickel went smoothly but peracetylation yielded a mixture of compounds. Two of them showed identical mass spectra and a third compound revealed three acetyl groups present in the molecule indicating a silyl group migration and partial cleavage of the silyl ether. Nevertheless, the expected product **115** was subjected to our deprotection conditions using deionized water at elevated temperatures and afforded compound **116** in excellent yields.



*Scheme 29. Deprotection sequence towards triol **116**.*

Alternatively, another approach with a different order of deprotection was adopted. After the reduction, a global deprotection under strong acidic reaction conditions gave compound **117** in over 90% yield. Selective acetylation of the amine functionalities using stoichiometric amounts of acetic anhydride or *N*-acetoxy phtalimide was not successful and a sequence of peracetylation followed by Zemplén saponification gave the desired product **116** (Scheme 30).



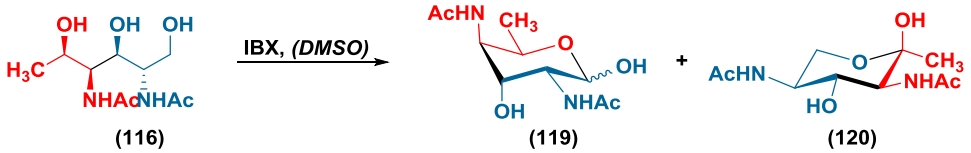
Scheme 30. Reversed deprotection/acetylation sequence.

The sugar alcohol **116** was a key compound and thus crucial for the synthesis. A differentiation between primary and secondary hydroxyl groups was essential for the successful selective oxidation step to the aldehyde. Several methodologies claim to utilize the differences in the reactivity. However, the polarity of our molecule limited the scope of applicable solvents.

Table 5 summarizes the applied protocols. TEMPO mediated oxidations offer the advantage to use water as solvent but overoxidation to the acid is difficult to avoid.[106] Anyway, neither catalytic procedures nor stoichiometric amounts of TEMPO led to oxidation and only starting material could be reisolated.

Dimethylsulfoxide (DMSO) belongs to the most polar solvents used in organic synthesis and is capable of dissolving unprotected carbohydrates. A major drawback of *o*-iodoxybenzoic acid (IBX) is the poor solubility in organic solvents other than DMSO, which was a possible solvent for our molecules. Furthermore, IBX oxidations show selectivity for primary hydroxyl groups over secondary ones.[107] According to literature, overoxidation of the resulting hemiacetal to the corresponding lactone should be prevented applying this reagent

To our surprise, the oxidation of triol **116** with IBX afforded an equimolar mixture of C1 (**119**) and C5 (**120**) oxidized product resulting in an aldose and a ketose in an overall yield of 55% (Scheme 31). Slow addition of the reagent overnight did not improve the selectivity. Since pure DMSO as solvent precluded low temperature, an aqueous mixture was used to enable application of 0 °C. However, low temperatures as well as raising the temperature to 80 °C did not improve the selectivity.



*Scheme 31. Oxidation of **116** with IBX.*

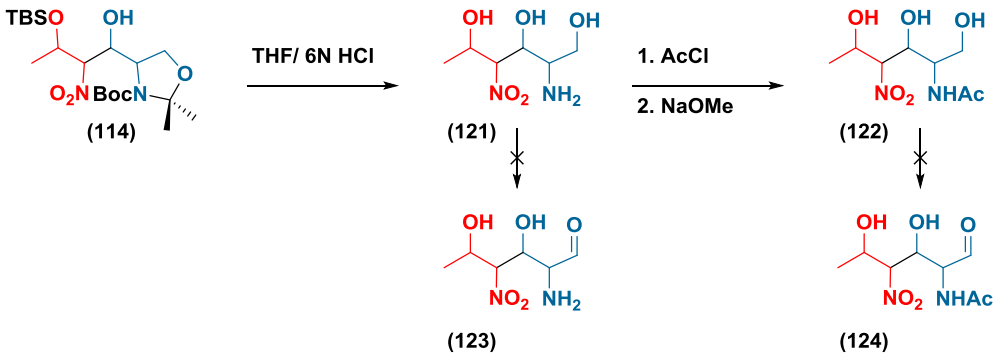
The advancement of IBX was the development of Dess Martin periodinane (DMP). It overcomes the problem of solubility and shows faster reaction rates. Therefore, the enhanced reactivity of this reagent was expected to shift the oxidation towards the primary alcohol. To our surprise, the opposite reaction was observed. After work up, a single product could be isolated in 67% yield and ^{1}H-NMR analysis proved the exclusive oxidation of the C5 hydroxyl group resulting in ketose **120** (Scheme 31).

entry	substrate	oxidant	conditions	yield 119 [%]
1	**116**	IBX	RT (DMSO)	28 (+27% **120**)
2	**116**	IBX	70°C (DMSO)	nd
3	**116**	IBX/	0°C (DMSO/H_2O)	nd
4	**116**	IBX (slow addition)	RT (DMSO)	nd
5	**116**	DMP	RT (DMSO)	67 (only **120)**
6	**116**	IBX β-cyclodextrin	RT (H_2O/acetone)	nd
7	**116**	NaOCl	RT (H_2O)	nd
8	**116**	TEMPO	0°C (H_2O)	nd

Table 5. Summary of the oxidation protocols tested. (nd= not detected).

Since the reaction kinetics did not allow a selective oxidation of the C1-OH, derivatisation with sterically demanding protecting groups was planned. The TBDPS as well as the triphenylmethyl group tend to selectively attach to primary hydroxyl groups. Subsequent protection of the remaining hydroxyl groups and hydrolysis of the C1 protecting group offered the possibility to access the primary position. However, this sequence failed, since the protection of the C1 hydroxyl could not be achieved in the first place. Similarly, the conversion into a cyclic acetal to enable differentiation between the hydroxyl groups was not successful and neither the 1,2 nor 1,3 protected compounds were obtained.

During our work with 3-deoxy-2-uloses, we demonstrated that primary hydroxyl groups can be converted into thioethers under tin chloride mediation using microwave conditions.[85d] The resulting sulfides are capable of undergoing the Pummerer rearrangement. Nevertheless, all efforts towards selective substitution with thiols resulted in complex product mixtures.



Scheme 32. Discrimination between C1 and C5 via different electronic environments.

As depicted in Scheme 32, the electronical environment adjacent to the C1 and C5 hydroxyl group was changed. This should contribute to their differentiation and selective oxidation. A major drawback of this route was the sensitivity towards treatment with base, since the nitro group caused side reactions and decomposition. Deprotection under acidic conditions afforded 4-nitro compound **121** in good yields. The oxidation of the primary alcohol with the free amine **121** could not be achieved at this stage (Table 6, entry 1). The *N*-acetyl protected derivative **122** was difficult to synthesize and the oxidation of the primary alcohol was not successful either (Table 6, entry 2-3).

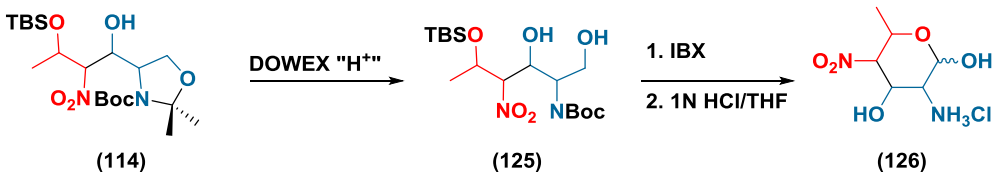
entry	substrate	oxidant	conditions	yield [%]
1	**121**	IBX	RT (DMSO)	nd
2	**122**	IBX	RT (DMSO)	<10
3	**122**	DMP	RT (DMSO)	nd
4	**122**	NaOCl	RT (H_2O)	oo

Table 6. Summary of the oxidation protocols tested. (nd= not detected, oo= overoxidation)

The limitation in the ‘3+3’ approach so far was the lack in selectivity during the final oxidation step caused by the perturbing C5 hydroxyl group. Consequently, this issue had to be addressed in an earlier step of the reaction sequence. After the nitroaldol reaction, compound **113** offered the possibility of selective deprotection of the different functionalities present.

The secondary TBS group was the first target and various fluoride based methodologies were tested. The application of TBAF and comparable basic conditions were not feasible because subsequent to the cleavage of the TBS group a retro aldol reaction occurred. In fact, we only observed decomposition of the molecule. Therefore, hydrogen fluoride, the HF-pyridine complex as well as $HSiF_6$ were applied in different solvents and stoichiometries, but neither of these conditions were successful in the selective deprotection of the silyl ether.

The differentiation of the various acid labile protecting groups was investigated. Acidic ion exchange resin proved to be successful in the cleavage of the acetonide, but kept the TBS group mainly unaffected (Scheme 33). The reaction time was crucial for the yield and reproducibility of **125**. The best results were obtained when Dowex W50 was used in a methanolic suspension which contained 10% water. The reaction was stopped as soon as cleavage of the TBS group started, indicated by an additional polar spot on the TLC.



(114) (125) (126)

Scheme 33. Successful reaction sequence towards deprotected carbohydrates.

Compound **125** was readily oxidized to the aldehyde with IBX in DMSO without side reactions such as overoxidation or epimerization. Immediate treatment with hydrochloric acid in THF afforded the unprotected carbohydrate **126** in excellent yields over two steps (Table 7).

3.3.1 Stereochemical and Mechanistic Considerations

The '3+3' approach allowed the combination of all possible enantiomers of the starting materials and therefore created different configurations in their D-and L-form, respectively. Starting from L-serine and (*R*)-**113**, the reaction sequence generated the D-*gulo* configurated product as a single isomer in 82% yield. Mechanistically, the absence of coordinating metal ion during the reaction should result in a higher contribution of steric and electronic interactions. The aldehyde and the nitro group tend to adopt an *anti*-alignment due to their dipoles, The preference for the *gulo* configuration can be rationalized as shown in Figure 25.

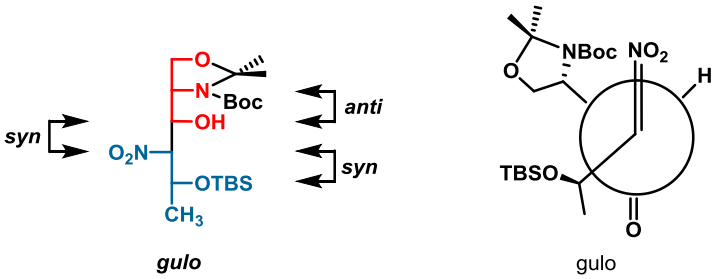


Figure 25. Proposed transition state.

The selective deprotection of *gulo*-**114** gave 54% of *gulo*-**125** (83% based on recovered starting material) and the oxidation/deprotection sequence gave the *gulo* configurated carbohydrate in nearly quantitative yield (Table 7, entry 1 & 4). This highly interesting sugar is the underlying hexose fragment of the 8-*epi*-legionaminic acid (**4**).

In contrast, the (*S*)-**113** enantiomer provided two diastereomers in an overall yield of 82% with L-*rhamno* and L-*ido* configuration, respectively (Figure 26, Table 6, entry 2-3 & 5-6).

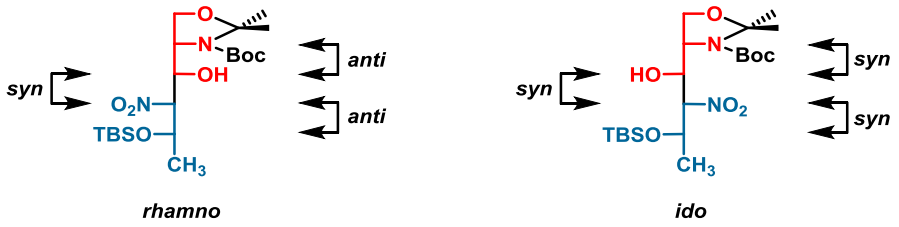


*Figure 26. Stereochemical outcome using L-serine and (S)-**113**.*

The *syn* relationship between the newly formed chiral centers is generated, but the inversed stereochemistry of the TBS protected alcohol enabled the attack from both sides of the carbonyl resulting in a 2:1 selectivity for the *rhamno* product.

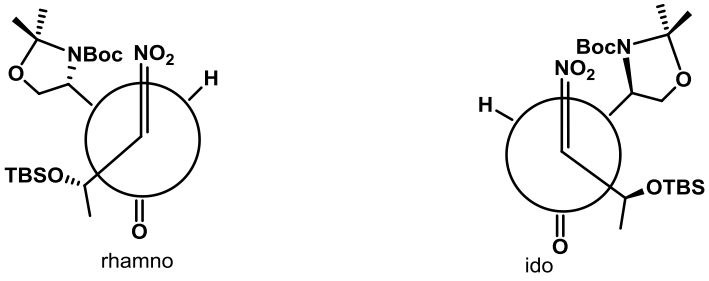


*Figure 27. Proposed transition states for (S)-**113** with L-**106**.*

The yield of the cleavage of the isopropylidene group was generally lower compared to the *gulo* derivative. The oxidation step provided the free carbohydrates in 83% for *rhamno* and 77% for the *ido* compound. The former configuration is necessary to obtain the correct stereochemistry for the legionaminic acid (**2**) and 4-*epi*-legionaminic acid (**3**), respectively.

entry	substrate	reagent	yield [%]
1	*gulo*-**114**	Dowex "H^+"	54 (83)
2	*rhamno*-**114**	Dowex "H^+"	38 (69)
3	*ido*-**114**	Dowex "H^+"	68 (76)
4	*gulo*-**125**	IBX	>95
5	*rhamno*-**125**	IBX	83
6	*ido*-**125**	IBX	77

Table 7. Overview of yields for the selective deprotection and final oxidation/deprotection sequence.

3.2.2 Assignment *via* ^{1}H-NMR

The relative configurations of the carbohydrates were determined by ^{1}H-NMR spectroscopy and analysis of their coupling constants. Table 8 summarizes the *J*-values.

entry	configuration	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
1	α-*gulo*	3.9	3.5	*nm*	3.0	6.4
2	β-*gulo*	8.7	3.0	2.8	1.9	6.5
3	α-*rhamno*	1.4	3.5	9.9	9.6	6.3
4	β-*rhamno*	1.6	4.2	10.5	9.4	6.1
5	α-*ido*	1.8	5.6	5.9	3.1	6.6
6	β-*ido*	2.1	5.5	6.2	3.5	6.5

Table 8. Coupling constants derived from ^{1}H-NMR spectra recorded at 600.13 MHz. (nm= not measurable).

The stereochemistry of the *gulo* configurated compound was determined using 2,4-diacetamido-2,4,6-trideoxy-D-gulose (**119**). The values and chemical shifts are consistent with the published data for this compound.[74]

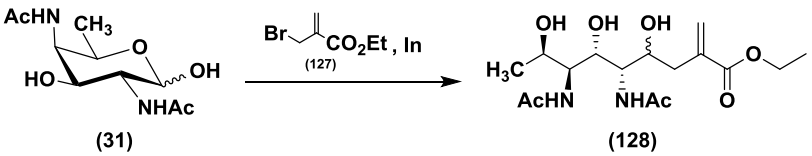
The major diastereomer, *rhamno*-**126**, resulting from the reaction of (*S*)-**113** with L-serine was investigated after the oxidation-deprotection sequence. The coupling constants are in agreement with the *rhamno* type sugars. The equatorial H2 caused small coupling constants for both anomer and differentiation was determined *via* the J_{CH}, which showed an increase of 10 Hz for the α-anomer. Additionally, the remaining *J*-values proved the axial position of H3 and H4. The absolute stereochemistry was already determined by the starting material.

In fact, the minor diastereomer, *ido*-**126**,was more difficult to resolve. From the theoretical point of view, the *altro*, *talo* or *ido* configuration were most likely because of the *syn* relation between the new chiral centers. The $J_{4,5}$ listed in Table 8 ruled out altrose, since the measured coupling constants differ form expected values according to the Karplus equation. Comparison of our findings with published data of *ido* configurated diamino hexoses or derivatives thereof revealed good agreement for this configuration.[108]

4. Indium Mediated Chain Elongation of Carbohydrates

4.1 Synthesis of Non-natural 3-Deoxy-2-nonulosonic Acids

The indium mediated chain elongation of unprotected hexoses offers access to the nonulosonic acid family. Applying allyl bromide derivative **127** the C1 to C3 fragment can be installed successfully. This Barbier-type reaction strongly depends on the reaction conditions. In fact, different sugars demand different solvent compositions as well as stoichiometries and sometimes additives are necessary to accelerate reaction rates.[85]



Scheme 34. Indium mediated chain elongation of the galacto derivative.

In order to reveal the best reaction conditions for substrate **31** (Scheme 8), various solvent compositions were applied (Table 9). Initially, aqueous ethanol (Table 8, entry 1&2) - the most common solvent mixture in this type of reaction - was tested. However, no product could be isolated. Similarly, anhydrous tetrahydrofurane (Table 9, entry, 3) and a mixture with diluted hydrochloric acid were not suitable (Table 9, entry 4). In general, acidic conditions accelerate reaction rates, whereas in this case the low pH caused decomposition of the *in situ* formed organoindium species before elongation took place.

In many cases, the indium mediated chain elongation requires aqueous reaction media. Since anhydrous THF did not lead to the desired product formation, mixtures with varying ratios were tested. Increasing the water content significantly influenced the yield obtaining up to 31% (Table 9, entry 11). In this case, additives showed rather negative effects (Table 9, entry 7-9).

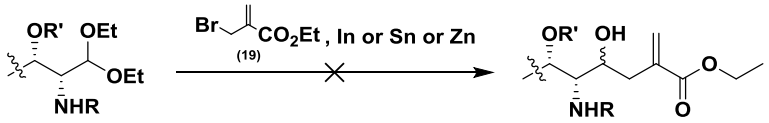
Pure water has been used as a solvent for this reaction (Table 9, entry 12). However, the allyl bromide component is only slightly soluble in aqueous reaction media. Raising the temperature to 60 °C enabled the application of this solvent and gave 47% of **128**.

In order to overcome the solubility problem, a 1:1 mixture of THF and water was applied at 60 °C and 85% of the desired product was isolated. The diastereoselectivity depends on the properties of the functional group adjacent to the carbonyl (see section 2.3). Nevertheless, it is known that the diastereoselectivity for these compounds is rather low[109] and a ratio of 2:1 was achieved.

entry	substrate	solvent	additive	temperature	yield
1	**31**	EtOH/H_2O= 2:5		rt	nd
2	**31**	EtOH/H_2O= 4:1		rt	nd
3	**31**	THF		rt	nd
4	**31**	THF/0.1 N HCl= 1:1		rt	nd
5	**31**	THF/H_2O= 5:2		rt	nd
6	**31**	THF/H_2O= 4:1		rt	nd
7	**31**	THF/H_2O= 4:1	NH_4I	rt	nd
8	**31**	THF/H_2O= 4:1	LiCl	rt	nd
9	**31**	THF/H_2O= 1:2	LiI	rt	traces
10	**31**	THF/H_2O= 1:4		rt	traces
11	**31**	**THF/H_2O= 1:1**		**rt**	**31**
12	**31**	**H_2O**		**60**	**47**
13	**31**	**THF/H_2O= 1:1**		**60**	**85**
14	**82**	EtOH/H_2O= 4:1		rt	nd
15	**82**	EtOH/H_2O= 4:1	NH_4I	rt	nd
16	**82**	THF/H_2O= 2:5	NH_4Cl	rt	nd
17	**82**	THF/H_2O= 1:5	Zn	rt	nd
18	**82**	THF/H_2O= 1:5	Sn	rt	nd
19	**83**	EtOH/0.1 N HCl= 5:1		rt	nd
20	**83**	EtOH/H_2O= 4:1		rt	nd
21	**83**	H_2O		rt	nd
22	**83**	H_2O	NH_4Cl	rt	nd
23	**83**	THF/0.1 N HCl= 3:2		rt	nd
24	**83**	THF/0.1 N HCl= 4:1		rt	nd
25	**83**	THF/H_2O= 4:1		rt	nd

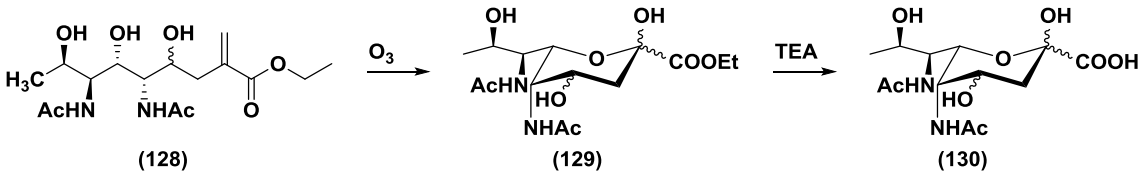
Table 9. Conditions applied in the indium reaction for various substrates. (nd= not detected)

During the reaction, a decrease of the pH value can be observed. This characteristic was tested for the possibility to perform the deprotection of compound **82** and the elongation in a one pot procedure (Scheme 35). In summary, all efforts to capitalize from the increasing proton concentration were not successful whether compound **82** or the diethyl acetal **83** were used as starting material (Table 9). Furthermore, the Barbier type reaction with tin or zinc, which tends to further decrease the pH value, was not applicable as well.



*Scheme 35. Attempts for the allylation of acetal **82** & **83**.*

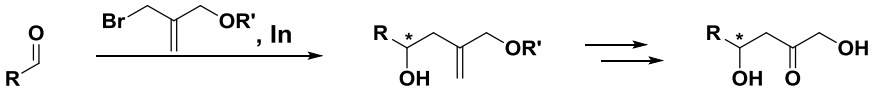
The last steps of the reaction sequence towards the free carbohydrate included an oxidation with ozone to generate the carbonyl compound, which immediately formed the pyranose hemiacetal **129**. Subsequent saponification with triethylamine gave the free carbohydrate **130** in 74% yield over two steps (Scheme 36).



Scheme 36. Ozonolysis and saponification.

4.2 Straightforward Synthesis of 3-Deoxy-2-uloses

Compared to 3-deoxy-2-ulosonic acids, the family of 3-deoxy-2-uloses has drawn less attention. Nevertheless, indium mediated chain elongations are the predominant methodologies to install the C1 to C3 unit in literature.[85d] Interestingly, the application of compound **131** or its protected derivative **132** has been scarcely examined.



Scheme 37. Reaction sequence towards 3-deoxy-2-uloses.

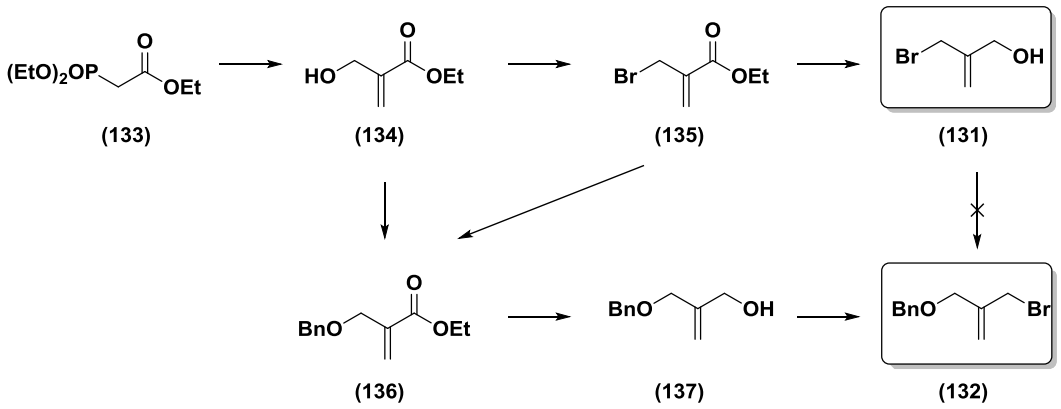
In contrast to published syntheses,[92] this new route did not convert the C1 into the hydroxyl group at a late stage, but installed the primary alcohol directly in the elongation step (Scheme 37). Therefore, critical reductions and excessive protecting group strategies were avoided. Since indium mediated reactions could be performed in aqueous media, unprotected carbohydrates were used as starting materials. Compound **131** or its benzyl protected derivative **132** were applied (Figure 28). Ozonolysis and reductive cleavage of the benzyl group in case of **132** gave the desired carbohydrates in a straightforward synthetic route.

(131) (132)

Figure 28. Allyl bromide derivatives applied to unprotected carbohydrates.

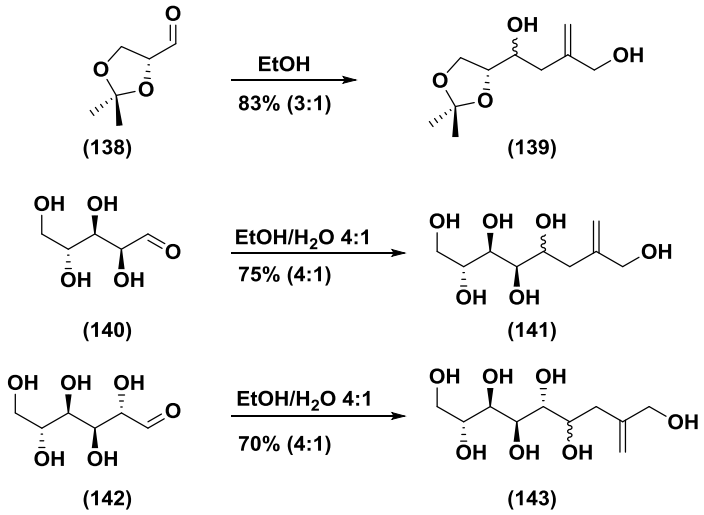
The allyl bromide components were synthesized starting from triethylphosphonoacetate (**133**) in a Horner-Wadsworth-Emmons reaction with formaldehyde (Scheme 38).[110] Ester **134** tended to polymerize and distillation at this stage was accompanied with a significant decrease in yield. Subsequent bromination with phosphorous tribromide gave compound **135** which could be easily purified.

The reduction to the alcohol with DIBALH demanded careful handling due to the low boiling point of the product **131**. During evaporation of the solvent as well as distillative purification, the pressure had to be controlled accurately in order to avoid loss of material.



Scheme 38. Synthesis of building blocks for the indium reaction.

With compound **131** in hand, its applicability in the indium mediated reaction with different carbohydrates was tested as shown in Scheme 39. Generally, the yield was high and the diastereoselectivities ranged from 3:1 to 4:1. Unfortunately, the diastereomers were not separable using either standard column chromatography or HPLC in normal or reversed phase (C18-column) mode. The peracetylated derivatives were synthesized and the purification procedures were repeated. Similarly, the diastereomers of these derivatives could not be separated.

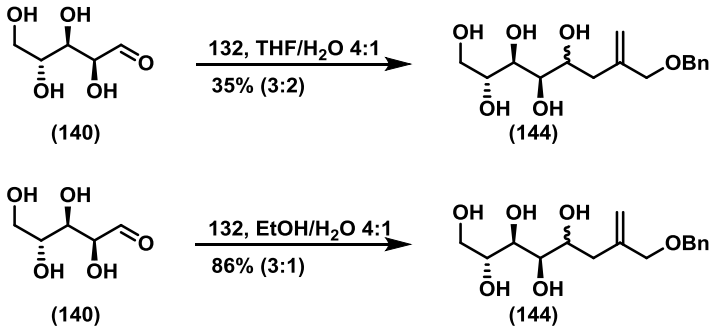


*Scheme 39. Indium mediated reaction of **131** with various sugars.*

Since the separation of the diastereomers generated during the elongation step was difficult, derivatisation to benzyl protected **132** was performed. Additionally, the volatility of compound **131** was reduced and the fluorescence of the aromatic system enabled UV-detection in the event of HPLC purification.

Two different synthetic routes led to the desired product **132** (Scheme 38). Since basic treatment of compound **134** had to be avoided, benzyl trichloroacetimidate was chosen to introduce the protecting group under acidic catalysis. Alternatively, bromination of the primary alcohol to yield bromide **135** followed by transformation into compound **136** by treatment with sodium benzylate was performed. After reduction of **136** with DIBALH in dichloromethane, an Appel reaction installed the bromine in 70% yield over two steps.

Arabinose was chosen as substrate for the allylation reaction with the benzyl derivative **132** (Scheme 40). Owing to the low solubility of compound **132** in water, the amount of organic solvent had to be adjusted. Ethanolic mixtures proved to give significantly better yields than tetrahydrofurane and 86% of the elongated compound **144** could be isolated.

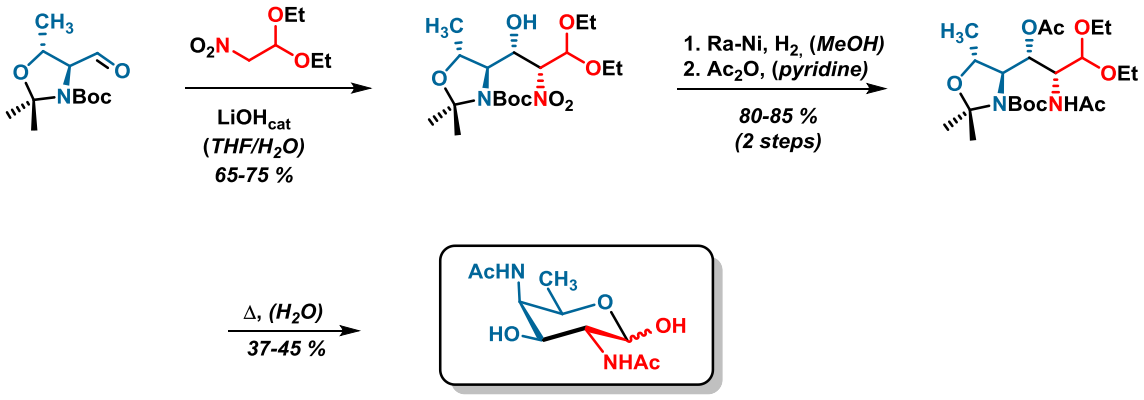


*Scheme 40. Indium mediated reaction of **132** with D-arabinose.*

SUMMARY

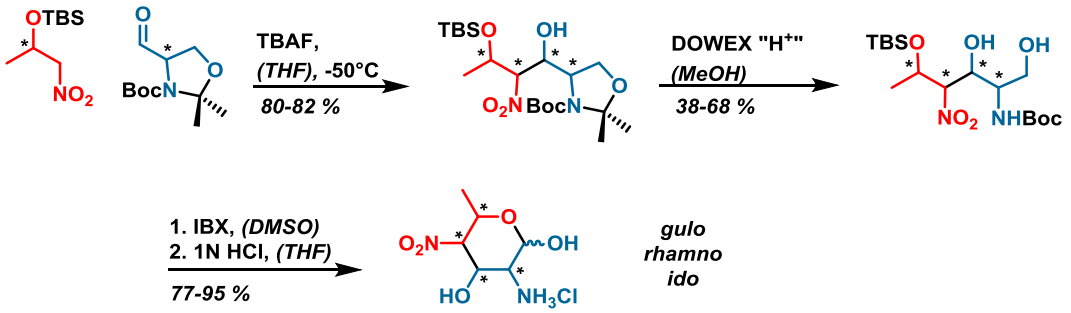
This work presents two closely related synthetic sequences towards the family of 2,4-diamino-2,4,6-trideoxy hexoses. The application of the nitroaldol reaction has been demonstrated as an excellent alternative to classic nucleophilic displacement strategies. Generally, two different nitro compounds have been used, classifying a '4+2' and a '3+3' approach.

2-Nitroacetaldehyde diethylacetal in combination with LiOH generated the *galacto* and the *talo* configurated carbon backbone, respectively (Scheme 41). The selectivity for the former compound depended on the coordinating properties of the lithium ion and could be tremendously increased upon the addition of water to the reaction medium. The reduction of the nitro group and subsequent acetylation followed by a global deprotection in deionized water at elevated temperatures yielded the di-*N*-acetylated target. Additionally, the reactions were performed on a gram scale.



Scheme 41. Synthesis of 2,4-diamino-2,4,6-trideoxy-D-galactose.

In contrast, the '3+3' approach demanded 1-nitro-2-propanol and a serine derived aldehyde for the construction of the hexose skeleton (Scheme 42). Careful control of the reaction conditions gave excellent yields and remarkable selectivities. The generation of the gulose derivative was achieved in 82% yield for a single diastereomer, whereas the *rhamnolido* ratio was 2:1 with a combined yield of 82%. Since the fully deprotected alcohols did not allow oxidation to the aldehyde in reasonable yields, selective cleavage of the acetonide using ion exchange resin and oxidation of the primary alcohol with o-iodoxybenzoic acid followed by acidic hydrolysis gave the free carbohydrates.



Scheme 42. Overview of the '3+3' approach.

Both approaches allow the crucial discrimination of the amine functionalities in the sugar. The galactose derivative enables differentiation after the reduction step, whereas the compounds from the '3+3' route can be distinguished *via* the oxidation states of the nitrogen.

The indium mediated chain elongation offers access to rare carbohydrate families. Using 2-(bromomethyl)acrylic ester, members of the 3-deoxy-2-nonulosonic acid family were synthesized. 2,4-Diacetamido-2,4,6-trideoxy-D-galactose served as starting molecule in the synthesis of the non-natural analogues 8-*epi*-pseudaminic acid and 4,8-*epi*-pseudaminic acid, respectively

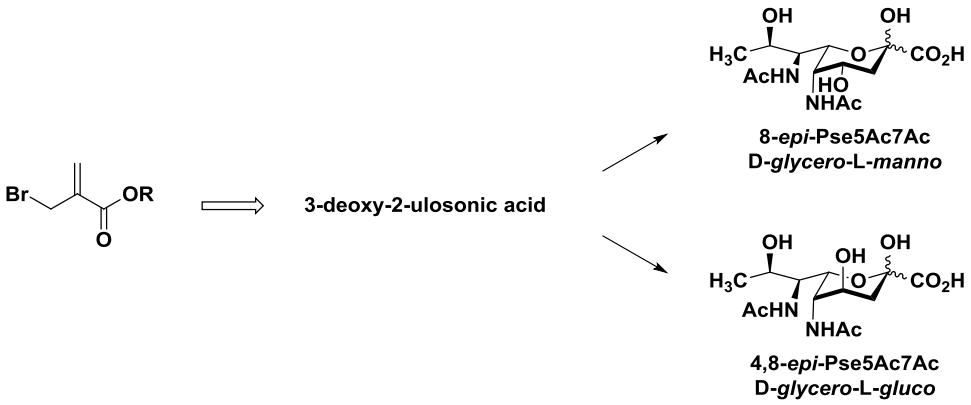


Figure 29. Strategy towards 3-deoxy-2-nonulosonic acids.

2-(Bromomethyl)prop-2-en-1-ol has been subjected to various starting materials in an indium mediated reaction to yield the biologically important reduced analogues of the ulosonic acids. Good yields and selectivities for the generation of the desired backbones were obtained throughout.

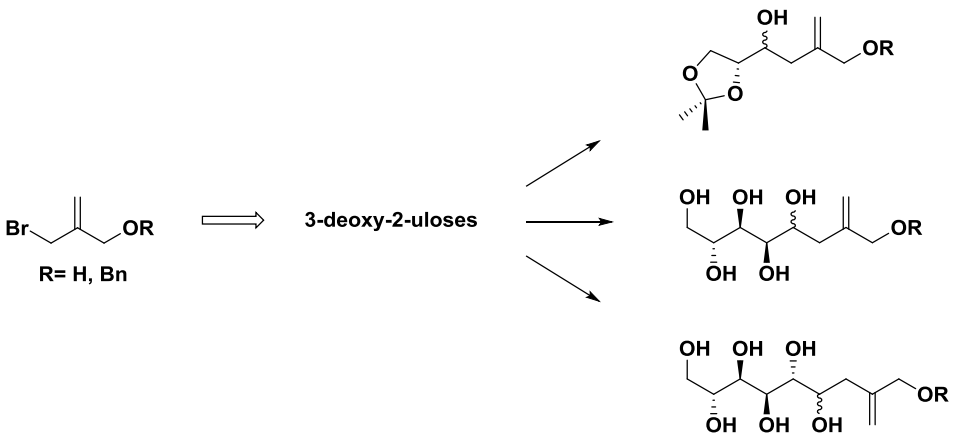


Figure 30. Strategy towards 3-deoxy-2-uloses.

OUTLOOK

The successful generation of the *gulo* and *rhamno* configurated backbones *via* the '3+3' approach allows the synthesis of natural bacterial sialic acids. However, in order to apply the allylation strategy, the nitro group has to be reduced prior to the indium mediated reaction. Since a reduction with the unprotected anomer of the carbohydrate will lead to an imino sugar, protecting groups have to be installed. Currently, two approaches are investigated. The first one addresses the selective derivatisation of the amine at C2 with various substituents to demonstrate the potential of the crucial nitrogen differentiation of these compounds. The introduction of an *N*-glycolyl group at C2 was achieved using acetoxyacetyl chloride. Subsequent protection of the hydroxyl groups will enable the reduction of the nitro functionality at C4.

Alternatively, the second route used a peracetylated derivative of compound **126** to directly access the 2,4-diacetamido compounds. Reaction with acetyl chloride was favorable, since basic reaction conditions led to decreasing yields and decomposition of the starting material. However, reductions with complex hydrides or hydrogen/metal systems (Pd, Ni) were not successful and metal mediated reductions (Zn, Fe, Sn, Sn^{2+}, Ni^{2+}) are currently investigated.

The indium mediated allylation generates a new chiral center during the elongation step, thus resulting in a diastereomeric mixture of products. Unfortunately, these compounds are hardly separable by standard column chromatography on silica gel. Consequently, purification has to be performed on HPLC systems either of the unprotected compounds or the acetylated derivatives, respectively. This limit of the methodology applied is currently under investigation in our laboratory and preliminary studies showed promising results.

ABSTRACT

Rare carbohydrates are essential molecules that regulate many biological processes. However, in many cases they are not accessible or isolatable from natural sources and chemical synthesis provides the predominant access of these molecules for investigations in the field of molecular biology. Especially polyamino-polydeoxy sugars are of great interest, since this class of carbohydrates regulates cell-cell and cell-environment communication, respectively.

Herein, we present two methodologies towards the *de novo* synthesis of these important sugars. We applied the well known nitroaldol reaction to amino acid derived aldehydes to generate the hexose backbones with various stereochemical configurations.

Thus, starting from L-threonine, the D-*galacto* configurated derivative was synthesized. This reaction strongly depended on the base and the solvent composition. The final deprotection of three different protecting groups to yield the free carbohydrate was achieved in an environmentally benign reaction using deionized water at elevated temperatures.

In order to expand the scope of this methodology, a second strategy was intended. The L-serine derived Garner's aldehyde served as starting material and 1-nitro-2-propanol was used for the generation of the backbone. Both enantiomers of the chiral nitro compound were successfully applied and gave excellent yields in the elongation step and the D-*gulo*, L-*rhamno* and L-*ido* configurations were obtained.

The indium mediated Barbier-type reaction of unprotected sugars is a powerful tool in carbohydrate chemistry. 2-(Bromomethyl)acrylic acid ethyl ester was used in a chain elongation reaction with 2,4-diacetamido-2,4,6-trideoxy-D-galactose (from our first project) to successfully synthesize two members of the 3-deoxy-2-nonulosonic acid family. Its reduced analogue, 2-(bromomethyl)prop-2-en-1-ol, was applied in the synthesis of various 3-deoxy-2-uloses with different chain lengths ranging from six to nine.

KURZFASSUNG

Höhere Kohlenhydrate sind essentielle Bestandteil des täglichen Lebens. Sie finden sich in vielen Organismen und unterschiedlichen Wirkungsstätten wieder. Im speziellen nehmen Polyamino-polydesoxyzucker durch ihre außergewöhnliche Position an den Enden von Glycokonjugaten der Zelloberfläche einzigartige Aufgaben im Bereich der Zellkommunikation wahr. Nicht zuletzt wegen dieser Bedeutung ist die Grundlagenforschung an diesen Molekülen im Fokus der Molekularbiologie. Um jedoch die ausreichende Versorgung mit diesen Kohlenhydraten zu gewährleisten, muss die Chemie entsprechende Verfahren der Synthese zur Verfügung stellen. Diese Dissertation beschäftigt sich zum einen mit zwei Synthesewegen, die durch eine Nitroaldolreaktion 2,4-Diamino-2,4,6-tridesoxyhexosen aufbauen, und im Folgenden mit der Synthese von 3-Desoxyzuckern.

Handelsübliche Aminosäuren dienten als Startmaterialien und wurden analog zum Protokoll von Garner *et al*. in Aldehyde transformiert. So lieferte L-Threonin nach der Reaktion mit 2-Nitroacetaldehyddiethylacetal ein D-*galacto* konfiguriertes Grundgerüst, welches auf elegante Weise zum freien Zucker umgesetzt werden konnte. Durch Erhitzen in entionisiertem Wasser konnten drei Schutzgruppen in einem einzigen Schritt abgespalten werden.

Der zweite Weg nützte L-Serin und 1-Nitro-2-propanol zum Aufbau des Zuckers. Beide Enantiomere des chiralen Alkohols fanden Verwendung und lieferten exzellente Ausbeuten. Auf diese Weise konnten D-*gulo*, L-*rhamno* und L-*ido* konfigurierte Derivate hergestellt werden.

Die Indium vermittelte Allylierung von Aldehyden bietet eine außergewöhnlich Möglichkeit um höhere Zucker zu synthetisieren. Sie toleriert ein breites Substratspektrum sowohl auf der Seite der Allylkomponente als auch auf Seite der Carbonylverbindung. 2-(Brommethyl)acrylsäureethylester wurde auf 2,4-Diacetamido-2,4,6-tridesoxy-D-galaktose angewendet und die Reaktion lieferte Zugang zu zwei Vertreter der biologisch äußerst wichtigen Nonulosonsäuren. Im Gegensatz dazu konnte mit Hilfe des reduzierten Analogons, dem 2-(Brommethyl)prop-2-en-1-ol, die Klasse der 3-Desoxy-2-ulosen synthetisiert werden. Verschiedene ungeschützte Zucker mit unterschiedlichen Kettenlängen wurden als Startmaterialien verwendet und ergaben die entsprechenden höheren Kohlenhydrate mit ausgezeichneten Ausbeuten und Selektivitäten.

ABBREVIATIONS

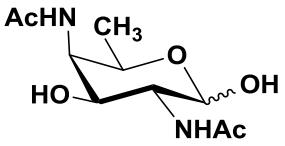
Ac	acetyl
Alt2Ac4Ac	2,4-diacetamido-2,4-dideoxy-D-altrose
AraN	4-amino-4-deoxy-L-arabinose
Bn	benzyl
Boc	*tert*-butyl carbamate
BuLI	*n*-butyl lithium
CM	cytoplasmic membrane
CMP	cytidine monophosphate
DAH	3-deoxy-D-arabino-heptulosonic acid
DCM	dichloromethane
DIBALH	diisobutylaluminium hydride
DMP	Dess Martin periodinane
DMSO	dimethylsulfoxide
equiv	equivalent
ESI	electrospray ionization
EtOH	ethanol
FAD	flavine adenine dinucleotide
Fru6P	D-fructose-6-phosphate
GalN	2-amino-2-deoxy-D-galactose
GalN	D-galactose
Glc	D-glucose
GlcN	D-glucosamine
GlcN6P	D-glucosamine-6-phosphat
GlcNAc	*N*-acetyl-D-glucosamine
GlcNAc6P	*N*-actyl-D-glucosamine-6-phosphate
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IBX	*ortho*-iodoxybenzoic acid
KDN	keto-deoxy neuraminic acid
KDO	3-deoxy-D-*manno*-2-octulosonic acid
Leg	legionaminic acid
Leg5Ac7Ac	5,7-di-*N*-acetyllegionaminic acid
LHMDS	lithium bis(trimethylsilyl)amide
LPS	lipopolysaccharide
Man	D-mannose
ManNAc	*N*-acetyl-D-mannosamine
MeOH	methanol
MOM	methoxymethyl
MurNAc	*N*-acetyl-D-muramic acid

NADPH	nicotinamide adenine dinucleotide phosphate
Neu5Ac	*N*-acetylneuraminic acid
NMR	nuclear magnetic resonance
NulO	nonulosonic acid
OPS	*O*-specific polysaccharide
PEP	phosphoenolpyruvate
PG	peptidoglycan
Pse	pseudaminic acid
Pse5Ac7Ac	5,7-di-*N*-acetylpseudaminic acid
RaNi	Rayney-nickel
Sia	sialic acid
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triehylamine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxy
THF	tetrahydrofurane
TLC	thin layer chromatography
UDP	uridine diphosphate

EXPERIMENTAL PROCEDURES OF SELECTED COMPOUNDS

General Methods

The NMR spectra were recorded either on a Bruker Avance DRX 400 at frequencies of 400.13 MHz for ^{1}H and 100.61 for ^{13}C or on a Bruker Avance III 600 at frequencies of 600.13 MHz for ^{1}H and at 150.90 MHz for ^{13}C, respectively. Multiplicities are assigned with s (singlet), d (doublet), t (triplet), q (quartet), br (broad signal) and cf (conformers show multiple signals in the spectrum). MS experiments were done on a Finnigan MAT 900 spectrometer. Flash chromatography was performed using Merck silica gel 60 (0.004-0.063 mm). TLC monitoring was done on Merck plates (silica gel 60 F254), compounds were visualized by treatment with a solution of ninhydrin (3 g in butanol (100 mL) / acetic acid (3 mL)), or with a solution of $(NH_4)_6Mo_7O_{24}.4H_2O$ (48 g) and $Ce(SO4)_2$ (2 g) in 10% H_2SO_4 (1 L) followed by heating. Solvents were distilled before use. Deionized water was purified using a Milli-Q® Reference A+ System. Optical rotations were measured on a Perkin Elmer Polarimeter 341. Chemicals were purchased in reagent grade.

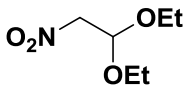


2,4-Diacetamido-2,4,6-trideoxy-D-galactose (31)

Compound **82** (3.15 g, 6.84 mmol) was dissolved in deionized water (3.15 L, *c* = 1 mg/mL) and refluxed for 12 hours using conventional heating in an oil bath. The solvent was removed and the crude product was purified by standard column chromatography (CH_2Cl_2/MeOH= 9:1, $R_{f(\mathbf{31})}$= 0.10) to obtain compound **31** as brownish solid. The free carbohydrate was dissolved in water (50 mL) and filtrated over an Isolute™ SPE column (MF C18, 500 mg) yielding **31** (623 mg, 2.53 mmol, 37 %).

$[\alpha]_D^{20}$ = +30.3 (*c* 5.7, H_2O); HRMS (ESI^+) *m/z* = 269.1117 $[M+Na]^+$ calcd. for $C_{10}H_{18}O_5N_2Na$: 269.1113.

^{1}H-NMR (D_2O, 600.13 MHz, ppm) α-anomer: δ_H 5.20 (dd, 1H, *J* = 3.7 Hz, *J* = 0.5 Hz, H-1) 4.36 (ddd, 1H, *J* = 6.5 Hz, *J* = 1.8 Hz, *J* = 0.5 Hz, H-5) 4.27 (dd, 1H, *J* = 4.4 Hz, *J* = 1.8 Hz, H-4) 4.07 (dd, 1H, *J* = 11.3 Hz, *J* = 4.4 Hz, H-3) 3.99 (dd, 1H, *J* = 11.3, Hz, *J* = 3.7 Hz, H-2) 2.11 (s, 3H, NC(O)$\underline{CH_3}$) 2.02 (s, 3H, NC(O)$\underline{CH_3}$) 1.10 (d, 3H, *J* = 6.5 Hz, H-6); β-anomer: δ_H 4.62 (d, 1H, *J* = 8.4 Hz, H-1) 4.23 (dd, 1H, *J* = 4.5 Hz, *J* = 1.5 Hz, H-4) 3.90 (dd, 1H, *J* = 6.4 Hz, *J* = 1.5 Hz, H-5) 3.86 (dd, 1H, *J* = 11.0 Hz, *J* = 4.5 Hz, H-3) 3.74 (dd, 1H, *J* = 11.0 Hz, *J* = 8,4 Hz, H-2) 2.10 (s, 3H, NC(O)$\underline{CH_3}$) 2.02 (s, 3H, N(O)$\underline{CH_3}$) 1.15 (d, 3H, *J* = 6.4 Hz, H-6); ^{13}C-NMR (D_2O, 150.90 MHz, ppm); α-anomer: δ_C 176.0 (N$\underline{C}$(O)CH_3) 175.0 (N$\underline{C}$(O)CH_3) 91.3 (C-1) 66.9 (C-3) 65.4 (C-5) 54.0 (C-4) 51.0 (C-2) 22.3 (NC(O)$\underline{CH_3}$) 22.2 (NC(O)$\underline{CH_3}$) 16.2 (C-6); β-anomer: δ_C 176.0 (N$\underline{C}$(O)CH_3) 175.3 (N$\underline{C}$(O)CH_3) 95.8 (C-1) 70.5 (C-3) 70.3 (C-5) 54.3 (C-2) 53.3 (C-4) 22.5 (NC(O)$\underline{CH_3}$) 22.2 (NC(O)$\underline{CH_3}$) 16.1 (C-6).

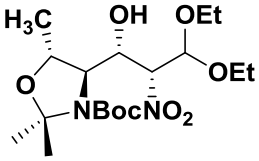


2-Nitroacetaldehyde diethylacetal (64)[111]

To a solution of triethyl orthoformate (50 mL, 0.3 mol) in nitromethane (80 mL, 1.49 mol, 5 equiv) anhydrous zinc chloride (2.5 g, 0.018 mol, 0.06 equiv) was added and the mixture was heated for 25 hours at 80 °C. The suspension was filtered twice through a folded filter and the liquid was concentrated at reduced pressure. Distillative purification (bp= 90 °C, 15 torr) yielded the desired compound (17.1 g, 0.105 mol, 35%) as colorless liquid.

The almost quantitative removal of solid was essential, since residual solid decreased the yield tremendously due to inclusions during distillation. Dilution with dichloromethane complicated the removal and aqueous extraction resulted in no phase separation.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.15 (t, *J* = 5.8 Hz, 1H, H1) 4.50 (d, *J* = 5.8 Hz, 2H, H2) 3.75 (dq, *J* = 7.0 Hz, *J* = 9.4 Hz, 2H, O$\underline{CH_2}CH_3$) 3.60 (dq, *J* = 7.0 Hz, *J* = 9.4 Hz, 2H, O$\underline{CH_2}CH_3$) 1.22 (t, *J* = 7.0 Hz, 6H, $OCH_2\underline{CH_3}$).

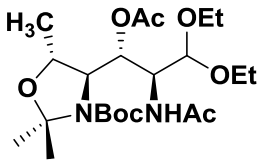


4-*N*-*tert*-Butyloxycarbonylamino-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-2-nitro-D-galactose diethylacetal (*syn*-78)

A sample of the diastereomeric mixture was separated after the nitro aldol reaction for the characterization of the intermediates of the major compound.

$[\alpha]_D^{20}$ = -24.6 (*c* 1.21, CH_2Cl_2); HRMS (ESI^+) *m/z* = 429.2216 $[M+Na]^+$ calcd. for $C_{18}H_{34}O_8N_2Na$ = 429.2213.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.10 (d, 1H, *J* = 7.3 Hz, H-1) 4.60 (dd, 1H, *J* = 2.6 Hz, *J* = 7.3 Hz, H-2) 4.25 (br, 1H, H-3) 4.15 (br, 1H, H-5) 3.91 (dd, 1H, *J* = 2.8 Hz, *J* = 5.3 Hz, H-4) 3.82 (qd, 1H, *J* = 7.0 HZ, *J* = 9.1 Hz, O$\underline{CH_2}CH_3$) 3.77 (qd, 1H, *J* = 7.0 HZ, *J* = 9.1 Hz, O$\underline{CH_2}CH_3$) 3.66 (qd, 2H, *J* = 7.0 Hz, *J* = 9.1 Hz, O$\underline{CH_2}CH_3$) 3.58 (qd, 2H, *J* = 7.0 Hz, *J* = 9.1 Hz, O$\underline{CH_2}CH_3$) 1.59 (br, 3H, C($\underline{CH_3}$)$_2$) 1.51 (s, 3H, C($\underline{CH_3}$)$_2$) 1.48 (s, 9H, C($\underline{CH_3}$)$_3$) 1.33 (d, 3H, *J* = 6.3 Hz, H-6) 1.24 (t, 3H, *J* = 7.0 Hz, OCH$_2\underline{CH_3}$) 1.17 (t, 3H, *J* = 7.0 Hz, OCH$_2\underline{CH_3}$); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 154.8 (cf, N$\underline{C}$(O)OC(CH$_3$)$_3$) 101.1 (C-1) 94.9 ($\underline{C}$(CH$_3$)$_2$) 88.5 (cf, C-2) 81.7 (cf, NC(O)$\underline{C}$(CH$_3$)$_3$) 71.9 (C-5) 69.3 (cf, C-3) 66.8 (cf, C-4) 65.4 (O$\underline{C}$H$_2$CH$_3$) 65.1 (O$\underline{C}$H$_2$CH$_3$) 28.7 (cf, C($\underline{C}$H$_3$)$_2$) 28.5 (C($\underline{C}$H$_3$)$_3$) 27.0 (cf, C($\underline{C}$H$_3$)$_2$) 20.4 (cf, C-6) 15.3 (OCH$_2\underline{C}$H$_3$) 15.2 (OCH$_2\underline{C}$H$_3$)

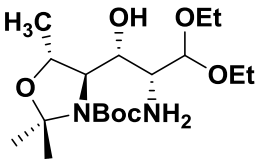


2-Acetamido-3-*O*-acetyl-4-*N*-*tert*-butyloxycarbonylamino-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-D-talose diethylacetal (*anti*-80)

The minor isomer was separated after the peracetylation step. For a detailed experimental procedure see compound **82**.

HRMS (ESI$^+$) *m/z* = 483.2680 [M+Na]$^+$ calcd. for $C_{22}H_{40}O_8N_2Na$: 483.2682.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.89 (br, 1H) 5.58 (br, 1H) 4.44 (br, 1H) 4.32 (br, 1H) 4.21 (br 1H) 3.80 (br, 2H) 3.54 (m, 2H) 3.37 (m, 1H) 2.08 (s, 3H) 2.02 (s, 3H) 1.56 (s, 3H) 1.50 (s, 9H) 1.39 (s, 6H) 1.18 (t, 6H); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 170.2 (C_q) 169.4 (C_q) 155.6 (CH) 93.9 (C_q) 80.4 (C_q) 71.8 (CH) 70.0 (CH) 64.6 (CH_2) 63.8 (CH) 63.2 (CH_2) 50.6 (CH) 29.3 (CH_3) 28.4 (C_3H_9) 27.7 (CH_3) 27.1 (CH_3) 23.5 (CH_3) 22.7 (CH_3) 21.2 (CH_3) 15.2 (CH_3) 14.9 (CH_3).

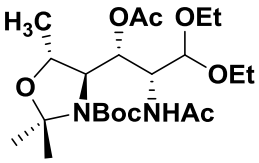


2-Amino-4-*N*-*tert*-butyloxycarbonylamino-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-D-galactose diethylacetal

For Experimental details see compound **82**.

$[\alpha]_D^{20}$ = -5.8 (*c* 0.92, CH_2Cl_2); HRMS (ESI^+) *m/z* = 377.2657 $[M+H]^+$ calcd. for $C_{18}H_{37}O_6N_2$ = 377.2652.

^{1}H-NMR ($CDCl_3$, 400.61 MHz, ppm) δ_H 4.45 (br, 1H, *J* = 6.6 Hz, H-1) 4.41 (m, 1H, H-5) 3.81-3.64 (m, 3H, H-3, O$\underline{CH_2}CH_3$) 3.61-3.49 (m, 3H, H-4, O$\underline{CH_2}CH_3$) 2.80 (d, 1H, *J* = 6.6 Hz, H-2) 1.62 (br, 3H, C($\underline{CH_3}$)$_2$) 1.48 (s, 9H, C($\underline{CH_3}$)$_3$) 1.43 (br, 3H, C($\underline{CH_3}$)$_2$) 1.31 (d, 3H, *J* = 6.5 Hz, H-6) 1.21 (t, 3H, *J* = 7.1 Hz, OCH$_2\underline{CH_3}$) 1.19 (t, 3H, *J* = 7.1 Hz, OCH$_2\underline{CH_3}$); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 153.8 (cf, N$\underline{C}$(O)OC(CH$_3$)$_3$) 104.3 (cf, C-1) 93.9 (cf, $\underline{C}(CH_3)_2$) 80.7 (NC(O)O$\underline{C}$(CH$_3$)$_3$) 75.1 (cf, C-5) 69.9 (cf, C-3) 65.1 (C-4) 64.9 (O$\underline{C}$H$_2$CH$_3$) 62.3 (cf, O$\underline{C}$H$_2$CH$_3$) 52.6 (C-2) 29.8 (cf, C($\underline{C}$H$_3$)$_2$) 28.7 (cf, C($\underline{C}$H$_3$)$_2$) 28.5 (NCOC($\underline{C}$H$_3$)$_3$) 22.1 (C-6) 15.5 (OCH$_2\underline{C}$H$_3$) 15.4 (OCH$_2\underline{C}$H$_3$).



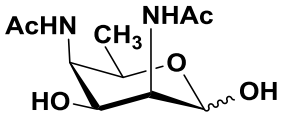
2-Acetamido-3-*O*-acetyl-4-*N*-*tert*-butyloxycarbonylamino-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-D-galactose diethylacetal (82)

Aldehyde **76**[112] (3.00 g, 12.33 mmol) and compound **64** (14.08 g, 86.31 mmol, 7 eq) were dissolved in a mixture of THF/H_2O= 3:2 (500 mL) and cooled to 0 °C. After addition of lithium hydroxide (30 mg, 0.1 eq), stirring was continued for 16 hours at 0 °C. The solvent was removed under reduced pressure and the residue was extracted with dichloromethane and washed with water. The organic phase was dried with $MgSO_4$ and the solvent was removed. The product was separated from the starting materials ($R_{f(\mathbf{64})}$= 0.67, $R_{f(\mathbf{76})}$= 0.59) using column chromatography on silica gel (hexanes/ethyl acetate= 4:1) yielding a mixture of diastereomers as pale yellow oil (3.71 g, 9.13 mmol 74 %, *galacto*/*talo*= 5:1, $R_{f(galacto)}$= 0.33, $R_{f(talo)}$= 0.46).

The diastereomeric mixture was dissolved in methanol (*c* = 10 mmol/L) and subjected to an H-Cube® hydrogenation reactor using a Raney nickel cartridge as catalyst. The reduction was performed using “full hydrogen”-mode with 0.7 mL/min flow at ambient temperature. After evaporation of the solvent, pyridine (3 mL/mmol), acetic acid anhydride (3 mL/mmol) and a catalytic amount of DMAP were added and the reaction was stirred over night at 0 °C. The solvent was removed and the crude product was dissolved in ethyl acetate and washed with water, followed by 0.5 N HCl and saturated NaCl-solution. The organic phase was dried over $MgSO_4$ and after removal of the solvent the diastereomeric mixture was obtained (3.78 g, 8.21 mmol, 90 %). The galactose derivative was purified using column chromatography on silica gel (hexanes:ethyl acetate= 1:2, $R_{f(\mathbf{82})}$= 0.17) yielding a pale yellow oil (3.15 g, 6.84 mmol, 56% from **76**).

$[\alpha]_D^{20}$ = -25.1 (*c* 3.45, CH_2Cl_2); HRMS (ESI^+) *m/z* = 483.2685 $[M+Na]^+$ calcd. for $C_{22}H_{40}O_8N_2Na$: 483.2682.

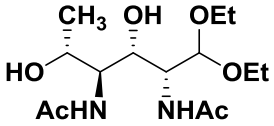
^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.77 (br, 2H, H-3, NHC(O)CH_3) 4.42 (br, 1H, H-5) 4.35 (br, 1H, H-1) 4.26 (ddd, 1H, *J* = 3.6 Hz, *J*= 4.0 Hz, *J* = 9.7 Hz, H-2) 3.79 (br, 1H, H-4) 3.68 (br, 1H, O$CH_2$$CH_3$) 3.59 (br, 1H, O$CH_2$$CH_3$) 3.47 (m, 2H, O$CH_2$$CH_3$) 2.04 (s, 3H, OC(O)$CH_3$) 1.98 (s, 3H, NC(O)$CH_3$) 1.54 (br, 3H, C($CH_3$)$_2$) 1.47 (br, 9H, C($CH_3$)$_3$) 1.36 (br, 3H, C($CH_3$)$_2$) 1.30 (d, 3H, *J* = 6.4 Hz, H-6) 1.16 (t, 3H, *J* = 7.1, OCH_2CH_3) 1.15 (t, 3H, *J* = 7.1, OCH_2CH_3); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 170.2 (OC(O)CH_3) 169.9 (NC(O)CH_3) 151.6 (cf, NC(O)C(CH_3)$_3$) 102.2 (C-1) 94.3 (cf, C(CH_3)$_2$) 80.6 (OC(CH_3)$_3$) 71.7 (cf, C-5) 70.0 (cf, C-3) 65.8 (C-4) 64.1 (cf, OCH_2CH_3) 62.9 (cf, OCH_2CH_3) 51.6 (C-2) 28.5 (C(CH_3)$_3$) 27.9 (cf, C(CH_3)$_2$) 26.9 (cf, C(CH_3)$_2$) 23.5 (NC(O)CH_3) 22.6 (cf, C-6) 21.3 (OC(O)CH_3) 15.3 (OCH_2CH_3) 15.2 (OCH_2CH_3);



2,4-Diacetamido-2,4,6-trideoxy-D-talose (*talo*-81)

The compound was synthesized according to compound **31**. The complex spectrum is in agreement with published data[74] and six different conformations can be assigned. Two pyranose conformations and 4 furanoses caused by the *N*-acetyl group on the hemiacetal forming nitrogen. For simplification, only the anomeric protons are listed.

^{1}H-NMR (D_2O, 600.13 MHz, ppm): δ_H 5.58 (β-fur, 3.5%) 5.51 (β-fur, 11.3%) 5.47 (α-fur, 12.1%) 5.38 (α-fur, 17.1%) 5.12 (α-pyr, 21.1%) 4.98 (β-pyr 34.9%).

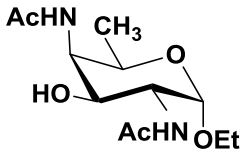


2,4-Diacetamido-2,4,6-trideoxy-D-galactose diethylacetal (83)

Compound **82** (100 mg, 0.22 mmol) was dissolved in water (c = 10 mg/mL) and stirred for 12 hours at 80 °C. After removal of the solvent, purification was performed on silica gel ($R_{f(\mathbf{83})}$= 0.61, CH_2Cl_2/MeOH= 9:1) to yield **83** as white solid (47 mg, 0.15 mmol, 68%).

$[\alpha]_D^{20}$ = -0.8 (*c* 1.2, H_2O); HRMS (ESI$^+$) *m/z* = 342.1841 $[M+Na]^+$ calcd. for $C_{14}H_{28}O_6N_2Na$ = 343.1845.

^{1}H-NMR (D_2O, 400.61 MHz, ppm) δ_H 4.68 (d, 1H, *J* = 7.2 Hz, H-1) 4.22 (dd, 1H, *J* = 1.2 Hz, *J* = 6.6 Hz, H-5) 4.18 (dd, 1H, *J* = 2.0 Hz, *J* = 10.1 Hz, H-3) 4.09 (dd, 1H, *J* = 2.0 Hz, *J* = 7.2 Hz, H-2) 3.90-3.75 (m, 2H, O$\underline{CH_2}CH_3$) 3.71-3.62 (m, 3H, O$\underline{CH_2}CH_3$, H-4) 2.04 (s, 3H, NC(O)$\underline{CH_3}$) 2.02 (s, 3H, NC(O)$\underline{CH_3}$) 1.26 (t, 3H, *J*= 7.1 Hz, $OCH_2\underline{CH_3}$) 1.19 (t, 3H, *J* = 7.1 Hz, $OCH_2\underline{CH_3}$) 1.14 (d, 3H, *J* = 6.6 Hz, H-6); ^{13}C-NMR (D_2O, 100.61 MHz, ppm) δ_C 173.9 (N$\underline{C}$(O)CH_3) 173.6 (N$\underline{C}$(O)CH_3) 102.6 (C-1) 67.9 (C-3) 65.1 (C-5) 64.7 (O$\underline{C}H_2CH_3$) 64.5 (O$\underline{C}H_2CH_3$) 54.9 (C-4) 52.0 (C-2) 22.1 (NC(O)$\underline{C}H_3$) 22.1 (NC(O)$\underline{C}H_3$) 19.3 (C-6) 14.6 ($OCH_2\underline{C}H_3$) 14.4 ($OCH_2\underline{C}H_3$).

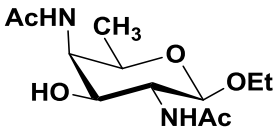


Ethyl-2,4-diacetamido-2,4,6-trideoxy-α-D-galactoside (84α)

Compound **84α** was isolated as a byproduct in the synthesis of **31**.

$R_{f(84\alpha)}$= 0.29 (CH_2Cl_2/MeOH= 9:1); HRMS (ESI^+) *m/z* = 297.1420 $[M+Na]^+$ calcd. for $C_{12}H_{22}O_5N_2Na$ = 297.1426.

$[\alpha]_D^{20}$ = +84.3 (c 2.1, H_2O); ^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H 4.87 (d, 1H, *J* = 3.5 Hz, H-1) 4.26 (m, 2H, H-4, H-5) 4.06 (dd, 1H, *J* = 3.8 Hz, *J* = 11.3 Hz, H-3) 4.03 (dd, 1H, *J* = 3.4 Hz, *J* = 11.3 Hz, H-2) 3.71 (qd, 1H, *J* = 7.1 Hz, *J*= 9.9 Hz, O$\underline{CH_2}CH_3$) 3.49 (qd, 1H, *J* = 7.1 Hz, *J* = 9.9 Hz, O$\underline{CH_2}CH_3$) 2.10 (s, 3H, NC(O)$\underline{CH_3}$) 2.02 (s, 3H, NC(O)$\underline{CH_3}$) 1.18 (t, 3H, *J* = 7.1 Hz, $OCH_2\underline{CH_3}$) 1.11 (d, 3H, *J* = 6.4 Hz, H-6); ^{13}C-NMR (D_2O, 150.90 MHz, ppm) δ_C 176.0 (N$\underline{C}$(O)CH_3) 174.9 (N$\underline{C}$(O)CH_3) 97.2 (C-1) 67.3 (C-3) 65.6 (C-5) 64.5 (O$\underline{C}H_2CH_3$) 53.9 (C-4) 50.6 (C-2) 22.2 (NC(O)$\underline{C}H_3$) 22.2 (NC(O)$\underline{C}H_3$) 15.9 ($OCH_2\underline{C}H_3$) 14.4 (C-6);

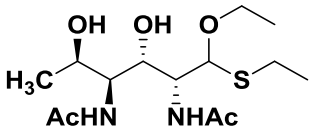


Ethyl-2,4-diacetamido-2,4,6-trideoxy-β-D-galactoside (84β)

Compound **84β** was isolated as a byproduct in the synthesis of **31**.

$R_{f(84\beta)}$= 0.18 (CH_2Cl_2/MeOH= 9:1); HRMS (ESI^+) *m/z* = 297.1422 $[M+Na]^+$ calcd. for $C_{12}H_{22}O_5N_2Na$ = 297.1426.

$[\alpha]_D^{20}$ = -51.9 (c 1.6, H_2O); ^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H 4.44 (d, 1H, *J* = 8.5, H-1) 4.23 (dd, 1H, *J* = 4.5 Hz, *J* = 1.6 Hz, H-4) 3.88 (qd, 1H, *J* = 1.6 Hz, *J*= 6.2 Hz, H-5) 3.87 (qd, 1H, *J* = 4.5 Hz, *J* = 11.0 Hz, O$\underline{CH_2}CH_3$), 3.86 (dd, 1H, *J* = 4.5 Hz, *J* = 11.0 Hz, H-3) 3.74 (dd, 1H, *J* = 11 Hz, *J* = 8.5 Hz, H-2) 3.65 (m, 1H, O$\underline{CH_2}CH_3$) 2.11 (s, 3H, NC(O)$\underline{CH_3}$) 2.02 (s, 3H, NC(O)$\underline{CH_3}$) 1.15 (d, 3H, *J* = 6.2 Hz, H-6) 1.14 (t, 3H, *J* = 7.1 Hz, $OCH_2\underline{CH_3}$); ^{13}C-NMR (D_2O, 150.90 MHz, ppm) δ_C 176.0 (N$\underline{C}$(O)CH_3) 175.2 (N$\underline{C}$(O)CH_3) 101.8 (C-1) 70.5 (C-3) 70.3 (C-5) 66.9 (O$\underline{CH_2}CH_3$) 53.3 (C-4) 53.2 (C-2) 22.5 (NC(O)$\underline{CH_3}$) 22.2 (NC(O)$\underline{CH_3}$) 16.0 (C-6) 14.6 ($OCH_2\underline{CH_3}$);



2,4-Diacetamido-2,4,6-trideoxy-D-galactose diethylhemithioacetal (86)

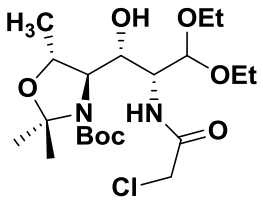
Compound **82** (100 mg, 0.22 mmol) was dissolved in ethyl mercaptane (5 mL) and heated to reflux for 3 hours. The solvent was removed and the product was purified using standard chromatography an silica gel (hexanes/ethyl acetate = 1:4, $R_{f(\mathbf{85})}$= 0.63) yielding a mixture of diastereomers (71 mg, 0.15 mmol, 68%). The mixture was dissolved in water (20 mL) and stirring was continued for 16 hours at 80 °C. After evaporation of the solvent, column chromatography on silica gel ($R_{f(\mathbf{86})}$= 0.54-0.66, dichloromethane/methanol= 19:1) yielded **86** as a diastereomeric mixture (0.8:1, 32 mg, 0.09 mmol, 61%).

HRMS (ESI$^+$) *m/z* = 375.1380 $[M+Na]^+$ calcd. for $C_{14}H_{28}O_4N_2S_2Na$: 375.1388.

^{1}H-NMR (D_2O, 400.13 MHz, ppm) δ_H 4.81 (CH) 4.76 (CH) 4.29 (CH) 4.26 (CH) 4.23(CH) 4.26 (CH) 4.14 (CH) 4.06 (CH_2) 3.95 (CH_2) 3.82 (CH_2) 3.80 (CH) 3.69 (CH_2) 3.67 (CH_2) 3.66 (CH_2) 2.69 (CH_2) 2.12 (CH_3) 2.08 (CH_3) 2.04 (CH_3) 2.01 (CH_3) 1.26 (CH_3) 1.18 (CH_3) 1.14 (CH_3); ^{13}C-NMR (D_2O, 100.61 MHz, ppm) δ_C 175.0 (C_q) 174.5 (C_q) 174.3 (C_q) 173.9 (C_q) 87.1 (CH) 85.7 (CH) 69.2 (CH) 67.8 (CH) 67.5 (CH) 65.6 (CH) 65.5 (CH_2) 65.1 (CH_2) 56.9 (CH) 55.5 (CH) 54.0 (CH) 53.0 (CH) 24.5 (CH_2) 24.0 (CH_2) 22.4 (CH_3) 22.3 (CH_3) 19.6 (CH_3) 19.5 (CH_3) 14.7 (CH_3) 14.5 (CH_3).

Experimental procedure of the deprotection of compound 86

Compound **86** (32 mg, 0.09 mmol) was dissolved in aqueous acetone (5 mL, 95% acetone, 5% water) and a solution of *N*-bromophtalimide (48 mg, 0.21 mmol, 2.4 equiv) in the same solvent (2 mL) was added dropwise. After the resulting yellow color had disappeared, the solvent was removed under reduced pressure and the residue was dissolved in water. Extraction with dichloromethane removed the phtalimide quantitatively as proven *via* TLC with UV-detection. The water was evaporated and the product (7 mg, 0.028 mmol, 31% (for **31**), **31**/**84**= 1:1) was purified on silica gel (dichloromethane/methanol= 4:1, $R_{f(\mathbf{31})}$= 0.10, $R_{f(\mathbf{84\beta})}$= 0.18, $R_{f(\mathbf{84\alpha})}$= 0.29).

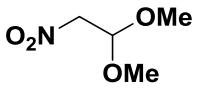


2-*N*-Chloracetamido-4-*N*-*tert*-butyloxycarbonylamino-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-D-galactose diethylacetal (88)

Compound *syn*-**78** was dissolved in methanol (*c* = 10 mmol/L) and subjected to an H-Cube® hydrogenation reactor using a Raney nickel cartridge as catalyst. The reduction was performed using "full hydrogen"-mode with 0.7 mL/min flow at ambient temperature. After evaporation, the reduced compound (70 mg, 0.19 mmol), pyridine (5 mL) and chloroacetic anhydride (155 mg, 0.91 mmol, 4.8 equiv) were added and the mixture was stirred for 20 min at 0 °C. Excess of anhydride was hydrolyzed with water and the product was extracted with dichloromethane. The solvent was removed under reduced pressure to yield crystalline **88** in sufficient purity (60 mg, 0.15 mmol, 81%).

HRMS (ESI$^+$) *m/z*= 475.2180 $[M+Na]^+$ calcd. for $C_{20}H_{37}N_2O_7ClNa$: 475.2187.

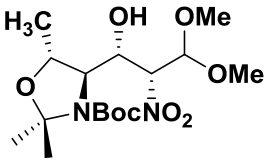
^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 4.61 (d, *J* = 3.5 Hz, 1H, H1) 4.48 (m, 1H, H5) 4.30 (m, 1H, H3) 4.05 (s, 2H, C(O)C$\underline{H}_2$Cl) 3.94 (dd, *J* = 3.5 Hz, *J* = 8.2 Hz, 1H, H2) 3.81 (m, 1H, $\underline{CH}_2CH_3$) 3.73 (m, 1H, $\underline{CH}_2CH_3$) 3.69 (m, 1H, H4) 3.58 (m, 1H, $\underline{CH}_2CH_3$) 3.50 (m, 1H, $\underline{CH}_2CH_3$) 1.59 (s, 3H, C(C$\underline{H}_3$)$_2$) 1.49 (s, 9H, OC(C$\underline{H}_3$)$_3$) 1.47 (s, 3H, C(C$\underline{H}_3$)$_2$) 1.29 (d, *J* = 6.1 HZ, 3H, H6) 1.21 (t, *J* = 7.2 Hz, 6H, $CH_2\underline{CH}_3$); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 165.8 ($\underline{C}$(O)CH_2Cl) 153.7 (N$\underline{C}$(O)O) 103.5 (C1) 94.5 ($\underline{C}$(CH$_3$)$_2$) 80.8 (O$\underline{C}$(CH$_3$)$_3$) 73.0 (C5) 68.5 (C3) 66.4 (C4) 65.5 (O$\underline{CH}_2$CH$_3$) 64.3 (O$\underline{CH}_2$CH$_3$) 51.7 (C2) 42.8 (C(O)$\underline{C}$H$_2$Cl) 28.9 (OC($\underline{C}$H$_3$)$_3$) 28.4 (C($\underline{C}$H$_3$)$_2$) 27.6 (OC($\underline{C}$H$_3$)$_3$) 20.8 (C6) 15.3 (OCH$_2\underline{C}$H$_3$).



2-Nitroacetaldehyde dimethylacetal (92)

Trimethyl orthoformate (10 mL, 91 mmol) was dissolved in nitromethane (50 mL, 0.93 mol, 10 equiv) and anhydrous zinc chloride (1 g, 7.3 mmol, 0.08 equiv) was added and the mixture was heated for 25 hours at 80 °C. The work up was performed as for compound **64** and distillation yielded the desired compound (2.6 g, 19.2 mmol, 21%) as colorless liquid.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.07 (t, *J* = 5.7 Hz, 1H, H1) 4.53 (d, *J* = 5.7 Hz, 2H, H2) 3.47 (s, 6H, O$\underline{C}H_3$).

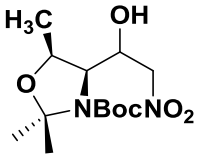


4-*N*-*tert*-Butyloxycarbonylamino-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-2-nitro-D-galactose dimethylacetal

Compound **76** (274 mg, 1.13 mmol) and 2-nitroacetaldehyde dimethylacetal (**92**, 837 mg, 6.2 mmol, 5.5 equiv) were dissolved in tetrahydrofurane/water (2:1, 20 mL). The mixture was cooled to 0 °C, LiOH (5 mg) was added and stirring was continued overnight. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic phase was washed with water and saturated NaCl-solution and dried over $MgSO_4$. The crude product was purified on silica gel to yield the target compound (209 mg, 0.55 mmol, 49%, galacto/talo = 3:1) as pale yellow oil.

$[\alpha]_D^{20}$= -15.7 (*c* 1.9, dichloromethane); HRMS (ESI$^+$) *m/z*= 401.1902 $[M+Na]^+$ calcd. for $C_{16}H_{30}N_2O_8Na$: 401.1900.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 4.97 (d, *J* = 7.6 Hz, 1H, H1) 4.60 (dd, *J* = 3.2 Hz, *J* = 7.6 Hz, 1H, H2) 4.25 (m, 1H, H3) 4.14 (m, 1H, H5) 3.89 (dd, *J* = 2.8 Hz, *J* = 5.2 Hz, 1H, H4) 3.50 (s, 3H, OC$\underline{H}_3$) 3.45 (s, 3H, OC$\underline{H}_3$) 2.94 (s, 3H, C(C$\underline{H}_3$)$_2$) 2.90 (s, 3H, C(C$\underline{H}_3$)$_2$) 1.48 (s, 9H, OC(C$\underline{H}_3$)$_3$) 1.33 (d, *J* = 6.3 Hz, 3H, H6); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 153.9 (N$\underline{C}$(O)O) 102.7 (C1) 95.0 ($\underline{C}$(CH$_3$)$_2$) 88.0 (C2) 81.6 (O$\underline{C}$(CH$_3$)$_3$) 71.8 (C5) 69.2 (C3) 66.7 (C4) 56.4 (O$\underline{C}$H$_3$) 56.1 (O$\underline{C}$H$_3$) 28.7 (C($\underline{C}$H$_3$)$_2$) 28.4 (OC($\underline{C}$H$_3$)$_3$) 27.0 (C($\underline{C}$H$_3$)$_2$) 20.7 (C6).



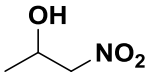
3-*N*-*tert*-Butyloxycarbonylamino-1,3,5-trideoxy-3-*N*,4-*O*-isopropylidene-1-nitro-L-ribo/arabino (98)

Aldehyde **89**[113] (250 mg, 1.03 mmol) was dissolved in tetrahydrofurane and nitromethane (275 µL, 5.14 mmol, 5 equiv) followed by the addition of TBAF (0.2 mL 1M in THF, 0.2 equiv). The reaction was stirred for 2 hours, the solvent was removed and the crude product was dissolved in dichloromethane. The solution was washed with water and saturated NaCl-solution and dried over $MgSO_4$. After evaporation of the solvent, the product was purified on silica gel (hexanes/ethyl acetate= 4:1) to give the desired product as an inseparable mixture of diastereomers (*syn*/*anti*= 1:1, 210 mg, 0.7 mmol, 67%).

HRMS (ESI$^+$) *m/z*= 475.2180 $[M+Na]^+$ calcd. for $C_{20}H_{37}N_2O_7ClNa$: 475.2187.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.43 (OH) 4.52 (CH) 4.46 (CH_2) 4.38 (CH) 4.31 (CH_2) 1.53 (CH_3) 1.51 (CH_3) 1.51 ((CH_3)$_3$) 1.40 (CH_3); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 155.3 (C_q) 93.2 (C_q) 82.6 (C_q) 80.3 (CH_2) 71.0 (CH) 69.7 (CH) 63.4 (CH) 28.3 ((CH_3)$_3$) 26.6 (CH_3) 23.8 (CH_3) 14.7 (CH_3).

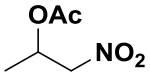
^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 4.58 (CH_2) 4.57 (CH) 4.39 (CH_2) 4.33 (CH) 4.17 (CH) 3.96 (CH) 2.85 (OH) 1.62 (CH_3) 1.56 (CH_3) 1.49 ((CH_3)$_3$) 1.46 (CH_3); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 155.1 (C_q) 93.5 (C_q) 81.4 (C_q) 80.1 (CH_2) 72.0 (CH) 69.1 (CH) 60.4 (CH) 28.3 ((CH_3)$_3$) 26.8 (CH_3) 24.5 (CH_3)14.6 (CH_3).



1-Nitro-2-propanol (105)

Acetic aldehyde (1.8 g, 0.041 mol) was dissolved in water (50 mL) and nitromethane (10 mL, 0.19 mol, 4.5 equiv), tetrabutylammonium iodide (150 mg, 0.41 mmol, 0.01 equiv) and caesium carbonate (100 mg, 0.3 mmol, 0.007 equiv) were added and stirred for 5 days at 0 °C. The reaction mixture was extracted several times with diethyl ether and the combined organic phases were dried over $MgSO_4$. Careful evaporation of the solvent gave the crude product, which was purified using standard column chromatography on silica gel (dichloromethane, R_f= 0.15) to yield racemic **105** as colourless liquid (3.2 g, 0.03 mol, 74%). Spectroscopical data agree with data reported.[101]

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 4.51 (m, 1H, H2) 4.42 (dd, *J* = 3.2 Hz, *J* = 13.3 Hz, 1H, H1a) 4.36 (dd, *J* = 8.3 Hz, *J* = 13.3 Hz, 1H, H1b) 2.52 (m, 1H, OH) 1.31 (d, *J* = 6.5 Hz, 3H, H3).

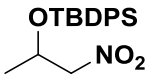


2-*O*-Acetyl-1-nitro-2-propanol (109)

Enzymatic procedure: To a solution of **105** (295 mg, 2.8 mmol) in tetrahydrofurane (5 mL), vinyl acetate (10 mL) and lipase from *Candida Rugosa* (44 mg) were added and the mixture was shaken for 7 days. The solution was filtered and the resulting crude product was purified on silica gel (hexanes/ethyl acetate= 4:1). $[\alpha]_D^{20}$ = 18 (*c* 8.0, $CHCl_3$; lit: 40.7 for (*R*)).[104]

Chemical procedure: Compound **105** (417 mg, 4.0 mmol) was dissolved in dichloromethane (5 mL) and acetic anhydride (0.4 mL) and pyridine (0.4 mL) were added. The solution was stirred overnight at 0 °C to give compound **109** (71 mg, 0.48 mmo, 12%) after purification on silica gel (hexanes/ethyl acetate= 4:1).

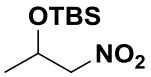
^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.52 (m, 1H, H2) 4.54 (dd, *J* = 7.9 Hz, *J* = 12.9 Hz, 1H, H1a) 4.46 (dd, *J* = 3.8 Hz, *J* = 12.9 Hz, 1H, H1b) 2.06 (s, 3H, CH_3) 1.37 (d, *J* = 6.5 Hz, 3H, H3).



2-*O*-*tert*-Butyldiphenylsilyl-1-nitro-2-propanol (112)

A solution of **105** (500 mg, 4.8 mmol), *tert*-butyldiphenylchlorosilane (1.4 g, 5.1 mmol, 1.1 equiv) and imidazol (350 mg, 5.1 mmol, 1.1 equiv) in dichloromethane (25 mL) was stirred overnight and compound **112** (1.04 g, 3 mmol, 64%) could be isolated after purification on silica gel (hexanes/ethyl acetate= 9:1).

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 7.69-7.57 (m, 10H, H_{ar}) 4.42 (m, 1H, H2) 4.34 (dd, *J* = 7.1 Hz, *J* = 11.2. Hz, 1H, H1a) 4.17 (dd, *J* = 3.9 Hz, *J* = 11.2. Hz, 1H, H1b) 1.05 (d, *J* = 6.3 HZ, 3H, H3) 0.95 (s, 9H, $C(C\underline{H}_3)_3$).



2-*O*-*tert*-Butyldimethylsilyl-1-nitro-2-propanol (113)

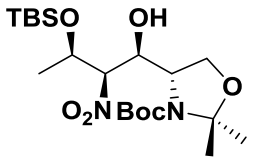
Compound **105** (3.2 g, 0.03 mol, 1 equiv) and *tert*-butyldimethylchlorosilane (4.97 g, 0.033 mol, 1.1 equiv) were suspended in dichloromethane (50 mL). After addition of imidazol (2.25 g, 0.033 mol, 1.1 equiv) the resulting mixture was stirred overnight at room temperature. The precipitate was removed by filtration and the solvent was removed under reduced pressure. Purification was performed using standard column chromatography on silica gel (ethyl acetate/hexanes= 1:4, R_f= 0.73) and yielded racemic **113** (6.38 g, 0.029 mol, 97%) as pale yellow oil. The separation of the enantiomers was achieved using chiral HPLC on a Chiracel® OD-H stationary phase (hexanes/2-propanol= 98:2). The (*R*)-**113** enantiomer eluted first ($[\alpha]_D^{20}$ = -43.7 (*c* 8.4, $CHCl_3$)) followed by (*S*)-**113** ($[\alpha]_D^{20}$ = +40.5 (*c* 6.5, $CHCl_3$)). The absolute configuration was determined by comparson with data reported.[104]

HRMS (ESI^+) *m/z*= 242.1191 $[M+Na]^+$ calcd. for $C_9H_{21}NO_3SiNa$: 242.1188.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 4.54 (m, 1H, H2) 4.34 (dd, *J* = 8.7 Hz, *J* = 11.4. Hz, 1H, H1a) 4.27 (dd, *J* = 3.2 Hz, *J* = 11.4. Hz, 1H, H1b) 1.23 (d, *J* = 6.4 HZ, 3H, H3) 0.85 (s, 9H, $C(C\underline{H}_3)_3$) 0.07 (s, 3H, $Si(C\underline{H}_3)_2$) 0.03 (s, 3H, $Si(C\underline{H}_3)_2$);

General procedure for the nitroaldol reaction

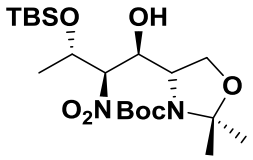
To a solution of aldehyde **106** (1.0 g, 4.36 mmol) in anhydrous tetrahydrofurane (60 mL) compound **113** (4.6 g, 21 mmol, 4.8 equiv) was added and cooled to -50 °C using a dry ice cooling bath. After the addition of tetrabutylammonium fluoride (0.5 mL 1M in THF, 0.12 equiv), the solution was stirred until the starting material disappeared (2-5 hours, ethyl acetate/hexanes= 1:4, $R_{f(\mathbf{106})}$= 0.34, $R_{f(\mathbf{113})}$= 0.71) while the temperature did not raise over -30 °C. After completion of the reaction, the solvent was removed under reduced pressure at 30 °C and the resulting residue was dissolved in ethyl acetate. The solution was washed with water and brine. The organic phase was dried over $MgSO_4$. Evaporation of the organic solvent yielded the crude product, which was purified using standard column chromatography on silica gel (ethyl acetate/hexanes= 4:1).



5-*O*-*tert*-Butyldimethylsilyl-2-*N*-*tert*-butyloxycarbonylamino-1-*O*,2-*N*-isopropylidene-4-nitro-2,4,6-trideoxy-D-gulitol (*gulo*-114)

$R_{f(gulo\text{-}\mathbf{114})}$= 0.46 (hexanes/ethyl acetate= 4:1; colourless oil (1.6 g, 3.57 mmol, 82%); HRMS (ESI$^+$) *m/z*= 471.2502 $[M+Na]^+$ calcd. for $C_{20}H_{40}N_2O_7SiNa$: 471.2502.

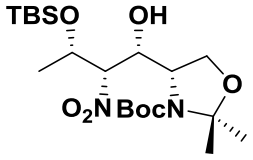
$[\alpha]_D^{20}$= -2.5 (*c* 7.4, dichloromethane); ^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 4.53 (dq, *J* = 6.2 Hz, *J* = 6.6 Hz, 1H, H5) 4.39 (m, 1H, H4) 4.21 (ddd, *J* = 3.5 Hz, *J* = 4.1 Hz, 1H, H3) 4.19 (m, 1H, H2) 3.97 (dd, *J* = 1.3 Hz, *J* = 9.9 Hz, 1H, H1a) 3.92 (m, 1H, H1b) 3.32-2.86 (2 bs (cf), 1H, OH) 1.57 (s, 3H, $C(C\underline{H}_3)_2$) 1.48 (s, 9H, $OC(C\underline{H}_3)_3$) 1.47 (s, 3H, $C(C\underline{H}_3)_2$) 1.32 (d, *J* = 6.2 Hz, 3H, H6) 0.85 (s, 9H, $SiC(C\underline{H}_3)_3$) 0.08 (s, 3H, $Si(C\underline{H}_3)_2$) 0.04 (s, 3H, $Si(C\underline{H}_3)_2$); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 153.4 ($N\underline{C}(O)O$) 94.2 ($\underline{C}(CH_3)_2$) 93.5 (C4) 81.3 ($O\underline{C}(CH_3)_3$) 69.9 (C3) 68.6 (C5) 63.4 (C1) 59.6 (C2) 28.5 ($OC(\underline{C}H_3)_3$) 27.0 ($C(\underline{C}H_3)_2$) 25.8 ($SiC(\underline{C}H_3)_3$) 24.1 ($C(\underline{C}H_3)_2$) 20.2 (C6) 18.1 ($Si\underline{C}(CH_3)_3$) -4.4 ($Si(C\underline{H}_3)_2$) -5.2 ($Si(C\underline{H}_3)_2$).



5-*O*-*tert*-Butyldimethylsilyl-2-*N*-*tert*-butyloxycarbonylamino-1-*O*,2-*N*-isopropylidene-4-nitro-2,4,6-trideoxy-L-rhamnitol (*rhamno*-114)

$R_{f(rhamno\text{-}114)}$= 0.54 (hexanes/ethyl acetate= 4:1; white solid (1.08 g, 2.4 mmol, 55%); HRMS (ESI^+) *m/z*= 471.2497 $[M+Na]^+$ calcd. for $C_{20}H_{40}N_2O_7SiNa$: 471.2502.

$[\alpha]_D^{20}$= -3.4 (*c* 0.75, dichloromethane); ^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 4.63 (m, 1H, H5) 4.37 (m, 1H, H4) 4.28 (m, 1H, H2) 4.20 (m, 1H, H3) 4.16 (m, 1H, H1a) 3.92 (dd, *J* = 5.9 Hz, *J* = 9.2 Hz, 1H, H1b) 3.58 (s, 1H, OH) 1.56 (s, 3H, $C(C\underline{H}_3)_2$) 1.50 (s, 3H, $C(C\underline{H}_3)_2$) 1.47 (s, 9H, $OC(C\underline{H}_3)_3$) 1. 1.31 (d, *J* = 6.3 Hz, 3H, H6) 0.87 (s, 9H, $SiC(C\underline{H}_3)_3$) 0.11 (s, 3H, $Si(C\underline{H}_3)_2$) 0.10 (s, 3H, $Si(C\underline{H}_3)_2$); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 153.4 ($N\underline{C}(O)O$) 94.7 ($\underline{C}(CH_3)_2$) 91.2 (C4) 81.6 ($O\underline{C}(CH_3)_3$) 69.9 (C5) 68.8 (C3) 64.1 (C1) 59.8 (C2) 28.8 ($OC(\underline{C}H_3)_3$) 27.8 ($C(\underline{C}H_3)_2$) 26.0 ($SiC(\underline{C}H_3)_3$) 26.0 ($C(\underline{C}H_3)_2$) 21.0 (C6) 18.2 ($Si\underline{C}(CH_3)_3$) -4.2 ($Si(C\underline{H}_3)_2$) -4.9 ($Si(C\underline{H}_3)_2$).



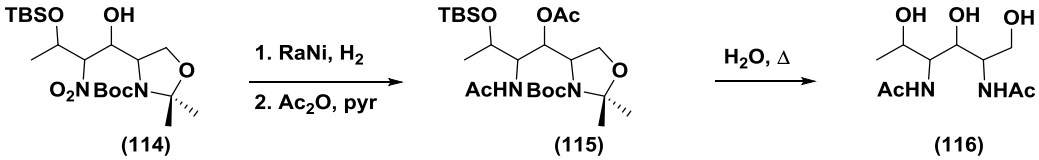
5-*O*-*tert*-Butyldimethylsilyl-2-*N*-*tert*-butyloxycarbonylamino-1-*O*,2-*N*-isopropylidene-4-nitro-2,4,6-trideoxy-L-iditol (*ido*-114)

$R_{f(ido\text{-}114)}$= 0.41 (hexanes/ethyl acetate= 4:1; colourless oil (528 mg, 1.18 mmol, 27%); HRMS (ESI^+) *m/z*= 471.2504 $[M+Na]^+$ calcd. for $C_{20}H_{40}N_2O_7SiNa$: 471.2502.

$[\alpha]_D^{20}$= -10.4 (*c* 7.0, dichloromethane); ^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 4.53 (m, 1H, H5) 4.40 (m, 1H, H4) 4.20 (m, 1H, H3) 4.14 (m, 1H, H2) 4.08 (m, 1H, H1a) 3.94 (m, 1H, H1b) 3.49 (m, 1H, OH) 1.57 (s, 3H, $C(C\underline{H}_3)_2$) 1.49 (s, 9H, $OC(C\underline{H}_3)_3$) 1.48 (s, 3H, $C(C\underline{H}_3)_2$) 1.38 (d, *J* = 5.9 Hz, 3H, H6) 0.85 (s, 9H, $SiC(C\underline{H}_3)_3$) 0.08 (s, 3H, $Si(C\underline{H}_3)_2$) 0.07 (s, 3H, $Si(C\underline{H}_3)_2$); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 94.2 ($\underline{C}(CH_3)_2$) 92.8 (C4) 81.3 ($O\underline{C}(CH_3)_3$) 69.7 (C3) 67.6 (C5) 63.4 (C1) 59.5 (C2) 28.3 ($OC(\underline{C}H_3)_3$) 27.0 ($C(\underline{C}H_3)_2$) 25.6 ($SiC(\underline{C}H_3)_3$) 23.8 ($C(\underline{C}H_3)_2$) 21.1 (C6)17.8 ($Si\underline{C}(CH_3)_3$) -4.6 ($Si(C\underline{H}_3)_2$) -5.3 ($Si(C\underline{H}_3)_2$).

General procedure for the synthesis of 116

Compound **114** was dissolved in methanol (*c* = 1 mg/mL) and the reduction was performed in an H-Cube® hydrogenation flow reactor using a Raney-nickel cartridge as catalyst (full hydrogen mode, flow= 0.7 mL/min). The solvent was removed and gave the desired compounds in excellent yields (93-98%).

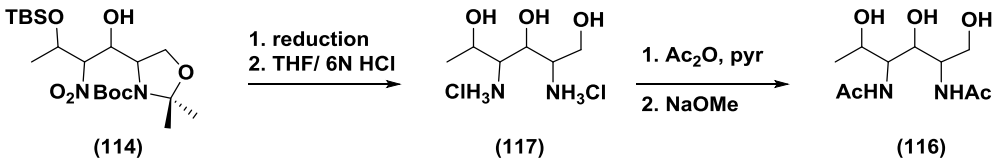


Route A): acetylation - deprotection

The crude product was dissolved in acetic anhydride/pyridine (1:1, *c* = 5 mL/mmol) and stirring was continued overnight to yield a mixture of compounds. Standard column chromatography on silica gel (hexanes/ethyl acetate= 2:1) was used to obtain the target compound. Compound **115** was deprotected using deionized water (*c* = 1 mg/mL) at 100 °C for 8 hours to give the target **116** (Table 10).

entry	starting material	product	yield [%]
1	*gulo*-**114**	*gulo*-**115**	31
2	*rhamno*-**114**	*rhamno*-**115**	28
3	*ido*-**114**	*ido*-**115**	35
4	*gulo*-**115**	*gulo*-**116**	82
5	*rhamno*-**115**	*rhamno*-**116**	69
6	*ido*-**115**	*ido*-**116**	73

Table 10. Yields obtained for route A.



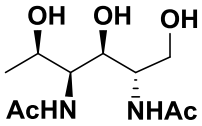
(114) (117) (116)

Route B): deprotection - acetylation

The crude product was stirred for 6 hours in a mixture of hydrochloric acid (6 N)/tetrahydrofurane (1:1). After evaporation, the product mixture was dissolved in deionized water. Subsequent neutralization was achieved with sodium hydroxide (0.5 N). The solvent was removed and the crude product was peracetylated using standard conditions (acetic anhydride/pyridine= 1:1, 5 mL/mmol). The crude compound was subjected to Zemplèn saponifiaction conditions using a catalytic amount of sodium methoxide in methanol to yield the 2,4-diacetamido derivative **116** (Table 11). Purification was achieved on silica gel (dichloromethane/methanol= 4:1).

entry	starting material	product	yield [%]
1	*gulo*-**114**	*gulo*-**117**	95
2	*rhamno*-**114**	*rhamno*-**117**	98
3	*ido*-**114**	*ido*-**117**	93
4	*gulo*-**117**	*gulo*-**116**	64
5	*rhamno*-**117**	*rhamno*-**116**	45
6	*ido*-**117**	*ido*-**116**	43

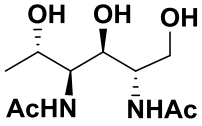
Table 11. Yields obtained for route B.



2,4-Diacetamido-2,4,6-trideoxy-D-gulitol (*gulo*-116)

$R_{f(gulo\text{-}\mathbf{116})}$= 0.16 (dichloromethane/methanol= 4:1); HRMS (ESI^+) *m/z*= 271.1265 $[M+Na]^+$ calcd. for $C_{10}H_{20}N_2O_5Na$: 271.1270.

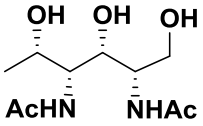
$[\alpha]_D^{20}$= -27.4 (*c* 1.6, H_2O); ^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H 3.99 (m, 1H, H3) 3.99 (m, 1H, H5) 3.83 (m, 1H, H4) 3.82 (m, 1H, H2) 3.73 (dd, *J* = 3.4 Hz, *J* = 11.8 Hz, H1a) 3.68 (dd, *J* = 5.4 Hz, *J* = 11.8 Hz, H1b) 2.02 (s, 3H, C(O)C$\underline{H_3}$) 1.96 (s, 3H, C(O)C$\underline{H_3}$) 1.20 (d, *J* = 6.5 Hz, 3H, H6); ^{13}C-NMR (D_2O, 150.90 MHz, ppm) δ_C 174.1 ($\underline{C}$(O)CH_3) 173.5 ($\underline{C}$(O)CH_3) 69.6 (C3) 68.6 (C5) 54.7 (C4) 52.2 (C2) 22.0 (C(O)$\underline{C}H_3$) 21.9 (C(O)$\underline{C}H_3$) 19.1 (C6).



2,4-Diacetamido-2,4,6-trideoxy-L-rhamnitol (*rhamno*-116)

$R_{f(rhamno\text{-}\mathbf{116})}$= 0.12 (dichloromethane/methanol= 4:1); HRMS (ESI^+) *m/z*= 271.1267 $[M+Na]^+$ calcd. for $C_{10}H_{20}N_2O_5Na$: 271.1270.

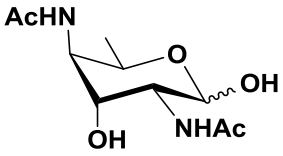
$[\alpha]_D^{20}$= -3.7 (*c* 0.9, H_2O); ^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H 4.16 (dd, *J* = 2.0 Hz, *J* = 10.0 Hz, 1H, H3) 3.89 (dt, *J* = 4.8, Hz, *J* = 6.4 Hz, 1H, H5) 3.81 (m, 1H, H2) 3.78 (m, 1H, H4) 3.76 (dd, *J* = 3.3 Hz, *J* = 12.1 Hz, 1H, H1a) 3.71 (dd, *J* = 5.2 Hz, *J* = 12.1 Hz, 1H, H1a) 2.00 (s, 3H, C(O)C$\underline{H_3}$) 1.98 (s, 3H, C(O)C$\underline{H_3}$) 1.19 (d, *J* = 6.4 Hz, 3H, H6); ^{13}C-NMR (D_2O, 150.90 MHz, ppm) δ_C 173.7 ($\underline{C}$(O)CH_3) 173.5 ($\underline{C}$(O)CH_3) 66.9 (C3) 66.6 (C5) 61.2 (C1) 54.9 (C4) 52.0 (C2) 22.0 (C(O)$\underline{C}H_3$) 21.9 (C(O)$\underline{C}H_3$) 19.1 (C6).



2,4-Diacetamido-2,4,6-trideoxy-L-iditol (*ido*-116)

$R_{f(ido\text{-}\mathbf{116})}$= 0.13 (dichloromethane/methanol= 4:1); HRMS (ESI^+) *m/z*= 271.1262 $[M+Na]^+$ calcd. for $C_{10}H_{20}N_2O_5Na$: 271.1270.

$[\alpha]_D^{20}$= -24.0 (*c* 1.5, H_2O); ^{1}H-NMR (D_2O, 400.13 MHz, ppm) δ_H 4.26 (dt, *J* = 1.3 Hz, *J* = 6.5 Hz, 1H, H5) 4.06 (m, 1H, H2) 3.83 (m, 1H, H3) 3.82 (m, 1H, H4) 3.80(dd, *J* = 3.6 Hz, *J* = 11.7 Hz, 1H, H1a) 3.69 (dd, *J* = 8.4 Hz, *J* = 11.7 Hz, 1H, H1b) 2.14 (s, 3H, C(O)C$\underline{H_3}$) 2.08 (s, 3H, C(O)C$\underline{H_3}$) 1.14 (d, *J* = 6.5 Hz, 3H, H6); ^{13}C-NMR (D_2O, 100.61 MHz, ppm) δ_C 174.6 ($\underline{C}$(O)CH_3) 174.5 70.9 (C3) 65.5 (C5) 60.1 (C1) 55.2 (C4) 53.5 (C2) 22.4 (C(O)$\underline{C}H_3$) 22.4 (C(O)$\underline{C}H_3$) 19.5 (C6).

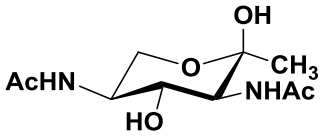


2,4-Diacetamido-2,4,6-trideoxy-D-gulose (119)

Compound **116** (30 mg, 0.12 mmol) was dissolved in dimethylsulfoxide (2 mL) and *ortho*-iodoxybenzoic acid (34 mg, 0.12 mmol, 1 equiv) was added. After 3 hours, the solvent was removed and the product was purified using standard column chromatography on silica gel (dichloromethane/methanol= 4:1) to yield an equimolar mixture of **119** (α:β**=** 1/5) and **120** (16 mg, 0.065 mmol, 54%). The spectroscopic data of **119** are in full agreement with data reported.[74]

HRMS (ESI^+) *m/z*= 269.1108 $[M+Na]^+$ calcd. for $C_{10}H_{18}N_2O_5Na$: 269.1113.

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (β-anomer, major): 4.94 (d, *J* = 3.9 Hz, 1H, H1) 4.30 (dd, *J* = 3.0 Hz, *J* = 6.4 Hz, 1H, H5) 3.94 (m, 1H, H3) 3.88 (m, 1H, H4) 3.85 (dd, *J* = 3.5 Hz, *J* = 3.9 Hz, 1H, H2) 2.09 (s, 3H, C(O)C$\underline{H_3}$) 2.04 (s, 3H, C(O)C$\underline{H_3}$) 1.18 (d, *J*= 6.6 Hz, 3H, H6); ^{13}C-NMR (D_2O 150.90 MHz, ppm) δ_C (β-anomer, major): 174.6 ($\underline{C}$(O)CH_3) 174.2 ($\underline{C}$(O)CH_3) 92.9 (C1) 68.7 (C3) 68.1 (C5) 53.3 (C4) 51.3 (C2) 21.9 (C(O)$\underline{C}H_3$) 21.8 (C(O)$\underline{C}H_3$) 15.6 (C6).



3,5-Diacetamido-1,3,5-trideoxy-L-fructose (120)

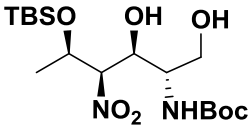
A solution of *gulo*-**116** (50 mg, 0.20 mmol) in dimethylsulfoxide (3 mL) was treated with Dess Martin periodinane (85 mg, 0.20 mmol, 1 equiv) and the reaction mixture was stirred for 3 hours. After removal of the solvent, the product was purified on silica gel (dichloromethane/methanol= 4:1) to yield compound **120** (33 mg, 0.13 mmol, 67%).

HRMS (ESI$^+$) *m/z*= 269.1119 $[M+Na]^+$ calcd. for $C_{10}H_{18}N_2O_5Na$: 269.1113.

^{1}H-NMR (D_2O, 400.13 MHz, ppm) δ_H (α-anomer, major): 4.33 (m, 1H, H5) 4.14 (dd, *J* = 4.4 Hz, *J* = 12.5 Hz, 1H, H6a) 4.07 (dd, *J* = 4.4 Hz, *J* = 10.9 Hz, 1H, H4) 3.99 (d, *J* = 10.9 Hz, 1H, H3) 3.66 (dd, *J* = 1.9 Hz, *J* = 12.5 Hz, 1H, H6b) 2.12 (s, 3H, C(O)C$\underline{H_3}$) 2.10 (s, 3H, C(O)C$\underline{H_3}$) 1.42 (s, 3H, H1); ^{13}C-NMR (D_2O, 100.61 MHz, ppm) δ_C (α-anomer, major): 175.4 ($\underline{C}$(O)CH_3) 175.2 ($\underline{C}$(O)CH_3) 98.4 (C2) 67.4 (C4) 62.0 (C6) 54.8 (C3) 50.5 (C5) 25.2 (C1) 22.4 (2x C(O)$\underline{C}H_3$).

General procedure for the selective deacetalisation

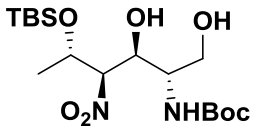
Compound **114** (320 mg, 0.71 mmol) was suspended in a mixture of dry methanol (25 mL) and water (0.25 mL). Dowex W50 ion exchange resin in H^+-form (650 mg) was added and the mixture was stirred for 3 to 12 hours until TLC showed an additional third polar spot (hexanes/ethylacetate= 1:1,R_f= 0.1-0.2, $R_{f(\mathbf{114})}$= 1, $R_{f(\mathbf{125})}$= 0.6-0.8). The resin was filtered off and the solvent was removed under reduced pressure. The product was purified on silica gel (ethyl acetate/hexanes= 1:2).



5-*O*-*tert*-Butyldimethylsilyl-2-*N*-*tert*-butyloxycarbonylamino-4-nitro-2,4,6-trideoxy-D-gulitol (*gulo*-125)

$R_{f(gulo\text{-}\mathbf{125})}$= 0.19 (ethyl acetate/hexanes= 1:2), colourless oil (156 mg, 0.38 mmol, 54 %, 83 % based on recovered starting material); HRMS (ESI^+) *m/z*= 431.2190 $[M+Na]^+$ calcd. for $C_{17}H_{36}N_2O_7SiNa$: 431.2189.

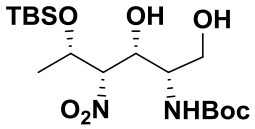
$[\alpha]_D^{20}$= -8.5 (*c* 6.5, dichloromethane); ^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.23 (bs, 1H, NH) 4.62 (m, 1H, H4) 4.52 (dq, *J* = 5.9 Hz, *J* = 6.6 Hz, 1H, H4) 4.22 (m, 1H, H3) 3.95 (m, 1H, H1a) 3.80 (m, 1H, H1b) 3.66 (bs, 1H, OH) 3.55 (m, 1H, H2) 3.13-2.83 (2 bs (cf), 1H, OH) 1.44 (s, 9H, $OC(C\underline{H}_3)_3$) 1.31 (d, *J* = 6.2 Hz, 3H, H6) 0.85 (s, 9H, $SiC(C\underline{H}_3)_3$) 0.08 (s, 3H, $Si(C\underline{H}_3)_2$) 0.04 (s, 3H, $Si(C\underline{H}_3)_2$); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 156.6 ($N\underline{C}(O)O$) 94.6 (C4) 81.2 ($O\underline{C}(CH_3)_3$) 70.2 (C3) 68.7 (C5) 62.8 (C1) 54.3 (C2) 28.8 ($OC(\underline{C}H_3)_3$) 26.2 ($SiC(\underline{C}H_3)_3$) 20.8 (C6) 18.6 ($Si\underline{C}(CH_3)_3$) -3.7 ($Si(C\underline{H}_3)_2$) -4.9 ($Si(C\underline{H}_3)_2$).



5-*O-tert*-Butyldimethylsilyl-2-*N-tert*-butyloxycarbonylamino-4-nitro-2,4,6-trideoxy-L-rhamnitol (*rhamno*-125)

$R_{f(rhamno\text{-}\mathbf{125})}$= 0.46 (ethyl acetate/hexanes= 1:2), white solid (111 mg, 0.27 mmol, 38%, 69% based on recovered starting material); HRMS (ESI^+) *m/z*= 431.2187 $[M+Na]^+$ calcd. for $C_{17}H_{36}N_2O_7SiNa$: 431.2189.

$[\alpha]_D^{20}$= -7.5 (*c* 0.4, dichloromethane); ^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.21 (s, 1H, NH) 4.60 (dd, *J* = 3.6 Hz, *J* = 5.1 Hz, 1H, H4) 4.54 (m, 1H, H5) 4.36 (m, 1H, H3) 4.01 (dd, *J* = 3.6 Hz, J= 11.5 Hz, 1H, H1a) 3.80 (m, 1H, H1b) 3.71 (m, 1H, H2) 1.44 (s, 9H, $OC(C\underline{H}_3)_3$) 1.31 (d, *J* = 6.1 Hz, 3H, H6) 0.88 (s, 9H, $SiC(C\underline{H}_3)_3$) 0.12 (s, 6H, $Si(C\underline{H}_3)_2$); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 156.0 ($N\underline{C}(O)O$) 91.7 (C4) 80.5 ($O\underline{C}(CH_3)_3$) 69.8 (C3) 67.6 (C5) 62.5 (C1) 53.2 (C2) 28.8 ($OC(\underline{C}H_3)_3$) 25.8 ($SiC(\underline{C}H_3)_3$) 20.6 (C6) 18.0 ($Si\underline{C}(CH_3)_3$) -4.5 ($Si(C\underline{H}_3)_2$) -5.1 ($Si(C\underline{H}_3)_2$).



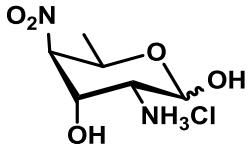
5-*O-tert*-Butyldimethylsilyl-2-*N-tert*-butyloxycarbonylamino-4-nitro-2,4,6-trideoxy-iditol (*ido*-125)

$R_{f(ido\text{-}\mathbf{125})}$= 0.32 (ethyl acetate/hexanes= 1:2), colourless liquid (198 mg, 0.48 mmol, 68%, 76% based on recovered starting material); HRMS (ESI^+) *m/z*= 431.2191 $[M+Na]^+$ calcd. for $C_{17}H_{36}N_2O_7SiNa$: 431.2189.

$[\alpha]_D^{20}$= -4.1 (*c* 0.5, dichloromethane); ^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.14 (s, 1H, NH) 4.48 (m, 1H, H5) 4.46 (m, 1H, H4) 4.22 (m, 1H, H3) 3.90 (m, 1H, H1a) 3.69 (m, 1H, H1b) 3.56 (m, 1H, H2) 2.48 (s, 1H, C3-OH) 1.36 (s, 9H, $OC(C\underline{H}_3)_3$) 1.28 (d, *J* = 6.2 Hz, 3H, H6) 0.77 (s, 9H, $SiC(C\underline{H}_3)_3$) 0.00 (s, 3H, $Si(C\underline{H}_3)_2$) -0.01 (s, 3H, $Si(C\underline{H}_3)_2$); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 156.4 ($N\underline{C}(O)O$) 92.9 (C4) 80.9 ($O\underline{C}(CH_3)_3$) 71.6 (C3) 69.1 (C5) 62.8 (C1) 53.4 (C2) 28.7 ($OC(\underline{C}H_3)_3$) 26.0 ($SiC(\underline{C}H_3)_3$) 21.5 (C6) 18.3 ($Si\underline{C}(CH_3)_3$) -4.7 ($Si(C\underline{H}_3)_2$) -4.8 ($Si(C\underline{H}_3)_2$).

General procedure for the oxidation-deprotection sequence

To a solution of **125** (90 mg, 0.22 mmol) in dimethylsulfoxide (4 mL), *ortho*-iodoxybenzoic acid (96 mg, 0.34 mmol, 1.6 equiv) was added and stirring was continued for 2 hours. After removal of the solvent, the crude product was dissolved in a mixture of tetrahydrofurane (5 mL) and hydrochloric acid (1N, 5 mL) and stirred for 5 hours. The solvent was evaporated and the product was purified using standard column chromatography on silica gel (dichloromethane/methanol= 4:1).



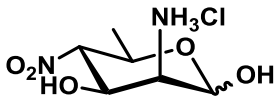
2-Amino-4-nitro-2,4,6-trideoxy-D-gulose (*gulo*-126)

$R_{f(gulo\text{-}\mathbf{126})}$= 0.23 (dichloromethane/methanol= 4:1); yellowish oil (48 mg, 0.21 mmol, 95 %).

$[\alpha]_D^{20}$= +27.1 (*c* 1.0, H_2O); HRMS (ESI^+) *m/z*= 193.0827 $[M\text{-}Cl]^+$ calcd. for $C_6H_{13}N_2O_5$: 193.0824.

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (α-anomer): 5.41 (d, *J* = 4.5 Hz, 1H, H1) 4.93 (dd, *J* = 2.8 Hz, *J* = 2.9 HZ, 1H, H4) 4.77 (dd, *J* = 2.9 Hz, *J* = 6.5 1H, H5) 4.63 (dd, *J*= 2.8 HZ, *J* = 3.4 Hz, 1H, H3) 4.12 (dd, *J* = 4.5 HZ, *J* = 3.4, 1H, H2) 1.25 (d, *J* = 6.5 Hz, 3H, H6); ^{13}C-NMR (D_2O, 150.90 MHz, ppm) δ_C (α-anomer): 89.3 (C1) 87.4 (C4) 67.3 (C5) 63.0 (C3) 47.2 (C2) 17.7 (C6).

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (β-anomer): 5.14 (d, *J* = 9.0 Hz, 1H, H1) 4.85 (m, 1H, H4) 4.71 (dd, *J* = 3.5 Hz, *J* = 9.0 Hz, 1H, H3) 4.52 (dd, *J* = 2.7 Hz, *J* = 6.5 Hz, 1H, H5) 3.80 (dd, *J* = 3.5 Hz, *J* = 9.0 Hz, 1H, H2) 1.27 (d, *J* = 6.5 Hz, 3H, H6); ^{13}C-NMR (D_2O, 150.90 MHz, ppm) δ_C (β-anomer): 92.1 (C1) 87.6 (C4) 68.3 (C5) 64.9 (C3) 52.1 (C2) 16.2 (C6).



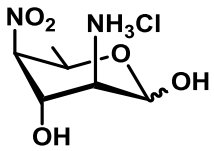
2-Amino-4-nitro-2,4,6-trideoxy-L-rhamnose (*rhamno*-126)

$R_{f(rhamno\text{-}\mathbf{126})}$= 0.57 (dichloromethane/methanol= 4:1); yellowish oil (42 mg, 0.18 mmol, 84%).

$[\alpha]_D^{20}$= -10.2 (*c* 0.14, H_2O); HRMS (ESI^+) *m/z*= 193.0820 $[M\text{-}Cl]^+$ calcd. for $C_6H_{13}N_2O_5$: 193.0824.

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (α-anomer): 5.21 (d, *J* = 1.4 Hz, 1H, H1) 4.66 (dd, *J* = 9.6 Hz, *J* = 9.9 Hz, 1H, H4) 4.63 (dd, *J* = 3.5 Hz, *J*= 9.9 Hz, 1H, H3) 4.48 (dq, *J* = 6.3 Hz, *J* = 9.6 Hz, 1H, H5) 3.32 (dd, *J* = 1.4 Hz, *J* = 3.5 Hz, 1H, H2) 1.28 (d, *J* = 6.3 Hz, 3H, H6); ^{13}C-NMR (D_2O, 150.90 MHz, ppm) δ_C (α-anomer): 94.7 (C1, J_{CH} = 175.5 Hz) 90.6 (C4) 67.2 (C3) 66.2 (C5) 54.2 (C2) 17.3 (C6).

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (β-anomer): 5.13 (d, *J* = 1.6 Hz, 1H, H1) 4.61 (dd, *J* = 9.4, *J* = 10.5, 1H, H4) 4.48 (dd, *J* = 4.2 Hz, *J* = 10.5 Hz, 1H, H3) 4.04 (dq, *J* = 6.1 Hz, *J* = 9.4 Hz, 1H, H5) 3.51 (dd, *J* = 1.6 Hz, *J* = 4.2 Hz, 1H, H2) 1.28 (d, *J* = 6.1 Hz, 3H, H6); ^{13}C-NMR (D_2O, 150.90 MHz, ppm) δ_C (α-anomer): 3.5 (C1, J_{CH} = 165.5 Hz) 90.1 (C4) 70.4 (C5) 69.3 (C5) 55.1 (C2) 17.3 (C6).

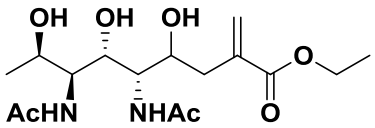


2-Amino-4-nitro-2,4,6-trideoxy-L-idose (*ido*-126)

$R_{f(ido\text{-}\mathbf{126})}$= 0.56 (dichloromethane/methanol= 4:1, inseparable mixture with *ido*-**123**); yellowish oil (39 mg, 0.21 mmol, 77%). HRMS (ESI^+) *m/z*= 193.0823 $[M\text{-}Cl]^+$ calcd. for $C_6H_{13}N_2O_5$: 193.0824.

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (α-anomer): 5.50 (dddd, *J* = 0.7 Hz, *J* = 0.7 Hz, *J* = 0.7 Hz, *J* = 1.8 Hz, 1H, H1) 5.20 (ddd, *J* = 5.9 Hz, *J* = 3.6 Hz, *J* = 0.7 Hz, 1H, H4) 4.71 (ddd, *J* = 0.7 Hz, *J* = 5.6 Hz, *J* = 5.9 Hz, 1H, H3) 4.68 (ddq, *J* = 0.7 Hz, *J* = 3.6 Hz, *J* = 6.6 Hz, 1H, H5) 3.95 (dd, *J* = 1.8 Hz, *J* = 5.6 Hz, 1H, H2) 1.27 (d, *J* = 6.6 Hz, 3H, H6); ^{13}C-NMR (D_2O, 150.90 MHz, ppm) δ_C 90.5 (C1, J_{CH} = 171.9 Hz) 88.0 (C4) 63.7 (C5) 59.8 (C3) 50.2 (C2) 15.3 (C6)

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (β-anomer): 5.152 (d, *J* = 2.1 Hz, 1H, H1) 5.150 (dd, *J* = 3.1 Hz, *J* = 6.1 Hz, 1H, H4) 4.61 (d, *J* = 5.6 Hz, *J* = 6.2 Hz, 1H, H3) 4.15 (dq, *J* = 3.1 Hz, *J* = 6.5 Hz, 1H, H5) 3.76 (dd, *J* = 2.1 Hz, *J* = 5.5 Hz, 1H, H2) 1.29 (d, *J* = 6.5 Hz, 3H, H6); ^{13}C-NMR (D_2O, 150.90 MHz, ppm) δ_C 91.5 (C1, J_{CH} = 167.2 Hz) 87.8 (C4) 68.4 (C5) 62.9 (C3) 51.4 (C2) 15.5 (C6).

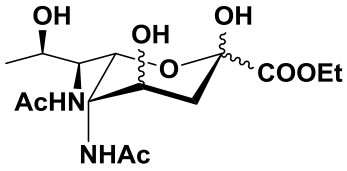


Ethyl-5,7-diacetamido-2,3,5,7,9-pentadeoxy-2-C-methylene-D-*glycero*-L-*gluco*-nonulosonate (*threo*-128)

2-(Bromomethyl)acrylic acid ethyl ester (**127**, 118 mg, 0.61 mmol, 3 equiv) was dissolved in tetrahydrofurane (5 mL) and indium shots (70 mg, 0.61 mmol, 3 equiv) were added. The mixture was heated in an ultrasound bath at 60 °C for 1 hour. Compound **31** (50 mg, 0.2 mmol) was dissolved in water (5 mL) and added to the reaction mixture and sonication was continued overnight at 60 °C. Residual indium was filtered off and the solvent was evaporated. Purification on silica gel (dichloromethane/methanol= 4:1) gave an inseparable mixture of diastereomers (62 mg, 0.17 mmol, 85%, *threo*/*erythro*= 2:1). A small amount of the major isomer was isolated for characterization.

HRMS (ESI$^+$) *m/z*= 383.1792 $[M+Na]^+$ calcd. for $C_{16}H_{28}N_2O_7Na$: 383.1794.

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (*threo*-isomer, major): 6.33 ($\underline{H_2}C=C$) 5.81 ($\underline{H_2}C=C$) 4.28 ($OC\underline{H_2}CH_3$) 4.23 (CH) 4.15 (CH) 4.07 (CH) 4.00 (CH) 3.70 (CH) 2.71 (CH_2) 2.40 (CH_2) 2.05 (CH_3) 2.04 (CH_3) 1.33 ($OCH_2C\underline{H_3}$) 1.14 (CH_3).

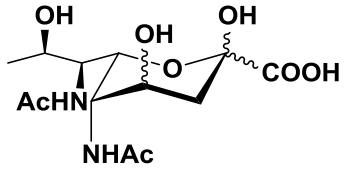


Ethyl-5,7-diacetamido-3,5,7,9-tetradeoxy-D-*glycero*-L-*gluco*-nonulosonate (*threo*-129)

Compound **128** (50 mg, 0.14 mmol) was dissolved in dichloromethane/methanol (1:1, 15 mL) and ozone was bubbled through the solution at -78 °C until a slight blue color appeared. Excess of ozone was removed by bubbling a stream of oxygen thrugh the solution and the reaction was treated with triphenylphosphine (50 mg, 0.19 mmol, 1.4 equiv). Most of the solvent was removed and the mixture was diluted with water to adjust the pH-value to seven with a sodium hydroxide solution (0.5 N). After removal of the solvent the crude product (45 mg, 0.12 mmol, 89%) was used in the next step without further purification.

HRMS (ESI$^+$) *m/z*= 385.1585 $[M+Na]^+$ calcd. for $C_{15}H_{26}N_2O_8Na$: 385.1587.

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (*threo*-isomer, major): 4.55 (CH) 4.25 ($OC\underline{H_2}CH_3$) 4.11 (CH) 3.96 (CH) 3.89 (CH) 3.82 (CH) 2.11 (CH_2) 2.08 (CH_2) 1.95 (CH_3) 1.91 (CH_3) 1.27 ($OCH_2C\underline{H_3}$) 1.05 (CH_3).



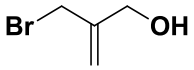
5,7-Diacetamido-3,5,7,9-tetradeoxy-D-*glycero*-L-*gluco/manno*-nonulosonic acid (*threo*-130)

Compound **129** (8 mg 0.022 mmol), was dissolved in H_2O/triethylamine (3:1).[109] After 2 hours at room temperature, the solvent was removed to yield the product as triethylamine salt (8 mg, 0.018 mmol, 83%).

HRMS (ESI$^-$) *m/z*= 333.1307 $[M-H]^-$ calcd. for $C_{13}H_{21}N_2O_8Na$: 333.1303.

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (*gluco*-isomer, major): 4.55 (CH) 4.22 (CH) 4.02 (CH) 3.94 (CH) 3.85 (CH) 2.15 (CH_2) 2.11 (CH_2) 2.03 (CH_3) 2.00 (CH_3) 1.13 (CH_3).

^{1}H-NMR (D_2O, 600.13 MHz, ppm) δ_H (*manno*-isomer, minor): 4.30 (CH) 4.24 (CH) 4.18 (CH) 3.93 (CH) 3.84 (CH) 2.18 (CH_2) 2.10 (CH_2) 2.05 (CH_3) 2.04 (CH_3) 1.13 (CH_3).



2-(Bromomethyl)prop-2-en-1-ol (131)

Compound **136**[110] (2.66 g, 13.8 mmol) was dissolved in dichloromethane (20 mL) and the mixture was cooled to -78 °C. DIBALH (29 mL 1M in DCM, 2.1 equiv) was added slowly over a period of 30 minutes. After completion, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2 hours. The solution was cooled to 0 °C and a saturated Na-K-tartrat solution (30 mL) was added and stirring was continued overnight. The aqueous phase was extracted with diethyl ether and the combined organic layers were dried over $MgSO_4$. Careful evaporation of the solvent gave the crude product (1.17 g, 7.7 mmol, 56%), which was used without purification in the next step. The spectroscopic data agree with data reported.[114]

MS (EI) *m/z*= 71.10 $[M\text{-}Br]^-$ calcd. for $C_4H_7O^+$: 71.05.

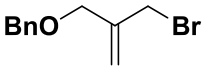
^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H (*threo*-isomer, major): 5.24 (H_2C=C) 5.19 (H_2C=C) 4.23 (CH_2Br) 3.98 (CH_2OH); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 145.2 (C_q) 116.1 (H_2C=) 64.0 (CH_2Br) 33.2 (CH_2OH).

General procedure for the allylation with 131

To a solution of aldehyde (**138**, **140**, **142**, 100 mg) in the corresponding solvent indium (1.5 equiv) and compound **131** (1.5 equiv) were added and sonicated (Table 12). The mixture was filtered through a pad of celite and concentrated *in vacuo*. Purification was achieved on silica gel to yield a diastereomeric mixture.

entry	aldehyde	solvent	reaction time [h]	purification	yield [%], (*syn*/*anti*)
1	**138**	EtOH	3	Hex:EE= 4/1	83 (dr= 3/1)
2	**140**	EtOH/H_2O= 4/1	12	Tol/Ac= 10/1	75 (dr= 4/1)
3	**142**	EtOH/H_2O= 4/1	18	Tol/Ac= 10/1	70 (dr= 4/1)

*Table 12. Reaction conditions and yields of the allylation reaction using **131**. (Hex= hexanes, EE= ethyl acetate, Tol= toluene, Ac= actone)*



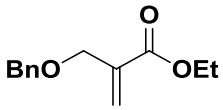
3-Bromo-2-(Benzyloxymethyl)prop-1-ene (132)

Route A) Alcohol **137** (500 mg, 2.8 mmol) and CBr_4 (1.46 g, 4.4 mmol, 1.6 equiv) were dissolved in dichloromethane (10mL) and cooled to 0 °C. A solution of PPh_3 (1.13 g, 4.3 mmol, 1.5 equiv) in dichloromethane (1 mL) was added slowly to the solution and stirring was continued overnight at room temperature. After removal of the solvent, the product was extracted with hexane, dried over $MgSO_4$ and the solvent was evaporated. The product was purified on silica gel to yield a colorless liquid (473 mg, 1.96 mmol, 70%).

Route B) Compound **137** (51 mg, 0.29 mmol) was dissolved in dichloromethane (7 mL) and cooled to -15 °C. After the addition of triphenylphosphine (90 mg, 0.34 mmol, 1.2 equiv), the mixture was stirred for 1 hour. *N*-Bromosuccinimide (54 mg, 0.3 mmol, 1.1 equiv) was added in portions over a period of 30 minutes. After 5 hours, the reaction was extracted with water followed by saturated NaCl-solution and the organic layer dried over $MgSO_4$. The solvent was removed and the product (30 mg, 0.12 mmol, 43%) was purified on silica gel (hexanes/ethyl acetate= 4:1).

HRMS (ESI^+) *m/z*= 263.0044 $[M+Na]^+$ calcd. for $C_{11}H_{13}OBrNa$: 263.0047.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 7.36-7.28 (5x H_{ar}) 5.36 (H_2C=) 5.27 (H_2C=) 4.54 (CH_2) 4.16 (CH_2) 4.05 (CH_2); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 142.4 (C_q) 138.1 (C_q) 128.5 (CH) 128.5 (CH) 127.8 (CH) 117.3 (CH_2) 72.5 (CH_2) 70.4 (CH_2) 33.1 (CH_2).



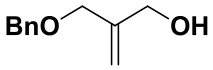
Ethyl-2(Benzyloxymethyl)acrylate (136)

Route A) Compound **134**[110] (1 g, 7.7 mmol,) and benzyl trichloroacetimidate (2.31 g, 9.15 mmol, 1.2 equiv) were dissolved in a mixture of dichloromethane/cyclohexane (1:1, 20 mL) and cooled to 0 °C. After the addition of trifluoromethanesulfonic acid (40 µL, 0.45 mmol, 0.06 equiv), the mixture was allowed to warm to room temperature and stirred for 3 hours. The acetamide was filtered through a pad of celite and the clear solution was washed with $NaHCO_3$ (1 N), water and saturated NaCl-solution. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. Purification was achieved on silica gel (hexanes/ethyl acetate= 35:1) to give compound **136** (920 mg, 4.18 mmol, 54%).

Route B) Benzyl alcohol (1.08 g, 10 mmol, 1.1 equiv) was dissolved in dry diethyl ether (40 mL) and sodium hydride (490 mg 55% dispersion in mineral oil, 11 mmol, 1.2 equiv) was added and the mixture was stirred for an additional hour. A solution of **135** (1.73 g, 9 mmol) in dry diethyl ether (40 mL) was added dropwise and stirring was continued for 2 hours followed by one hour at reflux temperature. The reaction mixture was extracted with water and the organic phase was washed with saturated NaCl-solution and dried over $MgSO_4$. After evaporation of the solvent, the product **136** (930 mg, 4.22 mmol, 47%) was purified using standard column chromatography (hexanes/ethyl acetate= 19:1).

HRMS (ESI^+) *m/z*= 243.0992 $[M+Na]^+$ calcd. for $C_{13}H_{16}O_3Na$: 243.0997.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 7.41-7.30 (5x H_{ar}) 6.37 (H_2C=) 5.97 (H_2C=) 4.63 (CH_2) 4.29 (CH_2) 4.26 (CH_2) 1.34 (CH_3); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 165.9 (C_q) 138.2 (C_q) 137.5 (C_q) 128.4 (CH) 127.7 (CH) 127.6 (CH) 125.6 (CH_2) 72.8 (CH_2) 68.5 (CH_2) 60.7 (CH_2) 14.2 (CH_3).



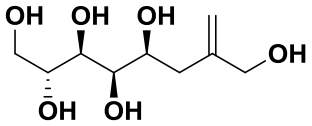
2-(Benzyloxymethyl)prop-2-en-1-ol (137)

To a solution of derivative **136** (1.73 g, 7.85 mmol) in dry dichloromethane (150 mL) at -78 °C, DIBALH (23.5 mL 1M in hexane, 3 equiv) was added dropwise. The mixture was stirred for an additional hour and subsequently allowed to warm to room temperature. The reaction was stopped by the addition of a saturated NH_4Cl-solution. The precipitate was removed by filtration and the organic phase washed with brine. After removal of the organic solvent, the crude product was used in the next reaction (1.37 g, 7.68 mmol, 98% (crude)).

HRMS (ESI^+) *m/z*= 201.0888 $[M+Na]^+$ calcd. for $C_{11}H_{14}O_2Na$: 201.0891.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 7.38-7.28 (5x H_{ar}) 5.21 (H_2C=) 5.16 (H_2C=) 4.53 (CH_2) 4.21 (CH_2) 4.11 (CH_2) 1.86 (OH).

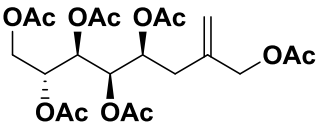
Since only the arabinose (**138**) derived compounds gave small amounts of diastereomerically pure product, the spectroscopic data of the major isomer for this series is listed below:



2,3-Dideoxy-2-C-methylene-D-*gluco*-octose (*threo*-141)

HRMS (ESI$^+$) *m/z*= 245.0999 [M+Na]$^+$ calcd. for $C_9H_{18}O_6Na$: 245.1001.

^{1}H-NMR (D_2O, 400.13 MHz, ppm) δ_H 5.20 (H_2C=) 5.09 (H_2C=) 4.14 (CH_2) 3.98 (CH) 3.87 (CH_2) 3.82 (CH) 3.76 (CH) 3.74 (CH_2) 3.69 (CH_2) 2.46 (CH_2) 2.26 (CH_2); ^{13}C-NMR (D_2O, 100.61 MHz, ppm) δ_C 144.6 (C_q) 113.0 (CH_2) 72.0 (CH) 71.4 (CH) 71.1 (CH) 70.7 (CH) 64.3 (CH_2) 62.8 (CH_2) 36.4 (CH_2).

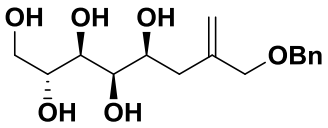


1,4,5,6,7,8-Hexaacetyl-2,3dideoxy-2-C-methylene-D-*gluco*-octose

Compound **141** was dissolved in acetic anhydride/pyridine (1:1, 5 mL/mmol) and the mixture was stirred overnight. After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed with water followed by hydrochloric acid (0.5 N) and saturated NaCl-solution. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

HRMS (ESI$^+$) *m/z*= 497.1637 [M+Na]$^+$ calcd. for $C_{21}H_{30}O_{12}Na$: 497.1635.

^{1}H-NMR ($CDCl_3$, 400.13 MHz, ppm) δ_H 5.43 (CH) 5.29 (CH) 5.19 (CH) 5.15 (CH_2) 5.07 (CH) 5.04 (CH_2) 4.62 (CH_2) 4.45 (CH_2) 4.25 (CH_2) 4.12 (CH_2) 2.47 (CH_2) 2.31 (CH_2) 2.13 (CH_3) 2.09 (CH_3) 2.07 (CH_3) 2.06 (CH_3) 2.05 (CH_3) 2.02 (CH_3); ^{13}C-NMR ($CDCl_3$, 100.61 MHz, ppm) δ_C 170.6 (C_q) 170.5 (C_q) 170.0 (C_q) 169.9 (C_q) 169.8 (C_q) 169.8 (C_q) 138.8 (C_q) 117.5 (CH_2) 70.8 (CH) 69.3 (CH) 68.7 (CH) 68.7 (CH) 66.3 (CH_2) 61.5 (CH_2) 34.8 (CH_2) 20.9 (CH_3) 20.8 (CH_3) 20.7 (CH_3) 20.7 (CH_3) 20.6 (CH_3) 20.5 (CH_3).



1-*O*-Benzyl-2,3-dideoxy-2-C-methylene-D-*gluco*-octose (*threo*-144)

To a solution of arabinose (**138**, 100 mg, 0.66 mmol) in ethanol/water (4:1, 15 mL), indium (114 mg, 1mmol, 1.5 equiv) and **132** (241 mg, 1 mmol, 1.5 equiv) were added and the mixture was sonicated overnight. The solution was filtered through a pad of celite and concentrated *in vacuo*. Purification was achieved on silica gel to yield a diastereomeric mixture (*erythro*/*threo*= 1:3, 177 mg, 0.57 mmol, 86%).

HRMS (ESI$^+$) *m/z*= 335.1475 $[M+Na]^+$ calcd. for $C_{16}H_{24}O_6Na$: 335.1471.

^{1}H-NMR (MeOH-d4, 400.13 MHz, ppm) δ_H (*gluco*-isomer, major) 7.36-7.27 (5x H_{Ar}) 5.16 (H_2C=) 5.09 (H_2C=) 4.51 (OCH_2Bn) 4.04 (CH_2) 3.94 (CH) 3.77 (CH) 3.73 (CH_2) 3.70 (CH) 3.65 (CH) 3.62 (CH_2) 2.46 (CH_2) 2.30 (CH_2).

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NMR-SPECTRA OF SELECTED COMPOUNDS

2-Nitroacetaldehyde diethylacetal (**64**) 119

4-Amino-4-*N*-*tert*-butyloxycarbonyl-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-2-nitro-D-galactose diethylacetal (*syn*-**78**) 119-120

2,4-Diamino-4-*N*-*tert*-butyloxycarbonyl-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-D-galactose diethylacetal 121-122

2-*N*-Acetyl-3-*O*-acetyl-2,4-diamino-4-*N*-*tert*-butyloxycarbonyl-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-D-galactose diethylacetal (**82**) 122-123

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2,4-Diacetamido-2,4,6-trideoxy-D-galactose diethylacetal (**83**) 125

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Ethyl-2,4-diacetamido-2,4,6-trideoxy-β-D-galactoside (**84β**) 127

2-Nitro-4-amino-4-*N*-*tert*-butyloxycarbonyl-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-D-galactose dimethylacetal 128-129

2-*N*-Chloracetamido-4-amino-4-*N*-*tert*-butyloxycarbonyl-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-D-galactose diethylacetal (**88**) 129-130

2-*N*-Acetyl-3-*O*-acetyl-2,4-diamino-4-*N*-*tert*-butyloxycarbonyl-2,4,6-trideoxy-4-*N*,5-*O*-isopropylidene-D-talose diethylacetal 131

3-Amino-3-*N*-*tert*-butyloxycarbonyl-1,3,5-trideoxy-3-*N*,4-*O*-isopropylidene-1-nitro-L-ribo/arabino (**98**) 132

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2-Amino-5-*O*-*tert*-butyldimethylsilyl-2-*N*-*tert*-butyloxycarbonyl-1,2-*O,N*-isopropylidene-4-nitro-2,4,6-trideoxy-D-gulitol (*gulo*-**114**) 133-134

2-Amino-5-*O*-*tert*-butyldimethylsilyl-2-*N*-*tert*-butyloxycarbonyl-4-nitro-2,4,6-trideoxy-D-gulitol (*gulo*-**125**) 135

2-Amino-4-nitro-2,4,6-trideoxy-D-gulose (*gulo*-**126**) 136

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2,4-Diacetamido-2,4,6-trideoxy-D-gulose (**119**) 138

3,5-diacetamido-1,3,5-trideoxy-L-fructose (**120**) 138-139

2-Amino-5-*O*-*tert*-butyldimethylsilyl-2-*N*-*tert*-butyloxycarbonyl-1,2-*O,N*-isopropylidene-4-nitro-2,4,6-trideoxy-L-rhamnitol (*rhamno*-**114**) 139-140

2-Amino-5-*O*-*tert*-butyldimethylsilyl-2-*N*-*tert*-butyloxycarbonyl-4-nitro-2,4,6-trideoxy-L-rhamnitol (*rhamno*-**125**) 140-141

2-Amino-4-nitro-2,4,6-trideoxy-L-rhamnose (*rhamno*-**126**) 142

2,4-Diacetamido-2,4,6-trideoxy-L-rhamnitol (*rhamno*-**116**) 143

2-Amino-5-*O*-*tert*-butyldimethylsilyl-2-*N*-*tert*-butyloxycarbonyl-1,2-*O,N*-isopropylidene-4-nitro-2,4,6-trideoxy-L-iditol (*ido*-**114**) 144

2-Amino-5-*O*-*tert*-butyldimethylsilyl-2-*N*-*tert*-butyloxycarbonyl-4-nitro-2,4,6-trideoxy-iditol (*ido*-**125**) 145

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5,7-diacetamido-3,5,7,9-tetradeoxy-D-*glycero*-L-*manno*-nonulosonic acid (*erythro*-**130**) 148
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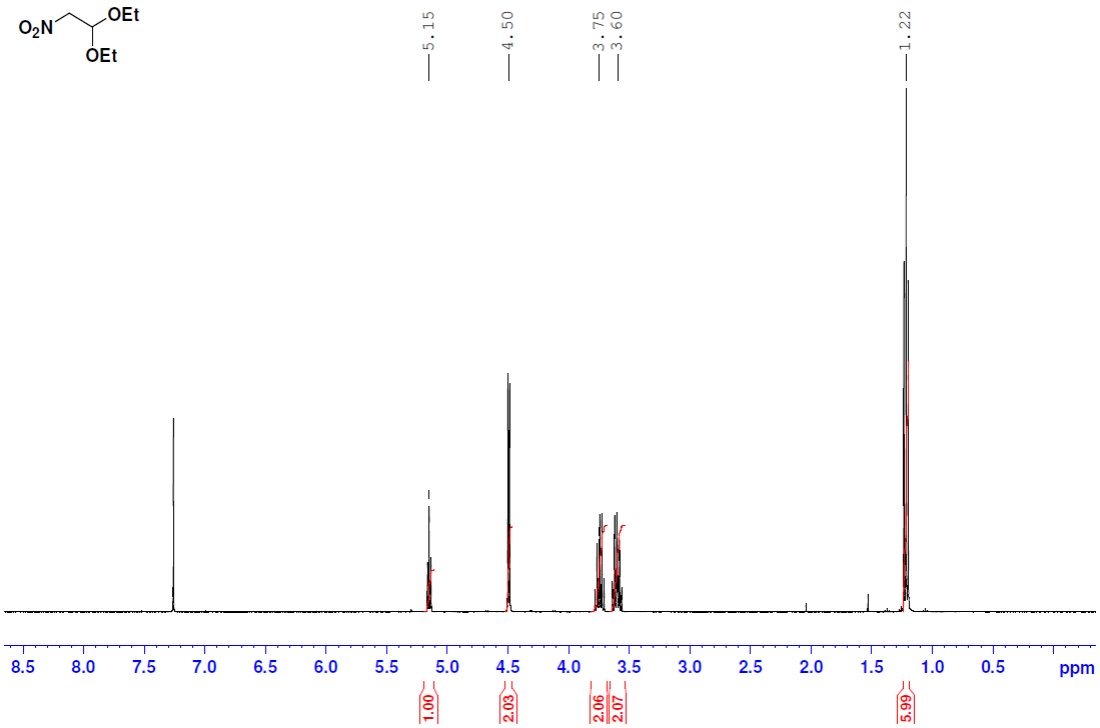
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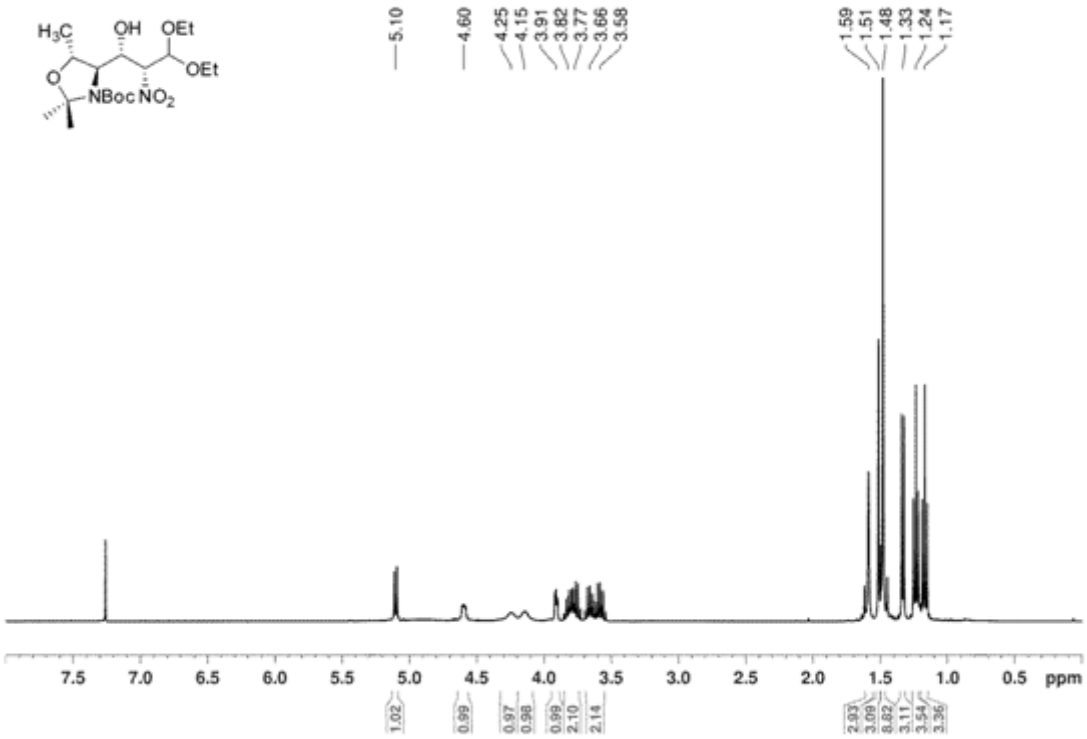
2.03
2.06
2.07
5.99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1.48
1.33
1.24
1.17
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.02
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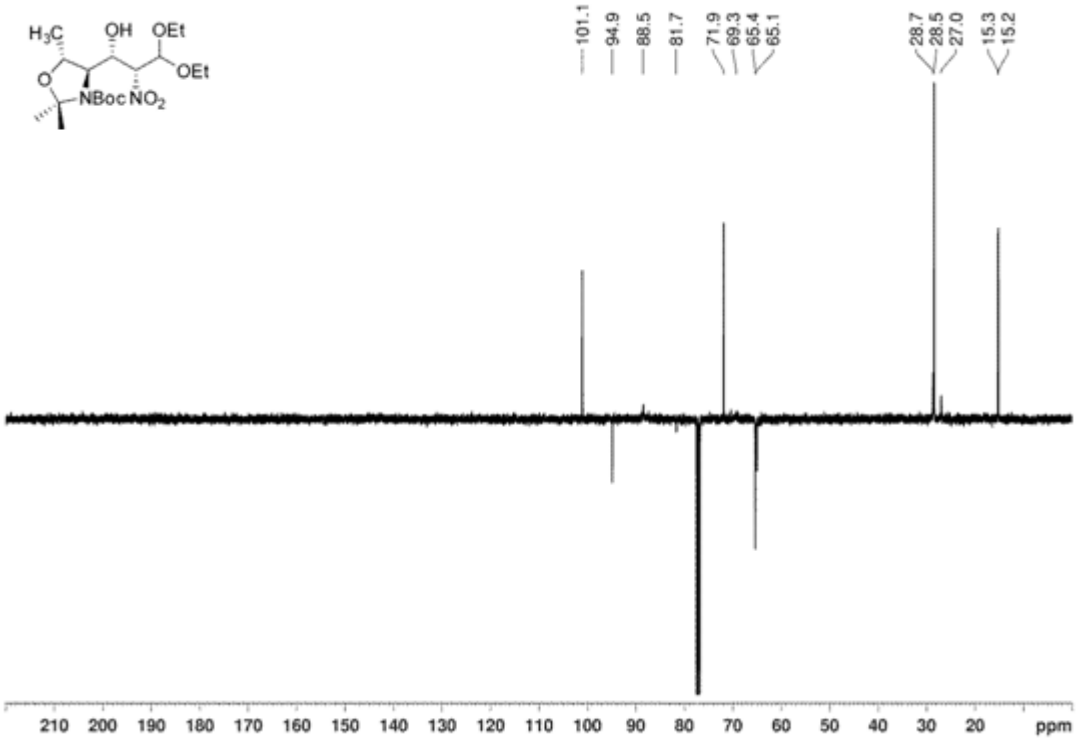
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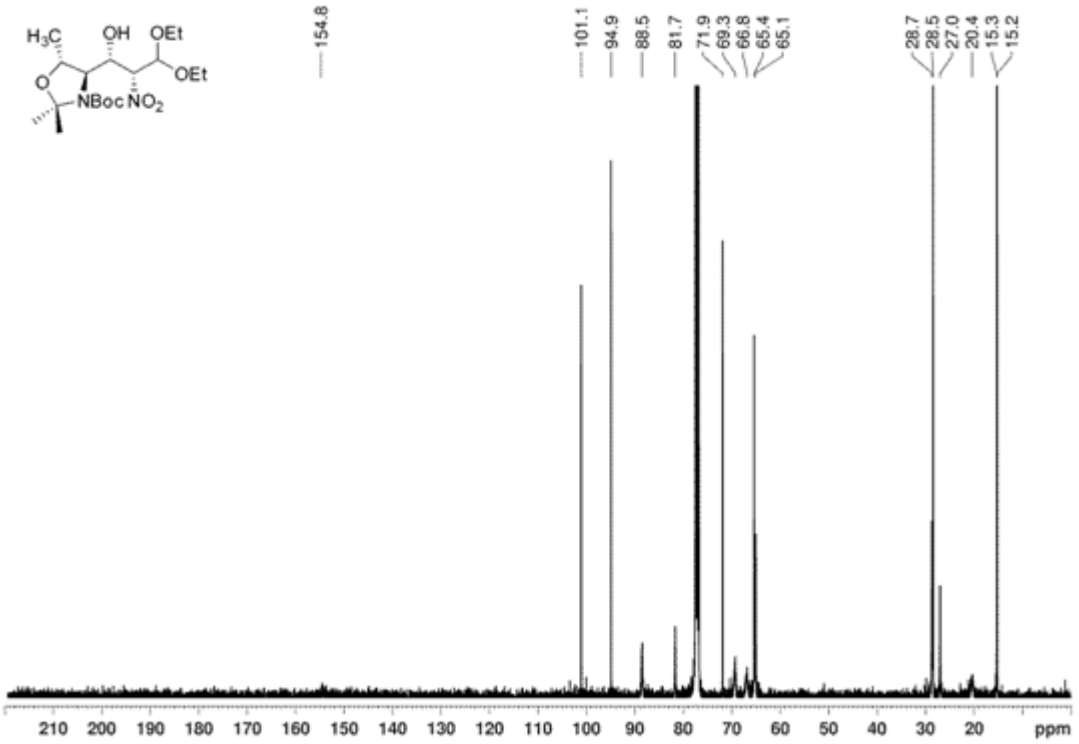
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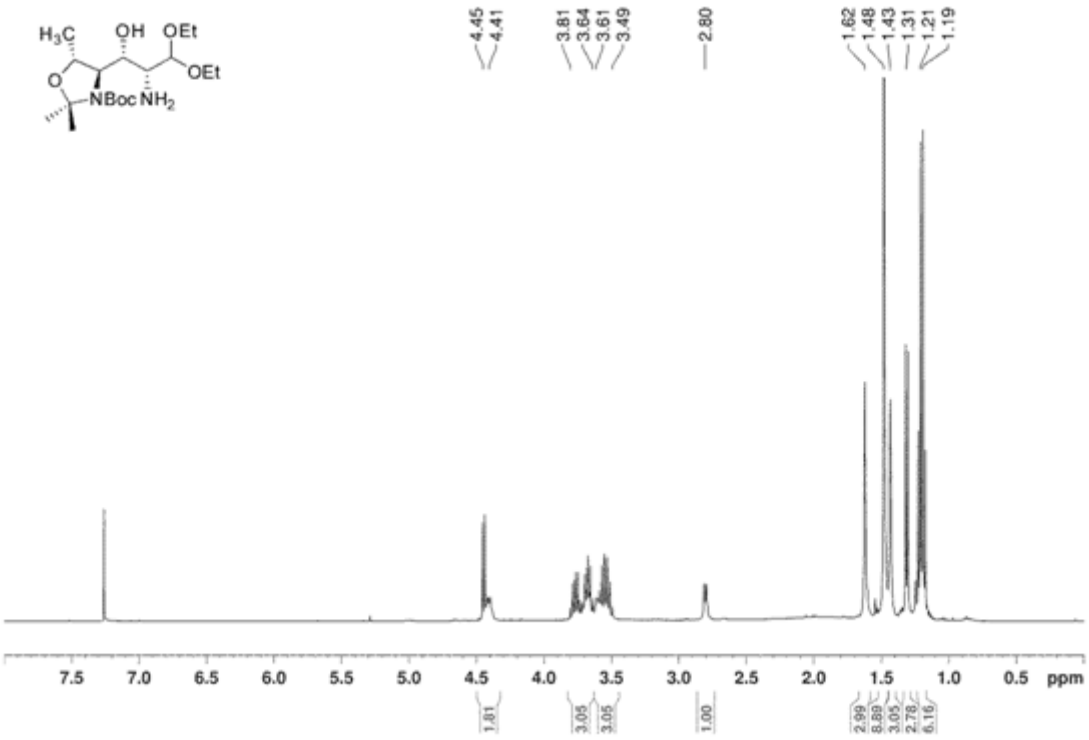
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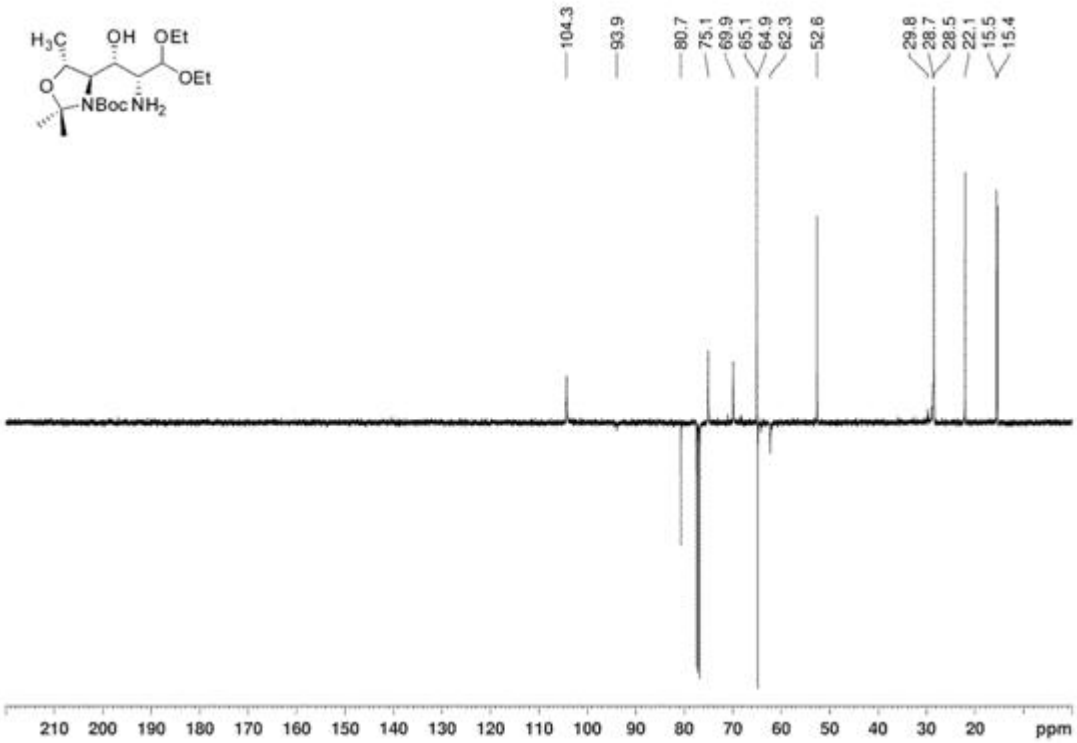
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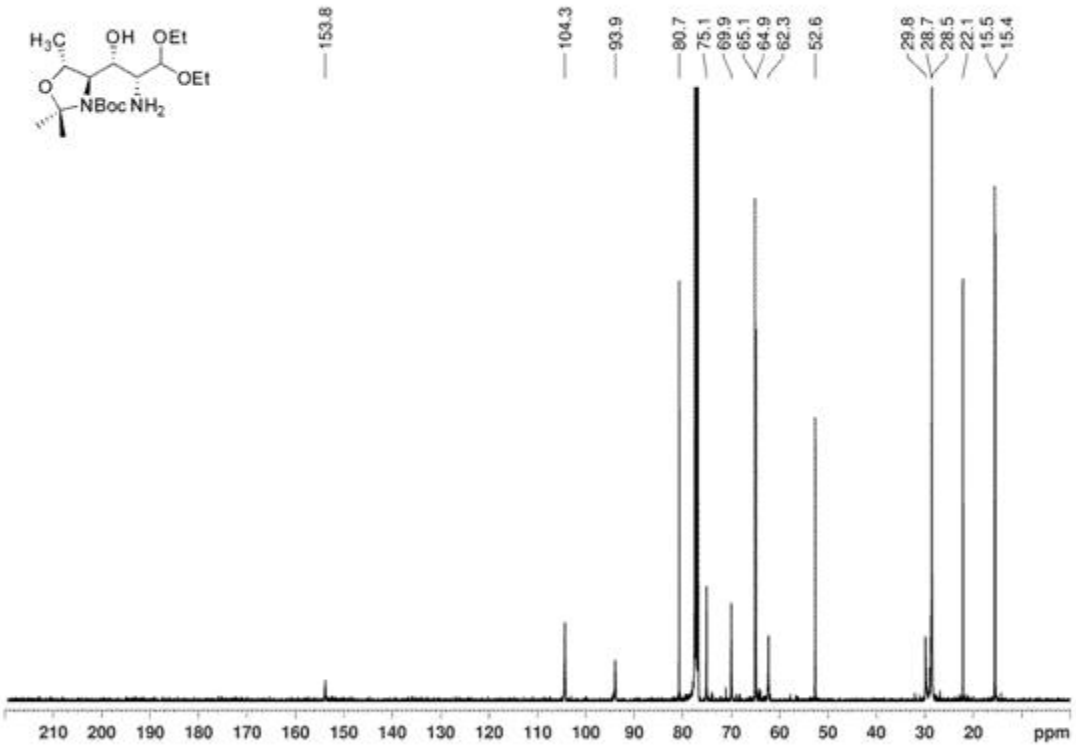
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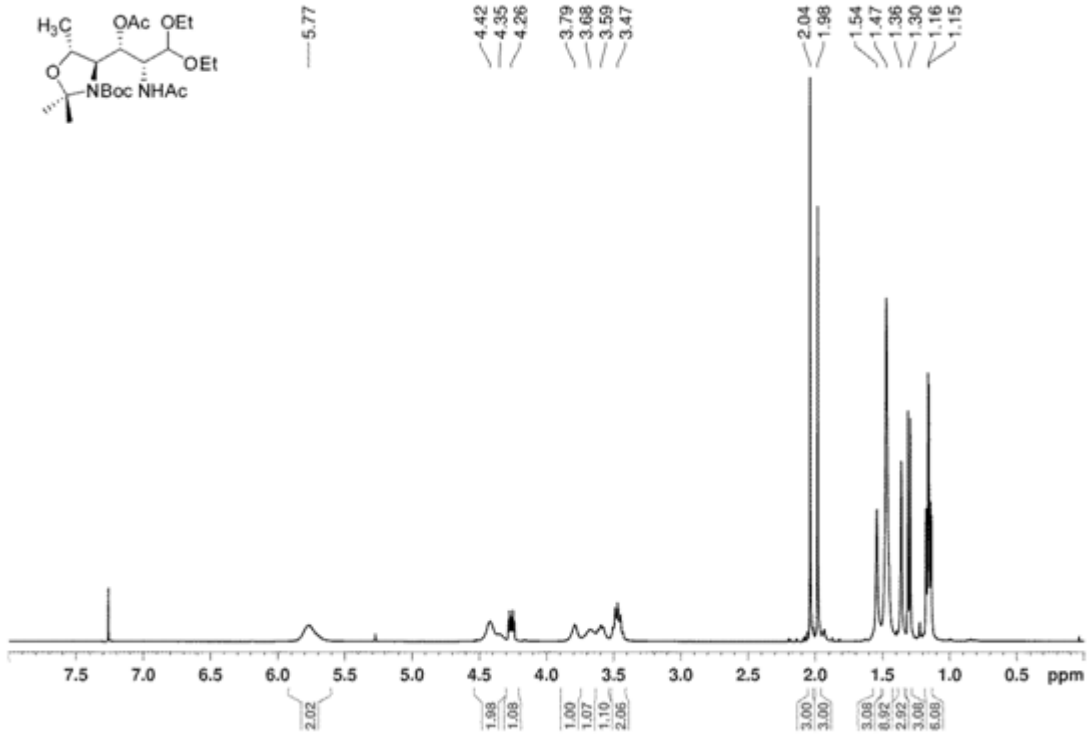
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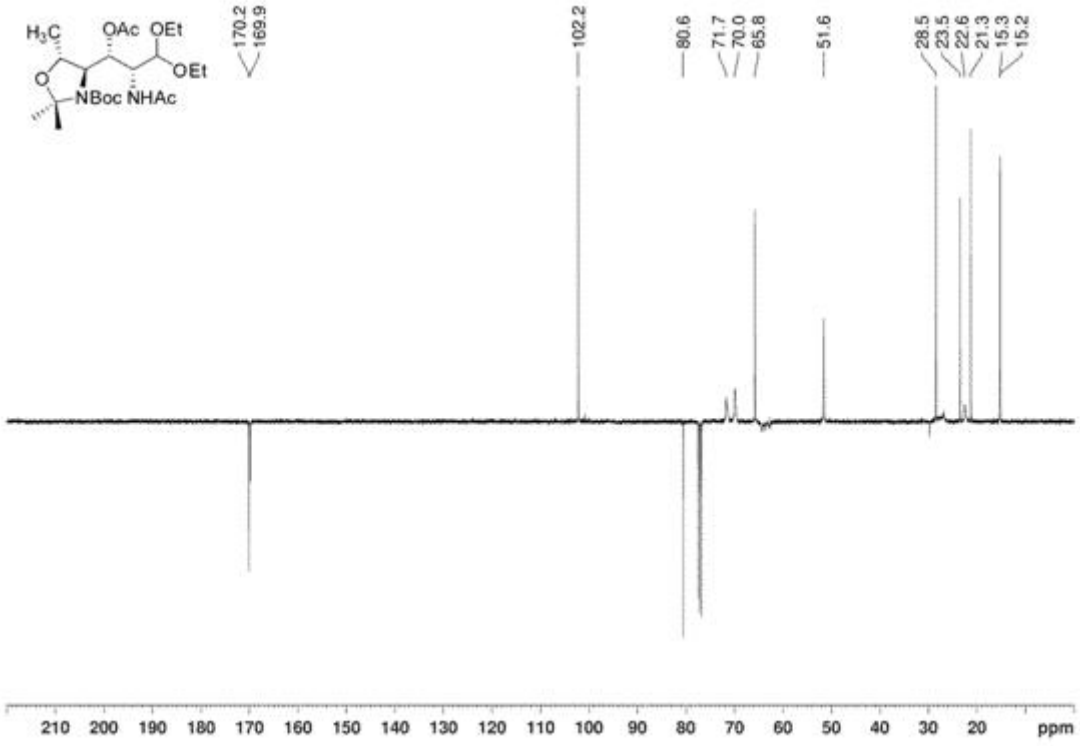
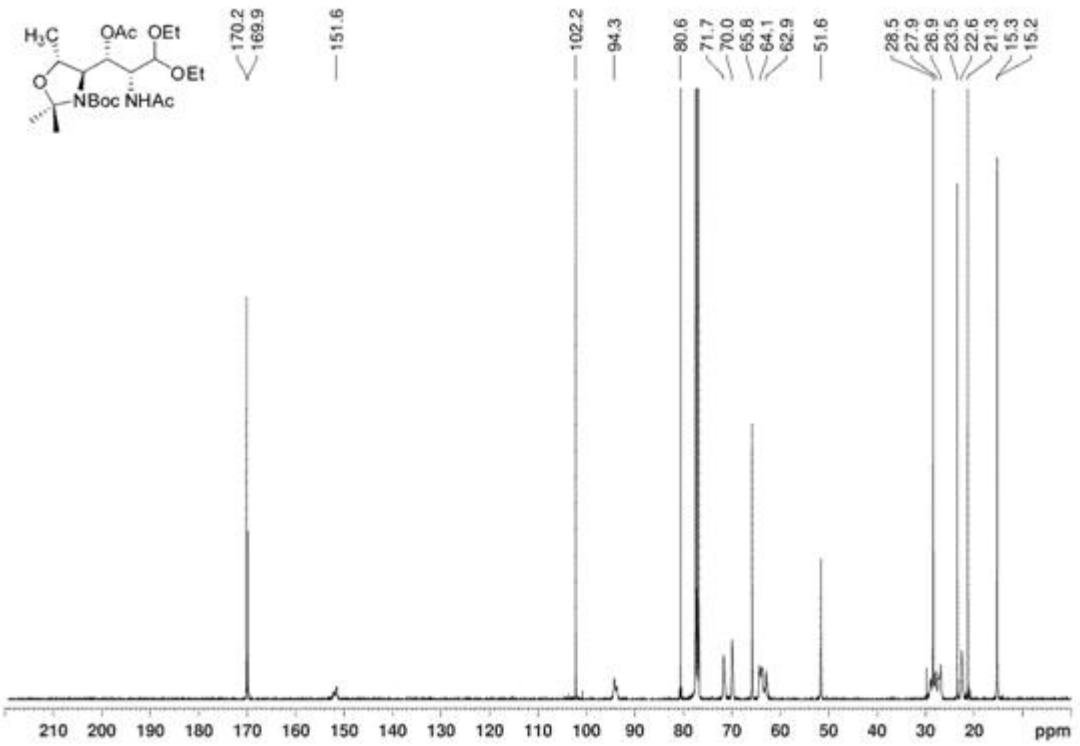
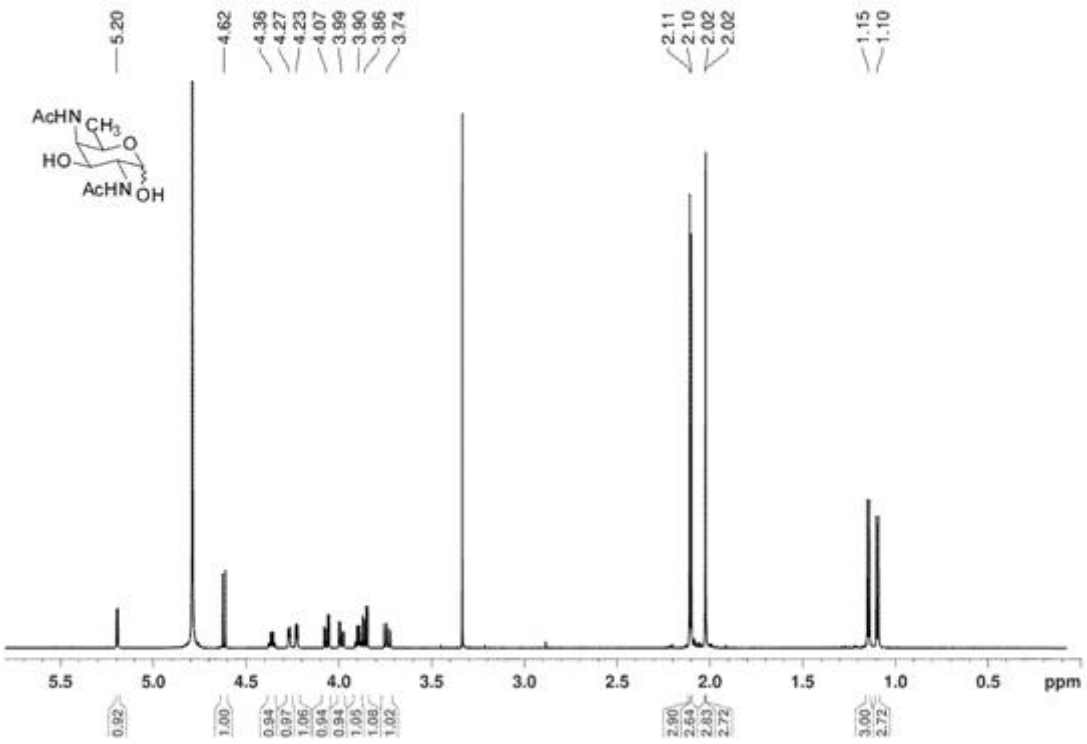
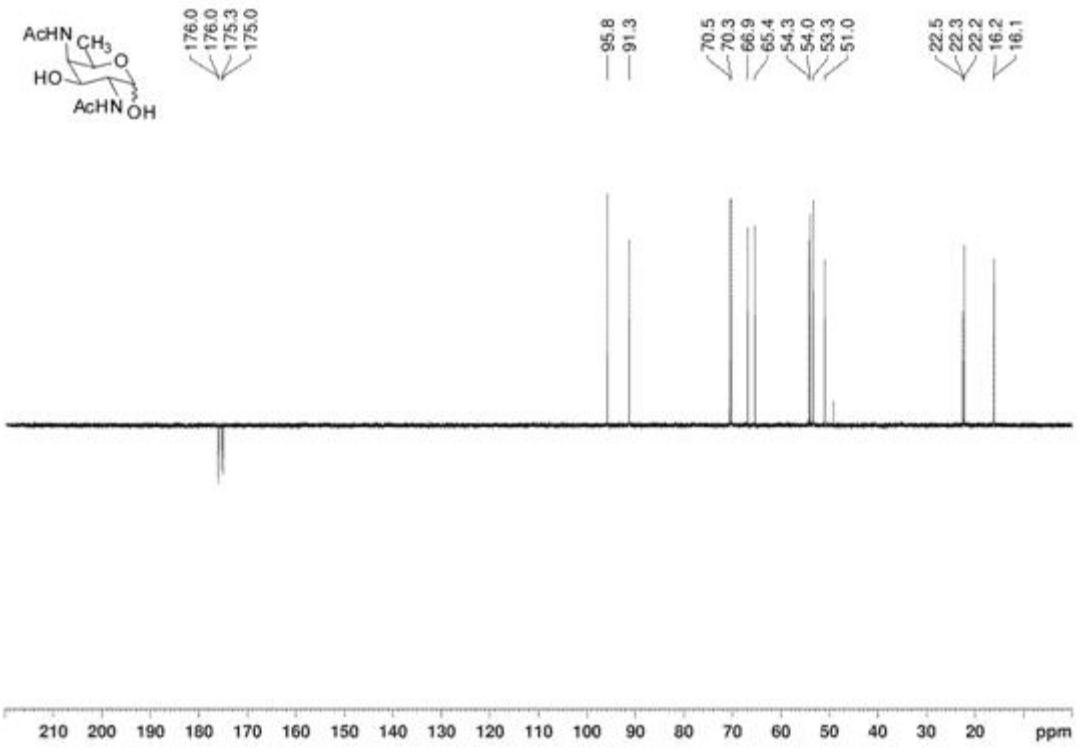
3.79
3.68
3.59
3.47
2.04
1.98
1.54
1.47
1.36
1.30
1.16
1.15
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.02
1.98
1.08
1.00
1.07
1.10
2.06
3.00
3.00
3.08
6.92
2.92
3.08
6.08

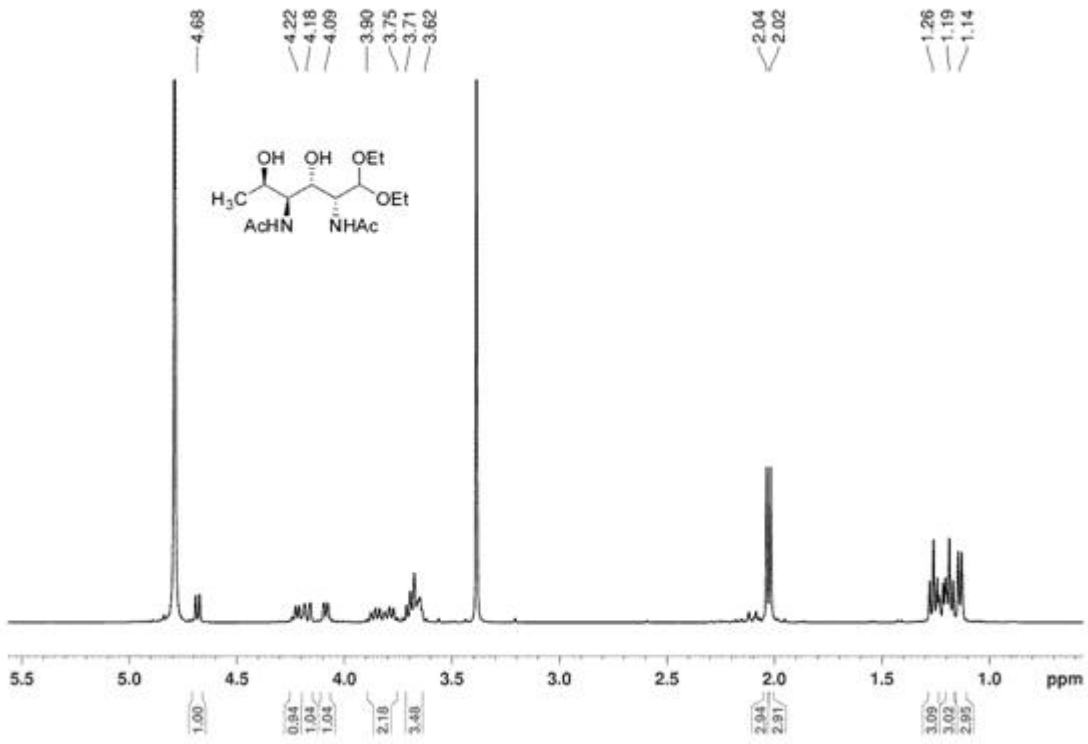

H3C
OAc
OEt
OEt
NBoc NHAc
170.2
169.9
102.2
80.6
71.7
70.0
65.8
51.6
28.5
23.5
22.6
21.3
15.3
15.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

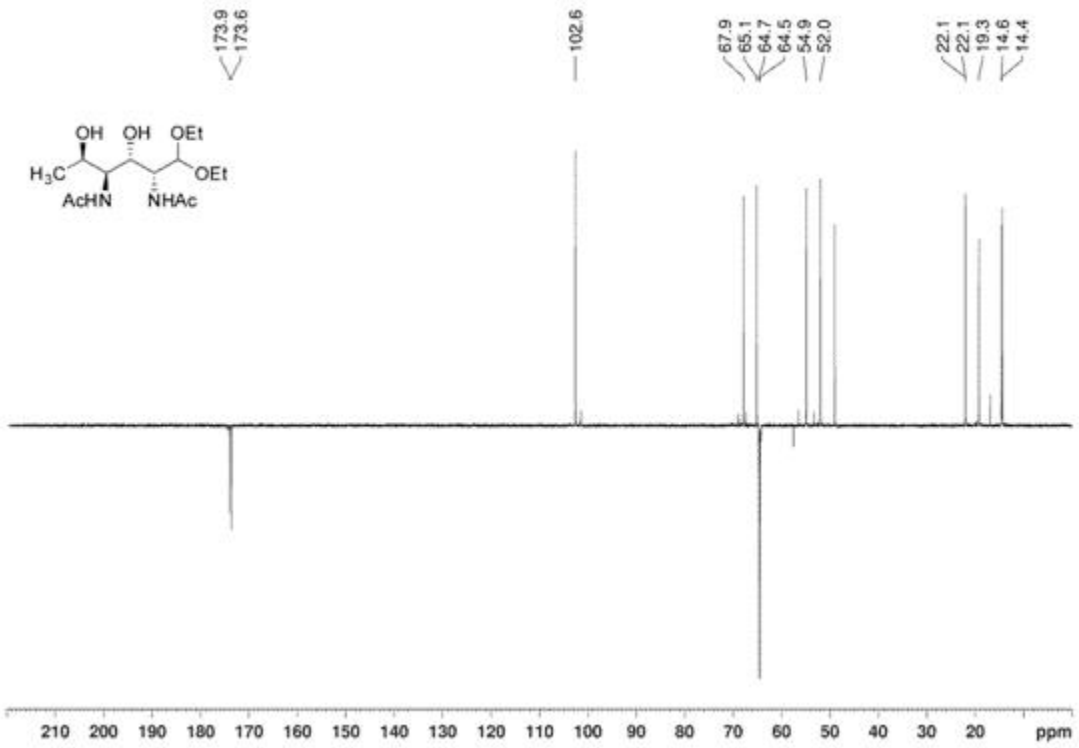
+

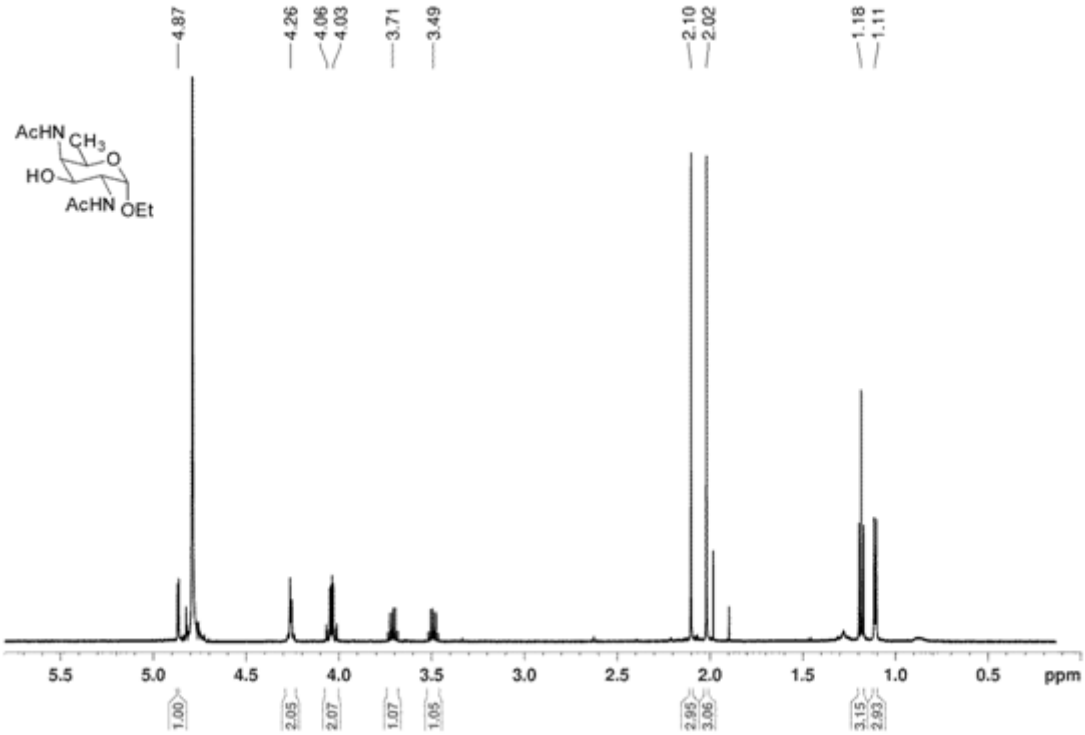

H3C
OAc
OEt
OEt
NBoc NHAc
170.2
169.9
151.6
102.2
94.3
80.6
71.7
70.0
65.8
64.1
62.9
51.6
28.5
27.9
26.9
23.5
22.6
21.3
15.3
15.2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

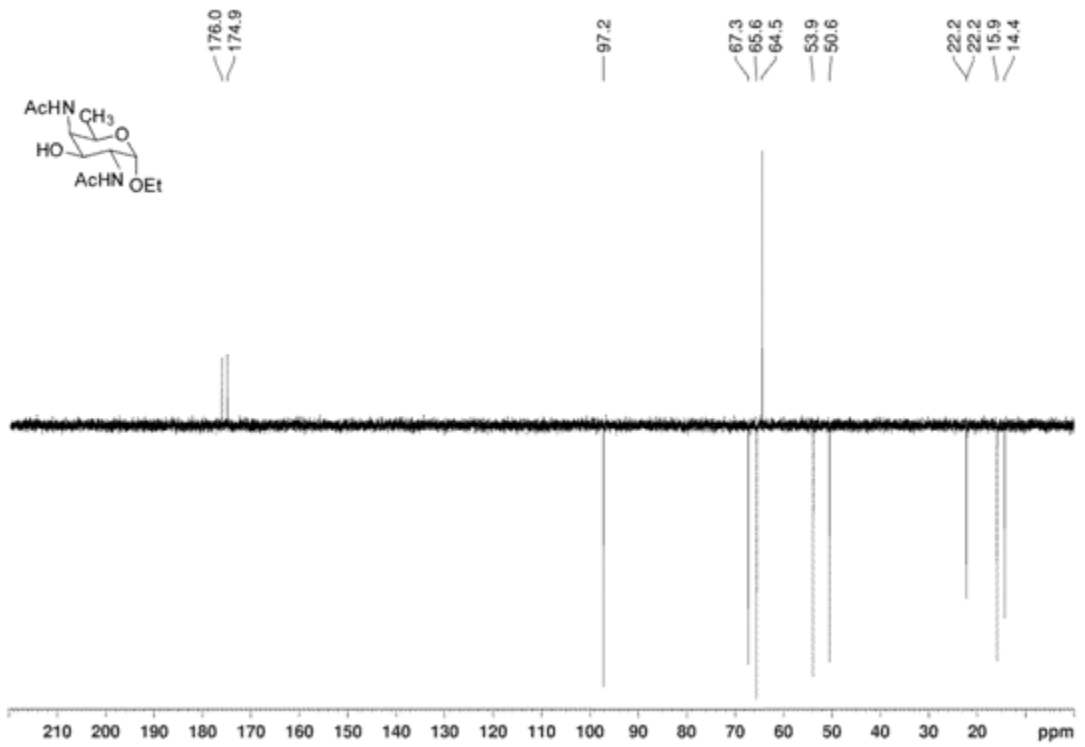

5.20
4.62
4.36
4.27
4.23
4.07
3.99
3.90
3.86
3.74
2.11
2.10
2.02
2.02
1.15
1.10
AcHN
CH3
O
HO
AcHN
OH
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.92
1.00
0.94
0.97
1.06
0.94
0.94
1.05
1.08
1.02
2.90
2.64
2.83
2.72
3.00
2.72

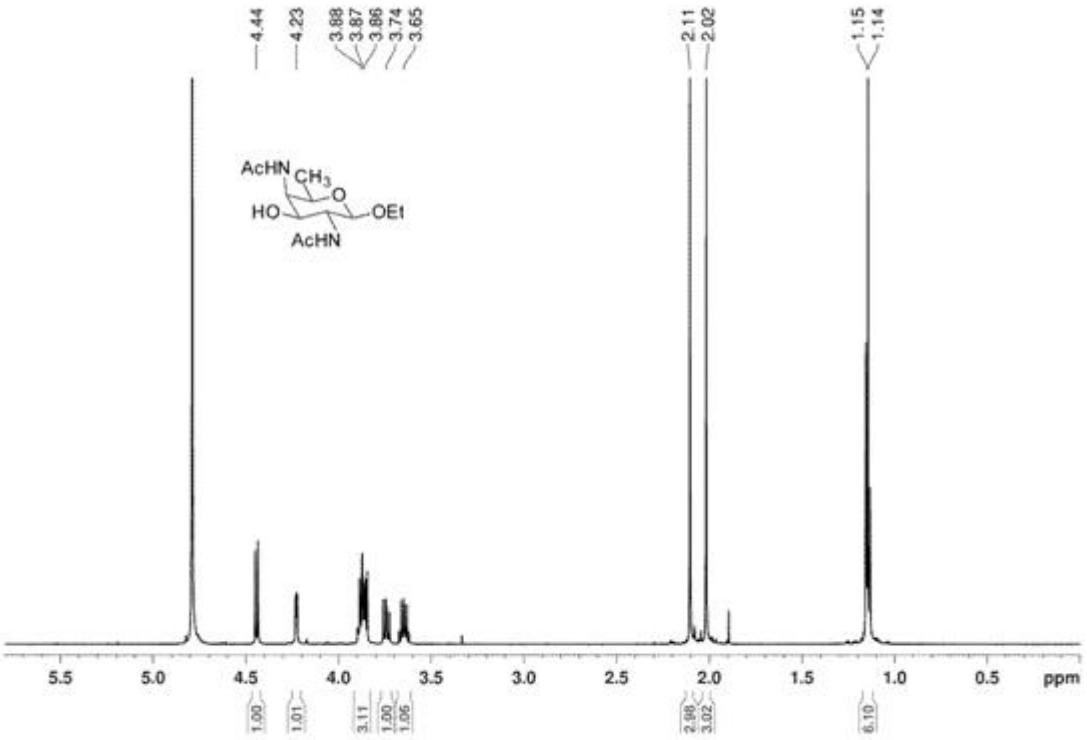

AcHN
CH3
O
HO
AcHN
OH
176.0
176.0
175.3
175.0
95.8
91.3
70.5
70.3
66.9
65.4
54.3
54.0
53.3
51.0
22.5
22.3
22.2
16.2
16.1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

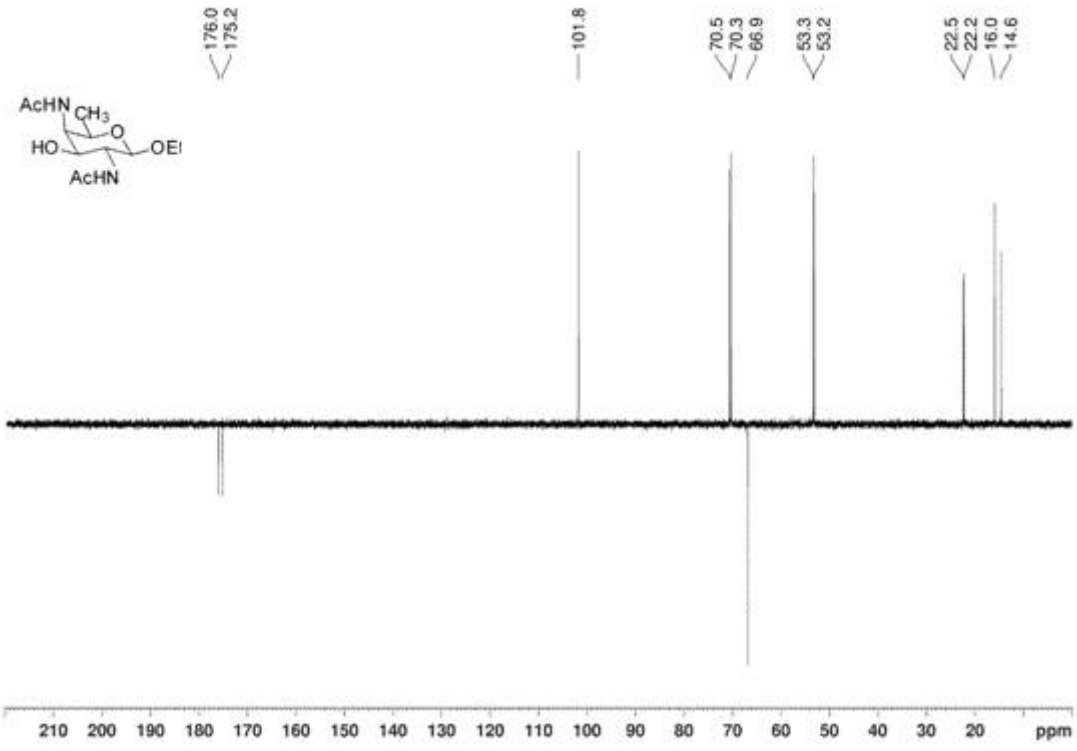

4.68
4.22
4.18
4.09
3.90
3.75
3.71
3.62
2.04
2.02
1.26
1.19
1.14
OH
OH
OEt
OEt
H3C
AcHN
NHAc
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
0.84
1.04
1.04
2.18
3.48
2.94
2.91
3.09
3.02
2.95

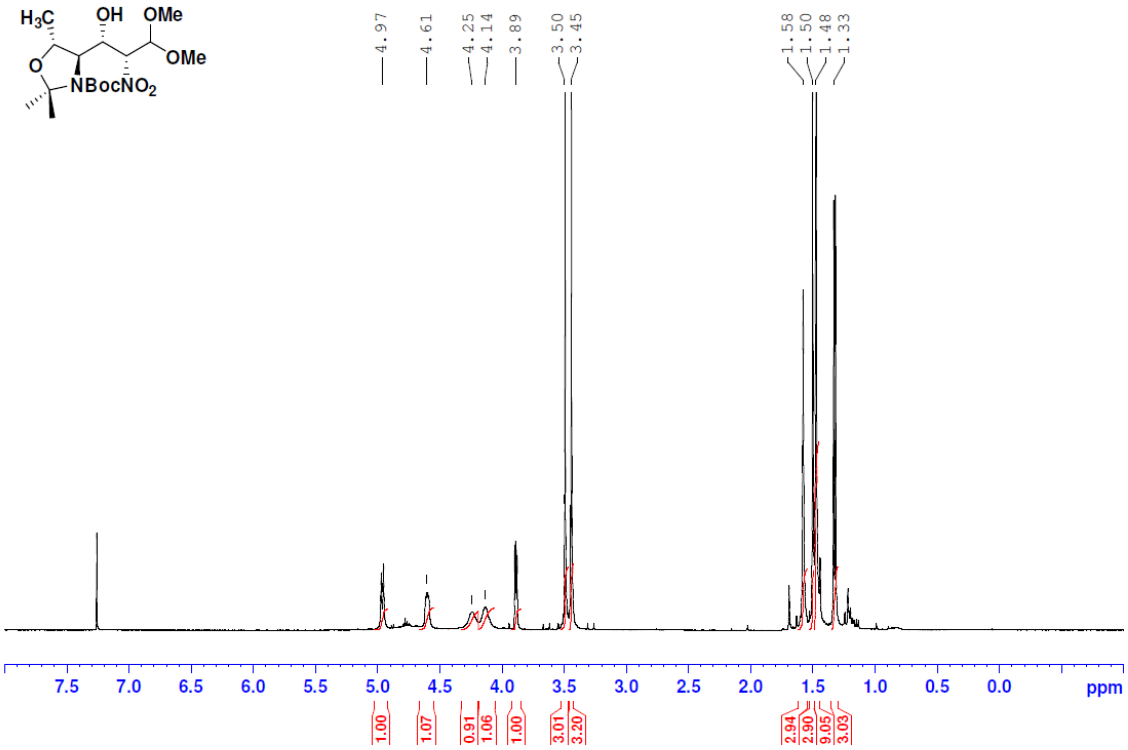

173.9
173.6
102.6
67.9
65.1
64.7
64.5
54.9
52.0
22.1
22.1
19.3
14.6
14.4
OH
OH
OEt
OEt
H3C
AcHN
NHAc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

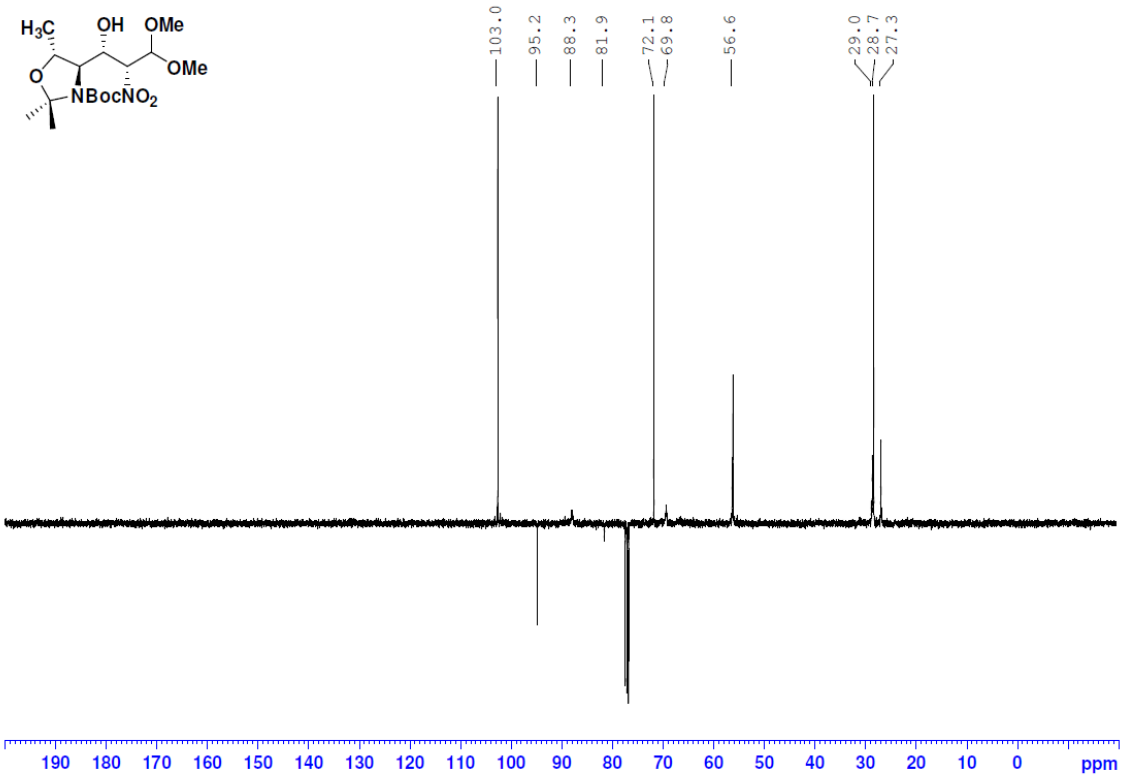

4.87
4.26
4.06
4.03
3.71
3.49
2.10
2.02
1.18
1.11
AcHN
CH3
O
HO
AcHN
OEt
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.05
2.07
1.07
1.05
2.95
3.06
3.15
2.93

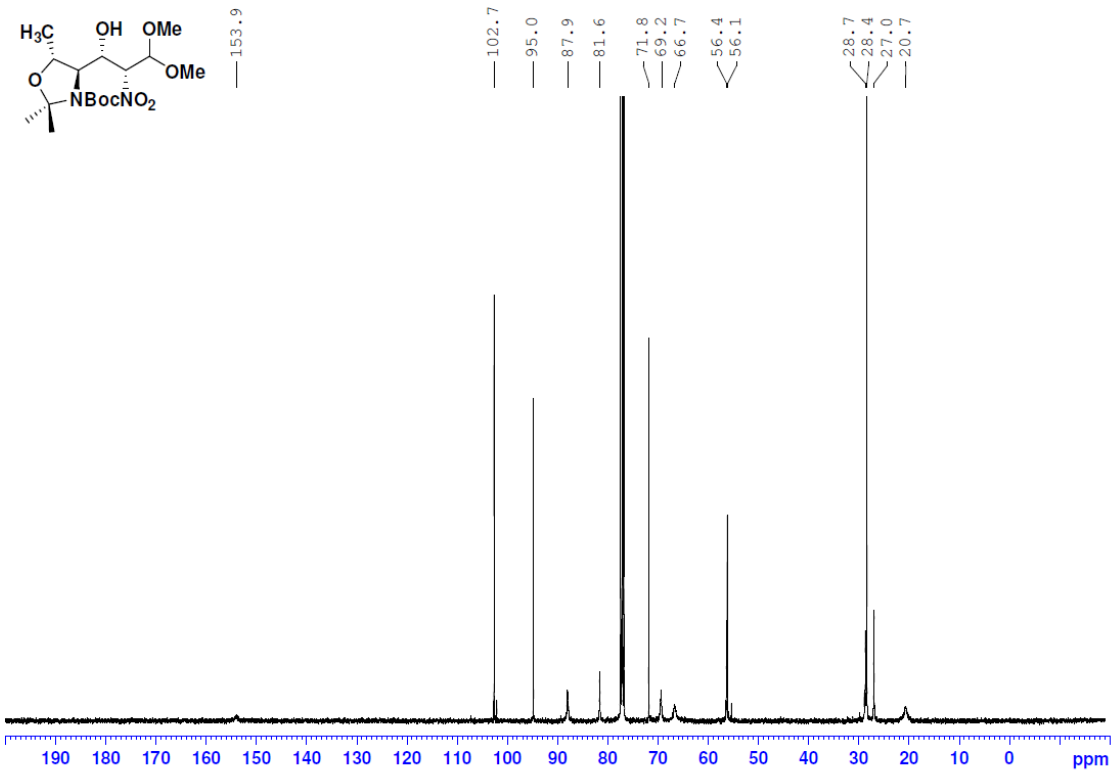

176.0
174.9
97.2
67.3
65.6
64.5
53.9
50.6
22.2
22.2
15.9
14.4
AcHN
CH3
O
HO
AcHN
OEt
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

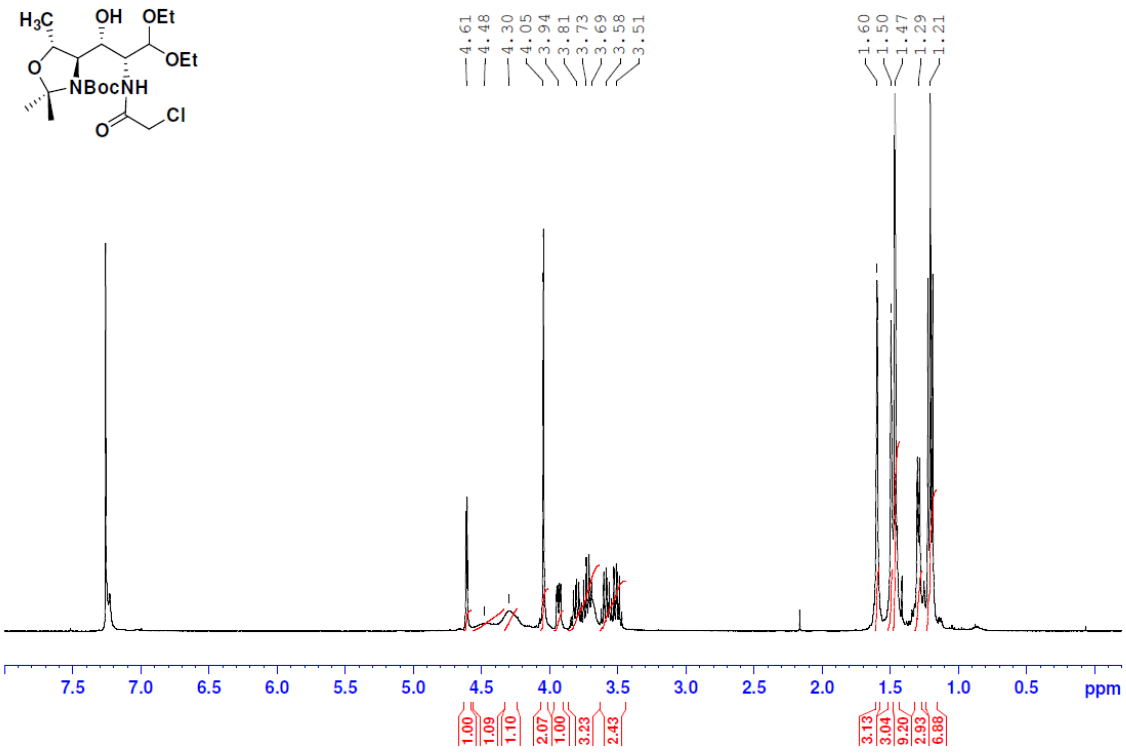

4.44
4.23
3.88
3.87
3.86
3.74
3.65
2.11
2.02
1.15
1.14
AcHN
CH3
O
HO
OEt
AcHN
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.01
3.11
1.00
1.06
2.98
3.02
6.10

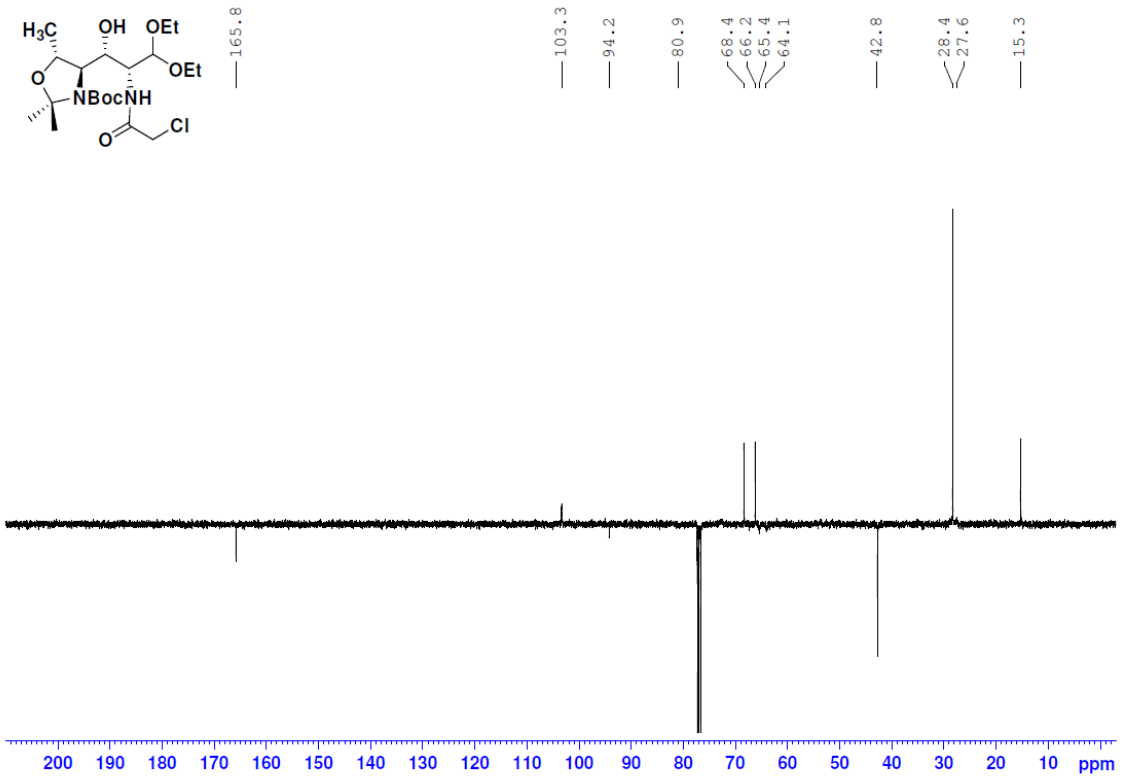

176.0
175.2
101.8
70.5
70.3
66.9
53.3
53.2
22.5
22.2
16.0
14.6
AcHN
CH3
O
HO
OEt
AcHN
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

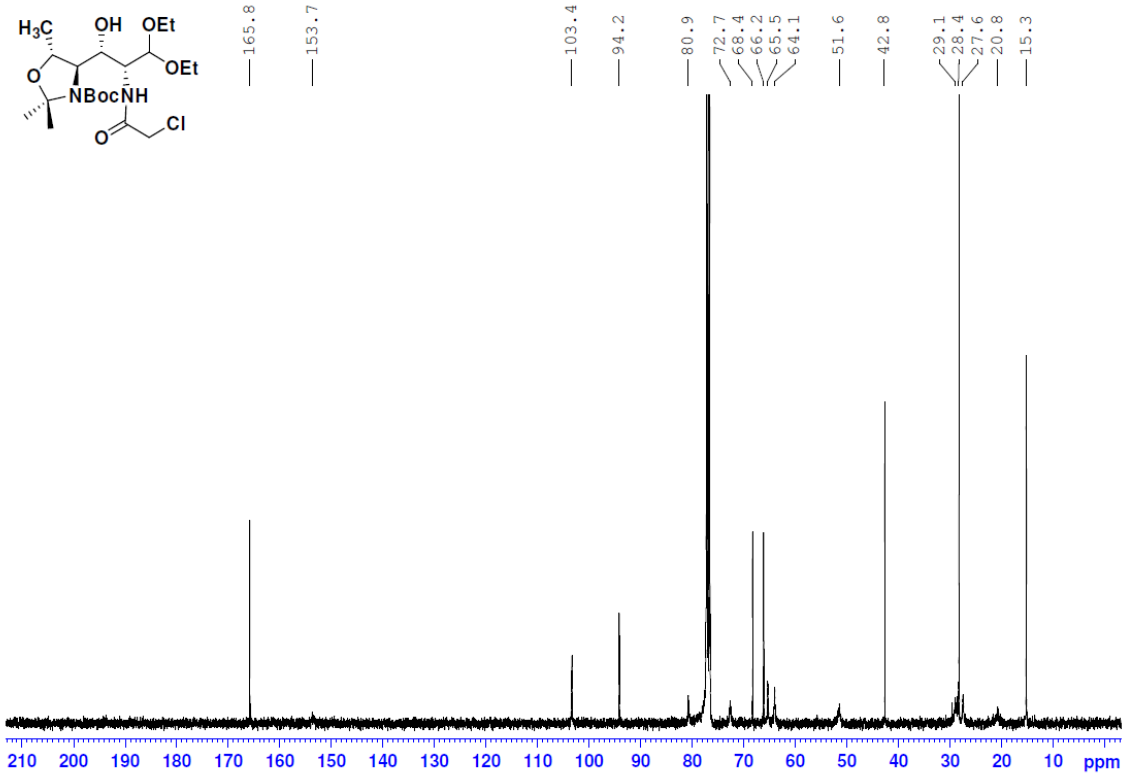

H3C
OH
OMe
OMe
O
NBocNO2
4.97
4.61
4.25
4.14
3.89
3.50
3.45
1.58
1.50
1.48
1.33
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.07
0.91
1.06
1.00
3.01
3.20
2.94
2.90
9.05
3.03

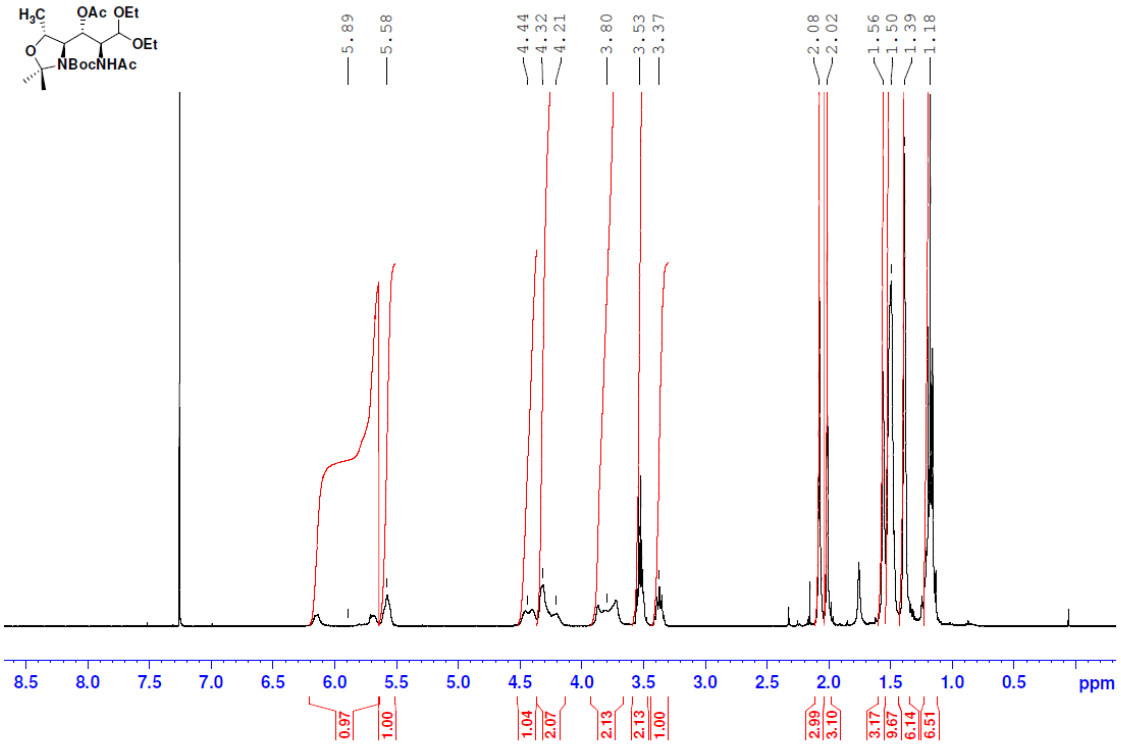

H3C
OH
OMe
OMe
O
NBocNO2
103.0
95.2
88.3
81.9
72.1
69.8
56.6
29.0
28.7
27.3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

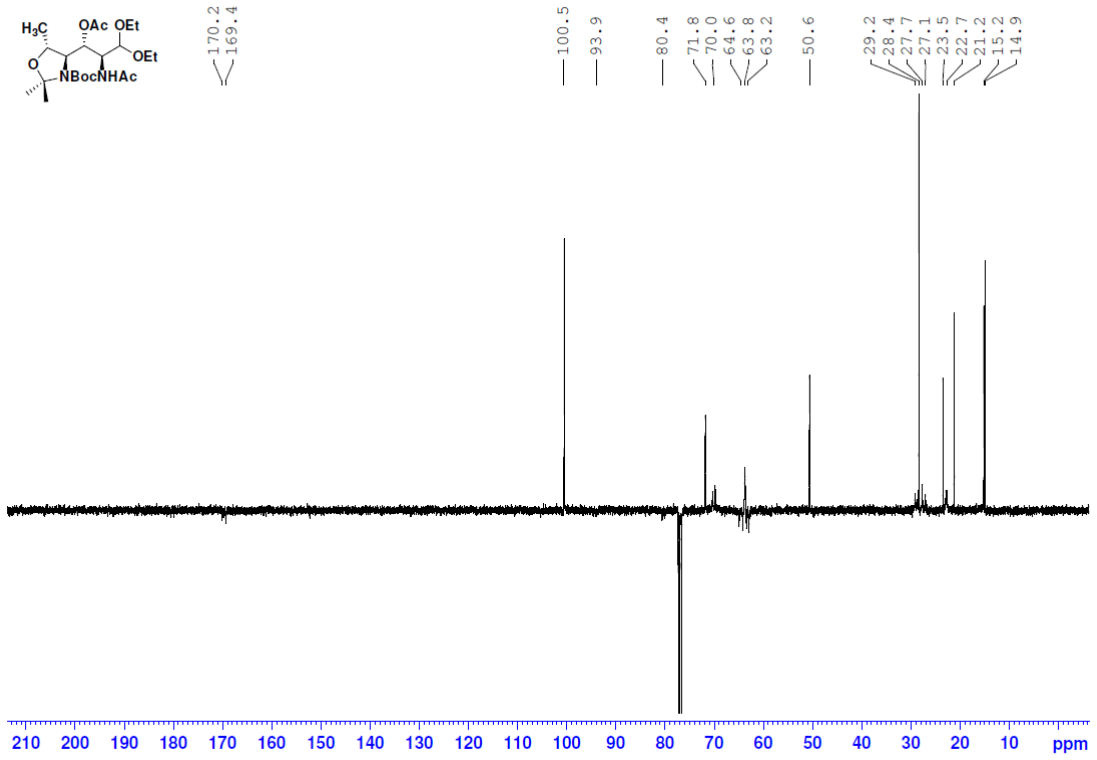

H3C
OH
OMe
OMe
O
NBocNO2
153.9
102.7
95.0
87.9
81.6
71.8
69.2
66.7
56.4
56.1
28.7
28.4
27.0
20.7
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

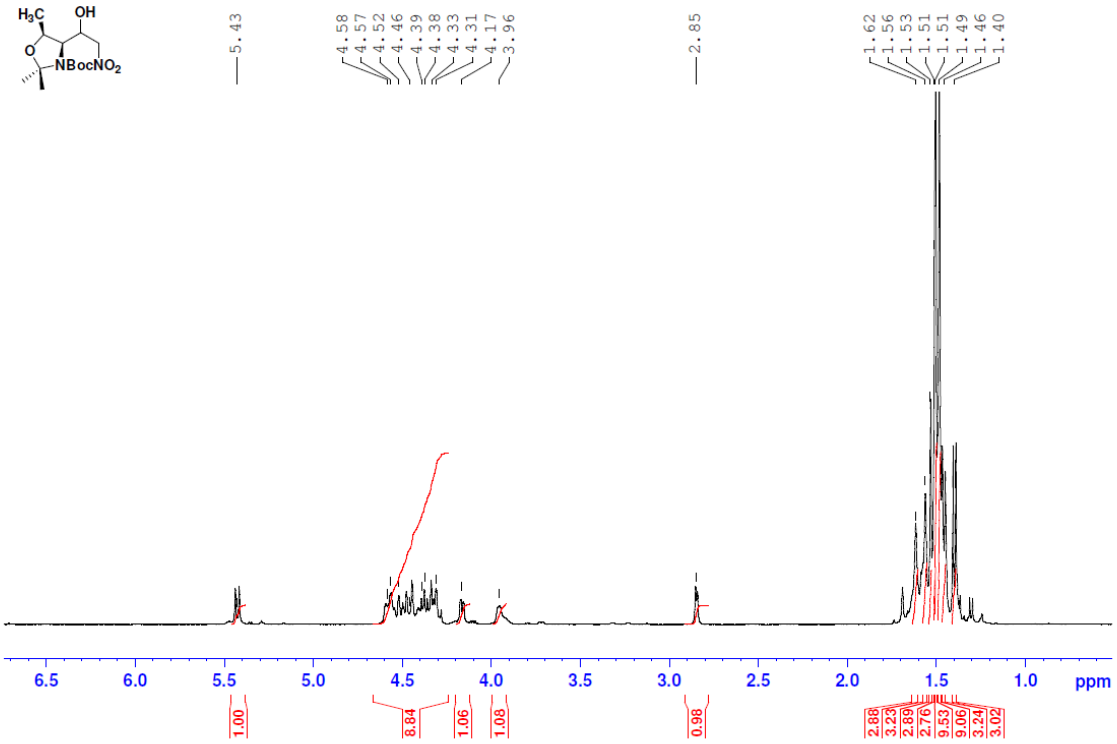

H3C
OH
OEt
OEt
O
NBocNH
Cl
O
4.61
4.48
4.30
4.05
3.94
3.81
3.73
3.69
3.58
3.51
1.60
1.50
1.47
1.29
1.21
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.09
1.10
2.07
1.00
3.23
2.43
3.13
3.04
9.20
2.93
6.88

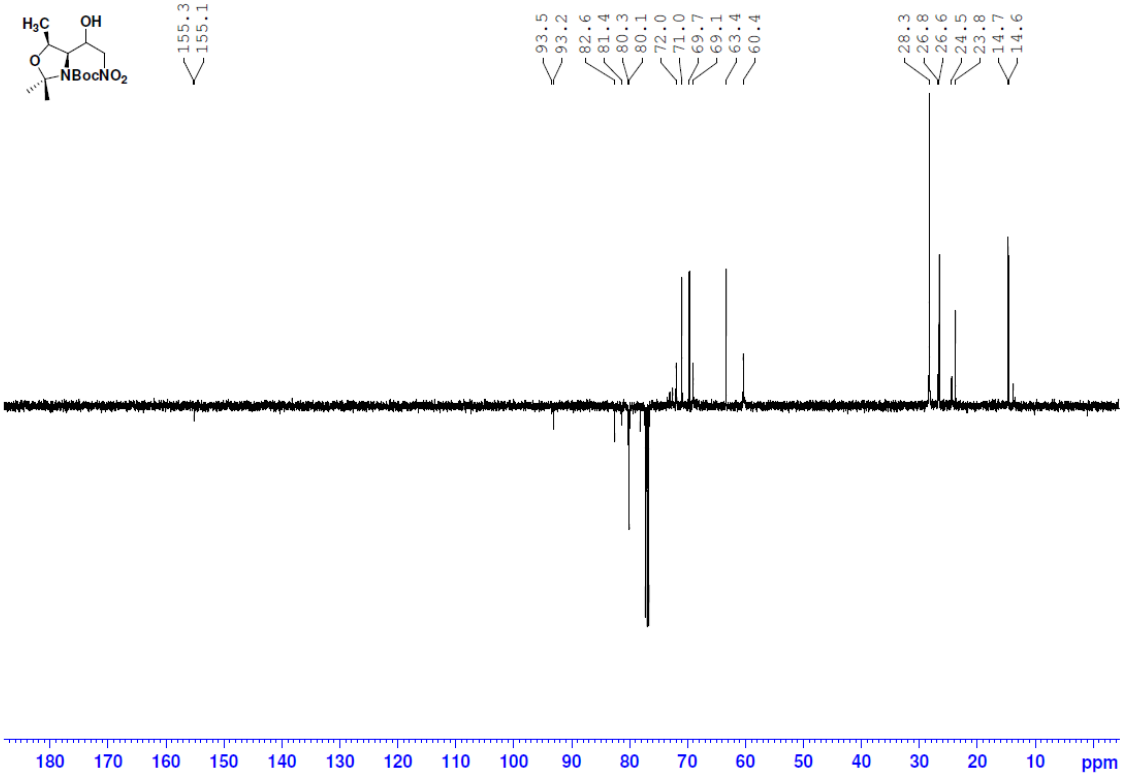

H3C
OH
OEt
OEt
O
NBocNH
O
Cl
165.8
103.3
94.2
80.9
68.4
66.2
65.4
64.1
42.8
28.4
27.6
15.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

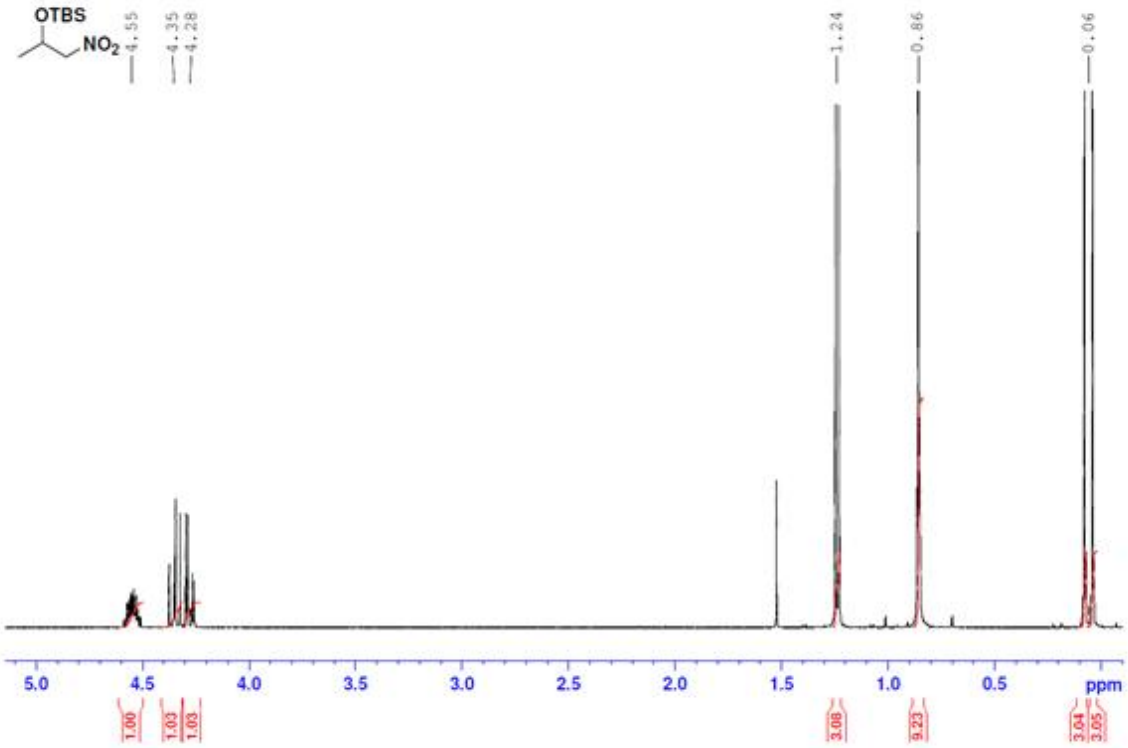

H3C
OH
OEt
OEt
O
NBocNH
O
Cl
165.8
153.7
103.4
94.2
80.9
72.7
68.4
66.2
65.5
64.1
51.6
42.8
29.1
28.4
27.6
20.8
15.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

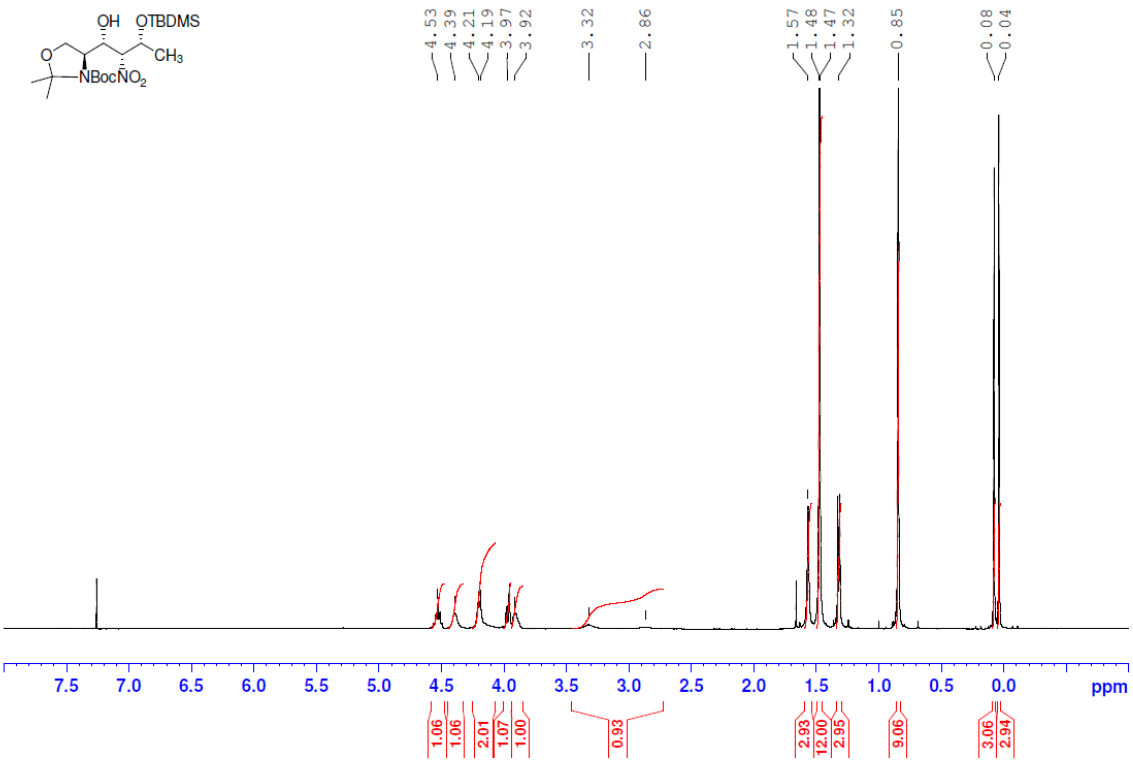

H3C
OAc OEt
OEt
O
NBocNHAc
5.89
5.58
4.44
4.32
4.21
3.80
3.53
3.37
2.08
2.02
1.56
1.50
1.39
1.18
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.97
1.00
1.04
2.07
2.13
2.13
1.00
2.99
3.10
3.17
9.67
6.14
6.51

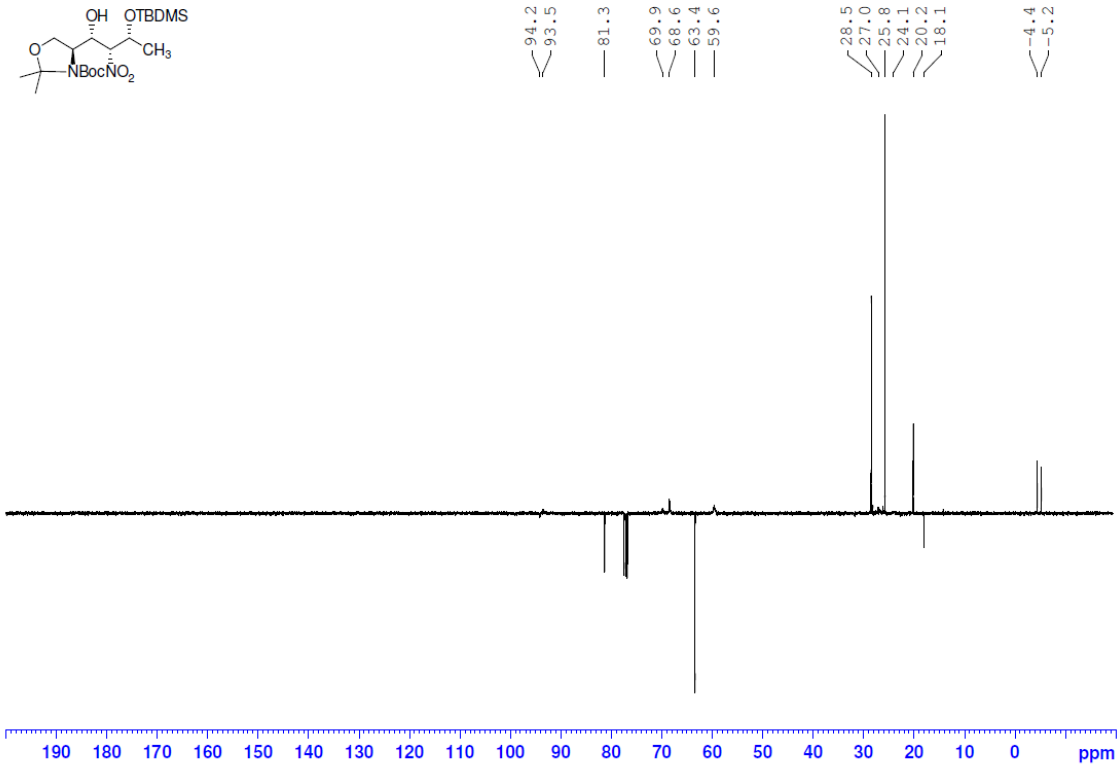

H3C
OAc OEt
OEt
O
NBocNHAc
170.2
169.4
100.5
93.9
80.4
71.8
70.0
64.6
63.8
63.2
50.6
29.2
28.4
27.7
27.1
23.5
22.7
21.2
15.2
14.9
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

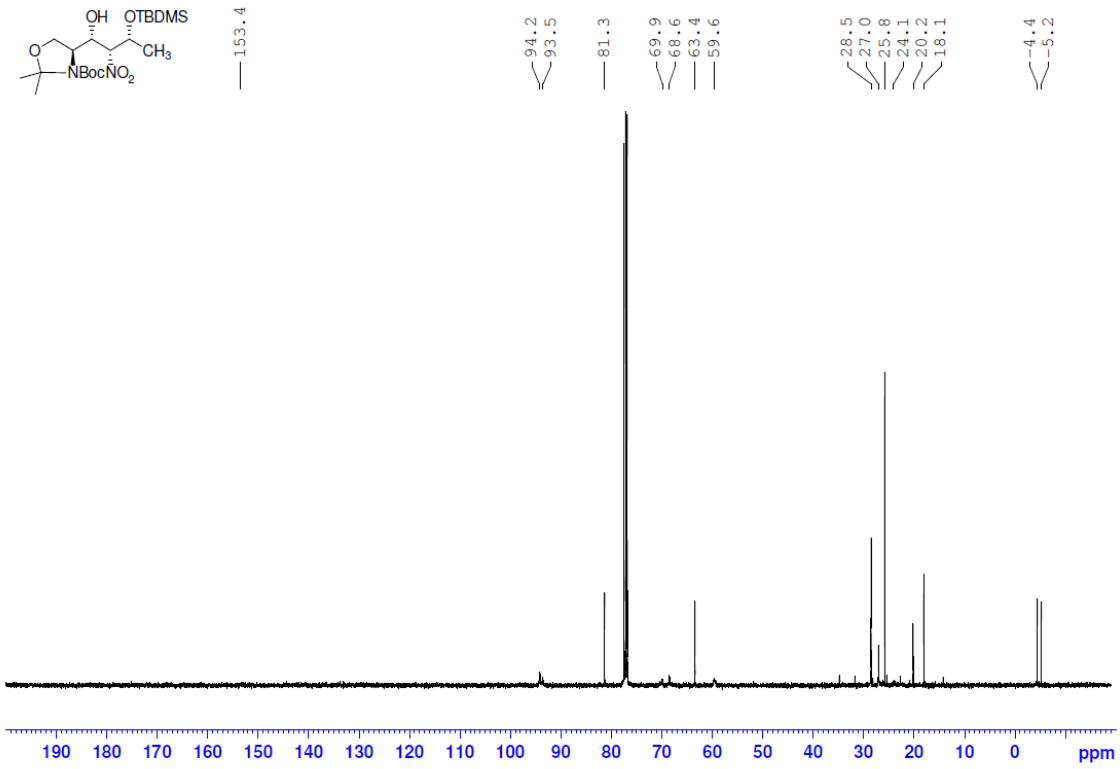

H3C
OH
O
NBocNO2
5.43
4.58
4.57
4.52
4.46
4.39
4.38
4.33
4.31
4.17
3.96
2.85
1.62
1.56
1.53
1.51
1.51
1.49
1.46
1.40
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
8.84
1.06
1.08
0.98
2.88
3.23
2.89
2.76
9.53
9.06
3.24
3.02

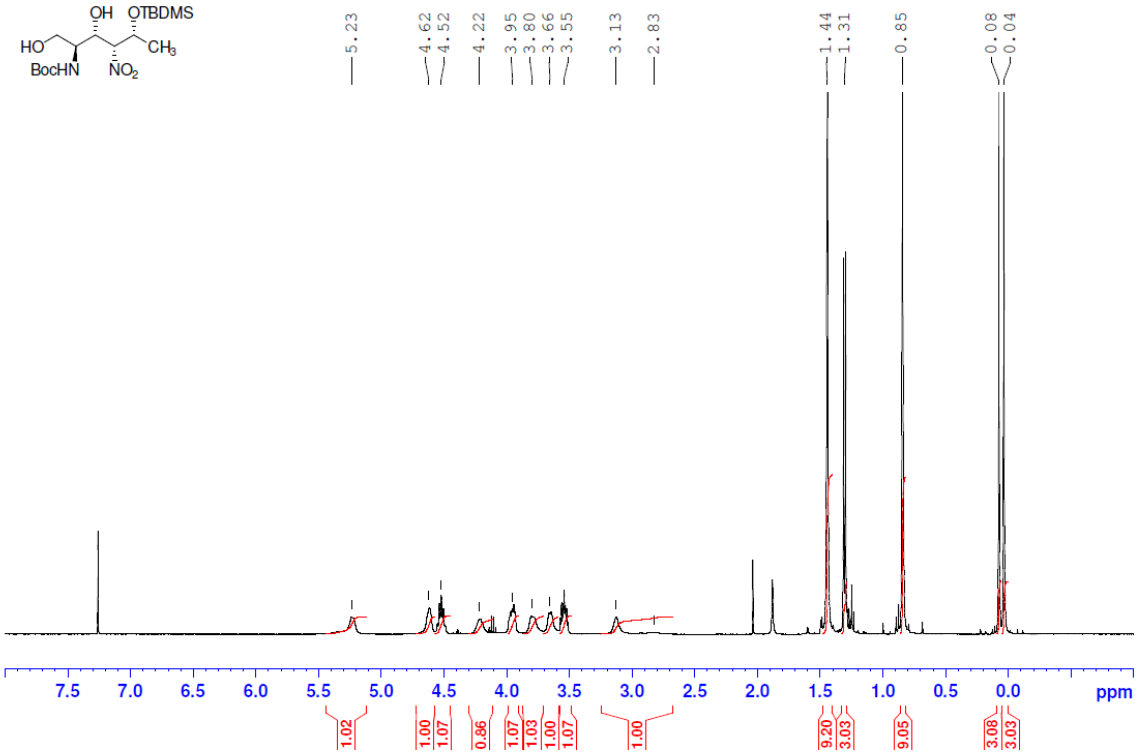

H3C
OH
O
NBocNO2
155.3
155.1
93.5
93.2
82.6
81.4
80.3
80.1
72.0
71.0
69.7
69.1
63.4
60.4
28.3
26.8
26.6
24.5
23.8
14.7
14.6
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

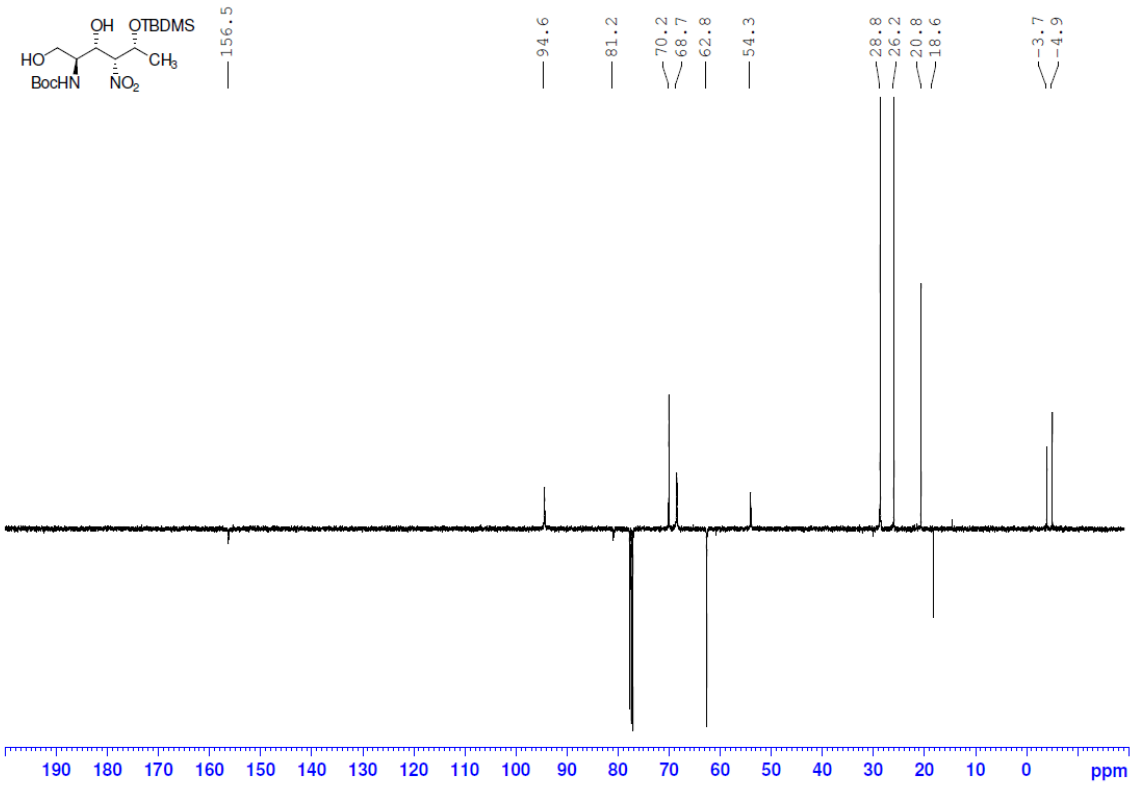

OTBS
NO2
4.55
4.35
4.28
1.24
0.86
0.06
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.03
1.03
3.08
9.23
3.04
3.05

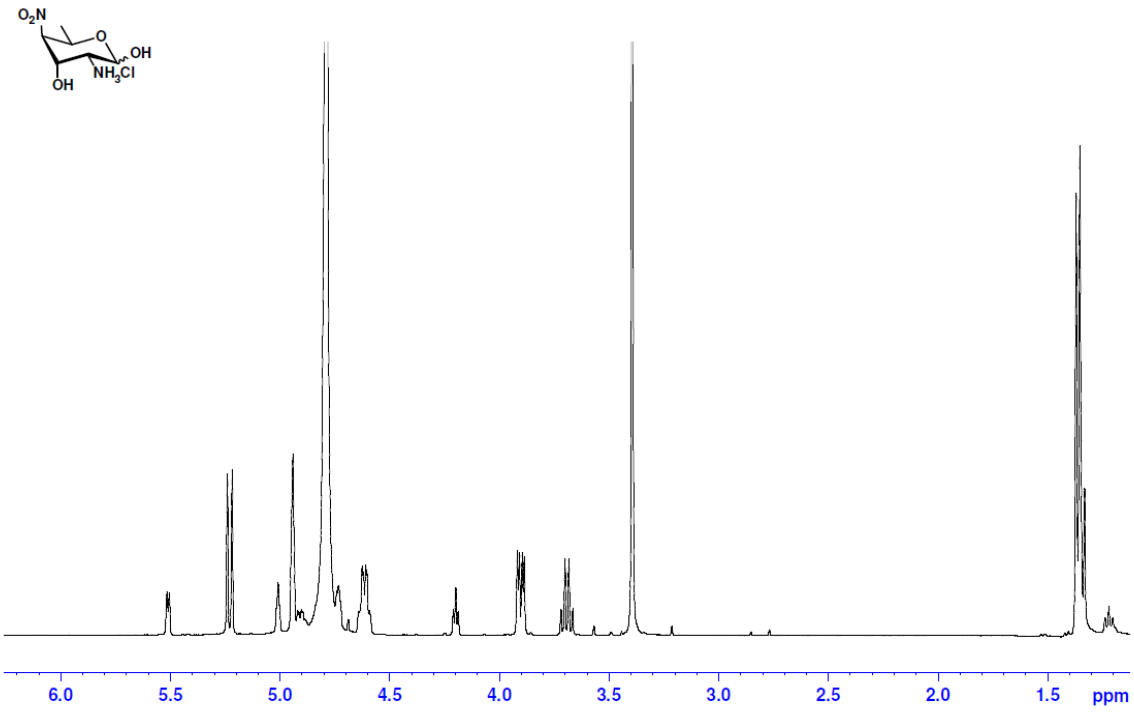

OH
OTBDMS
CH3
NBocNO2
4.53
4.39
4.21
4.19
3.97
3.92
3.32
2.86
1.57
1.48
1.47
1.32
0.85
0.08
0.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.06
1.06
2.01
1.07
1.00
0.93
2.93
12.00
2.95
9.06
3.06
2.94

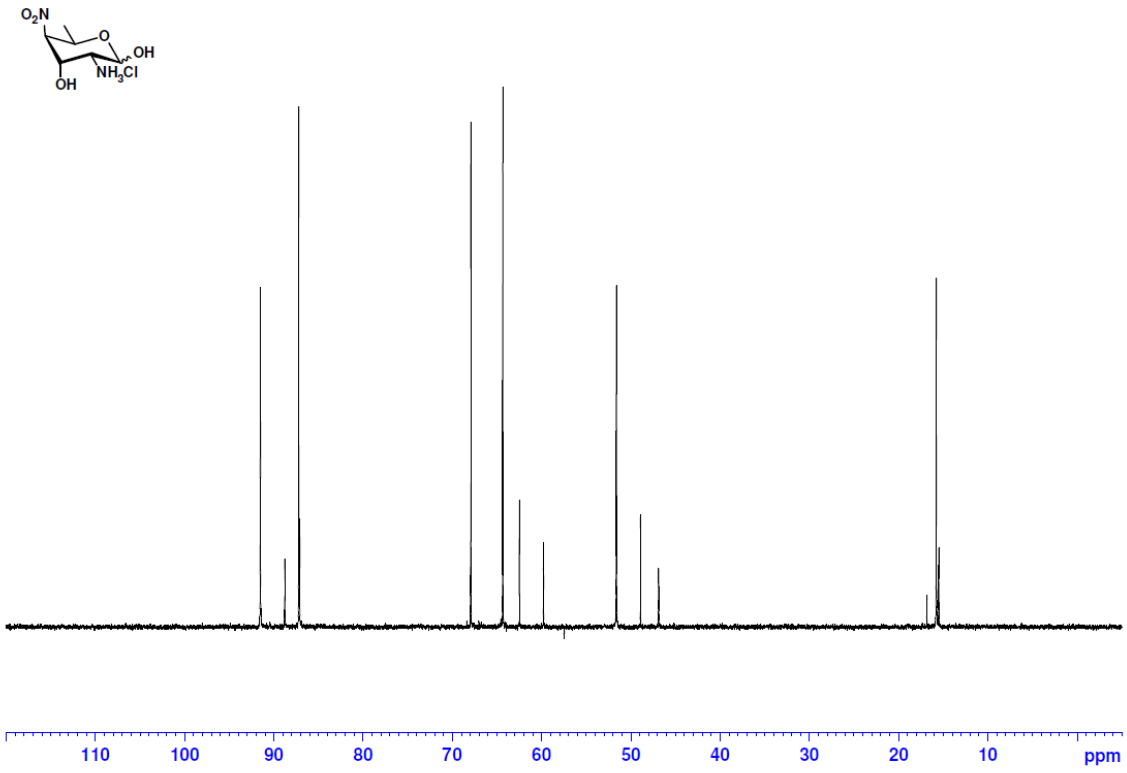

OH
OTBDMS
CH3
O
NBocNO2
94.2
93.5
81.3
69.9
68.6
63.4
59.6
28.5
27.0
25.8
24.1
20.2
18.1
-4.4
-5.2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

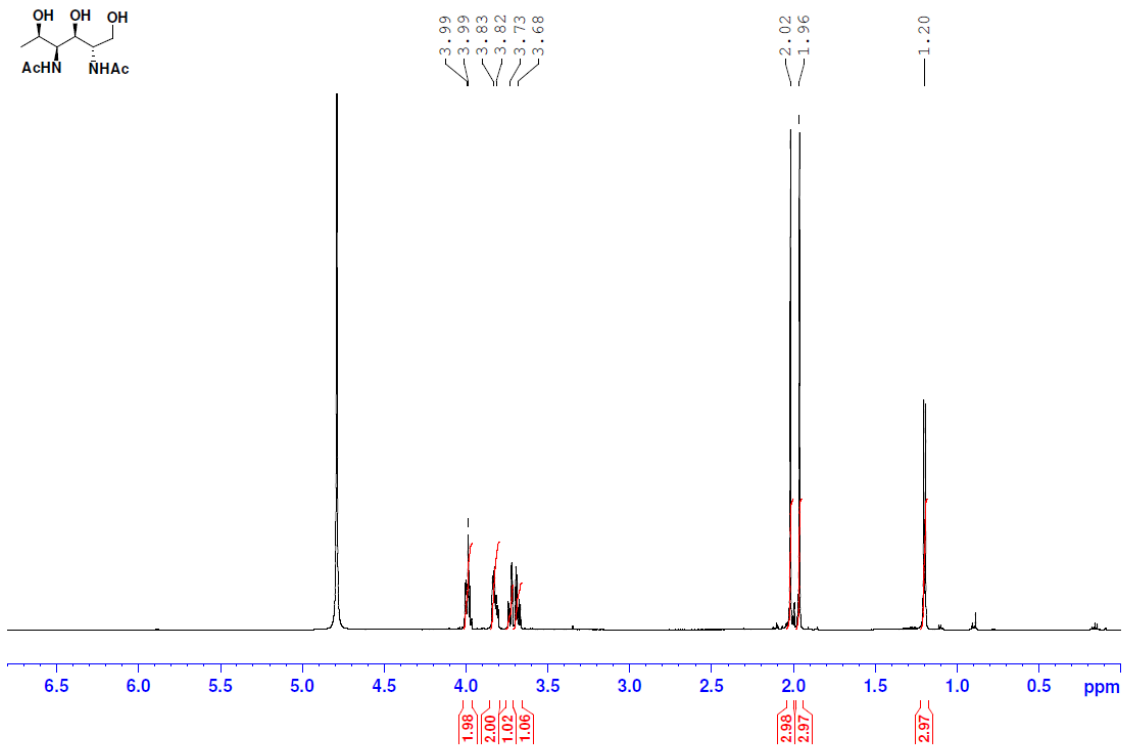

OH
OTBDMS
CH3
O
NBocNO2
153.4
94.2
93.5
81.3
69.9
68.6
63.4
59.6
28.5
27.0
25.8
24.1
20.2
18.1
-4.4
-5.2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

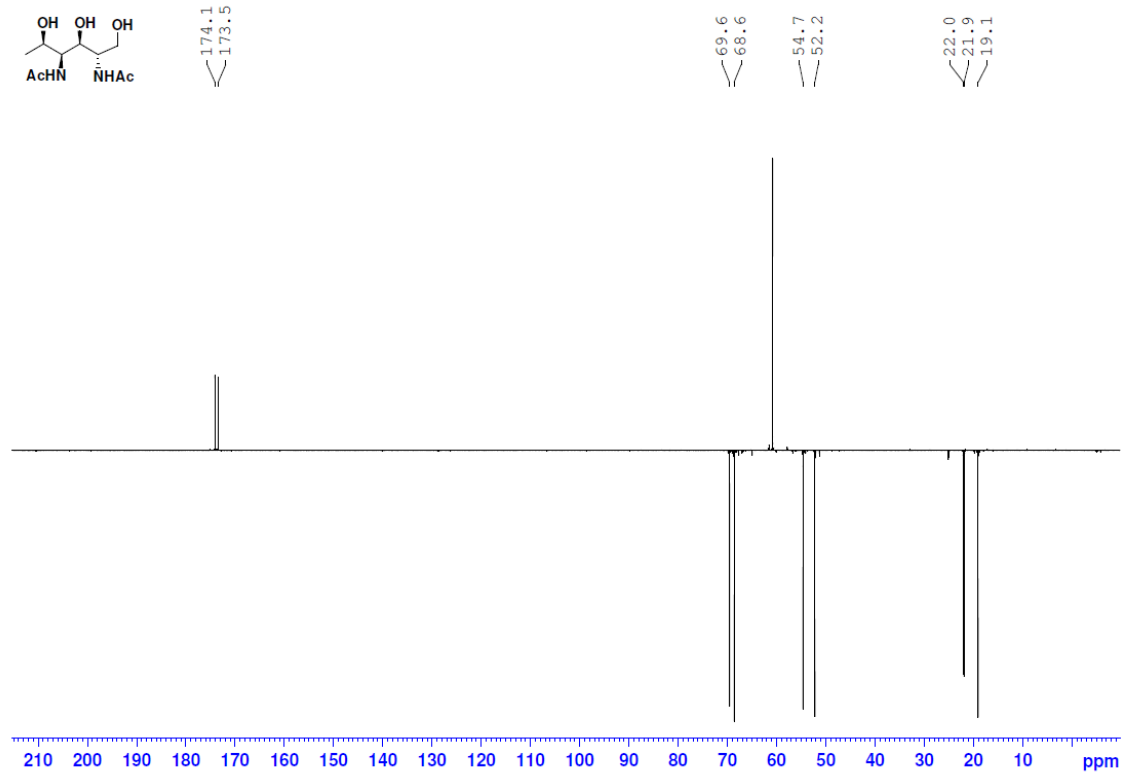

OH
OTBDMS
HO
BocHN
CH3
NO2
5.23
4.62
4.52
4.22
3.95
3.80
3.66
3.55
3.13
2.83
1.44
1.31
0.85
0.08
0.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.02
1.00
1.07
0.86
1.07
1.03
1.00
1.07
1.00
9.20
3.03
9.05
3.08
3.03

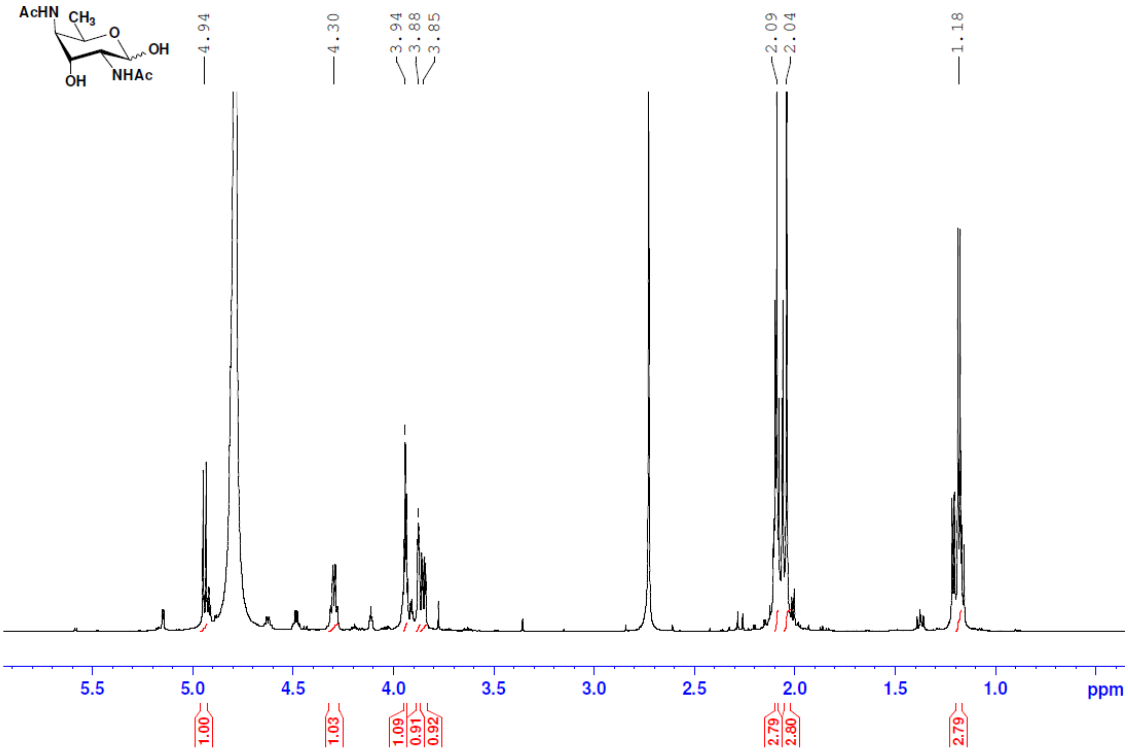

OH
OTBDMS
HO
BocHN
CH3
NO2
156.5
94.6
81.2
70.2
68.7
62.8
54.3
28.8
26.2
20.8
18.6
3.7
-4.9
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

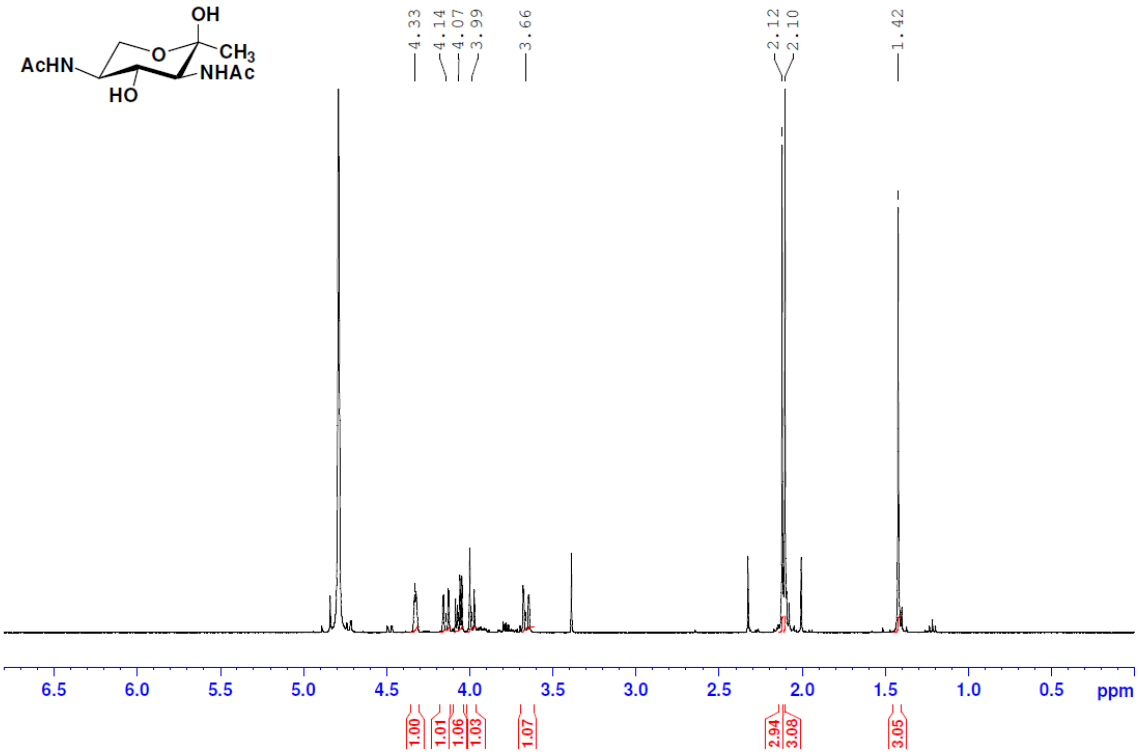

O2N
O
OH
NH3Cl
OH
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

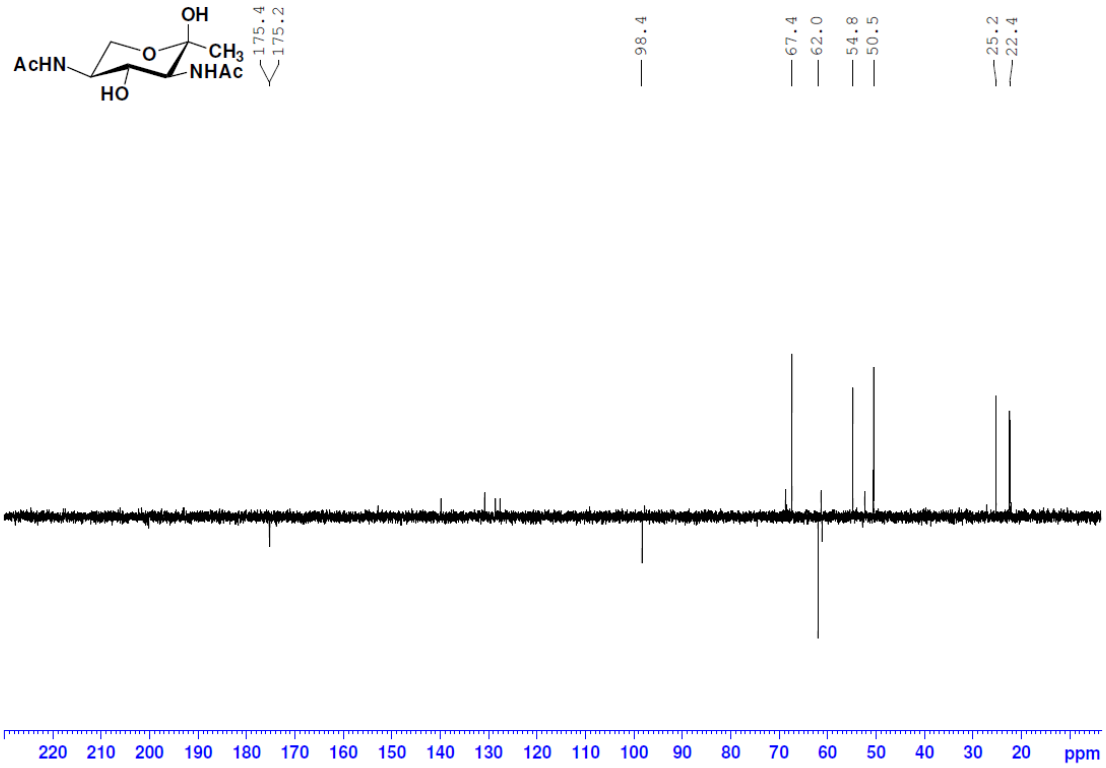

O2N
O
OH
NH3Cl
OH
110
100
90
80
70
60
50
40
30
20
10
ppm

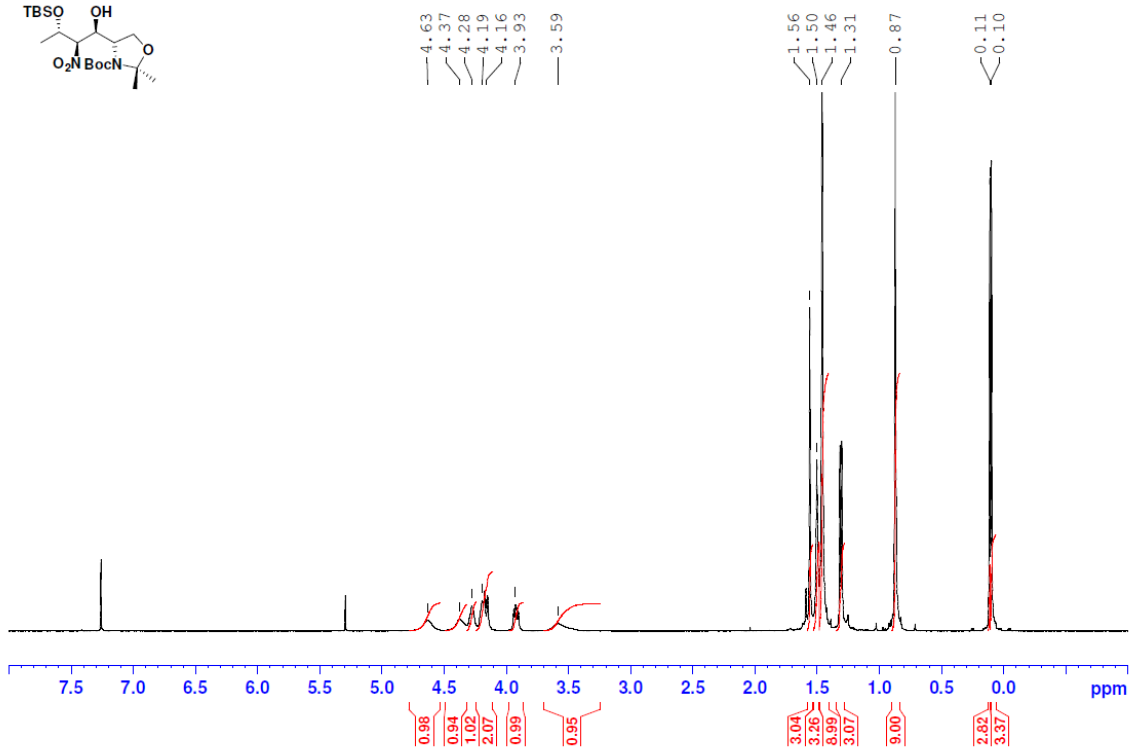

OH
OH
OH
AcHN
NHAc
3.99
3.99
3.83
3.82
3.73
3.68
2.02
1.96
1.20
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.98
2.00
1.02
1.06
2.98
2.97
2.97

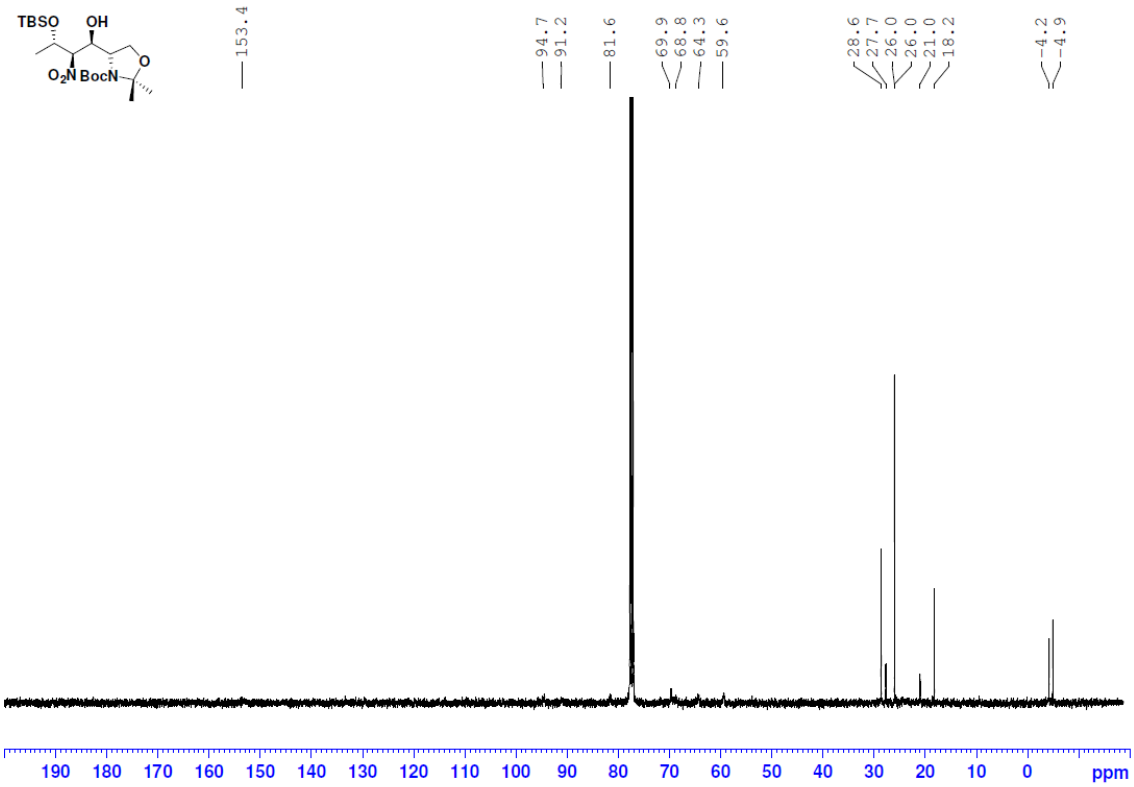

OH
OH
OH
AcHN
NHAc
174.1
173.5
69.6
68.6
54.7
52.2
22.0
21.9
19.1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

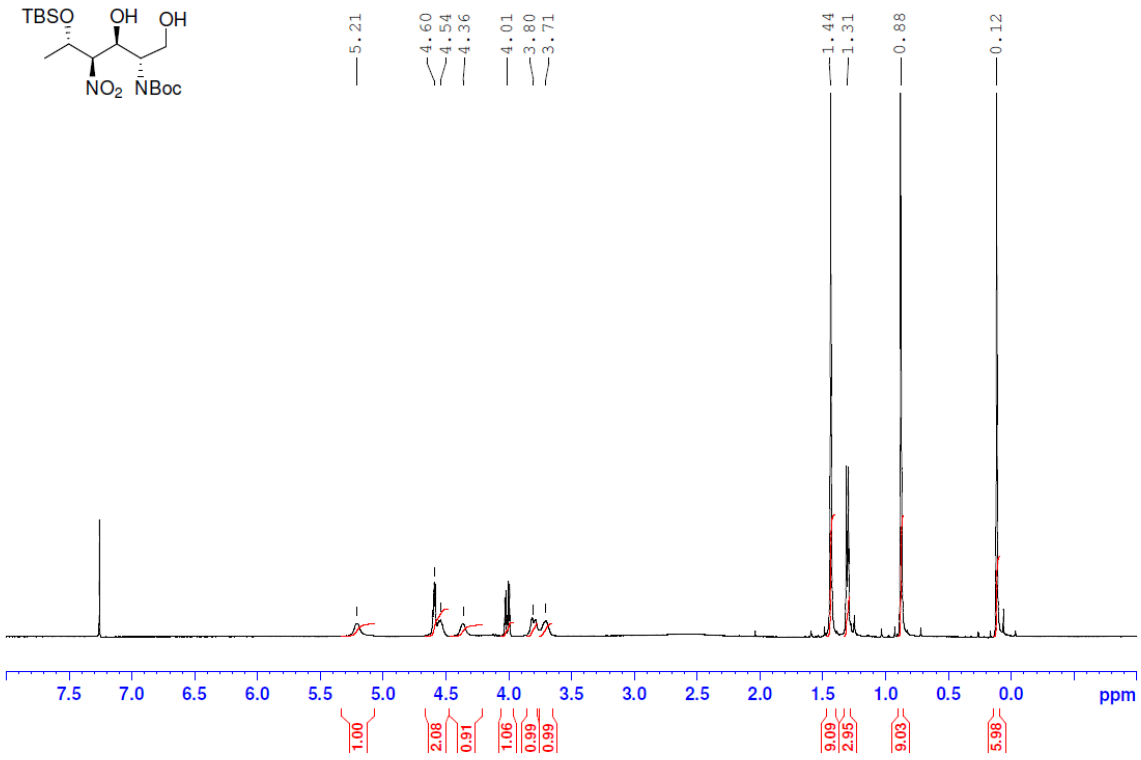

AcHN
CH3
O
OH
OH
NHAc
4.94
4.30
3.94
3.88
3.85
2.09
2.04
1.18
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.03
1.09
0.91
0.92
2.79
2.80
2.79

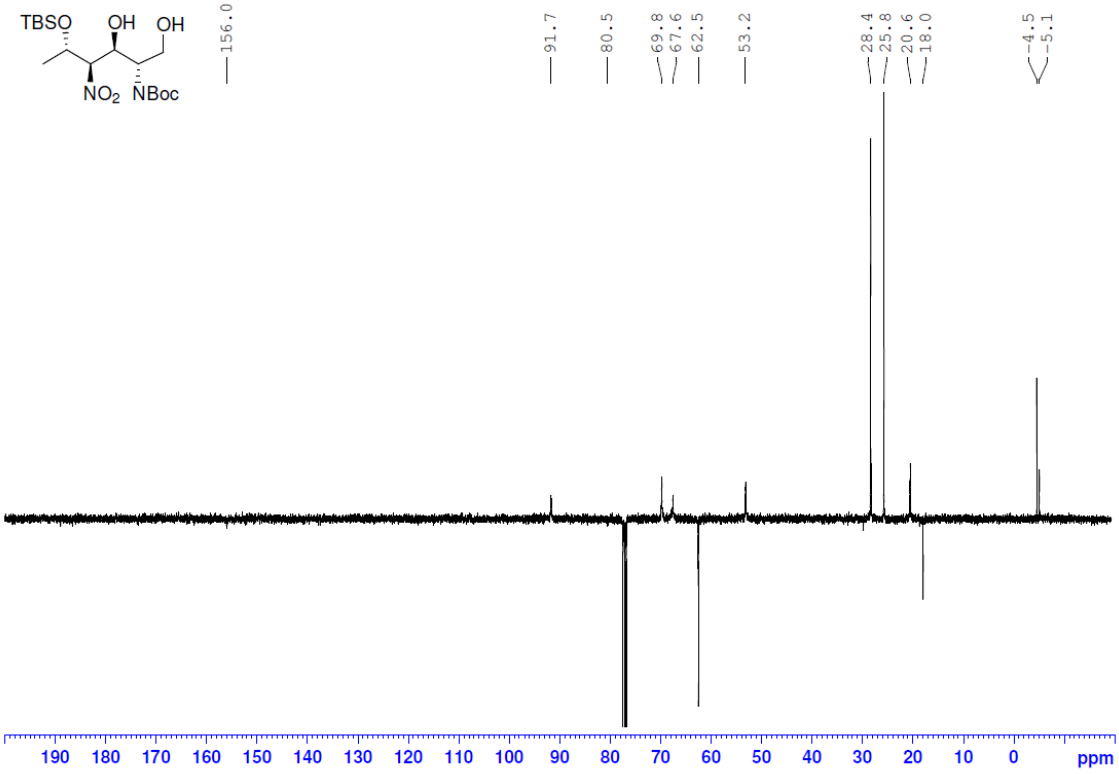

OH
AcHN
O
CH3
NHAc
HO
4.33
4.14
4.07
3.99
3.66
2.12
2.10
1.42
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.01
1.06
1.03
1.07
2.94
3.08
3.05

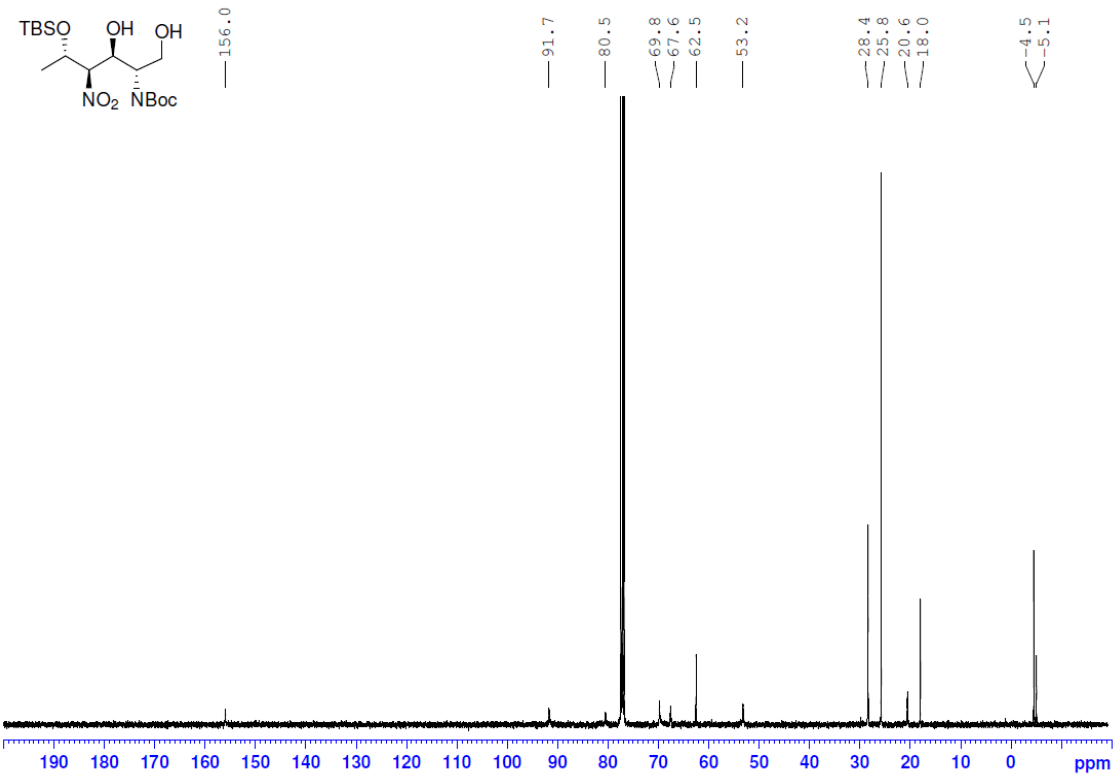

OH
AcHN
O
CH3
NHAc
HO
175.4
175.2
98.4
67.4
62.0
54.8
50.5
25.2
22.4
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

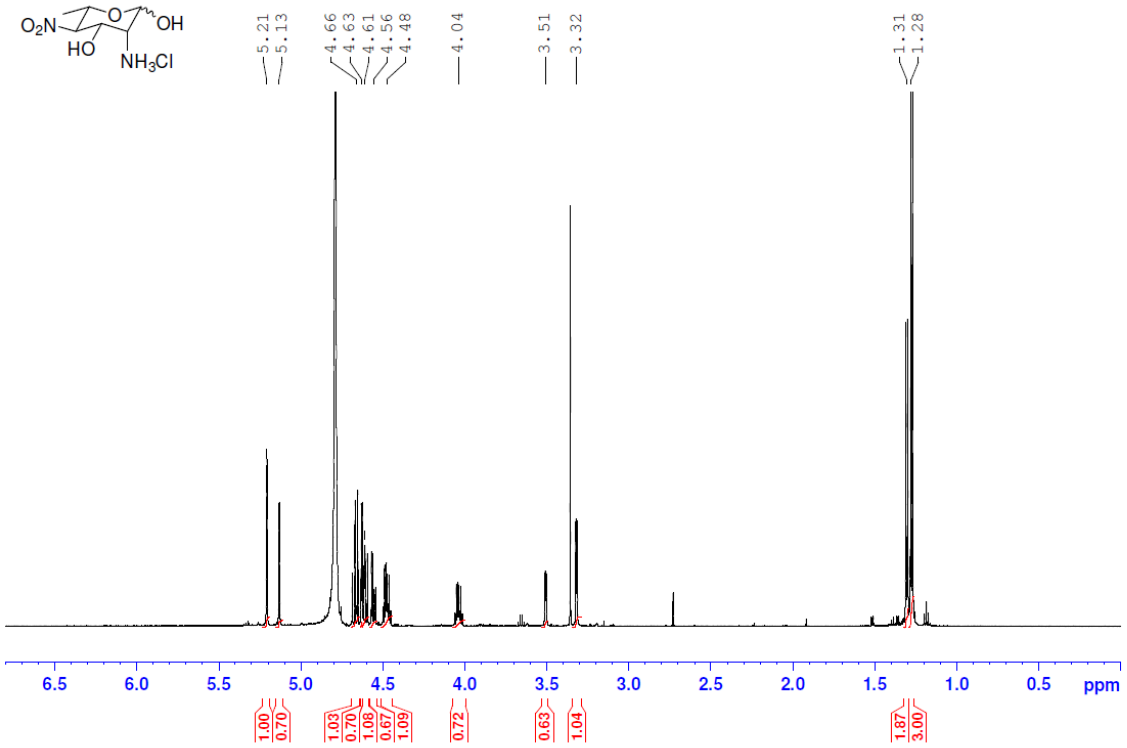

TBSO
OH
O2N BocN
O
4.63
4.37
4.28
4.19
4.16
3.93
3.59
1.56
1.50
1.46
1.31
0.87
0.11
0.10
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.98
0.94
1.02
2.07
0.99
0.95
3.04
3.26
8.99
3.07
9.00
2.82
3.37

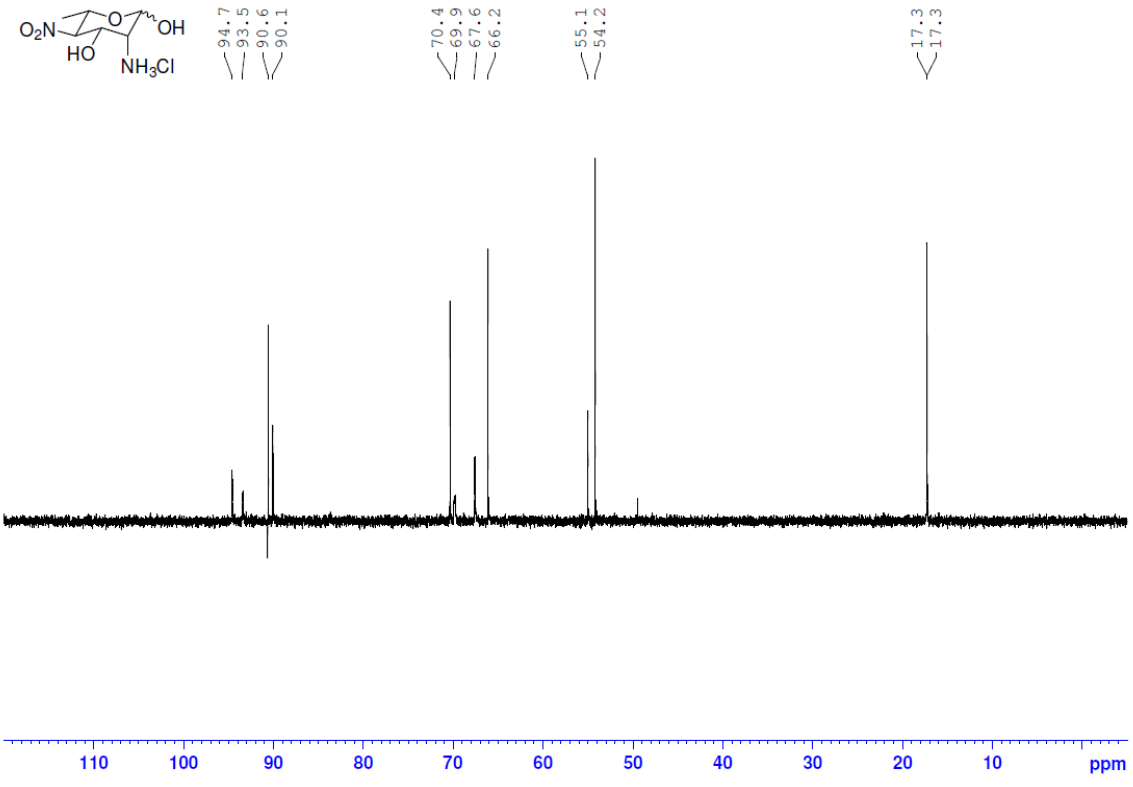

TBSO
OH
O2N BocN
O
153.4
94.7
91.2
81.6
69.9
68.8
64.3
59.6
28.6
27.7
26.0
26.0
21.0
18.2
-4.2
-4.9
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

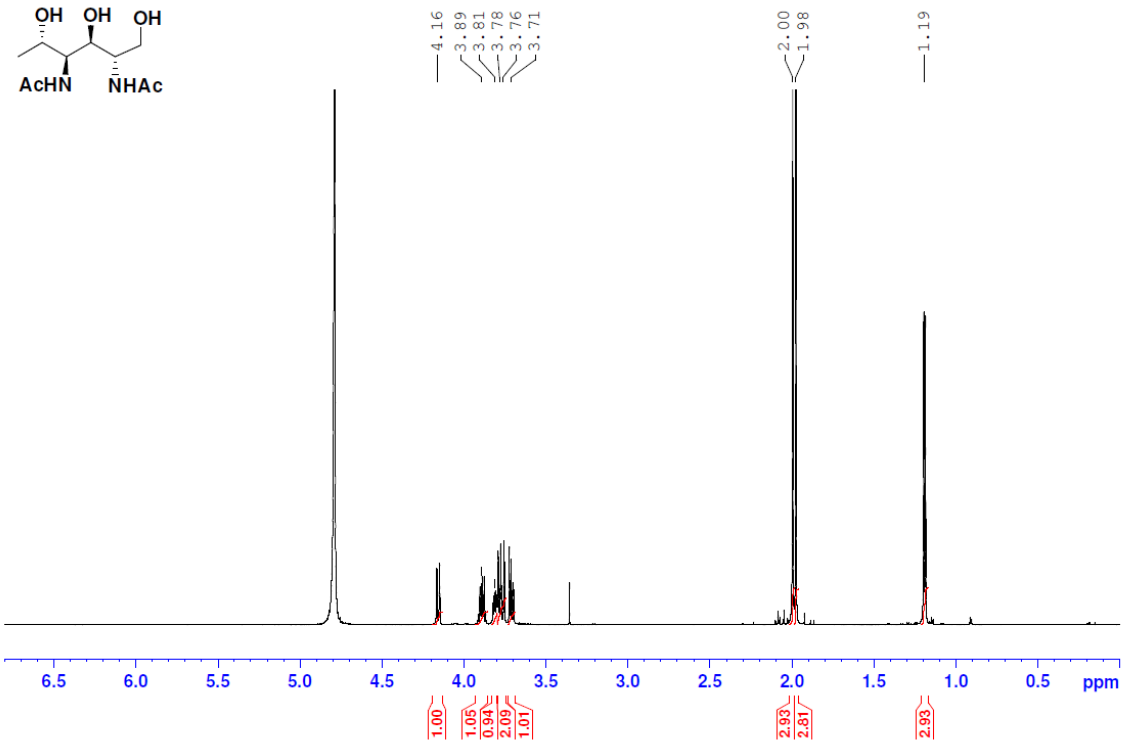

TBSO
OH
OH
NO2
NBoc
5.21
4.60
4.54
4.36
4.01
3.80
3.71
1.44
1.31
0.88
0.12
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
2.08
0.91
1.06
0.99
0.99
9.09
2.95
9.03
5.98

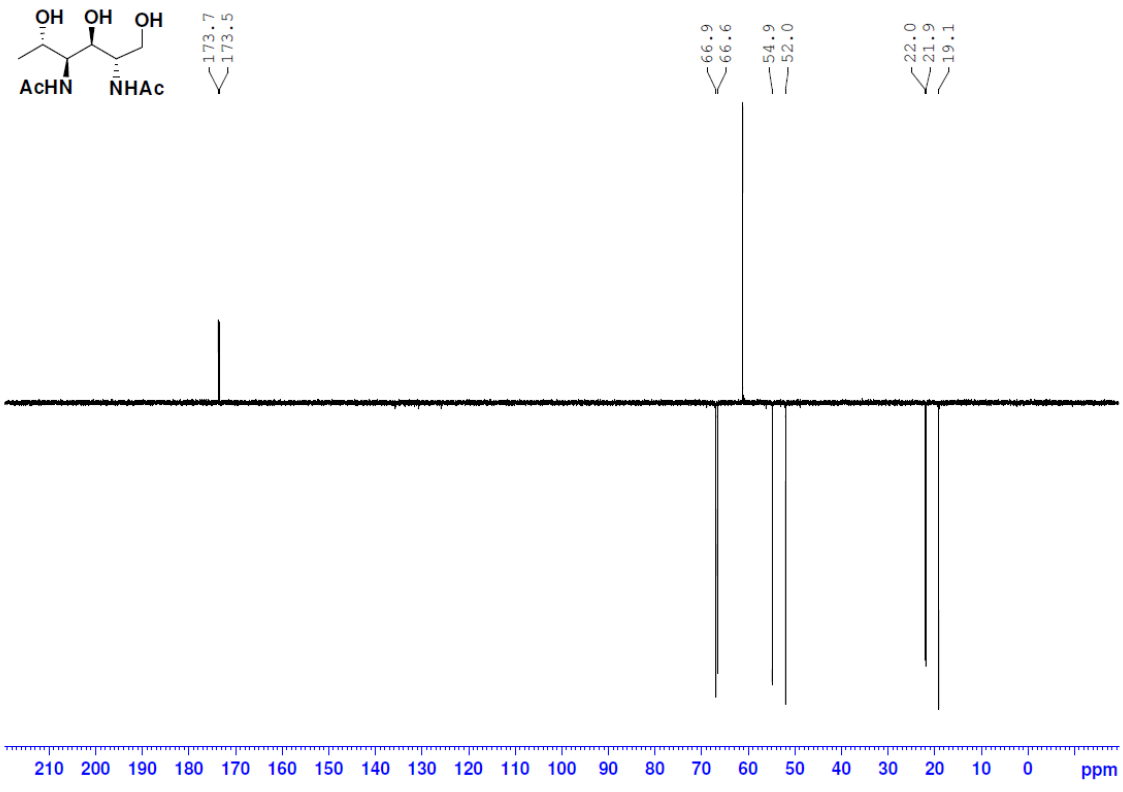

TBSO
OH
OH
NO2
NBoc
156.0
91.7
80.5
69.8
67.6
62.5
53.2
28.4
25.8
20.6
18.0
-4.5
-5.1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

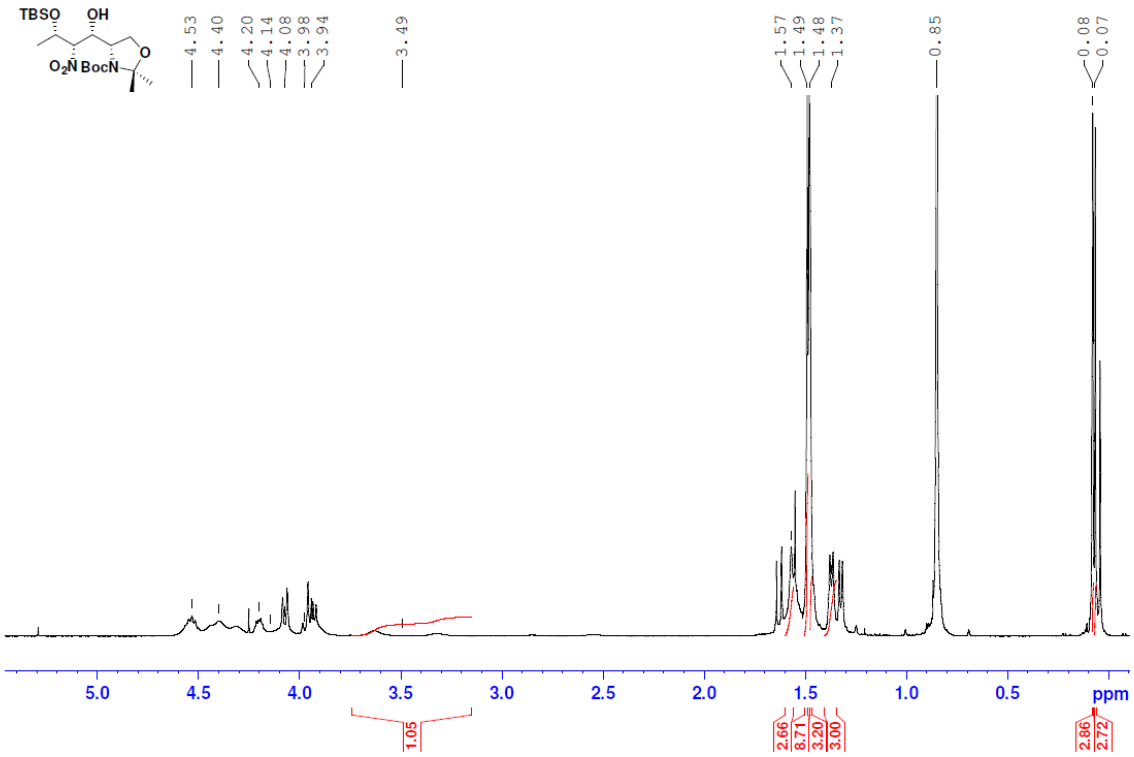

TBSO
OH
OH
NO2
NBoc
156.0
91.7
80.5
69.8
67.6
62.5
53.2
28.4
25.8
20.6
18.0
-4.5
-5.1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

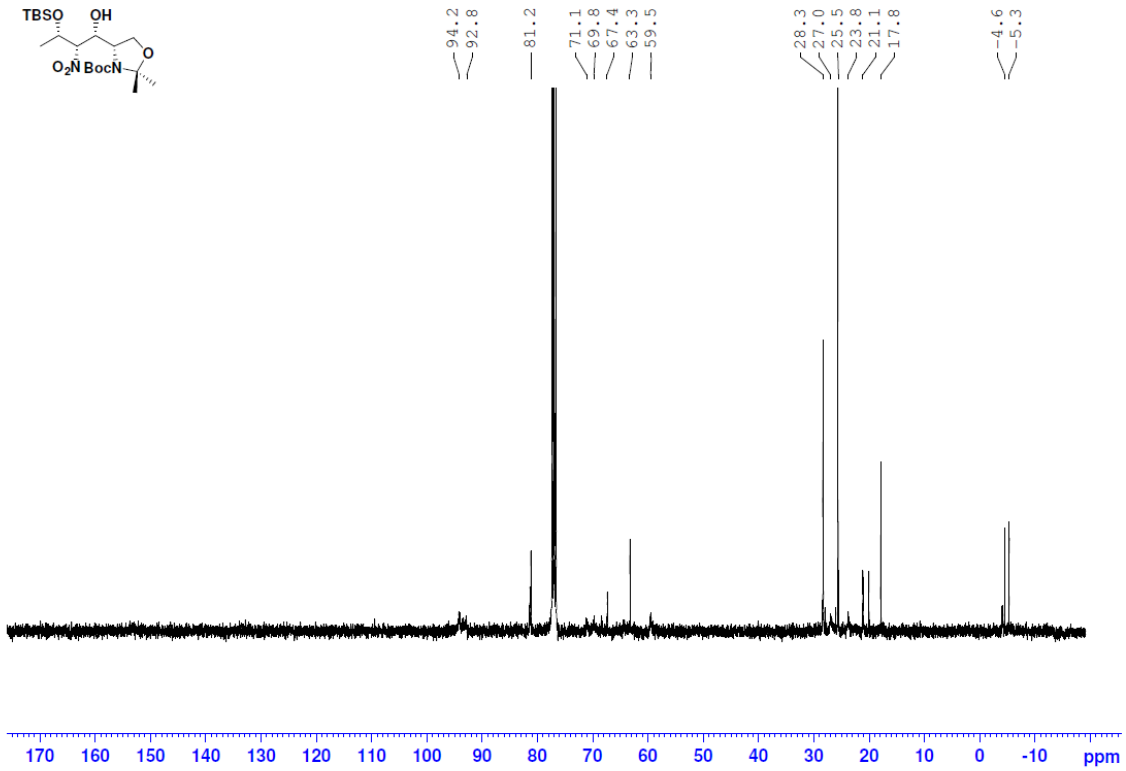

O2N
OH
HO
NH3Cl
5.21
5.13
4.66
4.63
4.61
4.56
4.48
4.04
3.51
3.32
1.31
1.28
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.70
1.03
0.70
1.08
0.67
1.09
0.72
0.63
1.04
1.87
3.00

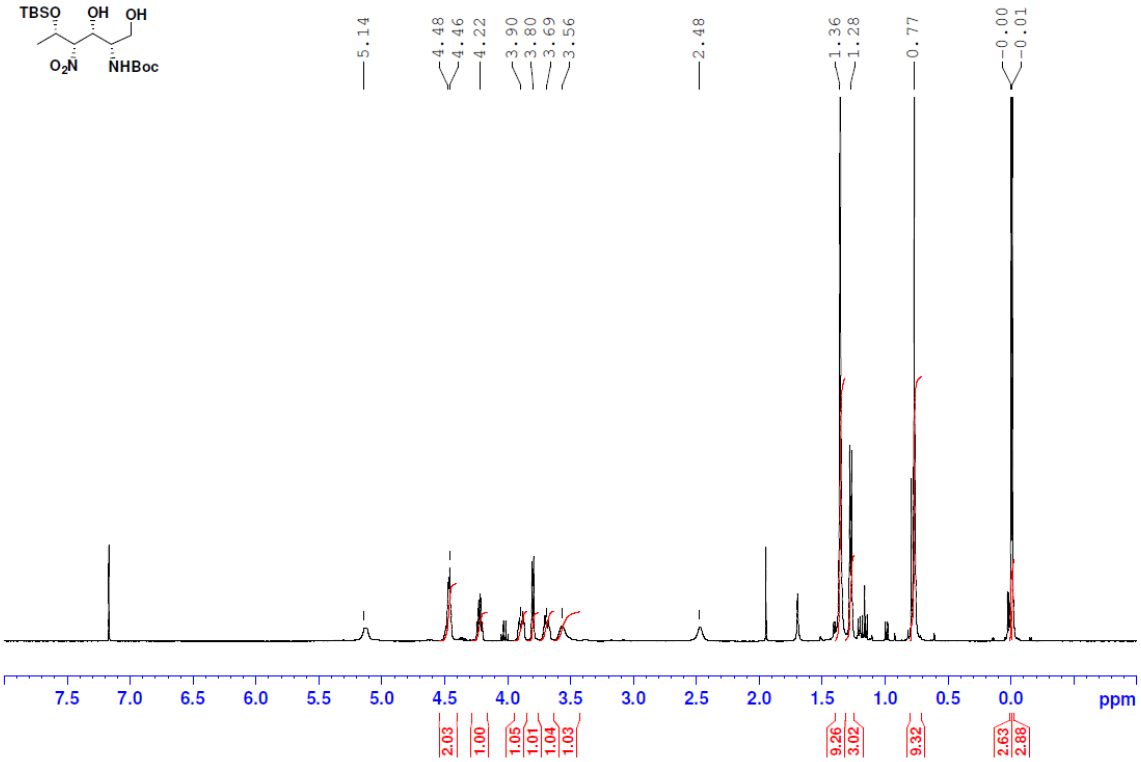

O2N
OH
HO
NH3Cl
94.7
93.5
90.6
90.1
70.4
69.9
67.6
66.2
55.1
54.2
17.3
17.3
110
100
90
80
70
60
50
40
30
20
10
ppm

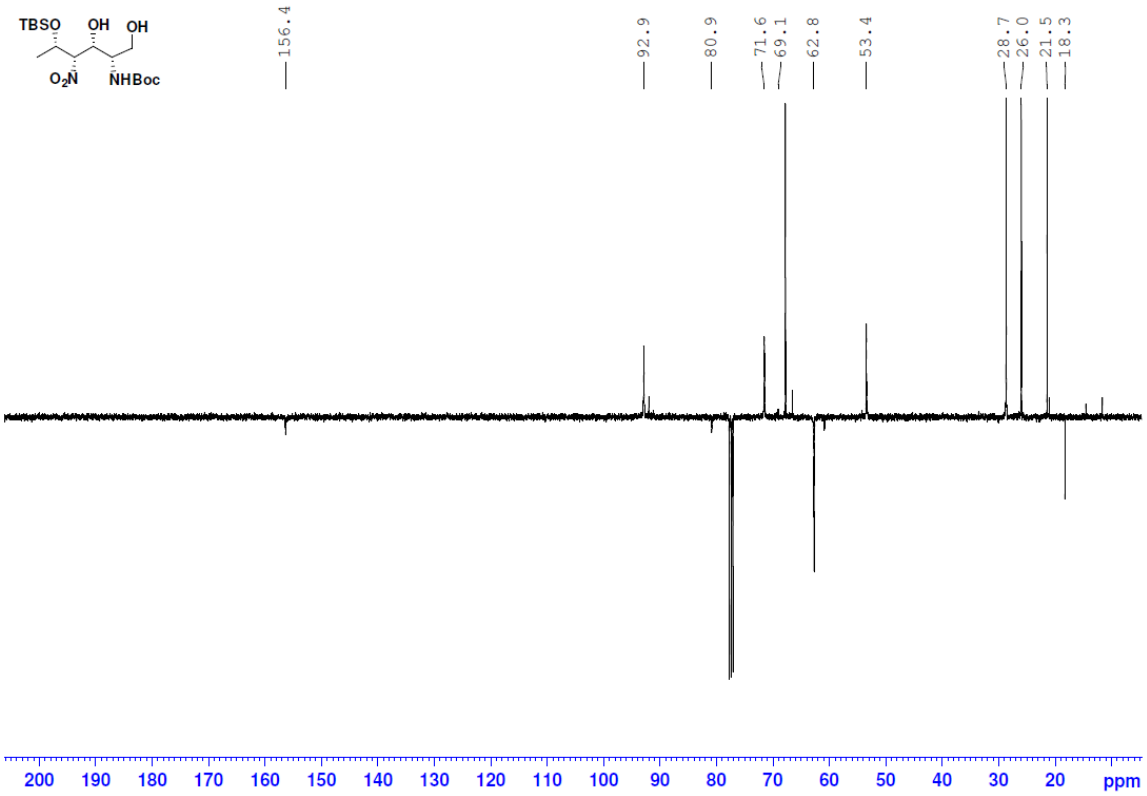

OH
OH
OH
AcHN
NHAc
4.16
3.89
3.81
3.78
3.76
3.71
2.00
1.98
1.19
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.05
0.94
2.09
1.01
2.93
2.81
2.93

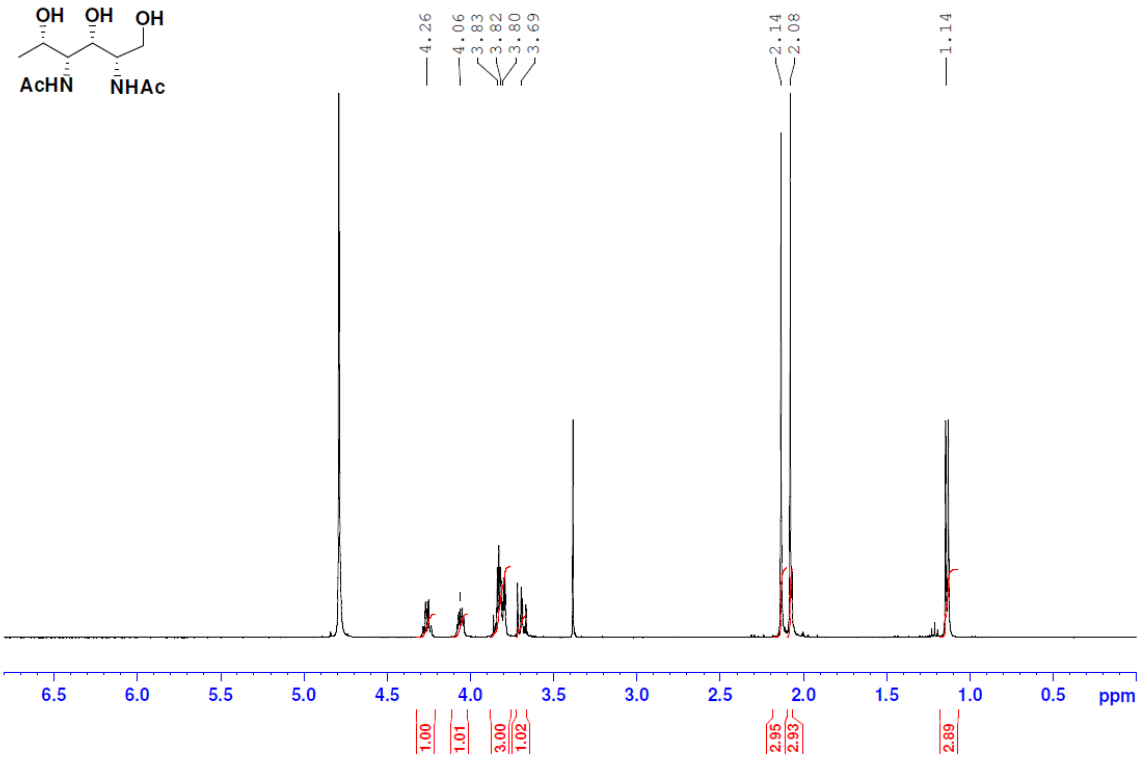

OH
OH
OH
AcHN
NHAc
173.7
173.5
66.9
66.6
54.9
52.0
22.0
21.9
19.1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

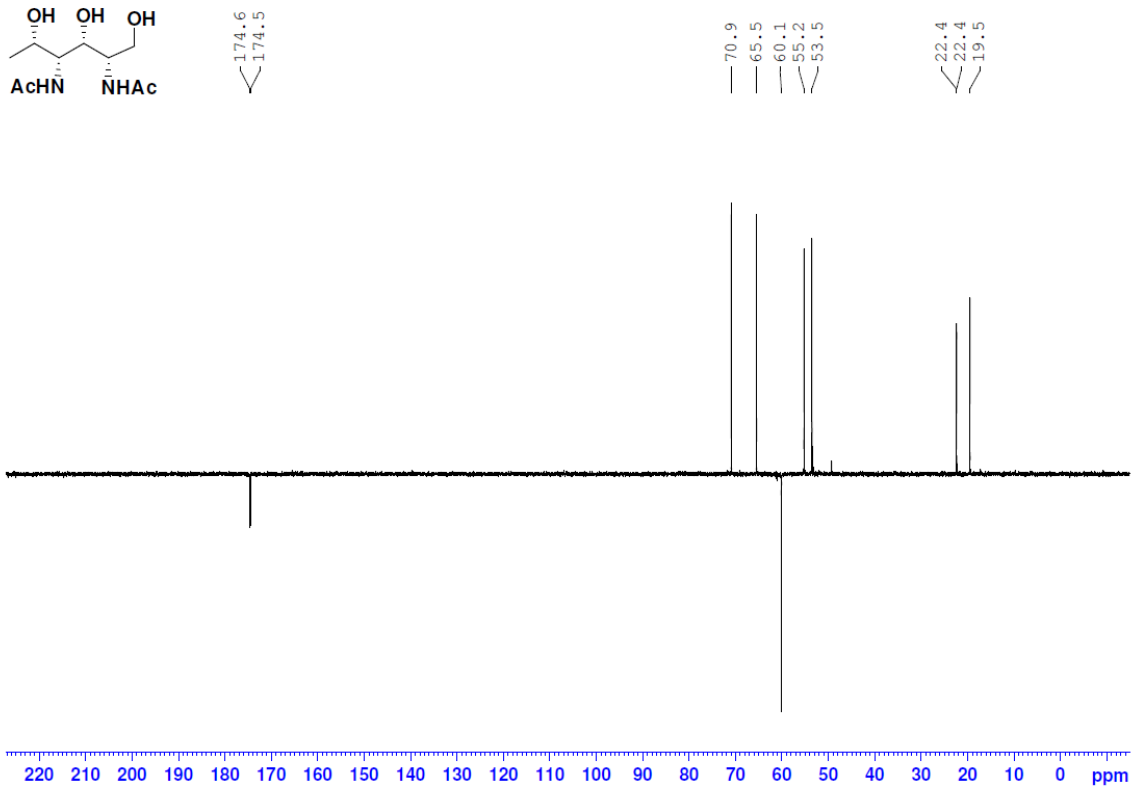

TBSO
OH
O2N BocN
4.53
4.40
4.20
4.14
4.08
3.98
3.94
3.49
1.57
1.49
1.48
1.37
0.85
0.08
0.07
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.05
2.66
8.71
3.20
3.00
2.86
2.72

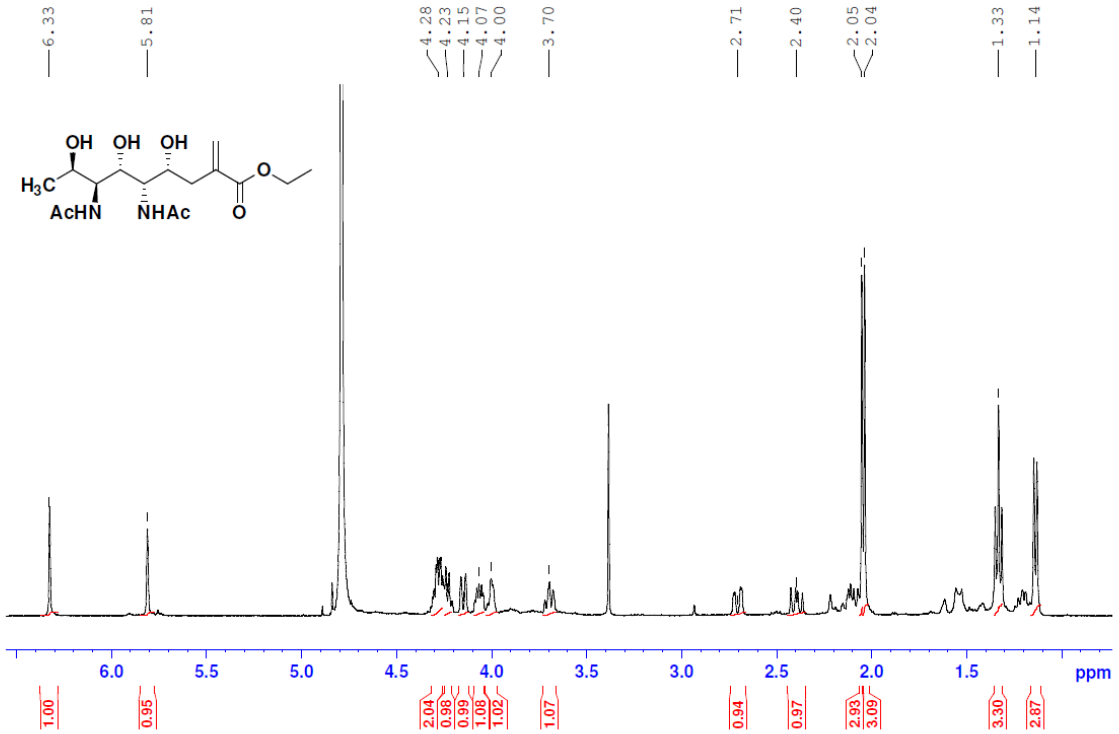

TBSO
OH
O2N BocN
94.2
92.8
81.2
71.1
69.8
67.4
63.3
59.5
28.3
27.0
25.5
23.8
21.1
17.8
-4.6
-5.3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

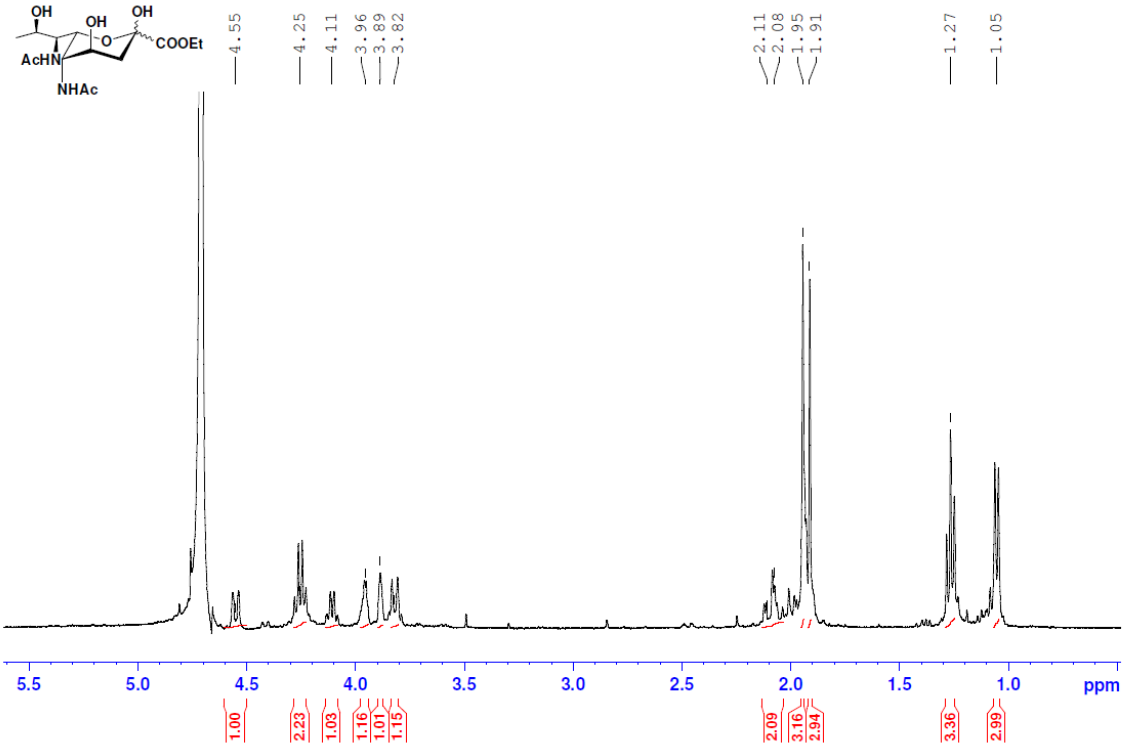

TBSO
OH
OH
O2N
NHBoc
5.14
4.48
4.46
4.22
3.90
3.80
3.69
3.56
2.48
1.36
1.28
0.77
0.00
0.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.03
1.00
1.05
1.01
1.04
1.03
9.26
3.02
9.32
2.63
2.88

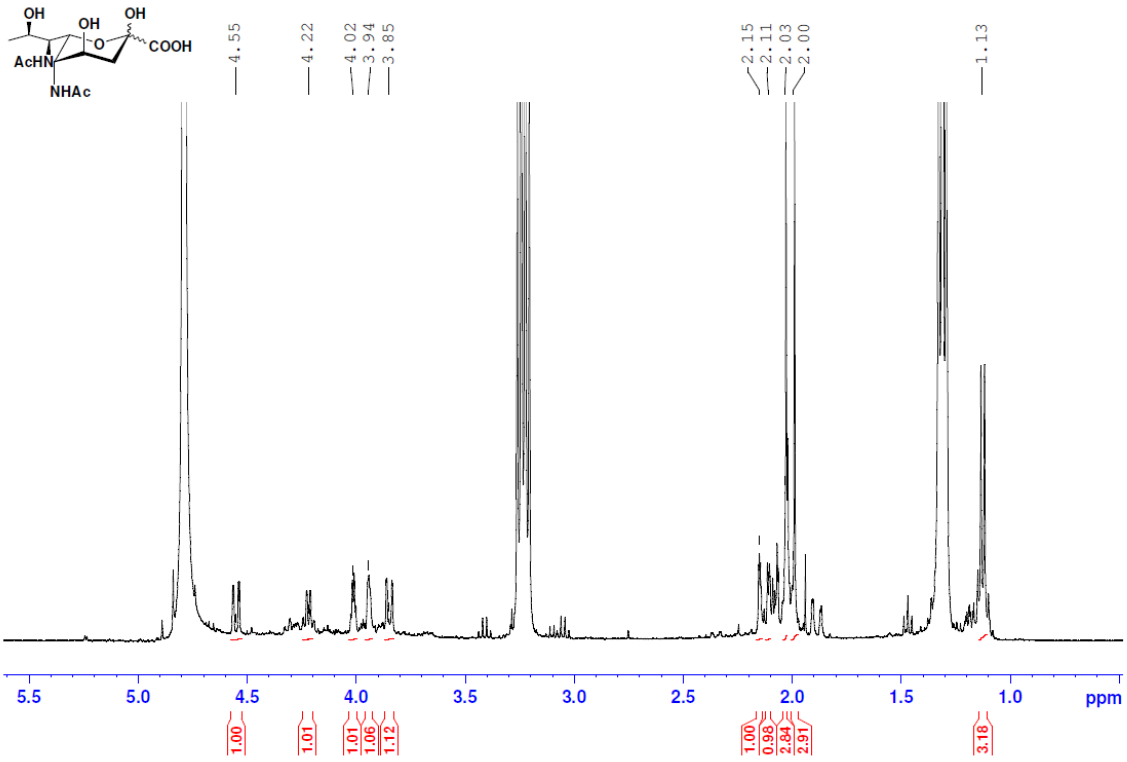

TBSO
OH
OH
O2N
NHBoc
156.4
92.9
80.9
71.6
69.1
62.8
53.4
28.7
26.0
21.5
18.3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

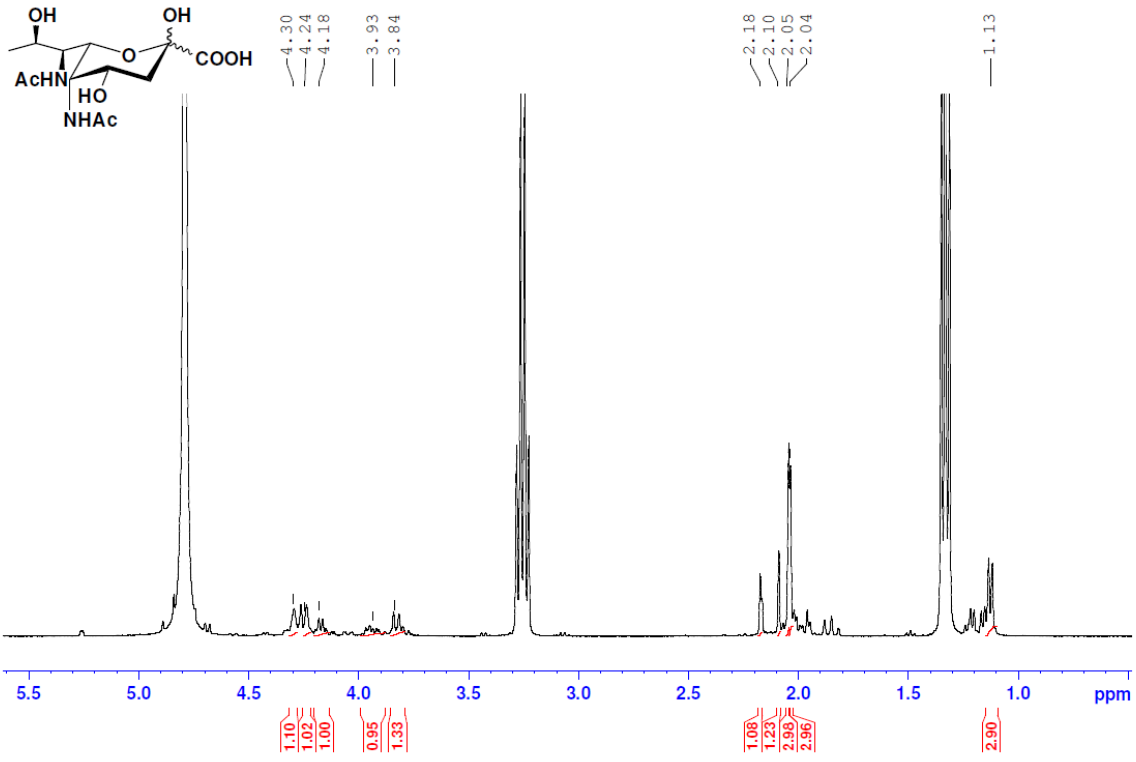

OH
OH
OH
AcHN
NHAc
4.26
4.06
3.83
3.82
3.80
3.69
2.14
2.08
1.14
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.01
3.00
1.02
2.95
2.93
2.89

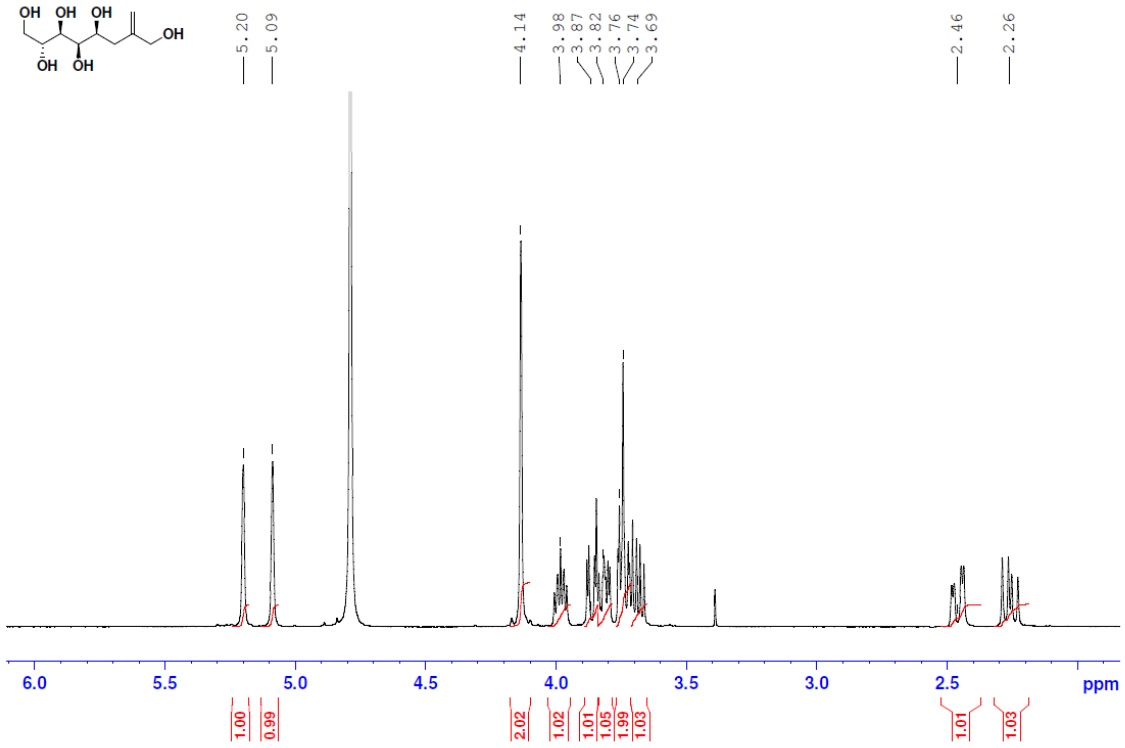

OH
OH
OH
AcHN
NHAc
174.6
174.5
70.9
65.5
60.1
55.2
53.5
22.4
22.4
19.5
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

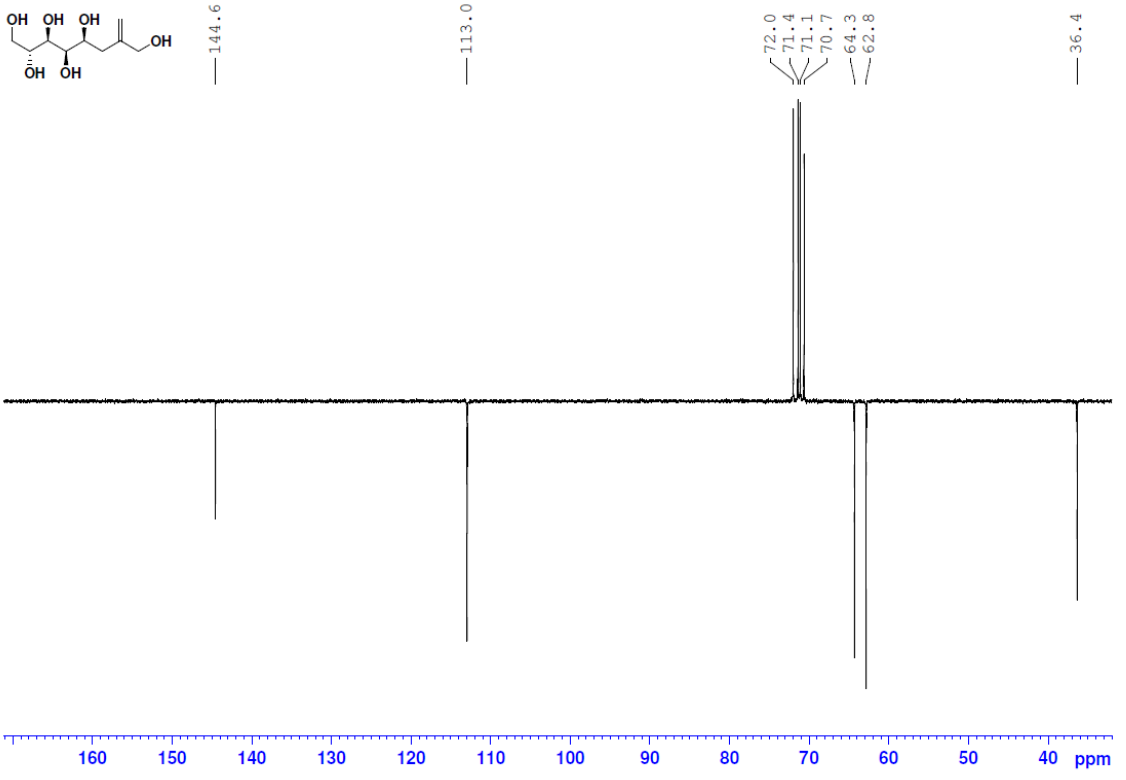

6.33
5.81
4.28
4.23
4.15
4.07
4.00
3.70
2.71
2.40
2.05
2.04
1.33
1.14
OH
OH
OH
H3C
AcHN
NHAc
O
O
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
0.95
2.04
0.98
0.99
1.06
1.02
1.07
0.94
0.97
2.93
3.09
3.30
2.87

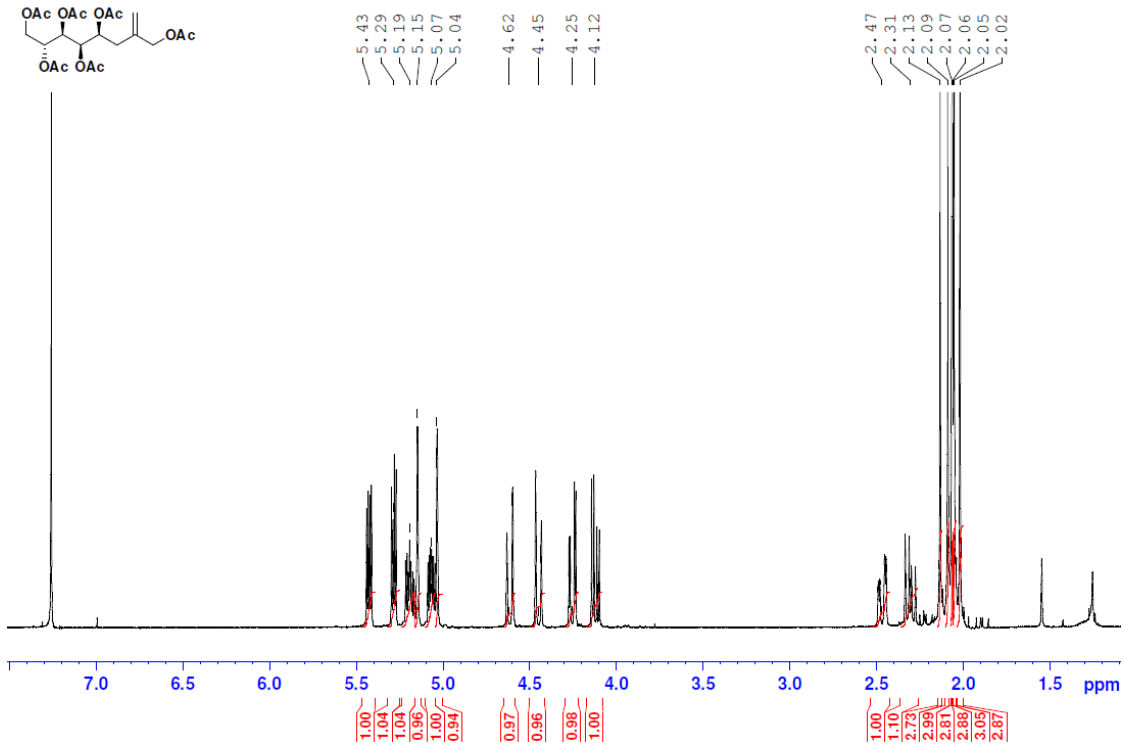

OH
OH
OH
COOEt
AcHN
NHAc
4.55
4.25
4.11
3.96
3.89
3.82
2.11
2.08
1.95
1.91
1.27
1.05
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
2.23
1.03
1.16
1.01
1.15
2.09
3.16
2.94
3.36
2.99


OH
OH
OH
COOH
AcHN
NHAc
4.55
4.22
4.02
3.94
3.85
2.15
2.11
2.03
2.00
1.13
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.01
1.01
1.06
1.12
1.00
0.98
2.84
2.91
3.18


OH
OH
COOH
AcHN
HO
NHAc
4.30
4.24
4.18
3.93
3.84
2.18
2.10
2.05
2.04
1.13
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.10
1.02
1.00
0.95
1.33
1.08
1.23
2.98
2.96
2.90


OH
OH
OH
OH
OH
OH
5.20
5.09
4.14
3.98
3.87
3.82
3.76
3.74
3.69
2.46
2.26
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
1.00
0.99
2.02
1.02
1.01
1.05
1.99
1.03
1.01
1.03


OH
OH
OH
OH
OH
OH
144.6
113.0
72.0
71.4
71.1
70.7
64.3
62.8
36.4
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


OAc OAc OAc
OAc
OAc OAc
5.43
5.29
5.19
5.15
5.07
5.04
4.62
4.45
4.25
4.12
2.47
2.31
2.13
2.09
2.07
2.06
2.05
2.02
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.04
1.04
0.96
1.00
0.94
0.97
0.96
0.98
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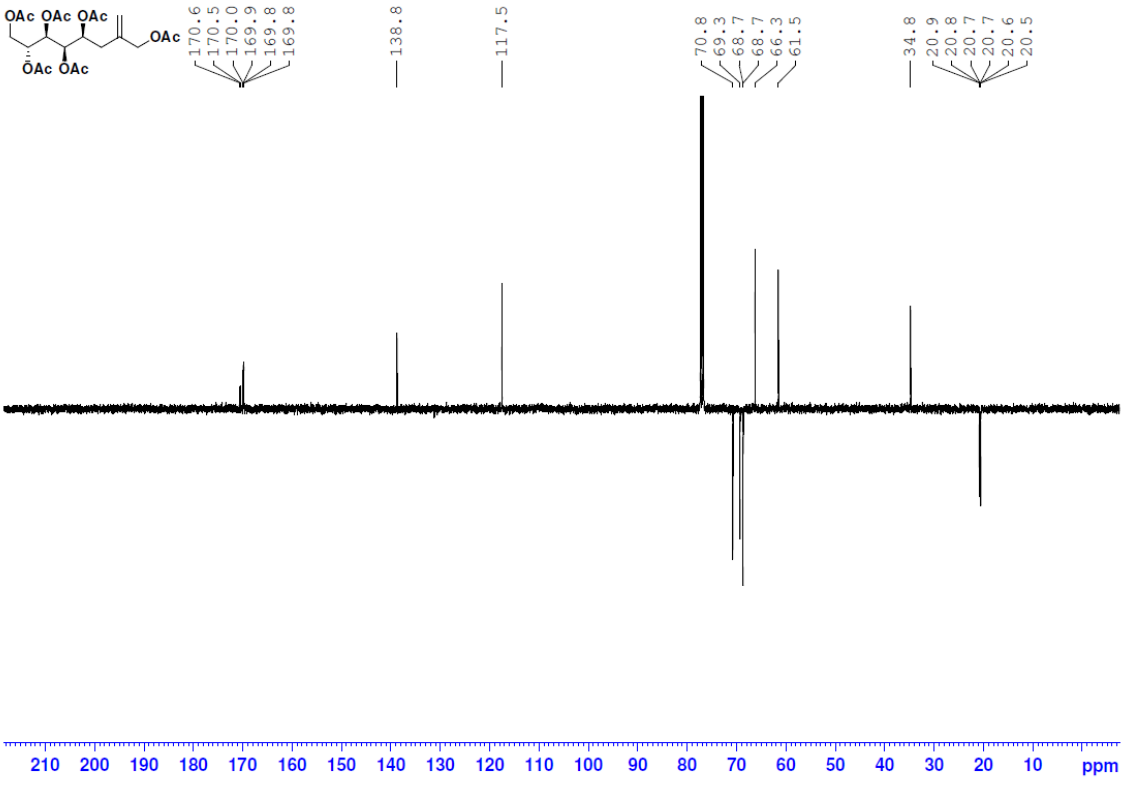
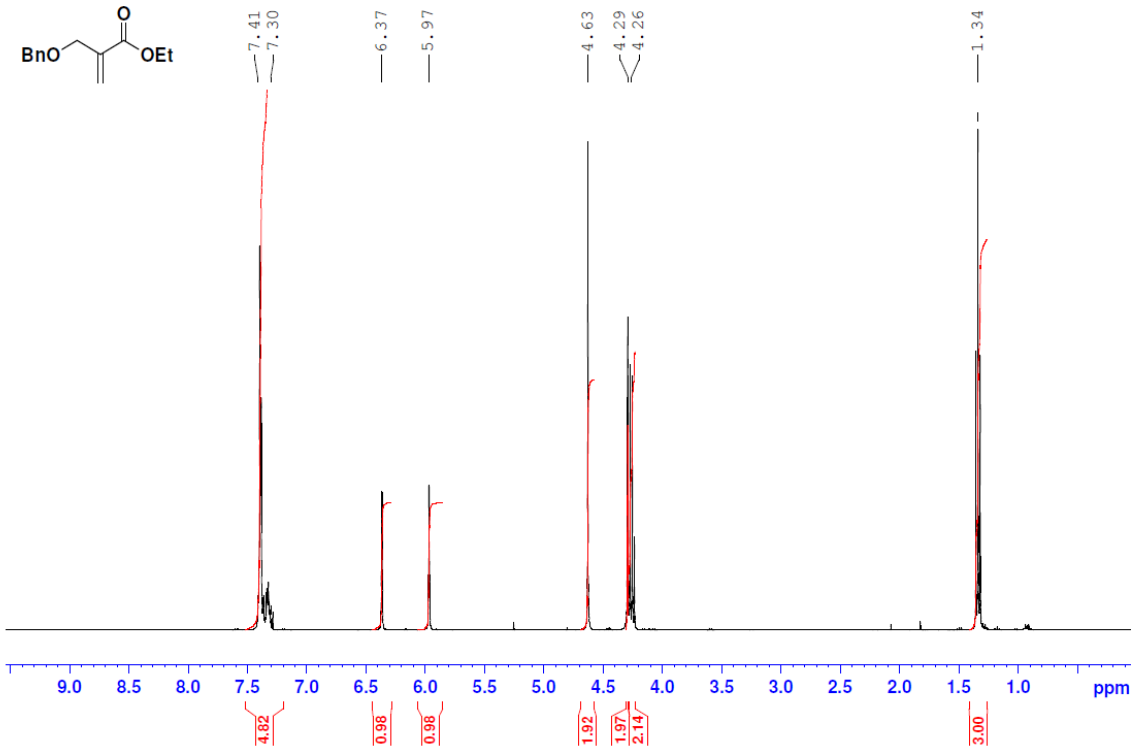
1.00
1.10
2.73
2.99
2.81
2.88
3.05
2.87


OAc OAc OAc
OAc
OAc OAc
170.6
170.5
170.0
169.9
169.8
169.8
138.8
117.5
70.8
69.3
68.7
68.7
66.3
61.5
34.8
20.9
20.8
20.7
20.7
20.6
20.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


BnO
OEt
7.41
7.30
6.37
5.97
4.63
4.29
4.26
1.34
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
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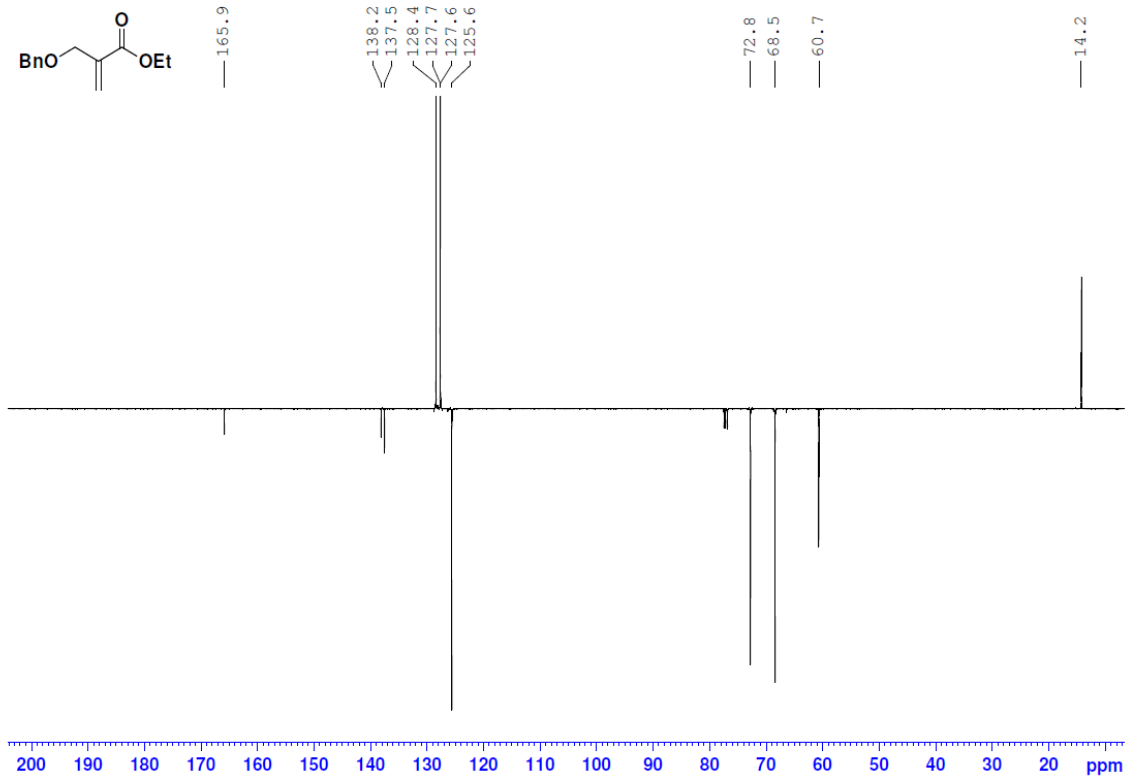
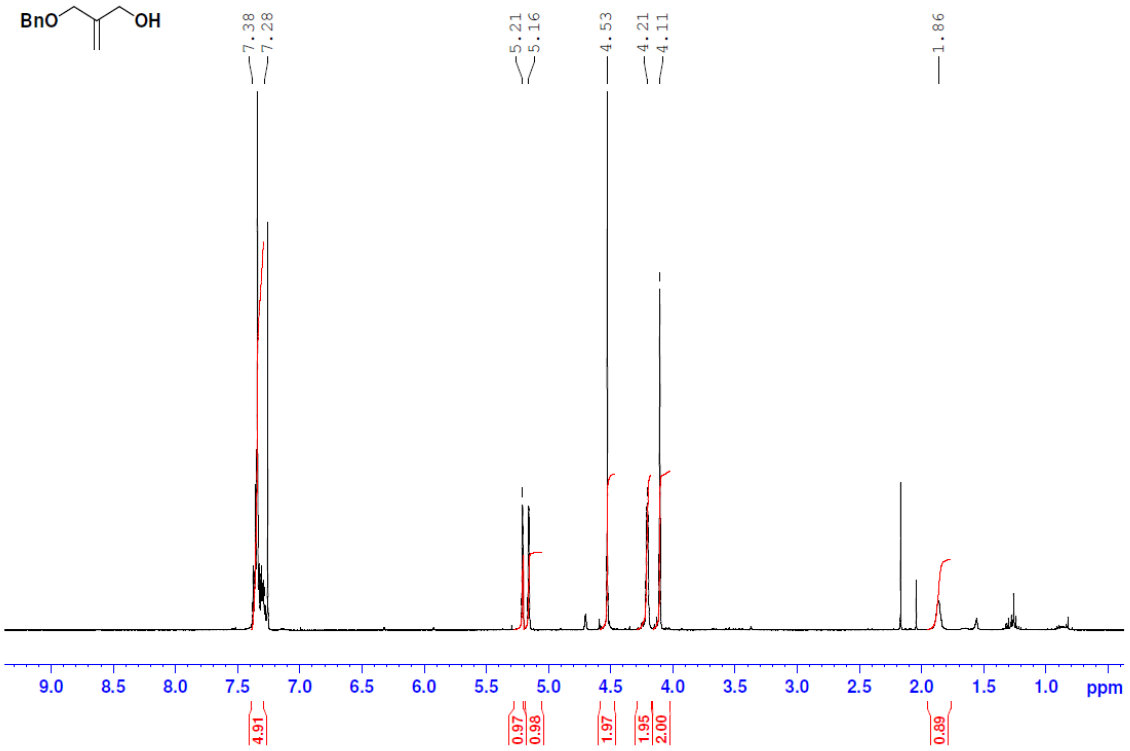
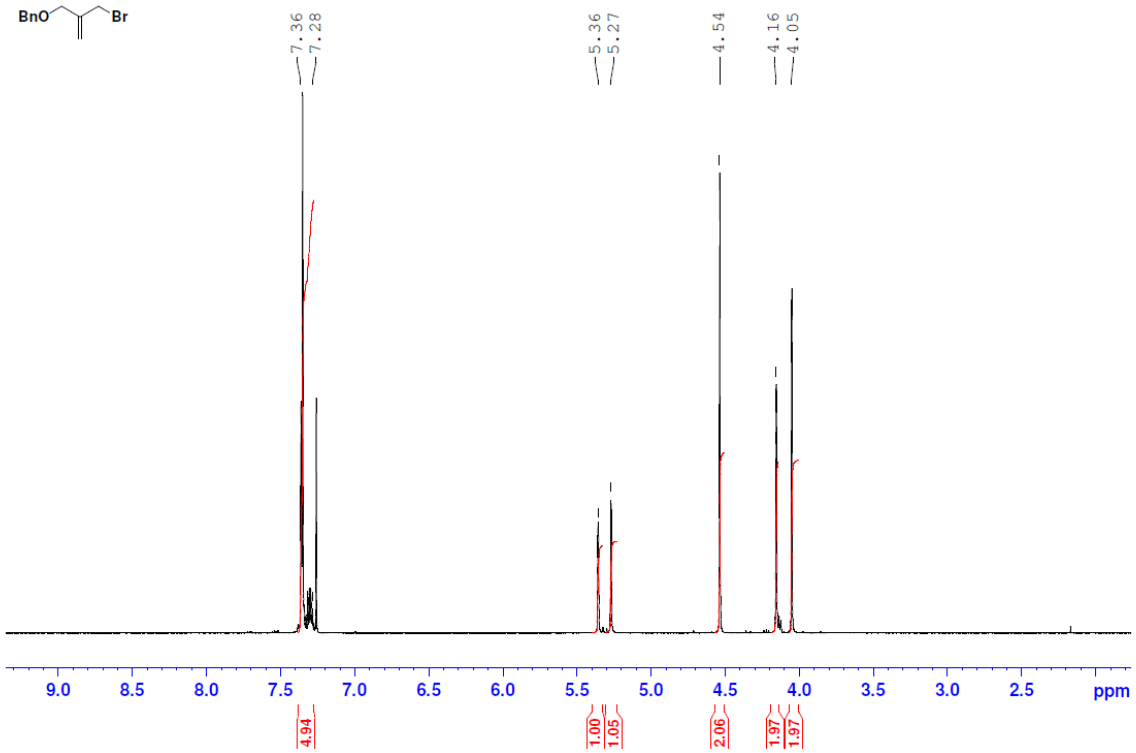
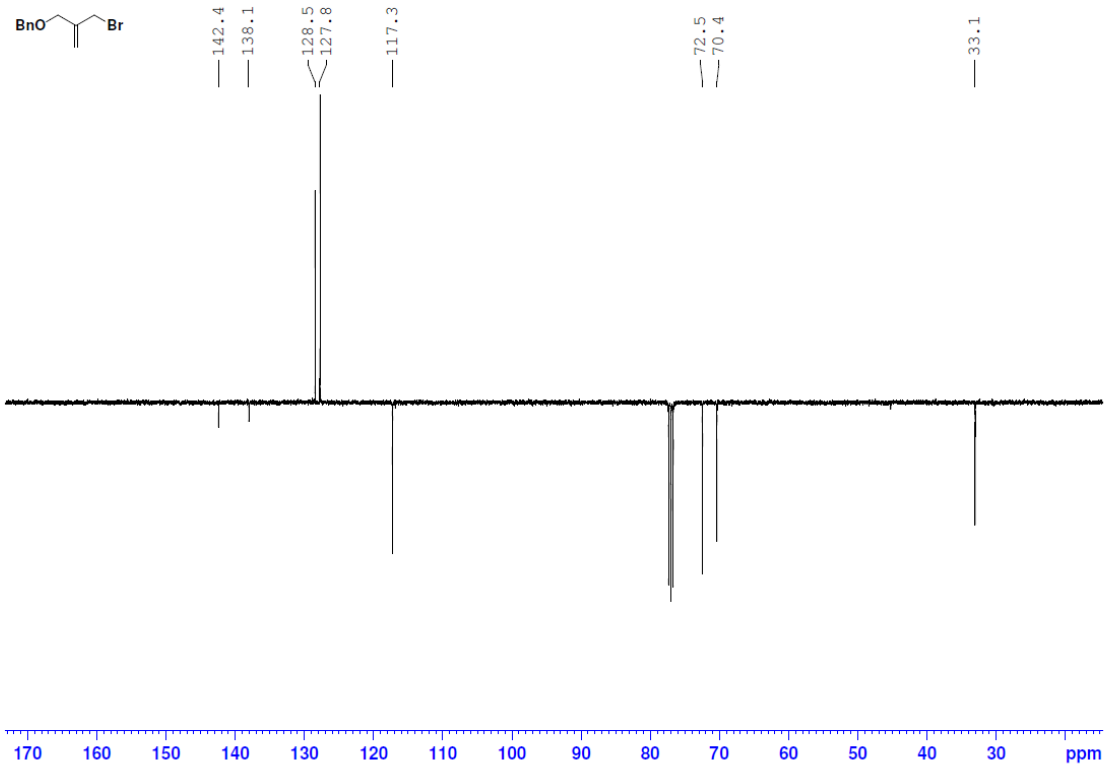
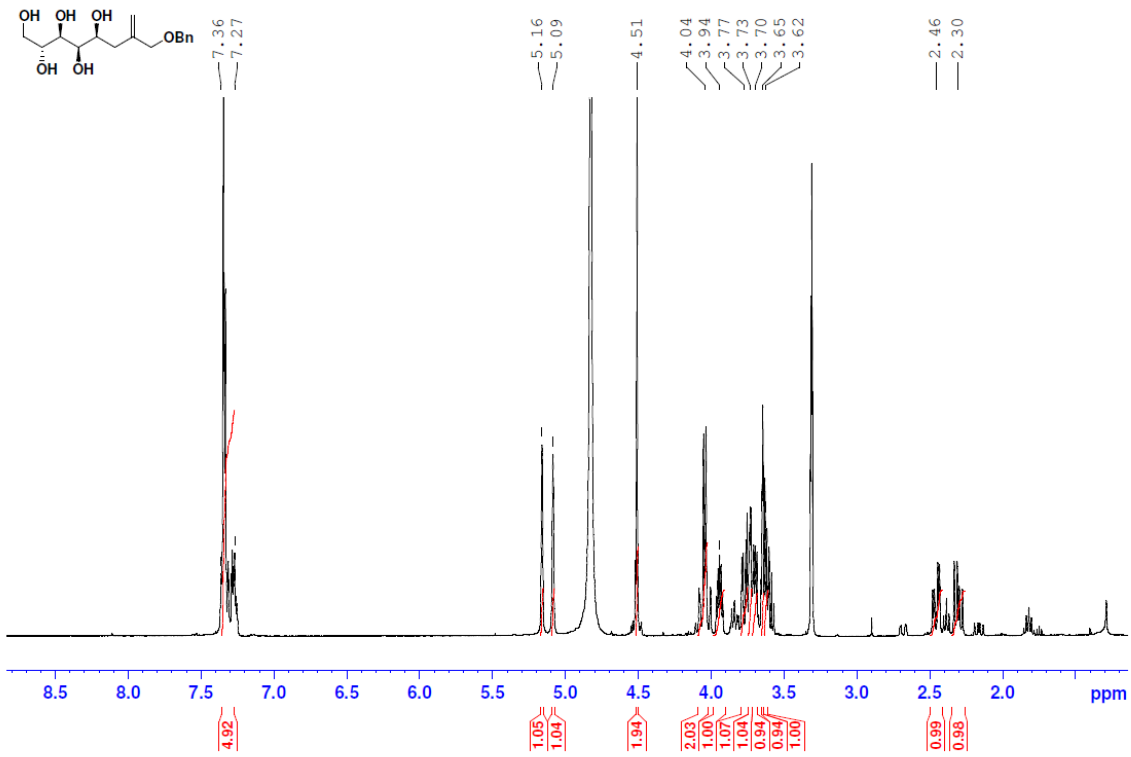
0.98
0.98
1.92
1.97
2.14
3.00


BnO
OEt
165.9
138.2
137.5
128.4
127.7
127.6
125.6
72.8
68.5
60.7
14.2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


BnO
OH
7.38
7.28
5.21
5.16
4.53
4.21
4.11
1.86
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
4.91
0.97
0.98
1.97
1.95
2.00
0.89


BnO
Br
7.36
7.28
5.36
5.27
4.54
4.16
4.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
4.94
1.00
1.05
2.06
1.97
1.97


BnO
Br
142.4
138.1
128.5
127.8
117.3
72.5
70.4
33.1
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm


OH OH OH
OBn
OH OH
7.36
7.27
5.16
5.09
4.51
4.04
3.94
3.77
3.73
3.70
3.65
3.62
2.46
2.30
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 ppm
4.92
1.05
1.04
1.94
2.03
1.00
1.07
1.04
0.94
0.94
1.00
0.99
0.98

LEBENSLAUF

Persönliche Daten

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Adresse	Nestroygasse 1/18, 1020 Wien
Geburtsdatum	27. März 1981
Staatsbürgerschaft	Österreich

Schulbildung

1987 - 1991	Volksschule II, 4800 Attnang-Puchheim
1991 – 1999	Bundesgymnasium Vöcklabruck, 4840 Vöcklabruck
2000 - 2001	Zivildienst im „Das Dorf Altenhof“, 4647 Altenhof a. H.

Hochschulausbildung

1999 - 2000	Studium der Technischen Chemie an der Johannes Kepler Universität Linz, 4020 Linz
2001 - 2007	Diplomstudium Chemie, mit Schwerpunkt Organische Chemie und Biochemie, Universität Wien, 1090 Wien
2007 - 2008	Diplomarbeit am Institut für Organische Chemie, 1090 Wien “Indium unterschrützte Allylierung von Kohlenhydraten: Synthese von 3-Desoxy-2-ulosen” (mit Auszeichnung bestanden)
2008 - 2013	Dr.-Studium der Naturwissenschaften Chemie am Insitut für Organische Chemie, 1090 Wien “Synthesis of Rare 2,4-Diamino-2,4,6-trideoxy Hexoses & Allylation Strategies Towards the Nonulosonic Acids and 3-Deoxy-2-uloses”

Universitäres

WS 2008 - SS 2008	Tutortätigkeit im Chemischen Grundpraktikum A - Laborsicherheit
WS 2009 - WS 2009	Lektor in den Chemischen Übungen für Ernährungswissenschafter und Biologen & im Biologisch-Chemischen Praktikum
2009	Forschungsstipendiums der Universität Wien
SS 2010- WS 2013	Lektor in den Chemischen Übungen für Ernährungswissenschafter und Biologen
2009	Mitorganisation beim „15th European Carbohydrate Symposium“ in Wien
2010 - 2014	Prae Doc / Universitätsassistent der Universität Wien, Institut für Organische Chemie, 1090 Wien
2011	Mitorganisation beim „21st International Symposium on Glycoconjugates“ in Wien

Berufserfahrung:

Sommer 1997	Braun Maschinenfabrik, 4840 Vöcklabruck
Sommer 1998	Firma Wessenthaler, 4800 Attnang-Puchheim
2000 - 2006 (jeweils im Sommer)	Lenzing AG, 4860 Lenzing, u.a. in den Bereichen „Lenzing Technik”, „Zellstofforschung”, etc.

Tagungsbeiträge

Vortrag im Rahmen des „12. Österreichischen Kohlenhydrat Workshop“ 2008 in Wien
„Indium-unterstützte Allylierung von Kohlenhydraten: Follow-Up Chemistry – Teil A“

Posterpräsentation im Rahmen des „15th European Carbohydrate Symposium“ 2009 in Wien (PA-073)
„A Short and Efficient Synthesis of 3-Deoxy-2-uloses“

Vortrag im Rahmen des „14. Österreichischen Kohlenhydrat Workshop“ 2010 in Wien
„Indium-mediated allylation: A convenient methodology to establish C3-synthons for the synthesis of 3-deoxy-2-uloses”

Posterpräsentation im Rahmen des „3rd EuCheMS Chemistry Congress“ 2010 in Nürnberg (VIIa.068)

„3-Deoxy-2-uloses: Permanganate Oxidation and Microwave Assisted Thioketalisation of Unreactive and Labile Carbohydrates“

Posterpräsentation im Rahmen des „21st International Symposium on Glycoconjugates“ 2011 in Wien (Nr 400)

„Pseudaminic and Legionaminic Acid: Synthesis of Sialic Acid Analogues“

Posterpräsentation im Rahmen der „14. Österreichischen Chemietage“ 2011 in Linz (PO-137)

„ Bioactive Carbohydrates: Synthesis of Deoxy-uloses and deoxy-ulosonic Acids

Posterpräsentation im Rahmen des „4rd EuCheMS Chemistry Congress“ 2012 in Prag (P-0446)

„Nitroaldol reaction as a key step in the synthesis of rare diamino sugars“

Posterpräsentation im Rahmen des „26th International Carbohydrate Symposium“ 2012 in Madrid (P-370)

„Synthesis of 2,4-Diacetamido-2,4,6-trideoxy Galactose: A Main Component of the Cell Wall of S. Pneumoniae“

Vortrag im Rahmen des „16. Österreichischen Kohlenhydrat Workshop“ 2012 in Wien

„5,7-Diacetamido-3,5,7,9-tetradeoxynonulosonic acids: Synthesis via an indium-mediated chain elongation of hexoses”

Vortrag im Rahmen des „17. Österreichischen Kohlenhydrat Workshop“ 2013 in Graz

„2,4-Diacetamido-2,4,6-trideoxy-D-galactose and its Application in the Synthesis of Sialic Acid Analogues”

Vortrag im Rahmen der „15. Österreichischen Chemietage“ 2013 in Graz (Nr 87)

„De Novo Synthesis of 2,4-Diacetamido-2,4,6-trideoxy Hexoses as key compounds to access the nonulosonic acid family“

Publikationen

„Synthetic Tools for Addressing Biological and Medicinal Chemical Questions."

Braitsch, M.; Fischer, M.; Hollaus, R.; Lentsch, C.; Lichtenecker, R.; Nagl, M.; Nowikow, C.; Schmölzer, C.; Schmid, W. *Joint Meeting on Medical Chemistry* **2009**, 21.

„Permanganate Oxidation Revisited: Synthesis of 3-Deoxy-2-uloses via Indium-Mediated Chain Elongation of Carbohydrates."

Schmölzer, C.; Fischer, M.; Schmid, W. *Eur. J. Org. Chem.* **2010**, 4886.

„Indium-Mediated Allenylation of Aldehydes and Its Application in Carbohydrate Chemistry: Efficient Synthesis of D-Ribulose and 1-Deoxy-D-ribulose."

Fischer, M.; Schmölzer, C.; Nowikow, C.; Schmid, W. *Eur. J. Org. Chem.* **2011**, 1645.

„Analysis of (poly-)phenols in commercially available red wines by means of LC-MS."

Hermann, G.; Jaitz, L.; Schmölzer, C.; Koellensperger, G.; Eder, R.; Hann, S. *Mitt. Klosterneuburg* **2012**, *62*, 13.

"Gram scale de novo synthesis of 2,4-diacetamido-2,4,6-trideoxy-D-galactose."

Schmölzer, C.; Nowikow, C.; Kahlig, H.; Schmid, W. *Carbohydr. Res.* **2013**, *367*, 1.
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Global Medical Discovery