Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Natural Sciences
Department of Chemistry

Johannes Tveit

Initial investigations into the synthesis of 1-*O*-(3-deoxy-3-linolenoyl-amide-sulfuquinovosyl) glycerol

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Supervisor: Nebojsa Simic
Co-supervisor: Sondre Nervik
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Declaration

I hereby declare that the work presented in this thesis has been conducted individually and in accordance of the rules and regulations of the Master in Chemistry (2 years) program at the Norwegian University of Science and Technology. The work was performed in the time between September 2019 and May 2021 and was supervised by associate professor Nebojša Simić and co-supervised by Ph.D. candidate Sondre Nervik.

Trondheim, 15$^{\text{th}}$ of May, 2021

Johannes Tveit

Preface

I wish to thank my supervisor, associate professor Nebojša Simić, and co-supervisor, Ph.D. candidate Sondre Nervik, for the opportunity to work on such an exciting project, and for the extensive guidance provided over the past two years. It has been a pleasure to work in this research group.

My colleagues in the lab; Petros Siapkaras, Ragnar Stene, Wojtek Swiergon, Michelle Vogts and Marcus de Bourg, as well as Sondre Nervik, have made this experience unforgettable. The topics of discussion, the way of speaking, the shared pain of failed experiments and general camaraderie were highly cherished. I would also like to thank Roger Aarvik for providing chemicals, materials and good moods, and Susana Villa Gonzalez for conducting mass spectrometry analysis.

Finally I wish to thank Marthe Kristine Sve, whose love and support has been crucial for me during this project.

Abstract

The work presented herein has been a part of the total synthesis research towards 1-*O*-(3-*O*-linolenoyl-6-deoxy-6-sulfo-α-D-glucopyranosyl)-glycerol (**1**) and its derivatives. The goal was to investigate methods for insertion of optically pure 1,2-*O*-isopropylidene-glycerol in the anomeric position of 2,4,6-tri-*O*-protected-3-azido-3-deoxy-α-D-glucopyranoses, with a focus on Schmidt glycosylation. Additionally, thioglucoside as glycosyl donor and oxidation of allyl moiety were looked into as alternative methods of introducing chirally pure glycerol moieties.

Starting from 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose, acetyl and benzyl protected glycosyl donors were synthesised. Schmidt glycosylation with acetyl lead exclusively to the β anomer. In the case of benzyl protected glycosyl donor, both product anomers were obtained. With both protecting groups, isomerization of the glycerol moiety presented a persistent challenge. It is unknown whether this was due to an undetermined factor or a general trend in Schmidt glycosylation. Initial testing of the benzyl protected phenyl thioglucoside donor indicated this donor to be unsuitable in this project.

As a proof of concept, the method deployed by the research group was tested on 3-azido-3-deoxy derivatives. Introduction of anomeric allyl ether through Fischer glycosylation with later oxidation of the double bond by Sharpless asymmetric dihydroxylation was successful, but did not provide a chirally pure glycerol moiety.

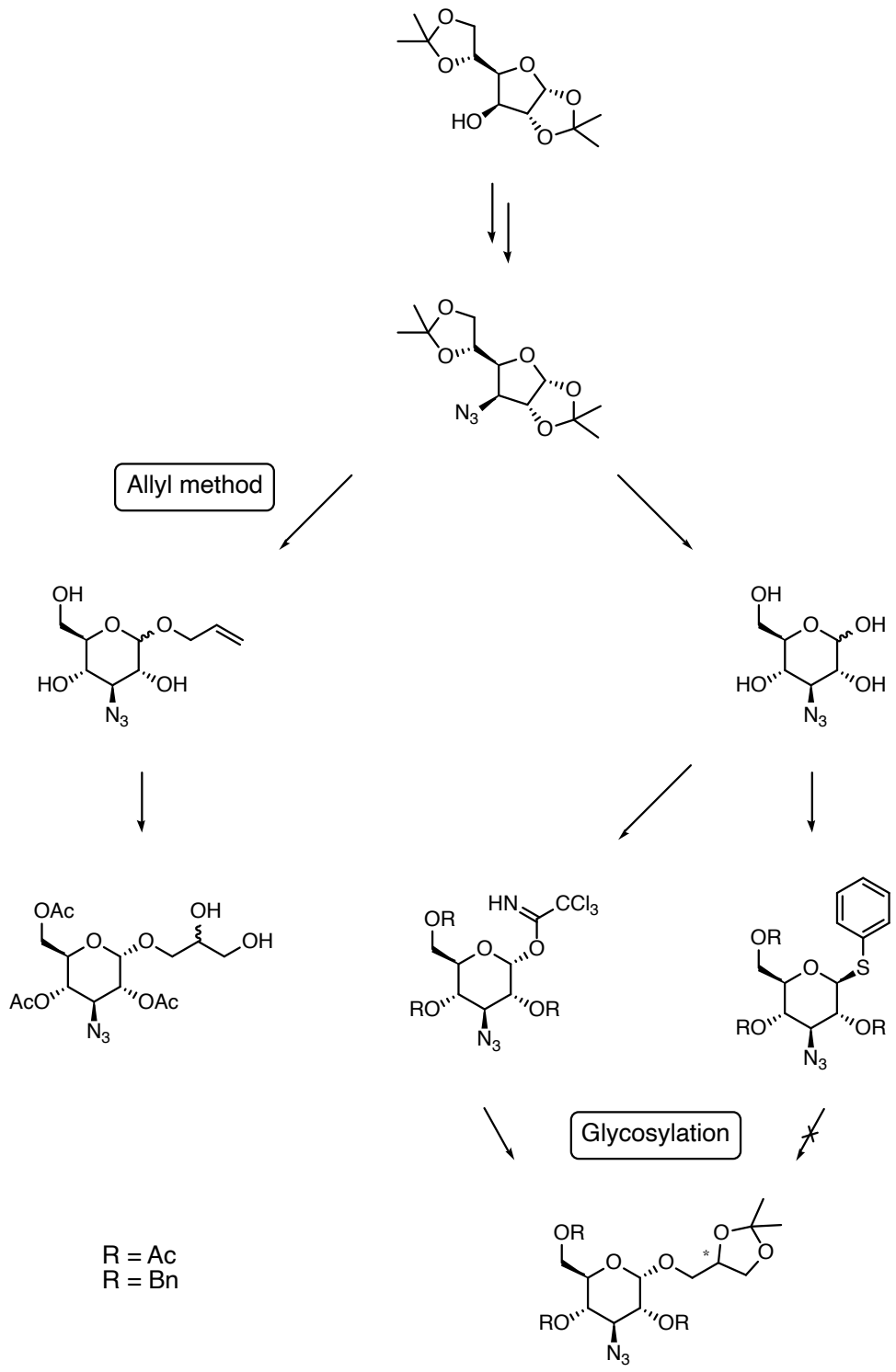
Sammendrag

Arbeidet som er presentert i denne oppgaven har vært en del av forskningen på totalsyntesen av 1-*O*-(3-*O*-linolenoyl-6-deoksy-6-sulfo-α-D-glukopyranosyl)-glyserol (**1**) og dets derivater. Målet med arbeidet var å undersøke metoder for å sette inn optisk ren 1,2-*O*-isoproyliden-glyserol i anomerisk posisjon av 2,4,6-tri-*O*-beskyttet-3-azid-3-deoksy-α-D-glukopyranose. Fokuset i arbeidet var på Schmidt glyckosylering, men bruk av tioglykosyl som glykosyldonor og oksidering av en allyl gruppe ble undersøkt som alternative metoder for å introdusere kiralt rent glyserol.

Acetyl- og benzyl-beskyttede glykosyl donorer ble laget fra 1,2;5,6-di-*O*-isopropyliden-α-D-glukofuranose. Schmidt glykosylering av acetylbeskyttede donorer førte eksklusivt til dannelse av β anomeren. Ved bruk av benzyl som beskyttelsesgruppe ble begge anomerene av produktet laget. Isomerisering av glyserolgruppen var et vedvarende problem med begge beskyttelsesgruppene. Det er uklart om dette var på grunn av en ukjent faktor som har blitt oversett eller om det er en generell trend ved Schmidt glykosylering. Innledende testing av benzylbeskyttet fenyltioglykosid indikerte at denne glykosyl donoren ikke var passende for dette prosjektet.

For å undersøke egnethet for 3-azid-3-deoksy derivater, ble metoden benyttet av forskningsgruppa utført. Allyleter ble introdusert ved Fischer glykosylering med påfølgende Sharpless asymmetrisk dihydroksylering. Dette resulterte i en glyserolgruppe som ikke var optisk ren.

Graphical abstract

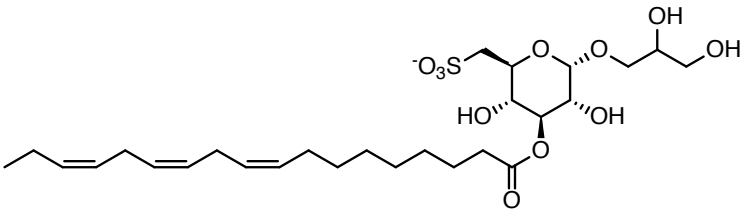


Contents

Symbols and Abbreviations

Abbreviation	**Explanation**
Ac_2O	Acetic anhydride
Ac	Acetate
ACN	Acetonitrile
$BF_3 \times Et_2O$	Boron trifluoride etherate
Bn	Benzyl
CCl_3CN	Trichloroacetonitrile
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	Dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	Dimethyl sulfoxide
FCC	Flash column chromatography
HPLC	High performance liquid chromatography
LA	Lewis acid
NIS	*n*-Iodosuccinimide
p-TsOH	*p*-Toluenesulfonic acid
PDC	Pyridinium dichromate
PG	Protecting group
rt	Room temperature (20 - 25 °C)
SM	Starting material
TCAI	Trichloroacetimidate
TLC	Thin-layer chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Ts	Tosyl / Toluensulfonyl

Numbered Compounds



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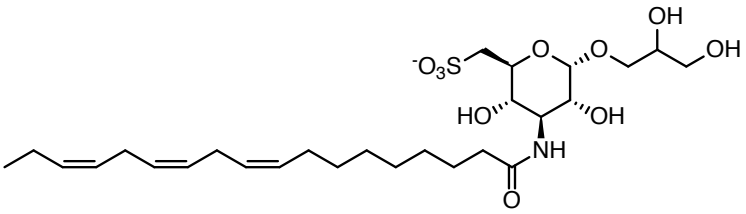

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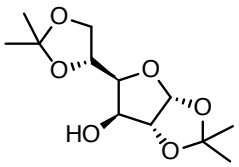

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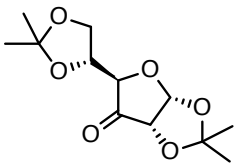

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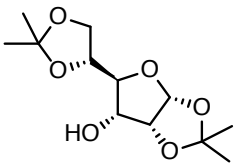

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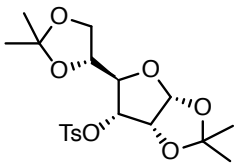

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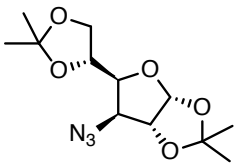

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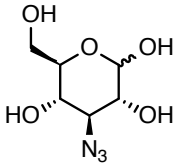

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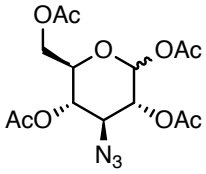

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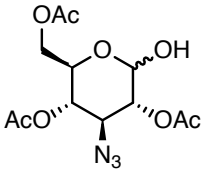

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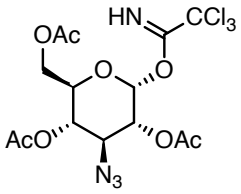

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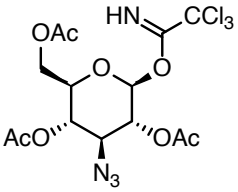

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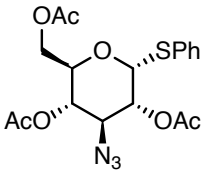

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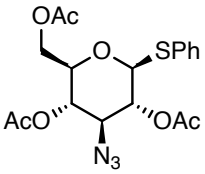

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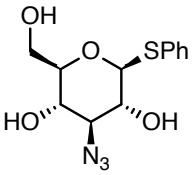

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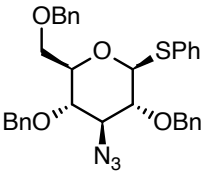

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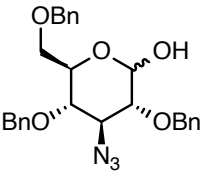

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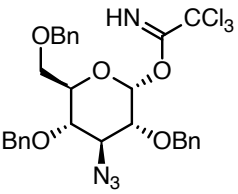

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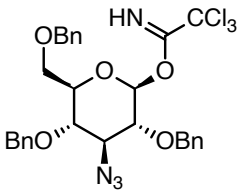

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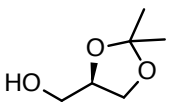

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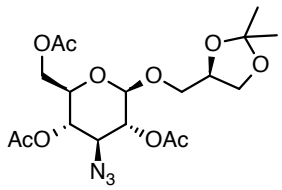

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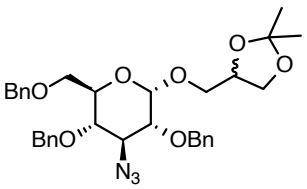

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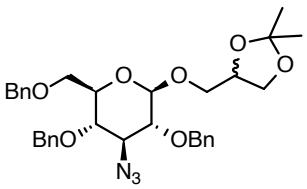

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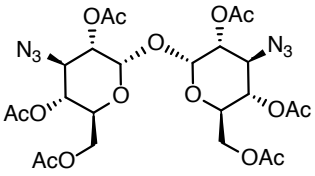

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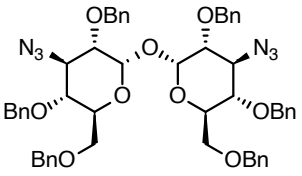

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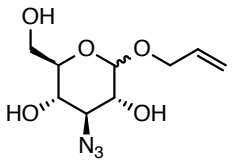

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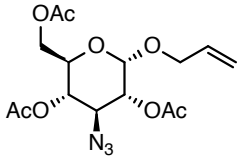

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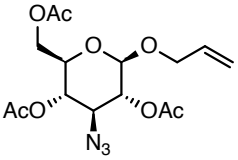

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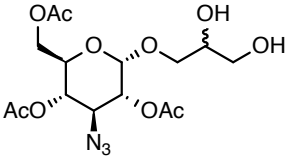

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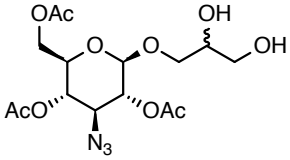

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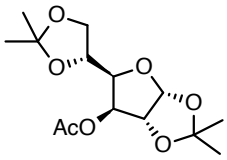

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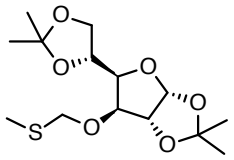


4b

1 Introduction

The use of plants for their therapeutic effect dates back to early man.[1] In ancient Greece, plants were studied and categorised. Several hundred years later, the first pure pharmacologically active compound from a plant, morphine, was isolated.[2] The purification and isolation of natural products was crucial to administration of precise dosages which did not vary with the age or source of the material.[2] During, and after, the 2nd World War microorganisms were also screened for compounds with pharmacological effect, due to the discovery of penicilin.[1,2] In the 1980s about 40% of the new drugs approved by the U.S. Food and Drug Administration were natural products or derived from natural products.[3] The isolation of natural compounds and synthesis of their derivatives is an important field in the development of pharmaceuticals today.

A group of natural products based on carbohydrates are the glycoglycerolipids, which are carbohydrates bearing a 1,2-diacyl-*sn*-glycerol moiety.[4] Glycogylcerolipids can be found in natural sources, including marine algea, cyanobacteria, and higher plants.[4–6] They have been shown to possess biological activities, such as anti-tumor, anti-viral and anti-inflammatory.[4,6] A subgroup of the glycoclycerolipids is the sulfoquinovosyl diacyl glycerols (SQDG), which has a sulfonic acid moiety instead of the 6-*O* moiety (Figure 1.1).

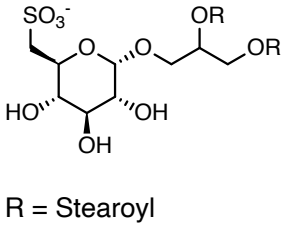
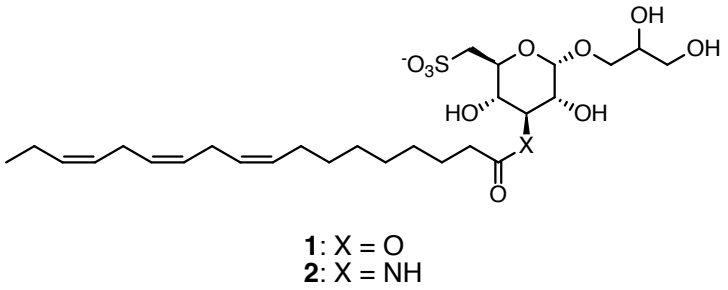


Figure 1.1. Example of SQDG.[7]

A novel compound, 1-*O*-(3-*O*-linolenoyl-6-deoxy-6-sulfo-α-D-glucopyranosyl)-glycerol (**1**, Figure 1.2), being structurally similar to SQDGs, was in 2015 isolated from the plant *Schlerochloa dura*, which has been applied in Serbian traditional medicine.[8] It was found

that **1** exhibited anti-inflammatory properties, by inhibiting release of arachidonic acid.[8] It was hypothesised that the inhibited release of arachidonic acid was due to **1** reducing the activity of the phospholipase A_2 enzyme.[8]



1: X = O
2: X = NH

Figure 1.2. 1-*O*-(3-*O*-linolenoyl-6-deoxy-6-sulfo-α-D-glucopyranosyl)-glycerol (**1**) extracted from *Schlerockloa dura*, and its amide derivative (**2**), the overall synthetic goal of this thesis.

The anti-inflammatory properties and structural similarity with SQDGs makes **1** interesting in the search for new drugs. Research into the total synthesis of **1** is conducted at the Department of Chemistry at the Norwegian University of Science and Technology. As a part of this research, the work presented herein studies the initial parts of the synthesis toward the amido-derivative (**2**), with focus on the glycosylation reaction and introduction of an enantiomerically pure glycerol moiety. It was suggested that an amide linkage could improve the potency of the novel compound **1**. An amide linkage could increase the stability towards hydrolysis, and consequently the substrate would spend longer time *in vivo*.[9] Additionally, he hydrogen on the amide could act as a hydrogen bond donor and affect the affinity towards the binding site.

1.1 General Carbohydrate Chemistry

Carbohydrates are a group of substances consisting of aliphatic polyhydroxy aldehydes or ketones, as well as their derivatives.[10,11] They can be divided into two groups, monosaccharides, and complex saccharides. Monosaccharides can not be split into smaller subunits by aqueous hydrolysis.[10,12] Complex saccharides, on the other hand, consist of two or more monosaccharides through a glycosidic bond, and can therefore be split into smaller

subunits by treatment with aqueous acids. The focus in this thesis is in the group of monosaccharides, and so the complex saccharides will not be payed much more attention.

1.1.1 Nomenclature

Monosaccharides in their simplest form contain only carbon, hydrogen and oxygen and have the formula $C_n(H_2O)_n$, however, derivatives often deviate from this general formula.[10,13] The skeletons of monosaccharides usually contain 5 or 6 carbon and are called pentoses and hexoses, respectively.[13] In nomenclature, pentoses and hexoses are further distinguished as aldose (aldehydes) and ketose (ketones) (Figure 1.3). A numbering system is utilized to aid nomenclature, where numbering starts such that the carbonyl group has the lowest possible number, usually 1 or 2.[13] A monosaccharide having a substituent on carbon number n would be called n-*C*-substituted. Similar if a substituent is at the hydroxy group of C-m, the monosaccharide is said to be m-*O*-substituted, see 3-*O*-methyl-D-glucopyranose (Figure 1.3). Additionally, monosaccharides are divided into the D- and L-series. If the highest numbered chiral carbon has the same configuration as D-glyceraldehyde, the monosaccharide is in the D-series.[10,13] If the carbon has the same configuration as L-glyceraldehyde belongs it to the L-series. Monosaccharides can exist

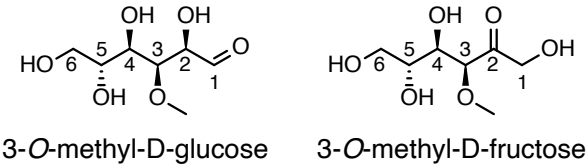
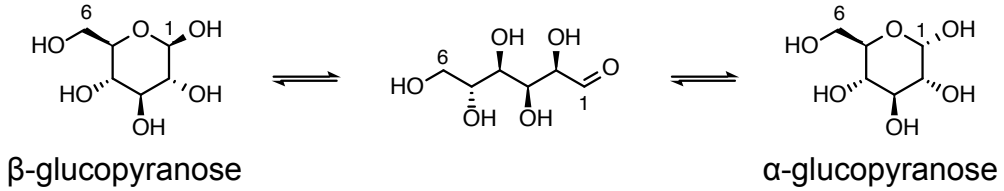


Figure 1.3. Numbering of aldohexose (left) and ketohexose (right).[13]

both as cyclic and acyclic, where cyclic is the most thermodynamically favourable for glucose derivatives and most other hexoses.[12,13] Cyclization occurs by nucleophilic attack of a hydroxy group on the carbonyl carbon in the acyclic species.[12] 5- and 6-membered rings are favoured due to their stability.[13,14] For glucose this would give the furanose and pyranose derivatives. At equilibrium in water, however, the furanose derivatives are undetectable by ^{1}H-NMR due to the pyranoses being much more thermodynamically stable.[12] Formation of the cyclic structure forms a new chiral center at the C-1 (anomeric center), resulting in two epimers, the α and β anomers (Scheme 1.1).



Scheme 1.1. Equilibrium between the open chain of glucose and the anomers of glucopyranose, with positions 1 and 6 marked.

1.1.2 Anomeric effect

The ratio between the α and β anomers of glucopyranose derivatives at equilibrium differ depending on the substituents.[10] Due to steric effect, larger substituents prefer to be in equatorial position as these provide less interactions with other ligands.[12,13,15] In the β configuration all the substituents are positioned equatorially. However, for unsubstituted glucose, the ratio of axial:equatorial positioning of the 1-OH is approximately 1:2.[10] When the 1-*O* substituent is replaced with a more electronegative substituent the anomeric ratio increases in the favour of the α anomer.[10] The phenomenon rising the amount of α anomer generally occurs when two heteroatoms are connected to a tetrahedral center.[10,12] This was coined "the anomeric effect" by Lemieux and Chü, and favours the orientation of heteroatoms in the axial configuration.[12]

To aid in distinguishing between the heteroatoms, a model using 1-substituted glucose will be employed in this section (see the structure in Figure 1.4). The 1-substituent, X, represents Br, Cl, F, N, O and S, while the endocyclic oxygen, O, can be substituted with N and S..[10,12] Several methods have been proposed to explain the anomeric effect, where two alternatives are the main models today: minimization of dipole moment and the stereoelectronic effect.[10–12] In the explanation with dipole moment, the nonbonding electrons of the endocyclic O forms a dipole which points in the exocyclic direction (Figure 1.4).[10] The bond between the anomeric carbon and the exocyclic X forms another dipole.[12] For β compounds these two dipoles are almost parallel, interacting energetically unfavourably with each other.[10] The dipole from the α anomer, however, points in another direction, and consequently the dipole interactions are less energetically unfavourable.[10,12]

A trend was found in the compounds which preferred the axial conformation.[12,16] They exhibited a shorter bond between the carbon and endocyclic O, and a longer bond be-

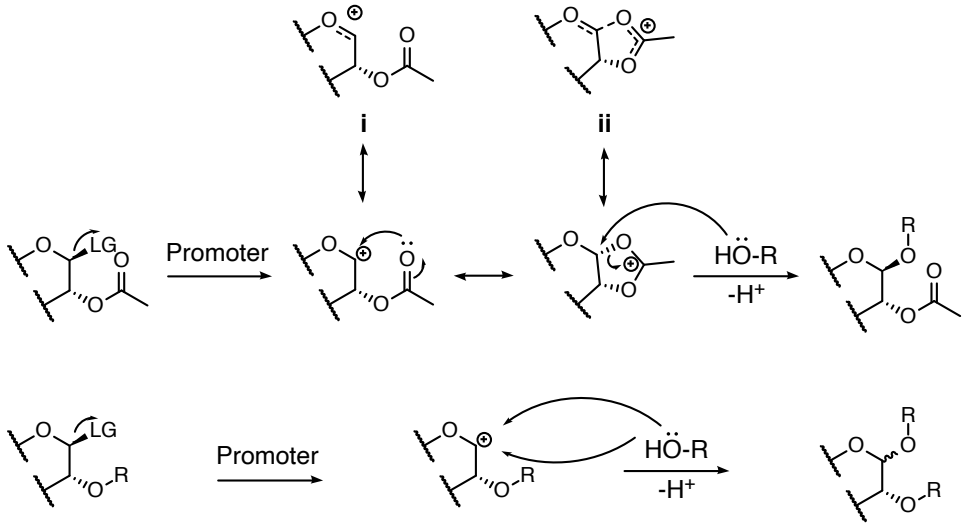
Figure 1.4. The dipole moment method to describe anomeric effect.[10,12,13]

Figure 1.5. Model to explain anomeric effect by use of orbital interactions.[10,12] Black orbital indicates an antibonding orbital, while the white orbital indicates a nonbonding orbital.

tween the carbon and exocyclic X.[12,16] This could not be explained by the dipole model, and to account for this the stereoelectronic explanation was suggested. In this concept the nonbonding electrons of the endocyclic O stand antiperiplanar to the bonding orbital of the substituent X, when X is in the axial position (Figure 1.5).[12] Thus, the nonbonding electrons stand synperiplanar to the antibonding orbital. An interaction between the nonbonding electrons and the antibonding orbital occurs, shortening the endocyclic bond and lengthening the exocyclic bond.[10,12] This does not occur when the anomeric substituent is in the equatorial position. Neither of the alternatives exclude the other, and so it is consensus that the stereoelectronic explanation is the main reason of the anomeric effect, while the dipole hypothesis, among other models attributes to some degree.[11,17] Some aspects of the anomeric effect is undisputed. Polar solvents decrease the anomeric effect.[18] This is probably due to the solvent stabilizing the dipole moment of the β anomer, thus making it less energetically unfavourable. The size of the anomeric substituent do not affect the anomeric effect noticeably.[12] A stronger electron withdrawing substituent in the the anomeric position will increase the anomeric effect.[12,13] This can also be reasoned by the dipole model.

1.1.3 Anchimeric assistance.

Anchimeric assistance, or neighboring group participation, is when a group near the reaction site affects the rate or stereochemical outcome of a nucleophilic displacement without the effect deriving from inductive, conjugative or steric reasons.[12,13] This occurs, for example, when the C-2 bears an *O*-acetyl group which can act as a nucleophile and disturb the displacement of a C-1 leaving group (LG) (Scheme 1.2). A promoter activates



Scheme 1.2. Example of how a nucleophile C-2 group affects the outcome of glycosylation while a non participating group does not.[10,12,19]

an LG, facilitating its departure, and forming an oxocarbenium ion (**i**).[12] The 2-*O* acetyl can stabilize the positive charge on C-1 by forming the ion **ii**. Due to steric hindrance the nucleophile attacks from the top, forming dominantly the 1,2-*trans* glycoside.[12,19] In addition to C-1, the nucleophile could attack at the C-2 or the carbonyl carbon in the acetyl, giving acyl migration or formation of orthoester, respectively.[10] Orthoesters can in some cases be isolated, but are usually rearranged to the desired glycoside.[12]

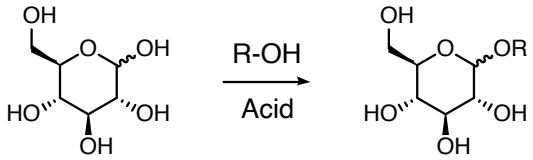
1.2 Glycosylation reactions

Glycosylation is the formation of a chemical bond between the anomeric carbon of a carbohydrate with the hydroxy group on another molecule.[13] The carbohydrate which

reacts at the anomeric position is called the glycosyl donor while the molecule with the hydroxy group is called the glycosyl acceptor. The formation of glycosidic bonds are among the most important reactions in carbohydrate chemistry.[13] This section covers a few selected glycosylation reactions which are relevant for this thesis.

1.2.1 Fischer

An early form of glycosylation was developed by Emil Fischer in 1893.[13,19,20] He refluxed glucose in methanol in the presence of hydrochloric acid (HCl) and produced both anomers of methyl-D- glucopyranoside. This gave rise to the method known as Fischer glycosylation. This is a simple form of glycosylation where, after protonation of the anomeric hydroxy, the monosaccharide acts as a glycosyl donor in the reaction with the solvent molecules, which act as glycosl acceptors (Scheme 1.3).[11,13] The thermodynamic



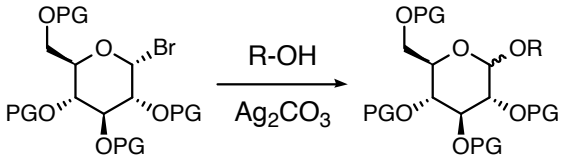
Scheme 1.3. Fischer glycosylation of α-D-glucose[11]

products are the anomers of the pyranose form, while the anomers of the furanose form can be isolated as the kinetic products.[11,13] Increasing the temperature or amount of acid is usually sufficient to ensure the thermodynamic product in good yields.[13] Fischer glycosylation can be useful when introducing small glycosyl acceptors but is not practical in the synthesis towards more complicated carbohydrates. The use of strong acids and high temperatures constitutes harsh reaction conditions. However, the selectivity towards the anomeric position reduces the amount of protection chemistry required. Many of the reagents are also inexpensive.

1.2.2 Königs-Knorr

Königs and Knorr developed, in 1901, an alternative method for glycosylation, which was considered more practical than Fischer glycosylation and is therefore still carried out today.[13,21] In the Königs-Knorr glycosylation, and later adaptions, the glycosyl donor is a fully protected glycosyl halide, while the glycosyl acceptor is a molecule which contain

a hydroxy group, (Scheme 1.4). Heavy metal salts (preferably silver or mercury) are utilized as promoters for the reaction.[12,19,22,23] The complexation of the anomeric bromide or chloride with heavy metal salts greatly improves their leaving group abilities.[11] The glycosylation can either happen by an S_N2 mechanism, or the formation of an oxocarbenium ion, which reacts with the hydroxy group of the glycosyl donor.[12] The reactivity of the Königs-Knorr reaction is dependent on the protecting groups (PG) employed, with the C-2 being most relevant.[12] Esters, which are elctron withdrawing, destabilize the formation of the previously mentioned oxocarbenium ion and consequently reduce the reactivity, compared to ether protecting groups.[23,24] The disadvantage of the Königs-Knorr glycosylation is the use of toxic and expensive heavy metal salts, and is usually avoided today. However, adaptions where Lewis acids and phase transfer catalysts function as promoters have been developed.[24]

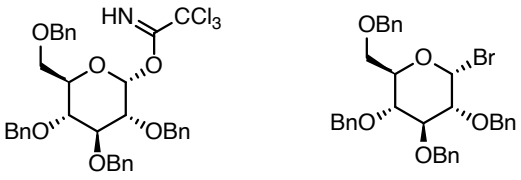


Scheme 1.4. Königs-Knorr glycosylation.[19]

1.2.3 Schmidt

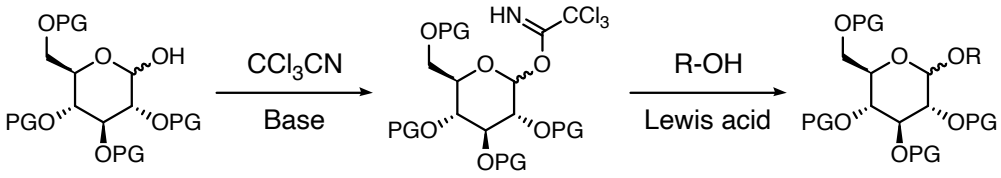
Schmidt glycosylation is one of the glycosylation techniques most frequently utilized today.[10] The method is also known as the trichloroacetimidate method and was heavily explored by Richard R. Schmidt in the 1980s.[23,25] Schmidt glycosylation is often preferred over the Königs-Knorr method as it does not need heavy metals to promote the reaction.[19,23] Additionally, the reagents often have superior shelf stability.[23] For example, the Schmidt trichloroacetimidate (TCAI) **iii** can be stored at +5 °C without any special precautions, while the glycosyl halide **iv** must be stored at -80 °C.[23,26] The Schmidt glycosylation is initiated by the formation of a TCAI glycosyl donor by reacting the anomeric hydroxy with trichloroacetonitrile (CCl_3CN) in the presence of a base.[13,23,27] Then the trichloroacetimide can react with the glycosyl acceptor promoted by a mild Lewis acid (Scheme 1.5).

Anomeric selectivity of the Schmidt TCAI can be achieved using either kinetic or thermo-



iii **iv**

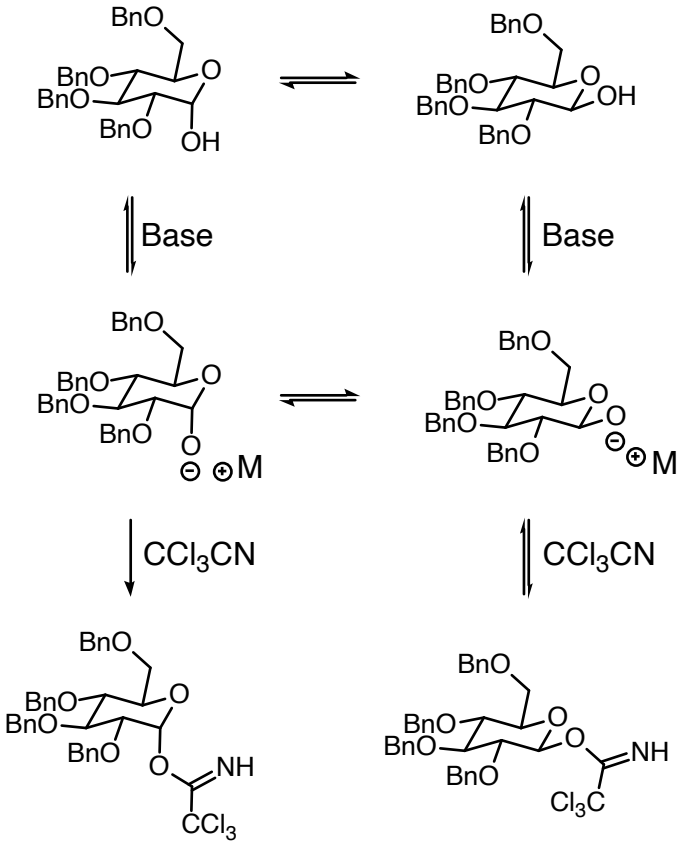
Figure 1.6. Example of glycosyl donors for the Schmidt method, **iii**, and for the Königs-Knorr method, **iv**[23,26]



Scheme 1.5. Schmidt glycosylation[19,23]

dynamic conditions. The β-trichloroacetimidate is rapidly formed, but undergoes a slow, base catalyzed anomerization to the α anomer due to the anomeric effect (Scheme 1.6).[13,23] Under thermodynamic conditions the α anomer can be isolated in good yields, while kinetic conditions provide the β anomer.[19,23] The base also affects the anomeric selectivity.[13,19] A weak base, like K_2CO_3, can easily catalyse the formation of the β trichloroacetimidate without having large effect on the retro-reaction, thus favoring the β product.[10,19,23] Stronger bases, like 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) or NaH, result in the formation of the more thermodynamically stable α anomer.

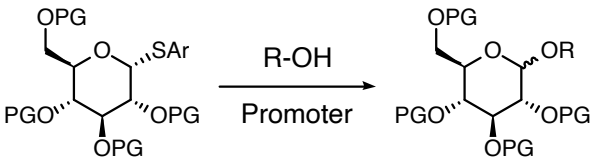
If the glycosyl acceptor is a Brønsted acid, no catalyst is required. When the glycosyl acceptor is an alcohol, however, the presence of a Lewis acid (LA) catalyst is usually needed.[23] Boron trifluoride etherate ($BF_3 \cdot Et_2O$) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) are the most common Lewis acids utilized as promoters today.[10,28] In the glycosylation reaction it is possible to alter the α/β selectivity of the product, as long as the TCAI does not have a participating group at the C-2.[29] If the C-2 carbon contains a participating group, the product is often almost exclusively the 1,2-trans product, β glucoside, due to anchimeric assistance.[23] When the C-2 contains a non-participating group, the anomeric selectivity is based on the Lewis acid or solvent.[19] A mild promoter like $BF_3 \cdot Et_2O$ will generally result in inversion at the anomeric carbon.[10,19,23] With the



Scheme 1.6. Formation of 2,3,4,6-*O*-tetrabenzyl-trichloroacetimidate[13,23]

stronger TMSOTf on the other hand, the solvent is more relevant.[19] Dichloromethane (DCM) and Et_2O will stabilize the oxocarbenium ion as β glucosides and consequently favor the α product.[19] In acetonitrile (ACN) an α-nitrilium ion is favoured, leading to the formation of β-glucoside.

1.2.4 Thioglycosides



Scheme 1.7. Example of thioglycosylation with a thioaryl at C-1 position[13]

Thioglycosides have a relatively high stability, are easily synthesised, and can serve as

glycosyl donors themselves, or be converted into other glycosyl donors.[24,30] This has made glycosylation with thioglycosides a widespread technique in oligosaccharide synthesis. The method uses a thioalkyl or thioaryl moiety at the C-1 position which, when activated, becomes a good leaving group. An *O*-nucleophile of another molecule can then react to form the glycoside (Scheme 1.7).[13] Only aryl thioglucosides was utilized in the work presented herein.

The sulfur atom in 1-thioglycosides, being a soft nucleophile, can react selectively with other soft electrophiles such as halogens, heavy metal cations and alkylating agents under mild conditions.[10,13] The hydroxy groups of carbohydrates, on the other hand, are hard nucleophiles and can react with hard reagents without affecting the soft anomeric thio-substituent. The high stability and ability to withstand most of the common protecting group manipulations required for carbohydrates, makes it possible to use thioaryls as a temporary protecting group for the anomeric position.[10,12,19]

When glycosylation using thioglycosides were first reported, the reactions were promoted by mercury salts.[28,30] Their breakthrough as glycosylation agents came when milder activation conditions were developed.[31–33] The field has since then been heavily studied to find conditions which address, among other things, anomeric selectivity and yield.[28] Several combinations of promoters have been reported to work with different glycosyl donors and acceptors.[13]

There are several similarities between glycosylation using thioglycosides and Schmidt glycosylation. The mechanism of both techniques are similar, and thus the same things which affect the anomeric ratio for Schmidt glycosylation are also relevant here. Anchimeric assistance can result in exclusively 1,2-*trans* product, while non participating protection groups yield more of the 1,2-*cis* product.[13,19] The solvent also affects anomeric ratio in the products. Diethyl ether (Et_2O) and DCM facilitates α glycoside, while ACN often leads to the β anomer.[19,34]

1.3 Protecting groups

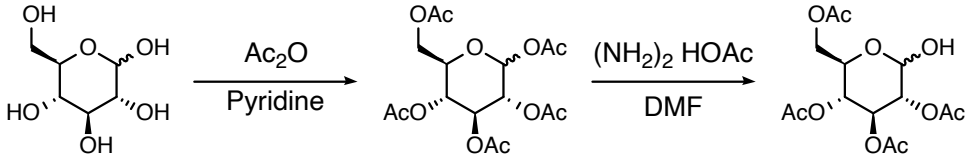
A great challenge in carbohydrate chemistry is achieving selectivity towards the desired functional group to be reacted.[12] In unprotected glucose there are 5 different free hydroxy

groups. Some selectivity can be found toward the primary hydroxy group due to steric hindrance.[13,19] The anomeric hydroxy group is a hemiacetal and is thus different than the other hydroxy groups in many aspects.[13] The anomeric hydroxy group can, for example, be replaced by an alkoxy group by treating the monosaccharide with an alcohol in the presence of a mineral acid (Fischer glycosylation, Section 1.2.1).[13] Protecting groups are often employed to ensure selectivity.[12]

The protecting groups employed in carbohydrate chemistry are the same as in other parts of organic chemistry.[10,19] When devising a protection strategy, many things must be considered. For example, a protecting group must be stable under the conditions utilized in subsequent reactions and easily introduced and cleaved in high stereoselectivity and yields. Orthogonal protecting groups are groups which can be removed in any order, under conditions which do not affect the other protecting groups.[12,19] This is generally required when multiple functional groups, which are not to be deprotected simultaneously, need to be protected. In addition to protect a functional group, protecting groups may affect other functionalities of a molecule.[10,12] They can, for example, sterically block other functional groups, or reduce reactivity of neighbouring positions by being electron donating or withdrawing.[10,12] There are numerous protecting groups available in organic chemistry.[35,36] A small selection of protecting groups relevant for this project is described in this section.

1.3.1 Acetyl

Acetyls are one of the most commonly applied protecting groups in carbohydrate chemistry.[37] This is due to the easy methods of introduction and removal in good yields, while simultaneously being stable against acidic conditions, and moderately stable under basic conditions.[10] Often, acetyl can be introduced under mild conditions, with little need of prior purification. This greatly aids purification and structure elucidation of polar compounds, as the hydroxy groups can be masked, decreasing the polarity. A disadvantage with acetyls is their tendency to migrate, both under acidic and basic condition.[10,35,37] This can be very problematic when another protecting group is removed, and acetyl migration leads to several products.



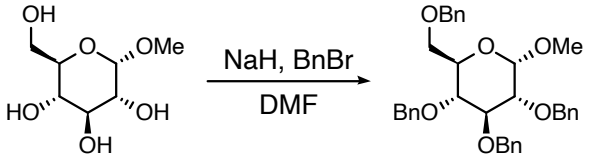
Scheme 1.8. Global acetylation followed by anomeric deacetylation.[19,38,39]

Introduction of the acetyl protecting group is usually carried out by acetic anhydride (Ac_2O) in pyridine (Scheme 1.8), and generally yields the same ratio of anomers as the parent sugar.[12,19,35] In special cases where the reaction rate is low, a catalytic amount of 4-dimethylaminopyridine can be added to accelerate the reaction.[12,35] Good yields of acetylation can also be achieved under acidic conditions.[10,19] With these conditions, the reaction probably operates under thermodynamic control, providing an increased amount of the more stable anomer.[19] The classical method for removal of the protecting group is known as the Zemplén procedure.[35,37,40] The ester is dissolved with a catalytic amount of NaOMe in dry MeOH, transesterifying the methylate. An advantage of the acetyl group is the possibility to selectively deprotect the anomeric position of a globally protected carbohydrate.[19,41] This simplifies selective introduction of non-selective groups at the anomeric position.

1.3.2 Benzyl ether

Benzyl ethers are often abbreviated BnOR and are frequently employed in carbohydrate chemistry due to their general stability and ease of introduction and removal.[35] The ether bonds tolerate a wide range of acidic and basic conditions, as well as many reducing and oxidizing agents.[12,35] This makes benzyl ethers excellent for long term protection of hydroxy groups.[10]

Benzyl ethers offer several methods for introduction, which include basic, neutral and acidic conditions, depending on the properties of the starting material (SM).[19] The standard method to introduce benzyl ethers in carbohydrate chemistry is a variant of the Williamson ether synthesis, using NaH and benzyl bromide (BnBr) in dimethylformamide (DMF) (Scheme 1.9).[10,15] The introduction of benzyl ethers usually proceed in good yields, and they can be introduced at several hydroxy groups simultaneously.[35]



Scheme 1.9. Global benzylation of α-methoxy glucopyranoside[42]

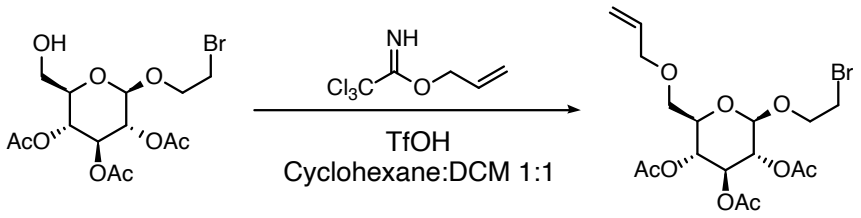
There are several orthogonal methods to cleave benzyl ethers.[35] The most common and mildest method is to cleave the ether by catalytic hydrogenolysis.[10,35] Birch reduction also removes benzyl ethers under mild conditions. Reductive removal is not always compatible with other functionalities in the sugar molecule. Azides or double bonds can be reduced and the palladium catalyst in catalytic hydrogenolysis can be poisoned by thio and amino groups.[10,35,43] Other methods of ether cleavage include the use of Lewis acids, dissolving metal reduction and oxidation.[35]

1.3.3 Allyl ether

Allyl ether is another ether protecting group frequently employed in carbohydrate chemistry.[35,36,43,44] They are robust and compatible with many of the reaction conditions found in sugar chemistry, whilst simultaneously having limitations towards strong electrophiles.[35] The double bond of the allyl ether provides an additional functionality compared to benzyl ethers, which are solely used for their protective capabilities.[15] The vinyl group can be utilized as a handle to further develop the parent molecule, for example by oxidation to an epoxide or by alkylation.[14,45]

The strongly basic Williamson ether synthesis can be utilized to introduce allyl ethers to a hydroxy group.[10,43] Where such conditions are not feasible, the use of acidic or nearly neutral can be employed.[19,44,46] An example of acidic conditions is to treat allyl alcohol with trichloroacetonitrile and then alkylate the carbohydrate catalysed by triflic acid (TfOH) (Scheme 1.10).[46] Fischer glycosylation can be employed to selectively introduce the allyl on the anomeric position.[47]

The classical method for the removal of this protecting group is by isomerization of the allyl ether to the more labile 1-propenyl ether, which can be removed by acidic hydrolysis, or oxidative cleavage.[36,43,48,49] Isomerization of the allyl moiety has been achieved



Scheme 1.10. Allylation of primary alcohol using acidic conditions.[46]

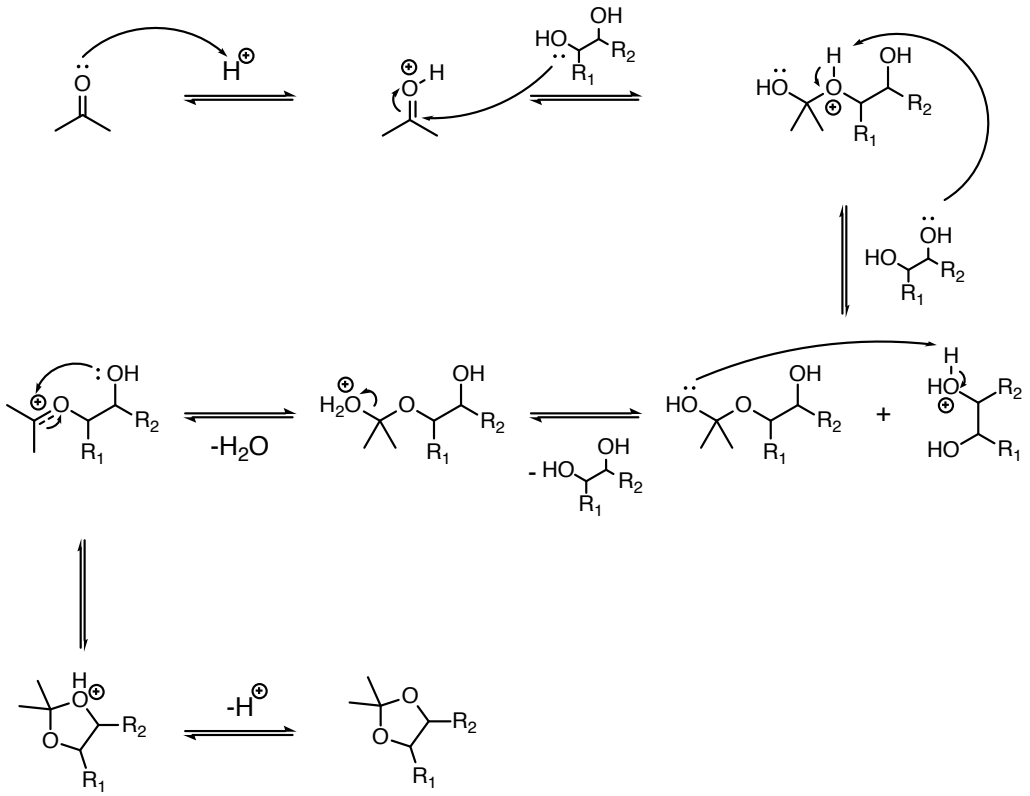
under strongly basic conditions such as potassium tert-butoxide in dimethyl sulfoxide (DMSO).[43,48,49] A more modern method to isomerize the ether is by use of transition metals, followed by hydrolysis of the 1-propenyl ether.[10,35] Wilkinson's catalyst, $RhCl(PPh_3)_3$, under netral aprotic conditons, or palladium on carbon under acidic conditions, are frequently reported in the literature.[43,49–51]

1.3.4 Isopropylidene acetal

The isopropylidene acetal, also known as acetonide, is one of the two most utilized protecting groups in carbohydrate chemistry for the protection of 1,2- and 1,3-diols.[19,35,36] It is a cyclic acetal which is stable under numerous conditions, including strong basic conditions, but it is fragile towards protic- and Lewis acids.[35]

The traditional method for formation of acetonides is by reacting a 1,2- or 1,3-diol with acetone, 2-methoxypropene or 2,2-dimethoxypropane in the presence of an acid catalyst.[19,35–37] The mechanism of formation of acetonide from acetone and a 1,2-diol is given in Scheme 1.11. There is some selectivity with regards to acetonides.[36] In cases where 1,2- and 1,3-diols can be protected, acetonide will favor the protection of 1,2-diols, and if multiple 1,2-diols are available the most thermodynamically stable product will dominate.[36]

The removal of acetonides is often achieved by acidic hydrolysis.[10,19,35] The acid strength and reaction time can vary, but one of the mildest methods involves pyridinium *p*-toluenesulfonate in aqueous media under gently heating.[35] Aqueous trifluoroacetic acid, acetic acid or dilute HCl are other methods which can remove acetonides rapidly.[10,19,52,53]

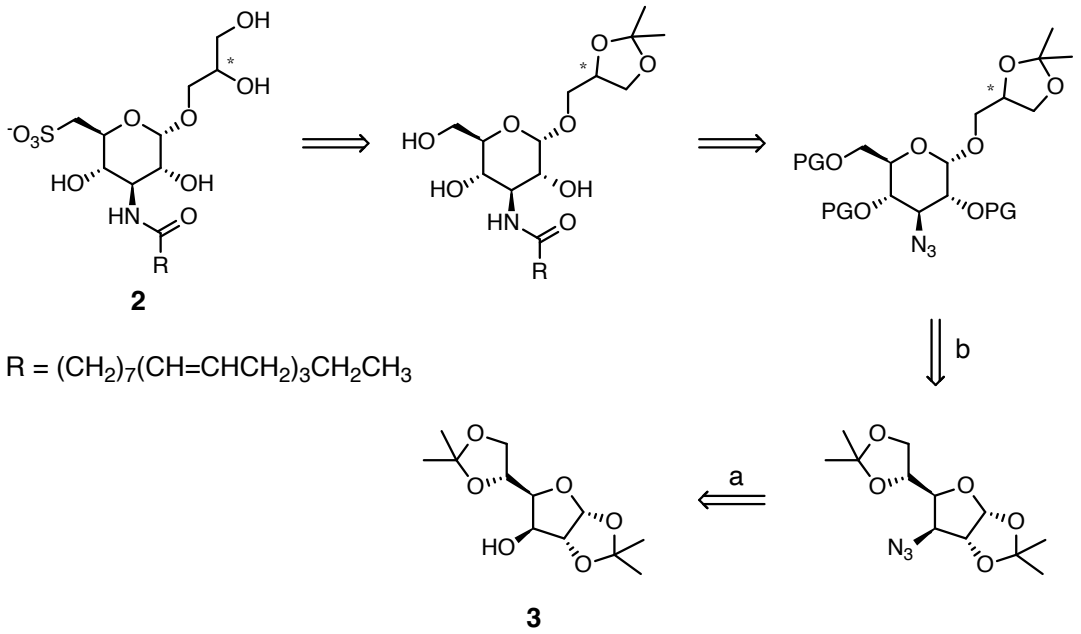


Scheme 1.11. Mechanism for the acid catalysed protection of a 1,2-diol by acetone as acetonide.[15,37]

1.4 Synthetic strategy

This project has looked into the synthesis towards the target compound **2**. A retrosynthetic plan for this synthesis is given in Scheme 1.12, where this work has focused on the introduction of an enantiomerically pure glycerol moiety, step b. Some focus has been given the initial step, a, as this was an unavoidable part in the synthesis towards the glycosylation reaction.

A synopsis for the introduction of glycerol moiety is given in Scheme 1.13. The plan was to explore the suitability of trichloroacetimidate glucosides and thioglucosides as glycosyl donors, with the goal to introduce optically pure 1,2-*O*-isoproylidene-glycerol. An alternative approach, already employed by the research group, was to oxidize an anomeric allyl ether to produce the glycerol moiety. Previous work on similar derivatives,

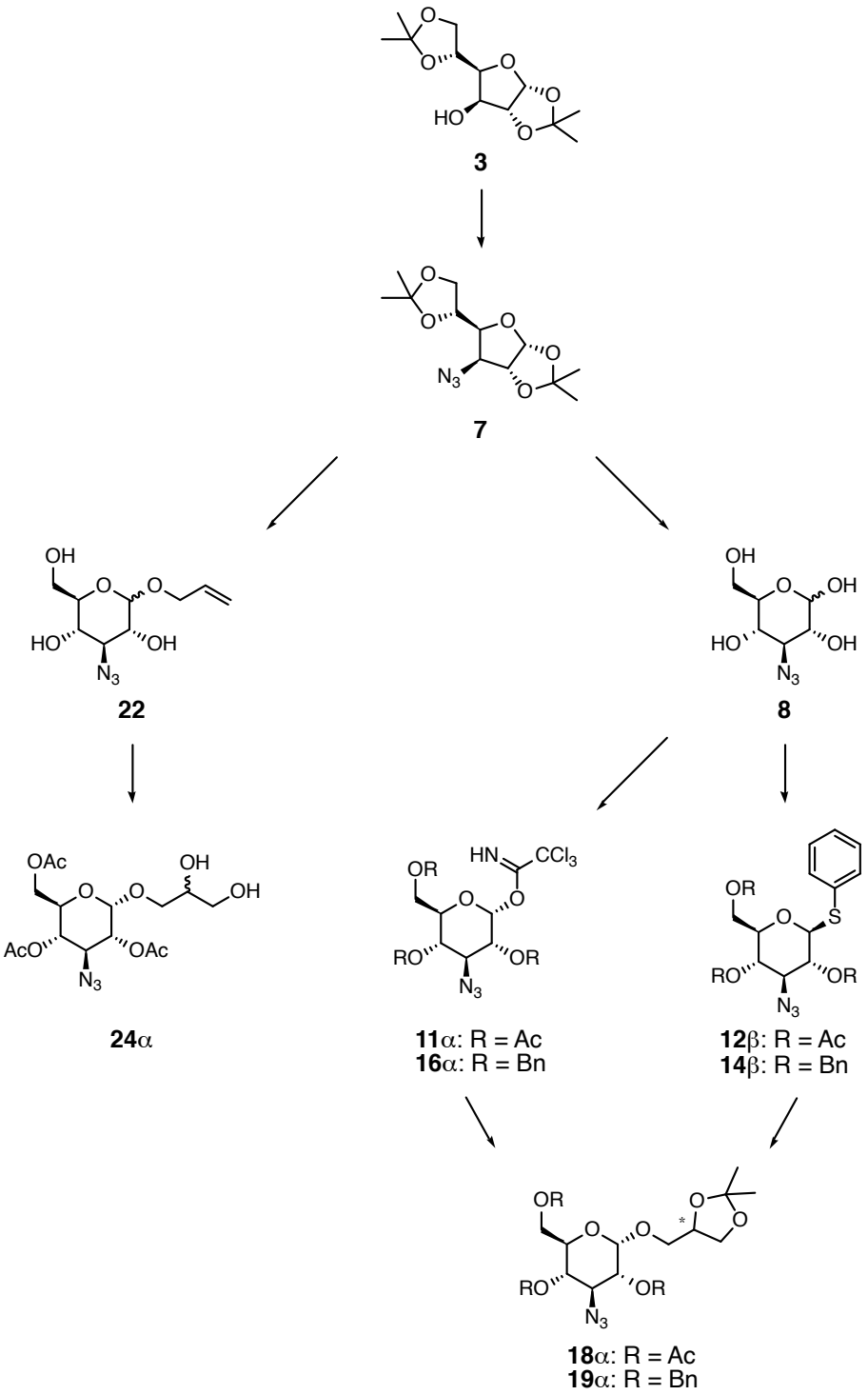


R = $(CH_2)_7(CH{=}CHCH_2)_3CH_2CH_3$

Scheme 1.12. Retrosynthetic plan to make the target compound, **2**, from the glucofuranose **3**.

however, has shown that this method does not provide a chirally pure glycerol moiety. Thus, this route was looked at as a proof of concept.

Azide was chosen in C-3 in structure **7** to act as a precursor to an amine which could be transformed to a fatty acid amide by aminolysis. The Staudinger reaction has been reported with success to reduce carbohydrate-azides to amines.[54,55] Two protection groups are employed on the carbohydrate backbone. The acetyl group was initially chosen due to ease of use and unknown degree of anchimeric assistance. Additionally, thiophenyl is usually introduced by reaction with an anomeric acetal.[12] Benzyl ethers were chosen due to being non-participating ethers during the glycosylation. Acetonide was chosen as protecting group on the glycerol moiety due to availability and ease of deprotection. Successful introduction by Schmidt glycosylation had also been reported in the literature on similar derivatives.[56–59]



Scheme 1.13. Synthetic routes towards regioselective introduction of acetonide protected glycerol moiety at anomeric position.

2 Results and Discussion

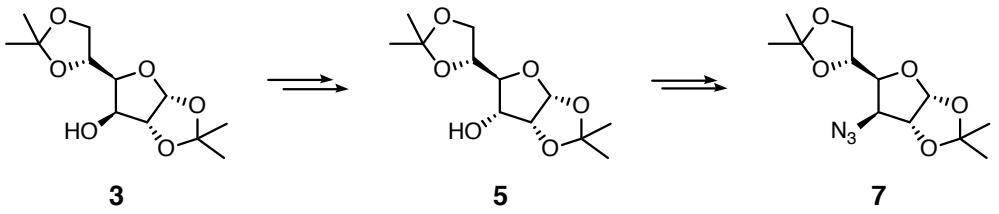
The work in this project was focused on the initial reactions in the total synthesis towards target compound **2**. It can be divided into 3 parts: Synthesis of glycosyl donors, investigation into glycosylation reactions, and an alternative method to introduce a glycerol moiety at the anomeric position. Although investigations into the glycosylation was the main goal of this project, much time has been spent on the synthesis toward the glycosyl donors. As most reactions proceeded in sufficient yields, little time was spent in the optimization of these reactions. Thus, further optimization is probably possible in most reactions. The purification of the glycosylation reactions was too difficult to provide sufficient quantitative data. This was due to the retention of isomers being too similar. Consequently, these studies were qualitative, to give an insight in the suitability of the glycosylation methods. Finally an alternative method to introduce a glycerol moiety is introduced. This work was purely carried out as a proof of concept, hence there is room for optimization of this part as well.

2.1 Synthesis of glycosyl donors

2.1.1 Introduction of 3-azido moiety to isopropylidene protected glucofuranose

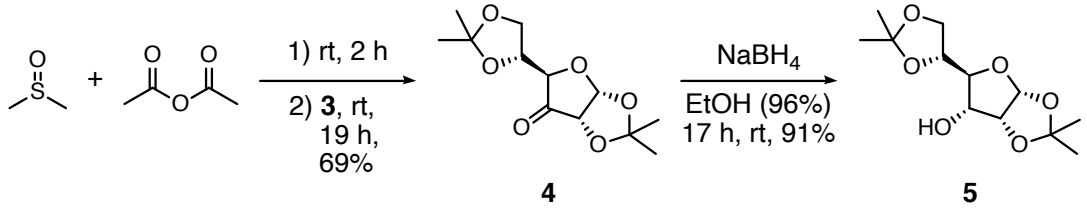
There are several methods to replace a hydroxy group with an azide.[60] This can be achieved by nucleophilic substitution with an azide anion after transforming the 3-hydroxy into a leaving group by substitution, usually in the form of a tosylate or triflate.[61–65] The hydroxy group could also be replaced in one step by the Mitsunobu reaction.[64] All these methods, however, lead to inversion.[14,61,64] Thus, it is necessary to first invert the glucofuranose to allofuranose (Scheme 2.1).

Inverting the glucofuranose **3** to the allofuranose **5** is often performed by oxidising the hydroxy to a ketone with a subsequent stereoselective reduction (Scheme 2.2). Vari-



Scheme 2.1. Synthetic strategy to make the azide **7** from **3**.

ous methods to oxidize the hydroxy group have been developed, where chromium-based oxidants or activated DMSO are frequently utilized.[66–69] An Albright–Goldman like oxidation was chosen due to the availability of the reagents and the simplicity of a potential scale up.[13,70,71] The chromium-based oxidant pyridinium dichromate (PDC) has been reported to produce quantitative yields where DMSO/Ac_2O only are reported with 81% desired product.[67,68] PDC is, however, a carcinogen, and was therefore avoided.



Scheme 2.2. Experimental procedure for inversion of alcohol at C-3 from **3** to **5**.

The oxidation of the glucofuranose **3** to ketone **4** was based on the method described by Mazur et al. (Scheme 2.2).[68] Multiple authors have reported purification by vacuum distillation.[68,69] This proved unfruitful in the initial attempt, likely due to subpar equipment, giving a crude product which had to be further purified by column chromatography. Compared to the yield of Mazur et al. (81%) this resulted in a poor yield of 36% (entry 1, Table 2.1).[68] In all subsequent reactions the product was purified by silica gel column chromatography.

Purification by column chromatography lead to the isolation of two byproducts. These were identified as the acetylated and the methylthio(methyl)-derivatives **4a** and **4b** (Figure 2.1), respectively, which are known from the literature as byproducts of this reaction.[68,70] To reduce the amount of acetylated byproduct it is possible to mix DMSO and Ac_2O prior to addition of starting material **3**.[68] Trying to minimize the acetylated

Table 2.1. Albright-Goldman oxidation of **3**. ΔTime indicates how long Ac_2O and DMSO was stirred together before the addition of starting material. Extractions are the number of extractions with DCM after the crude product was concentrated under reduced pressure. Constant reaction conditions: Ac_2O (8 mL/g), DMSO (12 mL/g), rt, 19 h after addition of **3**.

Entry	ΔTime [h]	Extractions	Yield [%]	**4a** [%]	**4b** [%]
1	1	3[a]	36	16	14
2	2	3	48	7	12
3	2	10	69	9	15

[a]Extractions were performed after attempted vacuum distillation.

byproduct, in the initial reaction, DMSO and Ac_2O were stirred for 1 h before adding starting material (entry 1, Table 2.1). However, the byproduct was still isolated in 16% yield. By increasing the time DMSO and Ac_2O were stirred before addition of starting material, the acetylated byproduct could be reduced to 7% (entry 2). Simultaneously, an increase in yield was observed. A further increase in yield was attempted by enhance the number of extractions prior to column chromatography. After the crude product had been diluted in water, it was extracted with DCM 10 times before washing with brine. The yield was increased to 69% by this number of extractions. Increasing the number of extractions was tested due to DMSO being miscible in both water and DCM. It was therefore assumed some product remained in the aqueous phase. Evaporation of all the DMSO and Ac_2O under reduced pressure could further improve the yield and remove the necessity of extraction.

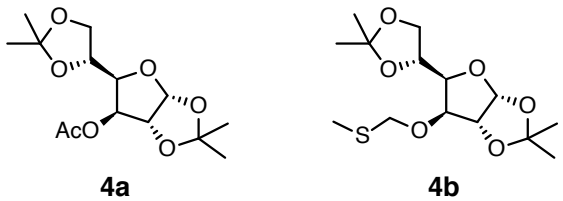


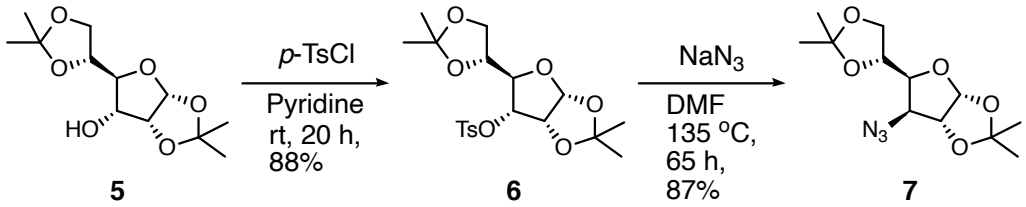
Figure 2.1. Acetyl- (**4a**) and (methylthio)methyl- (**4b**) derivatives of **3**. Common byproducts from the oxidation of **3** with DMSO and Ac_2O[70,72]

The methylthio(methyl) derivative, **4b**, is the product of the Pummerer rearrangement.[70] From the Swern oxidation this rearrangement is found to be dependent on temperature.[70]

The amount of byproduct **4b** formed in these reactions was stable around 14%. For further optimization, the effect of temperature could be investigated. However, with sufficient amount of intermediate in hand, this was not pursued.

The reduction towards allofuranose **5** was based on the procedures of Desmukh et al. and Guo et al. (Scheme 2.2).[66,73] However, longer reaction times than those reported were required for full conversion. This was evident from TLC monitoring, which showed presence of the starting material after 2 h. The reaction was left overnight and the prolonged reaction time was well tolerated, yielding the allofuranose **5** in 91%.

Insertion of the azide at C-3 was achieved by an S_N2 reaction from the tosylate **6** (Scheme 2.3). Replacement of the hydroxy group in one step under Mitsunobu conditions reportedly gives low yields (19%) and was therefore not considered.[64] Methods based on triflate and tosylate leaving groups seemed much more suitable, and with comparable high yields (84-90%) reported in the literature.[74–76] Due to availability of the reagents, the tosylation route was selected, employing the conditions described by Williams and Jones.[76]



Scheme 2.3. Synthetic plan for the insertion of azide in **5**.

Due to the properties of the tosylate as a leaving group and the small size of the azide nucleophile, it was expected that the substitution towards **7** should proceed smoothly. The literature, however, reports the need for either 150 °C for 4 h or 135 °C for up to 52 h.[61–65] Employing 152 °C for 6 h resulted in a meagre yield of 42% (entry 1, Table 2.2), prompting an investigation into the effects of time, temperature and amount of nucleophile.

Increased reaction time (22 h) resulted in a slightly improved yield (entry 2). A reduction of the temperature to 135 degrees gave further increase in yield (entry 3). This is likely a result of fewer byproducts formed at the lower temperature, as evinced by TLC monitoring

Table 2.2. S_N2-substitution of 3-OTs with azide in **6**. Constant parameters: 1 mmol scale, 5 mL DMF.

Entry	Time [h]	Temp [°C]	NaN_3 [Eqv.]	Product [%]
1	6	150	5	42
2	22	150	5	50
3	22	135	5	65
4	22	135	18	74
5	45	135	18	80
6	65	135	5	79
7[a]	65	135	10	87

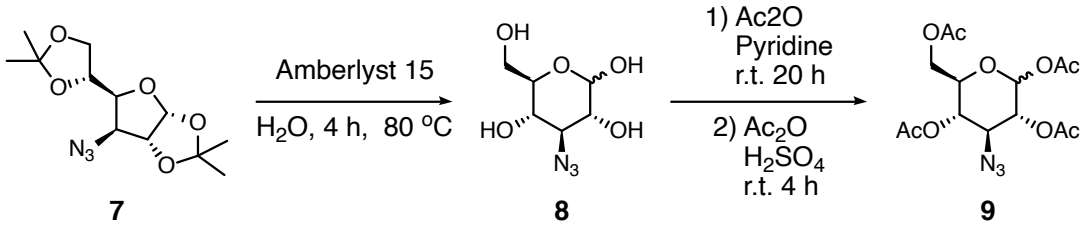
[a] 6 mmol scale

showing a cleaner reaction. The temperature was therefore set to 135 °C for all subsequent experiments. A massive increase in the amount of added azide and/or further increase in reaction time elevated the yield even more (entries 4-6). From the entries with the same amount of reagent it is clear that increase in reaction time improves the yield of the reaction. By comparison of entries 5 and 6 it is shown that an increase in amount of reagent can give similar yields as a longer reaction time.

The best result was seen with 10 equivalents of NaN_3 and 65 h reaction time at 135 °C, giving azide **7** in 87% yield (entry 7). However, as previously noted, the reaction time can be reduced and still give sufficient results (80%) by increasing the amount of NaN_3. Recovery of unreacted starting material was easily achieved by changing the eluent in flash column chromatography from 9:1 to 3:1 *n*-pentane:EtOAc.

2.1.2 Acetyl protected trichloroacetimidate

3-Azido-3-deoxy glycopyranose (**8**) was synthesised by stirring of **7** in H_2O at 80 °C overnight, giving quantitative yields as a racemic mixture of the anomers (Scheme 2.4). During this reaction the acetals were hydrolysed and the carbohydrate backbone was rearranged to the more stable pyranose form. The reaction mixture was, after drying, sufficiently pure to proceed without further purification.



Scheme 2.4. Rearrangement of **7** followed by acetylation.

To acetylate the glucopyranose **8**, two different methods were considered, basic and acidic conditions (Scheme 2.4). Basic conditions, as described by Manta et al., yielded 47% of the acetylated glucopyranose **9** (entry 1, Table 2.3).[61] The yield was elevated by increasing the amount of Ac_2O (entry 2). Acidic conditions, reported by Anjum et al., initially yielded 79% (entry 3).[41] Under these conditions extraction with DCM followed by washing with H_2O was sufficient purification. On larger scales, the yield was increased up to 91% (entries 4 and 5).

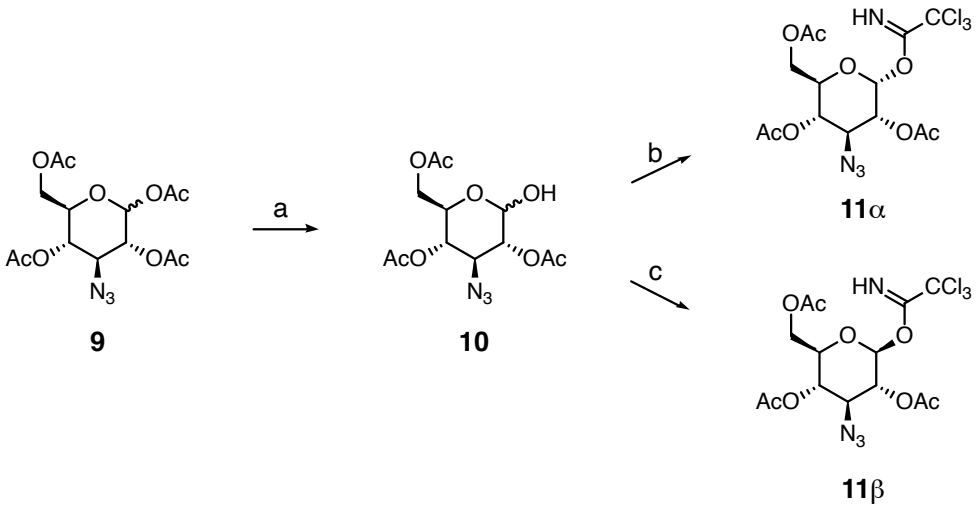
Table 2.3. Acetylation of **8**. Method A: Pyridine (25 mL/g), 20 h. Method B: H_2SO_4 (0.08 eqv.), 4 h. Constant reaction conditions: Ac_2O (25 eqv.), **8** (0.1 g), rt.

Entry	Method	Yield [%]
1	A	47
2	A[a]	57
3	B	79
4	B[b]	84
5	B[c]	91

[a] 60 eqv. Ac_2O [b] 0.3 g scale

[c] 0.9 g scale

Synthesis of the TCAI **11**, from the tetra-acetylated glucoside **9**, was carried out by anomeric deprotection with subsequent insertion of trichloroacetimide, to give either α or β configuration, depending on the reaction conditions (Scheme 2.5). Removal of the anomeric acetyl group was executed by reacting the starting material, **9**, with NH_4OAc in DMF at rt. This was a successful method affording the desired product as a mixture of both anomers in 70 - 75% yield (Table 2.4). Scaling up and prolonging the reaction time had no noteworthy impact on yield or anomeric ratio.



Scheme 2.5. a) NH_4OAc (2.1 eqv.), DMF, rt, 28 h. b) DBU (0.1 eqv.), CCl_3CN (3.2 eqv.), DCM, rt, 25 h. c) K_2CO_3 (2.7 eqv.), CCl_3CN (1.3 eqv.), DCM, rt, 3 h.

Table 2.4. Anomeric deprotection of **9**. Constant reaction conditions: NH_4OAc (2.1 eqv.), DMF (9 mL/g).

Entry	**9** [mg]	time [h]	Yield [%]
1	80.1	22	70
2	305	20	72
3	496	28	75
4	753	41	71

After the anomeric position was deprotected, the Schmidt glycosyl donor **11** could be prepared. It was believed that, alongside anchimeric assistance, the choice of solvent and Lewis acid employed during the glycosylation reaction were the dominant factors in determining the stereochemistry of the glycosylated product, **18**.[19] Therefore it was first aimed to make the α-anomer of the glycosyl donor, **11**. Anjum et al. reported this reaction in good yields using cesium carbonate ($CsCO_3$) as a base catalyst for 4 hours.[41] After 4 h TLC monitoring showed incomplete conversion and the reaction was allowed to proceed for a total of 25 h (entry 1, Table 2.5). TLC analyses still showed some presence of starting material after 25 h, but the reaction was stopped and purified giving **11α** in 54% yield. ^{1}H-NMR indicated that the product was pure, however, high performance

liquid chromatography (HPLC) analysis clearly showed the presence of two compounds. It was initially believed that the impurity derived from the reagent, CCl_3CN, as HPLC analysis revealed the presence of the same impurity in the reagent. Later it was concluded that the sample was pure, but had reacted with the water in the eluent, explaining the two different signals in the HPLC analysis. This was confirmed by ^{1}H-NMR of the β compound, **11β**. One NMR-sample was run twice with a 16 h time gap. An increase of the signal at 2.17 ppm indicated the formation of some byproduct /Figure 2.2).

Table 2.5. Synthesis of trichloroacetimide **11** from the 1-OH glucopyranose **10**. Constant reaction parameters: Base (0.15 eqv.), DCM (20 mL/g), rt, N_2-atmosphere.

Entries	**10** [mg]	Base	CCl_3CN [eqv.]	Time [h]	Yield α/β [%]
1	85.5	$CsCO_3$	10.7	25	54/-[a]
2	49.5	DBU	3.2	25	81/-[a]
3	371	K_2CO_3[b]	1.2	3	26/3[c]
4	183	DBU	1.3	48	78/-[a]

[a]The beta anomer was not isolated [b]2.7 eqv. [c]Calculated yield of the β anomer was 23% by NMR-assay

Considering the amount of CCl_3CN utilized, 54% was deemed an unsatisfactory yield. Thus, DBU was employed as base, while decreasing the amount of reagent added (entry 2). This resulted in a satisfactory yield of 81% of the α anomer.

To form the β-anomer of trichloroacetimidate **11**, K_2CO_3 and a shorter reaction time were chosen, seeking to favor the kinetic product.[19,23] An excess of K_2CO_3 was employed in an attempt to ensure an anomeric ratio favoring the β product. By NMR-assay the yield of the β anomer was calculated to 23%. However, due to coelution with unreacted starting material, only 3% of the pure anomer was isolated. The α anomer was isolated in 26% yield. According to Schmidt et al., the β anomer of TCAI is formed rapidly and then slowly anomerizes to the α anomer.[23] This indicates that a shorter reaction time could increase the yield of **11β**. Further investigation into the formation of the β anomer was abandoned when it proved an unsuitable glycosyl donor due to anchimeric assistance (as described later, Section 2.2).

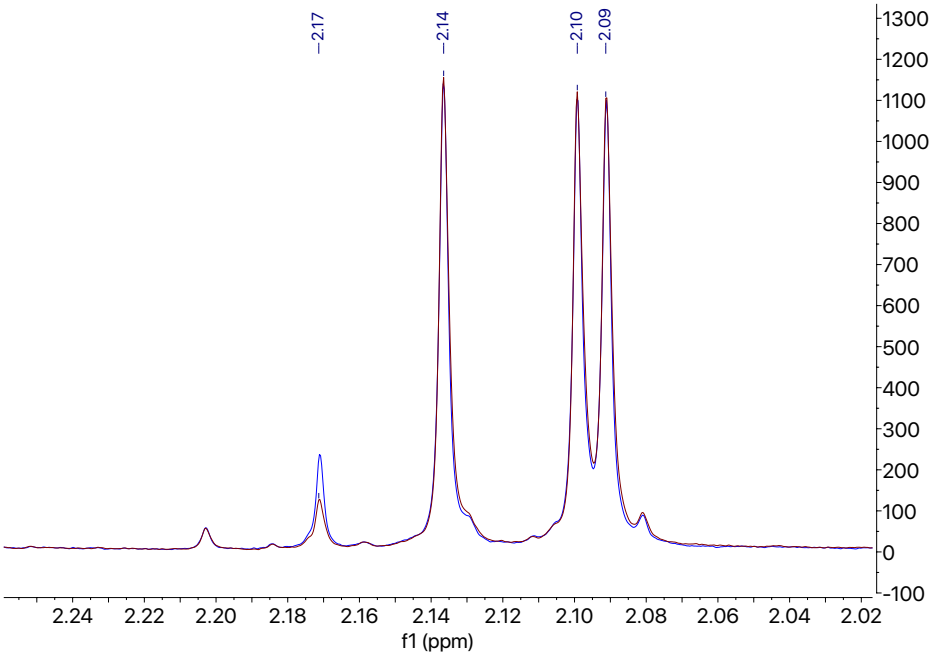
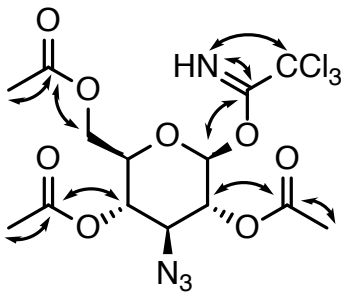


Figure 2.2. Stacked ^{1}H-NMR spectrum of **11β**, taken with 16 h between. The red spectrum was obtained first, while the blue was taken 16 h later.



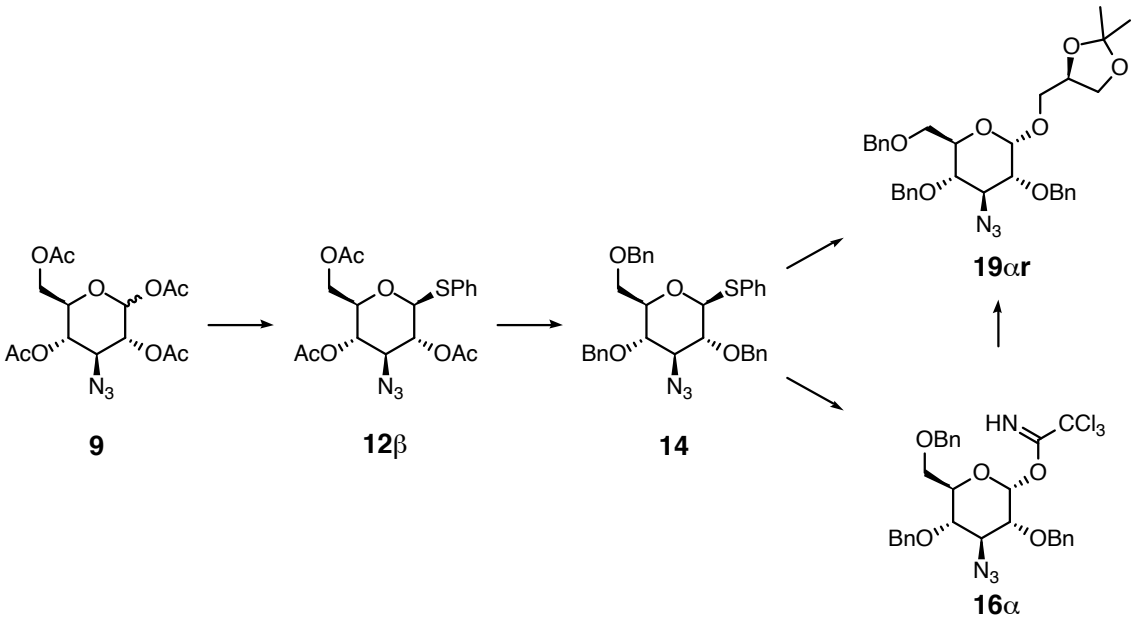
11β

Figure 2.3. Selected long range couplings seen by HMBC

The β anomer of **11** was not reported in the literature, and consequently the compound had to be fully characterised (see appendix A.1). The molecular formula was confirmed by high resolution mass spectrometry (HRMS), and the structure elucidated by ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC and HMBC. The configuration was confirmed by the coupling constant $J_{\mathrm{H1,H2}}$, which was found to be 8.1 Hz. From HMBC the substituents could be placed, due to long range coupling, as shown in figure Figure 2.3.

2.1.3 Benzyl protected thio glycosyl donor

It was decided to try another protecting group at the 2-*O* position to avoid anchimeric assistance. Ethers are commonly used as protecting groups when neighboring group participation is to be avoided in glycosylation reactions.[19] Thus, benzyl like ethers were chosen as a prominent protecting group. A new synthetic plan using benzyl ether was devised (Scheme 2.6).

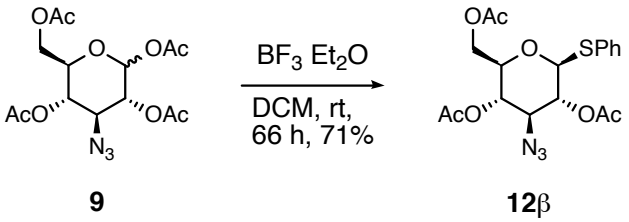


Scheme 2.6. Revised synthetic plan for the glycosylation at 1-position.

To alter the protecting groups in the molecule without affecting the protecting group at the 1-*O* position, an orthogonal protecting group had to be placed here. Thiophenyl was chosen on account of its high stability and ability to act as a glycosyl donor itself.[12,19]

The tetra-acetylated glucoside **9** was treated with thiophenol yielding both anomers of the sulphide **12** (Scheme 2.6). The first attempt to make the thioether resulted in a yield of 35% of the β sulfide **12β** with 29% recovered pure α starting material, **9α** (entry 1, Table 2.6). This indicated that the reaction rate of the **9α** anomer was slower than the rate of the **β** anomer. A longer reaction time was explored to improve the yield. Disappointingly, after 66 h, full conversion had not been achieved, and after termination of the reaction and column chromatography the products were obtained in a yield of 48% β and 5% α (entry 2).

According to Deng et al., the use of sonication during synthesis of fully acetylated phenyl thioglycopyranoside from α-glucose pentaacetate drastically shortened the reaction time and improved the yield.[77] Sonication did indeed boost the reaction rate, however, TLC monitoring clearly showed the formation of several byproducts after 30 minutes. The reaction was terminated and after column chromatography the desired **12β** was isolated in 19% yield, with 59% recovered starting material. Additional investigation into the use of sonication was not conducted due to increased formation of byproducts and difficulty in purification. Ultimately, it was decided that the best way to increase the yield of **12β** was to optimize the preceding reaction (**8** → **9**). As the starting material **9β** had a higher reaction rate than **9α**, starting with pure β would probably result in better yields in a shorter time.



9 **12**β

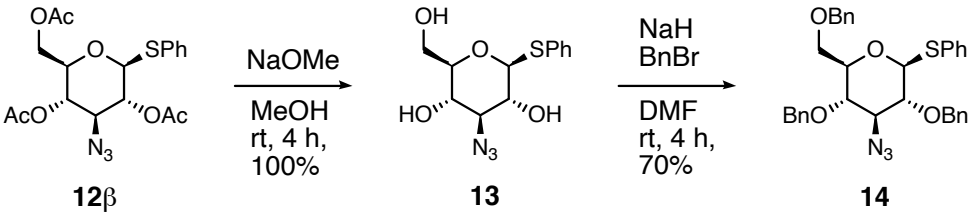
Scheme 2.7. Synthesis of sulfide **12β** in 71% yield with respect to recovered starting material. .

Hydrolysis of the acetyl groups in **12**, providing **13**, proceeded smoothly in quantitative yields (Scheme 2.8). The subsequent protection of the hydroxy groups with benzyl ethers yielded the glycosyl donor **14** in 70% yield.

Table 2.6. Sulfidation of tetraacetylated glucoside **9**. Constant reaction parameters: $BF_3 \cdot Et_2O$ (5 eqv.), DCM (10 mL/g), rt.

Entry	**9** [g]	Time [h]	Yield **12β** [%]	Yield **12β**[a] [%]	Yield **12α** [%]
1	0.471	24	35	49	3
2	1.070	66	48	71	5
3[b]	0.150	0.5	19	46	1

[a] With respect to recovered **9**. [b] The reaction was performed under ultra sound sonication.

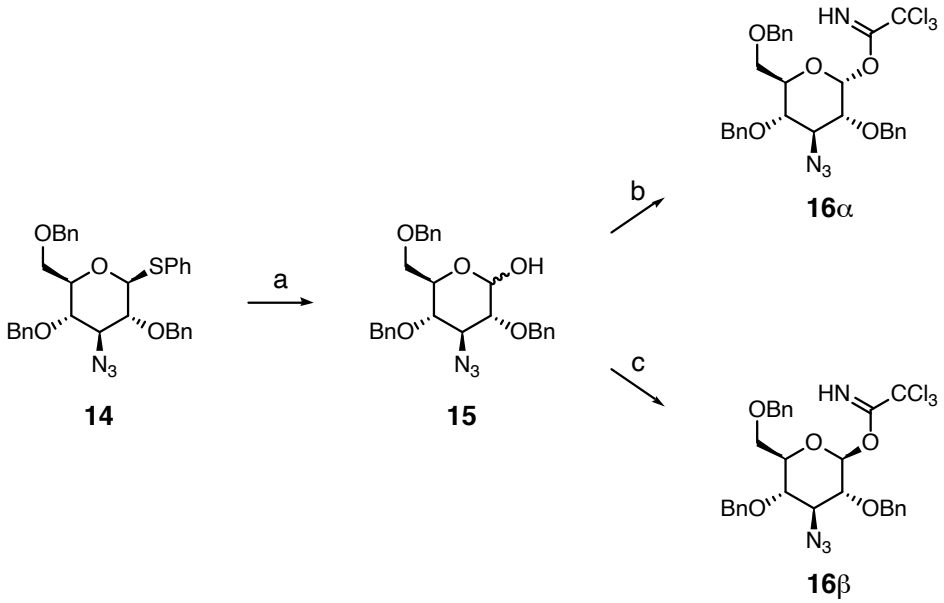


Scheme 2.8. Experimental procedure for conversion of acetyl protected glucoside **12** to benzyl protected glucoside **14**.

2.1.4 Benzyl protected trichloroacetimidate

To transform the thioglucoside glycosyl donor **14** into the Schmidt donor **16**, the thiophenyl was first hydrolysed before a trichloroacetimide was reacted into the anomeric position (Scheme 2.9). Vetter et al. reported the removal of thio phenyl in 80% yield within 30 minutes by use of *n*-bromosuccinimide in acetone/H_2O.[78] After 4 h under these conditions, the presence of starting material was evident, by TLC analysis, (Table 2.7, entry 1). In the course of parallel glycosylation work (see section 2.2), reaction conditions for rapid glycosylation of **14** were discovered. By performing the reaction in DCM with water as a glycosyl acceptor, *n*-iodosuccinimide (NIS) as promoter and TMSOTf as catalyst, the yield was increased to 79% in 2 h (entry 2). These conditions also worked well on a gram scale (entry 3).

The conditions employed in the synthesis of acetylated trichloroacetimidate **11** were also employed to prepare benzylated derivatives (Table 2.8). Again the nature of the base and the length of the reaction determined the major product. With DBU as base, the



Scheme 2.9. a) NIS (1.9 eqv.), TMSOTf (0.14 eqv.), DCM/H_2O (95/5 v/v), rt, 2.5 h, 79% b) DBU (0.15 eqv.), CCl_3CN (3.0 eqv.), DCM, rt, 20 h, 61% c) K_2CO_3 (0.13 eqv.), CCl_3CN (2.7 eqv.), DCM, rt, 4 h, 16%

α anomer was the major product (41%) after 20 h (entry 1). Doubling the reaction time resulted in almost 50% increase in the yield (61%) (entry 2). The β anomer was not observed under these conditions. Conversely, with K_2CO_3 as base in a much shorter reaction (4 h), the β anomer was the major product, albeit at a low yield of 16% (entry 3).

The purification of **16α** was easily achieved by eluting the crude product through a short pad of silica. In purification of the β product, the presence of the closely eluting α anomer necessitated a longer column. It was then observed that both the α and β anomer reacted on the silica gel. This was seen by TLC, when an additional set of co-eluting compounds with distinct differences in retention from the product were observed after column chromatography. The starting material eluted after both product anomers, but with a higher R_f-value than the byproducts of α and β, indicating the formation of more polar byproducts during column chromatography. From ^{1}H-NMR of the fractions containing imidate **16β**, the byproduct was determined to account for about 8% of the desired compound (see Figure 2.4). The presence of a small singlet at 8.49 ppm led to

Table 2.7. Hydrolysis of thioether **14** to **15**. Conditions A: Acetone/H_2O (90/10, v/v), NBS (2 eqv.), N_2-atmosphere. Conditions B: DCM/H_2O (95/5, v/v), NIS (2 eqv.), TMSOTf (0.14 eqv.), N_2-atmosphere

Entry	**14** [mg]	Conditions	Time [h]	Yield [%]
1	171	A	4	43[a]
2	341	B	2	79
3	1110	B	2	75

[a] Not full conversion, 13% recovered starting material.

Table 2.8. Synthesis of trichloroacetimidate **16** from glucoside **15**. Constant reaction parameters: Base (0.15 eqv.), CCl_3CN (3 eqv.), DCM (15 mL/g), rt, N_2-atmosphere

Entry	SM [mg]	Base	Time [h]	Yield α/β [%]
1	210	DBU	20	42/-[a]
2	317	DBU	41	61/-[a]
3	696	K_2CO_3	4	2/16

[a] the β anomer was not observed.

the hypothesis that the byproduct could be the rearranged trichloroacetamide derivative (**16B**, Figure 2.5), since this also has one proton in a similar chemical environment. The rearrangement of trichloroacetimidates to their amide isomer is known to take place under acidic conditions.[79,80] It was therefore hypothesised that the slightly acidic silica gel could facilitate this rearrangement. The large difference in R_f-values was remarkable (Table 2.9). It is unknown if the rearrangement would cause such a contrast in retention properties. Thus, it is possible, some other alterations have happened, and the byproduct is something else.

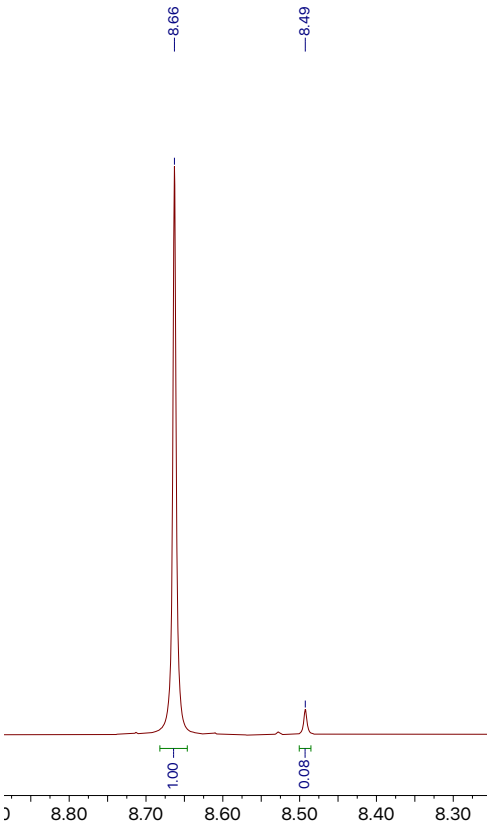


Figure 2.4. Part of the ^{1}H-NMR of **16β**, zoomed in at the region where the presence of byproduct is clearly visible. The full spectrum is given in Figure A.9

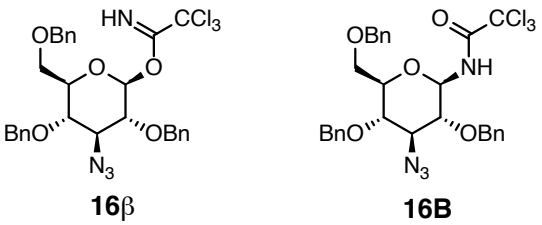


Figure 2.5. Presumed rearranged byproduct (**16B**) from **16β** after column chromatography.

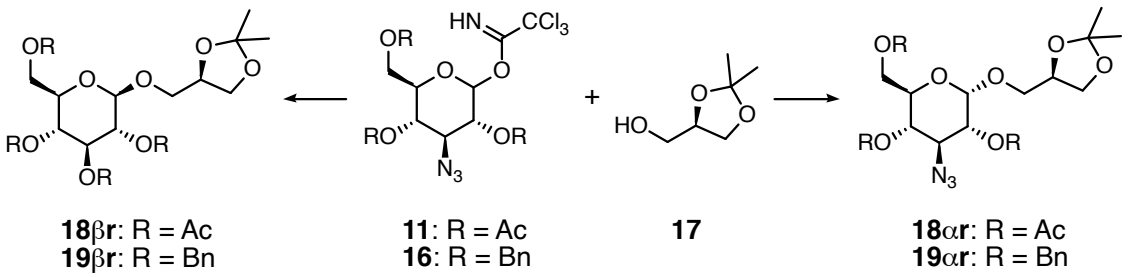
Table 2.9. Retention factors, in *n*-pentane:Et_2O 2:1, of compounds eluting successively during the purification of **16β**.

Compound	R_f	R_f of byproduct
16α	0.38	0.11
16β	0.32	0.09
15	0.15	-

2.2 Glycosylation reactions

In the total synthesis, employed by the research group, towards the target compound **1**, the glycerol moiety is introduced by oxidation of an allyl ether. This results in a mixture of the R- and S-isomers, which is strenuous to separate. In pursue of alternative methods to introduce an enantiomerically pure glycerol moiety, the Schmidt glycosylation was investigated. Glycosylation using thioglucosides as glycosyl donor was looked into as well. Due to problematic purifications the studies were purely qualitative.

2.2.1 Schmidt glycosylation



18β**r**: R = Ac
19β**r**: R = Bn

11: R = Ac
16: R = Bn

17

18α**r**: R = Ac
19α**r**: R = Bn

Scheme 2.10. Schmidt glycosylation of glycosyl donors **11** and **16** with glycosyl acceptor **17**.

Schmidt glycosylation was, in this work, initially attempted on the trichloroacetimide **11α** using TMSOTf as Lewis acid, (Scheme 2.10). After 20 h the desired product **18α** was not observed in the ^{1}H-NMR (entries 1 and 2, Table 2.10). However, the β anomer was found. The reactions were carried out with TMSOTf, 0.3 eqv. and 0.04 eqv. (entries 1 and 2 respectively). ^{1}H-NMR of the semi-purified β products indicated isomerization of

the glycerol moiety when 0.3 eqv. Lewis acid was employed, while no isomerization was observed with 0.04 eqv. Lewis acid (Figure 2.6).

Table 2.10. Qualitative study on Schmidt glycosylation using trichloroacetimide **11** or **16** with glycosyl acceptor **17**. Constant conditions: Lewis acid (0.3 eqv.), **17** (1.4 eqv.), N_2-atmosphere, 0 °C → rt, 20 h. Isomerization was observed on the glycerol moiety of the desired products.

Entry	Glycosyl donor	Lewis acid	Anomer Product
1	**11α**	TMSOTf	β
2	**11α**	TMSOTf [a]	β[b]
3	**11α**	$BF_3 \cdot Et_2O$	-[c]
4	**11β**	$BF_3 \cdot Et_2O$	-[c]
5	**16α**	TMSOTf	α/β
6[d]	**16α**	TMSOTf	α/β
7	**16α**	TMSOTf [a]	α/β
8	**16β**	$BF_3 \cdot Et_2O$	α/β

[a]0.04 eqv. Lewis acid. [b]No isomerization was observed.

[c]No desired product was observed. [d]Reaction time was 1 h.

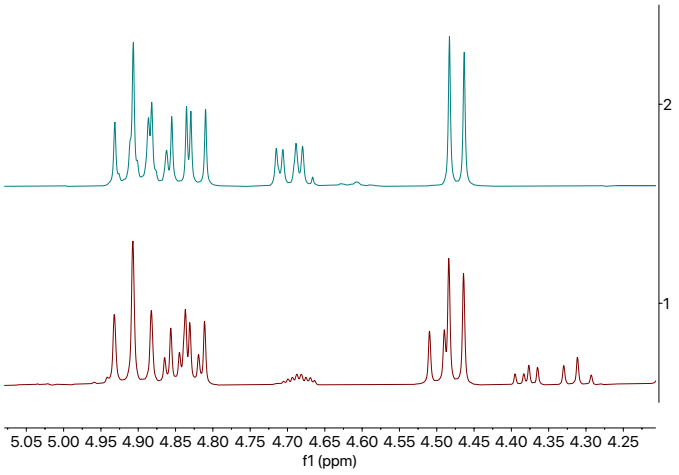
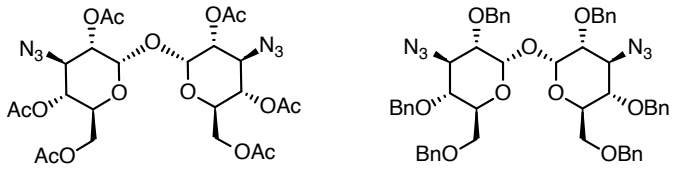


Figure 2.6. ^{1}H-NMR of impure samples of **18β** indicating isomerisated product. 0.3 Eqv. (bottom spectrum) or 0.04 eqv. (top spectrum) Lewis acid was added in the reaction. The numbers 1 and 2 corresponds to entries 1 and 2 in Table 2.10. The signal at 4.48 ppm derives from the anomeric proton.

As TMSOTf did not provide the α anomer, the Lewis acid was changed to the frequently employed $BF_3 \cdot Et_2O$ to see if this could impact the outcome. Since $BF_3 \cdot Et_2O$ favors inversion to a higher degree than TMSOTf, both anomers of the starting material were tested (entries 3 and 4). The results did at first seem promising; in both reactions the main product seemed to be an α-sugar containing two methyl groups. However, the sugar compound only contained two acetyl groups, and thus could not be the desired product, **18α**. It was therefore not given more attention and remains unidentified. A minor product in the reactions with $BF_3 \cdot Et_2O$ was assumed to be the self-glycosylated **20** (Figure 2.7). ^{1}H-NMR indicated two α signals, a total of 14 protons in the sugar region 3.5-5.8 ppm, and six acetyl groups (spectrum is given in Figure A.27). The acetyl groups were divided in three singlets, indicating symmetry or similar chemical environment. This led to the hypothesis of self-glycosylation. The large difference between the α proton shifts are probably due to the two glucosides having different dihedral angles towards the electron pairs of the oxygen. Similar observations was found in the case of $BF_3 \cdot Et_2O$ and benzylated glycosyl donor, which are presented later in this section.



20 **21**

Figure 2.7. Self-glycosylated products found when $BF_3 \cdot Et_2O$ was utilized as Lewis acid during Schmidt glycosylation.

The anchimeric assistance of the 2-*O*-acetyl was concluded to be too great to produce any α anomer of the glucoglycerol **18**, as expected from the literature.[10–13] It was proceeded to test Schmidt glycosylation of the benzylated trichloroacetimides **16α** and **β**. With TMSOTf as Lewis acid promoter, both anomers of the desired product were observed on ^{1}H-NMR (entry 5). HPLC analysis of the crude product indicated isomerization of the products, where 4 products eluted close together (Figure 2.8). Due to the similar retention of the anomers, purification by silica gel column chromatography proved difficult, though a few pure β and some α-enriched fractions were obtained. NMR analysis of these fractions confirmed isomerization of the acetonide, as a total of eight signals were present in the region of 1.25-1.37 ppm, indicating four sets of acetonide methyl groups (Figure 2.9).

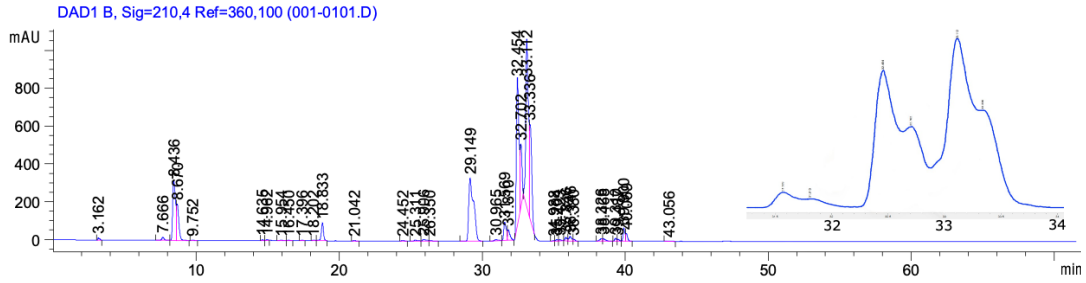


Figure 2.8. Chromatogram (method A) of crude **19**. The area where the products elute is magnified.

In order to minimize isomerization, shortening the reaction time and lowering the amount of Lewis acid was attempted, but to no avail (entries 6 and 7). Employing $BF_3 \cdot Et_2O$ as Lewis acid also gave isomerized products (entry 8). Additionally with $BF_3 \cdot Et_2O$, a small amount of the self-glycosylated disaccharide **21** was isolated (Figure 2.7). This was similar to the results for the acetylated derivatives. Self-glycosylation was observed in the presence of $BF_3 \cdot Et_2O$ there as well, but not with TMSOTf.

Isomerization seems to happen unrelated to reaction time, the Lewis acid or protecting groups employed. Multiple authors have reported successful Schmidt glycosylations using chirally pure acetonides without encountering isomerization issues.[56–59] Moreover, one Schmidt glycosylation reaction carried out in this project also proceeded without any observed isomerization, (entry 2). Thus it seems possible to avoid isomerization.

Initially the source of isomerization was suggested to be some kind of impurity. The glycerol **17** was pure by NMR analysis (Figure A.10), and consequently another explanation had to be found. One method to deprotect acetals is by acid catalysed hydrolysis.[14,15] The isomerization was proposed to occur by partial deprotection and reprotection of the acetonide, as shown in Scheme 2.11. This, however, requires either an acidic proton or another electrophile acting similarly as the proton. The reactions were performed in dry DCM with either TMSOTf or $BF_3 \cdot Et_2O$ as promoter under N_2 atmosphere with molecular sieves. There should not be any acidic protons. TMSOTf is reported to hydrolyse to TfOH.[81,82] Consequently, if there is H_2O in the reaction mixture, TfOH could lead to partial deprotection. The solvent, glycerol **17** and trichloroacetamides, **11** and **16**, were unlikely to contain H_2O . The solvent was collected from a solvent purification system, the glycosyl acceptor **17** was freshly bought, and H_2O was not seen in the NMR analysis

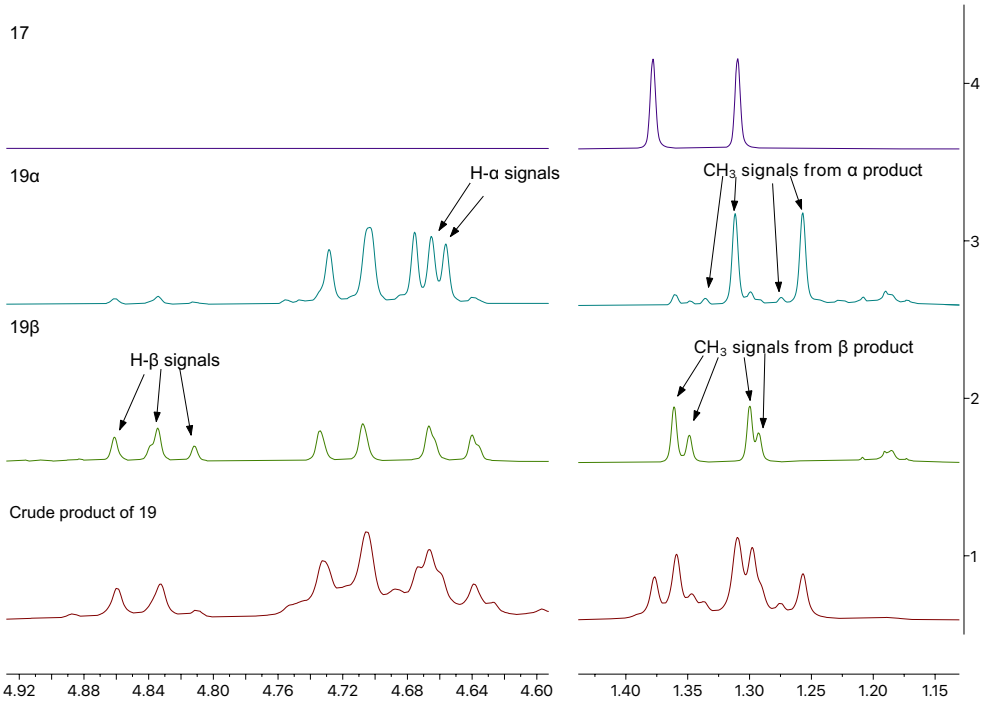
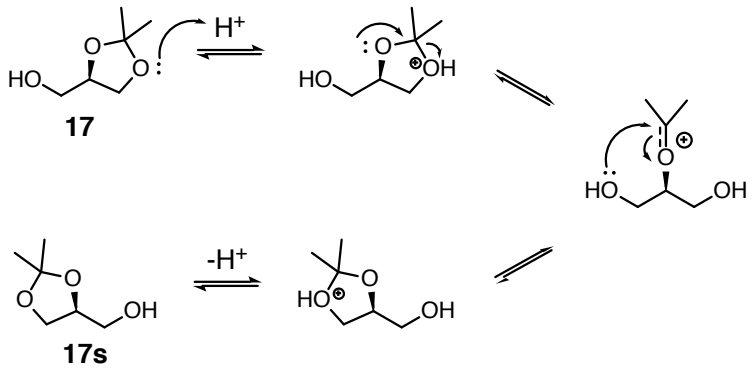


Figure 2.9. ^{1}H-NMR of compounds **17** (spectrum 4), **19** α(spectrum 3), β (spectrum 2) and crude product (spectrum 1).

(Figure A.10). No H_2O was used during synthesis or purification of the TCAIs. The purity and water content of the Lewis acids was not analyzed, and thus, there could be H_2O or other impurities present. This is deemed unlikely, as isomerization is observed with both Lewis acids.

The glycosyl donors, **11** and **16** not being sufficiently pure could be an explanation. The purification of **16** showed the decomposition of product on the column. The products were consequently not completely pure (Figure 2.4). This decomposed byproduct is assumed to be the rearranged amide (**16B**, figure Figure 2.5), but it is not identified, and therefore it is unknown how and if it could affect isomerization of the acetonide.

In the literature, the racemization of benzylidene acetal is reported to happen due to partial ring opening.[83] The mechanism presented by Harangi et al., is disappointingly inadequate in explaining racemization of acetals bearing two equal substituents, like



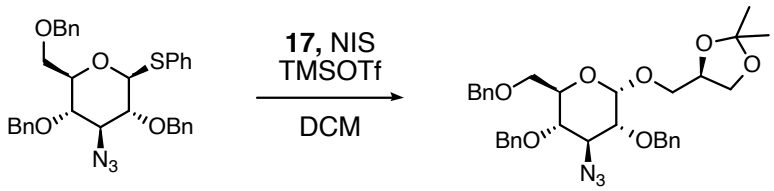
Scheme 2.11. Possible mechanism for acid catalysed isomerization of **17** to **17s**.[15]

acetonides.[83] Nevertheless, Lewis acid promoted racemization of acetonide **17** has been reported in the literature, due to intramolecular acyl migration.[59,84,85] Gordon and Danishefsky found, during glycosylation with fluoride glycosyl donor, that isomerization of the isopropylidene glycerol took place, but could be avoided by the use of additives.[84] In the case of Königs Knorr glycosylation, the isopropylidene glycerol **17** has been seen to racemise due to acyl migration.[85–88]

From the results of this project it seems like isomerization should occur during Schmidt glycosylation using acetonide, while retention of stereochemistry is the deviation. It is doubtful that this is the case, as retention of stereochemistry is reported multiple times in the literature and was observed once in this project.[56–59] Thus it seems more likely that isomerization occurs due to some unknown factor or impurity. The benzylated derivative, 1,2-di-*O*-benzylglycerol, of the acetonide **17** have been reported to not undergo racemization.[85,88] This could be utilized instead of the acetonide to avoid the problem.

2.2.2 Thioglucoside as glycosyl donor

The glycosylation of a fully benzylated derivative of **14** with **17** has been reported by Yagami et al., using TfOH as promotor at -80 °C to produce the β anomer as the main product.[89] Wanting to reduce the number of reactions in the overall synthesis, it was qualitatively tested if glycosylation could be achieved from the thioglucoside **14** (Scheme 2.12). Using the conditions described by Wang et al. as a starting point, longer reaction time and higher temperature was employed with the intent to improve both yield and anomeric ratio.[90]



14 **19αr**

Scheme 2.12. Attempted glycosylation using **14** as glycosyl donor.

Wang et al. activated the glycosyl donor with NIS and TMSOTf prior to addition of the acceptor. When monitoring by TLC it was evident that **14** was fully consumed/activated within 30 minutes. **17** was then added to the solution and stirred for the time given in Table 2.11. After 4 h the reaction was quenched giving the 1-hydroxy **15** as the major product, while no stereoisomer of **19** was observed (entry 1, Table 2.11). As there was

Table 2.11. Attempted glycosylation towards **19** directly from thioglucoside **14**. No desired product was observed in any entry. Conditions A: NIS (1.3 eqv.), TMSOTf (1.2 eqv.), **17** (1.4 eqv., added 30 minutes after NIS and TMSOTf). Conditions B: **17** (0.6 eqv., added at the same time as the other reagents.), NIS (2.0 eqv.), TMSOTf (0.4 eqv.) Constant conditions: **14** (0.1 mmol), N_2-atmosphere, mol.sieves.

Entry	Conditions	Time	Temperature
1	A	4	0
2	A	20	0 °C → rt
3	B	20	0 °C → rt

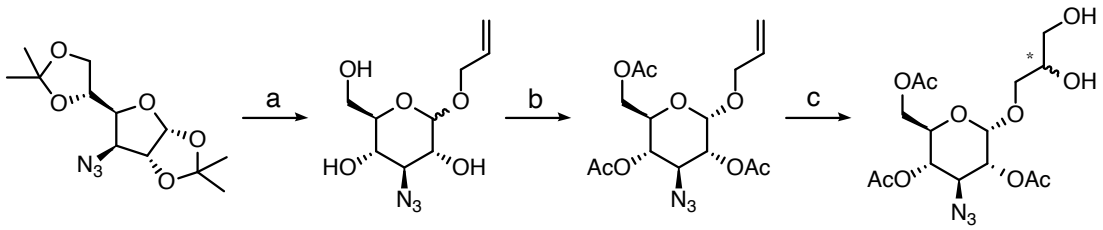
no trace of the desired product it was speculated that the intermediate had not reacted with any glycosyl acceptor until the work up. During work up it was exposed to H_2O, which would explain why the non-glycosylated **15** was the major product. Employing higher temperature and longer reaction time to increase the probability of glycosylation prior to the work up, was unfruitful (entry 2).

Seeing that no glucoside **19** had been observed in the previous two reactions, an experiment with the glycosyl acceptor as limiting agent was performed. The glycosyl acceptor was added at the same time as TMSOTf and NIS. The reaction was monitored by TLC and ^{1}H-NMR analysis of the reaction mixture after full consumption of the starting

material revealed that the methyl signals from the acetonide was lacking. Further investigation into the nature of the byproducts were not undertaken. Instead, since none of the attempted glycosylation reactions performed with the thioglucoside yielded the desired product, it was concluded that thioglucoside **14** was unsuitable as a glycosyl donor for this project. It is noted that only TMSOTf and NIS were investigated as promoters. Thus, under other conditions glycosylation between this glycosyl donor and acceptor may work. This was nevertheless not looked into.

2.3 Allyl method

An alternative method to introduce a glycerol moiety in the anomeric position, already utilized by the research group, is presented in Scheme 2.13. This method has yet not provided satisfactort R-/S-selectivity, but is presented herein as a proof of concept applicable also for 3-azido-3-deoxy glycopyranosides. The method involves acid catalyzed concomitant rearrangement and Fischer glycosylation to insert allyl ether in the anomeric position, with subsequent acetylation of the hydroxy groups. Sharpless asymmetric dihydroxylation is then applied to transform the double bond to a diol, providing the glycerol moiety.



Scheme 2.13. Alternative method to introduce glycerol moiety at anomeric position. a) Allyl alcohol, HCl, reflux, 30 min b) Pyridine, Ac_2O rt, overnight, 53% total yield over 2 steps c) AD-mix-β, t-BuOH/H_2O, 0 °C → rt, 22 h, 45%.

The allyl group was introduced by refluxing the starting material in allyl alcohol with catalytic amounts of HCl, producing **22** as an anomeric mixture. The high polarity of the compound made purification by silica column laborious and it was not attempted as the research group had previously found that it made little to no impact on the subsequent

reactions on similar derivatives. ^{1}H-NMR of the crude **22** showed α/β ratio of 65:35.

Direct acetylation of **22** with Ac_2O in pyridine overnight rendered **23** in a total yield of 53% over two steps. This compound provided baseline separation of the product anomers by column chromatography, giving 32% **23α** and 21% **23β** over two steps. A total yield of 53% was considered low in comparison to other derivatives made by the research group.[91] The fractions after column chromatography which did not contain the desired product were therefore collected and once again subjected to Ac_2O and pyridine overnight. No desired product was found, however, the 3-azido-3-deoxy glucopyranose **9** (Scheme 2.4) was isolated from the new crude product. This indicates that the reaction to form **22** were not completed, and some rearranged, unglycosylated intermediate (**8**, Scheme 2.4) still was present in the crude, which would attribute to the overall low yield.

Sharpless asymmetric dihydroxylation was carried out on both anomers of **23**. AD-mix-β was used as the research group had found this to give a better selectivity towards one of the isomers compared to AD-mix-α. From Table 2.12 it is seen that the **23β** highly favoured one of the isomers, while the α anomer resulted in a better yield. This is in accordance with the trend the research group has seen on 3-*O*-benzylated derivatives. These reactions were only conducted once as a proof on concept, and could probably be optimized with regards to both yield and selectivity.

Table 2.12. Synthesis of **24** from **23**. Constant parameters: 0.16 g SM, AD-Mix-β (1.40 g/mmol), H_2O:t−BuOH (94 mL/g, 1:1 v:v), 0 °C → rt.

Anomer	Time [h]	Yield [%]	Isomer ratio[a]
β	29	27	94:6
α	22	45	72:28

[a]It is unknown which isomer is in excess

The use of the allyl moiety is a facile method to introduce a glycerol moiety at the anomeric position, which works for the 3-azido-3-deoxy-glucopyranose. Although the separation of anomers **23α** and **β** is simple, the separation of R- and S-isomers is terrible. There was no separation by HPLC (method A), and the compounds eluted as one symmetrical peak. On similar derivatives, the research group has found that separability is improved a little by masking the diol with isopropylidene. The separability is, however,

not improved enough to get clean fractions. Thus, this method need optimization if it is to produce chirally pure glucoglycerols.

3 Conclusion and Further Work

The synthesis of the different glycosyl donors proved successful and mainly in sufficient yields. The most problematic reactions were the introduction of thiophenyl to the anomeric position, and the synthesis of β TCAIs. Insertion of thiophenol was heavily time consuming, and only gave mediocre yields. Optimization of previous reactions was deemed the most promising aspects to increase the yield and shorten the reaction time. The formation of β imidates worked, but the yields were low. Optimization with regards to base, temperature and yield should be performed, if these products are to be made again.

Schmidt glycosylation with TMSOTf on acetylated derivatives produced exclusively the β glucoside, due to anchimeric assistance. This was overcome by changing the protecting groups to benzyl ether. Investigation into the reaction conditions, and effect of protecting groups, to increase the ratio of α anomer is needed. $BF_3 \cdot Et_2O$, as promoter, did not produce the desired acetylated glycoside, but was successful for the benzylated imidates. Additionally, indications of self glycosylation was observed when $BF_3 \cdot Et_2O$ was employed. Isomerization of the glycerol moiety during the reaction revealed itself to be a persistent problem. The cause of isomerization was not determined, but either some unknown impurity or the Lewis acid were regarded as the most likely reasons. Change of the glycoside acceptor to 1,2-di-*O*-benzyl-glycerol appear to be the most promising method to overcome isomerization. The purification of the glycosylated product was difficult. Partial separation of the β was achieved by use of enormous amounts of silica. The separation of R- and S-isomers were, however, unsuccessful. Initial testing into the suitability of glycosylation by thioglucoside **14** were unfruitful and not further investigated in this project. Although, for further investigations the exploration of other promoters could be rewarding.

Introduction of a glycerol moiety by oxidation of an allyl ether was successful. The product was, as expected, not optically pure. Optimization of the reaction conditions could greatly improve yield, and possibly isomeric selectivity.

The remaining parts of the synthetic path towards target compound **2** is still unexplored. The immediate problem is the removal of benzyl ether in the presence of azide. This can be problematic and reaction conditions, as well as the use of other benzyl like ethers, need to be explored. The work presented herein has explored the initial synthetic steps towards the amido derivative (**2**) of **1**. From this, the complexity of the synthesises towards both compounds are better understood, and consequently, the work can aid in the path toward said compounds.

4 Experimental

4.1 General information

All chemicals were bought from Sigma Aldrich and used without further purification. Anhydrous solvents were collected from a Braun "MB SPS-800 Solvent Purification System". Solvents were evaporated on a rotary evaporator in a water bath at 40°C or 60°C. Temperatures below or above rt was achieved by ice or oil bath.

4.1.1 Separation techniques

Thin layer chromatography was conducted by using silica gel on aluminium (60Å, F254, Merck). Aromatic compounds was visualised by UV (254 nm), while non-aromatic compounds were visualised by $KMnO_4$ staining.

Flash column chromatography (FCC) was performed using silica gel (40-63 µm, 60 Å, Merck). Mobile phase composition is mentioned in each case.

Analytical HPLC was carried out using an Agilent Technology "1290 Infinity" instrument with a G4220B binary pump, G4226A autosampler, G1316A column compartment and G1315D diode array detector (DAD). An Agilent "Zorbax Bonus-RP", 250 x 4.6 mm, 5µm column was used as column, with an Agilent "Zorbax Bonus-RP", 12.5 x 4.6 mm, 5µm guard column. Automation and processing was performed using Agilent Technologies ChemStation for LC and CE systems (version: B.04.03 SP1[87]) software. The flow was 1 mL/min and the column temperature was 25 °C. The acetonitrile was analytical (HPLC) grade while the H_2O was *Milli-Q* purified.

Method A: A linear gradient of acetonitrile:H_2O starting at 20:80 and going to pure ACN after 50 minutes, followed by 15 minutes pure ACN.

4.1.2 Spectroscopy

NMR spectra were carried out on a Bruker 600 MHz "Avance III" with a 5 mm cryogenic CP-TCI Z-gradient probe, operating at 600 MHz for 1H-NMR and 150 MHz for 13C-NMR, or a Bruker 400MHz "Avance III HD" with a 5mm SmartProbe Z-gradient probe. Chemical shifts are given in δ (ppm), relative to TMS, and coupling constants (J) are given in Hertz. All spectra were processed with MestReNova 14.2.0.

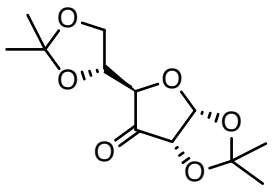
IR spectra were recorded as a thin layer of solid, using a Bruker "Alpha FTIR ECO-ATR" spectrometer with OPUS software.

Optical rotation was measured using an Anton Paar "MCP 5100" polarimeter, with a 2.5 mm stainless steel sample holder, using the sodium D-line (589 nm), at 20°C.

Accurate mass determination in positive and negative mode was performed on a "Synapt G2-S" Q-TOF instrument from Water TM. Samples were ionized by the use of ASAP probe (APCI) or ESI probe. No chromatographic separation was used previous to the mass analysis. Calculated exact mass and spectra processing was done by Waters TM Software Masslynx V4.1 SCN871.

4.2 Synthetic procedures

4.2.1 1,2:5,6-Di-*O*-isopropylidene-3-keto-α-D-ribo-3-hexulofuranose (4)



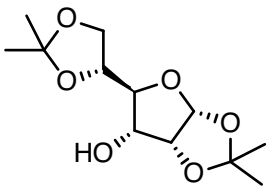
4

Dry DMSO (120 mL) and Ac_2O (60 mL) were combined and stirred at rt. After 2 hours 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**, 10.1 g, 38.8 mmol) was added to

the solution and stirred for 19.5 h at rt. The reaction mixture was concentrated under reduced pressure. The residue was diluted in H_2O and extracted with DCM (10 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated to give a crude product. The crude product was purified by FCC (2:1 → 1:2 *n*-pentane:Et_2O) to give **4** (69%, 6.87 g, 26.6 mmol) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 6.07 (d, J = 4.5 Hz, 1H), 4.33 - 4.27 (m, 3H), 3.94 - 3.98 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H), 1.27 (s, 6H). The NMR is consistent with previously reported data.[92]

4.2.2 1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose (5)

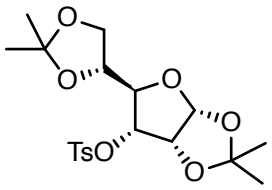


5

To a solution of ketone **4** (6.87 g, 26.6 mmol) in EtOH (96%, 40 mL) at 0 °C $NaBH_4$ (2.54 g, 67.2, 2.5 eq) was added portionwise over a 5 minute period. The solution was slowly warmed to rt and stirred for 17 h. The reaction was quenched by addition of excess NH_4Cl and stirred until there were no visible bubbling. The reaction mixture was concentrated under reduced pressure and diluted with H_2O. The solution was extracted with DCM, and the organic phases were washed with water and brine. The extract was dried over Na_2SO_4, filtered and evaporated to yield a crude product. The crude product was purified by FCC (2:1 → 1:3 *n*-pentane/Et_2O) to give **5** (91%, 6.33 g, 24.3 mmol) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): 5.75 (d, J = 3.9 Hz, 1H) 4.55 (dd, J = 3.9, 5.2 Hz, 1H), 4.24 (td, J = 4.7, 6.5 Hz, 1H), 4.04 - 3.92 (m, 3H) 3.75 (dd, J = 4.7, 8.5 Hz, 1H) 2.47 (d, J = 8.4 Hz, 1H) 1.51 (s, 3H) 1.40 (s, 3H) 1.32 (s, 3H) 1.31 (s, 3H). NMR matches literature data.[93]

4.2.3 1,2:5,6-Di-*O*-isopropylidene-3-*O*-tosyl-α-D-glucofuranoside (6)

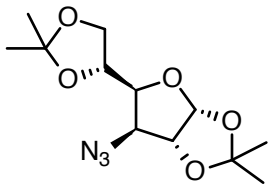


6

TsCl (1.92 g, 10.1 mmol, 1.4 eq) was added to a solution of allofuranose **5** (1.89 mg, 7.25 mmol) in pyridine (8 mL), and stirred at rt for 20 h. Excess ice water was added to the solution and the precipitate was filtered off. The precipitate was recrystallized in MeOH and H_2O to afford **6** in 88% yield (2.65 g, 6.40 mmol) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.87 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 5.76 (d, J = 3.4 Hz, 1H), 4.67 - 4.63 (m, 2H), 4.21 - 4.17 (m, 1H), 4.16 - 4.13 (m, 1H), 3.93 (dd, J = 8.4, 6.8 Hz, 1H), 3.78 (dd, J = 8.5, 6.5 Hz, 1H), 2.45 (s, 3H), 1.53 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H). The ^{1}H-NMR matches reported data[62]

4.2.4 3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (7)



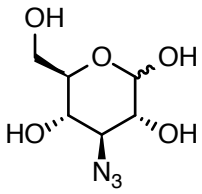
7

Tosylate **6** (400 mg, 0.968 mmol) and NaN_3 (622 mg, 9.57 mmol) was added to DMF (5 mL) and stirred at 135 °C for 68 h. The solvent was removed under reduced pressure and the residue was dissolved in H_2O and extracted with EtOAc. The organic phases was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude was

purified by FCC (*n*-pentane:EtOAc 9:1) to produce **7** (87%, 240 mg, 0,838 mmol) as a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 5.86 (d, J = 3.7 Hz, 1H) 4.62 (d, J = 3.7 Hz, 1H), 4.28 - 4.21 (m, 1H), 4.14 (dd, J = 8.6, 6.0 Hz, 1H), 4.12 - 4.08 (m, 2H) 3.98 (dd, J = 8.7, 4.8 Hz, 1H), 1.51 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H). ^{1}H-NMR was in accordance with previously reported literature.[94]

4.2.5 3-Azido-3-deoxy-D-glucopyranose (8)

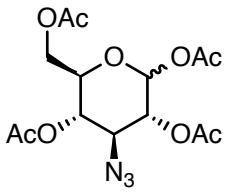


8

The azide **7** (1.26 g, 4.42 mmol) was dissolved in H_2O (11 mL) and added Amberlyst 15 (0.5 g). The mixture was stirred at 80 °C for 22 h. The mixture was filtered and the solvent was evaporated under reduced pressure to give an anomeric mixture of **8** in 100% yield (0.906 g, 4.41 mmol, 50:50 α:β) as a clear oil.

^{1}H-NMR (400 MHz, D_2O): 5.08 (d, J = 3.6 Hz, 1H), 4.56 (d, J = 7.9 Hz, 1H), 3.77 - 3.51 (m, 6H), 3.45 - 3.29 (m, 5H), 3.15 - 3.09 (m, 1H). NMR is consistent with available literature data.[95]

4.2.6 1,2,4,6-Tetra-*O*-acetyl-3-azido-3-deoxy-D-glucopyranoside (9)

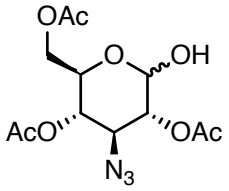


9

The 3-azido-3-deoxy glucopyranose **8** (0.906 g, 4.41 mmol) was added to a solution of H_2SO_4 (11 µL, 0.38 mmol) in Ac_2O (11.0 mL, 116 mmol) and stirred at rt for 4 h. H_2O (30 mL) was added to quench the reaction. The solution was extracted with EtOAc, washed with H_2O and $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness under reduced pressure. This gave **9** an an anomeric mixture in 91% yield (1.507 g, 4.04 mmol, 57:43 α:β) as a clear oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 6.24 (d, J = 3.6 Hz, 1H), 5.60 (d, J = 8.3 Hz, 0.75H), 5.00 - 4.93 (m, 2.5H), 4.88 (dd, J = 10.7, 3.6 Hz, 1H), 4.20 - 4.12 (m, 2H), 4.07 - 3.95 (m, 2.75H), 3.90 (t, J = 10.4 Hz, 1H), 3.72 (ddd, J = 10.0, 4.7, 2.0 Hz, 1H), 3.62 (t, J = 10.0 Hz, 0.75H), 2.12 (s, 3H), 2.07 (s, 3H), 2.06 (s, 2.3H), 2.05 (s, 2.3H), 2.04 (s, 2.3H), 2.03 (s, 6H), 2.02 (s, 2.3H). NMR is in accordance with reported literature.[96]

4.2.7 2,4,6-Tri-*O*-acetyl-3-azido-3-deoxy-D-glucopyranose (10)

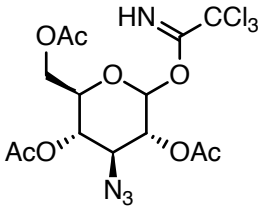


10

NH_4OAc (216 mg, 2.81 mmol) was added to a solution of tetra-acetate **9** (496 mg, 1.33 mmol) in DMF (4.1 mL). After the solution had been stirred at rt for 28 h, the solvent was removed under reduced pressure. The residue was purified by column chromatography (3:2 *n*-pentane:EtOAc) providing an anomeric mixture of **10** as a clear syrup (75%, 329 mg, 0.99 mmol, 85:15 α:β).

^{1}H-NMR(400 MHz, $CDCl_3$): 5.46 (bt, 1H, J= 3.6 Hz), 4.95 (m, 1.2H), 4.77 (m, 1.2H), 4.67 (dd, 0.2H, J= 8.1, 9.0 Hz), 4.21 – 4.04 (m, 4.8H), 3.70 (m, 0.4H), 3.43 (d, 0.2H, J= 9.1 Hz), 2.83 (d, 1H, J= 3.6 Hz), 2.18 (s, 0.6H), 2.17 (s, 3H), 2.13 (s, 3.6H), 2.09 (s, 3.6H). NMR is consistent with earlier reported data[74]

4.2.8 2,4,6-Tri-*O*-acetyl-3-azido-3-deoxy-α/β-D-glucopyranosyl trichloroacetimidate (11)



11

α anomer: A solution of **10** (49.5 mg, 0.149 mmol) and CCl_3CN (70 µL, 0.485 mmol) in DCM (1.0 mL) with molecular sieves (4Å) a under N_2-atmosphere was cooled to 0 °C. A catalytic amount of DBU (2.3 µL, 0.0142 mmol) was added to the solution, which was slowly warmed to rt and stirred for 25 h. The solvent was removed under reduced pressure, and the crude product was directly eluted through a short pad of silica (*n*-pentane:EtOAc 4:1) to yield pure **11α** (81%, 57.3 mg, 0.120 mmol) as a clear syrup.

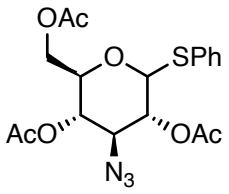
^{1}H-NMR (400 MHz, $CDCl_3$): 8.64 (s, 1H), 6.46 (d, J = 3.6 Hz, 1H), 5.01 (t, J = 10.1 Hz, 1H), 4.91 (dd, J = 3.6, 10.6 Hz, 1H), 4.18 - 4.12 (m, 1H), 4.08 - 3.97 (m, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H). Proton spectrum was in accordance with earlier reported data.[97]

β anomer: To a stirred solution of the 1-OH glucopyranose **10** (371 mg, 1.12 mmol), K_2CO_3 (425 mg, 3.07 mmol) and molecular sieves in DCM (6 mL) under a N_2-atmosphere at 0 °C was added CCl_3CN (0.2 mL, 1.4 mmol). After 3 h at rt the mixture was filtered and evaporated to give a crude product. Purification by FCC (*n*-pentane:EtOAc 6:1 → 2:1) resulted in pure **11β** (15.5 mg, 32.6 µmol, 3%) as a white solid.

HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. 497.0010 for $C_{14}H_{17}N_4O_8Cl_3Na$, found 497.0013; $[\alpha]_D^{20}$ = 21.3 ° (*c* 0.61, CH_2Cl_2); IR (cm^{-1}): 3449, 3334, 2960, 2927, 2109, 1748, 1681, 1432, 1374, 1217, 1153, 1071, 1037, 969, 891, 838, 798, 646, 600, 560; ^{1}H-NMR (600 MHz, $CDCl_3$): 8.64 (s, 1H, NH), 5.75 (d, J = 8.1 Hz, 1H, H-1), 5.16 (dd, J = 8.1, 10.2 Hz, 1H, H-2), 5.04 (t, J = 9.8 Hz, 1H, H-4), 4.21 (dd, J = 4.5, 12.5 Hz, 1H, H-6a), 4.08 (dd, J = 2.5, 12.5 Hz, 1H, H-6b), 3.78 (ddd, J = 2.5, 4.5, 9.8 Hz, 1H, H-5), 3.65 (t, J = 10.0

Hz, 1H, H-3), 2.07 (s, 3H, Me), 2.03 (s, 3H, Me), 2.02 (s, 3H, Me); ^{13}C-NMR (150 MHz, $CDCl_3$): 170.8 (CO), 169.3 (CO), 168.8 (CO), 161.2 (C=N), 95.9 (C-1), 90.5 (C-Cl_3), 73.8 (C-5), 70.1 (C-2), 68.1 (C-4), 64.3 (C-3), 61.7 (C-6), 20.9 (Me), 20.8 (Me), 20.7 (Me).

4.2.9 2,4,6-Tri-*O*-acetyl-3-azido-3-deoxy-1-phenylthio-α/β-D-glucopyranoside (12)



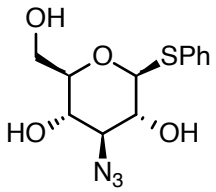
12

$BF_3 \cdot Et_2O$ (1.8 mL, 14.6 mmol) was added to a solution of thiophenol (0.40 mL, 3.91 mmol, 1.4) and sulfide **9β** (1.07 g, 2.88 mmol) in dry DCM (10 mL). The reaction progressed at rt for 66 h. The reaction was quenched by the addition of $NaHCO_3$ and extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by FCC (*n*-pentane:EtOAc:DCM 6:1:1 - 5:1:1) to give **12** as a pure α-sulfide (5%, 64 mg, 0.15 mmol, 8% with respect to recovered SM) and pure β-sulfide (48%, 586 mg, 1.38 mmol, 71% with respect to recovered SM) as white solids.

α-anomer: ^{1}H-NMR(400 MHz, $CDCl_3$): 7.39 - 7.35 (m, 2H), 7.26 - 7.20 (m, 3H), 5.82 (d, J = 5.7 Hz, 1H), 4.89 (dd, J = 10.6, 5.6 Hz, 1H), 4.88 (t, J = 10.0 Hz, 1H), 4.42 (ddd, J = 10.1, 5.3, 2.3 Hz, 1H), 4.15 (dd, J = 12.4, 5.3 Hz, 1H), 3.96 (dd, J = 12.4, 2.4 Hz, 1H), 3.87 (t, J = 10.2 Hz, 1H), 2.11 (s, 3H), 2.08 (s, 3H), 1.94 (s, 3H).

β-anomer: ^{1}H-NMR(400 MHz, $CDCl_3$): 7.45 - 7.40 (m, 2H), 7.27 - 7.22 (m, 2H), 4.86 (q, J = 9.7 Hz, 2H), 4.59 (d, J = 10.0 Hz, 1H), 4.15 - 4.07 (m, 2H), 3.64 - 3.56 (m, 2H), 2.11 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H). Both anomers' NMR matches previously reported spectra[98]

4.2.10 3-Azido-3-deoxy-1-phenylthio-β-D-glucopyranoside (13)

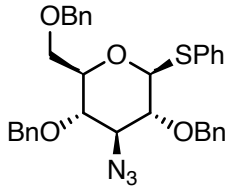


13

NaOMe (29.8 mg, 0.572 mmol) was added to a solution of **12β** (585 mg, 1.38 mmol) in MeOH (12 mL). The solution was stirred at rt for 4.5 h before an excess of dry Amberlyst 15 was added to quench the reaction. The reaction mixture was filtered and evaporated to dryness after it had stirred for 5 minutes. This resulted in the unprotected thioglucoside **13** (100%, 404 mg, 1.38 mmol) as a white solid.

^{1}H-NMR(400 MHz, d_4−Methanol): 7.46 - 7.43 (m, 2H), 7.24 - 7.14 (m, 3H), 4.53 (d, J = 9.5 Hz, 1H), 3.75 (dd, J = 2.0, 12.0 Hz, 1H), 3.56 (dd, J = 5.5, 12.0 Hz, 1H), 3.28 - 3.23 (m, 2H), 3.18 - 3.09 (m, 2H). NMR is in accordance with earlier reported data.[96]

4.2.11 3-Azido-3-deoxy-2,4,6-tri-*O*-benzyl-1-phenylthio-β-D-glucopyranoside (14)



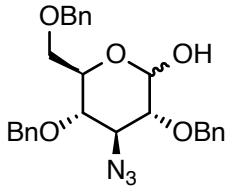
14

To a cooled solution at 0 °C of **13** (125 mg, 0.428 mmol) and BnBr (0.20 mL, 1.7 mmol) in DMF (2.0 mL) was NaH (53.2 mg, 2.22 mmol, 60%) added portion wise. The reaction mixture was heated to rt and stirred for 4 h before it was quenched with MeOH (0.5 mL). The solvents were concentrated under reduces pressure, diluted in H_2O and extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered and evaporated to

dryness. The crude product was purified by FCC (*n*-pentane:EtOAc 9:1) to give **14** (70%, 171 mg, 0.301 mmol) as a pale yellow solid.

^{1}H-NMR(400 MHz, $CDCl_3$): 7.52 - 7.48 (m, 2H), 7.41 - 7-37 (m, 2H), 7.33 - 7.16 (m, 16H), 4.83 (d, J = 10.1 Hz, 1H), 4.73 (d, J = 10.7 Hz, 1H), 4.68 (d, J = 10.1 Hz, 1H), 4.55 - 4.53 (m, 2H), 4.51 - 4.45 (m, 2h), 3.71 - 3.63 (m, 2H), 3.56 - 3.50 (m, 2H), 3.45 - 3.38 (m, 2H), 3.26 (t, J = 9.5 Hz, 2H). NMR matched reported data.[96]

4.2.12 3-Azido-3-deoxy-2,4,6-tri-*O*-benzyl-α/β-D-glucopyranose (15)

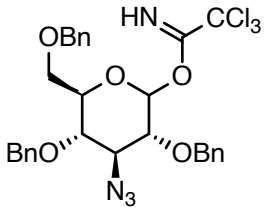


15

A solution of **14** (341 mg, 0.600 mmol) and NIS (256 mg, 1.14 mmol) in DCM (14 mL) was added H_2O (0.7 mL). The mixture was cooled to 0 °C before TMSOTf (15 µL, 0.083 mmol) was added and stirred at rt for 2 h. Na_2SO_3 (293 mg, 2.32 mmol) was added and stirred until the solution turned clear. The reaction mixture was diluted with H_2O and extracted with DCM. The combined organic phases were washed with $NaHCO_3$ and brine before they were dried over Na_2SO_4, filtered and evaporated. Eluting the crude product through a silica gel column (*n*-pentane:Et_2O 2:1) yielded **15** (79%, 224 mg, 0.472 mmol) as a white solid.

^{1}H-NMR(400 MHz, $CDCl_3$): 7.35 - 7.10 (m, 24H) 5.11 (bt, J = 2.9 Hz, 1H), 4.85 (d, J = 11.0 Hz, 0.5H), 4.73 - 4.66 (m, 3H), 4.62 - 4.58 (m, 1.5H), 4.52 (d, J = 12.1 Hz, 1H), 4.50 (d, J = 12.1 Hz, 0.5H), 4.45 - 4.35 (m, 3H), 3.92 (ddd, J = 2.2, 3.6, 10.2 Hz, 1H), 3.81 (t, J = 9.9 Hz, 1H), 3.65 - 3.25 (m, 7.5H), 3.13 (dd, J = 7.7, 9.8 Hz, 0.5H), 3.03 (d, J = 2.2 Hz, 1H). ^{1}H-NMR is in accordance with literature data.[78]

4.2.13 3-Azido-3-deoxy-2,4,6-tri-*O*-benzyl-α/β-D-glucopyranosyl trichloroacetimidate (16)



16

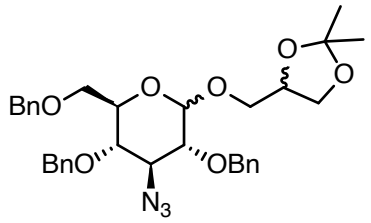
α anomer: To a stirred solution of **15** (317 mg, 0.666 mmol) in dry DCM (5 mL) with molecular sieves (4Å) under a N_2-atmosphere was CCl_3CN (0.2 mL, 1.22 mmol) and DBU (15 µL, 0.10 mmol) added dropwise. The solution was stirred at rt for 20 h before it was filtered and evaporated under reduced pressure. The crude product was eluted through a short pad of silica (*n*-pentane:Et_2O 5:1) to furnish **16α** (250 mg, 0.403 mmol, 61%) as a pale orange syrup.

^{1}H-NMR (600 MHz, $CDCl_3$): 8.53 (s, 1H), 7.29 - 7.20 (m, 13H), 7.17 - 7.14 (m, 2H), 6.39 (d, J = 3.4 Hz, 1H), 4.74 (d, J = 10.5 Hz, 1H), 4.67 - 4.60 (m, 2H), 4.54 (d, J = 12.0 Hz, 1H), 4.42 (d, J = 10.6 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 3.92 - 3.85 (m, 2H), 3.71 (dd, J = 3.0, 11.0 Hz, 1H), 3.59 - 3.48 (m, 3H). The NMR data is in accordance with earlier reported data.[78]

β anomer: 15 (696 mg, 1.46 mmol) and K_2CO_3 (27.0 mg, 0.20 mmol) were dissolved in dry DCM (9 mL) with molecular sieves under a N_2 atmosphere. To this solution CCl_3CN (0.4 mL, 3.99 mmol) was added and it was stirred at rt for 3.5 h. The reaction mixture was filtered and evaporated under reduced pressure before it was purified by FCC (4:1 → 2:1 *n*-pentane:Et_2O). This gave **16β** (146 mg, 0.236 mmol) in 16% yield as a clear syrup.

^{1}H-NMR (600 MHz, $CDCl_3$): 8.77 (s, 1H), 7.34 - 7.26 (m, 15H), 5.81 (d, 1H, J = 7.8 Hz), 4.96 (d, 1H, J = 10.7 Hz), 4.82 (t, 2H, J = 11.2 Hz), 4.66 (d, 1H, J = 12.1 Hz), 4.61 - 4.55 (m, 2H), 3.79 - 3.76 (m, 2H), 3.71 - 3.57 (m, 4H). ^{1}H-NMR was consistent with previously reported data.[78]

4.2.14 1,2-*O*-isopropyliden-3-*O*-(3-azido-3-deoxy-2,4,6-tri-*O*-benzyl-α/β-D-glucopyranosyl)-(R/S)-glycerol (19)



19

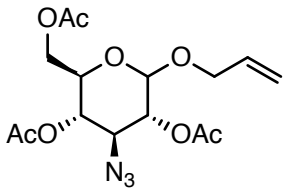
The trichloroacetimide **16α** (89.9 mg, 145 µmol) was dissolved in dry DCM (1.2 mL) with molecular sieves (4Å) under a N_2-atmosphere. The solution was cooled to 0 °C prior to addition of glycosyl acceptor **17** (27 µL, 217 µmol) and TMSOTf (1 µL, 6 µmol). The reaction was allowed to progress at rt for 24 h before it was quenched with $NaHCO_3$ (aq.). The water phase was extracted with DCM before the combined organic phases were washed with brine, dried over Na_3SO_4, filtered and dried under reduced pressure. The crude product was purified by FCC (*n*-pentane:EtOAc 5:1) to give **19** (48 mg, 82 µmol, 57%) as a mixture of anomers and isomers as a clear syrup.

α anomer: HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. 612.2686 for $C_{33}H_{39}N_3O_7Na$, found 612.2687; IR (cm^{-1}): 3087, 3063, 3031, 2985, 2922, 2868, 2105, 1732, 1496, 1454, 1369, 1327, 1260, 1206, 1152, 1070, 1045, 1029, 910, 840, 736, 697, 609, 553, 532, 515, 467; ^{1}H-NMR (600 MHz, $CDCl_3$): 7.32 - 7.20 (m, 13H, Ar), 7.15 - 7.11 (m, 2H, Ar), 4.72 (d, J = 10.5, 1H, benzylic), 4.69 (d, J = 12.2, 1H, benzylic), 4.66 (d, J = 3.5, 1H, H-1), 4.56 - 4.53 (m, 2H, benzylic), 4.40 (d, J = 12.2, 1H, benzylic), 4.36 (d, J = 10.5, 1H, benzylic), 4.19 (p, J = 5.9, 1H, H-2'), 3.97 (dd, J = 6.4, 8.5, 1H, H-1'a), 3.83 (t, J = 9.8, 1H, H-3), 3.71 - 3.67 (m, 2H, H-1'b, H-5), 3.65 (dd, J = 3.2, 10.6, 1H, H-6a), 3.60 (dd, J = 5.4, 10.0, 1H, H-3'a), 3.52 (dd, J = 2.0, 10.6, 1H, H-6b), 3.38 (t, J = 9.8, 1H, H-4), 3.33 - 3.27 (m, 2H, H-2, H-3'b), 1.34 (s, 3H, Me), 1.27 (s, 3H, Me); ^{13}C-NMR (150 MHz, $CDCl_3$): 137.9 (Ph-q), 137.8 (Ph-q), 137.7 (Ph-q), 128.68 (Ar), 128.66 (Ar), 128.63 (Ar), 128.61 (Ar), 128.58 (Ar), 128.54 (Ar), 128.4 (Ar), 128.24 (Ar), 128.22 (Ar), 128.19 (Ar), 128.13 (Ar), 128.04 (Ar), 128.02 (Ar), 109.6 ($\underline{C}Me_2$) 96.8 (C-1) 78.1 (C-2) 76.4 (C-4) 75.1

(benzylic) 74.2 (C-2') 73.8 (benzylic) 73.1 (benzylic) 70.1 (C-5) 69.4 (C-3') 68.2 (C-6) 67.1 (C-1') 65.4 (C-3) 27.0 (Me) 25.5 (Me)

β anomer: HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. 612.2686 for $C_{33}H_{39}N_3O_7Na$, found 612.2687; IR (cm^{-1}): 3089, 3064, 3031, 2986, 2930, 2871, 2103, 1497, 1454, 1379, 1369, 1311, 1261, 1211, 1160, 1147, 1066, 1050, 1028, 1002, 934, 910, 840, 735, 696, 646, 620, 595, 551, 514, 463, 427; ^{1}H-NMR (600 MHz, $CDCl_3$): 7.37 - 7.33 (d, J = 7.4 Hz, 2H, Ar), 7.31 - 7.20 (m, 11H, Ar), 7.17 - 7.15 (m, 2H, Ar), 4.85 (d, J = 10.8 Hz, 1H, benzylic), 4.72 (d, J = 10.7 Hz, 1H, benzylic), 4.65 (d, J = 10.7 Hz, 1H, benzylic), 4.55 (d, J = 12.2 Hz, 1H, benzylic), 4.46 (d, J = 12.2 Hz, 1H, benzylic), 4.43 (d, J = 10.6 Hz, 1H, benzylic), 4.36 (d, J = 7.8 Hz, 1H, H-1), 4.26 (p, J = 6.0 Hz, 1H, H-2'), 4.00 (dd, J = 6.4, 8.3 Hz, 1H, H-1'a), 3.80 (dd, J = 5.9, 10.2 Hz, 1H, H-3'a), 3.70 (dd, J = 5.9, 8.3 Hz, 1H, H-1'b), 3.63 - 3.57 (m, 3H, H-6a,b, H-3'b), 3.49 - 3.44 (m, 1H, H-3)„ 3.37 - 3.33 (m, 2H, H-4, H-5), 3.21 (dd, 7.7, 9.7 Hz, 1H, H-2), 1.36 (s, 3H, Me), 1.30 (s, 3H, Me); ^{13}C-NMR (150 MHz, $CDCl_3$): 138.0 (Ph-q), 137.9 (Ph-q), 137.7 (Ph-q), 128.64 (Ar), 128.62 (Ar), 128.58 (Ar), 128.54 (Ar), 128.4 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 109.7 ($\underline{C}Me_2$), 104.0 (C-1), 79.9 (C-2), 76.4 (C-4), 75.6 (C-5), 75.0 (benzylic), 74.8 (benzylic), 74.6 (C-2'), 73.7 (benzylic), 71.3 (C-3'), 68.6 (C-3, C-6), 67.1 (C-1'), 27.1 (Me), 25.5 (Me).

4.2.15 Allyl 2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-α/β-D-glucopyranoside (23)



23

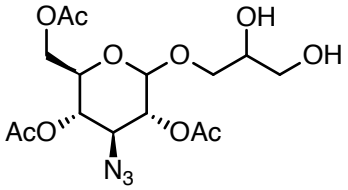
The azido glucofuranose **7** (521 mg, 1.82 mmol) was dissolved in allyl alcohol (7 mL) and added HCl (0.2 mL, 37%). The solution was heated to reflux and stirred for 30 minutes. The solvent was removed under reduced pressure to give the allyl glucopranoside **22** (463 mg, 1.89 mmol, 104%, α:β 65:35) as a crude mixture.

The crude **22** was dissolved in pyridine (5 mL) and Ac_2O (5 mL) and stirred at rt for 17 h. The sovent was removed under reduced pressure. The crude product was diluted in H_2O and extracted with DCM. The combined organic phases were washed with $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated. Column chromatography (*n*-pentane:EtOAc 6:1 → 4:1) resulted in pure **23α** (216 mg, 0.582 mmol, 32%) and pure **23β** (141 mg, 0.379 mmol, 21%) as two clear oils.

α anomer: HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. 394.1226 for $C_{15}H_{21}N_3O_8Na$, found 394.1230; $[\alpha]_D^{20}$ = 132° (*c* 1.17, CH_2Cl_2); IR (cm^{-1}): 2921, 2853, 2108, 1026, 1744, 1429, 1366, 1215, 1161, 1036, 927, 768, 602, 549, 511, 487, 422; ^{1}H-NMR (600 MHz, $CDCl_3$): 5.82 (m, 1H, allylic), 5.25 (dd, J = 1.2, 17.2 Hz, 1H, allylic), 5.18 (d, J = 10.4 Hz, 1H, allylic), 5.02 (d, J = 3.6 Hz, 1H, H-1), 4.87 (t, J = 10.0 Hz, 1H, H-4), 4.69 (dd, J = 3.6, 10.5 Hz, 1H, H-2), 4.13 (m, 2H, allylic, H-6a), 4.00 (dd, J = 2.4, 12.4 Hz, 1H, H-6b), 3.96 (m, 2H, allylic, H-3), 3.90 (ddd, J = 2.5, 4.7, 10.0 Hz, 1H, H-5), 2.08 (s, 3H, Me), 2.06 (s, 3H, Me), 2.03 (s, 3H, Me). ^{13}C-NMR (150 MHz, $CDCl_3$): 170.1 (CO). 170.0 (CO), 169.4 (CO), 133.2 ($\underline{C}H{=}CH_2$), 118.5 ($CH{=}\underline{C}H_2$), 94.6 (C-1), 71.7 (C-2), 69.0 (allylic), 68.6 (C-4), 67.8 (C-5), 62.1 (C-6), 61.2 (C-3), 20.9 (2 × Me), 20.8 (Me).

β anomer: HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. 394.1226 for $C_{15}H_{21}N_3O_8Na$, found 394.1230; $[\alpha]_D^{20}$ = -4.5 ° (*c* 1.1, CH_2Cl_2); IR (cm^{-1}): 2956, 2883, 2105, 1744, 1429, 1371, 1212, 1167, 1123, 1037, 990, 927, 893, 705, 646, 600, 558, 486; ^{1}H-NMR (600 MHz, $CDCl_3$): 5.77 (m, 1H, allylic), 5.20 (dq, J = 1.5, 17.2 Hz, 1H, allylic), 5.14 (dq, J = 1.5, 10.5 Hz, 1H, allylic), 4.92 (t, J = 9.9 Hz, 1H, H-4), 4.88 (dd, J = 7.9, 10.5 Hz, 1H, H-2), 4.43 (d, J = 7.9 Hz, 1H, H-1), 4.26 (ddt, J = 1.5, 4.8, 13.2 Hz, 1H, allylic), 4.15 (dd, J = 4.9, 12.3 Hz, 1H, H-6a), 4.06 (dd, J = 2.5, 12.3 Hz, 1H, H-6b), 4.02 (ddt, J = 1.4, 6.1, 13.2 Hz, 1H, allylic), 3.56 (m, 2H, H-3, H-5), 2.06 (s, 3H, Me), 2.05 (s, 3H, Me), 2.02 (s, 3H, Me); ^{13}C-NMR (150 MHz, $CDCl_3$): 169.7 (CO), 168.1 (CO), 168.0 (CO), 132.3 ($\underline{C}H{=}CH_2$), 116.6 ($CH{=}\underline{C}H_2$), 98.7 (C-1), 71.6 (C-5), 70.1 (C-2), 68.8 (allylic), 67.5 (C-4), 63.3 (C-3), 61.0 (C-6), 19.73 (Me), 19.70 (Me), 19.64 (Me).

4.2.16 1-*O*-(3-azido-3-deoxy-2,4,6-tri-*O*-acetyl-α/β-D-gluco-pyranosyl)–glycerol (24)



24

α anomer: The allyl ether **23α** (188 mg, 0.398 mmol) was dissolved in *tert*-butanol (*t*-BuOH):H_2O (20 mL, 1:1 v:v) and cooled to 0 °C. To this solution AD-mix-β (584 mg) was added, and it was stirred for 22 h while slowly warmed to rt. Na_2SO_3 was added at 0 °C and stirred until the solution turned clear. The mixture were extracted with DCM, and the organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane:Et_2O 1:1 → 0:1) to yield an isomeric mixture of **24α** (73.4 mg, 0.181 mmol) in 45% as a clear syrup.

HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. 428.1281 for $C_{15}H_{23}N_3O_{10}Na$, found 428.1283; $[\alpha]_D^{20}$ = 111° (*c* 0.97, CH_2Cl_2); IR (cm^{-1}): 3476, 2939, 2884, 2119, 1746, 1433, 1371, 1223, 1163, 1115, 1037, 984, 902, 863, 770, 649, 601, 554, 490; ^{1}H-NMR (600 MHz, $CDCl_3$): 5.03 (d, J = 3.6 Hz, 0.3H, H-1), 5.01 (d, J = 3.6 Hz, 0.7H, H-1), 4.89 - 4.83 (m, 1H, H-4), 4.72 - 4.68 (m, 1H, H-2), 4.17 - 4.09 (m, 1H, H-6a), 4.06 - 4.00 (m, 1H, H-6b), 3.96 - 3.83 (m, 3H, H-3, H-5, H-2'), 3.76 (dd, J = 4.0, 10.4 Hz, 0.7H, H-1'a) 3.71 - 3.64 (m, 1.5H, H-3'a, H-1'a) 3.62 - 3.54 (m, 1.5H, H-3'b, H-1'b) 3.57 (dd, J = 6.4, 10.4 Hz, 1H, H-1'b) 2.50 (bs, OH) 2.09 (s, 3H, Me), 2.06 (s, 3H, Me), 2.03 (s, 3H, Me); ^{13}C-NMR (150 MHz, $CDCl_3$): *Major isomer*: 170.9 (CO) 169.90 (CO) 169.42 (CO) 96.2 (C-1) 71.60 (C-2) 70.59 (C-1') 70.41 (C-2') 68.56 (C-4) 67.87 (C-5) 63.76 (C-3') 62.1 (C-6) 61.12 (C-3) 20.86 (Me) 20.80 (Me) 20.79 (Me) *Minor isomer*: 170.9 (CO) 169.95 (CO) 169.44 (CO) 95.9 (C-1) 71.62 (C-2) 70.52 (C-2') 70.37 (C-1') 68.60 (C-4) 67.92 (C-5) 63.73 (C-3') 62.1 (C-6) 61.06 (C-3) 20.85 (Me) 20.80 (Me) 20.79 (Me)

β anomer: A stirred solution of allyl ether **23β** (128 mg, 0.272 mmol) in *t*-BuOH:H_2O

(10 mL, 1:1, v:v) at 0 °C was added AD-mix-β (366 mg). The solution was slowly warmed to rt and stirred for 28 h before being quenched with Na_2SO_3. After the solution had turned clear it was extracted with DCM. The combined portions of DCM was washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. Column chromatograht (*n*-pentane:Et_2O 1:1 → 0:1) gave the glycerol **24β** (30.0 mg, 0.0740 mmol, 27%) as a clear syrup.

HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. 428.1281 for $C_{15}H_{23}N_3O_{10}Na$, found 428.1283; $[\alpha]_D^{20}$ = -21.5 ° (*c* 0.37, CH_2Cl_2); IR (cm^{-1}): 3455, 2937, 2887, 2107, 1746, 1431, 1374, 1318, 1220, 1170, 1039, 894, 601, 559; ^{1}H-NMR (600 MHz, $CDCl_3$): 4.90 (t, J = 9.9 Hz, 1H, H-4), 4.84 (dd, J = 7.9, 10.0 Hz, 1H, H-2), 4.43 (d, J = 7.9 Hz, 1H, H-1), 4.11 (d, J = 4.0 Hz, 2H, 6-Ha,b), 3.80 - 3.74 (m, 2H, H-1'a, H-2'), 3.73 - 3.69 (m, 1H, H-1'b), 3.64 - 3.60 (m, 2H, H-5, H-3'a), 3.58 (t, J = 10.2 Hz, 1H, H-3), 3.55 - 3.50 (m, 1H, H-3'b), 2.96 (bs, 1H, OH), 2.19 (bs, 1H, OH), 2.08 (s, 3H, Me), 2.06 (s, 3H, Me), 2.03 (s, 3H, Me); ^{13}C-NMR (150 MHz, $CDCl_3$): 170.8 (CO), 169.5 (CO), 169.3 (CO), 101.7 (C-1), 72.9 (C-1'), 72.8 (C-5), 71.3 (C-2), 70.5 (C-2'), 68.5 (C-4), 64.2 (C-3), 63.5 (C-3'), 62.0 (C-6), 20.85 (Me), 20.83 (Me), 20.75 (Me).

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A Spectroscopic data

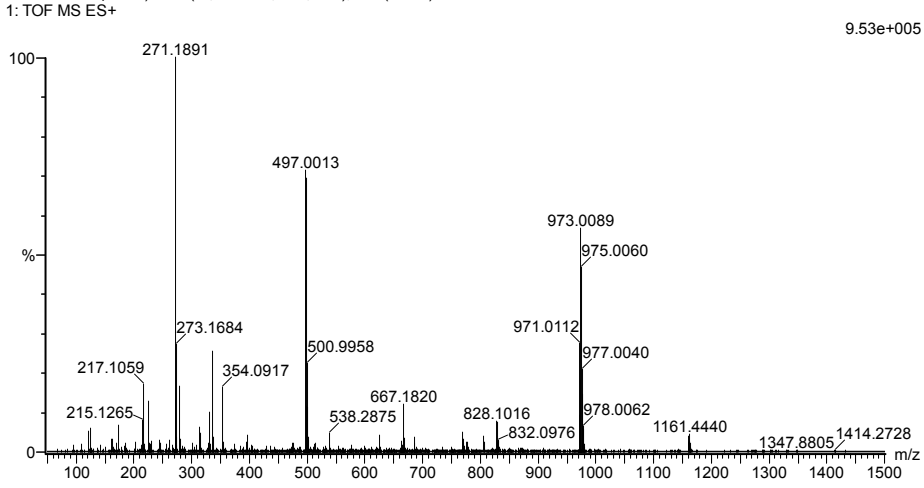
A.1 Spectroscopic data for compound 11β

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -10.0, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 6

Monoisotopic Mass, Even Electron Ions
5636 formula(e) evaluated with 12 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-10 O: 0-10 Cl: 0-3 Na: 0-1

2020-340 48 (0.463) AM2 (Ar,35000.0,0.00,0.00); Cm (48:54)
1: TOF MS ES+



Minimum:				-10.0				
Maximum:		5.0	2.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
497.0013	497.0010	0.3	0.6	6.5	1908.0	0.038	96.28	C14 H17 N4 O8 Cl3 Na
	497.0007	0.6	1.2	10.5	1911.2	3.292	3.72	C12 H12 N10 O6 Cl3

Figure A.1. HRMS (ESI+) of **11β**.

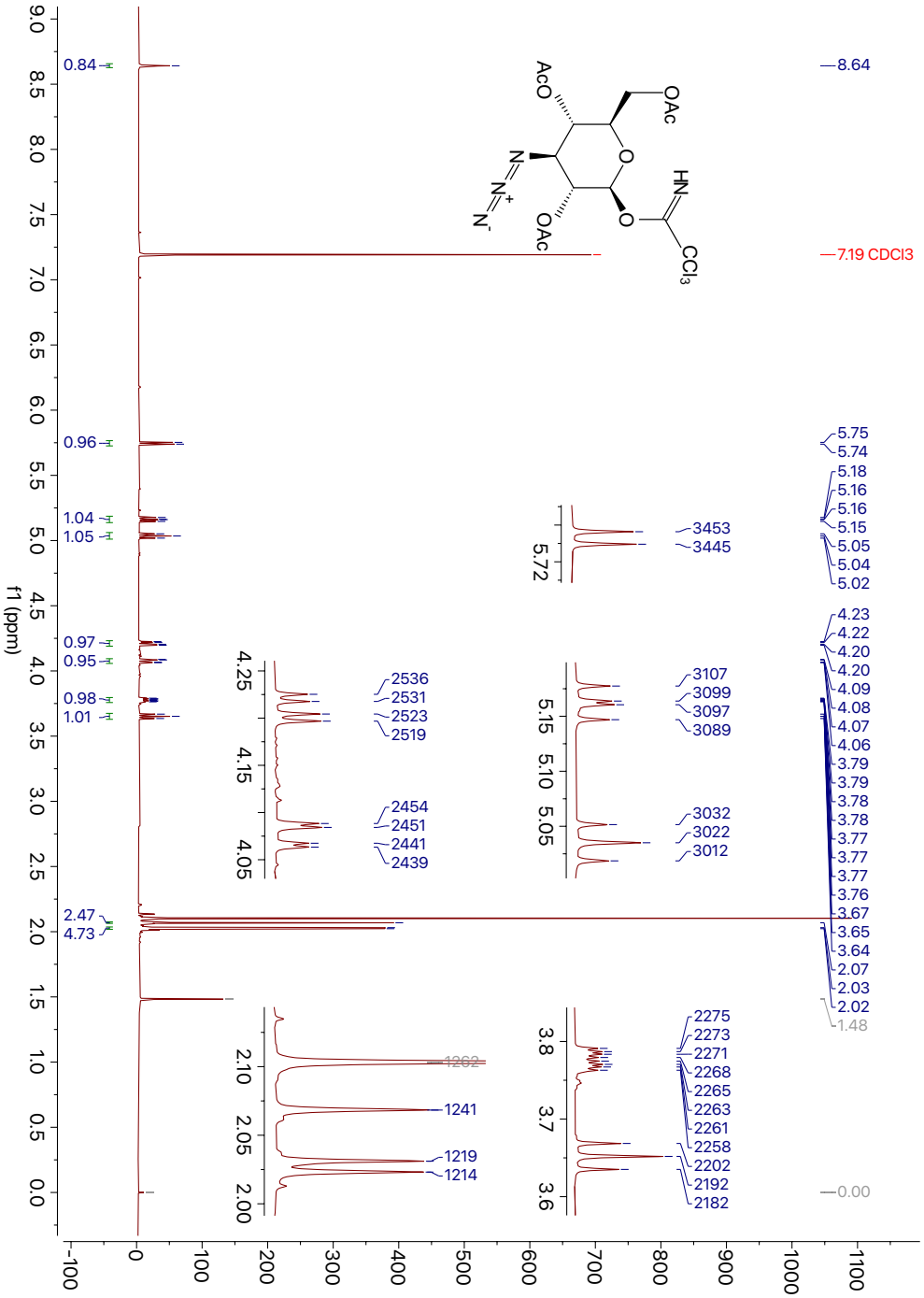


Figure A.3. ^{1}H-NMR spectrum of **11β**.

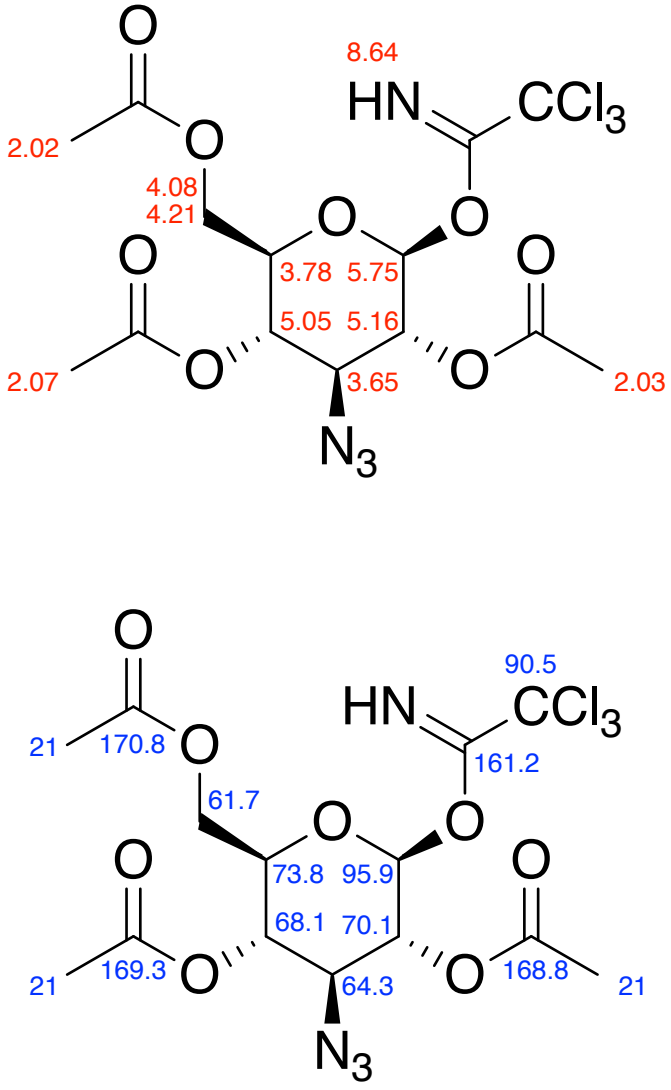


Figure A.2. Assigned ^{1}H- (red) and ^{13}C- (blue) shifts of **11β**.

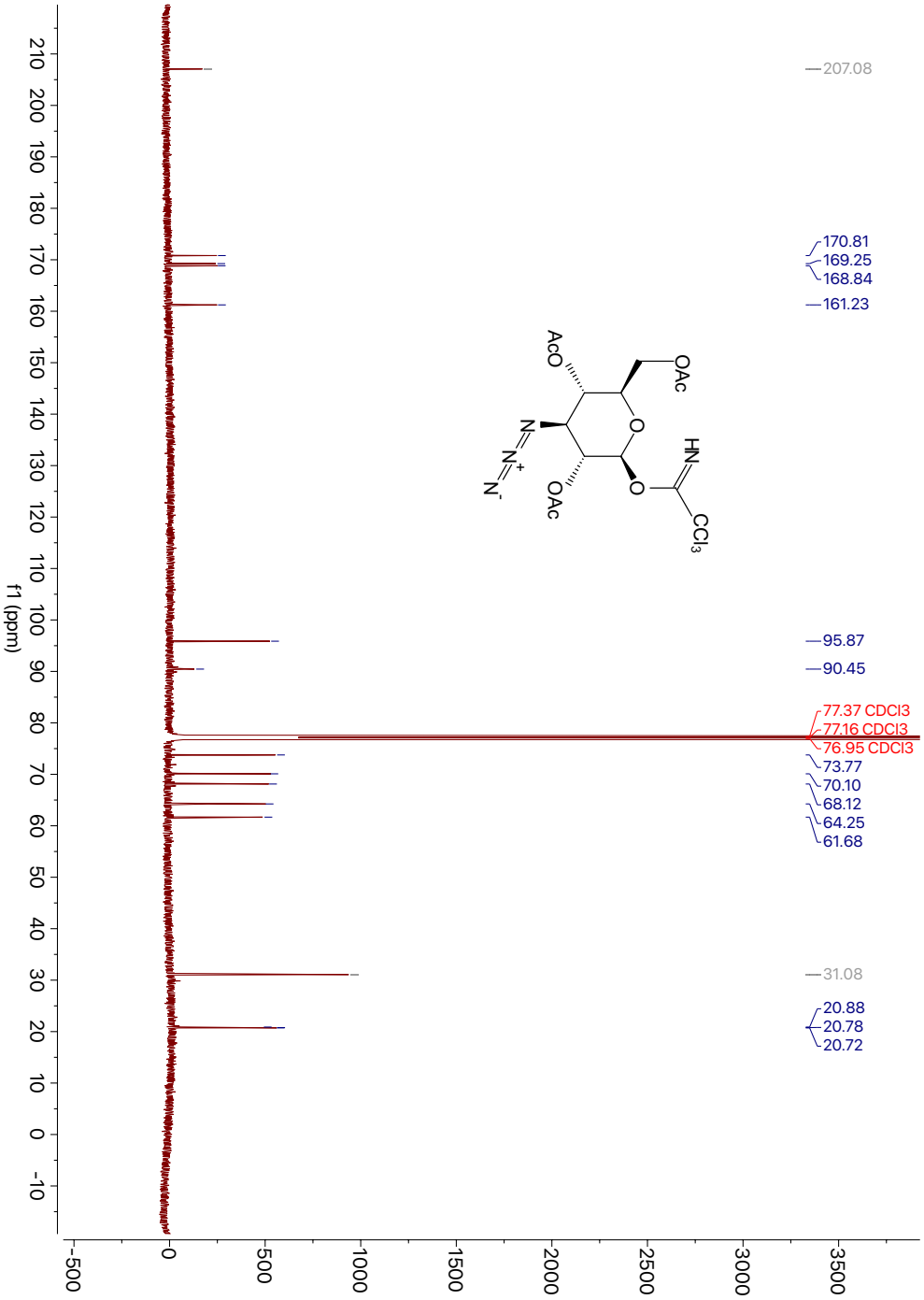


Figure A.4. ^{13}C-NMR spectrum of **11β**.

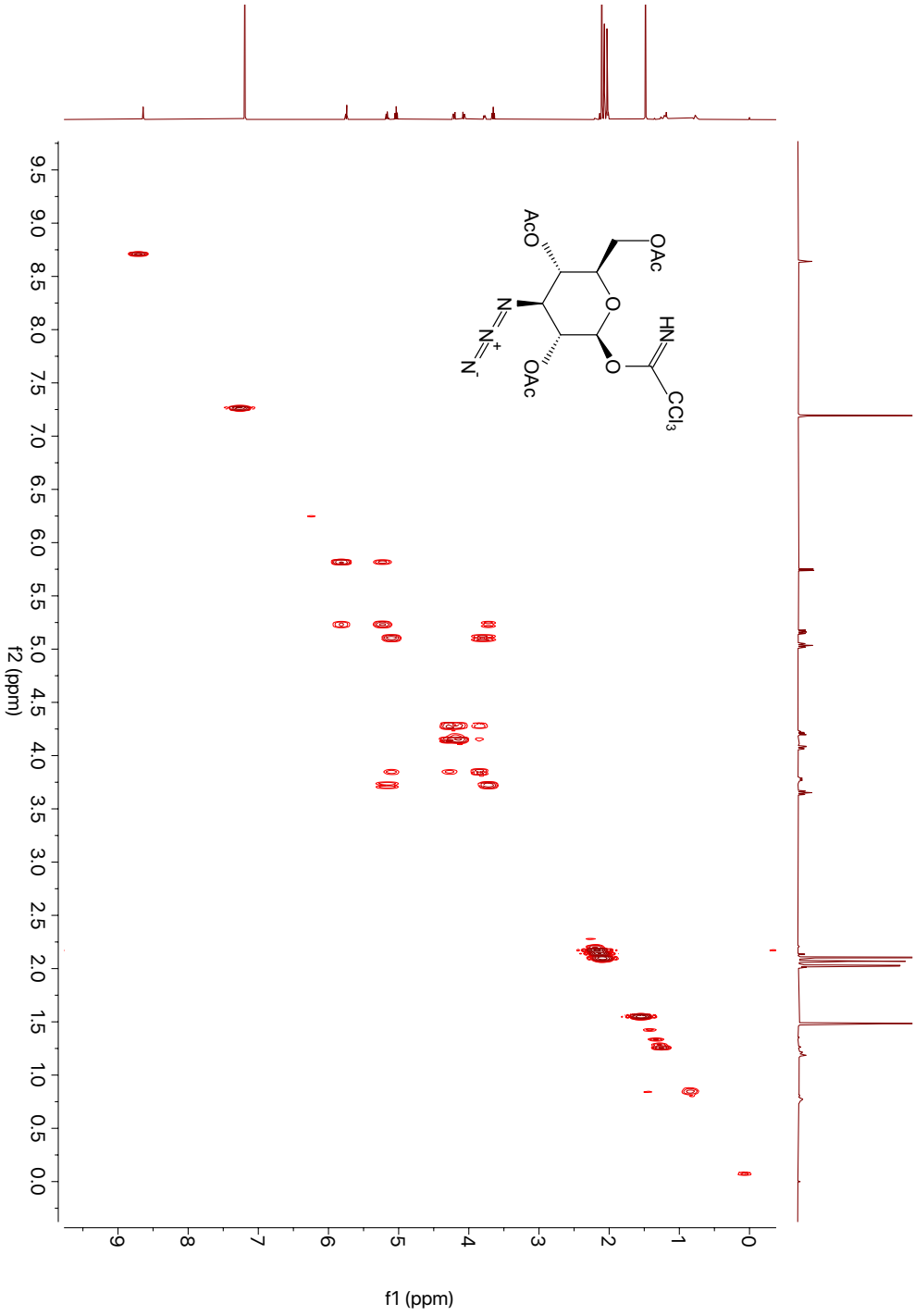


Figure A.5. COSY spectrum of **11β**.

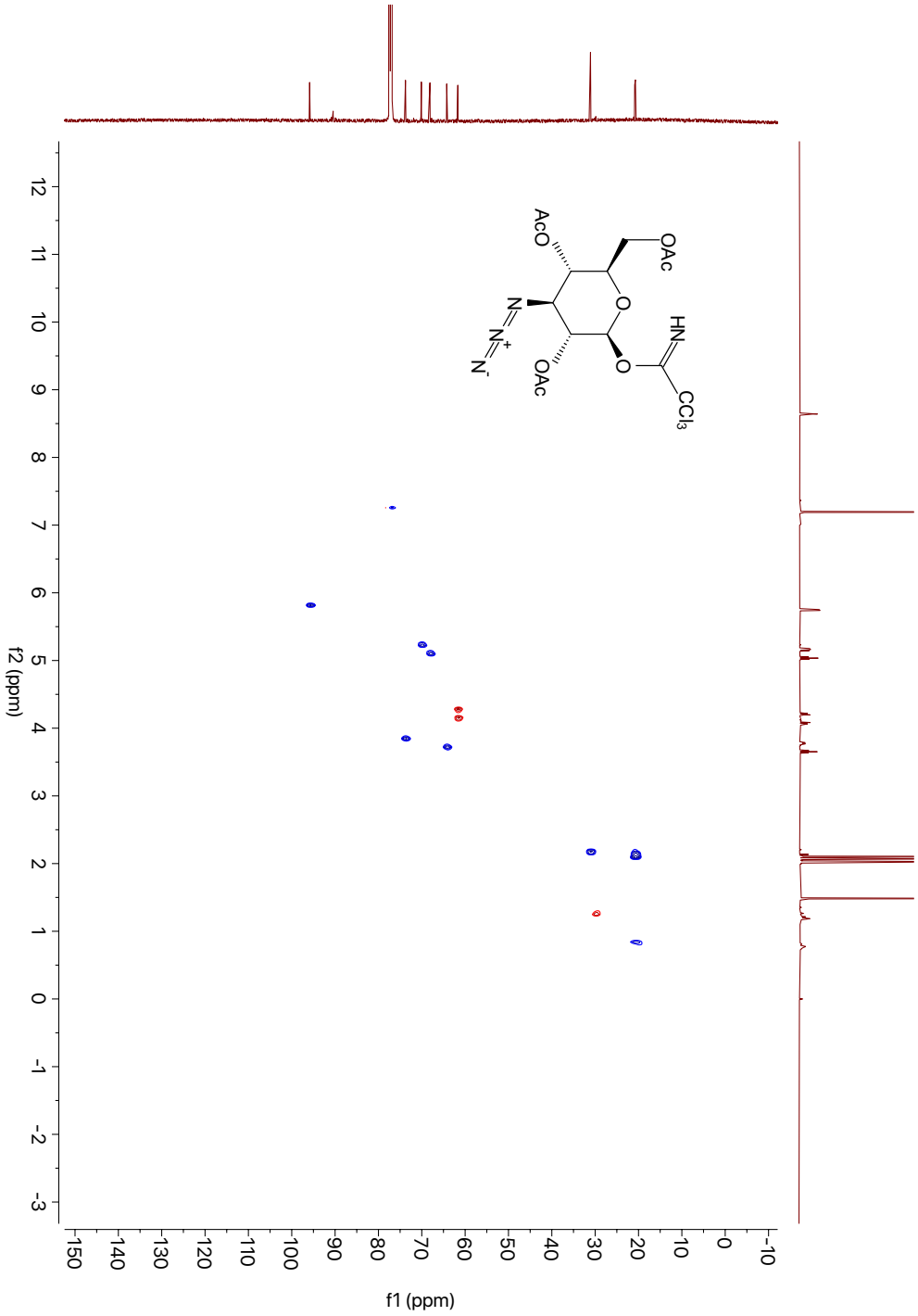


Figure A.6. HSQC spectrum of **11β**.

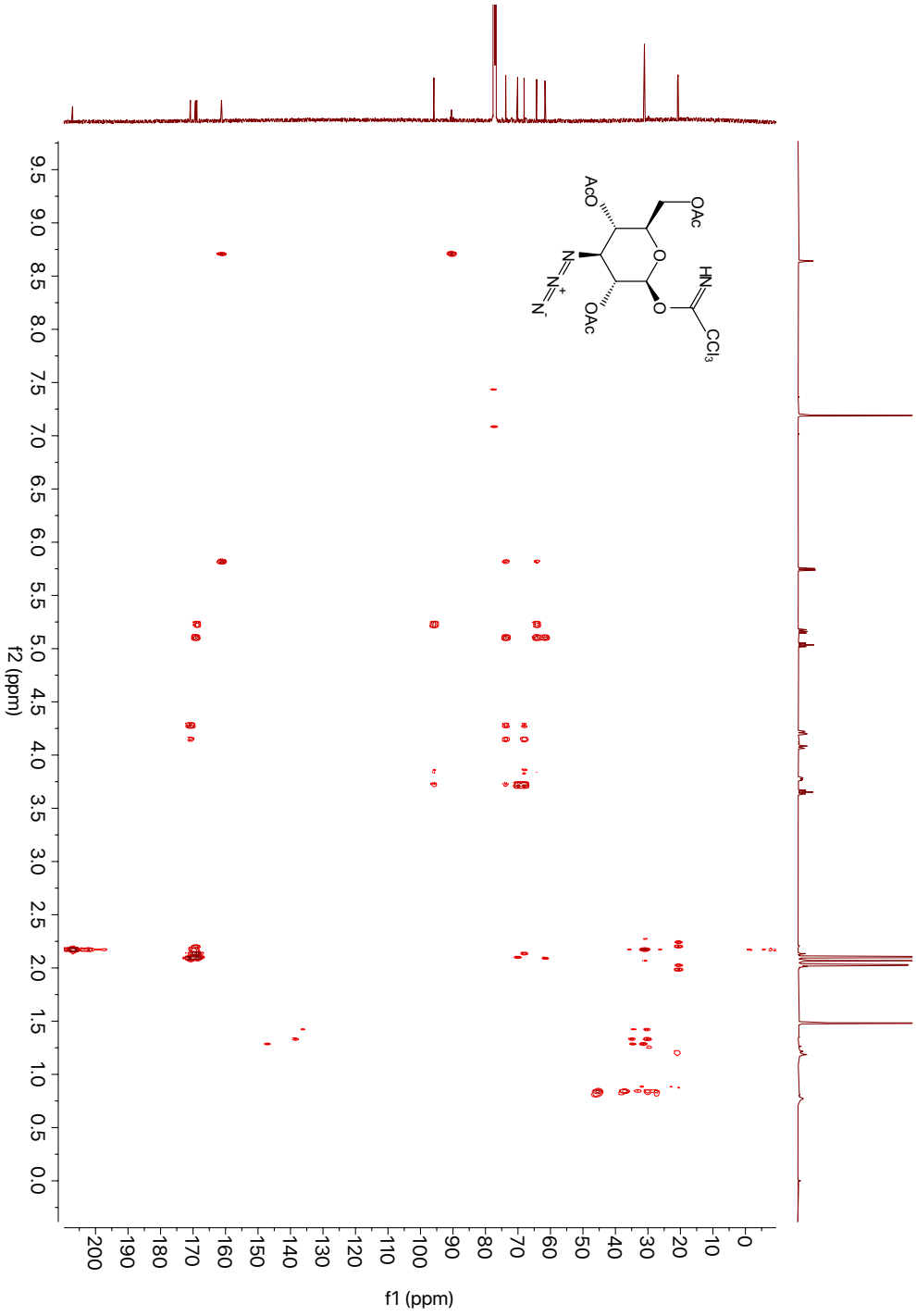


Figure A.7. HMBC spectrum of **11β**.

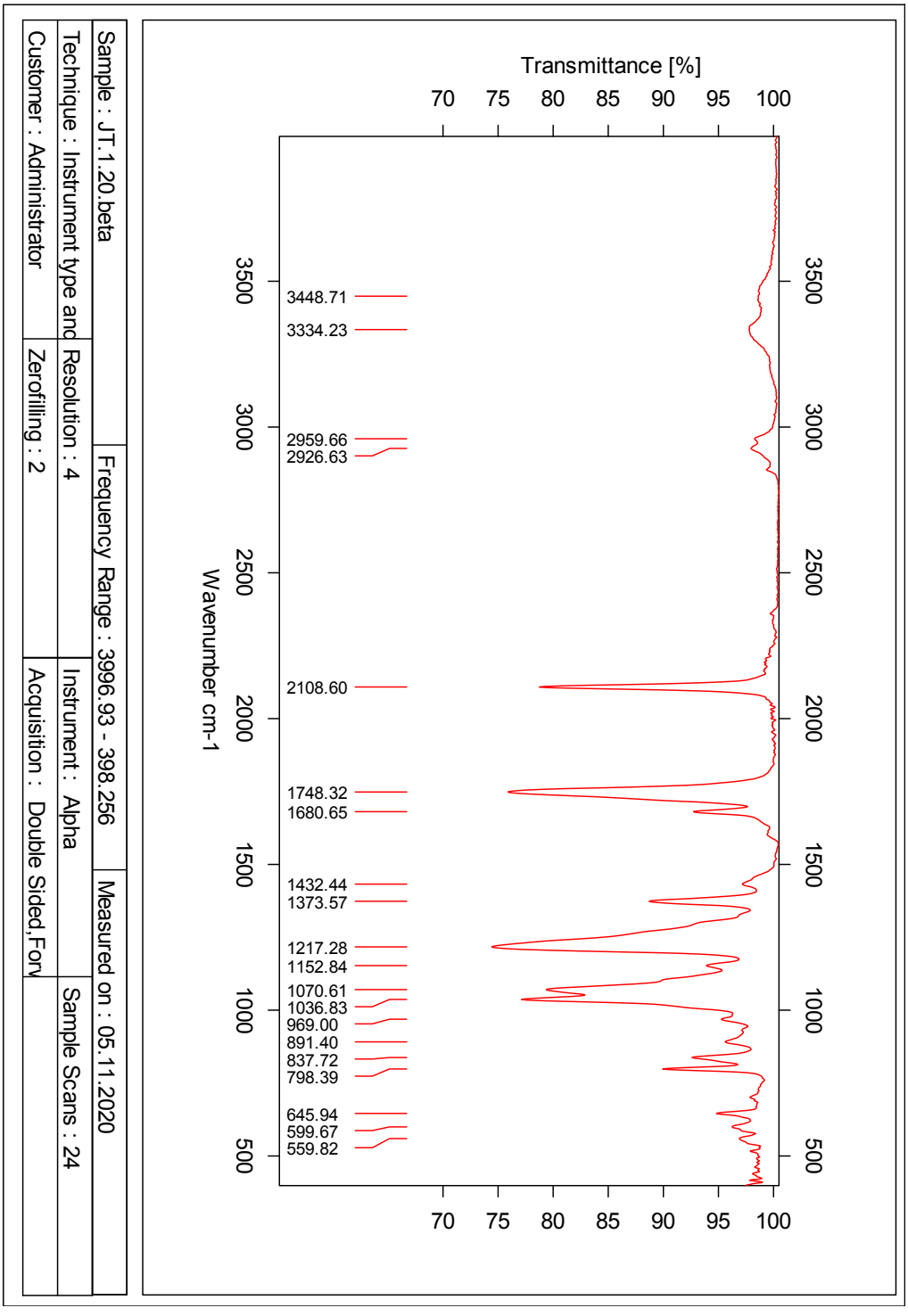


Figure A.8. IR spectrum of **11β**.

A.2 Spectroscopic data for compound 16β

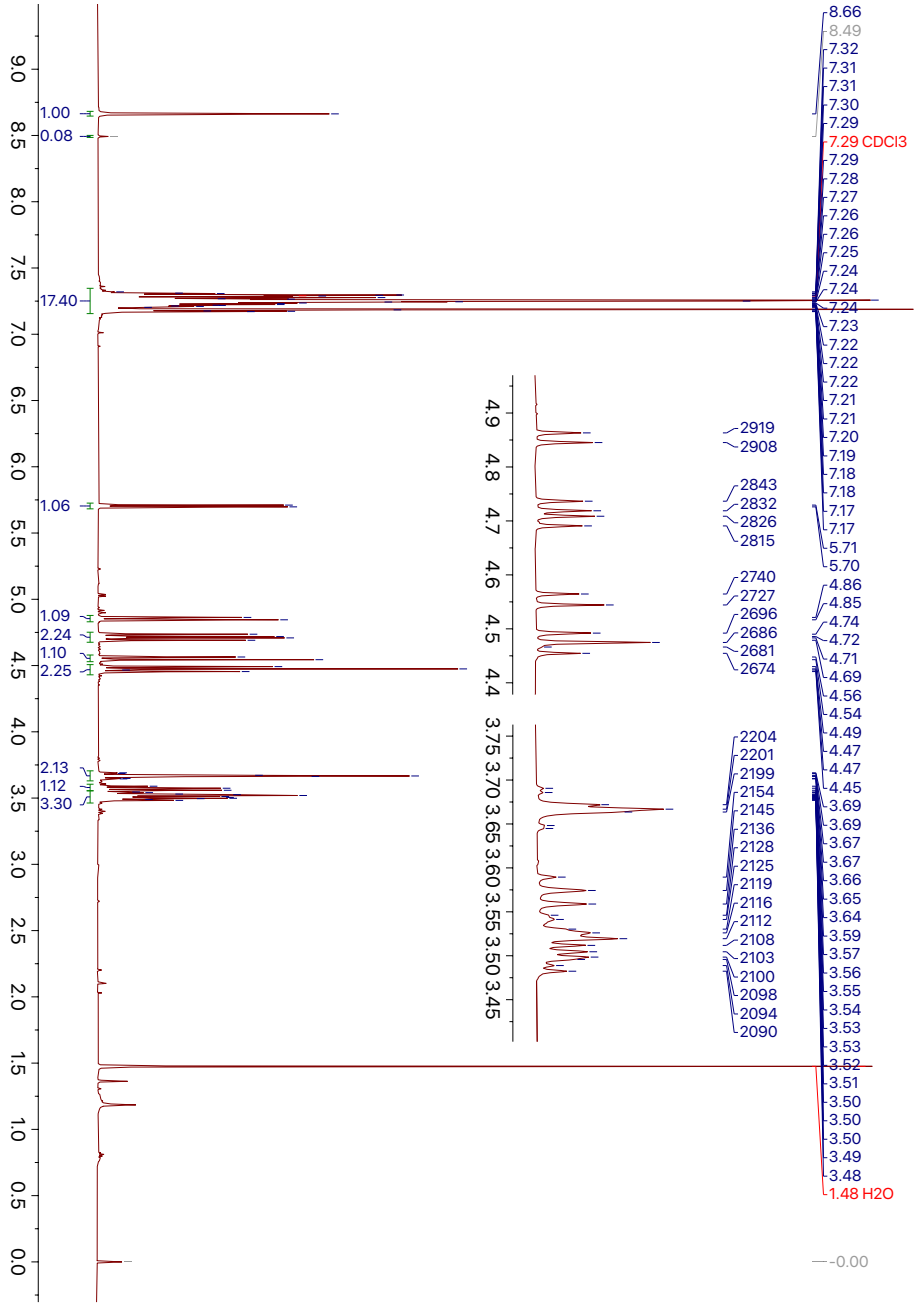


Figure A.9. ^{1}H-NMR spectrum of **16β**.

A.3 Spectroscopic data for compound 17

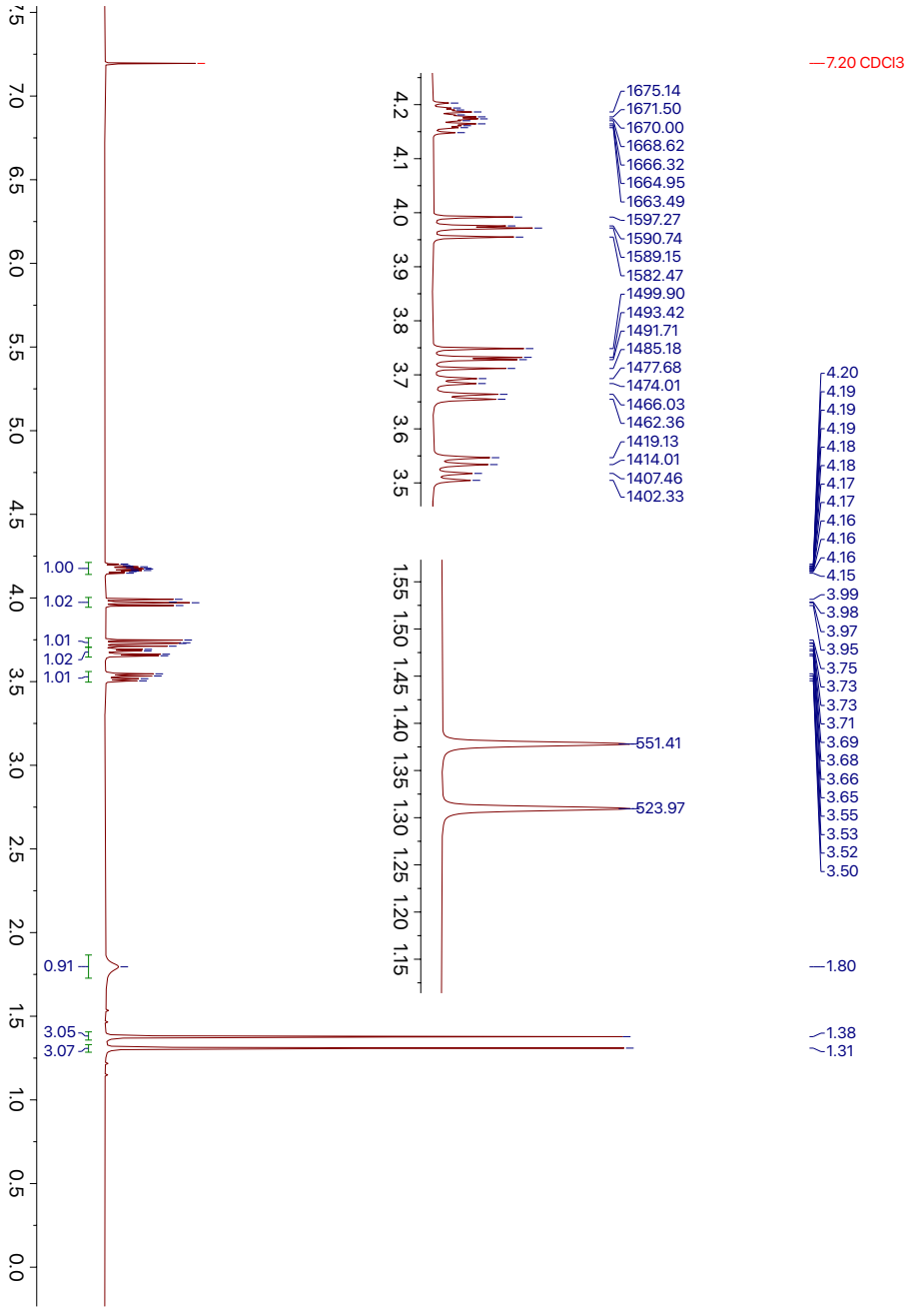


Figure A.10. ^{1}H-NMR spectrum of **17**.

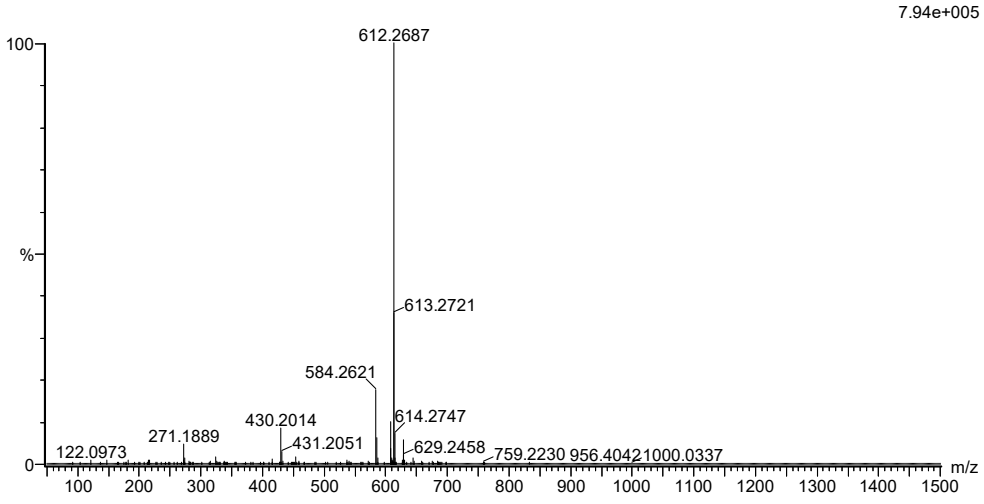
A.4 Spectroscopic data for compound 19α

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2004 formula(e) evaluated with 7 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-7 O: 0-10 Na: 0-1 Au: 0-1

2021-259 73 (0.692) AM2 (Ar,35000.0,0.00,0.00); Cm (73:75)
1: TOF MS ES+



Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
612.2687	612.2686	0.1	0.2	15.5	636.5	0.273	76.09	C33 H39 N3 O7 Na
	612.2688	-0.1	-0.2	0.5	643.8	7.569	0.05	C19 H42 N3 O5 Na Au

Figure A.11. HRMS (ESI+) of **19α**.

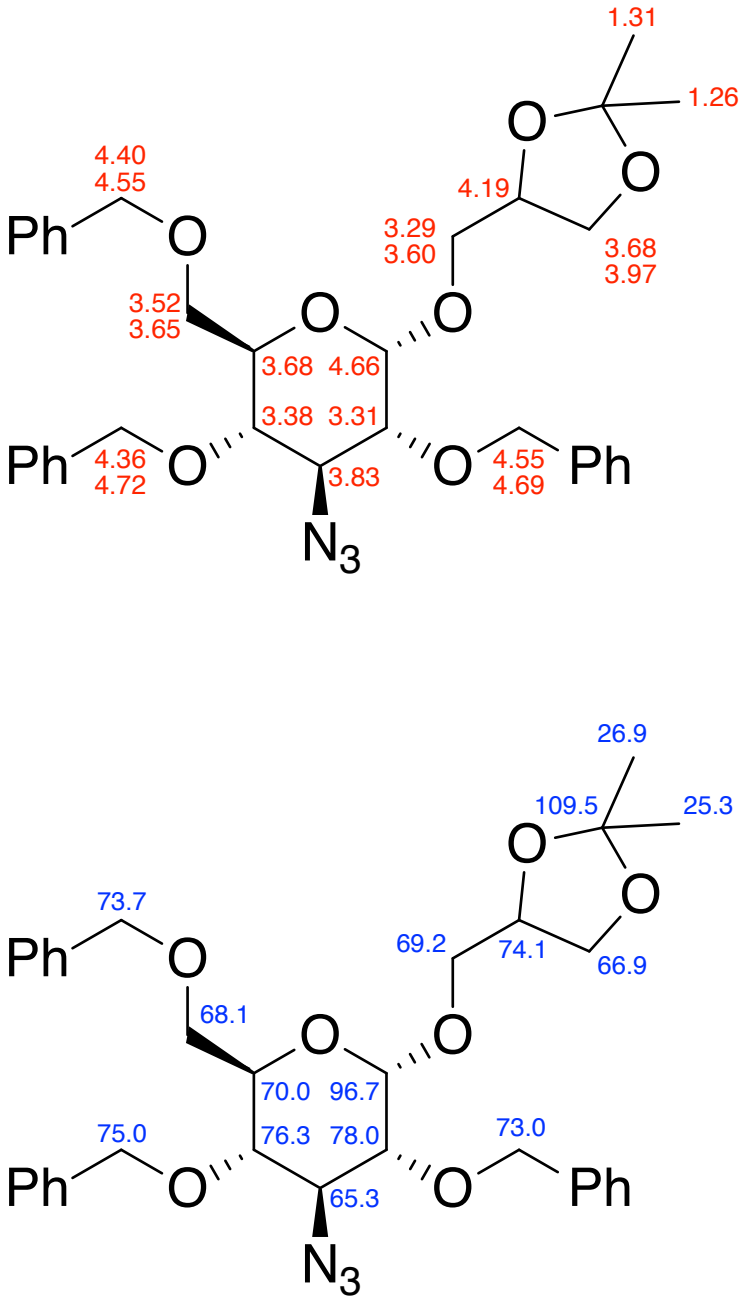


Figure A.12. Assigned ^{1}H- (red) and ^{13}C- (blue) shifts of **19α**.

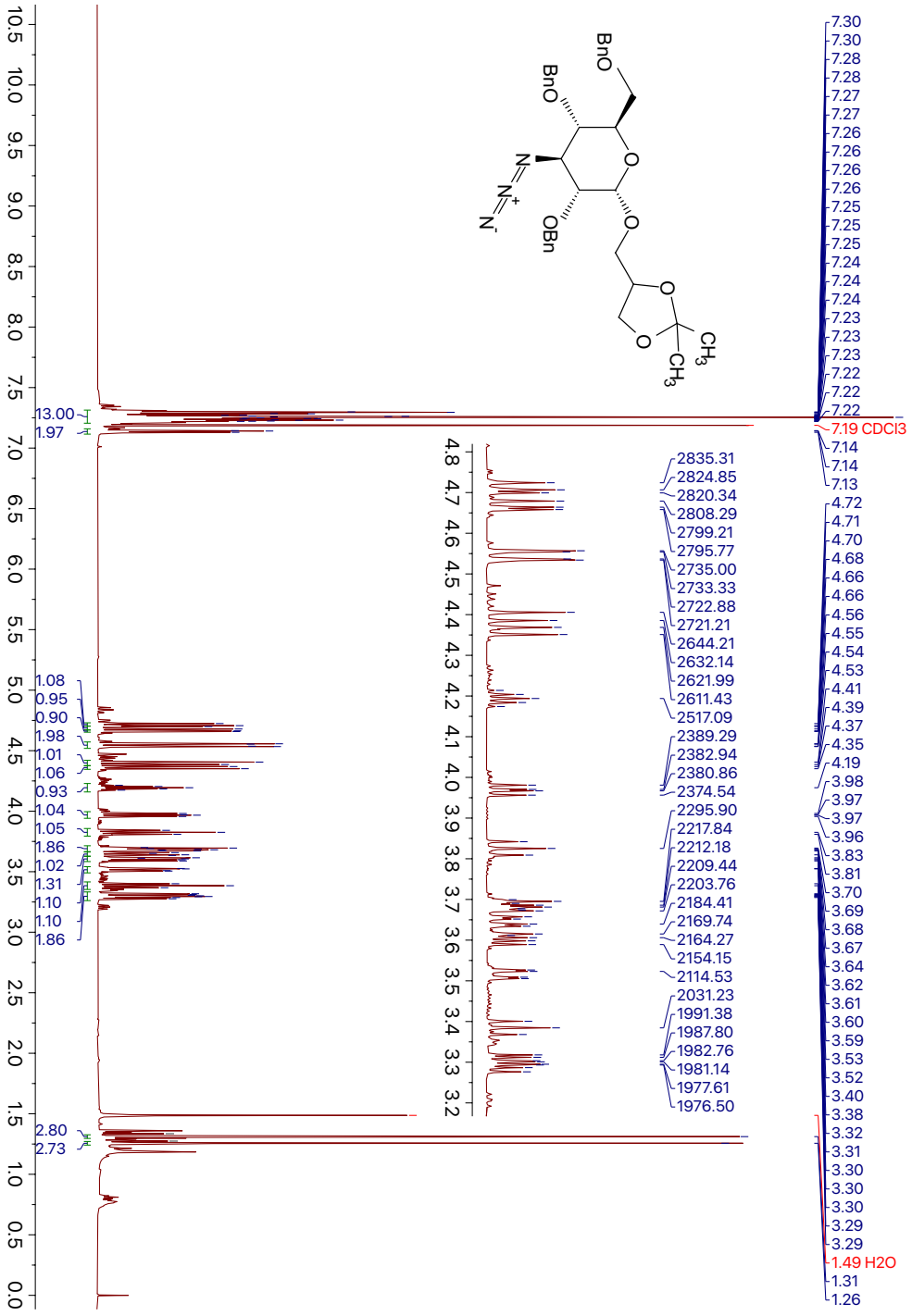


Figure A.13. ^{1}H-NMR spectrum of **19α**.

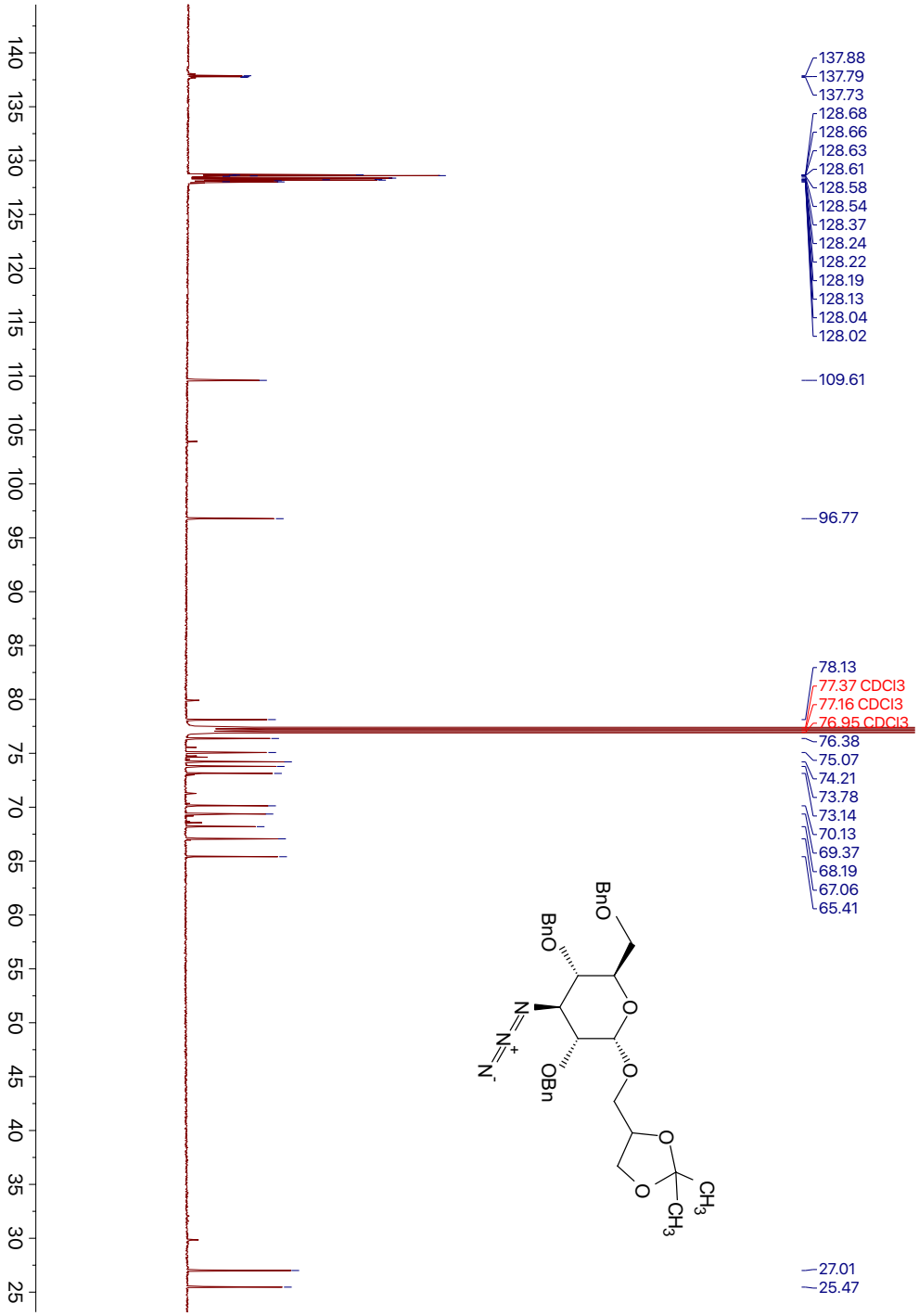


Figure A.14. ^{13}C-NMR spectrum of **19α**.

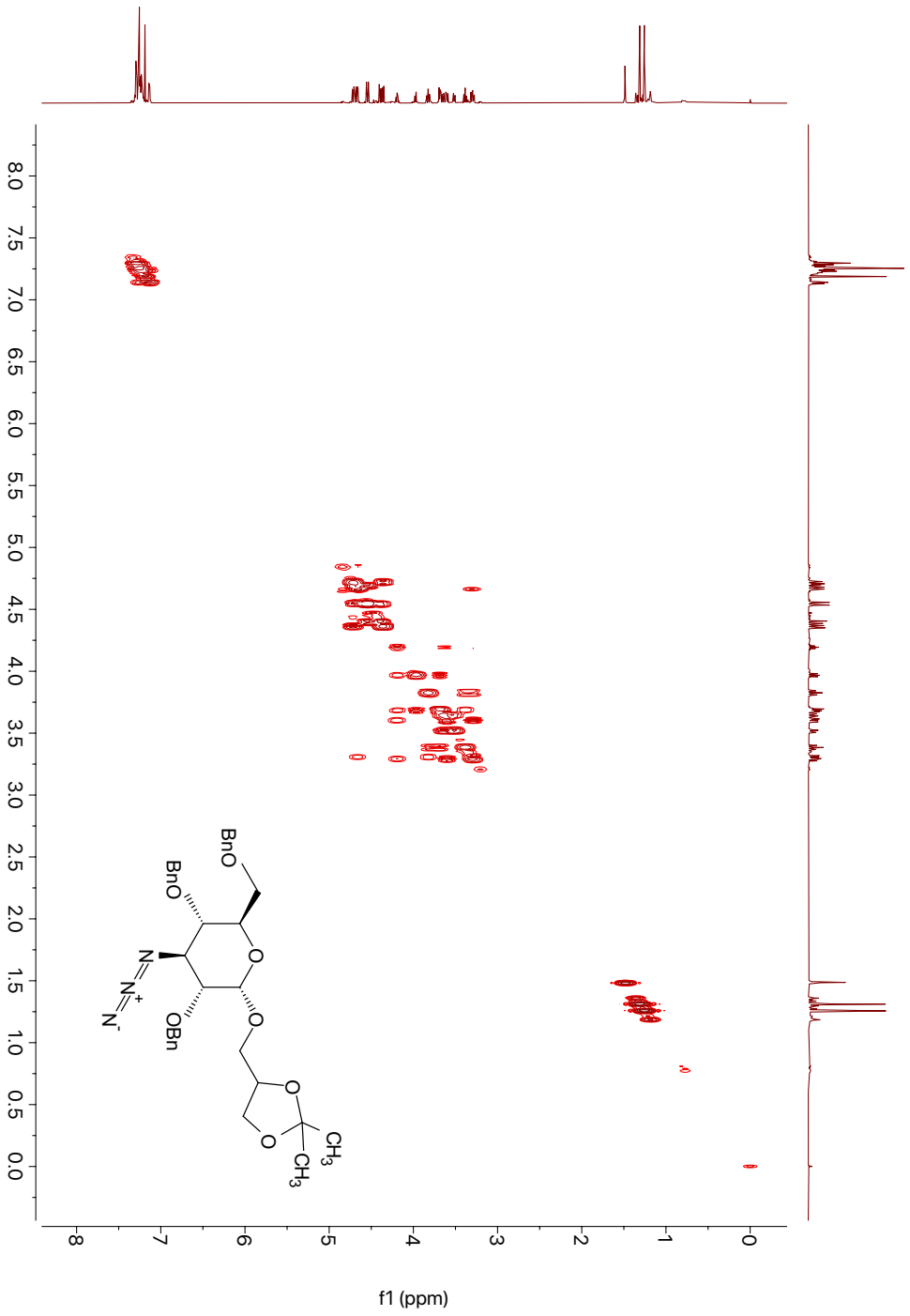


Figure A.15. COSY spectrum of **19α**.

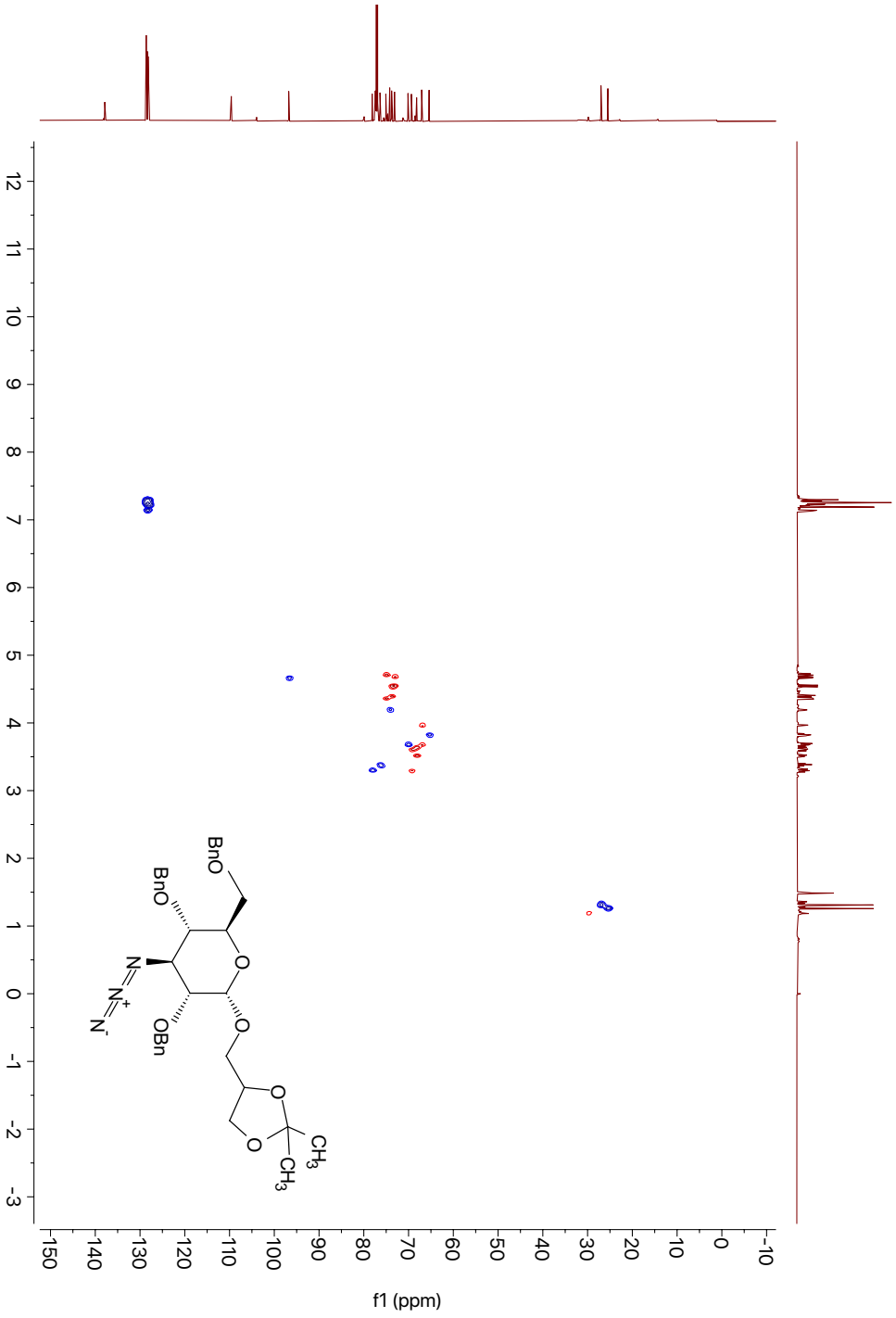


Figure A.16. HSQC spectrum of **19α**.

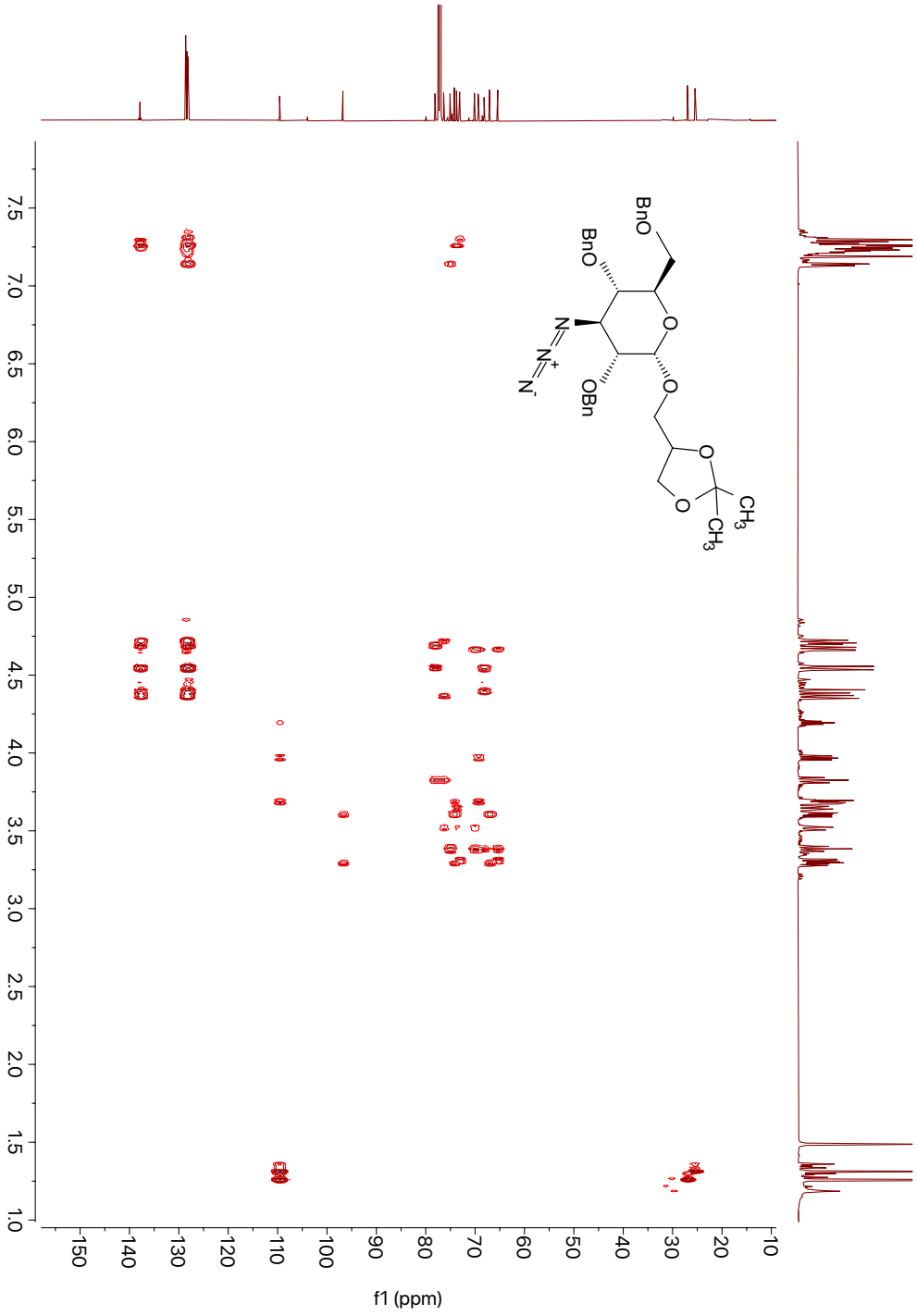


Figure A.17. HMBC spectrum of **19α**.

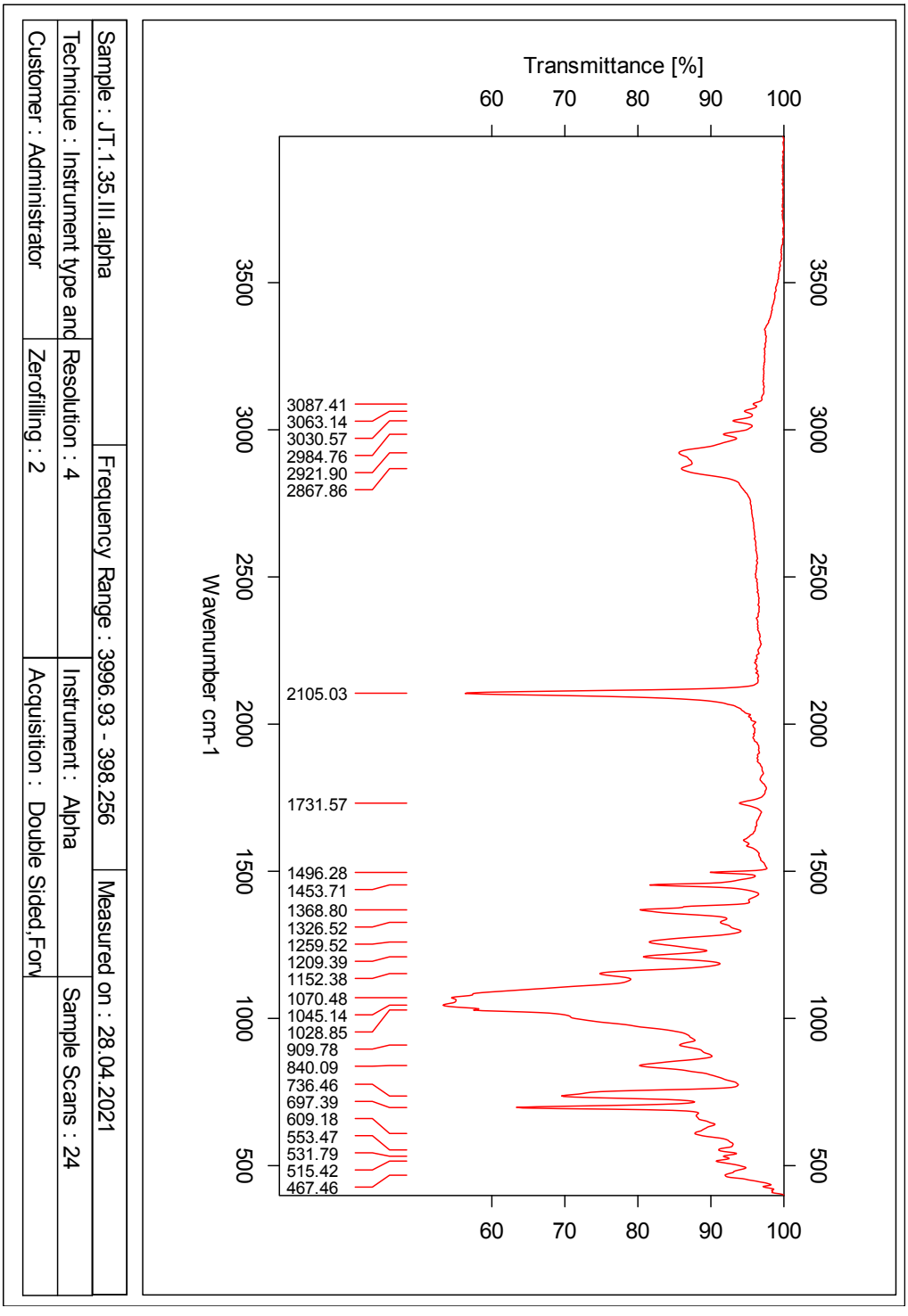


Figure A.18. IR spectrum of **19α**.

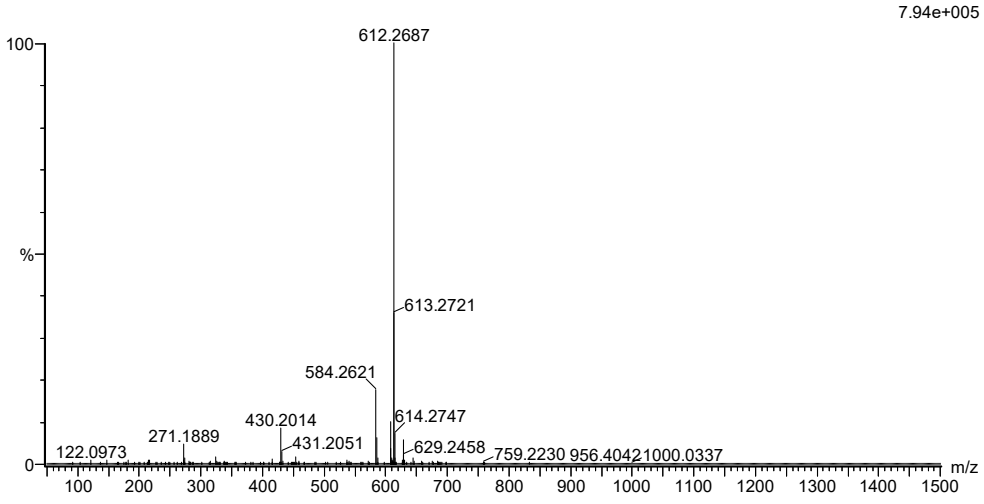
A.5 Spectroscopic data for compound 19β

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
2004 formula(e) evaluated with 7 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-7 O: 0-10 Na: 0-1 Au: 0-1

2021-259 73 (0.692) AM2 (Ar,35000.0,0.00,0.00); Cm (73:75)
1: TOF MS ES+



Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
612.2687	612.2686	0.1	0.2	15.5	636.5	0.273	76.09	C33 H39 N3 O7 Na
	612.2688	-0.1	-0.2	0.5	643.8	7.569	0.05	C19 H42 N3 O5 Na Au

Figure A.19. HRMS (ESI+) of **19β**.

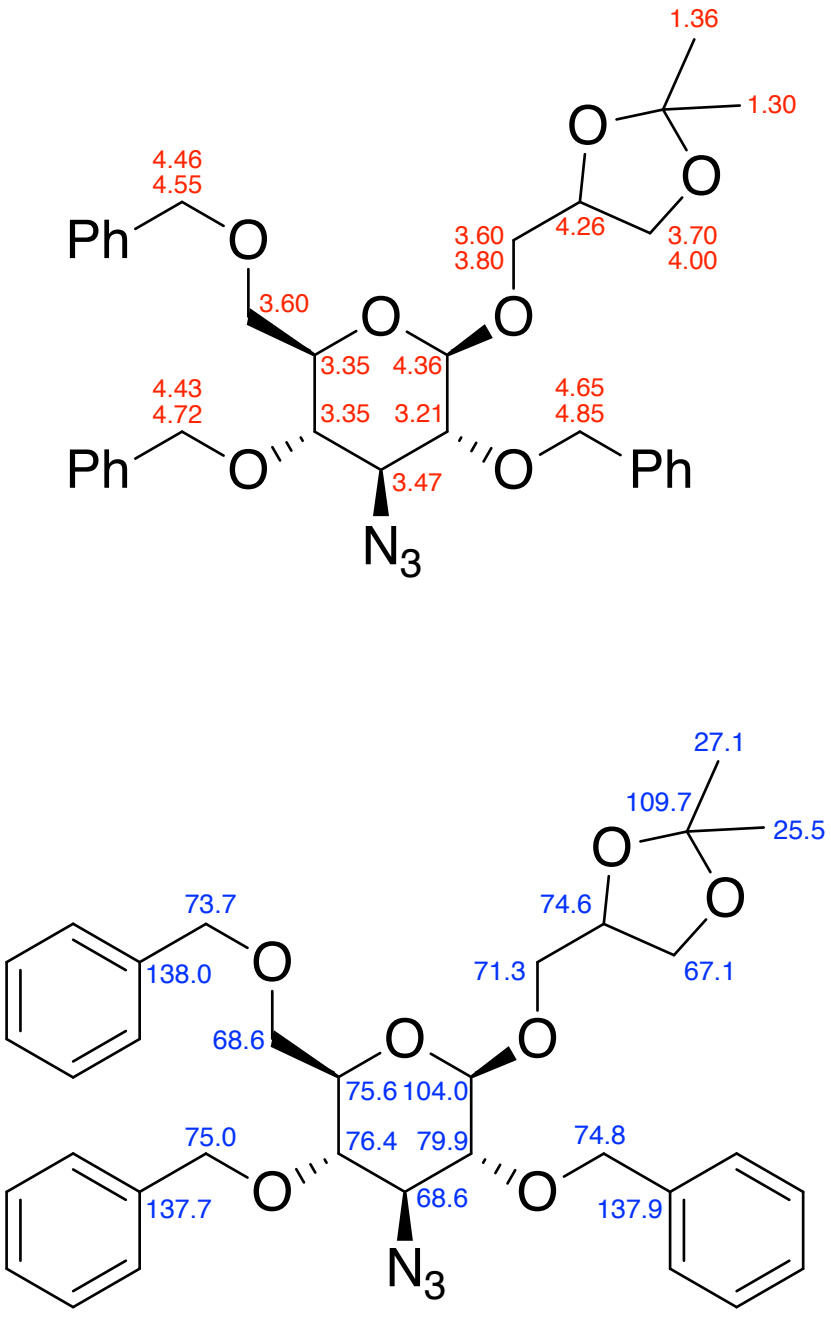


Figure A.20. Assigned ^{1}H- (red) and ^{13}C- (blue) shifts of **19β**.

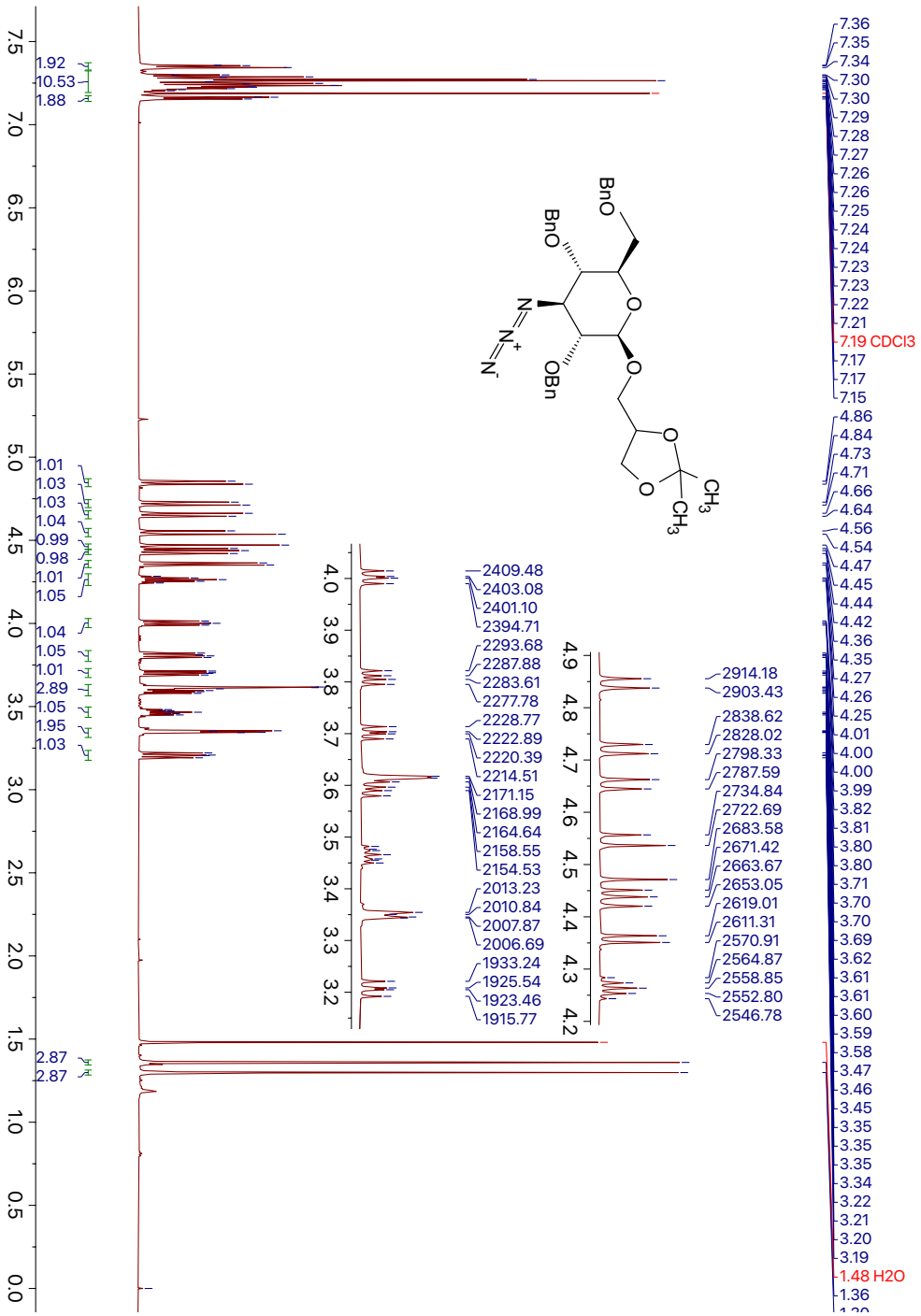


Figure A.21. ^{1}H-NMR spectrum of **19β**.

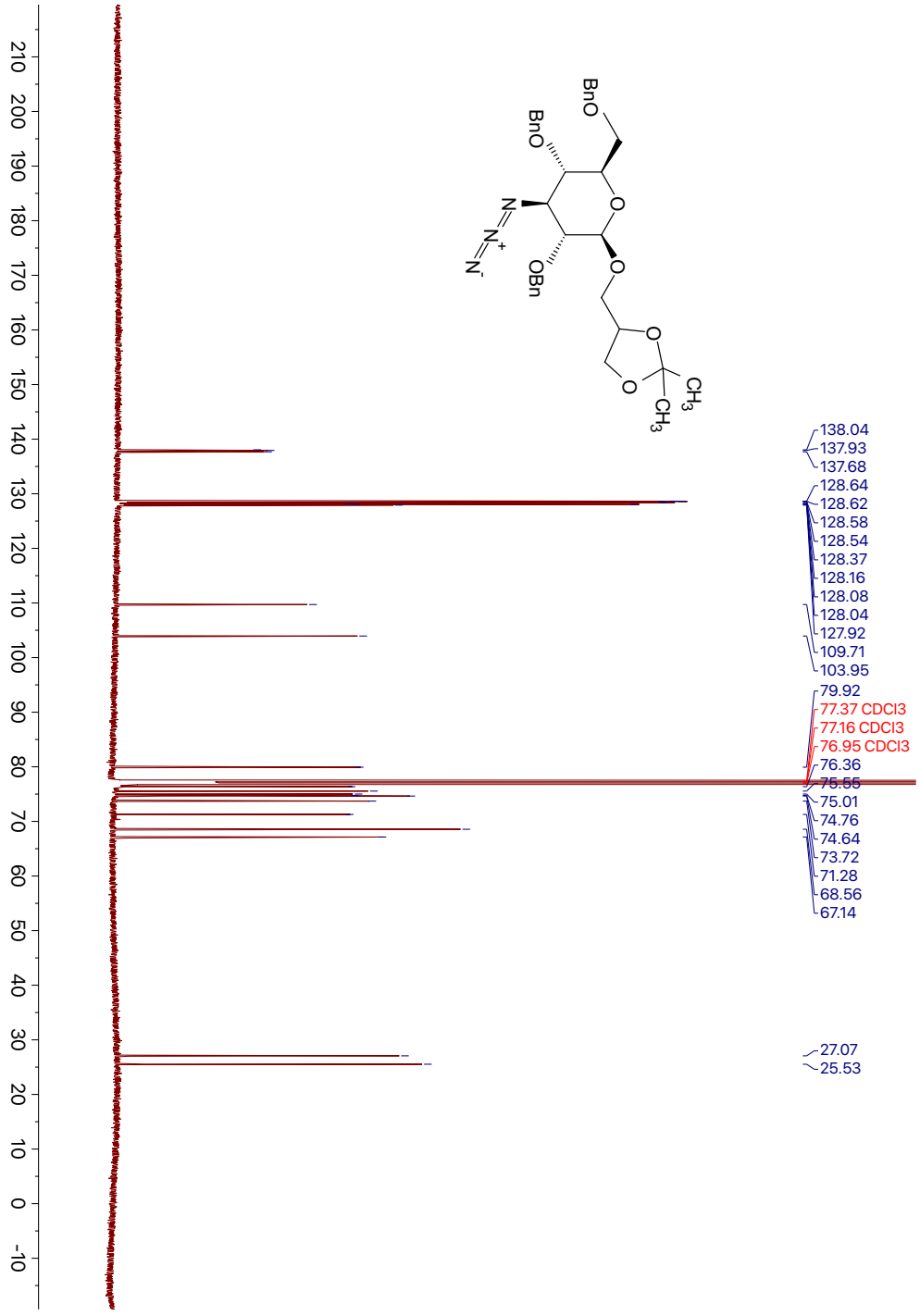


Figure A.22. ^{13}C-NMR spectrum of **19β**.

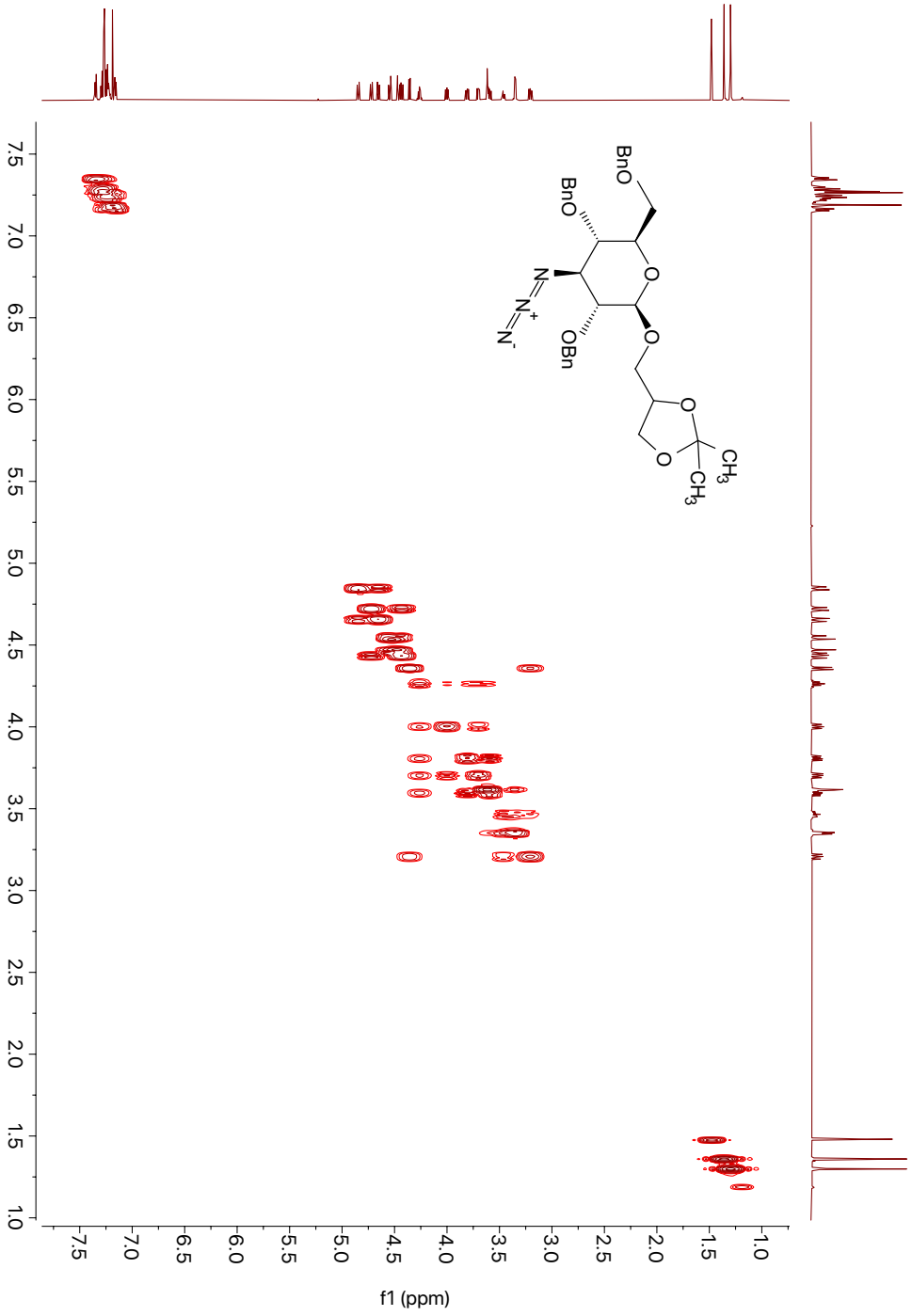


Figure A.23. COSY spectrum of **19β**.

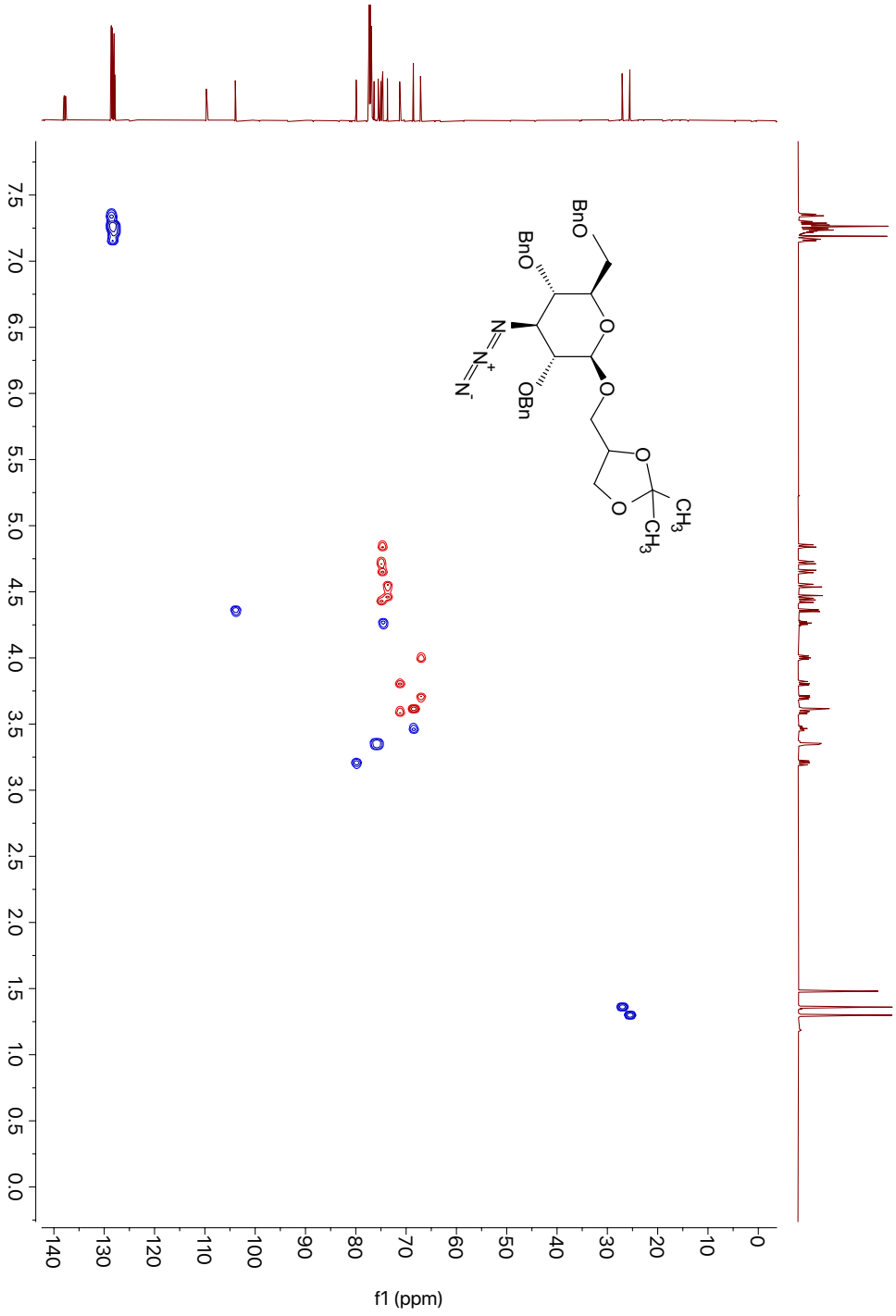


Figure A.24. HSQC spectrum of **19β**.

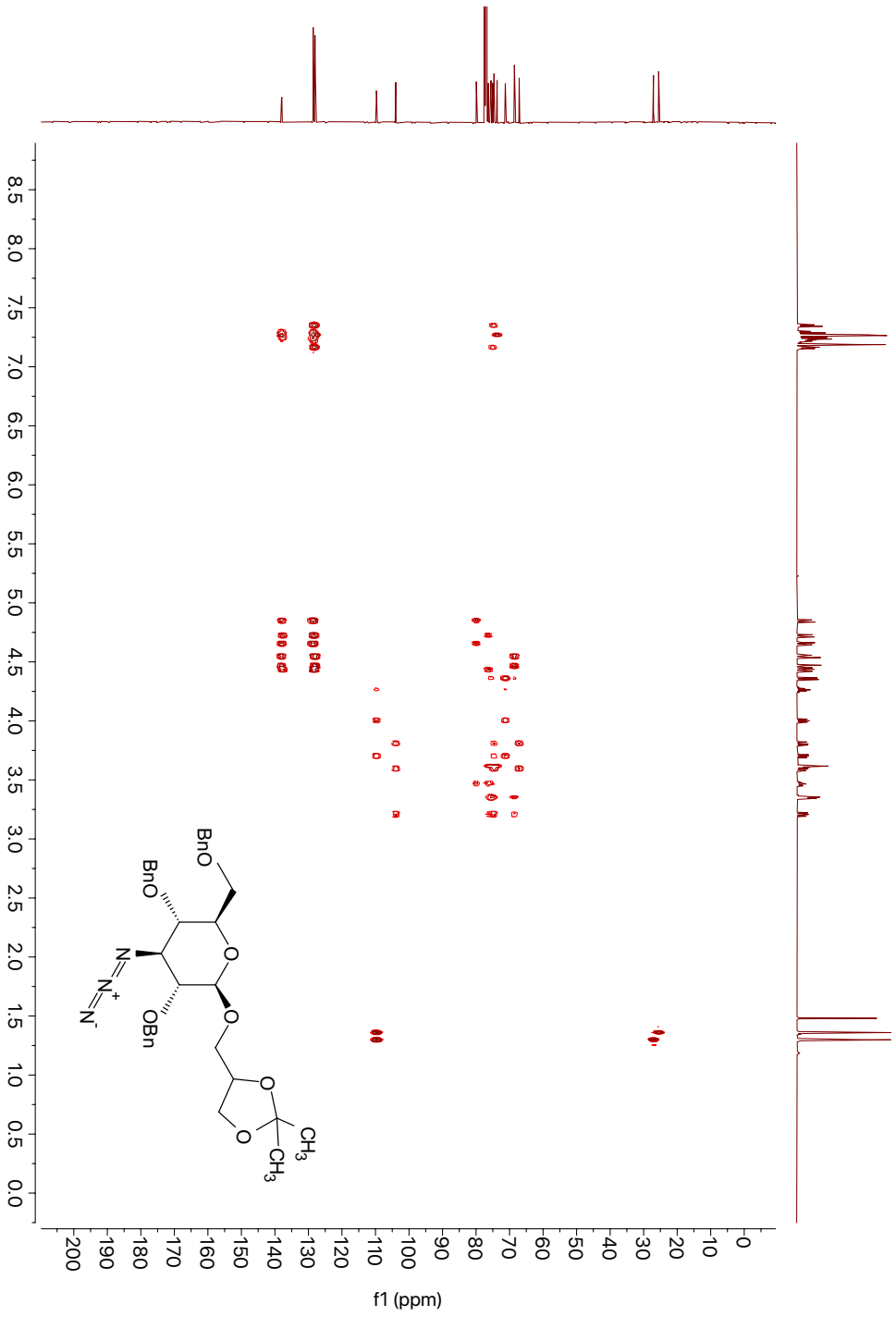


Figure A.25. HMBC spectrum of **19β**.

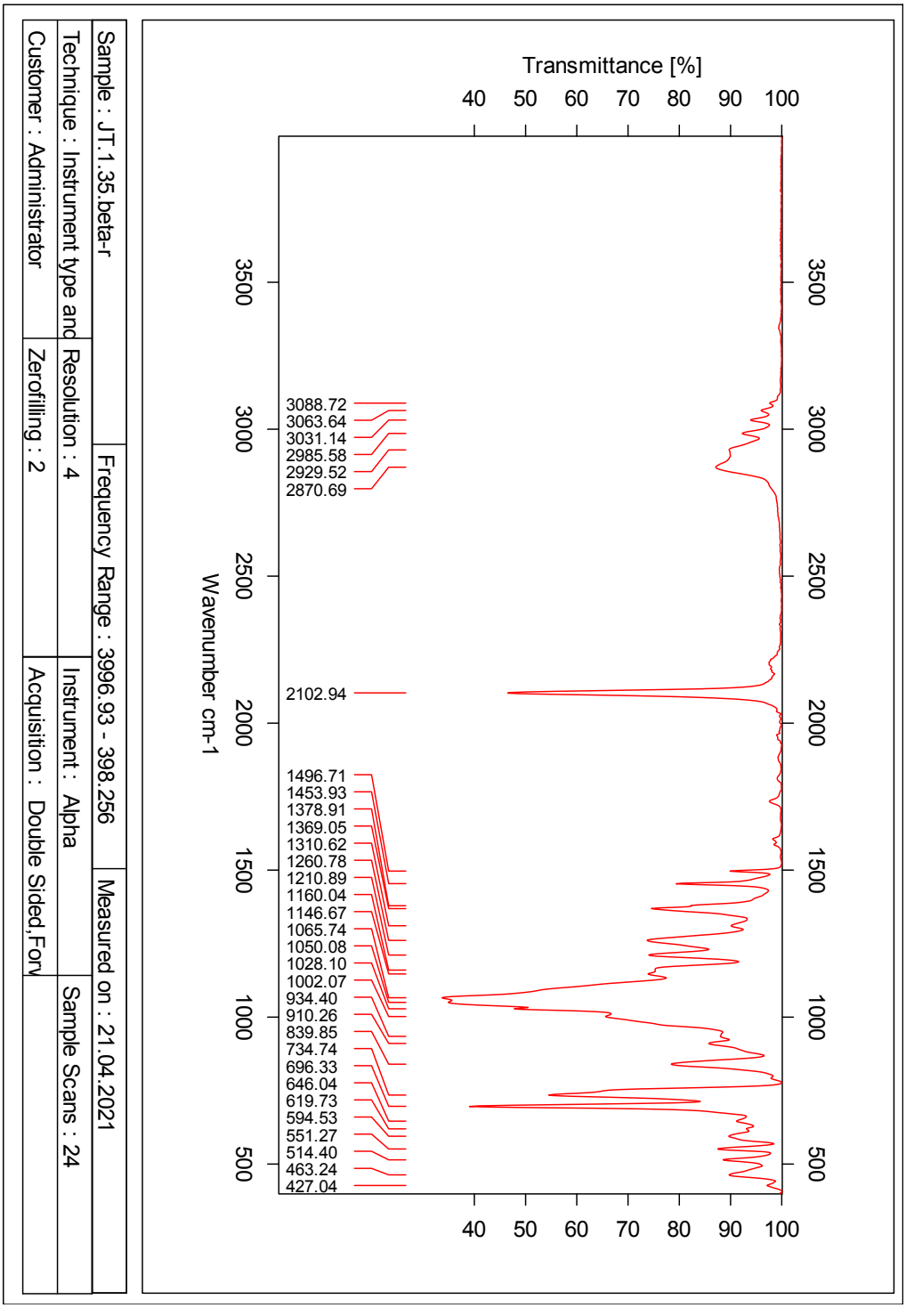


Figure A.26. IR spectrum of **19β**.

A.6 Spectroscopic data for compound 20

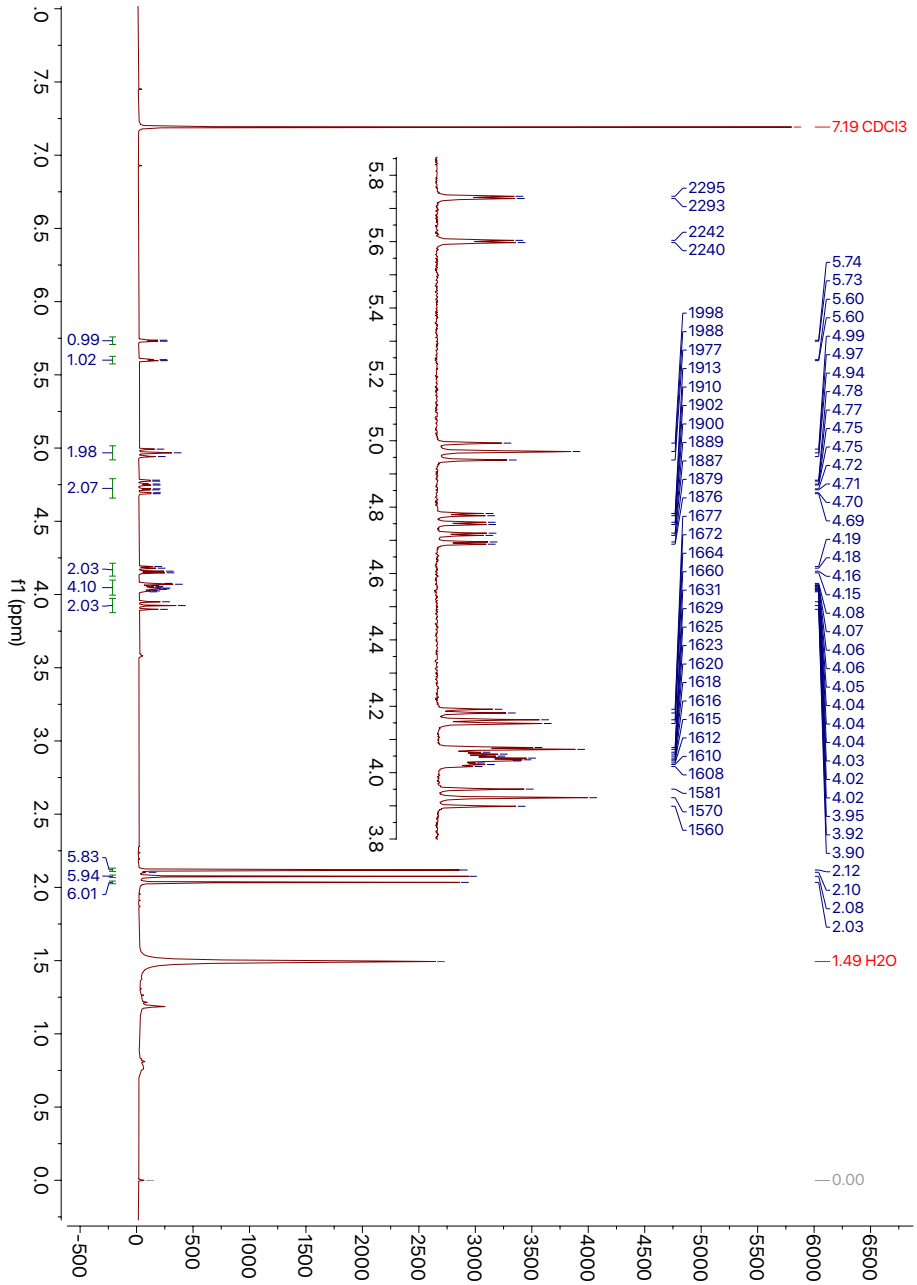


Figure A.27. ^{1}H-NMR spectrum of **25α**.

A.7 Spectroscopic data for compound 21

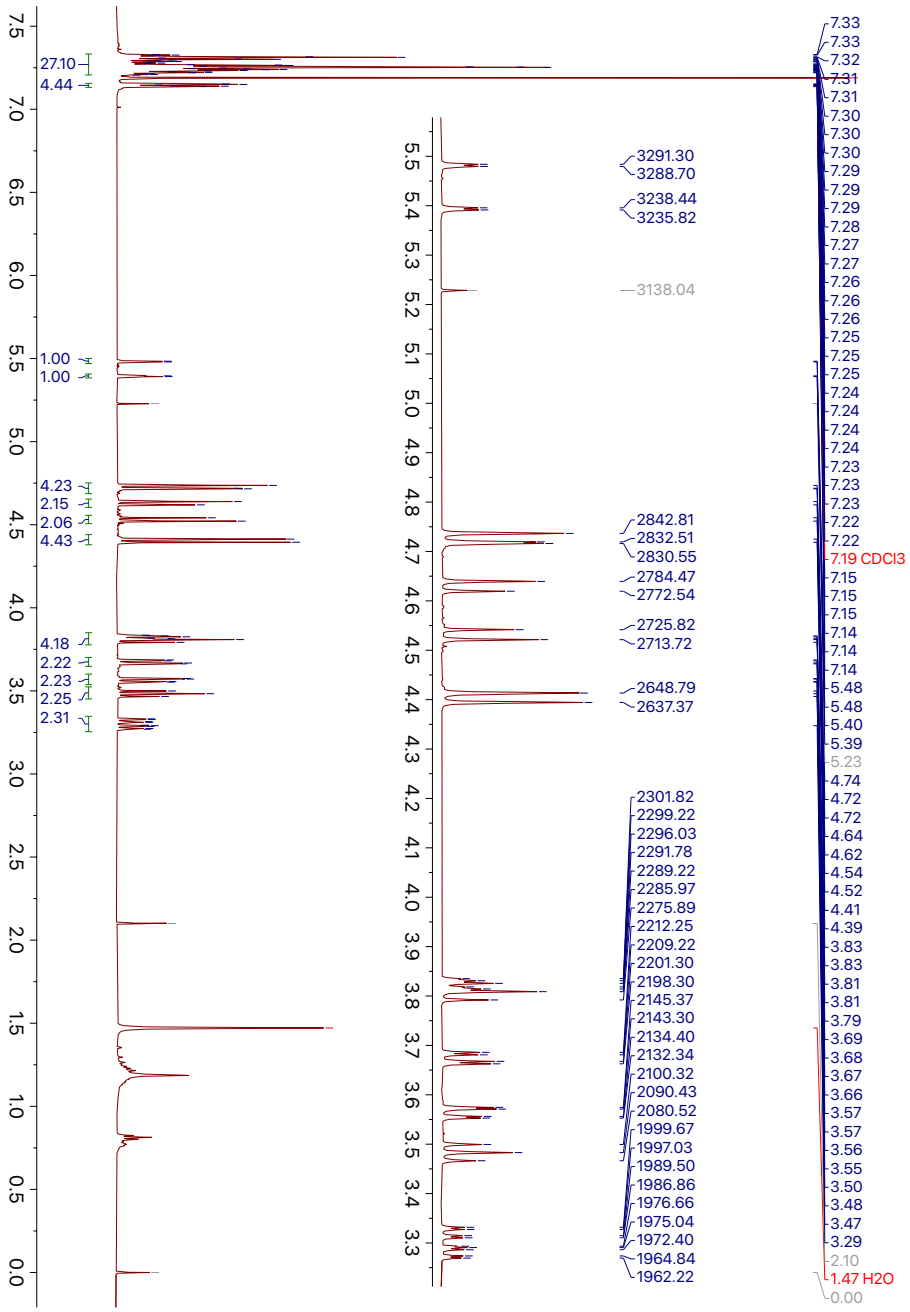


Figure A.28. ^{1}H-NMR spectrum of **25a**.

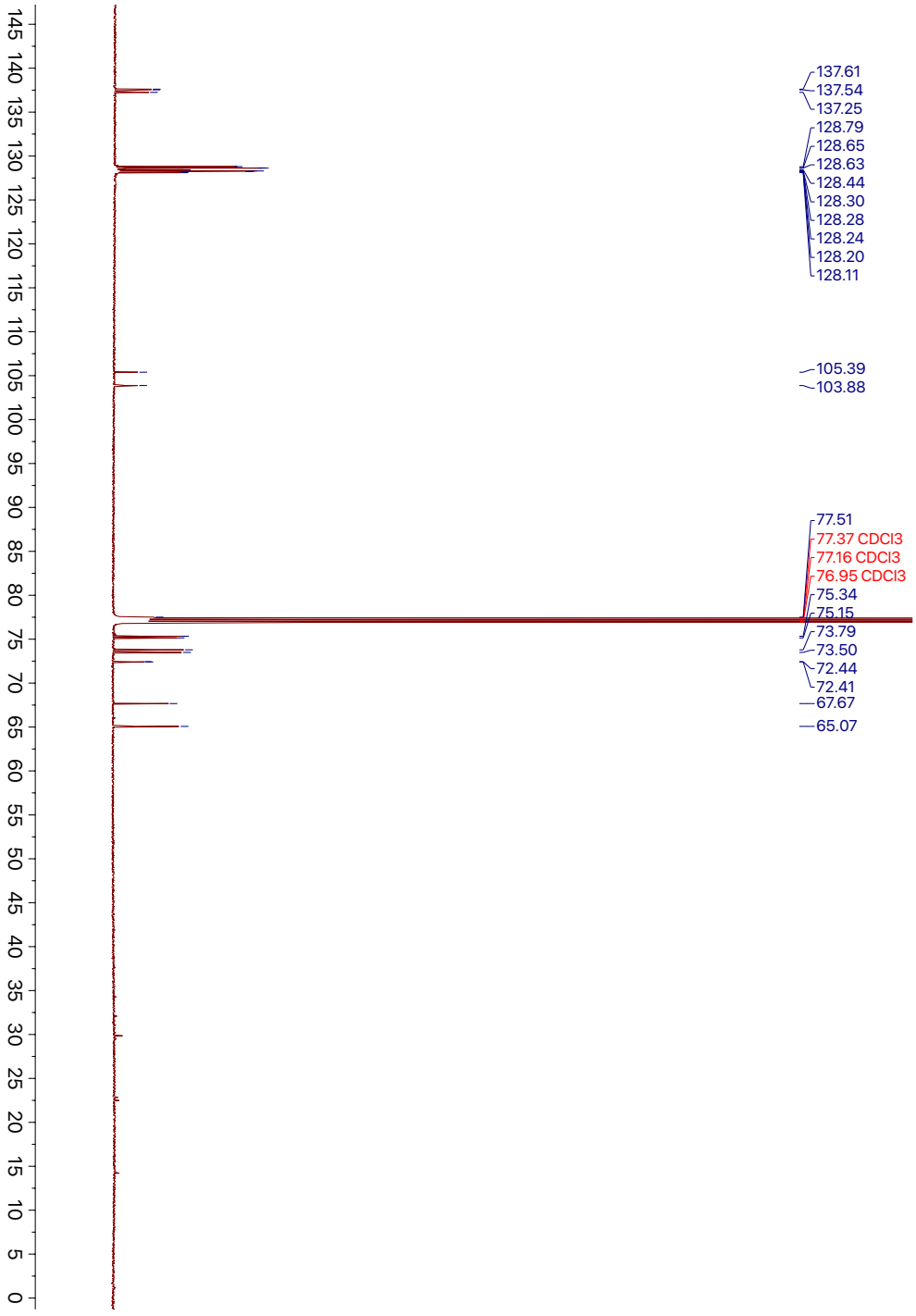


Figure A.29. ^{13}C-NMR spectrum of **25α**.

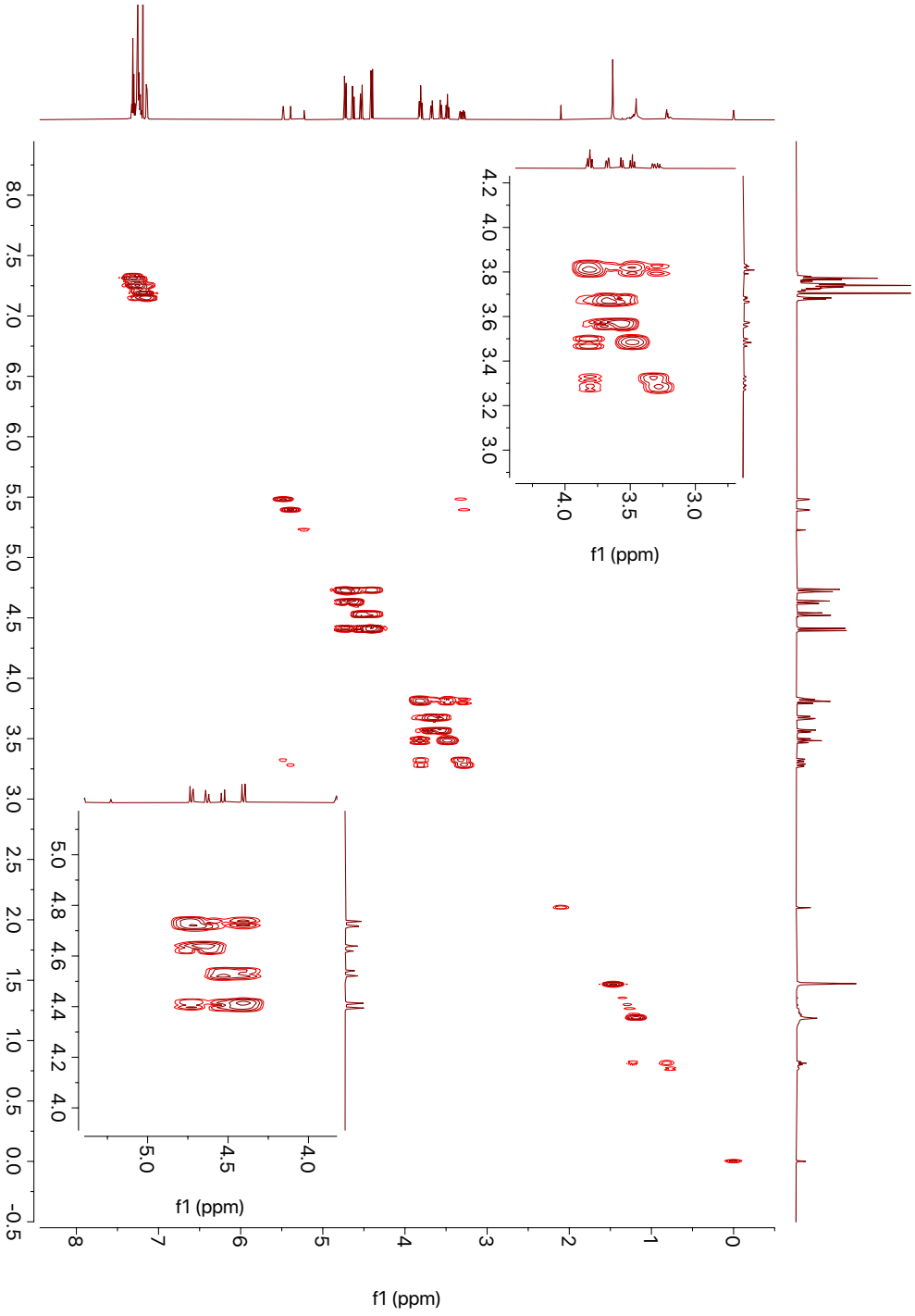


Figure A.30. COSY spectrum of **25α**.

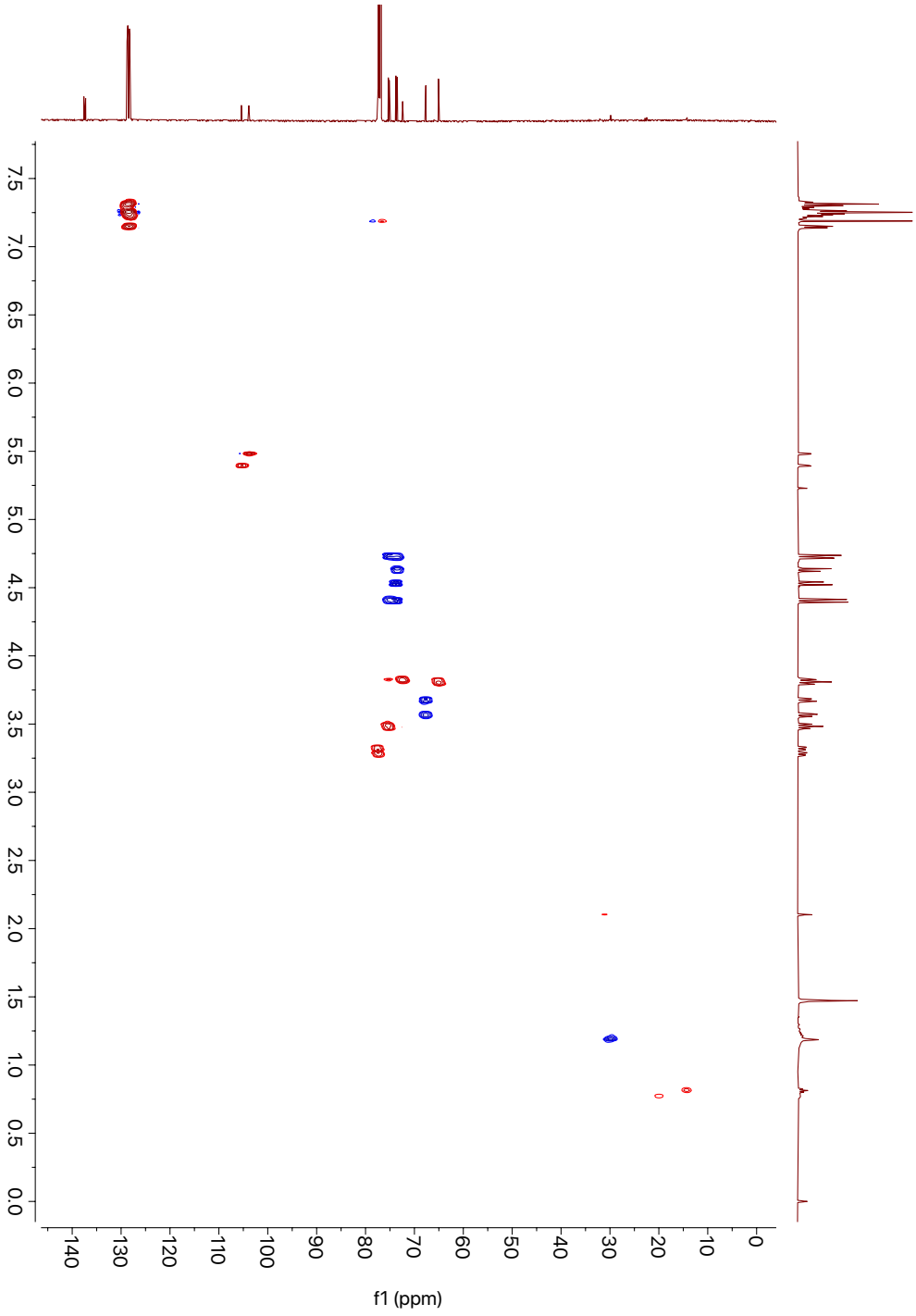


Figure A.31. HSQC spectrum of **25α**.

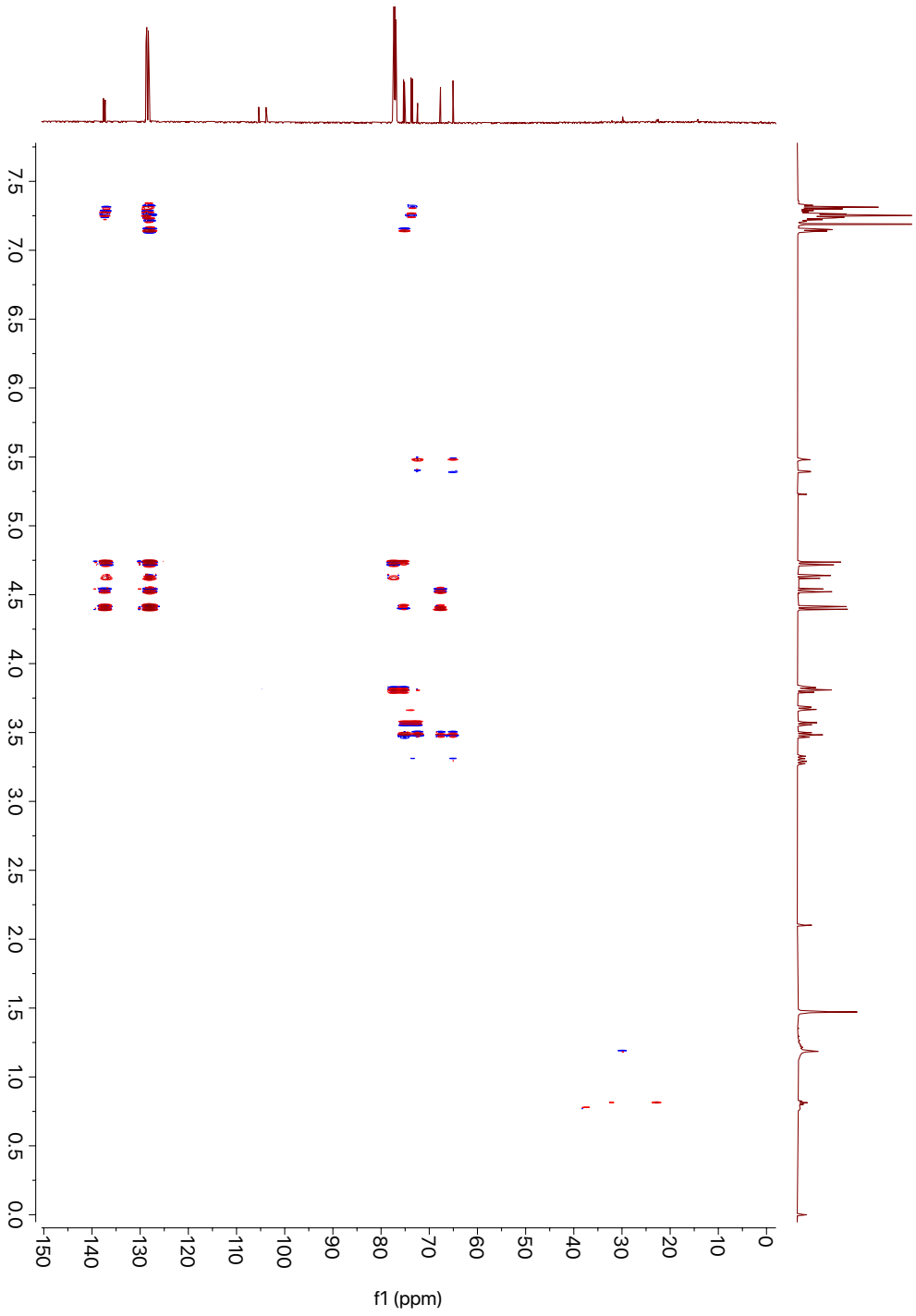


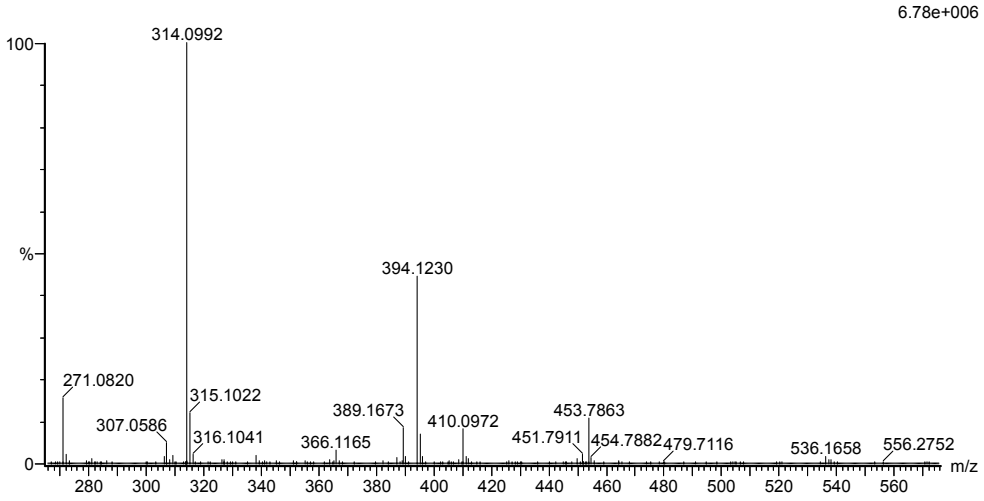
Figure A.32. HMBC spectrum of **25α**.

A.8 Spectroscopic data for compound 23α

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -50.0, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 6

Monoisotopic Mass, Even Electron Ions
2072 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-10 O: 0-10 Na: 0-1
2020 414 63 (0.604) AM2 (Ar,35000.0,0.00,0.00); Cm (52:67)
1: TOF MS ES+



Minimum:				-50.0				
Maximum:		5.0	2.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
394.1230	394.1226	0.4	1.0	6.5	2709.0	0.463	62.93	C15 H21 N3 O8 Na
	394.1224	0.6	1.5	10.5	2709.6	0.992	37.07	C13 H16 N9 O6
	394.1232	-0.2	-0.5	22.5	2719.6	11.004	0.00	C29 H16 N O

Figure A.33. HRMS (ESI+) of **23α**.

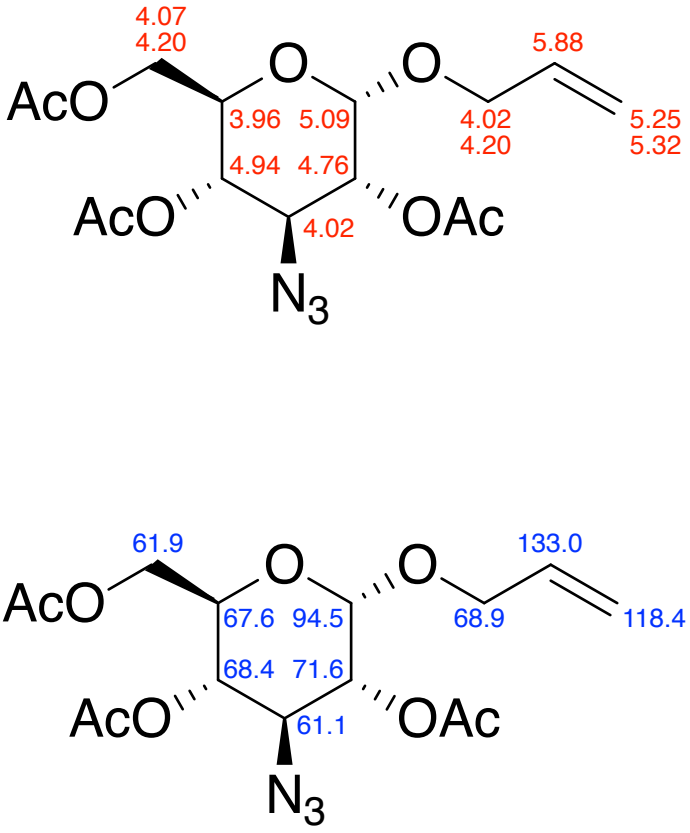


Figure A.34. Assigned ^{1}H- (red) and ^{13}C- (blue) shifts of **23α**.

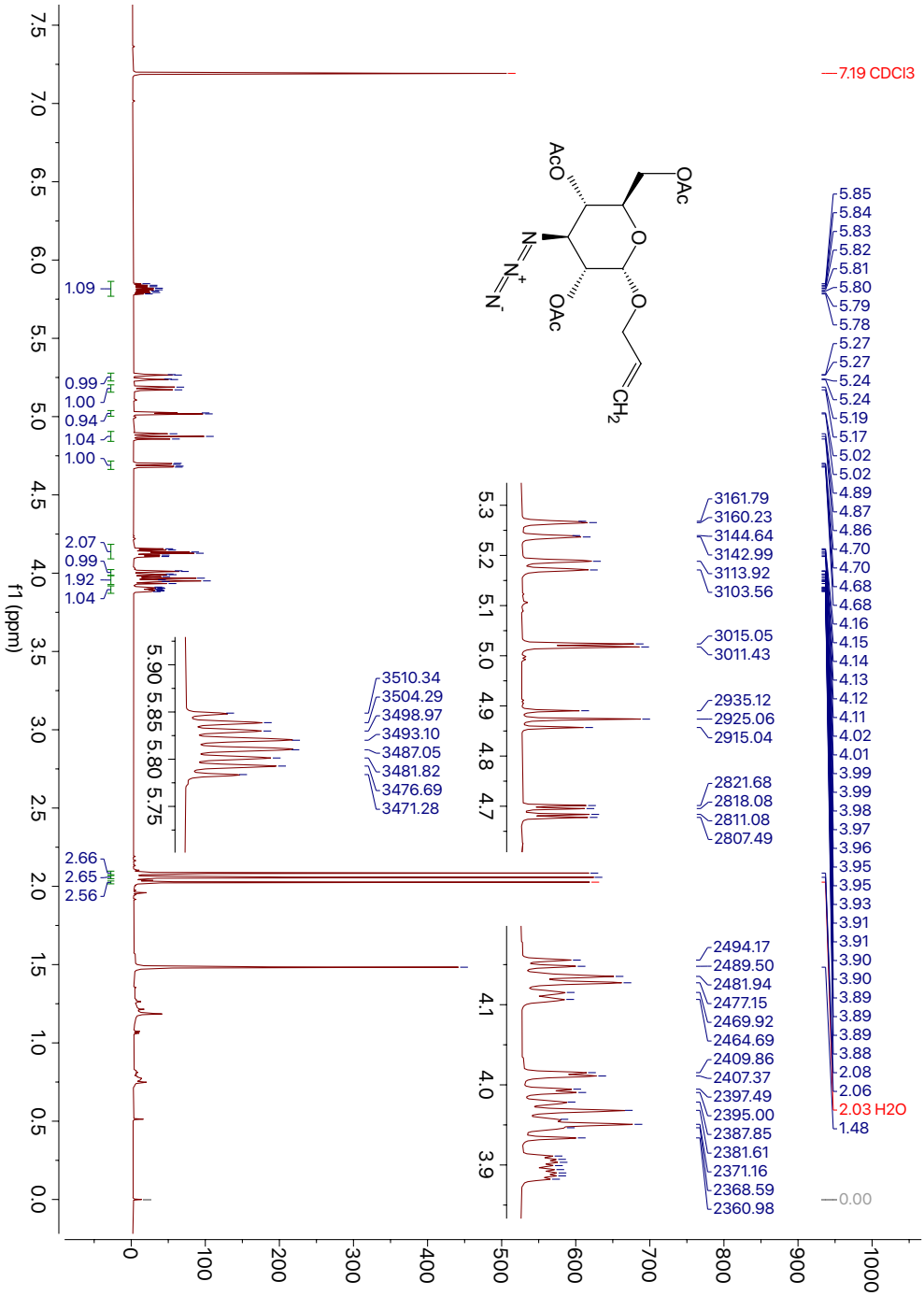


Figure A.35. ^{1}H-NMR spectrum of **23α**.

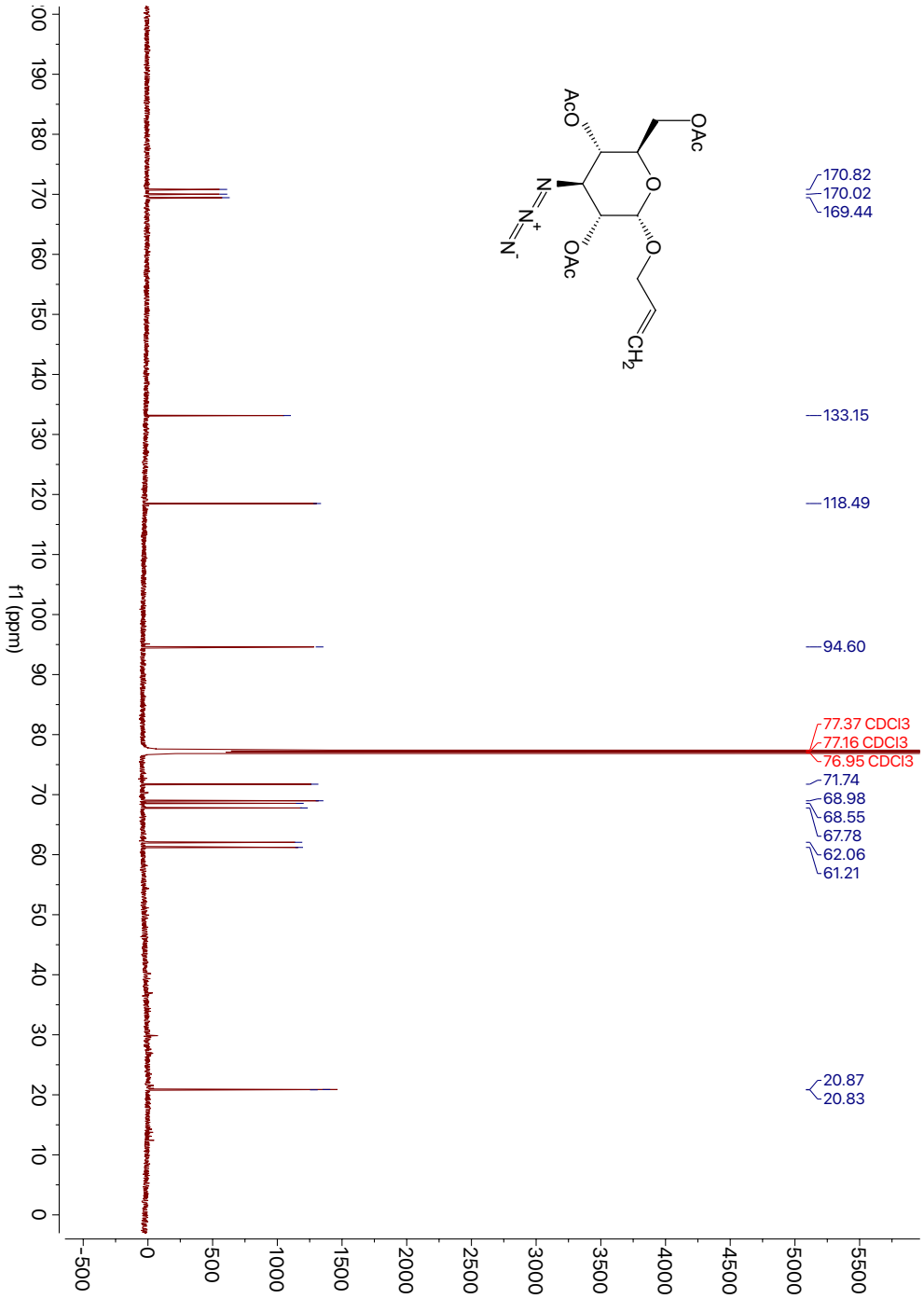


Figure A.36. ^{13}C-NMR spectrum of **23α**.

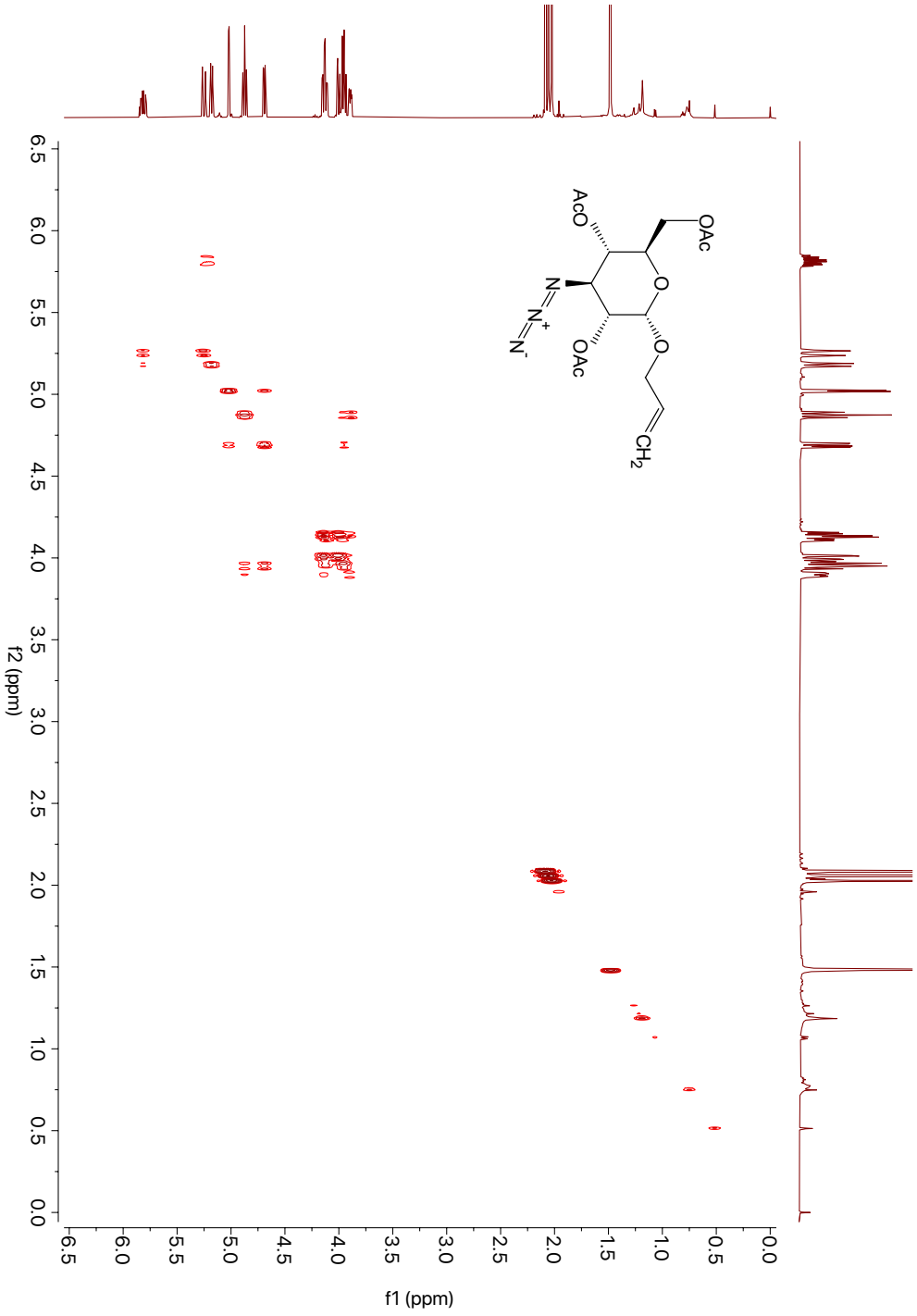


Figure A.37. COSY spectrum of **23α**.

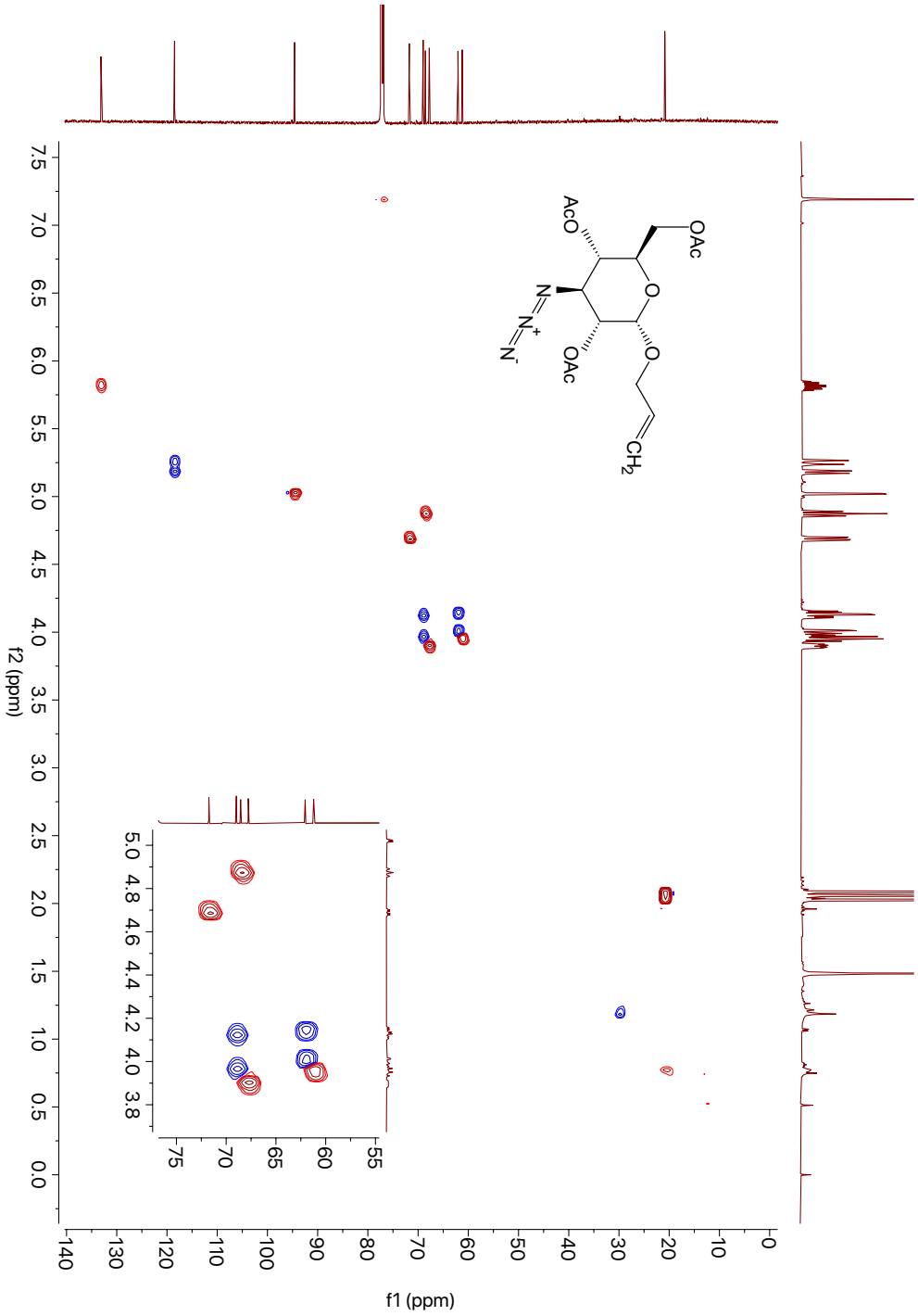


Figure A.38. HSQC spectrum of **23α**.

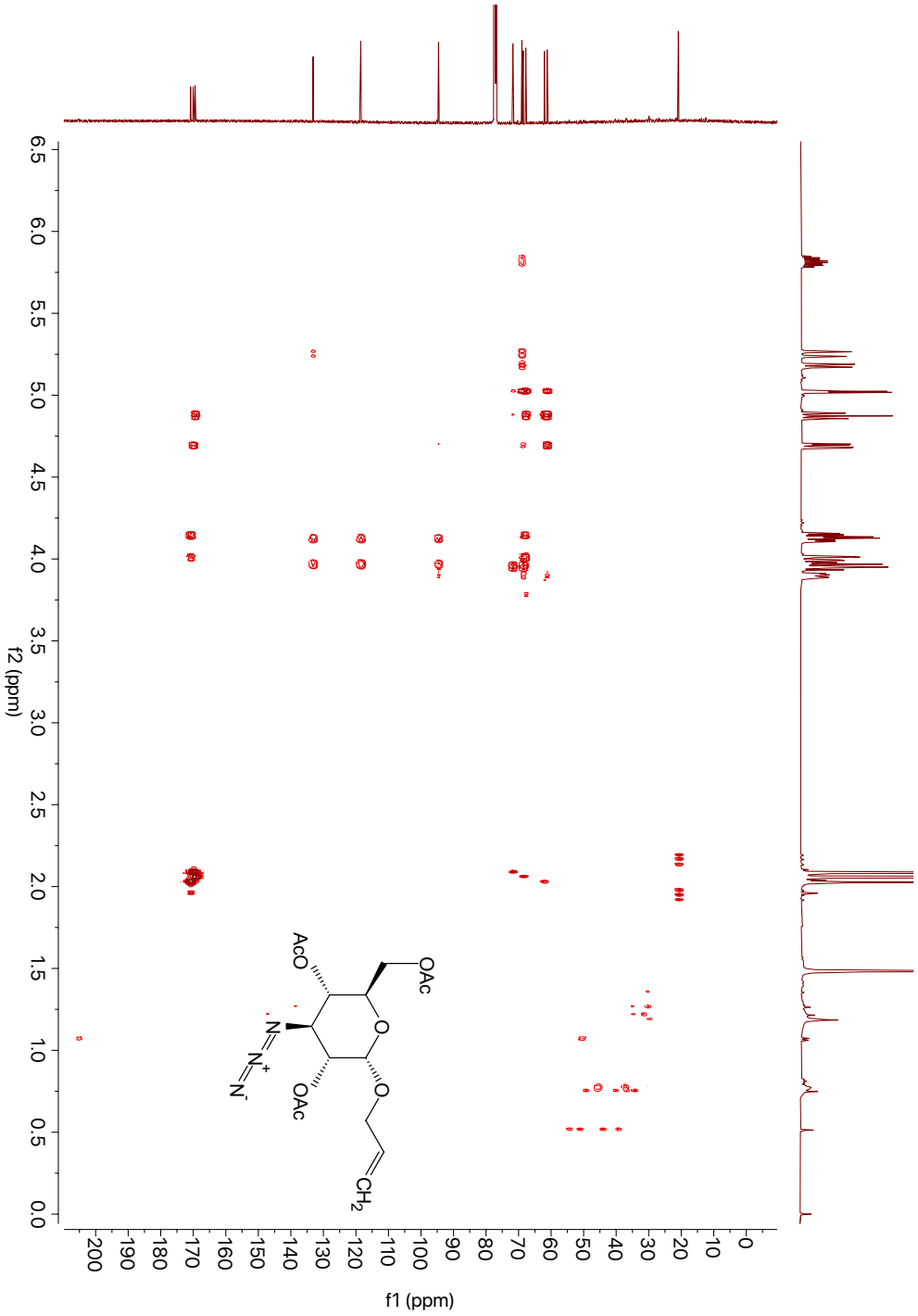


Figure A.39. HMBC spectrum of **23α**.

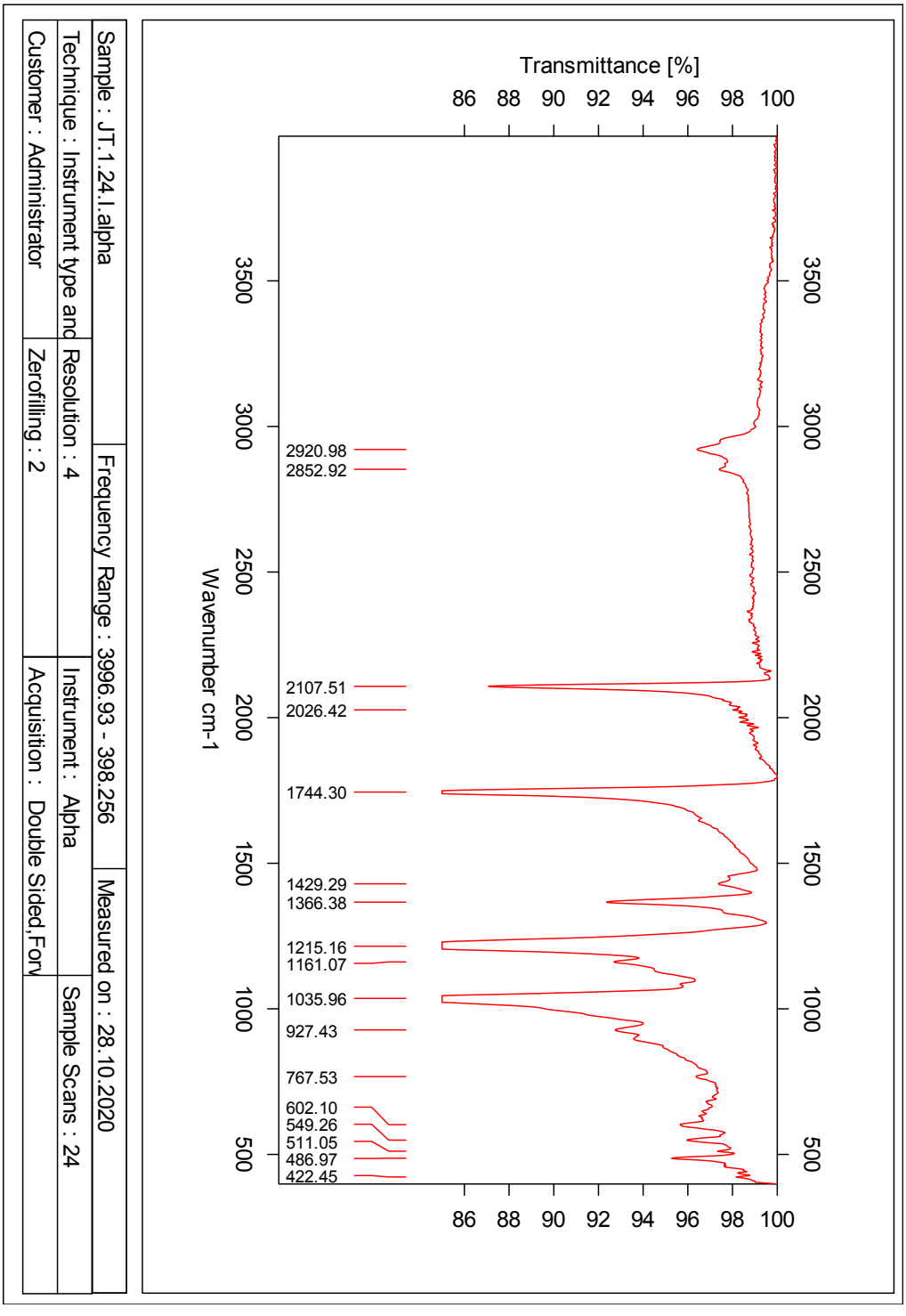


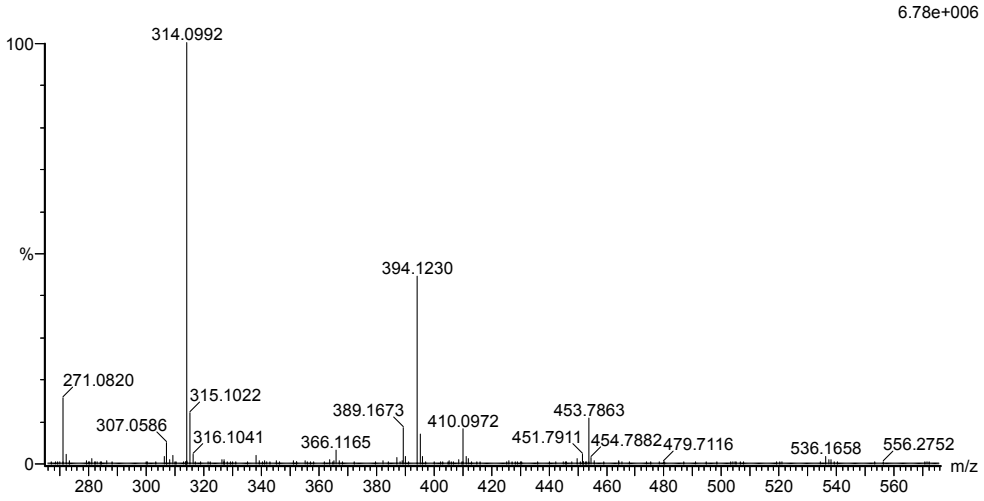
Figure A.40. IR spectrum of **23α**.

A.9 Spectroscopic data for compound 23β

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -50.0, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 6

Monoisotopic Mass, Even Electron Ions
2072 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-10 O: 0-10 Na: 0-1
2020 414 63 (0.604) AM2 (Ar,35000.0,0.00,0.00); Cm (52:67)
1: TOF MS ES+



Minimum:				-50.0				
Maximum:		5.0	2.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
394.1230	394.1226	0.4	1.0	6.5	2709.0	0.463	62.93	C15 H21 N3 O8 Na
	394.1224	0.6	1.5	10.5	2709.6	0.992	37.07	C13 H16 N9 O6
	394.1232	-0.2	-0.5	22.5	2719.6	11.004	0.00	C29 H16 N O

Figure A.41. HRMS (ESI+) of **23β**.

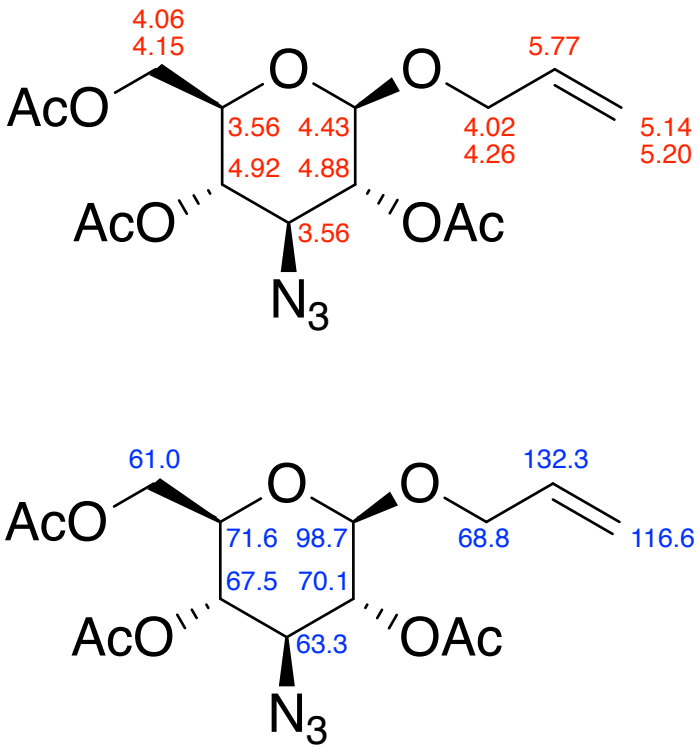


Figure A.42. Assigned ^{1}H- (red) and ^{13}C- (blue) shifts of **23β**.

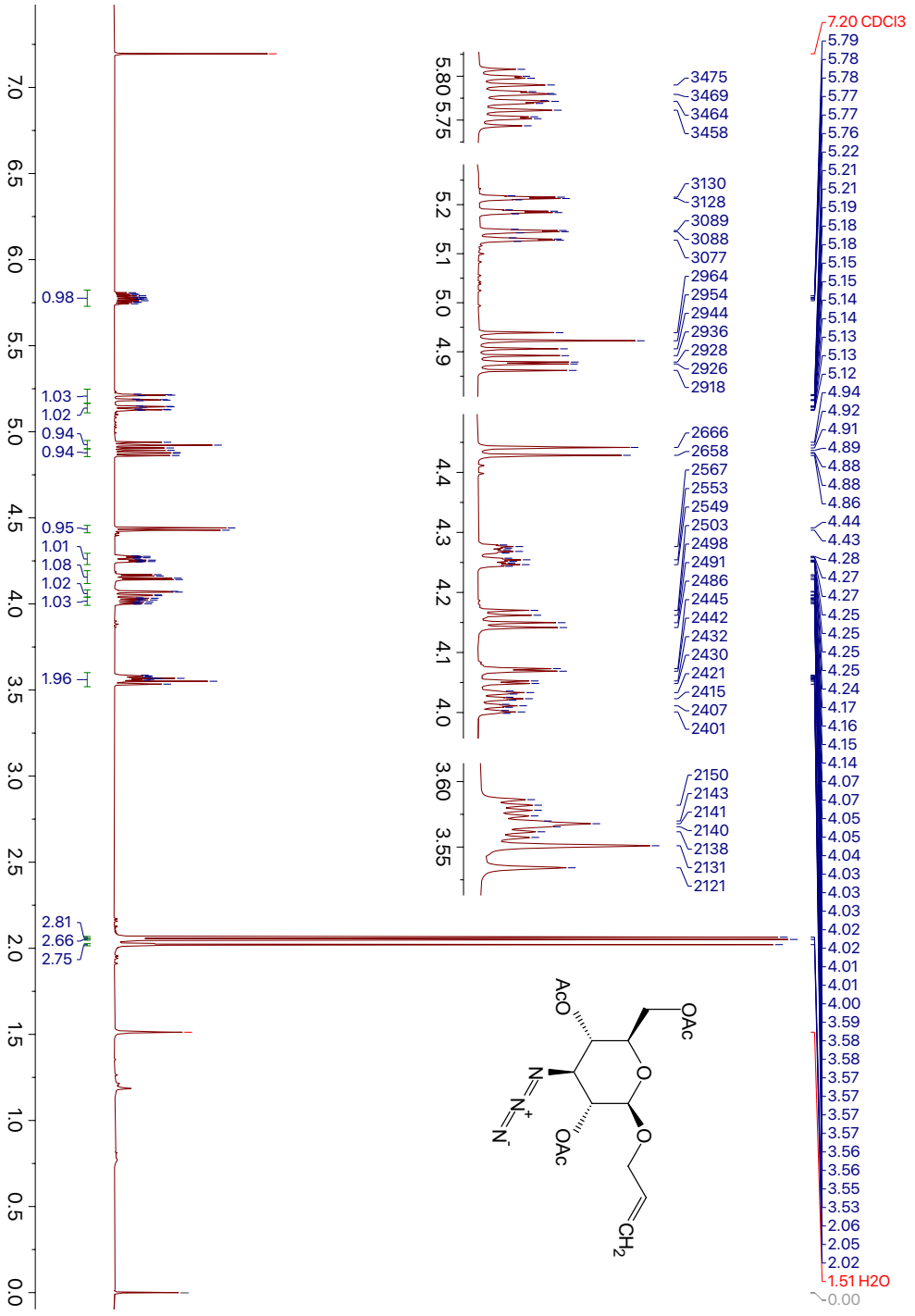


Figure A.43. ^{1}H-NMR spectrum of **23β**.

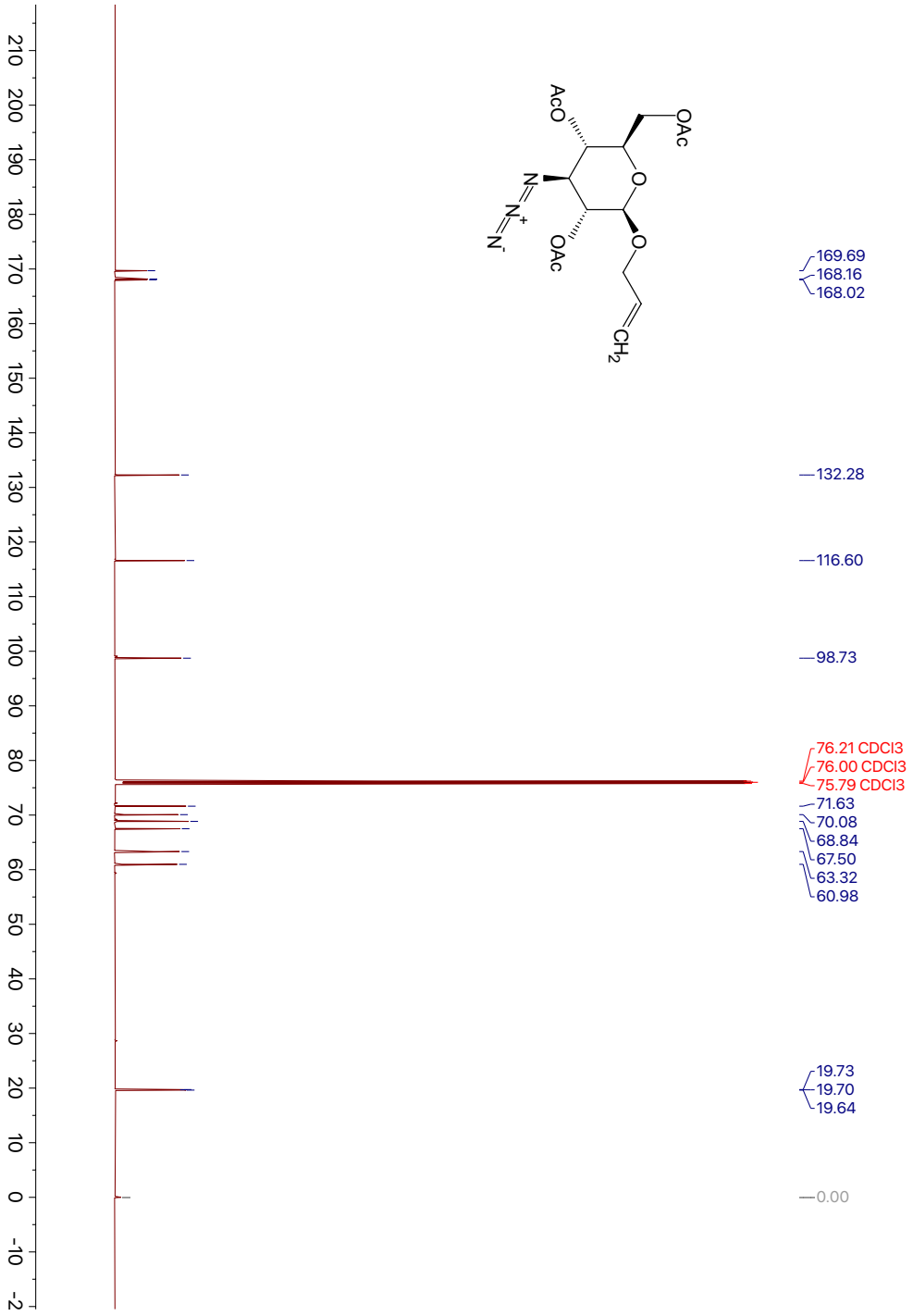


Figure A.44. ^{13}C-NMR spectrum of **23β**.

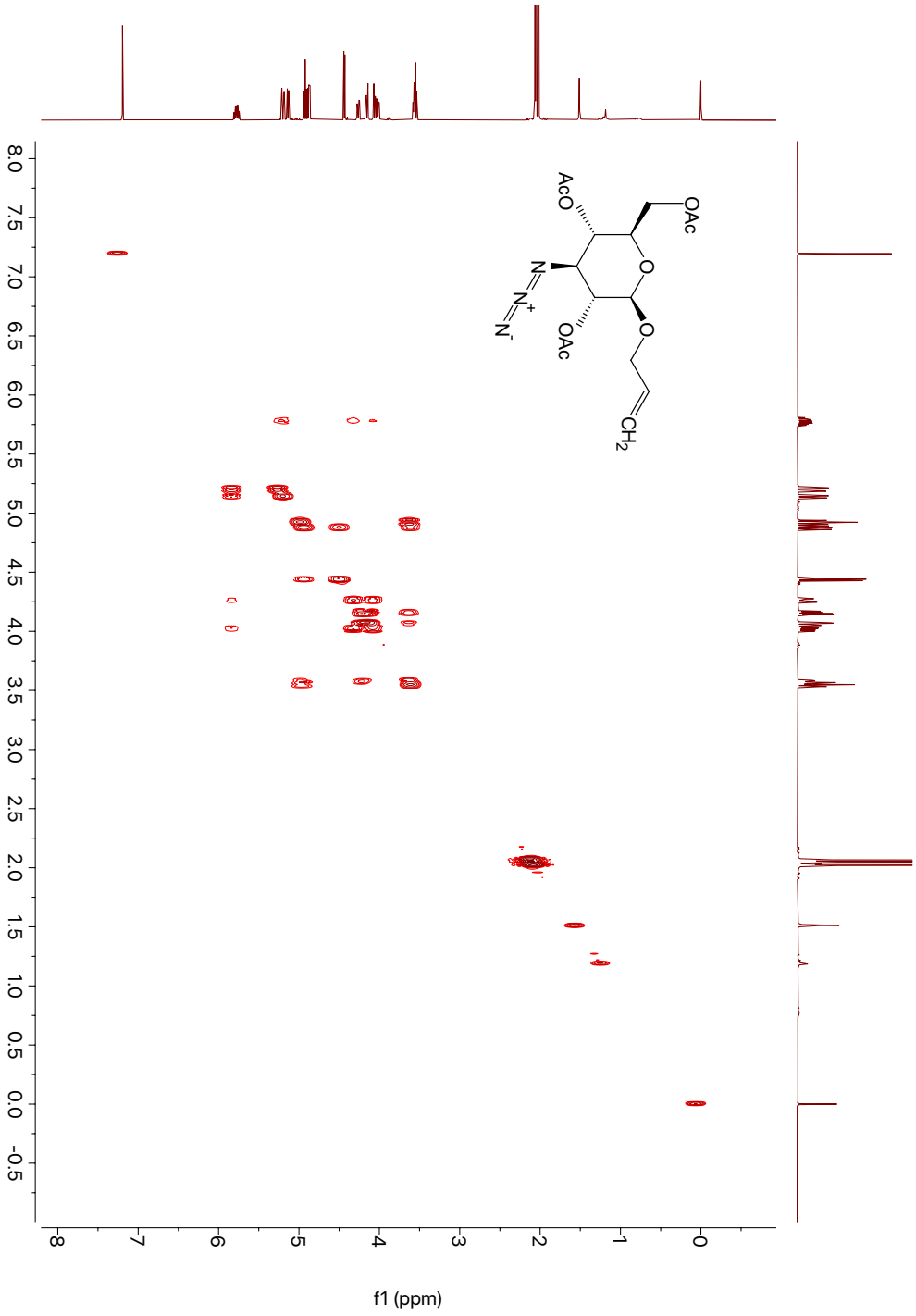


Figure A.45. COSY spectrum of **23β**.

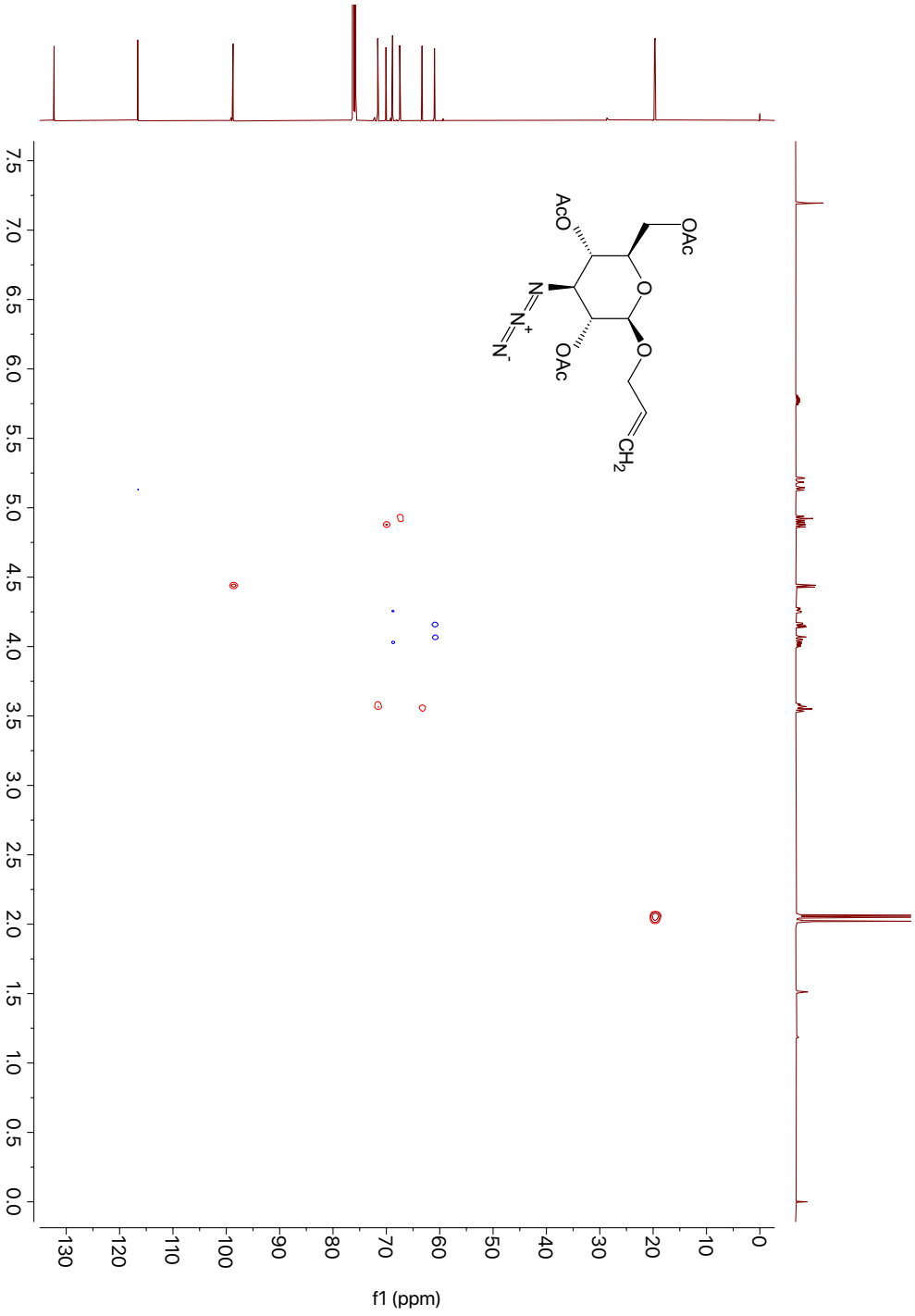


Figure A.46. HSQC spectrum of **23β**.

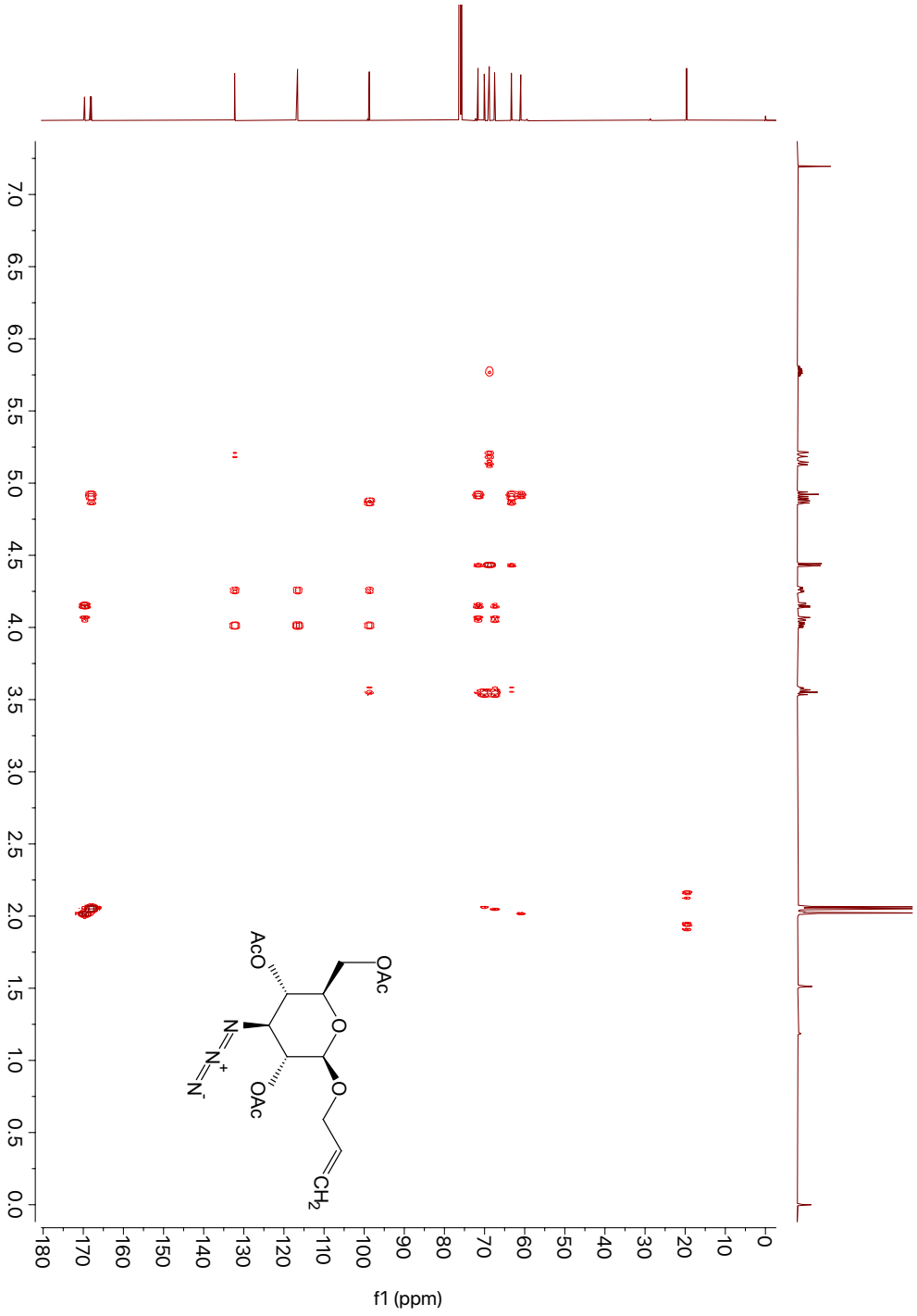


Figure A.47. HMBC spectrum of **23β**.

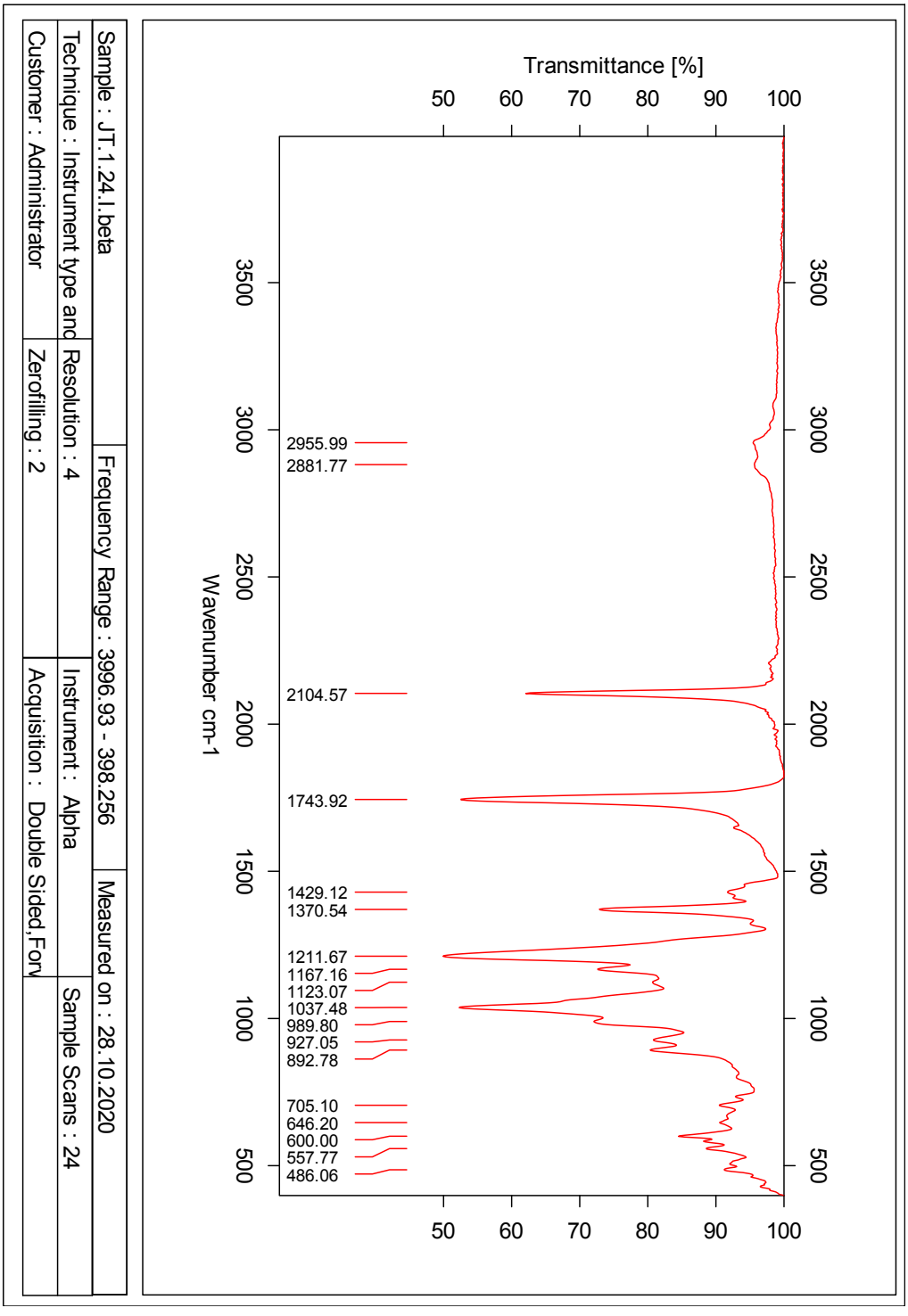


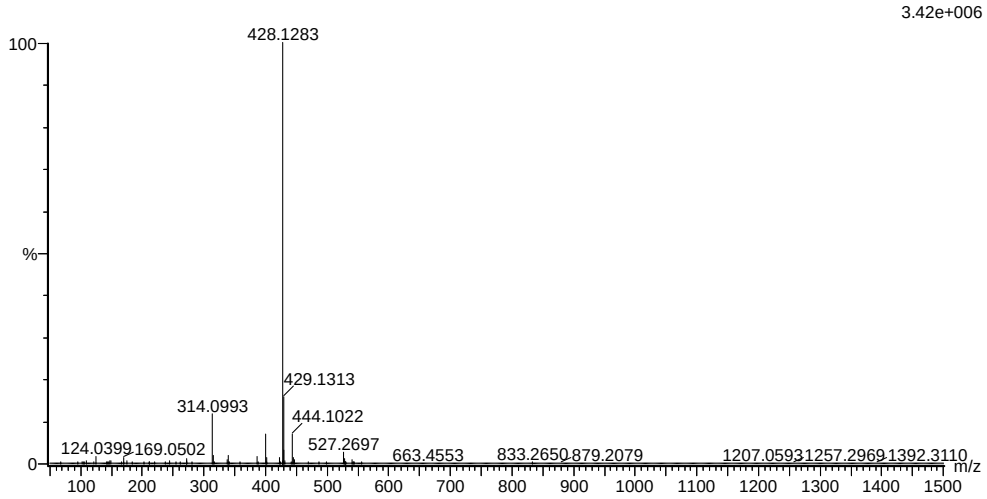
Figure A.48. IR spectrum of **23β**.

A.10 Spectroscopic data for compound 24α

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -10.0, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 6

Monoisotopic Mass, Even Electron Ions
786 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-5 O: 0-10 Na: 0-1
2021-228 95 (0.901) AM2 (Ar,35000.0,0.00,0.00); Cm (95:101)
1: TOF MS ES+



Minimum:				-10.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
428.1283	428.1281	0.2	0.5	5.5	2211.4	0.000	100.00	C15 H23 N3 O10 Na
	428.1287	-0.4	-0.9	21.5	2227.3	15.836	0.00	C29 H18 N O3

Figure A.49. HRMS (ESI+) of **24α**.

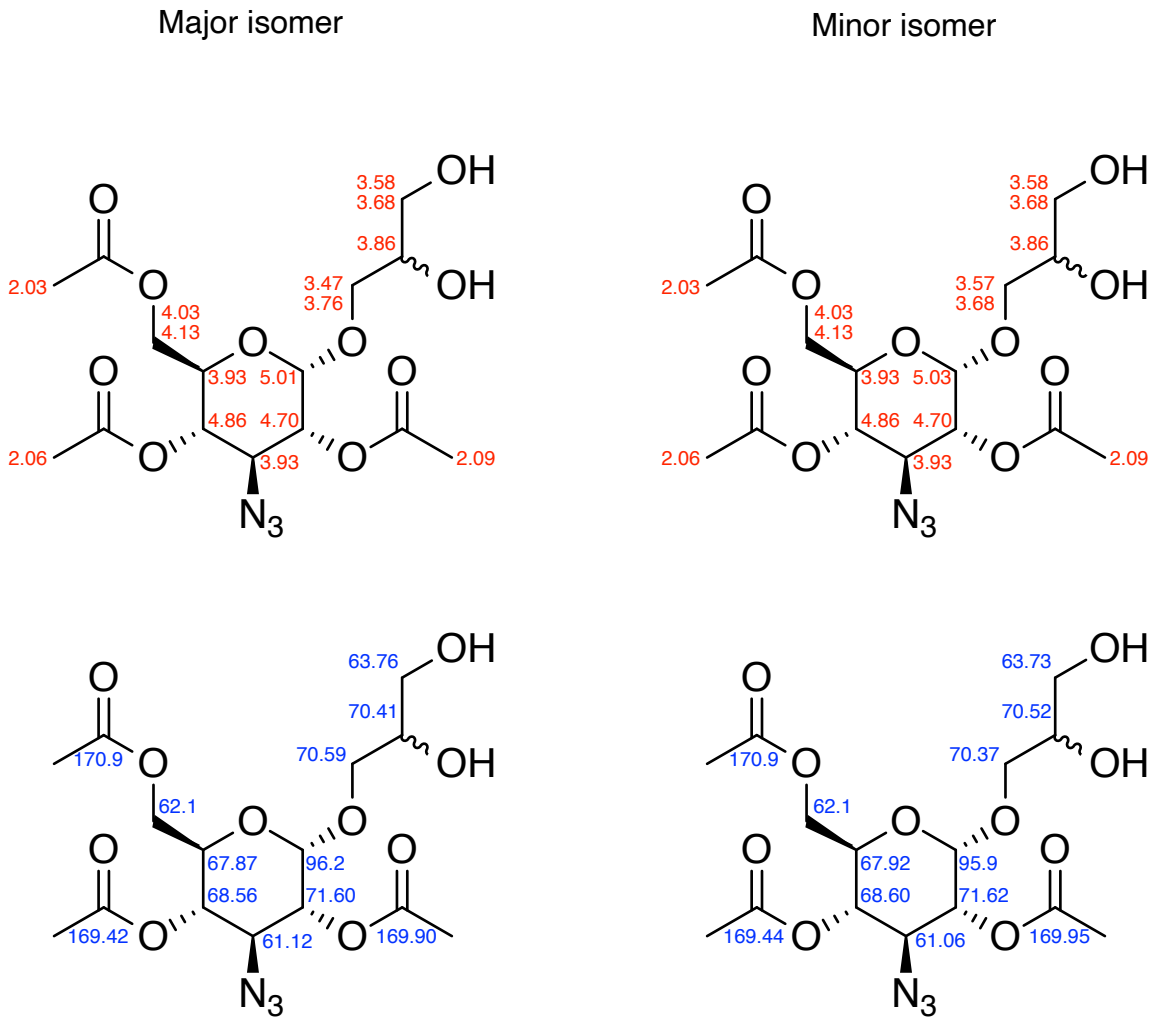


Figure A.50. Assigned ^{1}H- (red) and ^{13}C- (blue) shifts of **24α**. It is unknown which is the r- or s-isomer.

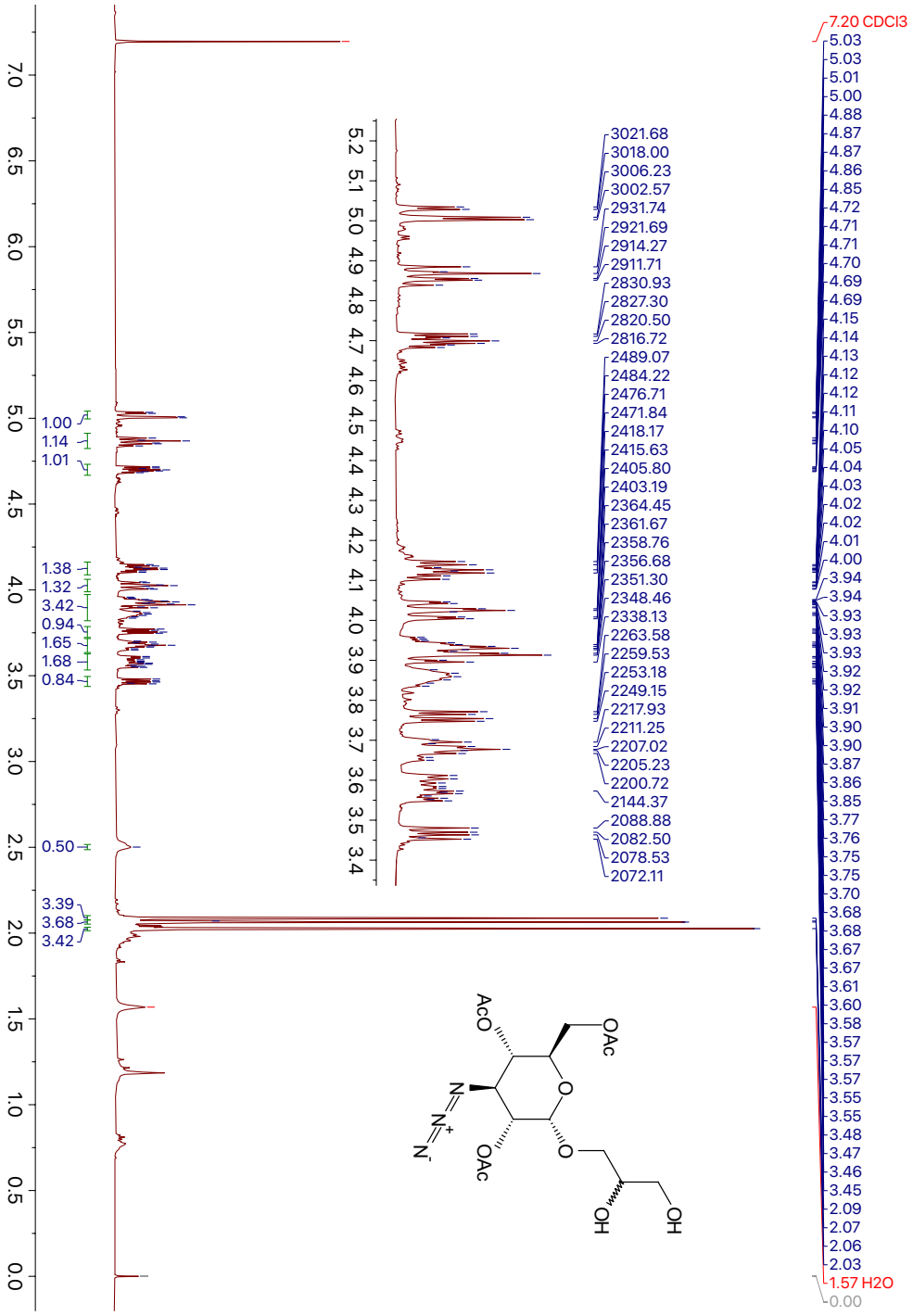


Figure A.51. ^{1}H-NMR spectrum of **24α**.

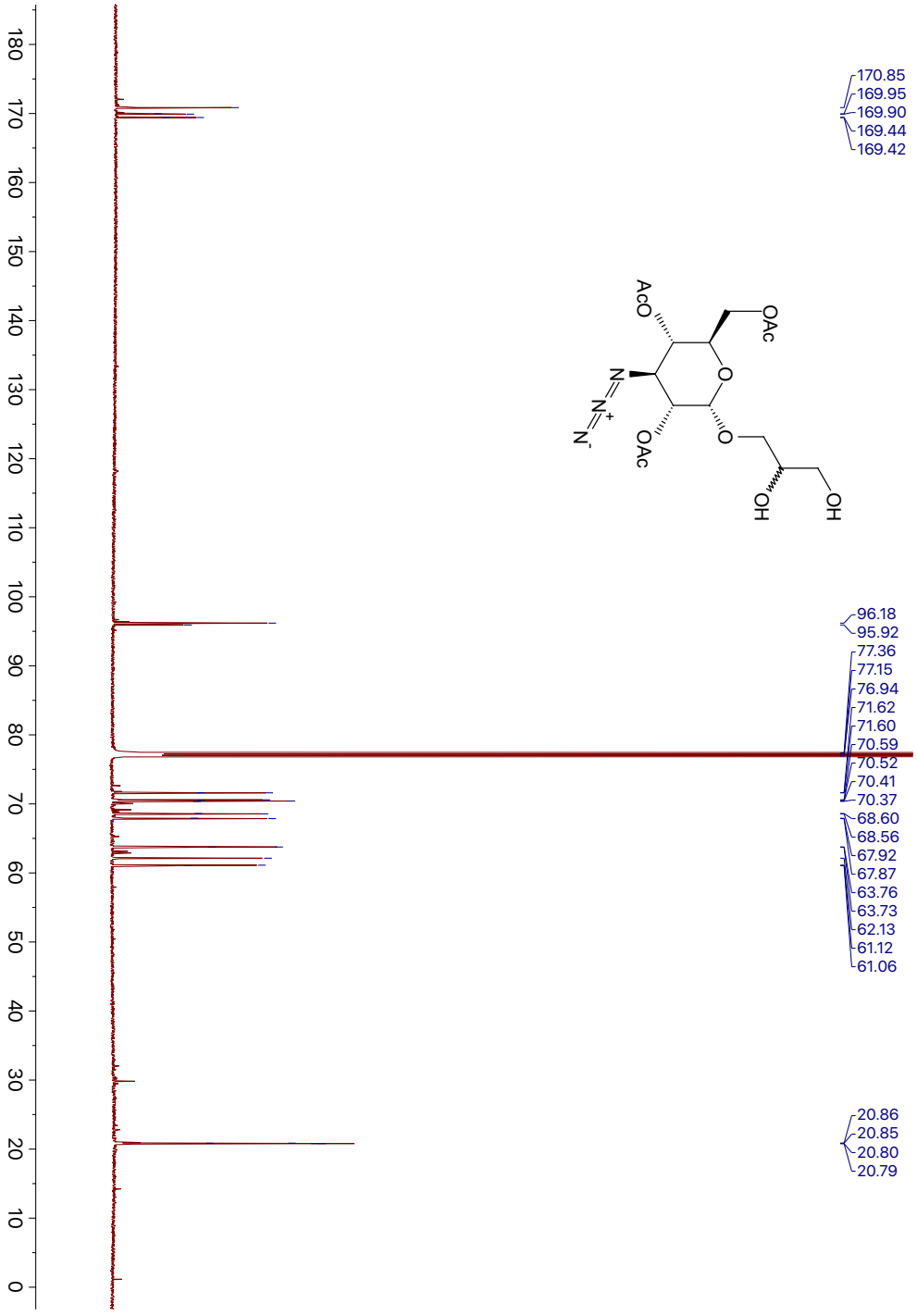


Figure A.52. ^{13}C-NMR spectrum of **24α**.

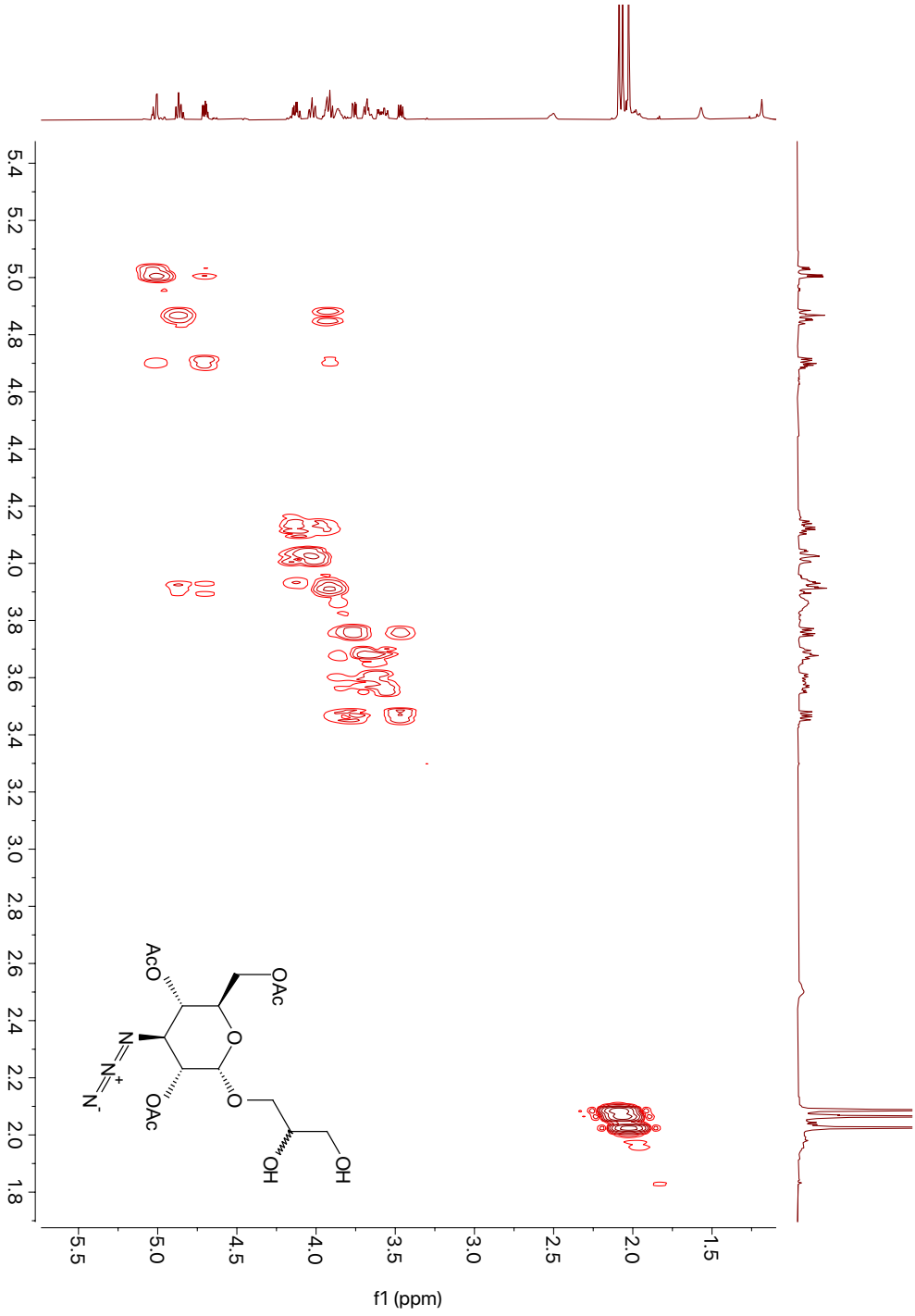


Figure A.53. COSY spectrum of **24α**.

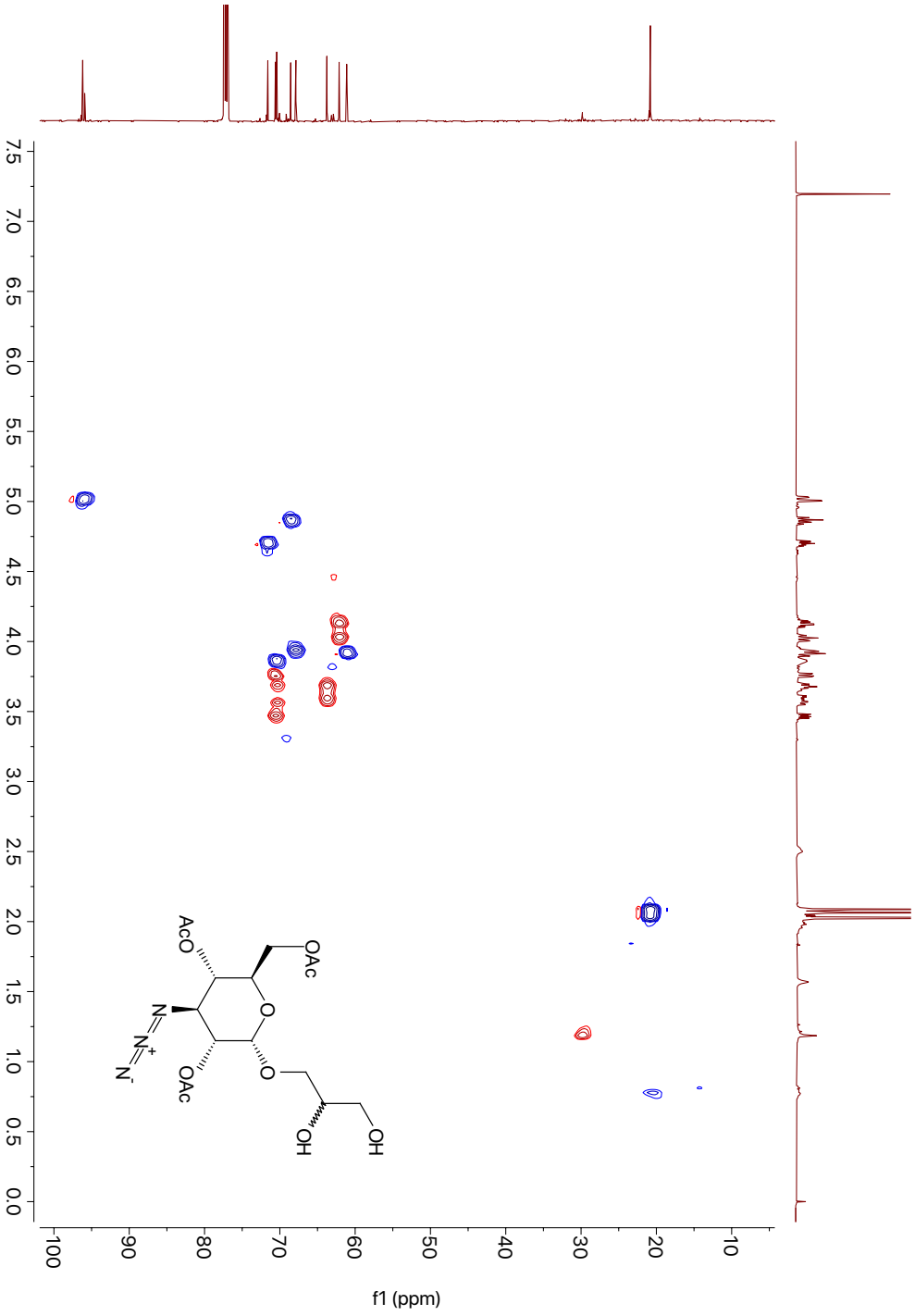


Figure A.54. HSQC spectrum of **24α**.

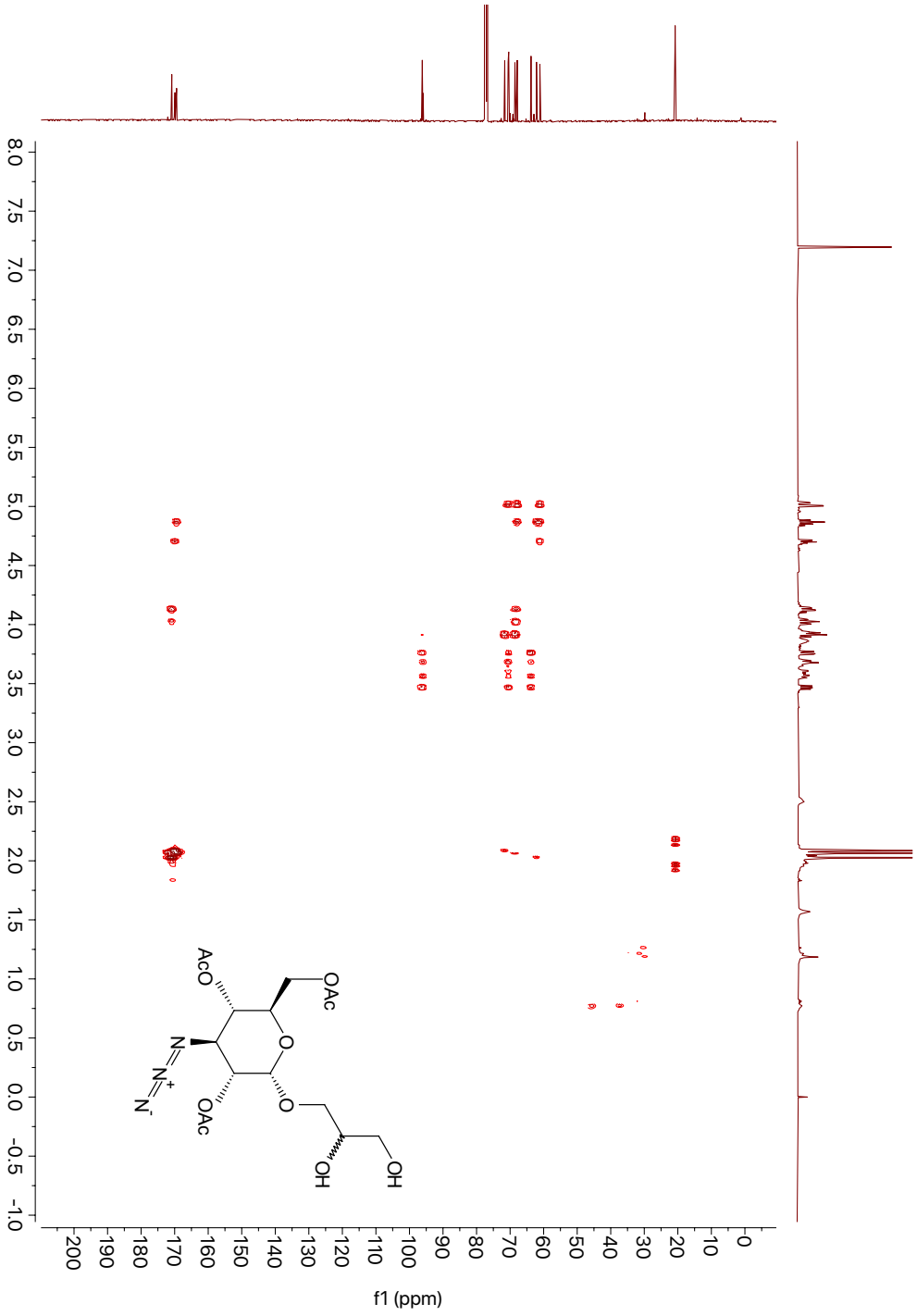


Figure A.55. HMBC spectrum of **24α**.

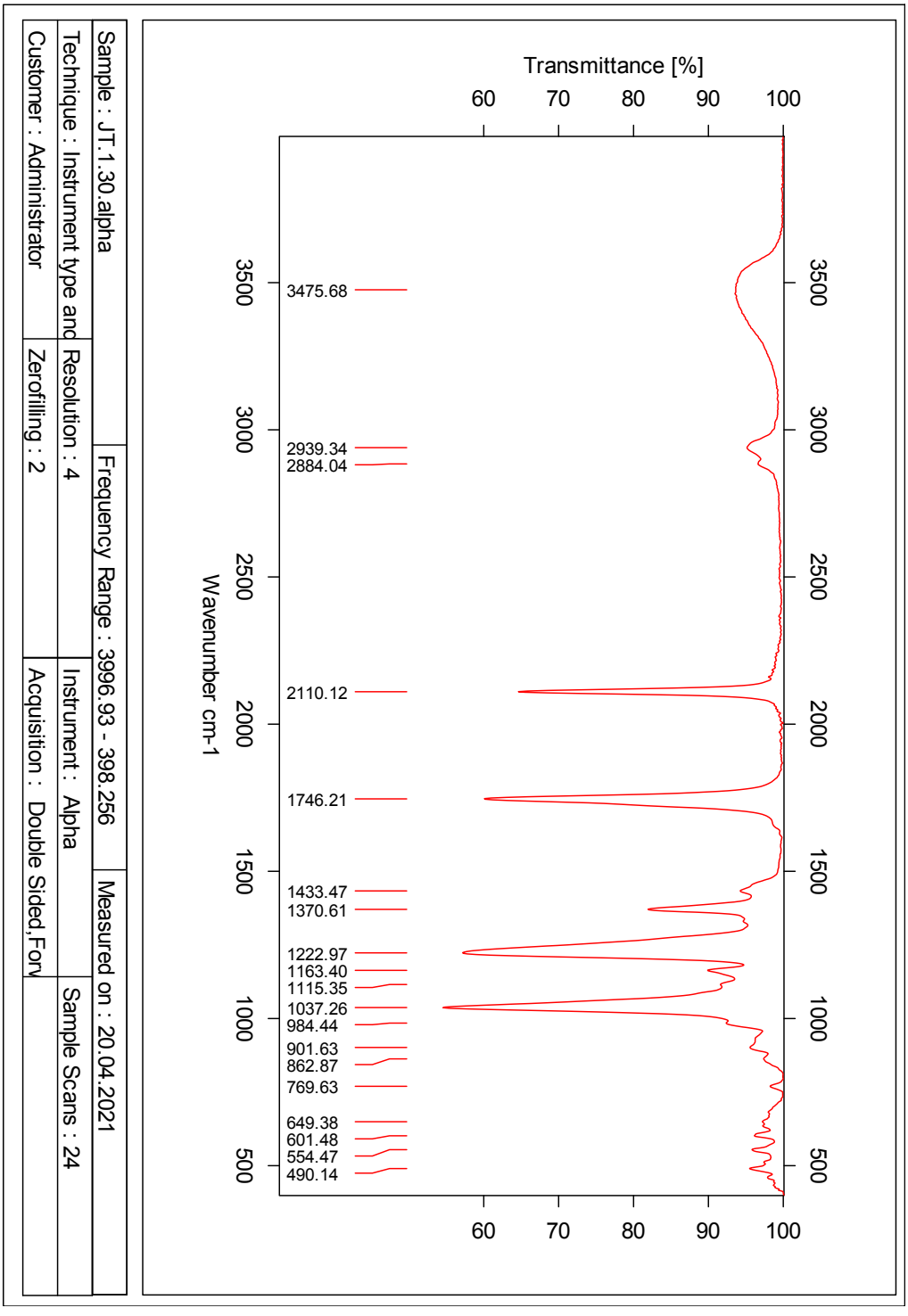


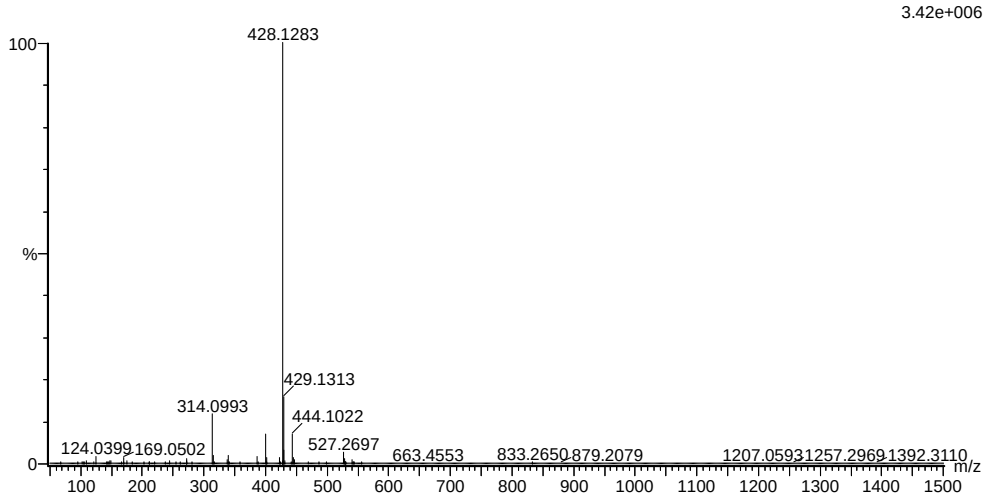
Figure A.56. IR spectrum of **24α**.

A.11 Spectroscopic data for compound 24β

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -10.0, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 6

Monoisotopic Mass, Even Electron Ions
786 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-5 O: 0-10 Na: 0-1
2021-228 95 (0.901) AM2 (Ar,35000.0,0.00,0.00); Cm (95:101)
1: TOF MS ES+



Minimum:				-10.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
428.1283	428.1281	0.2	0.5	5.5	2211.4	0.000	100.00	C15 H23 N3 O10 Na
	428.1287	-0.4	-0.9	21.5	2227.3	15.836	0.00	C29 H18 N O3

Figure A.57. HRMS (ESI+) of **24β**.

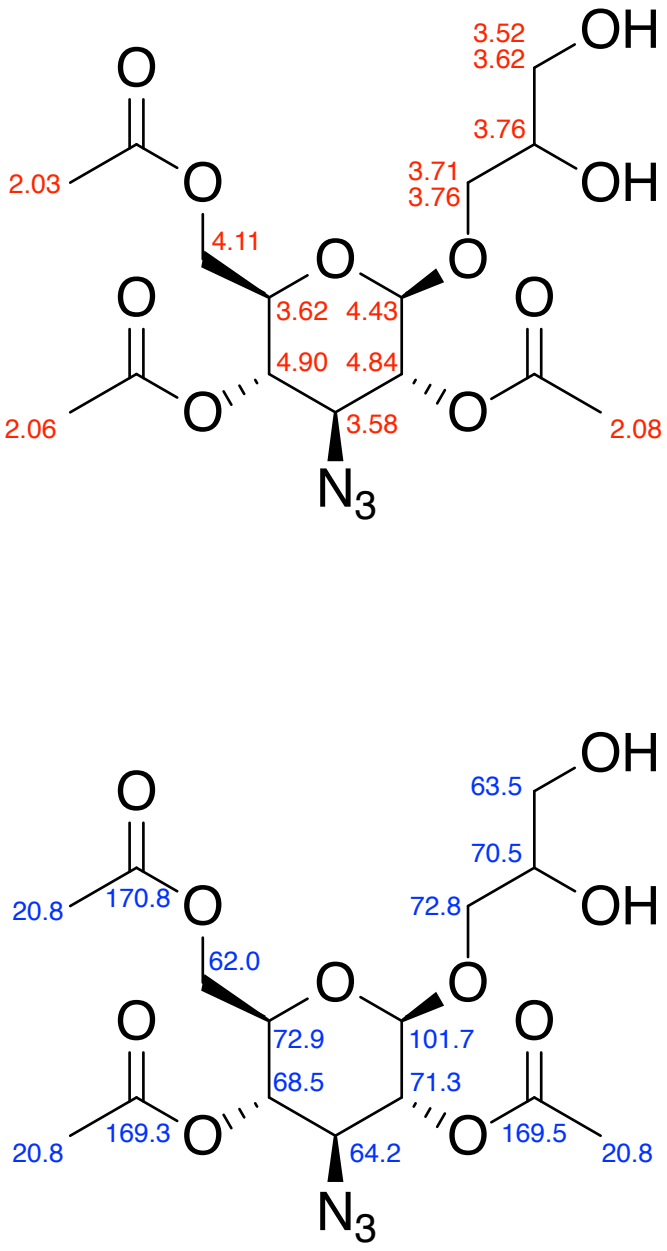


Figure A.58. Assigned ^{1}H- (red) and ^{13}C- (blue) shifts of **24β**.

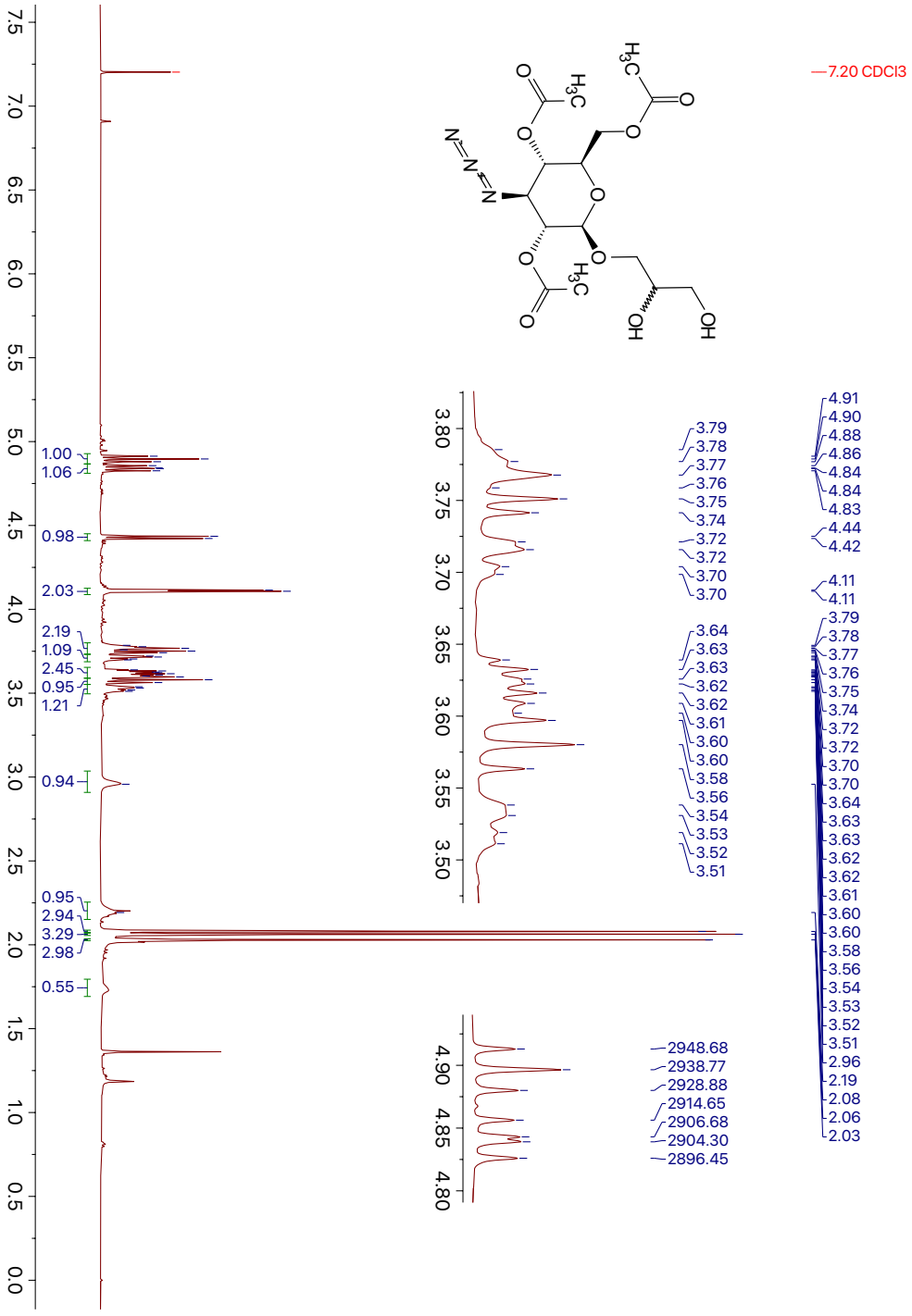


Figure A.59. ^{1}H-NMR spectrum of **24β**.

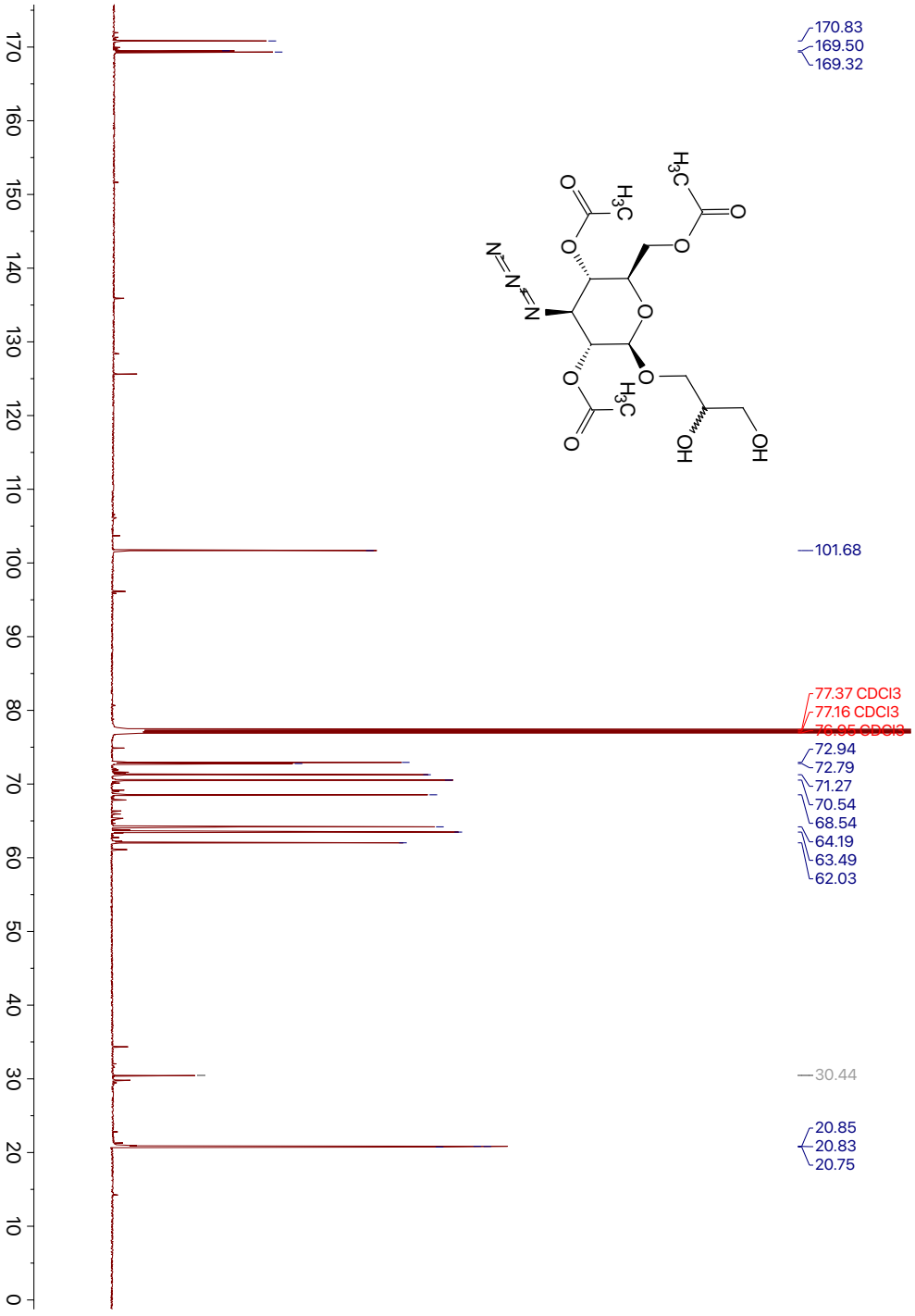


Figure A.60. ^{13}C-NMR spectrum of **24β**.

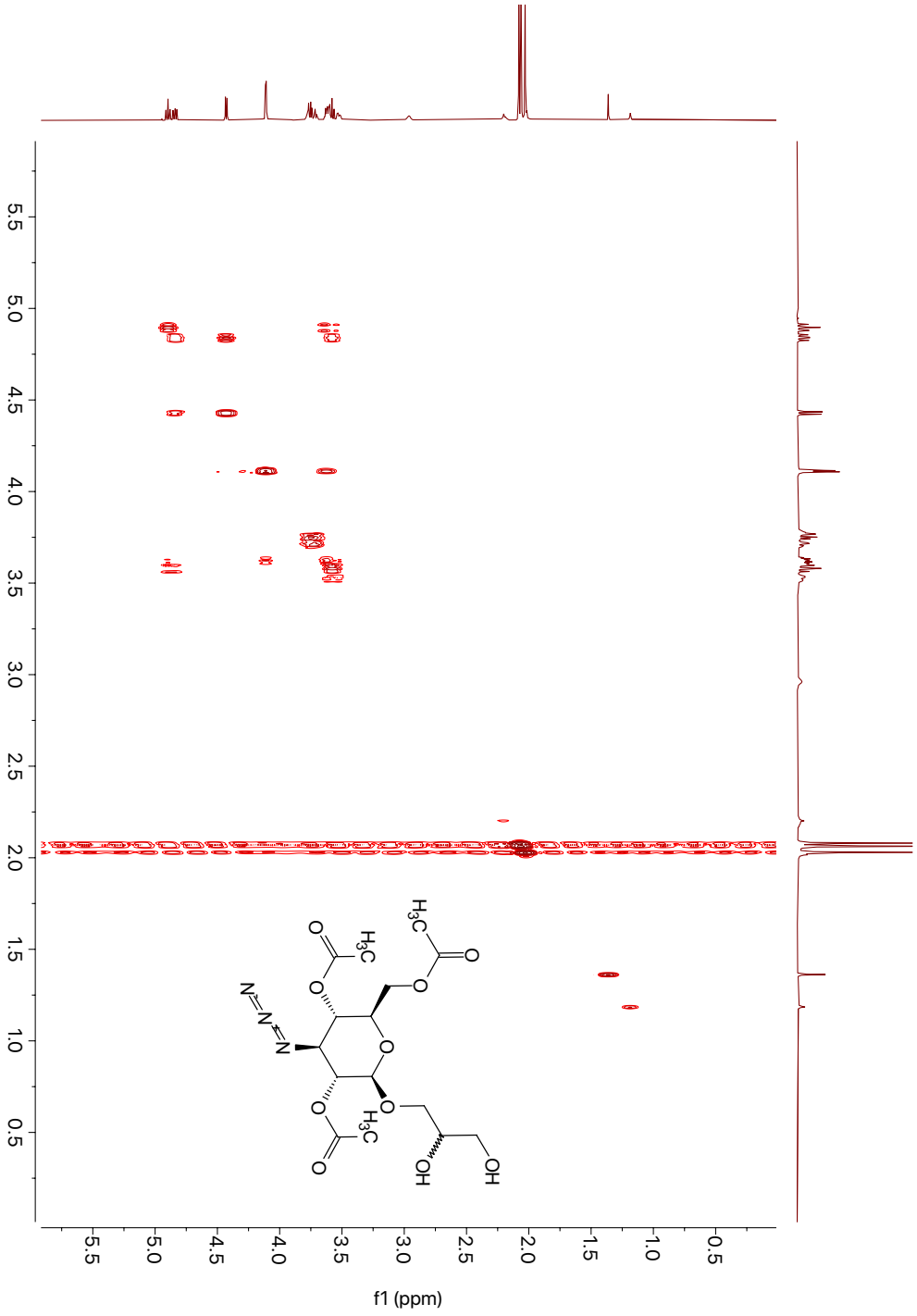


Figure A.61. COSY spectrum of **24β**.

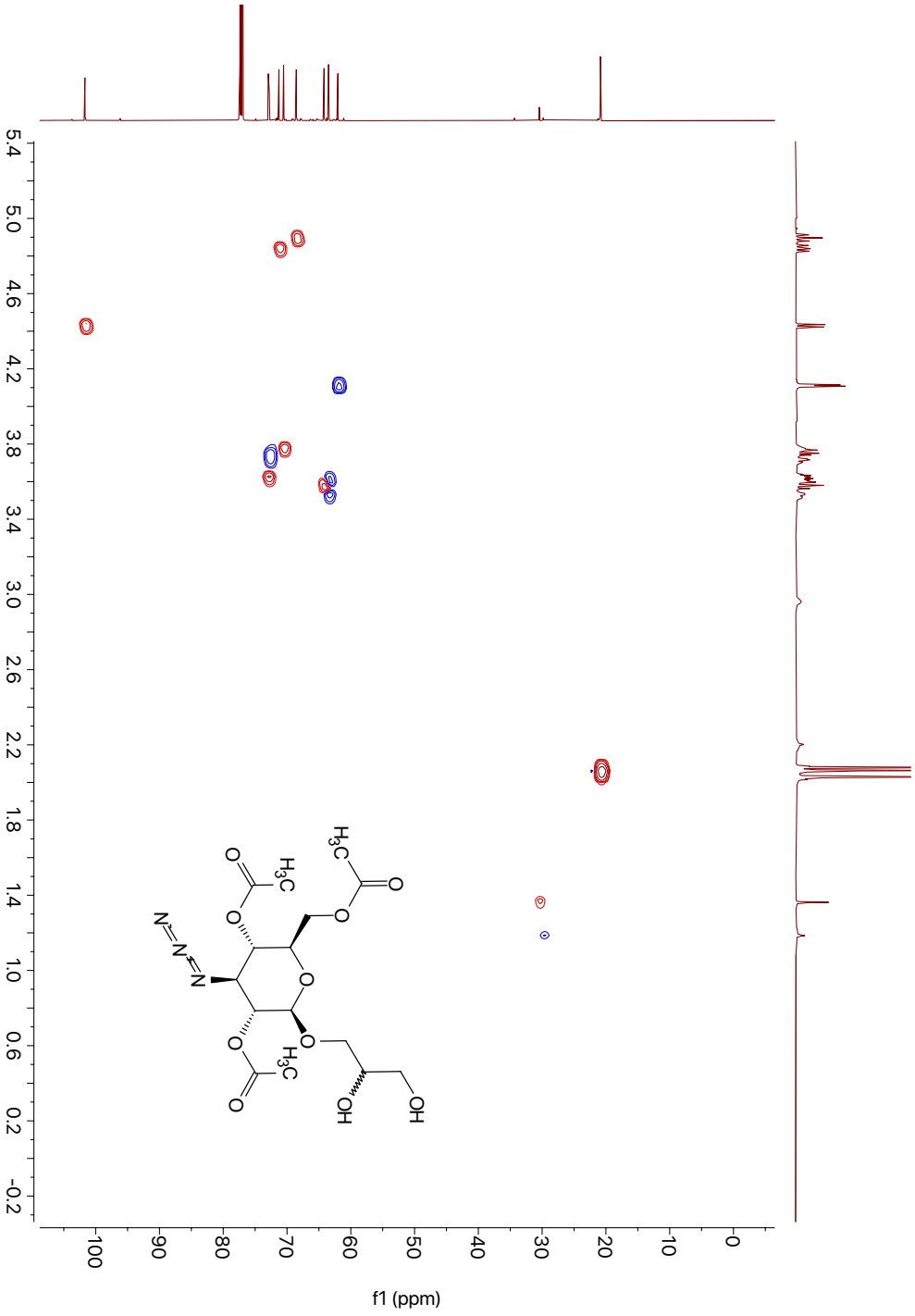


Figure A.62. HSQC spectrum of **24β**.

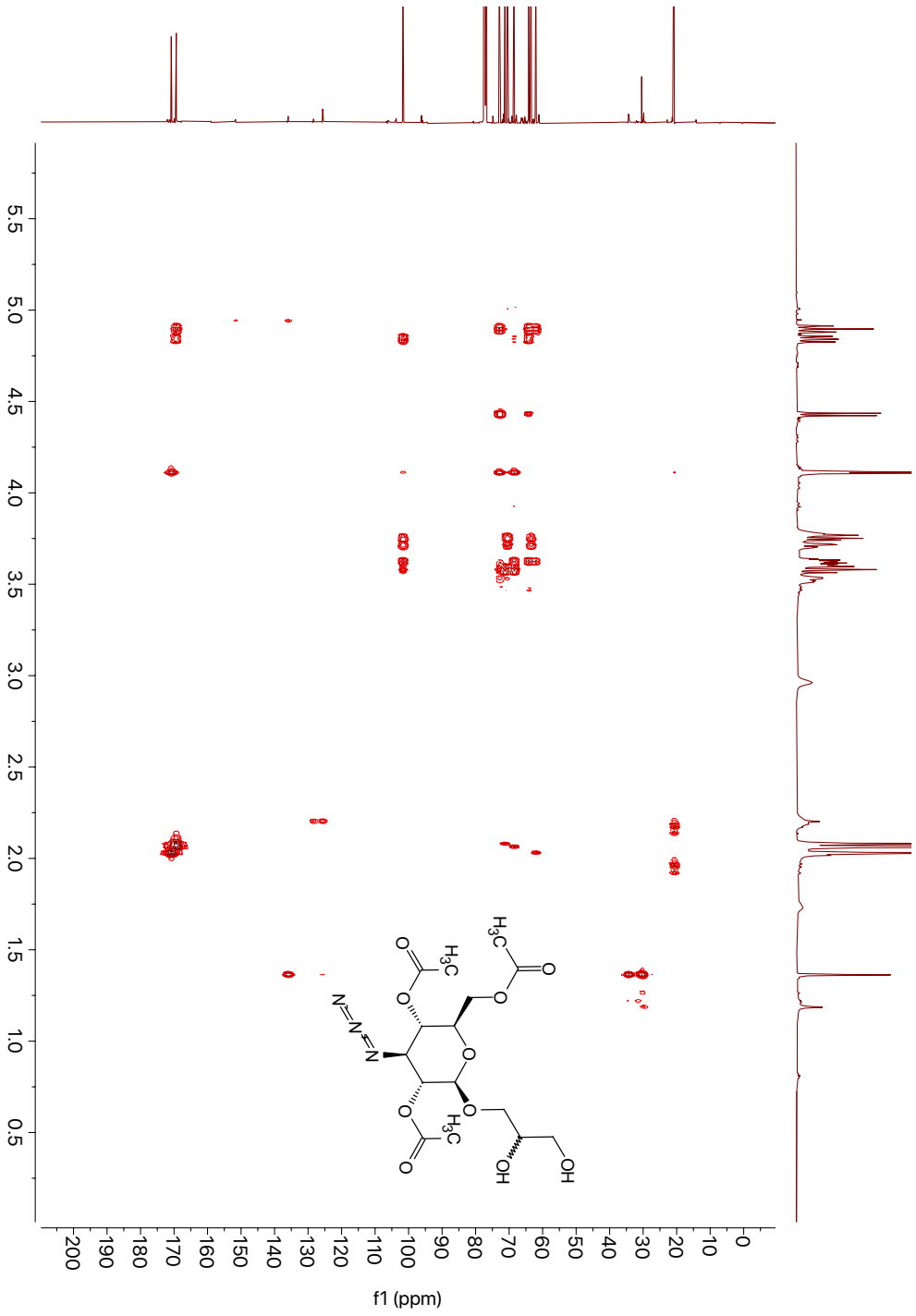


Figure A.63. HMBC spectrum of **24β**.

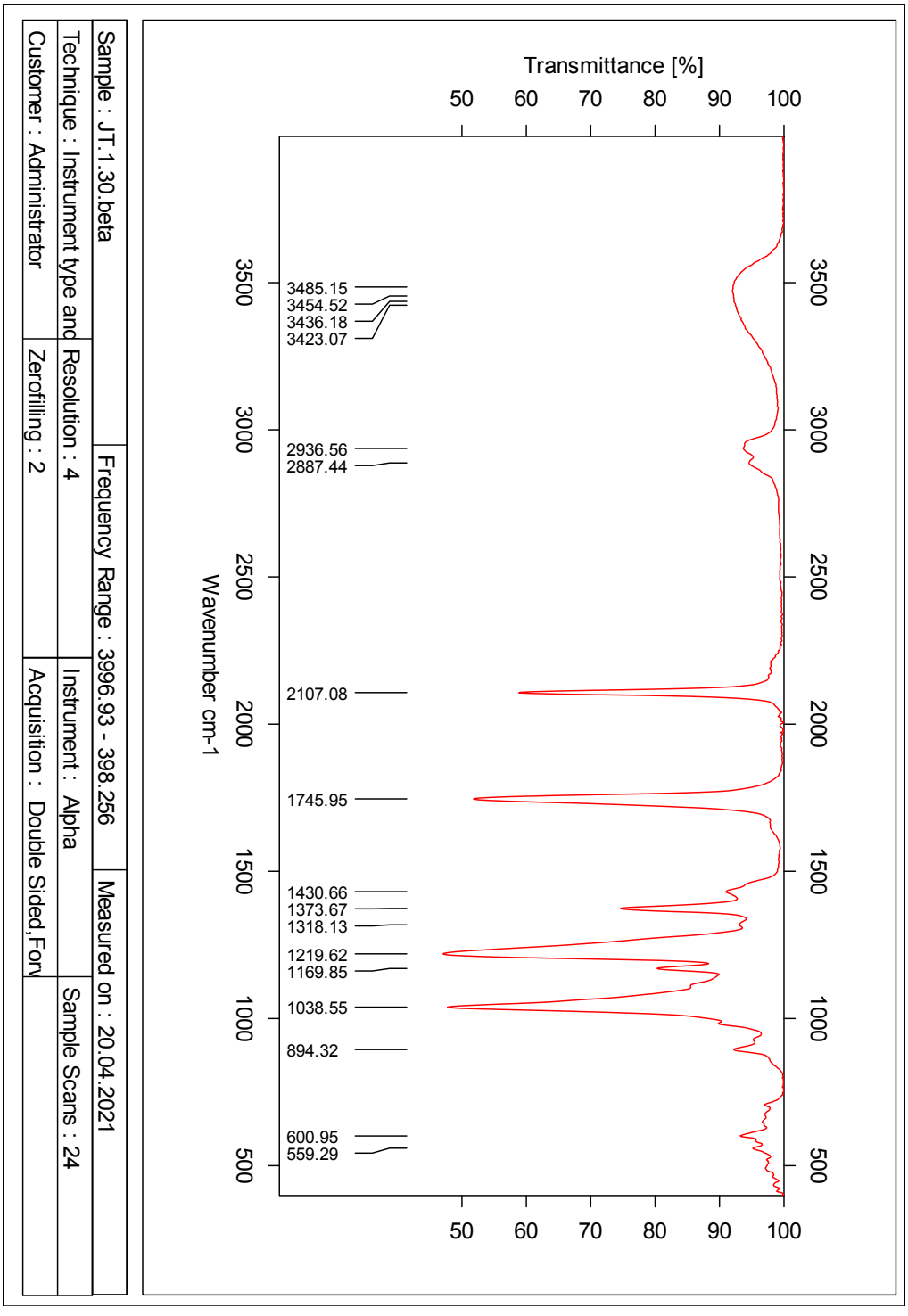


Figure A.64. IR spectrum of **24β**.

Johannes Tveit

Initial investigations into the synthesis of 1-*O*-(3-deoxy-3-linolenoyl-amide-sulfuquinovosyl) glycerol

NTNU
Norwegian University of
Science and Technology