TECHNISCHE UNIVERSITÄT WIEN

DIPLOMA THESIS

INDIUM MEDIATED ACYLOXYALLYLATION OF ALDOSES – SYSTEMATIC STUDY AND TARGET-ORIENTED SYNTHESIS

carried out for the purpose of obtaining the degree 'Diplom-Ingenieur', by

Lara Maltrovsky, BSc

[redacted]

under the supervision of

Associate Prof. Dipl.-Ing. Dr.techn. Michael Schnürch

Dipl.-Ing. Dr.techn. Christian Stanetty

Institute of Applied Synthetic Chemistry, E163

submitted at TU Wien, Faculty of Technical Chemistry

Vienna, 02.12.2022

Per aspera ad astra.

ACKNOWLEDGMENTS

The work on this thesis concludes a period of my life I look back on with mixed feelings. The past five years definitely were a challenging time, however they taught me a lot and gave me the possibility to make many experiences which strongly formed me as the person I am today. I am deeply grateful that I had people by my side who accompanied and supported me along the way, and I do not think that I can ever properly express how much that meant to me. Therefore, I would like to take the opportunity and at least thank all of those, who made this thesis possible.

First of all, I want to thank *Christian Stanetty* for the supervision of my master thesis, the trust in me by giving me the opportunity to work on this project, all the advice he provided concerning my practical lab work and his guidance during the writing process of my thesis. He was the one introducing me to the very special world of sugar chemistry, in which I had the pleasure to gain a deeper insight over the course of the last 12 months.

Furthermore, I would like to thank *Univ.Prof. Dr.techn. Marko Mihovilovic* for the possibility to conduct my master thesis in the BSC research group and *Associate Prof. Dr.techn. Michael Schnürch* for the qualified input during our group seminars as well as his willingness to act as my main examiner.

Next, I want to thank *Nina Biedermann* for always having a helping hand and for being the go-to person, when I had a question, as well as *Christoph Suster*, *Hubert Kalaus*, *Verena Scheibelreiter* and everyone else from the G20 lab for making the countless hours in the lab more enjoyable and for lending an ear to my problems.

I want to thank the whole BSC research group for their warm welcome when I started my thesis last December and the great working environment I was able to experience in this past year, for making the lunch breaks entertaining and for good talks with and without a beer. Special thanks go to all the HPLC-MS and NMR operators for the multiple measurements.

Also, I would like to thank *Lisa Laa*, who turned from my favorite lab partner during our bachelor studies to a very close friend, even though we ended up in different areas. I highly appreciate our hikes, tennis sessions and coffee dates which always were a highlight during especially stressful times and helped me to clear my mind and refocus.

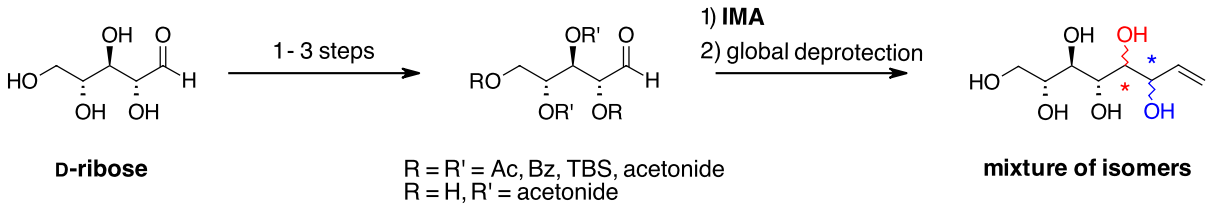
A very special mention goes to my friends in Denmark, *Mikel Gomes*, *Sina Maschek* and *Boris Mondet*. I am immensely grateful for your friendship and the countless hours of conversations and thousands of text messages, for you listening to my occasional complaints and self-doubts and for making Copenhagen a home away from home for me.

Last but not least I want to thank my parents, my sister, and my boyfriend who were by my side during all my ups and downs. They were the ones bringing me back down to earth when I was close to having a nervous breakdown and staying interested in my work even though they sometimes had no clue what I was talking about and who always managed to lift my spirit after long and exhausting lab days by good food and just being there for me. I cannot be thankful enough for your endless support and your confidence in me letting me find my way in life!

ABSTRACT

The indium mediated acyloxyallylation (IMA) of aldoses was introduced by *Madsen et al.* in 2005 and constitutes a valuable tool for the elongation of reducing sugars by two carbon atoms (upon ozonolysis). While the IMA leads to four possible diastereomers, the mainly observed isomer was the product with *lyxo*-configuration, representing a *syn*-orientation in respect to the former 2-OH-group and an *anti*-addition to the aldehyde. The research group already developed a target-oriented synthesis of L-*glycero*-D-*manno*-heptose exploiting the already described primarily formed isomer. However, in the course of this work also a first identification of the other three diastereomers was possible. Hereinafter, *Draskovits et al.* engaged in an in-depth methodological investigation of the IMA of unprotected and 2,3-*O*-isopropylidene protected tetroses which furnished a pronounced diastereodivergence depending on whether a protecting group is used or not. It was found that the stereochemistry of the products is connected to chelation at the 2-OH group but is independent of the configuration of the starting material.

As first part of the thesis, this study is now expanded to the more generally accessible class of protected sugar aldehydes, and the composition of the product mixture of the IMA with starting materials bearing a variety of commonly used protecting groups was investigated.

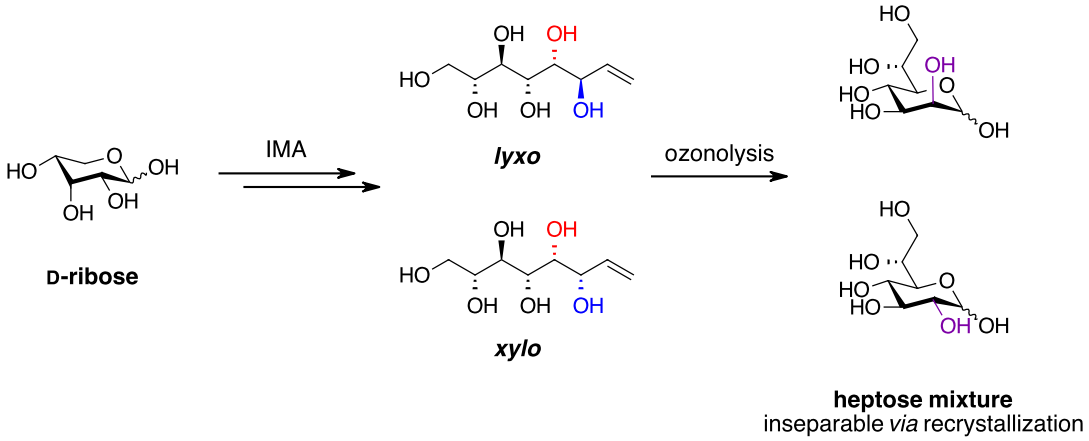


A family of *ribo*-configured protected sugar aldehydes was successfully prepared and subjected to the IMA. The effect of the different protecting groups onto the diastereomeric ratio was determined from the ^{1}H-NMR spectra of the obtained product mixtures upon complete deprotection. Within the investigation, diastereodivergence was indeed found depending on whether the starting materials did bear protecting groups at the O2-position or not. It was shown that only acetonide protection delivers a synthetically useful selectivity for the *anti*/*anti*-configuration, thus exhibiting a pronounced diastereodivergence compared to the unprotected cases. Extension from the *erythro*-configured ribose scaffold to the *threo*-configured arabinose confirmed a high degree of generality in respect to the vicinal stereochemistry.

As second part of the thesis, and to further investigate possible applications of the IMA, a new route for the synthesis of the rare bacterial sugar D-*glycero*-D-*manno*-heptose from D-ribose was developed and focus was laid on a column-free thus tentatively scalable synthesis pathway.

The starting point of the planned reaction sequence was the large scale synthesis of crystalline 1,2,3,4,6,7-hexa-*O*-acetyl-L-*glycero*-α-D-*manno*-heptopyranose, the stable and non-hygroscopic storage form of L-*glycero*-D-*manno*-heptose, established by *Stanetty and Baxendale* where the primarily formed enitol can be isolated due to its high crystallinity. The IMA of D-ribose leads to the formation of two main isomers in *lyxo*- and *xylo*-configuration in a ratio of 1.6:1. However, a simple separation of the diastereomers *via* recrystallization was not successful for this case. Therefore, a procedure based on the introduction of isopropylidene groups as the key transformation exploiting

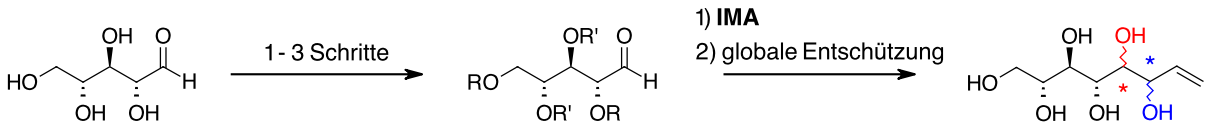
the stereochemical difference regarding the 2-OH-group of the two isomers was successfully applied. A column-free synthesis of DD-heptose was accomplished on small scale and its upscaling is currently under investigation.



KURZFASSUNG

Die indium-mediierte Acyloxyallylierung (IMA) von Aldosen wurde 2005 von *Madsen et al.* erstmals beschrieben und stellt ein wertvolles Instrument für die Verlängerung von reduzierenden Zuckern um zwei Kohlenstoffatome dar (nach anschließender Ozonolyse). Obwohl die IMA zur Bildung von vier möglichen Diastereomeren führen kann, ist das Hauptprodukt jenes mit *lyxo*-Konfiguration, bei dem eine *syn*-Orientierung in Bezug auf die ehemalige 2-OH-Gruppe und eine *anti*-Addition an den Aldehyd vorliegt. In der Arbeitsgruppe wurde bereits eine zielorientierte Synthese von L-*glycero*-D-*manno*-Heptose entwickelt, die auf der Weiterverwendung des isolierten *lyxo*-konfigurierten Hauptprodukts basiert. Weiters wurden erstmals auch die anderen auftretenden Isomere identifiziert. Auf diesen Ergebnissen aufbauend, führten *Draskovits et al.* eine umfassende methodologische Untersuchung der IMA von ungeschützten und 2,3-*O*-isopropylidengeschützten Tetrosen durch, welche eine ausgeprägte Diastereodivergenz abhängig davon, ob eine Schutzgruppe verwendet wurde oder nicht, gezeigt hat. Weiters wurde herausgefunden, dass die Stereochemie der Produkte stark von einer Chelatisierung ausgehend von der 2-OH-Gruppe beeinflusst wird, die Konfiguration der Startmaterialien hingegen keine ausschlaggebende Rolle spielt.

Als erster Teil dieser Arbeit wird diese Studie nun auf die leichter zugängliche Klasse der geschützten Zuckeraldehyde erweitert und die Zusammensetzung des Produktgemisches der IMA in Hinblick auf Startmaterialien untersucht, die verschiedene, häufig verwendete Schutzgruppen tragen.

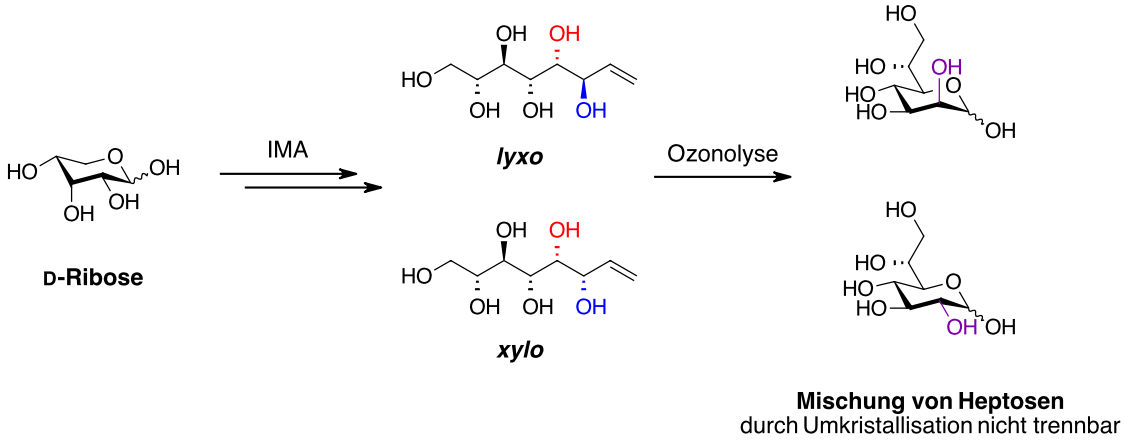


D-Ribose **Produktgemisch**

Zunächst wurde erfolgreich eine Auswahl von *ribo*-konfigurierten geschützten Zuckeraldehyden hergestellt, welche dann als Startmaterialien für die IMA verwendet wurden. Der Effekt der unterschiedlichen Schutzgruppen auf das Diastereomerenverhältnis wurde über die ^{1}H-NMR Spektren der erhaltenen, vollständig entschützten Produktgemische bestimmt. Im Rahmen der Untersuchung wurde auch im Fall der von Ribose abgeleiteten Verbindungen eine Diastereodivergenz festgestellt, die davon abhängt, ob die Edukte eine Schutzgruppe an der O2-Position aufweisen oder nicht. Es wurde gezeigt, dass nur die Acetonid-Schützung eine synthetisch verwertbare Selektivität für die *anti*/*anti*-Konfiguration aufweist, und dementsprechend eine deutlich hervorstechende Diastereodivergenz verglichen mit den Fällen besitzt, die keine Schutzgruppe an der O2-Position tragen. Eine Ausweitung des *erythro*-konfigurierten Ribose-Rückgrats zu der *threo*-konfigurierten Arabinose bestätigt außerdem einen hohen Grad an Generalität im Hinblick auf die vicinale Stereochemie.

Als zweiter Teil der Arbeit und um die möglichen Anwendungen der IMA weiter zu untersuchen, wurde eine neue Syntheseroute für den bakteriellen Zucker D-*glycero*-D-*manno*-Heptose ausgehend von D-Ribose entwickelt. Hierbei wurde der Fokus auf eine säulenfreie Synthese gelegt, um durch die Vermeidung von aufwändigen Reinigungsschritten eine einfache Skalierbarkeit der Reaktionen zu ermöglichen.

Der Startpunkt der geplanten Reaktionssequenz war die von *Stanetty and Baxendale* etablierte Synthese der kristallinen 1,2,3,4,6,7-hexa-*O*-acetyl-L-*glycero*-α- D-*manno*-Heptopyranose, der stabilen und nicht-hygroskopischen Lagerform von L-*glycero*-D-*manno*-Heptose, bei der das benötigte Hauptisomer auf Grund seiner hohen Kristallinität durch Umkristallisieren isoliert werden kann. Die IMA von D-Ribose führt zur Ausbildung von zwei Hauptisomeren in *lyxo*- und *xylo*-Konfiguration im Verhältnis 1.6:1. Allerdings ist in diesem Fall eine einfache Trennung der Diastereomere durch Umkristallisieren ohne Erfolg. Stattdessen wurde eine Reaktionssequenz angewandt, die auf der Einführung von Isopropylidengruppen basiert und die stereochemischen Unterschiede der beiden Isomere in Bezug auf die Position der 2-OH-Gruppe ausnutzt. Tatsächlich konnte mit Hilfe dieser Strategie die säulenfreie Synthese von DD-*manno*-Heptose erfolgreich in kleinem Maßstab durchgeführt werden, die Skalierung der Route wird derzeit noch untersucht.



ABBREVIATIONS

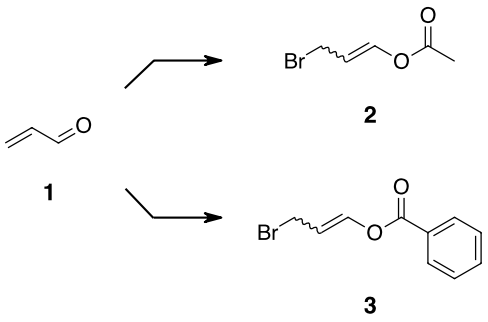
Ac	acetyl
Bn	benzyl
Bz	benzoyl
CMW	mixture of chloroform, methanol, and water
conc.	concentrated
COSY	correlated spectroscopy (2D-NMR)
δ	chemical shift (in ppm)
d	doublet
DABCO	1,2-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DMAPA	3-(dimethylamino)-1-propylamine
DMF	dimethylformamide
DMP	2,2-dimethoxypropane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DP	degree of polymerization
EA	ethyl acetate
Et_2O	diethyl ether
EtOH	ethanol
equiv.	equivalent
HMBC	heteronuclear multiple bond correlation (2D-NMR)
HPLC-MS	high performance liquid chromatography mass spectrometry
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence (2D-NMR)
IMA	indium mediated acyloxyallylation
J	coupling constant
Kdo	3-deoxy-D-*manno*-2-octulosonic acid
LP	petroleum ether
LPS	lipopolysaccharides
m	multiplet
MeOH	methanol
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
OCC	open-chain content
PCM	phase change material
q	quartet
s	singlet
t	triplet
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin-layer chromatography

GENERAL SCHEMES

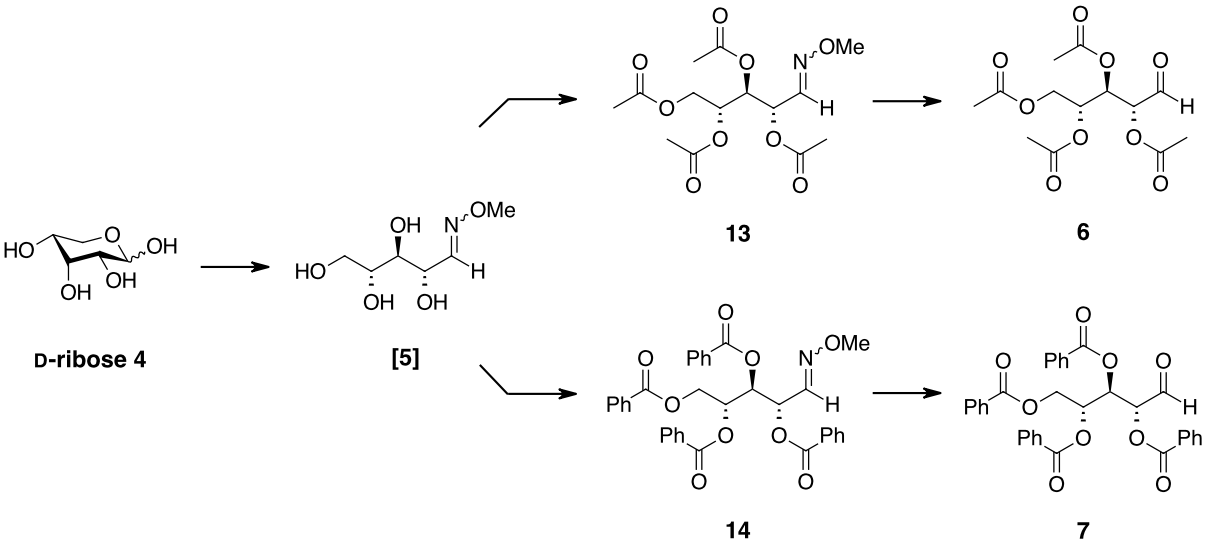
In this thesis all compounds prepared or used as starting materials are numbered in bold Arabic numerals in order of their appearance. For unisolated intermediates additional square brackets were used. Chemical structures which are only shown for clarification purposes (see chapter 1. Introduction) are numbered in bold Roman numerals.

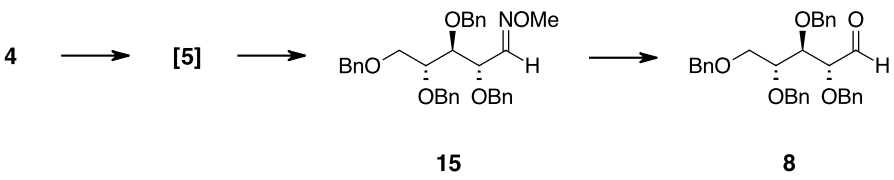
Indium mediated acyloxyallylation of aldoses – Systematic study

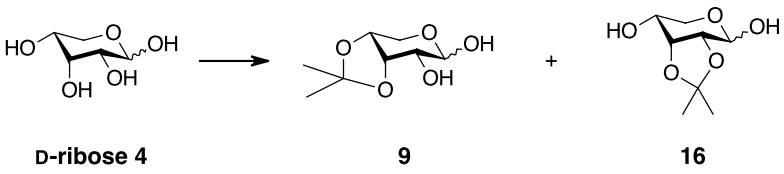
Preparation of the elongation reagents



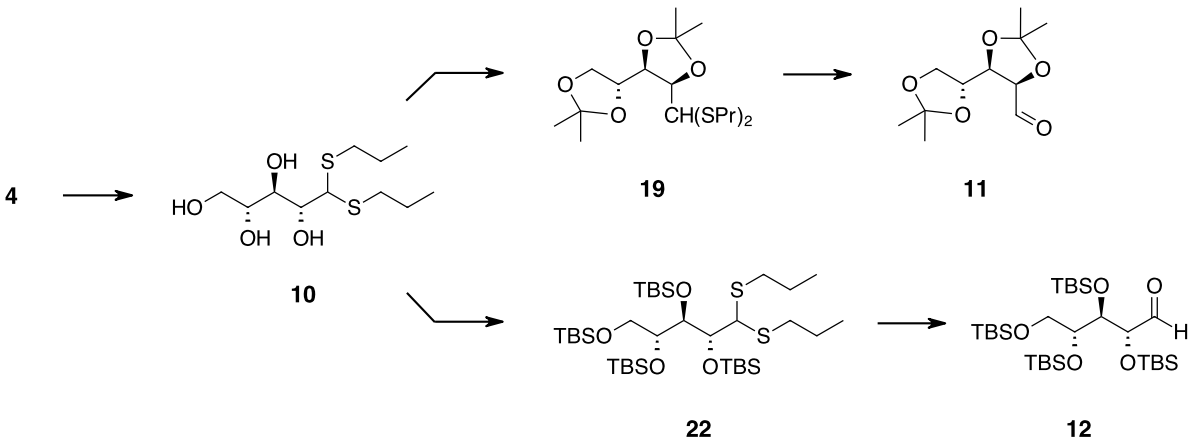
Preparation of the protected sugar aldehydes



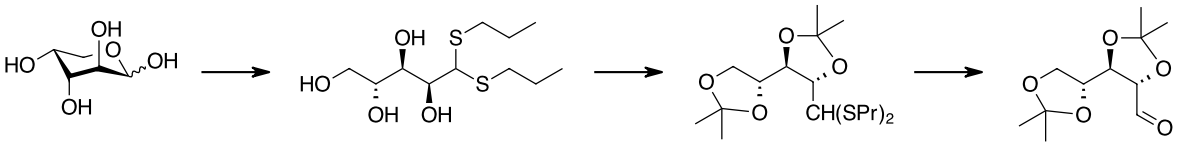




D-ribose 4 **9** **16**

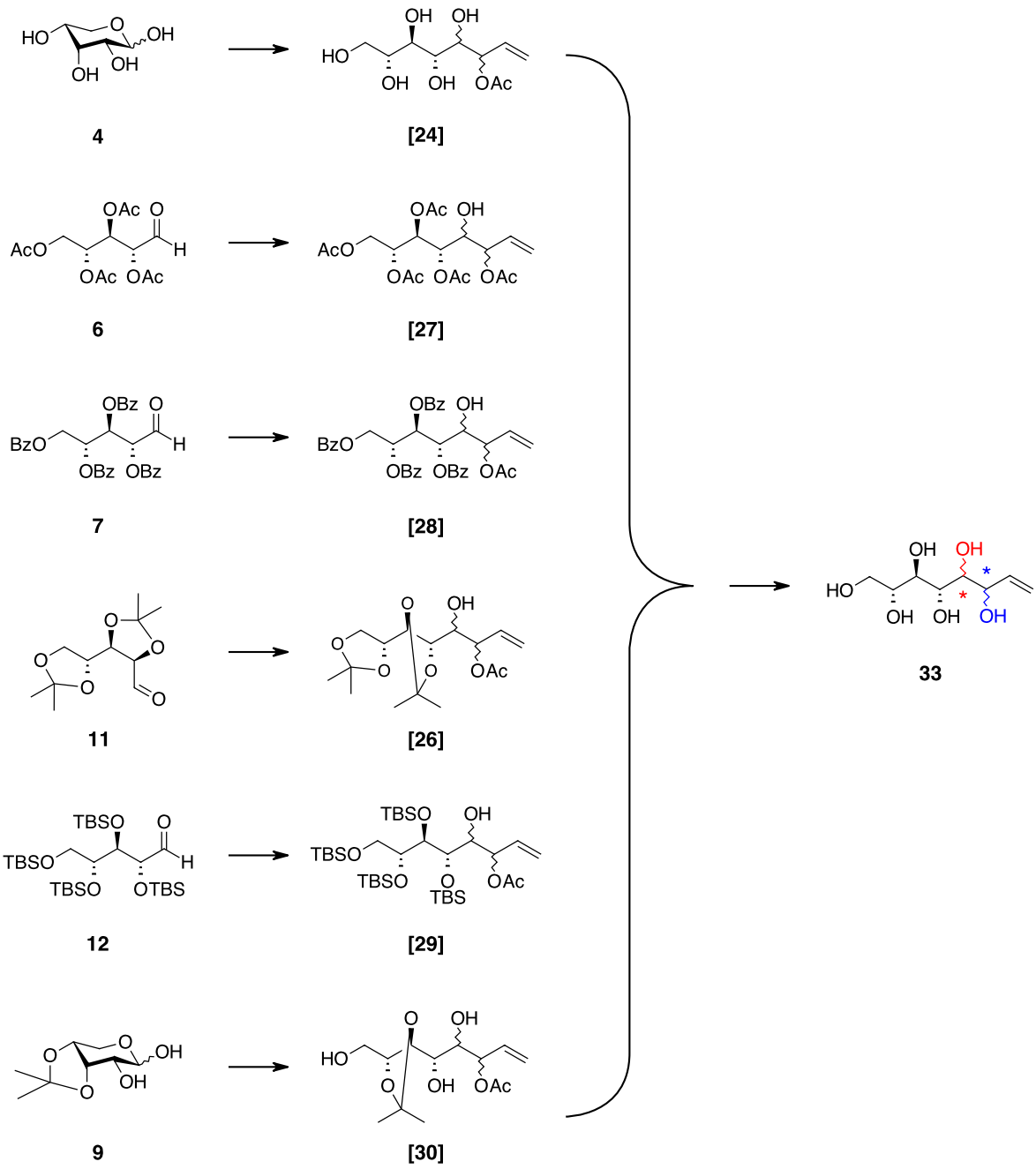


10 **19** **11** **22** **12**

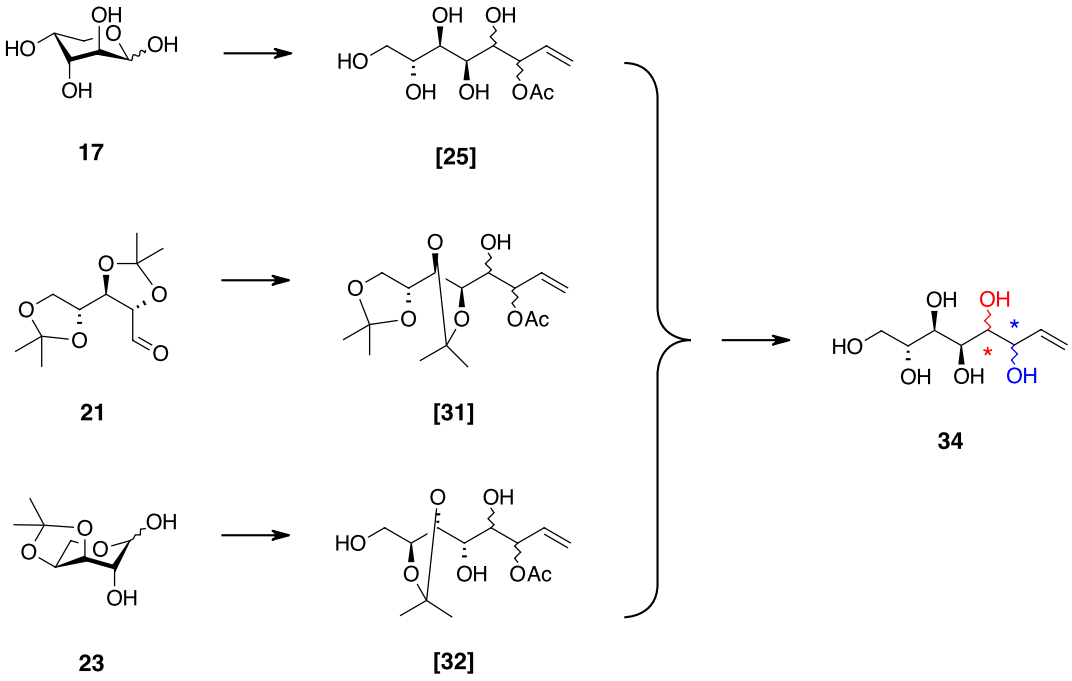


D-arabinose 17 **18** **20** **21**

IMA of the sugar aldehydes (*ribo*-series)

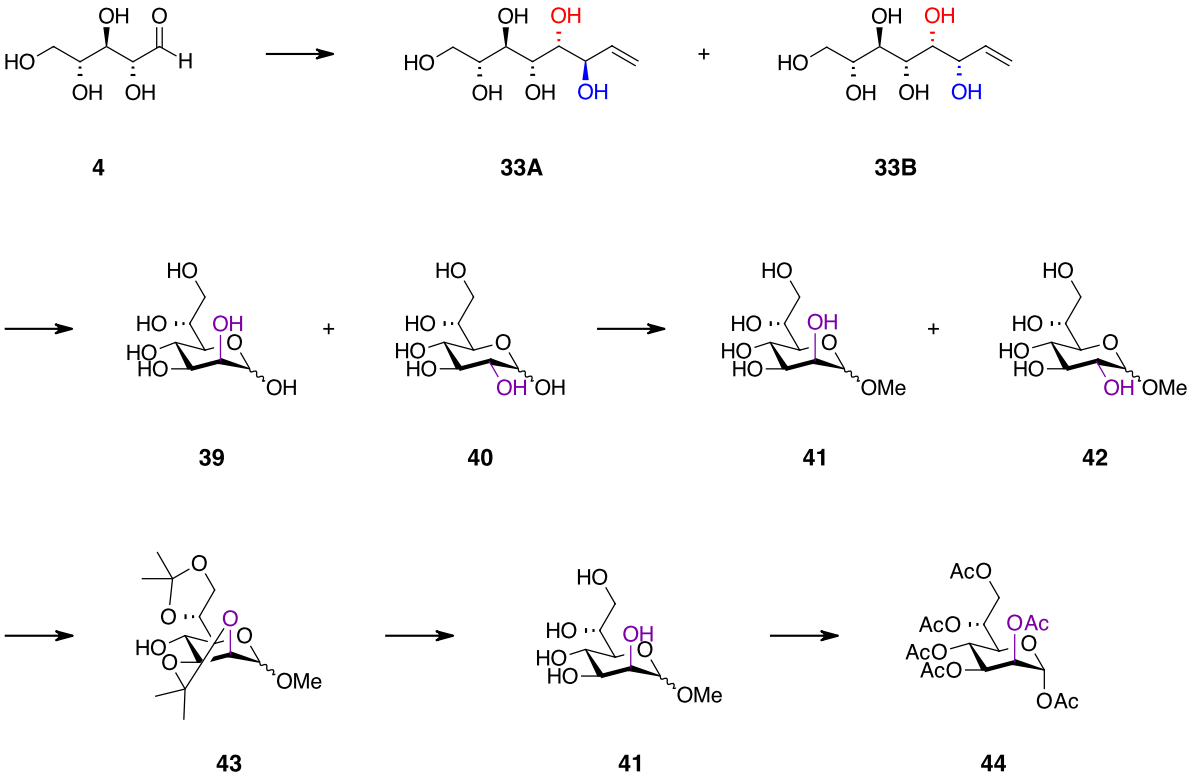


IMA of the sugar aldehydes (*arabino*-series)



Indium mediated acyloxyallylation of aldoses – Target-oriented synthesis

Synthesis of D-*glycero*-D-*manno*-heptose



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1. Introduction

1.1 Carbohydrates

1.1.1 General information

Carbohydrates form the largest group of natural products. They play a role in a wide range of biological processes and are responsible for structural stability as well as energy storage in both plants and animals. The name 'carbohydrate' refers to the former misconception that these compounds only consist of the element carbon and water, having a general structure of $C_x(H_2O)_y$.[1] However, the carbohydrate family was found to be much more diverse and includes next to monosaccharides, oligosaccharides, and polysaccharides also derived substances, which can be synthesized from or hydrolyzed to monosaccharides.[2]

1.1.2 Structure and classification

Carbohydrates can be grouped in monomeric carbohydrates like monosaccharides and polymeric carbohydrates which are called oligosaccharides (DP = 2-10) or polysaccharides (DP > 10) depending on their degree of polymerization (DP). The elementary building blocks are chiral polyhydroxyalkanals or polyhydroxyalkanones which often adopt a cyclic hemiacetal form.[2]

The monosaccharides are classified according to their number of carbon atoms and their carbonyl functionality. The length of the carbon chain is indicated by using the terms trioses (3 carbon atoms), tetroses (4), pentoses (5), hexoses (6), etc., whereas the classification into aldoses or ketoses depicts whether their acyclic form comprises an aldehyde moiety or a keto group (see Figure 1). Aldoses are also referred to as 'reducing sugars' due to the ease of oxidizing their aldehyde functionality. Furthermore, monosaccharide units can be divided depending on the size of their ringforms into typically pyranoses (6-membered ring) and furanoses (5-membered ring).[3]

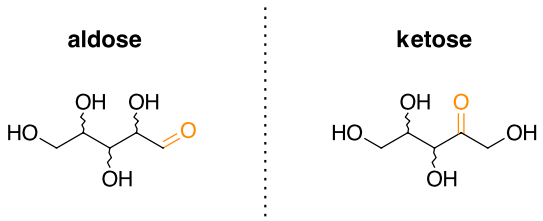


Figure 1: Classification of pentoses according to their carbonyl functionality

For the parent sugars, all non-carbonyl carbon atoms along the sugar chain are substituted with a hydroxy group. This creates a high number of stereocenters, allowing for a wide range of possible carbohydrate structures. The so called Fischer projection is used instead of the *R,S* system which is generally applied to designate the stereochemistry of a chiral center in chemical compounds.[4] In the Fischer projection, the carbon chain is drawn vertically in a straight line, with the carbon in the highest oxidation state (carbonyl group) pointing upwards. The substituents are drawn left and right and are directed out of the plane towards the observer. The hydroxy group of the asymmetric center which is the furthest away from the carbonyl functionality determines the configuration of the monosaccharide. If it is facing to the right hand side, the sugar is in the D-form, whereas it is called a L-sugar if the hydroxy group is directed to the left hand side.[2] For aldoses the number of different

possible structures is 2^{n-2} with n being the number of respective carbon atoms. Within a series of structures with equal chain length always two sugars are enantiomers, having the same relative but an inverted absolute stereochemistry (see Figure 2 for all pentoses as example).[3]

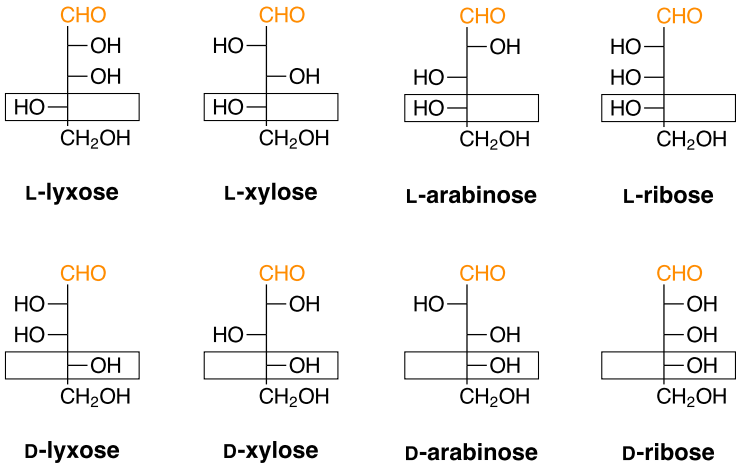


Figure 2: D- and L-form of all possible aldopentoses (Fischer projection)

1.1.3 Nomenclature of higher carbon sugars

Monosaccharides with up to six carbon atoms are assigned trivial names (e.g. D-ribose) which are preferred over their systematic names (e.g. D-*ribo*-pentose). When it comes to sugars with longer chain length like heptoses, octoses, etc. no trivial names are defined anymore, and the systematic name needs to be generated by adding two or more configurational prefixes to the stem name. Therefore, the carbon sugar is divided into groups of four chiral centers starting from the chiral center proximal to C1. The prefixes which correspond to the parent sugars are cited in reverse order, beginning with the prefix of the group which is furthest away from C1 (and may consist of less than four chiral centers). In the end the length descriptor is added.[5] Figure 3 shows two examples for the generation of the systematic name of a higher carbon sugar using the described methodology.

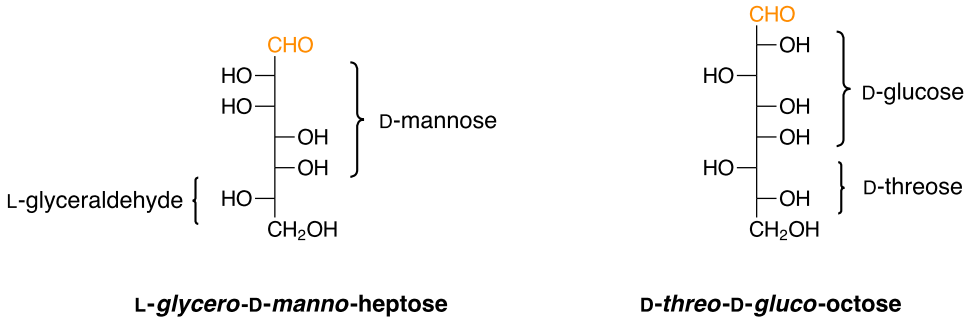


Figure 3: Nomenclature of higher carbon sugars

1.1.4 Configurational isomers

Stereoisomers are molecules with the same chemical formula and bond structure which differ only in the geometrical arrangement of their atoms and functional groups. An overview about different configurational isomers, including enantiomers, diastereomers, epimers, and anomers, is important to distinguish between certain sugar structures:

- **Enantiomers** are isomers which act like mirror images. The so-called chiral compounds possess the same physical properties except for the direction of the rotation of plane-polarized light. Examples are the D- and L-form of different sugars (see Figure 2).

- **Diastereomers** are all stereoisomers which are not enantiomers. These compounds differ in one or more stereocenters and in contrast to enantiomers, they show varying physical properties e.g. melting point, boiling point, refractive index, etc. (see Figure 2).

- **Epimers** are a specific kind of diastereomers. The term is used in respect to diastereomeric sugars which only differ in one chiral center. L-arabinose and L-ribose, for example, are epimers which have a different configuration on the second carbon atom (see Figure 2).

- **Anomers** are sugar-isomers in their hemiacetal or hemiketal form which differ in the configuration on the carbon atom which was the carbonyl functionality in the open-chain form. This carbon atom is also called the anomeric carbon. A popular example are the anomers α-D-glucopyranose and β-D-glucopyranose (see Figure 4).[6]

1.1.5 Ring-chain tautomerism

1.1.5.1 Hemiacetal/hemiketal formation

Due to the structural features of sugars, namely the presence of a carbonyl functionality as well as several hydroxy groups, they can undergo an intramolecular cyclisation reaction leading to the formation of cyclic hemiacetals or hemiketals depicted in Figure 4.

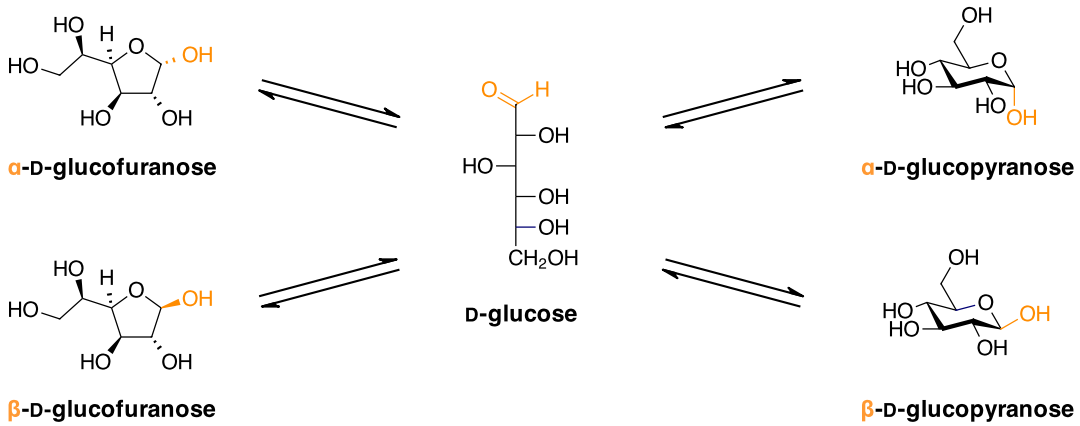


Figure 4: Hemiacetals of D-glucose formed via internal cyclization

The cyclisation reaction is especially favored in the case of relatively strain-free rings consisting of five or six atoms including an oxygen atom. Thus, aldoses and ketoses in aqueous solutions give slowly equilibrating mixtures of multiple sugar species. In there, the cyclic forms of the sugar are dominating whereas the open-chain form only represents a very small percentage. The cyclic forms of the carbohydrates are called furanoses if the rings are five-membered and pyranoses if it concerns the six-membered equivalents. The names are derived from the Hantz-Widman nomenclature for the corresponding unsaturated heterocycles furan and pyran.[4] The internal cyclisation reaction of one of the hydroxy groups of a monosaccharide with the aldehyde or keto group introduces a new chiral center which is located next to the endocyclic oxygen atom which is called the anomeric center. This leads to two possible diastereomers which are distinguished using the anomeric prefixes α (alpha) and

β (beta). They refer to the relative configuration of the hydroxy group at the anomeric carbon atom in respect to the one at the D/ L-center.[7]

1.1.5.2 Mutarotation and open-chain content (OCC) of aldoses

As mentioned before, aldoses can form hemiacetals *via* an internal cyclisation reaction and are predominantly present in solutions as this cyclic (furanoid and pyranoid) structures. Due to the reversibility of the transformation an equilibration of the anomeric forms can take place which is called mutarotation.[8]

The proportion of the acyclic form which is present in an aqueous solution is known as the open-chain content (OCC) of a sugar and it is typically significantly below 1% except for tetroses which have a relatively high open-chain content and equilibrate at around 90% of the cyclic form being present.[9] The merit of the open-chain content allows for a broader understanding of the varying reactivity and stability of the open-chain aldehydes of different aldoses.[10] A small value which represents a low amount of aldehyde present in the solution can account for slowing down reactions which require the availability of the aldehyde moiety. An example is the elongation of reducing sugars *via* the indium mediated acyloxyallylation (IMA), where reduced reactivity could be observed for sugars with more than six carbon atoms compared to their shorter-chain analogue D-lyxose which has a considerably higher open-chain content.[9]

1.2 General methods for the elongation of aldoses

Carbohydrate chemistry has played an important role in organic chemistry for far more than a century.[11] The use of carbohydrates was observed in various synthesis routes targeting natural products since carbohydrates serve as well suited enantiopure starting materials.[12] However, only few carbohydrates are readily available from natural sources. Therefore, the possibility of altering the chain length of sugars by dehomologation (shortening of the sugar chain) and elongation and thus allowing for interconversion of easily accessible carbohydrates into much-needed building blocks poses a powerful synthetical tool.[13]

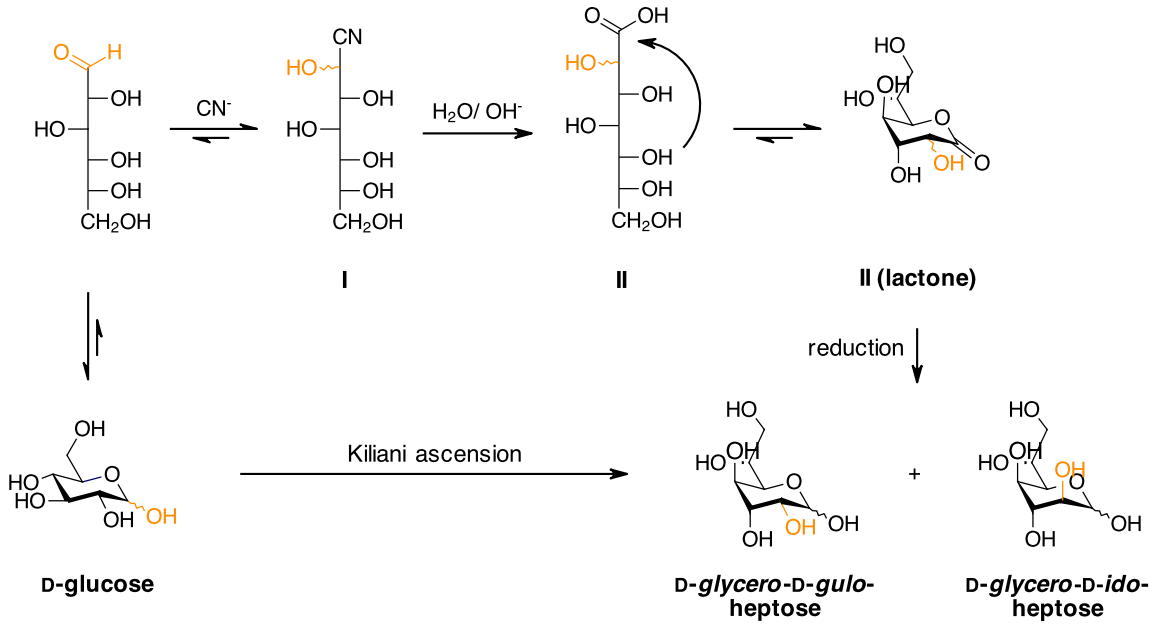
This chapter describes a selection of different methods for the elongation of carbohydrates bearing an aldehyde moiety. The discussed types of elongation of the carbon-backbone of these so-called aldoses takes place by addition of different elongation reagents to the carbon atom of the carbonyl functionality. A new carbon-carbon bond is formed at the anomeric center. The major challenge of this transition is the control of the diastereoselectivity of the newly obtained product, which largely depends on the nature of the carbohydrate substrate, the used nucleophile, or the reaction conditions. Furthermore, most of the elongation reactions make an at least partial protection of the aldoses necessary, what leads to a more elaborate and complex overall synthesis.[14]

1.2.1 Addition of carbanions

1.2.1.1 Kiliani ascension

In 1886 one-carbon elongation of aldoses upon addition of cyanide as the elongation reagent was reported by *Heinrich Kiliani*.[15] This reaction which is commonly known as Kiliani ascension is one of the oldest tools for chain extension in carbohydrate chemistry.[14]

Scheme 1 shows the Kiliani ascension of D-glucose, an aldose with six carbon atoms. In the first step, a cyanide is added to the carbonyl functionality to give epimeric cyanohydrins **I**. These intermediates undergo hydrolysis to the corresponding aldonic acids **II** which form lactones. Reduction of the lactones under mild acidic conditions results in a mixture of two epimeric heptoses bearing one more carbon atom than the starting material.[11]

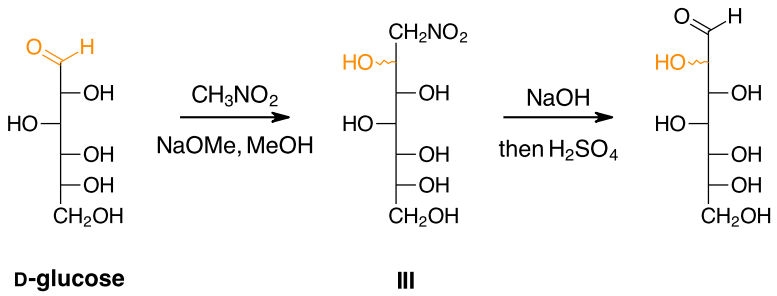


Scheme 1: One-carbon elongation of D-glucose via the Kiliani ascension

The nucleophilic attack of the cyanide can happen from two sides which creates a new stereocenter in the generated product. The C2 epimeric aldonic acids which are subsequently reduced to the corresponding aldoses are formed in a 1:1 to 3:1 ratio. The separation *via* crystallization of suitable derivates is possible but usually furnishes only moderate yields.[14] Nonetheless, the Kiliani ascension is a reliable and commonly used elongation procedure for the synthesis of monosaccharides with ^{13}C- and ^{14}C-labelling.[11]

1.2.1.2 Fischer-Sowden homologation

The Fischer-Sowden homologation[16] poses another classical way of elongating a sugar by one carbon atom. In this transformation, the aldoses are reacted with nitromethane and sodium hydroxide in methanol leading to two one-carbon elongated epimeric 1-deoxy-1-nitroalditols **III** (see Scheme 2) which are typically separated by fractional crystallization. The nitro compounds are then converted into aldehydes by a Nef reaction.[14]

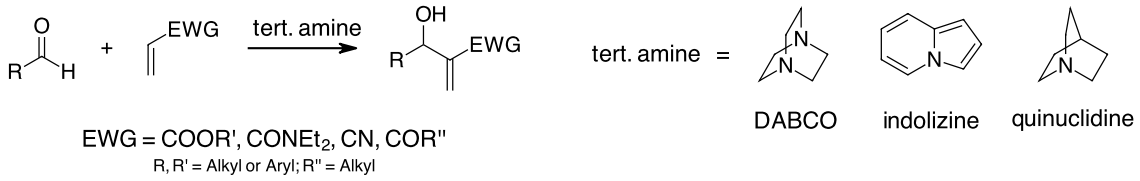


Scheme 2: One-carbon elongation of D-glucose via Fischer-Sowden homologation

The Fischer-Sowden homologation proves to be useful in providing the desired product if the usually preferred Kiliani ascension is obstructed by a tenacious separation process or does not give the target compound as the major epimer.[14]

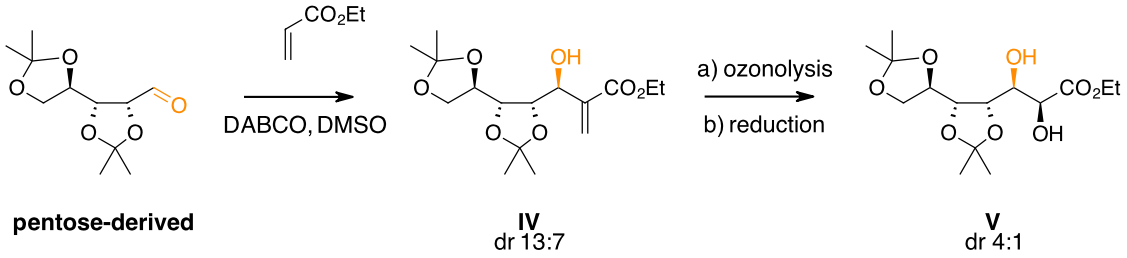
1.2.1.3 Baylis-Hillman reaction

The Baylis-Hillman reaction is attributed to a German patent filed in 1972[17] which describes the reaction of activated alkenes, like α,β-unsaturated esters, amides, nitriles and ketones, with different aldehydes using tertiary bicyclic amides as catalysts.[18] The general reaction mechanism is displayed in Scheme 3.



Scheme 3: General mechanism of the Baylis-Hillman reaction

To perform the reaction, a sugar derived aldehyde as well as an electron-deficient olefin are needed, which are typically reacted with a tertiary amine like DABCO in either DMSO or a dioxane/water-mixture. Due to the chirality of carbohydrates, substrate-controlled, stereoselective Baylis-Hillman reactions are possible and fully hydroxylated higher-carbon sugars can be prepared in relatively few steps upon ozonolysis.[14] Scheme 4 shows the Baylis-Hillman reaction of a pentose-derived sugar aldehyde with acetonide protecting groups. Addition of ethyl acrylate yields two epimeric products **IV** in a diastereomeric ratio of 13:7. Ozonolysis followed by reduction with sodium borohydride converts the terminal olefin into a hydroxy group with a 4:1 selectivity favoring the *syn*-configuration in respect to the newly introduced stereocenter on the former C1 (see Scheme 4). Further deprotection and subsequent reduction of compound **V** results in a heptose with a two-carbon elongated carbon chain compared to the starting material.[19]

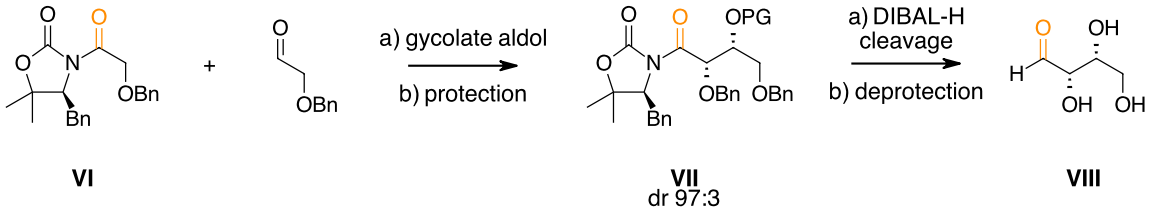


Scheme 4: Baylis-Hillman reaction of a protected sugar aldehyde[19]

1.2.1.4 Chain extension based on aldol reactions

Aldol reactions mediated by aldolases are responsible for the monosaccharide biosynthesis in nature, however, the same reaction type can likewise be used for an elongation of aldoses under laboratory conditions. To obtain a pronounced stereochemical control during the aldol reaction, chiral auxiliaries can be used amongst others.[14]

Especially aldol reactions applying an oxazolidinone auxiliary (Evans aldol) proved to be highly stereoselective procedures for extending the carbon chain in carbohydrates (see Scheme 5). The reactions can be easily carried out using either lithium or boron enolates and result in an elongation of the starting materials by two carbon atoms.[14]

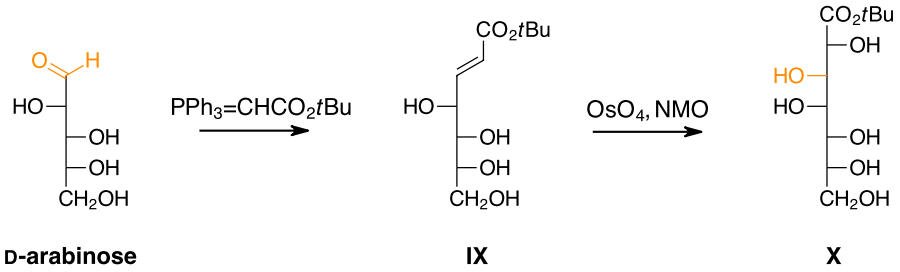


Scheme 5: Chain elongation by chiral auxiliary aldol reaction[20]

1.2.2 Chain elongation by olefination

1.2.2.1 Chain elongation with phosphorane-based ylides

Phosphorane ylides are frequently applied in extension of aldoses at the C1 position. The most common olefination method is the classical Wittig reaction. The type of Wittig reagent is selected depending on whether protected aldose hemiacetals or unprotected aldoses are used. Transformations of the latter require a polar solvent, such as dioxane or dioxane/DMF, and can only be performed with stabilized or semi-stabilized ylides to prevent fragmentation of the starting material by a retro-aldol reaction. The Wittig reaction results in α,β-unsaturated esters which can be dihydroxylated in a diastereoselective fashion to give higher-carbon sugars bearing a two-carbon elongated carbon chain.[14]



Scheme 6: Sequential Wittig reaction and dihydroxylation of D-arabinose

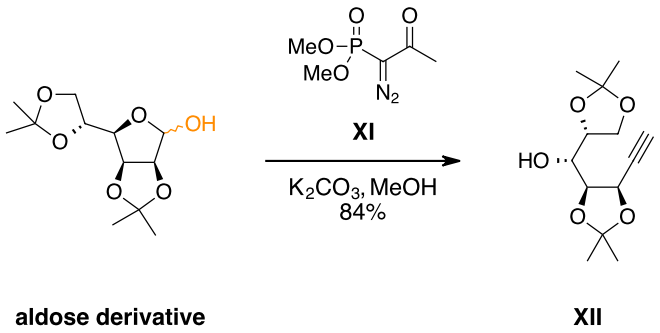
Scheme 6 shows the two-step Wittig-dihydroxylation procedure with D-arabinose. The Wittig reaction carried out with a *tert*-butyl ester stabilized phosphorane gives exclusively the (*E*)-configured product **IX** which is subsequently dihydroxylated using osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) to obtain aldonate **X**. The method is particularly effective for aldoses with *threo*-configuration since a good diastereoselectivity (5:1-8:1) can be observed for the dihydroxylation step affording the corresponding 2,3,4,5-*galacto*-configured aldonic acids.[21]

1.2.2.2 Chain elongation with phosphonate-based ylides

The Horner-Emmons olefination reaction with stabilized phosphonates such as $(EtO)_2P(O)CH_2CO_2Et$ furnishes (*E*)-α,β-unsaturated esters in very good stereoselectivity. The transformation is especially useful for the synthesis of higher sugars with more than 10 carbon atoms by olefination of the aldehyde of C5 or C6 sugars with a stabilized phosphorus ylide at the non-reducing end of the monosaccharide. The Horner-Emmons approach is preferred over the Wittig olefination due to the simpler preparation and the higher reactivity of the phosphonate ylides in comparison to the corresponding phosphoranes.[14]

Another possibility for the elongation of the carbon chain is the reaction of sugar aldehydes to terminal alkynes using dimethyl-1-diazo-2-oxopropylphosphonate **XI**.[22] This so called Ohira-Bestmann reagent

undergoes cleavage of the acetyl group by *in situ* methanolysis in a basic methanolic solution to generate dimethyl(diazomethyl)phosphonate which then reacts with an aldose derivate to form the one-carbon extended ald-1-ynitol **XII** (see Scheme 7). The one-step synthesis works most effectively with protected aldoses where good yields can be obtained, but also tolerates free hydroxyl groups.[23]

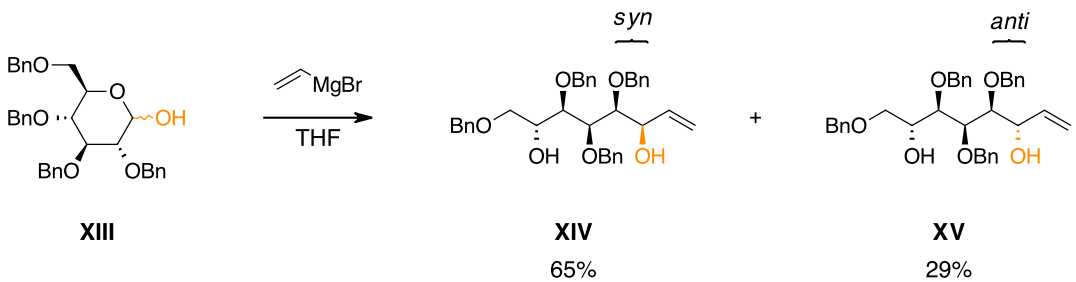


*Scheme 7: Elongation of aldose derivatives with the Ohira-Bestmann reagent **XI**[14]*

1.2.3 Organometallic addition reactions

The addition of organometallic reagents to a variety of carbohydrates is a well exploited and commonly used method for the extension of the carbon chain and the synthesis of higher-carbon sugar derivatives. The simple reaction is characterized by high stereoselectivity and convenient chemical yields in most cases, however, the prediction of the stereochemical outcome (*syn*/*anti* ratio) can be challenging.[24] Depending on the applied organometallic reagent, either protected sugar aldehydes, protected/unprotected carbohydrate hemiacetals or protected aldonolactones can be used as substrates for the elongation reaction. The addition of an organometallic reagent to the aldehyde moiety results in the formation of a new stereocenter. The *syn*/*anti*-ratio is closely linked to whether or not chelation is possible as well as to the nature of the chelating species. Therefore, the control of the stereochemistry in the product is significantly impacted by various factors, namely the choice of reaction conditions, the used organometallic species, and the carbohydrate substrate.[14]

1.2.3.1 Elongation with organomagnesium, organolithium or organozinc reagents



*Scheme 8: Addition of vinylmagnesium bromide to 2,3,4,6-tetra-O-benzyl-D-glucopyranose **XIII**[25]*

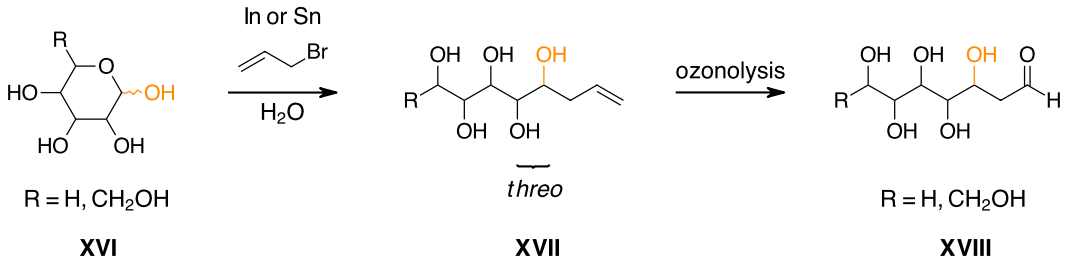
Organomagnesium and organolithium reagents generally require anhydrous reaction conditions since they are prone to hydrolysis. Usually, aprotic solvents such as ether or THF are used. Hence, the sugar substrates need full or at least partial protection, also to avoid solubility issues in the required solvents. Regarding the stereochemical reaction outcome, organomagnesium reagents normally favor 1,2-chelation and lead to the 1,2-*syn* (*threo*) diastereomer as the major product (see Scheme 8). However, since the diastereoselectivity of the Grignard addition is influenced by the chelation with the OH-group on C2 it is often only moderate with e.g. isopropylidene groups where the oxygen atom participates

less effectively. Furthermore, although the reaction conditions of the organometallic addition reactions are constantly optimized, one must keep in mind that it may be difficult to transfer results even to similar substrates.[14]

The lithium cation shows a less effective chelating effect than organomagnesium and the addition of organolithium reagents to protected sugars aldehydes only affords a modest diastereoselectivity. The stereochemistry of the product is highly substrate-dependent and cannot easily be influenced by altering the reaction conditions. Organozinc reagents can be applied in special cases, when alkynyllithium reagents exhibit insufficient selectivity for the addition to a protected aldose aldehyde. Transmetallation to the corresponding zinc reagent may enhance the favored formation of the 1,2-*syn* (*threo*) reaction product.[14]

1.2.3.2 Tin and indium mediated allylation

Contrary to other organometallic addition reactions, allylations with tin and indium can be carried out under aqueous conditions using water or alcohols as reaction medium. Thus, the classical substrate requirements of full or at least partial protection of the aldose hemiacetals or aldehydes can be omitted. With unprotected aldoses **XVI**, the addition is controlled by 1,2-chelation and results in a predominant formation of the 1,2-*syn* (*threo*) product **XVII** (see Scheme 9). Subsequent ozonolysis of the allylation product yields the corresponding 2-deoxy sugar **XVIII**. The use of more finely powdered metals increases the reactivity, indium leads to a faster reaction rate as well as enhanced yields in comparison to tin. When applying the indium mediated allylation to aldoses with isopropylidene and TBS groups a much weaker 1,2-chelation can be observed.[14] Consequently, the 1,2-*anti* product with *erythro* relationship between the newly formed hydroxyl group and the one originally present on C2 of the initial aldehyde is found as the major isomer.[26] This primary formation of the corresponding Cram product with the protected aldehydes can be attributed to the dominance of the steric effects, the reaction proceeding under effective non-chelation control.[27]



XVI **XVII** **XVIII**

Scheme 9: Indium and tin mediated allylation of unprotected sugars

Besides allyl bromide, also more functionalized allylic bromides such as 2-(bromomethyl)acrylates and 2-(bromomethyl)acrylic acid can be used for the indium mediated elongation reaction. Subsequent ozonolysis of the resulting olefins afford 3-deoxy-2-ulosonic esters/acids in good overall yields.[14]

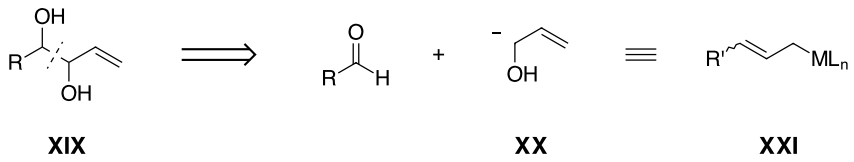
Palmelund and Madsen introduced the indium mediated allylation of unprotected pentoses and hexoses with 3-bromopropenyl esters giving rise to alditols with a terminal olefin. Here, ozonolysis of the reaction products results in the corresponding heptoses and octoses, respectively.[28] This so called indium mediated acyloxyallylation (IMA), is described in the next chapter (see 1.3 Indium mediated acyloxyallylation (IMA)) in more detail.

1.3 Indium mediated acyloxyallylation (IMA)

The indium mediated acyloxyallylation (IMA) constitutes a useful tool for the direct elongation of reducing sugars by two carbon atoms (upon ozonolysis). As this thesis deals with the fundamentals as well as possible applications of the reaction, this chapter provides an in-depth look into its development and its strengths but also its limitations and challenges.

1.3.1 Acyloxyallylation of aldehydes

As previously mentioned, chain elongation of aldoses *via* indium mediated allylation with allyl bromide and subsequent ozonolysis results in 2-deoxy sugars. For the direct synthesis of 'standard' carbohydrates, a different reagent is required to act as a nucleophile in the allylation procedure in order to obtain alk-1-ene-3,4-diols as reaction products. These *syn* and *anti* 1-ene-3,4-diols **XIX** are valuable building blocks regarding the total synthesis of various polyoxy natural products. Scheme 10 shows the retrosynthetic analysis of these compounds, which reveals a regioselective addition of a 1-hydroxy allyl anion **XX** to aldehydes as suitable reaction pathway.[29]

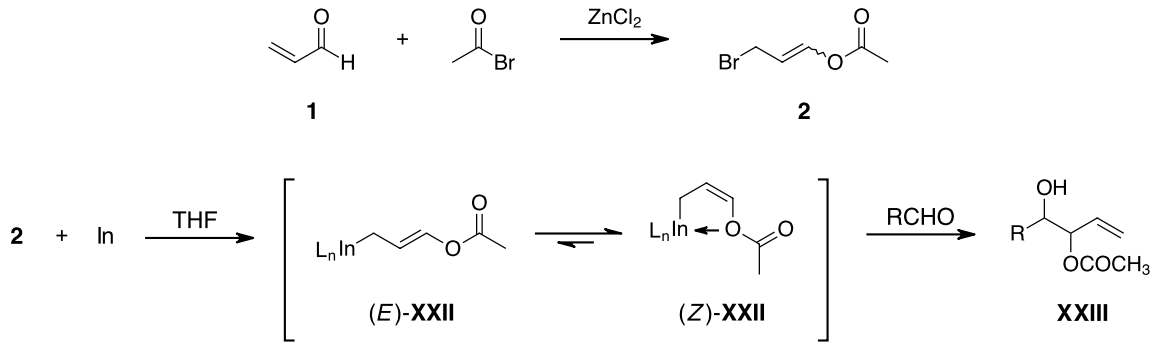


XIX **XX** **XXI**

Scheme 10: Retrosynthetic analysis of an alk-1-en-3,4-diol

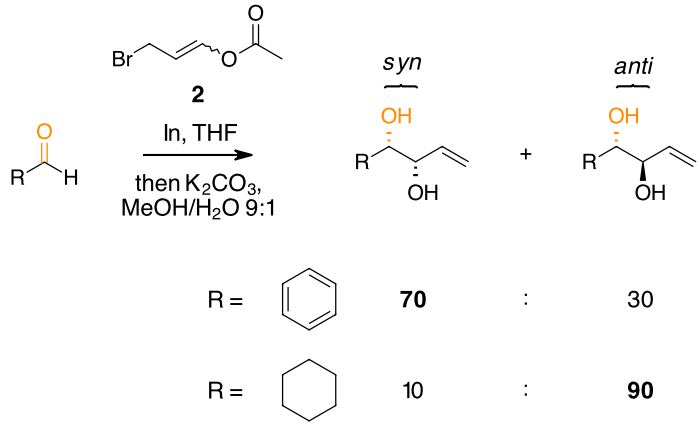
3-substituted allylic organometallic reagents **XXI** represent fitting synthetic equivalents for the required synthon **XX**, however, preparation of these derivatives usually necessitates metalation with alkyllithium bases as well as subsequent transmetalation. This limits the possible applications and makes these reagents unsuitable for the elongation of unprotected sugars where aqueous conditions are required due to solubility issues.[29] A more practical protocol was developed by *Lombardo et al.* which is based on the 1,4-haloacylation of acrolein **1**. Herein, the organometallic species **XXIII** is obtained by oxidative addition of metallic indium to the carbon-halogen bond of an adequate 3-heterosubstituted allyl bromide, for example 3-bromo-1-propenyl acetate **2** or 3-bromo-1-propenyl benzoate **3**.[30]

Scheme 11 depicts the preparation of the elongation reagent 3-bromo-1-propenyl acetate **2** which can be synthesized on multigram scale. The exposure to indium powder in THF leads to formation of 3-acetoxy allyl indium species **XXII** that successively react with aldehydes to generate 1-ene-3-acetoxy-4-ols **XXIII** in high yield.[29]



*Scheme 11: Preparation of 3-bromo-1-propenyl acetate **2** and generation of the 1-en-3-acetoxy-4-ol **XXIII***

The 3-halo-1-alkoxyprop-1-enes **2** and **3** were first used in addition reactions to simple prochiral aldehydes. It was found that the diastereoselectivity of the acetoxyallylation mediated by indium powder mainly depends on whether saturated or unsaturated aldehydes are used. Aliphatic, unconjugated aldehydes display *anti* stereoselectivity, while conjugated, unsaturated aldehydes clearly exhibit the inverse *syn* stereopreference (see Scheme 12).[30]

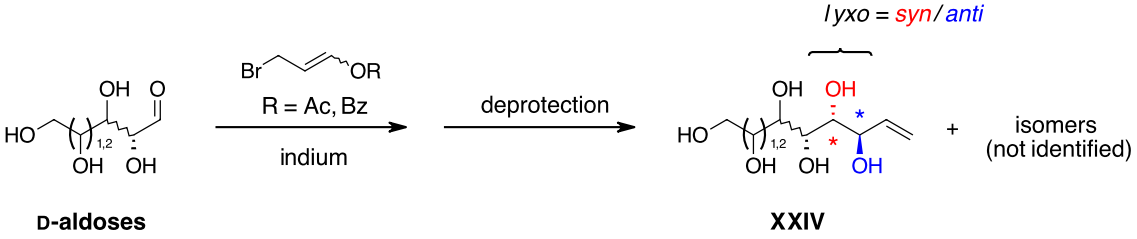


Scheme 12: Diastereoselectivity in the indium mediated Grignard route to alk-1-ene-3,4-diols[30]

The acyloxyallylation of aldehydes can be performed using two different routes. For the Grignard protocol, the organometallic species is pre-formed by stirring indium powder and the elongation reagent (usually in a 1:1.5 molar ratio) in anhydrous THF before adding the aldehyde. In contrast, Barbier conditions are needed if the reaction is performed in water to inhibit Wurtz dimerization of the 3-halo-1-alkoxyprop-1-enes. For this one-pot procedure, the elongation reagent is directly added to the stirred mixture of indium powder and the aldehyde in the polar solvent. Both routes showed the same stereochemical trend in regard to the formed reaction products.[30]

1.3.2 Implementation in carbohydrate chemistry

Palmelund and Madsen[28] were the first to apply the acyloxyallylation strategy on unprotected aldoses, and thereby introduced the concept to carbohydrate chemistry in 2005. Their proof-of-concept study showed the applicability of the indium mediated acyloxyallylation on reducing sugars using D-pentoses and D-hexoses as starting materials (see Scheme 13). The obtained corresponding enitols could be converted into two-carbon elongated sugars *via* subsequent ozonolysis.[28]



*Scheme 13: IMA of D-aldoses affording the lyxo-configured product **XXIV** as the main isomer*

The elongation reaction was performed in ethanol or a dioxane/water mixture under Barbier conditions to assure dissolution of the sugars. When the reaction products were deesterified in the workup, a mixture of diastereomers was obtained. While the studied transformation can lead to four different diastereomers in total, all of the aldoses used gave the enitol **XXIV** with *lyxo*-configuration at positions 3, 4, and 5 as the major isomer. The compound is representing a *syn*-orientation in respect

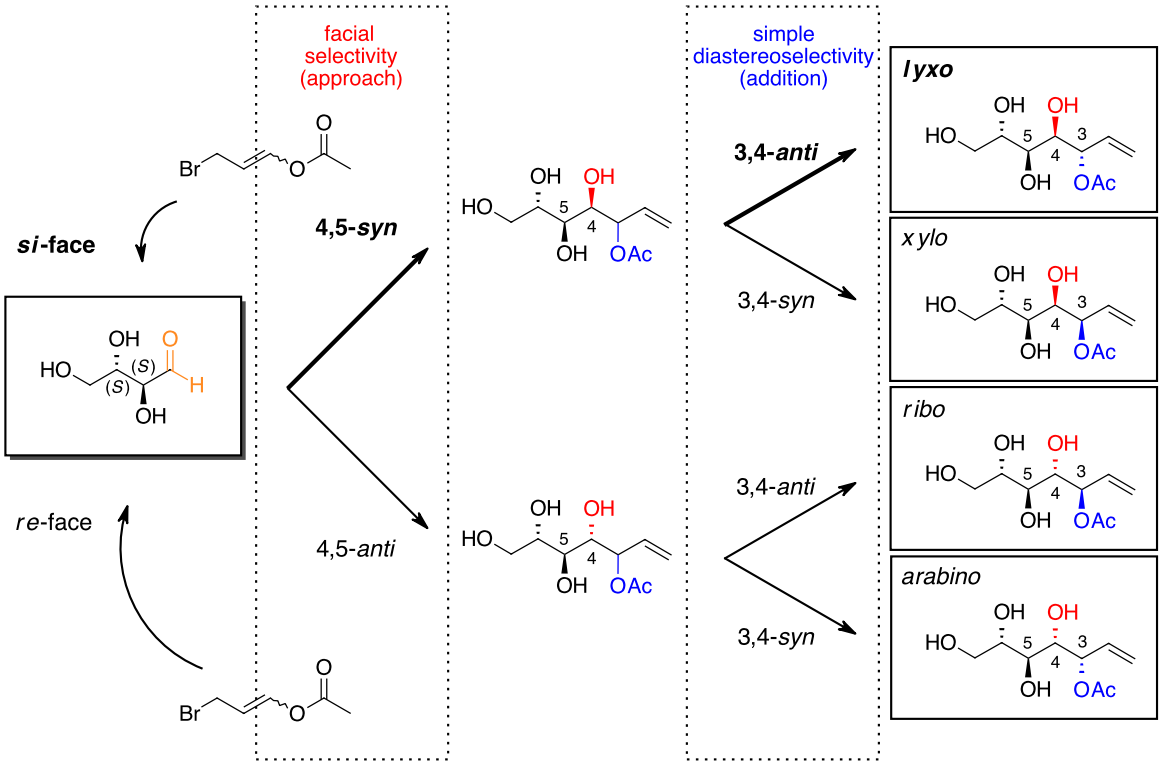
to the former 2-OH group and an *anti*-addition to the aldehyde.[28] The latter is in agreement with the findings of *Lombardo et al.* for saturated aldehydes[30], however, the predominant *syn*-orientation in regard to the former C2-stereocenter is a specific feature for unprotected reducing sugars as starting materials and is consistent with the influence of the possible chelation with the OH-group on the carbon atom next to the aldehyde moiety which has already been described before (see 1.2.3.2 Tin and indium mediated allylation).

1.3.3 Wurtz-type coupling

When the elongation procedure was performed with the readily available C6 sugars galactose, glucose and mannose, a decreased reactivity of the hexoses in comparison to the pentoses was observed,[28] which can be ascribed to their lower open chain content.[9] Furthermore, using ethanol as reaction solvent an acid-catalyzed Fisher glycosylation took place instead of the desired enitol formation, therefore the solvent was changed to a dioxane/water mixture.[28]

However, especially in water, Wurtz-type dimerization of the elongation reagent was observed which makes the application of a Barbier protocol necessary where the reagent and the indium powder are directly added to a stirred mixture of the aldehyde dissolved in the reaction medium. The fast formation of the Wurtz-type byproducts is explained by the acidic hydrolysis of the indium salts which are formed during the indium mediated acyloxyallylation reaction which lowers the pH value of the reaction mixture up to 3. Under this conditions, the enolester functionality of the 3-halo-1-alkoxyprop-1-enes is sensitive to hydrolysis.[30] However, if an aldehyde is present, nucleophilic addition to the carbonyl group of the organometallic species is faster than the Wurtz-type coupling and decomposition of the reagent is inhibited.[31]

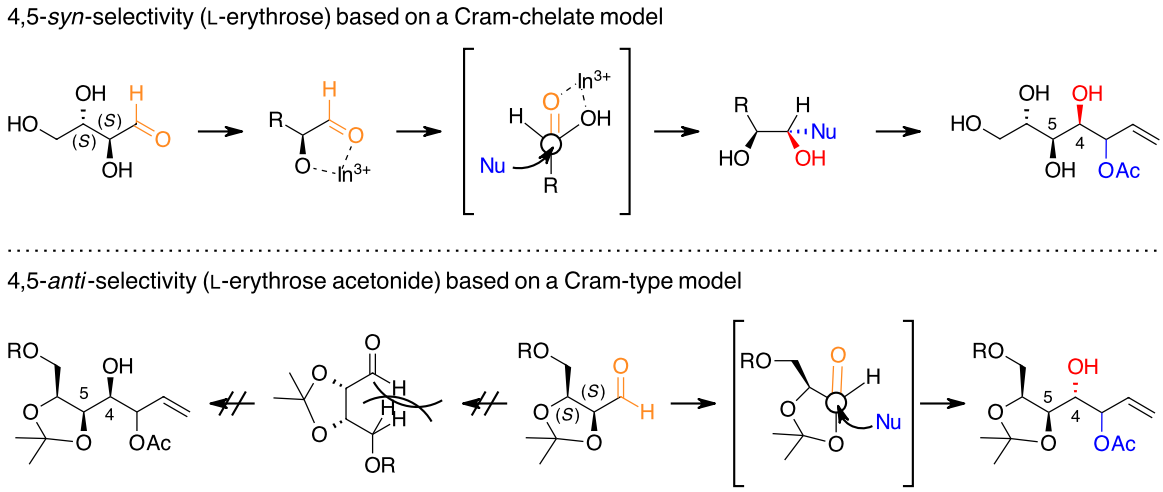
1.3.4 Methodology of the IMA of aldoses



Scheme 14: Depiction of the two types of selectivity observed in the IMA of L-erythrose with color-coding of for the substrate (red) and reagent (blue) derived stereocenters; the path to the main product is marked bold[32]

Within our group, an in-depth methodological investigation of the acyloxyallylation of unprotected and protected tetroses was performed by *Draskovits et al.*[32] in 2018. Hereby, the epimeric tetroses L-erythrose and D-threose and the corresponding 2,3-*O*-isopropylidene protected derivatives were successfully applied to the indium mediated acyloxyallylation to examine the diastereoselectivity of the reaction depending on the structure of the starting material. The usage of tetroses enabled unambiguous identification of the hexose-products (upon ozonolysis) by comparison with readily available reference materials.

The facial selectivity for the *si*-face and the *re*-face of the aldehyde can be rationalized by a Cram-chelate model or a Cram-type model, respectively (see Scheme 15), while the *anti*-selectivity in the addition step is consistent with the mechanistic model which *Lombardo and Trombini*[30] described for the acyloxyallylation of achiral aliphatic aldehydes.[32]



Scheme 15: Reasoning for the facial selectivity in the IMA relating to the dependence of a 2,3-O-isopropylidene protection

This work had followed up on the work of *Stanetty and Baxendale* who elucidated the stereochemistry of the three elongation products of the indium mediated acyloxyallylation of L-lyxose in their case study towards bacterial L-*glycero*-D-*manno*-heptose at scale using 3-bromo-1-propenyl acetate **2** as reagent (see 1.3.5.1 Application of the IMA in the synthesis of bacterial sugars). The diastereomeric mixture was constituted of three of the four possible isomers, namely the *lyxo* isomer (65%), the *xylo* isomer (25%), and the *ribo* isomer (10%).[33] The *syn*/*anti*-configuration of the main product was in accordance with the original study by *Madsen et al.*[28] and the selectivity between the four isomers in consistence with the later findings of *Draskovits et al.*[32].

1.3.5 Applications of the IMA

1.3.5.1 Application of the IMA in the synthesis of bacterial sugars

Bacterial lipopolysaccharides (LPS) are components of the outer cell membrane of Gram-negative bacteria. It comprises lipid A as well as a covalently linked core region which consists of up to 15 sugars with LD-heptoses and 3-deoxy-D-*manno*-2-octulosonic acid (Kdo) as major constituents (see Figure 5).[34] Among these, especially L-*glycero*-D-*manno*-heptose plays an important role due to its function as mediator for various interactions with the human immune system. Since the core regions are highly conserved structurally, both, the sugar and its biochemical epimeric precursor D-*glycero*-D-*manno*-heptose constitute a target for the development of new antibiotics and vaccines.[35]

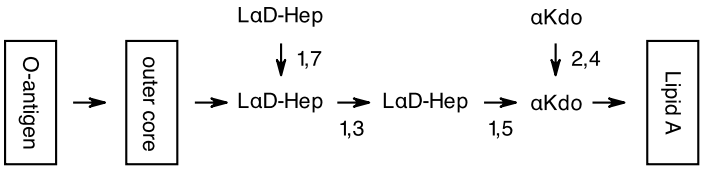
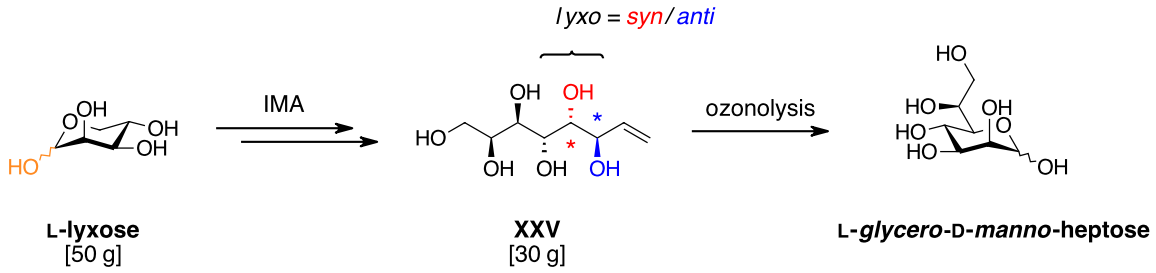


Figure 5: Exemplary structure of LPS with the LD-heptose containing inner core region (phosphorylation not shown)[35]

Historically, to access the parent LD- and DD-heptoses a 6-8 step synthesis from shorter, commercially available sugars was required. However, this significantly hampered the research in this important area.[35] In 2015, *Stanetty and Baxendale*[33] developed a short and scalable synthesis of L-*glycero*-D-*manno*-heptose, exploiting the *lyxo*-configuration of the predominantly formed diastereomer **XXV** in the indium mediated acyloxyallylation of aldoses described by *Palmelund and Madsen*[28] (see Scheme 16).



Scheme 16: Convenient and scalable preparation of L-glycero-D-manno-heptose via IMA of L-lyxose

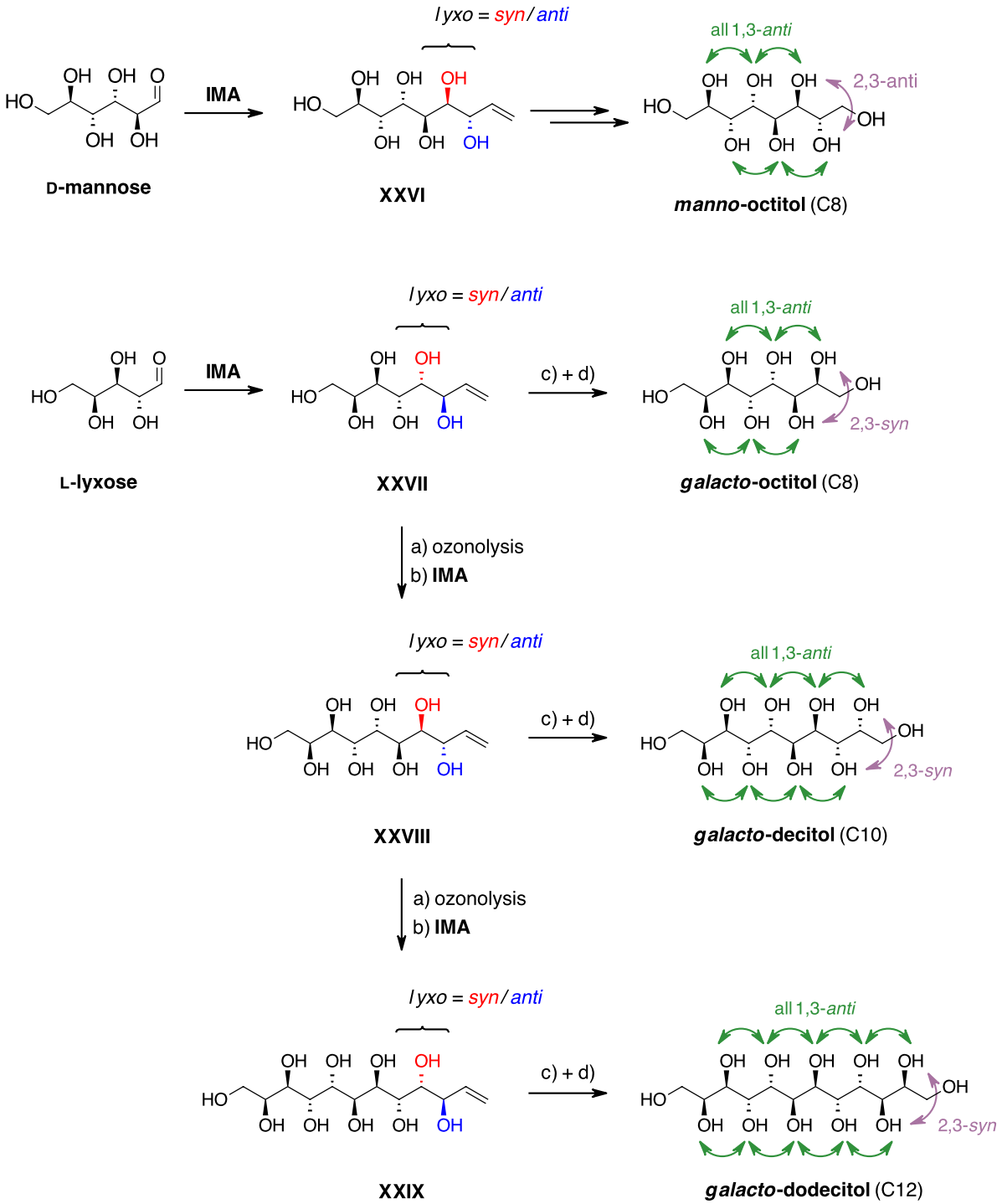
The target compound in its fully acetylated, bench-stable storage form (1,2,3,4,6,7-hexa-*O*-acetyl-L-*glycero*-D-*manno*-heptopyranose) is obtained in a highly convenient four-step sequence from L-lyxose, requiring only two recrystallizations.[33]

1.3.5.2 Synthesis of non-natural sugar alcohols

Natural sugar alcohols can be found in fruits, vegetables, mushrooms and in human organisms, however, on industrial scale they are usually formed by reduction of reducing sugars by catalytic hydrogenation.[36] They consist of a straight carbon chain with a hydroxyl group on each carbon atom and the number of hydroxyl groups determines the name of the sugar alcohol (tetritols, pentitols, hexitols, heptitols, etc.). Especially hexitols and derived compounds are of use in the food industry as well as for pharmaceuticals, textiles, cosmetics, and polymers.[37]

In recent years, sugar alcohols became increasingly interesting regarding a possible application as phase change materials (PCMs) for thermal energy storage. They are promising materials because of their ability to store large amounts of energy by using the latent heat of a phase change, e.g. solid to liquid. This high storage capacity is paired with a safer handling compared to other PCMs and particularly of use since the melting points are in a range suitable for solar process heat or waste heat recovery.[38] In a computational study from 2016 by *Inagaki and Ishida*[39] exceptionally large thermal storage densities of up to 450-500 kJ/kg were predicted for non-natural sugar alcohols fulfilling three general guidelines: a linear carbon backbone, a 1,3-*anti*-relationship of all hydroxyl groups, and an even number of carbon atoms. The calculated values for the so-called '*manno*-series' were investigated in our research group already, and a new series of stereochemically defined sugar alcohols with 8, 10, and 12 carbon atoms in the chain based on the naturally occurring galactitol was designed. For the synthesis of the compounds, the indium mediated acyloxyallylation was selected to access the higher sugar species. Its high diastereoselectivity was essential to achieve the necessary *syn*-relationship

between the two hydroxyl groups at the terminal stereocenters and to obtain the opposed distribution of all neighboring substituents (see Scheme 17).[40]

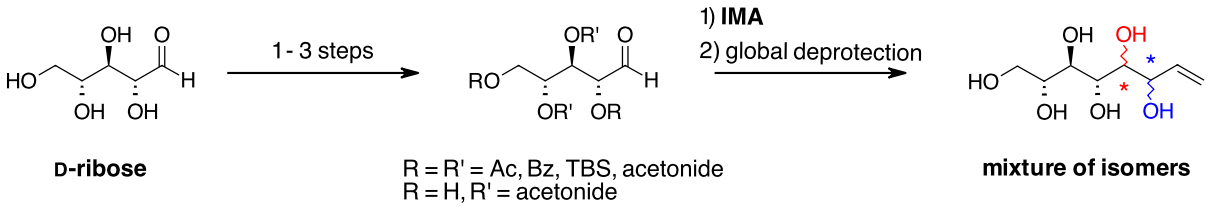


Scheme 17: Synthesis of non-natural sugar alcohols using the IMA; c) selective dihydroxylation, d) inversion by Mitsunobu

1.4 Aim of the thesis

Draskovits and Stanetty engaged in an in-depth methodological investigation of the indium mediated acyloxyallylation of unprotected L-erythrose and D-threose and a protected version thereof which furnished a pronounced diastereodivergence for these two pairs of compounds.[32]

The primary aim of this thesis was an expansion of this study to a more generally accessible class of starting materials to investigate the influence of a variety of commonly used protecting groups onto the diastereoselectivity of the indium mediated acyloxyallylation (IMA) of aldoses. Protected sugar aldehydes were chosen as substrates for the studied reaction as they can be synthesized from all sugars alike. For the primary investigation, D-ribose was selected as stereochemical pattern as the two main isomers formed from ribose have already been identified en route to an attempted short synthesis of DD-heptose.



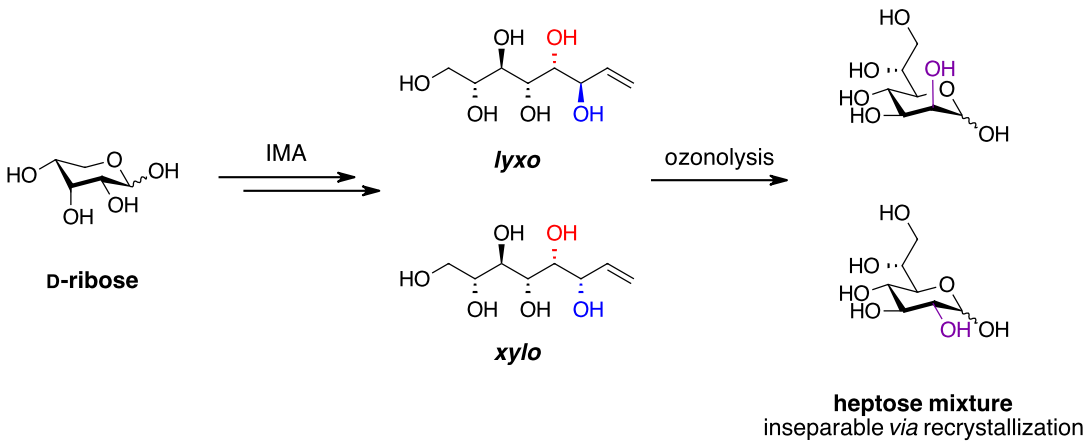
Scheme 18: Indium mediated acyloxyallylation of ribo-configured sugar aldehydes

The first task was the preparation of different protected sugar aldehydes synthesized from commercially available D-ribose. Based on a selection of commonly used protecting groups the respective aldoses bearing acetyl, benzoyl, benzyl, TBS and acetonide protection should be obtained in 1-3 steps starting from the reducing sugar. Afterwards, they should be subjected to IMA and the diastereomeric ratios of the four possible elongation products should be determined from the ^{1}H-NMR spectra upon complete deprotection (see Scheme 18). The evaluation of the found ratios then provides a basis for statements about the dependence of the reaction outcome on the used protecting group.

As a next step, it was planned to confirm the generality of the findings from these initial experiments by repetition of the IMA using sugar aldehydes with '*threo*'-configuration as starting materials. Therefore, synthesis of a protected sugar aldehyde based on D-arabinose and the protecting group, which proved to be best suitable in terms of reaction outcome should be performed and the obtained compound should then be subsequently used for IMA. The results of this elongation reaction are expected to be comparable to the ones of the ribose-case. Furthermore, commercially available partially protected sugars as well as the unprotected aldose should be applied.

For the second part of this thesis, we wanted to focus on practice-related aspects of the studied reaction. Following the target oriented synthesis of L-*glycero*-D-*manno*-heptose by *Stanetty and Baxendale*[33], the application of the indium mediated acyloxyallylation for the synthesis of the bacterial sugar D-*glycero*-D-*manno*-heptose using D-ribose as starting material should be examined. The envisaged synthesis pathway is based on the work of *Stanetty and Baxendale*[33] who used the afore-noted reaction for the preparation of L-*glycero*-D-*manno*-heptose from L-lyxose exploiting the configuration of the predominantly formed diastereomer. In contrast to the described procedure in which simple recrystallization afforded the final product, for D-*glycero*-D-*manno*-heptose a different way will have to be found to separate the two main isomers produced during the course of the elongation reaction. Starting from D-ribose, we expect a mixture of D-*glycero*-D-*manno*-heptose and D-

glycero-D-*gluco*-heptose to be formed upon ozonolysis of the enitols which is inseparable *via* recrystallization (see Scheme 19).



Scheme 19: Application of the IMA for the synthesis of D-glycero-D-manno-heptose

Starting from the enitol mixture after IMA a reaction sequence comprising methyl glycoside formation and acetonide protection as the key steps should be applied for the differentiation of the formed diastereomers. To achieve a time-efficient synthesis despite the required additional steps, it was planned to use an approach where no elaborate purification is applied and the respective crude material is used immediately in the following reaction. That means that ideally after deprotection and full acetylation of the target compound only a final recrystallisation should be necessary to obtain the pure target compound, thus paving the way for facile (commercial) access to this important bacterial sugar.

2. Results and Discussion

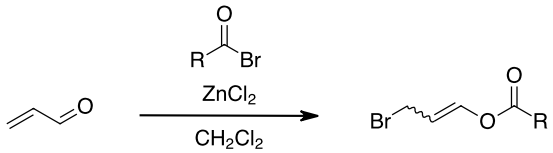
2.1 Indium mediated acyloxyallylation of aldoses – Systematic study

This part of the thesis describes the investigation of the influence of a variety of commonly used protecting groups onto the diastereoselectivity of the indium mediated acyloxyallylation (IMA) of aldoses. Hereby, the initial study of *Draskovits and Stanetty*[32] who examined the elongation reaction with protected and unprotected tetroses was expanded to a more generally accessible class of starting materials.

The use of protected aldopentoses is attributed to the goal of making universally applicable predictions for the reaction outcome dependent on the protecting group of the starting material. Contrary to their parent reducing sugars which possess variable degrees of open-chain contents (OCC) depending on their individual characteristics, protected sugar aldehydes have 100% OCC. The protecting groups prevent the hemiacetal formation which is a common feature of regular aldoses and hence facilitate the reaction with the aldehyde moiety, making them more similar to classical carbonyl compounds, nonetheless they are viable surrogates for semi-protected carbohydrates with an equilibrating anomeric center.

2.1.1 Preparation of the elongation reagents

In the course of this work, two 3-bromo-1-propenyl esters were synthesized, namely 3-bromo-1-propenyl acetate **2** and 3-bromo-1-propenyl benzoate **3**, which are known to act as elongation reagents in the indium mediated acyloxyallylation of aldoses.[28] The preparation of these compounds was carried out according to a literature protocol[30] using acrolein as starting material to which acetyl bromide/benzoyl bromide is added employing zinc chloride as a catalyst for the ester formation (see Scheme 20). Different to the described procedure the acrolein was used without previous distillation as reported by *Stanetty and Baxendale*[33] in their paper about the large scale synthesis of L-*glycero*-D-*manno*-heptose.



*Scheme 20: Synthesis of the 3-bromo-1-propenyl esters **2** and **3***

For the synthesis of the 3-bromo-1-propenyl esters low temperatures were applied due to the exothermic behavior of the reaction once the catalyst is added to the mixture of the commercially available acid bromides and acrolein **1**. Initiation of the reaction was signaled by a significant rise of the temperature from -30 °C up to +15 °C. Afterwards, it dropped again and the mixture was kept at that temperature with external cooling until full conversion of the starting material was confirmed *via* ^{1}H-NMR measurement.

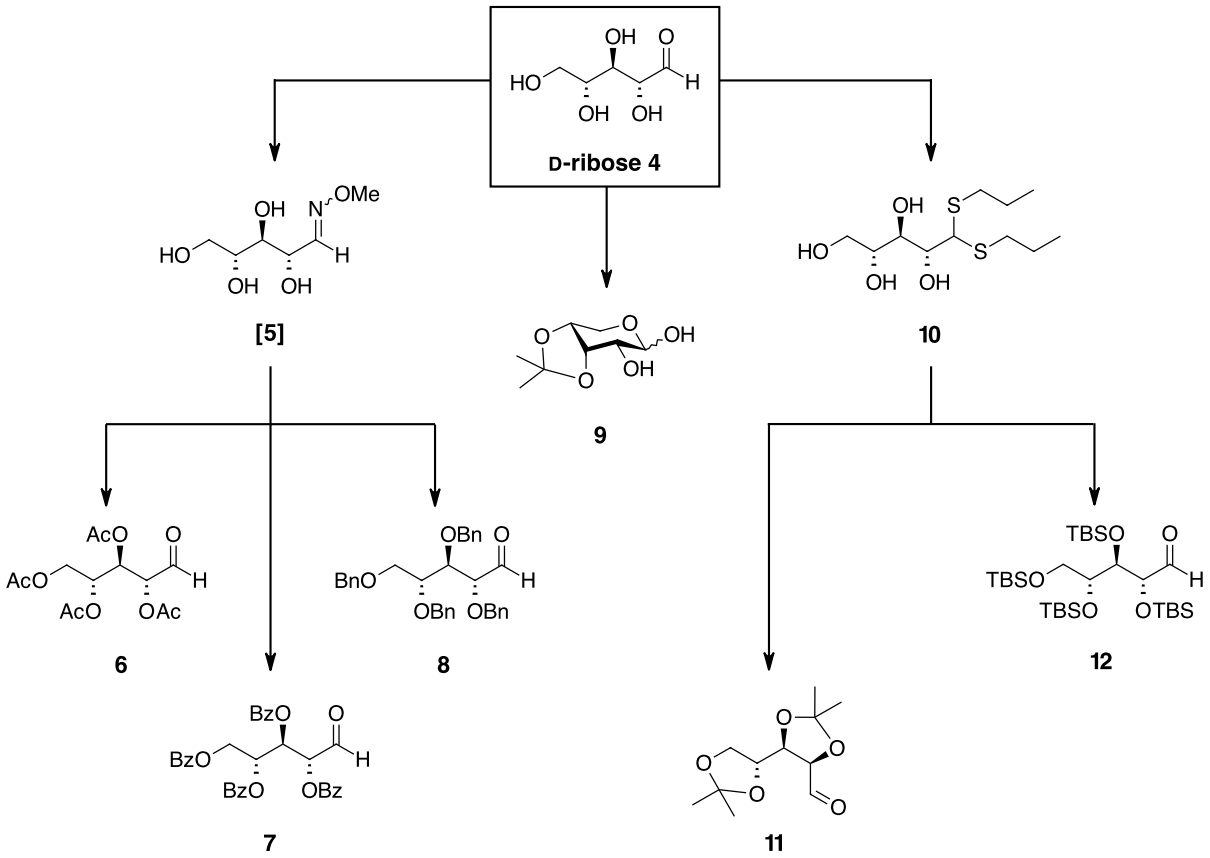
Purification of the acetate **2** was accomplished by distillation whereby only 42% of the theoretical yield could be recovered, while the benzoate **3** was purified *via* column chromatography which afforded a

white solid in 80% yield. Distillation of the 3-bromo-1-propenyl ester resulted in a significant loss of material. A probable cause for that could be polymerization of the elongation reagent in the distilling flask containing the crude product leading to a rubber-like black residue. However, earlier experiments performed by *Stanetty* showed that the elongation reagent prior distillation was not applicable for the indium mediated acyloxyallylation with ribose as starting material due to increased ethyl riboside formation. So, the diminished yield due to the purification procedure had to be conceded to facilitate investigation of the IMA reaction of interest. Anyway, for the methodological study only small amounts of the reagent were necessary.

The prepared elongation reagents were stored in the freezer at -18 °C under argon to avoid decomposition of the compounds. However, despite those preventive measures the formation of HBr was observed upon longer storage of the esters. Since reproducible results were achieved also after storing the reagent for several months, the acid generation did not seem to have an impact on the indium mediated acyloxyallylation which can be attributed to the overstoichiometric usage in comparison to the sugar aldehyde.

2.1.2 Preparation of the protected sugar aldehydes

Different protecting groups which are commonly used in the scope of sugar chemistry were selected for the synthesis of the protected sugar aldehydes with *ribo*-configuration which embody the starting materials for the indium mediated acyloxyallylation. The following scheme gives an overview of the prepared compounds using D-ribose **4** as the educt (see Scheme 21). The applied reaction conditions leading to the depicted compounds are described in the next chapters in more details.

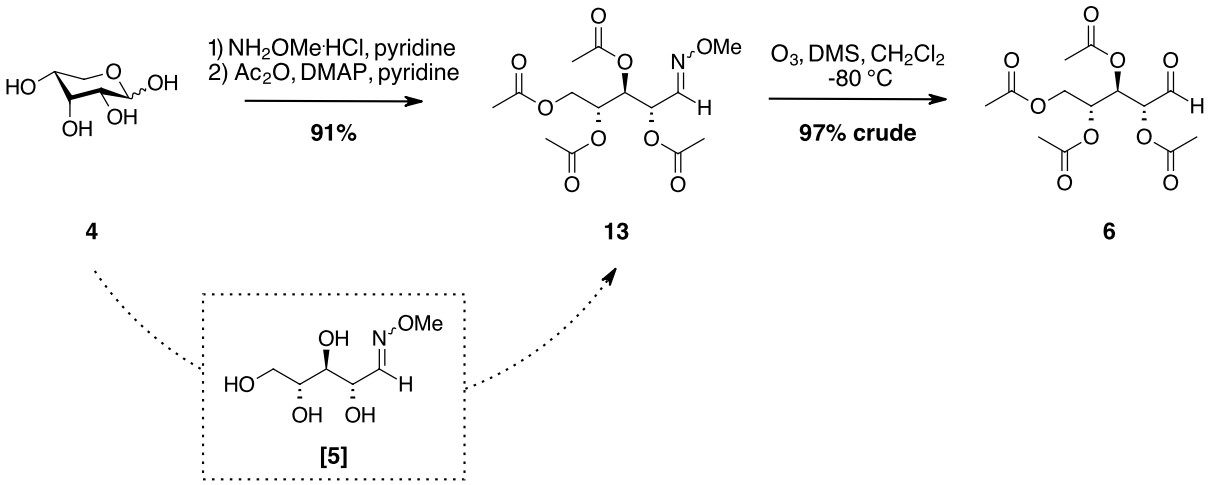


Scheme 21: Overview of the prepared protected ribo-configured sugar aldehydes

To make sure that the findings are also applicable to other sugars and even compounds outside the realm of carbohydrate chemistry, not only sugar aldehydes based on D-ribose were prepared, but also an example based on D-arabinose was tested. The big difference between those compounds is the configuration of the parent aldoses. Ribose possesses an '*erythro*'-configuration while arabinose shows a '*threo*'-configuration along its carbon backbone. For the mentioned examination, the sugar aldehyde with acetonide protection was selected to be resynthesized from arabinose as starting material. The decision was based on the finding that this protecting group resulted in the most significant selectivity of the elongation reaction towards one major product when comparing all investigated *ribo*-configured protected sugar aldehydes (see 2.1.3.4 Diastereomeric ratios of the product mixtures).

2.1.2.1 Synthesis of the acetyl protected sugar aldehyde

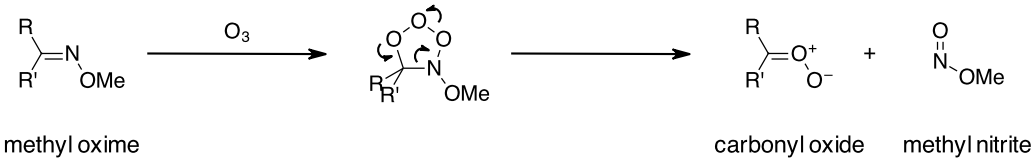
To obtain the protected open chain sugar **6**, a reaction sequence consisting of methyloxime formation, acetyl protection of the hydroxy groups and cleavage of the methyloxime *via* ozonolysis following a literature procedure[41] was applied (see Scheme 22).



*Scheme 22: Synthesis of the acetyl protected sugar aldehyde **6***

The formation of the methyloxime **13** happened *via* reaction intermediate **[5]** which was not isolated but directly subjected to acetylation. The procedure yielded 91% of the fully acetylated compound **13** which was in compliance with the literature. Afterwards an ozonolysis reaction was performed to furnish the deprotected aldehyde.

The use of ozonolysis for the deprotection of the methyloxime-protected aldoses is described as a high-yielding and efficient method for the generation of acyclic sugar aldehydes. It only produces volatile and water-soluble side products and is performed under very mild reaction conditions.[41] The cleavage of methyloximes by ozone occurs *via* a cyclic transition state formed by a 1,3-dipolar cycloaddition reaction. The primary ozonide then rearranges to give methyl nitrite and carbonyl oxide,[42] a zwitterionic compound which consequently reacts to the corresponding aldehyde after addition of a reducing agent.[43] The mechanism of the ozonolysis is depicted in Scheme 23.



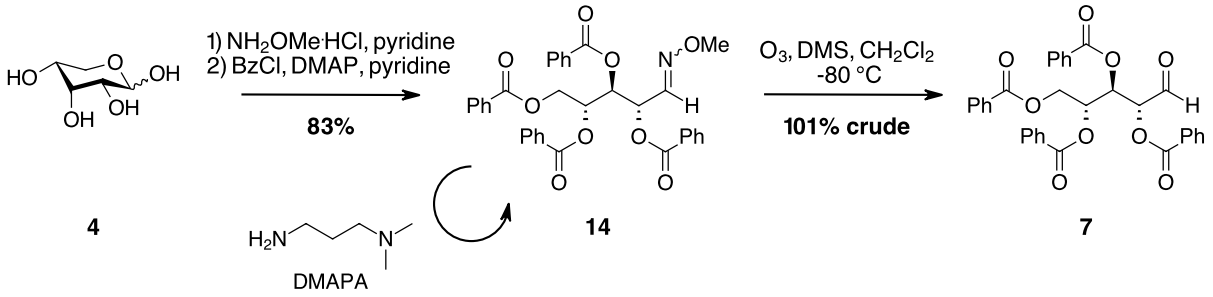
Scheme 23: Mechanism of the ozonolysis of methyl oximes

In the second step, the ozonolysis of the oxime to the aldehyde, a problem arose. The transformation of the methyloxime seemed to only proceed very slowly and ozone had to be bubbled through the reaction solution for several hours before TLC suggested full conversion of the starting material. However, after the reduction with dimethyl sulfide and the extractive workup remaining methyloxime was visible in the ^{1}H-NMR spectrum again. The same result was obtained after repeating the experiment. As stated in the paper, the acetylated *aldehydo*-sugars are unstable to silica gel and purification *via* column chromatography to separate the product from the leftover starting material was not possible.[41] So, the target compound **6** was obtained in a crude yield of 97% in a purity of approximately 85%.

A possible reason for the fault-prone TLC monitoring for this specific ozonolysis reaction could be that the reaction temperature of -78 °C which was stated in the literature procedure[41] was actually too cold and significantly slowed down the cleavage of the methyloxime. When the sample for the TLC measurement was drawn, it warmed up and the reaction proceeded so that the TLC showed complete consumption of the methyl oxime. To confirm this hypothesis the reaction would have to be performed again at a higher temperature of about -60 °C.

2.1.2.2 Synthesis of the benzoyl protected sugar aldehyde

The synthesis of the benzoyl protected sugar aldehyde was performed in the same fashion as the preparation of the acetyl protected sugar aldehyde (2.1.2.1 Synthesis of the acetyl protected sugar aldehyde).[41] First, reaction intermediate **[5]** was formed which was benzoylated *in situ* by the addition of benzoylchloride, afterwards the methyl oxime was transformed into the target aldehyde *via* ozonolysis (see Scheme 24).



*Scheme 24: Synthesis of the benzoyl protected sugar aldehyde **7***

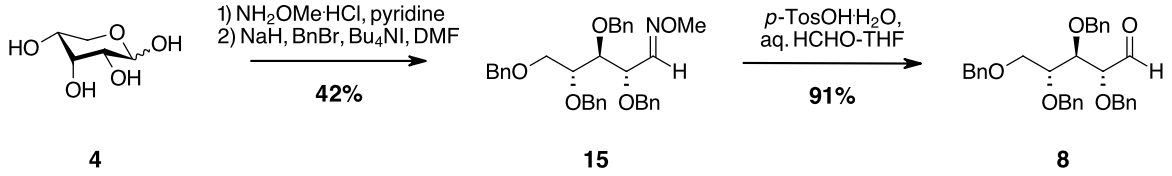
Compound **14** was purified by flash chromatography giving two fractions of the target material of which one showed an impurity in the aromatic region of the ^{1}H-NMR spectrum. Instead of performing an additional column chromatography run, the mixed fraction was treated with 3-(dimethylamino)-1-propylamine (DMAPA), a reagent which can be used to remove excess reagents such as benzoyl chloride, tosyl chloride, and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride.[44] It is described that simple stirring of the reaction mixture with DMAPA for 30 minutes followed by an acidic workup eliminates the unwanted byproducts. Hence, the fraction containing the impurity was dissolved in dichloromethane, stirred with DMAPA and afterwards washed with hydrochloric acid to remove the formed amines. This procedure significantly reduced the amount of leftover reagent and after the treatment with DMAPA only traces of the impurity could be detected.

The benzoylated methyloxime was then subjected to ozonolysis, however also in this case it was discovered that the full conversion of the starting material which was suggested by TLC was not real and remaining starting material was visible in the ^{1}H-NMR spectrum beside the benzoylated sugar

aldehyde upon workup. The target compound **7** was obtained in a crude yield of 101% in a purity of approximately 75% containing residual methyloxime and DMSO.

2.1.2.3 Synthesis of the benzyl protected sugar aldehyde

The benzyl protected sugar aldehyde was prepared in three steps *via* the temporary masking of the aldehyde moiety as a methyloxime, benzyl protection of the hydroxy groups and regeneration of the aldehyde by acidic cleavage of the oxime treating it with *p*-toluenesulfonic acid monohydrate in a mixture of 36-38% aqueous formaldehyde and THF (see Scheme 25).[45] For compound **15** the achieved yield of 42% (for two steps) is significantly lower than the 81% yield stated in the paper even though the procedure had been followed carefully. However, enough of the benzylated methyl oxime was obtained in the first attempt, therefore no repetition was performed to improve the reaction output.



4 **15** **8**

*Scheme 25: Synthesis of the benzylated sugar aldehyde **8***

In contrast to the methyloximes **13** and **14**, where the methyloxime was cleaved *via* ozonolysis, for the benzylated compound **15** an acidic hydrolysis was used which was described for various benzylated methyloximes by *Norimura et al.*[45] in 2017. The deprotection of the aldehyde moiety which afforded the benzyl protected sugar aldehyde **8** worked without any problems and the target compound in the form of a yellow oil was obtained in a very high yield and mostly pure according to ^{1}H-NMR.

Compound **8** was not fully part of the methodological investigation of the IMA due to difficulties regarding the cleavage of the benzyl groups being incompatible with the olefine, which was required intact for the comparative analysis of the diastereomers (see 2.1.3.1 General procedure for the IMA and downstream processing of the reaction products).

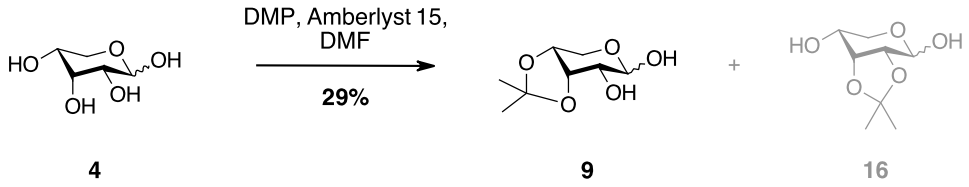
2.1.2.4 Synthesis of the acetonide protected sugar aldehydes

Three different acetonide protected sugar aldehydes were synthesized as starting materials for the indium mediated acyloxyallylation. First, the 3,4-*O*-isopropylidene protected ribose as well as the fully acetonide protected *ribo*-configured sugar aldehyde were prepared and later also a sugar aldehyde bearing two isopropylidene protecting groups derived from D-arabinose was synthesized to evaluate the impact of a *threo*-configuration of the sugar scaffold onto the outcome of the IMA.

Literature research afforded a rather simple experimental procedure for the formation of partially acetonide protected aldopentoses using an acetonation reaction catalyzed by the sulfonic acid catalyst Smopex-101 H^+. In the paper at hand, the aldoses were treated with a twofold molar excess of 2,2-dimethoxypropane (DMP) in dimethylformamide in the presence of the catalyst overnight at ambient temperature. For L-ribose as starting material, this protocol provided a 1:1 mixture of the kinetically favored 3,4-*O*-isopropylidene-L-ribopyranose, together with the thermodynamically favored 2,3-*O*-isopropylidene-L-ribofuranose.[46]

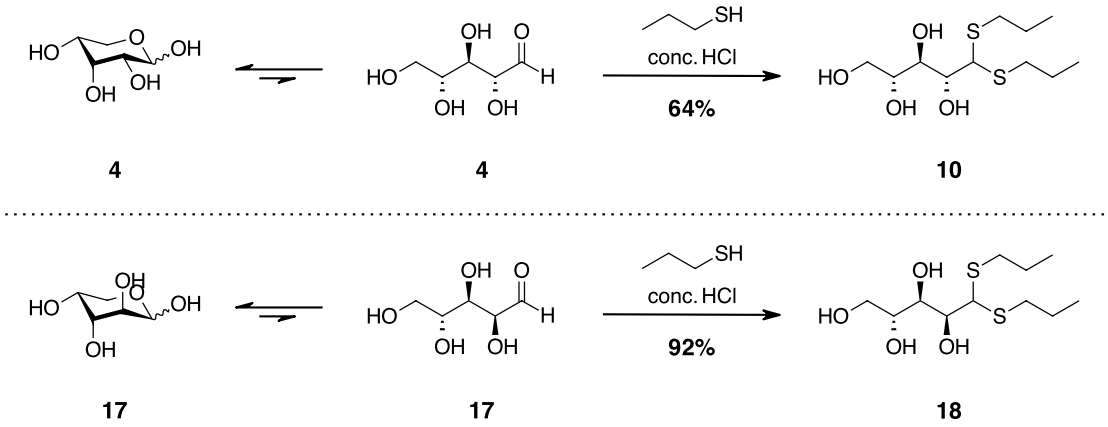
The reaction was adapted for D-ribose using the commercially available solid-supported sulfonic acid catalyst Amberlyst 15(H) which was also found to be suitable for the acetonation reaction. However, even though the reaction mixture was stirred at room temperature for 48 hours no complete conversion of the starting material could be observed. It was decided to do the workup anyway, and

column chromatography was used to separate the product mixture and afforded the 3,4-*O*-isopropylidene protected D-ribose **9** in 29% yield as white needles and the simultaneously formed unwanted 2,3-*O*-isopropylidene protected D-ribose **16** in 46% yield as a colorless oil. The missing 25% yield can be attributed to the remaining starting material, whereas the extended reaction time presumably led to the increased formation of the thermodynamically favored reaction product resulting in a shift of the 1:1 ratio stated by *Forsman and Leino*[46] away from the target compound.



Scheme 26: Synthesis of D-ribose derivatives bearing only one acetonide protecting group

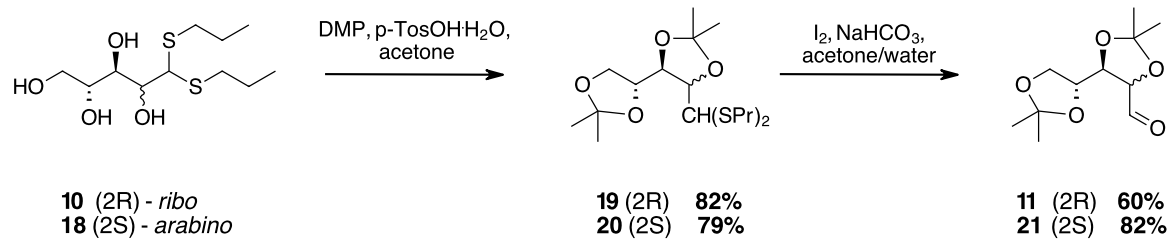
For the preparation of the fully acetonide protected sugar aldehydes the aldehyde functionality of the aldose was first protected as the respective dithioacetal. Hence, the sugar was treated with 1-propanethiol, using concentrated hydrochloric acid both as catalyst and as solvent for the reaction (see Scheme 27). Both D-ribose **4** and D-arabinose **17** were used as starting materials for the dithioacetal formation. For the ribose case, the reaction yielded 64% of a white solid which was compliant with the literature[47]. In comparison to that, a significantly increased reactivity was observed when arabinose was used as an educt. The reaction mixture turned into a sludge within 15 minutes and the product **18** was collected by suction filtration in a yield of 92%.



*Scheme 27: Synthesis of D-ribosedi(propylthio)acetal **10** and D-arabinosedi(propylthio)acetal **17***

The formation of the dithioacetals **10** and **18** was followed by an acid-catalyzed isopropylidene protection of the free hydroxy groups with DMP in acetone yielding about 80% of compound **19** and of compound **20**, respectively. The last step was the cleavage of the dithioacetal while the isopropylidene moieties were retained. Again, it was followed the procedure described by *Bender et al.* for the preparation of diisopropylidene ribose.[47] Since thioacetals are stable under acidic and basic conditions, deprotection to the corresponding carbonyl often requires specific treatment.[48] In contrast to other publications for the preparation of the targeted sugar aldehyde[49] instead of the commonly used but toxic mercury salts oxidative cleavage with elemental iodine and sodium bicarbonate as a mild base was applied (see Scheme 28). Purification *via* column chromatography was necessary due to contamination of the target compounds with residues of the thioacetal protecting group even after the extractive workup. The sugar aldehydes were obtained as clear, colorless oils in

a yield of 60% for compound **11** and 82% for compound **21**. The received products were pure according to ^{1}H-NMR.



10 (2R) - *ribo*
18 (2S) - *arabino*

19 (2R) **82%**
20 (2S) **79%**

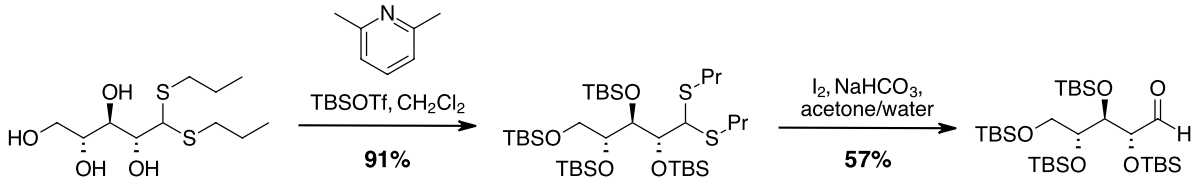
11 (2R) **60%**
21 (2S) **82%**

*Scheme 28: Synthesis of the acetonide protected sugar aldehydes **11** and **21***

2.1.2.5 Synthesis of the TBS protected sugar aldehyde

For the preparation of the TBS protected sugar aldehyde the same precursor as for the acetonide protection was used. The D-ribosedi(propylthio)acetal **10** was treated with TBDMS triflate and 2,6-lutidine at 0 °C affording the TBS protected dithioacetal **22** in a high yield.[50] 2,6-lutidine is a commonly used sterically hindered base for the protection of hydroxy groups as silyl ethers. An excess of it is removed during the workup by extraction with aqueous $CuSO_4$-solution.

The deprotection of the aldehyde was performed in a similar fashion as for the acetonide protected species before, using elemental iodine and sodium bicarbonate as reagents, yielding after column chromatography 57% of pure product plus a mixed fraction with about 80% purity according to ^{1}H-NMR totalling over 90% of targeted product **12** being formed.



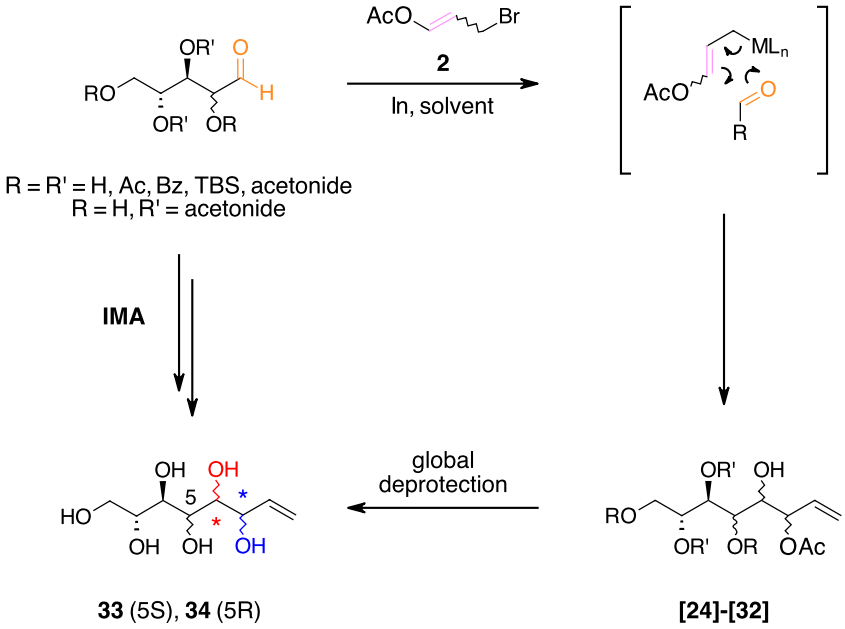
10 **22** **12**

*Scheme 29: Synthesis of the TBS protected sugar aldehyde **12***

2.1.3 IMA of the sugar aldehydes

2.1.3.1 General procedure for the IMA and downstream processing of the reaction products

The prepared sugar aldehydes (see 2.1.2 Preparation of the protected sugar aldehydes) were used as starting materials for the indium mediated acyloxyallylation. The same reaction was also applied to the commercially available aldopentoses D-ribose and D-arabinose as well as the partially acetonide protected arabinose derivative 3,4-*O*-isopropylidene-L-arabinose **23**.



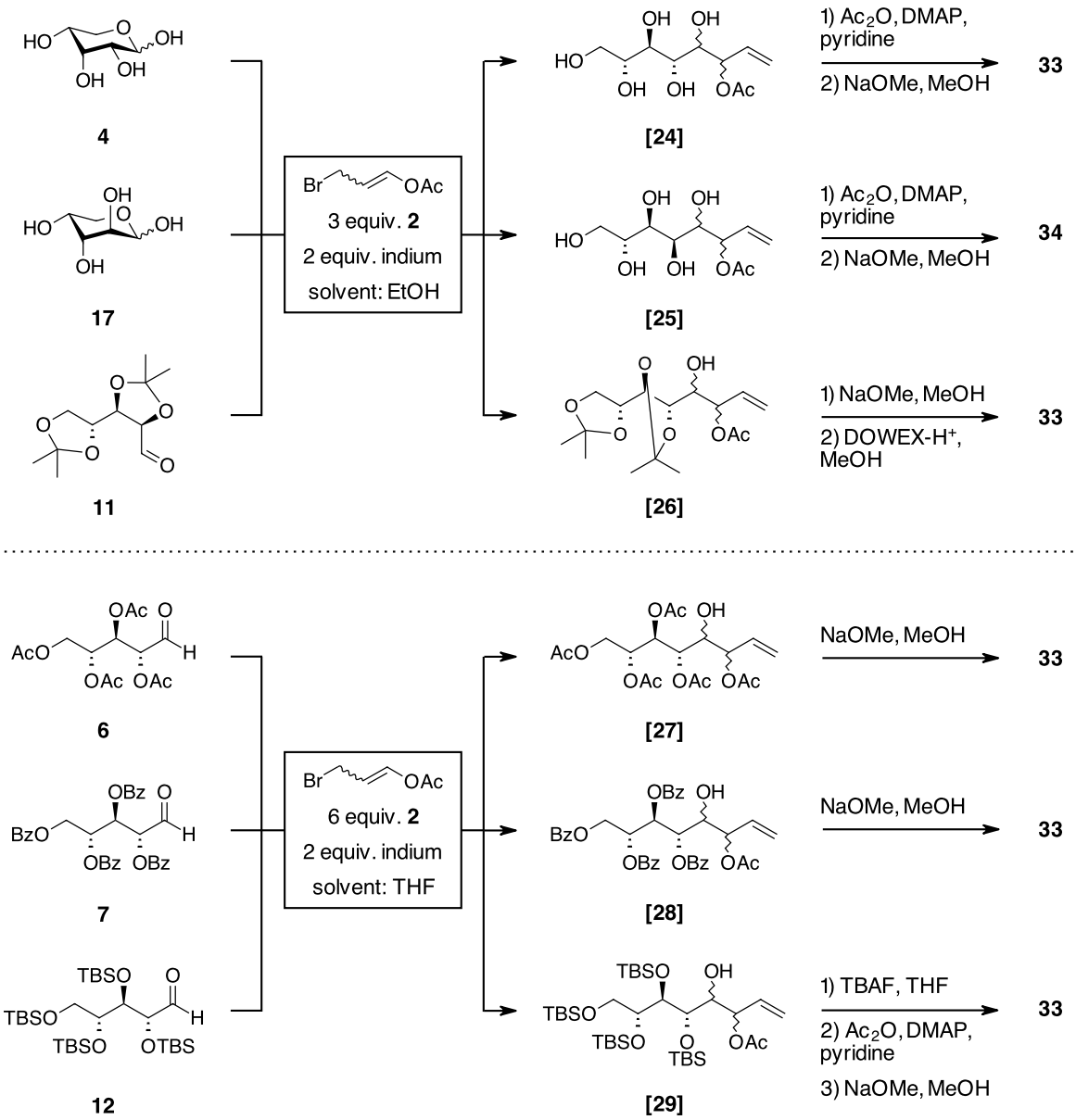
Scheme 30: General mechanism of the indium mediated acyloxyallylation (IMA)

Scheme 30 shows the general mechanism for the indium mediated acyloxyallylation of aldoses and aldose derivatives. The starting material, in our case an aldopentose derivative, is reacted with 3-bromo-1-propenyl esters **2** or **3** working as elongation reagents and indium as a mediator of the reaction. First, chelation between the metal and the elongation reagent is observed. The double bond of the coordination compounds attacks at the aldehyde moiety leading to the formation of a partially protected enitol with two new stereocenters. Due to the nature of the reaction four possible diastereomers can be obtained. The product mixture is then subjected to global deprotection of the hydroxy groups to furnish the target compounds, the corresponding octenitols **33** and **34**, respectively.

The experiments with the protected sugar aldehydes were focused on the investigation of the ratio between the diastereomers formed during the elongation reaction and were therefore only performed on a milligram scale deploying 0.2 mmol of starting material at a time. For the IMA indium powder in a purity of 99.99% and ~325 mesh was used as an indium source. According to *Palmelund and Madsen* the dispersion of the indium powder can have a significant impact on the coupling reaction and consequently the conversion of the reaction.[28] However, the quality was found to be sufficient for the applied compounds, likely as in our case either pentoses with high open-chain content or sugar aldehydes were the starting materials and thus comparably reactive.

Specific downstream processing of the obtained materials: Due to the nature of the different starting materials, the reaction procedure was adapted depending on the use of protecting groups and the nature thereof. An example is the use of the reaction solvent: Absolute ethanol was used for the IMA

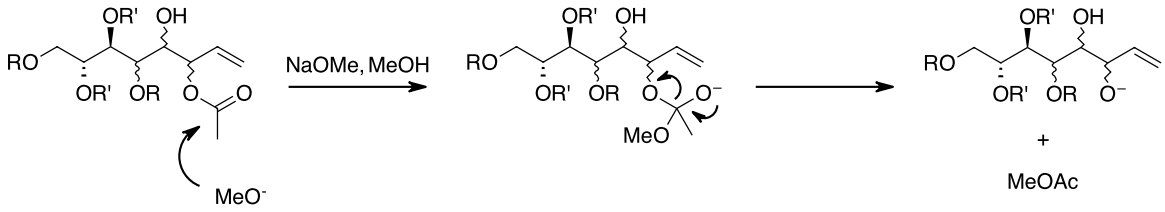
of the unprotected aldoses **4** and **17** and the acetonide protected sugar aldehydes **9**, **11**, **21** and **23**, whereas solubility issues resulting in the observation of only partial conversion in ethanol made a change to anhydrous THF as reaction medium necessary for the other prepared compounds. Furthermore, the double number of equivalents of the elongation reagent was found to enhance the conversion for some of the reactions performed in THF. To enable better comparison, the amount of six equivalents of the 3-bromo-1-propenyl ester was therefore applied for all further experiments. Another noteworthy point is the workup of the IMA. To remove indium related byproducts formed during the reaction an aqueous extraction was applied. An advantage of the fully protected sugar aldehydes was their solubility in the organic layer, while the water-soluble indium residues stayed in the aqueous phase. In contrast, enitols **[24]**, **[25]**, **[30]**, and **[32]**, the reaction products of the unprotected aldoses and the partially acetonide protected compounds, had to be acetylated prior to the extraction to avoid distribution of the formed reaction intermediate in both layers and significant loss of product after the workup. The different reaction and deprotection conditions are depicted in Scheme 31.



*Scheme 31: Reaction conditions for the IMA of the protected sugar aldehydes and respective deprotection conditions for the obtained partially protected enitols **[24]-[29]***

In Scheme 31 only the IMA of the *ribo*-configured acetonide protected sugar aldehyde **9** is illustrated. However, the *arabino*-configured acetonide protected sugar aldehyde **21** reacts under analogous conditions, while for the partially acetonide protected sugar derivatives 3,4-*O*-isopropylidene-D-ribose **9** and 3,4-*O*-isopropylidene-L-arabinose **23** an additional acetylation step was performed ahead of the extractive workup. To cleave the acetonide protecting groups simple stirring in MeOH under acidic conditions overnight at room temperature was sufficient for all mentioned compounds.

Zemplén deacetylation: Due to the use of 3-bromo-1-propenyl acetate **2** the partially protected enitols formed in the course of the elongation reaction comprise at least one acetyl group (see Scheme 31). Therefore, Zemplén deacetylation poses a crucial step in the terms of global deprotection to the mixture of the targeted octenitols. Since this deacetylation procedure was applied in every performed reaction sequence, on this point, a short overview of the reaction which was first reported by *Zemplén and Kuntz* in 1924 is given below (see Scheme 32). For Zemplén deacetylation *O*-acetyl protected sugar derivatives are treated with a catalytic amount of sodium methoxide in methanol at room temperature which leads to a transesterification reaction forming methyl acetate and subsequently to an efficient restoring of the hydroxy groups on the carbohydrate. Furthermore, this type of deprotection usually gives almost quantitative yields.[51]



Scheme 32: Mechanism of the catalytic Zemplén deacetylation displayed for the partially O-acetyl protected enitol

The diastereomeric ratios (see 2.1.3.4 Diastereomeric ratios of the product mixtures) were determined from the crude product mixtures upon global deprotection. Since the experiments were aimed at the generation of information for a methodological study on the diastereoselectivity, on the small scale no special attention was paid to the enhancement of the yield/recovery of the reaction products and no further purification of the obtained enitols was performed.

Attempted analysis of the diastereomers derived from the benzylated sugar aldehyde 8: The benzyl protected sugar aldehyde **8** was subjected to the elongation reaction as well and TLC monitoring showed full conversion for the IMA. However, the deprotection of the crude product mixture to the octenitols **33** proved to be difficult, since the standard procedure for the cleavage of benzyl groups, hydrogenation using palladium on charcoal as a catalyst, led also to reduction of the double bond. That made the determination of the diastereomeric ratio *via* ^{1}H-NMR not possible anymore because the applied method is based on the signals of the allylic hydrogen H3 which shows distinct shifts in the case of the different enitols. Another deprotection method which was tried was the cleavage of the benzyl groups by treatment with boron trichloride at low temperatures under argon atmosphere. However, the obtained NMR proved to be inconclusive. Also a close observation of the NMR spectrum of the benzylated enitol did not indicate a significant stereoselectivity towards a single product, so it was ultimately decided to abandon this compound in favor of focusing on the impact of the other protecting groups on the IMA instead.

2.1.3.2 Identification of the products of the IMA

While the generation of the unprotected enitol mixtures *via* the indium mediated acyloxyallylation and subsequent global deprotection is described in the preceding chapter (see 2.1.3.1 General procedure for the IMA and downstream processing of the reaction products), this chapter deals with the identification of the obtained isomers to enable a definite assignment of the respective stereochemical configuration.

Due to the introduction of two new stereocenters during the studied transformation four different diastereomers can be formed in total. For the ribose scaffold this corresponds to the four compounds depicted in Figure 6.

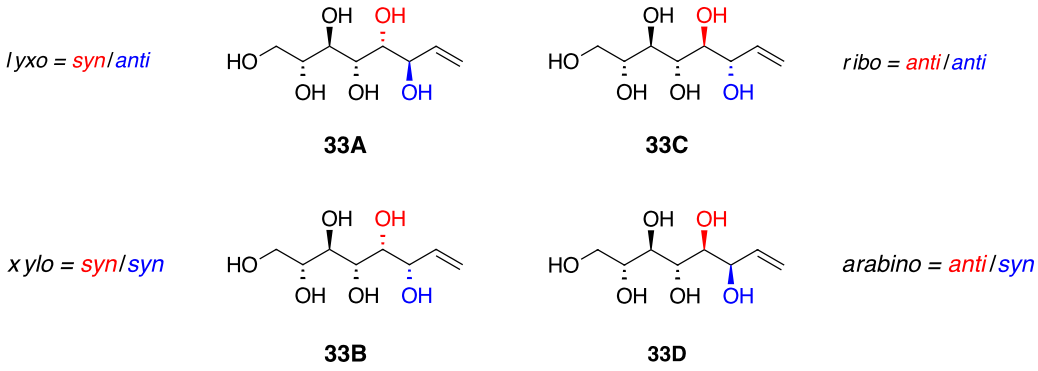
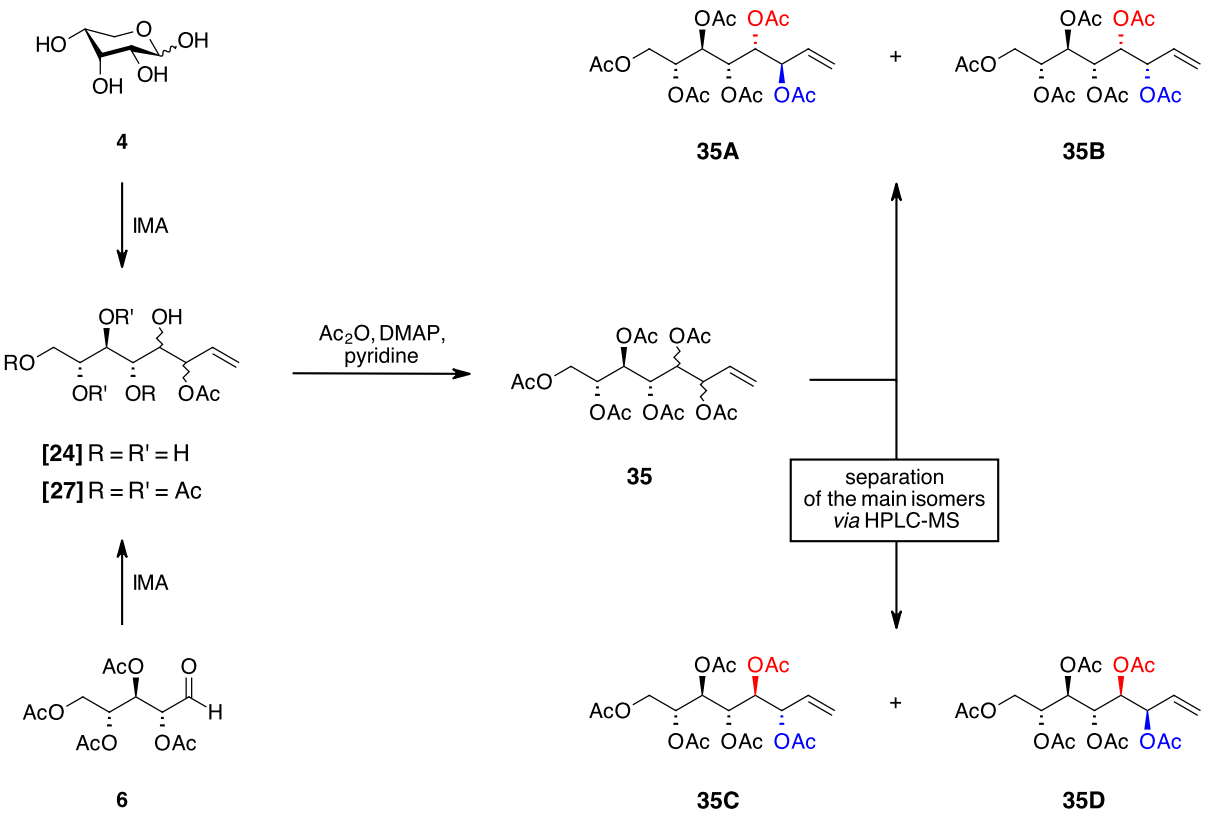


Figure 6: Possible reaction products of the IMA of D-ribose

It is stated in literature that in the case of unprotected aldoses, the mainly observed isomer is the product with *lyxo*-configuration **A**, representing a *syn*-orientation in respect to the former 2-OH-group and an *anti*-addition to the aldehyde. This was already described by *Palmelund and Madsen* in their paper about the chain elongation of aldoses by indium mediated coupling with 3-bromo-1-propenyl esters. However, in the scope of their work only the nature of the major diastereomer was elucidated.[28]

Structural identification of the formed diastereomers: In this thesis, the configuration of all four possible diastereomers formed by IMA of D-ribose and D-ribose derivatives (see Figure 6) was confirmed by either comparison of the isolated compounds with ^{1}H-NMR spectra of reliable reference material (for **33A** and **33B**) or determination of the stereochemistry after the ozonolysis reaction to the corresponding heptoses (for **33C** and **33D**). For the isolation of the obtained diastereomers the crude product mixtures of the IMA of the unprotected aldose **4** and the acetyl protected sugar aldehyde **6** were fully acetylated and the peracetates **35** of the main two respective isomers were separated *via* preparative HPLC (for further information about the used instrument see 5.1.6 HPLC-MS) as it is displayed in Scheme 33. These product mixtures were chosen since they contain **33A** and **33B** or **33C** and **33D** as the main isomers whereas the other two isomers are only present in minor amounts (see Figure 7 and Figure 8, respectively).

The exact composition of the used product mixtures is described in 2.1.3.4 Diastereomeric ratios of the product mixtures in more detail. However, for a better understanding of the reaction outcome the focus is first laid on the elucidation of the structures of the four diastereomers which can be formed during the IMA.



Scheme 33: Separation of the main peracetates for the purpose of the elucidation of their stereochemistry

Identification of 33A and 33B *via* isolation and comparison: For the elucidation of the stereochemistry of the formed isomers **33A** and **33B** the crude enitol mixture **[24]** derived from the IMA of D-ribose **4** with 3-bromo-1-propenyl acetate **2** was treated with acetic anhydride and a catalytic amount of DMAP. For the separation of the obtained peracetates **35** *via* HPLC-MS HPLC grade acetonitrile and water, containing 0.1% formic acid, were used as eluents. First, a number of analytical runs had to be performed to find the ideal conditions in terms of gradients. Then, 50 mg of the peracetates were dissolved in HPLC grade acetonitrile and the mode was switched to preparative runs. Due to problems with the instrument and the fraction collector occurring during the runs, some of the material was lost. However, about 1 mg of the peracetate of the minor isomer (first peak) and 10 mg of the peracetate of the major isomer (second peak) was isolated. The substance was then subjected to Zemplén deacetylation and the corresponding ^{1}H-NMR spectrum was compared to a spectrum of *lyxo*-configured reference material CS-411/1 which was available from earlier experiments performed by *Stanetty* who already elucidated its stereochemistry based on the corresponding heptose.

The comparison of the spectra measured in D_2O (see Figure 7) showed a high degree of conformity of the isolated enitol and the reference material, hence the *lyxo*-configuration of the obtained enitol **33A** was confirmed. Furthermore, the successful separation of the other main isomer **33B** is visible by comparison with the spectrum of the enitol mixture obtained from the IMA of D-ribose **4** which reveals the signals for both compounds as well as a small signal for the third isomer **33C** with *ribo*-configuration which is also visible in the spectrum for the isolated compound **33A**.

Especially the signals for H3 (the allylic hydrogen) and H2 (-C**H**=CH_2) are easily distinguishable due to the difference in the chemical shift and marked with the descriptors **A** and **B**. The configuration of the second diastereomer **33B** was similarly known through earlier experiments in the research group, so

the minor isomer could be assigned to the *xylo*-configuration exhibiting a *syn*-orientation in respect to the former 2-OH-group and a *syn*-addition to the aldehyde.

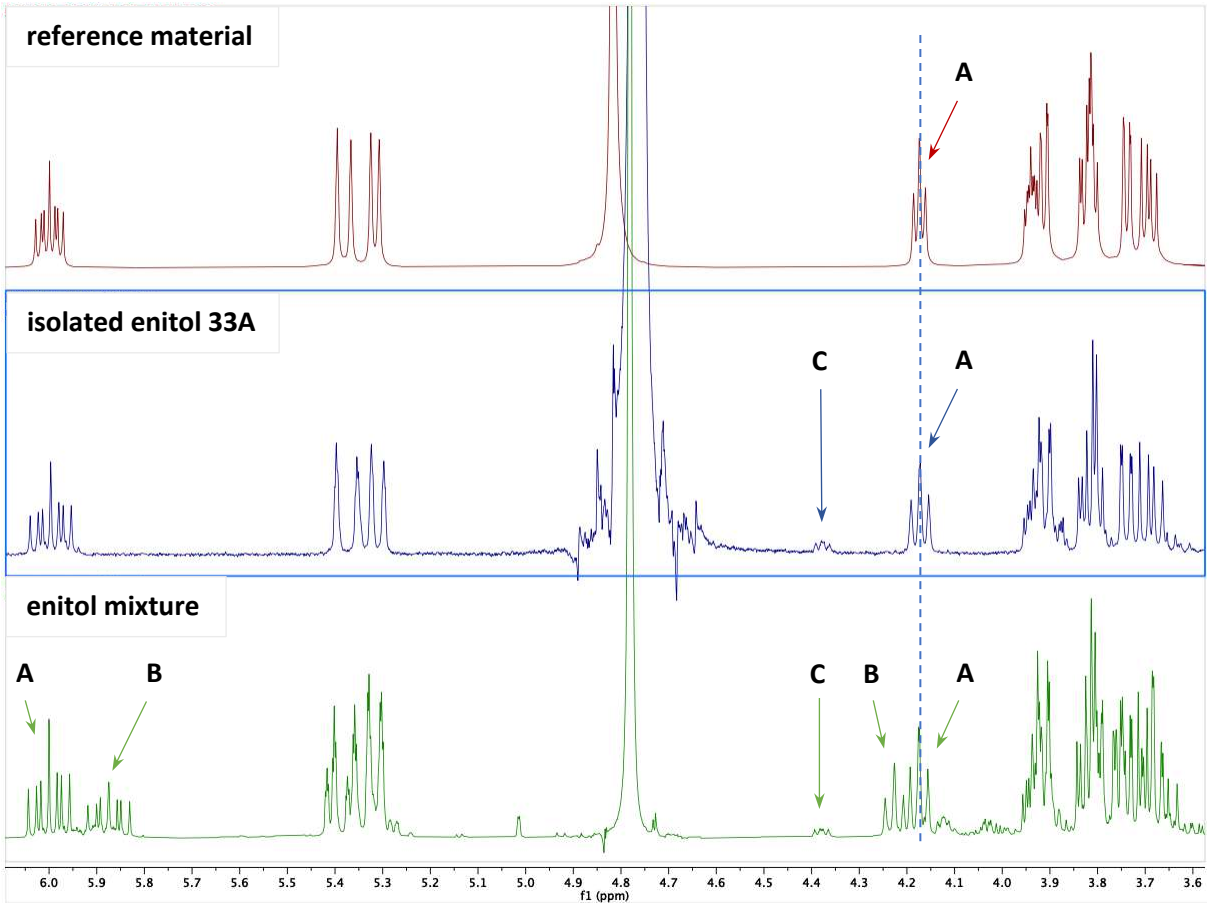


*Figure 7: Comparison of the ^{1}H-NMR spectra of the enitol mixture obtained from the IMA of D-ribose, the isolated enitol **33A** and a reference material with lyxo-configuration (bottom to top) measured in D_2O*

Identification of 33C and 33D *via* isolation and ozonolysis to the reducing sugar: For the elucidation of the stereochemistry of the formed isomers **33C** and **33D**, the crude enitol mixture **[27]** derived from the IMA of the acetyl protected sugar aldehyde **6** was chosen because the two isomers were substantial components of the crude mixture there. Further, there is the additional advantage of the ease of the generation of the peracetate species **[27]** by simple acetylation. In comparison, for the crude enitol mixtures of the other prepared protected sugar aldehydes an additional deprotection step to cleave the respective original protecting groups would have been necessary before the acetyl groups could have been introduced.

The separation of the peracetates was again performed *via* HPLC-MS leading to 10 mg of a yellowish solid for the first peak and 7 mg for the second peak visible in the HPLC-MS chromatogram. The successfully isolated compounds were deacetylated under Zemplén conditions to give the respective octenitols **33C** and **33D**. After the deprotection, all obtained material was dissolved in D_2O and ^{1}H-NMR spectra were measured. This revealed that the fractions which were collected for the first peak apparently also contained small amounts of unwanted compounds beside the targeted peracetate. The spectrum for the other isomer, however, seemed pure except for a small signal corresponding to isomer **A** which could not be separated (see Figure 8).

To identify the structure of the two remaining compounds, the received octenitols were subjected to ozonolysis in a mixture of water/acetone at 0 °C following a literature protocol[33] to transform them into the respective heptoses (see 4.2.26 D-*Glycero*-D-*altro*-heptose (36) and 4.2.27 D-*Glycero*-D-*allo*-heptose (37)). Due to the small amount of material used which was recovered from the NMR tubes, one drop of the indicator Sudan red was sufficient, and decoloration of the reaction solution was already achieved after 10 minutes.

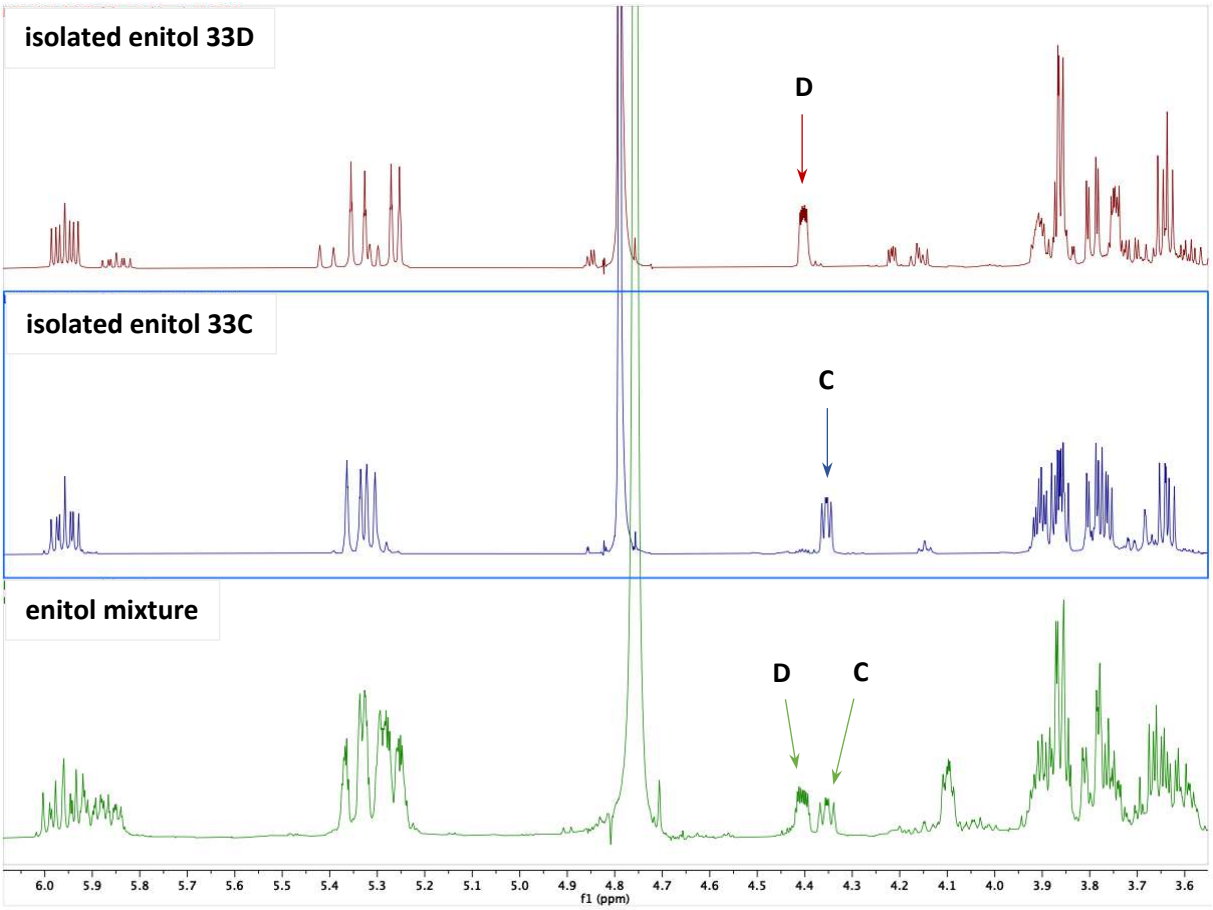
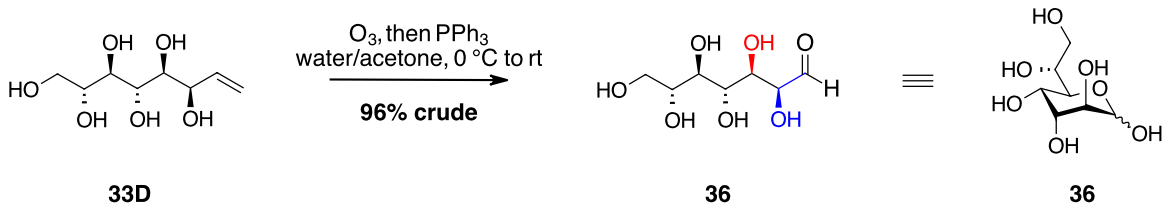


*Figure 8: Comparison of the 1H-NMR spectra of the enitol mixture obtained from the IMA of the acetyl protected sugar aldehyde and the isolated enitols **33C** and **33D** (bottom to top) measured in D_2O*

The ozonolysis was tried for compound **33D** first, ensuring the successful application of the procedure to such a small scale. The reaction to the corresponding heptose **36** is shown in Scheme 34.



*Scheme 34: Transformation of the octenitol **33D** to the corresponding heptose **36** via ozonolysis*

The stereochemistry of the obtained aldose was elucidated *via* the ^{1}H-NMR spectrum. Due to the impurities, there were a large number of overlapping signals visible in the range of 3.5 to 4.3 ppm which made a full characterisation of the compound very difficult. However, four distinct signals in a ratio of 13%:20%:40%:27% could be observed in the anomeric region which are in accordance with the

anomeric hydrogens of the four existing anomers of D-altrose, β-altrofuranose, α-altrofuranose, β-altropyranose, and α-altropyranose (see Figure 9). The corresponding signals in the ^{13}C-NMR spectrum (see Figure 10) were assigned using the HSQC-spectrum of D-altrose.

The comparison with the altrose scaffold suggests that the respective octenitol **33** is in *arabino*-configuration **D**, representing an *anti*-orientation in respect to the former 2-OH-group and a *syn*-addition to the aldehyde.

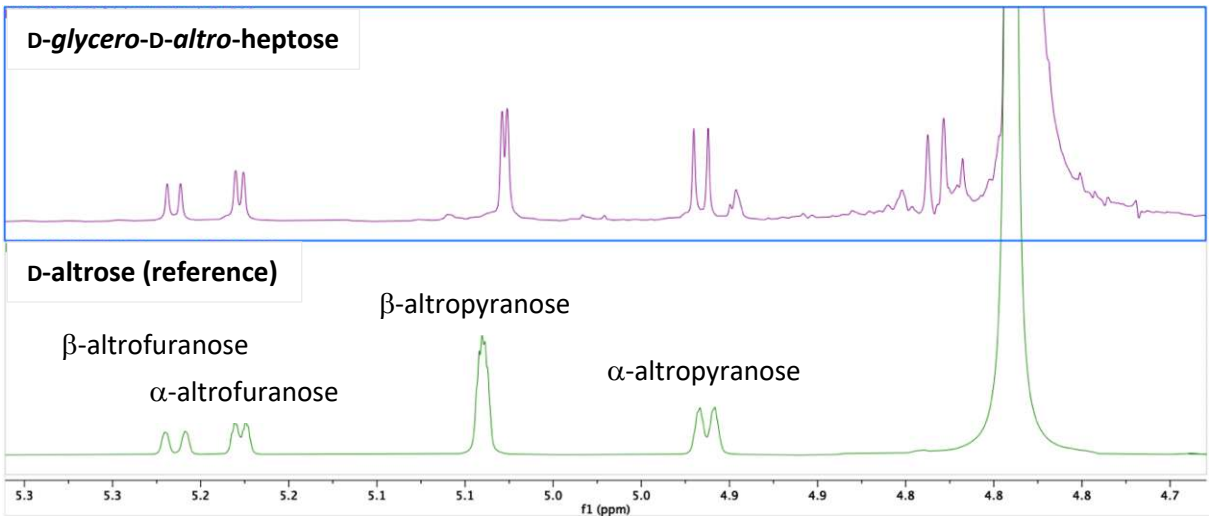


*Figure 9: Comparison of the ^{1}H-NMR spectrum of D-altrose (bottom) with the obtained heptose **36** (top) measured in D_2O*

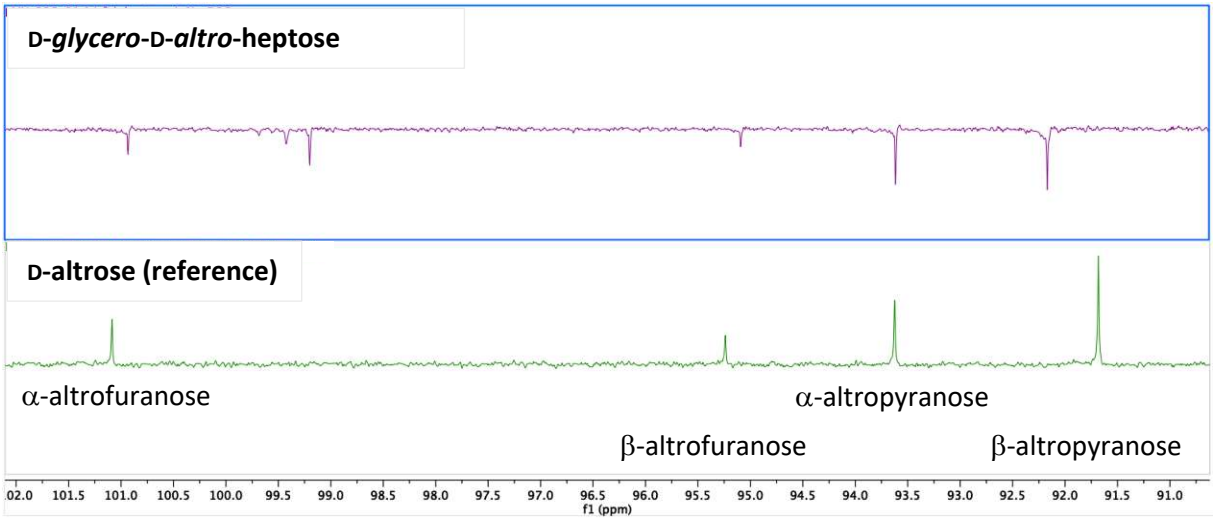
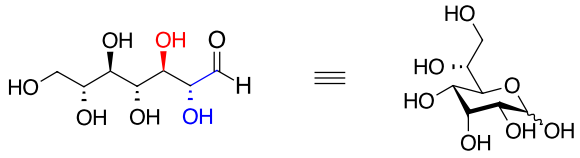


*Figure 10: Comparison of the ^{13}C-NMR spectrum of D-altrose (bottom) with the obtained heptose **36** (top) measured in D_2O*

Afterwards, the ozonolysis reaction was repeated with octenitol **33C** to give the corresponding heptose **37** which is depicted in the following figure (see Figure 11).

Again, the ^{1}H-NMR spectrum was used to work out the configuration of the compound at hand. The obtained aldose **37** was compared to a reference spectrum of D-allose, the hexose of which the cyclic sugar scaffold of the obtained heptose was expected to consist of. The two spectra show a high accordance (see Figure 12). Furthermore, the stereochemistry of the received heptose could be confirmed by investigation of the relevant ^{1}H-^{1}H coupling constants of the hydrogens based on the

Karplus equation. Therefore, the cyclic form of the sugar which is adopted preferably over the open chain form has to be considered, which is shown in Figure 11. The large coupling constant (J = 8.2 Hz) for the anomeric hydrogen signal at 4.83 ppm suggests that the main anomer exhibits the β-form, where the anomeric hydrogen is axial, whereas the hydroxy group occupies the equatorial position. Thus, hydrogen H2 on the far right with a chemical shift of 3.37 ppm must be axial as well. Beside the large coupling constant with H1, H2 also possesses a smaller coupling constant of 3.1 Hz, implying that the adjacent hydrogen H3 (δ = 4.12 ppm) stands equatorial.



37 **37**

*Figure 11: Heptose **37** derived from octenitol **33C***

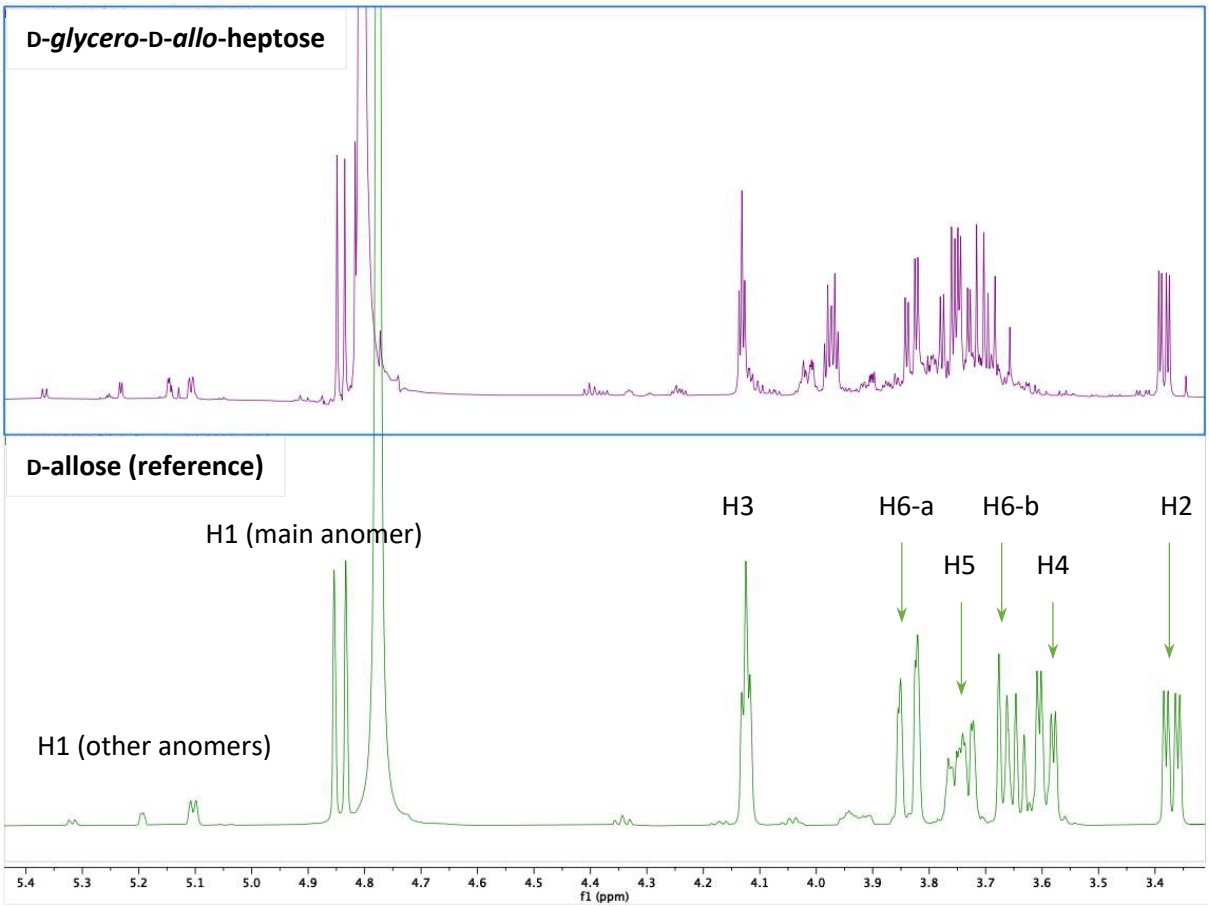


*Figure 12: Comparison of the ^{1}H-NMR spectrum of D-allose (bottom) with the obtained heptose **37** (top) measured in D_2O*

This arrangement is compliant with the predicted *anti*-orientation in respect to the former 2-OH-group and the *anti*-addition to the aldehyde, corresponding to the octenitol in *ribo*-configuration **C**.

2.1.3.3 Side product formation during the IMA

For all indium mediated acyloxyallylation reactions the formation of an unknown side product was observed. Figure 13 displays the side product formation in the IMA of selected compounds. Especially in the case of using the acetyl protected sugar aldehyde **6** as a starting material, the signal which can be attributed to a hydrogen atom of the side product (δ = 4.13 ppm) is clearly visible and outnumbers the enitol signals with its intensity. Therefore, this reaction was chosen to investigate the nature of the formed side product.

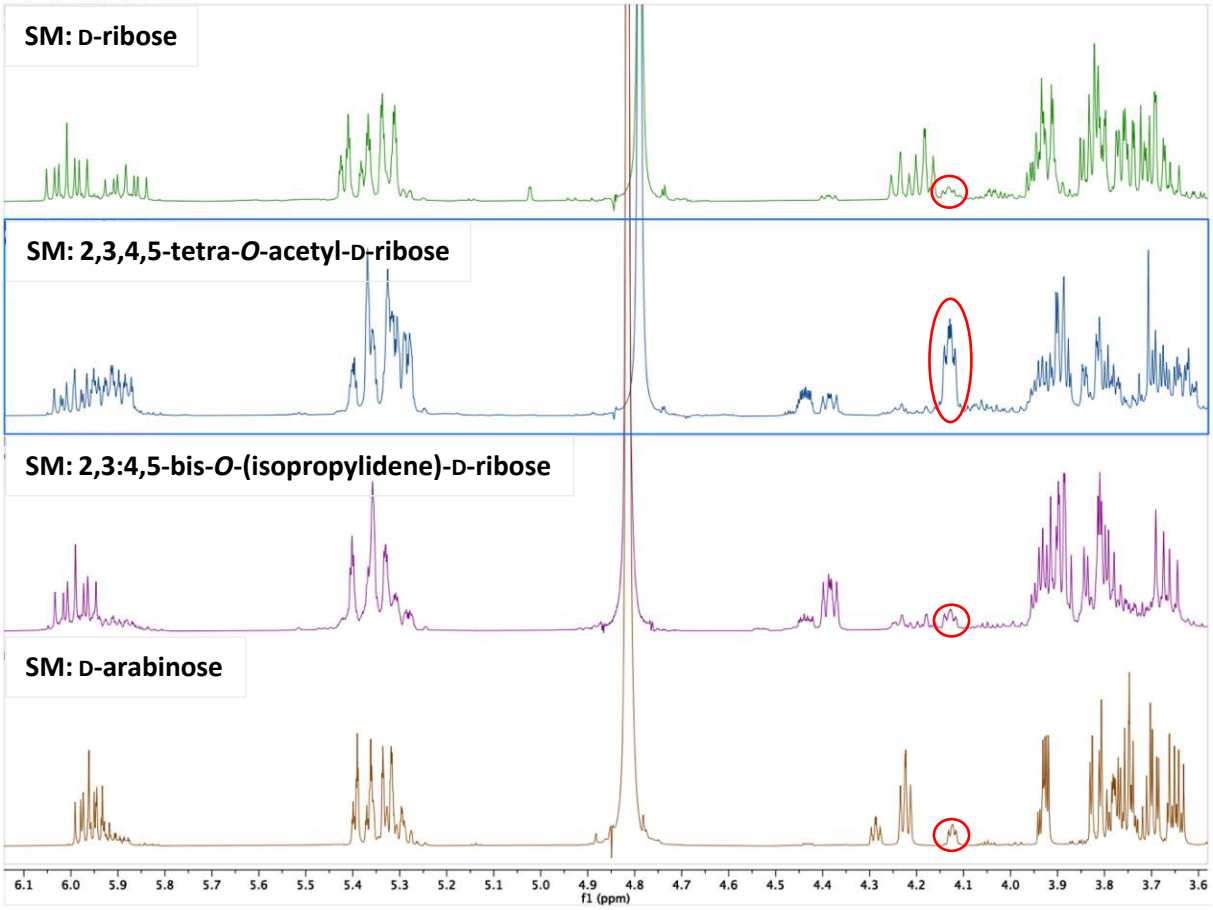


*Figure 13: Depiction of the side product formation in selected IMA reactions using D-arabinose **16**, the ribo-configured acetonide protected sugar aldehyde **11**, the ribo-configured acetyl protected sugar aldehyde **6**, and D-ribose **4** as starting material (bottom to top) measured in D_2O*

For the examination of the side product, 56 mg of the crude octenitol mixture received by IMA of **6** and subsequent Zemplén deacetlyation were applied to column chromatography on silica gel using DCM:MeOH 9:1 as eluent. TLC of the obtained fractions showed a black, more apolar spot for the earlier fractions which corresponds to the unknown side product as well as the characteristic violet, more polar spot for the enitols which are eluted a bit later. About 5 mg of the side product were isolated. Furthermore, 38 mg pure enitols (**33C** + **33D**) were obtained. NMR measurements of the substances were performed. Figure 14 shows an overlay of the two received ^{1}H-NMR spectra. 'Subtracting' the signals of the pure enitols, it can be concluded that the remaining signals marked A, B, and C belong to the side product. Furthermore, a section of the ^{13}C-NMR spectrum of the side product is attached, which displays five distinct carbon signals.

According to their chemical shift, signals B and C correspond to hydrogens bound to carbon atoms connected with a double bond. The ratio of the intensities of the signals which is 1:2, suggests a terminal double bond. This is confirmed by the chemical shifts of the signals B and C in the ^{13}C-NMR spectrum which were linked to the signals B and C in the ^{1}H-NMR spectrum *via* an HSQC experiment. It must be noted that always two carbon signals were connected to one of the hydrogen signals. Therefore, the signal intensity of signal A was set to 2.00, which led to four hydrogens for the two CH_2 groups (B) and two hydrogens for the two CH groups (C) after deduction of the corresponding multiple of 0.8 connected to the hydrogen atoms of the terminal double bond of the enitol residues which lie underneath signals B and C and distort the integral value. Signal A with a positive intensity in the DEPT spectrum can be attributed to two carbon atoms even though only a single signal is visible in the ^{13}C-NMR spectrum since the affiliated signal in the ^{1}H-NMR spectrum belongs to two chemically equivalent hydrogen atoms having the same chemical shift.

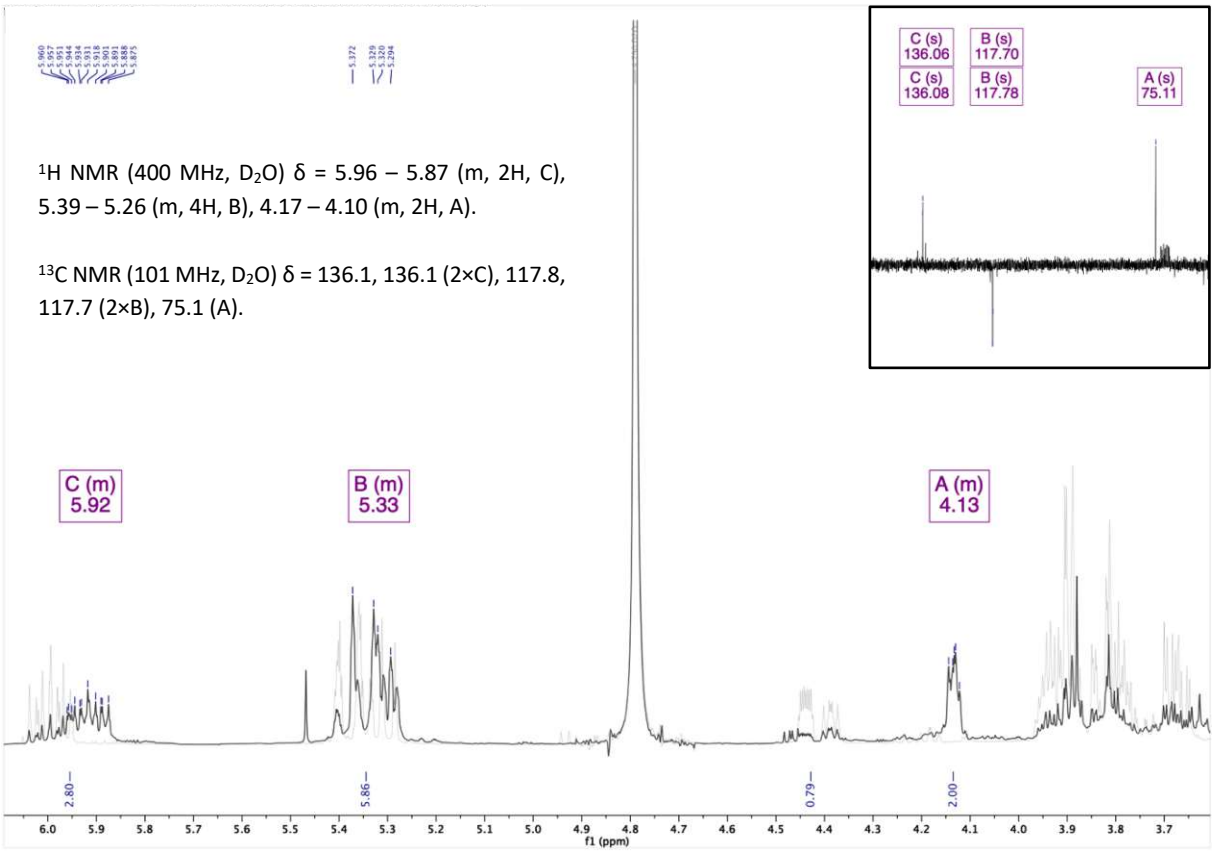
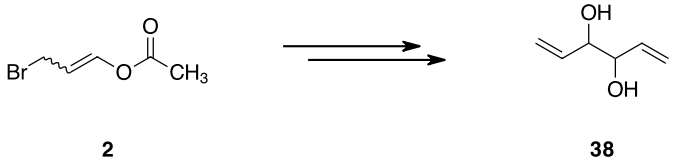


*Figure 14: Overlay of the ^{1}H-NMR spectra of the enitols **33C** and **33D** (light grey) and the isolated side product (dark grey) after column chromatography including the relevant section of the corresponding ^{13}C-NMR spectrum*

It is assumed that the formed side product is the dimer **38** derived of the elongation reagent as it is depicted in the following scheme (see Scheme 35). The side product is deacetylated in the same way as the targeted octenitols and can thus be found in the crude product mixture.



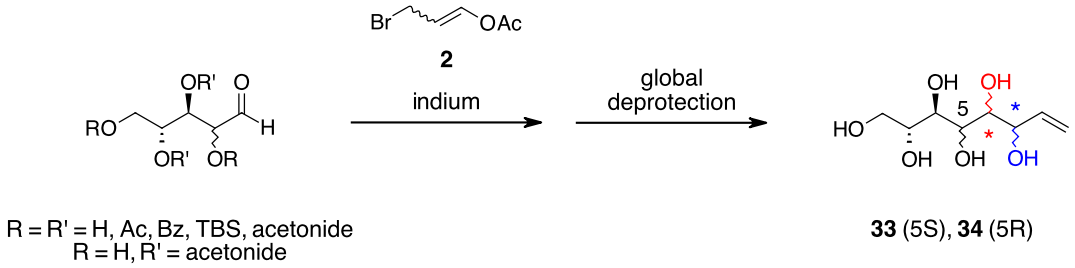
2 **38**

*Scheme 35: Side product formation by dimerization of the elongation reagent **2***

2.1.3.4 Diastereomeric ratios of the product mixtures dependent on the used protecting groups

With the relevant species all identified, the discussion of the first big task of this thesis, the investigation of the ratio between the formed isomers during the indium mediated acyloxyallylation of protected sugar aldehydes, can be reported. Hereby, special focus was laid upon whether or not a pronounced diastereoselectivity for the elongation reaction could be found using a particular protecting group based on earlier findings by *Draskovits and Stanetty*.[32]

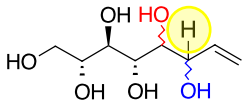
For the examination of the formed isomers, the indium mediated acyloxyallylation was performed with 3-bromo-1-propenyl acetate **2** as the elongation reagent (see Scheme 36).



Scheme 36: Indium mediated acyloxyallylation of various sugar derivatives

The outcome of the IMA of the unprotected sugars D-ribose **4** and D-arabinose **17** is known and had been described in literature.[28] Nevertheless, those reactions were performed in the laboratory as well, since they were used as control reactions to verify the quality of the prepared elongation reagent **2**. Furthermore, they served as a basis to compare if there is a facial diastereodivergence between related protected and unprotected structures.

The ratios between the four possible diastereomers were determined from the ^{1}H-NMR spectra of the obtained product mixtures upon complete deprotection. For that purpose, the signals of the allylic hydrogen atom next to the double bond (see Figure 15) were utilized since these signals show a distinct shift depending on the nature of the diastereomer and thus make an integration of the signals without overlapping possible. Similar suitability of these diagnostic region was observed before. Exemplary ^{1}H-NMR spectra are shown below (see Figure 16).



33

Figure 15: Highlighted allylic hydrogen H3 which is used as diagnostic region

Figure 16 shows the ^{1}H-NMR spectra of the enitol mixtures of the IMA of D-ribose **4** as well as of the acetonide and acetyl protected sugar aldehyde, **11** and **6**, respectively. The respective signals of the allylic hydrogen H3 are marked with a red rectangle. Right of these signals the peak of the formed side product **38** (see 2.1.3.3 Side product formation) is visible.

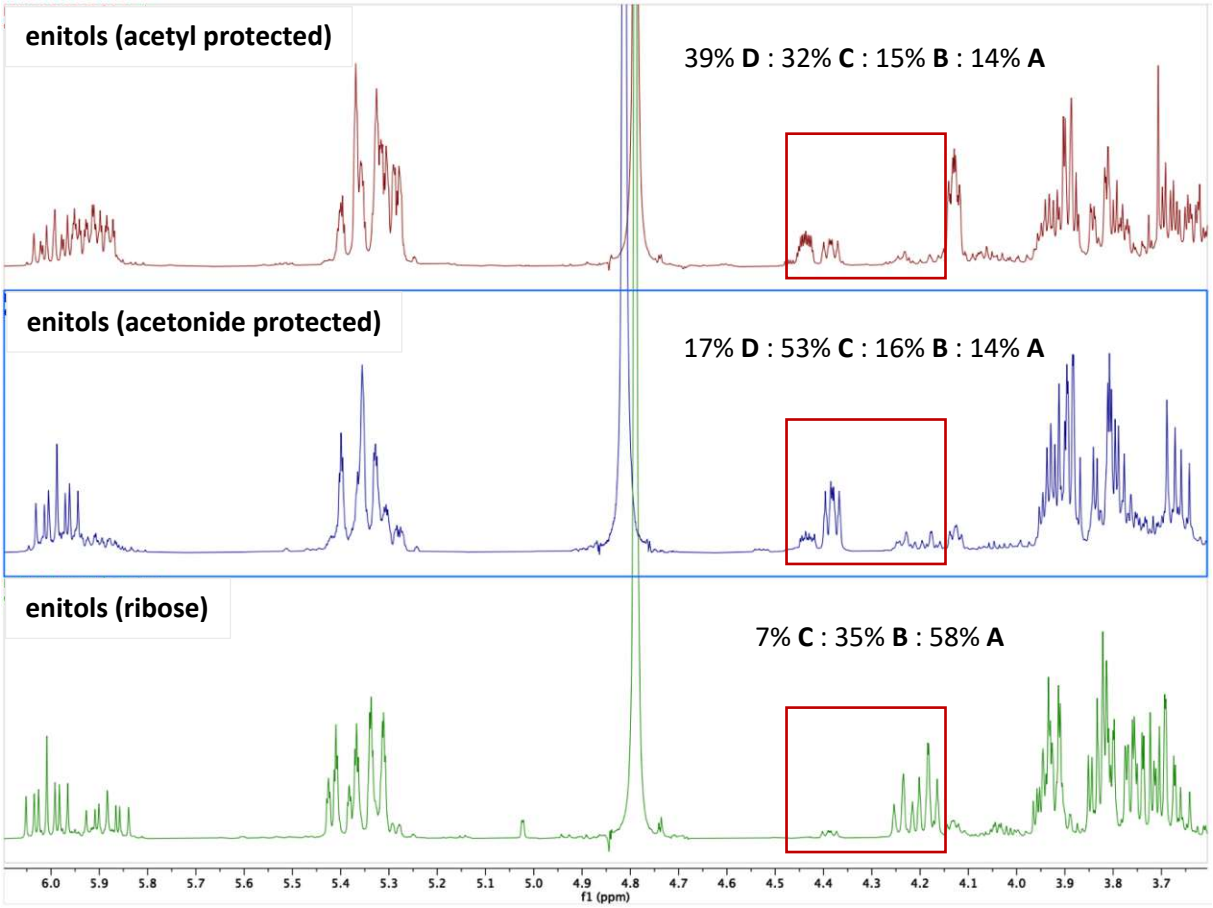
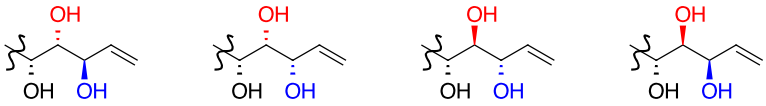


*Figure 16: Comparison of the ^{1}H-NMR spectra of the product mixtures obtained by IMA of D-ribose **4**, the acetonide protected sugar aldehyde **9** and the acetyl protected sugar aldehyde **6** (bottom to top) measured in D_2O*

The diastereomeric ratio was calculated from the integrals of the diagnostic allylic position H3. The results for the unprotected ribose and for the protected sugar aldehydes are depicted in the following table (see Table 1):

Table 1: Diastereomeric ratios of the obtained enitol mixtures starting from the ribose derived compounds



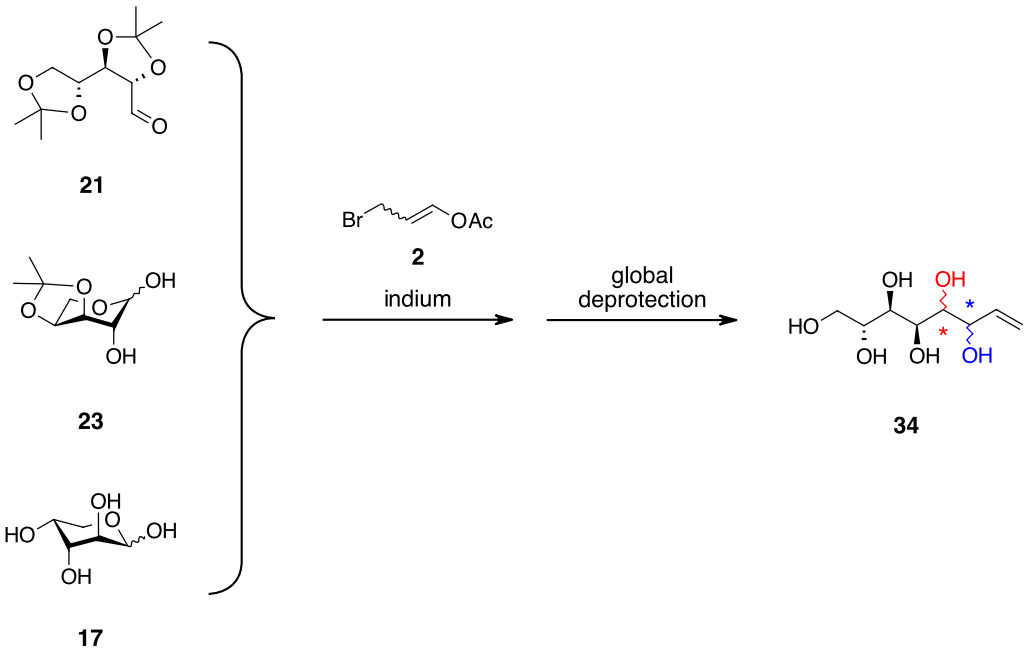
protecting group	starting material	**A** *syn/anti*	**B** *syn/syn*	**C** *anti/anti*	**D** *anti/syn*
-	ribose	**58%**	35%	7%	-
3,4-acetonide	ribose	**60%**	24%	10%	6%
2,3;4,5-acetonide	ribose	14%	16%	**53%**	17%
acetyl	ribose	14%	15%	**32%**	**39%**
benzoyl	ribose	17%	15%	**30%**	**38%**
TBS	ribose	22%	22%	27%	29%

Compound **33A** with *lyxo*-configuration (*syn*/*anti*) was found to be the main isomer for D-ribose **4** and 3,4-*O*-isopropylidene-D-ribose **9**, probably due to the chelation with the OH-group on C2. In contrary, full protection of the reducing sugar led to a shift towards increased formation of enitols **C** and **D** which show *ribo*- (*anti*/*anti*) and *arabino*-configuration (*anti*/*syn*), respectively. In the case of the protected sugar aldehydes, the OH-group on the C2 bears a protecting group, so the chelation is presumably inhibited and the sterically more favorable *anti*-addition to the aldehyde is preferred. This diastereodivergence was also described for protected tetroses.[32]

In terms of diastereoselectivity however, the acetyl, benzoyl and TBS protected sugar aldehydes showed no exploitable results since these starting materials led to formation of the octenitols **33C** and **33D** in a ratio of about 1:1. Of the used protecting groups only the acetonide protection of D-ribose delivers a reasonable opposing selectivity of the elongation reaction towards a major product with *ribo*-configuration.

2.1.3.5 Testing for generality

To confirm the generality of the findings, the IMA was also performed using compounds possessing a '*threo*'-configuration of the sugar backbone instead of relying only on ribose as a sugar with '*erythro*'-configuration as starting material. For these reactions D-arabinose **17**, 3,4-*O*-isopropylidene-L-arabinose **23** and the acetonide protected sugar aldehyde **21** were deployed resulting in the octenitols **34** (see Scheme 37).



*Scheme 37: Indium mediated acyloxyallylation of D-arabinose **17** and the arabinose derivatives **21** and **23***

In Figure 17 the ^{1}H-NMR spectra of the enitol mixtures of the IMA of D-arabinose **17** and the arabinose derivatives **21** and **23** are shown, where the respective signals of the allylic hydrogen H3 are marked with a red rectangle. Also here, the peak of the formed side product **38** (see 2.1.3.3 Side product formation) is visible to the right of these signals. The assignment of the signals was done analogous to the assignment for the ribose derived enitols based on earlier findings that the signals of the obtained diastereomers always appear in the same order with the signal for the enitol in *lyxo*-configuration being the most upfield and thus having the lowest ppm-value of all isomers. The chemical shift of the diagnostic H3 signal assigned to this compound **A** is in consistence with the literature[28].

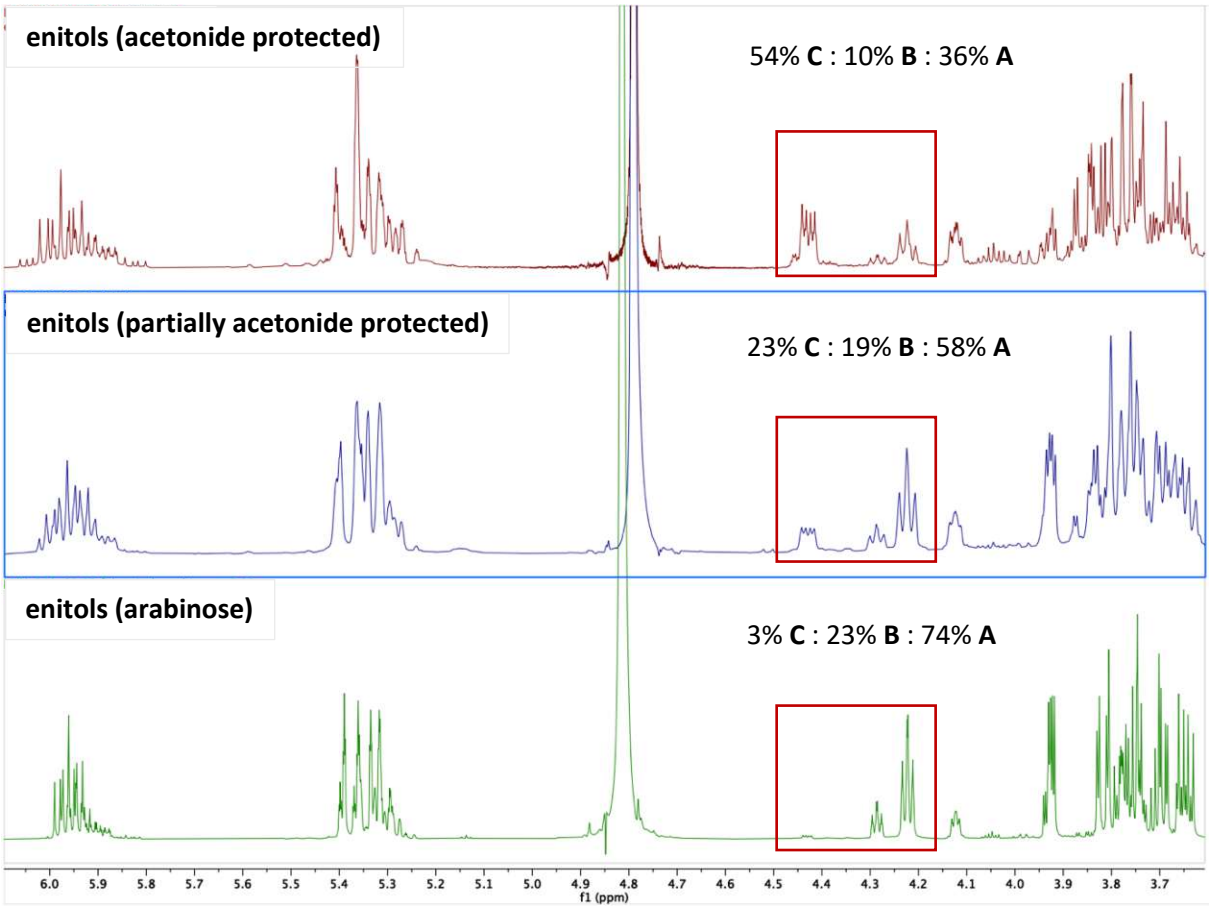


*Figure 17: Comparison of the ^{1}H-NMR spectra of the product mixtures obtained by IMA of D-arabinose **17**, 3,4-O-isopropylidene-L-arabinose **23** and the acetonide protected sugar aldehyde **21** (bottom to top) measured in D_2O*

Table 2 displays the diastereomeric ratios obtained in the performed experiments including the data for the arabinose derived compounds (marked in red).

Table 2: Diastereomeric ratios of the obtained enitol mixtures including the results for the arabinose derived compounds

protecting group	starting material	**A** *syn/anti*	**B** *syn/syn*	**C** *anti/anti*	**D** *anti/syn*
-	ribose	**58%**	35%	7%	-
	arabinose	**74%**	23%	3%	-
3,4-acetonide	ribose	**60%**	24%	10%	6%
	arabinose	**58%**	19%	23%	-
2,3;4,5-acetonide	ribose	14%	16%	**53%**	17%
	arabinose	36%	10%	54%	-
acetyl	ribose	14%	15%	**32%**	**39%**
benzoyl	ribose	17%	15%	**30%**	**38%**
TBS	ribose	22%	22%	27%	29%

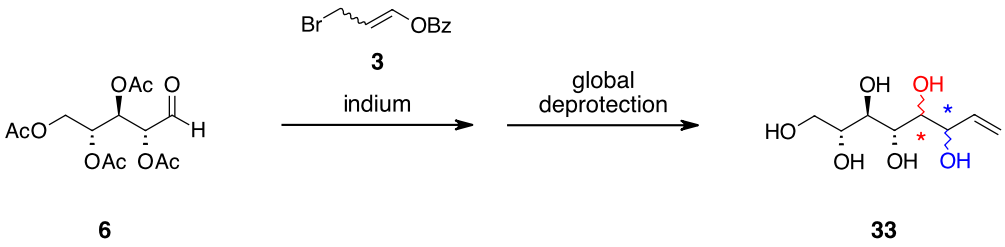
The same trend towards the *lyxo*-configured isomer **A** which was described before could be observed when using D-arabinose **17** and the arabinose derivative 3,4-*O*-isopropylidene-L-arabinose **23** as starting materials. These results are in accordance with the literature, which states that the *lyxo*-configured product is the major diastereomer for reactions with unprotected aldoses.[28, 32] The fully acetonide protected arabinose **21** also showed compliance with the results obtained for the *ribo*-

configured sugar aldehydes in terms of a shift towards product **C** with *anti*/*anti*-configuration. However, the effect is not as significant as with the ribose derived analogue.

2.1.3.6 Exchange of the elongation reagent with ribose derived compounds

All before-mentioned reactions were performed with 3-bromo-1-propenyl acetate **2** as elongation reagent. However, *Palmelund and Madsen* described in their paper about the indium mediated chain elongation of aldoses that the use of the more stable and sterically demanding reagent 3-bromo-1-propenyl benzoate **3** results in an improved diastereoselectivity, increasing for example the selectivity of the IMA of D-ribose from a ratio a 1.5:1 **A**:**B** to 3.5:1 in favor of the *lyxo*-configured product.[28]

When the indium mediated elongation reaction of the acetyl protected sugar aldehyde **6** resulted in a formation of the main products, the octenitols **33C** and **33D** in a ratio of about 1:1, the exchange of the original elongation reagent to 3-bromo-1-propenyl benzoate **3** was tried to enhance the diastereoselectivity for one of the obtained enitols (see Scheme 38).



*Scheme 38: IMA of the acetyl protected sugar aldehyde **6** using 3-bromo-1-propenyl benzoate **3** as elongation reagent*

However, the diastereomeric ratio was not found to change distinctly, in terms of the main products only a slight increase from 39% to 43% of the enitol with *arabino*-configuration (*anti*/*syn*) was visible in the ^{1}H-NMR spectrum. Besides, there was a small variation in the ratio of the minor octenitols **33A** and **33B**. To further investigate the IMA with **3**, the elongation reaction was repeated using 3,4-*O*-isopropylidene-D-ribose **9** as starting material. Also in this case the diastereomeric ratio did not show a considerable difference (see Table 3).

Table 3: Comparison of the diastereomeric ratios received with different elongation reagents

protecting group	elongation reagent	**A** *syn/anti*	**B** *syn/syn*	**C** *anti/anti*	**D** *anti/syn*
acetyl	acetate **2**	14%	15%	**32%**	**39%**
	benzoate **3**	18%	7%	**32%**	**43%**
3,4-acetonide	acetate **2**	**60%**	24%	10%	6%
	benzoate **3**	**60%**	25%	7%	8%

The outcome suggested that an exchange of the elongation reagent from 3-bromo-1-propenyl acetate **2** to 3-bromo-1-propenyl benzoate **3** does not have a pronounced effect on the diastereoselectivity of the indium mediated acyloxyallylation under chelating and non-chelating conditions.

The finding of the significantly increased diastereoselectivity for the main isomer could also not be reproduced by *Draskovits and Stanetty*, who tried the replacement of 3-bromo-1-propenyl acetate with the corresponding benzoate in the case of the IMA of D-lyxose. The enhancement they experienced was way less significant, changing the original diastereomeric ratio of 65:25:10 to 70:20:10.[32]

2.2 Indium mediated acyloxyallylation of aldoses – Target-oriented synthesis

This chapter deals with the development of a column-free thus scalable synthetic approach towards the rare bacterial sugar D-*glycero*-D-*manno*-heptose based on the indium mediated acyloxyallylation of aldoses, a reaction which poses a useful tool for the preparation of higher sugar species. This pathway should avoid laborious purification steps so that synthesis at scale is possible.

The reaction sequence of the target-oriented synthesis is based on the established route towards LD-heptose which exploits the formation of the *lyxo*-configured enitol as the major isomer in the IMA of L-lyxose. There, the desired enitol can be separated from the other diastereomers by selective crystallization.[33] To obtain the target compound D-*glycero*-D-*manno*-heptose, D-ribose **4** instead of L-lyxose is used as starting material to ensure the right configuration of the hydroxy group on the C6 of the heptose. The indium mediated elongation reaction produces two main isomers, **33A** in *lxyo*-configuration (*syn*/*anti*) and **33B** in *xylo*-configuration (*syn*/*syn*), of which the first one is the precursor of the desired material. However, in contrast to the synthesis of L-*glycero*-D-*manno*-heptose, the isolation of the targeted enitol with *manno*-configuration *via* recrystallization is not successful because the second isomer with *gluco*-configuration crystallizes as well. Therefore, a new synthetic pathway leading to the separation of the isomers had to be developed to enable the isolation of pure D-*glycero*-D-*manno*-heptose.

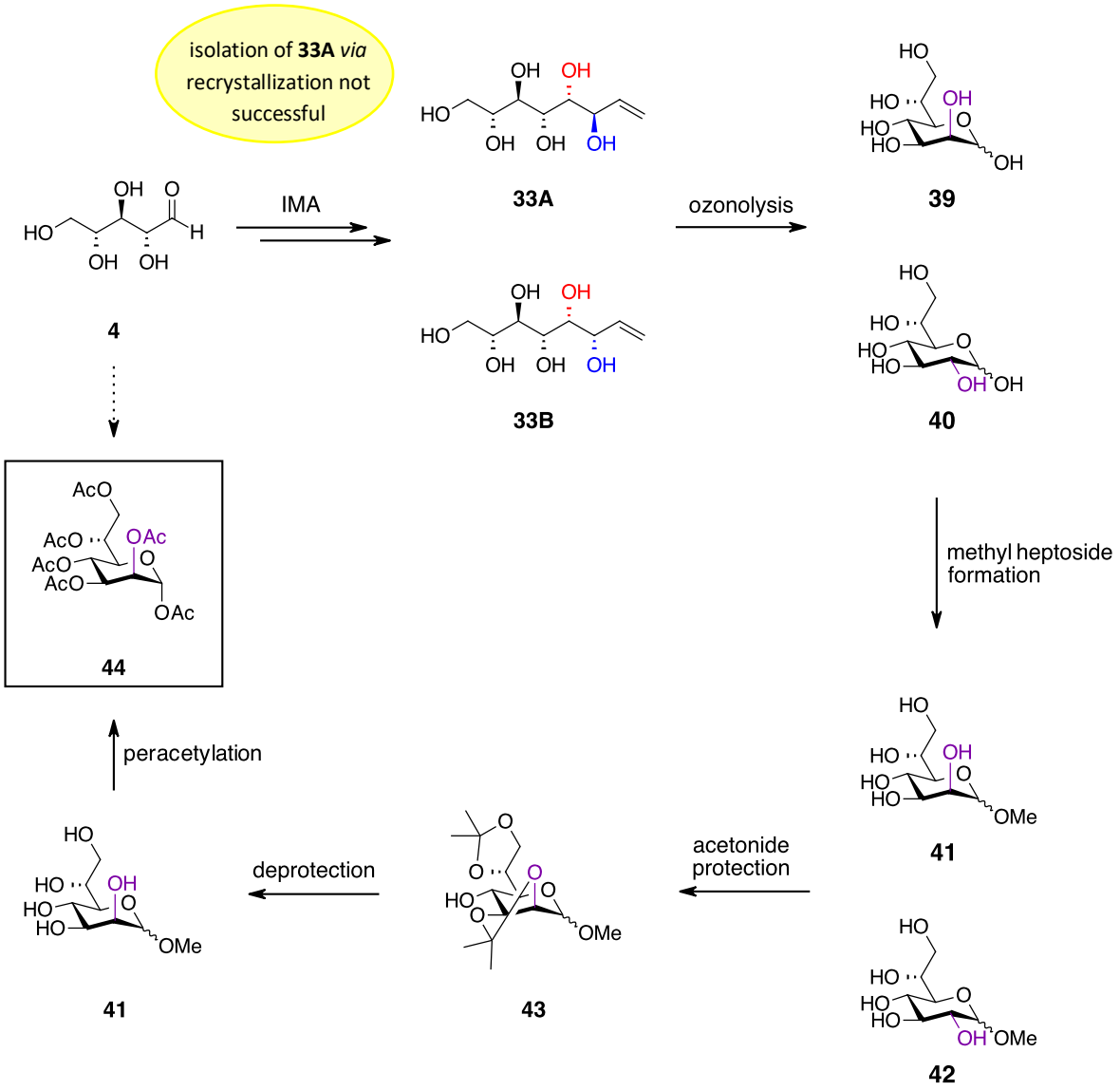
The synthetic approach rests upon the differences in the stereochemistry of the *manno*-configured and the *gluco*-configured reaction products. Due to the varying positions of the hydroxy groups, a discrimination *via* the introduction of isopropylidene groups is possible. While the desired compound with *manno*-configuration exhibits two acetonide protecting groups and dissolves in the organic layer, the *gluco*-configured compound only forms one acetonide and therefore remains water-soluble. The separation then happens *via* aqueous extraction (see 2.2.1.4 Separation via acetonide protection).

2.2.1 Column-free synthesis of D-*glycero*-D-*manno*-heptose – Proof-of-concept

As already mentioned, the starting point of the planned synthesis route is the large scale synthesis of crystalline 1,2,3,4,6,7-hexa-*O*-acetyl-L-*glycero*-α-D-*manno*-heptopyranose performed by *Stanetty and Baxendale*[33]. They developed a short and scalable route using the indium mediated diastereoselective acyloxyallylation of L-lyxose as the key step. Protection of the targeted compound L-*glycero*-D-*manno*-heptose as a peracetate led to a stable, crystalline, and non-hygroscopic material which made the compound easy to handle, suitable for shipping and for long-time storage. For the IMA, 3-bromo-1-propenyl acetate **2** was used, because the acetyl bromide needed for its preparation is less expensive than the benzoyl bromide, which is applied in the synthesis of the benzoate, which is an advantage if the target compound is going to be produced on a larger scale.

The indium mediated acyloxyallylation of D-ribose **4** resulted the formation of **33A** and **33B** in the ratio of 1.6:1 as it was already observed in earlier experiments. The separation of the two diastereomers *via* recrystallization similarly to the procedure used for the synthesis of L-*glycero*-D-*manno*-heptose was already attempted by *Stanetty* but could not be performed successfully even though various recrystallization conditions were applied. Therefore, the received isomer mixture was first subjected to ozonolysis to give a mixture of heptoses **39** and **40**. Then, the crude material was transformed into the corresponding methyl heptosides **41** and **42** to protect the hydroxygroup at C1. Afterwards, isopropylidene groups were introduced to enable the separation of the unwanted sugar derivative *via* aqueous extraction. So, the desired methyl 2,3:6,7-bis-*O*-(isopropylidene)-D-*glycero*-D-*manno*-

heptoside **43** could be isolated and was then deprotected under acidic conditions and finally peracetylated to give the bench-stable 1,2,3,4,6,7-hexa-*O*-acetyl-D-*glycero*-α-D-*manno*-heptopyranose **44** as a white, crystalline material after a final recrystallization (see Scheme 39).

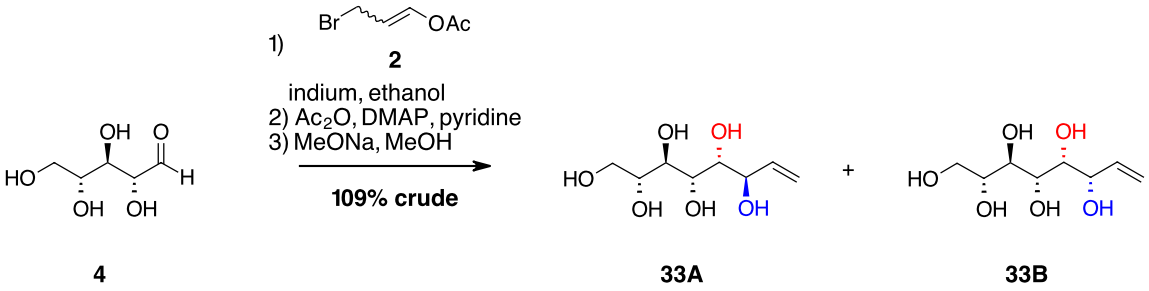


*Scheme 39: Six-step synthesis of 1,2,3,4,6,7-hexa-O-acetyl-D-glycero-α-D-manno-heptopyranose **44***

Compound **44** poses an ideal storage form of the desired bacterial sugar. Only a simple Zemplén deacetylation is necessary to furnish the unprotected D-*glycero*-D-*manno*-heptose from its peracetate.

2.2.1.1 IMA of D-ribose

The indium mediated acyloxyallylation of D-ribose **4** with 3-bromo-1-propenyl acetate **2** as elongation reagent led to the formation of the two previously described main products **33A** and **33B** (see Scheme 40). To remove indium residues, an acetylation-deacetylation sequence was applied leading to a crude yield of 109%, consisting dominantly of the unprotected enitols.



*Scheme 40: Indium mediated acyloxyallylation of D-ribose **4***

The main isomers were found in the ratio of 1.6:1 **A**:**B** according to the ^{1}H-NMR spectrum (see Figure 18). The major diastereomer **33A** with *lyxo*-configuration corresponds to the target compound D-*glycero*-D-*manno*-heptose upon ozonolysis. The found results were in consistence with the purely analytical ones reported above.

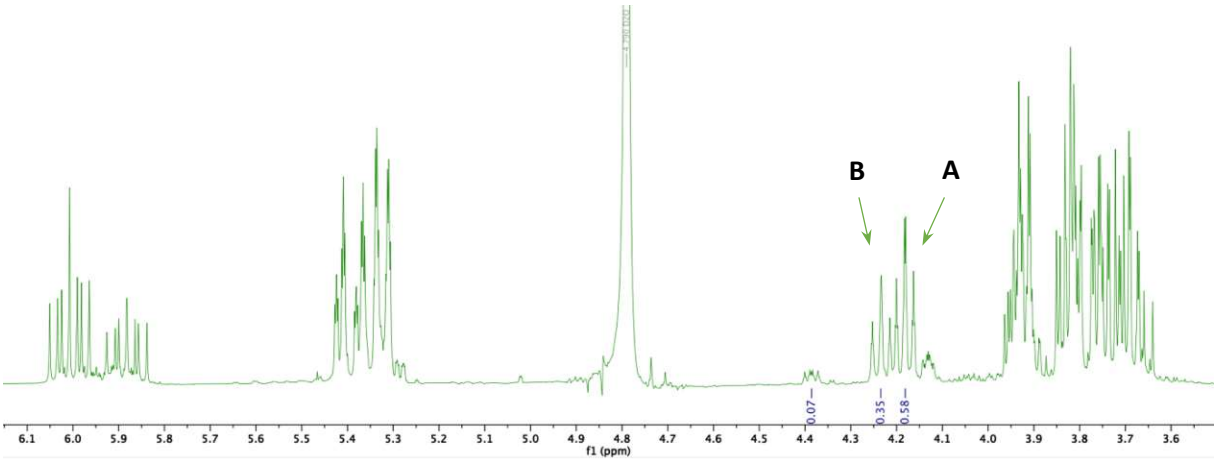
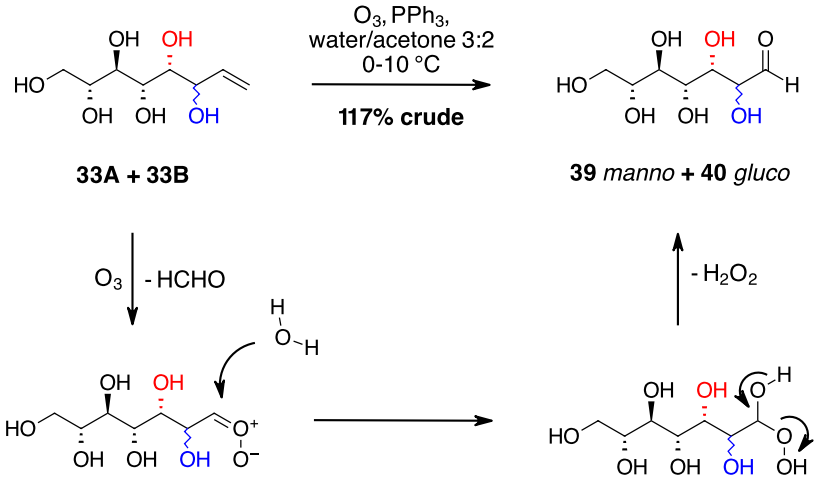


*Figure 18: ^{1}H-NMR spectrum of the enitol mixture obtained by the IMA of D-ribose **4***

2.2.1.2 Ozonolysis of the isomer mixture

For the ozonolysis of the water-soluble enitols, a mixture of water/acetone (3:2) was used as reaction medium which enabled a high solubility of **33A** and **33B** as well as the use of the lipophilic indicator Sudan red (III) to monitor the consumption of the starting material. The temperature was kept below 10 °C to achieve fast conversion to the corresponding heptose because it was described that higher temperatures or a higher water content significantly slow down the reaction.[33] The following scheme shows the mechanism of the ozonolysis of the enitols to the corresponding aldoses (see Scheme 41).

When alkenes are subjected to ozonolysis in mixtures of water and an organic solvent (like acetone), the water works as trap for the transient carbonyl oxides and leads to a release of H_2O_2 in stochiometric amounts which minimizes the formation of peroxides.[33] The decomposition of H_2O_2 was achieved by addition of triphenyl phosphine resulting solely in lipophilic byproducts which were removed during the extractive workup with dichloromethane, so that the corresponding heptoses, D-*glycero*-D-*manno*-heptose **39** and D-*glycero*-D-*gluco*-heptose **40**, remained in the aqueous layer and could be isolated in 117% crude yield in respect to the amount of D-ribose (in mol) used in the IMA.



*Scheme 41: Mechanism of the ozonolysis of the mixture of enitols **33A** and **33B** to the corresponding heptoses*

The two different aldoses can be differentiated *via* ^{1}H-NMR by the coupling constants of the signals for the anomeric hydrogen atom H1 (see Figure 19). In the case of the D-*glycero*-D-*gluco*-heptose **40** the coupling constant is significantly larger than for the heptose **39** with *manno*-configuration of the ring system. This is because the hydrogen atom at C2 of the *gluco*-configured heptose is in an axial position, while the hydrogen atom at C2 for the *manno*-configuration is positioned equatorial. For the compounds two anomeric signals in each case are visible in the ^{1}H-NMR spectrum which can be attributed to the α-anomer and the β-anomer, respectively. The signal of the α-anomer can generally be found at higher ppm values than the one of the β-anomer.

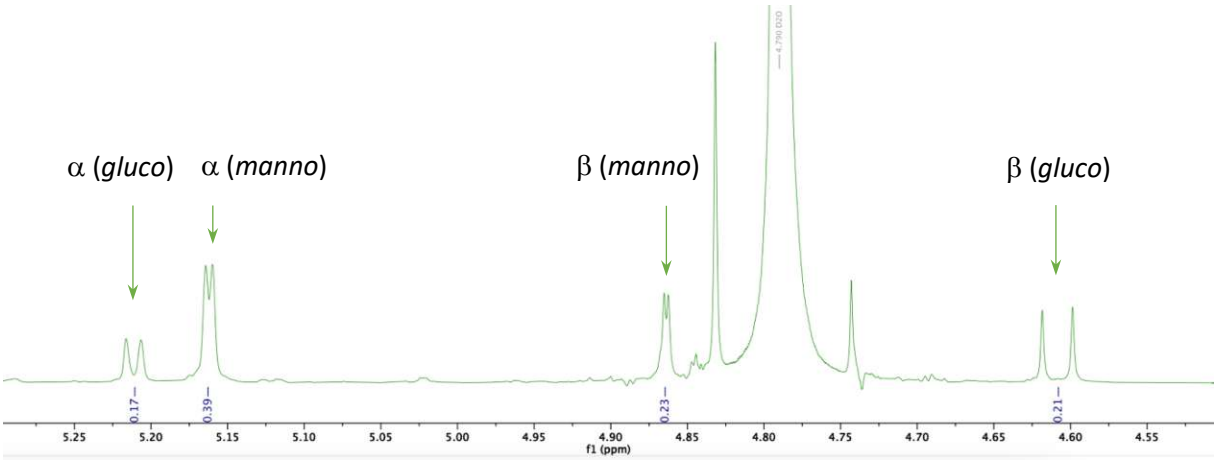
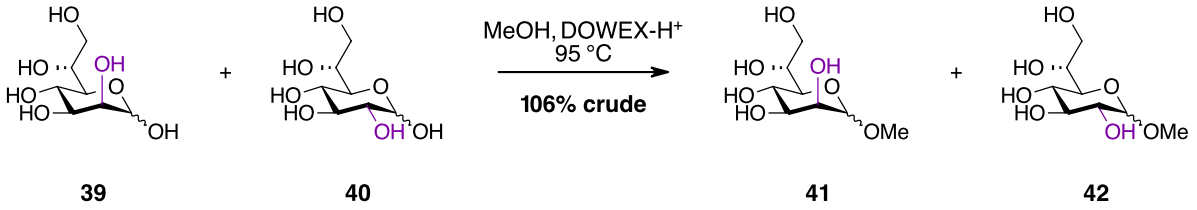


Figure 19: ^{1}H-NMR spectrum of the heptose mixture obtained by ozonolysis

2.2.1.3 Methyl heptoside formation

The formation of the methyl heptosides **41** and **42** poses a crucial step in the reaction sequence since it inhibits reaction with the hydroxy group at C1. This is particularly important in the follow-up reaction, where isopropylidene groups were introduced (see 2.2.1.4 Separation via acetonide protection).

The crude heptose mixture obtained *via* ozonolysis was directly applied to the methyl heptoside formation. Therefore, the crude material was heated to reflux under acidic conditions in methanol as the reaction solvent which gave a mixture of methyl D-*glycero*-D-*manno*-heptoside **41** and methyl D-*glycero*-D-*gluco*-heptoside **42** (see Scheme 42).



39 40 41 42

*Scheme 42: Formation of the methyl heptosides **41** and **42***

Advantage of the use of DOWEX-H^+ as proton source is the ease of the removal of the catalyst by simple filtration of the reaction mixture. Afterwards, the target compounds could be isolated through rotary evaporation of the methanol in a crude yield of 106%. The mixture of the methyl heptosides was used in the next reaction without further purification. Analysis *via* ^{1}H-NMR however clearly suggests full conversion of the reducing sugars to the corresponding methyl pyranosides, which can be clearly distinguished and assigned due to coupling constants and shifts, respectively (see Figure 20).

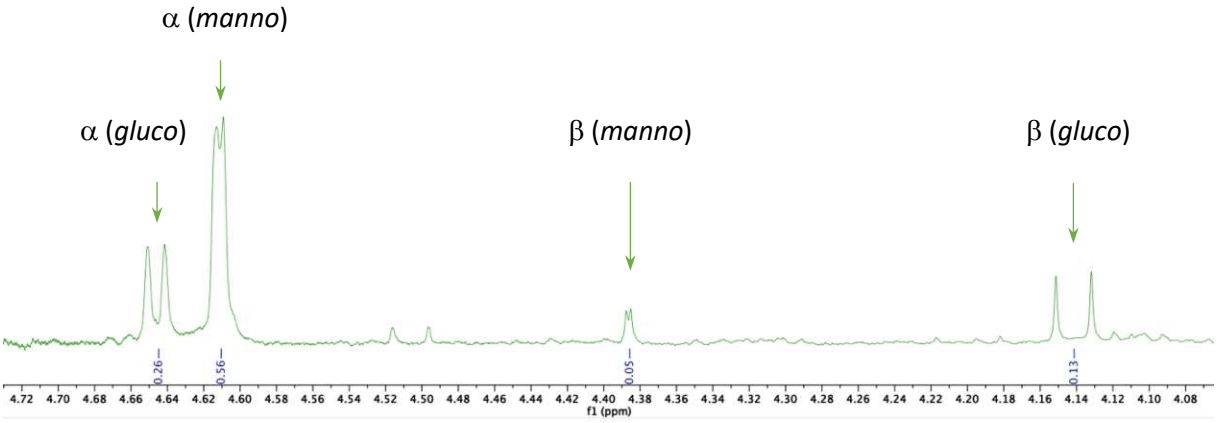


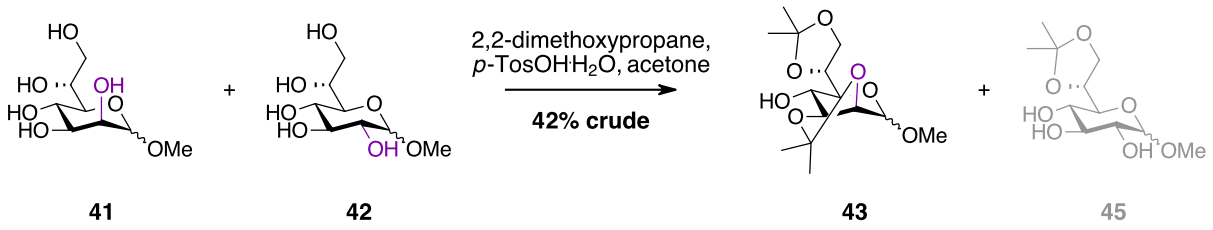
*Figure 20: ^{1}H-NMR spectrum of the methyl heptosides **41** and **42** in manno- and gluco-configuration*

2.2.1.4 Separation via acetonide protection

The acetonide protection by introduction of isopropylidene groups is the key step in the developed reaction sequence enabling a facile separation of the product mixture *via* aqueous extraction. The separation is based on the differentiating behavior of the two compounds **41** and **42** in respect to the number of introduced isopropylidene groups due to their stereochemical configuration. In the case of the methyl D-*glycero*-D-*manno*-heptoside **41** the hydroxy group on C2 is axial, whereas the same hydroxy group is in an equatorial position for methyl D-*glycero*-D-*gluco*-heptoside **42** corresponding to the positioning of the hydroxy groups in the related sugars mannose and glucose, respectively. The introduction of an isopropylidene group between hydroxy groups of a ring system is selective, a *cis* relationship of the neighbouring hydroxy groups is needed. That means, that compound **41** with *manno*-configuration of the ring system exhibits two possible locations for acetonide protection, namely between the hydroxy groups on C2 and C3 as well as between the hydroxy groups on C6 and C7 which do not participate in the ring formation, resulting in target compound methyl 2,3:6,7-bis-*O*-(isopropylidene)-D-*glycero*-D-*manno*-heptoside **43**. In contrast, for compound **42** only the hydroxy groups on C6 and C7 are accessible for acetonide protection tentatively leading to the formation of methyl 6,7-*O*-(isopropylidene)-D-*glycero*-D-*gluco*-heptoside **45** (see Scheme 43). Because of the large number of free hydroxy groups when only one isopropylidene group is in place, the latter compound

is water-soluble and can be found in the aqueous layer, while the desired product **43** which only bears one free hydroxy group dissolves in the organic solvent used for the extractive workup of the reaction.

The *cis*-selectivity of the acetonide protection also explains the importance of the formation of the methyl heptosides (see 2.2.1.3 Methyl heptoside formation) prior to the introduction of the isopropylidene groups. Because the α-anomer of D-*glycero*-D-*gluco*-heptose **40** bears a free hydroxy group in axial position on C1, introduction of more than one isopropylidene group would be possible if this compound would be directly used as starting material. The result would be an incomplete separation of the two isomers. However, this reaction and consequently the formation of a product mixture is prevented through the protection of the respective hydroxy group on C1 as a methoxy group.



*Scheme 43: Synthesis of methyl 2,3:6,7-bis-O-(isopropylidene)-D-glycero-D-manno-heptoside **43***

The introduction of the isopropylidene groups is depicted in Scheme 43. Due to the use of acetone as reaction solvent, only an understoichiometric amount of DMP is needed for the acetonide protection. The target compound methyl 2,3:6,7-bis-*O*-(isopropylidene)-D-*glycero*-D-*manno*-heptoside **43** was obtained in 42% crude yield and was directly used in the next reaction, the formation of the peracetate. The low yield can be attributed to the separation of the other isomer, which made up for about 40% of the initial product mixture. Calculated in respect to the theoretical content of the *manno*-configured isomer in the enitol mixture (~60%) a crude yield of 70% was achieved. For the remaining 30% it was assumed that not all the starting material **41** was converted into the target compound **43** but that there was the possibility that some of the methyl heptoside was transformed into a compound equivalent to compound **45**, bearing only one isopropylidene group. This only partially acetonide protected version of the target material was then found together with the *gluco*-configured compound in the aqueous phase.

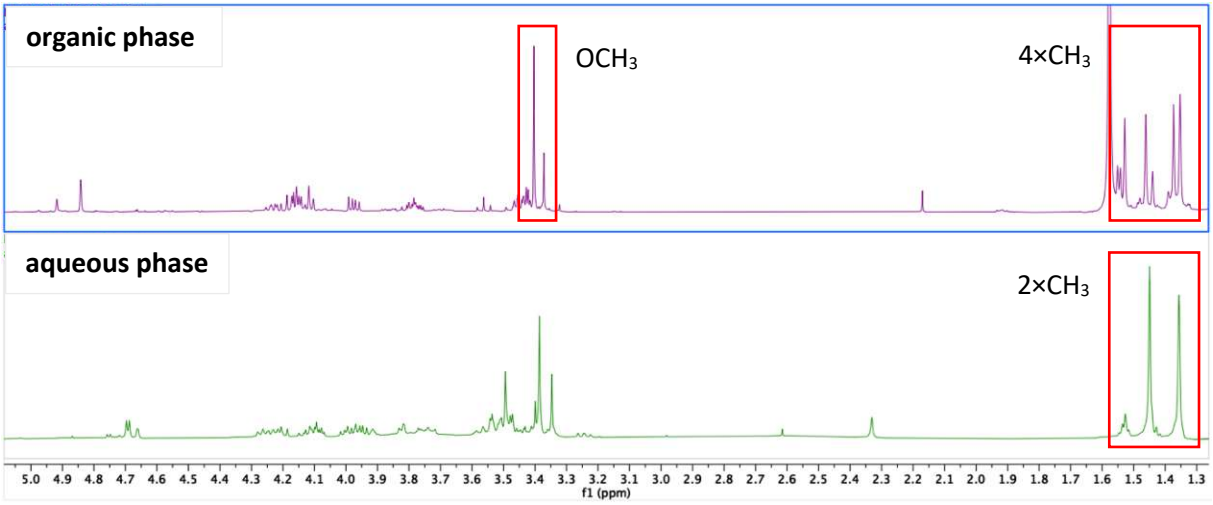


Figure 21: ^{1}H-NMR spectra of the material obtained from the organic phase (top) and the aqueous phase (bottom) measured in $CDCl_3$

Figure 21 displays the ^{1}H-NMR spectra of the compounds isolated from the organic phase and aqueous phase, respectively. For the material obtained from the organic phase, the four large singlet signals in the area of 1.3-1.6 ppm indicate the installation of two isopropylidene groups on the molecule, each with two CH_3-groups. Another singlet at about 3.4 ppm corresponds to the methoxy group which is attached to the anomeric carbon. This is compliant with methyl 2,3:6,7-bis-*O*-(isopropylidene)-D-*glycero*-D-*manno*-heptoside **43** as target compound. Also in this reaction, the α- and the β-anomer can be formed.

Measurement of the ^{1}H-NMR spectrum of the material obtained from the aqueous phase confirmed the assumed formation of species with only one isopropylidene-group installed in the molecule. In contrast to the spectrum of compound **43** depicted above the region around 1.4 ppm displayed only two singlet signals corresponding to the two CH_3 groups of the acetonide.

The isolated compound **43** was then subjected to deprotection, where the isopropylidene groups were cleaved under acidic conditions by stirring with DOWEX-H^+ in methanol to afford the corresponding *manno*-configured methyl heptoside **41** in 120% crude yield. Figure 22 shows the ^{1}H-NMR spectrum of the deprotected compound in contrast to the spectrum of the methyl heptoside mixture composed of two anomers each with *manno*- and *gluco*-configuration, respectively. It is clearly visible that the separation of the isomers *via* acetonide protection and aqueous extraction was successful, and the isolated material only contains the targeted species whereas the signals for the *gluco*-configured methyl heptoside are disappeared. The small signal at about 4.5 ppm can probably be attributed to the small amounts of the third isomer formed during the IMA which exhibits an *allo*-configuration. However, it is negligible since its peracetate does not solidify in the final recrystallization step.

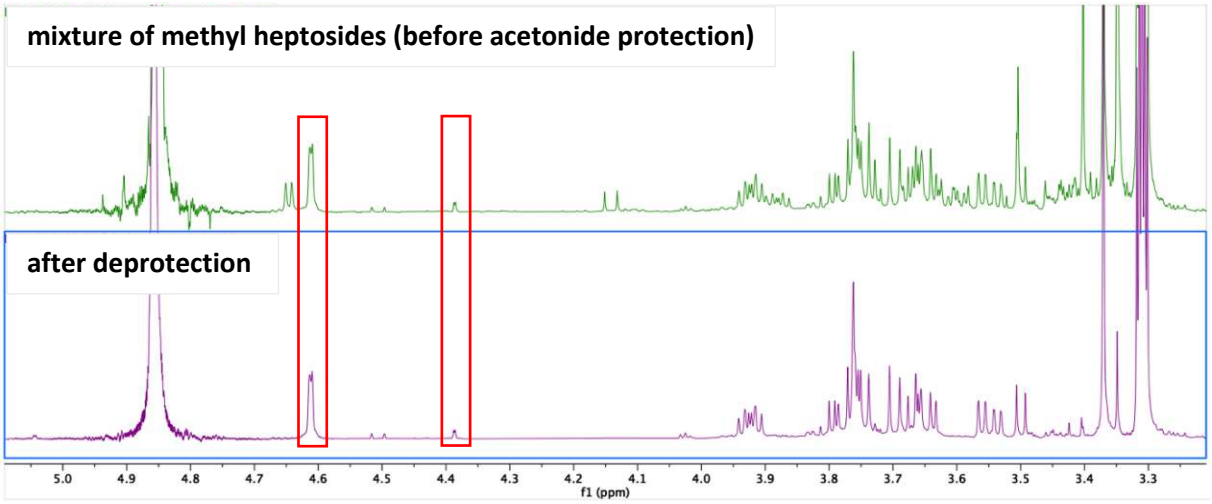
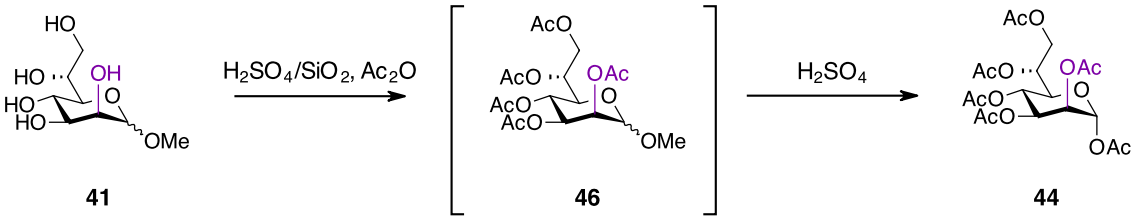


*Figure 22: ^{1}H-NMR spectra of the methyl heptoside mixture prior acetonide protection (top) and the isolated manno-configured methyl heptoside **41** after deprotection (bottom) measured in MeOD*

2.2.1.5 D-glycero-α-D-manno-heptose hexaacetate

The methyl D-*glycero*-D-*manno*-heptoside **41** was used in a concurrant acetylation/acetolysis step to obtain the final product 1,2,3,4,6,7-hexa-*O*-acetyl-D-*glycero*-α-D-*manno*-heptopyranose **44**. A catalytic amount of SiO_2/H_2SO_4[52] in acetic anhydride furnished the acetylated methyl heptoside **46** as a reaction intermediate. Subsequent addition of concentrated sulfuric acid resulted in complete acetolysis overnight, leading almost exclusively (α:β 9:1 according to ^{1}H-NMR) to the α-configured heptose hexaacetate **44** (see Scheme 44).



*Scheme 44: Preparation of the D-glycero-D-manno-heptose hexaacetate **36***

The crude material obtained *via* peracetylation solidified during evaporation of the solvent and 54 mg of the pure product (α:β 98:2 according to ^{1}H-NMR) were received in a single recrystallization from boiling ethanol in an overall yield of 12% (four steps from the heptose mixture after ozonolysis) or 20% in respect to the 60% of *manno*-configured product in the initial enitol mixture. Due to the small scale, it was not tried to isolate a second crop from the mother liquid, total possible recoveries over the series of steps will be determined as soon as scale up was successful.

Except for the final recrystallization, the whole reaction sequence was performed using the crude material obtained in the preceding step for the next reaction.

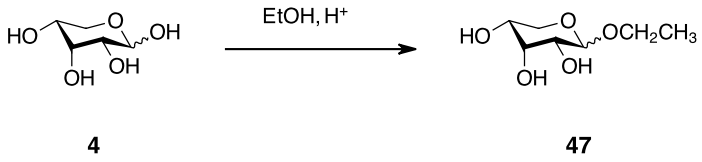
2.2.2 Attempted upscaling

After successful preparation of the bacterial sugar D-*glycero*-D-*manno*-heptose on milligram scale, the analogous upscaling of the synthesis yielding gram quantities of the target compound was attempted. Therefore, the developed route was repeated starting with 3 g and 12 g D-ribose, respectively. However, upscaling of the synthesis pathway proceeded less smoothly. The problems which arose performing the different reaction steps are described in the following subchapters in greater detail.

2.2.2.1 Ethyl riboside formation during IMA

Preparation of 3-bromo-1-propenylacetate: For the indium mediated acyloxyallylation of multigram quantities of D-ribose a significant amount of the elongation reagent 3-bromo-1-propenyl acetate **2** was required. So, the synthesis of the elongation reagent was performed twice starting with 50 mL acrolein (stabilized, 90%) each. However, the loss of product during distillation was even more drastic than when performing the preparation on a smaller scale (see 2.1.1 Preparation of the elongation reagents) and yields below 30% were reached in both experiments. For the synthesis of the larger amount of reagent a different, but also already opened bottle of acrolein **1** was used than for the initial preparation. So, a deviating quality of reaction educt could possibly be a reason for the differing results. Another possibility is decomposition of 3-bromo-1-propenyl acetate **2** during the distillation beside the earlier observed polymerization. However, due to a shortage of acrolein (cannot be reordered), the reaction could not be repeated with fresh acrolein as starting material and the prepared reagent had to be used for the IMA of the pentose.

IMA of ribose at scale: Effective stirring was identified as a critical requirement to achieve complete conversion of the starting material.[33] Therefore, a mechanical stirrer was used to ensure sufficient homogenization of the reaction mixture despite the high amount of used indium. However, even though the vigorous stirring, formation of ethyl ribosides **47** was observed in the reaction mixture (see Scheme 45). It is supposed that an acid-catalyzed Fischer glycosidation occurred caused by the drop of the pH value after addition of the elongation reagent and subsequent attack of the ethanol used as reaction solvent at the anomeric position of the aldose. For the IMA with 3 g D-ribose **4** about 8% of the product mixture was made up of ethyl ribosides, for the IMA with 12 g starting material even 14% of ethyl ribosides were observed.



4 **47**

Scheme 45: Acid-catalyzed ethyl riboside formation during the IMA

In Figure 23 the ^{1}H-NMR spectra of the obtained products are compared with the spectrum of the enitol mixture of the experiment on milligram scale, where no distinct ethyl riboside formation after the IMA is visible.

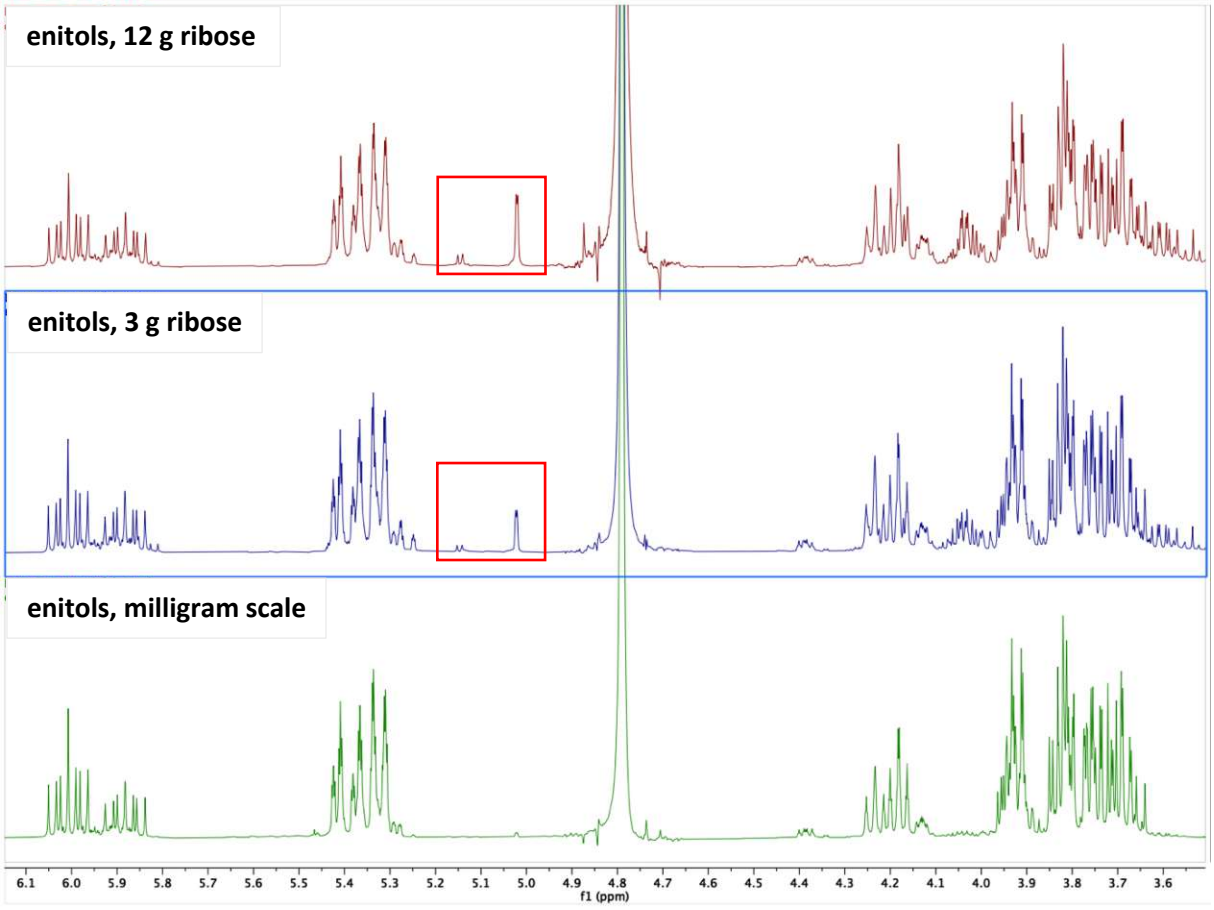


Figure 23: Ethyl riboside formation during the IMA (corresponding signals are marked with a red rectangle) measured in D_2O

2.2.2.2 Ozonolysis on large scale

Ozonolysis of the obtained enitol mixtures led to the corresponding heptoses, D-*glycero*-D-*manno*-heptose **39** and D-*glycero*-D-*gluco*-heptose **40**. In Figure 24 the ^{1}H-NMR spectrum of the heptose mixture obtained *via* ozonolysis on milligram scale is compared with the spectra of the product mixtures received from the experiments on gram scale (bottom to top). In the latter are beside the four anomeric signals of both heptoses also some smaller impurities and the signal of the ethyl riboside **47** (marked in red) visible, which was formed in the indium mediated acyloxyallylation of D-ribose **4**. The ratio between the sugars of *manno*- and *gluco*-configuration remained largely untouched after the ozonolysis of the enitols.

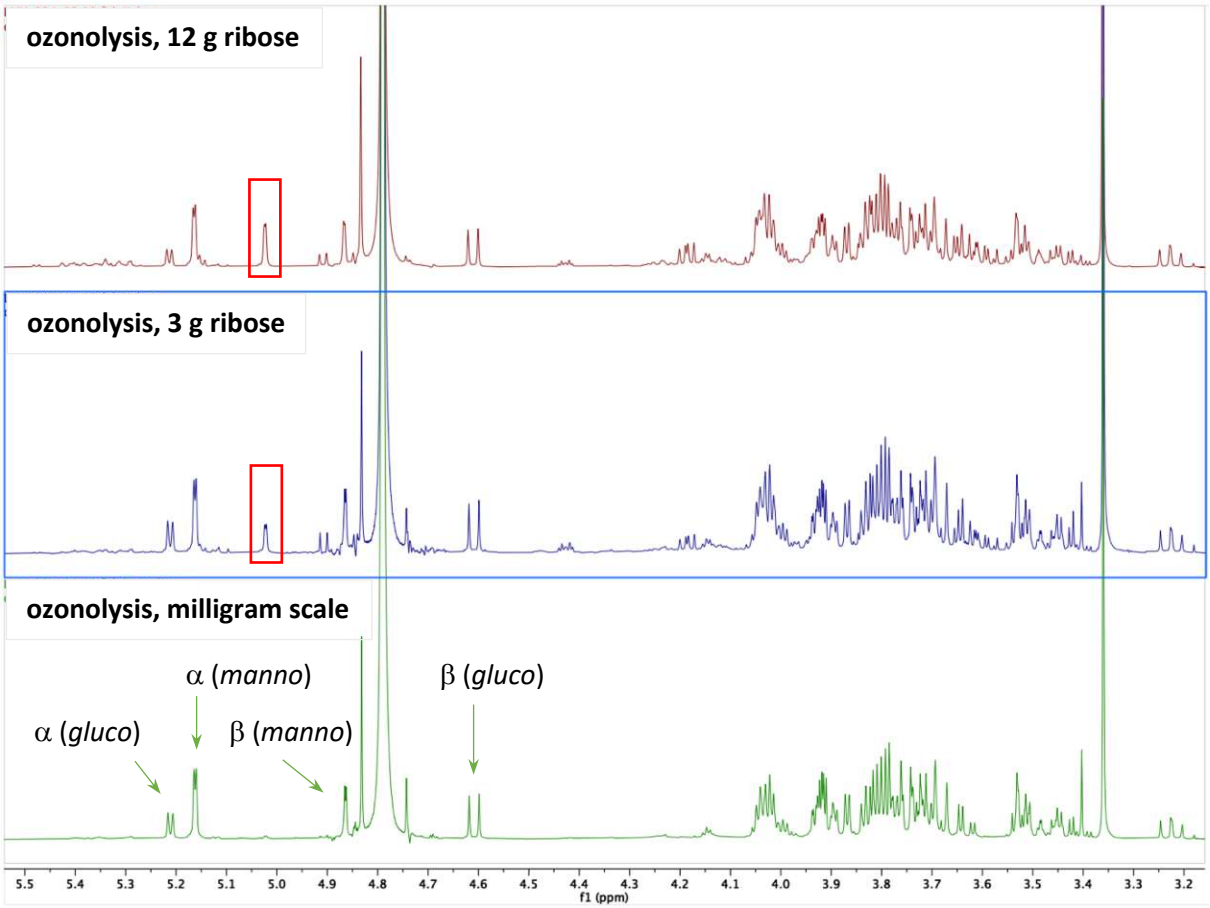


Figure 24: Comparison of the ^{1}H-NMR spectra of the obtained heptose mixtures via ozonolysis measured in D_2O

2.2.2.3 Methyl heptoside formation on large scale

The comparison of the ^{1}H-NMR spectra of the obtained product mixtures after the heptoside formation shows that only on the milligram scale a rather pure mixture of the possible anomers was received. The spectra for the experiments performed on larger scale display a multitude of signals linked to minor impurities, however the four distinct peaks for the target product with *manno*-configuration as well as the *gluco*-configured isomer are still visible (see Figure 25).

For the methyl heptoside formation the crude material from the preceding reaction step, the ozonolysis, was directly used. The methoxy group was installed in methanol under acidic conditions. On large scale the experimental procedure was adopted, and the reaction mixture was not only heated to reflux overnight but was left to stir for up to 24 hours. As described in 2.2.1.3 Methyl heptoside formation, the formation of the methyl heptosides is a very crucial step before the separation of the isomers can be attempted *via* an aqueous workup after introduction of the isopropylidene groups. Therefore, an elongation of the reaction time was applied for the greater amount of starting material to ensure full conversion of the aldoses.

The ethyl ribosides **47** which were not affected by the ozonolysis reaction but were extracted together with the obtained heptoses probably were converted to methyl ribosides during the methyl heptoside formation making up for some of the additional signals.

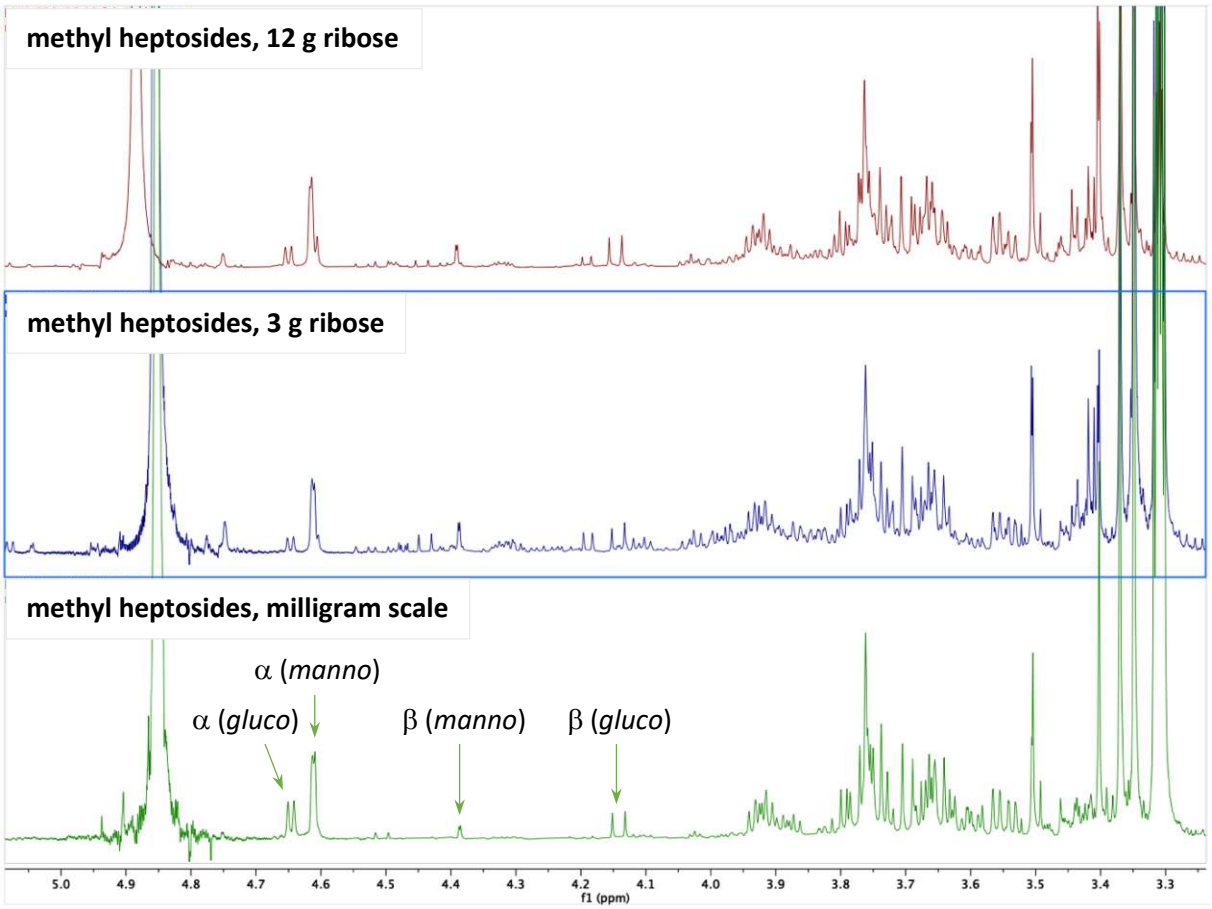


Figure 25: Comparison of the ^{1}H-NMR spectra of the obtained methyl heptosides measured in MeOD

2.2.2.4 Isopropylidene formation and separation by aqueous extraction

For the acetonide protection a mixture of DMP and acetone and a catalytic amount of *p*-toluenesulfonic acid monohydrate was used. In comparison to the milligram scale, where TLC monitoring showed that the reaction was finished after 3.5 hours of stirring at room temperature, the two larger batches did not show complete conversion after this time and on the next morning there was still a shadow of starting material left. For the middle batch more reagents were added and stirring was continued, however no improvement could be achieved. Because the *gluco*-configured side product only bears one isopropylidene group beside three free hydroxy groups, this compound (as well as remaining starting material) can be removed by extraction with water. On the contrary, the target compound with the two integrated isopropylidene groups dissolves in the organic layer and can be isolated by evaporation of the solvent under reduced pressure, if any bis-protected *gluco*- or *allo*-species were present, they would likely be in this fraction.

Figure 26 shows a comparison of the ^{1}H-NMR spectra for all three batches after the acetonide protection of the crude methyl heptosides.

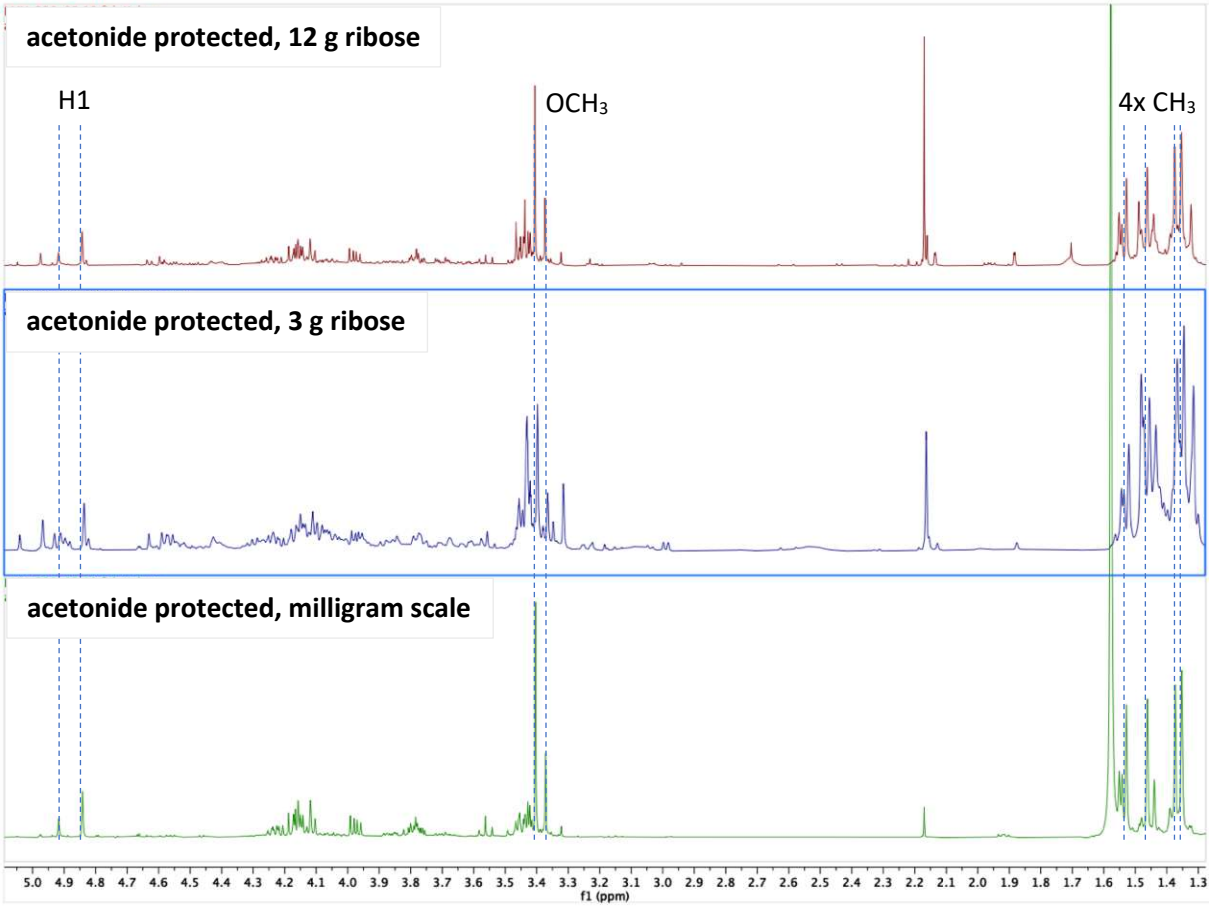


Figure 26: Comparison of the ^{1}H-NMR spectra of material obtained from the organic phase after the acetonide protection of the methyl heptoside mixture and separation via aqueous extraction measured in $CDCl_3$

The material which was obtained by evaporation of the organic layer was subjected to deprotection under acidic conditions to cleave the isopropylidene groups leading to the already known methyl heptoside **41**. Figure 27 shows the ^{1}H-NMR spectra of the received compound **41** for all three experiments in comparison with a reference spectrum showing the mixture of methyl heptosides obtained in the methyl heptoside formation on milligram scale. It is clearly visible that all signals which belong to the *gluco*-configured methyl heptosides vanished after the separation *via* aqueous extraction and only the signals corresponding to the *manno*-configured methyl heptosides were left which are marked with a red rectangle.

The impurities particularly visible in the spectrum of the 3 g batch were already acquired during the previous reaction steps. Next to the undesired ethyl riboside formation during the IMA, the additional signals can potentially be attributed to furanoses formed following the reaction pathway whose chemical shift is different to the one of the targeted pyranose forms. However, despite the complexity of the spectra of these mixtures, it is apparent that all *gluco*-configured methyl pyranosides were successfully removed at this stage.

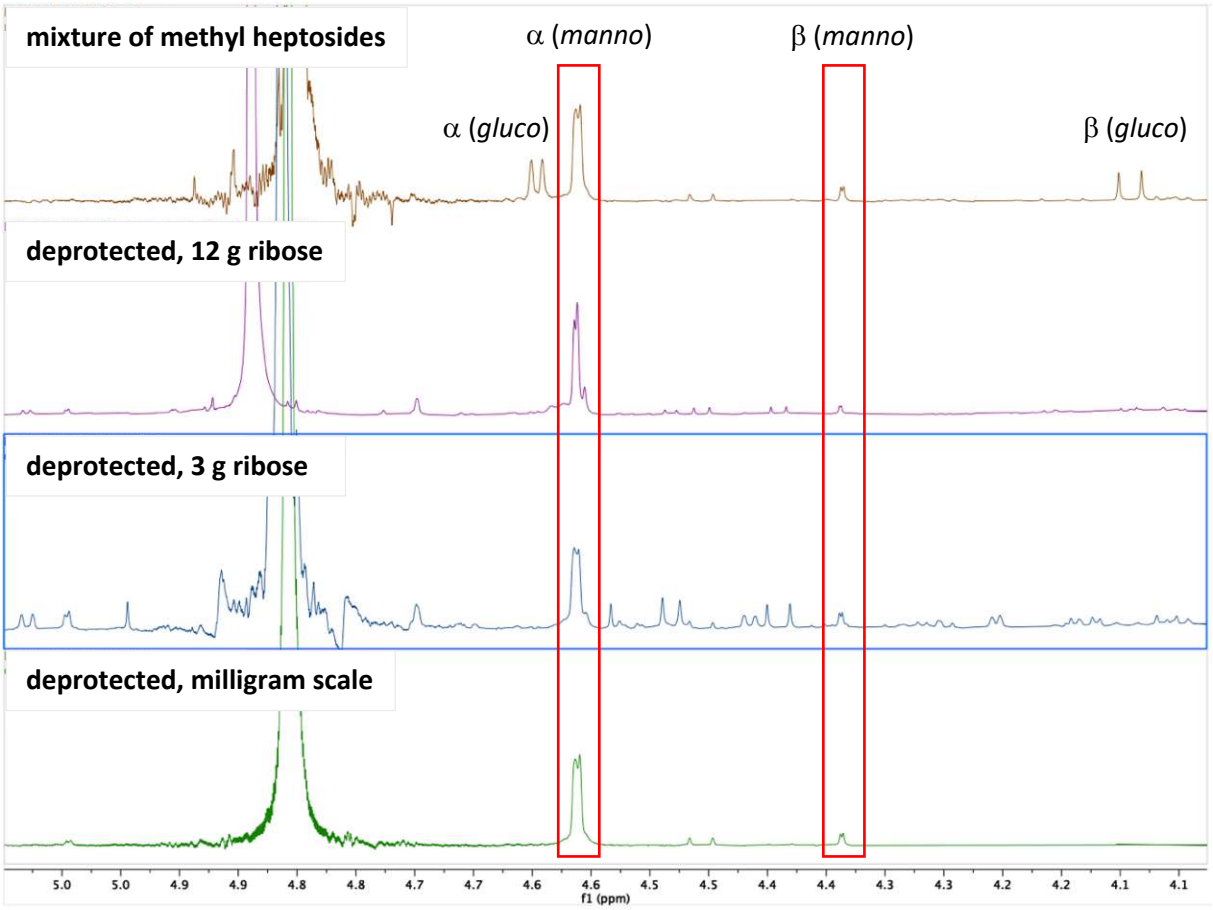


*Figure 27: Comparison of the deprotected compound **41** after separation of the isomers via aqueous extraction with a reference spectrum of the methyl heptoside mixture **41** (manno) + **42** (gluco) measured in MeOD*

2.2.2.5 Acetylation/acetolysis and recrystallization

In general, for the upscaling of the synthesis pathway the reactions were performed with the batch starting from 3 g D-ribose **4** first, and only after confirmation of the successful transformation *via* ^{1}H-NMR it was repeated with the larger batch starting from 12 g D-ribose. Since separation of the two isomers seemed to be the key step in the reaction sequence and the ^{1}H-NMR spectra depicted in Figure 27 showed that no *gluco*-configured methyl heptosides were left after deprotection, the final step, a concomitant acetylation/acetolysis, was performed for both batches simultaneously. It was assumed that the remaining impurities could be removed by recrystallization from boiling ethanol as it was the case on the milligram scale.

However, after measuring the ^{1}H-NMR spectra of the white solid obtained after recrystallization, it was noticed that it did not only compose of one but two sugar derivatives which strongly differed from the result obtained on milligram scale (see Figure 28). It was assumed that instead of pure 1,2,3,4,6,7-hexa-*O*-acetyl-D-*glycero*-α-D-*manno*-heptopyranose **36** a mixture of the target compound and the *gluco*-configured isomer had been received. This hypothesis was confirmed by deprotection of the peracetates under Zemplén conditions and comparison of the measured ^{1}H-NMR spectra using the heptose mixture furnished by ozonolysis of the enitols as a reference.

Rationalization of the problems and trouble-shooting: First, an incomplete separation during the aqueous extraction was supposed to be the reason for the significant amount of *gluco*-configured heptose hexaaacetate. However, consultation of the corresponding 2D spectra after deprotection

revealed no hidden peaks and supported that the starting material for the acetylation/acetolysis reaction was mainly D-*glycero*-D-*manno*-methyl heptoside **41** containing minor impurities due to the utilization of the crude material of the preceding experiments without purification throughout the entire reaction sequence.

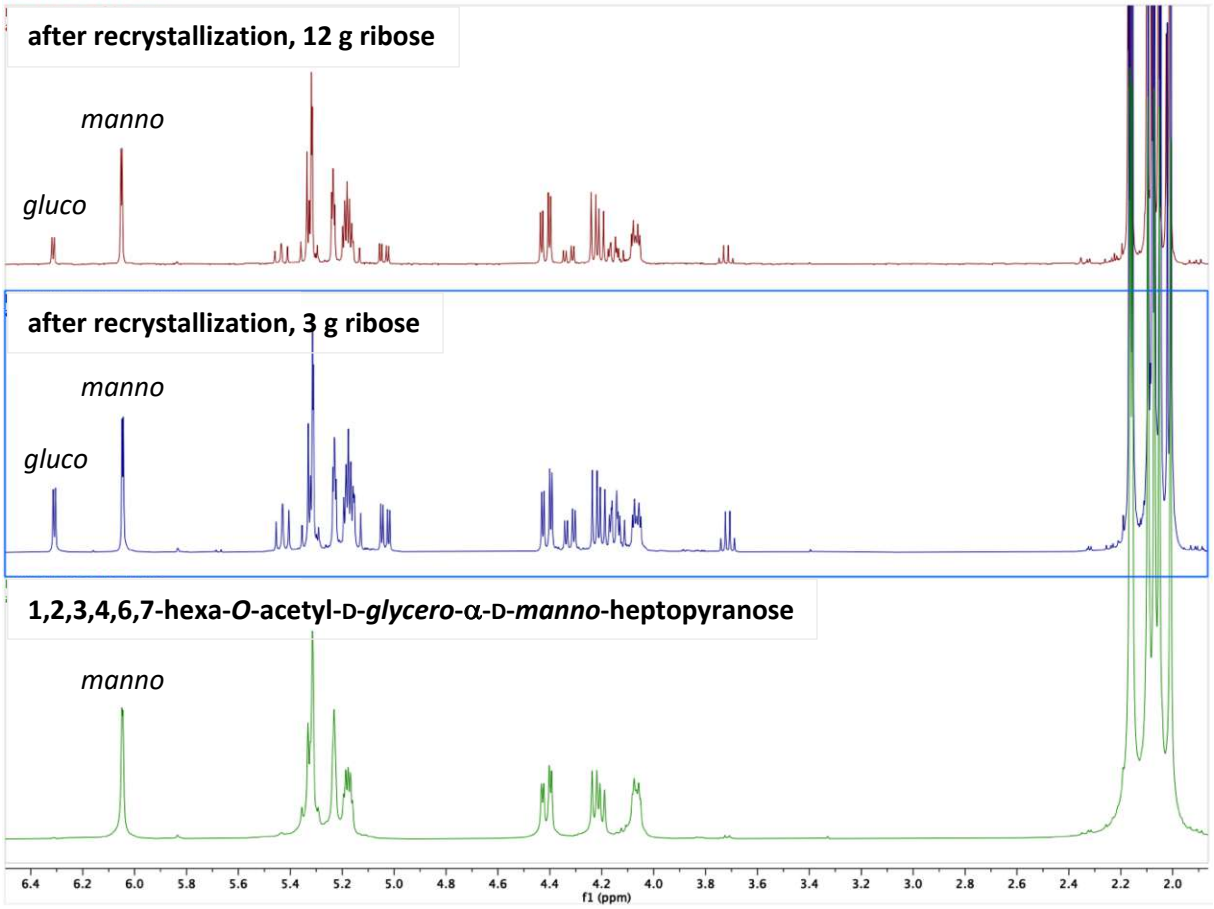


Figure 28: ^{1}H-NMR spectra of the obtained material after recrystallization from boiling ethanol measured in $CDCl_3$

Another possibility for the occurrence of the peracetate with *gluco*-configuration is an epimerization during the acetolysis. It was found in literature that some unsubstituted pyranose sugars can be transformed into their C2 epimers under certain conditions e.g. in an acetolysis medium containing a high concentration of acetic acid.[53] This issue was further investigated by *Sowa*, with the aim to circumvent an inadvertent formation of side products through this acetolysis-inversion reaction. He, amongst others, describes the epimerization of 1.0 g D-mannose in a mixture of acetic acid, acetic anhydride and sulfuric acid (30 mL:4 mL:1.5 mL) yielding a mixture of D-glucose and D-mannose in a 0.3 to 1 ratio. It is stated that the tautomerization might occur with the formation of relatively large amounts of furanoses, for which the inversion at the central carbon probably proceeds through a transient tricyclic system of five-membered rings *via* cyclic acetoxonium intermediates. So, only little change in position is required for the atoms which are directly involved. The accumulated data suggests that only monosaccharides with a *cis*-2,3 configuration of the furanose form epimerize in an acetolysis medium.[54]

The used acetylation/acetolysis medium which was applied in the performed reaction was acetic anhydride together with sulfuric acid. The acetolysis conditions differ from the ones described in the

paper[54] where additionally a very high amount of acetic acid was used. However, the elevated temperatures upon addition of sulfuric acid might still have led to the formation of the C2 epimer in the acetolysis mixture. Fact is, that after the acetylation/acetolysis reaction and the subsequent workup the *gluco*-configured heptose hexaacetate and the target compound **44** (α-anomer) were found in a ratio of 23:77 for the middle batch and in a slightly better ratio of 11:89 for the large batch. The the α:β ratio of the product was 93:7 according to ^{1}H-NMR (see Figure 29).

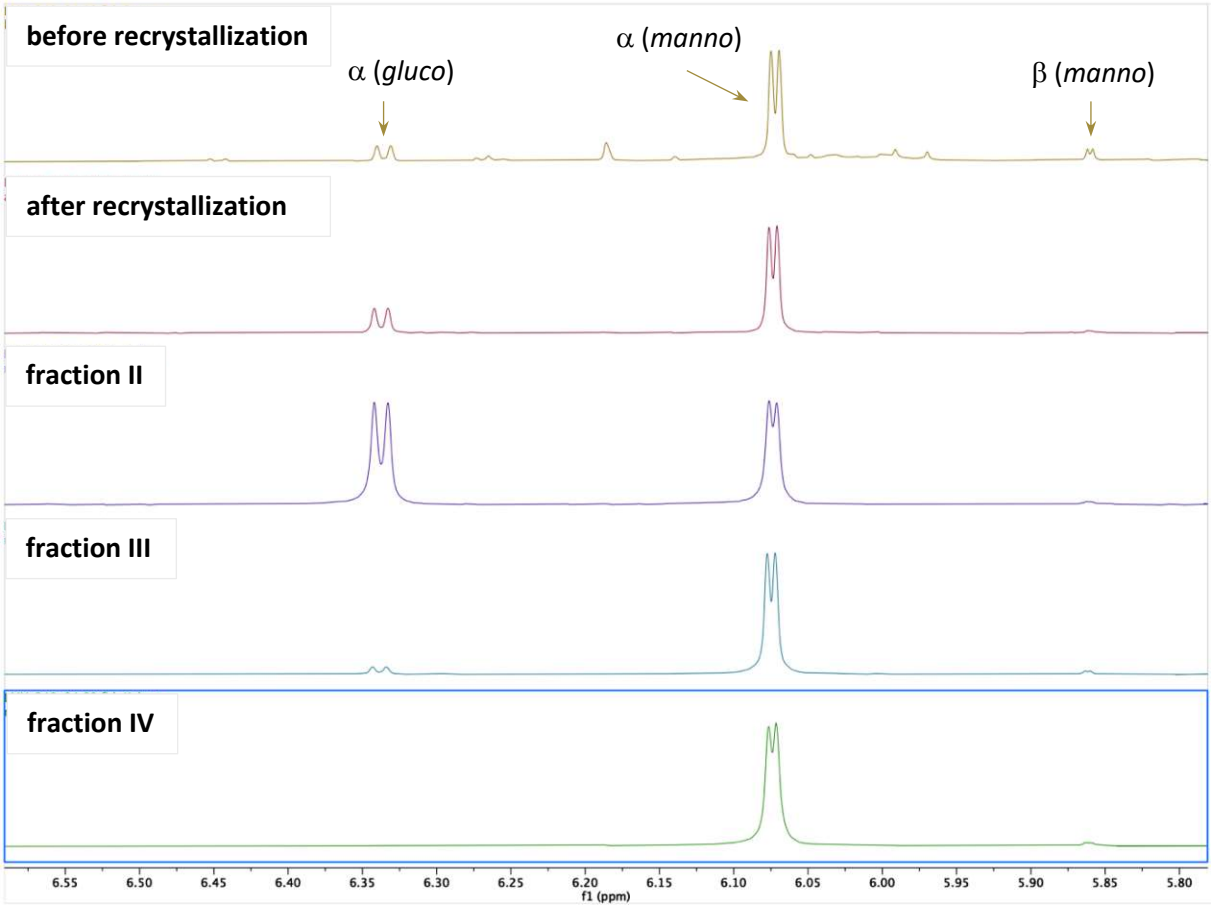


Figure 29: Comparison of the ratio of gluco:manno for the different recrystallization attempts and the obtained product before recrystallization (top) displayed for the large batch

Recrystallization from boiling ethanol led to the accumulation of the *gluco*-configured side product as shown in Figure 29, a known phenomenon which was the reason for the required development of this synthetic extra-loop for discrimination. For the large batch, the obtained white solid showed a ratio of 20:80 *gluco*:*manno* while the α:β ratio of the product changed to 98:2 according to ^{1}H-NMR. The first recrystallization of the received 16.1 g of brown oily crude material afforded only 2.7 g of white solid. After the weekend, another fraction of 80 mg was isolated from the mother liquor, this time with a ratio of about 1:1 *gluco*:*manno*. Due to time reasons, not all of the ethanol of the mother liquor could be evaporated after suction filtration and the brown solution was kept at room temperature overnight. On the next morning a third fraction of 744 mg consisting mostly of target material could be collected (9:91 *gluco*:*manno*).

Since ^{1}H-NMR measurements revealed that a significant amount of the targeted *manno*-compound **44** remained in the 11 g of concentrated mother liquor, another recrystallization attempt was performed. However, upon cooling of the solution only a brownish oil separated from the ethanol. The procedure

was repeated with more solvent (20 mL ethanol) leading to the same result, the emerging of a brown oil. However, while the mixture was stored in the fridge over the weekend small crystals started to grow in the oily phase. Isolation of the crystals *via* suction filtration furnished 680 mg of pure 1,2,3,4,6,7-hexa-*O*-acetyl-D-*glycero*-α-D-*manno*-heptopyranose **44** as a fine white solid.

Recrystallization was also tried with diethyl ether, but no crystal formation was observed. Even though the mother liquor still contains target material, further recrystallizations from the crude yellow oil remained unsuccessful. This might be attributed to the higher amount of impurities than on the milligram scale which inhibit the desired crystal growth.

3. Conclusion and outlook

A family of *ribo*-configured protected sugar aldehydes with acetyl, benzoyl, acetonide, TBS and benzyl protection was prepared and subjected to the indium mediated acyloxyallylation (IMA). Within the investigation it was found diastereodivergence depending on whether the starting materials (2-OH) did bear protecting groups or not. The effect of different protecting groups was examined and a protection *via* acetonides was found to be most suitable to shift the reaction outcome towards a *ribo*-configuration **C**, representing an *anti*-orientation in respect to the former 2-OH-group and an *anti*-addition to the aldehyde. Furthermore, the indium mediated acyloxyallylation was also applied to arabinose and arabinose derivatives to confirm that the findings are independent of the configuration of the starting material. The experiments showed that the trends can be transferred likewise to sugar aldehydes with '*threo*'-configuration.

The successful application of the reaction on protected aldoses is encouraging and the findings hopefully help to promote a more frequent consideration of the indium mediated acyloxyallylation as a suitable synthetic solution for a two-carbon elongation within and even beyond the scope of carbohydrate chemistry for chiral aldehydes.

In terms of the application of the indium mediated acyloxyallylation, the synthesis of D-*glycero*-D-*manno*-heptose was investigated. The preparation of the heptose hexaacetate, the bench-stable storage form of the targeted bacterial sugar, was successfully accomplished on a milligram scale. The synthesis followed a newly developed procedure for the separation of the two main isomers formed during the IMA based on the introduction of isopropylidene groups as the key transformation. Thereby, the stereochemical difference between the *manno*- and the *gluco*-configured methyl heptoside regarding the OH-group on C2 was exploited to enable the isolation of the desired compound *via* aqueous extraction. Furthermore, we succeeded in evolving a column-free reaction pathway by directly using the obtained crude material in the next reaction step and thus avoiding laborious purification procedures.

Despite the found synthetic solution proved to be suitable for the preparation of DD-heptose in principle, the attempted synthesis on large scale showed that for a successful upscaling of the reaction pathway an optimization of the reaction conditions will be necessary.

4. Experimental part

4.1 General methods

4.1.1 Reagents and solvents

The used chemicals were bought from commercial sources with a purity greater than 95% if not stated differently and were used without further purification. Water-free solvents were available at the institute from a PureSolv solvent purification system by Innovative Technology, or commercial sources that were stated as water-free and stored in bottles with a septum and over molecular sieve. Ratios of liquids used as solvents or as eluents are given as volume ratios.

4.1.2 TLC

TLC analysis for reaction monitoring and analyzing fractions from column chromatography was performed on silica gel 60 F_{254}-plates. The spots were visualized using UV light (254 nm) or by staining the plates with anisaldehyde solution (180 mL EtOH, 10 mL anisaldehyde, 10 mL H_2SO_4 conc., 2 mL CH_3COOH), potassium permanganate solution (3.0 g $KMnO_4$, 20.0 g K_2CO_3, 250 mg KOH, 300 mL H_2O), or cerium molybdate solution ("Mostain", 21 g $(NH_4)_6Mo_7O_{24}{\cdot}4\ H_2O$, 1 g $Ce(SO_4)$, 231 mL H_2SO_4 conc., 500 mL H_2O).

4.1.3 Column chromatography

Column chromatography for purification purposes was performed with silica gel 60 (43-60 µm). The used column sizes and eluents were adapted to the corresponding separation problem.

4.1.4 Specific rotation

A modular circular polarimeter (Anton Paar MCP 500) with a 100 mm long cuvette of a 3 mm diameter was used for measuring the specific rotation of chiral compounds. Specific rotations were measured at 20 °C if not stated differently and a wavelength of 589 nm with the noted solvent of HPLC purity or higher and with the concentration being given in g/100 mL.

4.1.5 HRMS

The HRMS analysis was carried out from solution of methanol or acetonitrile or water or a mix of these by using an Agilent G7167B multi sampler, an Agilent G7120A binary pump with degasser, an Agilent G7116B oven and Agilent 6545 Q-TOF mass spectrometer equipped with a dual AJS ion score. The measurements were performed with ESI in positive mode.

5.1.6 HPLC-MS

HPLC-MS analysis was performed on a Nexera X2® UHPLC system (Shimadzu®, Kyoto, Japan) comprised of LC-30AD pumps, a SIL-30AC autosampler, CTO-20AC column oven, and DGU-20A5/3 degasser module. Detection was accomplished by concerted efforts of SPD-M20A photo diode array, a RF-20Axs fluorescence detector, an ELS-2041 evaporative light scattering detector (JASCO®) and finally *via* LCMS-2020 mass spectrometer.

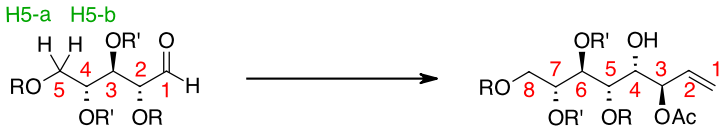
Separation *via* HPLC-MS was carried out using an Autopurification system from Waters with an ACQUITY QDa detector, combined with a 2998 Photodiode array detector. Separation was conducted with a XSELECT CSH C18 5 µm 4.6 x 150 mm column for analytical samples and a XSELECT CSH Prep

C18 5 µm OBD 30 x 150 mm column for preparative runs. HPLC grade acetonitrile and water, containing 0.1% formic acid, were used as eluents.

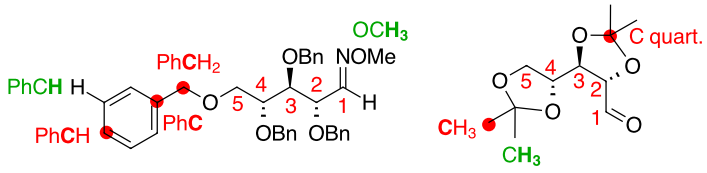
4.1.7 NMR

NMR spectra were recorded from $CDCl_3$, CD_3OD, CD_2Cl_2 or D_2O solutions. The analysis was done at 297 K using a Bruker Avance Ultra Shield 400 MHz sprectrometer. For 600 MHz ^{1}H-NMR and 151 MHz ^{13}C-NMR an Avance III HD 600 spectrometer was used. All spectra were calibrated to the solvent residual peak.[55] Chemical shifts (δ) are reported in ppm, coupling constants (*J*) were expressed in Hz. Assignments were based on 2D-spectra (COSY, HSQC and HMBC experiments).

For all sugar species, numbering of the carbon atoms consistently starts from the (former) reducing end of the sugar:



When necessary, special descriptors were used to further specify the assignment of a signal:



4.1.8 Melting points

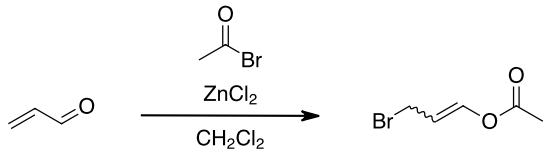
Melting points were recorded with the Kofler methods on a Reichert Thermogalen Hot Stage Microscope with a Leica Galen III microscope and a mercury thermometer covering the range 20 °C to 230 °C. For the microscopic investigation of the melting process a heating rate of 2.0 °C/min was used.

4.1.9 Ozone generation

Ozone enriched oxygen was generated using a Triogen LAB2B Ozone generator.

4.2 Experimental procedures - Systematic study

4.2.1 3-Bromo-1-propenyl acetate (2)



1 **2**

C_3H_4O $C_5H_7BrO_2$
MW: 56.06 g/mol MW: 179.01 g/mol

Procedure:

Acrolein **1** (90%, 10 mL, 135 mmol, 1.0 equiv.) was dissolved in dry DCM (54 mL) and cooled to -40 °C using an acetone/liquid N_2 cooling bath (precipitation of a white solid). Acetyl bromide (9.6 mL, 128 mmol, 0.95 equiv.) was added over a few minutes, followed by zinc chloride (no pre-activation, 190 mg, 1.39 mmol, 0.01 equiv.) at -30 °C. The reaction solution turned orange and the temperature started to rise quickly up to +15 °C, after which it dropped again and the reaction mixture was stirred at -20 °C for 30 minutes. An aliquot (60 µL) was worked up (Et_2O/$NaHCO_3$) and concentrated under reduced pressure. ^{1}H-NMR of the sample revealed complete conversion of the acrolein.

Workup:

The reaction mixture was cooled to -30 °C and added to a mixture of water and ice (50 mL). The mixture was transferred into a separatory funnel and the phases were separated, leading to a milky green organic layer and a clear acidic aqueous layer. The organic layer was washed with water (3× 50 mL, still acidic). The combined aqueous phases were back-extracted with fresh DCM (2× 25 mL). The organic layer was extracted twice with saturated $NaHCO_3$ solution (80 mL in total, until basic) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated to leave the crude material as a dark brown liquid (~20.5 g) which was stored under argon in the freezer at -18 °C.

The crude material was purified by distillation (b.p. = 75-77 °C, 7 mbar) to obtain 10.17 g of the target compound **2** as a mixture of isomers (*E*/*Z*=3:7). According to ^{1}H-NMR the material contains minor impurities, but the spectral data is in consistence with the literature[30]. The colorless, slightly yellow liquid was stored under argon at -18 °C.

Yield	10.17 g (42%)
Appearance	colorless, slightly yellow oil
Boiling point	75-77 °C, 7 mbar, Lit: 69-71 °C, 22 Torr[30]
R_f-value	0.74 (LP:EA 4:1, anisaldehyde)

NMR

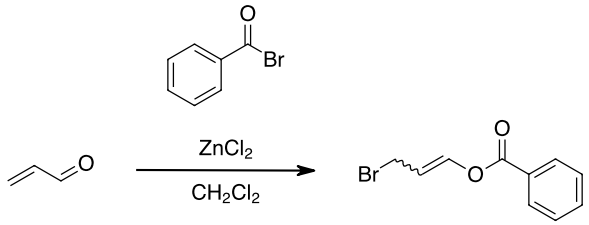
Z-Isomer:
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 (dt, *J* = 6.3, 0.9 Hz, 1H, H1), 5.23 (td, *J* = 8.4, 6.3 Hz, 1H, H2), 4.08 (dd, *J* = 8.4, 0.9 Hz, 2H, H3), 2.20 (s, 3H, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.3 (**C**=O), 137.2 (C1), 109.6 (C2), 23.7 (C3), 20.7 (**C**H_3).

E-Isomer:
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (dt, *J* = 12.4, 1.1 Hz, 1H, H1), 5.70 (dt, *J* = 12.4, 8.4 Hz, 1H, H2), 3.98 (dd, *J* = 8.4, 1.0 Hz, 1H, H3), 2.15 (s, 3H, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.7 (**C**=O), 139.3 (C1), 111.4 (C2), 28.6 (C3), 20.8 (**C**H_3).

4.2.2 3-Bromo-1-propenyl benzoate (3)



1

C_3H_4O
MW: 56.06 g/mol

3

$C_{10}H_9BrO_2$
MW: 241.08 g/mol

Procedure:

Acrolein **1** (90%, 1 mL, 13.5 mmol, 1.0 equiv.) was dissolved in dry DCM (34 mL) and cooled to -30 °C using an acetone/liquid N_2 cooling bath. Benzoyl bromide (1.6 mL, 12.8 mmol, 0.95 equiv.) was added dropwise, followed by zinc chloride (no pre-activation, 25 mg, 0.14 mmol, 0.01 equiv.) at -30 °C. The cooling bath was submerged and the temperature started to rise slowly. The stirred mixture was allowed to reach 0 °C and was stirred at this temperature for 2.5 hours during which the reaction solution turned orange. An aliquot (100 µL) was worked up (Et_2O/$NaHCO_3$) and concentrated under reduced pressure. ^{1}H-NMR of the sample revealed full conversion of the acrolein.

Workup:

Aqueous saturated $NaHCO_3$-solution (25 mL) was slowly added to the reaction mixture. The mixture was transferred into a separatory funnel using dichloromethane and the phases were separated, leading to a milky green organic layer and a clear acidic aqueous layer. The aqueous phase was extracted with another portion of fresh DCM (2× 50 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated to leave the crude material (3.102 g) as a dark green-brown liquid. The crude was stored under argon in the freezer at -18 °C.

The crude material solidified in the freezer giving a brown solid which was dissolved in DCM. The pure product was obtained by column chromatography (60 g SiO_2, LP:EA 9:1) as a colorless liquid that solidified in the freezer. The target compound **3** is a mixture of isomers (*E*/*Z*=3:4) and pure according to ^{1}H-NMR. The spectral data is in consistence with literature[30]. It was stored under argon at -18 °C.

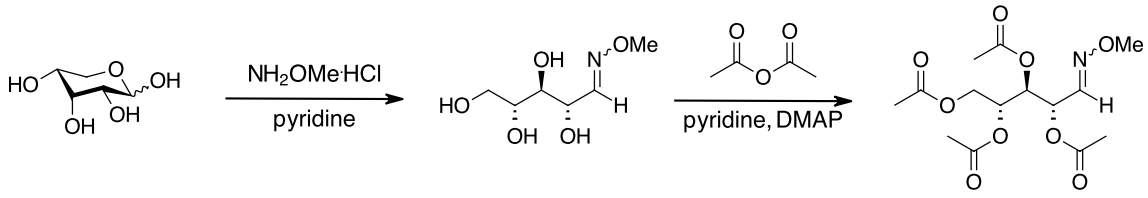
Yield	2.592 g (80%)
Appearance	white solid
Melting point	42-43 °C (LP:EA), Lit: 74-76 °C (pentane) for the pure (*E*)-isomer[30]
R_f-value	0.78 (LP:EA 4:1, anisaldehyde)

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 – 8.04 (m, 2H, C_6H_5 (*E*/*Z*)), 7.68 (dt, *J* = 12.4, 1.0 Hz, 1H, H1 (*E*)), 7.69 – 7.58 (m, 1H, C_6H_5 (*E*/*Z*)), 7.54 – 7.46 (m, 2H, C_6H_5 (*E*/*Z*)), 7.44 (dt, *J* = 6.2, 0.7 Hz, 1H, H1 (*Z*)), 5.90 (dt, *J* = 12.3, 8.4 Hz, 1H, H2 (*E*)), 5.39 (td, *J* = 8.4, 6.2 Hz, 1H, H2 (*Z*)), 4.21 (dd, *J* = 8.4, 0.8 Hz, 1H, H3 (*Z*)), 4.07 (dd, *J* = 8.4, 1.0 Hz, 1H, H3 (*E*)).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.3, 162.9 (2×**C**=O), 139.6 (C1 (*E*)), 137.7 (C1 (*Z*)), 134.1 (C_6H_5), 134.0 (C_6H_5), 130.3 (C_6H_5), 130.2 (C_6H_5), 128.9 (C_6H_5), 128.8 (C_6H_5), 112.0 (C2 (*E*)), 110.2 (C2 (*Z*)), 28.7 (C3 (*E*)), 23.7 (C3 (Z)).

4.2.3 2,3,4,5-Tetra-*O*-acetyl-D-ribose methyloxime (13)



4 $C_5H_{10}O_5$ MW: 150.13 g/mol

[5] $C_6H_{13}NO_5$ MW: 179.17 g/mol

13 $C_{14}H_{21}NO_9$ MW: 347.32 g/mol

Procedure:

A 100 mL round-bottom flask was charged with D-ribose **4** (2.000 g, 13.3 mmol, 1.0 equiv.) and *O*-methylhydroxylamine hydrochloride (1.356 g, 15.9 mmol, 1.2 equiv.). The flask was flushed with argon, then dry pyridine (30 mL) was added and the solids dissolved immediately. The yellow-brown reaction solution was stirred at room temperature and conversion was controlled *via* TLC ($CHCl_3$:MeOH:H_2O 14:7:1, anisaldehyde). After 2.25 hours the starting material was not visible anymore. A spatula of DMAP and acetic anhydride (7.7 mL, 80.6 mmol, 6.1 equiv.) were added to the reaction mixture and it was stirred at room temperature overnight. TLC on the next morning showed full conversion of the intermediate **[5]** to the fully acetylated compound.

Workup:

The reaction mixture was transferred into a 500 mL separatory funnel. Ethyl acetate (90 mL) was added and the organic layer was repeatedly washed with aqueous $CuSO_4$-solution (5%, 300 mL in total) until the aqueous layer remained light blue. The organic layer was washed with brine (2× 30 mL) and dried over anhydrous Na_2SO_4. It was filtered and the solvent was removed under reduced pressure to give 4.204 g of a brown oil. The crude was not purified. However, ^{1}H-NMR revealed a pure product **13.**

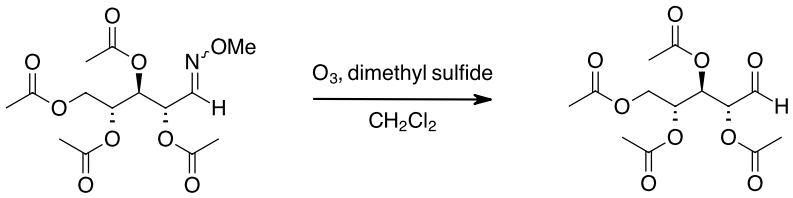
Yield	4.204 g (91%)
Appearance	brown oil
Optical rotation	$[\alpha]_D^{20}$ = +39.7 (*c* 1.0, CH_2Cl_2)
R_f-value	0.36 (LP:EA 2:1, anisaldehyde)
HRMS ($^+$ESI-TOF)	*m/z* $[M+H]^+$ calc. for $C_{14}H_{22}NO_9$ 347.1216, found 347.1228

NMR (mixture of diastereomers ~3:1, major isomer)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 6.9 Hz, 1H, H1), 5.59 (dd, *J* = 6.9, 4.1 Hz, 1H, H2), 5.46 (dd, *J* = 7.2, 4.1 Hz, 1H, H3), 5.17 (ddd, *J* = 7.3, 5.2, 3.0 Hz, 1H, H4), 4.32 (dd, *J* = 12.4, 3.0 Hz, 1H, H5-b), 4.15 (dd, *J* = 12.4, 5.1 Hz, 1H, H5-a), 3.85 (s, 3H, OC**H₃**), 2.09 (s, 6H, 2×COC**H₃**), 2.08, 2.05 (2×s, 2×3H, 2×COC**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.7, 169.7, 169.6, 169.4 (4×**C**=O), 144.0 (C1), 70.1 (C3), 69.7 (C2), 69.2 (C4), 62.3 (O**C**H₃), 61.7 (C5), 21.0, 20.9, 20.8, 20.8 (4×CO**C**H₃).

4.2.4 2,3,4,5-Tetra-*O*-acetyl-D-ribose (6)



13

$C_{14}H_{21}NO_9$
MW: 347.32 g/mol

6

$C_{13}H_{18}O_9$
MW: 318.28 g/mol

Procedure:

2,3,4,5-Tetra-*O*-acetyl-D-ribose methyloxime **13** (1.000 g, 2.88 mmol, 1.0 equiv.) was weighted into a 500 mL three-necked flask and was dissolved in DCM (200 mL). The flask was connected to the ozone generator and a washing bottle containing a freshly prepared aqueous KI-solution (10% w/w). The reaction mixture was cooled down to -80 °C in an acetone/N_2-bath and ozone was bubbled through the stirred solution (flow: 6) which became dark blue. The temperature was held between -80 °C and -50 °C and conversion was controlled *via* TLC (LP:EA 1:1, anisaldehyde). For that, the ozone generator was switched off again and the reaction solution was purged with oxygen and nitrogen for two minutes each. TLC was measured of the colorless reaction solution. After 5.5 hours TLC showed no starting material anymore and DMS (2.33 mL, 31.7 mmol, 11 equiv.) was added. The stirred reaction mixture was allowed to warm up to room temperature overnight.

Workup:

The green reaction solution was transferred into a 1000 mL separatory funnel and washed with a brine-$NaHCO_3$ solution (1:1 v/v, 3× 150 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 893 mg of a white solid. ^{1}H-NMR revealed that even though the TLC during the reaction monitoring suggested complete conversion some starting material was left next to the target compound. The aldehyde **6** had a purity of approximately 85% according to ^{1}H-NMR.

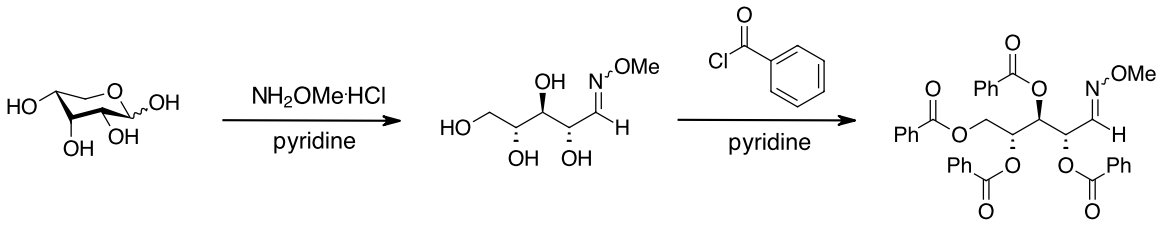
Yield	893 mg crude (97%, 85% purity)
Appearance	white solid
R_f-value	0.39 (LP:EA 1:1, anisaldehyde)

NMR

^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.50 (s, 1H, H1), 5.61 (dd, *J* = 9.0, 2.4 Hz, 1H, H3), 5.45 (d, *J* = 2.4 Hz, 1H, H2), 5.30 (ddd, *J* = 9.0, 4.1, 2.6 Hz, 1H, H4), 4.36 (dd, *J* = 12.6, 2.6 Hz, 1H, H5-a), 4.17 (dd, *J* = 12.6, 4.1 Hz, 1H, H5-b), 2.20, 2.10, 2.07, 2.01 (4×s, 4×3H, 4×COC**H₃**).

^{13}C NMR (151 MHz, $CDCl_3$) δ = 193.0 (C1), 170.7, 169.9, 169.6, 169.2 (4×**C**=O), 76.8 (C2), 68.3 (C3, C4), 61.5 (C5), 20.8 (CO**C**H_3), 20.8 (2×CO**C**H_3), 20.6 (CO**C**H_3).

4.2.5 2,3,4,5-Tetra-*O*-benzoyl-D-ribose methyloxime (14)



4

$C_5H_{10}O_5$
MW: 150.13 g/mol

[5]

$C_6H_{13}NO_5$
MW: 179.17 g/mol

14

$C_{34}H_{29}NO_9$
MW: 595.59 g/mol

Procedure:

A 100 mL round-bottom flask was charged with D-ribose **4** (2.000 g, 13.3 mmol, 1.0 equiv.) and *O*-methylhydroxylamine hydrochloride (1.361 g, 16.0 mmol, 1.2 equiv.). The flask was flushed with argon, then pyridine (30 mL) was added and the solids dissolved immediately. The yellow-brown reaction solution was stirred at room temperature and conversion of the starting material was controlled *via* TLC ($CHCl_3$:MeOH:H_2O 14:7:1, anisaldehyde). After 2 hours TLC showed complete conversion. Benzoyl chloride (9.5 mL, 81.1 mmol, 6.1 equiv.) was added to the solution under ice-bath cooling. A white precipitate formed and the reaction mixture was stirred at room temperature overnight. TLC on the next morning revealed full conversion of the intermediate **[5]**.

Workup:

The reaction mixture was transferred into a 500 mL separatory funnel. Ethyl acetate (120 mL) was added and the organic layer was repeatedly washed with aqueous $CuSO_4$-solution (5%, 220 mL in total) until the aqueous layer remained light blue. The dark green organic layer was washed twice with a brine solution (90 mL in total), dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to give a green oil (10.94 g crude product).

The crude material was purified via flash chromatography (100 g SiO_2, LP:EA 3:1, ~50 mL fractions) to obtain the target compound **14** as clear, very sticky oil (4.618 g) in 97% purity according to ^{1}H-NMR (ethyl acetate residues). Another fraction of 3.043 g still contained impurities and was treated with DMAPA. After a successful try of the procedure with 50 mg of the material, the colorless oil was dissolved in DCM (25 mL) and DMAPA (0.260 mL) was added. The solution was stirred for 30 minutes before it was diluted with DCM and washed thrice with hydrochloric acid (1 M, 3× 25 mL), aqueous saturated bicarbonate solution and then brine. The organic layer was dried with Na_2SO_4, filtered and evaporated to dryness giving the product as a colorless oil (2.277 g) in 92% purity according to ^{1}H-NMR. Traces of solvents and a small amount of the contamination could still be seen in the spectrum.

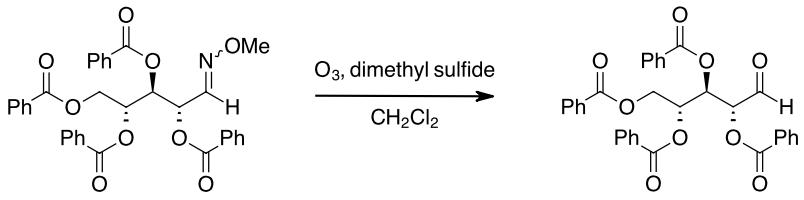
Yield	6.575 g (83%, 92% purity)
Appearance	colorless oil
Optical rotation	$[\alpha]_D^{20}$ = +11.1 (*c* 1.0, CH_2Cl_2)
R_f-value	0.34 (LP:EA 4:1, anisaldehyde)
HRMS ($^+$ESI-TOF)	*m/z* $[M+Na]^+$ calc. for $C_{34}H_{29}NaNO_9$ 595.1840, found 595.1867

NMR (mixture of diastereomers ~2.5:1, major isomer)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 7.95 (m, 8H, 8×PhC**H**), 7.65 – 7.49 (m, 5H, H1, 4×PhC**H**), 7.49 – 7.37 (m, 8H, 8×PhC**H**), 6.18 (dd, *J* = 7.2, 3.9 Hz, 1H, H3), 6.11 (dd, *J* = 6.6, 3.9 Hz, 1H, H2), 5.92 (ddd, *J* = 7.2, 5.5, 3.2 Hz, 1H, H4), 4.90 (dd, *J* = 12.3, 3.3 Hz, 1H, H5-a), 4.57 (dd, *J* = 12.3, 5.5 Hz, 1H, H5-b), 3.78 (s, 3H, OC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 165.3, 165.2, 165.2 (4×**C**=O), 144.1 (C1), 133.8, 133.6, 133.6, 133.3 (4×Ph**C**), 130.1, 130.1, 130.1, 130.1, 130.1, 130.1, 129.9, 129.9, 129.6, 129.4, 129.3, 129.2, 128.8, 128.8, 128.7, 128.7, 128.7, 128.7, 128.5, 128.5 (20×Ph**C**H), 71.4 (C3), 70.9 (C2), 70.0 (C4), 62.8 (C5), 62.3 (O**C**H$_3$).

4.2.6 2,3,4,5-Tetra-*O*-benzoyl-D-ribose (7)



14

$C_{34}H_{29}NO_9$
MW: 595.59 g/mol

7

$C_{33}H_{26}O_9$
MW: 566.55 g/mol

Procedure:

2,3,4,5-Tetra-*O*-benzoyl-D-ribose methyloxime **14** (1.000 g, 1.68 mmol, 1.0 equiv.) was weighted into a 500 mL three-necked flask and was dissolved in DCM (200 mL). The flask was connected to the ozone generator and a washing bottle containing a freshly prepared aqueous KI-solution (10% w/w). The reaction solution was cooled down to -80 °C in an acetone/N_2-bath. Ozone was bubbled through the stirred solution (flow: 8) which became dark blue. The temperature was held between -80 °C and -50 °C and conversion was controlled *via* TLC (LP:EA 3:1, anisaldehyde). For that, the ozone generator was switched off again and the reaction solution was purged with oxygen and nitrogen for two minutes each. TLC was measured of the colorless reaction solution. After 8 hours TLC showed no starting material anymore and DMS (1.4 mL, 18.5 mmol, 11 equiv.) was added. The stirred reaction mixture was allowed to warm up to room temperature overnight.

Workup:

The slightly yellow reaction mixture was transferred into a 1000 mL separatory funnel and extracted with a brine-$NaHCO_3$ solution (1:1 v/v, 150 mL). The turbid organic phase was then washed with brine (4× 50 mL) to break the formed emulsion. Afterwards, it was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 959 mg of a beige solid. ^{1}H-NMR revealed impurities, traces of DMSO and starting material beside the target compound **7** giving a purity of approximately 75%.

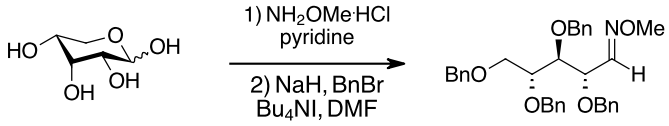
Yield	959 mg crude (101%, 75% purity)
Appearance	beige solid
R_f-value	0.32 (LP:EA 3:1, anisaldehyde)

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.57 (s, 1H, H1), 8.14 – 7.91 (m, 8H, 8×PhC**H**), 7.67 – 7.30 (m, 12H, 12×PhC**H**), 6.30 (dd, *J* = 9.2, 2.3 Hz, 1H, H3), 6.11 (ddd, *J* = 9.2, 4.7, 2.9 Hz, 1H, H4), 5.88 (d, *J* = 2.3 Hz, 1H, H2), 4.91 (dd, *J* = 12.5, 2.8 Hz, 1H, H5-a), 4.52 (dd, *J* = 12.5, 4.7 Hz, 1H, H5-b).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 195.0 (C1), 166.2, 165.7, 165.1, 164.9 (4×**C**=O), 134.1, 134.0, 134.0, 133.4 (4×Ph**C**), 130.3, 130.3, 130.3, 130.1, 130.1, 130.1, 130.1, 130.1, 129.9, 129.9, 129.9, 128.9, 128.9, 128.9, 128.9, 128.9, 128.8, 128.8, 128.6, 128.6 (20×Ph**C**H), 77.6 (C2), 70.7 (C3), 68.9 (C4), 62.7 (C5).

4.2.7 2,3,4,5-Tetra-*O*-benzyl-D-ribose methyloxime (15)



4

$C_5H_{10}O_5$
MW: 150.13 g/mol

15

$C_{34}H_{37}NO_5$
MW: 539.66 g/mol

Procedure:

A 100 mL round-bottom flask was charged with D-ribose **4** (2.002 g, 13.3 mmol, 1.0 equiv.) and *O*-methylhydroxylamine hydrochloride (1.359 g, 15.9 mmol, 1.2 equiv.). The flask was flushed with argon and pyridine (30 mL) was added. The yellow-brown reaction solution was stirred at room temperature for 2.25 hours until TLC ($CHCl_3$:MeOH:H_2O 14:7:1, anisaldehyde) showed complete conversion of the starting material. The reaction mixture was concentrated under reduced pressure to give a brownish oil which was transferred into a 250 mL three-necked round bottom flask and dissolved in dry DMF (66 mL, 0.2 M). The mixture was cooled to 0 °C. NaH (60% in paraffin oil, 5.320 g, 133 mmol, 10 equiv.) was added portionwise to the stirred mixture under continued ice-bath cooling (H_2 formation). The mixture was stirred at 0 °C for 1 hour. Then benzylbromide (12.9 mL, 106 mmol, 8.0 equiv.) was added *via* a dropping funnel. The reaction mixture turned orange and started to foam again. Therefore, the addition was paused for some minutes and continued after the gas formation decreased. After finishing the addition, a solid formed, which dissolved while the mixture was allowed to warm up to room temperature. Then, tetrabutylammonium iodide (1.244 g, 3.3 mmol, 0.2 equiv.) was added. After 2 hours TLC ($CHCl_3$:MeOH:H_2O 14:7:1/LP:EA 2:1, anisaldehyde) indicated full conversion.

Workup:

Excessive reagent was quenched by the addition of ice water (70 mL, formation of H_2). The mixture was diluted with ethyl acetate (70 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (2× 70 mL). The pooled organic phases were washed with water (2× 50 mL) and brine (2× 30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The oily crude material was diluted in acetonitrile (40 mL), washed with *n*-hexane (3× 20 mL) and evaporated again, giving a brown-black oily liquid (14.13 g). The crude material was purified *via* column chromatography (100 g SiO_2, LP:EA 20:1) to give 2.994 g of the target compound **15** as a yellow oil. The ^{1}H-NMR spectrum shows minor impurities, the spectral data of the material is in accordance with literature[45].

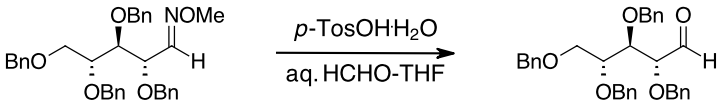
Yield	2.994 g (42%)
Appearance	yellow oil
Optical rotation	$[\alpha]_D^{24}$ = +14.0 (*c* 1.0, $CHCl_3$), Lit: +21.4 (*c* 1.0, $CHCl_3$)[45]
R_f-value	0.58 (LP:EA 4:1, anisaldehyde)
HRMS ($^+$ESI-TOF)	*m/z* $[M+Na]^+$ calc. for $C_{34}H_{37}NaNO_5$ 539.2670, found 539.2691

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 8.1 Hz, 1H, H1), 7.34 – 7.26 (m, 20H, 20×PhC**H**), 4.80 (d, *J* = 11.4 Hz, 1H, PhC**H**H (O3)), 4.69 (d, *J* = 11.4 Hz, 1H, PhC**H**H (O4)), 4.63 (d, *J* = 11.5 Hz, 2H, PhCH**H** (O3)), PhC**H**H (O2)), 4.59 (d, *J* = 11.4 Hz, 1H, PhCH**H** (O4)), 4.49 (bs, 2H, PhC**HH** (O5)), 4.44 (d, *J* = 11.8 Hz, 1H, PhCH**H** (O2)), 4.35 (dd, *J* = 8.1, 4.0 Hz, 1H, H2), 3.97 (dd, *J* = 6.7 Hz, 4.0, 1H, H3), 3.89 (s, 3H, OC**H$_3$**), 3.75 – 3.71 (m, 1H, H4), 3.71 – 3.63 (m, 2H, H5-a, H5-b).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.8 (C1), 138.5, 138.5, 138.5, 138.1 (4×Ph**C**), 128.5, 128.5, 128.5, 128.4, 128.4, 128.4, 128.4, 128.2, 128.2, 128.2, 128.1, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.7, 127.7 (20×Ph**C**H), 79.9 (C3), 78.1 (C4), 77.3 (C2), 74.2 (Ph**C**H$_2$ (O3)), 73.5 (Ph**C**H$_2$ (O5)), 72.7 (Ph**C**H$_2$ (O4)), 71.1 (Ph**C**H$_2$ (O2)), 69.6 (C5), 61.9 (O**C**H$_3$).

4.2.8 2,3,4,5-Tetra-*O*-benzyl-D-ribose (8)



15

$C_{34}H_{37}NO_5$
MW: 539.66 g/mol

8

$C_{33}H_{34}O_5$
MW: 510.63 g/mol

Procedure:

To a stirred solution of 2,3,4,5-tetra-*O*-benzyl-D-ribose methyloxime **15** (250 mg, 0.46 mmol, 1.0 equiv.) in a mixture of THF and 36-38% formaldehyde (2.5:1, 4.6 mL, 0.1 M) at room temperature was added *p*-toluenesulfonic acid monohydrate (90 mg, 0.46 mmol, 1 equiv.). The mixture was stirred overnight and TLC (PE:EA 4:1, anisaldehyde) on the next morning revealed that some starting material was left. Additional *p*-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol, 0.1 equiv.) was added and the reaction was stirred for another 4.25 hours when TLC showed complete conversion of the starting material.

Workup:

The reaction was quenched with saturated aqueous $NaHCO_3$-solution (20 mL) and transferred into a separatory funnel. It was extracted with ethyl acetate (3× 20 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified *via* column chromatography (19 g SiO_2, hexane:EA 10:1 to 100% EA) giving 215 mg of the target compound **8** as a yellow oil. The ^{1}H-NMR spectrum revealed some minor impurities, the spectral data of the material is in accordance with the literature[45].

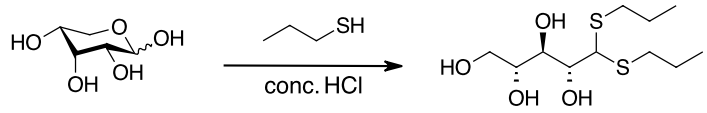
Yield	215 mg (91%)
Appearance	yellow oil
Optical rotation	$[\alpha]_D^{27}$ = +13.8 (*c* 1.0, $CHCl_3$), Lit: +13.0 (*c* 1.0, $CHCl_3$)[45]
R_f-value	0.52 (LP:EA 4:1, anisaldehyde)
HRMS ($^+$ESI-TOF)	*m/z* $[M+H]^+$ calc. for $C_{33}H_{35}O_5$ 510.2405, found 510.2421

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.48 (d, *J* = 0.9 Hz, 1H, H1), 7.35 – 7.16 (m, 18H, 18×PhC**H**), 7.23 – 7.19 (m, 2H, 2×PhC**H**), 4.75 – 4.66 (m, 4H, 2×PhC**H$_2$**), 4.58 (d, *J* = 11.5 Hz, 2H, PhC**H$_2$**), 4.51 – 4.44 (m, 4H, 2×PhC**H$_2$**), 4.11 – 4.08 (m, 1H, H2), 4.00 (dd, *J* = 8.6 Hz, 2.3, 1H, H3), 3.89 (ddd, *J* = 9.0 Hz, 4.4, 2.2, 1H, H4), 3.69 (dd, *J* = 10.6 Hz, 2.5, 1H, H5-a), 3.60 (dd, *J* = 10.6 Hz, 4.5, 1H, H5-b).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.3 (C1), 138.4, 138.2, 137.8, 137.6 (4×Ph**C**), 128.6, 128.6, 128.5, 128.5, 128.5, 128.5, 128.4, 128.4, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.7 (20×Ph**C**H), 82.6 (C2), 80.7 (C3), 76.9 (C4), 73.5, 73.3, 73.0, 72.8 (4×Ph**C**H$_2$), 69.3 (C5).

4.2.9 D-Ribosedi(propylthio)acetal (10)



4

$C_5H_{10}O_5$
MW: 150.13 g/mol

10

$C_{11}H_{24}O_4S_2$
MW: 284.44 g/mol

Procedure:

D-Ribose **4** (8.004 g, 53.3 mmol, 1.0 equiv.) was suspended in conc. HCl (8 mL) while being cooled to 0 °C with an ice-bath. 1-propanethiol (11.1 mL, 117 mmol, 2.2 equiv.) was added to the solution. The reaction mixture was vigorously stirred at room temperature for 1.5 hours. Then, water (64 mL) was added and the stirring of the solution was continued for 1 hour. Afterwards, 3 M NaOH (40 mL) was added at 0 °C. The solution was stirred at that temperature for 30 minutes which lead to the whole flask being filled with a white solid.

Workup:

The reaction mixture was transferred into a suction filter. The filter cake was washed with hexane (3× 40 mL) and water (4× 40 mL) and dried under reduced pressure. The wettish solid was then transferred into a desiccator. It was dried for 5 days to give 9.721 g of the target compound **10** as a white solid. The material was pure according to ^{1}H-NMR and with spectral data in consistence with the literature[47].

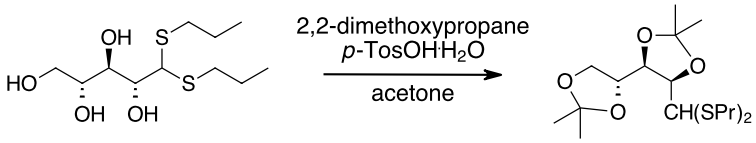
Yield	9.721 g (64%)
Appearance	white solid
Melting point	83.5-84 °C (water), Lit: 82 °C[47]
Optical rotation	$[\alpha]_D^{20}$ = -7.3 (*c* 1.0, CH_2Cl_2) , Lit: -11.7° (*c* 0.05, CH_2Cl_2)[47]
R_f-value	0.65 ($CHCl_3$:MeOH:H_2O 14:7:1, anisaldehyde)
HRMS ($^+$ESI-TOF)	*m/z* $[M+Na]^+$ calc. for $C_{11}H_{24}NaO_4S_2$ 284.1116, found 284.1132

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.19 (d, *J* = 3.5 Hz, 1H, H1), 3.99 – 3.89 (m, 2H, H3, H4), 3.89 – 3.82 (m, 3H, H2, H5), 2.78 – 2.56 (m, 4H, C**H₂**CH_2CH_3), 1.72 – 1.56 (m, 4H, CH_2C**H₂**CH_3), 1.01 (td, *J* = 7.3, 1.2 Hz, 6H, CH_2CH_2C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 74.6 (C2), 73.2 (C4), 72.8 (C3), 63.5 (C5), 55.7 (C1), 34.0, 33.7 (2×**C**$H_2CH_2CH_3$), 23.1, 22.9 (2×CH_2**C**H_2CH_3), 13.7, 13.7 (2×CH_2CH_2**C**H_3).

4.2.10 2,3:4,5-Bis-*O*-(isopropylidene)-D-ribosedi(propylthio)acetal (19)



10 **19**

$C_{11}H_{24}O_4S_2$
MW: 284.44 g/mol

$C_{17}H_{32}O_4S_2$
MW: 364.57 g/mol

Procedure:

A solution of D-ribosedi(propylthio)acetal **10** (1.501 g, 5.27 mmol, 1.0 equiv.), 2,2-dimethoxypropane (13 mL, 103 mmol, 19.5 equiv.) and *p*-TosOH·H_2O (100 mg, 0.53 mmol, 0.1 equiv.) in acetone (35 mL) was stirred for 2.5 hours at ambient temperature until TLC (hexane:MTBE 10:1, anisaldehyde) revealed complete conversion.

Workup:

The turbid solution was diluted with aqueous Na_2CO_3-solution (5%, 20 mL) resulting in a clear solution. It was transferred into a separatory funnel and extracted with DCM (3× 20 mL, 1× 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to give 2.02 g crude material which contained residues of 2,2-dimethoxypropane. The crude material was purified by column chromatography (120 g SiO_2, hexane:MTBE 10:1) to yield the title compound **19** as a colorless oil (1.581 g). The material contains minor impurities according to ^{1}H-NMR and spectral data is in consistence with the literature[47].

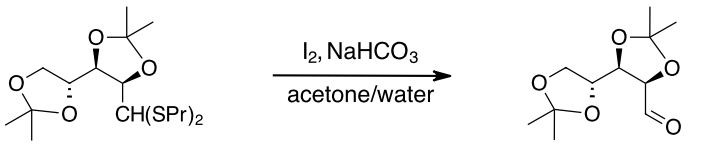
Yield	1.581 g (82%)
Appearance	colorless oil
Optical rotation	$[\alpha]_D^{20}$ = -85.3 (*c* 1.0, CH_2Cl_2), Lit: -93.1° (*c* 0.07, CH_2Cl_2)[47]
R_f-value	0.37 (hexane:MTBE 10:1, anisaldehyde)
HRMS ($^+$ESI-TOF)	*m/z* $[M+H]^+$ calc. for $C_{17}H_{33}O_4S_2$ 364.1742, found 364.1756

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.62 (dt, *J* = 9.2, 5.9 Hz, 1H, H4), 4.53 (dd, *J* = 6.4, 4.2 Hz, 1H, H2), 4.24 (d, *J* = 4.2 Hz, 1H, H1), 4.14 (dd, *J* = 8.7, 6.2 Hz, 1H, H5-a), 4.09 (dd, *J* = 9.3, 6.5 Hz, 1H, H3), 3.91 (dd, *J* = 8.6, 5.7 Hz, 1H, H5-b), 2.82 – 2.56 (m, 4H, 2×C**H₂**CH_2CH_3), 1.74 – 1.57 (m, 4H, 2×CH_2C**H₂**CH_3), 1.49, 1.41 (2×s, 2×3H, 2×C**H₃**), 1.34 (s, 6H, 2×C**H₃**), 1.00 (td, *J* = 7.3, 3.7 Hz, 6H, 2×CH_2CH_2C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 110.0, 109.4 (2×C quart.), 81.6 (C2), 79.3 (C3), 73.5 (C4), 68.6 (C5), 51.2 (C1), 33.6, 33.0 (2×**C**$H_2CH_2CH_3$), 27.1, 26.9, 25.7, 25.0 (4×**C**H_3), 23.0, 22.7 (2×CH_2**C**H_2CH_3), 14.1, 14.0 (2×CH_2CH_2**C**H_3).

4.2.11 2,3:4,5-Bis-*O*-(isopropylidene)-D-ribose (11)



19 **11**

$C_{17}H_{32}O_4S_2$ $C_{11}H_{18}O_5$
MW: 364.57 g/mol MW: 230.26 g/mol

Procedure:

2,3:4,5-Bis-*O*-(isopropylidene)-D-ribosedi(propylthio)acetal **19** (200 mg, 0.55 mmol, 1.0 equiv.) was dissolved in a mixture of acetone/water (5 mL/0.5 mL). The solution was cooled in an ice-bath and $NaHCO_3$ (210 mg, 2.47 mmol, 4.5 equiv.) and iodine (280 mg, 1.10 mmol, 2.0 equiv.) were added. The resulting dark brown reaction mixture was stirred at room temperature. After two hours additional $NaHCO_3$ (47 mg, 0.55 mmol, 1.0 equiv.) and iodine (139 mg, 0.55 mmol, 1.0 equiv.) were added. Then, the mixture was stirred for another two hours. TLC (LP:EA 3:1, anisaldehyde) showed full conversion of the starting material.

Workup:

The reaction mixture was treated with $Na_2S_2O_3$-solution (20%, 60 mL) which immediately led to a decoloration of the dark brown solution. It was transferred into a separatory funnel and the aqueous phase was extracted with ethyl acetate (3× 30 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to give a yellow liquid. ^{1}H-NMR measurement revealed the formation of two different aldehyde species and leftovers of the thioacetal protecting group, so the crude was purified *via* column chromatography (10 g SiO_2, LP:EA 4:1 + 0.1% triethylamine) yielding 76 mg of the target compound **11** as a clear, colorless liquid in a purity of about 95% according to ^{1}H-NMR and with spectral data in consistence with the literature[47].

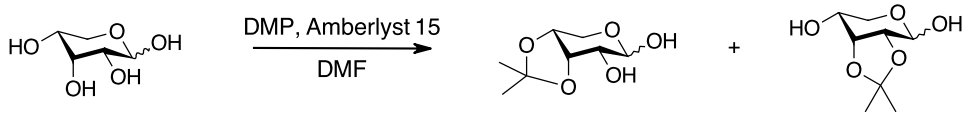
Yield	76 mg (60%)
Appearance	clear, colorless liquid
Optical rotation	$[\alpha]_D^{20}$ = -1.7 (*c* 0.3, CH_2Cl_2), $[\alpha]_D^{20}$ = -5.8° (0.4 g/L, CH_2Cl_2)[47]
R_f-value	0.40 (LP:EA 4:1, anisaldehyde)

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.73 (d, *J* = 1.9 Hz, 1H, H1), 4.61 (dd, *J* = 6.8, 1.9 Hz, 1H, H2), 4.31 (dd, *J* = 8.6, 6.8 Hz, 1H, H3), 4.16 – 4.06 (m, 2H, H4, H5), 3.96 – 3.86 (m, 1H, H5), 1.54, 1.41, 1.38, 1.31 (4×s, 4×3H, 4×C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.8 (C1), 111.4 (C quart. (O2, O3)), 110.3 (C quart. (O4, O5)), 81.9 (C2), 78.9 (C3), 73.7 (C4), 67.7 (C5), 27.5, 26.9, 25.6, 25.3 (4×**C**H_3).

4.2.12 3,4-*O*-isopropylidene-D-ribose (9) and 2,3-*O*-isopropylidene-D-ribose (16)



4

$C_5H_{10}O_5$
MW: 150.13 g/mol

9

$C_8H_{14}O_5$
MW: 190.19 g/mol

16

$C_8H_{14}O_5$
MW: 190.19 g/mol

Procedure:

To a solution of D-ribose **4** (1.500 g, 9.99 mmol, 1.0 equiv.) in DMF (25 mL) was added 2,2-dimethoxy propane (2.52 mL, 20.0 mmol, 2.0 equiv.). The reaction was initiated by addition of Amberlyst 15(H) ion exchange resin (160 mg, 0.5 mmol, 0.05 equiv.) and the reaction mixture was stirred at room temperature overnight. At the next morning TLC (CMW 7:3:0.5, anisaldehyde) only revealed partial conversion of the starting material and the reaction mixture was therefore stirred for another night.

Workup:

After 48 hours of reaction time still no full conversion of the starting material could be observed. So, the reaction was stopped by filtration and the solvent and excess of reagent were removed by evaporation using the high vacuum pump (4 mbar, 55 °C water bath temperature) to give 2.2 g of crude material. It was purified *via* column chromatography (140 g SiO_2, LP:EA 1:2 to 100% EA) which provided after evaporation of the solvents:

- 552 mg of **9** as white needles after coevaporation from ethyl acetate
- 879 mg of **16** as a colorless oil

The ^{1}H-NMR spectrum of **9** contains some minor impurities while the spectrum of **16** shows traces of ethyl acetate. Spectral data for both compounds is in accordance with the literature[46].

3,4-*O*-isopropylidene-D-ribose (9)

Yield	552 mg (29%)
Appearance	white needles
Melting point	113-115 °C (LP:EA), 116-119 °C for the L-isomer[46]
Optical rotation	$[\alpha]_D^{24}$ = -55.8 (*c* 1.0, CH_3OH), Lit: $[\alpha]_D^{24}$ = +61.4 (*c* 0.97, CH_3OH) for the L-isomer[46]
R_f-value	0.22 (LP:EA 1:10, anisaldehyde)

NMR

^{1}H NMR (400 MHz, MeOD) 4.88 (d, *J* = 6.9 Hz, 1H, H1), 4.51 (dd, *J* = 6.9, 3.3 Hz, 1H, H3), 4.28 (ddd, *J* = 6.9, 3.4, 3.4 Hz, 1H, H4), 3.79 (dd, *J* = 12.7, 3.4 Hz, 1H, H5-a), 3.57 (dd, *J* = 6.9, 3.3 Hz, 1H, H2), 3.52 (dd, *J* = 12.7, 3.5 Hz, 1H, H5-b), 1.47, 1.34 (2×s, 2×3H, 2×C**H**$_3$).

^{13}C NMR (101 MHz, MeOD) δ = 110.8 (C quart.), 95.4 (C1), 76.2 (C3), 75.0 (C4), 70.9 (C2), 63.9 (C5), 27.1, 25.4 (2×**C**H_3).

2,3-*O*-isopropylidene-D-ribose (16)

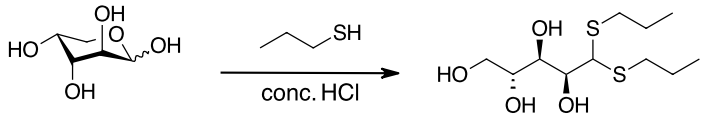
Yield	879 mg (46%)
Appearance	colorless oil
Optical rotation	$[\alpha]_D^{24}$ = -23.9 (*c* 1.0, $CHCl_3$), Lit: $[\alpha]_D^{24}$ = +21.3 (*c* 1.02, $CHCl_3$) for the L-isomer[46]
R_f-value	0.51 (LP:EA 1:4, anisaldehyde)

NMR

^{1}H NMR (400 MHz, MeOD) δ = 5.26 (s, 1H, H1), 4.77 (dd, *J* = 5.9 Hz, 1.0, 1H, H3), 4.52 (d, *J* = 5.9 Hz, 1H, H2), 4.19 (ddd, *J* = 5.5, 4.3, 1.0 Hz, 1H, H4), 3.66 – 3.56 (m, 2H, H5), 1.44, 1.31 (2×s, 2×3H, 2×C**H₃**).

^{13}C NMR (101 MHz, MeOD) δ = 113.2 (C quart.), 104.0 (C1), 88.6 (C4), 87.9 (C2), 83.4 (C3), 64.3 (C5), 26.7, 25.0 (2×**C**H_3).

4.2.13 D-Arabinosedi(propylthio)acetal (17)



17

$C_5H_{10}O_5$
MW: 150.13 g/mol

18

$C_{11}H_{24}O_4S_2$
MW: 284.44 g/mol

Procedure:

D-Arabinose **17** (2.018 g, 13.2 mmol, 1.0 equiv.) was suspended in conc. HCl (2 mL) while being cooled to 0 °C with an ice-bath. 1-propanethiol (2.8 mL, 30.0 mmol, 2.2 equiv.) was added to the stirred solution in one portion. The reaction mixture was vigorously stirred until formation of a white solid. Additional conc. HCl (2 mL) was added, then the precipitate was suspended in water (16 mL) and the mixture was stirred for 30 more minutes. Afterwards, 3 M NaOH (20 mL) was added at 0 °C.

Workup:

The reaction mixture was transferred into a suction filter. The filter cake was washed with hexane (3× 20 mL) and water (3× 20 mL). The wettish solid was dried under high vacuum for two hours and stored in the desiccator overnight. 3.456 g of target compound **18** were obtained as a white solid which only contained minor impurities according to ^{1}H-NMR.

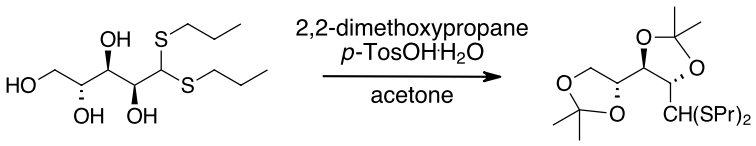
Yield	3.456 g (92%)
Appearance	white solid
Melting point	130-132 °C (water), Lit: 131-131.5 °C[56]
Optical rotation	$[\alpha]_D^{25}$ = -13.7 (*c* 0.5, CH_3OH), Lit: $[\alpha]_D^{25}$ = -12.57 (*c* 2.93, CH_3OH)[56]
R_f-value	0.73 (CMW 7:3:0.5, anisaldehyde)
HRMS ($^+$ESI-TOF)	*m/z* $[M+Na]^+$ calc. for $C_{11}H_{24}NaO_4S_2$ 284.1116, found 284.1130

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.04 (dd, *J* = 6.7, 1.3 Hz, 1H, H3), 4.03 (d, *J* = 9.2 Hz, 1H, H1), 3.87 – 3.78 (m, 3H, H4, H5-a, H5-b), 3.76 (dd, *J* = 9.2, 1.2 Hz, 1H, H2), 2.79 – 2.56 (m, 4H, 2×C**H$_2$**CH_2CH_3), 1.74 – 1.57 (m, 4H, 2×CH_2C**H$_2$**CH_3), 1.01 (td, *J* = 7.3, 4.0 Hz, 6H, 2×CH_2CH_2C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 73.1 (C4), 70.7 (C3), 70.7 (C2), 64.3 (C5), 56.4 (C1), 33.9, 31.4 (2×**C**$H_2CH_2CH_3$), 23.1, 22.8 (2×CH_2**C**H_2CH_3), 13.8, 13.7 (2×CH_2CH_2**C**H_3).

4.2.14 2,3:4,5-Bis-*O*-(isopropylidene)-D-arabinosedi(propylthio)acetal (20)



18

$C_{11}H_{24}O_4S_2$
MW: 284.44 g/mol

20

$C_{17}H_{32}O_4S_2$
MW: 364.57 g/mol

Procedure:

D-Arabinosedi(propylthio)acetal **18** (1.004 g, 3.53 mmol, 1.0 equiv.) and *p*-TosOH·H_2O (79 mg, 0.41 mmol, 0.12 equiv.) were dissolved in acetone (25 mL). 2,2-dimethoxypropane (9 mL, 71.0 mmol, 20.0 equiv.) was added and the mixture was stirred for 3 hours at ambient temperature until TLC (hexane:MTBE 10:1, anisaldehyde) revealed complete conversion.

Workup:

The turbid solution was diluted with aqueous Na_2CO_3-solution (5%, 25 mL). It was transferred into a separatory funnel and extracted with DCM (3× 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to give 1.21 g crude material which contained residues of 2,2-dimethoxypropane. The crude material was purified by column chromatography (90 g SiO_2, hexane:MTBE 10:1) to yield the title compound **20** as a clear oil (1.018 g). The material was pure according to ^{1}H-NMR and with spectral data in consistence with the literature[56].

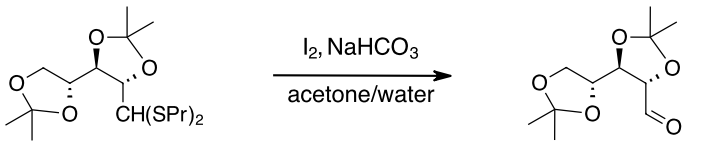
Yield	1.018 g (79%)
Appearance	clear, colorless liquid
Optical rotation	$[\alpha]_D^{25}$ = +84.8 (*c* 1.0, CH_3OH), Lit: $[\alpha]_D^{25}$ = +81.49 (*c* 1.0, CH_3OH)[56]
R_f-value	0.54 (LP:MTBE 8:1, anisaldehyde)
HRMS ($^+$ESI-TOF)	*m/z* $[M+Na]^+$ calc. for $C_{17}H_{32}NaO_4S_2$ 364.1742, found 364.1758

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.29 (dt, *J* = 4.8, 2.7 Hz, 1H, H2), 4.17 – 4.11 (m, 1H, H5-a), 4.10 – 4.05 (m, 2H, H3, H4), 4.01 (d, *J* = 2.8 Hz, 1H, H1), 3.98 – 3.93 (m, 1H, H5-b), 2.79 – 2.59 (m, 4H, 2×C**H$_2$**CH_2CH_3), 1.64 (dp, *J* = 14.3, 7.3 Hz, 4H, 2×CH_2C**H$_2$**CH_3), 1.45, 1.41, 1.38, 1.34 (4×s, 4×3H, 4×C**H$_3$**), 1.01 (td, *J* = 7.3, 5.4 Hz, 6H, 2×CH_2CH_2C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 110.4, 109.8 (2×C quart.), 84.5 (C2), 79.3 (C3), 77.3 (C4), 67.9 (C5), 53.1 (C1), 33.4, 33.1 (2×**C**$H_2CH_2CH_3$), 27.5, 27.2, 26.7, 25.4 (4×**C**H_3), 22.9, 22.8 (2×CH_2**C**H_2CH_3), 13.8, 13.8 (2×CH_2CH_2**C**H_3).

4.2.15 2,3:4,5-Bis-*O*-(isopropylidene)-D-arabinose (21)



20 **21**

$C_{17}H_{32}O_4S_2$ $C_{11}H_{18}O_5$
MW: 364.57 g/mol MW: 230.26 g/mol

Procedure:

2,3:4,5-Bis-*O*-(isopropylidene)-D-ribosedi(propylthio)acetal **20** (803 mg, 2.20 mmol, 1.0 equiv.) was dissolved in a mixture of acetone/water (20 mL/2 mL). The solution was cooled in an ice-bath and $NaHCO_3$ (850 mg, 10.0 mmol, 4.5 equiv.) and iodine (1.117 g, 4.40 mmol, 2.0 equiv.) were added. The resulting dark brown reaction mixture was stirred at room temperature. After two hours additional $NaHCO_3$ (201 mg, 2.37 mmol, 1.1 equiv.) and iodine (563 mg, 2.22 mmol, 1.0 equiv.) were added. Then, the mixture was stirred for another five hours. TLC (LP:EA 3:1, anisaldehyde) showed full conversion of the starting material.

Workup:

The reaction mixture was treated with $Na_2S_2O_3$-solution (20%, 20 mL) which immediately led to a decoloration of the dark brown solution. It was transferred into a separatory funnel and the aqueous phase was extracted with ethyl acetate (5× 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to give an orange oil. ^{1}H-NMR measurement showed that the material was contaminated with the cleaved thiole, so the crude was purified *via* column chromatography (58 g SiO_2, LP:EA 4:1 + 0.1% triethylamine) yielding 413 mg of the target compound **21** as a clear, colorless oil, which was pure according to ^{1}H-NMR.

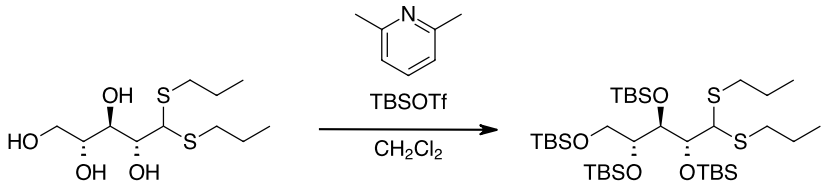
Yield	413 mg (82%)
Appearance	clear, colorless oil
Optical rotation	$[\alpha]_D^{25}$ = -8.7 (*c* 2.0, $CHCl_3$), Lit: $[\alpha]_D^{25}$ = -15.0 (*c* 2.0, $CHCl_3$)[57]
R_f-value	0.58 (LP:EA 1:2, anisaldehyde)

NMR

^{1}H NMR (400 MHz, CDCl3) δ = 9.76 (d, *J* = 1.0 Hz, 1H, H1), 4.41 (dd, *J* = 6.1 Hz, 1.0, 1H, H2), 4.20 – 4.11 (m, 2H, H4, H5-a), 4.07 (td, *J* = 6.1, 1.3 Hz, 1H, H3), 4.02 – 3.93 (m, 1H, H5-b), 1.48, 1.42, 1.38, 1.35 (4×s, 4×3H, 4×C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.0 (C1), 112.0, 110.2 (2×C quart.), 83.4 (C2), 77.9 (C3), 76.6 (C4), 67.1 (C5), 27.1, 26.8, 26.4, 25.2 (4×**C**H_3).

4.2.16 2,3,4,5-Tetra-*O*-(*tert*-butyldimethylsilyl)-D-ribosedi(propylthio)acetal (22)



10

$C_{11}H_{24}O_4S_2$
MW: 284.44 g/mol

22

$C_{35}H_{80}O_4S_2Si_4$
MW: 741.49 g/mol

Procedure:

D-Ribosedi(propylthio)acetal **10** (1.499 g, 5.27 mmol, 1.0 equiv.) was suspended in dry DCM (12 mL) and cooled to 0 °C with an ice-bath. 2,6-lutidine (3.1 mL, 26.3 mmol, 5.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.5 mL, 23.7 mmol, 4.4 equiv.) were added dropwise over the course of 10 minutes. The clear solution was stirred for 30 minutes at 0 °C and then for 3 hours at room temperature.

Workup:

After TLC (LP:EA 3:1/ 100% hexane, anisaldehyde) revealed complete conversion, the salmon-colored reaction solution was diluted with water (40 mL) and the product was extracted with DCM (3× 30 mL). The organic layer was washed with aqueous $CuSO_4$-solution (5%; 200 mL in total) to remove excess 2,6-lutidine. It was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a yellow-brown liquid which solidified upon standing. The crude material was purified by column chromatography (150 g SiO_2, 100% hexane, then hexane:EA 10:1). Evaporation of the eluent yielded the title compound **22** as a white solid. The material was pure according to ^{1}H-NMR and with spectral data in consistence with the literature[50].

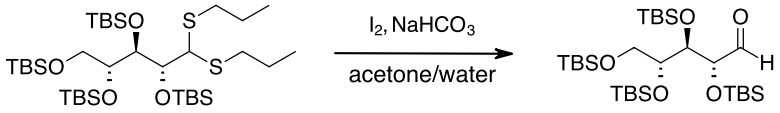
Yield	3.535 g (91%)
Appearance	white solid
Melting point	76-77 °C (hexane:EA)
Optical rotation	$[\alpha]_D^{20}$ = +11.5 (*c* 1.0, CH_2Cl_2)
R_f-value	0.27 (100% hexane, anisaldehyde)

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.19 (ddd, *J* = 7.4 Hz, 4.0, 1.1, 1H, H4), 4.10 (d, *J* = 1.4 Hz, 1H, H1), 4.07 (dd, *J* = 8.5, 1.1 Hz, 1H, H3), 3.89 (dd, *J* = 8.5, 1.4 Hz, 1H, H2), 3.69 (dd, *J* = 10.5, 3.9 Hz, 1H, H5-a), 3.58 (dd, *J* = 10.5, 7.5 Hz, 1H, H5-b), 2.79 – 2.67 (m, 1H, C**H**HCH$_2$CH$_3$), 2.65 – 2.53 (m, 1H, CH**H**CH$_2$CH$_3$), 2.54 – 2.42 (m, 2H, C**H$_2$**CH$_2$CH$_3$), 1.67 – 1.55 (m, 4H, 2×CH$_2$C**H$_2$**CH$_3$), 1.02 – 0.95 (m, 6H, 2×CH$_2$CH$_2$C**H$_3$**), 0.94 0.92, 0.90, 0.89 (4×s, 4×9H, 4×Si-C(C**H$_3$**)$_3$), 0.27, 0.21, 0.17, 0.14, 0.12, 0.10, 0.05 (8×s, 8×3H, 8×Si(C**H$_3$**)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 78.4 (C3), 77.9 (C2), 73.8 (C4), 64.2 (C5), 57.2 (C1), 35.2, 33.8 (2×**C**$H_2CH_2CH_3$), 26.6, 26.5, 26.4, 26.3 (12×Si-C(**C**$H_3)_3$), 23.4, 23.0 (2×CH_2**C**H_2CH_3), 18.9, 18.7, 18.6, 18.5 (4×C quart.), 14.0, 13.8 (2×CH_2CH_2**C**H_3), -2.8, -3.3, -3.4, -4.1, -4.2, -5.1, -5.2 (8×Si(**C**$H_3)_2$).

4.2.17 2,3,4,5-Tetra-*O*-(*tert*-butyldimethylsilyl)-D-ribose (12)



22

$C_{35}H_{80}O_4S_2Si_4$
MW: 741.49 g/mol

12

$C_{29}H_{66}O_5Si_4$
MW: 607.18 g/mol

Procedure:

2,3,4,5-Tetra-*O*-(*tert*-butyldimethylsilyl)-D-ribosedi(propylthio)acetal (200 mg, 0.27 mmol, 1.0 equiv.) was dissolved in a mixture of acetone/water (9.0 mL/0.9 mL). The reaction mixture was cooled in an ice-bath and $NaHCO_3$ (105 mg, 1.21 mmol, 4.5 equiv.) and iodine (138 mg, 0.54 mmol, 2.0 equiv.) were added. The resulting dark brown reaction mixture was stirred at room temperature overnight. TLC (100% hexane, anisaldehyde) on the next morning revealed only partial conversion. A second portion of $NaHCO_3$ (23 mg, 0.27 mmol, 1.0 equiv.) and iodine (70 mg, 0.27 mmol, 1.0 equiv.) was added and the mixture was stirred at ambient temperature for additional 4.5 hours when TLC showed complete conversion of the starting material.

Workup:

The reaction mixture was treated with $Na_2S_2O_3$-solution (20%, 60 mL) which immediately led to a decoloration of the dark brown solution. It was transferred into a separatory funnel and the aqueous phase was extracted with ethyl acetate (3× 30 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum to give a yellow liquid. The crude was purified *via* column chromatography (30 g SiO_2, 100% hexane to hexane:EA 10:1). Since TLC showed two spots for the first five product fractions, they were evaporated separately giving 80 mg of a clear oil which was a mixture of product and traces of the cleaved mercaptan (~80% purity according to ^{1}H-NMR). The eluent was then changed to hexane:EA 10:1 and the following fractions were combined and concentrated under reduced pressure to give 94 mg of a clear oily liquid which solidified in the fridge. The product **12** was pure according to ^{1}H-NMR and with spectral data in consistence with the literature[50].

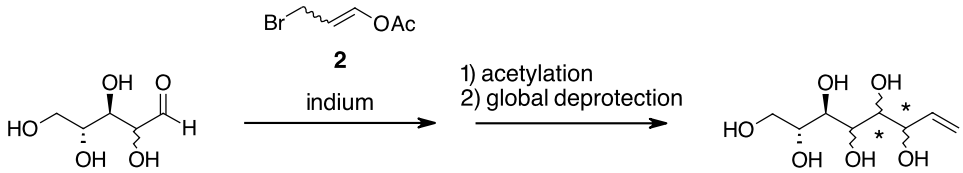
Yield	94 mg (57%)
Appearance	white solid
Melting point	48-51 °C (hexane:EA)
Optical rotation	$[\alpha]_D^{20}$ = -17.0 (*c* 1.0, CH_2Cl_2)
R_f-value	0.33 (hexane:EA 40:1, anisaldehyde)

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.64 (d, *J* = 1.6 Hz, 1H, H1), 4.31 (dd, *J* = 3.4 Hz, 1.7, 1H, H2), 4.04 – 3.98 (m, 1H, H3), 3.90 – 3.83 (m, 1H, H4), 3.71 (dd, *J* = 10.4, 5.4 Hz, 1H, H5-a), 3.56 (dd, *J* = 10.4, 5.6 Hz, 1H, H5-b), 0.91, 0.90, 0.89, 0.86 (4×s, 4×9H, 4×Si-C(C**H**$_3$)$_3$), 0.12 – 0.04 (m, 24H, 8×Si(C**H**$_3$)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 202.3 (C1), 78.1 (C2), 77.8 (C3), 75.4 (C4), 64.8 (C5), 26.2, 26.1, 26.1, 26.0 (12×Si-C(**C**H_3)$_3$), 18.5, 18.5, 18.3, 18.3 (4×C quart.), -4.1, -4.3, -4.4, -4.8, -5.1, -5.2 (8×Si(**C**H_3)$_2$).

4.2.18 General procedure for the IMA of unprotected aldoses



4 (2R), **17** (2S)

$C_5H_{10}O_5$
MW: 150.13 g/mol

33 (5S), **34** (5R)

$C_8H_{16}O_6$
MW: 208.21 g/mol

IMA:

D-Ribose **4**/ D-arabinose **17** (60 mg, 0.4 mmol, 1.0 equiv.) was weighted into a 10 mL round-bottom flask and absolute ethanol (2 mL) was added. The reaction mixture was heated to 45 °C and it was waited until the sugar was completely dissolved. Then, 3-bromo-1-propenyl acetate **2** (218 mg, 1.2 mmol, 3.0 equiv.) and in immediate succession indium (91 mg, 0.8 mmol, 2.0 equiv.) was added to the vigorously stirred reaction mixture. TLC (CMW 14:7:1, anisaldehyde) after 10 minutes showed product formation (violet, more apolar spot on TLC), however also a shadow of the starting material remained visible. After 20 minutes the reaction mixture was filtered over a filter paper when still warm and the solvent was evaporated to give a white residue.

Acetylation:

It was dissolved in pyridine (1.5 mL) and acetic anhydride (580 µL, 6.0 mmol, 15 equiv.) was added under ice-bath cooling leading to the formation of some white solid. Afterwards, a small amount of DMAP was added to the milky solution which became clear. The yellow reaction mixture was stirred until TLC showed full conversion of the reaction intermediate (violet spot) to a very apolar species. MeOH (1.5 mL) was added under ice-bath cooling to quench the reagent and the reaction mixture was stirred for a couple of more minutes. It was diluted with ethyl acetate (20 mL), extracted with water (20 mL), 1 N HCl (2× 10 mL, pH ~1), saturated $NaHCO_3$ solution (2× 10 mL, pH basic) and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a clear yellow oil.

Global deprotection:

The residue was taken up in MeOH (2 mL) and treated with NaOMe (30% in MeOH, 15 drops) until pH ~11. The mixture was stirred at room temperature until TLC indicated complete deacetylation. The reaction mixture was neutralized by the addition of Dowex-H^+ (MeOH washed). The solution was filtered and the methanol was evaporated to give a clear, yellow oil. ^{1}H-NMR was measured to evaluate the ratio of the formed isomers **33** derived from D-ribose and **34** derived from D-arabinose.

Appearance	yellowish oil
R_f-value	0.31 (CMW 7:3:0.5, anisaldehyde; violet spot)

NMR: D-ribose as starting material

^{1}H-NMR revealed the formation of three isomers: **A** with *lyxo* configuration (*syn/anti*), **B** with *xylo* configuration (*syn/syn*) and **C** with *ribo* configuration (*anti/anti*). The ratio of the main isomers is 1.6:1 **A**:**B**. The following NMR code contains the respective letter if a clear assignment of a signal to one of the three isomers was possible.

^{1}H NMR (400 MHz, D_2O) δ = 6.01 (ddd, *J* = 17.3, 10.5, 6.9 Hz, 1H, H2 (**A**)), 5.88 (ddd, *J* = 17.5, 10.5, 7.4 Hz, 1H, H2 (**B**)), 5.45 – 5.30 (m, 2H, H1-a, H1-b), 4.39 (m, 1H, H3 (**C**)), 4.23 (t, *J* = 7.6 Hz, 1H, H3 (**B**)), 4.22 – 4.14 (t, *J* = 7.1 Hz, 1H, H3 (**A**)), 3.98 – 3.87 (m, 2H, H5, H7), 3.87 – 3.79 (m, 2H, H6, H8-a), 3.79 – 3.63 (m, 2H, H4, H8-b).

For the main isomer:

^{13}C NMR (101 MHz, D_2O) δ = 137.4 (C2), 117.9 (C1), 72.6 (C7), 72.3 (C3), 71.8 (C4), 71.5 (C6), 69.7 (C5), 62.0 (C8).

NMR: D-arabinose as starting material

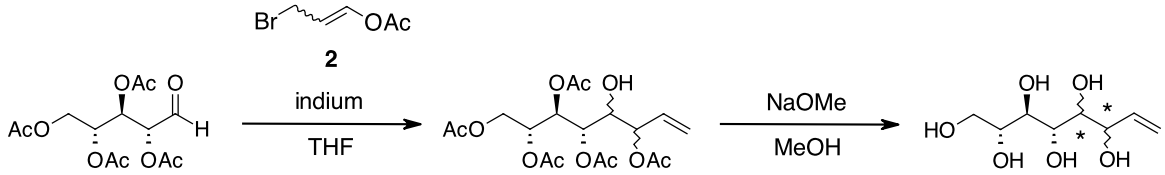
^{1}H-NMR revealed the formation of three isomers which are assumed (partly based on the literature[28]) to have *lyxo* configuration (*syn/anti*) for isomer **A**, *xylo* configuration (*syn/syn*) for isomer **B** and *ribo* configuration (*anti/anti*) for isomer **C**. The ratio of the main isomers is 3.2:1 **A**:**B**.

^{1}H NMR (600 MHz, D_2O) δ = 5.98 – 5.90 (m, 1H, H2), 5.39 – 5.28 (m, 2H, H1-a, H1-b), 4.41 (dd, *J* = 7.1, 3.5 Hz, 1H, H3 (**C**)), 4.28 – 4.24 (m, 1H, H3 (**B**)), 4.22 – 4.18 (m, 1H, H3 (**A**)), 3.92 – 3.89 (m, 1H), 3.81 – 3.60 (m, 5H).

For the main isomer:

^{13}C NMR (101 MHz, D_2O) δ = 135.9 (C2), 118.4 (C1), 74.6, 72.5, 71.9, 71.0, 68.9, 62.7 (C8).

4.2.19 IMA of 2,3,4,5-tetra-*O*-acetyl-D-ribose **6** towards **33**



6 **[27]** **33**

$C_{13}H_{18}O_9$
MW: 318.28 g/mol

$C_{18}H_{26}O_{11}$
MW: 418.39 g/mol

$C_8H_{16}O_6$
MW: 208.21 g/mol

IMA:

To anhydrous THF (2 mL, 0.1 M) in an argon-flushed 10 mL round-bottom flask was added indium powder (47 mg, 0.4 mmol, 2.0 equiv.). Then, 3-bromo-1-propenyl acetate **2** (215 mg, 1.2 mmol, 6.0 equiv.) was added to the vigorously stirred mixture, followed by the aldehyde **6** (75 mg, 0.2 mmol, 1.0 equiv.) dissolved in a small amount of THF in one portion. The reaction mixture was vigorously stirred for 10 minutes, after which TLC (LP:EA 1:1, anisaldehyde) was measured which showed complete conversion of the free aldehyde. The reaction mixture was filtered and the filtrate was evaporated, leaving a clear, slightly yellow oil. The oil was dissolved in ethyl acetate (15 mL) and washed with water (2× 10 mL) and brine. It was dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent gave a clear oil.

Global deprotection:

The oil was dissolved in MeOH (1 mL) and treated with NaOMe (30% in MeOH, 15 drops) until pH ~10. The mixture was stirred overnight. TLC on the next morning indicated complete deacetylation. The reaction mixture was neutralized by the addition of Dowex-H^+ (MeOH washed). The solution was filtered and the methanol was evaporated to give a clear, yellow oil.

To achieve better spectra the enitols were dissolved in water (2 mL) and extracted with diethyl ether (2× 2mL). The aqueous phase was washed with hexane and the water was evaporated. NMR of the obtained oil was measured to evaluate the ratio of the formed isomers **33**.

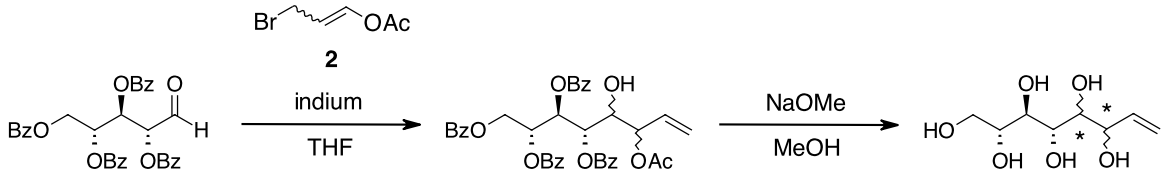
Appearance yellow oil
R_f-value 0.31 (CMW 7:3:0.5, anisaldehyde; violet spot)

NMR

^{1}H NMR (400 MHz, D_2O) δ = 6.07 – 5.85 (m, 1H, H2), 5.43 – 5.26 (m, 2H, H1-a, H1-b), 4.46 – 4.42 (m, 1H, H3 (**D**)), 4.41 – 4.35 (m, 1H, H3 (**C**)), 4.26 – 4.22 (m, 1H, H3 (**B**)), 4.18 (t, *J* =7.5 Hz, 1H, H3 (**A**)), 3.99 – 3.61 (m, 6H).

Note: Compound **6** was also reacted with 3-bromo-1-propenyl benzoate **3** instead of 3-bromo-1-propenyl acetate **2** (see 2.1.3.6 Exchange of the elongation reagent with ribose derived compounds). In this case, the reaction was performed analogous to the procedure described above.

4.2.20 IMA of 2,3,4,5-tetra-*O*-benzoyl-D-ribose **7** towards **33**



7 **[28]** **33**

$C_{33}H_{26}O_9$
MW: 566.55 g/mol

$C_{38}H_{34}O_{11}$
MW: 666.67 g/mol

$C_8H_{16}O_6$
MW: 208.21 g/mol

IMA:

To anhydrous THF (2 mL, 0.1 M) in an argon-flushed 10 mL round-bottom flask was added indium powder (47 mg, 0.4 mmol, 2.0 equiv.). Then, 3-bromo-1-propenyl acetate **2** (215 mg, 1.2 mmol, 6.0 equiv.) was added to the vigorously stirred mixture, followed by the aldehyde **7** (154 mg, 0.2 mmol, 1.0 equiv.) dissolved in a small amount of THF in one portion. The reaction mixture was vigorously stirred for 10 minutes, then TLC (LP:EA 2:1, anisaldehyde) was measured which showed complete conversion of starting material. The reaction mixture was filtered and the filtrate was evaporated, leaving a yellow oil. The oil was dissolved in ethyl acetate (20 mL) and washed with water (3× 10 mL) and brine. It was dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent gave a clear oil.

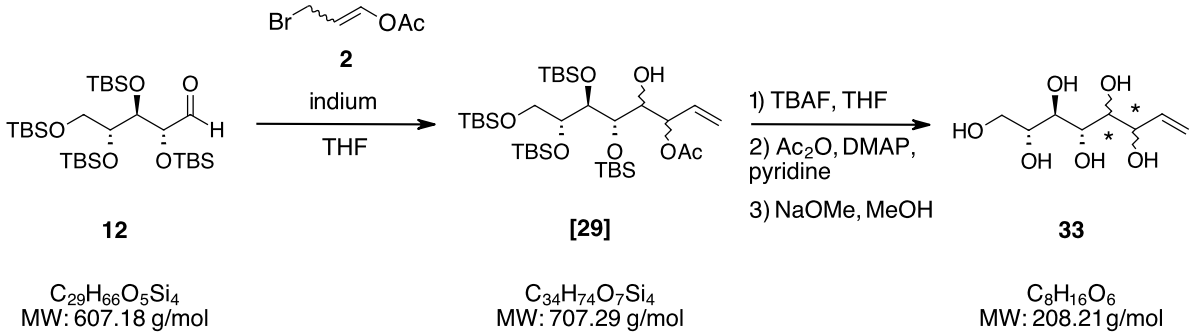
Global deprotection:

The oil was subjected to Zemplén deacetylation. It was dissolved in MeOH (1 mL). Then, NaOMe (30% in MeOH, 20 drops) was added under stirring at room temperature until pH~11. The mixture was stirred until TLC showed full conversion of the reaction intermediate to the unprotected species. The reaction solution was neutralized with Dowex-H^+ (MeOH washed) and filtered. The resin remaining in the filter was rinsed with additional MeOH and the solvent was evaporated to give the enitols as a yellow oily material.

To achieve better spectra the enitols were dissolved in water (2 mL) and extracted with diethyl ether (2× 2mL). The aqueous phase was washed with hexane and the water was evaporated. ^{1}H-NMR of the obtained oil was measured to evaluate the ratio of the formed isomers **33**.

Appearance	yellow oily material
R_f-value	0.31 (CMW 7:3:0.5, anisaldehyde; violet spot)

4.2.21 IMA of 2,3,4,5-tetra-*O*-(*tert*-butyldimethylsilyl)-D-ribose **12** towards **33**



12

$C_{29}H_{66}O_5Si_4$
MW: 607.18 g/mol

[29]

$C_{34}H_{74}O_7Si_4$
MW: 707.29 g/mol

33

$C_8H_{16}O_6$
MW: 208.21 g/mol

IMA:

To anhydrous THF (2 mL, 0.1 M) in an argon-flushed 10 mL round-bottom flask was added indium powder (47 mg, 0.4 mmol, 2.0 equiv.). Then, 3-bromo-1-propenyl acetate **2** (215 mg, 1.2 mmol, 6.0 equiv.) was added to the vigorously stirred mixture, followed by the aldehyde **12** (135 mg, 0.2 mmol, 1.0 equiv.) dissolved in a small amount of THF in one portion. The reaction mixture was vigorously stirred for 10 minutes, then TLC (LP:Et_2O 1:1, anisaldehyde) was measured which showed only partial conversion of starting material. The reaction was stirred overnight but apparently did not reach full conversion, so the reaction mixture was filtered and the filtrate was evaporated, leaving a brownish oil. The oil was dissolved in ethyl acetate (20 mL) and washed with water (3× 10 mL) and brine. The aqueous phase was back-extracted with ethyl acetate (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent gave a clear, yellow oil.

Global deprotection:

The residue was dissolved in THF (20 mL) and cooled in an ice-bath under argon atmosphere. Tetrabutylammonium fluoride (1.0 M in THF, 0.22 mL, ~1.1 equiv.) were added at 0 °C and the mixture was stirred for 3.5 hours. Then, THF was evaporated and the resulting brown oil was dissolved in water (20 mL). It was extracted with diethyl ether (2× 10 mL) and washed with hexane. The water was lyophilized overnight.

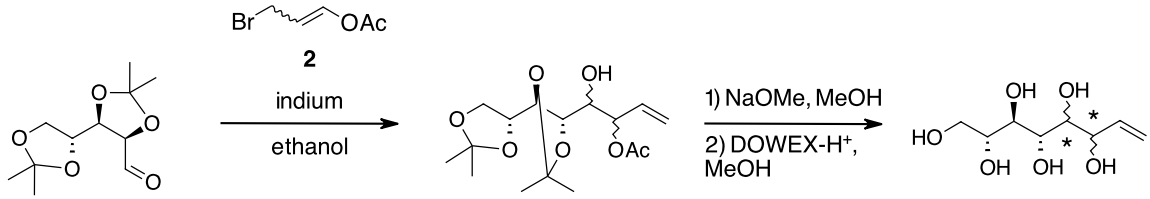
The obtained brown oil was acetylated again to separate the deprotected intermediate from remaining tetrabutyl ammonium fluoride *via* extraction. It was dissolved in pyridine (1.5 mL) and acetic anhydride (0.34 mL, ~18 equiv.) as well as a spatula tip of DMAP was added. The reaction mixture was stirred at room temperature for 4 hours, when full conversion of the intermediate was observed. Then, MeOH (1 mL) was added to quench the excess reagent. It was diluted with ethyl acetate (20 mL) and extracted with water (10 mL) and 1 N HCl (2× 10 mL, pH ~1). The combined organic layers were washed with $NaHCO_3$-solution (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a yellow oil.

The residue was taken up in MeOH (1 mL) and treated with NaOMe (30% in MeOH, 15 drops) until pH~10 was reached and stirred at room temperature. After 4 hours, TLC (CMW 7:3:0.5, anisaldehyde) was measured which showed full conversion to the targeted enitols **33**. The reaction mixture was then neutralized by the addition of Dowex-H^+ and filtered. The resin which remained in the filter was washed with fresh methanol to give a brown, sticky oil.

To achieve better spectra the enitols were dissolved in water (2 mL) and extracted with diethyl ether (2× 2mL). The aqueous phase was washed with hexane and the water was evaporated. NMR of the obtained oil was measured to evaluate the ratio of the formed isomers **33**.

Appearance	brown, sticky oil
R_f-value	0.31 (CMW 7:3:0.5, anisaldehyde; violet spot)

4.2.22 IMA of 2,3:4,5-bis-*O*-(isopropylidene)-D-ribose **11** towards **33**



11

$C_{11}H_{18}O_5$
MW: 230.26 g/mol

[26]

$C_{16}H_{26}O_7$
MW: 330.37 g/mol

33

$C_8H_{16}O_6$
MW: 208.21 g/mol

IMA:

Absolute ethanol (2 mL, 0.1 M) was heated to 45 °C in an argon-flushed 10 mL round-bottom flask. In immediate succession, first 3-bromo-1-propenyl acetate **2** (110 mg, 0.6 mmol, 3.0 equiv.), indium (47 mg, 0.4 mmol, 2.0 equiv.) and subsequently aldehyde **11** (46 mg, 0.2 mmol, 1.0 equiv.) as a solution in little ethanol was added in one portion. The reaction mixture was vigorously stirred for 10 minutes, then TLC (LP:EA 4:1, anisaldehyde) was measured which showed complete conversion of the starting material. The reaction mixture was filtered while still warm and the filtrate was evaporated, leaving a clear, slightly yellow oil. The oil was dissolved in ethyl acetate (15 mL) and washed with water (3× 10 mL) and brine. It was dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent gave a yellow-orange oil.

Global deprotection:

The oil was dissolved in MeOH (1 mL) and treated with NaOMe (30% in MeOH, 10 drops) until pH ~10. The color of the reaction mixture changed to a light pink and it was stirred at room temperature overnight. TLC (LP:EA 2:1, anisaldehyde) on the next morning indicated complete deacetylation. The reaction mixture was neutralized by the addition of Dowex-H^+ (MeOH washed). After filtration, additional Dowex-H^+ resin (MeOH washed) was added to the filtrate until a pH<2 was determined and the reaction mixture was stirred overnight. TLC (CMW 7:3:0.5 and LP:EA 2:1, anisaldehyde) on the next day revealed conversion to the fully unprotected enitols. The resin was then filtered, washed with MeOH and the solvent was evaporated to give the enitols as a flesh-colored oil.

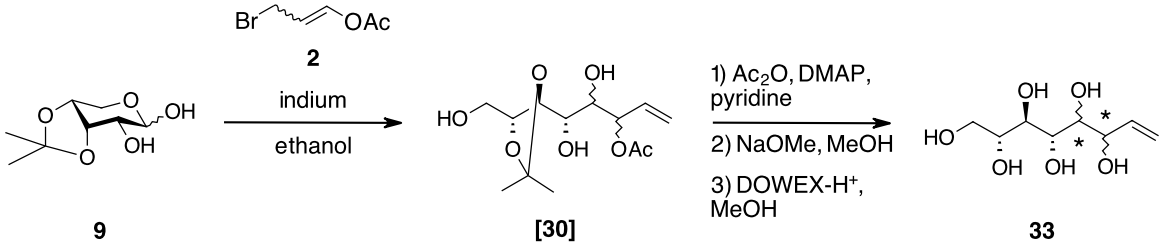
To achieve better spectra the enitols were dissolved in water (2 mL) and extracted with diethyl ether (2× 2mL). The aqueous phase was washed with hexane and the water was evaporated. NMR of the obtained oil was measured to evaluate the ratio of the formed isomers **33**.

Appearance flesh-colored oil
R_f-value 0.31 (CMW 7:3:0.5, anisaldehyde; violet spot)

NMR

^{1}H NMR (400 MHz, D_2O) δ = 6.04 – 5.79 (m, 1H, H2), 5.40 – 5.23 (m, 2H, H1-a, H1-b), 4.44 – 4.39 (m, 1H, H3 (**D**)), 4.39 – 4.34 (m, 1H, H3 (**C**)), 4.23 – 4.18 (m, 1H, H3 (**B**)), 4.18 – 4.13 (m, 1H, H3 (**A**)), 3.94 – 3.60 (m, 6H).

4.2.23 IMA of 3,4-*O*-isopropylidene-D-ribose **9** towards **33**



9 $C_8H_{14}O_5$ MW: 190.19 g/mol

[30] $C_{13}H_{22}O_7$ MW: 290.31 g/mol

33 $C_8H_{16}O_6$ MW: 208.21 g/mol

IMA:

Absolute ethanol (2 mL, 0.1 M) was heated to 45 °C in an argon-flushed 10 mL round-bottom flask. In immediate succession, first 3-bromo-1-propenyl acetate **2** (110 mg, 0.6 mmol, 3.0 equiv.), indium (47 mg, 0.4 mmol, 2.0 equiv.) and subsequently aldehyde **9** (38 mg, 0.2 mmol, 1.0 equiv.) as a solution in little ethanol was added in one portion. The reaction mixture was vigorously stirred for 10 minutes, then TLC (LP:EA 1:4, anisaldehyde) was measured which showed complete conversion of the starting material. After 20 minutes the reaction mixture was filtered while still warm and the filtrate was evaporated, leaving a clear oil.

The crude material **[30]** was subjected to acetylation to ensure full organic solubility of the reaction intermediates. The acetylation procedure can be found under 4.2.18 General procedure for the IMA of unprotected aldoses**.**

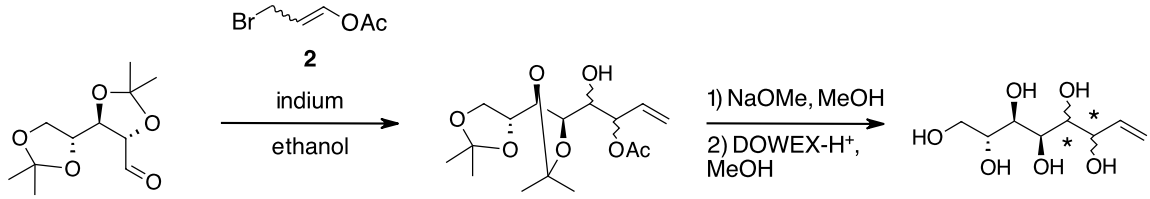
Global deprotection:

The residue was dissolved in MeOH (1 mL) and treated with NaOMe (30% in MeOH, 10 drops) until pH ~10. The reaction mixture was stirred at room temperature for 1 hour, when TLC (LP:EA 1:4, anisaldehyde) indicated complete deacetylation. The reaction mixture was neutralized by the addition of Dowex-H^+ (MeOH washed). After filtration, additional Dowex-H^+ resin (MeOH washed) was added to the filtrate until a pH<2 was determined and the reaction mixture was stirred for 3 hours. TLC (CMW 7:3:0.5 and LP:EA 1:4, anisaldehyde) on the next day revealed conversion to the fully unprotected enitols. The resin was then filtered, washed with MeOH and the solvent was evaporated to give the enitols **33** as a red-brown oily material.

Appearance	red-brown oily material
R_f-value	0.31 (CMW 7:3:0.5, anisaldehyde; violet spot)

Note: Compound **9** was also reacted with 3-bromo-1-propenyl benzoate **3** instead of 3-bromo-1-propenyl acetate **2** (see 2.1.3.6 Exchange of the elongation reagent with ribose derived compounds). In this case, the reaction was performed analogous to the procedure described above.

4.2.24 IMA of 2,3:4,5-bis-*O*-(isopropylidene)-D-arabinose **21** towards **34**



21 $C_{11}H_{18}O_5$ MW: 230.26 g/mol

[31] $C_{16}H_{26}O_7$ MW: 330.37 g/mol

34 $C_8H_{16}O_6$ MW: 208.21 g/mol

IMA:

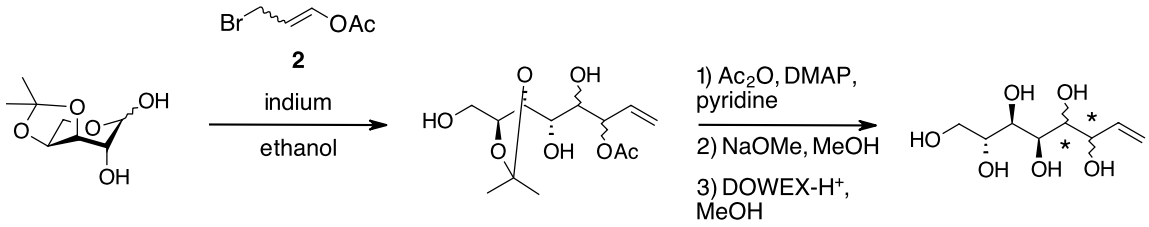
Absolute ethanol (4 mL, 0.1 M) was heated to 45 °C in an argon-flushed 10 mL round-bottom flask. In immediate succession, first 3-bromo-1-propenyl acetate **2** (215 mg, 0.6 mmol, 3.0 equiv.), indium (47 mg, 0.4 mmol, 2.0 equiv.) and subsequently aldehyde **21** (92 mg, 0.4 mmol, 1.0 equiv.) as a solution in little ethanol was added in one portion. The reaction mixture was vigorously stirred for 10 minutes, then TLC (LP:EA 1:2, anisaldehyde) was measured which showed complete conversion of the starting material. The reaction mixture was filtered while still warm and the filtrate was evaporated, leaving a clear, pink oil. The oil was dissolved in ethyl acetate (20 mL) and washed with water (3× 10 mL) and brine. It was dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent gave a yellow oil.

Global deprotection:

The oil was dissolved in MeOH (1.5 mL) and treated with NaOMe (30% in MeOH, 15 drops) until pH ~10 was reached. The mixture was stirred overnight at room temperature. TLC (LP:EA 1:2, anisaldehyde) on the next morning indicated complete deacetylation (more polar, violet spot). The reaction mixture was neutralized by the addition of Dowex-H^+ (MeOH washed). After filtration, additional Dowex-H^+ resin (MeOH washed) was added to the filtrate until a pH<2 was determined and the reaction mixture was stirred overnight. TLC (CMW 7:3:0.5, anisaldehyde) on the next day revealed conversion to the fully unprotected enitols **34**. The resin was then filtered, washed with MeOH and the solvent was evaporated to give the enitols as a red-brown oil.

Appearance	red-brown oil
R_f-value	0.31 (CMW 7:3:0.5, anisaldehyde; violet spot)

4.2.25 IMA of 3,4-*O*-isopropylidene-L-arabinose **23** towards **34**



23 $C_8H_{14}O_5$ MW: 190.19 g/mol

[32] $C_{13}H_{22}O_7$ MW: 290.31 g/mol

34 $C_8H_{16}O_6$ MW: 208.21 g/mol

IMA:

Commercially available 3,4-*O*-isopropylidene-L-arabinose **23** (76 mg, 0.4 mmol, 1.0 equiv.) was weighted into a 10 mL round-bottom flask and absolute ethanol (2 mL, 0.1 M) was added. The reaction mixture was heated to 45 °C and the sugar dissolved immediately. Then, 3-bromo-1-propenyl acetate **2** (219 mg, 1.2 mmol, 3.0 equiv.) and in immediate succession indium (91 mg, 0.8 mmol, 2.0 equiv.) was added to the vigorously stirred reaction mixture. TLC (CMW 7:3:0.5 and LP:EA 1:4, anisaldehyde) after 10 minutes showed formation of the partially protected enitols as well as full conversion of the starting material. The reaction mixture was filtered while still warm and the filtrate was evaporated, leaving a clear, slightly pink oil.

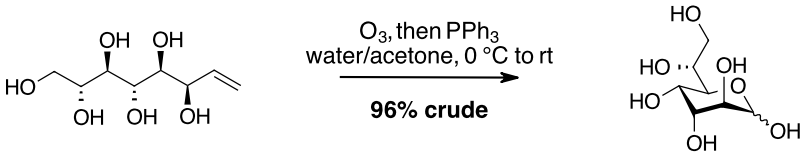
The crude material **[32]** was subjected to acetylation to ensure full organic solubility of the reaction intermediates. The acetylation procedure can be found under 4.2.18 General procedure for the IMA of unprotected aldoses**.**

Global deprotection:

The resulting oil was dissolved in MeOH (2 mL) and treated with NaOMe (30% in MeOH, 15 drops) until pH ~11. The mixture was stirred at room temperature until TLC (LP:EA 1:4, anisaldehyde) indicated complete deacetylation. The reaction mixture was then neutralized by the addition of Dowex-H^+ (MeOH washed). After filtration, additional Dowex-H^+ resin was added to the filtrate until a pH<2 was determined and the reaction mixture was stirred overnight. TLC (CMW 7:3:0.5 and LP:EA 4:1, anisaldehyde) on the next day revealed conversion to the fully unprotected enitols. The resin was then filtered, washed with MeOH and the solvent was evaporated to give the enitols **34** as a red-brown oily material.

Appearance	red-brown oily material
R_f-value	0.31 (CMW 7:3:0.5, anisaldehyde; violet spot)

4.2.26 D-*Glycero*-D-*altro*-heptose (36) confirming the stereochemistry of 33D



33D **36**

Note: The starting material, the unprotected entiol **33D**, was obtained from the fully acetylated form of the reaction intermediate **[27]** derived from the acetyl protected sugar aldehyde **6** after IMA and acetylation (see 4.2.19 IMA of 2,3,4,5-tetra-*O*-acetyl-D-ribose **6** towards **33**)**.** Preparative HPLC was applied to separate the two mainly formed isomers and subsequent Zemplén deacetylation of the isolated compound furnished the pure diastereomer **33D**. For more details see chapter 2.1.3.2 Identification of the products of the IMA .

Procedure:

In a microwave vial the 1,2-Dideoxy-D-*glycero*-D-*altro*-oct-1-enitol **33D** (3.4 mg, 0.016 mmol, 1 equiv.) was taken up in H_2O/acetone (3:2, 120 µL/80 µL) giving a yellowish solution. 1 drop of Sudan red (III) in acetone was added which stained the reaction mixture pink. The mixture was cooled to 0 °C with an ice-bath. Then, ozone was bubbled through (flow: 1) through a syringe. The outcoming gas was passed through a washing bottle containing a freshly prepared aqueous KI-solution (10% w/w). After 10 minutes, the pink color had vanished and the ozone generator was switched off. O_2 was bubbled through the solution for 4 minutes. A TLC (CMW 7:3:0.5, anisaldehyde) was measured which showed complete conversion of the starting material, therefore PPh_3 (10 mg, 0.038 mmol, 2.4 equiv.) was added, followed by additional acetone (0.4 mL, to dissolve the PPh_3). The reaction solution was stirred at room temperature overnight.

Workup:

The next day, a peroxide test (KI-starch paper) was performed which showed that no peroxide was present in the solution anymore. The reaction mixture was transferred into a 10 mL flask with acetone and water and concentrated under reduced pressure (200 mbar) which led to formation of a white solid. The aqueous layer was transferred into an eprouvette. Then, the white solid was dissolved in DCM and was transferred as well. The aqueous phase was extracted with DCM (2× 2 mL). The organic phase turned pink and the aqueous phase became very turbid but the phases separated without any problems. The aqueous phase was then washed with ethyl acetate (2 mL) and diethyl ether (2 mL). The now clear aqueous phase was washed with hexane (1 mL) once to remove residual organic solvents and evaporated *via* lyophilization. 3.3 mg of **36** were obtained as an off-white solid.

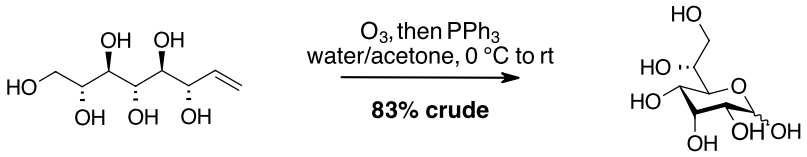
Yield	3.3 mg (96% crude)
Appearance	off-white solid
R_f-value	0.16 (CMW 7:3:0.5, anisaldehyde)

NMR

Since the starting material was not totally pure a full characterisation *via* NMR was not possible due to the high number of overlapping signals. However, the ^{1}H-NMR spectrum confirmed conversion of the starting material to the respective aldose with *altro*-configuration. Four signals in the anomeric region were observed which showed the very similar chemical shifts and ratios compared to the ^{1}H-NMR spectrum of altrose measured in D_2O, thus confirming the stereochemical composition of **36** and consequently enitol **33D**.

^{1}H NMR (600 MHz, D_2O) δ = 5.27 (d, *J* = 4.6 Hz), 5.23 (d, *J* = 2.7 Hz), 5.08 (d, *J* = 1.9 Hz), 4.97 (d, *J* = 4.8 Hz).

4.2.27 D-*Glycero*-D-*allo*-heptose (37) confirming the stereochemistry of 33C



33C **37**

Note: The starting material, the unprotected entiol **33C**, was obtained from the fully acetylated form of the reaction intermediate **[27]** derived from the acetyl protected sugar aldehyde **6** after IMA and acetylation (see 4.2.19 IMA of 2,3,4,5-tetra-O-acetyl-d-ribose **6** towards **33**)**.** Preparative HPLC was applied to separate the two mainly formed isomers and subsequent Zemplén deacetylation of the isolated compound furnished the pure diastereomer **33C**. For more details see chapter 2.1.3.2 Identification of the products of the IMA .

Procedure:

In a microwave vial the 1,2-Dideoxy-D-*glycero*-D-*allo*-oct-1-enitol **33C** (2.5 mg, 0.016 mmol, 1 equiv.) was taken up in H_2O/acetone (3:2, 120 µL/80 µL) giving a yellowish solution. 1 drop of Sudan red (III) in acetone was added which stained the reaction mixture pink. The mixture was cooled to 0 °C with an ice-bath. Then, ozone was bubbled through (flow: 1) through a syringe. The outcoming gas was passed through a washing bottle containing a freshly prepared aqueous KI-solution (10% w/w). After 10 minutes, the pink color had vanished and the ozone generator was switched off. O_2 was bubbled through the solution for 4 minutes. A TLC (CMW 7:3:0.5) was measured which showed complete conversion of the starting material, therefore PPh_3 (8 mg, 0.032 mmol, 2 equiv.) was added, followed by additional acetone (0.4 mL, to dissolve the PPh_3). The reaction solution was stirred at room temperature overnight.

Workup:

The next day, a peroxide test (KI-starch paper) was performed which showed that no peroxide was present in the solution anymore. The reaction mixture was transferred into a 10 mL flask with acetone and water and concentrated under reduced pressure (200 mbar) which led to formation of a white solid. The aqueous layer was transferred into an eprouvette. Then, the white solid was dissolved in DCM and was transferred as well. The aqueous phase was extracted with DCM (2× 2 mL). The organic phase turned pink and the aqueous phase became very turbid but the phases separated without any problems. The aqueous phase was then washed with ethyl acetate (2 mL) and diethyl ether (2 mL). The now clear aqueous phase was washed with hexane (1 mL) once to remove residual organic solvents and evaporated *via* lyophilization. 2.1 mg of **37** were obtained as an off-white solid.

Yield	2.1 mg (83% crude)
Appearance	off-white solid
R_f-value	0.16 (CMW 7:3:0.5, anisaldehyde)

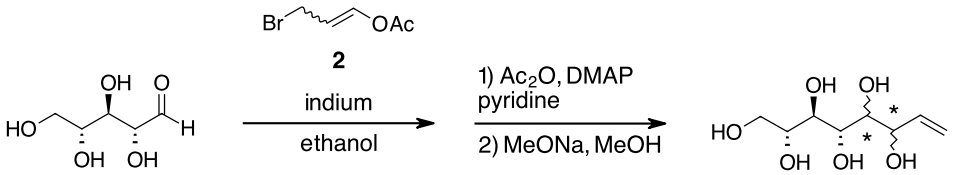
NMR

^{1}H NMR (600 MHz, D_2O) δ = 4.83 (d, *J* = 8.2 Hz, 1H, H1), 4.12 (t, *J* = 3.0 Hz, 1H, H3), 3.96 (dt, *J* = 7.6, 3.4 Hz, 1H, H6), 3.82 (dd, *J* = 10.3, 3.3 Hz, 1H, H5), 3.75 (dd, *J* = 12.0, 3.5 Hz, 1H, H7-a), 3.72 (dd, *J* = 10.2, 3.0 Hz, 1H, H4), 3.68 (dd, *J* = 12.0, 7.5 Hz, 1H, H7-b), 3.37 (dd, *J* = 8.2, 3.1 Hz, 1H, H2).

^{13}C NMR (151 MHz, D_2O) δ = 93.5 (C1), 73.7 (C5), 72.0 (C6), 71.2 (C3), 71.0 (C2), 67.5 (C4), 61.6 (C7).

4.3 Target-oriented synthesis of D-*glycero*-D-*manno*-heptose

4.3.1 1,2-Dideoxy-D-*glycero*-D-*manno*-oct-1-enitol (33A) and 1,2-dideoxy-D-*glycero*-D-*gluco*-oct-1-enitol (33B)



4

$C_5H_{10}O_5$
MW: 150.13 g/mol

33A + 33B

$C_8H_{16}O_6$
MW: 208.21 g/mol

IMA:

D-Ribose **4** (500 mg, 3.33 mmol, 1.0 equiv.) was weighted into a 50 mL round-bottom flask and the flask was flushed with argon. Absolute ethanol (20 mL, 2.5% solution) was added. The reaction mixture was heated to 45 °C and it was waited until the ribose was completely dissolved. Then, 3-bromo-1-propenyl acetate **2** (1.781 g, 9.99 mmol, 3.0 equiv.) and in immediate succession indium (768 mg, 6.66 mmol, 2.0 equiv.) was added to the vigorously stirred reaction mixture (magnetic stirrer at highest level). TLC (CMW 7:3:0.5, anisaldehyde) after 10 minutes showed formation of the target compound (violet, more apolar spot on TLC). After 20 minutes the reaction mixture was filtered over a filter paper when still warm and the solvent was evaporated to give 2.67 g of the crude intermediate.

Acetylation:

The crude material was dissolved in pyridine (10 mL) and acetic anhydride (4.8 mL, 50 mmol, 15 equiv.) was added under ice-bath cooling. Then, a small amount of DMAP was added to the milky white solution. The mixture was stirred overnight at room temperature. TLC on the next morning indicated full conversion of the starting material. MeOH (5 mL) was added to the yellow solution under ice-bath cooling to quench the remaining reagent. The reaction mixture was stirred for 5 more minutes and was then diluted with ethyl acetate (60 mL), extracted with water (40 mL), 1 N HCl (4× 40 mL, pH ~1), saturated $NaHCO_3$ solution (40 mL) and brine (10 mL), dried over Na2SO4 and concentrated under reduced pressure. Coevaporation from MeOH gave a clear, yellow oil (1.843 g).

Deacetylation:

The residue was taken up in MeOH (8 mL) and treated with NaOMe until pH~10 (~120 mg). The reaction mixture was stirred for 3.25 h at room temperature until TLC indicated complete deacetylation (violet spot with R_f-value identical to ribose). The reaction solution was neutralized by addition of Dowex-H^+ resin. It was filtered and the solvent was evaporated. The crude material was distributed between water (10 mL) and DCM (3× 5 mL). The turbid aqueous phase was then washed with hexane (5 mL) to remove residual DCM. The water was evaporated *via* lyophilization to give 758 mg of a yellowish solid. The crude material was directly used in the next step.

^{1}H-NMR was measured which revealed the ratio of the main isomers to be 1.6:1 **A**:**B** with small amounts of diastereomer **33C**. Also, formation of the side product **38** (see 2.1.3.3 Side product formation) was observable.

Yield 758 mg (109% crude yield)
Appearance yellowish solid
R_f-value 0.34 (CMW 7:3:0.5, anisaldehyde; violet spot)

NMR

^{1}H NMR (400 MHz, D_2O) δ = 6.01 (ddd, *J* = 17.3, 10.5, 6.9 Hz, 1H, H2 (**A**)), 5.88 (ddd, *J* = 17.4, 10.0, 6.8 Hz, 1H, H2 (**B**)), 5.44 – 5.30 (m, 2H, H1-a, H1-b), 4.41 – 4.37 (m, 1H, H3 (**C**)), 4.23 (t, *J* = 7.6 Hz, 1H, H3 (**B**)), 4.21 – 4.15 (m, 1H, H3 (**A**)), 3.97 – 3.89 (m, 2H, H5, H7), 3.86 – 3.79 (m, 2H, H6, H8-a), 3.79 – 3.63 (m, 2H, H4, H8-b).

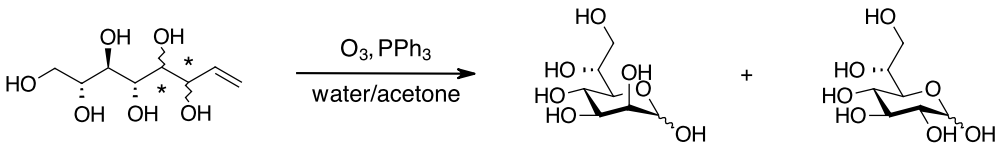
Isomer **A**:

^{13}C NMR (101 MHz, D_2O) δ = 137.4 (C2), 117.9 (C1), 72.6 (C7), 72.3 (C3), 71.8 (C4), 71.5 (C6), 69.7 (C5), 62.0 (C8).

Isomer **B**:

^{13}C NMR (101 MHz, D_2O) δ = 136.1 (C2), 118.7 (C1), 74.2 (C3), 72.6, 72.5, 71.6, 70.4, 61.9 (C8).

4.3.2 D-*Glycero*-D-*manno*-heptose (39) and D-*glycero*-D-*gluco*-heptose (40)



33A + 33B

$C_8H_{16}O_6$
MW: 208.21 g/mol

39

$C_7H_{14}O_7$
MW: 210.18 g/mol

40

$C_7H_{14}O_7$
MW: 210.18 g/mol

Procedure:

A 50 mL three-necked round-bottom flask was charged with the crude enitol mixture of **33A** and **33B** (693 mg, ~3.33 mmol, 1.0 equiv.). It was dissolved in in a mixture of water/acetone (3:2, 9 mL/6 mL). The yellow, clear solution was cooled to 0 °C with an ice-bath. 5 drops of Sudan red (III) in acetone were added which stained the solution pink. Then, ozone (flow: 4) was bubbled through the reaction mixture through a gas inlet. The outcoming gas was passed through a washing bottle containing a freshly prepared aqueous KI-solution (10% w/w). After 0.5 hours the pink color had vanished and the ozone generator was switched off. O_2 and argon were bubbled through the solution for 2 minutes each. A TLC ($CHCl_3$:MeOH:H_2O 14:7:1, anisaldehyde) was measured which showed complete conversion. PPh_3 (1.750 g, 6.66 mmol, 2.0 equiv.) was added as well as some acetone (~10 mL) to increase the solubility of the PPh_3. The solution was allowed to warm up to room temperature and was stirred overnight.

Workup:

The next day, a peroxide test (KI-starch paper) was performed which showed that no peroxide was present in the solution anymore. The reaction mixture was transferred into a 100 mL flask with acetone and water and concentrated under reduced pressure (200 mbar) which led to the formation of a white solid. It was then transferred into a separatory funnel. The white solid which remained in the flask was dissolved in DCM and transferred as well. The aqueous phase was extracted with DCM (20 mL). The organic phase turned slightly yellow, and the aqueous phase became very turbid but the phases separated without any problems. The aqueous phase was then extracted with ethyl acetate (2× 10 mL) and hexane (5 mL) and the water was evaporated. The residue was evaporated from ethanol thrice to give a yellow oil which was dried at 6 mbar to receive 821 mg of an off-white sticky solid. The ^{1}H-NMR spectrum showed traces of solvent and formaldehyde. Nonetheless, the crude was used in the next step without further purification.

Yield	821 mg (117% crude yield)
Appearance	off-white solid
R_f-value	0.14 (CMW 7:3:0.5, anisaldehyde)

NMR

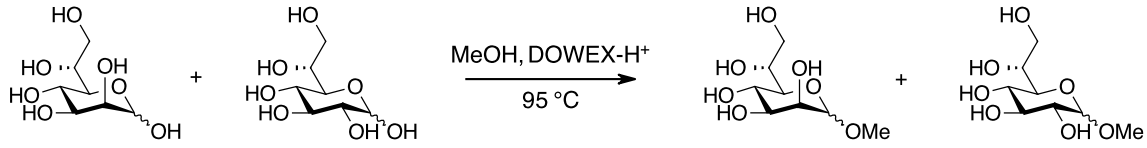
The ^{1}H-NMR spectrum of the product mixture confirmed formation of the respective heptoses showing four distinct signals in the anomeric region which can be related to the H1 of α-D-*glycero*-D-*manno*-

heptose (41%), β-D-*glycero*-D-*manno*-heptose (23%), α-D-*glycero*-D-*gluco*-heptose (16%), and β-D-*glycero*-D-*gluco*-heptose (20%). Unambiguous assignment of the other signals was not possible due to overlapping and a lack of conclusive 2D spectra.

Signals of the anomeric hydrogen H1:

^{1}H NMR (400 MHz, D_2O) δ = 5.21 (d, *J* = 3.9 Hz, 1H, H1 α-D-*glycero*-D-*gluco*-heptose), 5.16 (d, *J* = 1.7 Hz, 1H, H1 α-D-*glycero*-D-*manno*-heptose), 4.86 (d, *J* = 1.1 Hz, 1H, H1 β-D-*glycero*-D-*manno*-heptose), 4.61 (d, *J* = 7.9 Hz, 1H, H1 β-D-*glycero*-D-*gluco*-heptose)

4.3.3 Methyl D-*glycero*-D-*manno*-heptoside (41) and methyl D-*glycero*-D-*gluco*-heptoside (42)



39 $C_7H_{14}O_7$ MW: 210.18 g/mol

40 $C_7H_{14}O_7$ MW: 210.18 g/mol

41 $C_8H_{16}O_7$ MW: 224.21 g/mol

42 $C_8H_{16}O_7$ MW: 224.21 g/mol

Procedure:

The mixture of heptoses (199 mg, ~0.95 mmol, 1.0 equiv.) was dissolved in MeOH (4 mL). Then, DOWEX-H^+ resin (MeOH washed, 200 mg) was added and the reaction solution was heated to 95 °C. It was stirred for 22 hours and the reaction progress was controlled *via* TLC measurements (CMW 7:3:0.5, anisaldehyde).

Workup:

The reaction mixture was filtered to remove the cation exchange resin. Afterwards the solvent was evaporated giving 225 mg the target compound as a mixture of the methyl heptosides **41** and **42**. The crude was directly used in the next step.

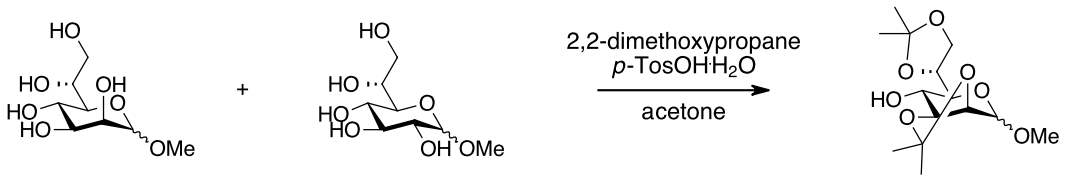
Yield	225 mg (106% crude yield)
Appearance	yellow oil
R_f-value	0.30 and 0.39 (CMW 7:3:0.5, anisaldehyde)

NMR

The ^{1}H-NMR spectrum of the product mixture confirmed formation of the target compounds, the respective methyl heptosides, showing four distinct signals for the anomeric hydrogen which can be assigned to methyl α-D-*glycero*-D-*manno*-heptoside (56%), methyl β-D-*glycero*-D-*manno*-heptoside (5%), methyl α-D-*glycero*-D-*gluco*-heptoside (26%), and methyl β-D-*glycero*-D-*gluco*-heptoside (13%). Unambiguous assignment of the other signals was not possible due to overlapping and lack of conclusive 2D spectra.

^{1}H NMR (400 MHz, MeOD) δ = 4.65 (d, *J* = 3.7 Hz, 1H, H1 methyl α-D-*glycero*-D-*gluco*-heptoside), 4.61 (d, *J* = 1.5 Hz, 1H, H1 methyl α-D-*glycero*-D-*manno*-heptoside), 4.39 (d, *J* = 1.0 Hz, 1H, H1 methyl β-D-*glycero*-D-*manno*-heptoside), 4.14 (d, *J* = 7.8 Hz, 1H, H1 methyl β-D-*glycero*-D-*gluco*-heptoside), 3.90 (m, 1H), 3.82 – 3.71 (m, 2H), 3.71 – 3.62 (m, 2H), 3.57 – 3.52 (m, 1H), 3.51 (m, 1H), 3.40 (s, 3H, OC**H$_3$** methyl α-D-*glycero*-D-*gluco*-heptoside), 3.37 (s, 3H, OC**H$_3$** methyl α-D-*glycero*-D-*manno*-heptoside).

4.3.4 Methyl 2,3:6,7-bis-*O*-(isopropylidene)-D-*glycero*-D-*manno*-heptoside (43)



41

$C_8H_{16}O_7$
MW: 224.21 g/mol

42

$C_8H_{16}O_7$
MW: 224.21 g/mol

43

$C_{14}H_{24}O_7$
MW: 304.34 g/mol

Procedure:

The crude heptoside mixture (212 mg, ~0.95 mmol, 1.0 equiv.) was dissolved in a mixture of acetone (7.7 mL) and 2,2-dimethoxypropane (0.096 mL, 0.76 mmol, 0.8 equiv.). A catalytic amount of *p*-toluenesulfonic acid (19 mg, 0.095 mmol, 0.1 equiv.) was added and the reaction mixture was stirred for 3.5 hours at room temperature until TLC analysis (CMW 7:3:0.5, then DCM:MeOH 97:3, anisaldehyde) indicated full conversion of the starting materials.

Workup:

The reaction was quenched with triethylamine (0.076 mL), diluted with DCM (30 mL), and washed with saturated $NaHCO_3$-solution (15 mL) and water (15 mL). The organic phase was washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to 124 mg of **43** as a yellow oil. The crude was directly used in the next step.

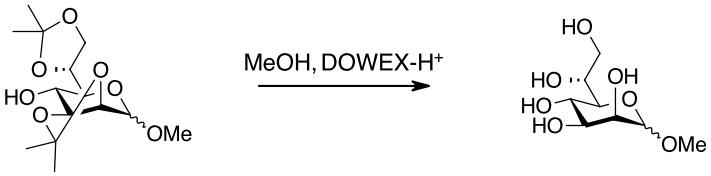
Yield	124 mg (42% crude yield)
Appearance	yellow oil
R_f-value	0.31 (DCM:MeOH 97:3, anisaldehyde)

NMR for the main anomer (ratio 1:2.3)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.84 (s, 1H, H1), 4.27 – 4.09 (m, 3H), 3.97 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.83 – 3.74 (m, 1H), 3.48 – 3.41 (m, 2H), 3.40 (s, 3H, OC**H₃**), 1.53, 1.46, 1.37, 1.36 (4×s, 4×3H, 4×C**H₃**).

For the second anomer signals at δ = 4.92 (s, 1H, H1) and δ =3.37 (s, 1H, OC**H₃**) were visible.

4.3.5 Methyl D-*glycero*-D-*manno*-heptoside (41)



43

$C_{14}H_{24}O_7$
MW: 304.34 g/mol

41

$C_8H_{16}O_7$
MW: 224.21 g/mol

Procedure:

The crude methyl 2,3:6,7-bis-*O*-(isopropylidene)-D-*glycero*-D-*manno*-heptoside (120 mg, ~0.39 mmol, 1 equiv.) was dissolved in methanol (3 mL) and DOWEX-H^+ resin was added until pH < 2. The reaction mixture was then stirred at room temperature overnight. On the next morning TLC (CMW 7:3:0.5, anisaldehyde) confirmed complete conversion to the unprotected species.

Workup:

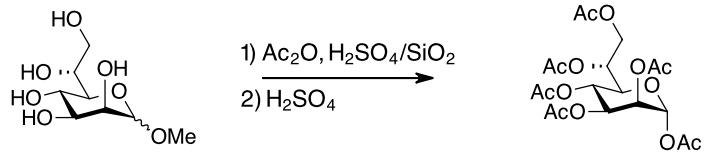
The reaction solution was filtered and the solvent was evaporated to give 105 mg of the crude methyl heptoside **41** as a flesh colored oil. The crude was directly used in the next step.

Yield	105 mg (120% crude yield)
Appearance	flesh colored oil
R_f-value	0.39 (CMW 7:3:0.5, anisaldehyde)

NMR for the main anomer (ratio 93:7 α:β)

^{1}H NMR (400 MHz, MeOD) δ = 4.61 (d, *J* = 1.6 Hz, 1H, H1), 3.92 (dt, *J* = 6.3, 3.8 Hz, 1H, 3.81 – 3.62 (m, 4H), 3.55 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.50 (d, *J* = 5.5 Hz, 1H), 3.37 (s, 3H, OC**H**$_3$).

4.3.6 D-*glycero*-α-D-*manno*-Heptose hexaacetate (44)



41

$C_8H_{16}O_7$
MW: 224.21 g/mol

44

$C_{19}H_{26}O_{13}$
MW: 462.40 g/mol

Procedure:

Acetic anhydride (0.54 mL, 5.6 mmol, 12 equiv.) was added to the crude methyl heptoside **41** (105 mg, ~0.47 mmol, 1.0 equiv.) and the reaction mixture was stirred for a few minutes. Then, H_2SO_4/SiO_2 (~3 mg, 1.6 mmol/g, <0.01 equiv.) was added under ice-bath cooling. After stirring the mixture for 3 hours at room temperature, a TLC (LP:EA 1:1, anisaldehyde) was measured which revealed complete conversion to the fully acetylated species. Sulfuric acid (0.017 mL, 0.3 mmol, 0.65 equiv.) was added and stirring of the dark brown reaction mixture was continued overnight.

Workup:

On the next morning, the reaction mixture was cooled with an ice-bath and neutralized by dropwise addition of DIPEA (0.11 mL, 0.6 mmol, 2 equiv. relative to H_2SO_4) which led to foaming and a color change from darkbrown to a lighter brown (pH ~6). The stirring was continued for 15 minutes. Afterwards, the reaction mixture was filtered (to remove the SiO_2) into a separatory funnel with ethyl acetate (4 mL). The solution was washed with water (2× 2 mL), HCl (1 M, 2× 3 mL, pH acidic) and water (2 mL) again. The combined aqueous layers were back-extracted with fresh ethyl acetate (2× 2 mL), the combined organic layers were washed with water (2 mL), saturated aqueous $NaHCO_3$-solution (2× 3 mL) and brine (1 mL) and dried over anhydrous Na_2SO_4. The solvents were evaporated and the residue was coevaporated from toluene and ethanol twice to give the crude material as yellow-white sticky solid (155 mg). The crude product was purified *via* recrystallization.

118 mg of the obtained material were transferred into a microwave vial and 2 drops (< 50 µL) of absolute EtOH were added. The mixture was heated with a heatgun. Heating furnished a clear yellow solution. The vial was put into an ice-bath and was then placed in the fridge. It was waited for 2 hours in which a sticky, chewy yellowish solid formed. The solid was transferred into a small suction filter and was washed with ice-cold EtOH to give the pure target compound **44** as a white solid (54 mg) in an anomeric ratio of 98:2 α:β according to ^{1}H-NMR and spectral data in consistence with literature[58].

Yield	54 mg (12% over 4 steps starting from the heptose mixture)
Appearance	white solid
Melting point	133-136 °C (EtOH), Lit: 139-140 °C[58]
Optical rotation	$[\alpha]_D^{24}$ = +59.0 (*c* 1.0, $CHCl_3$), Lit: $[\alpha]_D$ = +66.0 (*c* 2.1, $CHCl_3$)[58]
R_f-value	0.47 (LP:EA 1:1, anisaldehyde)
HRMS ($^+$ESI-TOF)	*m/z* $[M+Na]^+$ calc. for $C_{19}H_{26}NaO_{13}$ 462.1372, found 462.1394

NMR

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.05 (d, *J* = 1.7 Hz, 1H, H1), 5.38 – 5.22 (m, 2H, H3, H4), 5.23 (t, *J* = 2.6 Hz, 1H, H2), 5.18 (dt, *J* = 6.8, 3.3 Hz, 1H, H6), 4.41 (dd, *J* = 12.1, 3.5 Hz, 1H, H7-a), 4.21 (dd, *J* = 12.0, 7.2 Hz, 1H, H7-b), 4.11 – 4.03 (m, 1H, H5), 2.16 (s, 6H, 2×C**H$_3$**), 2.10, 2.07, 2.05, 2.01 (4×s, 4×3H, 4×C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.7, 170.1 (2×**C**=O), 170.1 (2× **C**=O), 169.8, 168.1 (2× **C**=O), 90.4 (C1), 72.0 (C5), 70.2 (C6), 68.9 (C4), 68.2 (C2), 66.4 (C3), 61.6 (C7), 21.0, 20.9, 20.9 (3×CO**C**H$_3$), 20.9 (2×CO**C**H$_3$), 20.8 (CO**C**H$_3$).

5. Appendix

5.1 Curriculum Vitae (CV)

LARA MALTROVSKY, BSc

[redacted]

EDUCATION

10/2020 -	**TU Wien** - MSc Technical Chemistry Master Thesis at the Institute of Applied Synthetic Chemistry, Research Group *Bioorganic Synthetic Chemistry*: 'Indium Mediated Acyloxyallylation of Aldoses - Systematic Study and Target-oriented Synthesis'
01/2020 - 01/2022	**TU Wien** - Minor Program Digital Skills
02/2021 - 06/2021	**DTU Danmarks Tekniske Universitet** Exchange Semester in Denmark (Erasmus+ programme)
10/2017 - 09/2020	**TU Wien** - BSc Technical Chemistry Bachelor Thesis at the Institute of Applied Synthetic Chemistry, Research Group *Bioorganic Synthetic Chemistry*: 'Gram-scale Mugineic Acid Total Synthesis'
2019/20, 2020/21	**Performance scholarship of TU Wien**
09/2012 - 06/2017	**College for Horticulture and Landscape Design** Specialization in Garden and Landscape Design

WORK EXPERIENCE

08/2021	**TU Wien** - Institute of Applied Synthetic Chemistry Four-week internship with a focus on bioorthogonal chemistry Research Group *Molecular Chemistry & Chemical Biology*
07/2020 - 08/2020	**TU Wien** - Institute of Applied Synthetic Chemistry Synthesis of chemical compounds for the ERC-funded project 'Wanted: Micro-nutrients! Phytosiderophore-mediated acquisition strategies in grass crops'
01/2020 - 03/2020	**TU Wien** - Institute of Applied Synthetic Chemistry Nine-week internship within the scope of my bachelor thesis
08/2019	**Borealis (Schwechat, AUT)** Gas chromatography, density determination of plastics

PUBLICATIONS AND CONFERENCES

19. - 22.09.2022	**19th Austrian Chemistry Days (Vienna, AUT)** Poster: Indium Mediated Acyloxyallylation of Sugar Aldehydes
07. - 08.07.2022	**25th Austrian Carbohydrate Workshop (Graz, AUT)** Poster: Indium Mediated Acyloxyallylation of Aldoses
09/2020	A Unified Approach to Phytosiderophore Natural Products Dr. Nikolas Kratena, Tobias Gökler, **Lara Maltrovsky**, Dr. Eva Oburger, Dr. Christian Stanetty* *Chemistry - A European Journal* **2020**, *27*, 577-580

ADDITIONAL QUALIFICATIONS

10/2019 -	**edutain e.U.** Tutoring in the subjects mathematics, chemistry
05/2022 - 06/2022	**TU Wien** Tutor in the 'Synthesis Laboratory Course'
08/2020 - 10/2022	**SFU Sigmund Freud PrivatUniversität** Tutoring basic general and organic chemistry
09/2020 - 06/2022	**CB Chemie GmbH** Creation of material safety data sheets using the software CHEMDOX
03/2019 - 11/2021	**IAESTE Vienna** Voluntary commitment in the areas Exchange Outgoing and Graphic Design

SKILLS

Languages	German (native), English (fluent), French (beginner)
IT-skills	Microsoft Office - Word, Excel, Powerpoint (ECDL) Adobe Photoshop & InDesign ChemDoodle, MestReNova, SciFinder, Reaxys Python (Basics)
Driving licence	B

INTERESTS

Singing	Choir *Neue Wiener Stimmen*
Sports	Ultimate Frisbee at *Mosquitos Klosterneuburg*

5.2 References

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