universität wien

DISSERTATION / DOCTORAL THESIS

Titel der Dissertation /Title of the Doctoral Thesis

„Contributions toward the synthesis of bioactive compounds“

verfasst von / submitted by

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angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Doktorin der Naturwissenschaften (Dr. rer. nat.)

Wien, 2018 / Vienna, 2018

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	A 796 605 419
Dissertationsgebiet lt. Studienblatt / field of study as it appears on the student record sheet:	Chemie / Chemistry
Betreut von / Supervisor:	Univ.-Prof. Dr. Walther Schmid †
Mitbetreut von / Co-Supervisor:	Univ.-Prof. Dr. Lothar Brecker

Dedication

To my father, who was always by my site.

I wish you could see me now.

Acknowledgements

At this point, I want to thank all the people that have supported me during my PhD. First, I want to thank the whole work group, especially Prof. Walther Schmid, who has given me the opportunity to work on this topic. Additionally, I want to thank Prof. Lothar Brecker for undertaking the supervision of this project after the unfortunate death of Walther Schmid. Of course, I also want to thank my colleague, Roman Lichtenecker. He has always lent me an ear and was a great support with my publications. Additionally, I want to thank Julia Schörghuber, Marilena Bisaccia, Manuel Gintner, Christian Denner, Frederik Weber and Gerlinde Benesch. I always had a great time with them, discussing work and private topics. A big thank you also to the whole team of the NMR-department, Hans-Peter Kählig, Susanne Felsinger and Ricarda Bugl for measuring the large number of NMRs.

Furthermore, I want to thank my family. My sister and my mother have always supported me, no matter how desperate I was. Although my father cannot see me anymore, he was an inspiring role model for me and I am very thankful for that. Not to forget my fiancé, Nino Trattnig, chemist on his own, who has always given me helpful council and knew how to build me up, when I was down. Finally, I want to thank everyone I have not mentioned namely. A high number of people are responsible for what I have achieved.

Table of contents

I Preface

This thesis is divided into two projects:

- Project I - Synthesis of GalNAc and IdoNAc
- Project II – Synthesis of ulosonic acid bioisosteres

In the chapters “Results and discussion”, “Experimental part” and “NMR spectra” of both projects the compounds will be numbered according to their first appearance in a scheme. This numbering will be continued until the end of project I and restarted for project II. Additionally, the order of procedure during the “Experimental part” and the NMR spectra will follow the logical order of reaction steps performed.

II Project I – Synthesis of GalNAc and IdoNAc

1 Introduction

1.1 Biological relevance of GalNAc and IdoNAc

N-Acetylgalactosamine (GalNAc) and *N*-acetylidosamine (IdoNAc) (Figure 1) belong to a ubiquitous group of compounds called amino sugars. This group is characterized by the substitution of one or more hydroxyl groups with an amine group functionality. In nature, this nitrogen is often masked by an acetyl group. Furthermore, they cannot be found as single components, but as part of oligo- or polysaccharides, as well as glycoproteins and proteoglycans.[1] During the last 150 years, many famous members, including *N*-acetylglucosamine (GlcNAc), -galactosamine and neuraminic acids (e.g. Neu5Ac) (Figure 1), have been isolated and their properties investigated in detail.[2–4]

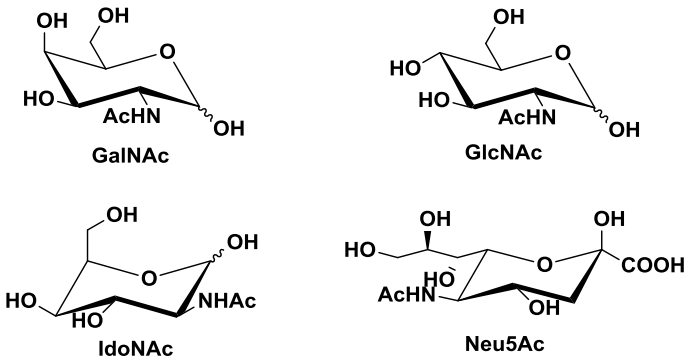


Figure 1: Four members of the amino sugar family: GalNAc, GlcNAc, IdoNAc and Neu5Ac.

Nowadays, there is a big difference in what is known about GalNAc and IdoNAc. Galactosamine, on the one hand, was one of the first identified amino sugars and has been investigated in detail, since that day. The literature about idosamine or IdoNAc, on the other hand, is rare. Although, several attempts for the synthesis of this compound have been published (see chapter 1.3), these publications include no information about their biological significance.

GalNAc can be found in a wide range of mammals, plants and invertebrates, e.g. as part of cell wall glycoproteins.[5,6] These proteins are involved in diverse biological processes. Intracellular, they influence the proper folding of newly synthesized proteins in the endoplasmic reticulum (ER). Extracellular, they serve as ligands for specific recognition processes towards e.g. enzymes, lectins or antibodies. In *O*-glycosylated glycoproteins, GalNAc becomes covalently α-linked to serine or threonine during post-translational modifications.[7–9] This core region glycan is also known as T

antigen nouvelle (Tn-antigen). Further attachment of a galactose β-1,3 towards this core region leads to the Thomsen-Friedenreich (TF)-antigen (Figure 2). These two immunodeterminants are overexpressed in a high number of different cancer cells, located in the breast, lung, colon, liver, prostate and gastric tissues.

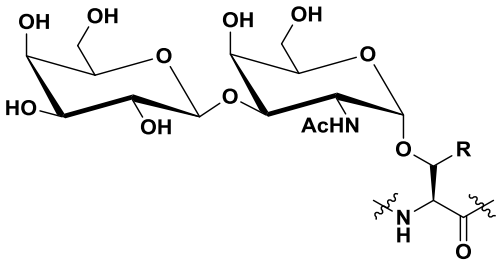


Figure 2: TF-antigen bound to the amino acid of a protein.

The TF-antigen also serves as the core region for the ABO and Lewis blood group determinants. Furthermore, GalNAc plays another important role as determinant for the blood group antigen A, where it is located at the terminal position. Whereas, on blood group antigen B this position is occupied by galactose and on blood group antigen 0 no carbohydrate is attached (Figure 3). These patterns are responsible for the recognition processes between blood cells and antibodies.[10–14]

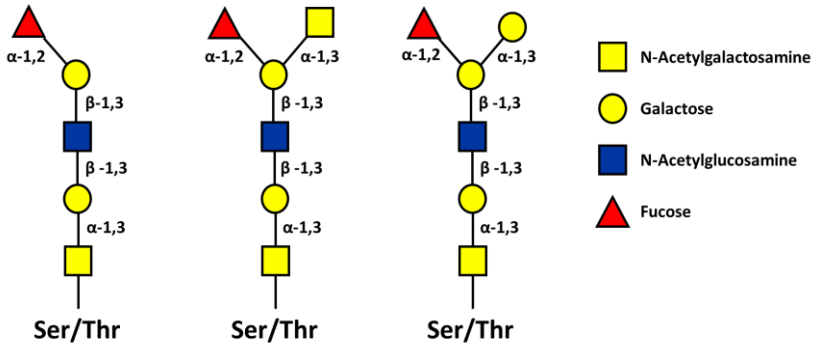


Figure 3: Blood group antigen 0, A and B (f.l.t.r).

Another examples for the importance of GalNAc is its presence in glycosaminoglycans (GAGs), unbranched polysaccharide chains consisting of repetitive disaccharide units.[15] These glycans are often covalently bound to proteins as part of the so-called proteoglycans. For instance, chondroitin sulfate, one member of the GAG family, is consisting of the alternating carbohydrates GalNAc (often sulfated on C-4 or C-6) and glucuronic acid (Figure 4A), linked to a proteoglycan through a tetrasaccharide (protein-Xyl-Gal-Gal-GlcA-GAG).[16–19] This proteoglycan is an important structural components of the cartilage and used in medicine for the treatment of osteoarthritis.[20–

[22] They can also be found in the brain matrix, where they influence the plasticity and neural growth as well as tumor growth.[23–25] Epimerization of the C-5 of glucuronic acid leads to iduronic acid and, consequently, to dermatan sulfate (Figure 4B).[26] Dermatan sulfate proteoglycans can also be found in the brain matrix, but they are even more common in the skin tissue. Here, they interact with growth factors and influence infections, fibrosis and wound repair.[27–29]

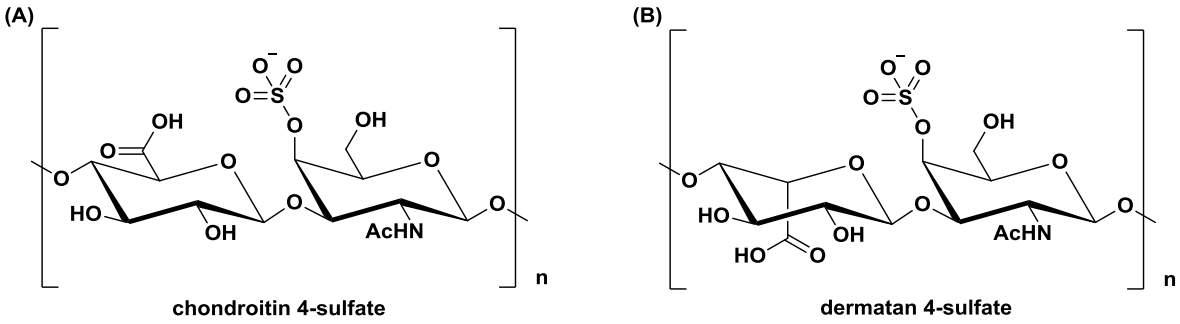
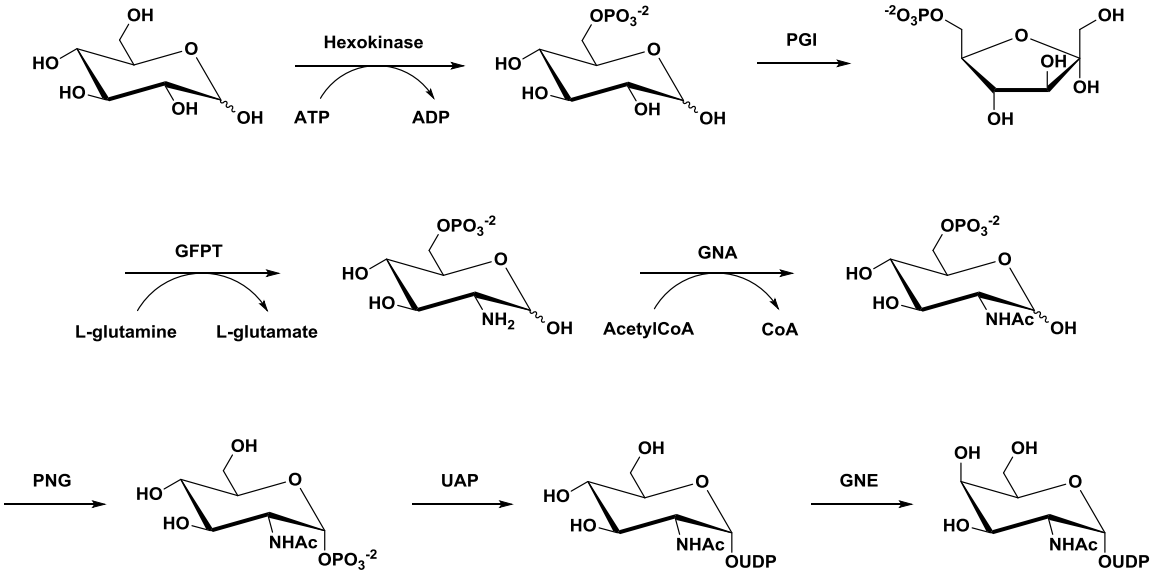


Figure 4: The two GalNAc containing GAGs: (A) chondroitin 4-sulfate and (B) dermatan 4-sulfate.

1.2 Biosynthesis of GalNAc

In most cases, glucose, taken up from diet, serves as precursor for the biosynthesis of amino sugars. After its transport through the cell membrane into the cytoplasm, hexokinase is phosphorylating glucose on C-6 under consumption of ATP (Scheme 1). Now, glucose-6-phosphate isomerase (PGI) is converting glucose-6-phosphate into fructose-6-phosphate. Subsequently, an amine is transferred from L-glutamine to fructose-6 phosphate by glutamine-fructose-6-phosphate transaminase (GFPT). The generated glucosamine-6-phosphate is acetylated by glucosamine-phosphate *N*-acetyltransferase (GNA). This enzyme is catalyzing the transfer of the acetyl from acetyl-CoA, which is also generated from glucose during the glycolytic pathway. After the conversion of glucosamine-6-phosphate to glucosamine-1-phosphate by phosphonoacetylglucosamine mutase (PGM), UMP is attached by UDP-*N*-acetylglucosamine diphosphorylase (UAP) to generate UDP-GlcNAc. Finally, this substrate is epimerized on C-4 by UDP-*N*-acetylglucosamine-4-epimerase (GNE) to generate UDP-GalNAc.[30–33]



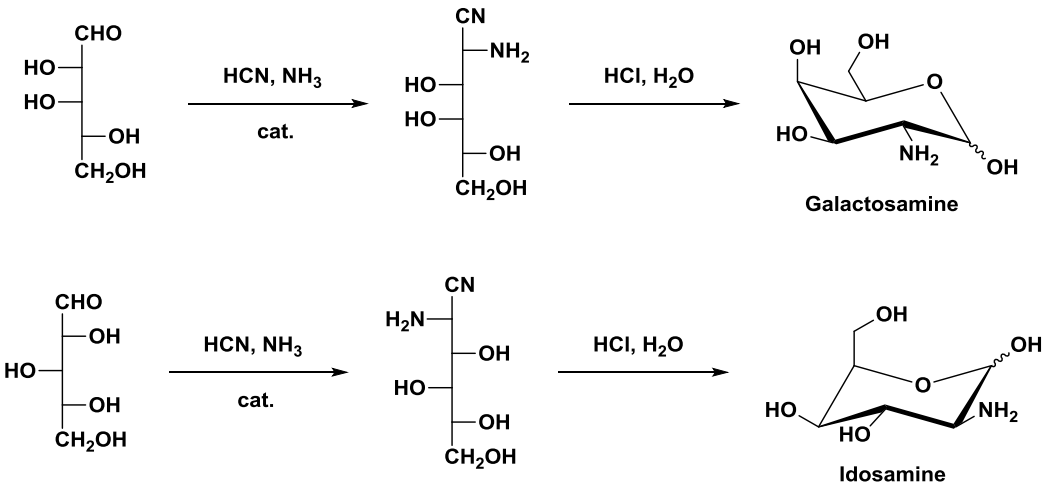
Scheme 1: Biosynthetic pathway of UDP-GalNAc.

For the biosynthesis of *O*-glycans, UDP-GalNAc is transported to the Golgi apparatus, where GalNAc-transferase 2 catalyzes the binding to the serine or threonine of a protein.[34]

1.3 Published strategies for the synthesis of 2-amino-2-deoxyhexoses

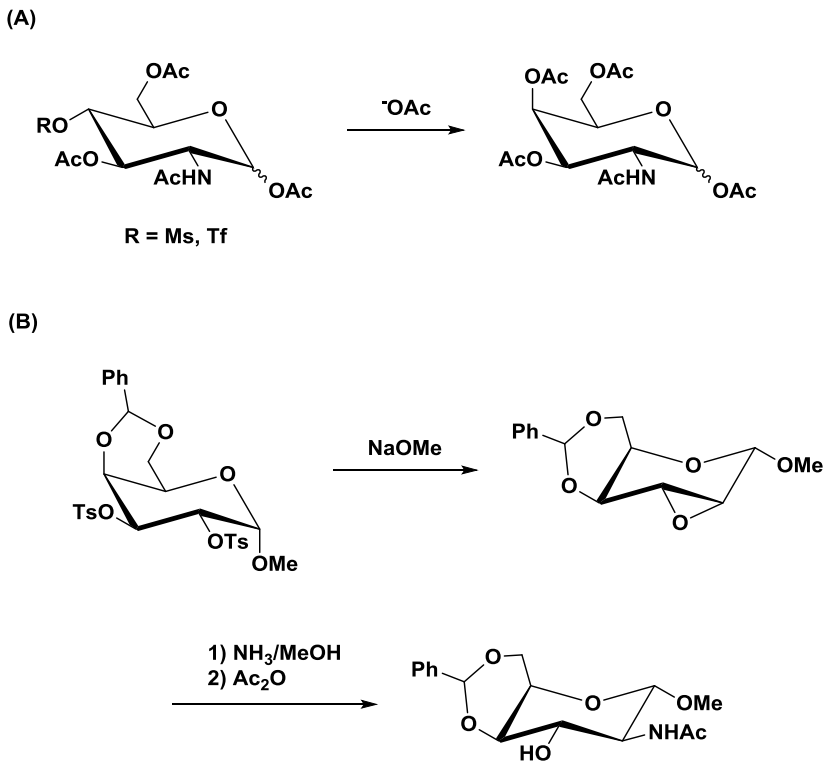
Several strategies for the synthesis of 2-amino sugars have been published, so far. With focus on the accessibility of GalNAc and IdoNAc the following chapter will highlight some of these approaches.

One of the most famous approaches is the Strecker synthesis.[35,36] Formerly used for the synthesis of amino acids, it can also be applied for the synthesis of amino sugars. Ammonia and hydrocyanic acid is reacting with a carbohydrate, leading to the introduction of an amine and the extension by a nitrile function. This is then catalytically reduced to the aldehyde (Scheme 2). These conditions for the introduction of the nitrogen functionality, usually, leads to the generation of a racemic mixture. To overcome this problem, several chiral catalysts for the synthesis of aminonitriles have been published over the last decades.[37,38]



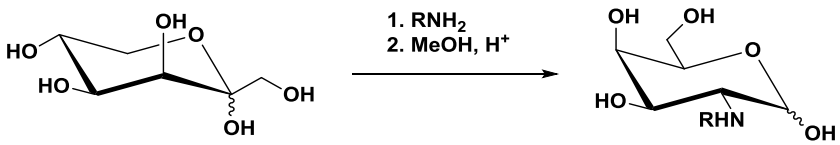
Scheme 2: Strecker synthesis of galactosamine and idosamine.

Another approach is the inversion of a stereocenter, e.g. on C-4, leading from *N*-acetylglucosamine to GalNAc.[39,40] For that reason, C-4 is mesylated or triflated to enable the S_N2 type substitution by an acetyl moiety (Scheme 3A). Although, GalNAc can be reached in just a few steps, the necessity of a 2-amino sugar as starting material leads to a low flexibility of this approach. Similarly, the parallel inversion of the stereocenters on C-2 and C-3 was published by Jeanloz *et al*. (Scheme 3B).[41] In this case, an epoxidation on galactose was performed, followed by a *trans*-opening and introduction of an amino acetyl group. Here, they could synthesize D-idosamine and D-talosamine.



Scheme 3: Inversion of the stereocenter on (A) C-4 and on (B) C-2 and C-3.

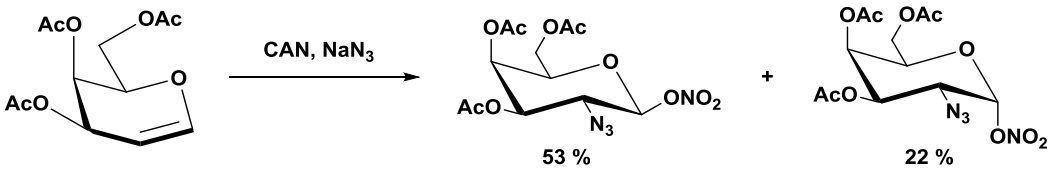
The Heyns rearrangement of ketoses[42–44] is another common approach towards amino sugars (Scheme 4). The reaction of a ketose with an amine source leads to the corresponding ketosamine, which subsequently rearranges to 2-amino-2-deoxysugars. In this case, D-galactosamine and D-talosamine were generated starting from D-tagatose. For steric reasons, the *galacto* configuration is highly preferred, resulting in almost no formation of the *talo* form. In theory, D-idosamine is reachable from D-sorbose. Unfortunately, the competitive reaction towards D-glucosamine is strongly preferred for the same reasons as in the synthesis of galactosamine, making the synthesis of idosamine challenging.



Scheme 4: General synthesis of D-galactosamine starting from D-tagatose.

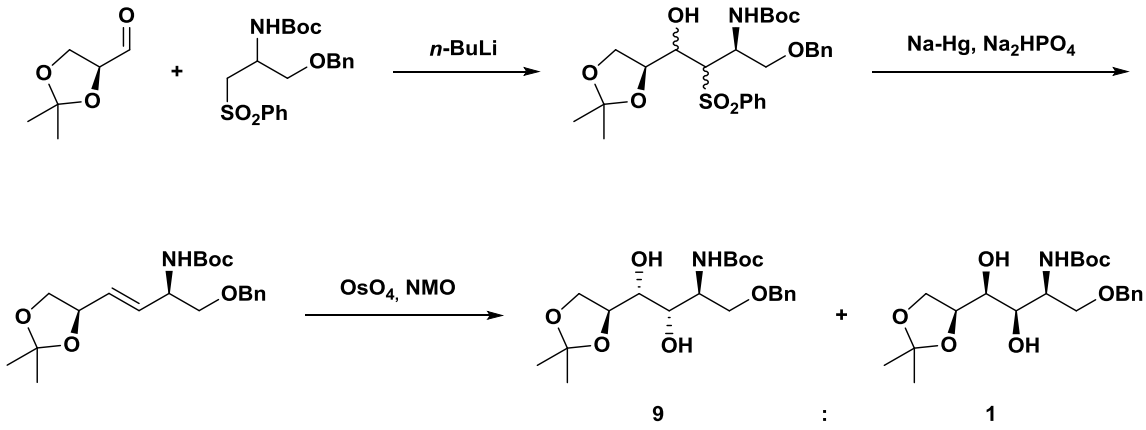
Another common method for the synthesis of 2-amino-2-deoxyhexoses is the use of glycals for the introduction of the desired nitrogen functionality on C-2.[45,46] This was achieved through the 2-iodoxybenzoic acid mediated generation of an oxazolidinone ring.[47] This cyclization induces a high stereoselectivity, but unfortunately, GalNAc is not reachable as only C-2, C-3 *cis*-products can

be created. By the azidonitration of galactal, Lemieux and Ratcliffe (Scheme 5) were successful in synthetizing D-galactosamine. Unfortunately, the selectivity of this reaction is rather low as the D-talose form is generated, as well.[46,48,49]



Scheme 5: Azidonitration of galactal published by Lemieux and Ratcliffe.

A fifth approach is the *E*-selective Julia-olefination of (*R*)- or (*S*)-2,3-isopropylideneglyceraldehyde with a second chiral building block containing the Boc-protected amine function, followed by dihydroxylation (Scheme 6).[50] This publication focuses on the synthesis of L-mannosamine, completely neglecting the possibility to synthesize L-idosamine. Nevertheless, the big advantage of this approach is that even some unnatural L-isomers are accessible, although, GalNAc is out of reach.



Scheme 6: Synthesis of L-*manno* and L-*ido* form *via* Julia olefination.

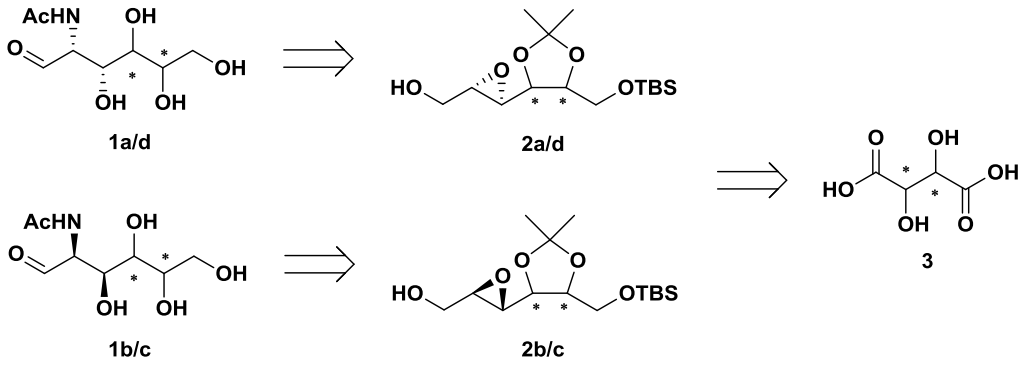
2 Results and discussion

2.1 Aim of the project

As pointed out previously, the flexible excess towards a broad library of aminosugars is still not possible (chapter 5). Although, several attempts for the synthesis of almost all members of this compound group have been published during the last decades,[42,51,52] there is still no concise route to give rise to all of them. Especially, IdoNAc has often been overseen, although, its biological activity is still unknown. Therefore, the aim of this project was to investigate a new and flexible approach towards aminosugars.

GalNAc **1** is involved in many different biological processes (chapter 1.1) and therefore, an ideal candidate as synthetic target. Tartaric acid **3** proofed to be the right starting material as it is affordable in both the unnatural D- and natural L-form. Furthermore, this rather small molecule already includes two of the four necessary stereogenic centers. In the end, building up the stereocenters on C-2 and C-3, as well as the regioselective introduction of an oxygen and nitrogen functionality results in the desired amino sugar (Scheme 7).

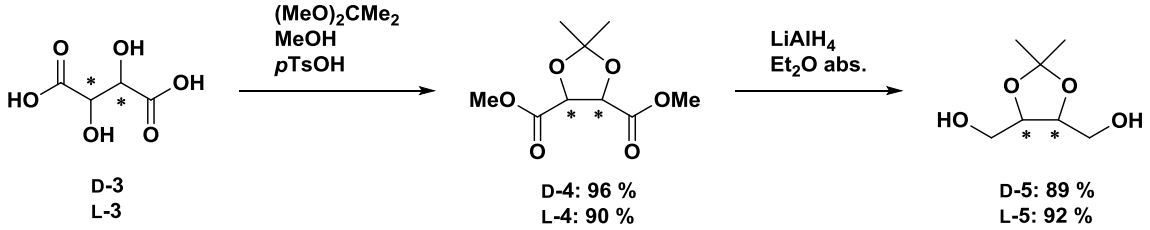
The key step for this approach has been the Sharpless epoxidation.[53] Therefore, the conversion of tartaric acid **3** to an unsaturated alcohol was necessary. With the following epoxidation, the final stereochemistry could have been defined, depending on the reaction conditions. Finally, the nitrogen functionality had to be introduced stereo- and regioselective.



Scheme 7: Retrosynthetic analysis for the presented approach towards aminosugars.

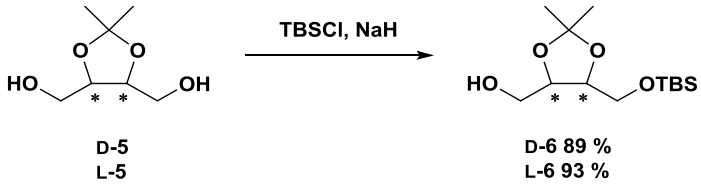
2.2 Synthesis of the unsaturated alcohol 8

As previously mentioned, D- and L-tartaric acid were chosen as starting material, because of their already present stereochemistry. Therefore, tartaric acids inherent C2 symmetry had to be broken, first. A monoprotection seemed to be the right tool. For this reason, an already published procedure was followed,[54] where the first step included the complete protection of tartaric acid **3** (Scheme 8). The diol was protected with an acetal, while the carboxylic acids were esterified, yielding compounds **D-4** and **L-4**. Now, these esters could be reduced with $LiAlH_4$ to gain D- and L-threitol **5** in 85 % and 83 % over two steps, respectively.



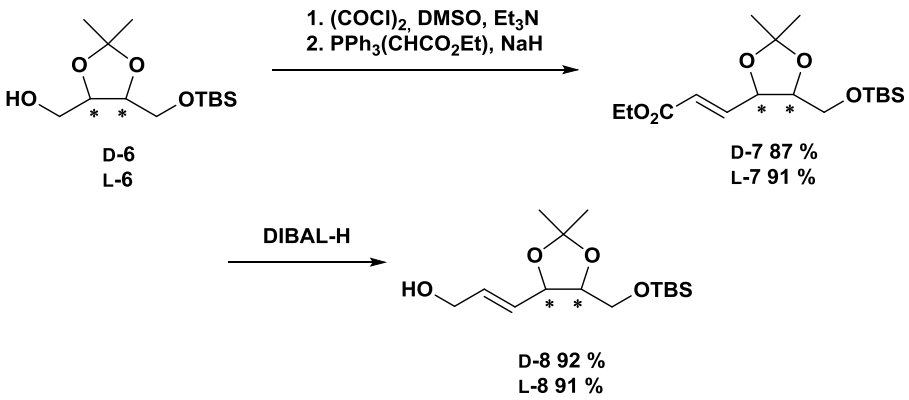
Scheme 8: Protection and reduction of tartaric acid 3.

For the selective protection of only one alcohol, first, a benzyl group was introduced. Unfortunately, full protection could not be avoided completely, resulting in a maximum yield of 76 % of monoprotected D-threitol. For this reason, we decided to perform *tert*-butyldimethylsilyl (TBS) protection (Scheme 9), yielding in 89 % and 93 % of the monoprotected D- and L-threitol **6**, respectively.



Scheme 9: TBS protection of threitol 5.

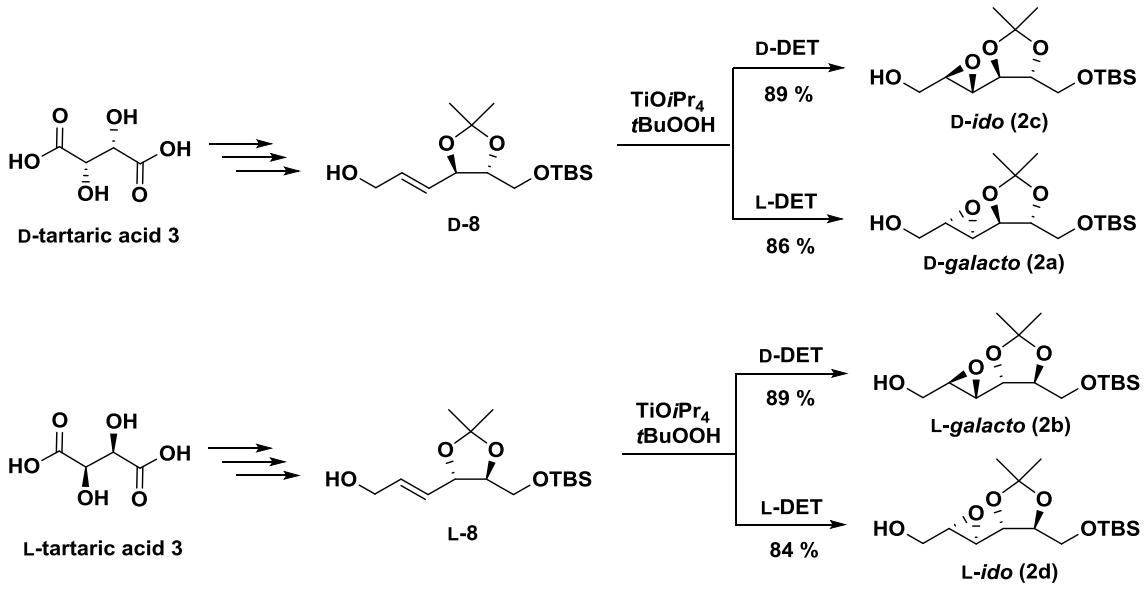
Now, an oxidation/elongation sequence had to be performed, including a Swern oxidation of the free alcohol to the aldehyde, followed by a Horner-Wadsworth-Emmons[55] (HWE) reaction (Scheme 10). Aldehydes are known to be very reactive and unstable, why we decided to perform the HWE reaction with the crude oxidation product. This resulted in the successful synthesis of the unsaturated esters **7** of both the D- and the L-isomer with yields of 87 % and 91 %, respectively. Finally, the ester was reduced to the alcohol **8** with DIBAL-H (92 % for **D-8** and 91 % for **L-8**).



Scheme 10: Swern/HWE sequence and DIBAL reduction towards unsaturated alcohol 8.

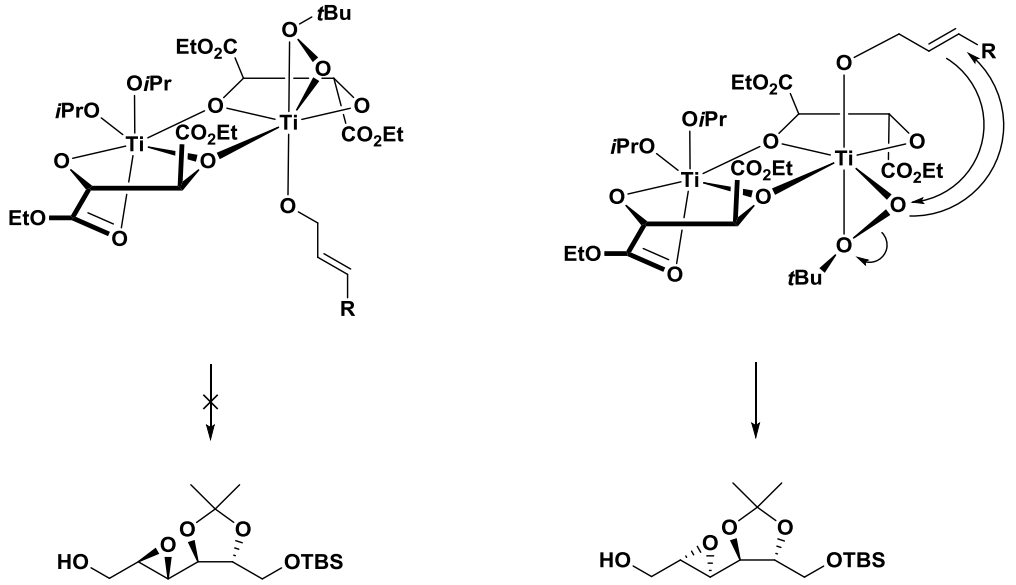
2.3 Sharpless epoxidation and stereoselective epoxide opening

The Sharpless epoxidation was the key step to generate the *galacto* or *ido* configuration (Scheme 11). This procedure was chosen because it ensures a high stereoselectivity for both diastereomers. Fortunately, this step was already published for the synthesis of Nojirimycin where the L-*ido* configuration (**2d**) had to be generated. We could adapt this approach and extent it to the synthesis of the L-*galacto* (**2b**), as well as the D-*ido* (**2c**) and D-*galacto* (**2a**) configuration. Interestingly, the yields for all for isomers are at the same range showing no influence of the neighboring functional groups. In fact, both *ido* isomers (**2c** and **2d**) have been received in comparable high yields, although these are the mismatched products,[56] due to the steric hinderance of the functional group on C-3. This unexpected outcome shows the high efficiency of the Sharpless epoxidation.



Scheme 11: Possible products during Sharpless epoxidation.

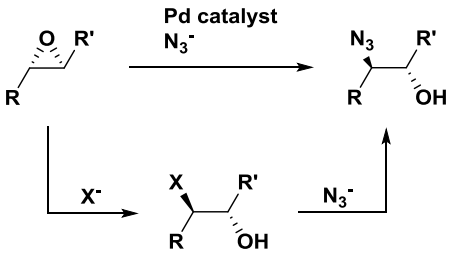
Mechanistically, a complex is built between the substrate, Ti(O*i*Pr)$_4$, diethyl tartrate (DET) and *tert*-butyl hydroperoxide (*t*BuOOH) (Scheme 12). Generally, only catalytical amounts of Ti(O*i*Pr)$_4$ and DET are necessary, but in this case stochiometric amounts had to be used to gain adequate yields (84 – 89 %). Here, DET acts as chiral mediator and therefore, determines the stereogenic outcome. This can be explained when taking a closer look to the complex geometry, when, for instance, the D-substrate is converted with the aid of L-DET. This leads to two possible complex geometries depending on the substitution of the substrate and *t*BuOOH, but the sterically less hindered transition state is strongly preferred. Subsequently, the D-*galacto* configuration (**2a**) is generated. Consequently, the use of D-DET results in the formation of the D-*ido* configuration (**2c**). Furthermore, when performing the reaction with **L-8**, the stereogenic outcome is interconverted; L-DET leads to the L-*ido* (**2d**) and D-DET to the L-*galacto* configuration (**2b**).



Scheme 12: Transition state during Sharpless epoxidation to form the D-*galacto* isomer (2a) using L-DET.

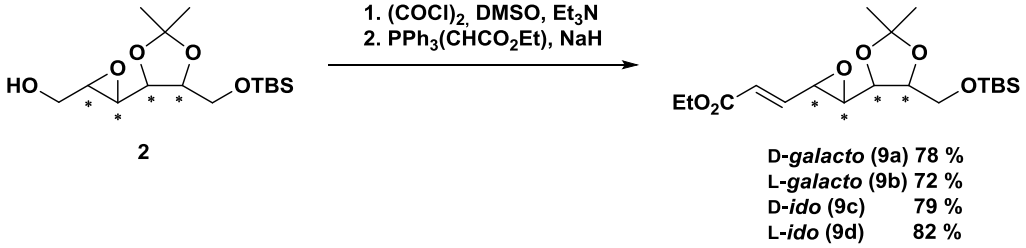
2.4 Selective introduction of the azide functionality

For the maintenance of the *galacto* and *ido* configuration, a *syn*-selective epoxide opening was crucial. For this reason, two possible approaches have been investigated (Scheme 13): On the one hand, a Pd-catalyzed *syn*-selective epoxide opening[57] and on the other hand, a two-step approach, where a leaving group is introduced *trans*-selective, followed by S_N2 substitution of an azide functionality.



Scheme 13: Two possible approaches for the *syn*-selective epoxide opening.

At this point, it has to be mentioned that for this and all following steps, the D-*galacto* isomer was used as the model compound, before adapting the improved reaction protocols to the residual isomers. Therefore, to perform the Pd-catalyzed *syn*-selective epoxide opening the formation of the α,β-unsaturated γ,δ-epoxy esters **9a** was required. Consequently, another Swern/HWE sequence had to be performed (Scheme 14) resulting in overall good yields (**9a-d** 72 – 82 %).



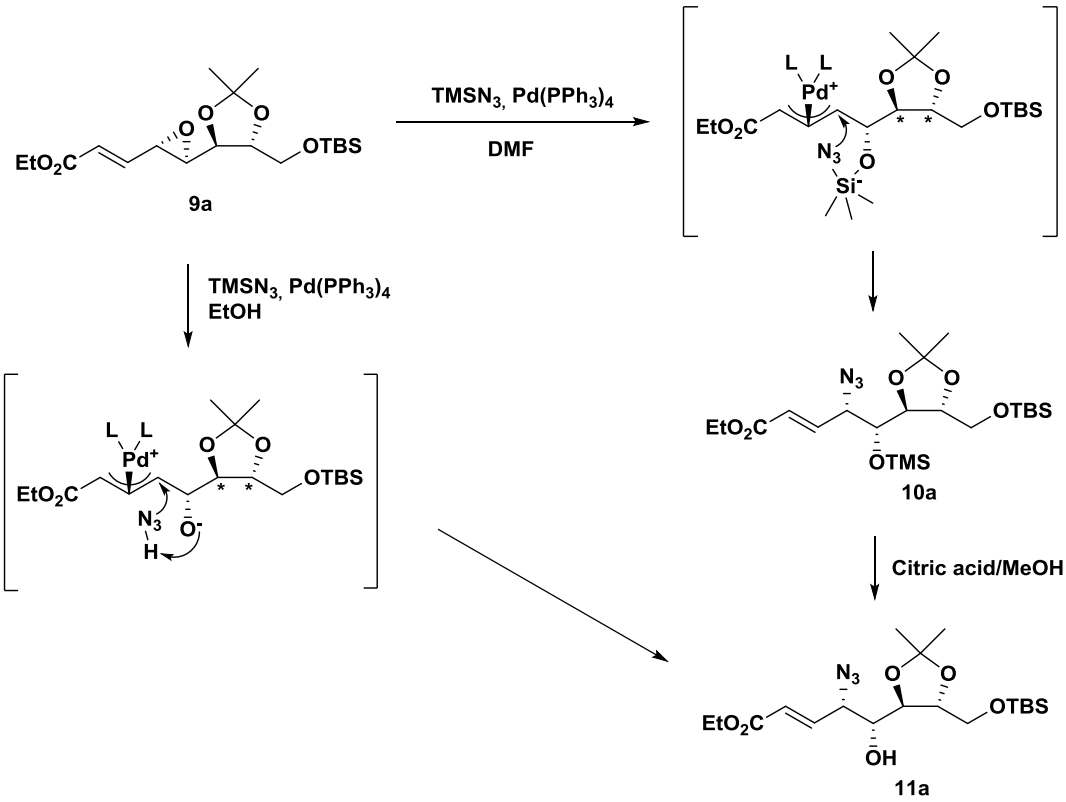
Scheme 14: Swern/HWE sequence to generate epoxy ester 9a-d.

Appealing to the knowledge of former group members, who already performed this reaction with different carbohydrates,[58,59] it was thought that using the standard condition – $TMSN_3$ (2 equiv), $Pd(PPh_3)_4$ (10 mol%) in dry, degassed THF, followed by quenching with citric acid in MeOH – would lead to adequate yields of the desired azides **11a-d** (Scheme 16). Unfortunately, when performing this reaction with epoxy ester **9a** only 45% of **11a** could be isolated. Consequently, optimization of the reaction conditions was required (Table 1). First trials with longer reaction time or different reaction temperatures, only, resulted in decreased yields. Changing the solvent to DMF, as published in case of low yields,[57] led to slightly better yields, but also to a mixture of TMS-protected (**10a**) and unprotected substrate (**11a**) (Scheme 15). Longer reaction times, only resulted in decreased yields. Further screening with MeCN, toluene or DCM was unsuccessful, as well.

Table 1: Reaction screening of the Pd-catalyzed epoxide opening of 9a.

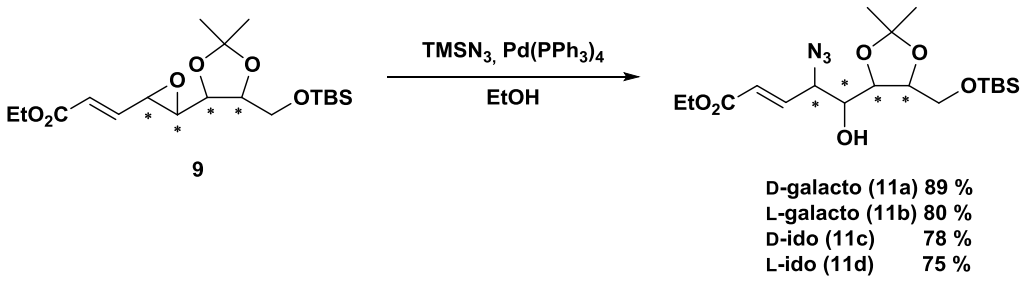
Solvent	Temp	Reaction time	Yield	Product
THF	r.t.	1 h	45 %	**11a**
THF	r.t.	3 h	35 %	**11a**
THF	0 °C	1 h	33 %	**11a**
THF	40 °C	1 h	23 %	**11a**
DMF	r.t.	1 h	51 %	**10a**
DMF	50 °C	2 h	51 %	**10a** (+ *trans*-isomer)
DMF	50 °C	3 h	35 %	**10a** (+ *trans*-isomer)
MeCN	r.t.	1 h	45 %	**10a**
Toluene	r.t.	1 h	54 %	**11a**
DCM	r.t.	1 h	49 %	**11a**
EtOH	r.t.	1 h	89 %	**11a**

Finally, when switching to EtOH, the desired azide **11a** could be isolated with a yield of 89 %. This dramatical increase, when using a protonated solvent, can be explained by taking a closer look to the postulated mechanism (Scheme 15): The Pd-catalyst binds to the double bond, forming a π-allyl complex. Simultaneously, the epoxide oxygen attacks $TMSN_3$. Finally, the azide attacks C-4 and acidic work-up leads to **11a**. This mechanism includes a double inversion of the stereocenter on C-4 and therefore, a retention, resulting in *syn*-products. When the reaction is performed in a protonated solvent like EtOH, $TMSN_3$ might *in situ* convert to HN_3. This highly reactive compound can perform the attack on C-4, while being deprotonated by the oxygen. Therefore, no acidic work-up is needed.



Scheme 15: Mechanisms for the Pd catalyzed epoxide opening towards 11a.

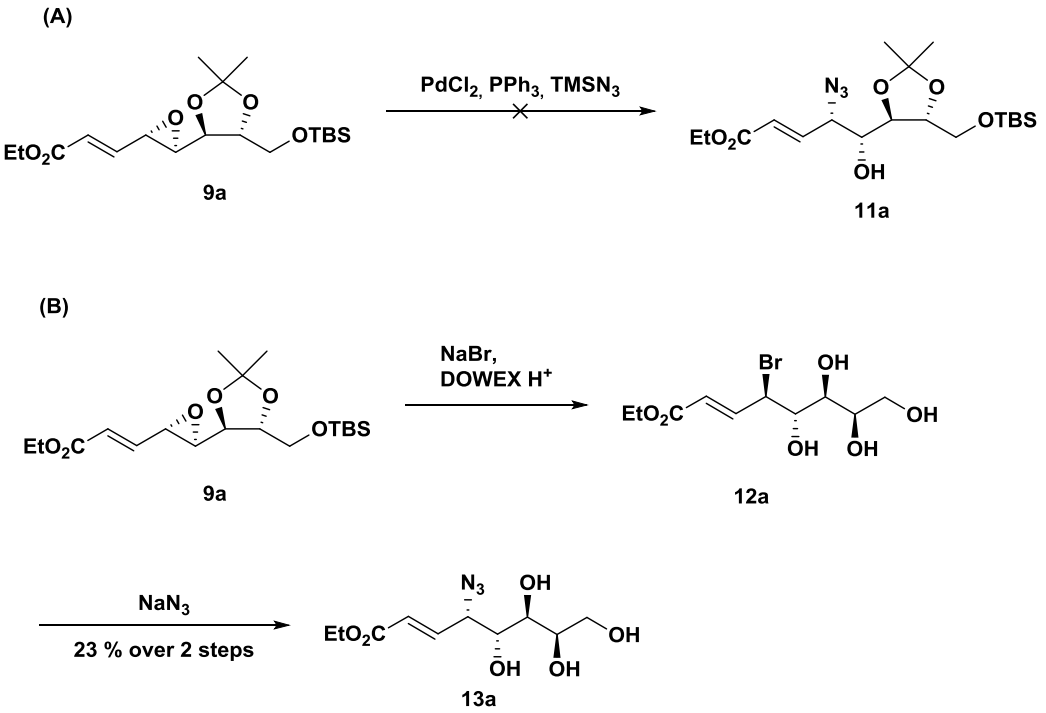
With the use of EtOH as solvent it was, furthermore, possible to overcome the problem of upscaling. When using aprotic solvents, a maximum amount of 100 mg substrate could be deployed. Bigger amounts led to a severe decrease of yield. With EtOH the reaction was performed in gram scale with overall good yields (Scheme 16).



Scheme 16: Pd-catalyzed *syn*-selective epoxide opening.

Parallel to the above described procedure, further attempts for the epoxide opening have been performed. Trials to generate the Pd-catalyst *in situ* from $PdCl_2$ and PPh_3, unfortunately, failed (Scheme 17A). Another approach, mentioned before, was the performance of a two-step route (Scheme 17B). In the first step, a bromide accomplished a nucleophilic attack on C-4, inverting this stereocenter and opening the epoxide (**12a**). Due to the acidic conditions, the protecting groups got lost. In the second step, another nucleophilic substitution by an azide led to the desired configuration (**13a**). This approach was performed with the D-*galacto* compound **9a** and resulted in

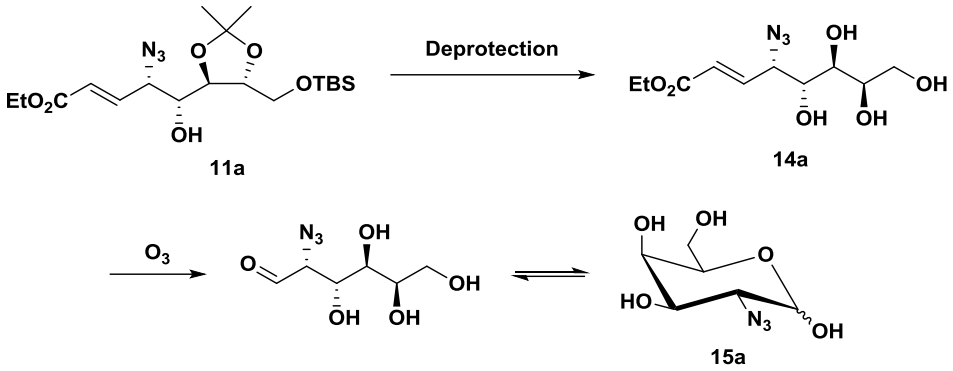
a yield of 23 % for **13a**. This rather low yield can be explained by an incomplete deprotection and a racemization of **12a**, which was observed, when this intermediate was stored overnight. Further attempts, using LiBr or LiI as nucleophile in the first step, failed. We concluded that, when comparing the results of the $Pd(PPh_3)_4$ approach with the *in situ* $Pd(PPh_3)_4$ and the two-step approach, the direct use of $Pd(PPh_3)_4$ is the most effective tool for our purposes.



Scheme 17: Epoxide opening performed (A) with *in situ* generated Pd-catalyst and (B) in two steps with NaBr and NaN_3.

2.5 Deprotection and Ozonolysis

With compounds **11a-d** in hand, the double bond had to be converted to the aldehyde. Ozonolysis seemed to be appropriate for this goal, but as free aldehydes are known to be very reactive and unstable, we decided to previously deprotect the substrate (Scheme 18). In this way, once the aldehyde is generated the compound can cyclize to the hemiacetal and stabilize itself. Therefore, screening for an accurate deprotection protocol was necessary.



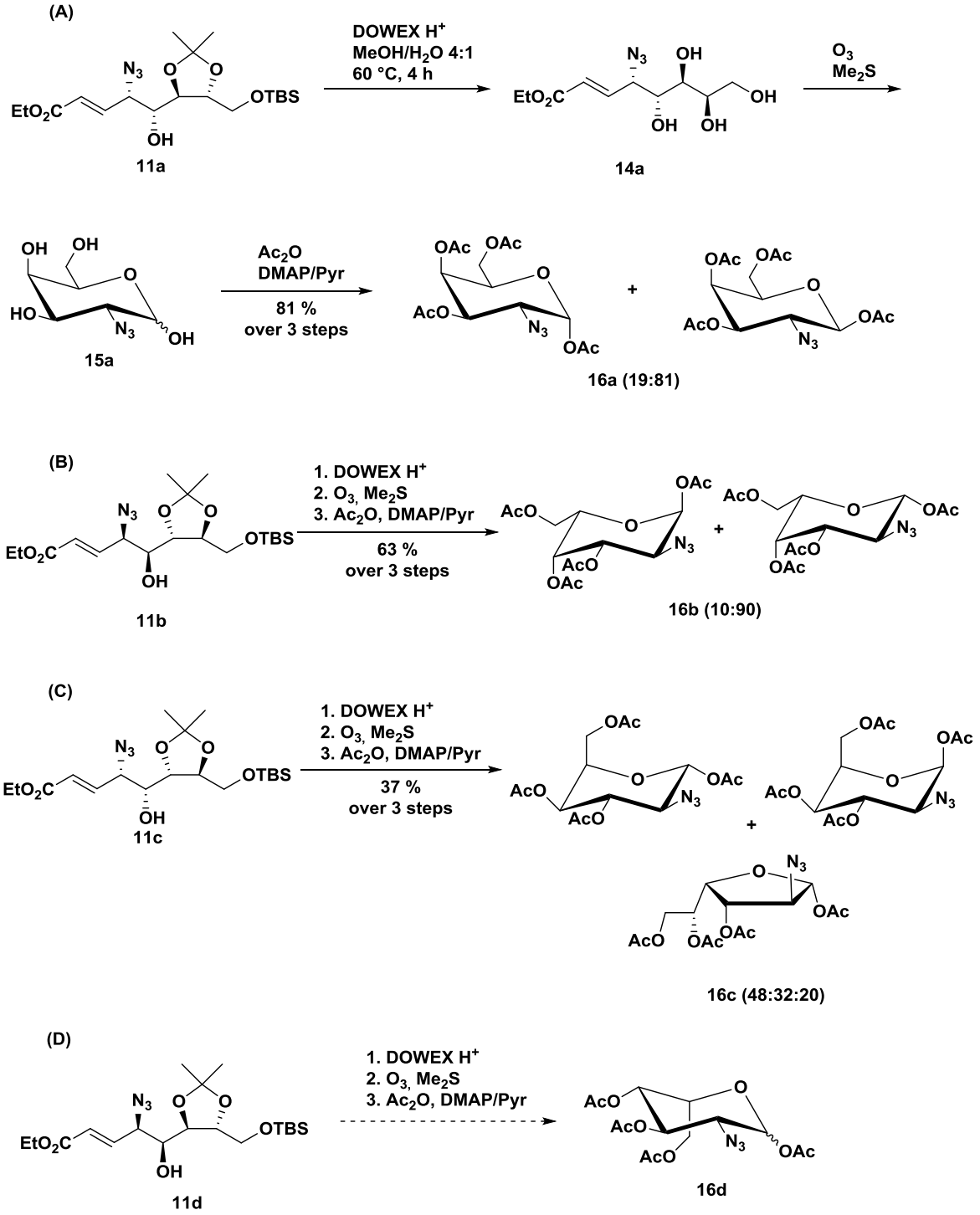
Scheme 18: Deprotection and ozonolysis of 11a.

For the complete deprotection of compound **11a**, different acidic conditions, including the use of TFA, HCl and DOWEX H^+, have been tested (Table 2). It was observed that under harsh conditions - high temperatures and/or high TFA and HCl concentrations - the double bond gets reduced or the compound decomposes. When performing the reaction at room temperature, a reaction time of, at least, 16 h is necessary to achieve acceptable yields. In comparison, high temperatures with a short reaction time lead to a somewhat selective cleavage of the TBS group resulting in 51 % of diol protected **15a**. Best results were achieved when using DOWEX H^+ as the proton source. In a mixture of MeOH/H_2O (4:1) the deprotection was accomplished either at room temperature in 3 days or at 60 °C in 4 h with almost quantitative yields.

Table 2: Reaction screening for the deprotection of 11a.

Solvents	Additive	Reaction time	Temp.	Yield (15a)
50 % TFA		16 h	r.t.	double bond lost
10 % TFA		16 h	r.t.	74 %
10 % TFA		30 min	100 °C	decomposed
10 % TFA/EtOH (1:4)		5 h	50 °C	35 %
1M HCl		30 min	100 °C	51 % diol protected
1M HCl		2 h	100 °C	27 %
1M HCl		5 h	100 °C	double bond lost
1M HCl/EtOH (1:4)		5 h	50 °C	38 %
1M HCl/EtOH (1:4)		16 h	r.t.	65 %
EtOH	DOWEX H^+	24 h	r.t.	50 %
EtOH	DOWEX H^+	4 h	90 °C	50 %
MeOH/H_2O (4:1)	DOWEX H^+	3 d	r.t.	95 %
MeOH/H_2O (4:1)	DOWEX H^+	4 h	60 °C	93 %
MeOH/H_2O (4:1)	DOWEX H^+	24 h	80 °C	89 %

Now, compound **14a** was submitted to ozonolysis yielding compound **15a** (Scheme 19A). The following peracetylation was performed to purify the product *via* silica chromatography, before performing the last reaction steps. Furthermore, the described reaction sequence was successfully adapted for the synthesis of the L-*galacto* isomer **16b** and the D-*ido* isomer **16c** (Scheme 19C). Unfortunately, the synthesis of the L-*ido* isomer **16d** (Scheme 19D) could not be realized any more, due to the lack of enough material. Nevertheless, the effective conversion of the D-*ido* isomer suggests that the reaction is adaptable for the L-*ido* isomer, as enantiomers possess the same physicochemical properties. This should also be the case for all following reaction steps.



Scheme 19: Deprotection, ozonolysis and peracetylation of (A) compound 11a, (B) 11b and (C) 11c; (D) theoretical approach towards 16d.

Interestingly, during NMR analysis of the D-*ido* isomer **16c** the α- (48 %) and β-pyranose form (32 %), as well as the α-furanose (20 %) was found, but not the β-furanose form (Figure 5). Although, it is known from literature[60] that idose occurs in both, pyranose and furanose form, the lack of β-furanose was unexpected.

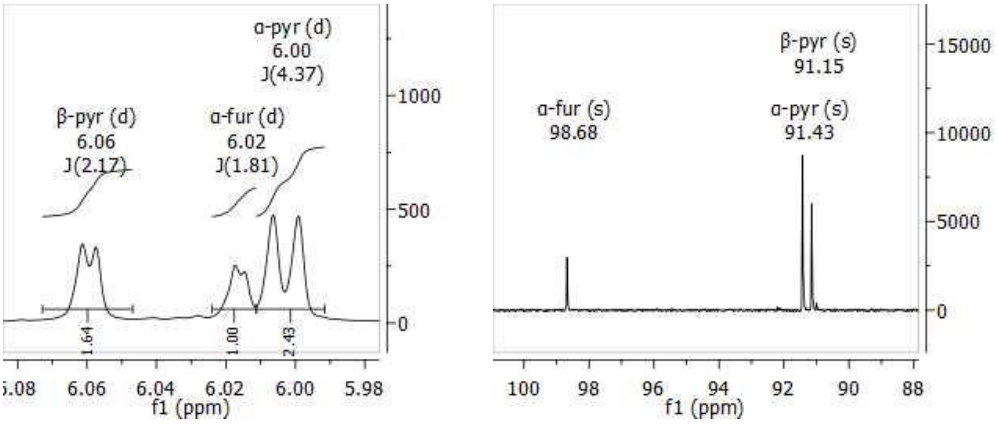
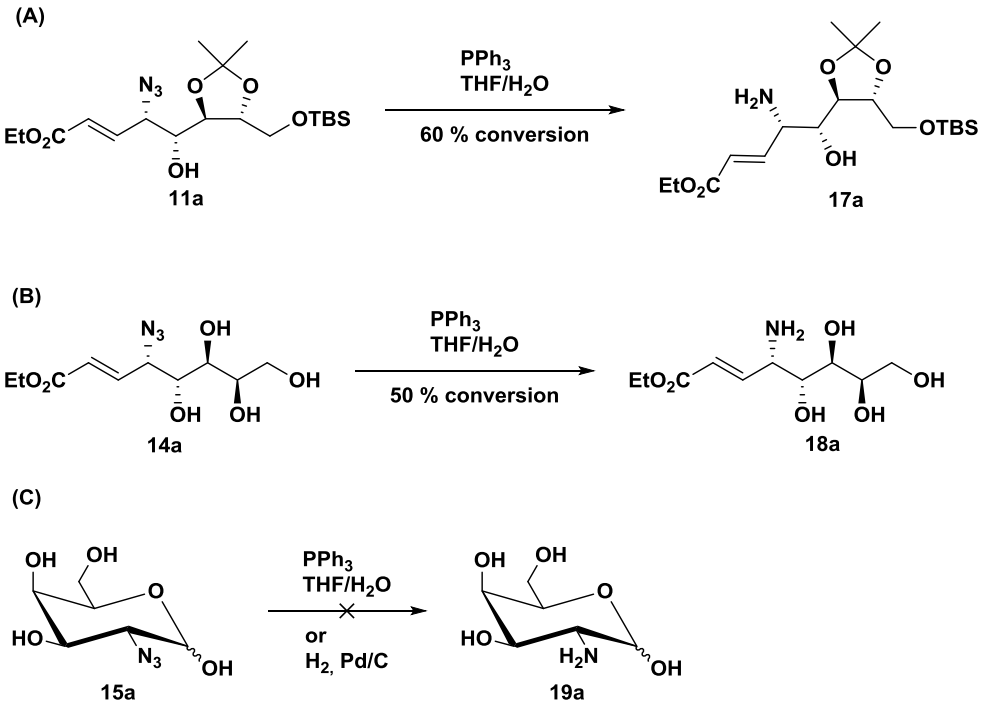


Figure 5: ^{1}H- and ^{13}C-NMR spectra of the anomeric signals of 16c.

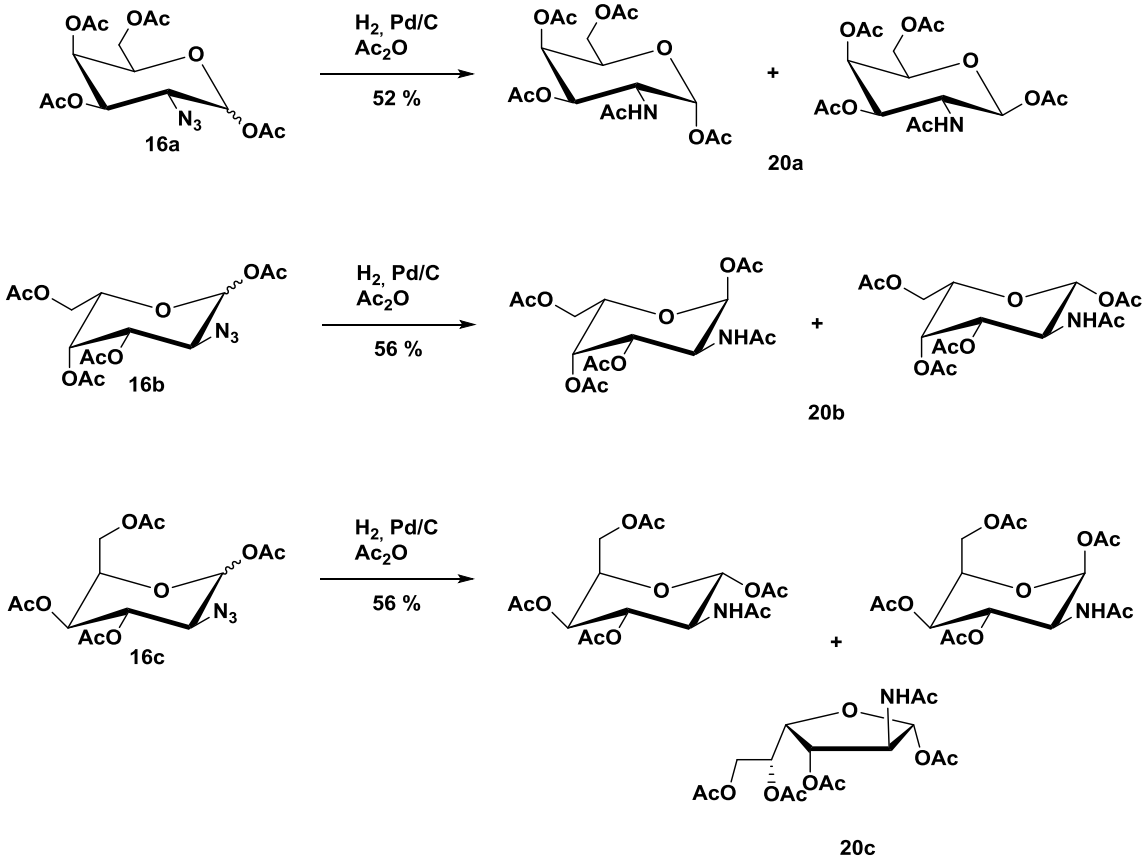
2.6 Azide reduction and final steps

The last steps included the formation of the amine functionality *via* azide reduction and selective deprotection of the hydroxyl groups. Attempts for the azide reduction of compound **11a** or **14a** *via* Staudinger reaction failed, due to incomplete conversion (Scheme 20A-B). Reduction of **11a** and **14a** with H_2 under Pd-catalysis was no option as the double bond would have been reduced, as well. Nevertheless, both reduction methodologies were tentatively applied for the reduction of compound **15a** (Scheme 20C). Unfortunately, it was not possible to isolate any compound **19a**.



Scheme 20: Staudinger reduction of compound 11a, 14a and 15a.

As the azide reduction of compounds **11a**, **14a** and **15a** was unsuccessful, Pd-catalyzed hydrogenolysis was performed with compound **16a**. Although the azide was completely reduced (indicated through NMR), acetyl migration was observed. Therefore, the reduction was performed in Ac_2O (Scheme 21). This resulted in 52 % of peracetylated D-galactosamine **20a**. The low yield can be explained by a partly adsorption of the generated amine on the activated charcoal, necessary for this reaction. The reaction protocol was successfully adapted for the synthesis of the peracetylated L-galactosamine **20b** and D-idosamine **20c**.



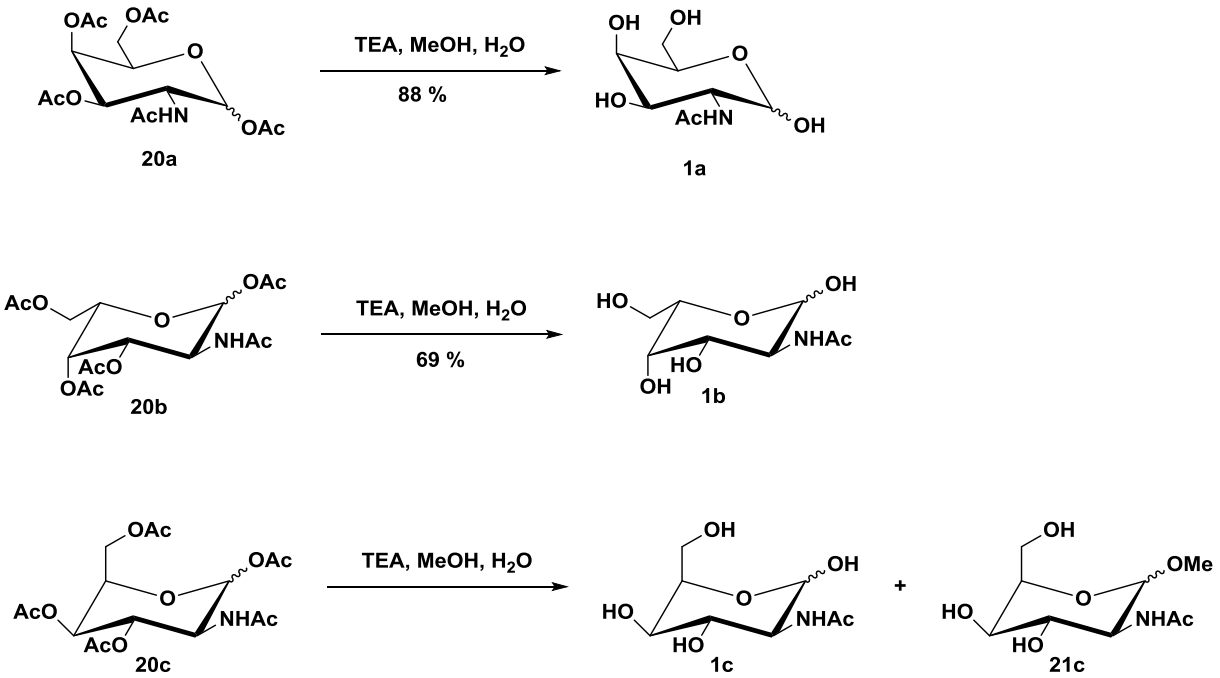
Scheme 21: Reductive acetylation of compounds 16a-c.

Finally, selective deprotection of the hydroxyl groups had to be performed without breaking the acetamide bond. Therefore, two deprotection protocols have been applied for the synthesis of the final amino sugars: On the one hand, Zemplén saponification using NaOMe in MeOH and on the other hand, deprotection in a mixture of Et_3N, MeOH and H_2O was performed (Table 3, Scheme 22). Both procedures, successfully, resulted in D-*N*-acetylgalactosamine **1a** and L-*N*-acetylgalactosamine **1b**. Unfortunately, deprotection of the peracetylated D-idosamine **20c** was not possible as a high amount of the methoxy glycoside **21c** was formed, as well. This was already determined *via* NMR analysis of the crude product, why no purification of compound **1c** was

performed. Here, further attempts for the deprotection would be necessary, which have not been performed anymore.

Table 3: Conditions and yield for deprotection of 20a-b.

Conditions	Yield (1a)	Yield (1b)
NaOMe/MeOH	63 %	71 %
Et_3N/MeOH/H_2O (1:10:10)	88 %	91 %



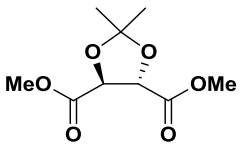
Scheme 22: Deprotection of 20a-c.

3 Experimental part

3.1 General methods

NMR spectra were recorded on a Bruker Avance DRX 400 (100.13 MHz for ^{1}H, 100.61 MHz for ^{13}C) or Bruker Avance III 600 (600.13 MHz for ^{1}H, 150.90 MHz for ^{13}C). Chemical shift (δ) are given in parts per million [ppm]. Abbreviations for the multiplicities are as followed: singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m). MS experiments were performed on a Finnigan MAT 900 spectrometer in ESI mode. IR spectra were verified on an ELMER FT-IR spectrometer. Optical rotations were measured on a Perkin Elmer Polarimeter 341. For flash chromatography Merck silica gel 60 (0.004 – 0.063 mm) was used. Merck plates (silica gel 60 F254) were used for TLC monitoring. The compounds were visualized under UV (254 nm), *via* treatment with a solution of 3 g $KMnO_4$, 20 g K_2CO_3 in 5 mL 5 % NaOH and 500 mL H_2O and subsequent heating. DCM, acetone, MeOH, EtOH, heptane and ethyl acetate were distilled before use. Dry DCM was prepared by filtration through an aluminium oxide column and stored over molecular sieves 4 Å. Other solvents and chemicals were purchased in reagent grade.

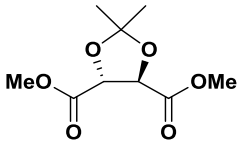
3.2 Dimethyl-2,3-*O*-isopropylidene-D-tartrate (**D-4**)



D-Tartaric acid (10 g, 66.63 mmol, 1 equiv) and *p*-toluenesulfonic acid (34 mg, 0.20 mmol, 0.003 equiv) were dissolved in dry MeOH (10 mL) in a flask equipped with reflux condenser and drying tube. 2,2-Dimethoxypropane (19 mL, 153.22 mmol, 2.3 equiv) was added and the mixture heated under reflux for 2 h. 2,2-Dimethoxypropane (9 mL, 72.58 mmol, 1.1 equiv) and cyclohexene (50 mL) were added and the solution slowly distilled *via* Vigreux column over 2 days. Again 2,2-Dimethoxypropane (0.8 mL, 6.45 mmol, 0.1 equiv) was added and distillation was continued until the temperature at the solvent head rose over 60 °C. After the solution cooled to room temperature, K_2CO_3 (92 mg, 0.67 mmol, 0.01 equiv) was added and the mixture stirred for an additional hour. The solvents were removed under reduced pressure and the resulting crude was purified by silica chromatography (heptane/ethyl acetate 3:1) to obtain tartrate **D-4** (13.89 g, 96 %) as a pale yellow oil: $[\alpha]^{20}_{D}$ = +47.3° (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 2 H, H-2 and

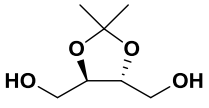
H-3), 3.82 (s, 6 H, OCH_3), 1.49 (s, 6 H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.18 (2 x C_q, C-1 and C-4), 114.00 (C_q, $\underline{C}(CH_3)_2$), 77.14 (2 x CH, C-2 and C-3), 52.92 (2 x CH_3, OCH_3), 26.44 (2 x CH_3, $C(\underline{C}H_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_9H_{14}O_6Na$ 241.0683; found 241.0681.

3.3 Dimethyl-2,3-*O*-isopropylidene-L-tartrate (L-4)



Compound **L-4** was synthesized from L-tartaric acid (10 g, 66.63 mmol) according to the procedure for compound **D-4** (chapter 3.2): yield 13.02 g (90 %); $[\alpha]^{20}_D$ = -47.4° (*c* 0.6, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 4.81 (s, 2 H, H-2 and H-3), 3.83 (s, 6 H, OCH_3), 1.50 (s, 6 H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.22 (2 x C_q, C-1 and C-4), 114.04 (C_q, $\underline{C}(CH_3)_2$), 77.17 (2 x CH, C-2 and C-3), 52.96 (2 x CH_3, OCH_3), 26.47 (2 x CH_3, $C(\underline{C}H_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_9H_{14}O_6Na$ 241.0683; found 241.0685.

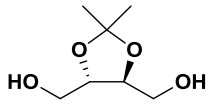
3.4 2,3-Di-*O*-isopropylidene-D-threitol (D-5)



$LiAlH_4$ (3.41 g, 89.82 mmol, 2 equiv) in dry THF (90 mL) was slowly added to a solution of **D-4** (9.80 g, 44.91 mmol, 1 equiv) in dry THF (145 mL) under argon at 0 °C. The mixture was heated under reflux for 1 h and quenched subsequently by the slow addition of H_2O (3.5 mL) at 0 °C, followed by 2 M NaOH (7 mL) and again H_2O (4 mL). The resulting solid was filtrated through Celite and washed with ethyl acetate. The solvents were removed under reduced pressure and purification of the obtained crude product by silica chromatography (heptane/ethyl acetate 1:4) yielded diol **D-5** (6.25 g, 89 %) as a pale yellow oil: $[\alpha]^{20}_D$ = +5.66° (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 3.91 (td, *J* = 2.8, 1.4 Hz, 2 H, H-2 and H-3), 3.69 (dt, *J* = 6.5, 4.7 Hz, 4 H, H-1 and H-4), 3.13 (dd, *J* = 6.5, 5.3 Hz, 2 H, OH), 1.38 (s, 6 H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.42 (C_q, $\underline{C}(CH_3)_2$), 78.16 (2 x CH, C-2 and C-3),

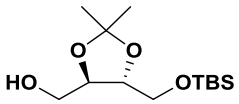
62.17 (2 x CH_2, C-1 and C-4), 27.17 (2 x CH_3, C($\underline{C}H_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_7H_{14}O_4Na$ 185.0784; found 185.0782.

3.5 2,3-Di-*O*-isopropylidene-L-threitol (L-5)



Compound **L-5** was synthesized from **L-4** (7.19 g, 32.93 mmol) according to the procedure for compound **D-5** (chapter 3.4): yield 4.90 g (92 %); $[\alpha]^{20}_D$ = -7.95° (*c* 1.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 4.00 (tt, *J* = 2.5, 1.5 Hz, 2 H, H-2 and H-3), 3.83 – 3.75 (m, 2 H, H-1 and H-4), 3.70 (dddd, *J* = 11.6, 7.4, 2.5, 1.3 Hz, 2 H, H-1 and H-4), 2.26 (dd, *J* = 6.9, 4.9 Hz, 2 H, OH), 1.43 (s, 6 H, $C(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 109.42 (C_q, $\underline{C}(CH_3)_2$), 78.14 (2 x CH, C-2 and C-3), 62.16 (2 x CH_2, C-1 and C-4), 27.17 (2 x CH_3, C($\underline{C}H_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_7H_{14}O_4Na$ 185.0784; found 185.0784.

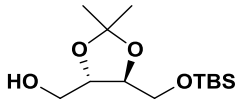
3.6 1-*O*-*tert*-Butyldimethylsilyloxy-2,3-di-O-isopropylidene-D-threitol (D-6)



NaH (111.67 mg of 60 % mineral oil dispersion, 2.11 mmol, 1 equiv) was added portionwise to a solution of TBSCl (418 mg, 2.77 mmol, 1 equiv) in dry THF (60 mL) under argon and stirred for 1 h. Subsequently, this mixture was added dropwise to a solution of **D-5** (450 mg, 2.77 mmol, 1 equiv) in dry THF (60 mL) under argon at 0°C and stirred for additional 18 h at r.t. The reaction was quenched by the slow addition of H_2O. The layers were separated and the water phase extracted three times with Et_2O. The combined organic phases were washed with brine and dried over $MgSO_4$. After evaporation of the solvents the crude product was purified by silica chromatography (heptane/ethyl acetate 9:1 to 5:1). Pure **D-6** (638 mg, 89 %) was received as a colorless oil: $[\alpha]^{20}_D$ = -17.00° (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.99 (d, *J* = 7.6 Hz, 1 H, H-3), 3.91 – 3.84 (m, 3 H, H-1a and H-2), 3.81 – 3.63 (m, 3 H, H-1b and H-4), 2.34 (dd, *J* = 8.2, 4.4 Hz, 2 H, OH), 1.42

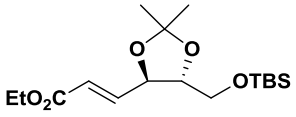
(s, 3 H, $C(CH_3)_2$), 1.40 (s, 3 H, $C(CH_3)_2$), 0.90 (s, 9 H, $C(CH_3)_3$), 0.09 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.26 (C_q, $\underline{C}(CH_3)_2$), 80.33 (CH, C-3), 78.29 (CH, C-2), 63.88 (CH_2, C-1), 62.92 (CH_2, C-4), 27.18 (CH_3, $C(\underline{C}H_3)_2$), 27.06 (CH_3, $C(\underline{C}H_3)_2$), 26.00 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.46 (C_q, $\underline{C}(CH_3)_3$), -5.34 (2 x CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{13}H_{28}O_4SiNa$ 299.1649; found 299.1643.

3.7 1-*O*-*tert*-Butyldimethylsilyloxy-2,3-di-O-isopropylidene-L-threitol (L-6)



Compound **L-6** was synthesized from **L-5** (5.2 g, 32.06 mmol) according to the procedure for compound **D-6** (chapter 3.6): yield 7.65 g (93 %); $[\alpha]^{20}_D$ = +15.96° (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 – 3.95 (m, 1 H, H-3), 3.87 (ttd, *J* = 6.1, 3.9, 1.7 Hz, 2 H, H-1a and H-2), 3.81 – 3.62 (m, 3H, H-1b and H-4), 2.36 (tdd, *J* = 8.7, 4.2, 1.6 Hz, 1 H, OH), 1.41 (s, 3 H, $C(CH_3)_2$), 1.40 (s, 3 H, $C(CH_3)_2$), 0.90 (s, 3 H, $C(CH_3)_3$), 0.08 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.26 (C_q, $\underline{C}(CH_3)_2$), 80.33 (CH, C-3), 78.29 (CH, C-2), 63.89 (CH_2, C-1), 62.93 (CH_2, C-4), 27.18 (CH_3, $C(\underline{C}H_3)_2$), 27.02 (CH_3, $C(\underline{C}H_3)_2$), 26.01 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.46 (C_q, $\underline{C}(CH_3)_3$), -5.33 (2 x CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{13}H_{28}O_4SiNa$ 299.1649; found 299.1643.

3.8 Ethyl-6-*tert*-butyldimethylsilyloxy-(4*R*,5*R*)-isopropylidenedioxy-(3*E*)-hexenoate (D-7)

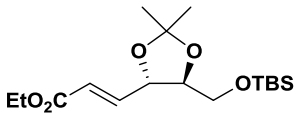


Oxalyl chloride (414 µL, 4.76 mmol, 2 equiv) was dissolved in DCM (3 mL) at -78 °C. After the dropwise addition of DMSO (676 µL, 9.52 mmol, 4 equiv) the mixture was stirred for 10 min. **D-6** (660 mg, 2.38 mmol, 1 equiv) dissolved in DCM (3 mL) was added slowly and stirring was continued for an additional hour. The reaction was quenched by the addition of Et_3N (2.0 mL, 14.27 mmol, 6 equiv) and was allowed to warm to r.t. The mixture was washed with water and the aqueous layer

extracted 3x with DCM. The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude aldehyde, which was used for the next step without further purification.

Sodium hydride (114 mg of a 60 % mineral oil dispersion, 2.85 mmol, 1.2 equiv) was dissolved in dry DCM (20 mL) under argon and cooled to 0 °C. Triethyl phosphonoacetate (1.978 mL, 2.85 mmol, 1.2 equiv) was added dropwise and the mixture was stirred at r.t. for 1 h. The primarily prepared intermediate, dissolved in dry DCM (8 mL), was added slowly and the solution stirred for additional 18 h. The reaction was quenched by pouring it into ice-water (100 mL). The layers were separated and the aqueous phase extracted 3x with DCM. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed and the crude ester purified through silica chromatography (heptane/ethyl acetate 9:1) yielding **D-7** (713 mg over 2 steps, 87 %) as a colorless oil: $[\alpha]^{20}_D$ = +3.04° (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, *J* = 15.7, 5.1 Hz, 1 H, H-3), 6.12 (dd, *J* = 15.7, 1.6 Hz, 1 H, H-2), 4.51 (ddd, *J* = 7.9, 5.1, 1.7 Hz, 1 H, H-4), 4.20 (q, *J* = 7.1 Hz, 2 H, $OC\underline{H}_2CH_3$), 3.85 – 3.73 (m, 3 H, H-5 and H-6), 1.43 (s, 3 H, $C(CH_3)_2$), 1.42 (s, 3 H, $C(CH_3)_2$), 1.29 (t, *J* = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 0.90 (s, 9 H, $C(CH_3)_3$), 0.08 (s, 3 H, $Si(CH_3)_2$), 0.07 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.25 (C_q, C-1), 144.85 (CH, C-3), 122.09 (CH, C-2), 110.03 (C_q, $\underline{C}(CH_3)_2$), 80.93 (CH, C-5), 77.98 (CH, C-4), 62.92 (CH_2, C-6), 60.63 (CH_2, $O\underline{C}H_2CH_3$), 27.08 (CH_3, $C(\underline{C}H_3)_2$), 26.95 (CH_3, $C(\underline{C}H_3)_2$), 26.01 (3 x CH_3, $C(\underline{C}H_3)_3$) 18.43 (C_q, $\underline{C}(CH_3)_3$), 14.38 (CH_3, $OCH_2\underline{C}H_3$), -5.24 (CH_3, $Si(CH_3)_2$), -5.31 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{32}O_5SiNa$ 367.1911; found 367.1907.

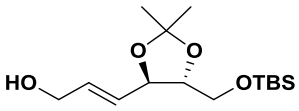
3.9 Ethyl-6-*tert*-butyldimethylsilyloxy-(4*S*,5*S*)-isopropylidenedioxy-(3*E*)-hexenoate (L-7)



Compound **L-7** was synthesized from **L-6** (7.74 g, 30.18 mmol) according to the procedure for compound **D-7** (chapter 3.8): yield 9.46 g (91 %); $[\alpha]^{20}_D$ = -2.31° (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dd, *J* = 15.7, 5.1 Hz, 1 H, H-3), 6.12 (dd, *J* = 15.7, 1.6 Hz, 1 H, H-2), 4.51 (ddd, *J* = 7.8, 5.1, 1.6 Hz, 1 H, H-4), 4.20 (qd, *J* = 7.1, 0.7 Hz, 2 H, $OC\underline{H}_2CH_3$), 3.85 – 3.70 (m, 3H, H-5 and H-6), 1.43 (s, 3 H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$), 1.29 (t, *J* = 7.2 Hz, 3 H, $OCH_2C\underline{H}_3$), 0.90 (s, 9H, $C(CH_3)_3$), 0.08 (s,

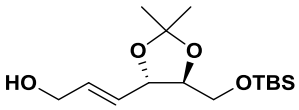
3 H, $Si(CH_3)_2$), 0.07 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.08 (C_q, $\underline{C}(CH_3)_2$), 144.68 (CH, C-3), 121.91 (CH, C-2), 109.91 (C_q, $\underline{C}(CH_3)$), 80.76 (CH, C-5), 77.81 (CH, C-4), 62.75 (CH_2, C-6), 60.46 (CH_2, $O\underline{C}H_2CH_3$), 26.91 (CH_3, $C(\underline{C}H_3)_2$), 26.78 (CH_3, $C(\underline{C}H_3)_2$), 25.84 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.27 (C_q, $\underline{C}(CH_3)_3$), 14.21 (CH_3, $OCH_2\underline{C}H_3$), -5.41 (CH_3, $Si(CH_3)_2$), -5.47 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{32}O_5SiNa$ 367.1911; found 367.1903.

3.10 (4*E*)-1-*O*-*tert*-Butyldimethylsilyl-4,5-dideoxy-2,3-*O*-isopropylidene-D-*threo*-hexen-1-ol (D-8)



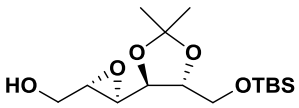
Compound **D-7** (6.66 g, 20.28 mmol, 1 equiv) was dissolved in cooled (0 °C), dry THF (60 mL) under argon and a 1 M solution DIBAL-H in toluene (60.83 mL, 60.83 mmol, 3 equiv) was added *via* syringe pump (0.45 mL/min). The mixture was stirred at r.t. for 18 h. By the slow addition of a sat. K-/Na-tartrate solution at 0 °C the reaction was quenched. This mixture was stirred until the two layers separated. The aqueous phase was extracted 3x with DCM and the combined organic layers were washed with brine. Drying over $MgSO_4$ followed by evaporation of the solvent and purification *via* silica chromatography (heptane/ethyl acetate 5:1 - 4:1) gave the unsaturated alcohol **D-8** (5.64 g, 92 %) as a colorless oil: $[\alpha]^{20}_D$ = +7.12° (*c* 1.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 5.98 (dtd, *J* = 15.5, 5.1, 1.0 Hz, 1 H, H-5), 5.76 (ddt, *J* = 15.5, 7.1, 1.6 Hz, 1 H, H-4), 4.38 (t, *J* = 7.1 Hz, 1 H, H-3), 4.22 – 4.13 (m, 2 H, H-6), 3.81 – 3.71 (m, 3 H, H-1 and H-2), 1.43 (s, 3 H, $C(CH_3)_2$), 1.41 (s, 3 H, $C(CH_3)_2$), 0.90 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 3 H, $Si(CH_3)_2$), 0.06 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.49 (CH, C-5), 128.65 (CH, C-4), 109.20 (C_q, $\underline{C}(CH_3)_2$), 81.50 (CH, C-2), 78.54 (CH, C-3), 63.01 (CH_2, C-6), 62.59 (CH_2, C-1), 27.24 (CH_3, $C(\underline{C}H_3)_2$), 27.07 (CH_3, $C(\underline{C}H_3)_2$), 26.03 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.49 (C_q, $\underline{C}(CH_3)_3$), -5.17 (CH_3, $Si(CH_3)_2$), -5.28 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{30}O_4SiNa$ 325.1806; found 325.1801.

3.11 (4*E*)-1-O-*tert*-Butyldimethylsilyl-4,5-dideoxy-2,3-*O*-isopropylidene-L-*threo*-hexen-1-ol (**L-8**)



Compound **L-8** was synthesized from **L-7** (8.49 g, 24.64 mmol) according to the procedure for compound **D-8** (chapter 3.10): yield 6.78 g (91 %); $[\alpha]^{20}_{D}$ = -2.68° (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.97 (dtd, *J* = 15.5, 5.2, 1.0 Hz, 1 H, H-5), 5.75 (ddt, *J* = 15.5, 7.1, 1.6 Hz, 1 H, H-4), 4.37 (dddd, *J* = 7.1, 6.2, 1.7, 0.9 Hz, 1 H, H-3), 4.17 (td, *J* = 5.6, 1.6 Hz, 2 H, H-6), 3.79 – 3.68 (m, 3 H, H-1 and H-2), 1.42 (s, 3 H, $C(CH_3)_2$), 1.41 (s, 3 H, $C(CH_3)_2$), 0.89 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 3 H, $Si(CH_3)_2$), 0.06 (s, 3 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 133.51 (CH, C-5), 128.62 (CH, C-4), 109.20 (C_q, $\underline{C}(CH_3)_2$), 81.50 (CH, C-2), 78.53 (CH, C-3), 62.99 (CH_2, C-6), 62.59 (CH_2, C-1), 27.23 (CH_3, $C(\underline{C}H_3)_2$), 27.07 (CH_3, $C(\underline{C}H_3)_2$), 26.03 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.48 (C_q, $\underline{C}(CH_3)_3$), -5.18 (CH_3,$Si(CH_3)_2$), -5.28 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{30}O_4SiNa$ 325.1806; found 325.1810.

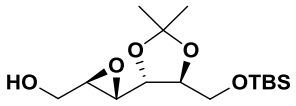
3.12 1-*O*-*tert*-Butyldimethylsilyl-4,5-dideoxy-(4*S*,5*S*)-epoxy-2,3-*O*-isopropylidene-D-*threo*-hexitol (**2a**)



Titanium(IV) isopropoxide (2.74 mL, 9.26 mmol, 1.4 equiv), was dissolved in dry DCM (50 mL) containing 4 Å molecular sieves (1.5 g) under argon at -78 °C. Diethyl-(L)-tartrate (1.59 mL, 9.26 mmol, 1.4 equiv) was added and the mixture stirred for 15 min. **D-8** (2 g, 6.61 mmol, 1 equiv) in dry DCM (10 mL) was added dropwise followed by a 5.5 M solution of *tert*-butyl hydroperoxide in nonane (2.4 mL, 13.22 mmol, 2 equiv). The solution was stirred for 18 h at -20 °C and quenched subsequently by the addition of 10 % solution of tartaric acid in water (25 mL). After stirring for an additional hour at r.t., the mixture was filtrated through a Celite pad, the layers separated and the organic layer washed with sat. $NaHCO_3$ solution. Drying over $MgSO_4$, removing of the solvent under reduced pressure and purification by silica chromatography (heptane/ethyl acetate 4:1) gave the epoxide **2a** (1.86 g, 86 %) as colorless oil: $[\alpha]^{20}_{D}$ = -16.19° (*c* 1.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) *δ*

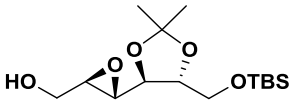
4.01 – 3.92 (m, 3 H, H-2 and H-3 and H-6a), 3.79 – 3.71 (m, 2 H, H-1), 3.72 – 3.65 (m, 1 H, H-6b), 3.24 – 3.15 (m, 2 H, H4 and H-5), 1.79 (dd, *J* = 7.5, 5.4 Hz, 1H, OH), 1.42 (s, 3 H, $C(CH_3)_2$), 1.41 (s, 3 H, $C(CH_3)_2$), 0.89 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 110.03 (C_q, $\underline{C}(CH_3)_2$), 79.12 (CH, C-2), 77.02 (CH, C-3), 63.56 (CH_2, C-1), 61.10 (CH_2, C-6), 56.14 (CH, C-5), 55.29 (CH, C-4), 27.05 (CH_3, $C(\underline{C}H_3)_2$), 26.89 (CH_3, $C(\underline{C}H_3)_2$), 26.03 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.50 (C_q, $\underline{C}(CH_3)_3$), -5.22 (CH_3, $Si(CH_3)_2$), -5.30 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{30}O_5SiNa$ 341.1755; found 341.1764.

3.13 1-*O*-*tert*-Butyldimethylsilyl-4,5-dideoxy-(4*R*,5*R*)-epoxy-2,3-*O*-isopropylidene-L-*threo*-hexitol (**2c**)



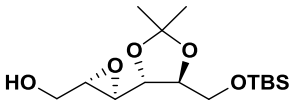
Titanium(IV) isopropoxide (2.74 mL, 9.26 mmol, 1.4 equiv), was dissolved in dry DCM (50 mL) containing 4 Å molecular sieves (1.5 g) under argon at -78 °C. Diethyl-(D)-tartrate (1.59 mL, 9.26 mmol, 1.4 equiv) was added and the mixture stirred for 15 min. **L-8** (2 g, 6.61 mmol, 1 equiv) in dry DCM (10 mL) was added dropwise followed by a 5.5 M solution of *tert*-butyl hydroperoxide in nonane (2.4 mL, 13.22 mmol, 2 equiv). The solution was stirred for 18 h at -20 °C and quenched subsequently by the addition of 10 % solution of tartaric acid in water (25 mL). After stirring for an additional hour at r.t., the mixture was filtrated through a Celite pad, the layers separated and the organic layer washed with sat. $NaHCO_3$ solution. Drying over $MgSO_4$, removing of the solvent under reduced pressure and purification by silica chromatography (heptane/ethyl acetate 4:1) gave the epoxide **2c** (1.87 g, 89 %) as colorless oil: $[\alpha]^{20}_D$ = +15.69° (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (ddd, *J* = 7.8, 6.0, 4.0 Hz, 1 H, H-2), 3.96 (ddd, *J* = 12.8, 4.5, 2.4 Hz, 1 H, H-6a), 3.91 (dd, *J* = 7.9, 4.7 Hz, 1 H, H-3), 3.84 (dd, *J* = 10.6, 3.9 Hz, 1 H, H-1a), 3.72 (dd, *J* = 10.6, 6.0 Hz, 1 H, H-1b), 3.69 – 3.63 (m, 1 H, H-6b), 3.19 (dt, *J* = 3.8, 2.3 Hz, 1 H, H-5), 3.14 (dd, *J* = 4.7, 2.3 Hz, 1 H, H-4), 1.69 (dd, *J* = 7.6, 5.0 Hz, 1 H, OH), 1.40 (s, *J* = 0.7 Hz, 3 H, $C(CH_3)_2$), 1.39 (s, *J* = 0.7 Hz, 3 H, $C(CH_3)_2$), 0.89 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.99 (C_q, $\underline{C}(CH_3)_2$), 78.41 (CH, C-2), 78.19 (CH, C-3), 63.65 (CH_2, C-1), 60.88 (CH_2, C-6), 55.77 (CH, C-5), 54.98 (CH, C-4), 27.16 (CH_3, $C(\underline{C}H_3)_2$), 26.80 (CH_3, $C(\underline{C}H_3)_2$), 26.05 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.51 (C_q, $\underline{C}(CH_3)_3$), -5.22 (CH_3, $Si(CH_3)_2$), -5.27 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{30}O_5SiNa$ 341.1755; found 341.1758.

3.14 1-*O*-*tert*-Butyldimethylsilyl-4,5-dideoxy-(4*R*,5*R*)-epoxy-2,3-*O*-isopropylidene-D-*threo*-hexitol (2b)



Compound **2b** was synthesized from **D-8** (3.15 g, 10.41 mmol) according to the procedure for compound **2c** (chapter 3.13): yield 2.97 g (89 %); $[\alpha]^{20}_{D}$ = +12.78° (*c* 1.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 3.99 – 3.91 (m, 3H, H-2 and H-3 and H-6a), 3.79 – 3.72 (m, 2H, H-1), 3.67 (ddd, *J* = 12.8, 7.4, 4.0 Hz, 1H, H-6b), 3.19 (ddd, *J* = 7.7, 4.1, 2.2 Hz, 2H, H-4 and H-5), 1.79 (dd, *J* = 7.5, 5.4 Hz, 1H, OH), 1.41 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$), 0.89 (s, 9H, $C(CH_3)_3$), 0.07 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 110.02 (C_q), 79.11 (CH), 76.99 (CH), 63.53 (CH_2), 61.11 (CH_2), 56.17 (CH), 55.29 (CH), 27.03 (CH_3), 26.87 (CH_3), 26.02 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.48 (C_q, $\underline{C}(CH_3)_3$), -5.23 (CH_3, $Si(CH_3)_2$), -5.28 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{30}O_5SiNa$ 341.1755; found 341.1751.

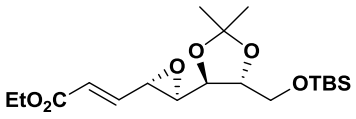
3.15 1-*O*-*tert*-Butyldimethylsilyl-4,5-dideoxy-(4*S*,5*S*)-epoxy-2,3-*O*-isopropylidene-L-*threo*-hexitol (2d)



Compound **2d** was synthesized from **L-8** (2 g, 6.61) according to the procedure for compound **2a** (chapter 3.12): yield 2.12 g (84 %); $[\alpha]^{20}_{D}$ = -12.22° (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 4.02 (ddd, *J* = 7.8, 6.0, 4.0 Hz, 1 H, H-2), 3.96 (ddd, *J* = 12.8, 4.7, 2.4 Hz, 1 H, H-6a), 3.91 (dd, *J* = 7.8, 4.7 Hz, 1 H, H-3), 3.84 (dd, *J* = 10.6, 3.9 Hz, 1 H, H-1a), 3.72 (dd, *J* = 10.6, 6.0 Hz, 1 H, H-1b), 3.69 – 3.60 (m, 1 H, H-6b), 3.19 (dt, *J* = 3.8, 2.3 Hz, 1 H, H-5), 3.14 (dd, *J* = 4.7, 2.3 Hz, 1 H, H-4), 1.69 (dd, *J* = 7.7, 5.1 Hz, 1 H, OH), 1.40 (s, 3 H, $C(CH_3)_2$), 1.39 (s, 3 H, $C(CH_3)_2$), 0.89 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 109.99 (C_q, $\underline{C}(CH_3)_2$), 78.41 (CH, C-2), 78.19 (CH, C-3), 63.65 (CH_2, C-1), 60.88 (CH_2, C-6), 55.77 (CH, C-5), 54.98 (CH, C-4), 27.16 (CH_3, $C(\underline{C}H_3)_2$), 26.80 (CH_3,

C($\underline{C}H_3)_2$), 26.05 (3 x CH_3, C($\underline{C}H_3)_3$), 18.51 (C_q, $\underline{C}(CH_3)_3$), -5.22 (CH_3, Si($CH_3)_2$), -5.27 (CH_3, Si($CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{30}O_5SiNa$ 341.1755; found 341.1762.

3.16 Ethyl-(2*E*)-8-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-(4*S*,5*S*)-epoxy-6,7-*O*-isopropylidene-D-*threo*-octa-2-enonate (**9a**)

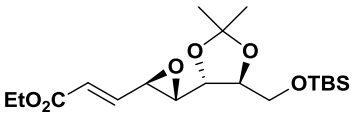


DMSO (2.9 mL, 41.33 mmol, 4 equiv) was added slowly to a solution of oxalyl chloride (1.8 mL, 20.66 mmol, 2 equiv) in dry DCM (35 mL) at -78 °C. After 15 min **2a** (3.29 g, 10.33 mmol, 1 equiv) in DCM (30 mL) was added dropwise and stirring continued for an additional hour. The reaction was quenched by the addition of Et_3N (8.6 mL, 61.99 mmol, 6 equiv) and allowed to warm up to r.t over 16 h. The mixture was washed with sat. NH_4Cl solution and brine. The solution was dried over $MgSO_4$, solvent removed under reduced pressure and the crude aldehyde used without further purification.

NaH (10 % in mineral oil, 496 mg, 12.40 mmol, 1.2 equiv) was dissolved in dry DCM (35 mL) under argon and cooled to 0°C. Triethyl phosphonoacetate (2.68 mL, 12.40 mmol, 1.2 equiv) was added slowly and the mixture stirred for 1 h at room temperature. Subsequently, the intermediate, dissolved in dry DCM (20 mL), was added and the solution stirred for 16 h. The reaction was quenched at 0°C by the slow addition of water. The phases were separated and the water phase extracted 3x with DCM. The organic phase was washed with brine and dried over $MgSO_4$. Removing of the solvents under reduced pressure and purification by silica chromatography (heptane/ethyl acetate 9:1) gave the unsaturated ester **9a** (3.10 g, 78 %) as a colorless oil: $[\alpha]^{20}_D$ = -7.57° (*c* 1.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.67 (dd, *J* = 15.7, 7.1 Hz, 1 H, H-3), 6.15 (d, *J* = 15.7 Hz, 1 H, H-2), 4.19 (q, *J* = 7.1 Hz, 2 H, O$\underline{C}H_2CH_3$), 3.98 (dt, *J* = 9.2, 4.7 Hz, 1 H, H-7), 3.93 (dd, *J* = 7.4, 4.5 Hz, 1 H, H-6), 3.78 (dd, *J* = 10.7, 4.0 Hz, 1 H, H-8a), 3.73 (dd, *J* = 10.7, 5.3 Hz, 1 H, H-8b), 3.52 – 3.49 (m, 1 H, H-4), 3.10 (dd, *J* = 4.2, 1.3 Hz, 1 H, H-5), 1.41 (s, 3 H, C($CH_3)_2$), 1.40 (s, 3 H, C($CH_3)_2$), 1.28 (t, *J* = 7.2 Hz, 3 H, $OCH_2C\underline{H}_3$), 0.89 (s, 9 H, C($CH_3)_3$), 0.07 (s, 6 H, Si($CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.59 (C_q, C-1), 143.44 (CH, C-3), 124.64 (CH, C-2), 110.20 (C_q, $\underline{C}(CH_3)_2$), 79.02 (CH, C-7), 77.14 (CH, C-6), 63.47 (CH_2, C-8), 60.82 (CH, C-5), 60.80 (CH_2, O$\underline{C}H_2CH_3$), 54.12 (CH, C-4), 27.02 (CH_3, C($\underline{C}H_3)_2$), 26.81 (CH_3, C($\underline{C}H_3)_2$), 26.02 (3 x CH_3, C($\underline{C}H_3)_3$), 18.48 (C_q, $\underline{C}(CH_3)_3$), 14.33 (CH_3, $OCH_2\underline{C}H_3$), -5.23 (CH_3,

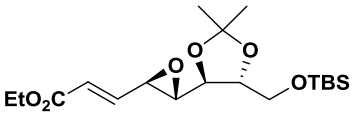
$Si(CH_3)_2$), -5.32 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{19}H_{34}O_6SiNa$ 409.2017; found 409.2016.

3.17 Ethyl-(2*E*)-8-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-(4*R*,5*R*)-epoxy-6,7-*O*-isopropylidene-L-*threo*-octa-2-enonate (9b)



Compound **9b** was synthesized from **2b** (1.31 g, 4.11 mmol) according to the procedure for compound **9a** (chapter 3.16): yield 1.15 g (72 %); $[\alpha]^{20}_D$ = +6.80° (*c* 1.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.67 (dd, *J* = 15.7, 7.1 Hz, 1 H. H-3), 6.15 (dd, *J* = 15.6, 0.8 Hz, 1 H, H-2), 4.20 (q, *J* = 7.1 Hz, 2 H, $OC\underline{H}_2CH_3$), 3.98 (ddd, *J* = 7.5, 5.3, 4.1 Hz, 1 H, H-7), 3.93 (dd, *J* = 7.5, 4.4 Hz, 1 H, H-6), 3.78 (dd, *J* = 10.7, 4.1 Hz, 1 H, H-8a), 3.74 (dd, *J* = 10.7, 5.4 Hz, 1 H, H-8b), 3.53 – 3.49 (m, 1 H, H-4), 3.11 (dd, *J* = 4.5, 2.0 Hz, 1 H, H-5), 1.41 (s, 3 H, $C(CH_3)_2$), 1.40 (s, 3 H, $C(CH_3)_2$), 1.28 (t, *J* = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 0.89 (s, 9 H, $C(CH_3)_3$), 0.07 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.60 (C_q, C-1), 143.44 (CH, C-3), 124.65 (CH, C-2), 110.21 (C_q, $\underline{C}(CH_3)_2$), 79.03 (CH, C-7), 77.15 (CH, C-6), 63.49 (CH_2, C-8), 60.83 (CH, C-5), 60.81 (CH_2, $O\underline{C}H_2CH_3$), 54.13 (CH, C-4), 27.03 (CH_3, $C(CH_3)_2$), 26.82 (CH_3, $C(CH_3)_2$), 26.02 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.49 (C_q, $\underline{C}(CH_3)_3$), 14.34 (CH_3, $OCH_2\underline{C}H_3$), -5.22 (CH_3, $Si(CH_3)_2$), -5.31 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{19}H_{34}O_6SiNa$ 409.2017; found 409.2025.

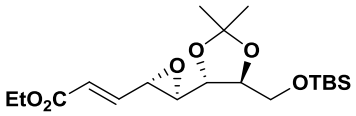
3.18 Ethyl-(2*E*)-8-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-(4*R*,5*R*)-epoxy-6,7-*O*-isopropylidene-D-*threo*-octa-2-enonate (9c)



Compound **9c** was synthesized from **2c** (2.47 g, 7.76 mmol) according to the procedure for compound **9a** (chapter 3.16): yield 2.37 g (79 %); $[\alpha]^{20}_D$ = +23.47° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (ddd, *J* = 15.7, 7.3, 0.7 Hz, 1 H, H-3), 6.15 (dd, *J* = 15.6, 0.8 Hz, 1 H, H-2), 4.20 (q, *J* = 7.1

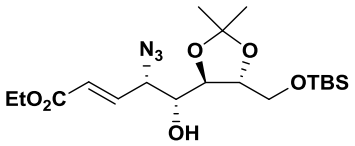
Hz, 2 H, OC$\underline{H}_2$CH$_3$), 4.05 (ddd, *J* = 7.6, 6.2, 3.9 Hz, 1 H, H-7), 3.99 (dd, *J* = 7.7, 3.9 Hz, 1 H, H-6), 3.85 (dd, *J* = 10.6, 3.9 Hz, 1 H, H-8a), 3.72 (dd, *J* = 10.6, 6.2 Hz, 1 H, H-8b), 3.53 (dt, *J* = 7.2, 1.3 Hz, 1 H, H-4), 3.05 (dd, *J* = 3.9, 2.0 Hz, 1 H, H-5), 1.39 (s, 6H, C(CH$_3$)$_2$), 1.29 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C$\underline{H}_3$), 0.89 (s, 9 H, C(CH$_3$)$_3$), 0.08 (s, 6 H, SI(CH$_3$)$_2$); ^{13}C NMR (150 MHz, CDCl$_3$) δ 165.68 (C$_q$, C-1), 143.74 (CH, C-3), 124.60 (CH, C-2), 110.15 (C$_q$, $\underline{C}$(CH$_3$)$_2$), 78.09 (CH, C-7), 77.72 (CH, C-6), 63.57 (CH$_2$, C-8), 60.82 (CH$_2$, O$\underline{C}$H$_2$CH$_3$), 60.31 (CH, C-5), 53.80 (CH, C-4), 27.19 (CH$_3$, C($\underline{C}$H$_3$)$_2$), 26.64 (CH$_3$, C($\underline{C}$H$_3$)$_2$), 26.04 (3 x CH$_3$, C($\underline{C}$H$_3$)$_3$), 18.50 (C$_q$, $\underline{C}$(CH$_3$)$_3$), 14.35 (CH$_3$, OCH$_2$$\underline{C}H_3$), -5.22 (CH$_3$, Si(CH$_3$)$_2$), -5.26 (CH$_3$, Si(CH$_3$)$_2$); HRMS (ESI) *m/z* [M + Na]$^+$ calcd for C$_{19}$H$_{34}$O$_6$SiNa 409.2017; found 409.2034.

3.19 Ethyl-(2*E*)-8-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-(4*S*,5*S*)-epoxy-6,7-*O*-isopropylidene-L-*threo*-octa-2-enonate (9d)



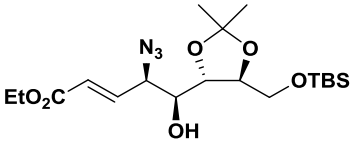
Compound **9d** was synthesized from **2d** (960 mg, 3.01 mmol) according to the procedure for compound **9a** (chapter 3.16): yield 956 mg (82 %); [α]$^{20}_D$ = -20.19° (*c* 1.1, CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$) *δ* 6.66 (dd, *J* = 15.7, 7.3 Hz, 1 H), 6.15 (d, *J* = 15.7 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.05 (ddd, *J* = 7.7, 6.2, 3.9 Hz, 1 H), 3.99 (dd, *J* = 7.8, 3.9 Hz, 1 H), 3.85 (dd, *J* = 10.6, 3.9 Hz, 1 H), 3.72 (dd, *J* = 10.6, 6.2 Hz, 1 H), 3.53 (dd, *J* = 7.3, 2.0 Hz, 1 H), 3.06 (dd, *J* = 4.0, 2.0 Hz, 1 H), 1.39 (s, 6 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (150 MHz, CDCl$_3$) *δ* 165.68 (C$_q$, C-1), 143.75 (CH, C-3), 124.60 (CH, C-2), 110.16 (C$_q$, $\underline{C}$(CH$_3$)$_2$), 78.09 (CH, C-7), 77.72 (CH, C-6), 63.56 (CH$_2$, C-8), 60.82 (CH$_2$, O$\underline{C}$H$_2$CH$_3$), 60.31 (CH, C-5), 53.80 (CH, C-4), 27.19 (CH$_3$, C(CH$_3$)$_2$), 26.64 (CH$_3$, C(CH$_3$)$_2$), 26.04 (3 x CH$_3$, C($\underline{C}$H$_3$)$_3$), 18.50 (C$_q$, $\underline{C}$(CH$_3$)$_2$), 14.35 (CH$_3$, OCH$_2$$\underline{C}H_3$), -5.22 (CH$_3$, Si(CH$_3$)$_2$), -5.26 (CH$_3$, Si(CH$_3$)$_2$); HRMS (ESI) *m/z* [M + Na]$^+$ calcd for C$_{19}$H$_{34}$O$_6$SiNa 409.2017; found 409.2023.

3.20 Ethyl-(2*E*)-4-azido-8-*O*-*tert*-butyldimethylsilyl-6,7-*O*-isopropylidene-2,3,4-trideoxy-D-*galacto*-octa-2-enonate (**11a**)



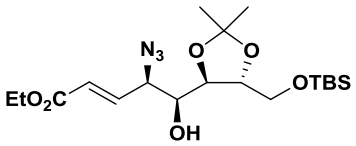
Compound **9a** (1.0 g, 2.59, 1 equiv) was dissolved in dry and degassed EtOH under argon. $Pd(PPh_3)_4$ (299 mg, 0.26 mmol, 0.1 equiv) and trimethylsilyl azide (0.68 mL, 5.17 mmol, 2 equiv) were added and the mixture stirred for 4 h. Subsequently, the orange solid was filtered off. The solvents were removed under reduced pressure and the crude product purified by silica chromatography (heptane/ethyl acetate 5:1) to receive compound **11a** (988 mg, 89 %) as a colorless oil: $[\alpha]^{20}_D$ = +3.78° (*c* 1.0, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 15.7, 6.8 Hz, 1 H, H-3), 6.16 (dd, *J* = 15.7, 1.4 Hz, 1 H, H-2), 4.22 (q, *J* = 7.1 Hz, 2 H, $OC\underline{H}_2CH_3$), 4.19 (d, *J* = 6.8 Hz, 1 H, H-5), 3.98 (dd, *J* = 9.6, 3.6 Hz, 1 H, H-8a), 3.93 –3.89 (m, 2 H, H-6 and H-7), 3.88 – 3.86 (m, 1 H, H-4), 3.68 (dt, *J* = 8.3, 2.5 Hz, 1 H, OH), 3.65 – 3.61 (m, 1 H, H-8b), 1.40 (s, 3 H, $C(CH_3)_2$), 1.38 (s, 3 H, $C(CH_3)_2$), 1.31 (t, *J* = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 0.91 (s, 9 H, $C(CH_3)_3$), 0.12 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.86 (C_q, C-1), 142.22 (CH, C-3), 124.74 (CH, C-2), 109.77 (C_q, $\underline{C}(CH_3)_2$), 80.25 (CH, C-6), 80.04 (CH, C-7), 74.94 (CH, C-4), 64.39 (CH_2, C-8), 62.93 (CH, C-5), 60.85 (CH_2, $O\underline{C}H_2CH_3$), 26.93 (CH_3, $C(\underline{C}H_3)_2$), 26.91 (CH_3, $C(\underline{C}H_3)_2$), 25.99 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.52 (C_q, $\underline{C}(CH_3)_3$), 14.37 (CH_3, $OCH_2\underline{C}H_3$), -5.41 (CH_3, $Si(CH_3)_2$), -5.42 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{35}N_3O_6SiNa$ 452.2193; found 452.2195; (IR) ν 3385, 2985, 2930, 2885, 2858, 2101, 1722, 1371, 1253, 1178, 1141, 1078, 1045 cm^{-1}.

3.21 Ethyl-(2*E*)-4-azido-8-*O*-*tert*-butyldimethylsilyl-6,7-*O*-isopropylidene-2,3,4-trideoxy-L-*galacto*-octa-2-enonate (**11b**)



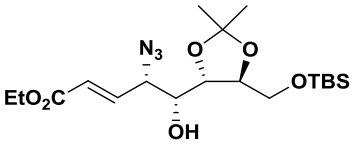
Compound **11b** was synthesized from **9b** (1.75 g, 4.53 mmol) according to the procedure for compound **11a** (chapter 3.20): yield 1.57 g (80 %); $[\alpha]^{20}_{D}$ = -2.76° (*c* 1.25, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.07 (dd, *J* = 15.7, 6.8 Hz, 1 H, H-3), 6.15 (dd, *J* = 15.7, 1.4 Hz, 1 H, H-2), 4.22 (q, *J* = 7.1 Hz, 2 H, $OC\underline{H}_2CH_3$), 4.20 – 4.17 (m, 1 H, H-5), 4.00 – 3.96 (m, 1 H, H-8a), 3.94 – 3.88 (m, 2 H, H-6 and H-7), 3.86 (dd, *J* = 2.7, 1.0 Hz, 1H, H-4), 3.68 (dt, *J* = 8.2, 2.4 Hz, 1 H, OH), 3.65 – 3.60 (m, 1 H, H-8b), 1.40 (s, 3 H, $C(CH_3)_2$), 1.38 (s, 3 H, $C(CH_3)_2$), 1.30 (t, *J* = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 0.91 (s, 9 H, $C(CH_3)_3$), 0.12 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 165.84 (C_q, C-1), 142.21 (CH, C-3), 124.73 (CH, C-2), 109.76 (C_q, $\underline{C}(CH_3)_2$), 80.24 (CH, C-6), 80.04 (CH, C-7), 74.94 (CH, C-4), 64.39 (CH_2, C-8), 62.93 (CH, C-5), 60.83 (CH_2, $O\underline{C}H_2CH_3$), 26.93 (CH_3, $C(\underline{C}H_3)_2$), 26.90 (CH_3, $C(\underline{C}H_3)_2$), 25.99 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.51 (C_q, $\underline{C}(CH_3)_2$), 14.37 (CH_3, $OCH_2\underline{C}H_3$), -5.42 (CH_3, $Si(CH_3)_2$), -5.43 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{35}N_3O_6SiNa$ 452.2193; found 452.2186; (IR) ν 3385, 2931, 2101, 1722, 1370, 1252, 1169, 1077, 1044 cm^{-1}.

3.22 Ethyl-(2*E*)-4-azido-8-*O*-*tert*-butyldimethylsilyl-6,7-*O*-isopropylidene-2,3,4-trideoxy-D-*ido*-octa-2-enonate (11c)



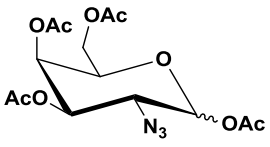
Compound **11c** was synthesized from **9c** (2.2 g, 5.69 mmol) according to the procedure for compound **11a** (chapter 3.20): yield 1.91 g (78 %); $[\alpha]^{20}_{D}$ = -14.64° (*c* 1.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.85 (dd, *J* = 15.6, 7.5 Hz, 1 H, H-3), 6.12 (dd, *J* = 15.6, 1.2 Hz, 1 H, H-2), 4.26 – 4.20 (m, 2 H, $OC\underline{H}_2CH_3$), 4.20 – 4.14 (m, 1 H, H-5), 4.10 (ddd, *J* = 7.9, 6.5, 3.9 Hz, 1 H, H-7), 3.98 (dd, *J* = 8.0, 2.0 Hz, 1 H, H-6), 3.83 (dd, *J* = 10.5, 3.9 Hz, 1 H, H-8a), 3.70 – 3.63 (m, 2 H, H-4 and H-8b), 2.62 (d, *J* = 8.7 Hz, 1 H, OH), 1.43 (s, 3 H, $C(CH_3)_2$), 1.39 (s, 3 H, $C(CH_3)_2$), 1.30 (t, *J* = 7.2 Hz, 3 H, $OCH_2C\underline{H}_3$), 0.88 (s, 9 H, $C(CH_3)_3$), 0.06 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 165.48 (C_q, C-1), 140.87 (CH, C-3), 125.59 (CH, C-2), 109.98 (C_q, $\underline{C}(CH_3)_2$), 78.47 (CH, C-6), 77.05 (CH, C-7), 71.99 (CH, C-4), 65.74 (CH, C-5), 63.57 (CH_2, C-8), 60.92 (CH_2, $O\underline{C}H_2CH_3$), 27.22 (CH_3, $C(\underline{C}H_3)_2$), 27.03 (CH_3, $C(\underline{C}H_3)_2$), 25.97 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.39 (C_q, $\underline{C}(CH_3)_3$), 14.33 (CH_3, $OCH_2\underline{C}H_3$), -5.37 (CH_3, $Si(CH_3)_2$), -5.40 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{35}N_3O_6SiNa$ 452.2193; found 452.2188; (IR) ν 3348, 2925, 2347, 2112, 1738, 1642, 1322, 1041 cm^{-1}.

3.23 Ethyl-(2*E*)-4-azido-8-*O*-*tert*-butyldimethylsilyl-6,7-*O*-isopropylidene-2,3,4-trideoxy-L-*ido*-octa-2-enonate (11d)



Compound **11d** was synthesized from **9d** (850 mg, 2.15 mmol) according to the procedure for compound **11a** (chapter 3.20): yield 692 mg (75 %); $[\alpha]^{20}_{D}$ = +13.04° (*c* 1.25, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.84 (dd, *J* = 15.6, 7.5 Hz, 1 H, H-3), 6.12 (dd, *J* = 15.6, 1.1 Hz, 1 H, H-2), 4.24 – 4.20 (m, 2 H, $OC\underline{H}_2CH_3$), 4.19 – 4.17 (m, 1 H, H-5), 4.09 (ddd, *J* = 7.9, 6.6, 3.9 Hz, 1 H, H-7), 3.97 (dd, *J* = 8.0, 2.0 Hz, 1 H, H-6), 3.83 (dd, *J* = 10.5, 4.0 Hz, 1 H, H-8a), 3.69 – 3.63 (m, 2 H, H-4 and H-8b), 2.63 (dt, *J* = 8.7, 1.4 Hz, 1 H, OH), 1.43 (s, 3 H, $C(CH_3)_2$), 1.39 (s, 3 H, $C(CH_3)_2$), 1.30 (t, *J* = 7.1 Hz, 3 H, $OCH_2C\underline{H}_3$), 0.88 (s, 9 H, $C(CH_3)_3$), 0.06 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.49 (C_q, C-1), 140.86 (CH, C-3), 125.58 (CH, C-2), 109.98 (C_q, $\underline{C}(CH_3)_2$), 78.44 (CH, C-6), 76.98 (CH, C-7), 71.93 (CH, C-4), 65.73 (CH, C-5), 63.52 (CH_2, C-8), 60.95 (CH_2, $O\underline{C}H_2CH_3$), 27.21 (CH_3, $C(\underline{C}H_3)_2$), 27.03 (CH_3, $C(\underline{C}H_3)_2$), 25.97 (3 x CH_3, $C(\underline{C}H_3)_3$), 18.38 (C_q, $\underline{C}(CH_3)_3$), 14.33 (CH_3, $OCH_2\underline{C}H_3$), -5.37 (CH_3, $Si(CH_3)_2$), -5.41 (CH_3, $Si(CH_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{35}N_3O_6SiNa$ 452.2193; found 452.2189; (IR) ν 3451, 2930, 2857, 2103, 1723, 1658, 1464, 1370, 1253, 1217, 1169, 1136, 1082, 1041 cm^{-1}.

3.24 2-Azido-1,3,4,6-deoxy-D-*galacto* pentaacetate (16a)



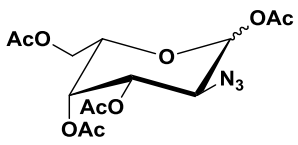
11a (2.0 g, 4.66 mmol, 1 equiv) was dissolved in 10 mL MeOH/H_2O (4:1). After the addition of DOWEX H^+ (approx. 1 g) the mixture was heated to 40 °C for 16 h. DOWEX H^+ was filtered off and the solvents removed under reduced pressure. The crude product was recrystallized from DCM and

heptane. The yellow solid was filtrated and dried under reduced pressure to give the unprotected compound, which was used without further purification.

The solid was dissolved in DCM/MeOH (9:1) and ozone was purged through at -78 °C until the solution became blue. Subsequently, oxygen was purged through until the blue color disappeared, again. DMSO (0.69 mL, 9.31 mmol, 2 equiv) was added and the solution stirred overnight. The solution, containing partly precipitated product, was removed and the product used without further purification.

The solid was dissolved in 10 mL Ac_2O/pyridine (1:1) under argon. DMAP (57 mg, 0.47 mmol, 0.1 equiv) was added and the mixture stirred overnight. The solvents were removed under reduced pressure and the crude product purified by silica chromatography (heptane/ethyl acetate 3:1) to receive compound **16a** (1.4 g, 81 %, α-*pyr*/β-*pyr* 14:86): ^{1}H NMR (600 MHz, $CDCl_3$) δ α: 6.31 (d, *J* = 3.6 Hz, 1 H, H-1), 5.47 (dd, *J* = 3.2, 1.3 Hz, 1 H, H-4), 5.31 (dd, *J* = 11.1, 3.2 Hz, 1 H, H-3), 4.30 – 4.25 (m, 1 H, H-5), 4.11 – 4.04 (m, 2 H, H-6), 3.93 (dd, *J* = 11.1, 3.6 Hz, 1 H, H-2), 2.17 (s, 3 H; Ac), 2.16 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.03 (s, 3 H, Ac); β: 5.54 (d, *J* = 8.5 Hz, 1 H, H-1), 5.37 (dd, *J* = 3.3, 0.9 Hz, 1 H, H-4), 4.88 (dd, *J* = 10.8, 3.3 Hz, 1 H, H-3), 4.16 – 4.08 (m, 2 H, H-6), 4.00 (td, *J* = 6.7, 1.1 Hz, 1 H, H-5), 3.83 (dd, *J* = 10.8, 8.5 Hz, 1 H, H-2), 2.20 (s, 3 H, Ac), 2.16 (s, 3 H, Ac), 2.06 (s, 3 H, Ac), 2.03 (s, 3 H, Ac); ^{13}C NMR (150 MHz, $CDCl_3$) δ α: 170.48 (C_q, Ac), 170.11 (C_q, Ac), 169.99 (C_q, Ac), 168.85 (C_q, Ac), 90.52 (CH, C-1), 68.86 (CH, C-5), 68.77 (CH, C-3), 66.94 (CH, C-4), 61.21 (CH_2, C-6), 56.92 (CH, C-2), 21.08 (CH_3, Ac), 20.79 (3 x CH_3, Ac), 20.76 (CH_3, Ac); β: 170.46 (C_q, Ac), 170.07 (C_q, Ac), 169.75 (C_q, Ac), 168.70 (C_q, Ac), 92.96 (CH, C-1), 71.82 (CH, C-5), 71.40 (CH, C-3), 66.25 (CH, C-4), 61.05 (CH_2, C-6), 59.75 (CH, C-2), 21.03 (CH_3, Ac), 20.79 (CH_3, Ac), 20.74 (CH_3, Ac), 20.72 (CH_3, Ac); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{19}N_3O_9Na$ 396.1019; found 396.1016; (IR) ν 2970, 2114, 1747, 1433, 1370, 1213, 1076, 1072 cm^{-1}.

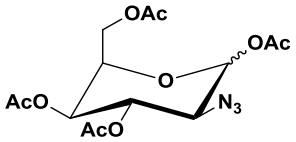
3.25 2-Azido-1,3,4,6-deoxy-L-*galacto* pentaacetate (16b)



Compound **16b** was synthesized from **11b** (1.56 g, 3.63 mmol) according to the procedure for compound **16a** (chapter 3.24): yield 854 mg (63 %; α-*pyr*/β-*pyr* 19:81); ^{1}H NMR (600 MHz, $CDCl_3$) δ

α: 6.31 (d, *J* = 3.6 Hz, 1 H, H-1), 5.48 – 5.45 (m, 1 H, H-4), 5.30 (ddd, *J* = 11.0, 3.3, 1.1 Hz, 1 H, H-3), 4.27 (t, *J* = 6.8 Hz, 1 H, H-5), 4.11 – 4.06 (m, 2 H, H-6), 3.93 (dd, *J* = 11.0, 3.6 Hz, 1 H, H-2), 2.17 (s, 3 H, Ac), 2.16 (s, 3 H, Ac), 2.06 (s, 3 H, Ac), 2.06 (s, 3 H, Ac); β: 5.54 (d, *J* = 8.5 Hz, 1 H, H-1), 5.38 – 5.35 (m, 1 H, H-4), 4.88 (dd, *J* = 10.8, 3.3 Hz, 1 H, H-3), 4.15 – 4.09 (m, 2 H, H-6), 4.00 (td, *J* = 6.7, 1.2 Hz, 1 H, H-5), 3.83 (ddd, *J* = 10.9, 8.5, 1.1 Hz, 1 H, H-2), 2.19 (s, 3 H, Ac), 2.16 (s, 3 H, Ac), 2.05 (s, 3 H, Ac), 2.03 (s, 3 H, Ac); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* α: 170.11 (C_q, Ac), 169.99 (C_q, Ac), 169.75 (C_q, Ac), 168.85 (C_q, Ac), 90.51 (CH, C-1), 68.86 (CH, C-5), 68.75 (CH, C-3), 66.94 (CH, C-4), 61.20 (CH_2, C-6), 56.91 (CH, C-2), 21.18 (CH_3, Ac), 20.06 (CH_3, Ac), 20.77 (CH_3, Ac), 20.72 (CH_3, Ac); β: 170.47 (C_q, Ac), 170.07 (C_q, Ac), 169.75 (C_q, Ac), 168.70 (C_q, Ac), 92.95 (CH, C-1), 71.81 (CH, C-5), 71.39 (CH, C-3), 66.26 (CH, C-4), 61.05 (CH_2, C-6), 59.74 (CH, C-2), 21.01 (CH_3, Ac), 20.77 (CH_3, Ac), 20.72 (CH_3, Ac), 20.70 (CH_3, Ac); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{19}N_3O_9SiNa$ 396.1019; found 396.1013; (IR) ν 2969, 2113, 1744, 1368, 1209, 1074, 1040 cm^{-1}.

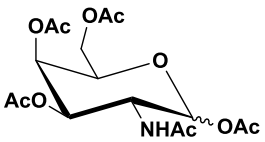
3.26 2-Azido-1,3,4,6-deoxy-D-*ido* pentaacetate (16c)



Compound **16c** was synthesized from **11c** (100 mg, 0.23 mmol) according to the procedure for compound **16a** (chapter 3.24): yield 32 mg (37 %; α-*pyr*/β-*pyr*/α-*fur* 50:31:19); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* α-*pyr*: 6.00 (d, *J* = 4.4 Hz, 1 H, H-1), 5.12 (dd, *J* = 6.4, 5.2 Hz, 1 H, H-3), 5.04 (dd, *J* = 5.2, 3.6 Hz, 1 H, H-4), 4.45 (ddd, *J* = 6.6, 5.2, 3.6 Hz, 1 H, H-5), 4.27 – 4.21 (m, 2 H, H-6), 3.65 (dd, *J* = 6.4, 4.4 Hz, 1 H, H-2), 2.12 (s, 3 H, Ac), 2.11 (s, 3 H, Ac), 2.11 (s, 3 H, Ac), 2.07 (s, 3 H, Ac); β-*pyr*: 6.06 (d, *J* = 2.4 Hz, 1 H, H-1), 5.25 (t, *J* = 4.6 Hz, 1 H, H-3), 4.87 (dd, *J* = 4.5, 3.0 Hz, 1 H, H-4), 4.35 (ddd, *J* = 7.2, 5.6, 3.1 Hz, 1 H, H-5), 4.19 – 4.13 (m, 2 H, H-6), 3.57 (dd, *J* = 4.6, 2.4 Hz, 1 H, H-2), 2.18 (s, 3 H, Ac), 2.13 (s, 3 H, Ac), 2.13 (s, 3 H, Ac), 2.04 (s, 3 H, Ac); α-*fur*: 6.02 (d, *J* = 1.8 Hz, 1 H, H-1), 5.32 (td, *J* = 6.3, 3.8 Hz, 1 H, H-3), 5.17 (dd, *J* = 6.0, 3.2 Hz, 1 H, H-4), 4.52 (t, *J* = 6.2 Hz, 1 H, H-2), 4.29 (dd, *J* = 12.0, 3.8 Hz, 1H, H-6a), 4.16 – 4.14 (m, 1H, H-5), 4.01 (dd, *J* = 12.0, 6.4 Hz, 1H, H-6b), 2.13 (s, 3 H, Ac), 2.11 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.03 (s, 3 H, Ac); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* α-*pyr*: 170.47 (C_q, Ac), 169.94 (C_q, Ac), 169.31 (C_q, Ac), 168.72 (C_q, Ac), 91.43 (CH, C-1), 68.94 (CH, C-3), 67.92 (CH, C-5), 67.63 (CH, C-4), 61.65 (CH_2, C-6), 58.27 (CH, C-2), 21.00 (CH_3, Ac), 20.85 (2 x CH_3, Ac), 20.69 (CH_3, Ac); β-*pyr*: 170.56 (C_q, Ac), 169.80 (C_q, Ac), 168.85 (C_q, Ac), 168.69 (C_q, Ac), 91.15 (CH, C-1),

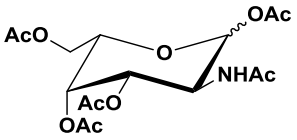
72.29 (CH, C-5), 68.17 (CH, C-3), 66.04 (CH, C-4), 62.13 (CH_2, C-6), 57.49 (CH, C-2), 20.98 (CH_3, Ac), 20.89 (CH_3, Ac), 20.80 (CH_3, Ac), 20.71 (CH_3, Ac); α-*fur*: 170.53 (C_q, Ac), 170.10 (C_q, Ac), 169.94 (C_q, Ac), 169.58 (C_q, Ac), 98.68 (CH, C-1), 78.96 (CH, C-2), 75.09 (CH, C-4), 69.27 (CH, C-3 or C-5), 69.19 (CH, C-3 or C-5), 62.58 (CH_2, C-6), 21.13 (CH_3, Ac), 21.12 (CH_3, Ac), 20.78 (CH_3, Ac), 20.76 (CH_3, Ac); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{19}N_3O_9SiNa$ 396.1019; found 396.1009; (IR) ν 2969, 2113, 1744, 1368, 1209, 1074, 1040 cm^{-1}.

3.27 2-Deoxy-2-D-aminogalactose pentaacetate (20a)



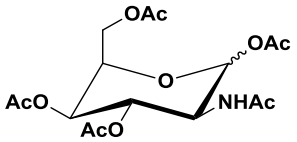
16a (200 mg, 0.54 mmol, 1 equ.) was dissolved in 3 mL Ac_2O. 20 mg Pd/C was added and a H_2-ballon attached to the flask. The mixture was stirred for 16 h before Ac_2O was removed under reduced pressure. The mixture was dissolved in warm EtOH/H_2O (1:1) and filtered through a Celite pad. The solvents were removed under reduced pressure and the crude product purified by silica chromatography (DCM/ethyl acetate/MeOH 7/2.5/0.5) to receive compound **20a** (108 mg, 52 %, α-*pyr*/β-*pyr* 26:74) as a colorless solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ α: 6.21 (d, *J* = 3.6 Hz, 1 H, H-1), 5.44 (d, *J* = 9.0 Hz, 1 H, NH), 5.42 (dd, *J* = 3.1, 1.2 Hz, 1 H, H-4), 5.22 (dd, *J* = 11.6, 3.1 Hz, 1 H, H-3), 4.72 (ddd, *J* = 11.6, 9.2, 3.6 Hz, 1 H, H-2), 4.25 – 4.22 (m, 1 H, H-5), 4.12 – 4.04 (m, 2 H, H-6), 2.17 (s, 6 H, Ac), 2.03 (s, 6 H, Ac), 1.95 (s, 3 H, Ac); β: 5.69 (d, *J* = 8.9 Hz, 1 H, H-1), 5.49 (d, *J* = 9.6 Hz, 1 H, NH), 5.37 (dd, *J* = 3.4, 1.2 Hz, 1 H, H-4), 5.08 (dd, *J* = 11.3, 3.4 Hz, 1 H, H-3), 4.44 (dt, *J* = 11.3, 9.3 Hz, 1 H, H-2), 4.18 – 4.08 (m, 2 H, H-6), 4.01 (td, *J* = 6.5, 1.2 Hz, 1 H, H-5), 2.16 (s, 3 H, Ac), 2.12 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 2.01 (s, 3 H, Ac), 1.93 (s, 3 H, Ac); ^{13}C NMR (150 MHz, $CDCl_3$) δ α: 171.38 (C_q, Ac), 170.56 (C_q, Ac), 170.38 (C_q, Ac), 170.21 (C_q, Ac), 168.94 (C_q, Ac), 91.49 (CH, C-1), 68.70 (CH, C-5), 67.97 (CH, C-3), 66.84 (CH, C-4), 61.45 (CH_2, C-6), 47.14 (CH, C-2), 23.34 (CH_3, Ac), 21.12 (CH_3, Ac), 20.91 (CH_3, Ac), 20.84 (CH_3, Ac), 20.82 (CH_3, Ac); β: 170.90 (C_q, Ac), 170.56 (C_q, Ac), 170.43 (C_q, Ac), 170.32 (C_q, Ac), 169.72 (C_q, Ac), 93.18 (CH, C-1), 72.00 (CH, C-5), 70.46 (CH, C-3), 66.48 (CH,C-4), 61.45 (CH_2, C-6), 49.93 (CH, C-2), 23.46 (CH_3, Ac), 21.05 (CH_3, Ac), 20.82 (2 x CH_3, Ac), 20.80 (CH_3, Ac); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{23}NO_{10}Na$ 412.1220; found 412.1223.

3.28 2-Deoxy-2-L-aminogalactose pentaacetate (20b)



Compound **20b** was synthesized from **16b** (200 mg, 0.54 mmol) according to the procedure for compound **20a** (chapter 3.27): yield 117 mg (56 %; α-*pyr*/β-*pyr* 57:43); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* α: 6.21 (d, *J* = 3.6 Hz, 1 H, H-1), 5.46 (d, *J* = 9.2 Hz, 1 H, NH), 5.42 (dd, *J* = 3.4, 1.3 Hz, 1 H, H-4), 5.21 (dd, *J* = 11.5, 3.3 Hz, 1 H, H-3), 4.72 (ddd, *J* = 11.6, 9.2, 3.7 Hz, 1 H, H-2), 4.23 (td, *J* = 6.8, 1.4 Hz, 1 H, H-5), 4.11 (dd, *J* = 11.3, 6.7 Hz, 2 H, H-6), 2.17 (s, 6H, Ac), 2.03 (s, 6 H, Ac), 1.95 (s, 3 H, Ac); β: 5.70 (d, *J* = 8.8 Hz, 1 H, H-1), 5.53 (d, *J* = 9.6 Hz, 1 H, NH), 5.37 (dd, *J* = 3.4, 1.1 Hz, 1 H, H-4), 5.08 (dd, *J* = 11.3, 3.4 Hz, 1 H, H-3), 4.44 (dt, *J* = 11.3, 9.2 Hz, 1 H, H-2), 4.16 (dd, *J* = 11.4, 6.6 Hz, 1 H, H-6a), 4.06 (dd, *J* = 11.3, 6.5 Hz, 1 H, H-6b), 4.02 (td, *J* = 6.5, 1.2 Hz, 1 H, H-5), 2.16 (s, 3 H, Ac), 2.12 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 2.01 (s, 3 H, Ac), 1.94 (s, 3 H, Ac); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* α: 171.35 (C_q, Ac), 170.54 (C_q, Ac), 170.37 (C_q, Ac), 170.21 (C_q, Ac), 168.94 (C_q, Ac), 91.49 (CH, C-1), 68.68 (CH, C-5), 67.96 (CH, C-3), 66.83 (CH, C-4), 61.43 (CH_2, C-6), 47.12 (CH, C-2), 23.32 (CH_3, Ac), 21.11 (CH_3, Ac), 20.90 (CH_3, Ac), 20.79 (2 x CH_3, Ac); β: 170.87 (C_q, Ac), 170.53 (C_q, Ac), 170.44 (C_q, Ac), 170.37 (C_q, Ac), 169.70 (C_q, Ac), 93.17 (CH, C-1), 71.96 (CH, C-5), 70.46 (CH, C-3), 66.47 (CH, C), 61.45 (CH_2, C-6), 49.88 (CH, C-2), 23.44 (CH_3, Ac), 21.04 (CH_3, Ac), 20.82 (2 x CH_3, Ac), 20.79 (CH_3, Ac); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{23}NO_{10}Na$ 412.1220; found 412.1217.

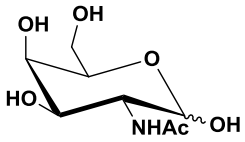
3.29 2-Deoxy-2-D-aminoidose pentaacetate (20c)



Compound **20c** was synthesized from **16c** (30 mg, 0.08 mmol) according to the procedure for compound **20a** (chapter 3.27): yield 18 mg (56 %; α-*pyr*/β-*pyr*/α-*fur* 49:33:18); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* α-*pyr*: 6.11 (d, *J* = 9.8 Hz, 1 H, NH), 5.93 (s, 1 H, H-1), 5.04 (t, *J* = 2.8 Hz, 1 H, H-4), 4.87 (t, *J* = 3.6 Hz, 1 H, H-3), 4.48 (td, *J* = 6.6, 2.1 Hz, 1 H, H-5), 4.31 (dt, *J* = 10.0, 2.9 Hz, 1 H, H-2), 4.11 (t, *J* = 6.2 Hz, 2 H, H-6), 2.14 (s, 3 H, Ac), 2.11 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.09 (s, 3 H, Ac), 2.04 (s, 3 H,

Ac); β-*pyr*: 6.06 (d, *J* = 9.7 Hz, 1 H, NH), 6.01 (d, *J* = 2.4 Hz, 1 H, H-1), 5.07 (t, *J* = 4.2 Hz, 1 H, H-4), 4.98 (t, *J* = 3.3 Hz, 1 H, H-3), 4.39 – 4.33 (m, 2 H, H-2 and H-5), 4.18 – 4.13 (m, 2 H, H-6), 2.12 (s, 3 H, Ac), 2.11 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 2.02 (s, 3 H, Ac), 1.99 (s, 3 H, Ac); α-*fur*: 6.27 (d, *J* = 8.2 Hz, 1 H, NH), 6.02 (d, *J* = 3.2 Hz, 1 H, H-1), 5.32 (dd, *J* = 6.9, 5.4 Hz, 1 H, H-3), 5.25 (dt, *J* = 7.1, 4.8 Hz, 1 H, H-5), 4.61 (ddd, *J* = 8.3, 5.4, 3.2 Hz, 1 H, H-2), 4.55 (dd, *J* = 6.9, 4.8 Hz, 1 H, H-4), 4.26 (dd, *J* = 11.9, 4.1 Hz, 1 H, H-6a), 4.05 (dd, *J* = 11.9, 7.1 Hz, 1 H, H-6b), 2.14 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 2.04 (s, 3 H, Ac), 1.98 (s, 3 H, Ac); ^{13}C NMR (150 MHz, $CDCl_3$) *δ* α-pyr: 170.59 (C_q, Ac), 169.71 (C_q, Ac), 169.04 (C_q, Ac), 168.68 (C_q, Ac), 168.66 (CH, Ac), 92.06 (CH, C-1), 67.36 (CH, C-3), 66.49 (CH, C-4), 66.04 (CH, C-5), 61.72 (CH_2, C-6), 46.32 (CH, C-2), 23.35 (CH_3, Ac), 20.99 (CH_3, Ac), 20.89 (CH_3, Ac), 20.84 (CH_3, Ac), 20.81 (CH_3, Ac); β-pyr: 170.34 (C_q, Ac), 170.17 (C_q, Ac), 170.02 (C_q, Ac), 168.76 (C_q, Ac), 168.57 (C_q, Ac), 90.80 (CH, C-1), 72.52 (CH, C-5), 68.48 (CH, C-4), 66.23 (CH, C-3), 61.94 (CH_2, C-6), 47.85 (CH, C-2), 23.35 (CH_3, Ac), 21.01 (CH_3, Ac), 20.91 (CH_3, Ac), 20.80 (CH_3, Ac), 20.74 (CH_3, Ac); α-fur: 170.62 (C_q, Ac), 170.55 (C_q, Ac), 170.36 (C_q, Ac), 169.89 (C_q, Ac), 168.93 (C_q, Ac), 98.76 (CH, C-1), 78.29 (CH, C-4), 75.05 (CH, C-3), 69.06 (CH, C-5), 62.70 (CH_2, C-6), 59.74 (CH, C-2), 23.18 (CH_3, Ac), 21.23 (CH_3, Ac), 21.16 (CH_3, Ac), 21.03 (CH_3, Ac), 20.87 (CH_3, Ac); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{23}NO_{10}Na$ 412.1220; found 412.1217.

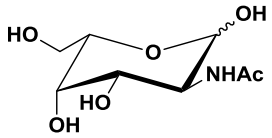
3.30 *N*-Acetyl-D-galactosamine (**1a**)



20a (115 mg, 0.30 mmol, 1 equiv) was dissolved in 3 mL MeOH/H_2O/Et_3N (10:10:1) and stirred for 16 h. The solvents were removed under reduced pressure and the crude product was recrystallized in MeOH/Et_2O to receive compound **1a** (57 mg, 88 %; α-*pyr*/β-*pyr* 56:44) as a colorless solid: $[\alpha]^{20}_D$ = +80.0° (*c* 1.0, H_2O); ^{1}H NMR (600 MHz, D_2O) *δ* α: 5.20 (d, *J* = 3.7 Hz, 1 H, H-1), 4.12 – 4.06 (m, 2 H, H-2 and H-5), 3.97 (d, *J* = 2.7 Hz, 1 H, H-4), 3.91 (t, *J* = 2.7 Hz, 1 H, H-3), 3.77 – 3.69 (m, 2 H, H-6), 2.02 (s, 3 H, Ac); β: 4.62 (d, *J* = 8.4 Hz, 1 H, H-1), 3.88 (d, *J* = 3.2 Hz, 1 H, H-4), 3.85 (dd, *J* = 10.8, 8.5 Hz, 1 H, H-2), 3.79 – 3.69 (m, 3 H, H-3 and H-6), 3.69 – 3.65 (m, 1H, H-5), 2.02 (s, 3 H, Ac); ^{13}C NMR (150 MHz, H_2O) *δ* α: 175.45 (C_q, Ac), 91.73 (CH, C-1), 71.28 (CH, C-5), 69.31 (CH, C-4), 68.12 (CH, C-3), 61.97 (CH_2, C-6), 51.00 (CH, C-2), 22.70 (CH_3, Ac); β: 175.72 (C_q, Ac), 96.14 (CH, C-1), 75.93 (CH,

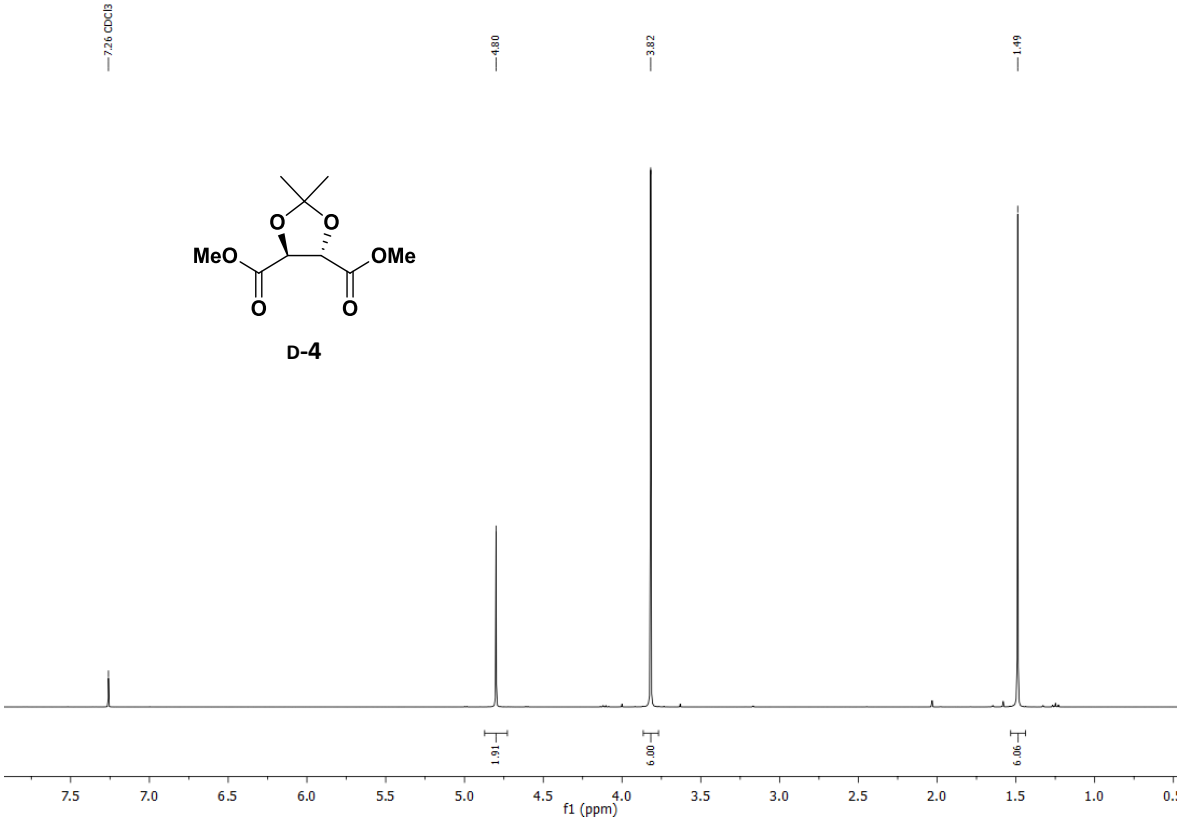
C-5), 71.87 (CH, C-3), 68.59 (CH, C-4), 61.74 (CH_2, C-6), 54.39 (CH, C-2), 22.95 (CH_3, Ac); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_8H_{15}NO_6Na$ 244.0797; found 244.0793.

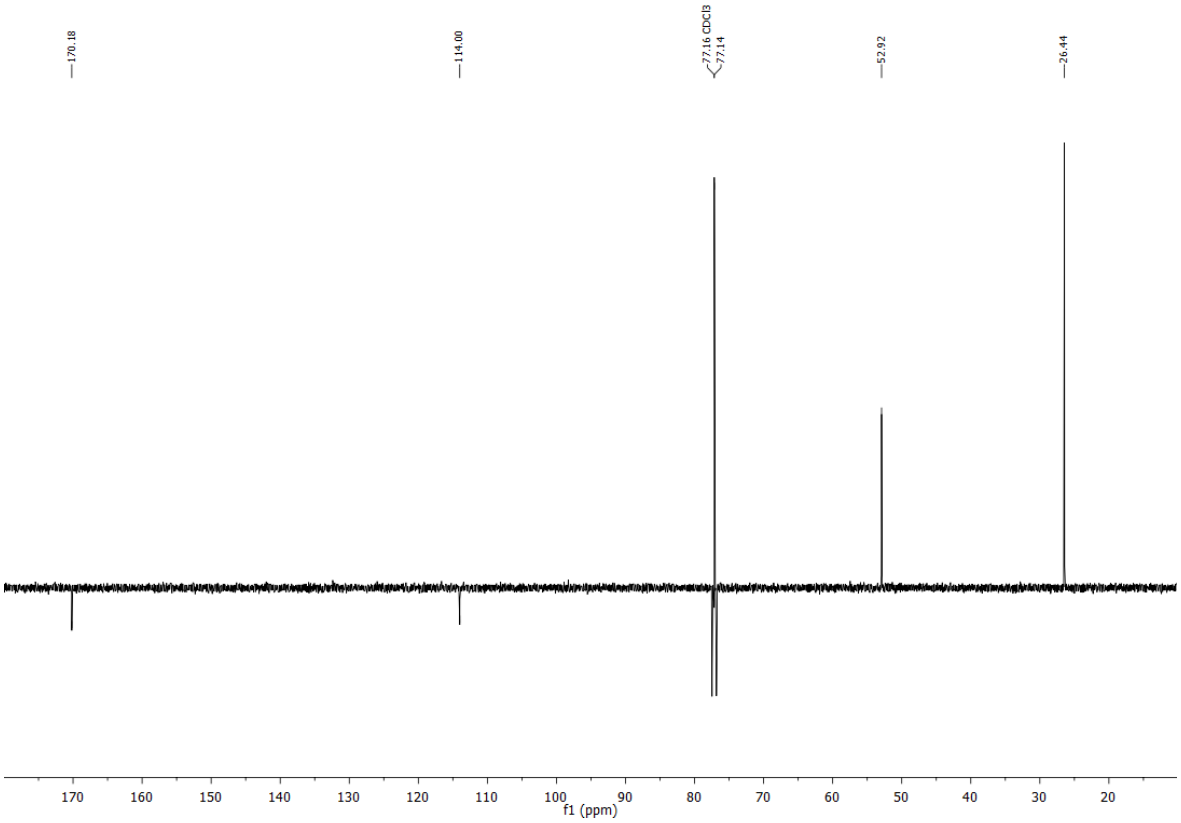
3.31 N-Acetyl-D-galactosamine (1b)

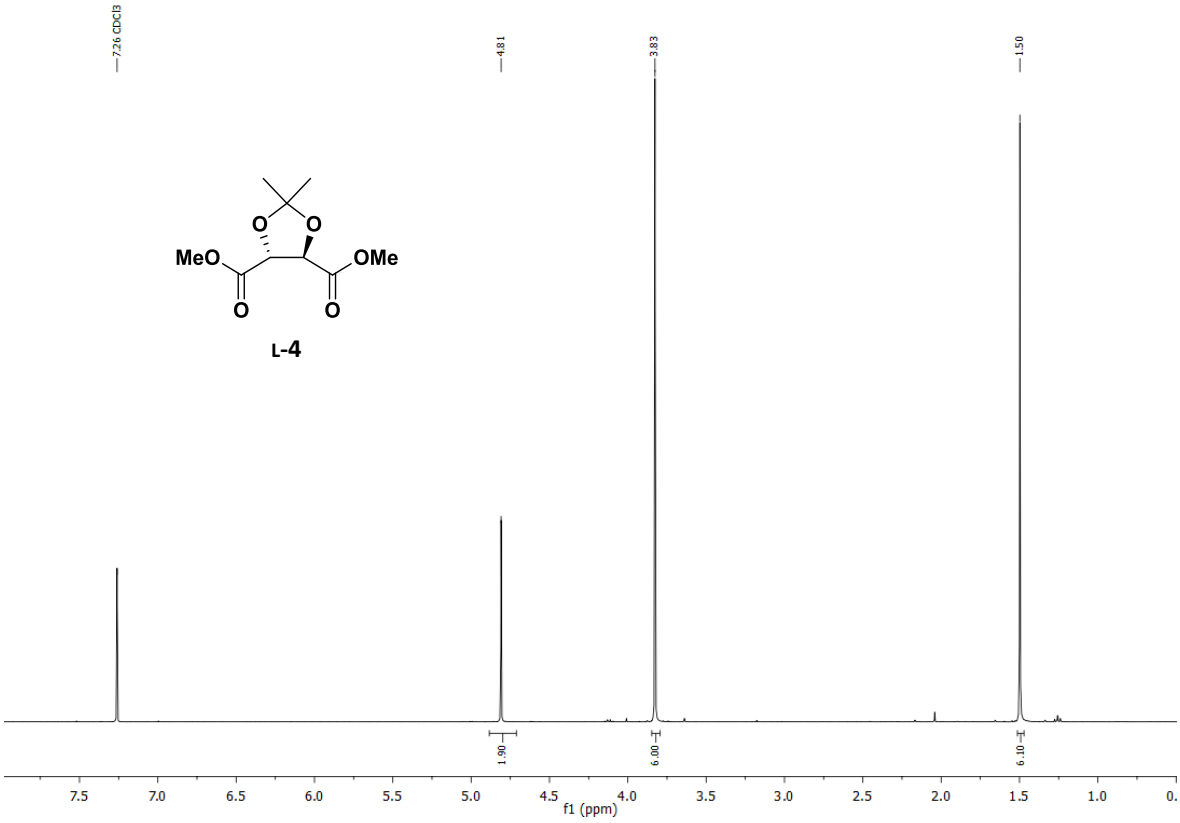


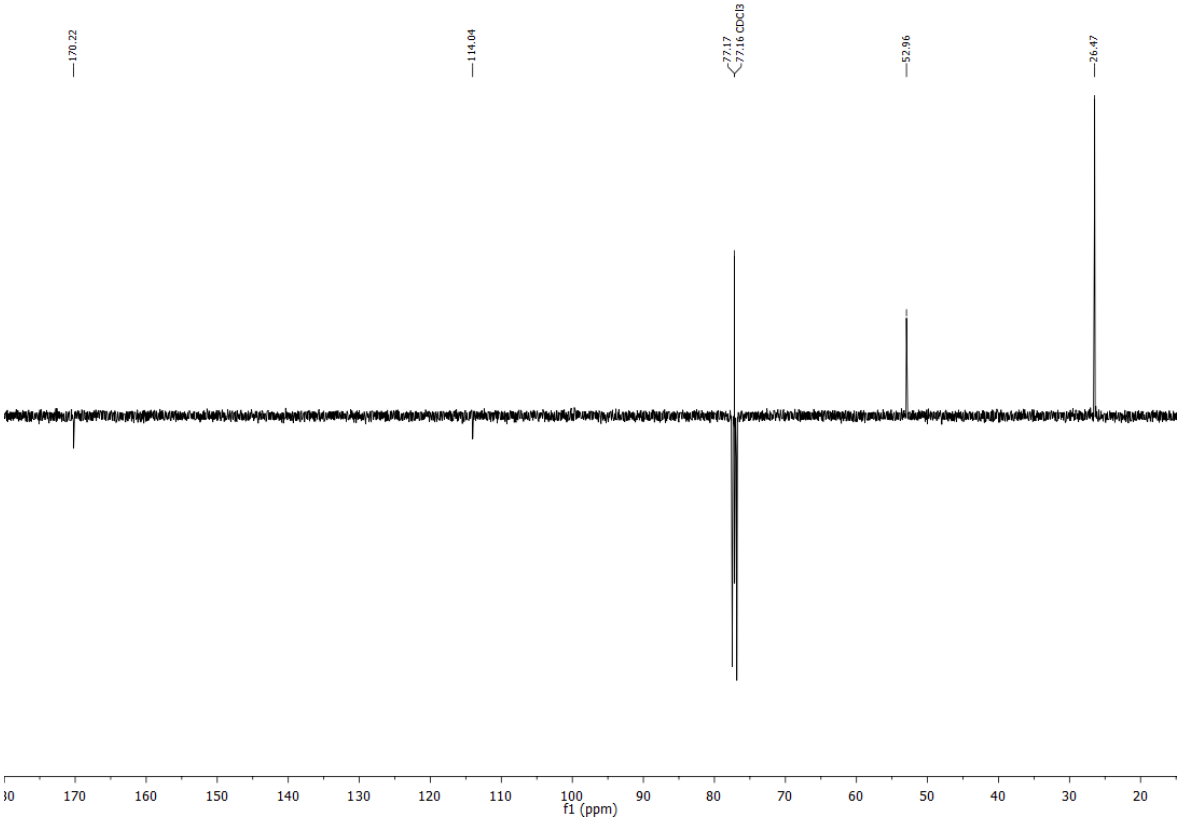
Compound **1b** was synthesized from **20b** (31 mg, 0.08 mmol) according to the procedure for compound **1a** (chapter 3.30): yield 16 mg (69 %; α-*pyr*/β-*pyr* 68:32); $[\alpha]^{20}_D$ = -71.5° (*c* 1.0, H_2O); ^1H NMR (600 MHz, D_2O) δ α: 5.23 (d, *J* = 3.8 Hz, 1 H, H-1), 4.15 – 4.08 (m, 2 H, H-2 and H-5), 4.01 – 3.97 (m, 1 H, H-4), 3.93 (t, *J* = 3.4 Hz, 1 H, H-3), 3.74 (d, *J* = 6.1 Hz, 2 H, H-6), 2.05 (s, 3 H, Ac); β: 4.64 (d, *J* = 8.4 Hz, 1 H, H-1), 3.91 (d, *J* = 3.2 Hz, 1 H, H-4), 3.87 (dd, *J* = 10.9, 8.5 Hz, 1 H, H-2), 3.81 – 3.71 (m, 3 H, H-3 and H-6), 3.71 – 3.66 (m, 1H, H-5), 2.04 (s, 3 H, Ac); ^{13}C NMR (150 MHz, H_2O) δ α: 175.44 (C_q, Ac), 91.74 (CH, C-1), 71.28 (CH, C-5), 69.32 (CH, C-4), 68.14 (CH, C-3), 61.98 (CH_2, C-6), 51.01 (CH, C-2), 22.72 (CH_3, Ac); β: 175.72 (C_q, Ac), 96.16 (CH, C-1), 75.93 (CH, C-5), 71.88 (CH, C-3), 68.60 (CH, C-4), 61.75 (CH_2, C-6), 54.41 (CH, C-2), 22.97 (CH_3, Ac); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_8H_{15}NO_6Na$ 244.0797; found 244.0788.

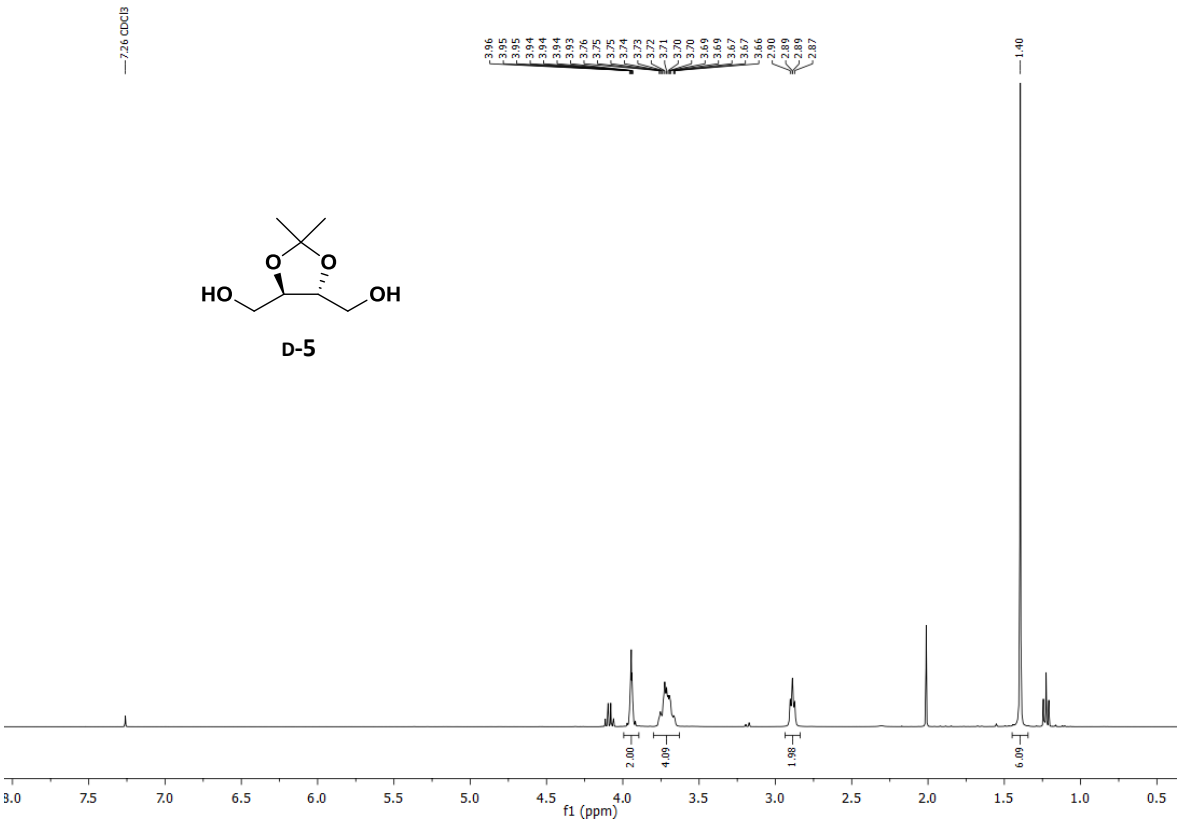
4 NMR spectra



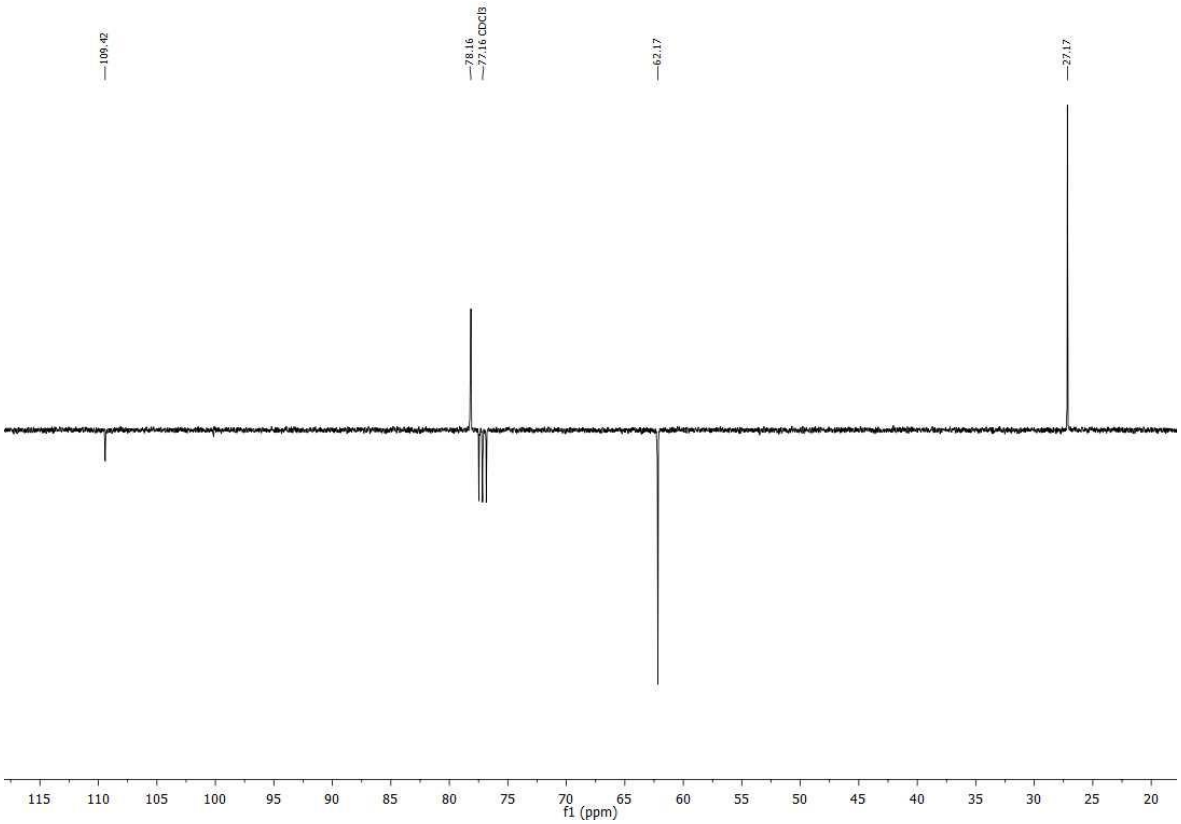


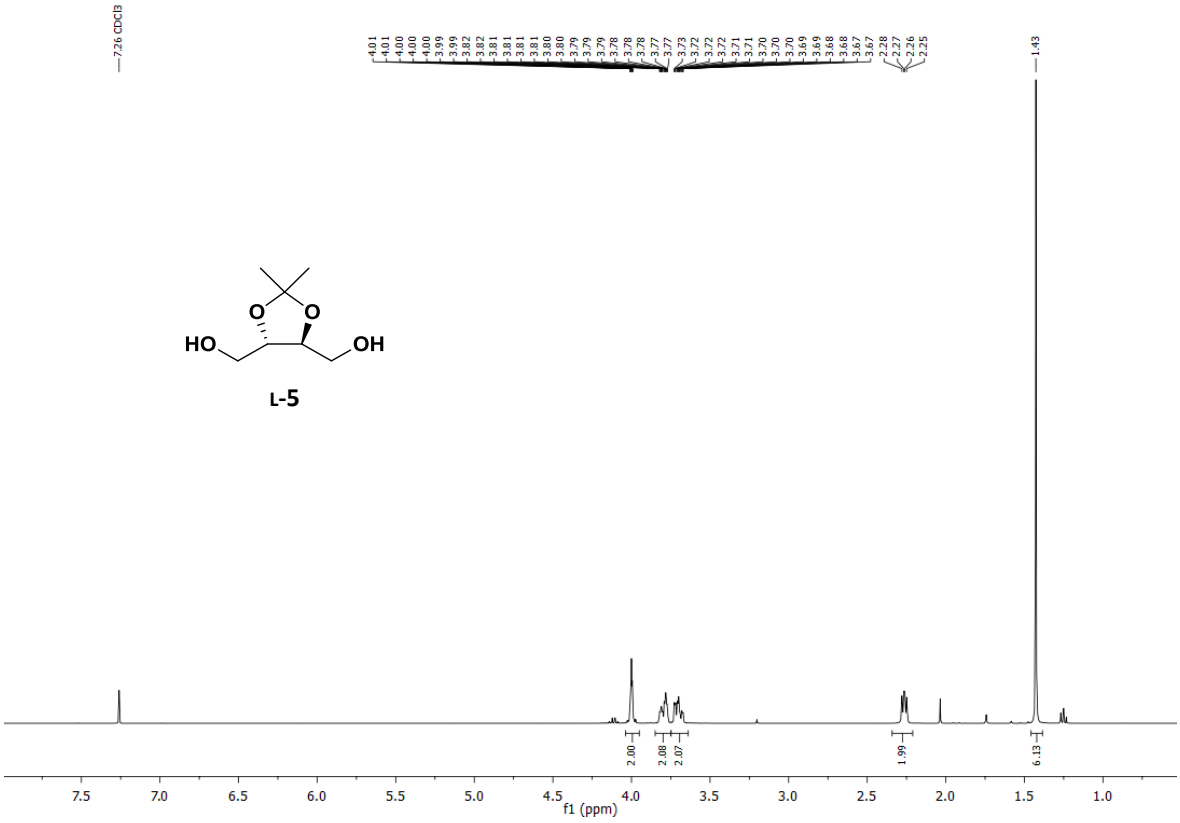

7.26 CDCl3
4.81
3.83
1.50
MeO
OMe
O
O
O
O
L-4
1.90
6.00
6.10
f1 (ppm)


170.22
114.04
77.17
77.16 CDCl3
52.96
26.47
f1 (ppm)


7.26 CDCl3
3.96
3.95
3.95
3.94
3.94
3.94
3.93
3.76
3.75
3.75
3.74
3.73
3.72
3.71
3.70
3.70
3.69
3.69
3.67
3.67
3.66
2.90
2.89
2.89
2.87
1.40
HO
OH
O
O
2.00
4.09
1.98
6.09
f1 (ppm)

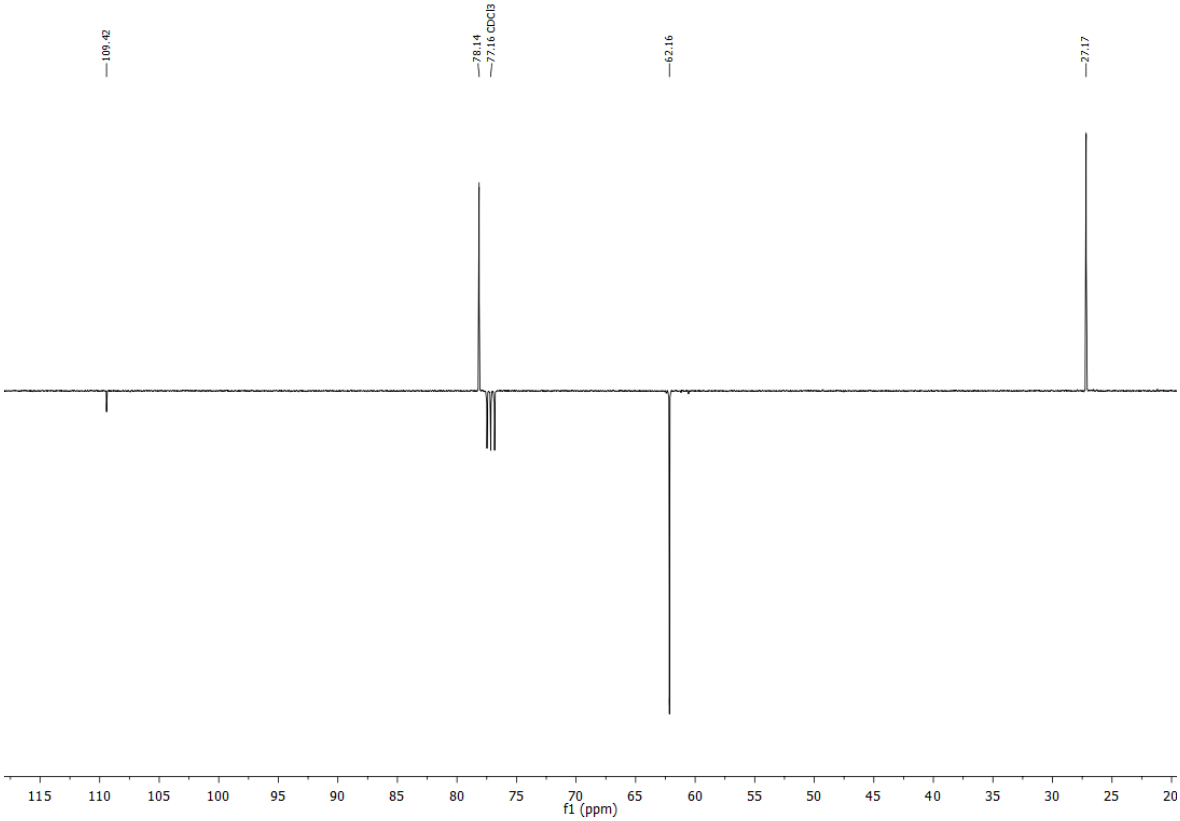
D-5

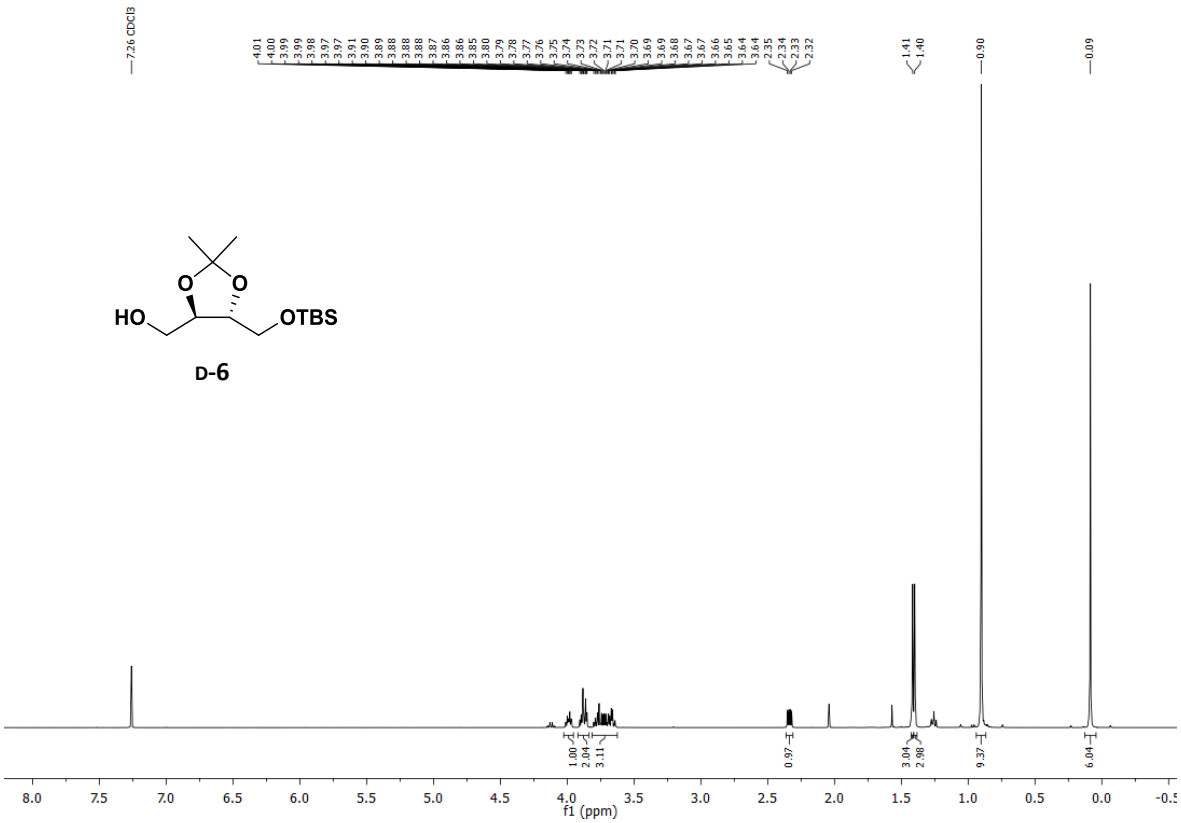

109.42
78.16
77.16 CDCl3
62.17
27.17
f1 (ppm)

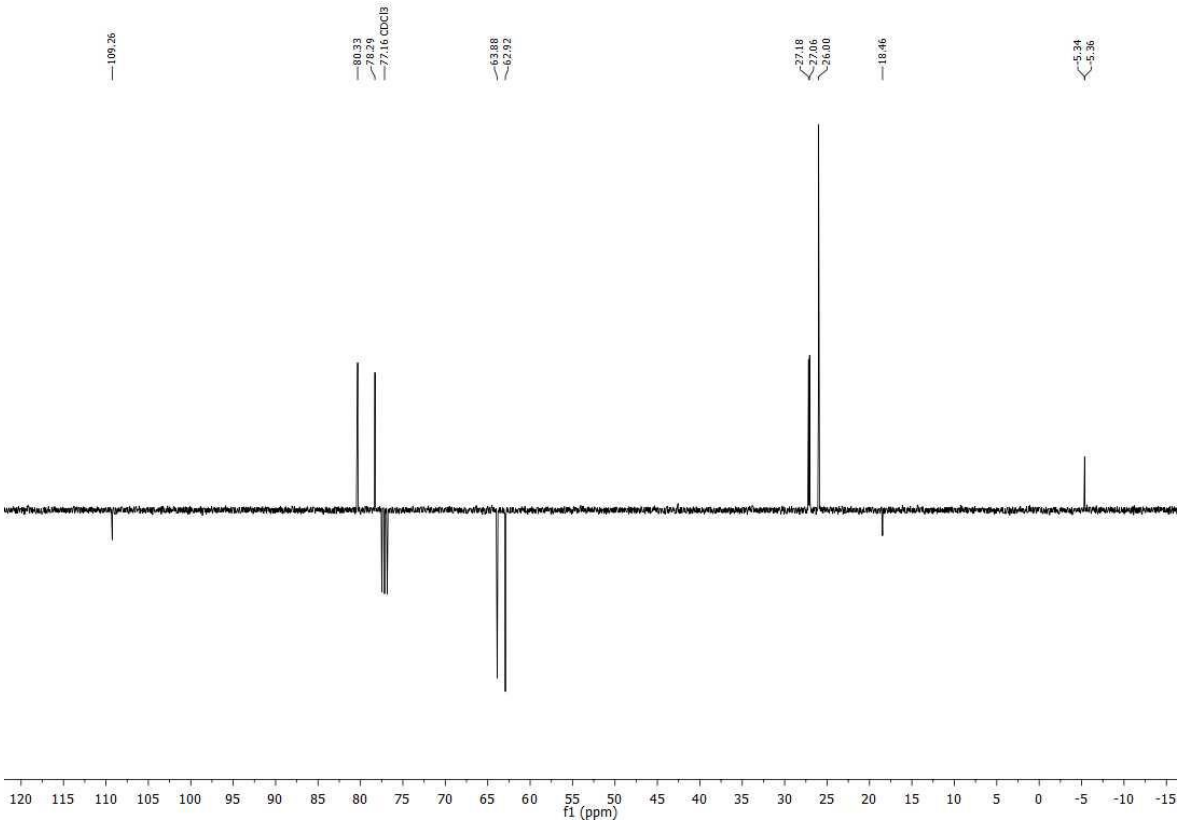

7.26 CDCl3
1.43
2.00
2.08
2.07
1.99
6.13
f1 (ppm)

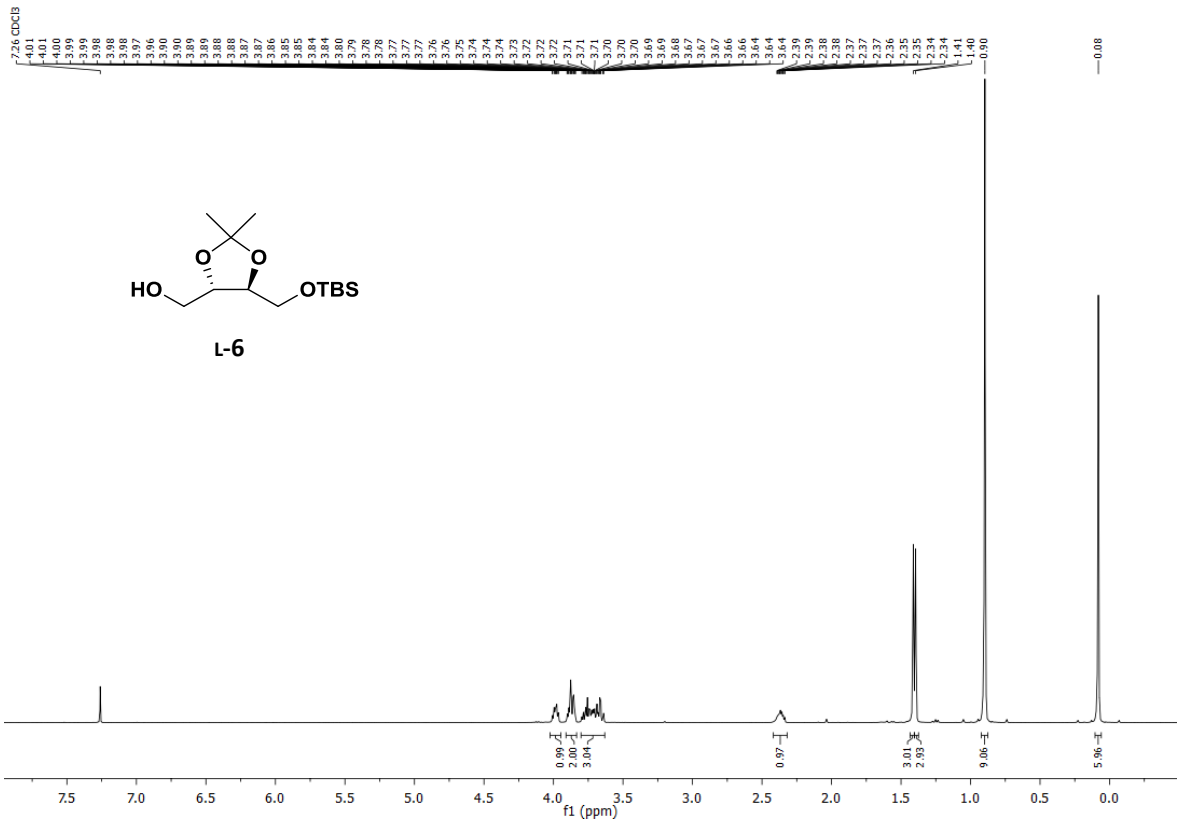
HO
OH

L-5

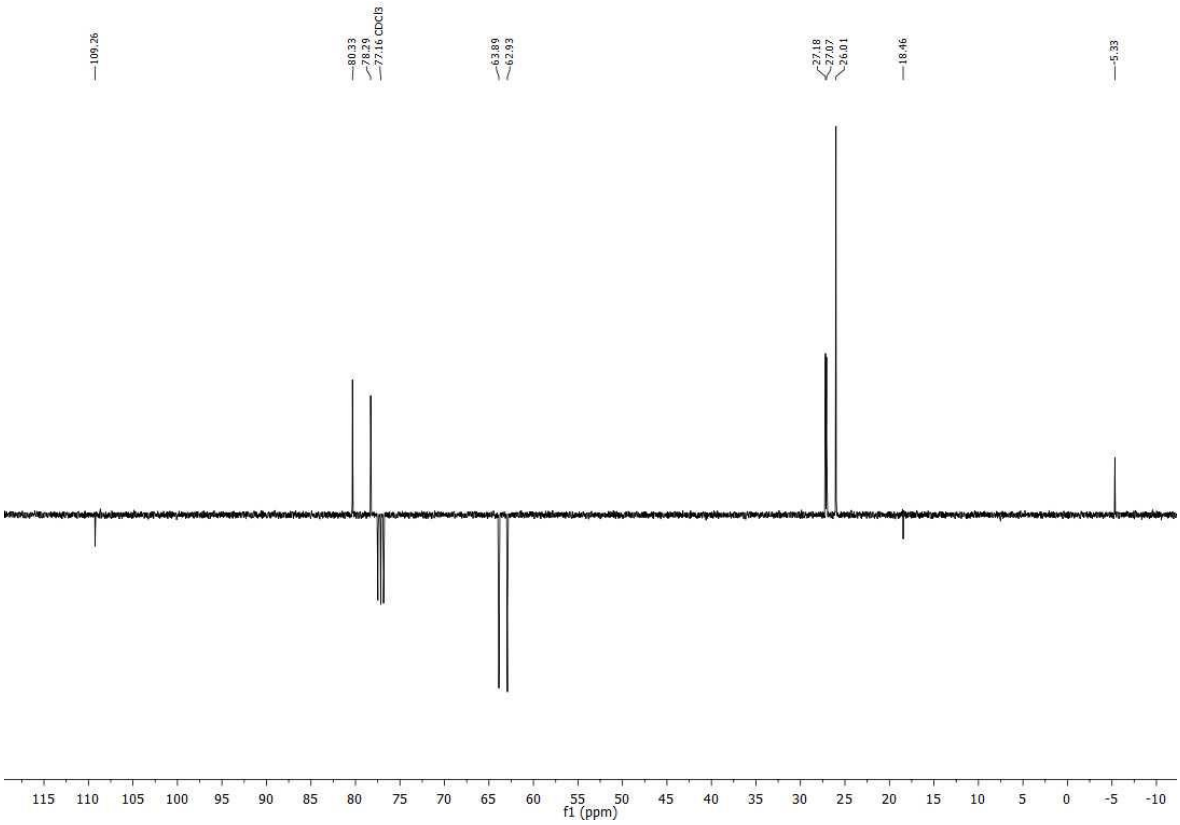

109.42
78.14
77.16 CDCl3
62.16
27.17
f1 (ppm)

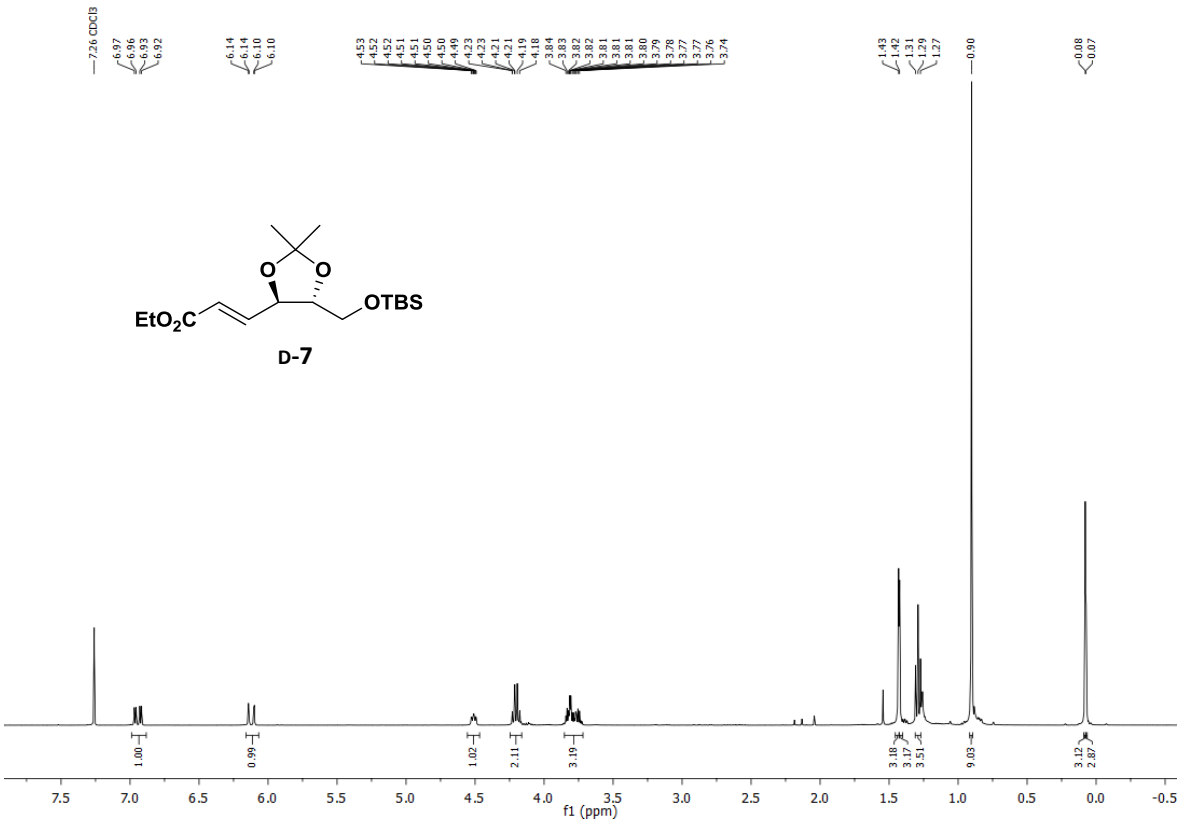

7.26 CDCl3
4.01
4.00
3.99
3.99
3.98
3.97
3.97
3.91
3.90
3.89
3.88
3.88
3.88
3.87
3.86
3.86
3.85
3.80
3.79
3.78
3.77
3.76
3.75
3.74
3.73
3.72
3.71
3.71
3.70
3.69
3.69
3.68
3.67
3.67
3.66
3.65
3.64
3.64
2.35
2.34
2.33
2.32
1.41
1.40
0.90
0.09
HO
O
O
OTBS
D-6
1.00
2.04
3.11
0.97
3.04
2.98
9.37
6.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

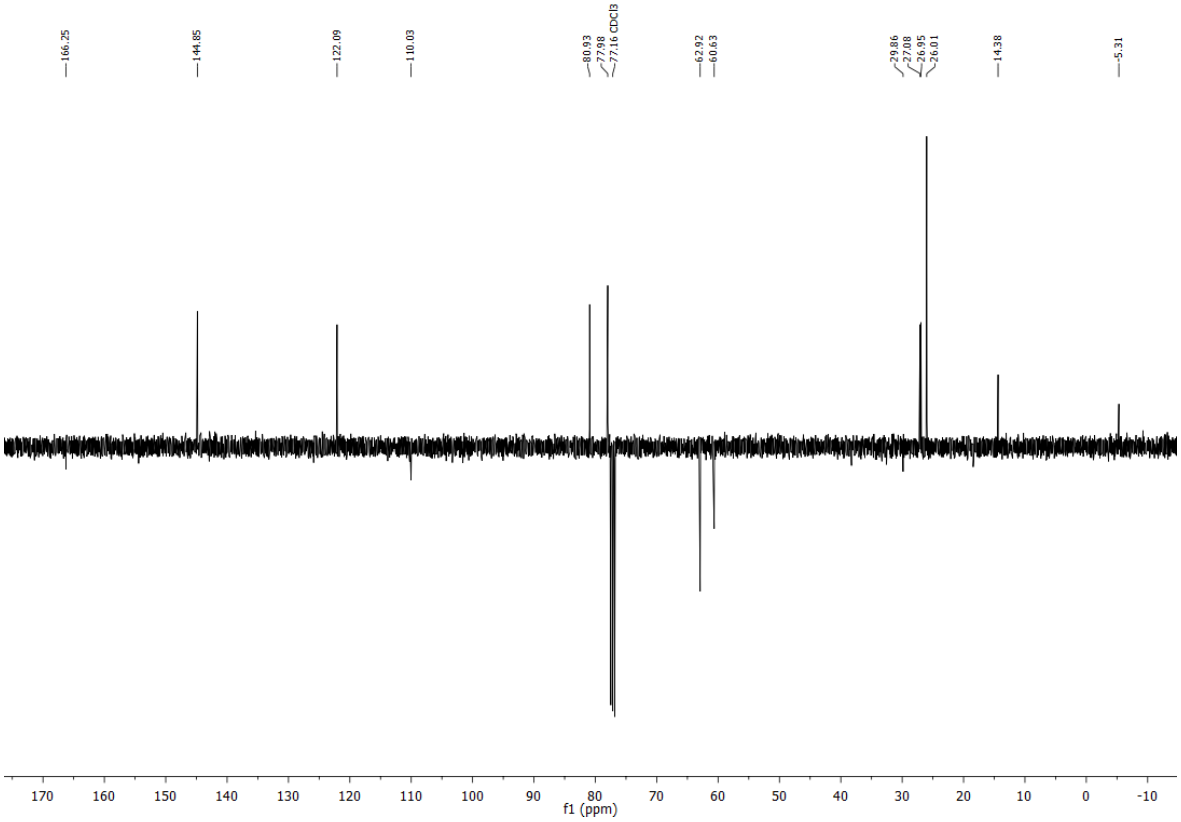

109.26
80.33
78.29
77.16 CDCl3
63.88
62.92
27.18
27.06
26.00
18.46
-5.34
-5.36
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
f1 (ppm)

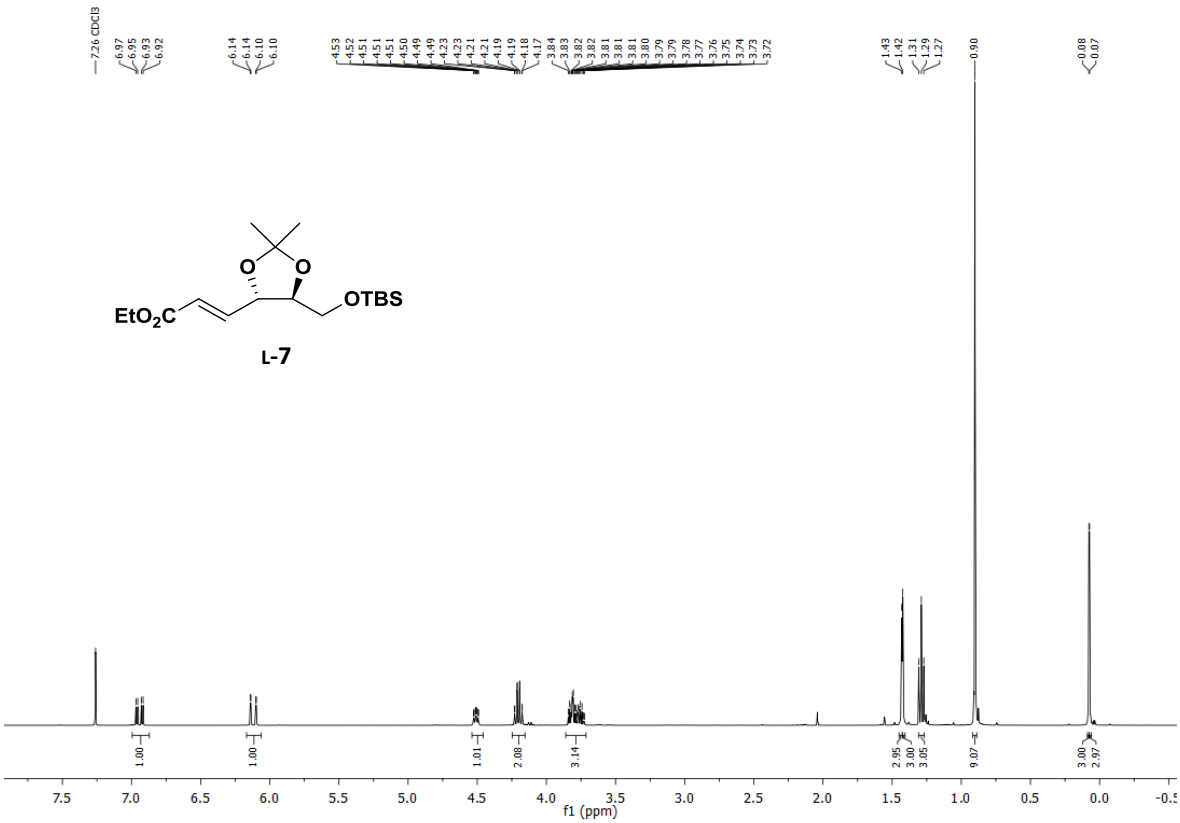


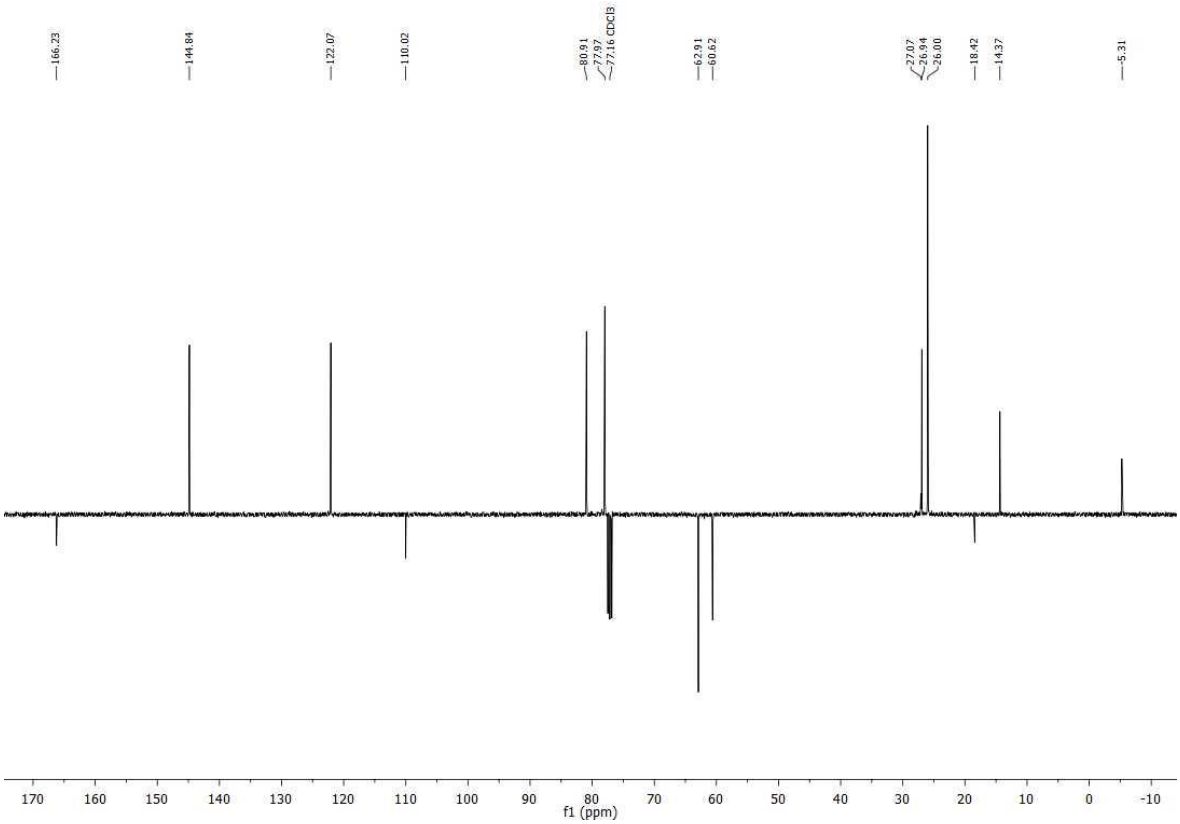
L-6




7.26 CDCl3
6.97
6.96
6.93
6.92
6.14
6.14
6.10
6.10
4.53
4.52
4.52
4.51
4.51
4.51
4.50
4.50
4.49
4.23
4.23
4.21
4.21
4.19
4.18
3.84
3.83
3.82
3.82
3.81
3.81
3.81
3.80
3.79
3.78
3.77
3.77
3.76
3.74
1.43
1.42
1.31
1.29
1.27
0.90
0.08
0.07
EtO2C
OTBS
D-7
1.00
0.99
1.02
2.11
3.19
3.18
3.17
3.51
9.03
3.12
2.87
f1 (ppm)

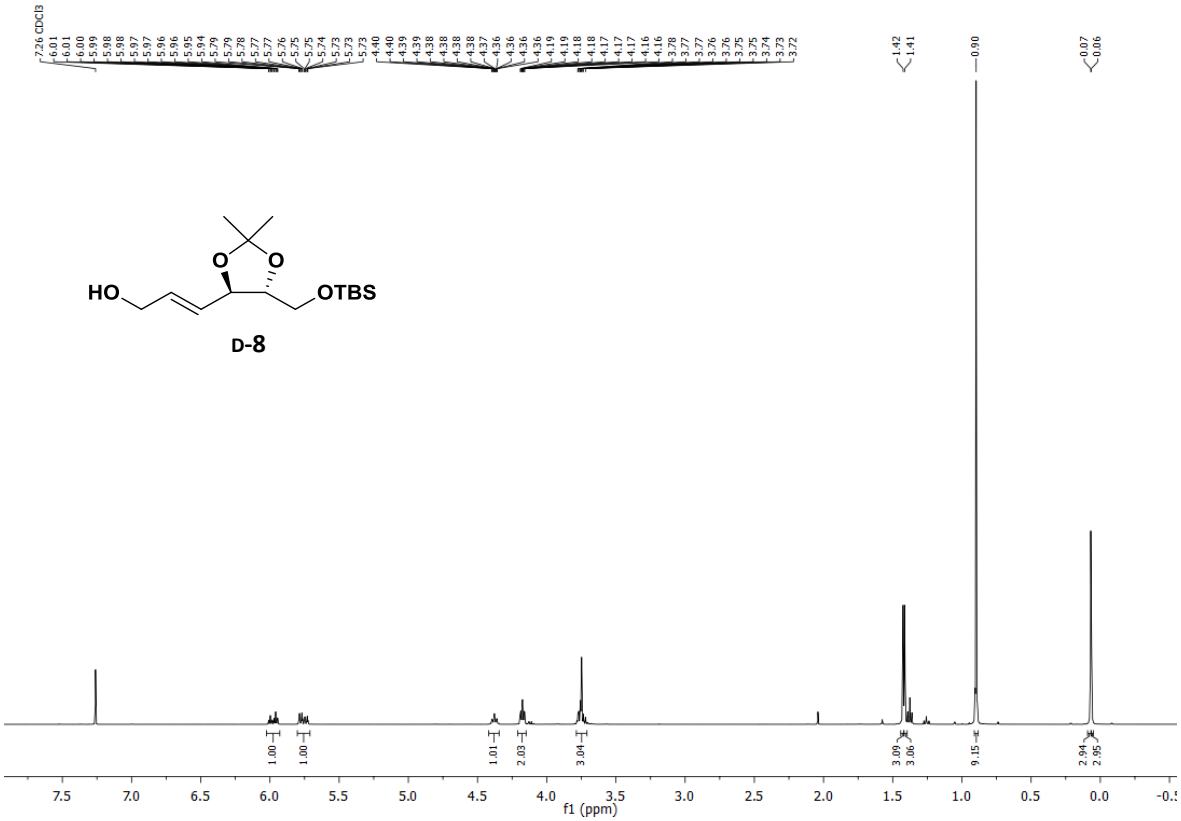

166.25
144.85
122.09
110.03
80.93
77.98
77.16 CDCl3
62.92
60.63
29.86
27.08
26.95
26.01
14.38
-5.31
f1 (ppm)


7.26 CDCl3
6.97
6.95
6.93
6.92
6.14
6.14
6.10
6.10
4.53
4.52
4.51
4.51
4.51
4.50
4.49
4.49
4.23
4.23
4.21
4.21
4.19
4.19
4.18
4.17
3.84
3.83
3.82
3.82
3.81
3.81
3.81
3.80
3.79
3.79
3.78
3.77
3.76
3.75
3.74
3.73
3.72
1.43
1.42
1.31
1.29
1.27
0.90
0.08
0.07
1.00
1.00
1.01
2.08
3.14
2.95
3.00
3.05
9.07
3.00
2.97
f1 (ppm)

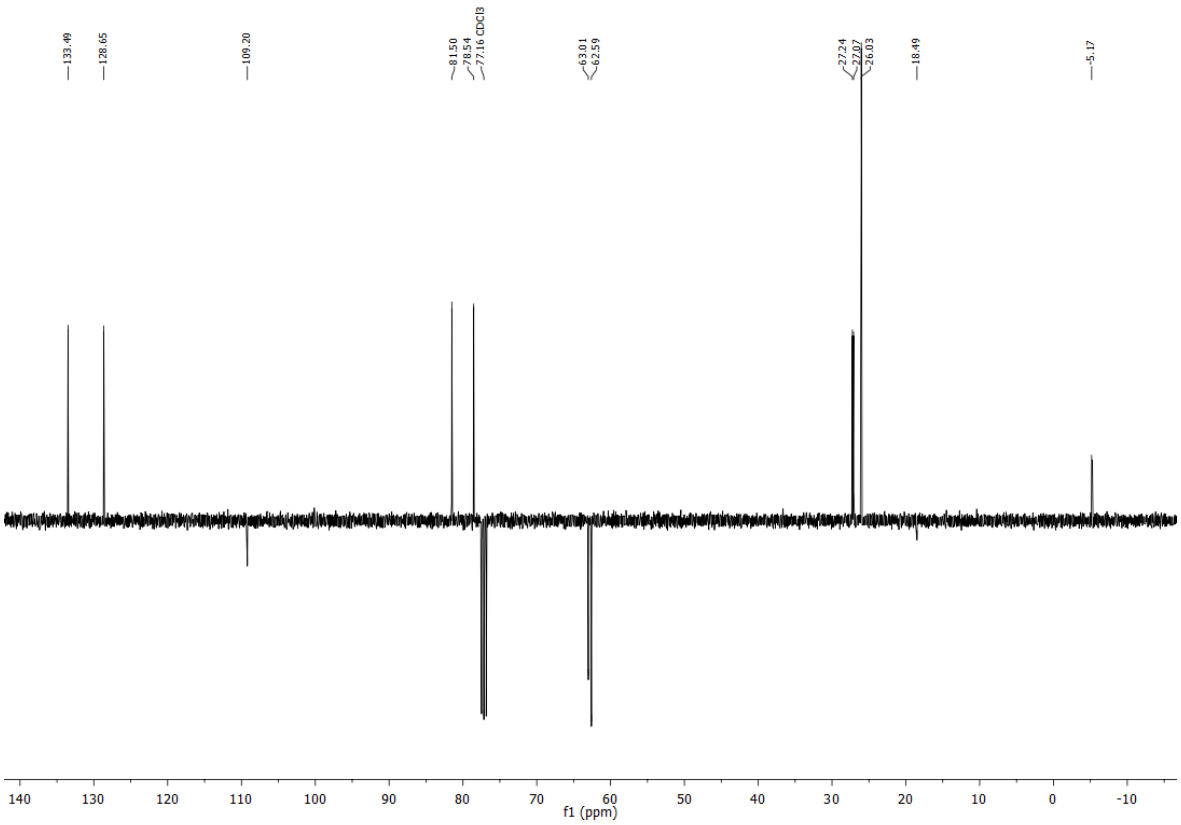

166.23
144.84
122.07
110.02
80.91
77.97
77.16 CDCl3
62.91
60.62
27.07
26.94
26.00
18.42
14.37
-5.31
f1 (ppm)

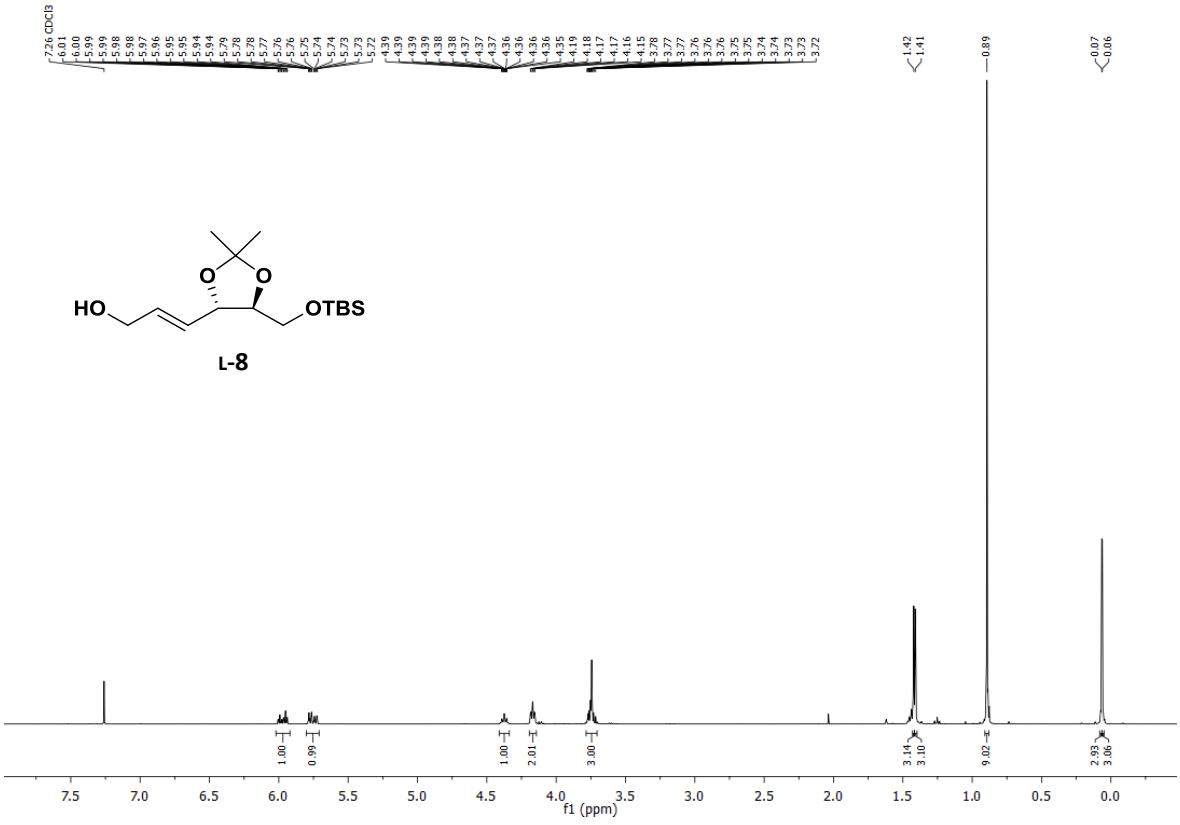
O
O
OTBS
EtO2C

L-7

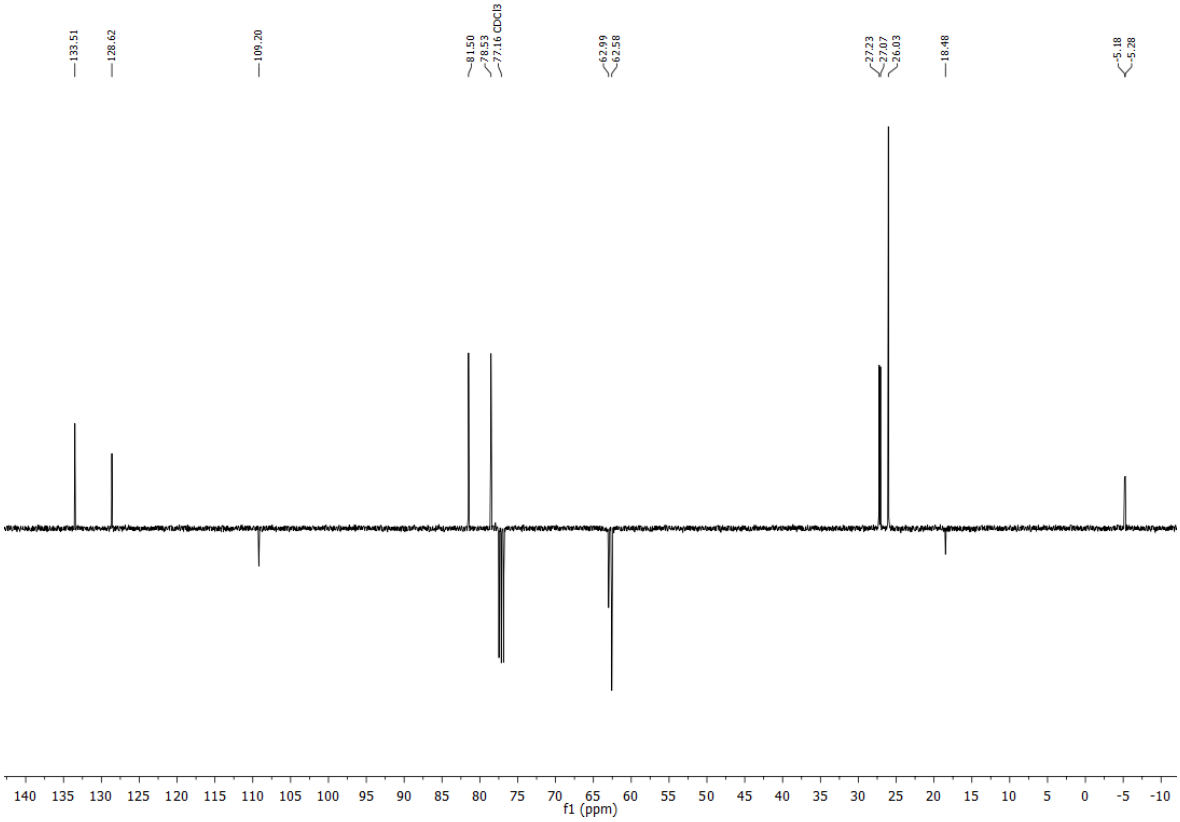


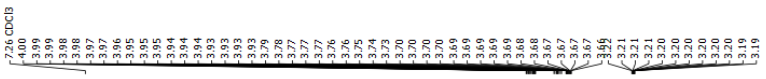
D-8

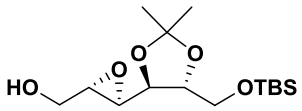




L-8

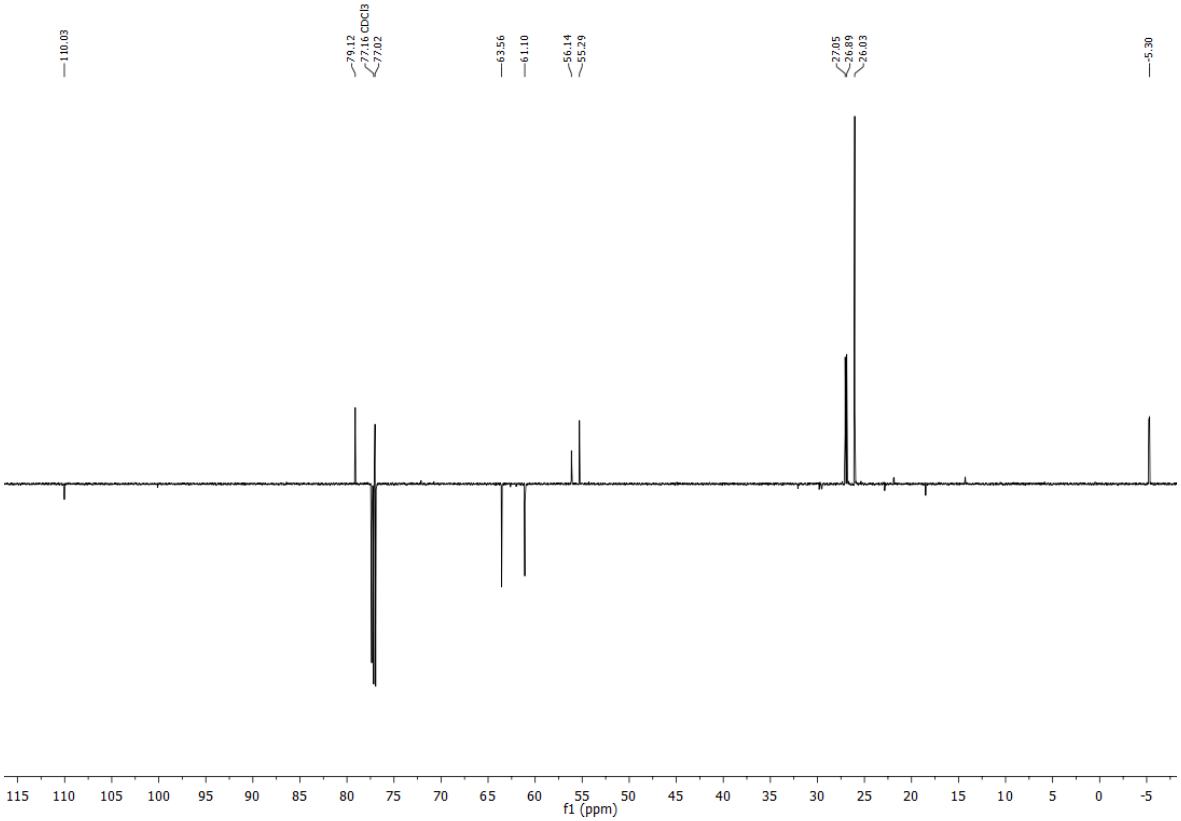


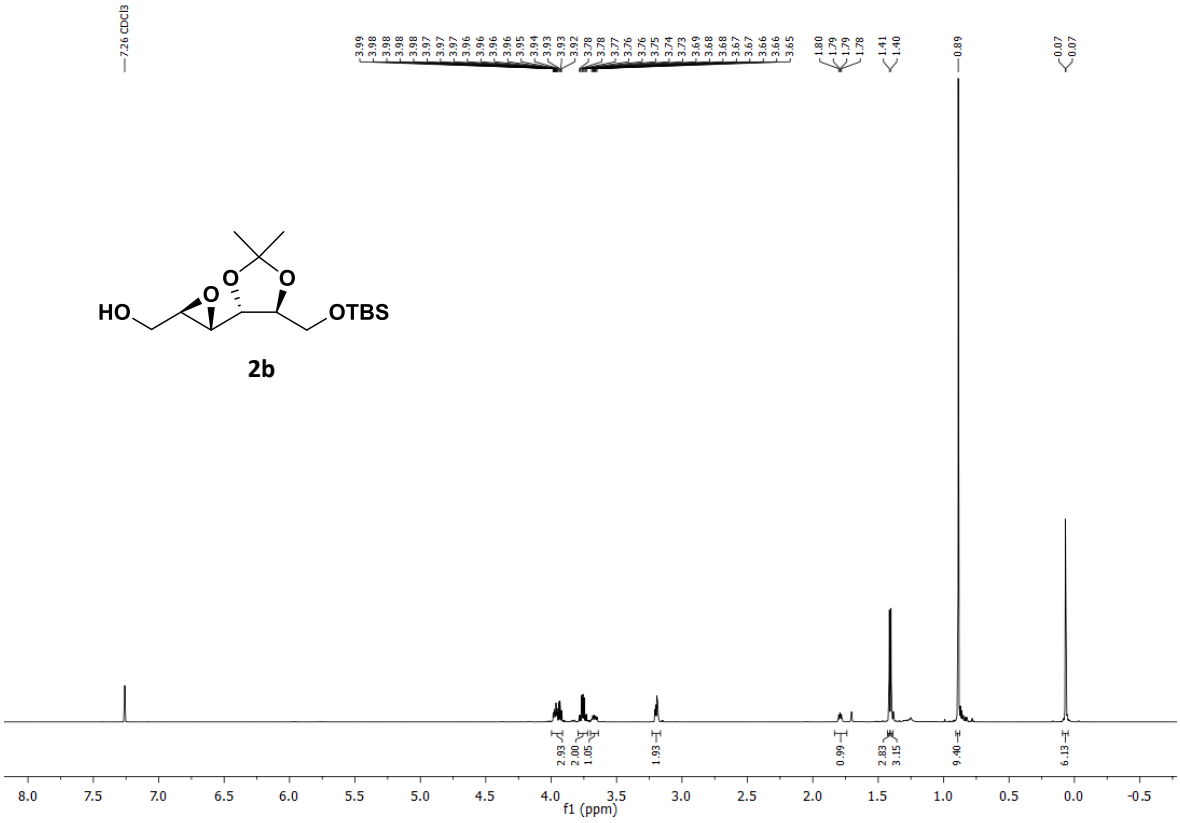



HO
O
O
O
OTBS

2a

3.03
2.08
1.07
2.00
3.06
2.96
9.18
6.01
f1 (ppm)


110.03
79.12
77.16 CDCl3
77.02
63.56
61.10
56.14
55.29
27.05
26.89
26.03
-5.30
f1 (ppm)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3.99
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3.98
3.98
3.98
3.97
3.97
3.97
3.96
3.96
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3.96
3.95
3.94
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3.92
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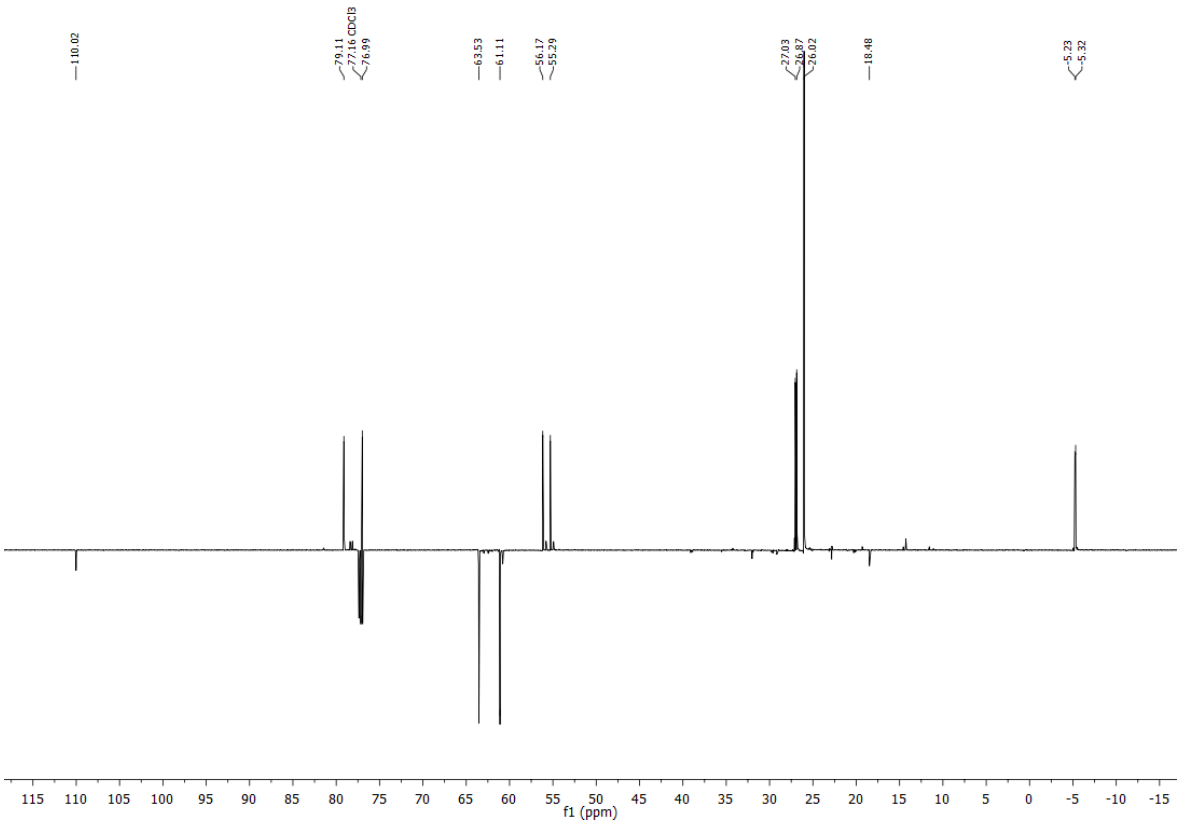
3.68
3.67
3.67
3.66
3.66
3.65
1.80
1.79
1.79
1.78
1.41
1.40
0.89
0.07
0.07
HO
O
O
O
OTBS
2b
2.93
2.00
1.05
1.93
0.99
2.83
3.15
9.40
6.13
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


110.02
79.11
77.16 CDCl3
76.99
63.53
61.11
56.17
55.29
27.03
26.87
26.02
18.48
-5.23
-5.32
115
110
105
100
95
90
85
80
75
70
65
60
55
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45
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35
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25
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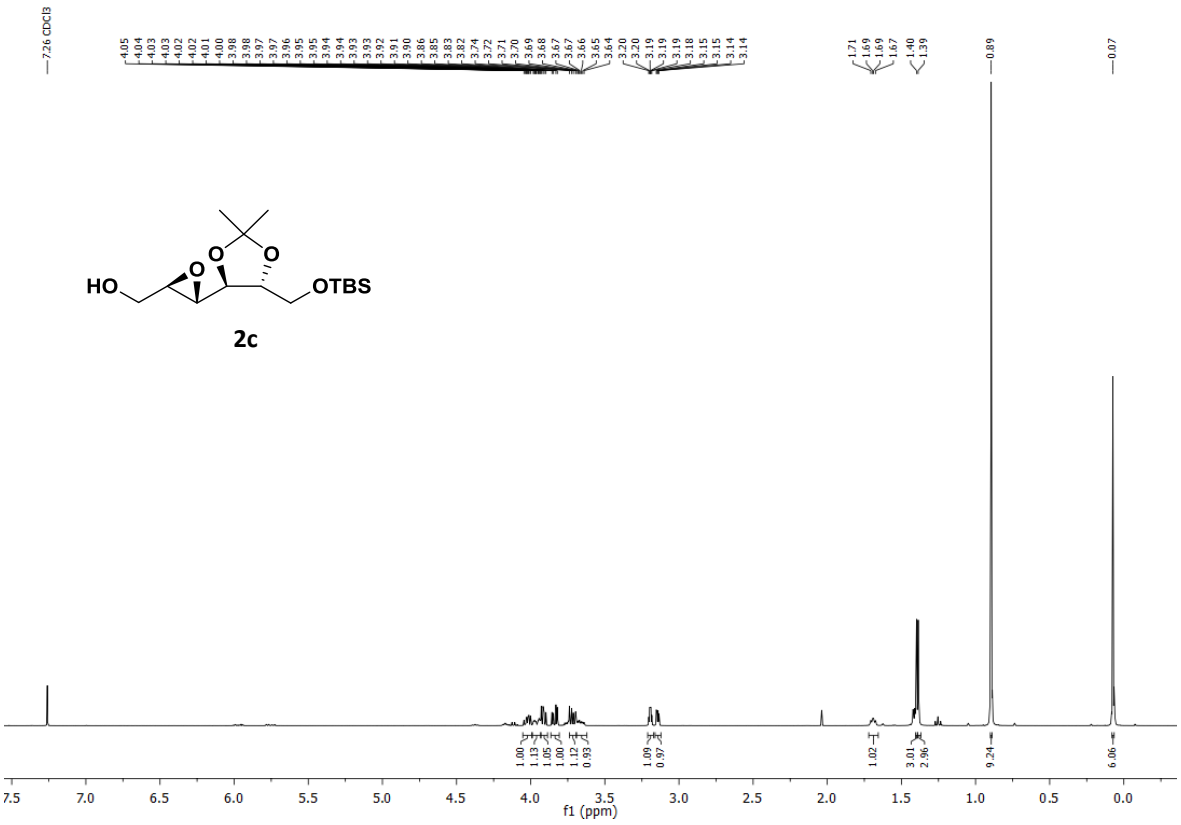
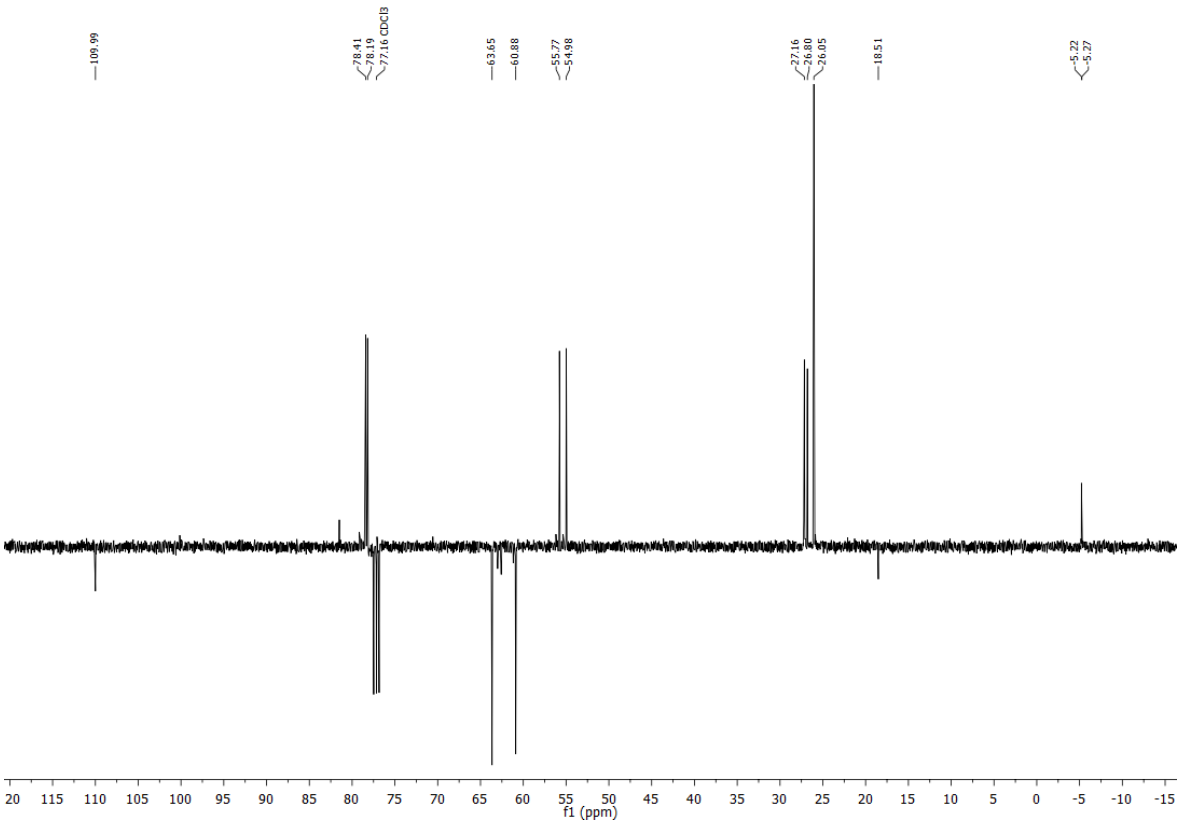
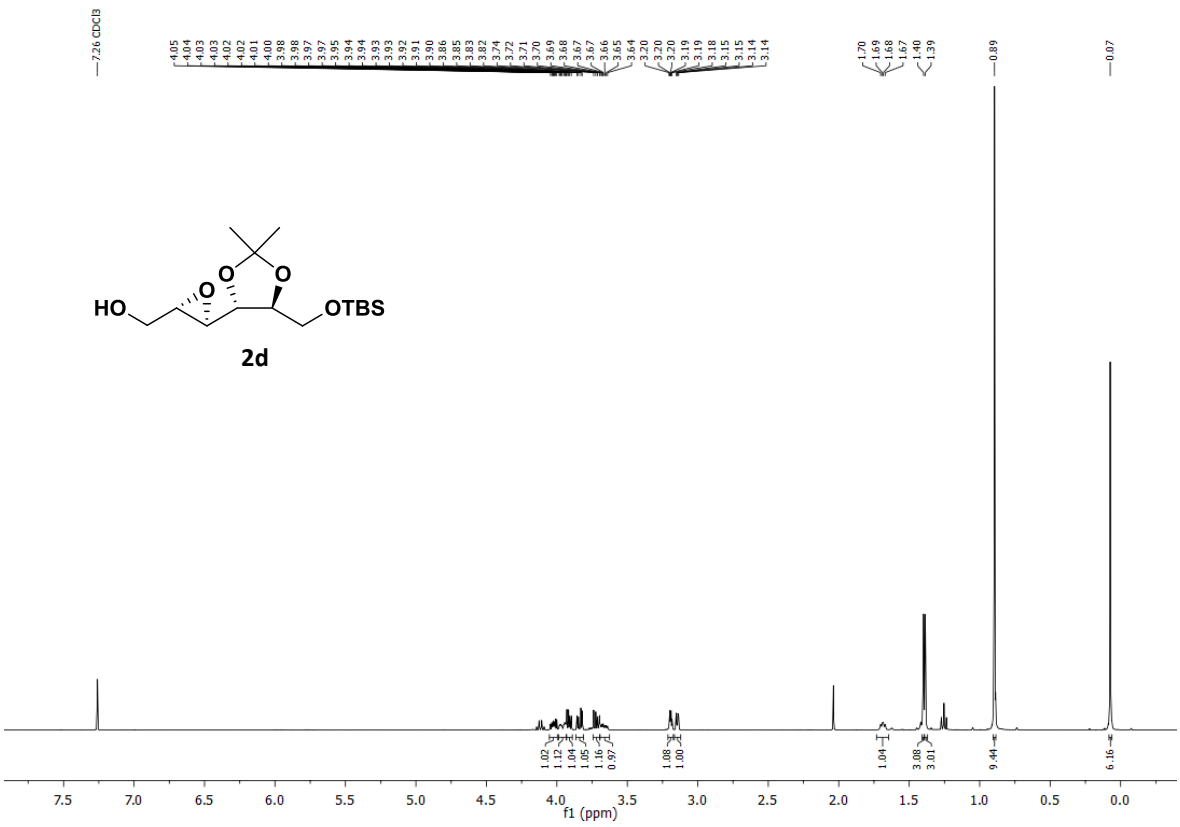
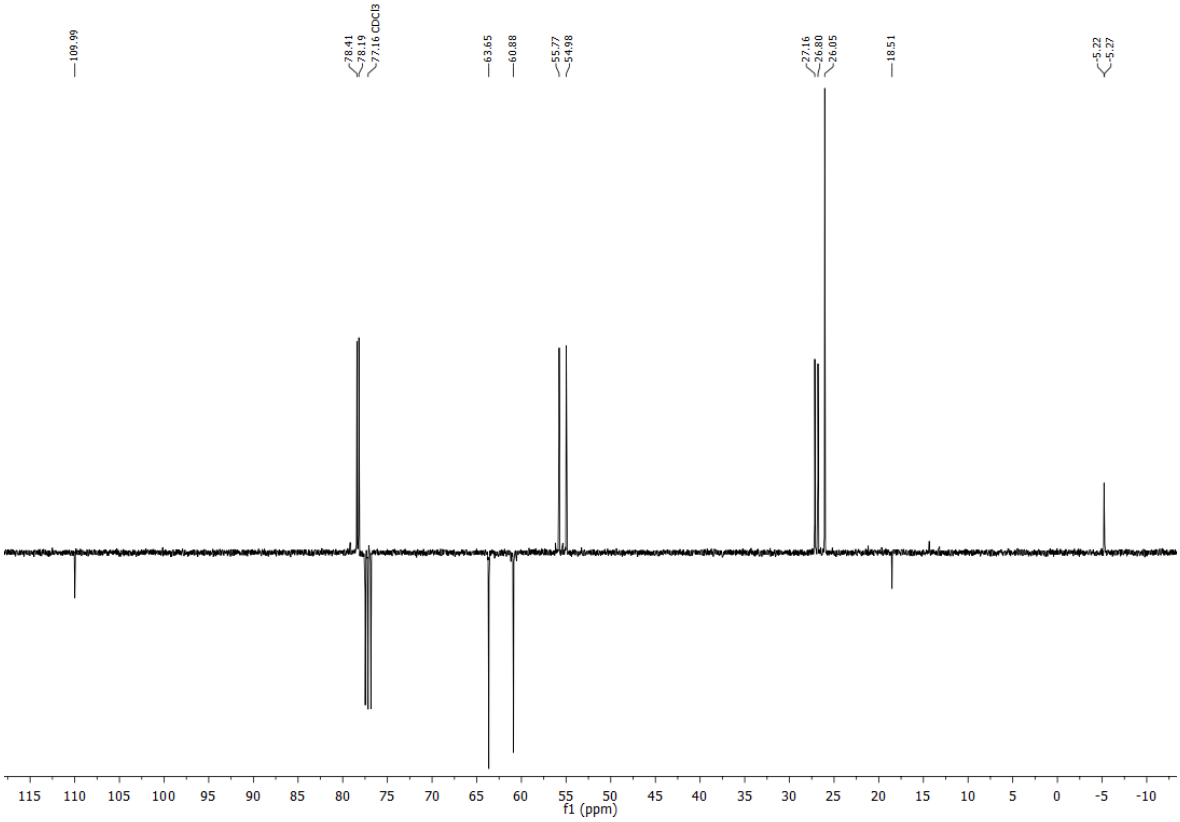
5
0
-5
-10
-15
f1 (ppm)

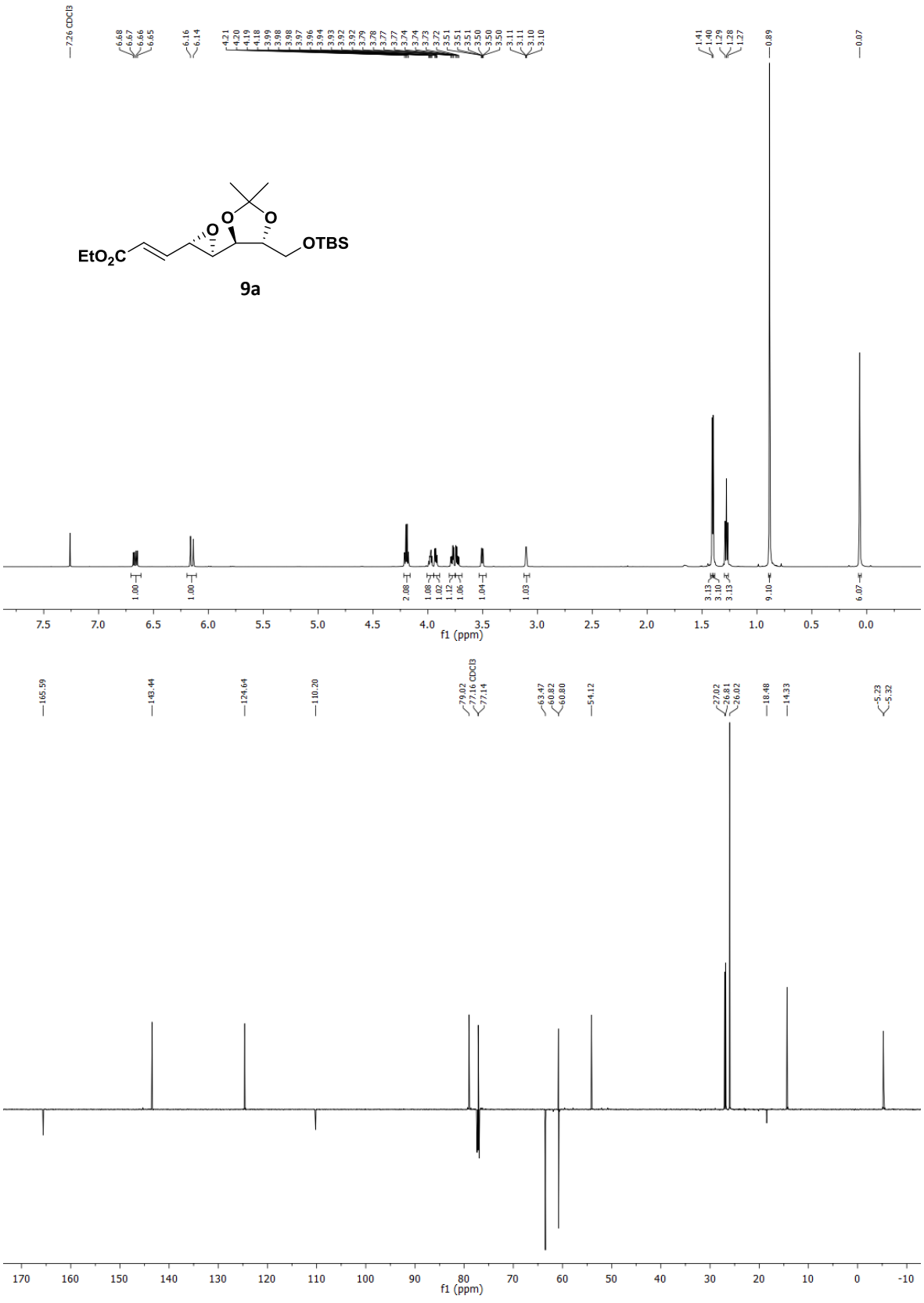


2c




HO
O
O
O
OTBS
2d
f1 (ppm)


f1 (ppm)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6.65
6.16
6.14
4.21
4.20
4.19
4.18
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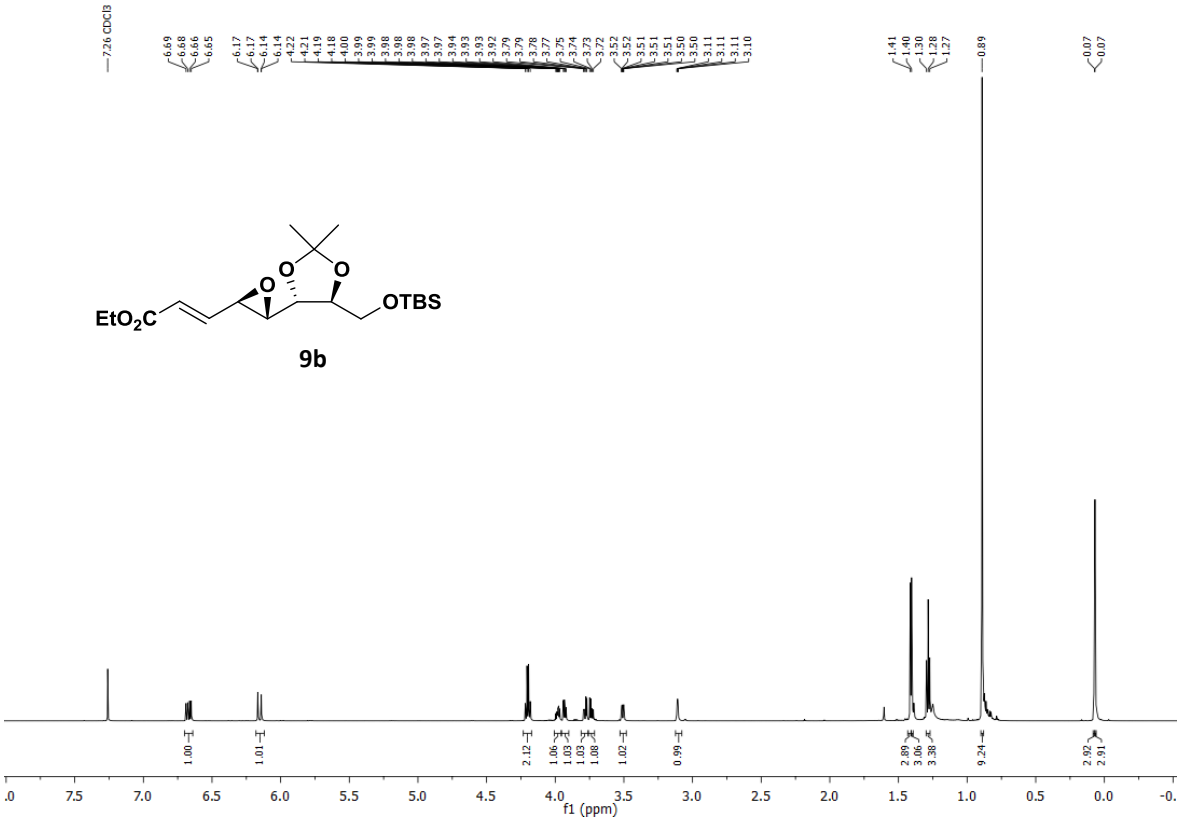
3.98
3.98
3.97
3.96
3.94
3.93
3.92
3.92
3.79
3.78
3.77
3.77
3.74
3.74
3.73
3.72
3.51
3.51
3.51
3.50
3.50
3.11
3.11
3.10
3.10
1.41
1.40
1.29
1.28
1.27
0.89
0.07
EtO2C
OTBS
9a
1.00
1.00
2.08
1.08
1.02
1.12
1.06
1.04
1.03
3.13
3.10
3.13
9.10
6.07
f1 (ppm)
165.59
143.44
124.64
110.20
79.02
77.16 CDCl3
77.14
63.47
60.82
60.80
54.12
27.02
26.81
26.02
18.48
14.33
-5.23
-5.32
f1 (ppm)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6.17
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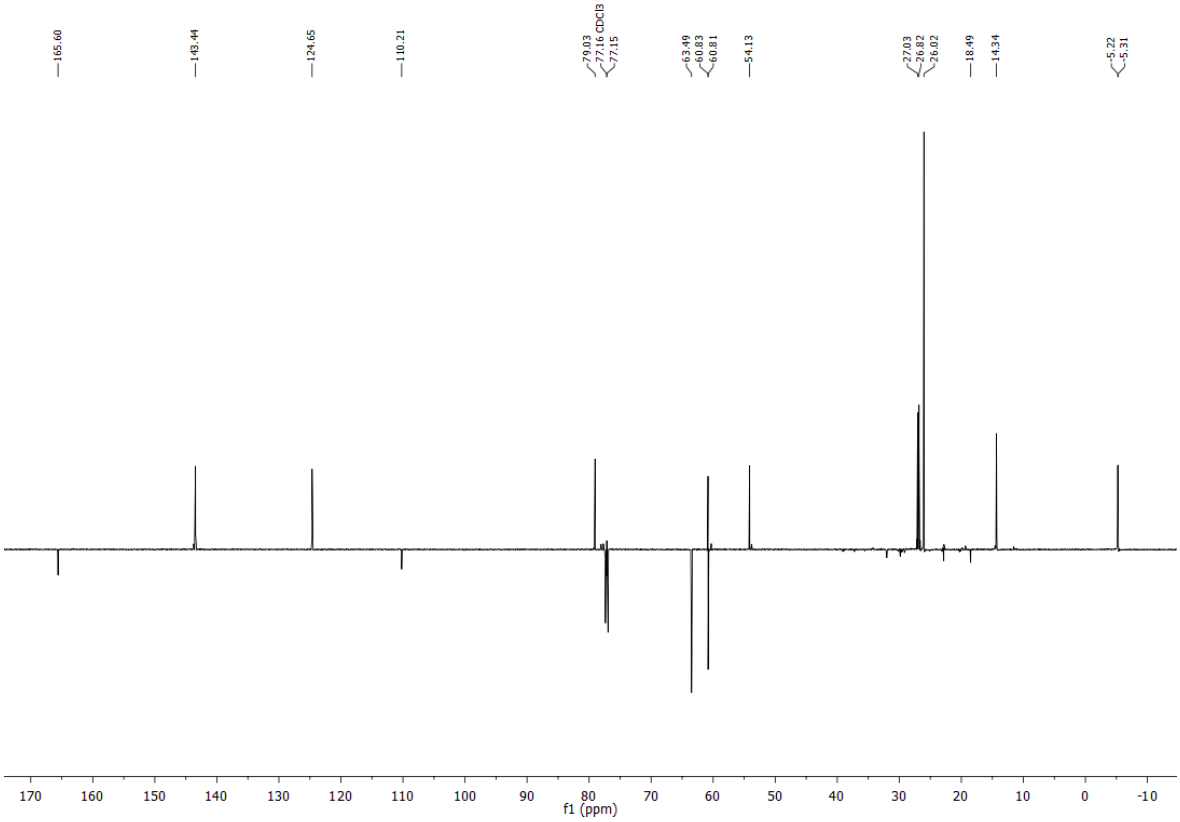
6.14
4.22
4.21
4.19
4.18
4.00
3.99
3.99
3.98
3.98
3.98
3.97
3.97
3.94
3.93
3.93
3.92
3.79
3.78
3.77
3.75
3.74
3.73
3.72
3.52
3.52
3.51
3.51
3.51
3.50
3.50
3.11
3.11
3.11
3.10
1.41
1.40
1.30
1.28
1.27
0.89
0.07
0.07
EtO2C
O
O
O
OTBS
1.00
1.01
2.12
1.06
1.03
1.03
1.08
1.02
0.99
2.89
3.06
3.38
9.24
2.92
2.91
f1 (ppm)

9b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143.44
124.65
110.21
79.03
77.16 CDCl3
77.15
63.49
60.83
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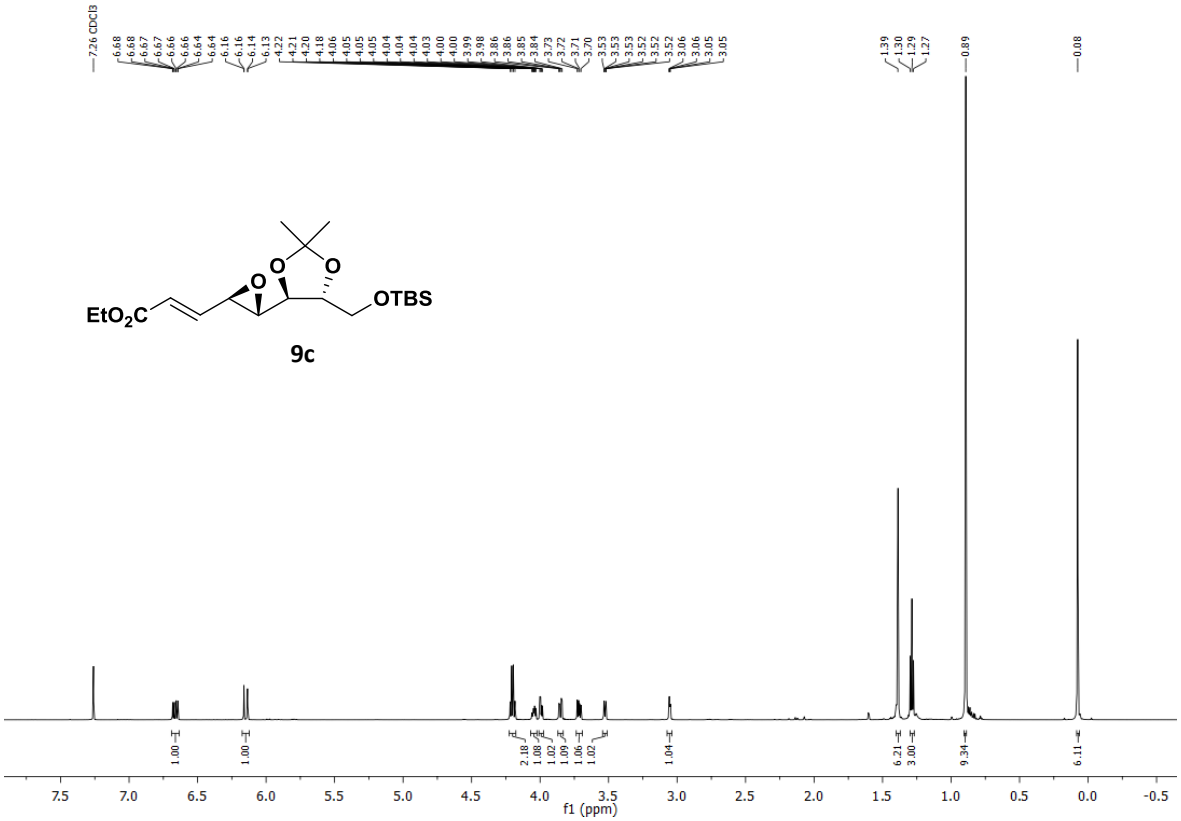
54.13
27.03
26.82
26.02
18.49
14.34
-5.22
-5.31
f1 (ppm)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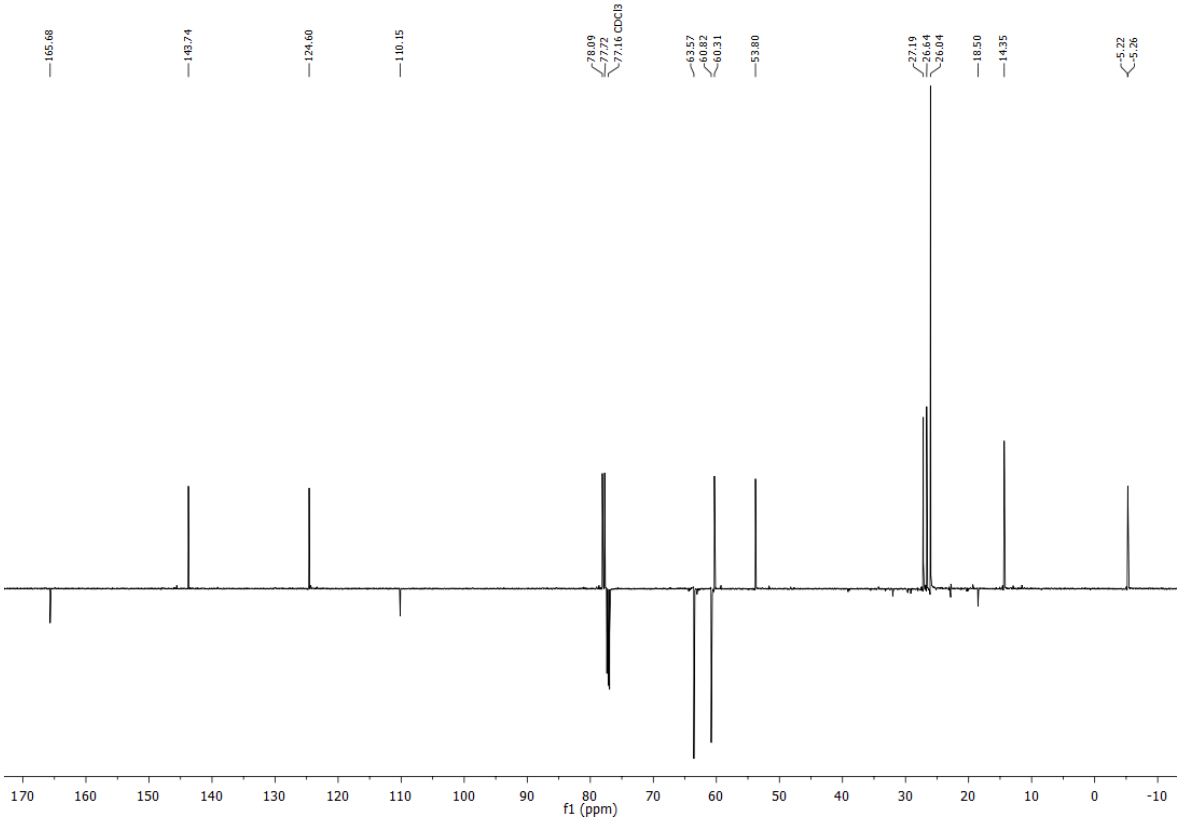
6.67
6.66
6.64
6.16
6.14
6.13
4.22
4.21
4.20
4.18
4.06
4.05
4.04
4.03
4.00
3.99
3.98
3.86
3.85
3.84
3.73
3.72
3.71
3.70
3.53
3.52
3.06
3.05
1.39
1.30
1.29
1.27
0.89
0.08
EtO2C
OTBS
9c
1.00
1.00
2.18
1.08
1.02
1.09
1.06
1.02
1.04
6.21
3.00
9.34
6.11
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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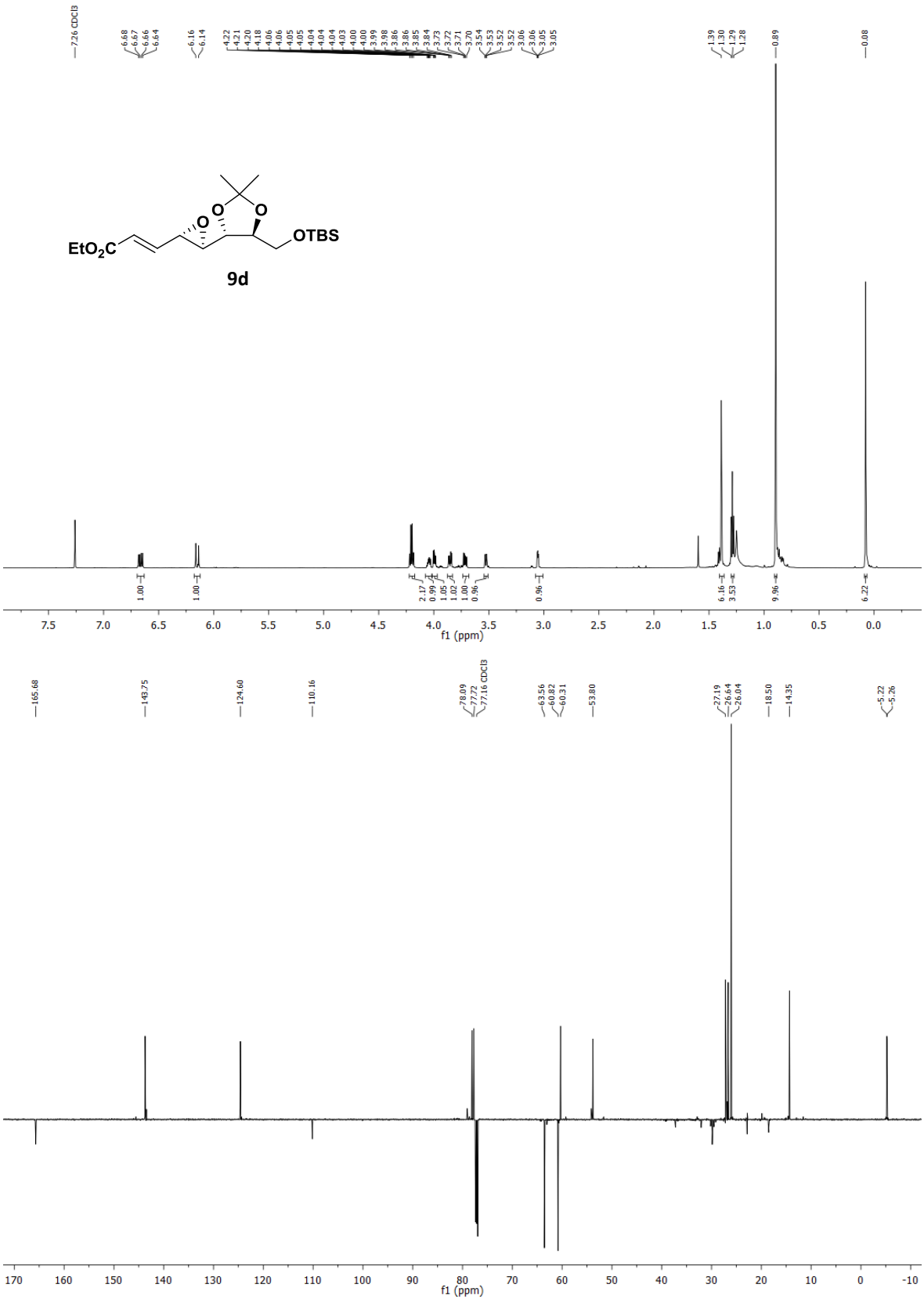
149.74
124.60
110.15
78.09
77.72
77.16 CDCl3
63.57
60.82
60.31
53.80
27.19
26.64
26.04
18.50
14.35
-5.22
-5.26
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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6.67
6.66
6.64
6.16
6.14
4.22
4.21
4.20
4.18
4.06
4.06
4.05
4.05
4.04
4.04
4.04
4.03
4.00
4.00
3.99
3.98
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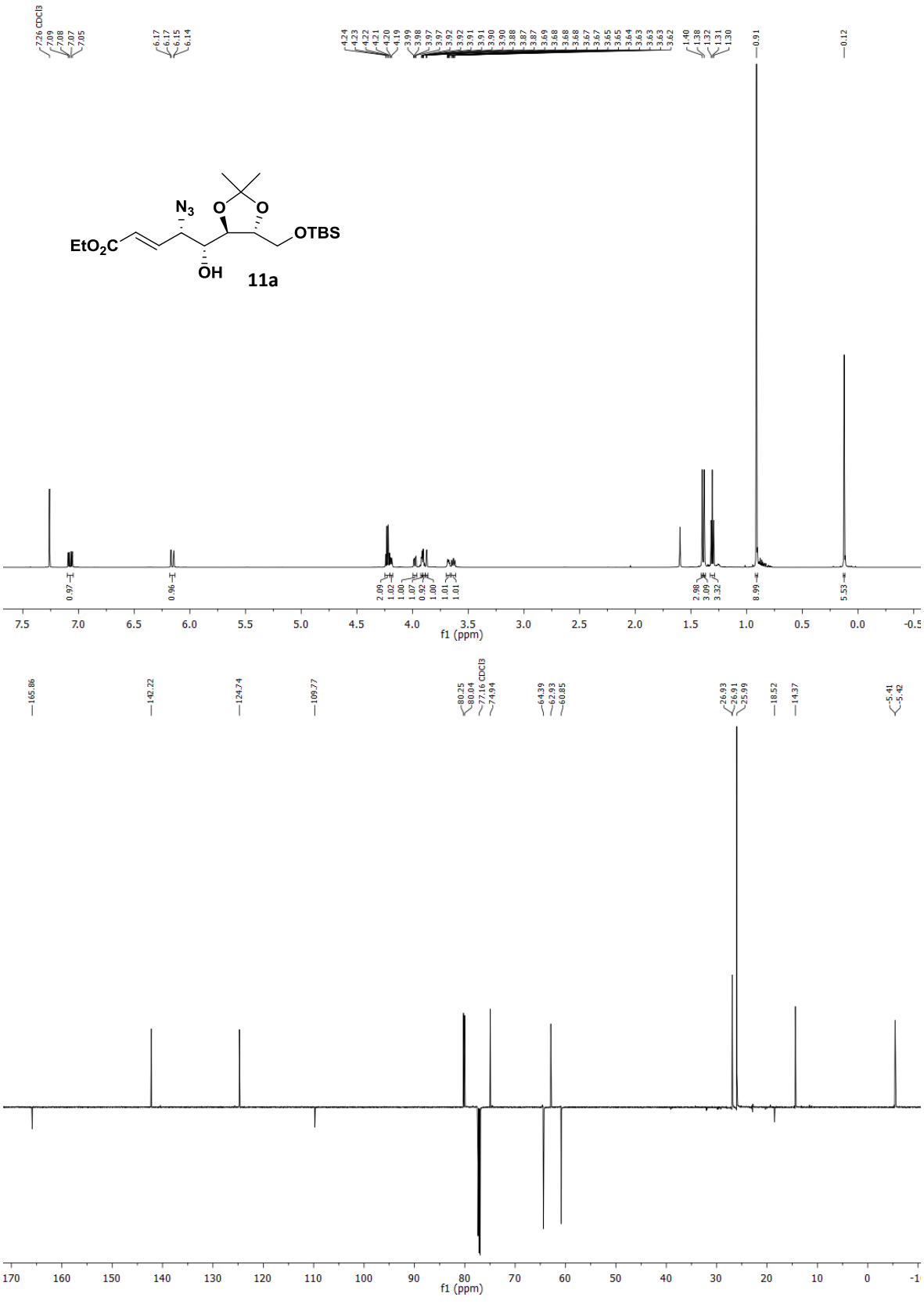
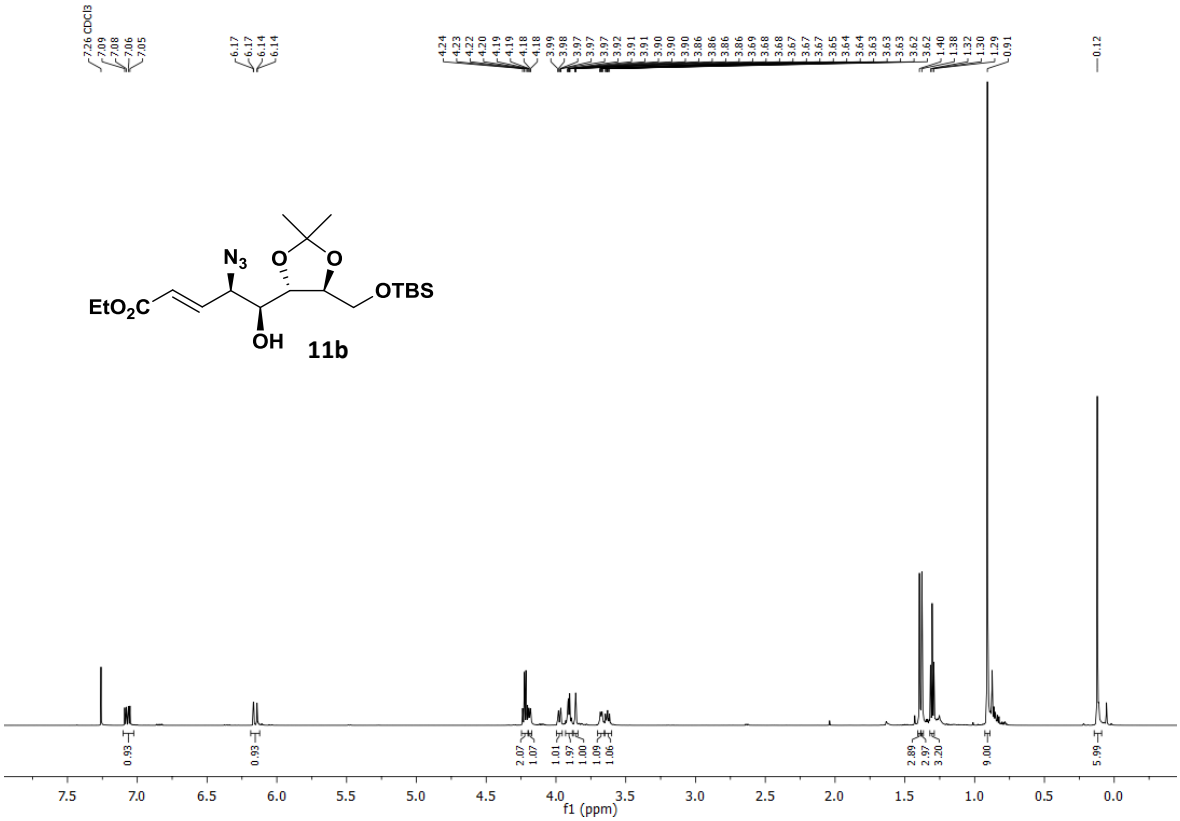
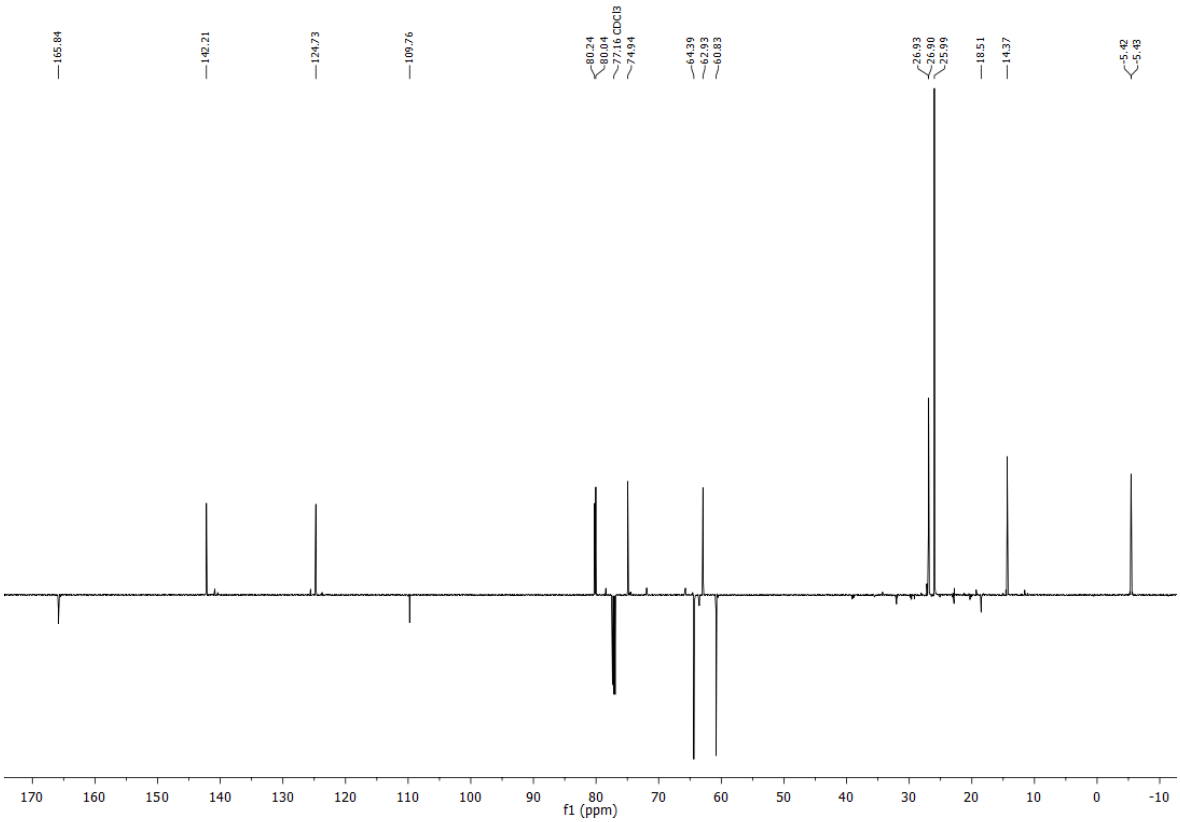
3.86
3.85
3.84
3.73
3.72
3.71
3.70
3.54
3.53
3.52
3.52
3.06
3.06
3.05
3.05
1.39
1.30
1.29
1.28
0.89
0.08
EtO2C
OTBS
9d
1.00
1.00
2.17
0.99
1.05
1.02
1.00
0.96
0.96
6.16
3.53
9.96
6.22
f1 (ppm)
165.68
143.75
124.60
110.16
78.09
77.72
77.16 CDCl3
63.56
60.82
60.31
53.80
27.19
26.64
26.04
18.50
14.35
-5.22
-5.26
f1 (ppm)


N3
O
O
EtO2C
OTBS
OH
11a
f1 (ppm)
f1 (ppm)


7.26 CDCl3
7.09
7.08
7.06
7.05
6.17
6.17
6.14
6.14
4.24
4.23
4.22
4.20
4.19
4.19
4.18
4.18
3.99
3.98
3.97
3.97
3.97
3.92
3.91
3.91
3.90
3.90
3.90
3.86
3.86
3.86
3.86
3.69
3.68
3.68
3.67
3.67
3.67
3.65
3.64
3.64
3.63
3.63
3.63
3.62
3.62
1.40
1.38
1.32
1.30
1.29
0.91
0.12
N3
O
O
OTBS
EtO2C
OH
11b
0.93
0.93
2.07
1.07
1.01
1.97
1.00
1.09
1.06
2.89
2.97
3.20
9.00
5.99
f1 (ppm)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142.21
124.73
109.76
80.24
80.04
77.16 CDCl3
74.94
64.39
62.93
60.83
26.93
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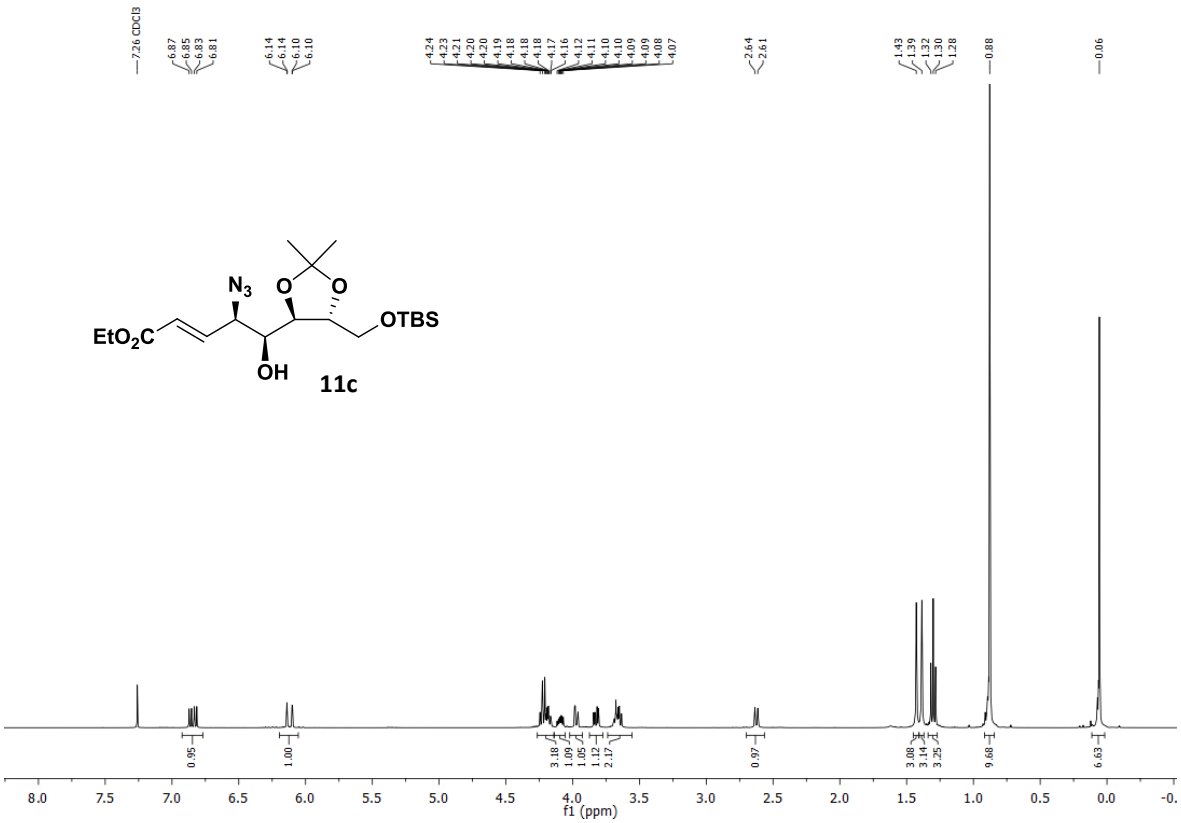
18.51
14.37
-5.42
-5.43
f1 (ppm)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6.83
6.81
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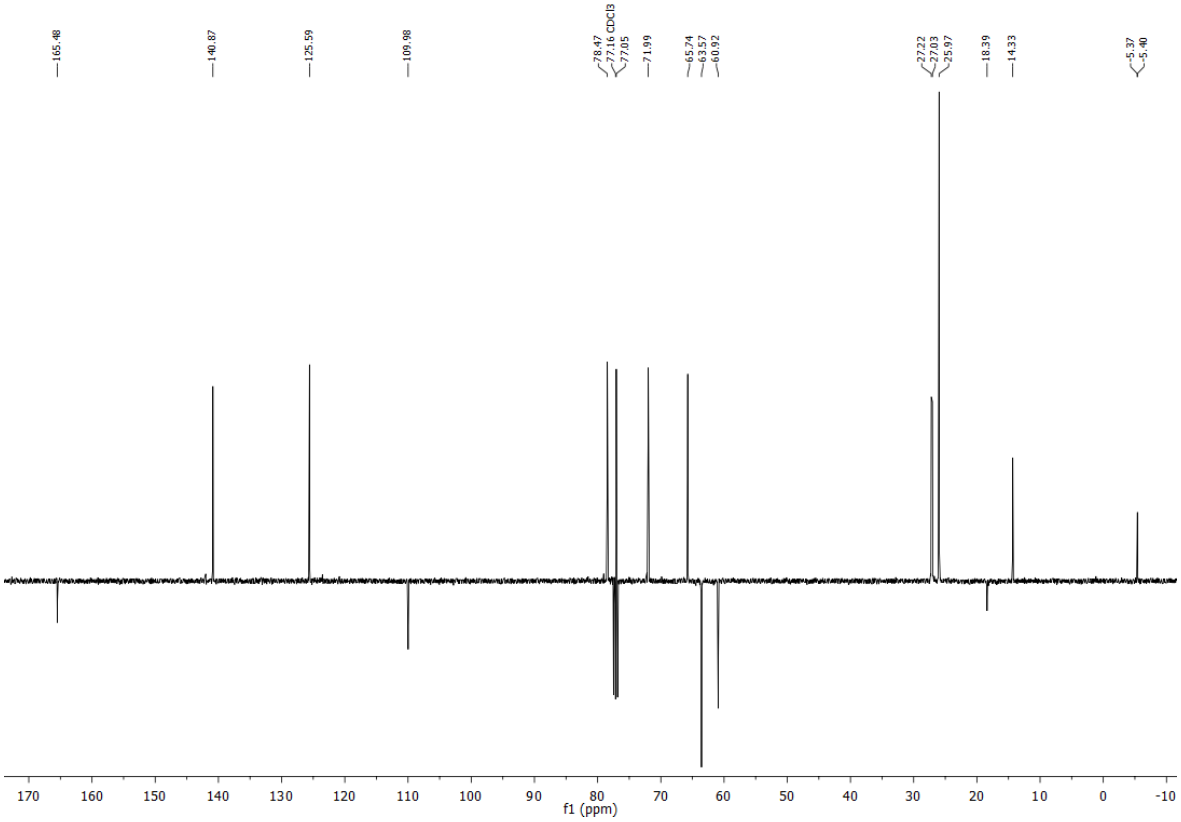
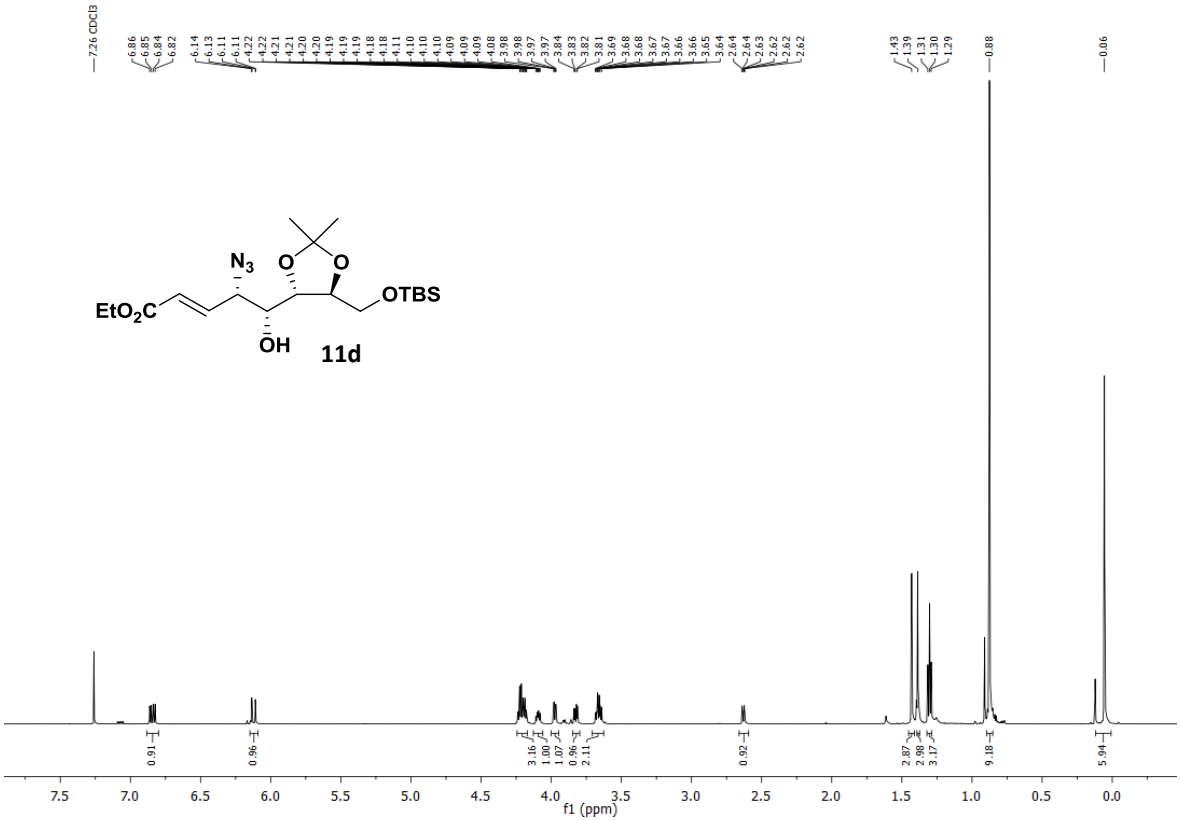
6.14
6.10
6.10
4.24
4.23
4.21
4.20
4.20
4.19
4.18
4.18
4.18
4.17
4.16
4.12
4.11
4.10
4.10
4.09
4.09
4.08
4.07
2.64
2.61
1.43
1.39
1.32
1.30
1.28
0.88
0.06
N3
O
O
OTBS
EtO2C
OH
11c
0.95
1.00
3.18
1.09
1.05
1.12
2.17
0.97
3.08
3.14
3.25
9.68
6.63
f1 (ppm)


165.48
140.87
125.59
109.98
78.47
77.16 CDCl3
77.05
71.99
65.74
63.57
60.92
27.22
27.03
25.97
18.39
14.33
-5.37
-5.40
f1 (ppm)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6.84
6.82
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6.13
6.11
6.11
4.22
4.21
4.21
4.20
4.20
4.19
4.19
4.19
4.18
4.18
4.11
4.10
4.10
4.09
4.09
4.08
3.98
3.98
3.97
3.97
3.84
3.83
3.82
3.81
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3.68
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3.66
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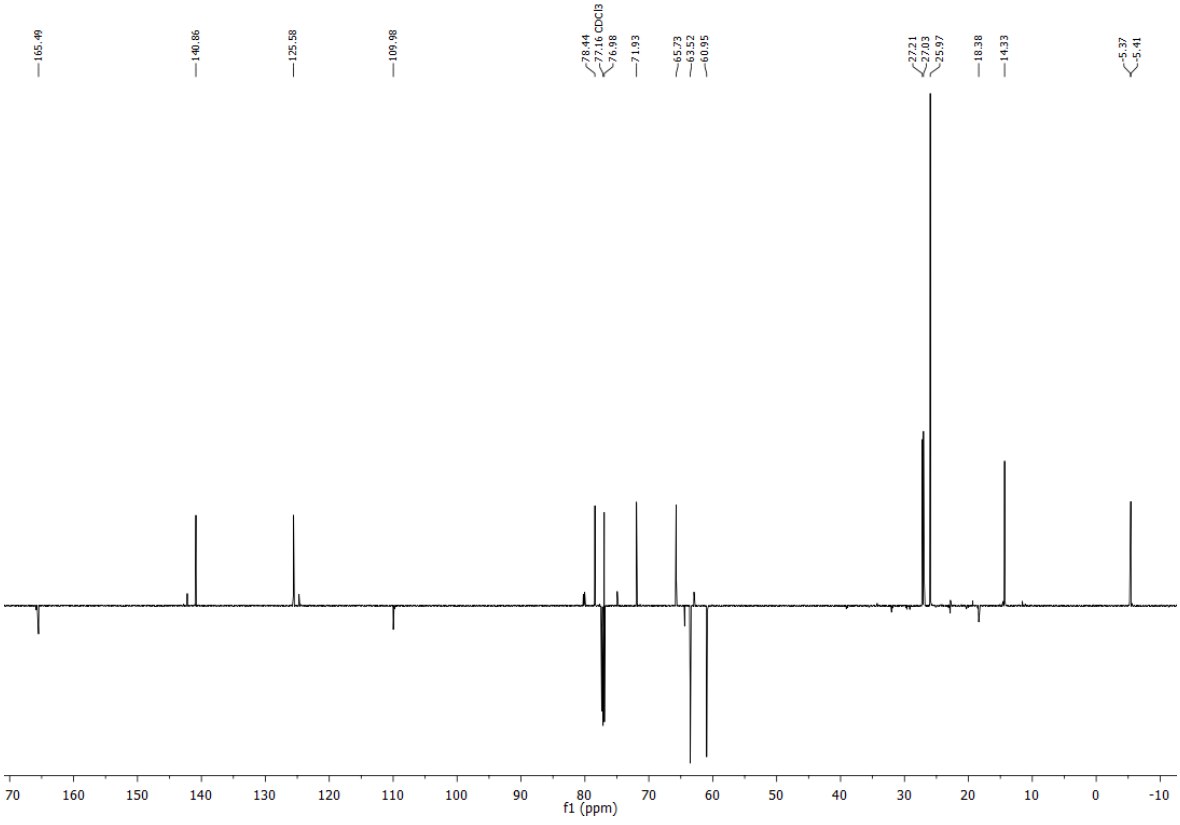
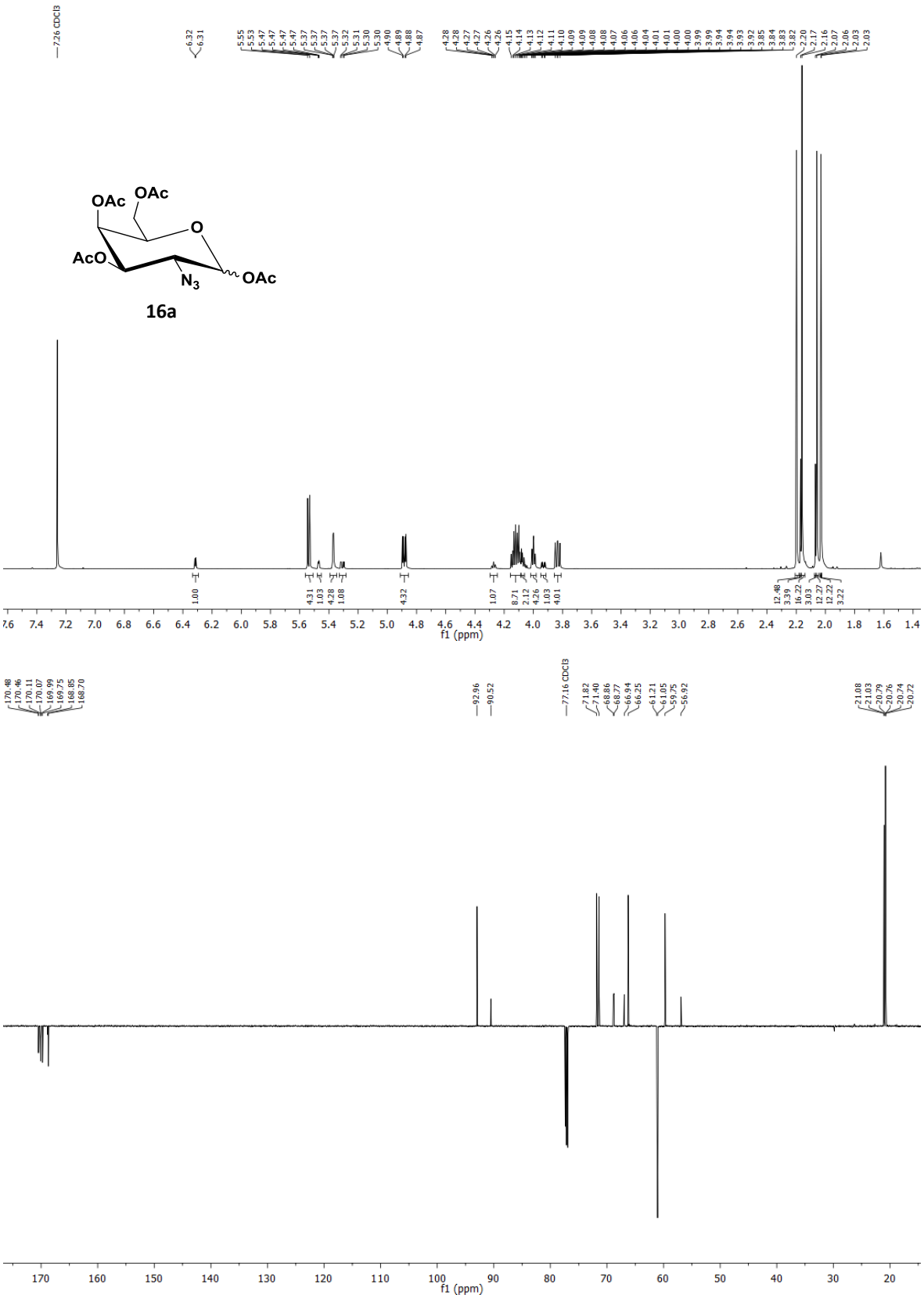
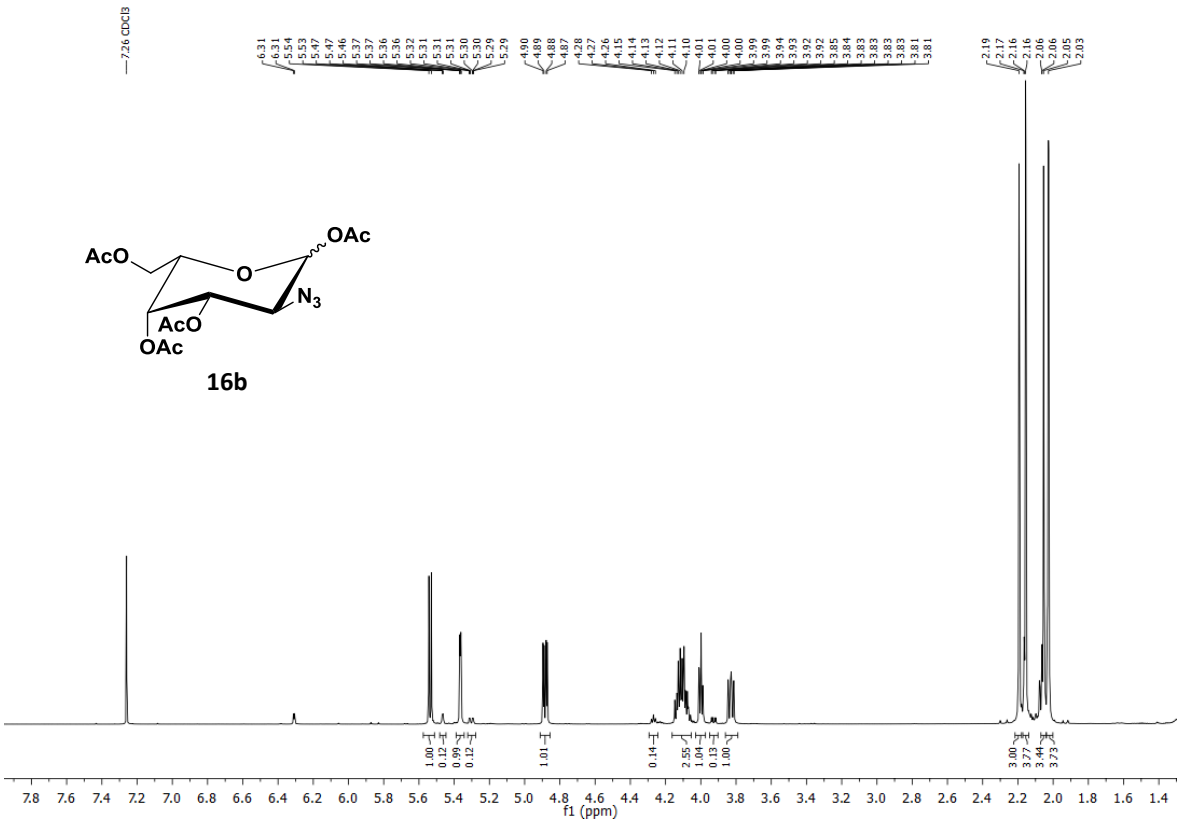
3.64
2.64
2.64
2.63
2.62
2.62
2.62
1.43
1.39
1.31
1.30
1.29
0.88
0.06
N3
O
O
EtO2C
OTBS
OH
11d
0.91
0.96
3.16
1.00
1.07
0.96
2.11
0.92
2.87
2.98
3.17
9.18
5.94
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

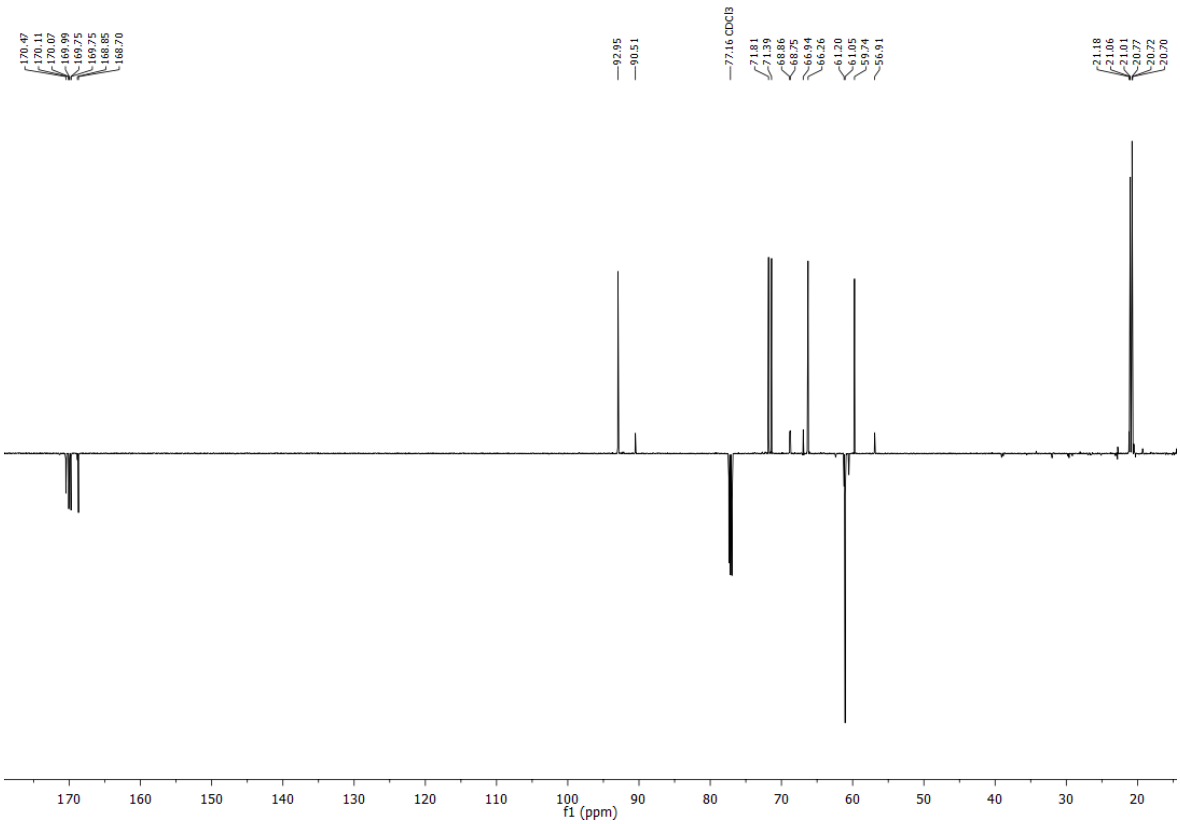

165.49
140.86
125.58
109.98
78.44
77.16 CDCl3
76.98
71.93
65.73
63.52
60.95
27.21
27.03
25.97
18.38
14.33
5.37
5.41
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

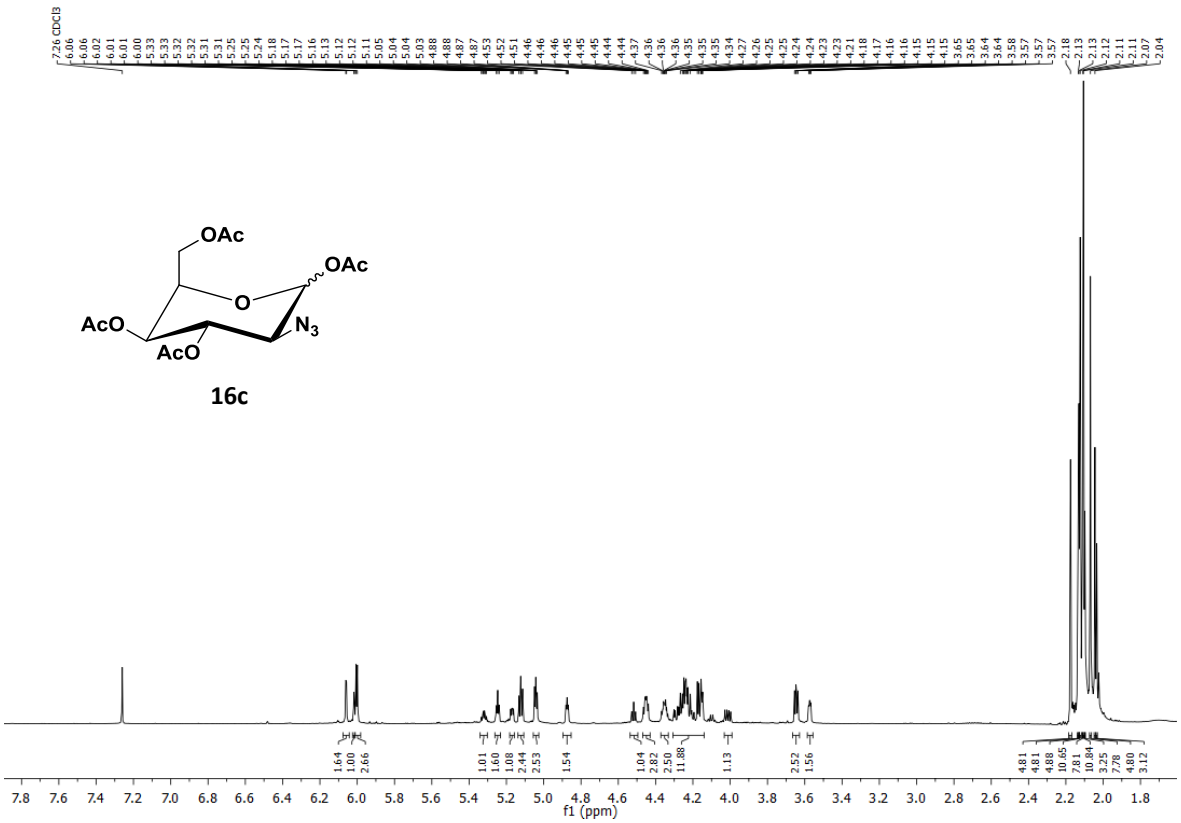


16a

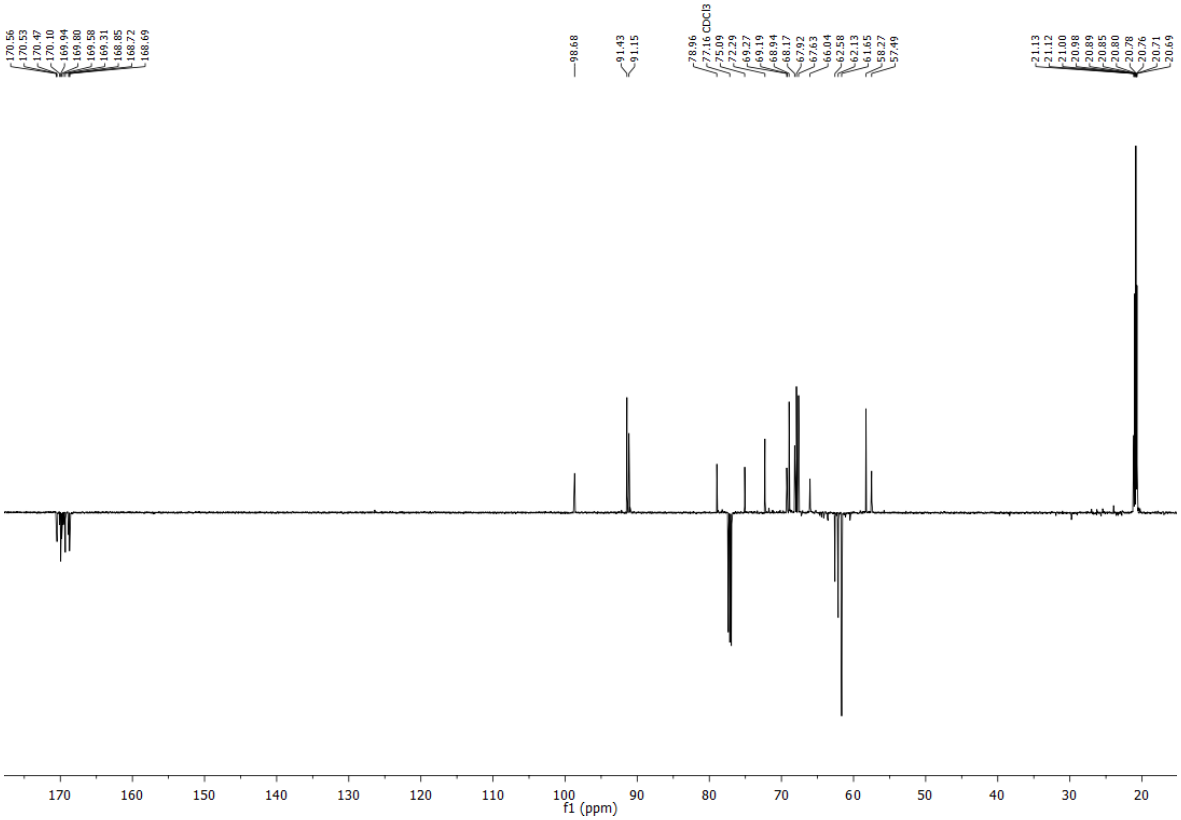

7.26 CDCl3
AcO
OAc
O
N3
AcO
OAc
f1 (ppm)

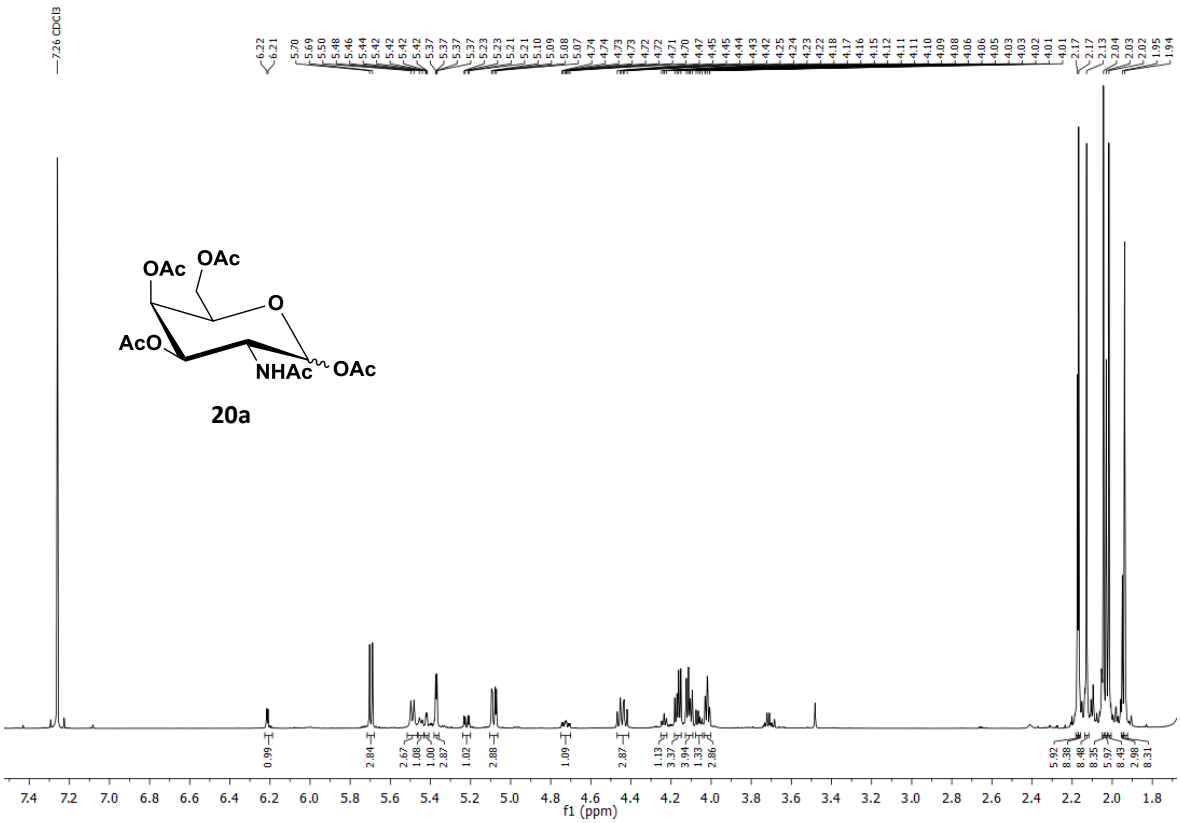
16b


77.16 CDCl3
92.95
90.51
f1 (ppm)

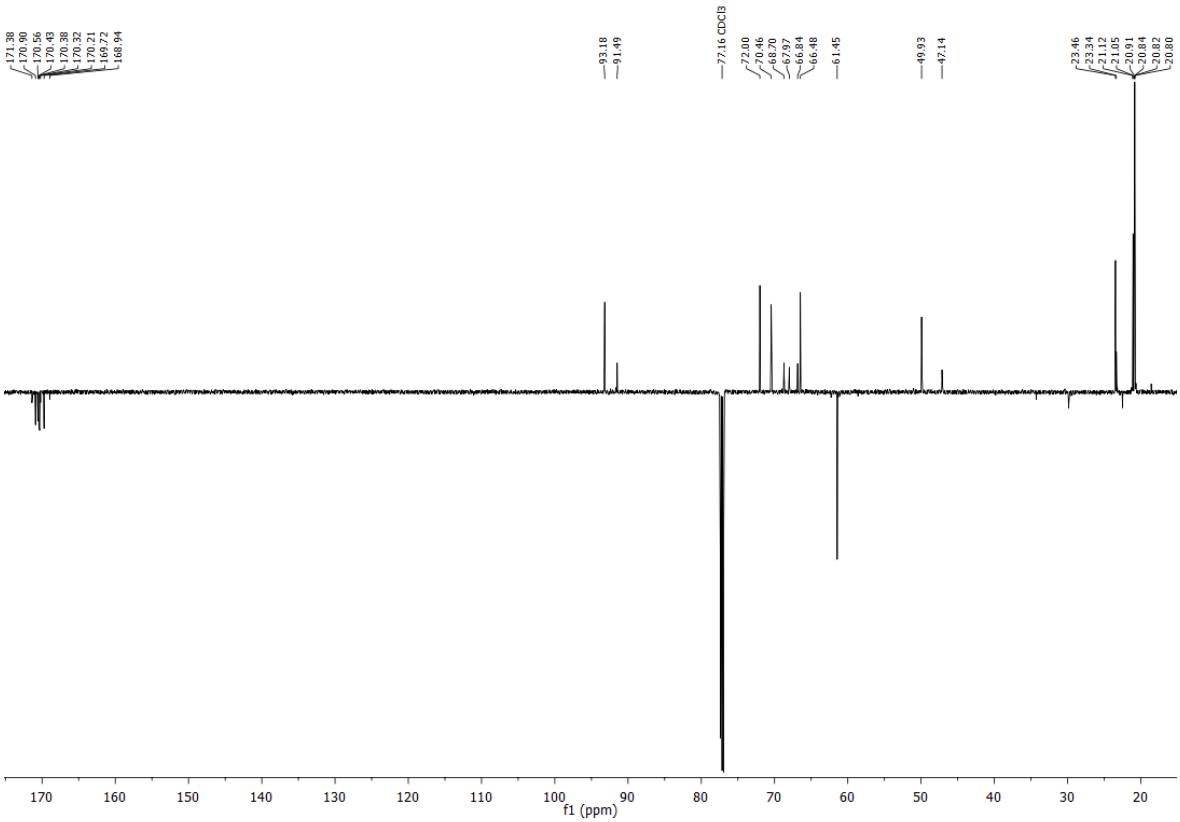


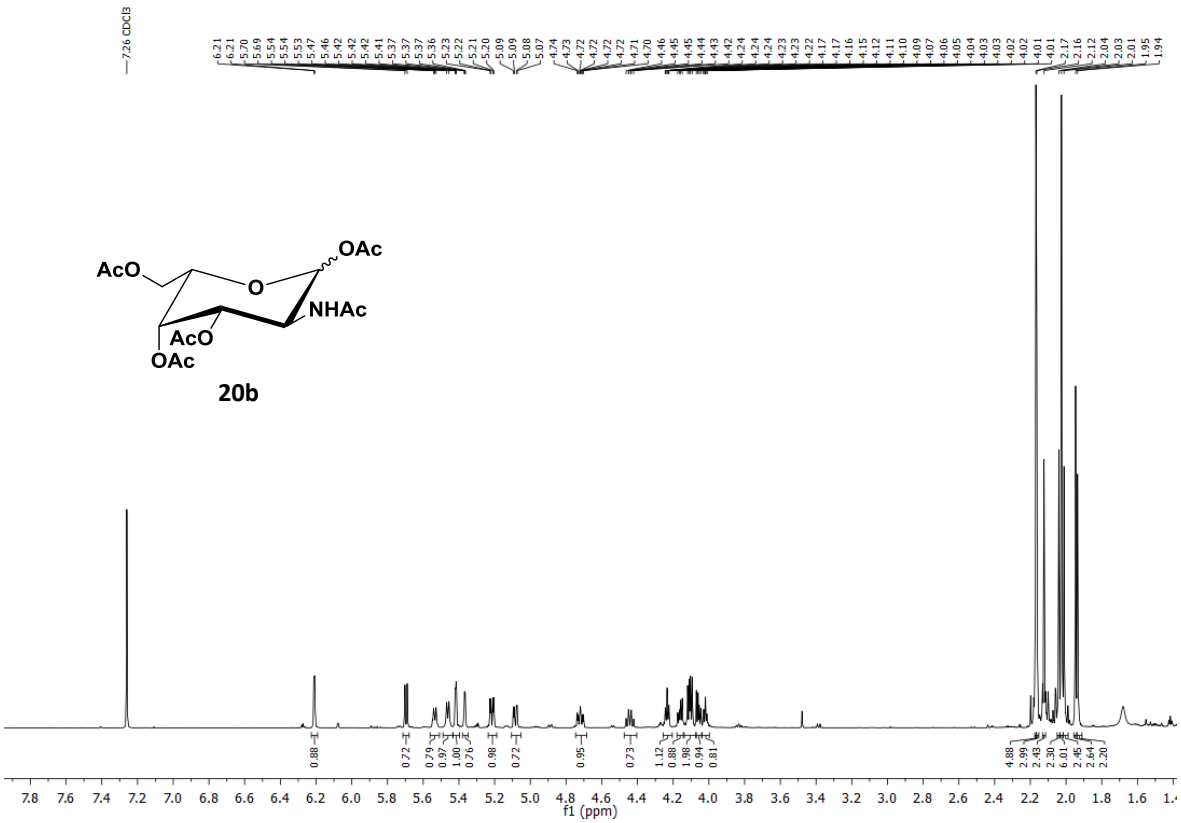
16c



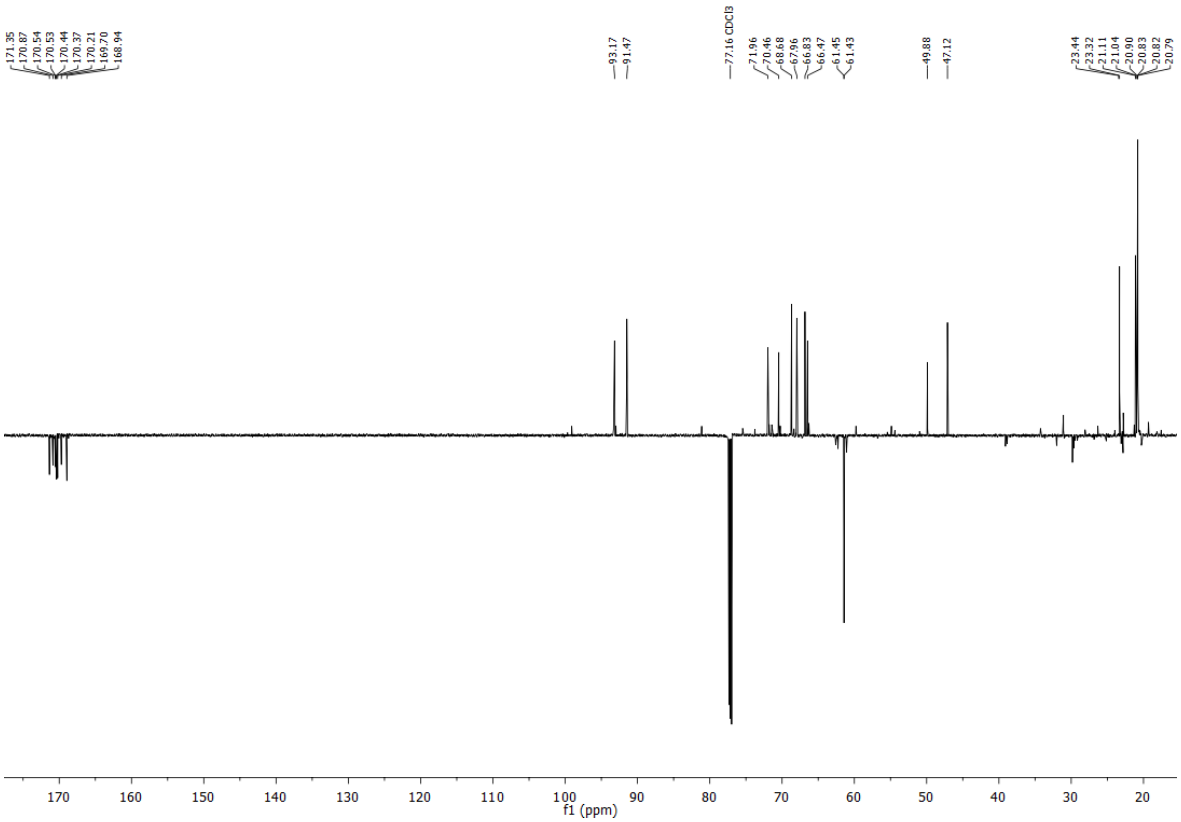


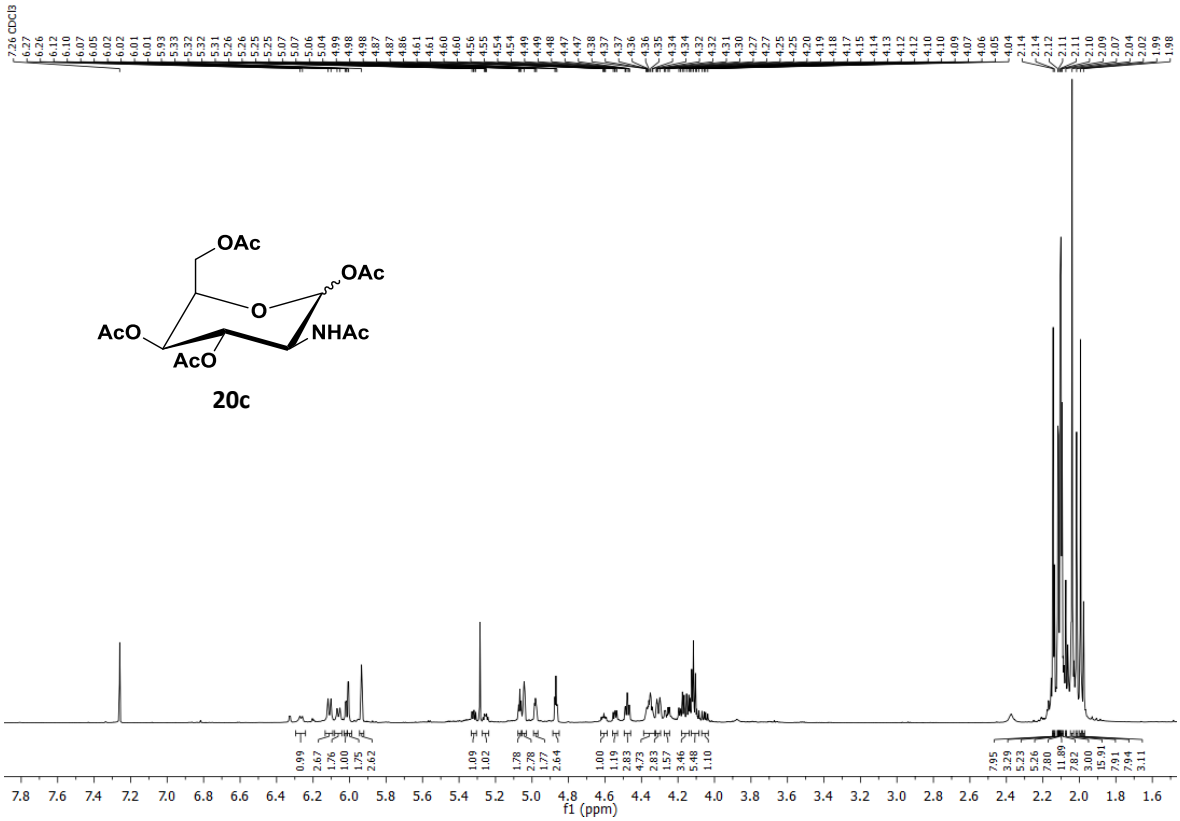
20a



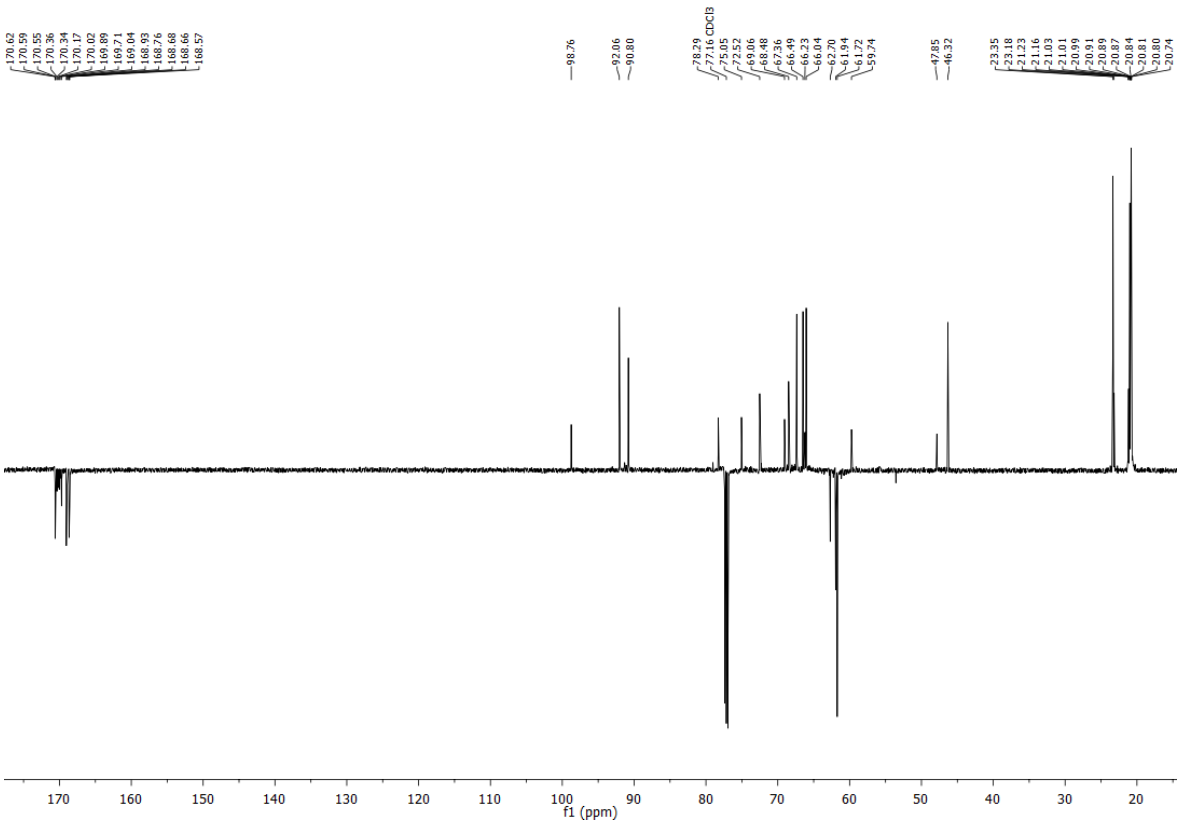


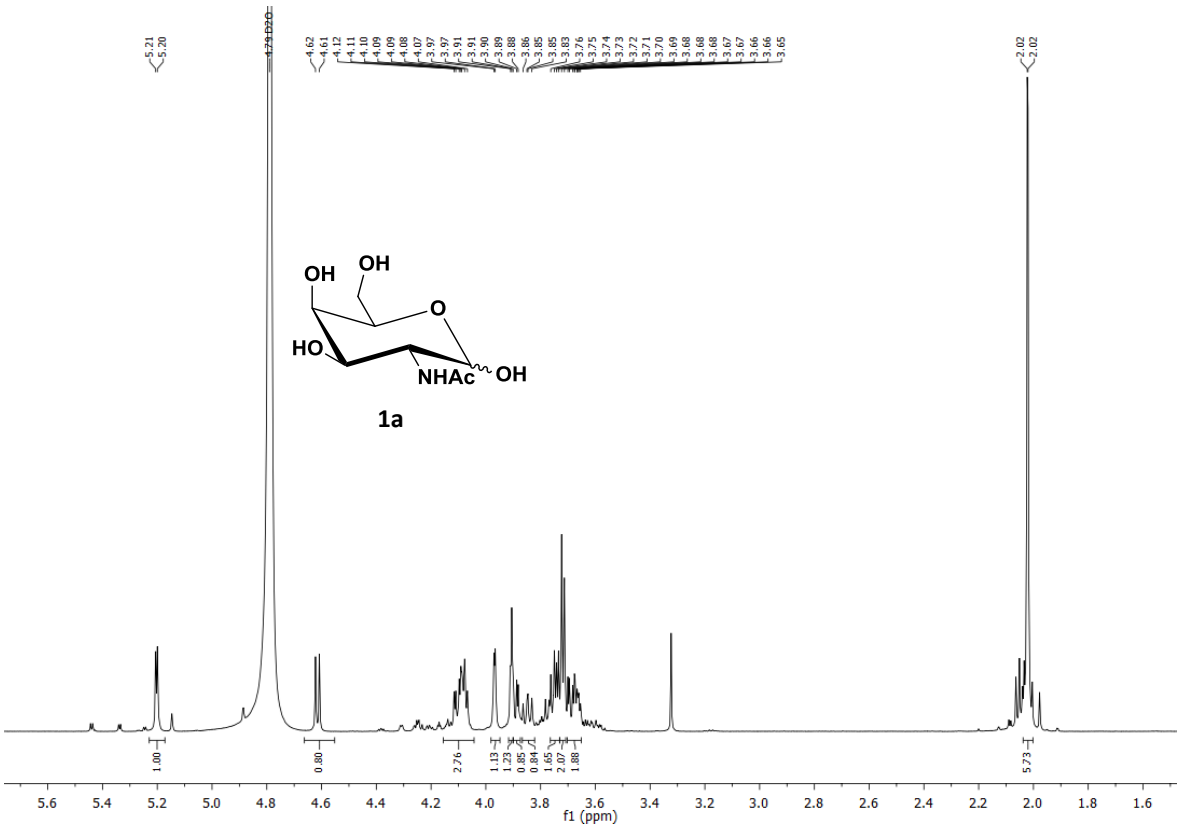
20b



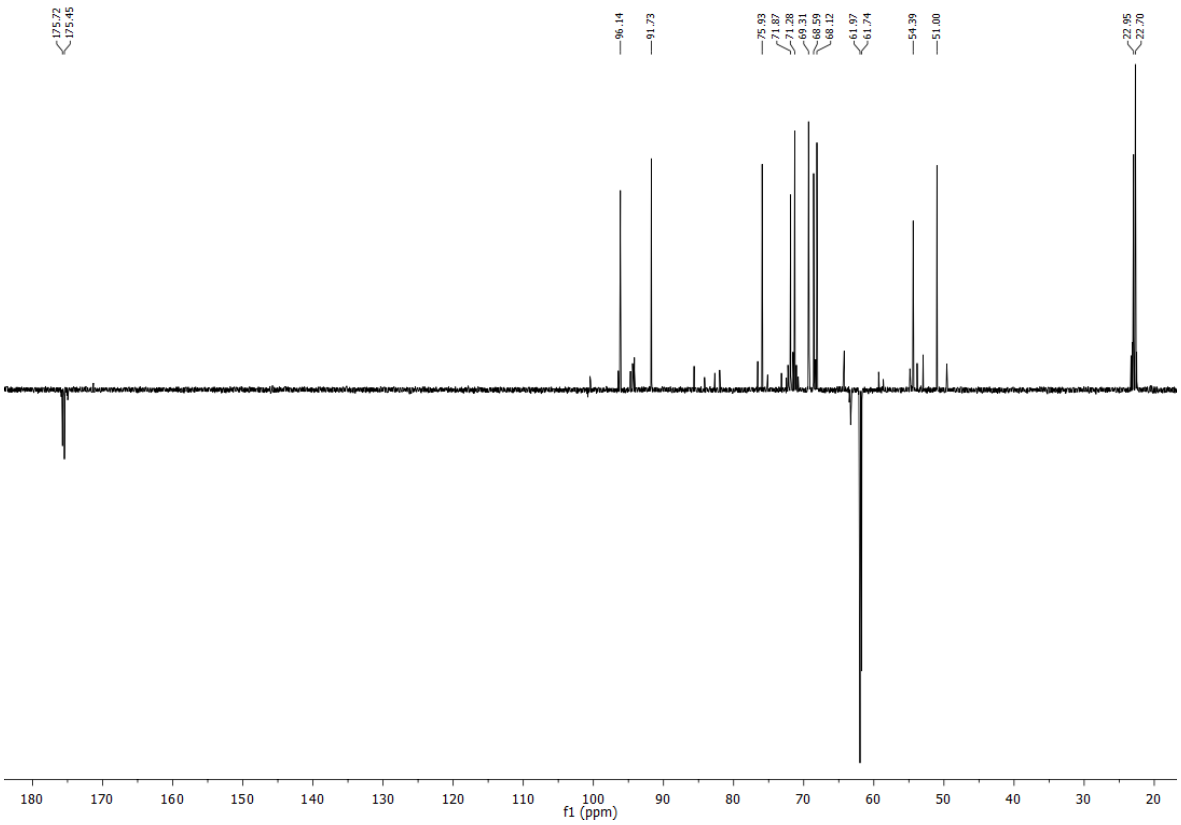


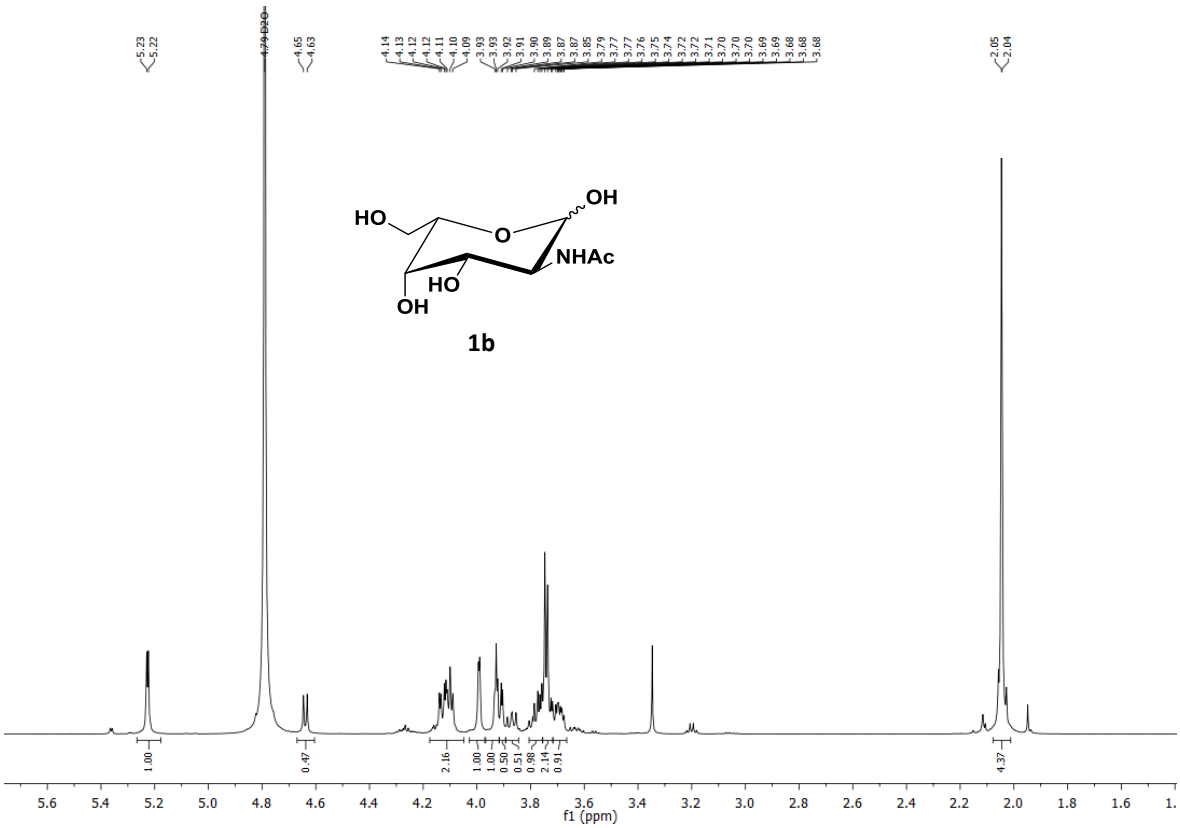
20c

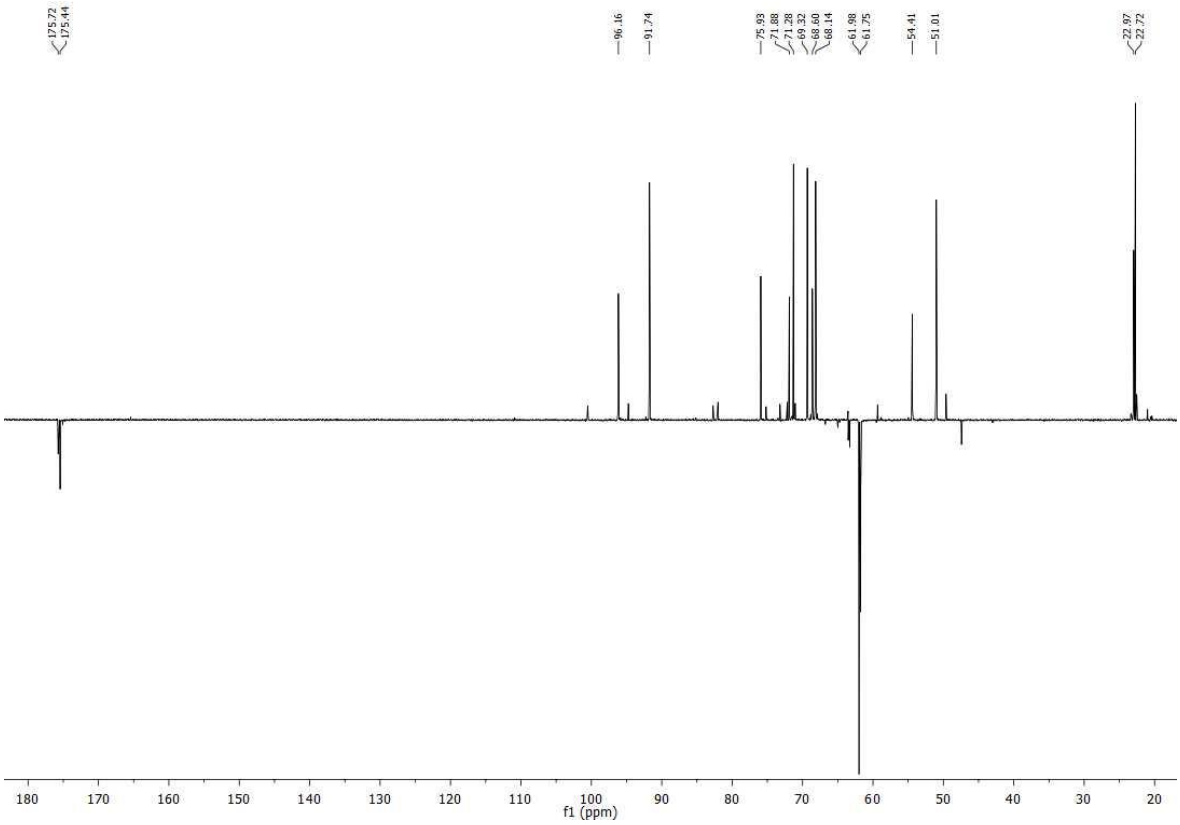




1a




HO
O
OH
NHAc
HO
OH
1b
f1 (ppm)


f1 (ppm)

III Project II – Synthesis of ulosonic acid bioisosteres

1 Introduction

1.1 Biological relevance of ulosonic acids

Ulosonic acids include all ketoses possessing a carboxylic function on C-1. Many well-known, biologically active ulosonic acid lack the hydroxyl group on C-3, e.g. 3-deoxy-D-*manno*-oct-2-ulosonic acid (Kdo), 2-keto-3-deoxynonic acid[61,62] (Kdn) or 3-deoxy-D-*arabino*-heptulosonic acid (Dah) (Figure 6).[63] Furthermore, the substitution by a nitrogen moiety is possible, resulting in the so-called sialic acids with *N*-acetylneuraminic acid (Neu5Ac) as the most famous member.[64] These compounds are only few examples of the ulosonic acid family, playing important roles in diverse biological processes.[65]

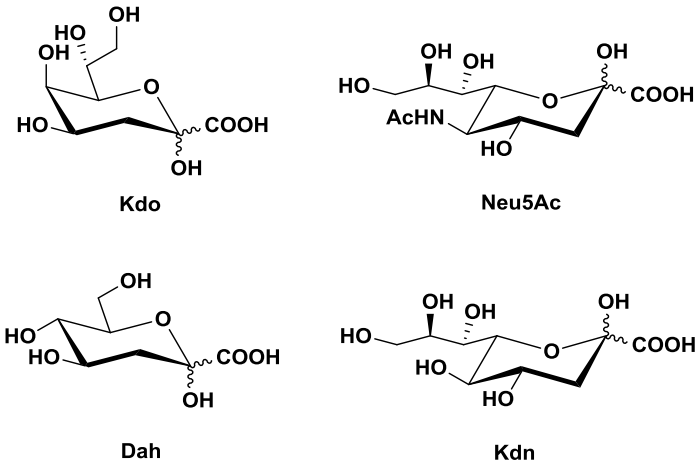


Figure 6: Members of the ulosonic acid family.

1.1.1 3-Deoxy-D-*manno*-oct-2-ulosonic acid (Kdo)

Kdo is an essential part of lipopolysaccharides (LPSs) (Figure 7), also known as endotoxins.[66–69] These amphiphilic macromolecules are located on the outer membrane of almost all Gram-negative bacteria and targeted by the mammalian immune system. They are divided into three regions: Lipid A, core region and *O*-specific chain. Lipid A, responsible for the toxicity of LPSs, consists of a β-1,6 linked disaccharide of partly phosphorylated glucosamine (GlcN). Furthermore, each GlcN is substituted on the positions 2, 3, 2' and 3' by fatty acid chains *via* acyl or amide linkages. This

substitution pattern can vary between species in length, number, order and saturation and serves as anchor connecting LPS with the cell membrane.[70–72]

The core region links lipid A to the *O*-specific chain and shows a high diversity of carbohydrates (Figure 7).[73] The inner core can contain up to three Kdos, with one α-ketosidically linked to position 6' of GlcN. Furthermore, the substitution pattern can be extended by heptoses, phosphates and hexuronic acids. This region is responsible for the recognition of several bacteria by antibodies and serum factors. Additionally, together with lipid A it is essential for the viability of bacteria. The outer core region is build up by branched oligosaccharide chains of common hexoses and shows antigenic properties. Finally, the *O*-specific chain consists of repeating units of heteropolysaccharide chains and works as major surface antigen.[74–76]

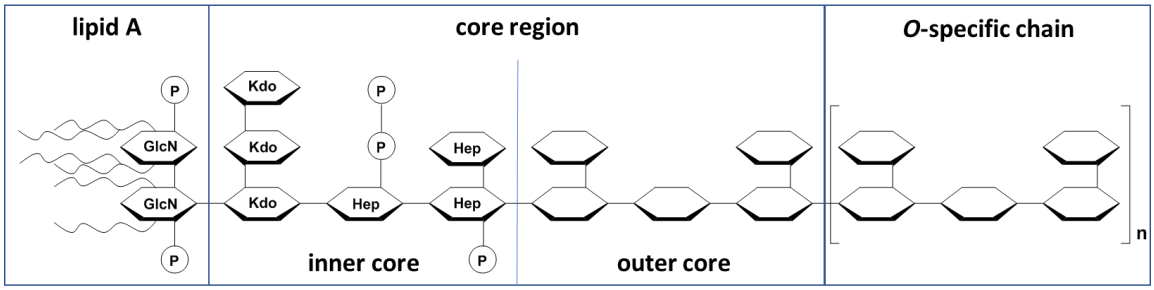
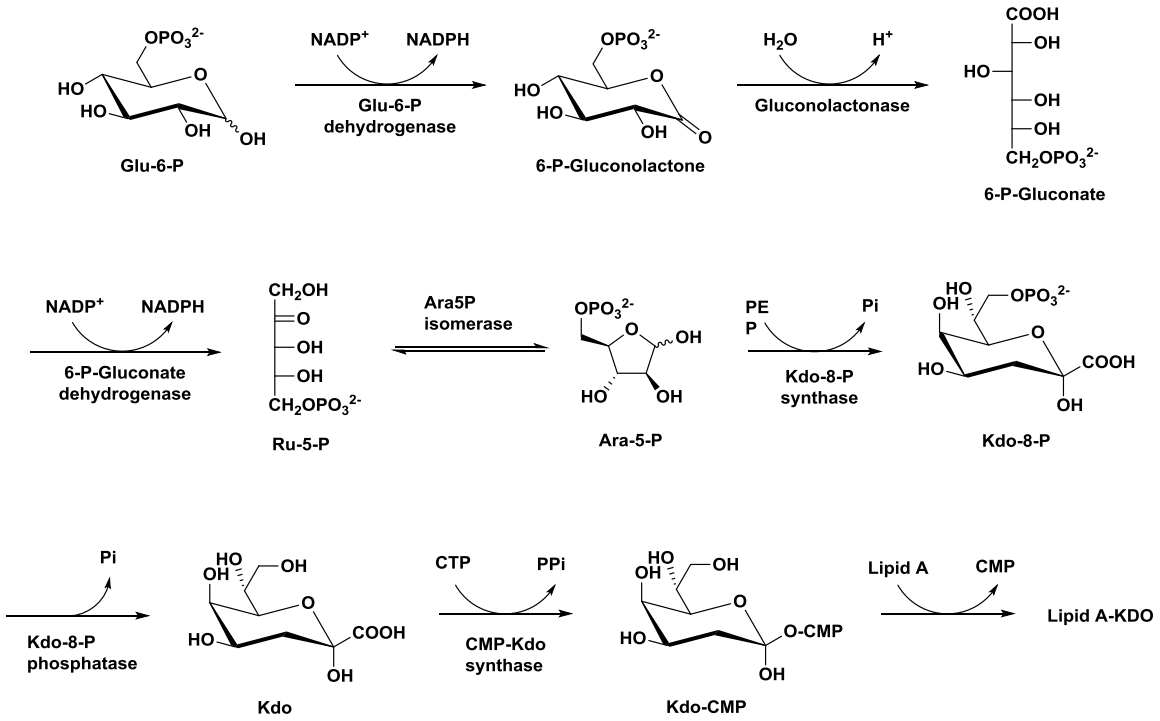


Figure 7: Schematic representation of lipopolysaccharide structure.

Biosynthetically, Kdo is, like many other carbohydrates, generated from glucose-6-phosphate (Glu-6-P) (Scheme 23).[77] As part of the pentose phosphate pathway, Glu-6-P is oxidized to D-ribulose-5-phosphate (Ru-5-P) over three steps.[78] In this so-called oxidative phase two equivalents of $NADP^+$ are reduced to NADPH to employ the necessary energy for this conversion through 6-P-gluconolactone and 6-P-gluconate. Now, Ru5P isomerizes to D-arabinose-5-phosphate (Ara-5-P)[79] and the following condensation of phosphoenolpyruvate (PEP) already leads to Kdo-8-phosphate (Kdo-8-P). The phosphate is hydrolyzed and the resulting Kdo is transformed into the activated nucleotide sugar by the attachment of Cytidine monophosphate (CMP). Finally, Kdo-CMP is transferred to lipid A under cleavage of CMP.[80]



Scheme 23: Biosynthesis of Kdo.

Release of LPS from the cell membrane leads to a response by the mammalian innate immune system.[81] The LPS-binding protein (LBP) transfers LPS to CD14, a surface glycoprotein located on macrophages and monocytes. Now, this complex is interacting with the Toll-like receptor (TLR) 4, the key mediator for this signal transduction in connotation with the myeloid differentiation factor 2 (MD-2).[82] This leads to a cascade of reactions in the cell, resulting in the production of lipid mediators (e.g. Prostaglandin E2), reduced oxygen species and cytokines (e.g. tumor necrosis factor). Balanced physiological level of these mediators, on the one hand, affects moderate fever, stimulation of the immune system and killing of microorganisms. Overexpression, on the other hand, can lead to high fever, hypertension, intravascular coagulation and even lethal shock.

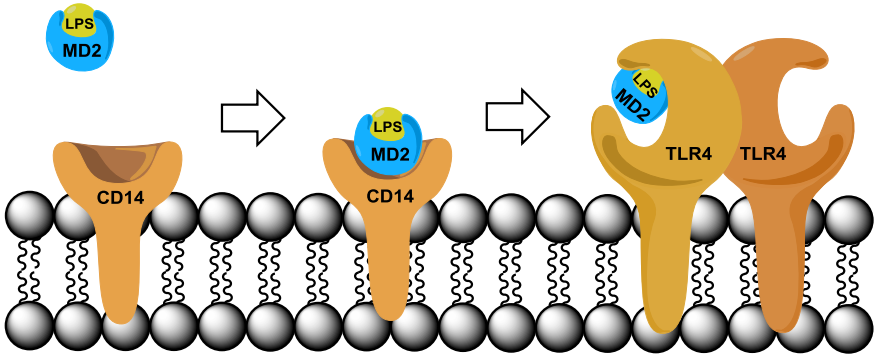
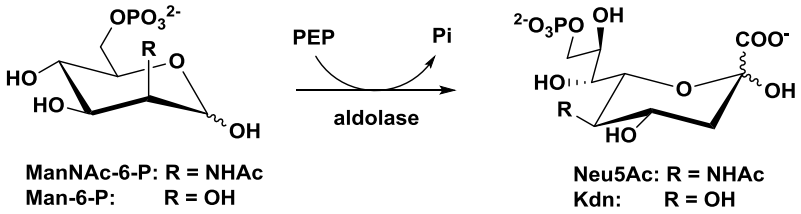


Figure 8: Illustration of the proteins on the cell surface involved in LPS recognition.

1.1.2 Sialic acids

The sialic acid (Sia) family includes, up to now, more than 50 known members and the number is still rising.[83–85] Neu5Ac was discovered as one of the first members of this family and is the most common sialic acid. This negatively charged monosaccharide is often located on the terminal position of glycolipids and glycoproteins on the cell surface. The biosynthetic pathway is similar to the Kdo pathway, described before, differing in the precursor: The reaction of *N*-acetylmannosamine-6-P (ManNAc-6-P) with phosphoenolpyruvate (PEP) results in the formation of Neu5Ac, whereas, the reaction of mannose-6-phosphate (Man-6-P) with PEP leads to Kdn (Scheme 24).

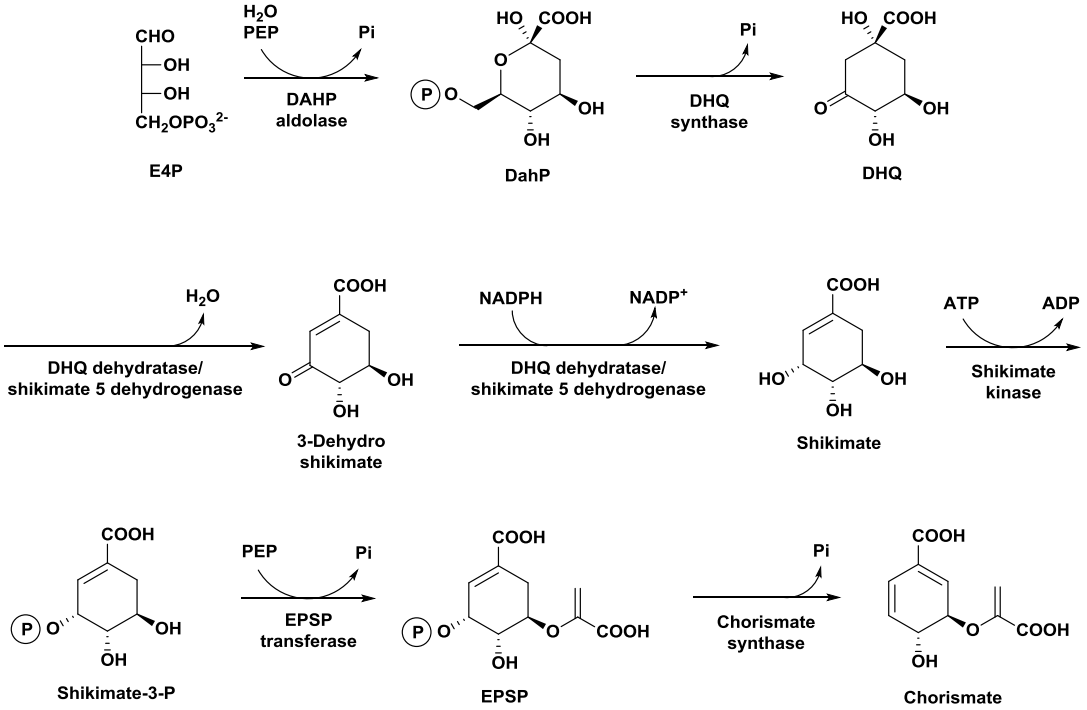


Scheme 24: Biosynthesis of Neu5Ac and Kdn.

Due to the negative charge, Sias are involved in binding and transport of different charged compounds and their position makes them preferable for cell recognition processes. On the one hand, they show masking properties. For example, desialylation of erythrocytes and thrombocytes leads to an immune response against them. Macrophages attack these now unmasked cells and remove them from the blood stream.[86] On the other hand, they can act as host ligands for protozoa, bacteria, toxins and viruses.[87–89] The influenza virus, for example, is covered with two proteins important for its replication: Neuraminidase and hemagglutinin. Both proteins are selective receptors for sialic acids. Hemagglutinin is responsible for binding of the virus to the host cell. The virus is taken up by the cell and replicates itself. To release the virus neuraminidase selectively cleaves the glycosidic bond between sialic acid and the next carbohydrate, galactose.[90–92] These are just a few examples for the importance of Sias. Their existence is also referred to processes during fertilization,[93,94] cardiovascular diseases,[95–97] cancer development[98–102] and many more.[103–105]

1.1.3 3-Deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DahP)

DahP plays an essential role in the so-called shikimate pathway, named after the first identified intermediate, isolated from *Illicium religiosum* (Japanese star anise). This pathway results in the synthesis of chorismate, a precursor for all aromatic amino acids and numerous metabolites like vitamins K_1, B_9 and E, as well as indole alkaloids and flavonoids.[106] First, (DAHP) is generated from erythrose-4-phosphate (E4P) and phosphoenolpyruvate (PEP) (Scheme 25). This substrate is then oxidized to 3-dehydroquinate (DHQ). Now, the same bi-functional enzyme – DHQ dehydratase/shikimate 5-dehydrogenase – is catalyzing the two reaction steps towards shikimate. Subsequently, phosphorylation of shikimate is followed by the transfer of another PEP leads to 5-enolpyruvylshikimate 3-phosphate (ESPS). Finally, phosphate is eliminated, yielding in chorismate.[106–109]



Scheme 25: Shikimate pathway in *E. coli*.

As shown in this chapter, besides Kdo, Kdn and Neu5Ac, DahP is an important member of ulosonic acids. Having excess towards this class of compounds and, especially, their derivatives could give new insights on their biological relevance.

1.2 Indium-mediated Barbier-type allylation in aqueous media

Indium-mediated allylation has proven to be a useful tool for the preparation of carbohydrates (chapter 1.2.3). Therefore, its application for the preparation of ulosonic acids (chapter 1.1) and their derivatives is obvious.

The use of organometallic reactions in aqueous media is preferred for many reasons. First, the handling with flammable organic solvents and working under inert conditions can be avoided. Furthermore, the masking of functional groups, e.g. hydroxyl groups, is not necessary to overcome unwanted side reactions or to overcome solubility problems. Therefore, this type of reaction perfectly suits for the application in carbohydrate chemistry. Another advantage is the possibility to influence the stereoselectivity through solvent effects. Finally, the use of water as an environmental friendly solvent is favored for the use in "green chemistry", gaining more and more importance during the last decades. [110–113]

1.2.1 Indium intermediates

For the reaction in aqueous media, only a limited number of metals are qualified, because they neither should react with water, nor should they generate insoluble oxides. During the last decades, several attempts with tin, zinc and lead have been published. The group around Li intensively focused on reactions in aqueous media and therefore, came across indium, which suits perfectly due to its chemical and physical properties.[114] This metal can be used in many organic solvents as well as in water, as it does not react with water. Furthermore, it is not toxic or oxidizes in the air. The ionization energy of indium (5.79 eV) is another favorable factor for its use as it is rather low compared to e.g. tin (7.34 eV), lead (7.43 eV) or zinc (9.39 eV).[115,116] This fact mostly makes it unnecessary to use a catalyst, heat or sonication for activation. A considerable disadvantage is the need to use quantitative amounts of indium. Although, the price dropped during the last years, 100 g indium powder still cost about € 1000, which makes upscaling troublesome. A possibility to overcome this problem could be the recycling of used indium by electrolysis.[117,118] Nevertheless, this metal is applicable for a high number of reactions, e.g. addition reactions,[119] radical reactions[120] or nucleophilic substitutions.[121]

During Barbier-type allylation, ketons or aldehydes react with an allyl or acryl halide, respectively. This reaction is mediated by a metal like, for example, tin or indium. Since the first publication of indium-mediated allylation by Araki *et al*. in 1987,[122] many different intermediates

have been postulated (Figure 9).[123] For example, they discovered an allylindium dichloride intermediate during the reaction of allylmagnesium bromide and indium trichloride with carbohydrates. Later, Chan and Yang[124] used NMR spectroscopy and transmetalation experiments to prove the existence of an In(I) intermediate and concluded its plausibility with the low first ionization potential (7.79 eV), but comparably high second ionization potential (18.87 eV). Another consideration was also that the reaction takes place on the surface of the metal including a single electron transfer from the metal to the carbonyl compound.[125]

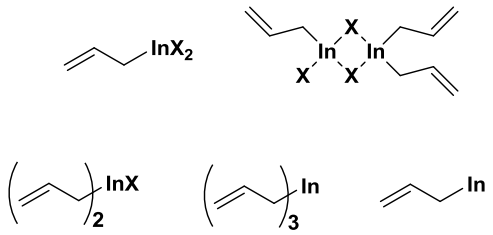
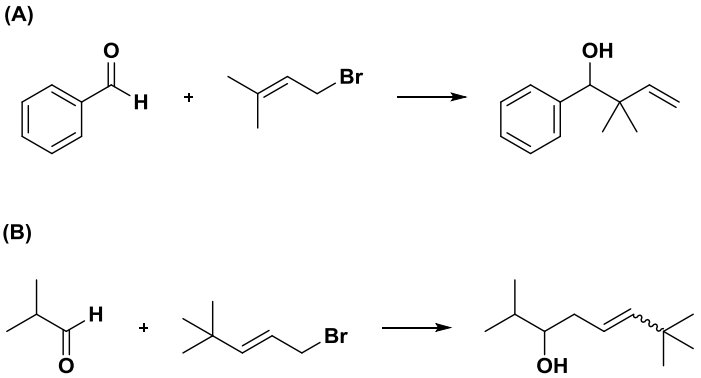


Figure 9: Intermediates postulated during the last decades.

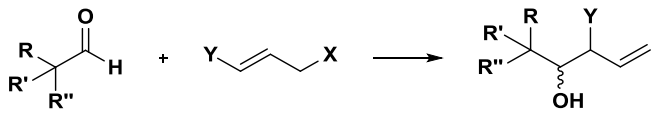
1.2.2 Selectivity of the In-mediated Barbier-type allylation

The regioselectivity of the In-mediated allylation is influenced by both steric and electronical effects.[126] In general, under aqueous conditions the C-C bond formation takes place on the higher substituted carbon (Scheme 26A). This is independent from the position of the allylic halogen. Nevertheless, the regioselectivity can be influenced by the size of the γ-substituents on the allylic halide. Investigations on this topic[127] led to the result that bulky groups, e.g. trimethylsilyl or *tert*-butyl, reverse the regioselectivity, leading to α-adducts (Scheme 26B). For example, in the case of the reaction of benzaldehyde and a γ,γ-disubstituted allyl bromide the γ-position is preferred. In comparison, in the reaction of isobutyraldehyde and isopropyl allyl bromide the steric hindrance is too high leading to the addition on the α-position.



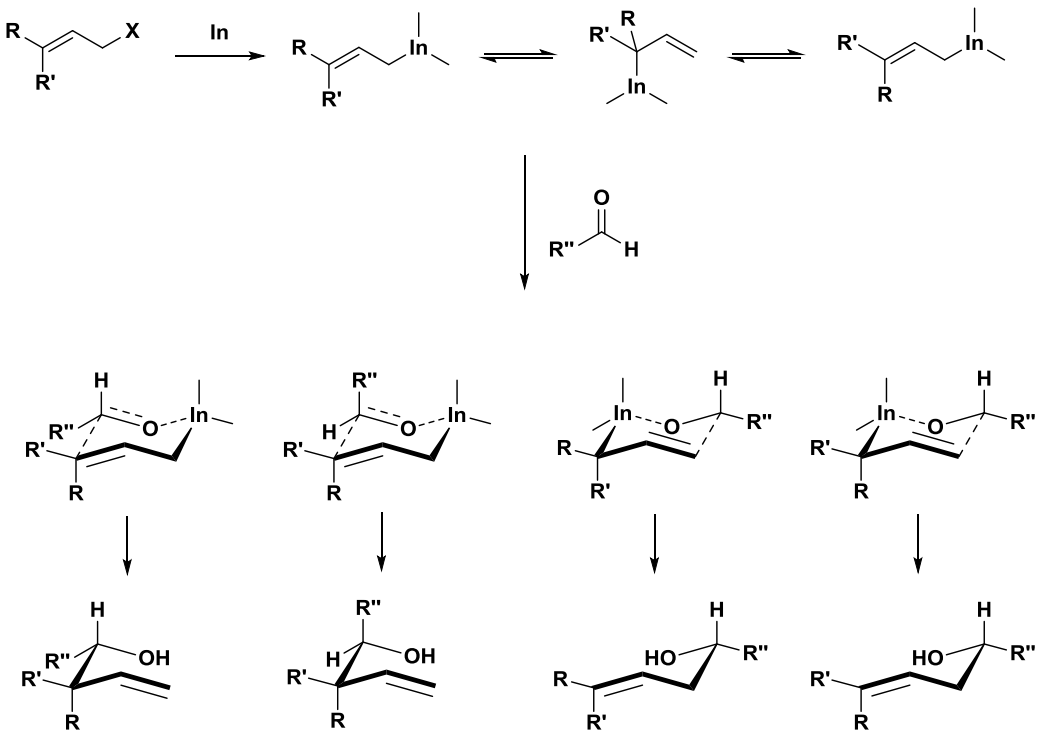
Scheme 26: (A) Addition of the higher substituted and (B) sterically hindered allyl bromide.

In the case of diastereoselectivity in aqueous media, the reaction can be differentiated into two types. In the first type, the allyl halide is substituted on the γ-position. This makes the diastereoselectivity dependent by both the substituent and the nature of the reacting aldehyde (Scheme 27). Here, the geometry of the double bond plays no role.



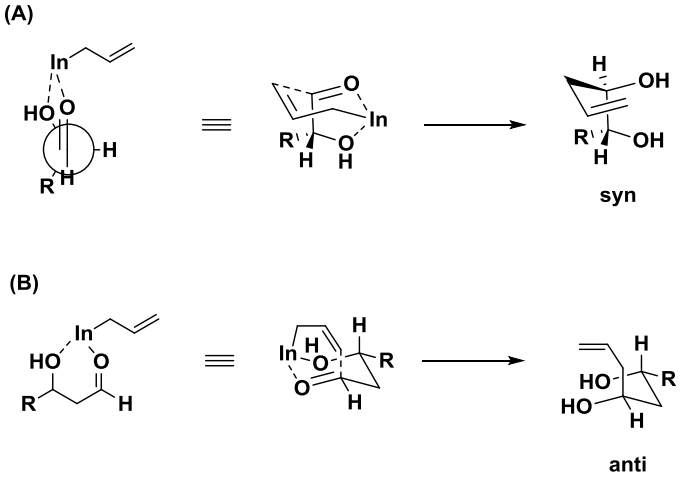
Scheme 27: Reaction of an aldehyde and γ-substituted allyl halide.

In general, the reaction is *syn*-selective when a chelating substituent is located on the α-position (Scheme 28). If steric hindrance is present, this effect can also be reversed leading to *anti*-products, if the α-substituent is very bulky. This selectivity can be explained through the Zimmermann-Traxler transition state.[125]



Scheme 28: Possible Zimmermann-Traxler transition states for the In-mediated allylation.

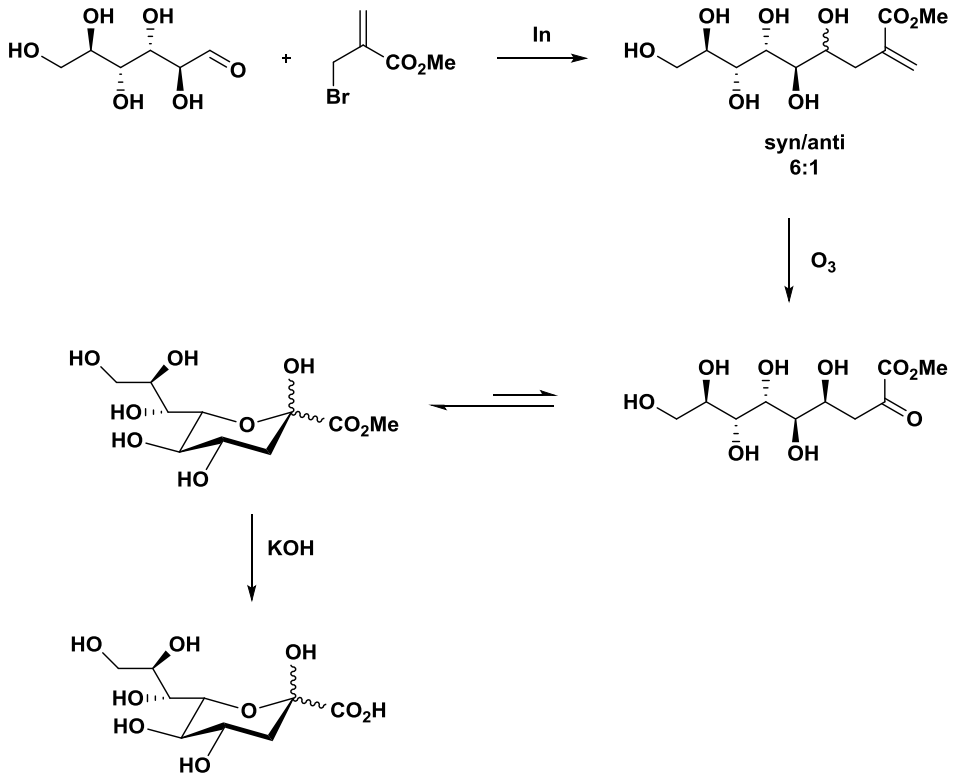
The diastereoselectivity of the second reaction type highly depends on the characteristics of the α-substituent. A strongly chelating substituent (e.g. hydroxyl or amine) preferably leads to *syn*-products. In the case of a non-chelating group (e.g. hydrogen or methyl) mostly *anti*-product are formed. Paquette *et al.*[128–130] investigated the influence of α- and β-substitution patterns of aldehydes on the allylation and described the stereoselectivity of this reaction using the Cram-model (Scheme 29). This model shows, on the one hand, how the chelating effect between the aldehyde, the α-substituent and the indium arranges the complex leading to *syn*-adducts.[131] On the other hand, chelating β-substituents lead to *anti*-adducts, because of this interaction.



Scheme 29: Cram-model of the addition of an (A) α- and (B) β-substituted aldehyde (bottom).

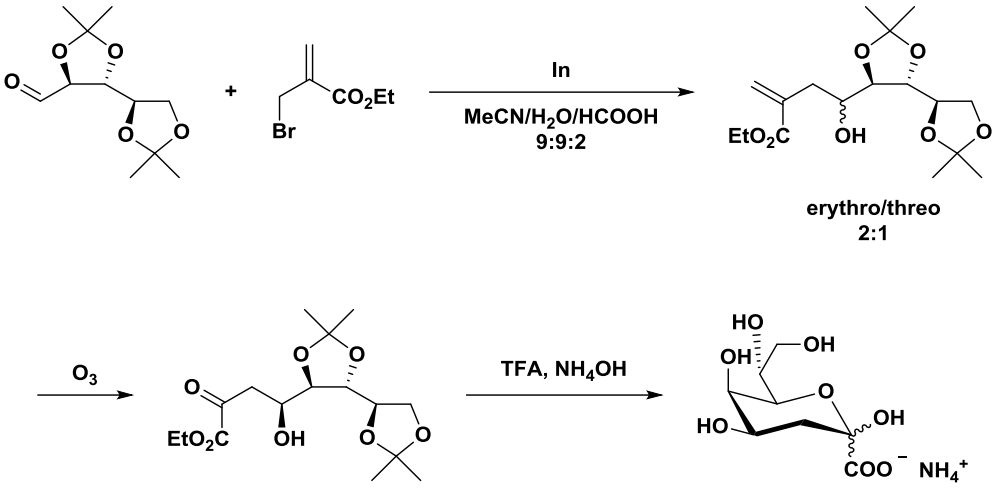
1.2.3 Applications for the In-mediated allylation

A high number of applications for the In-mediated allylation has been published during the last decades.[132,133] Especially for carbohydrate chemistry, this type of reaction is interesting, because of the already mentioned applicability to work in aqueous media. Therefore, Chan and Li[134] published the first synthesis of 2-keto-3-deoxynononic acid (Kdn) in aqueous medium (Scheme 30). Key step is the In-mediated allylation preferably leading to *syn*-product, because of the chelating effect of the free hydroxyl group in α-position. Subsequent ozonolysis and saponification, finally, leads to KDO without the need of protecting groups.[135]



Scheme 30: Synthesis of Kdn by Chan and Li.

Whitesides and his group used this reaction for the synthesis of ulosonic acids like *N*-acetylneuraminic acid (Neu5NAc) and 3-deoxy-D-*manno*-oct-2-ulosonic acid (Kdo).[136–138] In the case of Kdo, it was necessary to mask the hydroxyl groups of the arabinose with acetonide to avoid the chelating effect and generate *anti*-selective conditions (Scheme 31).



Scheme 31: Synthesis of Kdo by Whitesides and coworkers.

Also, the group around Schmid has gained a lot of experience in the field of In-mediated allylation during the last decades. They have used it not only for the synthesis of ulosonic acid, e.g. 3-deoxy-d-*arabino*-2-heptulosonic acid (Dah),[139] but also for the synthesis of deoxy carbohydrates[140–142], amino sugars[58,143–145] and higher carbohydrates[59,146,147].

Many more applications for the In-mediated allylation can be mentioned.[148–150] For example, in 1998 this methodology was used by Yi *et al*.[151,152] for the synthesis of (+)-goniofufurone (Figure 10), belonging to the group of styryl lactones known for their cytotoxicity.[153] Another example is its application for the synthesis of β-lactams[154,155] (Figure 10), which are interesting synthons for biologically active compounds.[156] Finally, also the possibility for an intramolecular ring closing should be mentioned.[157] Interestingly, a high tendency towards *exo*-products was observed in this case, as well as the construction of the smaller of the two possible ring systems.

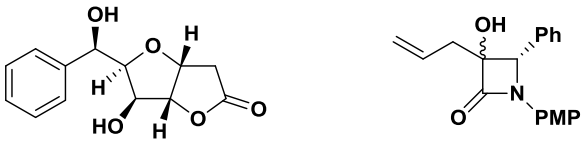


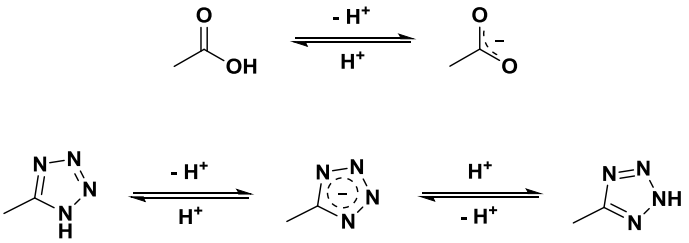
Figure 10: (+)-Gonifufurone (left side) and β-Lactam (right side).

1.3 Tetrazole as bioisostere for carboxylic acid

In medicinal chemistry, the use of bioisosteres is an important tool to positively manipulate the metabolic stability of drugs without affecting their biological properties. For example, the substitution of hydrogen by fluorine may prolong the drug's half-life, but should have no influence

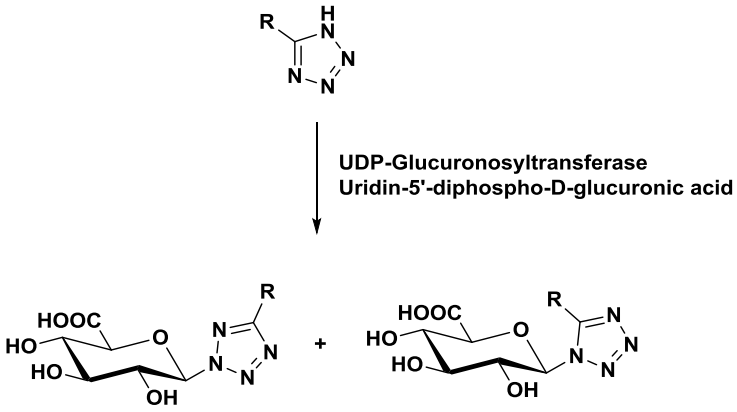
on its efficiency. This principle can also be adapted for carboxylic acid. This functional group is present in numerous bioactive compounds (e.g. amino acids or ulosonic acids) and is therefore, an interesting target for bioisosteric substitution.[158] Beside functional groups like hydroxamic acid, phosphonic acid and sulfonic acid, tetrazole proofed to be a good candidate for bioisosteric replacement for many reasons.[159]

First, the p*K*a values of tetrazoles (4.5 – 4.9) and carboxylic acids (4.2 – 4.4) are comparable, due to mesomeric stabilization. Subsequently, both moieties are ionized at physiological pH. Tetrazoles also display the same planar structure as carboxylic acids. Although, they are slightly larger, mutagenesis studies and X-ray crystal structures revealed that tetrazoles can form two hydrogen bonds within the active site of a protein.[160] This can partly be explained by the existence of both 1*H*- and 2*H*-tautomeric forms of tetrazole when comprising a free N-H bond (Scheme 32).



Scheme 32: Comparison of neutral and deprotonated carboxylic acid and tetrazole structures.

Not only the common properties, but also the differences between tetrazoles and carboxylic acids can be of use for medicinal chemistry. For example, tetrazole compounds have up to 10 times higher lipophilicity and therefore, higher membrane permeability. Measurements of the Caco-2 (Caucasian colon adenocarcinoma) cell permeability of ten different compounds showed significantly higher rates when carboxylic acid is replaced by tetrazole in the molecule.[161,162] Furthermore, tetrazoles major advantage is their high metabolic stability. On the one hand, tetrazole compounds seem to be stable during most of the Phase II biotransformations (conjugation with e.g. coenzyme A or glutathione). These transformations lead to higher hydrophilicity of the substrates and usually facilitate their biliary excretion.[163] On the other hand, *N*-glucuronidation, a common Phase II biotransformation, of tetrazoles was observed by Perrier *et al* (Scheme 33).[164] Although, these investigations indicate a fast excretion of tetrazole compounds, the high metabolic stability could be explained by enterohepatic recirculation mechanisms. Once a metabolite is biliary excreted, reabsorption and hydrolysis in the intestinal mucosa could result in additional assimilation in a second pass.



Scheme 33: *N*-Glucuronidation of tetrazole metabolite.

The replacement of a carboxylic acid by a tetrazole gave rise to several approved drugs used for a wide range of diseases (Figure 11). For example, nowadays Losartan is one of the most common drugs for the treatment of hypertension. It acts as angiotensin II receptor agonist and shows, compared to other investigated bioisosteres, several times higher efficiency during peroral administration.[163,165] Two further members of this type of drugs are Valsartan[166] and Irbesartan,[167] both exposing a tetrazole moiety.

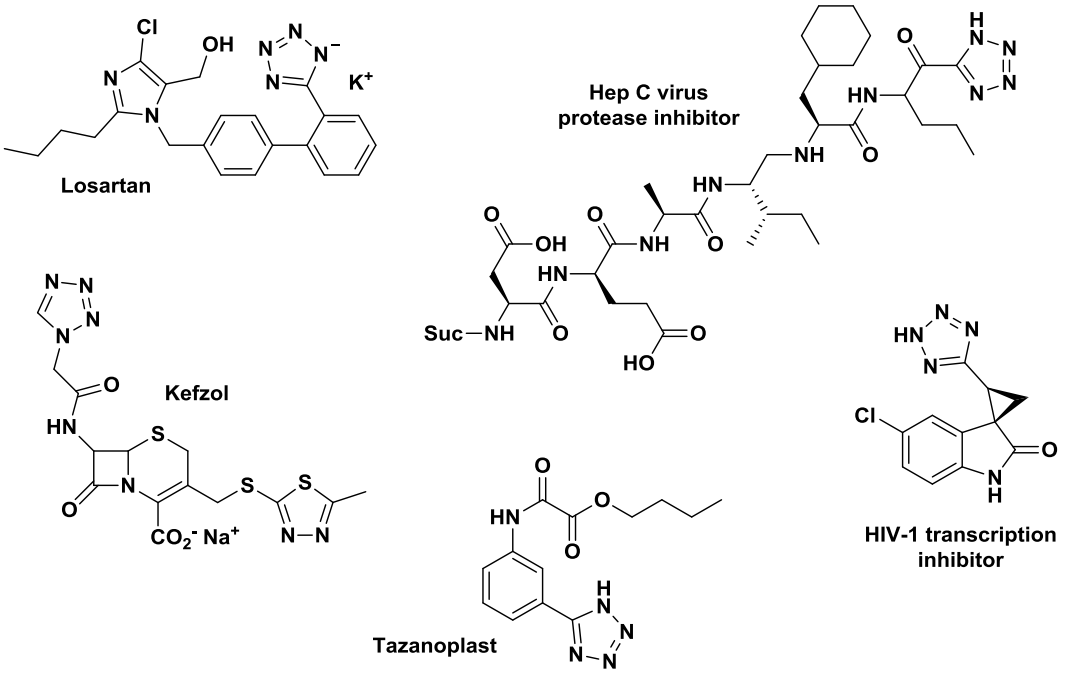


Figure 11: Examples for tetrazole containing drugs in clinical use.

Another example for a tetrazole containing drug is Kefzol (Cefazolin).[168] This compound shows antimicrobial and anti-inflammatory activity. Although it is no longer used frequently in human medicine, it is of high importance in veterinary medicine. Furthermore, new and promising

generations of this compound class (e.g. Cefamandole and Latamoxef) have been launched on the market during the last years.[169]

Also on the field of antiviral drugs, tetrazole-containing compounds play an essential role. Substrates on the base of peptides, acting as Hepatitis C virus protease inhibitor, have been published.[170] Likewise, for the treatment of AIDS several tetrazole compounds have been investigated in detail.[171,172]

Tazanoplast, as one last example, is a successful antihistaminic agent used for the treatment of acute reversible airway obstruction.[173] The list of applications for tetrazole-containing drugs published until now goes on and the is still growing,[174–177] e.g. antitumor agents,[178] central nervous system stimulants[179] or magnetic resonance imaging contrast agents.[180]

A publication by Ionescu *et al*.[181] gives another interesting example for the application possibilities of tetrazole carbohydrates. In this case, they replaced the phosphate in the mannose-6-phophate (M6P) by a tetrazole (Figure 12). M6P plays an important role in angiogenesis, the generation process of new blood vessels from pre-existing ones. Inhibition of this process is a useful tool in cancer therapy.[182] In vivo investigations with chick chorioallantoic membrane assays showed that mannose-6-phosphate has an inhibitory effect of 68 % compared to a phosphate-buffered saline control.

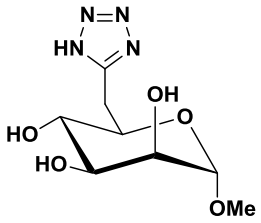
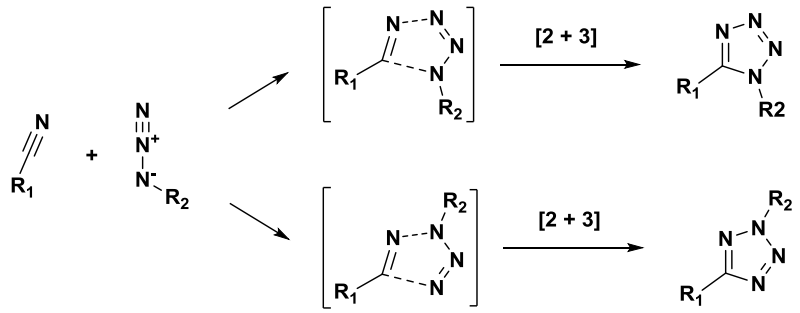


Figure 12: Tetrazole derivative of mannose-6-phosphate by Ionescu *et al*.

1.3.1 Mechanism of tetrazole formation from azide and nitrile

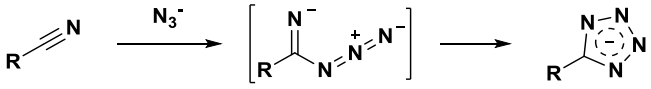
The most common way for the synthesis of a tetrazole is the [2 + 3] cycloaddition of an azide with a nitrile. Mechanistically, this cycloaddition can proceed either concerted or through an intermediate; this was shown by density functional theory (DFT) calculations.[183] In the case of a neutral azide, e.g. an organic azide, the concerted [2 + 3] mechanism is strongly preferred, leading to two different isomers, the 1,5- and the 2,5-substituted tetrazole (Scheme 34). Furthermore, the

calculations showed a high influence of nitrile substituents on the reaction barriers, with the more electronegative substituent resulting in lower barriers.



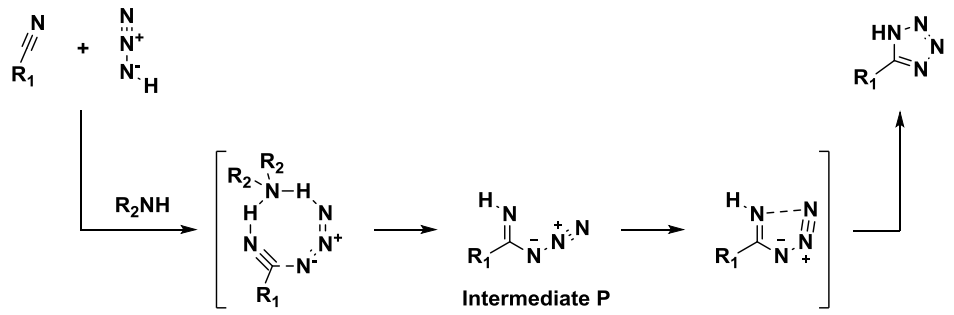
Scheme 34: Mechanism for the concerted tetrazole formation.

When using an anionic azide, e.g. NaN_3, two different transition states are possible, presuming that the cation plays no role in the mechanism. On the one hand, the same concerted [2 + 3] cycloaddition as with a neutral azide is possible. On the other hand, a two-step mechanism can occur where the nitrile is attacked nucleophilic by the azide, and the tetrazole ring closed, subsequently (Scheme 35). DFT calculations[183] showed that the stability of this intermediate is depending on the substituents on the nitrile: strong electron-withdrawing groups, e.g. RSO_2^- or F^-, stabilize it.



Scheme 35: Mechanism for tetrazole formation when using an anionic azide.

A third mode of reaction is the involvement of a proton (Scheme 36). Depending on the neutral or anionic conditions, this proton is provided from e.g. NH_3 or NH_4^+. For both cases, the formation of a so-called intermediate P is highly probable as DFT calculations[183] exhibited a high stability compared to free reactants. Again, this stability shows similar dependents on the substituents on the nitrile as for the proton-free mechanisms.

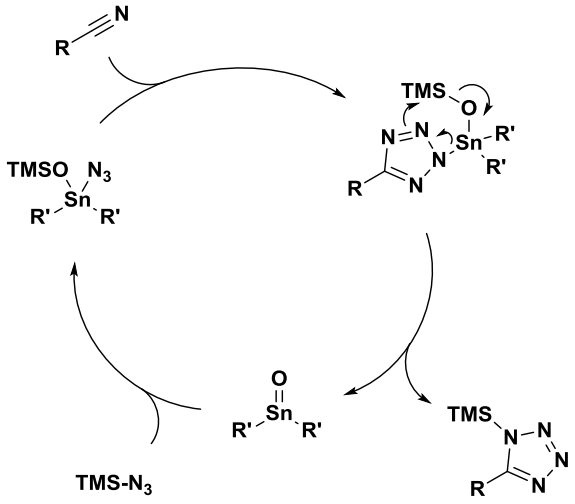


Scheme 36: Mechanism for proton-involved tetrazole formation.

1.3.2 Published tetrazole synthesis starting from nitrile

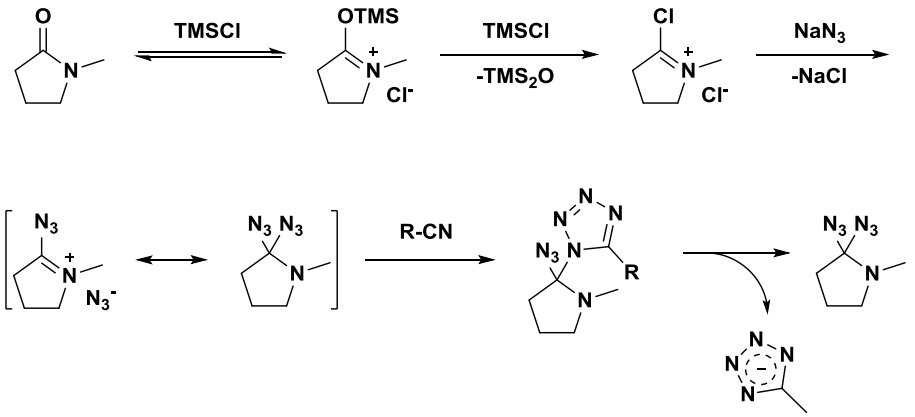
In practice, HN_3 would be the logical reagent for tetrazole synthesis,[184] but it is highly explosive and toxic,[185] making its use problematic. *In situ* generation and continuous flow procedures proofed to be the accurate tool to handle this volatile compound. Over the last years, several continuous flow procedures[186,187] in aqueous media have been published, where HN_3 is generated in situ from NaN_3 and acetic acid. Reaction screening of a high number of aliphatic, aromatic and heteroaromatic nitriles has resulted in overall high yields.

A safer source for an azide is $TMSN_3$.[188] This compound is sensitive to hydrolysis and, therefore, must be handled under water-free conditions. Generally, a catalytical amount of Bu_2SnO is used to activate $TMSN_3$ (Scheme 37).[189] A comparable approach is the use of Bu_3SnN_3. This compound can be generated in situ from Bu_3SnCl and NaN_3,[190] but the direct use is much more common.[191]



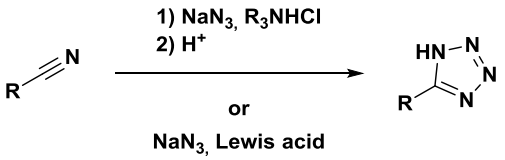
Scheme 37: Mechanism of tetrazole formation using $TMSN_3$ and Bu_2SnO.

Another procedure published by Kappe and coworkers.[192] uses TMSCl and NaN_3 in *N*-methyl-2-pyrrolidone (NMP). In this microwave-assisted approach, NMP plays an essential role not only as solvent, but also as mediator. In their proposed mechanism (Scheme 38), NMP is reacting with TMSCl to a Vilsmeier-Haack-type intermediate. Subsequently, the chlorides are replaced by azides to generate an ionic dihydropyrrolium azide, supposedly existing in equilibrium with its covalent isomer. This highly active species can now undergo [2 + 3] cycloaddition with nitriles.



Scheme 38: Proposed mechanism of tetrazole formation by Kappe and coworkers.

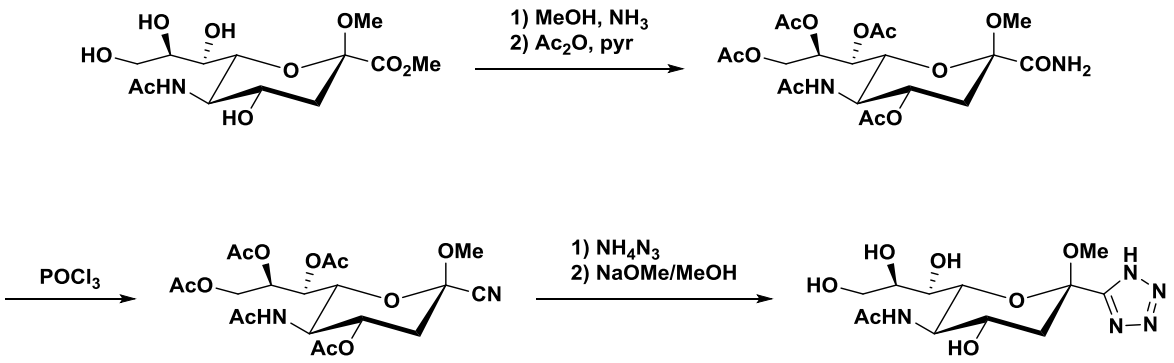
The most common source for the introduction of azides is NaN_3. In combination with NH_4Cl or Et_3NHCl (Scheme 39), the reaction is usually performed in a polar, aprotic solvent (e.g. toluene or DMF). Often, high temperatures and long reaction times (up to several days) are necessary to achieve acceptable yields.[193] Therefore, microwave irradiation was applied. With this method, reaction times can be drastically reduced.[194,195] Likewise, the use of Lewis acids like $ZnCl_2$ or $ZnBr_2$ proofed to be ideal mediators for this reaction (Scheme 39).[196] Here, the reaction is performed in aqueous media and can also either be heated conventionally or under microwave irradiation. $AlCl_3$ as another strong Lewis acid was used as well for the formation of tetrazole. In this case, of course, water has to be avoided and therefore, THF was used as solvent.[197]



Scheme 39: Tetrazole formation using NaN_3 and either ammonium salt or Lewis acid.

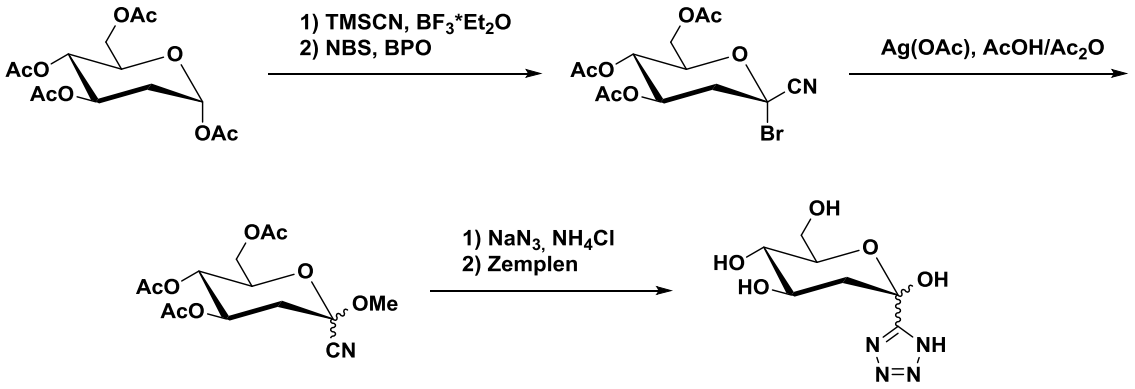
1.3.3 Published approaches towards tetrazole ulosonic acids

In 1986, Schmid *et al*.[198] published the synthesis of the tetrazole isostere of Neu5Ac. They could transform the ester function into a tetrazole in five steps (Scheme 40). First, the ester was converted into an amide, followed by peracetylation of the compound. Now, a nitrile was generated on this position with $POCl_3$. This could then undergo [2 + 3] cycloaddition with NH_4N_3 to form the tetrazole ring. The reaction was performed in a sealed tube to avoid sublimation of the potentially explosive azide. Finally, Zemplén saponification was used to deprotect the compound.



Scheme 40: Synthesis of tetrazole Neu5Ac by Schmid *et al*.

Another member of the ulosonic acid family – Dah – was derivatized by Buchanan *et al*.[199] Their approach started with peracetylated 2-deoxy-D-arabinose (Scheme 41), which was converted into methyl glycoside.[200] Subsequently, tetrazole formation was performed with NaN_3, before the final deprotection *via* Zemplén saponification led to the formation of Dah.



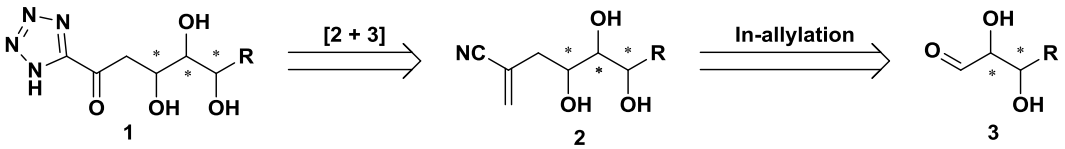
Scheme 41: Synthesis of tetrazole Dah by Buchanan *et al*.

2 Results and discussion

2.1 Aim of the project

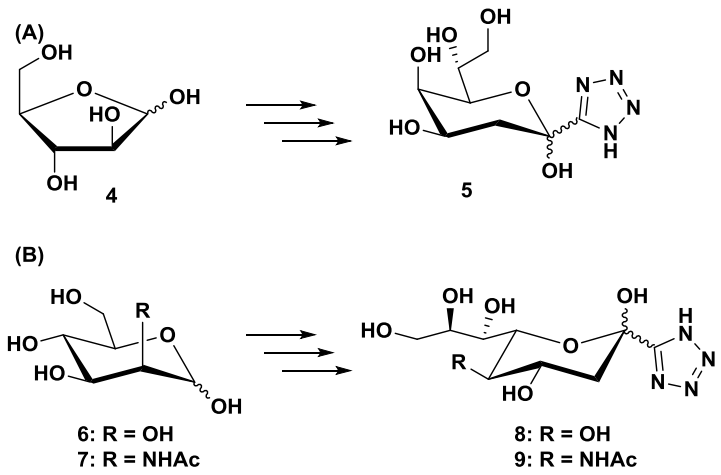
The biological importance of ulosonic acids, shown in chapter 1.1, is beyond doubt. Therefore, excess towards their derivatives could provide new insights in their metabolic behavior. As the carboxylic acid function plays a key role in biological interactions of these compounds, a conversion of this functionality was the logical conclusion.

The carboxylic acid of an ulosonic acid should be replaced by a tetrazole, because this functionality has proven to be an interesting candidate as bioisostere (chapter 1.3). The [2 + 3] cycloaddition of nitriles with azides is a well-known methodology to generate tetrazoles (chapter 1.3.2) and should be adapted for the synthesis of tetrazole isosteres of ulosonic acids (Scheme 42). The nitrile **2** should be synthesized *via* In-mediated allylation of carbohydrate **3** and bromoacrylonitrile. At this step, the stereochemical outcome is crucial and therefore, the reaction conditions must be adapted.



Scheme 42: Retrosynthetic analysis of the synthesis of tetrazole isosteres of ulosonic acids.

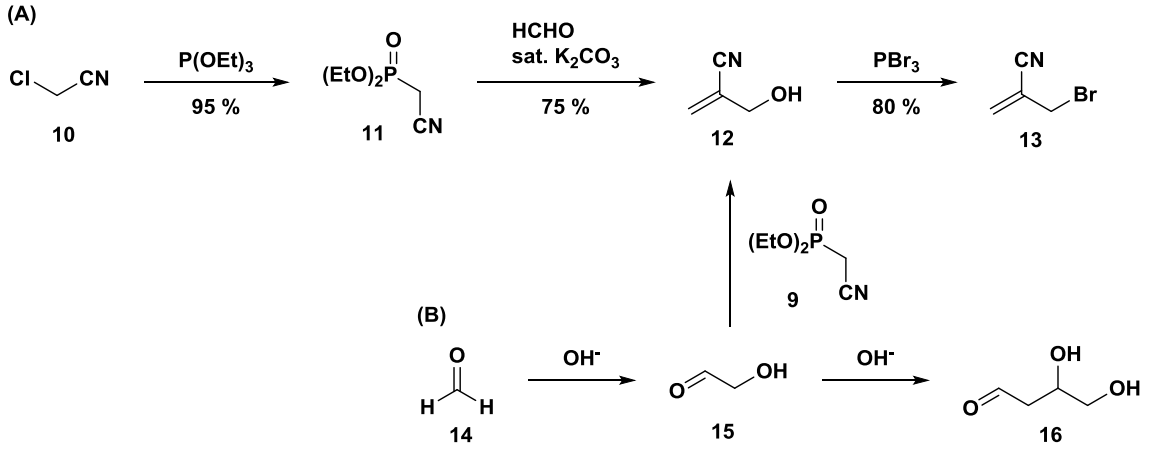
This reaction protocol should be improved using D-arabinose as starting material, resulting in the formation of the tetrazole derivative of Kdo (Scheme 43A). Furthermore, it should be adapted for the synthesis of the Kdn derivative **8** from D-mannose **6** and Neu5Ac derivative **9** from D-*N*-acetylmannosamin **7** (Scheme 43B).



Scheme 43: Synthesis of (A) Kdo derivative (5) and (B) derivatives of Kdn (8) and Neu5Ac (9).

2.2 Synthesis of 2-(bromomethyl)acrylonitrile 13

For the In-mediated allylation, the synthesis of 2-(bromomethyl)acrylonitrile **13** was necessary. Fortunately, its preparation has been published already (Scheme 44A).[201] Here, **13** was generated over two steps from purchasable diethyl phosphonoacetonitrile **11**. Likewise, this compound can be synthesized from chloroacetonitrile **10** and triethyl phosphite in almost quantitative yields. The next step was performed with both, the purchased and self-prepared compound **11** and no difference in reaction behavior could be observed. Mechanistically, this step included a self-condensation of formaldehyde, followed by a HWE[55] reaction with **11** (Scheme 44B). Critical point in this reaction is the formation of intermediate **15**, as further condensation cannot be avoided completely, which is leading to condensation products like **16**.



Scheme 44: Synthesis of 2-(bromomethyl)acrylonitrile 11.

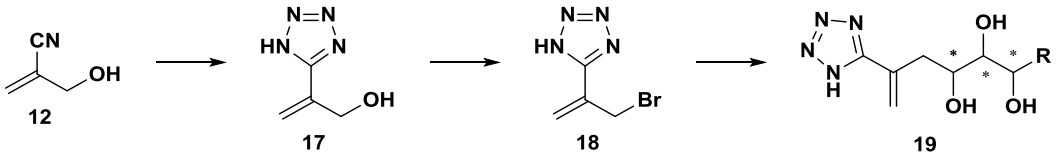
Nevertheless, compound **12** was obtained in good yields and submitted to bromine substitution with PBr_3. This volatile and highly reactive compound had to be handled carefully, as polymerization was observed during the reaction, as well as, during storage, provoked by high temperatures and acidic conditions. Attempts for avoiding this side product, by the addition of pyridine as buffer, failed (Table 4). Also, the use of CBr_4 or *N*-bromosuccinimide (NBS) as bromine source was unsatisfactory. Although, polymerization could not be avoided completely and separation of the polymer was not possible, compound **13** was used for the In-mediated allylation.

Table 4: Screened conditions for bromination of 12.

Conditions	Yield (13)
PBr_3	66 %
PBr_3, pyridine	26 %
CBr_4, PPh_3	25 %
NBS	15 %

2.2.1 Attempts for the tetrazole formation from acrylonitrile 12

Introduction of a tetrazole on compound **12** (Scheme 45) was desirable for two reasons. First, unwanted side reactions on the nitrile function, like saponification, could be avoided during the next steps. Second, for building up the tetrazole function on a later stage (Scheme 42) it might be necessary to adapt the reaction conditions on the different nitrile sugars (**2**) used. In comparison, with compound **17** the tetrazole functionality would be implemented already through the In-mediated allylation, resulting right away in compound **19**.



Scheme 45: Formation of tetrazole 17.

Therefore, several conditions for the [2 + 3] cycloaddition of **12** with an azide have been tested (Table 5). Unfortunately, impeccable characterization of compound **12** was not possible. Due to its small mass, this compound was outside the range of selectivity of mass spectrometry. Furthermore, the assignment through NMR spectroscopy failed as the quaternary carbon of the tetrazole was not visible in ^{13}C-NMR spectra. Although shift movements have been observed in ^{1}H-NMR spectra, a final determination *via* 2D-NMR without this quaternary carbon was not possible. Nevertheless, the ^{1}H-NMR spectra of all screened reaction conditions showed high amounts of by-products, why the preparation of compound **17** was discarded.

Table 5: Screened condition for the formation of 17.

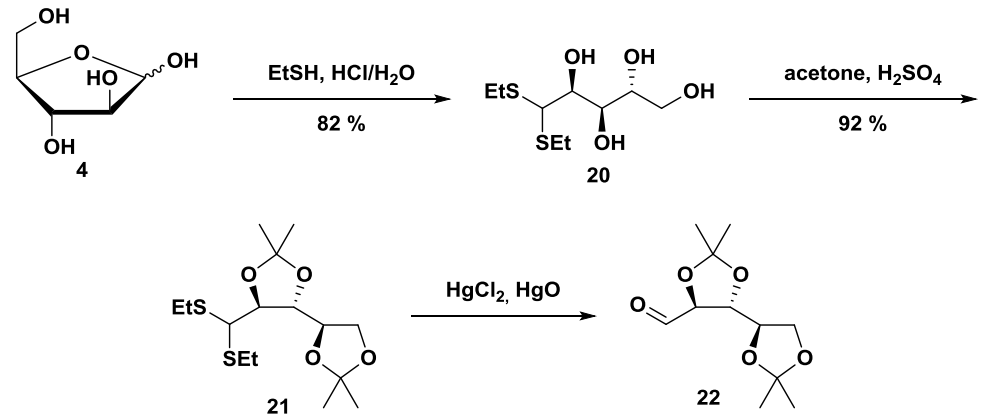
Conditions
NaN_3; ZnBr
NaN_3; NH_4Cl
NaN_3, Et_3NHCl
NaN_3, DOWEX H^+
$TMSN_3$, Bu_2SnO

2.3 Indium-mediated Allylation

2.3.1 In-mediated allylation of compound 22

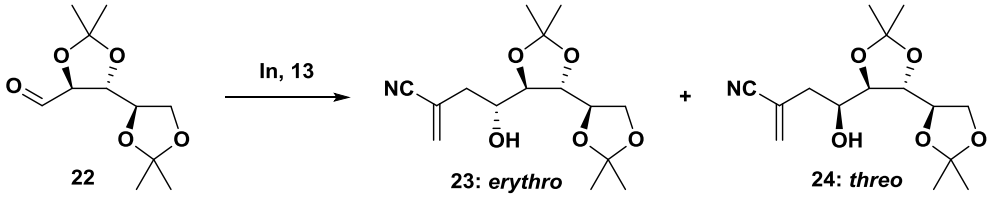
As mentioned before (chapter 2.1), D-arabinose **4** was used for the synthesis of tetrazole derivative of Kdo **5**. For the elongation of this compound and introduction of the nitrile functionality, In-mediated allylation was performed. As described in chapter 1.2.2, the stereochemical outcome of this allylation is strongly depending on the chelating properties of the carbohydrate. For the synthesis of **5**, *erythro*-selectivity during allylation was preferred. Therefore, **4** had to be protected selectively in the open chain form (Scheme 46) to suppress chelation and generate the Felkin-Anh product **23** (Scheme 47).[202]

First, D-arabinose was forced into the open chain form by the generation of a thioacetal (Scheme 46). Subsequently, the hydroxyl functions were protected *via* isopropylidene. Deprotection of the aldehyde was achieved by the use mercury salt. Attempts for avoiding these highly toxic compounds, by using NBS, were unsuccessful as no pure **22** could be isolated. Furthermore, to protect the highly reactive aldehyde, compound **22** was used for the next step without purification *via* silica chromatography.



Scheme 46: Protocol for the preparation of 22.

To determine appropriate reaction conditions for the allylation of **22** (Scheme 47), not only in terms of yield, but also the ratio of *erythro* **23** to *threo* **24** configuration, reaction screening was required (Table 6). First, the reaction was performed in solvent mixtures of EtOH and H_2O, as good experiences have been made with these mixtures.[203] Unfortunately, the yields were rather low. The addition of $Er(OTf)_3$ or $Yb(OTf)_3$ as catalyst, as well as the performance at higher temperature resulted only in slightly better yields. Interestingly, when the reaction is run in pure EtOH the ratio between *erythro* and *threo* is interconverted.



Scheme 47: In-mediated allylation of 22.

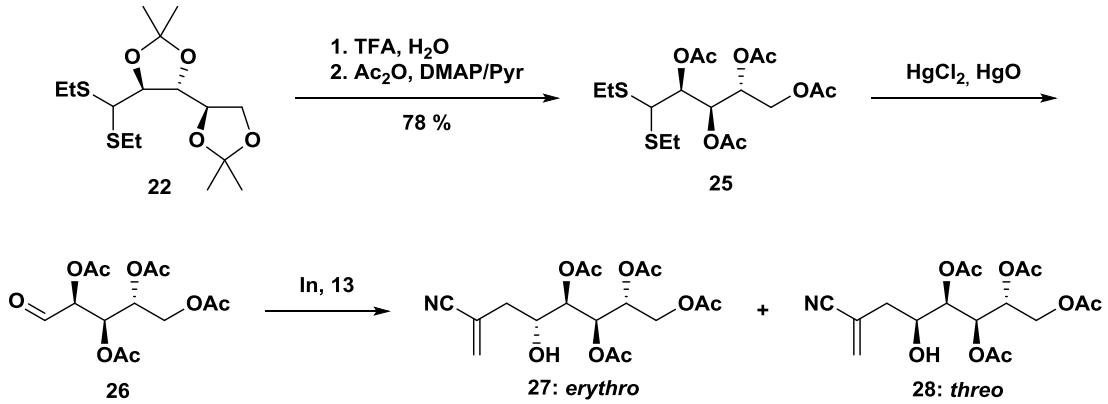
Therefore, EtOH was replaced by solvents like THF or MeCN. In this case, NMR spectroscopy show a high number of unidentified by-product and no product could be isolated. The use of MeCN was already reported for the synthesis of Kdo *via* In-mediated allylation (Scheme 31).[138] Therefore, its tentatively use for this allylation was obvious, but resulted in only pure diastereomeric ratio and yield. Finally, attempts with a mixture of DMF and H_2O (6:4) resulted in yields of 53 % over two steps, independent of the reaction temperature. The reaction was also performed in gram scale, without observing any decrease in yield. Otherwise, the use of catalytic amounts of $Yb(OTf)_3$ resulted in decreased yields.

Table 6: Screened reaction conditions for the In-mediated allylation of 22.

Solvents		Temp.	Additives	Ratio 23/24*	Isolated Yield (23)**
EtOH/H_2O	4:1	r.t.		1.6:1	17 %
EtOH/H_2O	4:1	r.t.	$Er(OTf)_3$	2:1	31 %
EtOH/H_2O	4:1	r.t.	$Yb(OTf)_3$	2:1	25 %
EtOH/H_2O	4:1	50 °C	$Er(OTf)_3$	1.8:1	43 %
EtOH/H_2O	4:1	50 °C	$Yb(OTf)_3$	1.7:1	42 %
EtOH/H_2O	1:1	r.t.		2:1	18 %
EtOH/H_2O	1:1	50 °C	$Er(OTf)_3$	1.2:1	15 %
EtOH/H_2O	1:1	50 °C	$Yb(OTf)_3$	1.1:1	15 %
EtOH/ 1 M HCl	25:4	50 °C		1.5:1	-
EtOH/ 1 M HCl	25:4	50 °C	$Yb(OTf)_3$	1:1	13 %
EtOH		r.t.		1:1.2	24 %
THF/H_2O	4:1	r.t.		n.d.	-
MeCN/H_2O	1:1	r.t.	10 % HCOOH	1.5:1	12 %
DMF/H_2O	6:4	r.t.		2:1	53 %
DMF/H_2O	6:4	r.t.	$Yb(OTf)_3$	2:1	45 %
DMF/H_2O	6:4	50 °C		1.9:1	53 %
DMF/H_2O	6:4	50 °C	$Yb(OTf)_3$	1.8:1	48 %

*Ratio determined by ^{1}H-NMR; **Yields determined over 2 steps; n.d. = not determinable.

Due to the low success during this screening procedure with compound **22**, parallel trials with acetylated compound **26** (Scheme 48) have been performed. Therefore, the protecting groups of **22** were switched to generate **26**. These electron-withdrawing acetyl groups highly destabilize a free aldehyde, why no purification was performed before the allylation.



Scheme 48: Preparation and In-allylation of 26.

Most of the conditions screened for the allylation of **26** resulted in no yield (Table 7). When the reaction was performed in THF and H_2O (1:1) at least 23 % of a mixture of **27** and **28** could be isolated. Unfortunately, NMR analysis after purification *via* silica chromatography, still, showed a high amount of impurities. Therefore, the determined yield is not corresponding with the isolated yield. The same applies to the reaction in acetone/H_2O (12:1). Only the reaction in MeCN/H_2O yielded in a clean, but inseparable, 2:1 mixture of **27** and **28**. Although the yields are rather low, compared to the allylation of **22**. Nevertheless, the obtained mixture was used, as well, for the application in tetrazole formation (chapter 2.4.1).

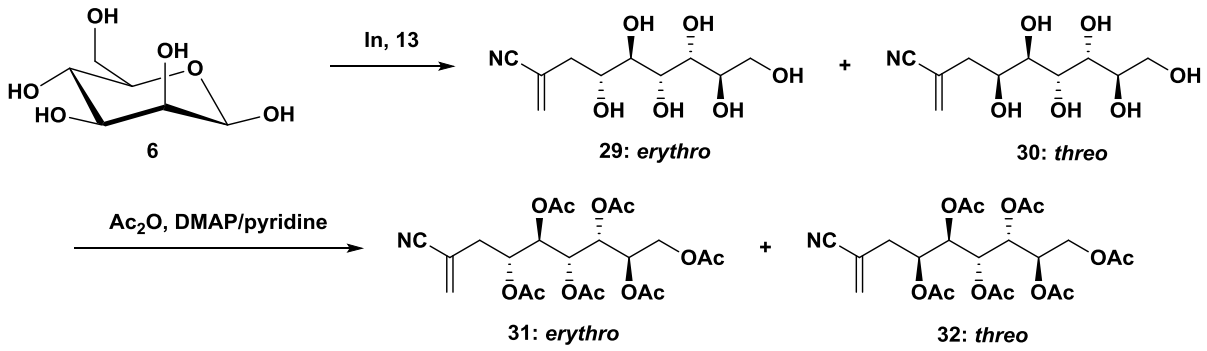
Table 7: Screened reaction conditions for the allylation of 26

Solvents		**Temp.**	**Isolated Yield (27 + 28)***	**Ratio 27/28****
EtOH/H_2O	4:1	r.t.	-	-
THF/H_2O	1:1	r.t.	23 %***	n.d.
THF/H_2O	2:1	r.t.	-	-
THF/0.1 M HCl	1:1	r.t.	-	-
MeCN/H_2O	4:1	50 °C	18 %	2:1
Acetone/H_2O	12:1	r.t.	18 %***	n.d.
DMF/H_2O	6:4	r.t.	-	-
DMF		r.t.	-	-

*Yields determined over 2 steps; **ratio determined by ^{1}H-NMR; ***containing unidentified impurities; n.d. = not determinable.

2.3.2 In-mediated allylation of 6

The In-mediated allylation was also applied for the synthesis of the Kdn derivative **8**. In contrast to the allylation for the synthesis of the Kdo derivative **5**, for the formation of **8** the *threo*-product **30** was desired (Scheme 49). The compounds inherent chelating properties should force the reaction towards **30**.



Scheme 49: In-mediated allylation of 6 and subsequent peracetylation.

Several solvent mixtures and reaction temperatures have been tested, resulting in different yields and ratio of **29** and **30** (Table 8). The conversion of compound **6** and achieved ratio of **29**/**30** was determined *via* NMR spectroscopy. Best results were achieved when using a solvent mixture of EtOH/H_2O (4:1) at 40 °C. Lower temperature leads to decreased yields and raising the temperature negatively influences the stereochemical outcome. Furthermore, the use of different solvent mixtures, such as DMF/H_2O, resulted in either low yield or, when using THF/H_2O, low amount of **30**.

Table 8: Screened reaction condition for the allylation of 6.

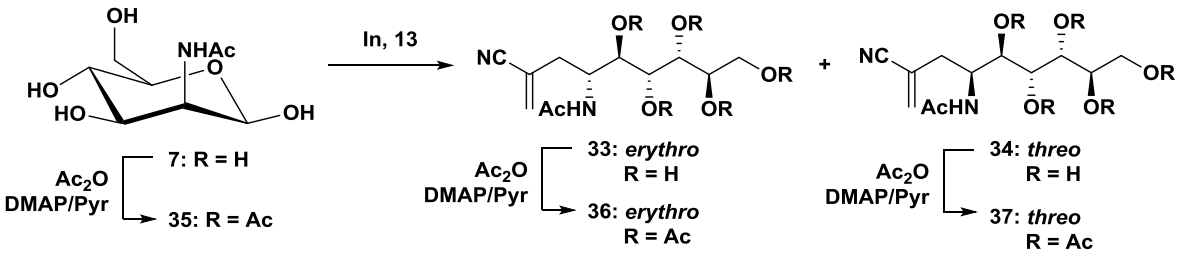
Solvents		Temp.	Conversion*	Ratio 29/30*
DMF/H_2O	6:4	r.t.	26 %	1:10
EtOH/H_2O	1:1	40 °C	64 %	1:5
EtOH/H_2O	4:1	r.t.	86 %	1:10
EtOH/H_2O	4:1	40 °C	98 %	1:10
EtOH/H_2O	4:1	60 °C	36 %	1:1
EtOH/H_2O	9:1	40 °C	60 %	1:5
EtOH/0.1 M HCl	4:1	40 °C	66 %	1:3
EtOH/0.1 M HCl	10:1	40 °C	83 %	1:3
THF/H_2O	1:1	r.t.	41 %	1:2
THF/0.1 M HCl	1:1	r.t.	30 %	1:3

*determined by NMR; reaction time: 24 h.

Unfortunately, separation of **29** and **30** was not possible. Additionally, yields higher than 100 % after work-up indicated the presence of indium. Therefore, the mixture was peracetylated to perform purification *via* silica chromatography (Scheme 49). This resulted in clean compound **32**. Both, the mixture of **29**/**30** and compound **32** were used for the tetrazole formation described in chapter 2.4.2.

2.3.3 In-mediated allylation of *N*-acetylmannosamine **7**

Also, attempts for the In-mediated allylation of *N*-acetylmannosamine **7** (Scheme 50) have been done. The assignment and integration of the NMR signals of **7**, **33** and **34** from the crude reaction mixture was difficult, due to a high number of unknown signals partly overlapping the compound signals. Therefore, no precise conversion of **7** or the ratio between **33** and **34** could have been determined.



Scheme 50: In-mediated allylation of 7.

Table 9: Screened reaction condition for the allylation of 7.

Solvents		Temp.
DMF/H_2O	6:4	r.t.
DMF/H_2O	6:4	40 °C
EtOH		r.t.
EtOH/H_2O	1:1	r.t.
EtOH/H_2O	1:1	40 °C
EtOH/H_2O	4:1	r.t.
EtOH/H_2O	4:1	40 °C
EtOH/H_2O	4:1	60 °C
EtOH/H_2O	6:1	r.t.
EtOH/H_2O	6:1	40 °C
EtOH/0.1 M HCl	4:1	40 °C
EtOH/0.1 M HCl	6:1	40 °C
EtOH/sat. NH_4Cl	4:1	r.t.
THF/H_2O	1:5	r.t.
THF/H_2O	1:1	40 °C

Furthermore, the crude mixture was peracetylated to isolate the possible products **36** and **37**. With these, an exact identification and determination of the ratio should have been possible. Unfortunately, only peracetylated mannosamine (**35**) could have been isolated. Therefore, the approach towards the Neu5Ac derivative (**9**) was discarded.

2.4 Tetrazole formation

2.4.1 Formation of tetrazole compounds 23 and 24

For the tetrazole formation (Figure 13), compound **23** has been used as the model compound. Different procedures for the [2 + 3] cycloaddition of **23** with an azide have been performed. (Table 10) During this screening, $TMSN_3$, Bu_3SnN_3 and NaN_3 have served as azide source, but only with NaN_3 it was possible to isolate the desired compound **38**.

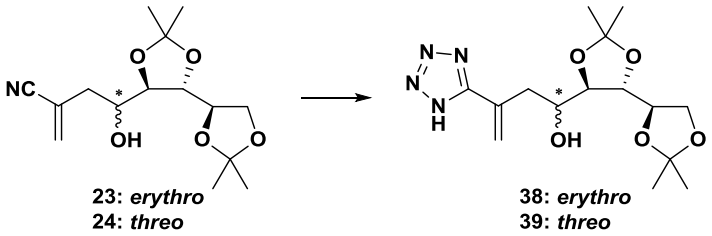


Figure 13: Formation of tetrazole 38 and 39.

The polarity of the used solvents had a high impact on the reaction, due to the solubility of the reagents. Therefore, with toluene a high amount of solid material in the flask was observed and no **38** could be identified *via* NMR. Although, the tetrazole formation has been performed tentatively in aqueous solutions, the use of water was not worthwhile. Beside the fact that its use can lead to the formation of highly explosive HN_3, it always resulted in the hydrolyzation of the nitrile functionality, leading to the carboxylic acid.

Another important parameter was the reaction temperature. When the temperature was too low, only the starting material (**23**) could be isolated. Too high temperatures led to the decomposition of **23**. Not even the use of microwave irradiation resulted in the formation of **38**. Therefore, the best results could be achieved at 110 °C using NaN_3 and NH_4HCl in toluene with a yield of 67 %. These conditions have been adapted successfully to the formation of **39** with a yield of 17 %.

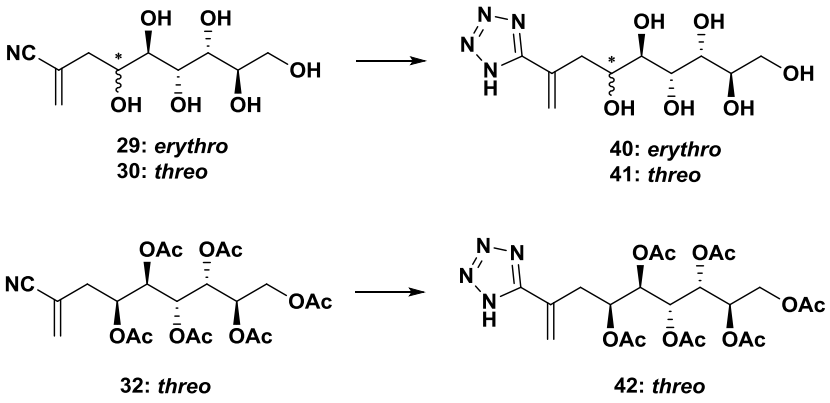
Table 10: Screened reaction conditions for the formation of 38.

Reagents	Solvents	Temp.		Reaction time	Yield (38)
NaN_3, NH_4Cl	Toluene	100 °C		18 h	-
NaN_3, NH_4Cl	DMF	150 °C		18 h	decomposed
NaN_3, NH_4Cl	DMF	100 °C		18 h	23 %
NaN_3, Et_3NHCl	DMF	90 °C		18 h	33 %
NaN_3, NH_4Cl	DMF	50 °C		18 h	-
NaN_3, Et_3NHCl	Toluene	90 °C		18 h	67 %
NaN_3, Et_3NHCl	DMF	130 °C	*mw*	3 h	decomposed
NaN_3, $ZnCl_2$	H_2O	100 °C		18 h	nitrile hydrolyzed
NaN_3, $ZnCl_2$	H_2O	100 °C	*mw*	5.5 h	decomposed
NaN_3, $ZnCl_2$	H_2O	130 °C	*mw*	90 min	decomposed
NaN_3, $ZnCl_2$	Dioxan	100 °C		18 h	-
NaN_3, $ZnCl_2$	DMF	120 °C		18 h	-
NaN_3, $ZnCl_2$	DMF	150 °C		18 h	-
NaN_3, $ZnBr_2$	THF	100 °C		18 h	-
NaN_3, $ZnBr_2$	NMP	100 °C	*mw*	75 min	-
NaN_3, $ZnBr_2$	THF/H_2O (1:5)	85 °C		18 h	nitrile hydrolyzed
NaN_3, $ZnBr_2$	DMF	160 °C		18 h	decomposed
NaN_3, $ZnBr_2$	DMF	150 °C	*mw*	40 min	decomposed
NaN_3, $ZnBr_2$	H_2O	150 °C	*mw*	25 min	decomposed
NaN_3, $ZnBr_2$	Isopropanol/H_2O (1:3)	100 °C		18 h	nitrile hydrolyzed
NaN_3, ZnO	THF/H_2O (1:5)	100 °C			nitrile hydrolyzed
NaN_3, I_2	2-butanone	75 °C	*mw*	2 h	-
$TMSN_3$, Bu_2SnO	Toluene	80 °C		24 h	-
$TMSN_3$, Bu_2SnO	Toluene	110 °C		24 h	-
$TMSN_3$, Bu_2SnO	DMF	120 °C		48 h	decomposed
NaN_3, TMSCl	NMP	120 °C	*mw*	3 h	decomposed
Bu_3SnN_3	Toluene	80 °C		24 h	-
Bu_3SnN_3	Toluene	30 °C		30 h	-

2.4.2 Formation of tetrazole compounds 40, 41 and 42

The reaction conditions for the formation of **38** and **39** have been adapted for the synthesis of the tetrazoles **40** and **41**. First trials with NaN_3 and Et_3NHCl in toluene were unsuccessful, due to the

low solubility of **29** and **30** in this solvent. Therefore, switching to more polar solvents was necessary. The use of DMSO, NMP or $PhNO_2$ was unsuccessful. Also, attempts of using the base Et_3N did not result in the desired products. Finally, with DMF 21 % of a 10:1 mixture of **40** and **41** could be isolated. In this case, a temperature of 110 °C was necessary. Lower temperatures resulted in no conversion and higher temperatures in the decomposition of the compounds. Furthermore, performing the reaction under microwave irradiation or the addition of 2 equivalents of EtOH did not increase the yield.



Scheme 51: Formation of tetrazole 40, 41 and 42.

Unfortunately, it was still not possible to separate compound **40** and **41**, and a complete clean up *via* anion exchange chromatography failed, as well. Nevertheless, the impure mixture was used for the next step.

Table 11: Screened reaction condition for the formation of 40 and 41.

Reagents	Solvents	Temp.	Reaction time	Yield (40 + 41)	Ratio (40/41)
NaN_3, Et_3NHCl	Toluene	90 °C	18 h	-	-
NaN_3, Et_3NHCl	Toluene (2 equiv EtOH)	90 °C	18 h	-	-
NaN_3, Et_3NHCl	DMF	90 °C	18 h	-	-
NaN_3, Et_3NHCl	DMF	110 °C	18 h	-	-
NaN_3, Et_3NHCl	DMF	110 °C	30 h	21 %	1:10
NaN_3, Et_3NHCl	DMF	170 °C	18 h	decomposed	-
NaN_3, Et_3NHCl	DMF (2 equiv EtOH)	90 °C	18 h	-	-
NaN_3, Et_3NHCl	DMF	50 °C	5 d	-	-
NaN_3, Et_3NHCl	DMF (2 equiv EtOH)	50 °C	5 d	-	-

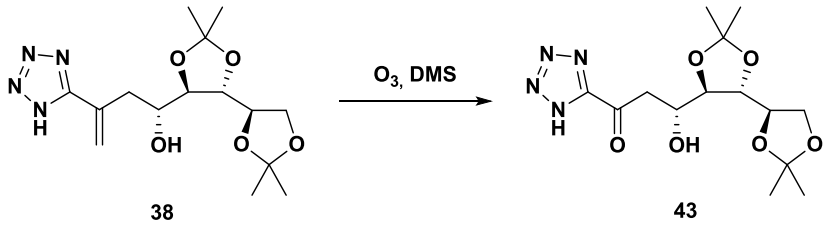
NaN_3, Et_3NHCl	DMF	50 °C	*mw*	2 h	-	-
NaN_3, Et_3NHCl	DMF	90 °C	*mw*	2 h	-	-
NaN_3, Et_3NHCl	DMF	150 °C	*mw*	30 min	decomposed	-
NaN_3, Et_3NHCl	NMP	90 °C		18 h	-	-
NaN_3, Et_3NHCl	Et_3N	90 °C		18 h	-	-
NaN_3, Et_3NHCl	DMSO	90 °C		18 h	-	-
NaN_3, Et_3NHCl	$PhNO_2$	90 °C		18 h	-	-

The almost sufficient reaction conditions for the formation of **40** and **41** were applied for the tetrazole formation using the peracetylated compound **32**. (Scheme 51) Unfortunately, no product (**42**) was formed. Switching to toluene as solvent resulted in no product, as well. Therefore, we had to quit this part of the project.

2.5 Ozonolysis

2.5.1 Ozonolysis of compounds 38 and 39

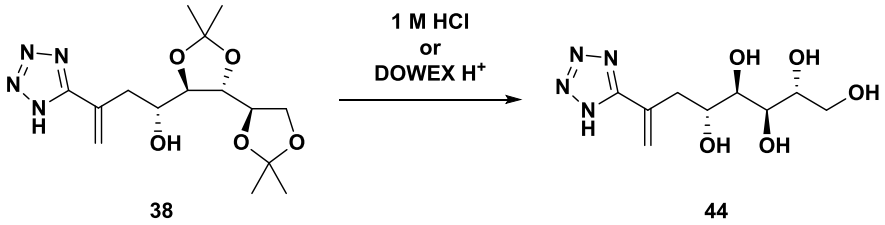
First attempt for the ozonolysis and resulting generation of the ketone functionality on C-2 have been done with compound **38**. (Scheme 52) Although, the first trial successfully resulted in clean **43**, this was not reproducible. NMR analysis always showed a mixture of **43** with several unknown compounds. To eliminate a possible source of side reactions, the pH of the solution was adjusted to a neutral range, but still no clean product could be isolated. Therefore, the deprotection of compound **38** was given priority. (Scheme 53)



Scheme 52: Ozonolysis of compound 38.

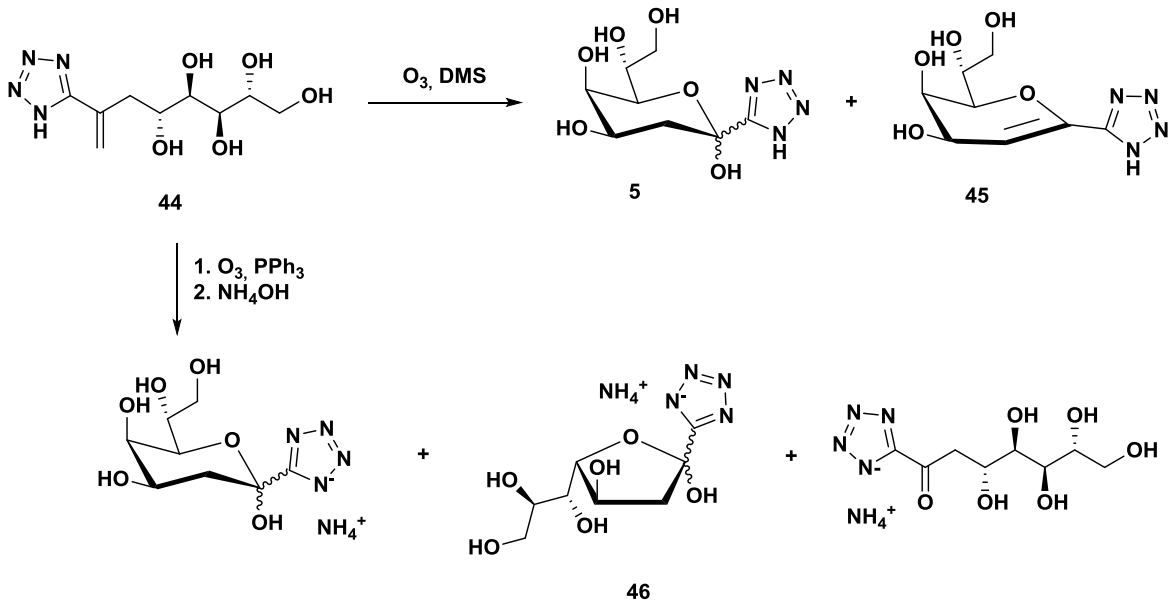
For the deprotection of **38**, 1 M HCl in THF/H_2O was used, first. This resulted in complete deprotection of **44**, confirmed *via* NMR. Unfortunately, with this methodology unwanted chloride salts, depending on the work-up (e.g. NaCl or NH_4Cl), are produced and difficult to separate.

Therefore, a deprotection protocol with DOWEX H^+ was applied. Although, the reaction time raised from 3 h to 16 h, clean compound **44** could be isolated quantitatively.



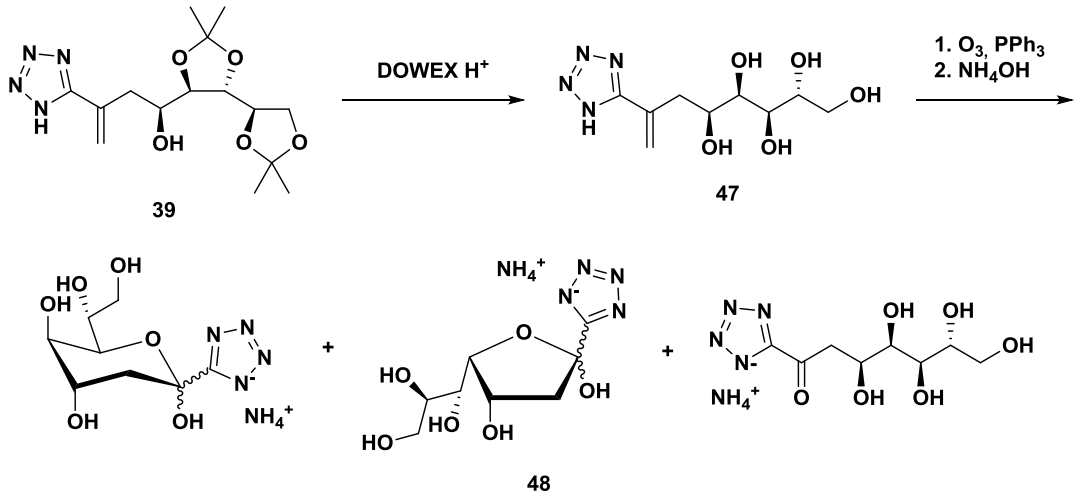
Scheme 53: Deprotection of compound 38.

When he final ozonolysis was performed (Scheme 54), dimethyl sulfide was used for the oxidation, resulting in DMSO as the only byproduct. It was believed that these two volatile compounds could easily be removed under reduced pressure, but DMSO was still visible in the NMR spectra. Additionally, NMR and MS analysis showed partly eliminated product (**45**). This can be explained through the acidic characteristics of this compound, promoting the elimination towards a conjugated π-system. To overcome this problem, compound **5** was converted into the ammonium salt directly after ozonolysis. This compound was more stable, although it still converted to the elimination product **45** over a period of several days. Unfortunately, it was not possible to completely remove DMSO. Consequently, we switch from DMS to PPh_3 for quenching the ozonolysis. This compound and its product (PPh_3O) are insoluble in water, why a simple extraction was sufficient to quantitatively gain the clean compound **46**. Interestingly, we not only observed a mixture of α- and β-pyranose and -furanose, but also a high amount of the open chain form.



Scheme 54: Ozonolysis of compound 44.

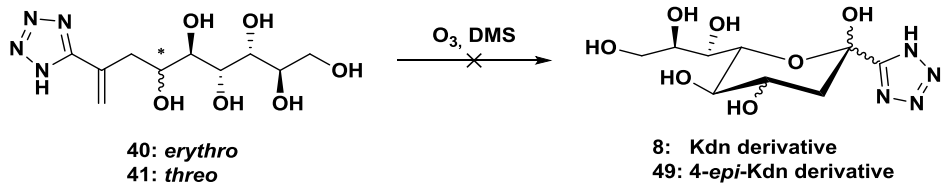
This procedure for the deprotection and ozonolysis was further applied for the ozonolysis of compound **39** and successfully resulted a quantitative amount of the 4-*epi*-Kdo derivative **48**. (Scheme 55) As before, we observed a mixture of α- and β-pyranose and -furanose, as well as the open chain form.



Scheme 55: Deprotection and ozonolysis of compound 39.

2.5.2 Ozonolysis of compounds 40 and 41

As described in chapter 2.4.2, the impure mixture of **40** and **41** was used for the ozonolysis. We wanted to perform the ozonolysis of this mixture. Unfortunately, no product (**8** and **49**) could be isolated.

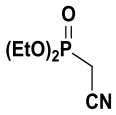


3 Experimental part

3.1 General methods

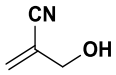
NMR spectra were recorded on a Bruker Avance DRX 400 (100.13 MHz for ^{1}H, 100.61 MHz for ^{13}C) or Bruker Avance III 600 (600.13 MHz for ^{1}H, 150.90 MHz for ^{13}C). Chemical shift (δ) are given in parts per million [ppm]. Abbreviations for the multiplicities are as followed: singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m). MS experiments were performed on a Finnigan MAT 900 spectrometer in ESI mode. IR spectra were verified on an ELMER FT-IR spectrometer. Optical rotations were measured on a Perkin Elmer Polarimeter 341. For flash chromatography Merck silica gel 60 (0.004 – 0.063 mm) was used. Merck plates (silica gel 60 F254) were used for TLC monitoring. The compounds were visualized under UV (254 nm), *via* treatment with a solution of 3 g $KMnO_4$, 20 g K_2CO_3 in 5 mL 5 % NaOH and 500 mL H_2O and subsequent heating or in an iodine chamber. DCM, acetone, MeOH, EtOH, heptane and ethyl acetate were distilled before use. Dry DCM was prepared by filtration through an aluminium oxide column and stored over molecular sieves 4 Å. Other solvents and chemicals were purchased in reagent grade.

3.2 Phosphonoacetonitrile diethyl ester (**11**)



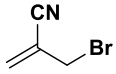
Chloroacetonitrile (50 mL, 0.79 mmol, 1 equiv) and $P(OEt)_3$ (175 mL, 1.58 mmol, 2 equiv) were heated to 150 °C for 2 h. Unreacted $P(OEt)_3$ was removed under reduced pressure and the resulting solution was distilled. The last fraction with bp 130-165 °C at 2 mm Hg contained the product **11** (112 g, 95 %) as colorless liquid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.19 (dqd, *J* = 8.9, 7.1, 2.0 Hz, 4 H, $OC\underline{H}_2CH_3$), 2.85 (d, *J* = 20.9 Hz, 2 H, H-2), 1.34 (t, *J* = 7.0 Hz, 6 H, $OCH_2C\underline{H}_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 112.74 (d, *J* = 11.2 Hz, C_q, C-1), 63.90 (d, *J* = 6.6 Hz, 2 x CH_2, $O\underline{C}H_2CH_3$), 16.47 (d, *J* = 143.7 Hz, CH_2, C-2), 16.32 (d, *J* = 5.9 Hz, 2 x CH_3, $OCH_2\underline{C}H_3$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_6H_{12}NO_3PNa$ 200.0447; found 200.0440.

3.3 2-(Hydroxymethyl)acrylonitrile (12).



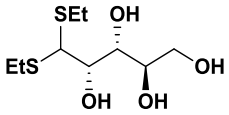
Saturated K_2CO_3 solution (9,9 mL, 67.8 mmol, 2 equiv) was added dropwise to a mixture of phosphonoacetonitrile diethyl ester **11** (10 g, 56.45 mmol, 1 equiv) and formaldehyde (37 % in water, 18.3 mL, 225.81 mmol, 4 equiv) while the temperature of the solution was kept between 35-40 °C. After completion, the solution was cooled immediately to 0 °C. Brine and Et_2O were added and the water phase extracted 3x with ether. The combined organic phases were dried over $MgSO_4$ and the solvents removed under reduced pressure. The crude product was purified through silica chromatography (heptane/ethyl acetate 3:1) to yield **12** (3.523 g, 75 %): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.03 (t, J = 1.8 Hz, 1 H, C=CH_2), 6.01 – 5.98 (m, 1 H, C=CH_2), 4.19 (t, J = 1.8 Hz, 2 H, H-3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 130.70 (CH_2, C=$\underline{C}H_2$), 122.68 (C_q, C-2), 117.30 (C_q, C-1), 62.44 (CH_2, C-3).

3.4 2-(Bromomethyl)acrylonitrile (13)



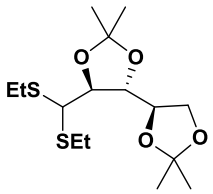
2-(Hydroxymethyl)acrylonitrile (**12**) (5.46 g, 65.71 mmol, 1 equiv) was dissolved in 100 mL dry Et_2O and cooled to -20 °C. PBr_3 (3.09 mL, 32.86 mmol, 0.5 equiv) was added dropwise. The solution was stirred for two hours at -20 °C, before being quenched by the addition of 100 mL H_2O. The mixture was extracted 3x with Et_2O, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified through silica chromatography (pentane/ethyl acetate 3:1) to yield **13** (7.58 g, 80 %) as colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.06 (s, 1 H, C=CH_2), 6.02 (s, 1 H, C=CH_2), 4.00 (s, 2 H, H-3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 133.62 (CH_2, C=CH_2), 120.32 (C_q, C-2), 117.13 (C_q, C-1), 29.62 (CH_2, C-3).

3.5 D-Arabinose diethyl dithioacetal (20)



To a solution of D-arabinose (10.00 g, 66.6 mmol, 1 equiv) in conc. hydrochloric acid (10 mL) was added dropwise ethane thiol (16.84 mL, 14.48 g, 233.1 mmol, 3.5 equiv) at 0 °C. After being stirred for 2.5 h at r.t., the mixture was cooled to 0 °C and filtered. The collected solid was washed with cold water (50 mL) and recrystallized from MeOH to give 14.00 g (82 %) of **20** as colorless plates: ^{1}H NMR (600 MHz, MeOD) δ 3.97 (d, J = 9.2 Hz, 1 H, H-1), 3.89 (dd, J = 8.6, 1.5 Hz, 1 H, H-3), 3.75 (dd, J = 9.2, 1.5 Hz, 1 H, H-2), 3.71 (dd, J = 11.2, 3.3 Hz, 1 H, H-5a), 3.59 (ddd, J = 8.9, 6.0, 3.3 Hz, 1 H, H-4), 3.52 (dd, J = 11.2, 6.1 Hz, 1 H, H-5b), 2.64 (dqd, J = 12.5, 7.5, 3.8 Hz, 2 H, SC$\underline{H}_2$CH$_3$), 2.61 – 2.53 (m, 2 H, SC$\underline{H}_2$CH$_3$), 1.16 (td, J = 7.4, 6.5 Hz, 6 H, SCH$_2\underline{C}$H$_3$); ^{13}C NMR (151 MHz, MeOD) δ 73.06 (CH, C-4), 72.66 (CH, C-2), 71.88 (CH, C-3), 65.08 (CH$_2$, C-5), 56.05 (CH, C-1), 25.30 (CH$_2$, S$\underline{C}$H$_2$CH$_3$), 25.29 (CH$_2$, S$\underline{C}$H$_2$CH$_3$), 14.84 (CH$_3$, SCH$_2\underline{C}$H$_3$), 14.79 (CH$_3$, SCH$_2\underline{C}$H$_3$); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_9H_{20}O_4S_2Na$ 279.0695; found 279.0698.

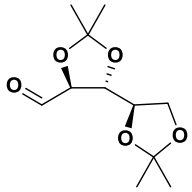
3.6 2,3:4,5-Di-*O*-isopropylidene-D-arabinose diethyl dithioacetal (21)



To a suspension of **20** (10.81 g, 42.17 mmol) in acetone (125 mL) at 0 °C was added concentrated sulfuric acid (1.5 mL). The resulting tan solution was warmed to room temperature and stirred for 16 h. The acidic mixture was neutralized by addition of 10 % NH_3 solution, and the precipitated solid was removed by filtration. The filtrate was removed and purified by silica chromatography (heptane/ethyl acetate 6:1) to afford 12.98 g (92%) of **21** as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.29 (dd, J = 6.6, 2.8 Hz, 1 H, H-2), 4.15 – 4.11 (m, 1 H, H-5a), 4.07 (dd, J = 5.8, 3.9 Hz, 2 H, H-3 and H-4), 4.03 (d, J = 2.7 Hz, 1 H, H-1), 3.97 – 3.93 (m, 1 H, H-5b), 2.78 – 2.65 (m, 4 H, SC$\underline{H}_2$CH$_3$), 1.44 (s, 3 H, C(CH$_3$)$_2$), 1.41 (s, 3 H, C(CH$_3$)$_2$), 1.37 (s, 3 H, C(CH$_3$)$_2$), 1.33 (s, 3 H, C(CH$_3$)$_2$), 1.26 (dt, J = 12.4, 7.4

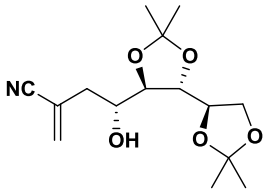
Hz, 6 H, $SCH_2C\underline{H}_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 110.34 (C_q, $\underline{C}(CH_3)_2$), 109.82 (C_q, $\underline{C}(CH_3)_2$), 84.47 (CH, C-2), 79.18 (CH, C-3), 77.24 (CH, C-4), 67.88 (CH_2, C-5), 52.41 (CH, C-1), 27.43 (CH_3, $C(\underline{C}H_3)_2$), 27.20 (CH_3, $C(\underline{C}H_3)_2$), 26.77 (CH_3, $C(\underline{C}H_3)_2$), 25.36 (CH_3, $C(\underline{C}H_3)_2$), 25.33 (CH_2, $S\underline{C}H_2CH_3$), 25.08 (CH_2, $S\underline{C}H_2CH_3$), 14.56 (CH_3, $SCH_2\underline{C}H_3$), 14.47 (CH_3, $SCH_2\underline{C}H_3$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{28}O_4S_2Na$ 359.1321; found 359.1316.

3.7 2,3:4,5-Di-*O*-isopropylidene-*aldehydo*-D-arabinose (22)



Compound **21** (1.5 g, 4.6 mmol, 1 equiv) was dissolved in acetone (16 mL) and H_2O (1.5 mL) HgO (2.3 g, 10.5 mmol, 2.5 equiv) and $HgCl_2$ (2.3 g, 8.3 mmol, 2 equiv) were added. The mixture was heated to 55 °C and stirred at this temperature for 3.5 h. After cooling to room temperature, the slurry was filtered through a Celite pad and the filtrate concentrated to dryness. The crude was taken up in dichloromethane (3 x 10 mL) and filtered again through Celite. The organic layers were washed with a 1 M solution of KI and then dried over $MgSO_4$. Removal of the solvent under vacuum gave 0.87 g (77 %) of aldehyde **22** as solid, which was used for the following step without further purification.

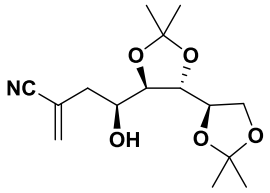
3.8 2,3-Dideoxy-5,6:7,8-di-*O*-isopropylidene-2-methylene-D-*manno*-octonitrile (23)



Compound **22** (300 mg, 1.30 mmol, 1 equiv), compound **13** (474 mg, 3.27 mmol, 2.5 equiv) and Indium powder (225 mg, 1.95 mmol, 1.5 equiv) were dissolved in 15 mL DMF/H_2O (6:4) and stirred

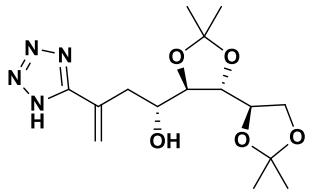
at 40 °C for 4 h. The solvents were removed and the crude product (erythro/threo 2:1) was purified by silica chromatography (heptane/ethyl acetate 5:1) to give 205 mg (53 %) of **23** as colorless crystals. $[\alpha]_D^{20}$ +5.27° (*c* 1.0, DCM); mp 32-35 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.97 (s, 1H, C=CH_2), 5.86 (s, 1H, C=CH_2), 4.19 (ddd, *J* = 8.5, 5.9, 2.1 Hz, 1H, H-8a), 4.07 – 3.97 (m, 2H, H-7 and H-8b), 3.89 – 3.82 (m, 2H, OH and H-4), 3.68 (dt, *J* = 6.0, 1.4 Hz, 2H, H-5 and H-6), 2.75 – 2.68 (m, 1H, H-3a), 2.38 (ddd, *J* = 14.5, 8.9, 1.8 Hz, 1H, H-3b), 1.44 (s, 3H, C(CH_3)$_2$), 1.36 (s, 3H, C(CH_3)$_2$), 1.34 (s, 6H, 2 x C(CH_3)$_2$); ^{13}C NMR (151 MHz, $CDCl_3$): δ 133.22 (CH_2, C=$\underline{C}H_2$), 119.77 (C_q, C-2), 118.94 (C_q, C-1), 110.52 (C_q, $\underline{C}(CH_3)_2$), 109.62 (C_q, $\underline{C}(CH_3)_2$), 82.62 (CH, C-5), 81.45 (CH, C-6), 77.19 (CH, C-7), 70.28 (CH, C-4), 68.15 (CH_2, C-8), 38.92 (CH_2, C-3), 26.86 (CH_3, C($\underline{C}H_3$)$_2$), 26.78 (CH_3, C($\underline{C}H_3$)$_2$), 26.51 (CH_3, C($\underline{C}H_3$)$_2$), 25.16 (CH_3, C($\underline{C}H_3$)$_2$); HRMS (ESI) m/z [M + Na]+ calcd for $C_{15}H_{23}O_5NNa$ 320.1468; found 320.1482; (IR) *v* 3441, 2987, 2936, 2883, 2224, 1622, 1456, 1433, 1373, 1213, 1153, 1065.

3.9 2,3-Dideoxy-5,6:7,8-di-*O*-isopropylidene-2-methylene-D-*gluco*-octonitrile (24)



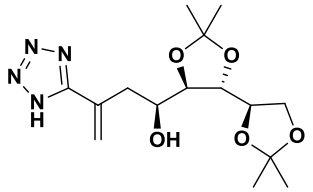
Compound **24** was synthesized from **13** (300 mg, 1.30 mmol) according to the procedure for compound **24** (chapter 3.8): yield 70 mg (18 %); mp 41-46 °C; $[\alpha]_D^{20}$ -9.90° (*c* 1.0, DCM); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.96 (s, 1H, C=CH_2), 5.84 (s, 1H, C=CH_2), 4.13 (dd, *J* = 8.7, 6.1 Hz, 1H, H-8a), 4.03 (ddd, *J* = 8.7, 6.0, 4.6 Hz, 1H, H-7), 3.99 – 3.93 (m, 2H, H-4 and H-8b), 3.90 (dd, *J* = 7.6, 2.4 Hz, 1H, H-6), 3.88 – 3.83 (m, 1H, H-5), 2.53 (dd, *J* = 14.6, 4.1 Hz, 1H, H-3a), 2.45 (dd, *J* = 14.6, 9.4 Hz, 1H, H-3b), 2.37 (d, *J* = 9.6 Hz, 1H, OH), 1.41 (s, 3H, CH_3, C(CH_3)$_2$), 1.39 (s, 3H, CH_3, C(CH_3)$_2$), 1.36 (s, 3H, CH_3, C(CH_3)$_2$), 1.32 (s, 3H, CH_3, C(CH_3)$_2$); ^{13}C NMR (151 MHz, CDCl3): δ 133.01 (CH_2, C=CH_2), 119.89 (C_q, C-2), 118.61 (C_q, C-1), 110.02 (C_q, $\underline{C}(CH_3)_2$), 109.89 (C_q, $\underline{C}(CH_3)_2$), 82.98 (CH, C-5), 77.41 (CH, C-6), 77.18 (CH, C-7), 68.26 (CH, C-4), 67.98 (CH_2, C-8), 39.82 (CH_2, C-3), 27.17 (CH_3, C($\underline{C}H_3$)$_2$), 27.05 (CH_3, C($\underline{C}H_3$)$_2$), 26.76 (CH_3, C($\underline{C}H_3$)$_2$), 25.25 (CH_3, C($\underline{C}H_3$)$_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{23}O_5NNa$ 320.1468; found 320.1471; (IR) *v* 3472, 2987, 2935, 2224, 1735, 1623, 1456, 1372, 1243, 1212, 1154, 1111, 1064.

3.10 5-(1,2-Dideoxy-5,6;7,8-di-O-isopropylidene-2-methylene-D-*manno*-heptosyl)-tetrazole (38)



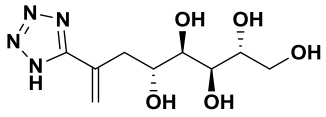
Compound **23** (1 g, 3.36 mmol, 1 equiv), NaN_3 (1.09 g, 16.82 mmol, 5 equiv) and Et_3NHCl (2.31 g, 16.82 mmol, 5 equiv) were dissolved in 10 mL dry toluene and stirred at 90 °C until the tlc showed completion of the reaction (approximately 18 h). After the mixture was cooled to 0 °C, ethyl acetate and 1 M HCl were added and the organic phase washed 3x with 1 M HCl. The organic phase was dried over $MgSO_4$ and the solvents removed. The crude product was purified by silica chromatography (heptane/ethyl acetate 1:1) to give 732 mg (64 %) of **38** as a colorless, amorphous solid. $[\alpha]_D^{20}$ -11.65° (*c* 1.0, DCM); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.41 (d, *J* = 1.1 Hz, 1H, C=CH_2), 5.70 (d, *J* = 1.1 Hz, 1H, C=CH_2), 4.24 – 4.16 (m, 1H, H-8a), 4.04 (m, 2H, H-7 and H-8b), 3.91 (ddd, *J* = 8.0, 6.8, 2.8 Hz, 1H, H-4), 3.70 – 3.63 (m, 2H, H-5 and H-6), 2.96 (ddd, *J* = 14.6, 2.7, 0.9 Hz, 1H, H-3a), 2.72 (ddd, *J* = 14.6, 6.8, 0.9 Hz, 1H, H-3b), 1.46 (s, 3H, CH_3, $C(CH_3)_2$), 1.39 (s, 3H, CH_3, $C(CH_3)_2$), 1.37 (s, 3H, CH_3, $C(CH_3)_2$), 1.34 (s, 3H, CH_3, $C(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.19 (C_q, C-1), 128.44 (C_q, C-2), 125.44 (CH_2, C=CH_2), 110.78 (C_q, $\underline{C}(CH_3)_2$), 109.66 (C_q, $\underline{C}(CH_3)_2$), 81.57 (CH, C-5 or C-6), 81.45 (CH, C-5 or C-6), 75.93 (CH, C-7), 72.69 (CH, C-4), 67.98 (CH_2, C-8), 38.09 (CH_2, C-3), 26.88 (CH_3, $C(\underline{C}H_3)_2$), 26.74 (CH_3, $C(\underline{C}H_3)_2$), 26.53 (CH_3, $C(\underline{C}H_3)_2$), 25.06 (CH_3, $C(\underline{C}H_3)_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{24}O_5N_4Na$ 363.1639; found 363.1642; (IR) *v* 3271, 2926, 2752, 1728, 1641, 1546, 1405, 1287, 1241, 1032, 1003.

3.11 5-(1,2-Dideoxy-5,6;7,8-di-O-isopropylidene-2-methylene-D-*gluco*-heptosyl)-tetrazole (**39**)



Compound **39** was synthesized from **24** (200 mg, 0.67 mmol) according to the procedure for compound **38** (chapter 3.10): yield 144 mg (63 %); $[\alpha]_D^{20}$ +13.71° (*c* 1.1, DCM); ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 6.30 (s, 1H, C=CH_2), 5.68 (s, 1H, C=CH_2), 4.15 (dd, *J* = 8.7, 6.2 Hz, 1H, H-8a), 4.05 (m, 2H, H-6 and H-7), 4.01 (dd, *J* = 7.1, 3.8 Hz, 1H, H-4), 3.97 (dd, *J* = 8.8, 4.9 Hz, 1H, H-8b), 3.90 (dd, *J* = 8.7, 7.0 Hz, 1H, H-5), 2.99 (dd, *J* = 14.8, 3.4 Hz, 1H, H-3a), 2.78 (dd, *J* = 14.8, 8.7 Hz, 1H, H-3b), 1.40 (s, 3H, CH_3, C(CH_3)$_2$), 1.38 (s, 3H, CH_3, C(CH_3)$_2$), 1.36 (s, 3H, CH_3, C(CH_3)$_2$), 1.32 (s, 3H, CH_3, C(CH_3)$_2$); ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 156.08 (C_q, C-1), 129.58 (C_q, C-2), 124.48 (CH_2, C=<u>C</u>H_2), 110.24 (C_q, <u>C</u>(CH_3)$_2$), 110.19 (C_q, <u>C</u>(CH_3)$_2$), 82.25 (CH, C-6), 78.13 (CH, C-5), 76.98 (CH, C-7), 71.14 (CH, C-4), 67.97 (CH_2, C-8), 38.75 (CH_2, C-3), 27.33 (CH_3, C(<u>C</u>H_3)$_2$), 27.26 (CH_3, C(<u>C</u>H_3)$_2$), 26.78 (CH_3, C(<u>C</u>H_3)$_2$), 25.25 (CH_3, C(<u>C</u>H_3)$_2$); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{24}O_5N_4Na$ 363.1639; found 363.1642; (IR) *v* 3119, 3985, 2866, 2759, 1552, 1371, 1215, 1156, 1118, 1067, 1015.

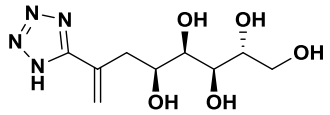
3.12 5-(1,2-Dideoxy-2-methylene-D-*manno*-heptosyl)-tetrazole (**44**)



Compound **38** (50 mg, 0.15 mmol, 1 equiv) was dissolved in 1 mL THF/H_2O (1:1) and DOWEX H^+ was added. This mixture was stirred at 60 °C for 18 h. After the ion exchange resin was filtered off, the solvent was removed under reduced pressure, giving 37 mg (97 %) of compound **44** as colorless, amorphous solid oil. $[\alpha]_D^{20}$ +9.93° (*c* 1.0, H_2O); ^{1}H NMR (600 MHz, D_2O) δ 5.98 (s, 1H, C=CH_2), 5.66 (d, *J* = 1.4 Hz, 1H, C=CH_2), 3.77 (ddd, *J* = 9.8, 8.5, 2.8 Hz, 1H, H-4), 3.72 (dd, *J* = 11.9, 2.8 Hz, 1H, H-8a), 3.69 (dd, *J* = 8.9, 1.3 Hz, 1H, H-6), 3.62 (ddd, *J* = 9.0, 6.3, 2.8 Hz, 1H, H-7), 3.58 (dd, *J* = 8.5, 1.3 Hz, 1H, H-5), 3.52 (dd, *J* = 11.9, 6.3 Hz, 1H, H-8b), 3.05 (ddd, *J* = 14.9, 2.9, 1.4 Hz, 1H, H-3a), 2.52 (dd, *J* = 14.8, 9.8 Hz, 1H, H-3b); ^{13}C NMR (151 MHz, D_2O) δ 155.59 (C_q, C-1), 128.79 (C_q, C-2), 124.10 (CH_2,

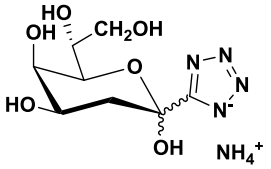
C=CH_2), 71.96 (CH, C-5), 70.73 (CH, C-7), 69.04 (CH, C-6), 68.57 (CH, C-4), 63.05 (CH_2, C-8), 37.40 (CH_2, C-3); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_9H_{16}O_5N_4H$ 261.1193; found 261.1191.

3.13 5-(1,2-Dideoxy-2-methylene-D-*gluco*-heptosyl)-tetrazole (47)



Compound **47** was synthesized from **39** (108 mg, 0.32 mmol) according to the procedure for compound **44** (chapter 3.12): yield 81 mg (98 %); $[\alpha]_D^{20}$ -10.10° (*c* 0.5, H_2O); ^1H NMR (600 MHz, D_2O) δ 5.92 (s, 1H, C=CH_2), 5.63 (s, 1H, C=CH_2), 3.85 (ddd, *J* = 9.3, 5.3, 3.9 Hz, 1H, H-4), 3.68 (dd, *J* = 11.7, 2.8 Hz, 1H, H-8a), 3.65 – 3.61 (m, H-5 and H-7), 3.60 (dd, *J* = 8.1, 2.2 Hz, 1H, H-6), 3.51 (dd, *J* = 11.7, 6.0 Hz, 1H, H-8b), 2.77 (dd, *J* = 8.1, 2.2 Hz, 1H, H-3a), 3.51 (dd, *J* = 11.7, 6.0 Hz, 1H, H-3b); ^{13}C NMR (151 MHz, D_2O) δ 155.28 (C_q, C-1), 128.35 (C_q, C-2), 124.09 (CH_2, C=CH_2), 71.55 (CH, C-5), 71.28 (CH, C-7), 70.82 (CH, C-6), 70.41 (CH, C-4), 62.55 (CH_2, C-8), 36.80 (CH_2, C-3); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_9H_{16}O_5N_4$ 259.1048; found 259.1046; (IR) *v* 3119, 2985, 2866, 2759, 1552, 1371, 1215, 1156, 1118, 1067, 1015.

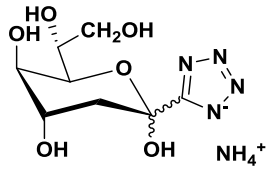
3.14 5-(2-Deoxy-D-*manno*-hept-1-ulosyl)-tetrazole (46)



Compound **44** (57 mg, 0.22 mmol, 1 equiv) was taken up in 4 mL MeOH/DCM (9:1). At -78 °C, O_3 was purged through the solution until it turned blue, followed by O_2 until the color vanished. Now, PPh_3 (86 mg, 0.33 mmol, 1.5 equiv) was added and the mixture stirred for an additional hour. The pH was adjusted to 7 by the addition of 1 M NH_4OH and the solvents removed under reduced pressure. The compound was taken up in H_2O and lyophilized to yield **46** (57 mg, 93 %) as a colorless, amorphous solid (mixture of open chain, α- and β-pyranose and furanose isomers 19:53:9:7:12). $[\alpha]_D^{20}$ +30.80° (*c* 1.0, H_2O); ^1H NMR (600 MHz, D_2O) for major α-pyranose form δ 4.07 (ddd, *J* = 12.1,

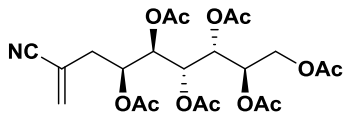
5.0, 2.9 Hz, 1H, H-4), 3.96 (d, *J* = 2.9 Hz, 1H, H-5), 3.88 (dd, *J* = 9.2, 1.1 Hz, 1H, H-6), 3.78 (ddd, *J* = 9.2, 5.8, 2.8 Hz, 1H, H-7), 3.69 (dd, *J* = 12.3, 2.8 Hz, 1H, H-8a), 3.51 (dd, *J* = 12.3, 5.8 Hz, 1H, H-8b), 2.09 (dd, *J* = 12.6, 5.0 Hz, 1H, H-3a), 1.97 (t, *J* = 12.6 Hz, 1H, H-3b); ^{13}C NMR (151 MHz, D_2O) for major α-pyranose form δ 164.64 (C_q, C-1), 94.33 (C_q, C-2), 70.67 (CH, H-6), 69.01 (CH, H-7), 66.07 (CH, C-5), 65.79 (CH, C-4), 62.79 (CH_2, C-8), 36.21 (CH_2, C-3); HRMS (ESI) *m/z* $[M - H]^-$ calcd for $C_8H_{13}N_4O_6$ 261.0841; found 261.0863; (IR) *v* 3719, 2936, 1688, 1419, 1382, 1208, 1160, 1135, 1065, 1007.

3.15 5-(2-Deoxy-D-*gluco*-hept-1-ulosyl)-tetrazole (48)



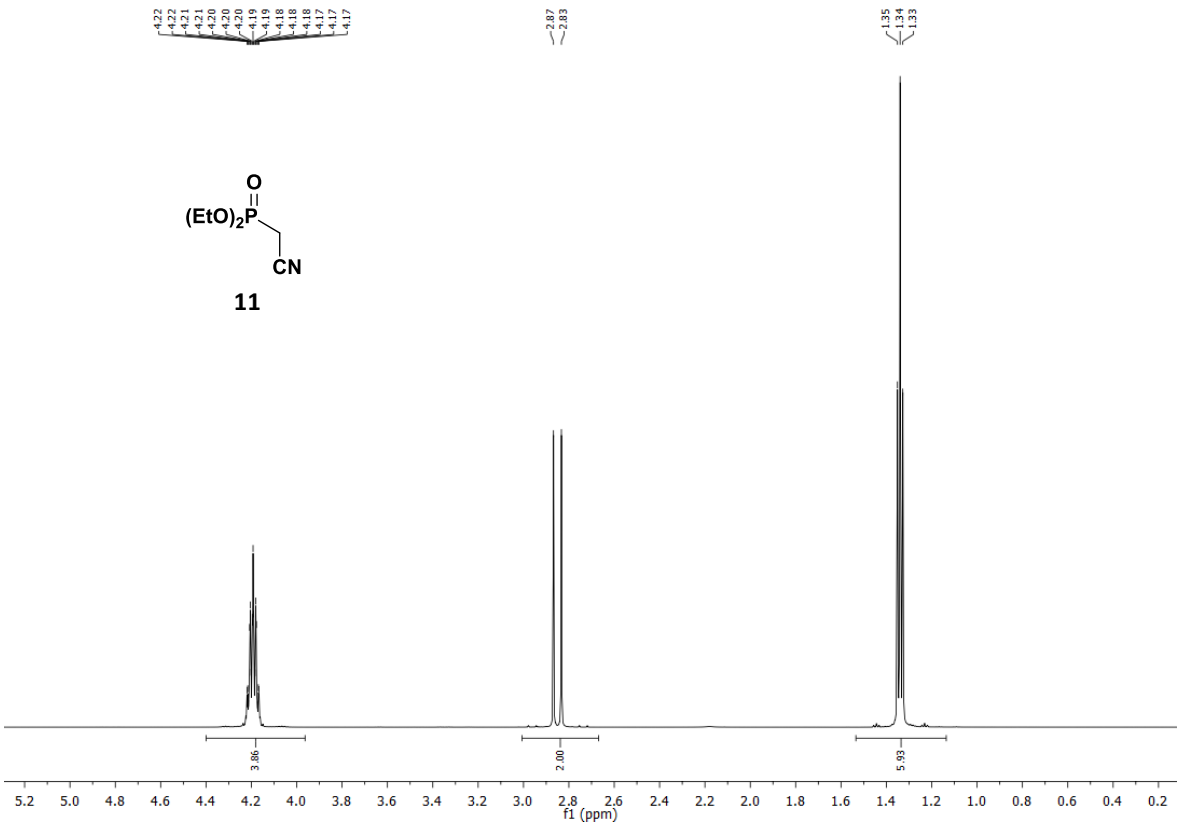
Compound **48** was synthesized from **47** (107 mg, 0.41 mmol) according to the procedure for compound **46** (chapter 3.14): yield 111 mg (97 %; mixture of open chain, α- and β-pyranose, α- and β-furanose isomers 78:17:<1:3:2); $[\alpha]_D^{20}$ +8.80° (*c* 1.0, H_2O); ^{1}H NMR (600 MHz, D_2O) for α-pyranose form δ 4.20 (dd, *J* = 9.1, 1.4 Hz, 1H, H-6), 4.01 (q, *J* = 3.6 Hz, 1H, H-4), 3.81 (dd, *J* = 5.9, 2.8, 1H, H-7), 3.79 (d, *J* = 3.3 Hz, 1H, H-5), 3.73 (d, *J* = 2.8 Hz, 1H, H-8a); 3.55 (dd, *J* = 5.9, 12.1 Hz, 1H, H-8b), 2.22 (dd, *J* = 15.1, 3.6 Hz, 1H, H-3a), 2.05 (dd, *J* = 15.1, 2.8 Hz, 1H, H-3b); ^{13}C NMR (151 MHz, D_2O) for α-pyranose form δ 160.95 (C_q, C-1), 94.01 (C_q, C-2), 69.24 (CH, C-7), 67.22 (CH, C-4), 66.75 (CH, C-6), 65.41 (CH, H-5), 62.77 (CH_2, C-8), 34.26 (CH_2, C-3); ^{1}H NMR (600 MHz, D_2O) for open-chain form δ 4.30 (q, *J* = 6.2 Hz, 1H, H-4), 3.72 – 3.68 (m, 1H, H-5 and H-8a)3.67 – 3.63 (m, 1H, H-7), 3.60 (dd, *J* = 8.1, 2.3 Hz, 1H, H-6), 3.52 (dd, *J* = 11.9, 6.3 Hz, 1H, H-8b), 3.32 (d, *J* = 6.4 Hz, 2H, H-3); ^{13}C NMR (151 MHz, D_2O) for open-chain form δ 193.44 (C_q, C-2), 164.62 (C_q, C-1), 71.77 (CH, C-5), 71.08 (CH, C-6), 70.95 (CH, C-7), 68.78 (CH, C-4), 62.63 (CH_2, C-8), 43.88 (CH_2, C-3); HRMS (ESI) *m/z* $[M - H]^-$ calcd for $C_8H_{13}N_4O_6$ 261.0841; found 261.0841; (IR) *v* 3181, 2924, 1688, 1422, 1380, 1013.

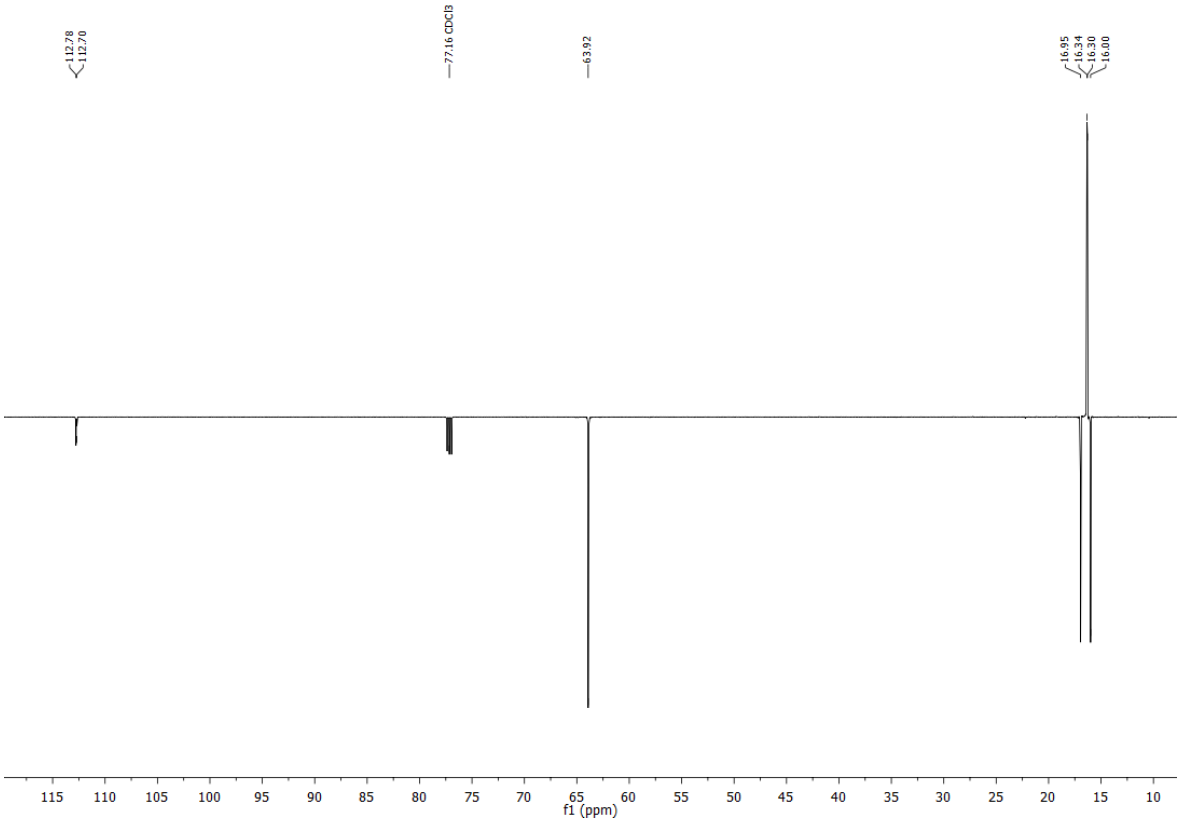
3.16 2-Methylene-1,2,3-trideoxy-D-*glycero*-D-*galacto*-nonulonitrile hexaacetate (32)

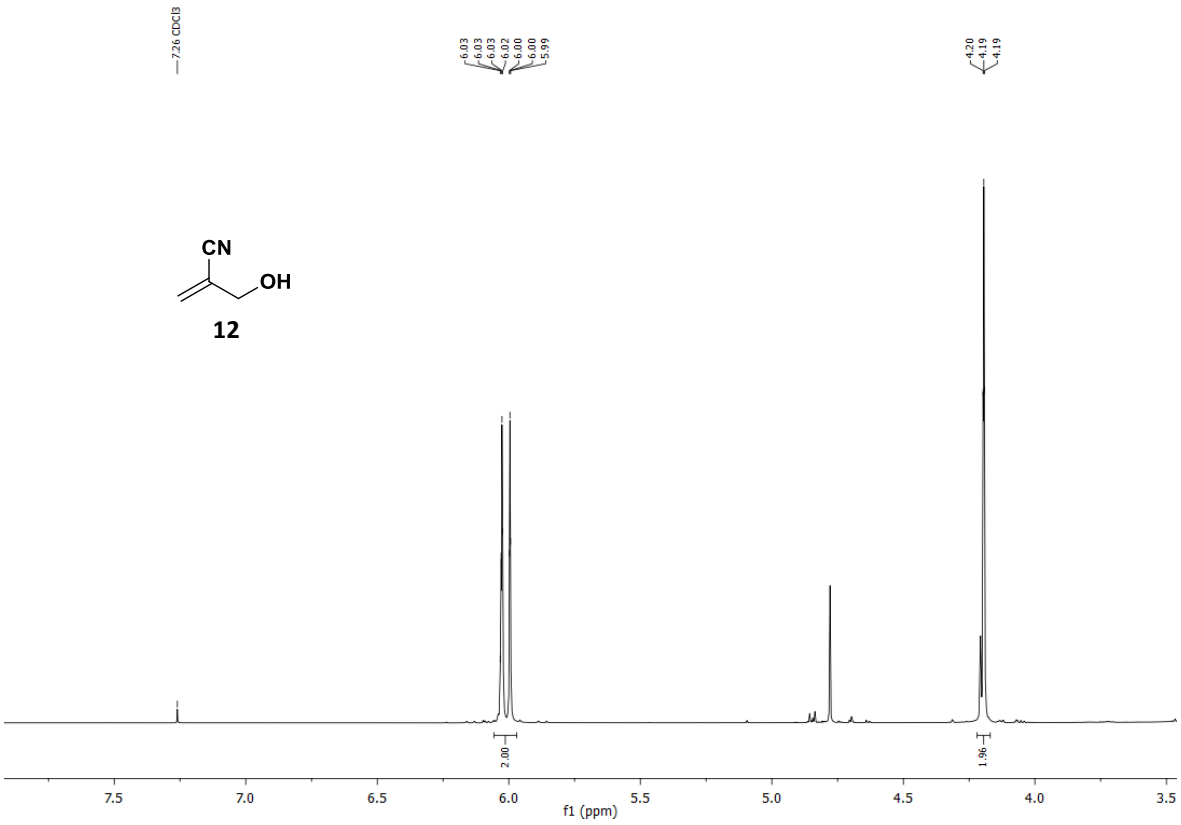


D-Mannose (25 mg, 0.14 mmol, 1 equiv), compound **13** (40 mg, 0.28 mmol, 2 equiv) and In powder (24 mg, 0.21 mmol, 1.5 equiv) were dissolved in 2 mL EtOH/H_2O (4:1) and stirred at 40 °C for 20 h. The solvents were removed and the crude product (erythro/threo 1:10) was purified by ion exchange chromatography (DOWEX HCO_2^-, eluted with H_2O; followed by DOWEX H^+, eluted with H_2O) to give a mixture of 366 mg of erythro (**29**) and threo (**30**) conformers (10:1, 53 %) as a colorless solid. The mixture was taken up in 2 mL Ac_2O/pyridine (1:1) and a catalytic amount of DMAP was added. This solution was stirred at room temperature for 18 h, before the solvents were removed under reduced pressure. The crude product purified by silica chromatography (heptane/ethyl acetate 1:1) to yield 36 mg (52 %) of compound **32** as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.89 (s, 1H, H-10a), 5.75 (s, 1H, H-10b), 5.44 (dd, *J* = 10.0, 1.9 Hz, 1H, H-6), 5.32 (dd, *J* = 8.9, 1.9 Hz, 1H, H-7), 5.17 (ddd, *J* = 9.0, 4.0, 1.9 Hz, 1H, H-4), 5.13 (dd, *J* = 10.1, 1.9 Hz, 1H, H-5), 4.96 (ddd, *J* = 8.5, 5.1, 2.8 Hz, 1H, H-8), 4.18 (dd, *J* = 12.5, 2.8 Hz, 1H, H-9a), 4.01 (dd, *J* = 12.6, 5.1 Hz, 1H, H-9b), 2.46 (dd, *J* = 14.5, 4.0 Hz, 1H, H-3a), 2.31 (dd, *J* = 14.5, 9.0 Hz, 1H, H-3b), 2.13 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.06 (d, *J* = 1.0 Hz, 6H, Ac), 2.05 (s, 3H, Ac), 2.02 (s, 3H, Ac); ^{13}C NMR (151 MHz, D_2O) *δ* 170.65 (C_q, Ac), 170.36 (C_q, Ac), 170.35 (C_q, Ac), 170.02 (C_q, Ac), 170.01 (C_q, Ac), 169.81 (C_q, Ac), 133.88 (CH_2, C=$\underline{C}H_2$), 118.46 (C_q, C-2), 118.08 (C_q, C-1), 69.31 (CH, C-5), 68.08 (CH, C-4 or C-8), 68.03 (CH, C-4 or C-8), 67.33 (CH, C-7), 66.75 (CH, C-6), 61.86 (CH_2, C-9), 36.84 (CH_2, C-3), 21.04 (CH_3, Ac), 20.93 (CH_3, Ac), 20.87 (CH_3, Ac), 20.80 (CH_3, Ac), 20.78 (CH_3, Ac), 20.73 (CH_3, Ac); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{29}O_{12}NNa$ 522.1582; found 522.1587.

4 NMR spectra



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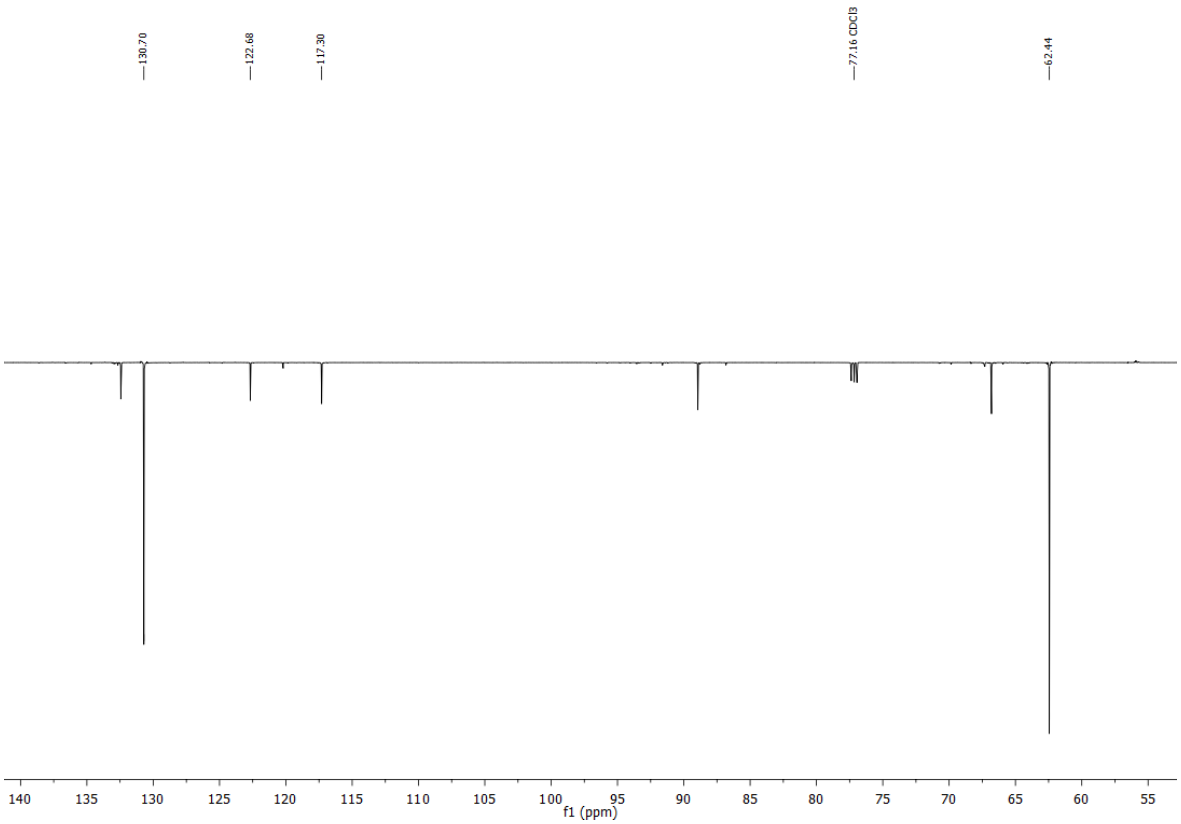
6.03
6.03
6.02
6.00
6.00
5.99
4.20
4.19
4.19
CN
OH
12
2.00
1.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
f1 (ppm)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117.30
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62.44
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120
115
110
105
100
95
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80
75
70
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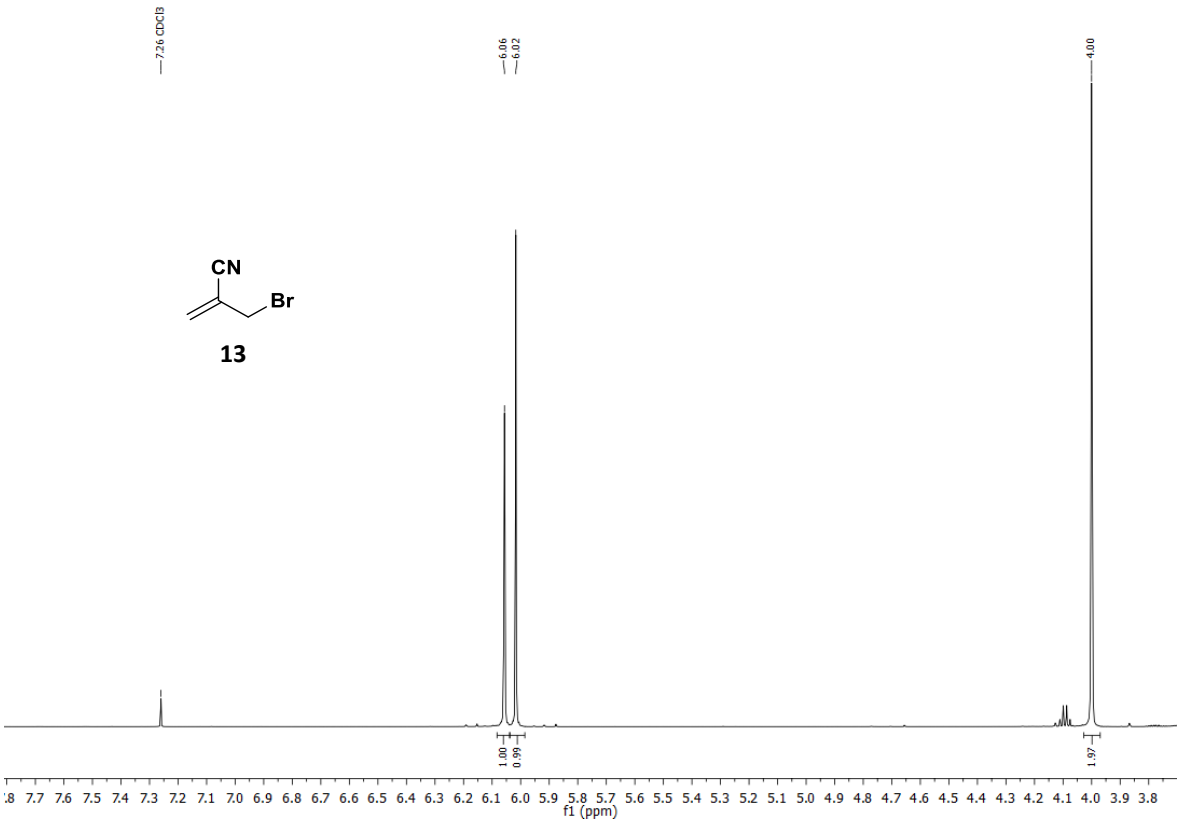
60
55
f1 (ppm)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4.00
CN
Br
13
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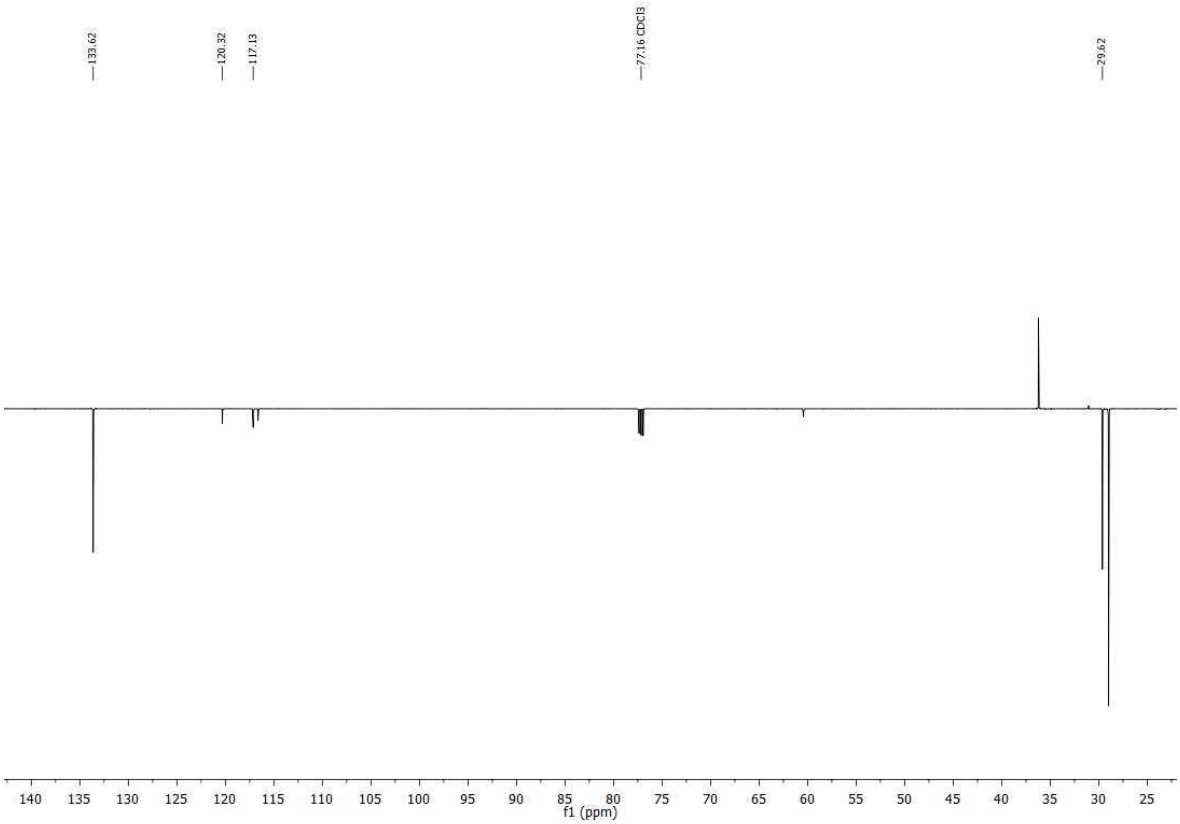
0.99
1.97
f1 (ppm)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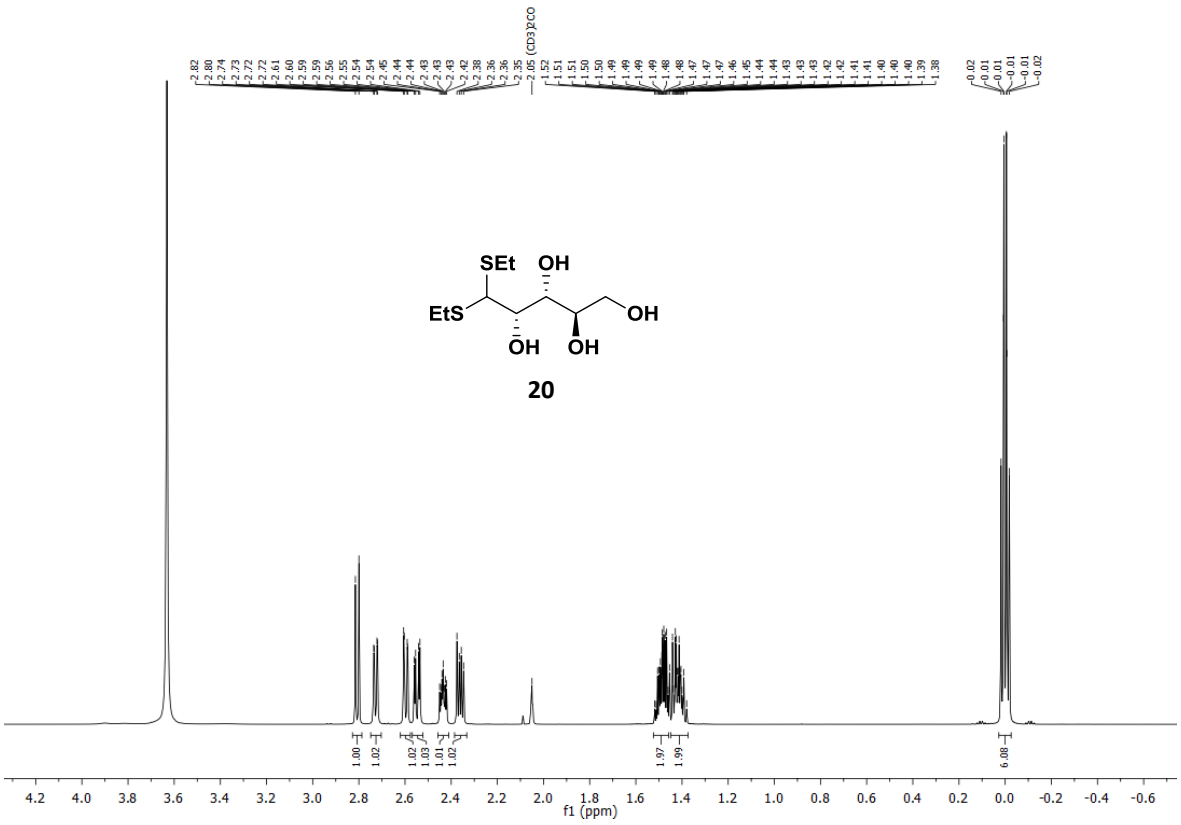
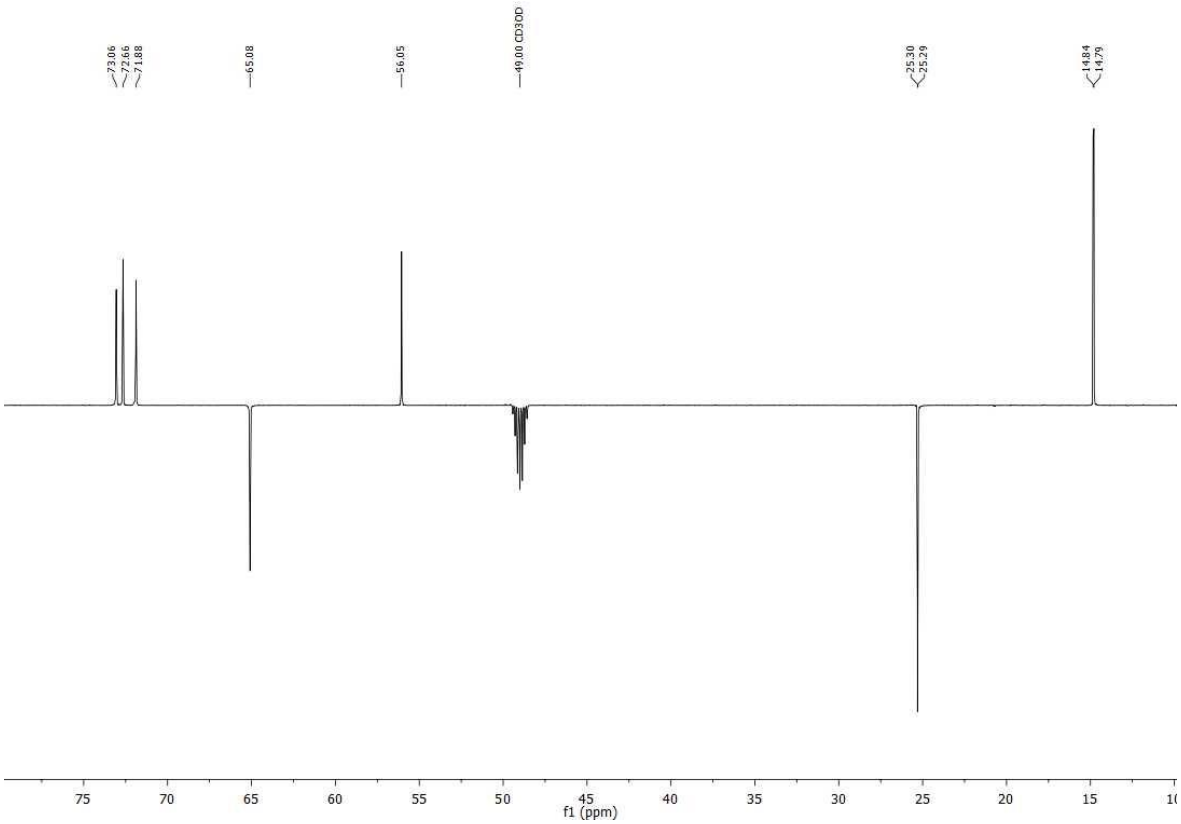
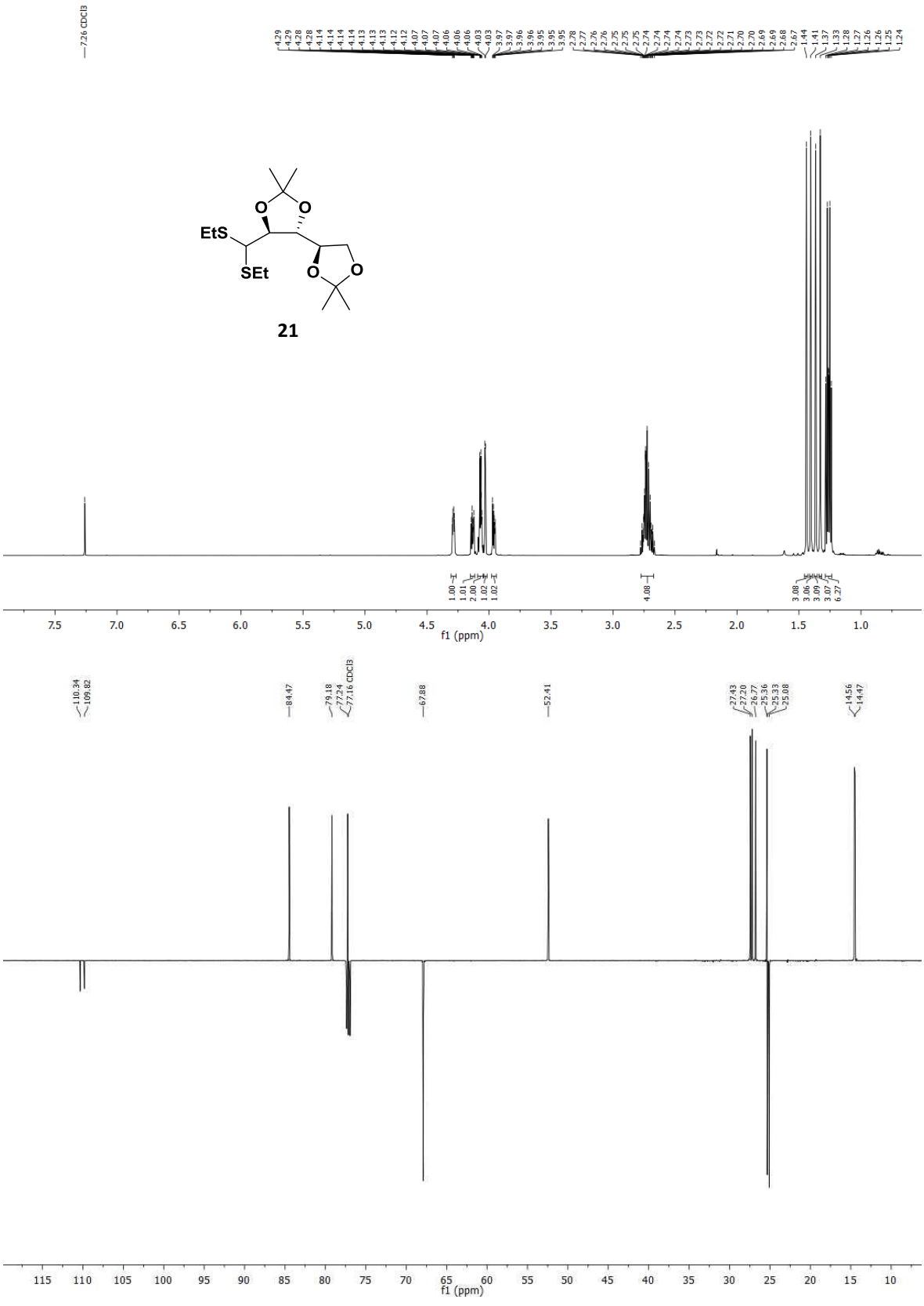
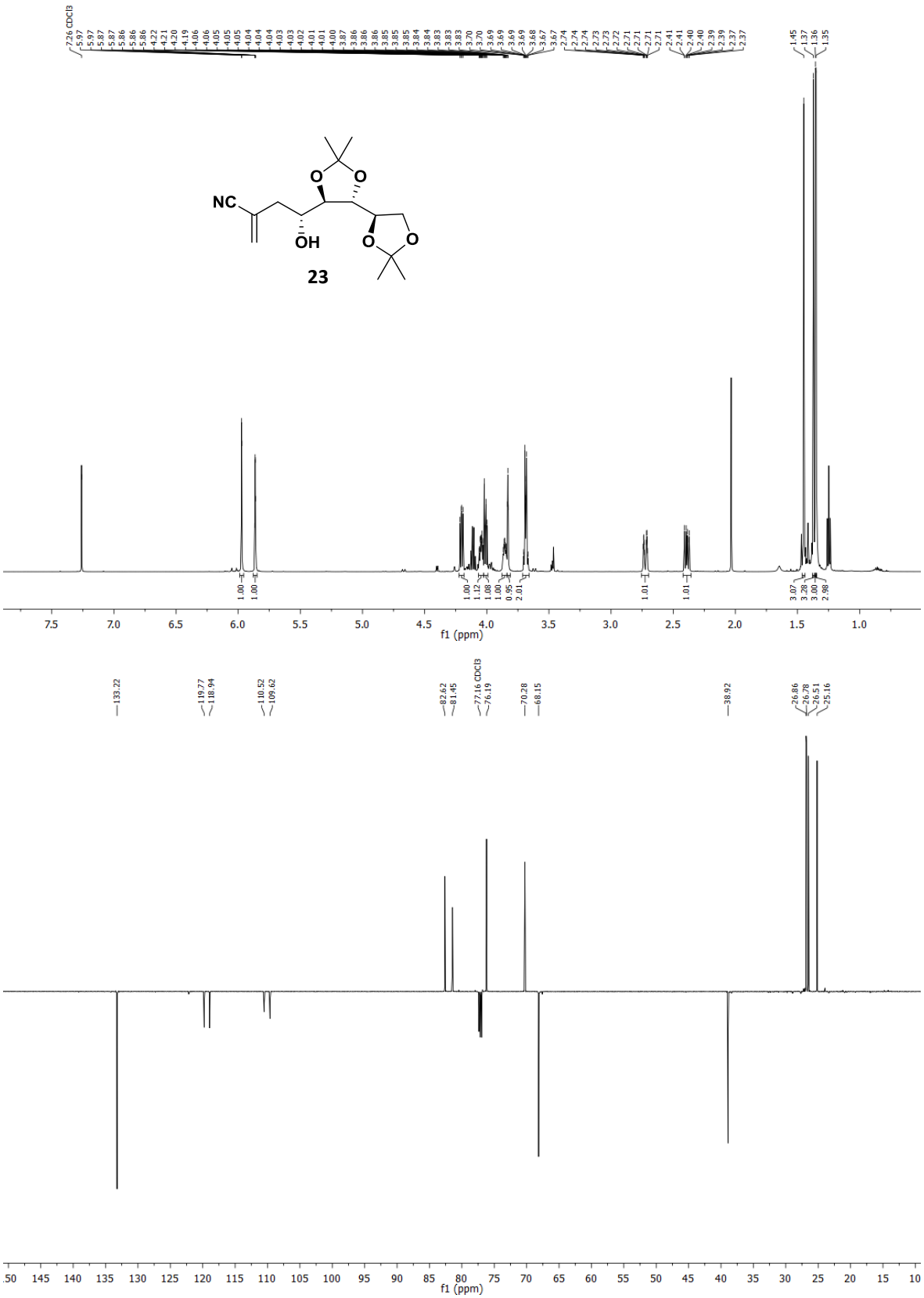
120.32
117.13
77.16 CDCl3
29.62
f1 (ppm)


SEt
OH
EtS
OH
OH
OH
20
f1 (ppm)


49.00 CD3OD
f1 (ppm)


7.26 CDCl3
4.29 4.29 4.28 4.28 4.14 4.14 4.14 4.13 4.13 4.12 4.12 4.07 4.07 4.07 4.06 4.06 4.06 4.03 3.97 3.97 3.96 3.96 3.95 3.95 3.95 2.78 2.77 2.76 2.76 2.75 2.75 2.74 2.74 2.74 2.74 2.73 2.73 2.72 2.72 2.71 2.70 2.70 2.69 2.69 2.68 2.67 1.44 1.41 1.37 1.33 1.28 1.27 1.26 1.26 1.25 1.24
EtS
SEt
O
O
O
O
21
1.00 1.01 2.00 1.02 1.02 4.08 3.08 3.06 3.09 3.07 6.27
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)
110.34 109.82 84.47 79.18 77.24 77.16 CDCl3 67.88 52.41 27.43 27.20 26.77 25.36 25.33 25.08 14.56 14.47
115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10
f1 (ppm)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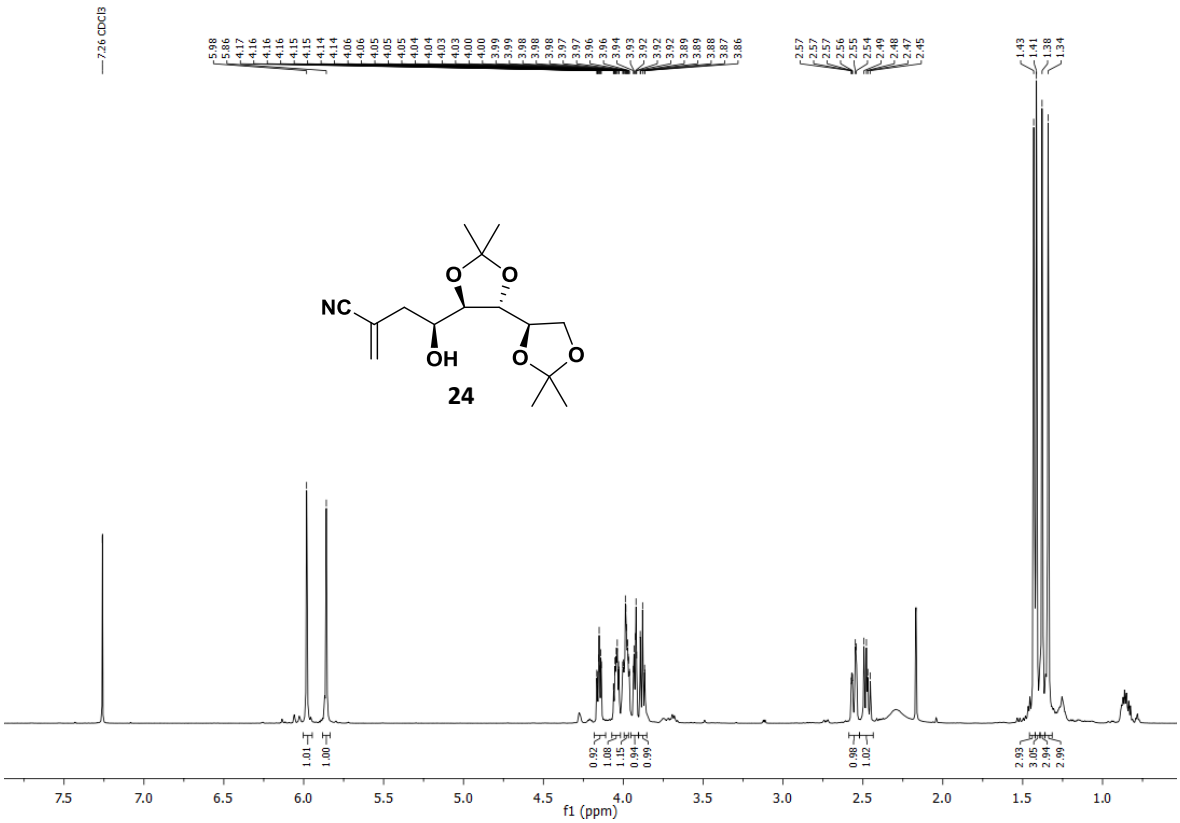
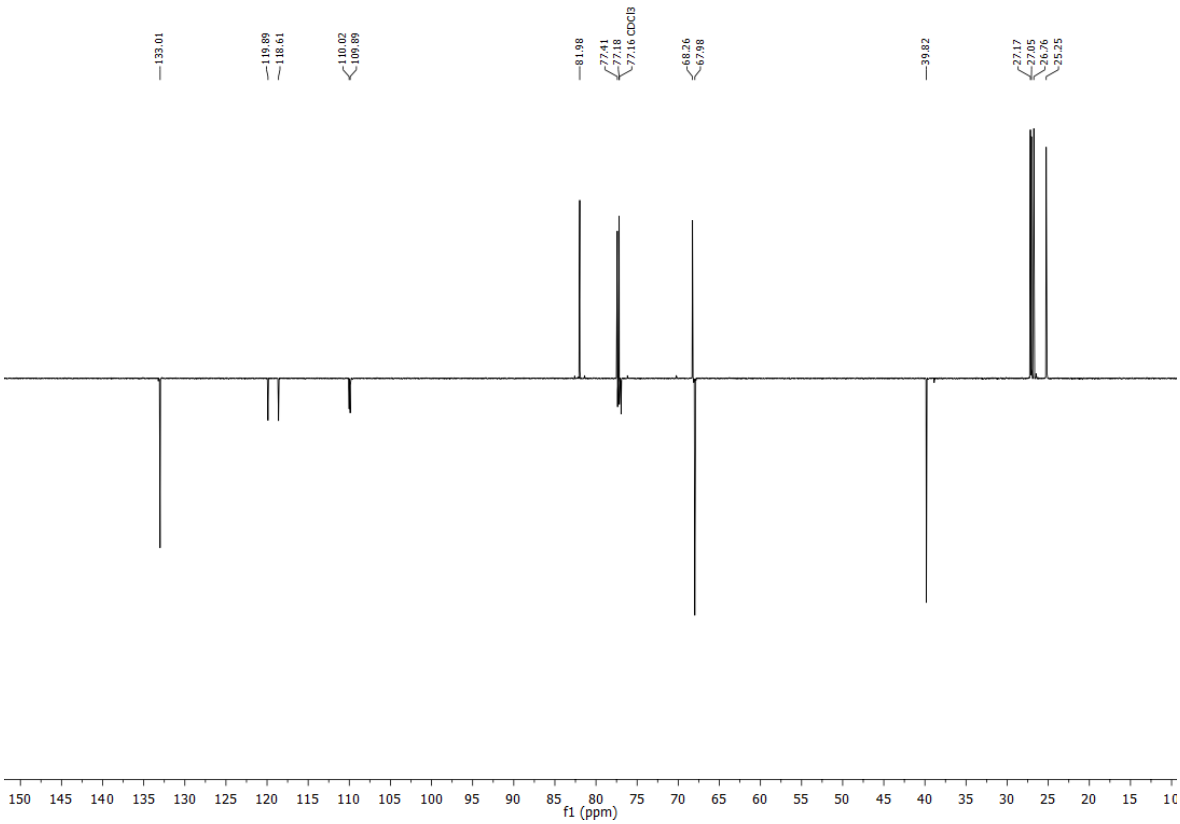
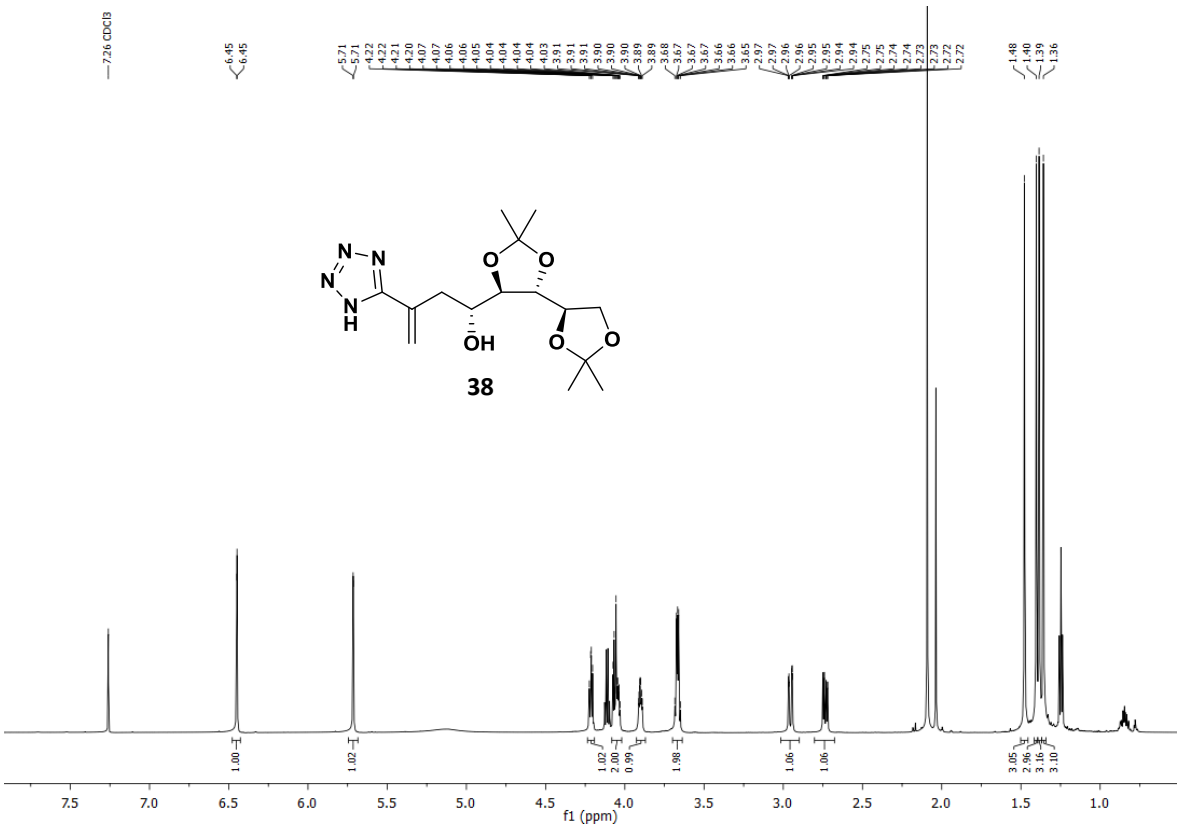
O
O
O
23
f1 (ppm)
f1 (ppm)



24

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6.45
5.71
5.71
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4.20
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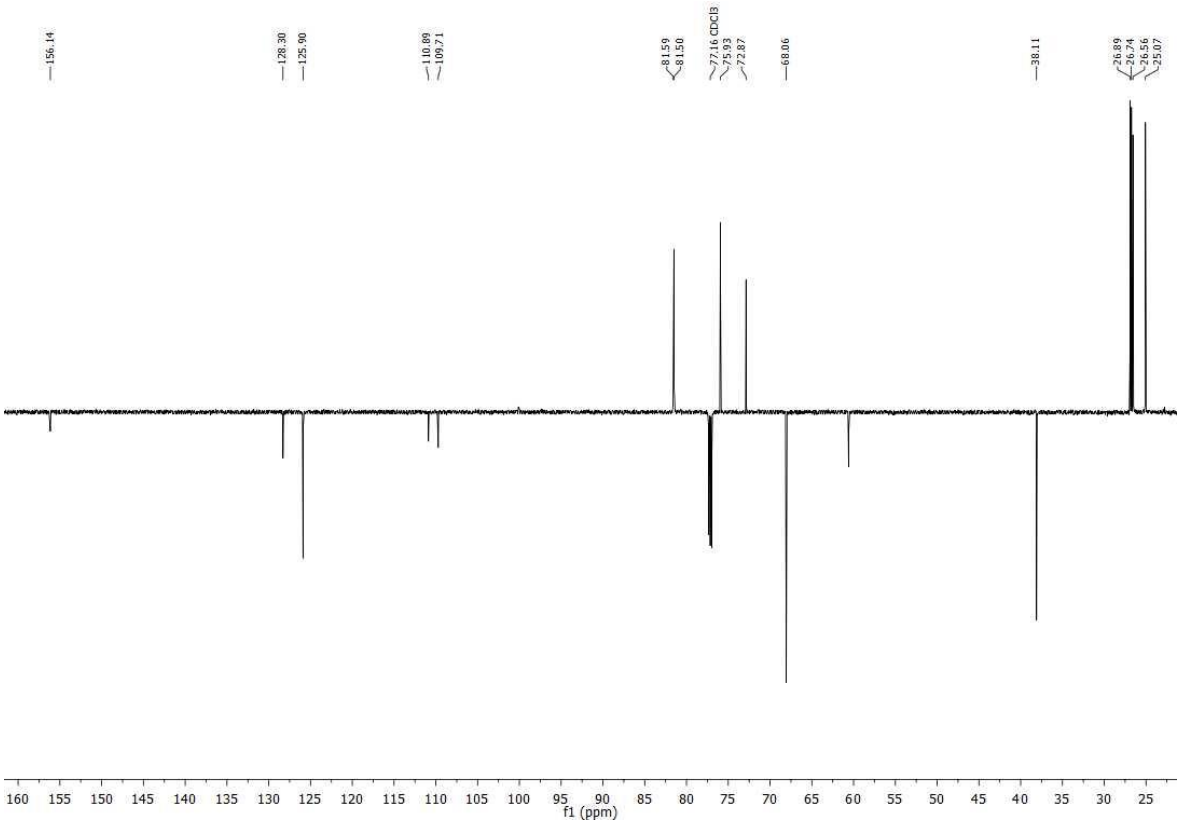
4.07
4.06
4.06
4.06
4.05
4.04
4.04
4.04
4.04
4.03
3.91
3.91
3.90
3.90
3.90
3.89
3.89
3.68
3.67
3.67
3.67
3.66
3.66
3.65
2.97
2.97
2.96
2.96
2.95
2.95
2.94
2.94
2.75
2.75
2.74
2.74
2.74
2.73
2.73
2.72
2.72
1.48
1.40
1.39
1.36
N
N
N
N
H
O
O
O
O
OH
38
1.00
1.02
1.02
2.00
0.99
1.98
1.06
1.06
3.05
2.96
3.16
3.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)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38.11
26.89
26.74
26.56
25.07
160
155
150
145
140
135
130
125
120
115
110
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100
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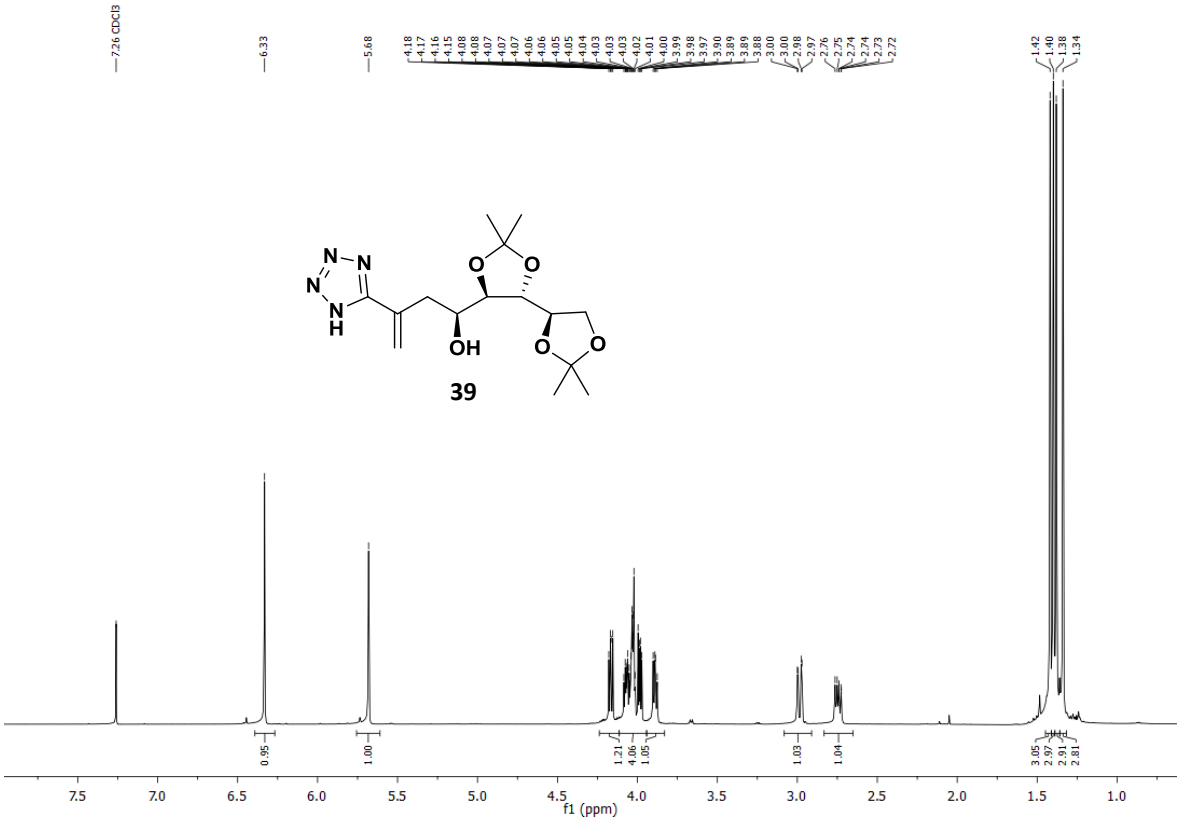
90
85
80
75
70
65
60
55
50
45
40
35
30
25
f1 (ppm)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4.05
4.05
4.04
4.03
4.03
4.03
4.02
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3.97
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3.89
3.89
3.88
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2.76
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2.73
2.72
1.42
1.40
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1.34
N
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N
H
O
O
OH
O
O
39
0.95
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1.21
4.06
1.05
1.03
1.04
3.05
2.97
2.91
2.81
7.5
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6.5
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4.5
4.0
3.5
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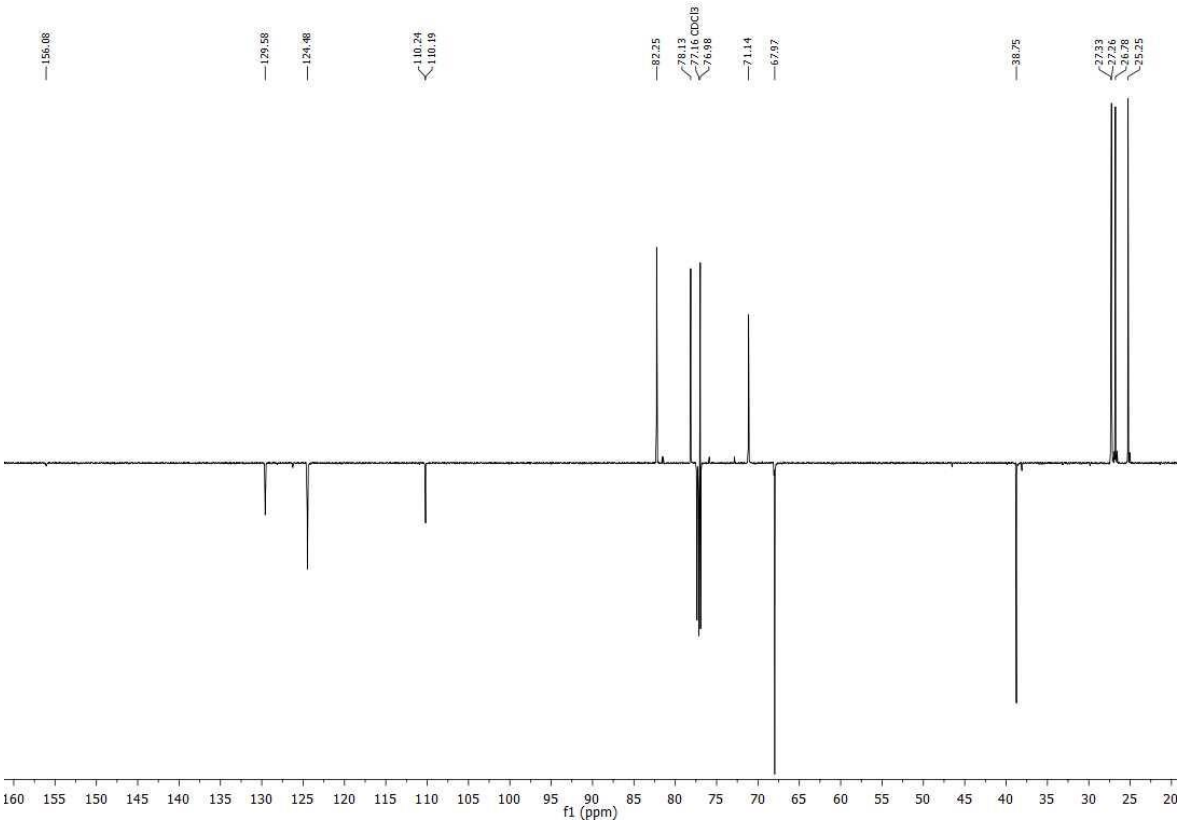
1.5
1.0
f1 (ppm)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27.26
26.78
25.25
160
155
150
145
140
135
130
125
120
115
110
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55
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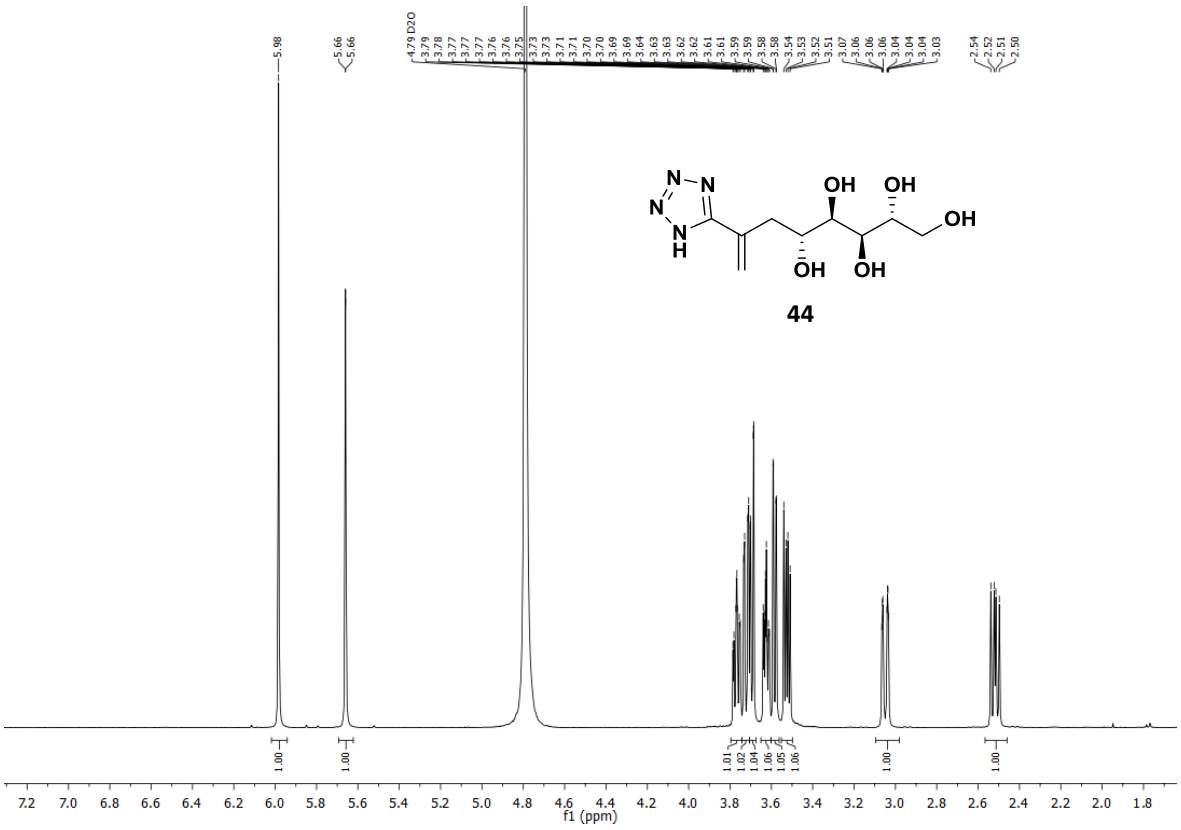
25
20
f1 (ppm)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3.73
3.73
3.71
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3.06
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3.04
3.04
3.04
3.03
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2.50
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N
N
H
OH
OH
OH
OH
OH
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1.00
1.01
1.02
1.04
1.06
1.05
1.06
1.00
1.00
7.2
7.0
6.8
6.6
6.4
6.2
6.0
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5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
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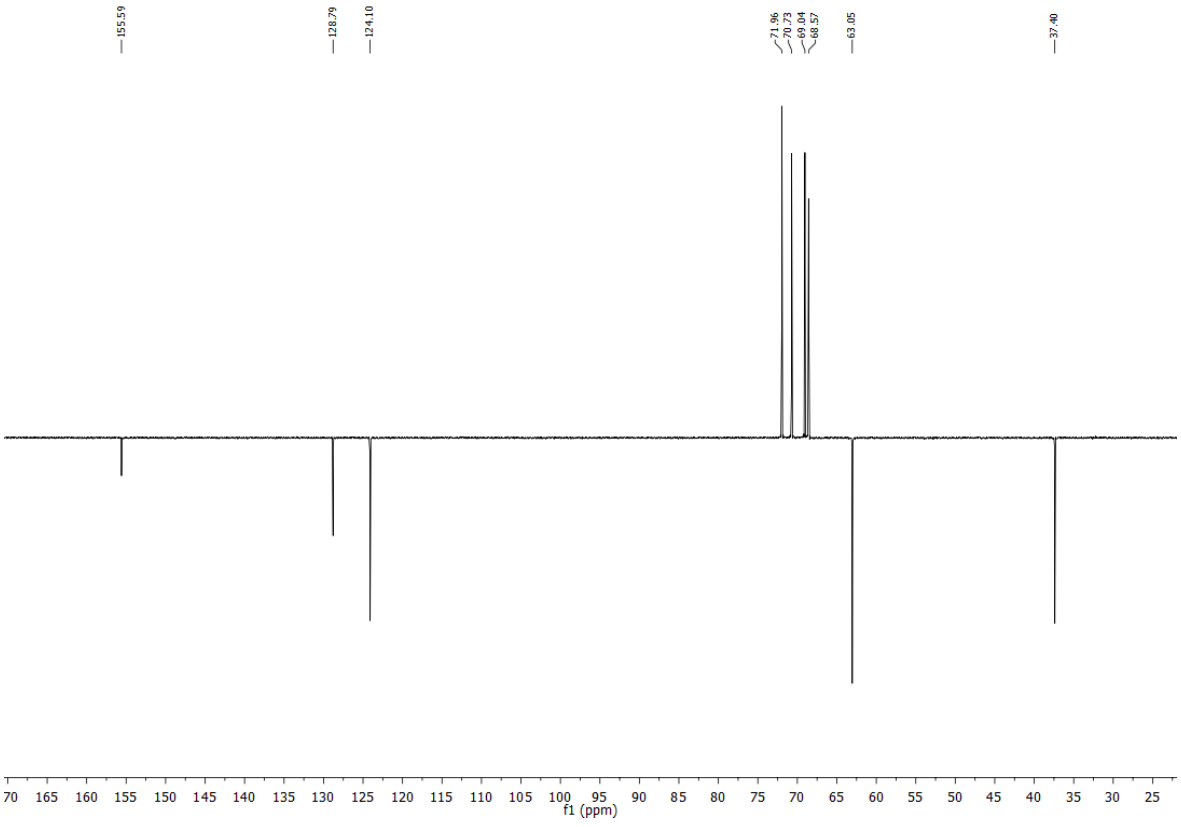
3.0
2.8
2.6
2.4
2.2
2.0
1.8
f1 (ppm)

44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69.04
68.57
63.05
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50
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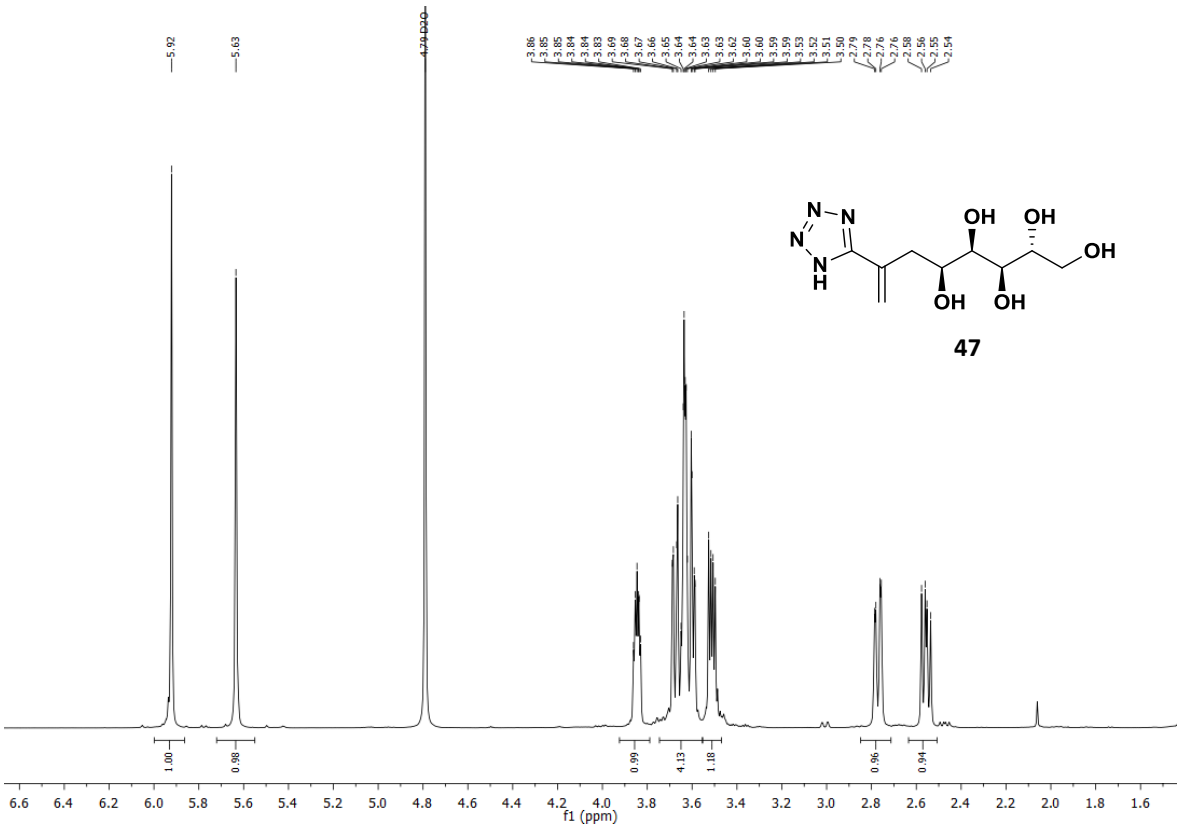
30
25
f1 (ppm)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3.52
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2.58
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0.98
0.99
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6.4
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6.0
5.8
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5.4
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5.0
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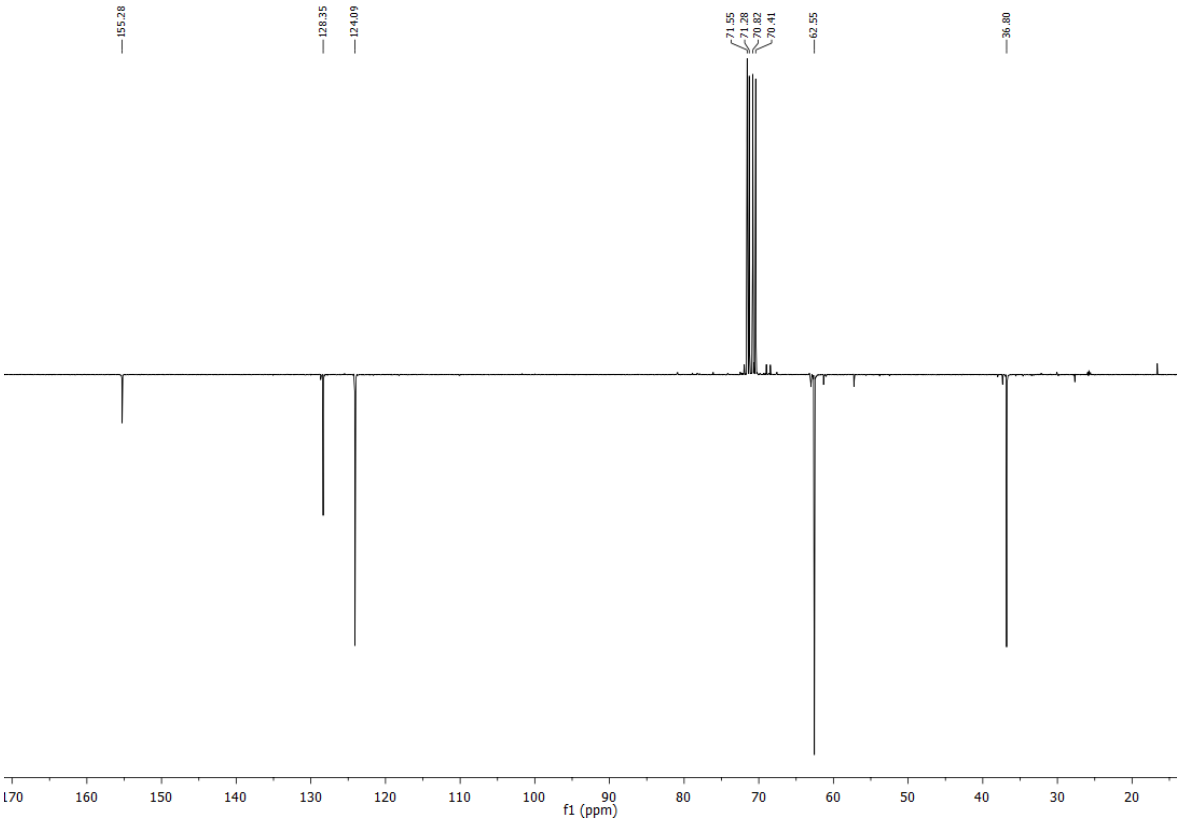
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
f1 (ppm)

N
N
N
N
H
OH
OH
OH
OH
OH

47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62.55
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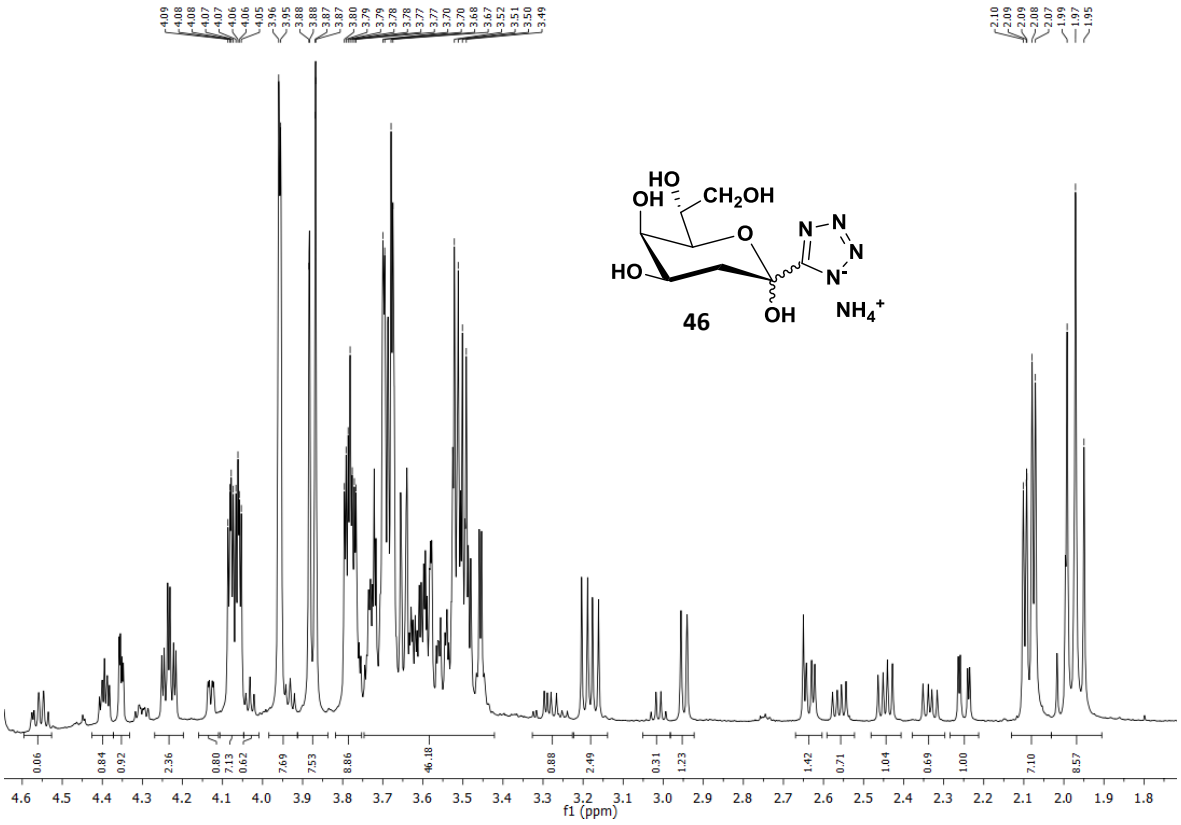
80
70
60
50
40
30
20
f1 (ppm)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CH2OH
O
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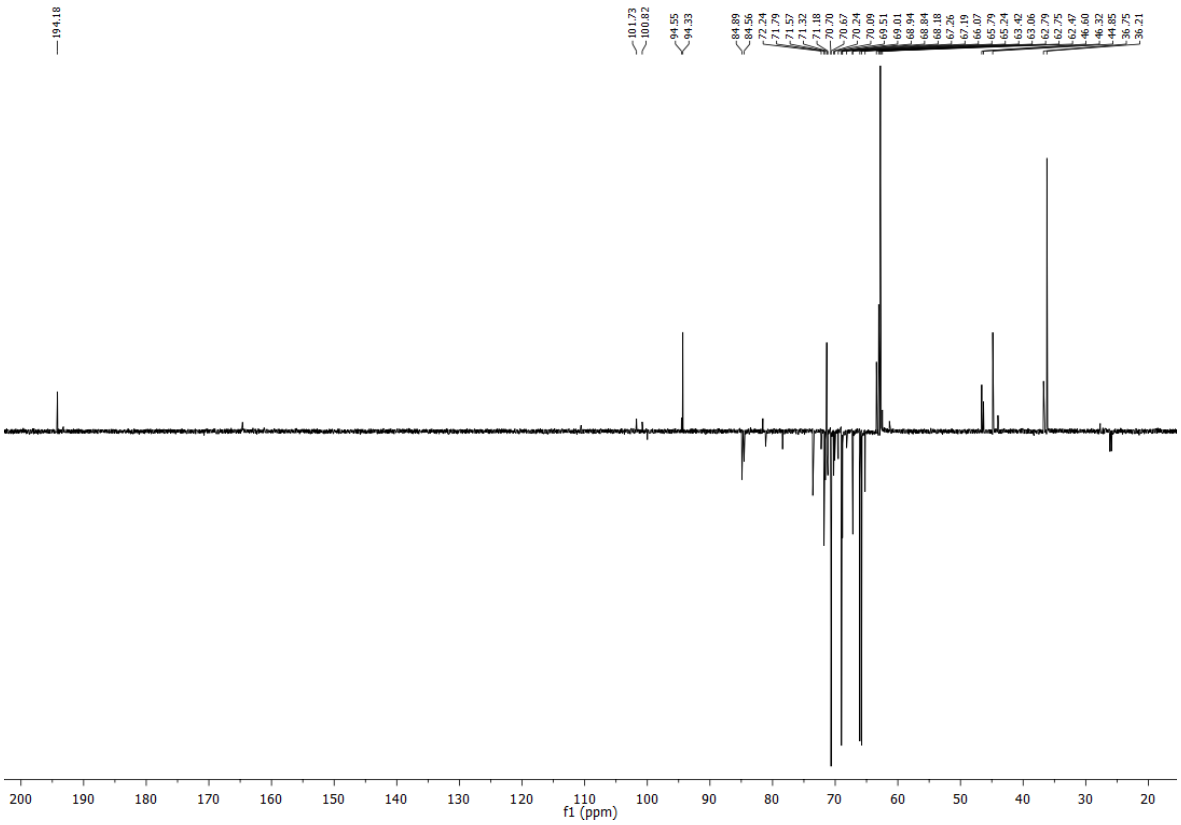
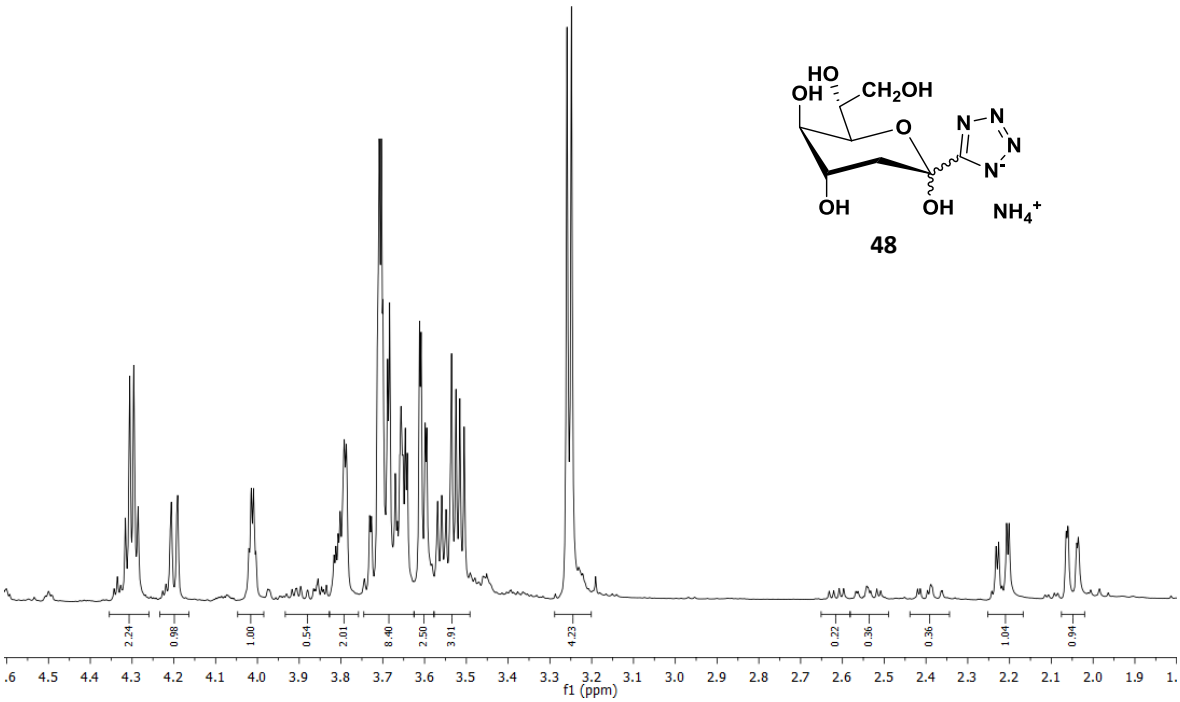
N
N
N
N-
OH
NH4+
46
f1 (ppm)


f1 (ppm)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CH2OH
O
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OH
OH
NH4+
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0.98
1.00
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2.01
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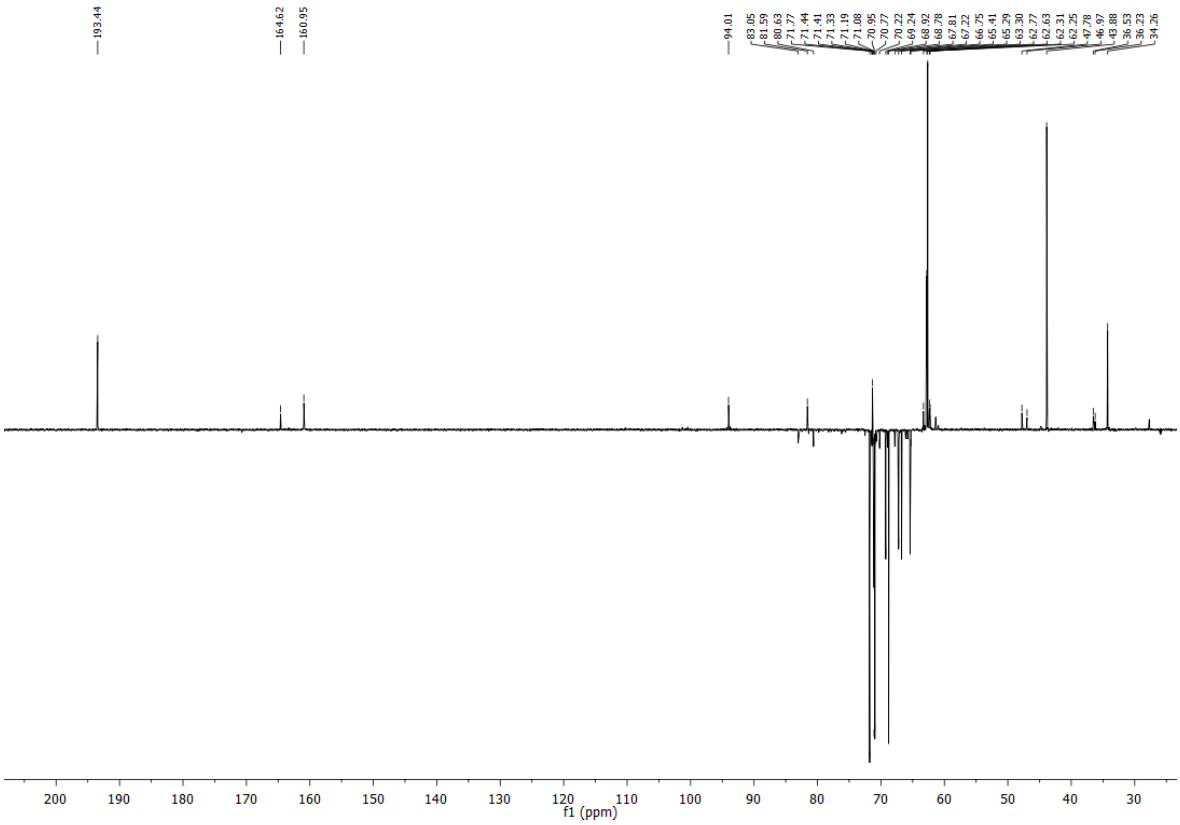
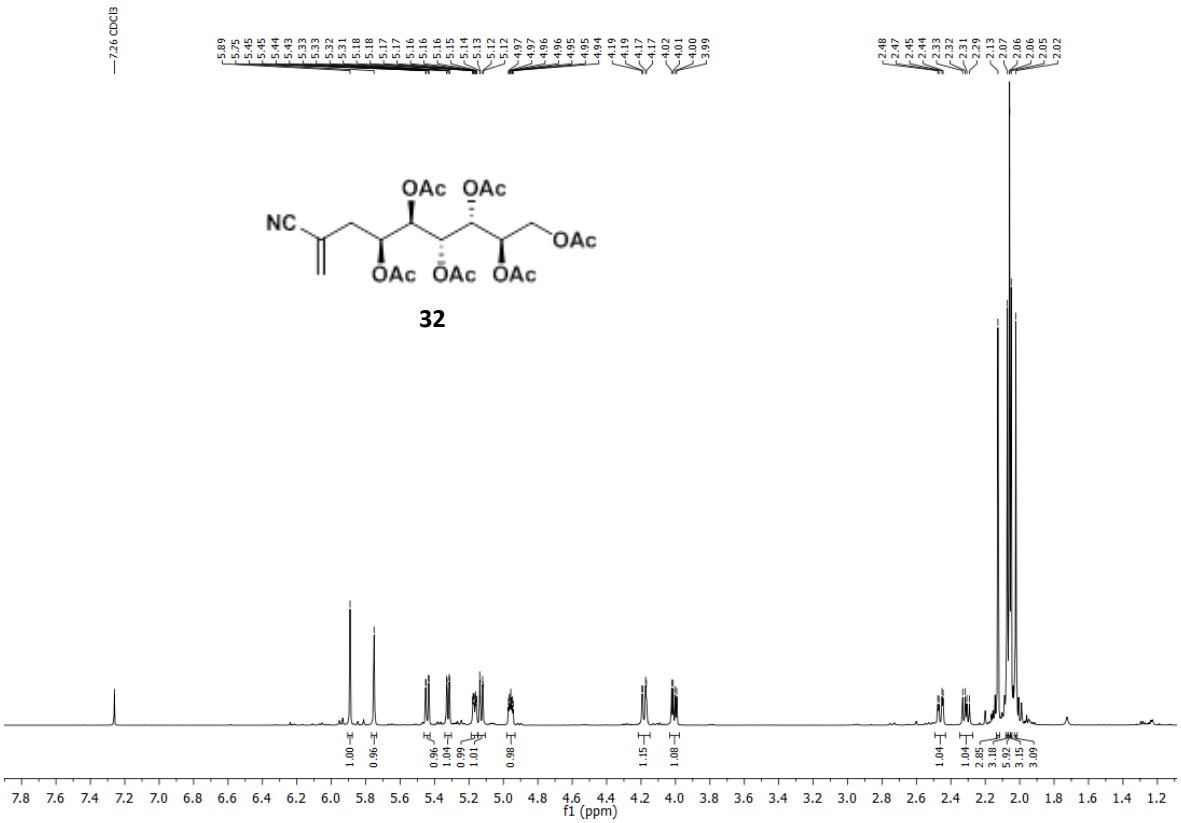
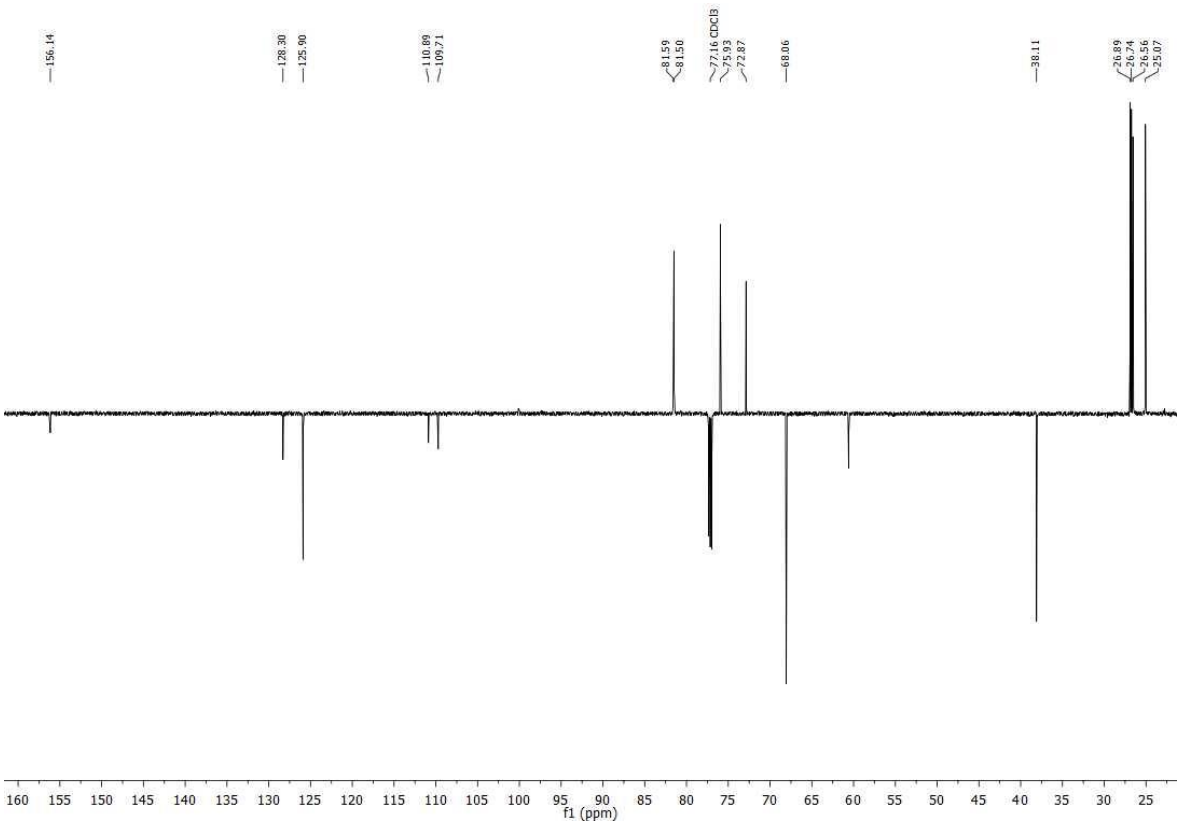
2.50
3.91
4.23
0.22
0.36
0.36
1.04
0.94
f1 (ppm)


193.44
164.62
160.95
94.01
f1 (ppm)


7.26 CDCl3
NC
OAc
OAc
OAc
OAc
OAc
OAc
f1 (ppm)

32


156.14
128.30
125.90
110.89
109.71
81.59
81.50
77.16 CDCl3
75.93
72.87
68.06
38.11
26.89
26.74
26.56
25.07
f1 (ppm)

IV Appendix

Abstract

This thesis consists of two projects. The first project comprises a flexible synthetic access towards *N*-acetylgalactosamine (GalNAc) and *N*-acetylidosamine (IdoNAc). GalNAc, as part of glycoproteins, can be found in a wide range of invertebrates, mammals and plants. It serves as link between the saccharide chain and the protein moiety. These proteins are known for their pivotal role in different receptor processes and cell-cell-interactions. Hence, a synthetical access towards this compound have been attracting a lot of interest. We have developed a novel route towards GalNAc, starting from the non-carbohydrate compound tartaric acid. This compound already provides two of the four desired stereogenic centers. In this synthesis, the carbohydrate backbone is build up *via* Horner-Wadsworth-Emmons (HWE) elongation of a previously oxidized threitol. After the compound is reduced, the oxygen moiety is introduced *via* Sharpless epoxidation. Another oxidation-HWE sequence paves the way for the Tsuji-Trost type epoxide opening, leading to a nucleophilic substitution of an azide. Taken together, this approach enables the establishment of the desired oxygen and nitrogen functions, both stereo- and regioselective. Furthermore, it shows an advantageous flexibility as it enables the synthesis of four different carbohydrate isomers. Not only was the D configuration of GalNAc synthesized, but also the unnatural L configuration. In addition, the D configuration of the peracetylated IdoNAc was prepared as a proof of concept.

The second project comprises a concise synthetic route towards ulosonic acid bioisosteres. Ulosonic acids are an important class of carbohydrates, including well known representatives as 3-deoxy-α-D-*manno*-oct-2-ulosonic acid (Kdo), 2-keto-3-deoxy-D-*glycero*-D-galactononic acid (Kdn) and *N*-acetylneuraminic acid (Neu5Ac). As part of the lipopolysaccharides (LPS) and capsular polysaccharides (CPS, K-antigen), these carbohydrates can be found on entirely all bacteria surfaces. We have developed a synthetic approach to access tetrazole derivatives of these compounds. Tetrazoles have shown to be ideal analogues for the bioisosteric replacement of carboxylic acids in several drugs, positively influencing their metabolic properties. The presented route features indium-mediated allylation with subsequent [2 + 3]-cycloaddition as key steps. After ozonolysis, this route leads to the tetrazole derivative of Kdo and its corresponding C-4 epimer. The route is flexible enough to be adapted to the preparation of further tetrazole bioisosteres of ulosonic acids as *N*-acetylneuraminic acid or 3-deoxy-D-*arabino*-heptulosonic acid.

Zusammenfassung

Diese Dissertation setzt sich aus zwei Projekten zusammen. Das erste Projekt umfasst einen flexiblen, synthetischen Zugang zu *N*-Acetylgalaktosamin (GalNAc) and *N*-Acetylidosamin (IdoNAc). GalNAc, als Teil von Glykoproteinen, kann in einer Vielzahl von Wirbeltieren, Säugetieren und Pflanzen gefunden werden. Es dient als Verbindung zwischen Proteinen deren Saccharidketten. Diese Proteine sind bekannt für ihre zentrale Rolle in den unterschiedlichsten Rezeptorprozessen und Zell-Zell-Interaktionen. Daher ist es von großem Interesse einen synthetischen Zugang zu diesen Verbindungen zu finden. Wir haben eine neue Synthese für GalNAc entwickelt, die von der Weinsäure ausgeht, da diese Verbindung bereits zwei der vier notwendigen stereogenen Zentren besitzt. In dieser Synthese wird das Kohlenhydratrückrad *via* Horner-Wadsworth-Emmons-Verlängerung (HWE-Verlängerung) eines zuvor oxidierten Threitols aufgebaut. Nachdem diese Verbindung reduziert wurde, wird die Sauerstofffunktion *via* Sharpless-Epoxidierung eingeführt. Eine weitere Oxidation-HWE-Sequenz macht eine Epoxidierung unter Tsuji-Trost-Bedingungen möglich, die zu einer nukleophilen Substitution eines Azids führt. Diese Vorgehensweise ermöglicht die stereo- und regioselektive Einführung einer Sauerstoff- und Stickstoff-Funktion. Weiters zeigt dieser Zugang eine hohe Flexibilität, da die Synthese von vier verschiedenen Kohlenhydratisomeren möglich ist. Es wurde nicht nur das D-, sondern auch das L-konfigurierte GalNAc synthetisiert. Als konzeptioneller Beweis wurde zusätzlich das peracetylierte L-IdoNAc hergestellt.

Das zweite Projekt umfasst einen synthetischen Zugang zu Ulosonsäure-Bioisosteren. Ulosonsäuren sind eine wichtige Gruppe der Kohlenhydrate, zu der bekannte Stellvertreter wie 3-Deoxy-α-D-*manno*-oct-2-ulosonsäure (Kdo), 2-Keto-3-deoxy-D-*glycero*-D-galactononsäure (Kdn) and *N*-Acetylneuraminsäure (Neu5Ac) gehören. Als Teil von Lipopolysacchariden (LPS) und Kapselpolysacchariden (CPS, K-Antigene) findet man diese Kohlenhydrate auf jeder Bakterienoberfläche. Wir haben einen synthetischen Zugang zu Tetrazolderivaten dieser Verbindung entwickelt. Tetrazole sind die idealen bioisosterischen Analoga für Carbonsäuren in der Medikamentenentwicklung, da sie deren metabolischen Eigenschaften positiv beeinflussen. Die hier vorgestellte Route beinhaltet eine Indium-mediierte Allylierung mit anschließender [2 + 3]-Cycloaddition als Schlüsselschritte. Nach einer anschließenden Ozonolyse wurde so Tetrazol-Kdo und sein C-4-Epimer hergestellt. Dieser Ansatz ist flexibel genug, um für die Herstellung weiteren Tetrazol-Bioisosteren von Ulosonsäuren, wie *N*-Acetylneuraminsäure (Neu5Ac) oder 3-Desoxy-D-*arabino*-heptulosonsäure adaptiert werden zu können.

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17th Austrian Chemical Days

University of Salzburg, Salzburg, Austria

Poster presentation: *A concise and flexible route towards ulosonic acid isosteres*

08/2016

28th International Carbohydrate Symposium

New Orleans, USA

Oral presentation: *N-Acetylgalactosamine: A novel and flexible approach starting from tartaric acid*

02/2016

20th Carbohydrate Workshop

BOKU, Wien, Austria

Oral presentation: *Synthesis of N-Acetylgalactosamine starting from tartaric acid*

09/2015

16th Austrian Chemical Days

University of Innsbruck, Innsbruck, Austria

Oral presentation: *Synthesis of N-Acetylgalactosamine starting from tartaric acid*

02/2014

18th Carbohydrate Workshop

TU Graz, Graz, Austria

Oral presentation: *Synthesis of N-Acetylgalactosamine starting from tartaric acid*