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Regioselective Protection and Functionalization of C-6 in The Synthesis Towards Sulfoquinovoses

Frithjof Andreas Bjørnstad

Chemistry
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Supervisor: Nebojsa Simic, IKJ

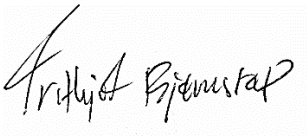
Norwegian University of Science and Technology
Department of Chemistry

Declaration

I hereby declare that the work presented in this master's thesis has been conducted in accordance of the rules and regulations for the MsChem (Master in Chemistry 2 year master's program) at the Norwegian University of Science and Technology. The work presented has been done individually under the supervision of Nebojša Simić and Sondre Nervik. The practical work has been performed in the period between September 2016 and May 2018.

Trondheim, May 20th, 2018

Frithjof Bjørnstad



Preface

This master's thesis has been performed at the Department of Chemistry at NTNU under the supervision of Associate Professor Nebojša Simić, and Ph.D student Sondre Nervik. I wish to thank both of my supervisors for the guidance given, their inspiration and patience over the past two years.

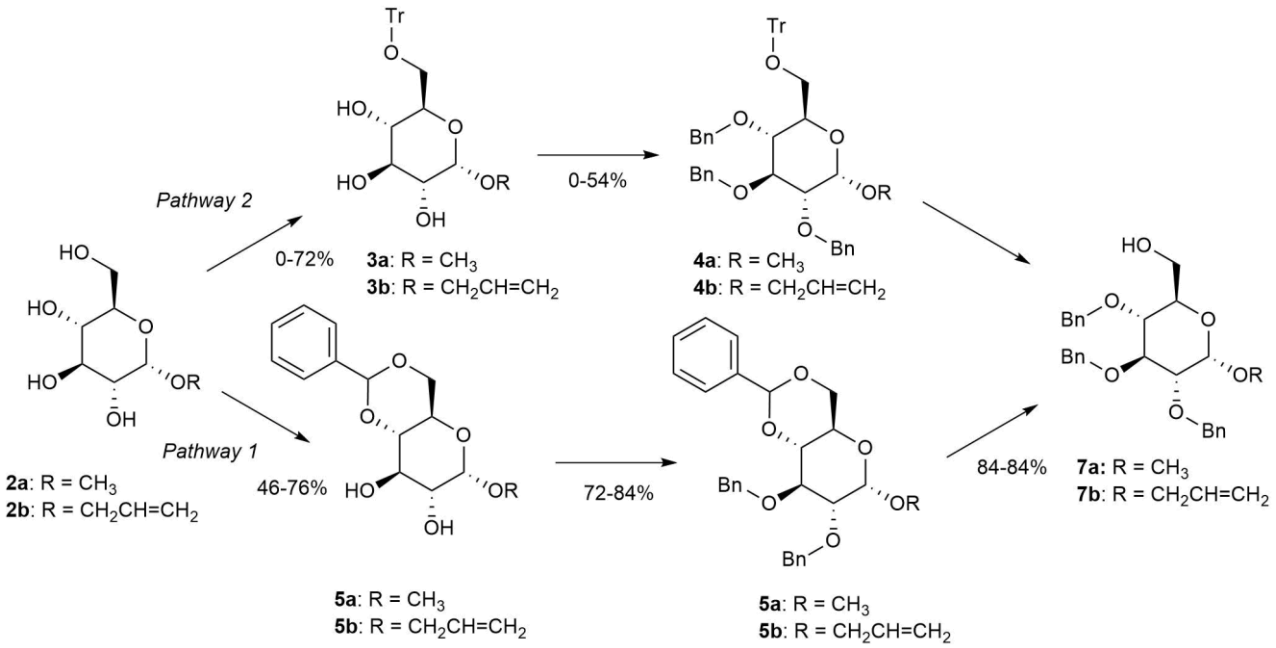
Being part of this research project has been an interesting experience. While the learning curve, working with these compounds, have been high, it has at the same time been extremely rewarding at times.

In addition, I wish to thank department engineer Roger Aarvik for supplying the materials needed and Susana Villa Gonzales for processing of MS results.

Lastly, I wish to thank my fiancée Idd Andrea Christensen and my family. You have all been a constant source of motivation and love. I could not have done this without you.

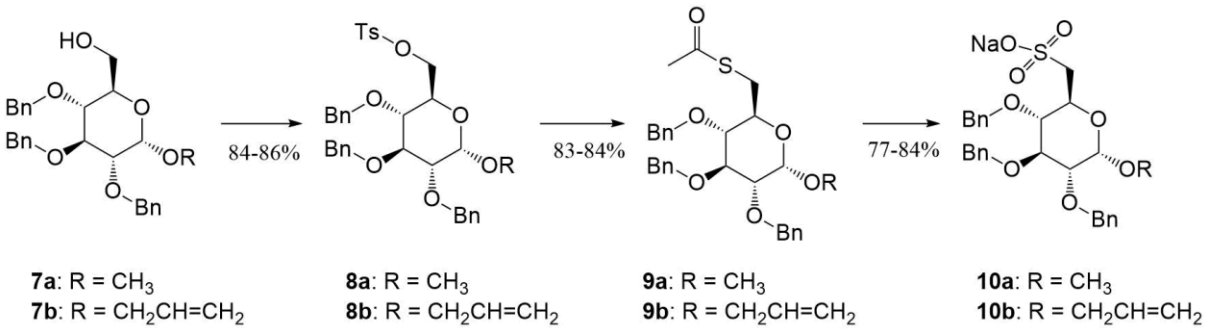
Abstract

The main goal of this thesis was to explore and compare two protection strategies yielding 2,3,4-tri-*O*-benzyl-*α*-*D*-glucopyranosides. Further work was done to functionalize the primary 6- hydroxyl position to a sulfonic acid moiety yielding sulfoquinovose derivates **10a/b**. Subordinate goals have been the optimization of the individual reactions for larger scale synthesis. Where possible, full spectroscopic characterization of intermediates, using appropriate NMR experiments was performed, enabling assignment of all relevant ^{13}C and ^{1}H shifts for most intermediates.



2,3,4-tri-*O*-benzyl-*α*-*D*-glucopyranoside intermediates **7a/b** were reached in 42-55% yield through pathway 1, employing acetal protection of O-6 and O-4, with a following simultaneous protection of O-2 and O-3 as benzyl ethers before regioselective ring cleavage, leaving the free hydroxyl at the primary position. High anomeric control was achieved, with no observable *β*-anomer for the methyl glucosides **5-7a**. After purification, and some optimization work, an anomeric ratio of 20:1 (*α: β*) was observed for allyl glucosides **5-7b**. Separation of the anomers was not attempted.

Mono-protection of the primary alcohol with a triphenylmethyl group was deemed a less suited pathway due to low initial yields of **4a** (54%) and unsuccessful purification and analysis of compounds **3b** and **4b,** attempting a wide array of purification techniques. The path was not explored further than intermediates **4a/b**.



7a: R = CH_3
7b: R = $CH_2CH{=}CH_2$

8a: R = CH_3
8b: R = $CH_2CH{=}CH_2$

9a: R = CH_3
9b: R = $CH_2CH{=}CH_2$

10a: R = CH_3
10b: R = $CH_2CH{=}CH_2$

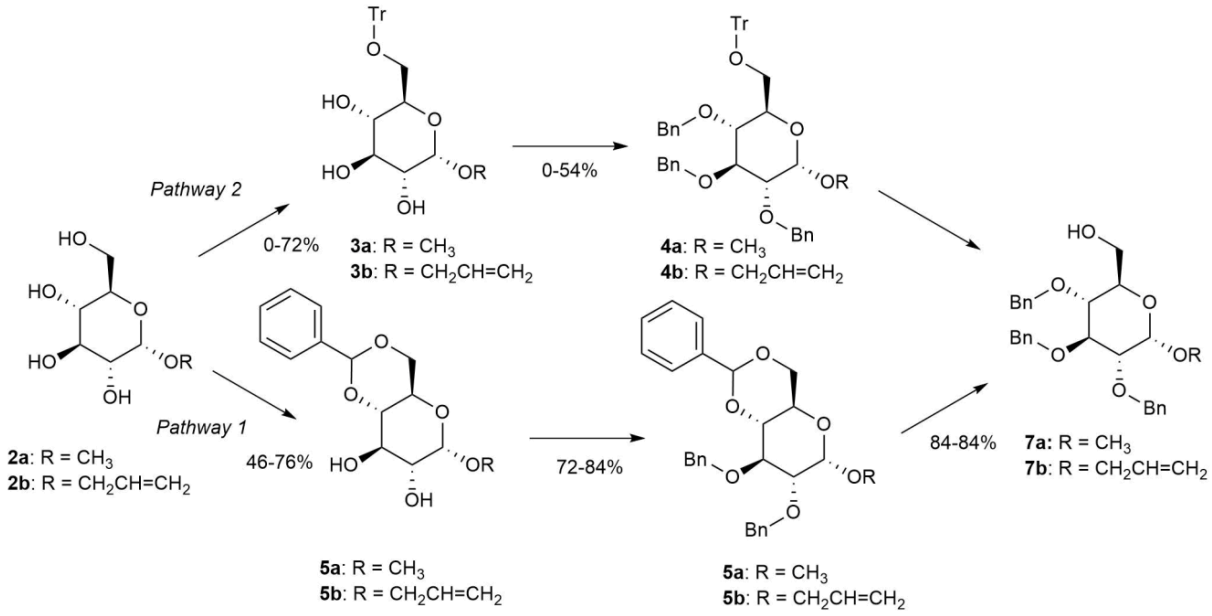
Further functionalization of the primary alcohol was performed by initial introduction of 4-toluenesulfonyl, yielding **8a**/**b** in 80-87%. Thioacetates **9a/b** (83-84%) were prepared using potassium thioacetate as a nucleophile. Oxidation of the thioacetates to the corresponding sulfoquinovose derivatives **10a/b** (77-85%) was performed with potassium peroxymonosulfate, requiring some optimization of workup procedures. Novel reactions in the protection of the formed sulfonic acid moiety as silyl ethers were unsuccessful, indicating a need for exploring other possibilities for the protection of sulfoquinovose derivates **10a/b**.

Effects of anomeric substituents were observed in the initial protection steps of the synthesis with the allyl glucosides, having yields 10-15% lower than that of the corresponding methyl glucopyranoses. In addition, differences in the oxidation of thioacetate **9a/b** were observed, with several problematic aspects in purification and analysis of **10b**.

Model substrates of tert-Butyldimethylsilyl(TBDMS)- and tert-butyldiphenylsilyl (TBPDS)-protected alcohols were procured. The substrates were subjected to the conditions employed in the oxidation of **9a/b** in order to assess the compatibility of the overall protection strategy of the research project. Both silyl ethers were found to withstand the conditions.

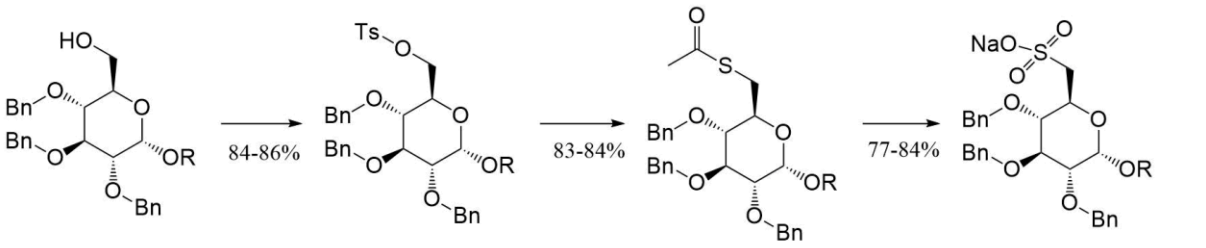
Sammendrag

Hovedformålet med denne masteroppgaven var å utforske og sammenligne to beskyttelses strategier for å oppnå 2,3,4-tri-*O* benzyl-*α*-*D*-glukopyranoser **7a/b,** med videre funksjonalisering av posisjon C-6 til en svovelsyre enhet. Optimalisering av opparbeidelse, rensning og analyse for syntese i større skala, har vært underordnete mål for arbeidet. Full spektroskopisk karakterisering av mellomprodukter, ved hjelp av egnete NMR eksperimenter ble utført, der alle relevante ^{13}C og ^{1}H signaler ble plassert.



2,3,4-tri-*O* benzyl-*α*-*D*-glukopyranoser **7a/b,** ble syntetisert med et totalt utbytte på 42-55% via strategi 1. Strategien baserer seg på beskyttelse av O-4 og O-6 som ett acetal, før simultan beskyttelse av O-2 og O-3 som benzyl etere, med en følgende regioselektiv ringåpning, resulterende i en fri hydroksyl gruppe på C-6. Høy anomerisk kontroll ble oppnådd, der ingen *β*-anomer ble observert for metyl glukosidene **5-7a**. Etter eksperimentering av opparbeidense og rensing, ble ett anomerisk forhold på 20:1 (*α: β*) observert for allyl glukosidene **5-7b**. Separasjon av anomerene ble ikke utført.

Beskyttelse av primær alkoholen på C-6 som en trifenylmetyl gruppe (strategi 2) ble observert som svært ineffektiv, med lave utbytter av **4a** (54%), mislykket rensning, og analyse av mellomproduktene **3b** og **4b**. Strategien ble av den grunn, ikke undersøkt videre.



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9a: R = CH_3
9b: R = $CH_2CH{=}CH_2$

10a: R = CH_3
10b: R = $CH_2CH{=}CH_2$

Funksjonalisering av primær alkoholen ble utført ved å først introdusere 4-toluensulfonyl på C-6 med ett utbytte av **8a/b** på 84-86%. Tioacetat **9a/b** (83-84%) ble syntetisert ved bruk av kalium tioacetat som nukleofil i enkle reproduserbare reaksjoner. Videre oksidering til de korresponderende sulfoquinovose derivatene **10a/b** (77-84%) ble gjennomført ved hjelp av kalium peroksymonosulfat (Oxone), med noe optimalisering av opparbeidelse prosedyrer. Beskyttelse av den dannede svovelsyre enheten som en silyl eter var ikke vellykket, og observasjoner fra forsøket tyder på at videre forskning på andre mulige beskyttelses strategier av sulfoquinovose derivatene **10a/b,** er nødvendig.

Effekten av anomerisk substituent ble i størst grad observert i de innledende beskyttelses trinnene av allyl glukosidene, der utbytter ble observert som 10-15% lavere enn i syntesen av de korresponderende metyl glukosidene. I tillegg ble det observert forskjeller i oksidasjonen av **9a/b**, der oksidasjon allyl tioacetat **9b** medførte en rekke utfordringer i rensing og analyse.

Modell substrater av tert-butyldimetylsilyl (TBDMS) og tert-butyldifenylsilyl (TBDPS) beskyttete alkoholer ble syntetisert. Substratene ble utsatt for de samme forholdene brukt i oksidasjonen av **9a/b** for å utforske kompatibiliteten i den overordnede beskyttelses strategien i forsknings prosjektet. Begge beskyttelsesgrupper ble observert som stabile.

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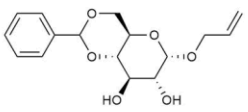
List of Compounds



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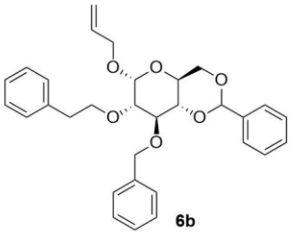

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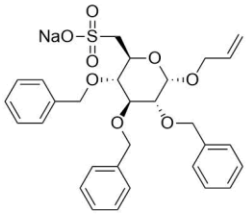

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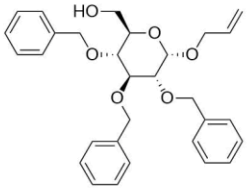

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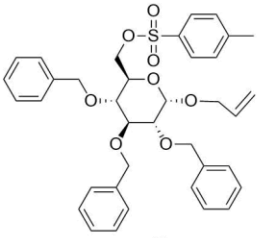

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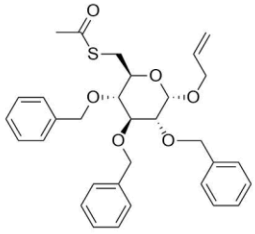

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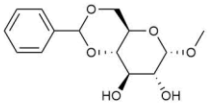

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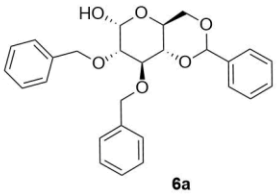

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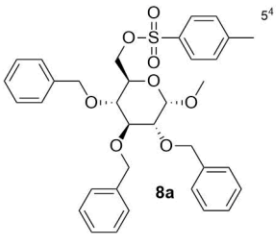

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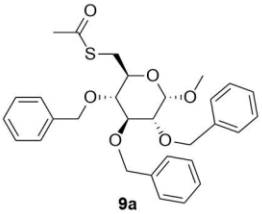

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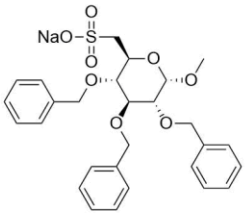

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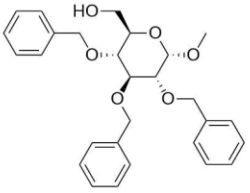

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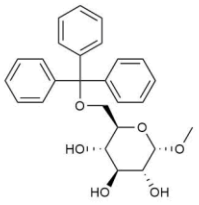

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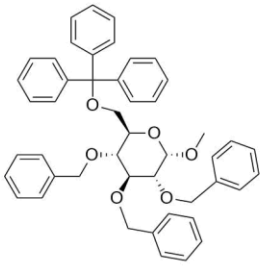

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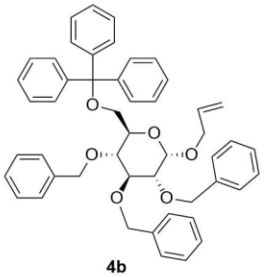

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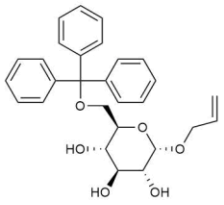

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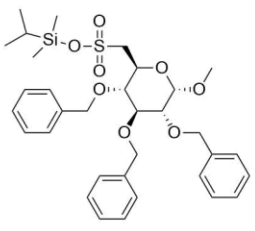


11a

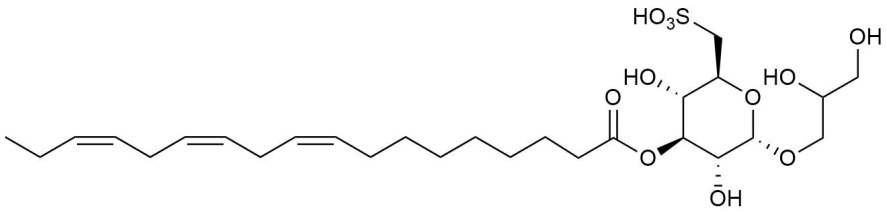
Symbols and Abbreviations

ACN	Acetonitrile
Bn	Benzyl bromide
br	Broad (IR)
$CDCl_3$	Deuterated-chloroform
conc.	Concentrated
COSY	Correlated spectroscopy
d	Doublet (NMR)
DCM	Dichloromethane
dd	Doublet of doublets (NMR)
ddd	Doublet of doublets of doublets (NMR)
DMAC	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dt	Doublet of triplets
Eq	Equivalents
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
HMBC	Heteronuclear Multi Bond Correlation
HPLC	High- performance liquid chromatography
HR	High resolution
HSQC	Heteronuclear Single Quantum Coherence
IR	Infrared Spectroscopy
J	Coupling constant [Hz]
m	Medium (IR absorption band)
m	*Meta*
m	Multiplet (NMR)
M^+	Molecular ion
Mesyl	Methane sulfonyl
min	Minutes
o	*Ortho*
Oxone	Potassium peroxymonosulfate
p	*Para*
ph	Phenyl
ppm	Parts per million
p-TsOH	*p*-toluene sulfonyl chloride
r.t	Room temperature
R_f	Retention factor
rx	Reaction
s	Singlett (NMR)
s	Strong (IR absorption band)
TCE	Trichloroethylene
TBDMS	Tert-butyl dimethyl silan
TBDMSOTf	Tert-butyldimethylsilyl trifuormethanesulfonate
TBDPS	Tert-butyl diphenyl silan
t-Bu	Tert-butyl
td	Triplet of doublets (NMR)

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TOCSY	Total correlation spectroscopy
Tosyl	Toluene sulfonyl
TrCl	Triphenylmethyl chloride
TsCl	4-Toluene Sulfonyl chloride
w	Weak (IR absorption band)

1. Introduction

The work performed in this thesis is part of a larger research project attempting total synthesis of compound **1c** (Figure 1). The target compound has been isolated from the plant *Schlerochloa dura*[1] and has shown to exhibit significant anti-inflammatory properties.[2] Further research into the biological activities of the compound and its derivatives is of great interest for further development of novel anti-inflammatory drug candidate(s). The synthesis of compound **1c** requires a series of steps, involving research into specific protection patterns, allowing for insertion of sulfur onto C-6, esterification of O-3 and oxidation of the allyl substituent in the anomeric position.



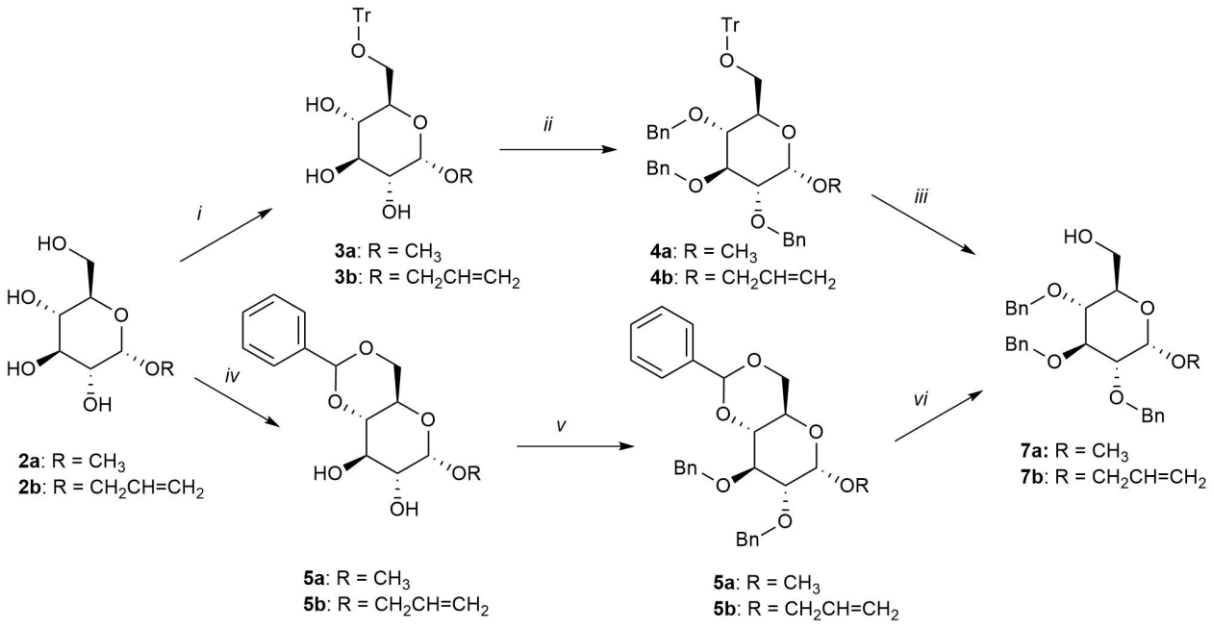
1c

Figure 1: The target molecule **1c** isolated from the plant *Schlerochloa dura*.

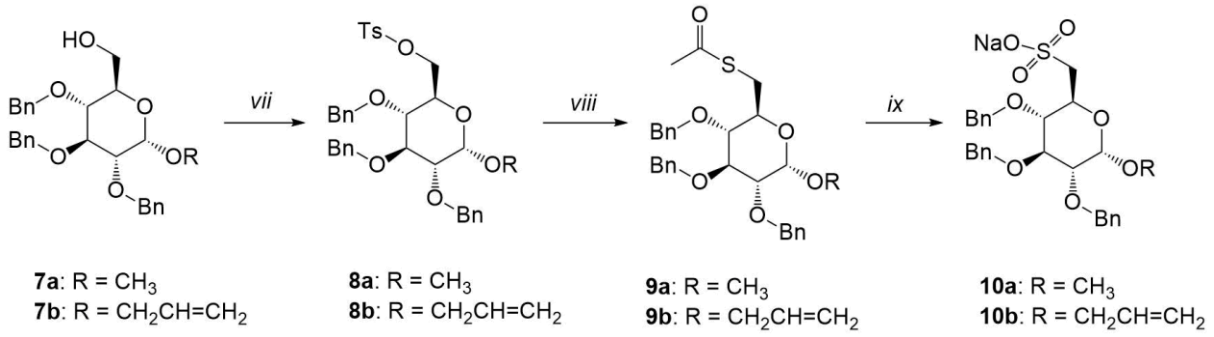
The main contribution of the work presented is research into the selective protection of *α-D*-glucopyranose derivatives, with subsequent insertion and oxidation of sulfur onto C-6. Investigation into optimization, anomeric control, purification and characterization of intermediates have been subordinate goals of the practical work.

Pathways to 3,4,5-tri-*O*-benzylated *α-D*-glucopyranose derivatives are described in literature.[3–7] However, inadequate spectroscopic data on intermediates, unfeasible and unpractical conditions for large-scale synthesis and general lack of data prompts further investigation. Functionalization of C-6 to an thioester is described in literature as relatively simple procedures for both the allyl and methyl derivates.[4,6,8,9] While oxidation of the thioacetate **9a** has been described,[6,9] oxidation of compound **9b** to **10b** has, to the best of our knowledge not been previously attempted.

The two protection strategies explored in this thesis are displayed in Scheme 1, while Scheme 2 shows the attempted method for the functionalization of C-6 yielding sulfoquinovose derivates **10a/b**.



Scheme 1: Protection strategies explored in the practical work. Reagents and conditions: *i*: TrCl, DMAP, pyridine 110°C, 2h. *ii*: BnBr, NaH, THF 60°C, 2h. *iii*: Not performed *iv*: $PhCH(OMe)_2$, *p*-TsOH, ACN/DMF, r.t, 5h. *v*: BnBr, NaH, THF, 60°C, 2h. *vi:* $LiAlH_4$-$AlCl_3$, CH_2Cl_2/diethyl ether, 50°C, 1h.



Scheme 2: Steps needed for the insertion of sulfur onto C-6. Reagents and conditions: *vii:* TsCl, pyridine r.t, 12h. *viii*: AcSOK, EtOH, reflux, 2h. *ix*: Oxone, NaOAc, HOAc, r.t, 12h.

2. Theory

2.1 Carbohydrates

Carbohydrates form a diverse group of compounds, ranging from simple C-5 and C-6 monosaccharides in the sugar backbone of DNA and RNA, to high-molecular carbohydrates and polysaccharides, such as cellulose and glycogen.[10,11] Historically, carbohydrates were defined as compounds with the empirical formula $C_n(H_2O)_m$, but today the definition has been broadened to incorporate aliphatic polyhydroxy aldehydes, ketones, and their derivatives.[10] Due to the presence of several functional groups in the molecule, carbohydrates contain multiple stereocenters, further diversifying the compounds.

Sugar chemistry was at its height in the latter part of 1980,[10] but have in recent years seen an increase in interest, due to their role in natural product chemistry, as well as their potential in drug design.

D-glucose is commonly used as a precursor to more complex and functionalized carbohydrates, including the target molecule in this project (**1c)**. The focus in the work presented will be on *D*-glucose derivatives. Other sugars or complex oligosaccharides will therefore not be discussed and are considered outside the scope of this thesis.

This section contains an overview of some of the most important and distinguishing aspects of sugar chemistry, carbohydrates in modern chemistry, protection chemistry, sulfonic acid derivatives and previous work relevant to the project.

2.2 Carbohydrates in natural product chemistry

Being the most abundant class of biomolecules in nature,[12] carbohydrates are involved in a wide array of biochemical reactions in cells, ranging from cell surface recognition, signal transduction and metabolism. Despite these compounds' central part in physiology, there has been a longstanding neglect from the drug development perspective, in comparison to proteins and nucleic acids.[13] With an increasing understanding of the glycobiology and the potential of carbohydrates in drug design, the focus on this field has seen vast increases in the last decades, not only in treatment but also in diagnostics.[14]

Changes in glycan structure are often considered hallmarks in disease progression, being associated with an inflammation, onset of cancers and several pathological conditions.[12] The changes in expression patterns of oligosaccharides, and glycoproteins have led to an increase in pharmaceutical research into glycan-based diagnostic techniques.[13] Carbohydrate-based therapeutics show promising clinical results and a vast number of carbohydrate drugs are in the stage of preclinical or clinical studies.[12]

Novel synthetic and biochemical methods have spurred extensive interest and investigation into the field of biomedical application of carbohydrate-based compounds[10,15]. In modern medicine, carbohydrates are in an increasing matter being exploited as important tools in the development of vaccines, therapeutics, and diagnostics.[13]

Naturally occurring polysaccharides and their corresponding degradation fragments, especially from eastern traditional medicinal herbs and fungi, have been showed to contain diverse structures with an array of bioactivities.[13,16]

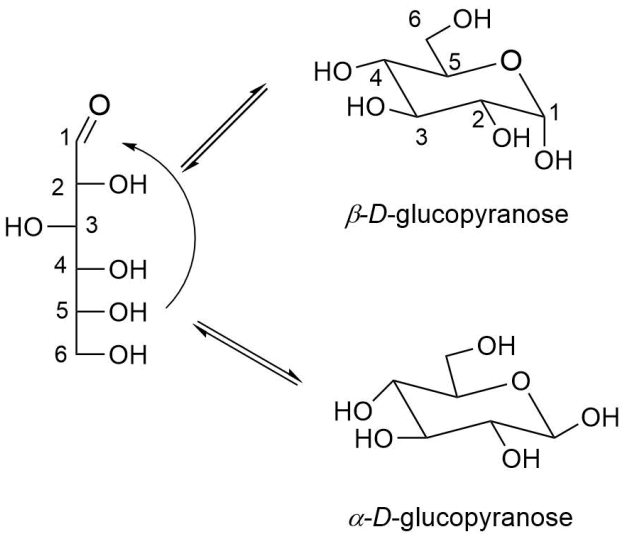
Successful carbohydrate based pharmaceuticals derived from glycan structures are currently on the market, examples being lentinan,[17] hyaluronic acid[13,17] and low-molecular-weight heparin[18] used to treat a variety of illnesses ranging from cancer to autoimmune related disorders.[12]

2.3 General concerns in carbohydrate chemistry

2.3.1 Carbohydrate Isomers

Monosaccharides can be divided into two main groups, depending on whether their acyclic form possesses an aldehyde (for aldoses), or a keto group (ketoses).[11] Further classification depends on the number of carbons and types of functionalities present.

D-glucose is the most abundant monosaccharide in nature,[10,19] and its derivatives have been studied in detail to a larger extent than for other saccharides. Like most other sugars, *D*-glucose will exist in a solution as a mixture of isomers.[11] The linear form of glucose and other hexoses are, in most cases, energetically unfavourable relative to its cyclic form.[19] Consequently, in aqueous solution, all monosaccharides with five or more carbons in the backbone will occur predominantly as its cyclic isomer.[11,20]



Scheme 3. Hemiacetal formation of d-glucose to *α-D*-glucopyranose and *β-D-g*lucopyranose. Formation of the 5 ring furanoses are not included but entail attack by the hydroxyl group of carbon 4.

The cyclization is initiated by nucleophilic attack of a hydroxyl group (O-5 for glucose) on the carbonyl atom in the acyclic species as seen in Scheme 3. Formation of the hemiacetal forms an asymmetric carbon atom at C-1, giving rise to two anomers: *α-D*-glucopyranose and *β-D*-glucopyranose, in the case of glucose. Ring formation involving the hydroxyl group on C-4 results in the 5-membered furanose isomer. This isomer is, however rare, observed to exist in below 0.3% at 27 °C in water, and is barely detectable by NMR.[21]

$^4C_1$ $^1C_4$

Figure 2: The two chair conformers of pyranoses.

Further classification of cyclic forms of 5- and 6- membered carbohydrates is based on the assumption that the geometry of the pyranose and furanose is similar to that of cyclohexane and cyclopentane, respectively.[21] The heteroatom causes a slight change in the molecular geometry due to the shorter character of the carbon-oxygen bond. There are several possible conformations the pyranoses can adopt, but the two most relevant ones are the chair conformations $^4C_1$ and $^1C_4$ illustrated in Figure 2. In relation to the plane of the chair, the numbers indicate the carbons located above or below the plane. Although these conformers differ in energy, this energy barrier is not high enough that it completely prevents conformational mobility.[11]

The vast majority of hexoses will adopt the $^4C_1$ due to two factors. Firstly, due to the destabilization nature of an axial hydroxyl group, especially the methyl hydroxyl.[11,19] The second factor is due to unfavourable *syn*-diaxial van der Waal interactions between the anomeric position and methyl hydroxyl group in the $^1C_4$ conformation, known as the Hassel-Ottar effect.[11,19,21] The free energy difference between the two chairs is approximately 25 kJ/mol[11,21]. Consequently, only one, the $^4C_1$ conformation of *D*–glucose is observed by NMR spectroscopy, verified by the *J* coupling constants of vicinal protons.[11]

2.3.2 Anomers and the anomeric effect

As described, the axial orientation of hydroxyl groups is unfavourable.[11] A fair assumption would then be that *D*-glucopyranose should be expected to be found predominantly in the β -anomer, where all the substituents are present in the equatorial position, in theory offering the highest stability. However, in aqueous solution, unsubstituted *D*-glucopyranose exists in a ratio of 36:64[19] of respectively the α and β anomer. This effect is even more pronounced in carbohydrates with halogens or, more generally, electronegative atoms with lone pairs in the anomeric position.[21] The effect is of such a magnitude that pyranoses with a halogen in the

anomeric position, will only be observed with its anomeric substituent in the axial orientation.[11]

This tendency of electronegative substituents to adopt an axial position in the $^4C_1$ conformer is referred to as the anomeric effect and is generally considered valid for all molecules with two or more heteroatoms linked to a tetrahedral center.[11]

There are two recognized explanations for the origins of this effect.[10] The first being due to unfavourable dipole-dipole interactions between the endocyclic sp^3 hybridized oxygen's nonbonding electron pairs, and the dipole from the anomeric substituent. These dipole moments are illustrated in Figure 3. This explanation is, however, lacking, since it does not account for observed differences in bond length and bond angles in the two anomers.[11]

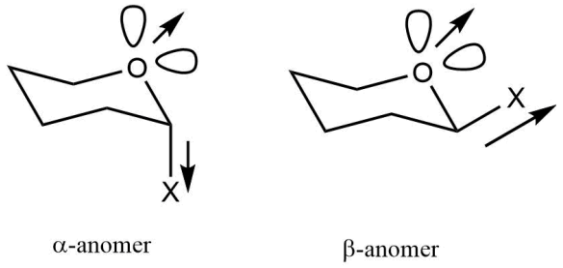


Figure 3: The dipole moments in the $^4C_1$ conformation of α and β-anomers.

The second explanation, based on stereoelectronic effects, is generally considered as the most complete explanation of the observed anomeric effect.[11,21] This explanation also considers the nonbonding electrons on the sp^3 endocyclic oxygen. These electrons occupy the axially oriented *p*-orbitals and are in the α-anomer oriented *syn*-periplanar to the antibonding orbital of the anomeric substituent. This results in mixing of the two orbitals, referred to as hyperconjugation,[10] leading to a shortening of the ring-O-C-1 bond, giving it more of a double bond character and lowering the overall energy of the system. There is still controversy concerning the explanation of the effect. This is largely due to the fact that the electron density redistribution in acetals, proposed by hyperconjugation, is not congruent with the known experimental chemistry of monosaccharides.[22]

The magnitude of this effect varies with the electron withdrawing properties on the anomeric substituent, as well as the polarity of the solvent. The size of the anomeric alkoxy group has shown to have little effect on the anomeric ratio.[19] In general, the more electronegative the anomeric substituent, the stronger preference it will have for the axial position.[23]

2.3.3 Analysis and separation of anomeric mixtures

As the *α* and *β*-anomers of *D*-glucose are diastereomeric, they are in principle readily distinguishable in NMR spectra.[11] The anomeric proton signals can be separated in ^{1}H-NMR as illustrated in Figure 4 below. The H-1 (equatorial) proton in *α*-*D*-glucose gives a peak around 5.2 ppm with a coupling constant of around J= 3.7 Hz with axial-equatorial coupling, whereas the H-1 (axial) proton of the β- form resonates at 4.6 ppm with J=7 Hz due to *trans*-diaxial coupling to the C-2 proton.[11,24] The equatorial position of the proton (*α*-anomer) is upfield due to it being in the plane with the endocyclic oxygen, contributing to de-shielding. Thus, the integrals of the peaks can be used to determine the molar distribution of the two anomers. This method will be effective for most *D*-pyranoses, provided that the two anomeric protons are clearly distinguishable. 2D-NMR experiments, such as TOCSY, can be applied where determination of anomeric ratio cannot be achieved with 1D methods.[24]

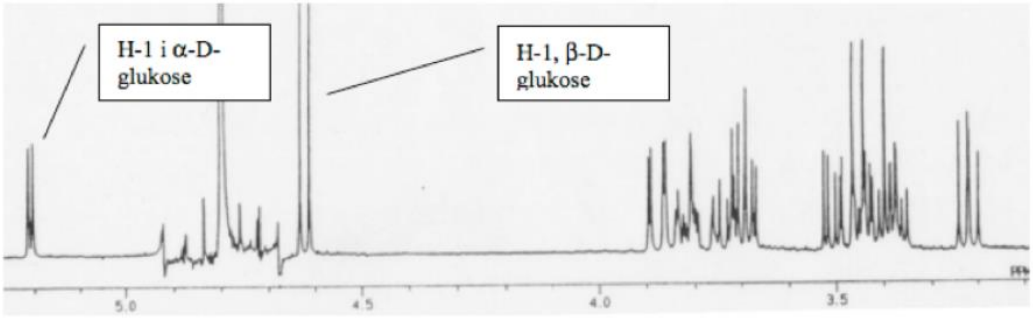


Figure 4: ^{1}H-NMR of D-Glucose in D_2O showing the clear distinguishability of the *α*- and *β*-anomer.[103]

Carbohydrates and their different anomers are readily separated by chromatographic methods[25] such as HPLC and preparative HPLC, depending on the properties of the compound in question. HPLC is a useful method for analytical separation of the anomers of sugars in a mutarotated system, and is a valuable supplement to NMR.[26] Lastly capillary electrophoresis chromatography has to some extent been employed in the analysis of mixtures of some carbohydrates.[25,27]

2.3.4 General trends in the reactivity of carbohydrates

A simplified way of looking at the reactivity of carbohydrates when considering S_N2 type reactions, is to consider each individual hydroxyl groups reactivity in relation to each other. In base catalysed reactions, where the alcohol is deprotonated, and acts as a nucleophile in alkylation or acetylation reactions, the order of reactivity can be simplified to

primary>equatorial>axial position on the sugar.[11] The proposed order of reactivity on this level is mainly due to steric factors and does not apply to all cases. For instance, C-1 in the ring inherits several of the properties of a carbonyl, seeing that in the open chain isomer of *D*-glucose, C-1 exists as a carbonyl carbon. The partial carbonyl character of the ring-O-C-1 bond makes the anomeric carbon more electrophile, causing higher reactivity with nucleophiles.[11]

Bulky reagents, such as triphenylmethyl chloride[19] or tosyl chloride,[4] will, due to steric factors almost predominantly react with the primary position in base catalysed S_N2 reactions, unless under harsh reaction conditions.[19,28,29]

A more comprehensive picture of the reactivity of the hydroxyl groups may, however, be attained from considering each groups acidity and nucleophilicity modulated by intramolecular H-bonds of the sugar molecule displayed in Figure 5.[30,31]

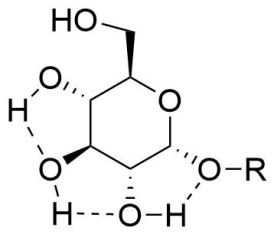
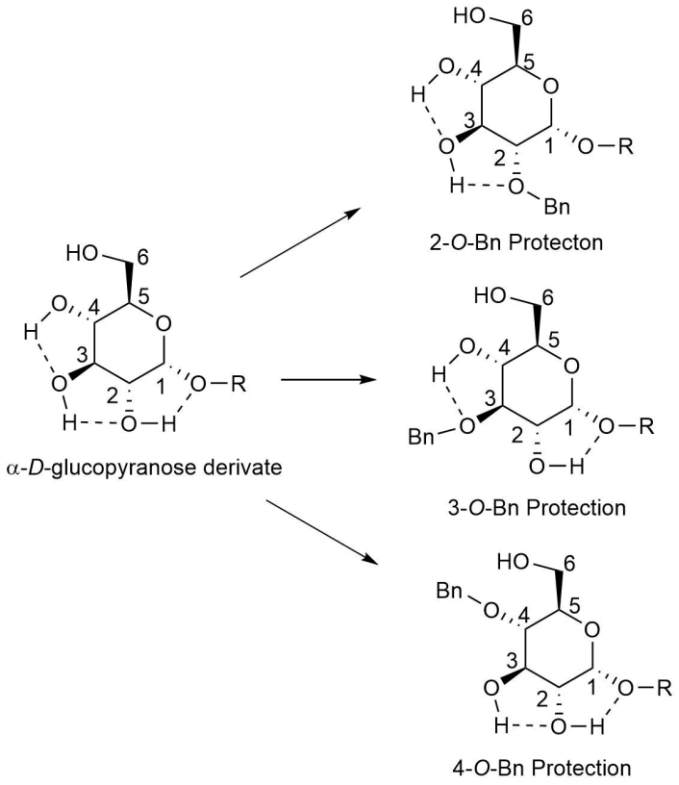


Figure 5: The proposed intramolecular H-bond network of the pyranose ring.

In recent literature, the relative differences in hydroxyl reactivity in acetylation reactions[30], as well as acidity,[31] have been compared in kinetic studies of *D*-glucopyranoside derivatives. In *β-D*-glucopyranosides, the 3-OH position has been observed to be more reactive, while in the *α*-anomer, the 4-OH position has shown increased reactivity towards mono-protection.[30] Effects in breaking the intramolecular H-bonding network in the carbohydrate molecule can explain this effect. Looking at the *α*-anomer and resulting products from mono-protection on each hydroxyl group, the enhanced reactivity of C-4 can be explained by looking at the relative possibility of forming an H-bonding network in each product illustrated in Scheme 4.



Scheme 4: Intramolecular H-bonding patterns resulting from mono-protection of α-D-glucopyranose derivatives.

Among the secondary OH groups, the reactivity of the 2-OH group is considerably reduced in comparison to 3-OH and 4-OH, due to resulting H bonding and the effectiveness of the resulting H-bond network. Breaking the H-bond between the proton on the 2-OH position and anomeric oxygens have been observed to be unfavourable, explaining the reduced reactivity of the C-2 hydroxyl group.[31] The difference in reactivity of 3-OH and 4-OH may be explained by the effect of the other hydroxyl groups H-bonding potential after protection of the position in question. 4-OH protection allows the C-3 hydroxyl to participate in the H-bonding network with 2-OH and the anomeric substituent, giving a more stable product. C-3 hydroxyl protection would break this network, completely destroying the H-bonding network from the 4-OH group to the anomeric oxygen.[30] This way of explaining reactivity is complex, controversial, and not yet completely understood.[30,32]

The relative reactivities of the hydroxyl groups are neither large enough, nor well enough understood to offer reliable selectivity in direct one-step protection reactions and are further complicated by additional substituents.[30]

2.4 Protection Chemistry

Due to the number of functional groups present in carbohydrates, protection chemistry is of practical importance in total synthesis working with sugars.[11] Furthermore, due to the fact that most of the functional groups on the molecule are of the same variety, being hydroxyl groups, the chemistry usually requires selective and orthogonal protection strategies.[19] The complexity arises in part from the further effects of the protection groups upon the molecule. Due to the number of large protection groups usually present in a fully protected sugar molecule, the effects introduced upon the molecule by these groups in terms of reactivity and further selectivity is often unclear and unpredictable.[11,23]

The protection groups most commonly employed for the protection of common alcohols, are usually, also suitable for protection of carbohydrate hydroxyl groups.[11] Depending on the functionality, the conditions needed for introduction and removal of the protection groups are also mostly similar. The biggest challenge in working with protection groups on carbohydrates is the number of protection groups needed and thus, the effect upon molecular properties such as polarity, solubility and reactivity the introduced groups have.[11,19]

For obvious reasons, the protection of the hydroxyl groups will be the main focus when discussing protection groups and strategies in this thesis. Protection of sulfonates and sulfonic acid derivatives will be mentioned briefly at the end of this section, while the protection of amines, carboxylic acid, carbonyls and other groups will not be discussed.

As the complexity of synthetic targets has increased, the ability to protect multiple alcohol groups in the same molecule and then sequentially deprotect them, allows individual alcohols in a polyhydroxylated compound to be modified. Due to employing both basic and acidic conditions, permanent protection groups, robust enough to survive multiple synthetic steps, have been important in this thesis.

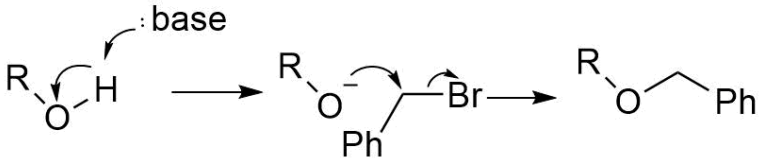
A common way of protecting hydroxyl groups are as ethers or esters, having various advantages and disadvantages. Esters are excellent protection groups with high selectivity, employed with a wide array of reagents.[11] For instance, in recent literature boronic esters have been applied in tandem with benzoyl groups in selective esterification of O-2 and O-3 on methyl-*α*-*D*-glucosides in high yields.[29,33] Regioselective mono acylation has been achieved using acetic acid or benzoic anhydride in triethylamine,[29,34] where high selectivity has been achieved in monoacylation by varying conditions, such as reagents, equivalents, and

temperature.[29]The problem with these groups are, however, their relative instability to basic conditions, oxidation agents, and their tendency to migrate, making them unsuited for the work in this project.[35,11]

Benzyl and silyl ethers are both resilient to a variety of conditions and have, in addition to being observed as fitting protection groups in the total synthesis of carbohydrate-based compounds,[4,36,37] been utilized extensively in previous work on the project.[38]

2.4.1 Benzyl ethers

Benzyl ethers are commonly used as protection groups in carbohydrate chemistry due to their ease of introduction, deprotection, as well as for their robust and stable nature .[11,19] The ether bonds survives a variety of basic and acidic conditions, hydride reducing and oxygenation agents,[23] whilst being easily removed by Pd catalyzed, hydrogenation reactions.[11,23,39] In addition, if other functionalities, liable to basic or acidic are present in the molecule, the group can be applied under basic, acidic, and neutral conditions. The most common, and highly effective procedure for the formation of benzyl ethers as a protecting group is based on a variant of the Williamson ether synthesis,[40] generating an alkoxide by treatment with strong base and subsequent nucleophilic attack on benzyl bromide in polar, aprotic solvents. The mechanism[19] for this reaction is shown in Scheme 5 below.

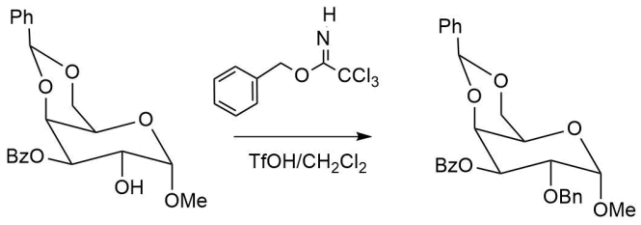


Scheme 5: The mechanism for introducing the benzyl ether protection group under basic conditions, using benzyl bromide as alkylation agent.

The rate of the reaction can be further accelerated by the addition of tetrabutylammonium iodide (Bu_4NI). It is suspected that the iodide replaces the bromide on benzyl bromide, generating benzyl iodine *in situ*, acting as a more potent alkylation agent.[19,41]

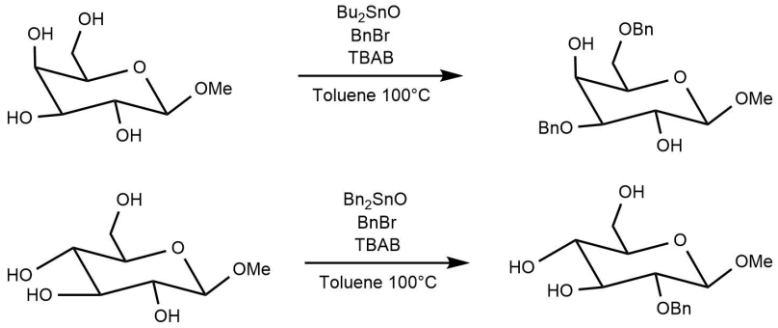
In general, the synthetic procedures are relatively straight forward, with high yields and allow for simultaneous benzylation of several hydroxyl groups.[19,23] This method of benzylation, can, however, only be applied, when other moieties on the molecule can withstand strong basic

conditions. Benzylation in mildly acidic conditions can be employed by using benzyl trichloroacetamide with a catalytic amount of triflic acid as shown in Scheme 6.[19] Though not as efficient, the combination of Ag_2O and benzyl bromide allows for benzylation in virtually neutral conditions.[19]



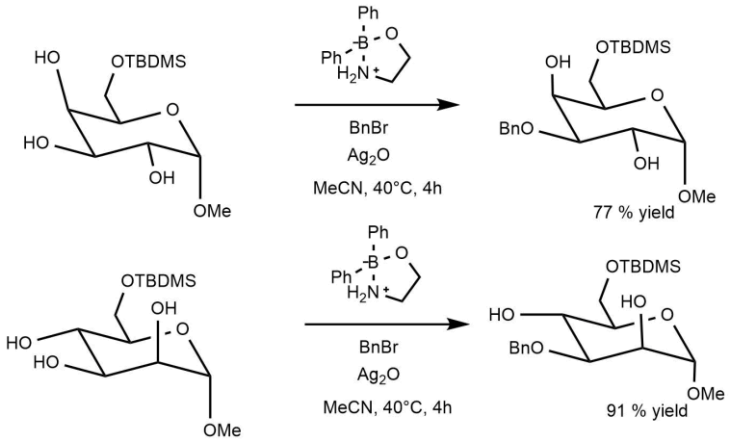
Scheme 6: Benzylation under mildly acidic conditions.

Regioselective benzylation of *D*-glucose derivatives have been developed using a variety conditions to tune selectivity. For instance, regioselective mono- and di-benzylation of O-3 and O-4 of monosaccharides has been achieved employing bromide ions in the form of tetra-n-butylammonium bromide (TBAB) in conjunction with activated tin catalysts (Scheme 7).[29]



Scheme 7: Regioselective mono- and di-benzylation of methyl-*β*-*D*-galacto- and glucopyranoside using bromide ions with a tin reagent.

Tin derivatives are highly toxic, making them poor candidates for industrial use, there is, however, a considerable amount of work being done, focusing on their applications in carbohydrate chemistry. Lastly, an interesting area, currently seeing extensive research is the use of boronates in regioselective benzylation reactions. Sugars readily form complexes with boronates.[29,34] These complexes have been utilized to selectively alkylate sugars with excellent yields and selectivity. Especially interesting, is the results achieved in working with 6-*O*-TBDMS protected glucopyranosides as illustrated in Scheme 8.[42]



Scheme 8. Regioselective benzylation of 6-*O*-TBDMS-*β*-*D*-galactopyranosides using diphenyl boronic acid.

Substituted benzyl ethers, such as *p*-methoxybenzyl and *p*-chlorobenzyl, show increased selectivity, compared to non-substituted benzyl ethers[33,43], but are less resilient and may decompose under harsh conditions.[19,23] On the other hand, *p*-aryl ethers also offer good selectivity, but are too stabile and often difficult to remove.[23] This does allow for some interesting ways of selective deprotection, but will not be discussed further in this section.

Deprotection of benzyl ethers is most commonly achieved through hydrogenation reactions involving palladium catalysts[4,6,19,41]. Alternatively, Birch-type reductions can be used to protect functionalities on the molecule affected by hydrogeneration reactions, but is not commonly employed in carbohydrate chemistry.[19] Regioselective cleavage of benzyl ethers have been attempted with Lewis acids such $FeCl_3$[44] and $SnCl_4$[45] with good selectivity. This is, however, only applicable when attempting regioselective deprotecting on groups in different orientations, where one benzyl group occupies a more sterically hindered orientation than the other. In addition, regioselective acetolysis has been shown to selectively dibenzylate the primary position on 2,3,4,6-*penta*-*O*- protected glycosides.[46]

Another advantage of the use of benzyl ethers as protection groups is the group's conjugated π-system, allowing for the use of UV detection when monitoring reactions on TLC. This, combined with the tendency to form crystalline compounds,[23,39] furthers the benefits of employing benzyl ethers as protection groups.

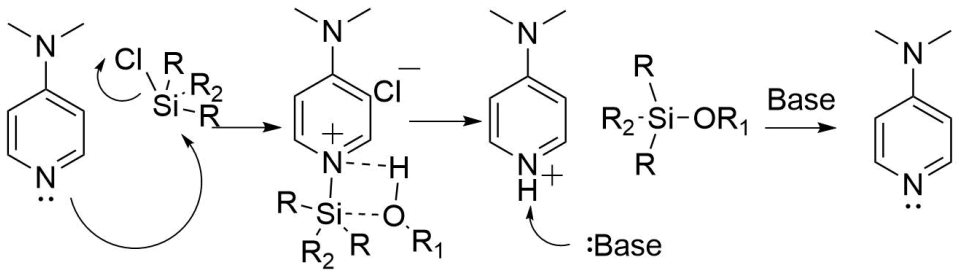
2.4.2 Silyl ethers

Silyl ethers have synthetic potential as protection groups due to the relative ease they can be introduced and removed, utilizing mild conditions[11,47,48]. Their relative stability to acidic and basic conditions can be finely tuned by varying the substituents on the silicon atom.[23]Generally, the more bulky and electronegative substituents present on silicone, the more stable the silyl ether will be towards acid hydrolysis.[23]

The silyl ether, in its simplest form, TMS (Trimethylsilyl) is widely used in chemistry as a temporary protection group, use as a permanent protection group, is, however, limited due to its liability to hydrolysis[39], and instability on silica columns.[11,49]

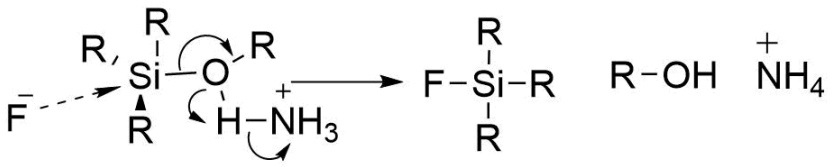
The tert-butyl-dimethyl silyl (TBDMS) and tert-butylphenyl silyl (TBDPS) are among the most commonly applied silyl ethers in carbohydrate chemistry[19,50]. These protection groups offer relatively high stability, and are robust in the presence of acidic and basic conditions.[39]

TBDMS and TBDPS are readily introduced by treatment with TBDMSCl and TBDPSCl in triethylamine or pyridine in the presence of a catalyst, such as DMAP or lutidine.[51-52] The suggested mechanism for introduction of silyl ethers, catalyzed by DMAP [53] is given in Scheme 9.



Scheme 9: Proposed mechanism for the DMAP catalyzed silylation of alcohols.

Silyl ethers can be cleaved by strong acidic or basic conditions, depending on the silicone substituents,[39] though the most reliable way of deprotection is usually by way of fluoride ions. Fluoride-induced deprotection is particularly useful, because the formation of the strong Si-F bond is a highly selective procedure.[11] Conditions used for this cleavage vary. For instance, NH_4F in methanol is a frequently used set of conditions,[54] but the selectivity can be tuned by altering cation, solvent or temperature.[47,48] The mechanism[54] for the deprotection of silyl ethers using fluorine ions in ammonium is displayed in Scheme 10.



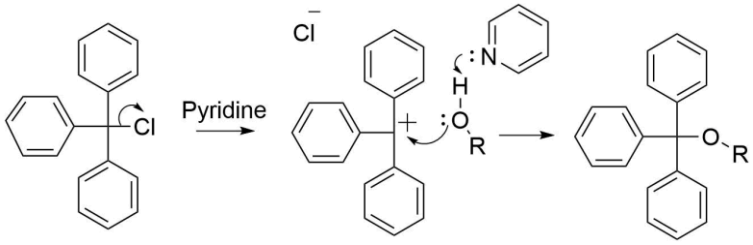
Scheme 10: Removal of the silyl protection group with ammonium fluoride [54]

Silyl ether stability, and therefore the ease of deprotection, can, as mentioned above, be adjusted by altering the substituents on the silicon atom.[48, 55] As a result, multiple hydroxyl groups in a single molecule can be protected as the same functional group, but with different reactivities.[47] Sequential selective de-protection, allows, in theory, each alcohol group to be deprotected, when it needs to be manipulated.[48]

Silyl ethers have not been used extensively in the protection chemistry performed in this thesis, but are being explored in other parts of the total synthesis project.[56] It is, however, important that the chemistry and conditions used are compatible with the silyl group. This will be discussed further in section 3.2.4 and in regard to future work.

2.4.3 Trityl ethers

Triphenylmethyl ethers, often referred to as a trityl moiety, are bulky protection groups, often employed for regioselective protection of the primary sugar hydroxyl.[11,57] Common methods of introducing the reagent involve using triphenylmethyl chloride (TrCl) in pyridine. The rate of the reaction is in itself slow, but increased rates are seen upon addition of DMAP in catalytic amounts.[19] The mechanism for the introduction of a trityl protection group is shown in Scheme 11.



Scheme 11: Mechanism for tritylation of a sugar hydroxyl group

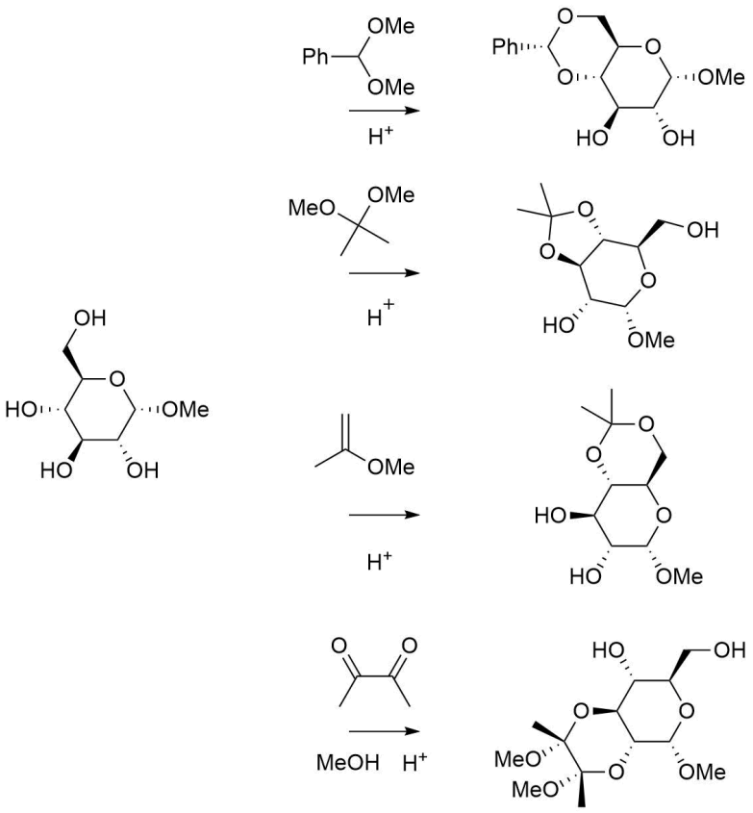
The triphenylmethyl ether is a bulky protection group, and is, for this reason it is not well suited for secondary hydroxyls. The trityl group, has however been shown to offer excellent

selectivity towards the primary position, and does, due to its bulky nature exhibit further possibilities in selectivity on other positions on the sugar ring.[32]

Trityl ethers can be cleaved with mild protic acids, or in the presence of Lewis acids, such as $ZnBr_2$-MeOH or $FeCl_3$.[19,23]

2.4.4 Acetal protecting groups

Acetal protection groups are often used for the selective protection 1,2 -*cis*, 1,3-*cis* and 4,6-*trans* diols of sugar derivates[19]. The two most commonly used acetals in the simultaneous protection of two hydroxyl groups on carbohydrates are benzylidene and isopropylidene acetals, used in a variety of synthetic pathways.[4,9,58–60] Cyclization happens by standard acetalization conditions, involving the acetals, and an acid catalyst. Examples of the most commonly used acetals, and their regioselectivity[11] is displayed in Scheme 12.

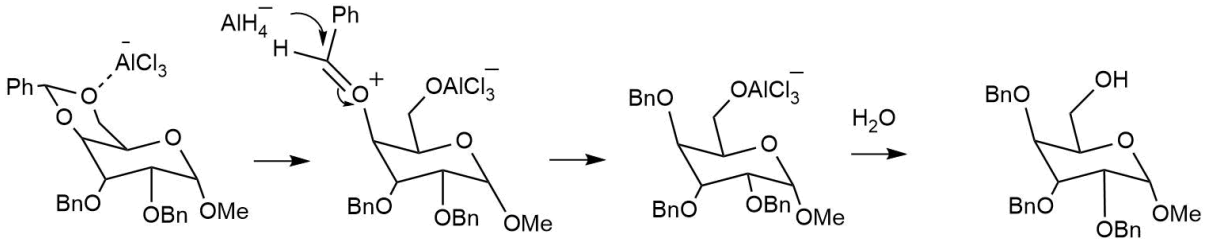


Scheme 12: Acetalization of methyl-*α*-*D*-glucopyranoside.[11]

Acetal protection groups are robust in the presence of base, but liable to strong acids, at extent depending on the properties of the acetal used.[11] The benzylidene acetal is commonly used for 4,6-*trans* protection of pyranose derivatives. It is easily introduced and offers high selectivity

and unproblematic removal. Introduction of the benzylidene acetal for *trans*-4,6 protection is commonly carried out in the presence of *p*-toluene sulfonic acid (*p*-TsOH) as a catalyst.[19,58]

The acetal group can easily be removed in mild aqueous conditions by hydrolysis, using AcOH, TFA/DCM/H_2O, or by catalytic hydrogenation.[19] Reagents allowing selective cleavage of the benzylidene acetal are described in literature, and used readily in synthesis of mono O-benzylated derivatives.[5] Treatment of 4,6-benzylidene derivatives with $LiAlH_4$-$AlCl_3$ selectively cleaves the less hindered O-*6*-CHPh position.[61] The mechanism for this selective reduction, using $LiAlH_4$ as the reducing agent, is shown in Scheme 13.[40,19]

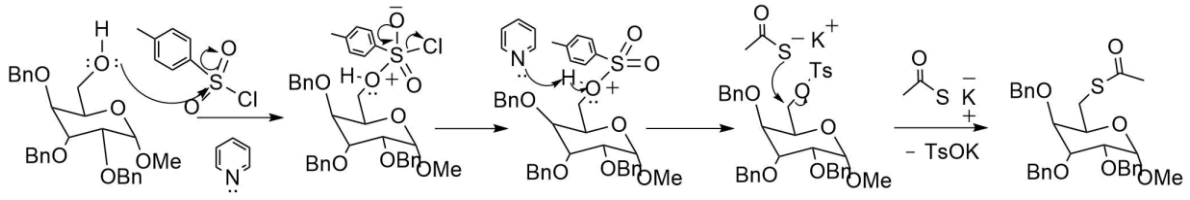


Scheme 13: Mechanism for the benzylidene acetal cleavage using $LiAlH_4$-$AlCl_3$.

Employing other reducing agents, such as $NaBH_3CN$-HCl, the selectivity of the ring-opening can be reversed leaving the free hydroxyl group at C-5.[5,23]

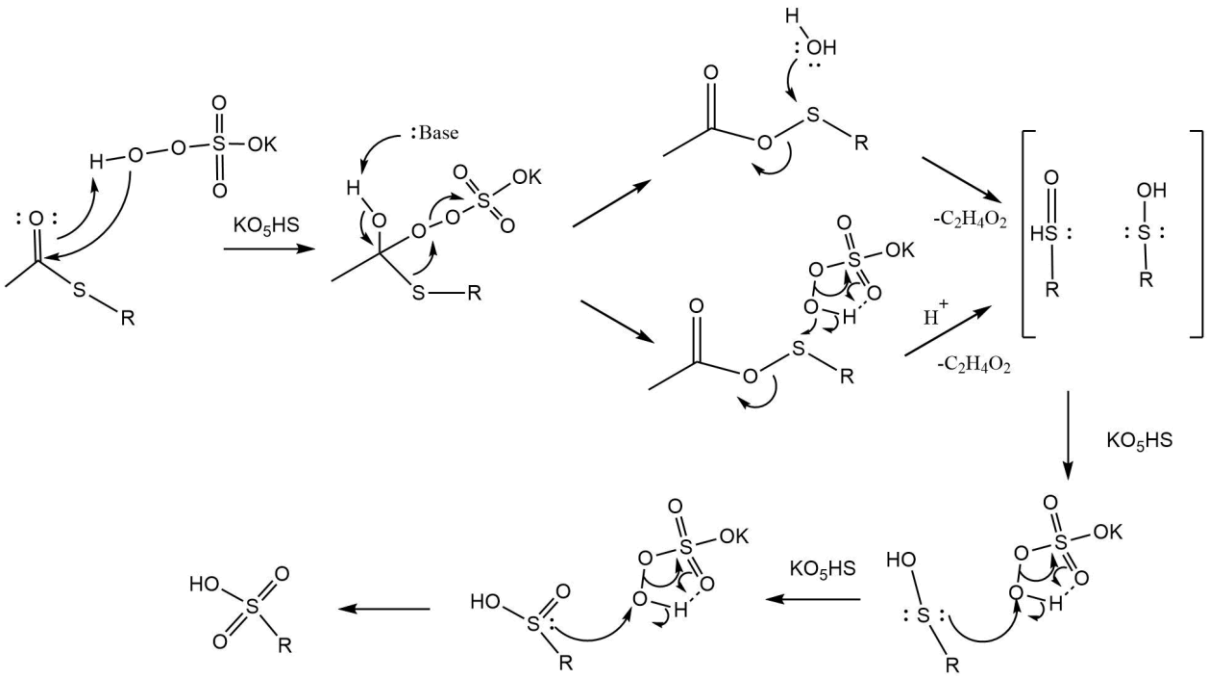
2.5 Sulfonic acid derivatives and insertion of sulfur

Methods for inserting sulfur into the C-6 alcohol are well documented, employing mild conditions with excellent yields.[4,6,8,9,37] These procedures usually proceed through initial introduction of a leaving group, such as tosyl or mesyl, followed by reaction with a thioacetate nucleophile, leading to the thioacetate substituent at the site of the former 6-hydroxyl group. The mechanism[23,40] of these initial steps is shown on Scheme 14.



Scheme 14: Proposed mechanism for the tosylation and insertion of sulfur onto C-6.

The following oxidation of the thioester to sulfonic acid derivatives, requires an oxidant in conditions mild enough to not lead to the deprotection on other sites. Peroxides, such as hydrogen peroxide, have been used successfully in the oxidation of thioacetates to sulfonic acid derivatives.[62] Potassium peroxomonosulfate, under the tradename Oxone,[63] has been observed to be an effective agent for the conversion of thioacetate into corresponding sulfonate compounds. Oxone has seen wide use as an oxidant in the last decade, due to its low cost, relatively mild conditions, and high yields.[63] The mechanism for this reaction is not well understood. However, based on a kinetic study, discussing intermediates in the oxidation of sulfones[64], and the mechanism of better understood peroxide oxidants,[65,66] a suggested mechanism is outlined in Scheme 15.



Scheme 15: Suggested mechanism for oxidation of a thioacetate to sulfonic acid using Oxone.

The suggested mechanism is based upon the proposed initial insertion of oxygen into the S-C bond with subsequent breakdown into sulfenic acid and acetic acid, as described in litterature.[64] It is worth mentioning that the step involving the cleavage of acetic acid may be initiated by the peroxymonosulfate ion acting as a nucleophile, instead of water. There is considerable evidence, however, that the presence of water speeds up the reaction, indicating its role as a nucleophile in the decarboxylation step.[64]

Due to its highly polar nature, the resulting sulfonic acid moiety is usually protected during multistep syntheses, as this simplifies the handling, solvability and purification of the sulfonate intermediates, as well as minimizes side reactions.[67]

Common protection groups applied for sulfonic acids are alkyl esters (mainly isopropyl, isobutyl)[67]. However, protection of sulfonates as simple esters is problematic, because sulfonate esters are potent electrophiles, possibly furthering side reactions[68]. To overcome this, allowing for solubility in standard organic solvents, and purification by conventional chromatography, sterically hindered protection groups, such as trifluoromethyl triflate (TFMT)[69] and phenyl triflates have been developed to protect the moiety. These groups are resistant to nucleophilic attack and are readily cleaved by trifluoracetic acid (TFA) in mild conditions.[69]

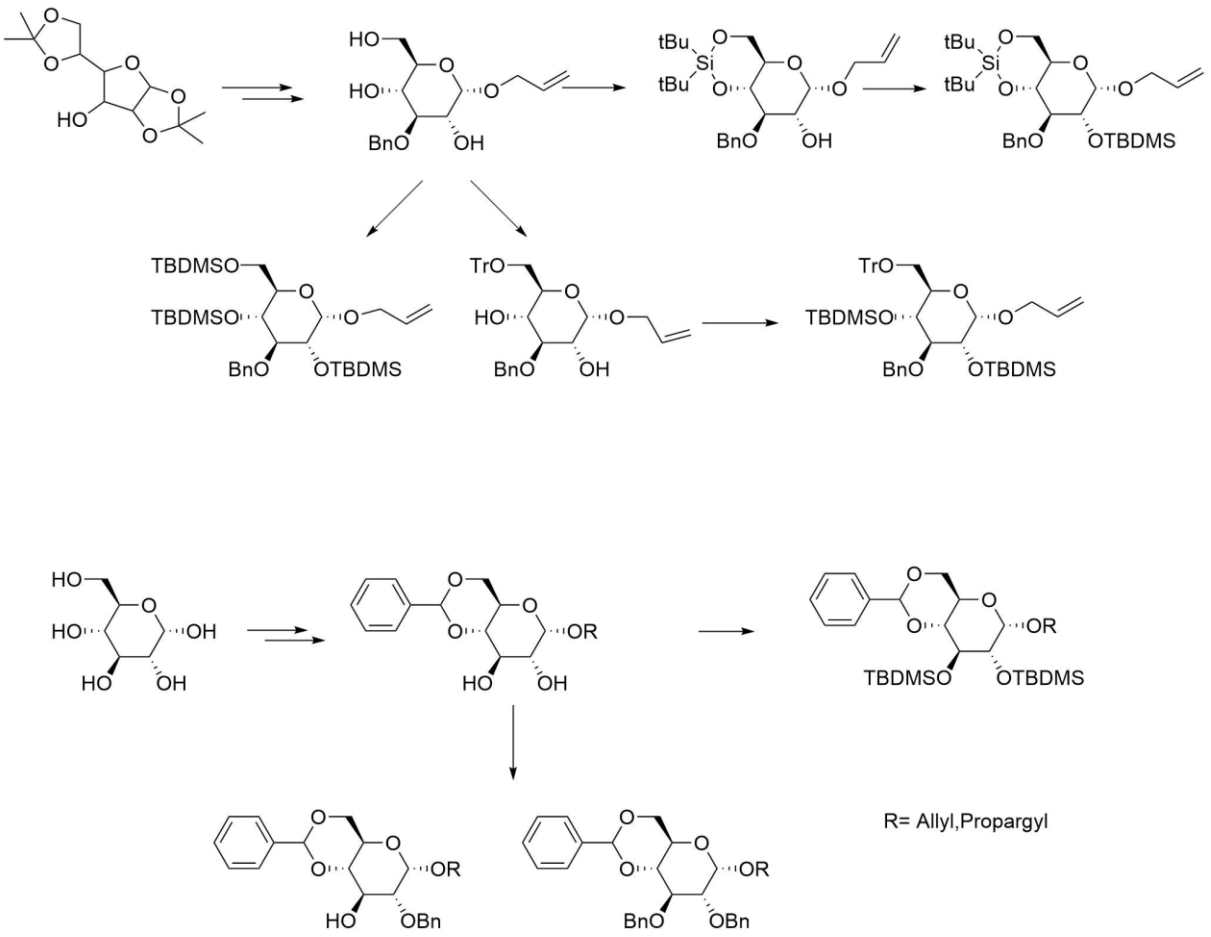
TMS has been successfully utilized as a protection group for sulfones,[70] but is not viable for this project, due to its instability under acidic conditions, and due to its known issues in silica chromatography[49]. Silyl ethers with bulky substituents on the silicone, such as TBDMS could, however, have potential as protection groups for the sulfonic acid moiety. In an aprotic environment, the silyl would inherit a partially positive charge, opening for a nucleophilic attack by the sulfonic acid moiety. Based on work with TBDMS-triflates[71], and the proven methods for silylation of sulfonic acid derivates employing TMSCl, this may allow for the protection of the sulfonic acid as an TDBMS ether, and would be of great value to the research project. This will be discussed further in section 3.2.4.

2.6 Actual status of knowledge

Previous research in the project has been conducted, experimenting with another pathway to protection patterns allowing for the esterification of O-3. The work has been based on solvent directed mono-benzylation of allyl 4,6-benzylidene glucopyranosides.[58] This has, however, proven to be a dead-end street, due to problems related to reproducing selectivity reported in the literature[58]. Extensive efforts into optimization of these selective mono-benzylations have shown promising increases in selectivity, but problems related to quenching the reactions has rendered this approach unsuitable for large scale synthesis.[38]

Other work on the project has focused on developing protection strategies based on insertion of various silyl ethers on 3-O-benzylated derivatives, obtained by using 1,2,5,6-di-*O*-isopropylidene-*α*-*D*-glucofuranose as starting material.[56] The current status and an overview of the work done is shown in Scheme 16.

In addition to exploration of other protection patterns, novel reactions attempting the esterification of O-3 and biotesting of intermediates are in their infant phase.



Scheme 16: Other research being conducted in the research project.

3. Results and discussion

This chapter is divided into three parts. Section 3.1 covers the protection strategies employed to obtain the 2,3,4-tri- *O*-benzyl protected glucosides **7a/b,** while section 3.2 describes functionalization of C-6, attempted protection of the resulting sulfoquinovose derivatives, as well as stability testing of two silyl ethers in the oxidation conditions employed.

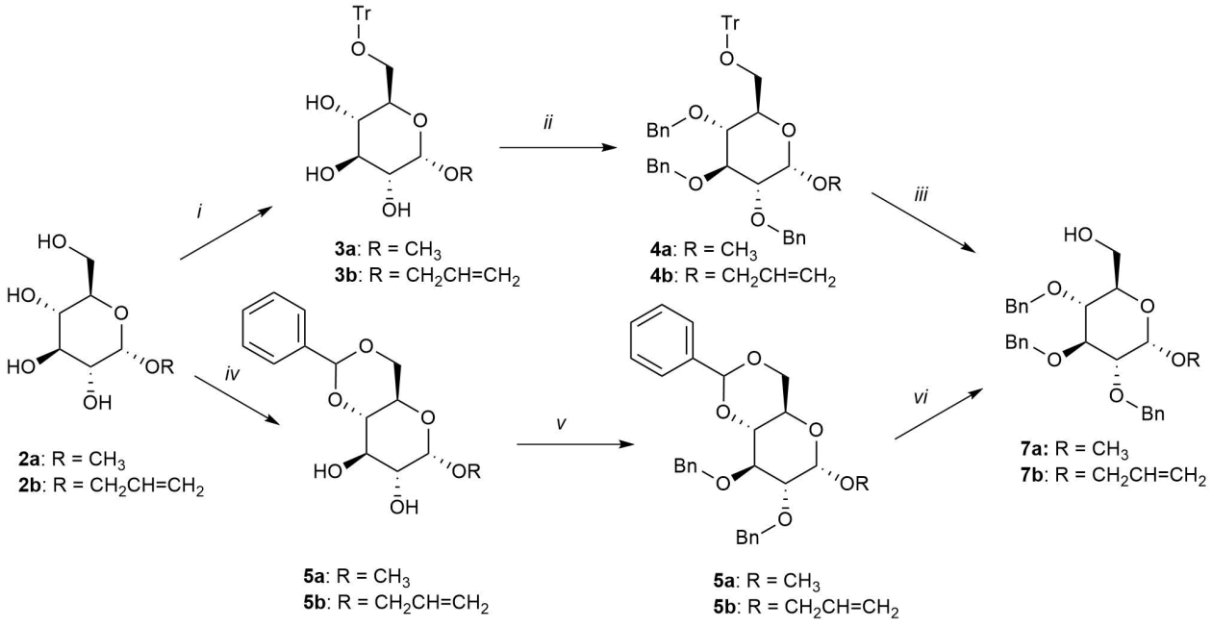
Lastly, section 3.3 deals with spectroscopic characterization of all intermediates with NMR and MS. All reactions were, where relevant, monitored by TLC and HPLC, as covered in the experimental section.

Known difficulties in working with a mix of anomers of the allyl glucosides prompted for experimentation on methyl glucosides.[38] Methyl-α-D-glucopyranoside is commercially available, making it ideal for trial reactions. In addition, better understanding of the effects of the anomeric substituent is of value in deciding upon further methods for functionalizing the C-1 substituent in the total synthesis of the target molecule **1c**.

3.1 Protection chemistry

In this section the two main routes towards the 2,3,4-tri-*O*-benzyl protected compounds **7a/b** (Scheme 17) and results from this work are presented. Strategy 1 is based on protecting the primary C-6-hydroxyl, as well as O-4 as a *trans*-4,6 benzylidene acetal, before protecting the C-2 and C-3 position as benzyl ethers. Further regioselective cleavage of the benzylidene acetal yields compounds **7a**/**7b**.

Strategy 2 proceeds through initial protection of the primary alcohol, with subsequent protection of O-2/O-3/O-4 as benzyl ethers, before deprotection of O-6, yielding the primary alcohol. This protection strategy is well documented on methyl α-*D*-glucopyranose derivatives[28,36,72]. Little research could be found, however, employing this method on allyl α-*D*-glucopyranose derivatives.



Scheme 17. Two routes to 2,3,4-tri-O-benzyl protected intermediates. Reagents and conditions: *i*: TrCl, DMAP, pyridine 110°C, 2h. *ii*: BnBr, NaH, THF 60°C, 2h. *iii*: Not attempted. *iv*: $PhCH(OMe)_2$, *p*-TsOH, ACN/DMF, r.t, 5h. *v:* BnBr, NaH, THF, 60°C, 2h. *vi*: $LiAlH_4$-$AlCl_3$, CH_2Cl_2/diethyl ether 50°C, 1h.

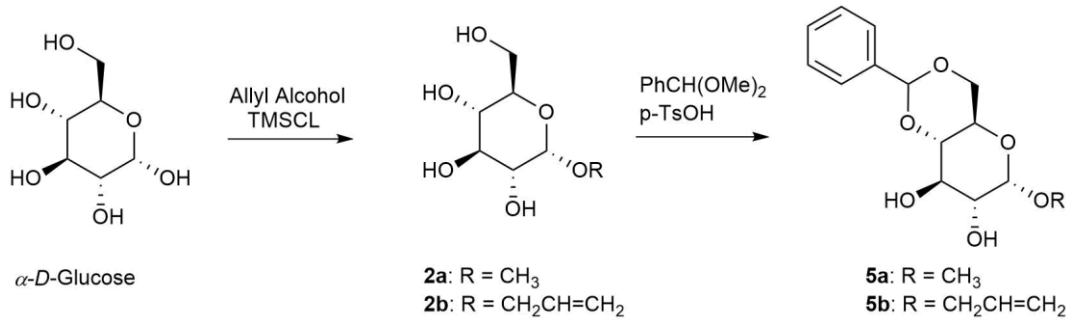
As mentioned in section 2.4, these pathways have previously been explored,[3–7] but the literature is still lacking in important details, such as complete NMR data, optimization work, and insight into large scale synthesis. For each step of the synthesis, optimizing the reactions has been attempted. Methods of purification, reaction conditions as well as collected yields will be discussed. At the end of the section, general effects, such as anomeric separation and observed effects of the anomeric substituents, will be covered.

3.1.1 Protection route 1: Acetal protection

Compound **5a** was prepared according to known literature procedures involving stirring of commercially bought methyl *α-D*-glucopyranose in benzylidene dimethyl acetal and catalytic amounts of *p*-TsOH.[16,58,73]

5b was prepared in a one-pot, two-step reaction according to literature[74], where *D*-glucose first undergoes acid-catalyzed glycosylation in neat allyl alcohol, giving compound **2b** in high yields. After evaporation, the crude product was reacted with benzylidene dimethyl acetal and a catalytic amount of *p*-TsOH to yield **5b.**[4,74]

The results for the glycosylation of *D*-glucose and following acetalization to **5b** are given in Table 2, while the results from acetalization of compound **2a** to **5a** are displayed in Table 1.



Scheme 18: Glycosylation of *α-D*-glucose using allyl alcohol and trimethylsilyl chloride (TMSCl) with the following acetalization employing benzaldehyde dimethyl acetal and p-toluene sulfonic acid (*p*-TsOH).

Table 1: Experiments ran for the acetalization of **2a**. All experiments are run in acetonitrile and a minimal amount of DMF to completely solve the reagents. Where no ratio is indicated, *α:β* ratio could not be scoped from NMR, indicating close to 100% *α*-anomer.

Entry	**Scale**	**Acetal [Eq]**	**p-TsOH [Eq]**	**Reaction time/temp**	**Purification**	**Yield [%]**	***α:β***
1	5.00 g	2.5	0.1	5h, r.t	Recrystallization	24%	-
2	5.00 g	2.5	0.1	8h, r.t	Recrystallization	33%	-
3	3.00 g	2.5	0.1	12h, r.t	Flash Chromatography	64%	1:16
4	5.00 g	2.5	0.1	12h, r.t	Recrystallization	76%	-
5	20.0 g	2.5	0.1	18h, r.t	Recrystallization	75%	-

The initial synthesis of **5a** gave substantially lower yields than those previously reported[16,73](Entry 1). Due to NMR and HPLC, indicating higher conversion than a mere 24%, the workup method and purification were suspected to cause loss of product. For this reason, multiple methods of workup were explored.

Common procedures for the workup and purification the benzylidene derivates **5a/b** involves precipitation from a saturated sodium bicarbonate solution or precipitation by addition of water to the reaction mixture. [16,58,73] Both of these methods were attempted as a way of

purification of compound **5a,** but yielded a mixture of compounds, needing further purification and was deemed unfit as a method of purification for the purposes in this thesis.

Attempts in recrystallizing in isopropanol yielded a mere 24% (Entry 1). This yielded a material pure enough for further synthesis, but clearly the loss of product was too large for the initial steps of a multi-step total synthesis project. The addition of water as an anti-solvent, (Entry 2) gave a slightly better yield. It should be noted that this reaction was given an extra three hours reaction time, and the increase in yield might simply be explained by higher degree of conversion. However, the presence of large amounts of α-anomer in the mother liquor indicates that this solvent system is too strong for recrystallization of **5a.**

Somewhat more successful was the use of a short silica plug, eluted with an ethyl acetate/*n*-pentane gradient, starting with pure pentane and ending with a ratio of 1:3 (Entry 3). TMSCl and excess of acetal were eluted at low polarities, with the product eluting as white crystals at the highest solvent polarity.

The best results were observed when recrystalizing from ethanol using water as anti-solvent. In large scale reactions for both **5a/b**, this purification method proved troublesome, due to residual solvents and co-precipitation of impurities when precipitating from small volumes. This was solved by tuning the amount of solvent and anti-solvent, and by vastly increasing the volume by trituration of the mixture before recrystallizing.

Being the first in a series of more complicated steps, a workup method for large-scale reactions was needed. Purification by silica gel, using flash chromatography would be effective on smaller scales, but is not a feasible or effective workup method for scales surpassing 2 grams. In addition, separation of anomers by silica is not as effective as trituration in ethanol. Although yields in this first step were sub-optimal, with 77% (Entry 4) being the highest attained, the reaction involves very little work and proved easy to reproduce in bulk (Entry 5).

A practical aspect and added benefit of recrystallizing the product is the different properties of the α and β anomers products, where the β-anomer is less crystalline. This enables partial removal of β-anomer during recrystallization. Comparing the α:β ratio attained from crystallisation against the observed ratio from products purified on silica, purification by recrystallization was deemed superior, due higher collected yields, time investment, and the absence of β-anomer observed in ^{1}H-NMR after purification.

The effect likely responsible for the observed difference in crystallinity of the anomers is covered in the theory section 2.3.4, concerning the H-bonding network of hexose derivatives. The *β*-anomer, having its anomeric oxygen in the equatorial plane creates a stronger intramolecular H-bond to its vicinal O-H on C-2, contributing to it being less crystalline. In the case of the *α*-anomer, the anomeric oxygen occupies the axial position, weakening this H-bond, possibly explaining the observed heightened crystallinity, due to a higher possibility of forming intermolecular H-Bonds.[30]

For compound **5a** no beta anomer was observed on NMR when purification by way of crystallization. Although the *β*-anomer is present in small amounts, the signals were indistinguishable and too low for quantification by NMR.

Reaction time and equivalents were to some extent altered to scope its effects (Entries 4 and 5). Monitoring the reaction on HPLC revealed full conversion at around 8 hours reaction time for compound **5a.**

Table 2: Experiments conducted with glycosylation and subsequent acetalization yielding **5b**. All glycosylation reactions are solved in neat allyl alcohol. All acetalization reactions are performed in acetonitrile and minimal amounts of DMF. All products were crystalized in ethanol using water as a solvent. The *α:β* of the crude product **2b** was scoped from ^{1}H-NMR.

Entry	**Scale**	**TMSCl [Eq]**	**Glycosylation conditions**	***α:β* of 2b crude**	**Acetal [Eq]**	***p*-TsOH [Eq]**	**Reaction time/temp**	**Yield [%]**	***α:β* 5b**
1	10.17 g	5	72h r.t	5:1	2.5	0.1	5h, r.t	14	12:1
2	8.4 g	5	72h r.t	5:1	2.5	0.1	12h, r.t	42	16:1
3	20.0 g	5	72h r.t	5:1	2.5	0.1	24h, r.t	46	20:1

Work done by Izumi et al,[74] investigating the attained ratio anomers in alkylation of the anomeric position of *D*-glucose, report high selectivity towards the *α*-anomer, when leaving the reaction to proceed over a period of 3 days, yielding the pure alpha anomer in 64% after acetalization.

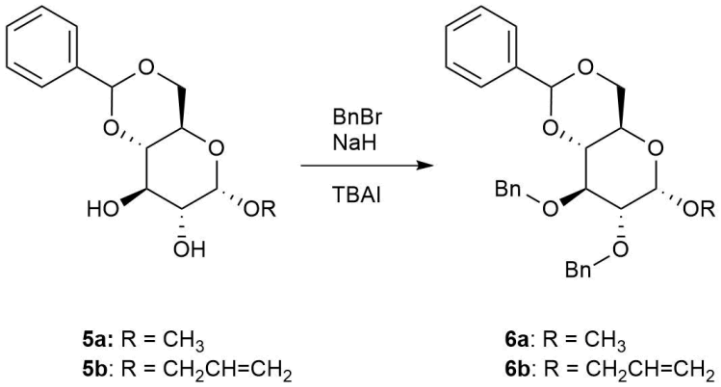
^{1}H-NMR analysis of the crude mixture of **2b** indicated an average *α:β* ratio of 5:1, while the observed ratio of **5b** after purification was, in most cases greater than 12:1. There was,

however, observed no change in anomeric ratio in samples taken when monitoring the reaction with samples taken every 15 minutes. Based on the constant ratio observed, it was concluded that it was unlikely that the decreased amount of *β*-anomer arises from anomerization during the acetalization reaction. A more likely explanation is that, as covered in the purification of **5a**, the *β*-anomer remains in the mother liquor after crystallization due to its lower crystallinity. This could also account relatively low collected yields of **5b**, whereas approximately 20% of the product is present as the *β*-anomer. Furthermore, a portion of the lost product can be explained by some portion of the α-anomer remaining in the mother liquor, seeing compete crystallization of the anomer is unlikely. The amount of α-anomer lost in the mother liquor could potentially be reduced by tuning of the recrystallization solvent system, but this was not pursued further due to sufficient yields for further synthesis. The findings in working with these reactions are in accordance with literature.[4,58,74]

In a similar manner as for compound **5a,** the reaction time for the acetalization of **5b** was varied and monitored. Low yields were observed with a reaction time of 5 hours (Entry 1) and from HPLC monitoring of the reaction, conversion was observed at 8 hours (Entry 2). A slight increase in yield was observed with the higher reaction time, as well as a better *α:β* ratio (Entry 3). This indicates a possible anomerization of the intermediate in the reaction mixture, favouring the *α* anomer. This would, however, require further experimentation to prove.

In the next step, the hydroxyl groups on C-2 and C-3 were benzylated under slightly modified conditions, based on previous literature and theory.[4,17,19,58]

The standard method for benzylation of both compound **5a** and **5b** utilizes an excess of base in a polar, aprotic solvent, with subsequent addition of either benzyl bromide, or benzyl chloride, in some cases with tetrabutylammonium salts added in catalytic amounts.[4,58,75] Table 3 displays the most noteworthy results from benzylation of **5a** and **5b**.



Scheme 19: Benzylation of compound **5a/b** using sodiumhydride (NaH) and benzyl bromide (BnBr) with catalytic amounts of tetrabutylammonium (TBAI) iodide.

Table 3: All reactions were performed in THF, and all products except two (Entries 5 and 11) were purified on silica. Products recovered in Entry 5 and 10 were recrystalized from isopropanol/water. $\alpha:\beta$ Ratios are given where possible. Where no ratio is given, the β-anomer was not detectable by NMR.

Entry	**R**	**Scale**	**NaH [Eq]**	**TBAI [Eq]**	**BnBr [Eq]**	**Reaction time/temp**	**Yield [%]**	***α:β***
1	CH_3	300 mg	3	0.10	3	1h, 80°C	52.7%	-
2	CH_3	400 mg	3	0.10	3	2h, 60°C	64.3%	-
3	CH_3	1.00 g	4.5	0.10	4	2h, 60°C	84.4%	-
4	CH_3	1.00 g	4.5	0.10	4	24h, r.t	79.5%	-
5	CH_3	10.00 g	5	0.10	5	2h, 60°C	54.2%	-
6	$CH_2CH=CH_2$	300 mg	3	0.10	3	1h, 80°C	59%	12:1
7	$CH_2CH=CH_2$	400 mg	3	0.10	3	2h, 60°C	67.9%	-
8	$CH_2CH=CH_2$	1.00 g	4.5	0.10	4	3h, 60°C	73.4%	20:1
9	$CH_2CH=CH_2$	1.00 g	4.5	0.10	4	2h, 60°C	72.0%	-
10	$CH_2CH=CH_2$	1.00 g	4.5	0.10	4	24h, r.t	56%	-
11	$CH_2CH=CH_2$	10.00 g	4.5	0.10	4	2h, 60°C	32%	-

By increasing the amount of base and benzyl bromide present as shown in Table 3, higher yields for the benzylation for both compound **5a** and **5b** were observed. The best results were achieved using 4 or more equivalents of base and benzyl bromide (Entries 3 and 9). Higher equivalents were not explored in this work, although it is unlikely to have any effect, as the presence of unreacted sodium hydride was noted upon quenching the reaction with water, and excess benzyl bromide was observed in the purification process. Covered in section 2.4.1 of the theory, TBAI may serve as a catalyst, replacing bromide on benzyl bromide, creating a more reactive alkylation reagent[11,19], and may work as a solid-to-liquid phase transfer catalyst, further increasing the rate of the reaction. Increasing the amount of TBAI may affect the rate of the reaction but was not deemed worth the time investment.

There is little consensus in literature as to the ideal reaction time and temperature, where reported conditions range from 24h at r.t to two hours at 60°C.[4,11,32,58,76,77] Following the benzylation of **5b** for three hours at 60°C, taking samples every 30 minutes for HPLC and NMR analysis, full conversion was observed between 90 and 120 minutes (Entry 8). The same time study was done for compound **5a** (Entry 3), with similar results.

Due to reported yields of over 90% in literature,[4] employing a longer reaction time at room temperature, reactions were run to test its effectiveness. Both **5a** and **5b** were subjected to a reaction period of 24 hours at r.t (Entries 4 and 10). Increased reaction time and lower temperatures were, however, not observed to improve the reaction in terms of yields or purity. The effect of reaction times upon the anomeric ratio is difficult to scope from the results. In most cases the amount of β-anomer is too low to be detected. Seeing the purification method employed does not separate anomers, these findings indicate little anomerization occurring during alkylation.

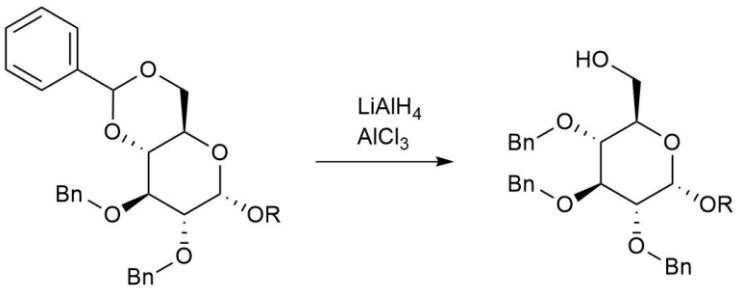
Benzylation of **5b** revealed by-products present in the crude reaction mixture (Entry 8). The mixture was analyzed with HPLC. The main α-product eluted at t_R=32.47min, with a small portion of β-anomer, observed at t_R= 33.01 min. The two mono-benzylated products were observed at t_R= 23.91 min for the O-2 protected derivate and 24.53 min for the O-3 derivate. The by-products were confirmed by comparison to previous work done on the project with the selective 2-O-benzylation of **5b**[38]**.** HPLC analysis of benzylation of the methyl glucoside **5a** revealed the same by-products, but in much smaller amounts, barely detectable by HPLC.

Due to extensive research previously done on the project, little optimization was needed for the method of purification of compound **5b**. Good results were attained purifying the crude

product on a silica column with 1:20 EtOAc/*n*-pentane as eluent yielding the dibenzylated product with a R_f value of 0.68. The two mono benzylated by-products were easily separated from **5b** due to their higher polarity, but were not successfully separable from each other on silica column without using high gradients. Compound **5a** was purified by using the same eluent system, though with a R_f value of 0.79, indicating a slightly lower polarity. This was also observed on reverse phase HPLC with the methyl glucosides, having slightly higher retention times.

Lastly, both compounds **5a/b** were successfully recrystallized from isopropanol and *n*-pentane (Entries 5 and 11). The low yields are due to incomplete precipitation. Attempting to further lower the solubility of the compounds by using weaker solvents or anti-solvents caused by-products to co-precipitate, deeming the method inferior to separation on silica.

Regioselective cleavage of the 4,6-*O*-benzylidene acetal of compound **6a/b** was reached in good yields using conditions from Tanka Et al.'s[5] work on regioselective cleavage using various Lewis acids. Results for the reactions are shown in Table 4.



6a: R = CH_3
6b: R = $CH_2CH{=}CH_2$

7a: R = CH_3
7b: R = $CH_2CH{=}CH_2$

Scheme 20. Selective ring-opening of the benzylidene ring of **6a/b** using lithium aluminium hydride ($LiAlH_4$) and aluminium chloride ($AlCl_3$).

Table 4: Results from the ring-opening of **6a** and **6b**. All reactions were performed in dry 4:7 diethyl ether:DCM. For both compound **8a** and **8b,** no *β*-anomer could be observed by NMR.

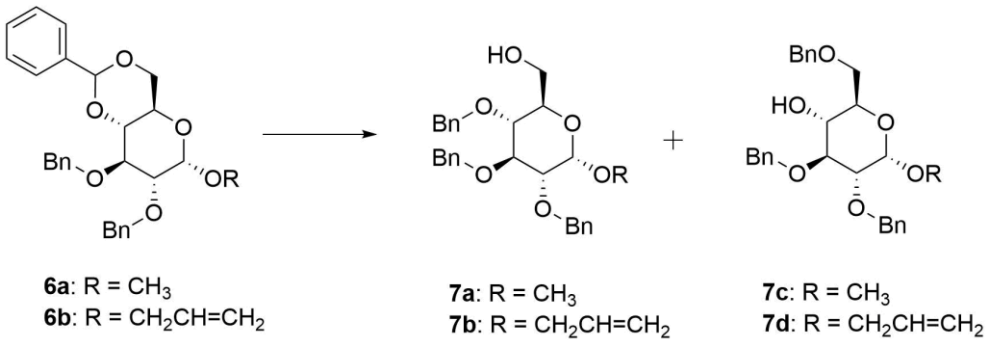
Entry	**R**	**Scale**	**$LiAlH_4$ [Eq]**	**$AlCl_3$ [Eq]**	**Reaction time/temp**	**Yield [%]**
1	CH_3	200 mg	4.7	4	2h	73%
2	CH_3	600 mg	4.7	4	2h	75%
3	CH_3	600 mg	2.5	2.5	2h	86%
4	CH_3	2.00 g	2.5	2.5	1h	66%
5	$CH_2CH{=}CH_2$	200 mg	4.7	4	2h	75%
6	$CH_2CH{=}CH_2$	600 mg	4.7	4	2h	79%
7	$CH_2CH{=}CH_2$	700 mg	2.5	2.5	2h	84%
8	$CH_2CH{=}CH_2$	1.00 g	2.5	2.5	1h	82%
9	$CH_2CH{=}CH_2$	1.00 g	1.5	1	2h	54%

In the work done by Tanka et al.[5] the effectivity and regioselectivity of a series of Lewis acids in the cleavage of benzylidene-protected glucosides was explored. The findings showed $LiALH_4$-$AlCl_3$ offering superior selectivity and ease of use, in comparison with other systems.[5] A combination of $LiAlH_4$ and $AlCl_3$ is reported to offer above 90% selectivity towards the free 6-hydroxyl derivative by several other sources.[4,9,75]

The conditions used by Tanka were initially mirrored, showing slightly less selectivity, and higher detectable amounts of the free C-4 hydroxyl by-product than reported.[5]

Initial results employing the exact conditions reported, yielded between 70-75% for both the allyl and methyl substrates, after purification on silica (Entries 1 and 5). Other sources report better yields and less by-products from using softer conditions, as low as 1.5 equivalents of $LiAlH_4$.[4]. For this reason, reactions were run, exploring the effects of altering the conditions.

Reactions employing equivalents as low 1.5, were not successful, as evidenced by substantially lowered yields (Entry 9). This may be due to present water residues in the sample, reacting with $LiAlH_4$. Following this, using low equivalents would require a dry environment to work efficiently. This was, however, not attempted in this work, but was countered by using higher amounts of reagents.



Scheme 21: Possible products from the ring-opening of compound **6a/b**

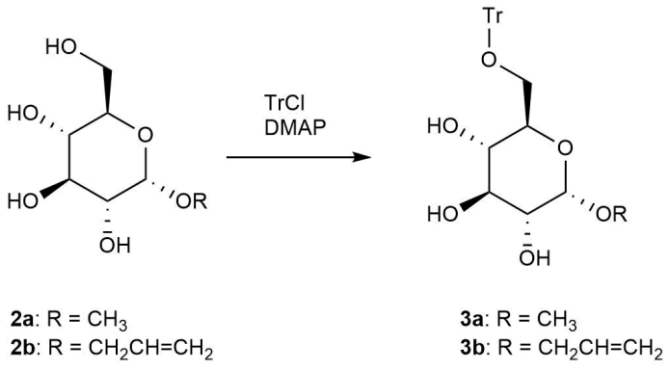
HPLC analyses from the reactions revealed that using fewer equivalents did not affect the overall conversion of compound **6a/b**, in comparison to using harsher conditions (Entries 2 and 6). On the other hand, using softer conditions were observed to increase selectivity, lowering the observed by-products (compound **7c/7d,** Scheme 21).

Following the reactions by HPLC, taking samples every 15 minutes, full conversion was observed after 30 minutes using 2.5 equivalents of $LiAlH_4$ and $AlCl_3$. (Entries 3 and 7).

Purification on silica using a gradient, starting with 1:15 and incrementally increasing polarity to 1:10 and lastly 1:5 EtOAc:*n*-pentane, allowed for separation of the by-products and eluted the main product without band broadening. A trial reaction of the next step in the tosylation of the free C-6 hydroxyl group was performed on the crude product of both **7a**/**7b** without purification, yielding interesting results. Comparing the reactivity of the free hydroxyl groups on **7a**/**7b** to the respective by-products **7c**/**7d**, the primary alcohol is in itself more reactive than the secondary. In addition, in **7c**/**7d** the free hydroxyl group is sterically hindered by two adjacent bulky benzyl ethers, further deactivating its reactivity with bulky reagents. This hypothesis was strengthened by analysis of the tosylation on the crude **7a/b,** where no tosylation of the 4-hydroxyl derivate was observed by HPLC or NMR. In addition to the large change in polarity in compound **7a/b** to **8a/b** in the tosylation reaction, the separation of the by-products **7c/d** can also be done in the next step in an eluent system of lower polarity. This would reduce the number of purification steps in the total synthesis without affecting further reactions.

3.1.2 Protection route 2: Mono-protection of the primary position

The initial tritylation reactions were run according to literature describing the procedure as a relatively simple, employing trityl chloride catalyzed with DMAP in pyridine.[32,78,79] The reaction was first attempted in a small scale, using the exact conditions reported (Entry 3), as shown in Table 5.



Scheme 22: Tritylation of **2a/b** employing triphenylmethyl chloride (TMSCl) and 4-dimethylaminopyridine (DMAP).

Table 5: Results from the tritylation of compound **2a** and **2b**. All reactions are run in pyridine and were added 10% DMAP.

Entry	R	Scale	TrCl [Eq]	Reaction time/temp	Purification	Yield [%]
1	CH_3	285 mg	1.2	110°C, 8h	Flash Chromatography	52%
2	CH_3	10.16 g	1.1	110°C, 8h	Recrystallizing	72%
3	$CH_2CH=CH_2$	2.30 g	1.5	110°C, 8h	Flash Chromatography	14%
4	$CH_2CH=CH_2$	1.81 g	1.5	110°C, 8h	Recrystallizing	-
5	$CH_2CH=CH_2$	500 mg	1.1	100°C, 1h	Flash Chromatography	-
6	$CH_2CH=CH_2$	510 mg	1.5	r.t 12 h	Flash Chromatography	-

Observations when monitoring the reactions TLC, indicated that most the starting materials were consumed in the reaction. This information led to the conclusion that other factors were responsible for the low yields collected (Entry 1). High amounts of by-products or loss of compounds in workup or separation were considered.

Different methods of purification were attempted, listed in Table 5. The best results were attained from recrystallization in isopropanol (Entry 2), giving the compound **3a** as small, white crystals in 72% yield.

Compound **2b** was prepared in line with literature,[74] using neat allyl alcohol and TMSCl, as covered in section 3.1.1. The anomeric ratio obtained was in agreement with previous observations: prolonged reaction times favoured the α-anomer as the main product.[74]

Initial purification of the allyl derivatives were attempted using the reported method by Webber et al,[80] involving recrystalizing in ethyl acetate and petroleum ether. Reproducing these results proved difficult, due to the compound not precipitating from the mixture without co-precipitation of by-products, thus, resulting in a yellow mixture of compounds, unfit for analysis. Use of flash chromatography proved to be ineffective, due to unexpected behaviour of the trityl group on the column, resulting in little to no separation. Several eluent systems, including 2:1-1:1 toluene:acetone and 1:5 EtOAc:*n*-pentane were tested in addition to recrystallization in: ethanol, isopropanol, water/*n*-pentane, and EtOAc/petroleum ether. None were, however, successful, yielding the same yellow mixture of compounds. While there are eluent systems reported to successfully purify the compound to be found in the literature,[81] the results could not be reproduced in our hands.

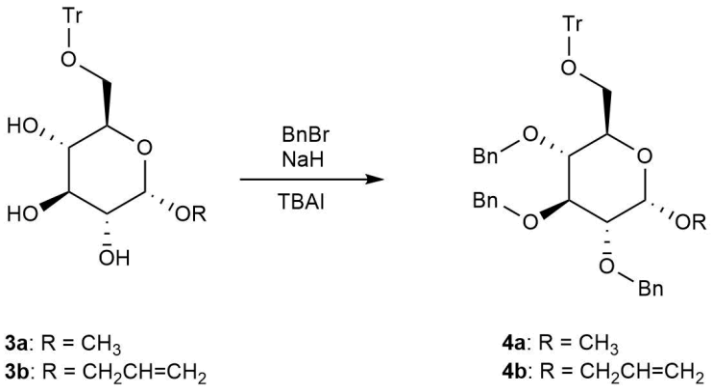
Some optimization work was attempted for compound **3b** (Entry 6). Little improvement was seen from altering the conditions, still resulting in a mixture of by-products, and offering the same difficulties in separation and purification.

Further investigation of this reaction would, in addition to finding suitable purification methods, involve varying the base used to catalyse the reaction. The mechanism for the reaction is displayed in chapter 2.4.3. DMAP is added to the reaction mixture increasing the basicity, in effect serving the role of a catalyst.[11] DABCO (1,4-diazabicyclo[2.2.2]octane) is another highly basic amine, and will like, DMAP, act as a catalyst in the tritylation reaction.[82] The use of DABCO has been reported with higher yields than DMAP for compound **2a**, but has not yet to the best of our knowledge been tested with the allyl substituent in the anomeric position. Experimentation with different bases were not explored in this thesis.

The work on this pathway was done in parallel to the work on pathway 1 (section 3.1.1). It quickly became evident that the trityl group offered several disadvantageous aspects, especially for substrates containing the allyl substituent in the anomeric position. This effect will be discussed further in section 3.1.3, looking at general traits in the anomeric substituents.

Despite pathway 2 being proven inferior to the alternative approach, triple benzylation of **3a** was attempted while continuing optimization work on the previous reaction. In addition, triple-benzylation of the crude reaction mixture of compound **3b** was attempted, in the belief that reducing the number of free hydroxyl groups would make the compound easier to purify.

The following reaction data is presented to underline the problems encountered with working with the triphenylmethyl protection group, and to further demonstrate the obvious advantages to the approach presented in section 3.1.1.



Scheme 23: Benzylation of **3a/b** using sodium hydride and benzyl bromide with catalytic amounts of tetrabutylammonium iodide

Table 6: Benzylation reactions of compounds **3a/b** to **4a/b**. All reactions are run in THF and were added 15% TBAI as a catalyst. All products were purified silica with 1:5 EtoAc:*n*-pentane. All reactions were purified by flash chromatography.

Entry	R	Scale	NaH [Eq]	BnBr [Eq]	Reaction time/temp	Yield [%]
1	CH_3	100 mg	4	3.5	2h, 60°C	46%
2	CH_3	900 mg	5	5	2h, 60°C	54%
3	CH_3	500 mg	4.5	4.5	24h, r.t	76%
3	$CH_2CH=CH_2$	200 mg	4	3.5	2h,60°C	-
4	$CH_2CH=CH_2$	500 mg	3.5	3.5	24h, reflux	--

Benzylation of compound **3a** was initially attempted using reported literature procedures[11,80,78]. In small-scale reactions, benzylation of **3a** yielded a yellow crude product (Entry 1). TLC indicated several by-products, but full conversion of the starting material. Although not proven by analysis, likely by-products are the mono- and di- protected derivatives. HPLC revealed 4 products in the crude reaction mixture eluting at t_R = 39.01, 34,14, 20.98 min and 15.33 min. No starting compound was observed. Although no method was employed to scope the relative molar ratio of the products, peak size indicated the highest peak at t_R = 39.01 as the major product, likely being the triple benzylated compound. The other peaks observed on HPLC are assumed to consist of the mono and di substituted products based on their elution time and NMR of the crude reaction mixture. Fully understanding and classification of this reaction would require extensive analysis of the by-products for verification of their structures, and was not deemed relevant due to the inefficiency of the pathway.

Baes on the assumption that by-products consist of mono and di substituted products, a second experiment was run with higher equivalents of base and benzyl bromide (Entry 2), in an attempt to force the reaction to completion. Somewhat better results were observed, with a yield of 54% of the desired compound. Lastly, a reaction time of 24h in r.t was explored based on a different source reporting yields as high as 85% (Entry 3).[7] Collected yields were substantially higher, and less by-products were observed.

Reported eluent systems, were found to be too polar to successfully purify the compound. For this reason, some experimentation was conducted. Several eluent systems were explored, with a gradient of eluents observed as most effective. Compound **4a** was successfully purified using a gradient of eluents starting with 1:40 EtOAc:*n*-pentane increasing to 1:20 and lastly 1:10. This successfully separated the by-products from the desired compound, but proved extremely time consuming, with **4a** eluting in fractions 41-42.

The only current available literature found describing the benzylation procedure of compound **3b** involves a 24 hour reaction time.[83] Due to problematic aspects of the purification of compound **3b**, one pot benzylation was attempted, starting from the crude product, believing that protecting the hydroxyl groups would result in a less polar compound, and therefore easier to purify on silica. After 2 hours at 60°C, a mixture of products was observed on TLC (Entry 3). The crude product was adsorbed on celite prior to application to the silica gel column in an attempt to counteract the observed problems on silica separation. This, however,

seemed to interfere with the retention, causing the purification process to fail, due to suspected to interactions between the trityl group and the celite, further complicating the purification of the compound. Application without celite was attempted, using reported procedures, but were also unsuccessful.

Employing the exact conditions and method of purification reported in litterature[83] did not improve recovered yields (Entry 4).

In summary, compound **3a/4a** was successfully synthesised according to literature. Problems were, however, encountered in purification, leading to extensive attempts in optimization of the purification method. Compound **3a** was successfully purified and analysed by NMR and MS. While compound **4a** could be somewhat purified on simple columns, complete separation on silica required high gradients of eluents and proved highly inefficient. Complete characterization of **4a** was, however, achieved. While the MS results for the compound include several by-products, the compound was identified, and was successfully purified on later in the project.

Compound **3b** and **4b** could not be purified to yield products pure enough for NMR or MS characterization. Several methods of purification were attempted, but were in vain. Due to time constraints and reasons covered above, time was not invested in full characterization of these compounds. Although preparative HPLC would most likely yield pure samples, suited for detailed analysis and characterization, it was not deemed a priority.

As a result of the complications encountered in purification, an array of observed by-products and low yields in each step compared to the other route to reach compound **7a/7b**, the pathway was not investigated further and deemed vastly inferior to the alternative approach covered in section 3.1.1.

3.1.3 Effect of anomeric substituent

Though not among the main objectives in this work, noteworthy differences in terms of reactivity and separation were observed dependent on the anomeric substituents on otherwise identical compounds.

Two major differences have been observed in the reactions covered in section 3.1. The overall yield of the reactions and properties in terms of polarity and solubility. The literature is scarce

concerning the effect of the anomeric substituent on reactivity or on physical properties, but this section will outline the observed differences.

Across most of the reactions studied in this thesis, the allyl glucosides have been reached in lower yields than that of the corresponding methyl glucosides.

A main contributing factor to the observed differences is most likely steric. The allylic substituent, being a bulkier group in comparison to the methyl substituent, may affect the reactivity of other positions in the molecule. The magnitude of this effect is, however, not well understood and would need further research. The steric differences could explain the increased number of biproducts observed in some reactions on allyl glycosides, in comparison to methyl glycosides, such as in the benzylation of **5b** and **3b**. In addition, the effect is likely in part responsible for the observed problems working with another bulky protection group, such as the trityl as outlined in section 3.1.2.

The largest differences in reactivity were seen on compounds such as **2a/b** or **5a/b**, with free hydroxyl groups, where the methyl glucoside intermediates were reached in 10-20% higher yields than the corresponding allyl glucoside. Smaller effects were seen on the following reactions involving ring-opening and functionalization of C-6, with a difference in yields between 2-5 % presented in section 3.2.

The observed differences between the two anomeric substituents indicate that the largest effect of the anomeric substituent in question, is upon the hydroxyl groups in its vicinity, indicating either a steric effect, or some form of interaction with the H-bonding network as covered in section 2.3.4. To better understand this effect, and to test its validity, further research into more bulky substituents and substituents with larger differences in electronic properties would be needed. Electronic effects of the substituents are not covered in this thesis due to lacking experimentation and data needed to comment on the subject.

A substantial difference between the ally- and methyl glucosides were observed in the oxidation of **9a/b**. This will, however, be discussed further in section 3.2.2.

3.1.4 Anomeric ratio and separation of anomers

Separation of the α and β anomers of each compound was not attempted. For the methyl glycosides the α:β ratio observed was too low to scope the molar ratio by NMR on all samples analyzed. This is most likely due to starting out with a pure commercially available α-anomer with no further reactivity at the C-1 position, leading to anomerization. Crystallization as a method of workup in the first two steps of the pathway, covered in section 3.1.1, would also, in effect, remove what little β-anomer amount formed in the first steps of the synthesis.

For the allyl glycosides, the β-anomer was observed by proton NMR, even after crystallization of compound **5b.** An anomeric ratio between 20:1 and 10:1 was observed in some intermediates where the β-anomer was detectable. Although not possible to observe by NMR, both anomers are likely present, with the β-anomer in small amounts.

Separation of anomers would be necessary in the total synthesis of compound **1c**, and the logical point to do this, based on the observations in this thesis, is after the ring-opening of the benzylidene acetal, before tosylation of C-6. HPLC analysis of an anomeric mix of **7b** showed the anomers as two peaks (not baseline-separated). The mixture was eluted with a water-acetonitrile gradient, starting with 80% water to 100% acetonitrile over 40 mins. Although an HPLC method using slower gradients may allow separation on preparative HPLC, this would, however, not be practical in a large scale/total synthesis context, meaning the anomers would likely have to be separated using silica gel chromatography.

Illustrated in section 2.6 of the thesis, other work has been conducted, experimenting with other protection patterns and protection groups.[56] Separation of an anomeric mixture of allyl 3-*O*-benzyl-4,6-ditertbutylsilylene glucose (Figure 6) has been achieved using high polarity systems (1:50 EtOAc:*n*-pentane).[56] The ease at which this compounds' two anomers can be separated likely arise due to the H-bond between the C-2 hydroxyl hydrogen and the anomeric oxygen, and the differences between the strength of this bond, dependent on the orientation of the anomeric oxygen. With a stronger bond between the anomeric oxygen and the hydrogen on the C-2 hydroxyl, as in the β-anomer (oxygen in the equatorial plane), the molecule will be less inclined to interact with the silica than the α-anomer, thus increasing the difference in retention of the anomers.

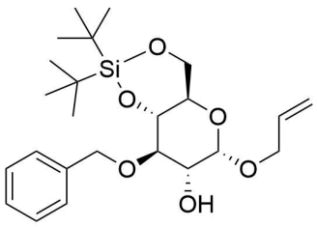


Figure 6: allyl 3-O-benzyl-4,6-ditertbutylsilylene glucose

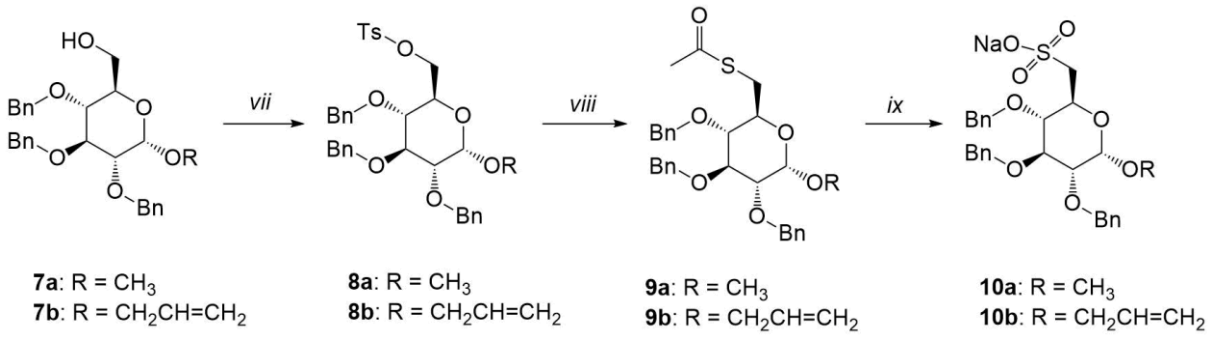
Separating anomers on silica may be more difficult where the anomers position has less direct impact on the compounds retention time on silica. **7a/b** would likely have much smaller differences in their R_f values, but the observed small *tR* on HPLC indicates that through some mechanism, the free hydroxyl group may affect the rate at which the two anomers elute. It should be noted that the distance between the 6-hydroxyl group and the anomeric oxygen result in poorer separation than the aforementioned 2-hydroxyl silylene derivative.

It could be advantageous to separate anomers as early as possible. This would minimize the number of possible by-products formed with the possibility to co-elute/co-precipitate, making purification more complex. Separation of an anomeric mixture in compounds with several free hydroxyl groups has previously been found to be less effective, even when using higher gradients.[38]

3.2 Insertion of sulfur, oxidation and sulfone protection

3.2.1 Insertion of sulfur

Methods for insertion of a sulfur atom onto C-6 are well documented in literature.[4,6,8,9,84] The most common methodology involves first functionalizing the hydroxyl into a good leaving group, before insertion of sulfur in the form of a thioester, or as a substituted thiol (Scheme 24).



Scheme 34: Steps needed for the insertion of sulfur onto C-6. Reagents and conditions: *vii:* TsCl, pyridine r.t, 12h. *viii*: AcSOK, EtOH, reflux, 2h. *ix*: Oxone, NaOAc, HOAc, r.t, 12h.

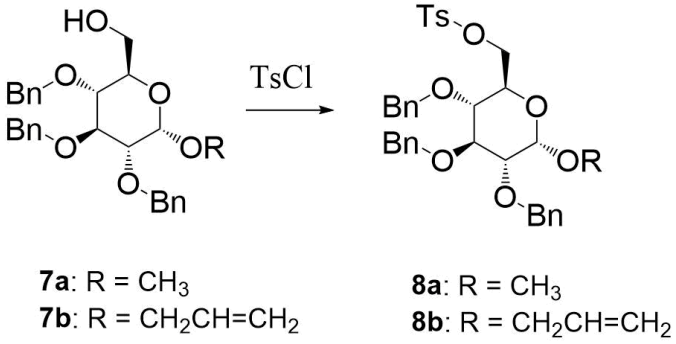
Novel reactions for protecting the resulting sulfonic acid derivative as a silyl ether, using conditions based on work done with TBDMSO triflates previously on the project,[56] will be presented at the end of the section.

Due to the relative simplicity and comprehensive literature available on the reactions, the tosylation and insertion of sulfur onto C-6 will be covered somewhat briefly.

Functionalization of the primary alcohol into a leaving group has been described employing several methods in literature. Most common is use of a sulfonyl chloride, either as 4-toluenesulfonyl chloride (Tosyl)[8] or, methanesulfonyl chloride (mesyl).[37] In addition, molecular iodine has been used to procure sugar iodides with further conversion to sugar thiols.[85] This method has, however, only been performed with the methyl glucosides and involves conditions less studied for compounds worked with in this project. The tosyl leaving group was chosen due to is seemingly simple introduction under mild conditions.[4,8]

Functionalisation of the primary alcohol to a tosyl group was performed as described in litterature[8]. Initial yields were slightly lower than reported for both **9a** and **9b,** with observed yields of about 70% (Entries 1 and 4).

TLC of the reaction mixture before purification revealed starting material present in the mixture, indicating only partial conversion (Entry 1). HPLC analysis of the same mixture confirmed the presence of unreacted compound **7a/b** and excess tosyl chloride but showed no substantial by-products.



7a: R = CH_3
7b: R = $CH_2CH{=}CH_2$

8a: R = CH_3
8b: R = $CH_2CH{=}CH_2$

Scheme 25: Tosylation of **7a/b** using 4-toluenesulfonyl chloride.

Table 7: Tosylation reactions on compound **7a/7b.** All reactions are performed in pyridine. For both compound **8a** and **8b** no β-anomer could be observed by NMR.

Entry	**R**	**Scale**	**TsCl [Eq]**	**Reaction time/temp**	**Yield [%]**
1	CH_3	200 mg	1.5	24h at r.t	73%
2	CH_3	200 mg	2.0	24h at r.t	78%
3	CH_3	2.7 g	2.0	24h at r.t	84%
4	$CH_2CH{=}CH_2$	300 mg	1.5	24h at r.t	64%
5	$CH_2CH{=}CH_2$	400 mg	2.0	24h at r.t	82%
6	$CH_2CH{=}CH_2$	500 mg	2.0	24h at r.t	86%

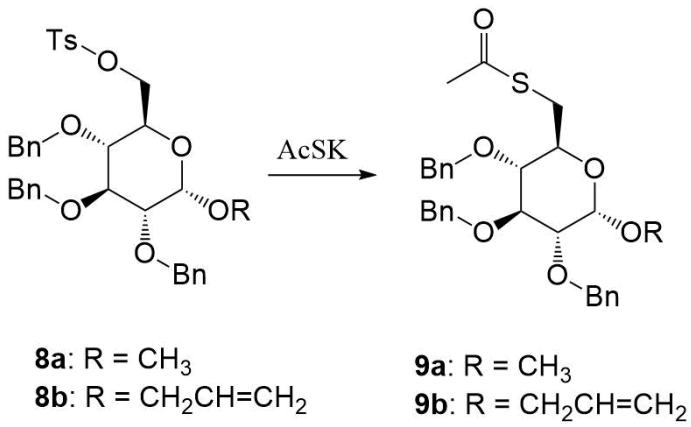
Harsher conditions, using more equivalents of TsCl (Entries 2 and 5), were observed to increase the yield by 10% confirmed by TLC and HPLC. The same effect may have been attained by increasing temperatures, but were not attempted.

Purification was done on silica using a gradient of solvents starting with 1:10 EtOAc:*n*-pentane increasing to 1:4 EtOAc:*n*-pentane, which effectively separated the starting materials and the products.

Although the reaction could likely be optimized further by experimenting with the use of catalysts such as DMAP/DABCO,[82,86] or by altering reaction conditions and workup, this was not prioritized, due to satisfactory yields for continuation of the synthesis under relatively mild conditions, with an unproblematic purification procedure.

For both compound **8a** and **8b** no *β*-anomer could be observed on NMR.

Due to its ease of introduction, possibility of oxidation[6,9,63,87] and well documented use,[6,8,9] a thioester was decided upon for a nucleophile in the thioesterfication. The sulfur atom acts as a nucleophile in a S_N2 type manner on C-6, with the tosyl group serving as a potent leaving group, as illustrated in the mechanism, portrayed in section 2.5.



8a: R = CH_3
8b: R = $CH_2CH{=}CH_2$

9a: R = CH_3
9b: R = $CH_2CH{=}CH_2$

Scheme 26: Thioesterfication of **8a/b** employing potassium thioacetate.

Table 8: Thioesterfication of compounds **8a/8b**. All reactions are performed in absolute EtOH.

Entry	R	Scale	KSAc [Eq]	Reaction time /temp	Yield [%]
1	CH_3	50 mg	2.6	3h, reflux	66.6%
2	CH_3	70 mg	2.6	5h, reflux	55%
3	CH_3	1.2 g	2.6	2h, reflux	83%
4	$CH_2CH{=}CH_2$	50 mg	2.6	3h, reflux	64%
5	$CH_2CH{=}CH_2$	150 mg	2.6	3h, reflux	81 %
6	$CH_2CH{=}CH_2$	600 mg	2.6	3h, reflux	84%

Conditions for generating the thioesters **9a/b** employing potassium thioacetate, are covered in litterature.[6,8,9] Due to the tosyl group being a stable and effective leaving group, relatively mild conditions could be utilized in absolute ethanol, without the use of a catalyst.

Initial yields were somewhat lower than reported in literature. Following the reaction by HPLC over a period of 5 hours, all starting material was consumed after 2 hours showing,

only one new product formed. This indicated that the low yields were due to problems in workup or in the purification.

Loss of product was discovered to be caused by inefficient extraction and mechanical loss during workup (Entries 1 and 4). This was, however, countered with increasing extraction volumes and by extracting from a larger amount of water, leaving less product left in the aqueous water/EtOH phase.

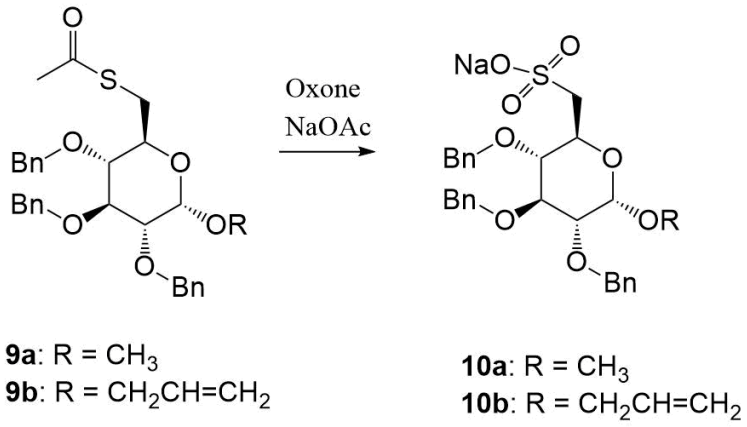
Purification was done successfully on silica column, using a gradient starting with 1:10 and increasing to 1:6 EtOAc:*n*-pentane, which yielded compound **9a/b** as a orange/yellow substance, with an extremely potent odour.

3.2.2 Oxidation of thioester derivates 9a and 9b

As presented in section 2.5, several oxidation reagents have been used in the oxidation of thioacetates.[62,63,88] Potassium peroxymonosulfate (Oxone)[63] was chosen due to relatively mild reaction conditions, ease of use, and lastly due to its potential use to further oxidise the alkene moiety[89] covered in the Future work section.

The first small scale oxidation reactions of thioacetates **9a/b** into sulfoquinovose derivates **10a/b** were performed according to literature for **9a**.[6,9] To the best of our knowledge, compound **10b** has not been described in literature, but assuming the effects of the anomeric substituent to be relatively small, the same conditions were applied for both substrates. Oxone, has however been used on similar compounds to, where the allyl group has been oxidized, prior to the oxidation of the thioacetate.[4,90] This will be discussed further in section 5.

The results from the oxidation of **9a/b** are presented in Table 9.



9a: R = CH_3
9b: R = $CH_2CH{=}CH_2$

10a: R = CH_3
10b: R = $CH_2CH{=}CH_2$

Scheme 27: Oxidation of **9a/b** using Oxone(potassium peroxymonosulfate) and sodium acetate.

Table 9: Oxidation reactions on **10a/10b**. All reactions are performed in glacial AcOH and quenched with Na_2CO_3 and $NaHCO_3$. Entry 10 was added 5 ml water to the reaction mixture.

Entry	**R**	**Scale [Eq]**	**Oxone [Eq]**	**NaOAc [Eq]**	**Reaction time/temp**	**Yield [%]**
1	CH_3	200 mg	4	20	8h, r.t	43%
2	CH_3	100 mg	4	20	8h, r.t	76 %
3	CH_3	200 mg	6	20	20h, r.t	76%
4	CH_3	125 mg	5	20	12h, r.t	75%
5	CH_3	125 mg	5	20	12h, r.t	84%
6	$CH_2CH{=}CH_2$	200 mg	4	20	8h, r.t	~ 32%
7	$CH_2CH{=}CH_2$	120 mg	5	20	12h, r.t	~ 63%
8	$CH_2CH{=}CH_2$	500 mg	5	20	12h, r.t	~ 77%
9	$CH_2CH{=}CH_2$	120 mg	4	20	12h, r.t	~ 67%
10	$CH_2CH{=}CH_2$	100 mg	4	20	12h, r.t	0%

Due to the large change in polarity and the ionic nature of the products **11a/b**, the crude product could not be analysed by standard reverse-phase HPLC. TLC was used to monitor the disappearance of compound **9a/b** to scope the reaction progress**.** Further literature search and experimentation revealed a potential problem in the workup procedure. After quenching the reaction with $NaHCO_3$, Na_2CO_3 and water, the literature procedures reported using EtOAc to extract the product. It has, however, been found in other sources that the formed sulfonates are soluble only in water and a few water-miscible organic solvents.[63] This may provide some explanation for the low yields observed in the first reactions, done for the allyl and methyl

thioesters **9a/b** (Entries 1 and 6). Further solubility testing of compound **10a/b** isolated from the first reactions revealed low to no solubility in EtOAc. Although extraction in EtOAc in theory still should work, as saturated solutions of $NaHCO_3$ and Na_2CO_3 are used to force the compound into the organic layer, it is likely an inefficient method of workup, especially when working in larger scales.

Two alternative methods of workup were developed based on the compounds' ionic character and insolubility in conventional organic solvents.

Based on experimentation with several solvents, compounds **10a/b** were found to be highly soluble in acetonitrile, while the carbonates and reagents used, were observed as insoluble. While extraction in this solvent would be unfeasible, due to its miscibility with water, cold filtration of a completely dry crude product after quenching would allow for separation of the product and other organic by-products from the reagents. Using a freeze dryer, the reaction mixture was quenched and subsequently dried over three days removing all solvents. The mixture was stirred with cold acetonitrile and filtrated three times. The acetonitrile was then removed to yield the crude product. Recovered yields were substantially increased by employing this method of workup (Entries 2, 3 and 5).

Another method of workup was developed based upon converting the sulfoquinovose derivatives from their salt to acids form by workup and extraction in acidic conditions. After quenching, the mixture was added HCl (37%) to make the solution acidic enough to protonate the sulfonic acid moiety. The exact pK_a of the sulfoquinovose derivative is not known, but using pK_a of similar compounds,[91] the pH needed to force the protonated form was determined to around pH= 1. The motivation for exploring this second way of workup was, in addition to the separation from reagents, the possibility of analysing the acid derivative on HPLC and NMR using the same conventional methods as for the previous derivatives. The process proved effective as a method of workup, yielding compounds **10a** in 75% yield (Entry 4). Conventional reverse-phase HPLC was employed initially to analyse the mixture, but proved unsuccessful. This is likely due to the ACN/H_2O system deprotonating the acid, reverting it to its sulfate form. HPLC analysis of sulfonic acid derivatives have been successfully employed using acid (FA) as additive in the eluent system.[69]. This, however, led to substantial baseline drift when applied in the analysis and could not be used as a method for monitor the reaction. This will be discussed further in the section concerning analysis of compound **10b**.

Lastly, another possible problem with this workup method was the strong acidic conditions needed, and thus the requirements they put on protection groups employed. Benzyl ethers are, in theory, robust enough to survive the acidic workup, but seeing other protection groups will be employed in the research project, these would also have to be as resilient. For instance, working with TBDMS ethers would not be suited in this method due to their liability to low pH in aqueous conditions.[39] For these reasons, as well as lower collected yields, the workup method was deemed less effective than freeze drying.

Tuning of the reaction time seemed to have little effect on observed yields for **10a**, with full conversion observed at 8 hours on TLC (Entry 2). Stability of other moieties on the compounds, as well the sugar rings stability to harsh oxidative conditions, were, however, of interest. For this reason, the effect of employing harsher conditions, using more equivalents of Oxone, and longer reaction times were explored (Entry 3). No effect was seen upon the sugar ring or other functionalities in the molecule, further demonstrating the mild nature of Oxone as a oxidant and the combability with carbohydrates and benzyl ethers.[4,6,9,63]

Sulfoquinovose derivative **10a** was successfully isolated using flash chromatography, employing a short silica plug, eluting with a gradient of EtOAc:*n*-pentane and lastly with 1:5 MeOH:EtOAc, yielding **10a** with no additional by-products observed.

Oxidation of **9b** proved less effective than for the corresponding methyl thioacetate. As mentioned above, the initial low yields were due to the efficiency of workup and was as for compound **10a,** substantially increased using the new methods of workup. In addition, similarly to compound **10a**, utilizing the freeze-drying method (Entries 8 and 9) was observed as a more effective method, than acidic workup in procuring the crude product (Entry 7).

Assuming thioester **9a** to be a good model substrate for the reaction, and due to little observable difference between the methyl and allyl analogs in the two previous reactions, conditions used in oxidation of **9a** were applied, and purification using silica was believed to be effective. For all reactions of **9b**, separation on silica was unsuccessful, yielding a mixture of compounds with similar polarity. Several eluent systems were tested, each proving fruitless. This is in accordance with literature, describing purification of sulfonic acid derivatives as problematic employing flash chromotography.[68,92] Although **10a** was successfully isolated, the observed purity of the collected product may be explained by to the absence of by-products, and not successful separation.

Sulfoquinovose derivative **10b** was identified both in NMR and on MS as the main product, but several additional compounds, with similar carbon and proton shifts, were observed by NMR. The yields given in Table 9 have been somewhat adjusted based on present impurities detected by ^{1}H-NMR. In order to get a clearer picture, and to possibly employ preparative HPLC to collect pure samples of the products, the HPLC method was modified by addition of 0.1% FA in the mobile phase in an attempt to keep the acid protonated on the column attempting to analyse the product on both salt and acid form. The same problems as for **10a** were, however, encountered, with substantial drift of the baseline, and no observable peaks. HPLC analysis of **10b** on its salt form was attempted using a different method, starting with 95% water in ACN for one hour, and gradually increasing the gradient to 95% ACN over a period of two hours. This was believed to effectively elute the salt, due to its solubility in water due to its ionic character. After an additional 30 min at 95% ACN no peaks were observed.

A possible explanation for the observed variety in yields and by-products from the oxidation reactions may be the proposed role of water in the mechanism. The mechanism of Oxone is described in detail in section 2.5. The addition of water has shown to increase the rate of the reaction substantially, as it may act as a nucleophile in the decarboxylation step.[64] The same article describes the reaction as extremely sensitive to the amount of water present in the solvent. Although all reactions were performed in dry conditions, trace amounts of water may, based on this theory, account for the variation in recovered yields observed employing otherwise similar conditions and workup. This cannot in itself explain the difference observed in working with the allyl and methyl thioesters **9a/b**, but was explored further.

Following the hypothesis that compound **9b** had not been fully oxidised, possibly explaining the observed by-products, water was added to the reaction mixture to test its effect (Entry 10). Workup and purification was performed using the freeze-drying method and were performed using the same amounts of reagents as for previous reactions. NMR analysis of the crude product revealed unexpected side reactions on other sites of the molecule, yielding a mixture of by-products and no observable amounts of the desired product **10b,** nor the starting material **9b**. Detailed analysis of the products were not carried out, but the allylic protons could not be observed in ^{1}H-NMR, indicating cleavage of the anomeric substituent. Due to time constraints, and having spent most of the starting material **9b**, further experimentation of the effect of water was not prioritized. From working with similar compounds, literature reports have suggested that longer reaction times, up to 72 hours, in dry conditions, may yield

better results in the oxidation reaction.[4] This would be a logic step in further investigating this reaction.

Due to the unsuccessful purification of **10b,** a pure sample for NMR analysis could not be obtained, addressed further in section 3.6.2.

In summary, the thioester derivate **9a** was successfully oxidised and isolated on silica to yield **10a.** Oxidation of **9b** resulted in a mixture of products, not separable on silica. HPLC of the isolated products was attempted on both salt and acid form, employing conventional eluents, systems with an acid additive, as well as highly polar eluent systems, in an attempt to understand the observed mixture of products. The findings from work with the oxidation of **9b** suggests that further protection may be necessary for successful purification and characterization. This conclusion is backed up by similar findings in the literature, describing the purification of similar compounds as problematic.[68,69,92] Further experimentation in developing an HPLC method for analysis of the products would likely give better insight into by-products, the course of the reaction as well as preparative sepparation. Capillary electrophoresis might be an effective way of analytical separation, and has previously been used to analyse mixtures of carbohydrates, containing sulfonic acid moieties.[25,27] This was, however, as covered, not possible due to time constraint.

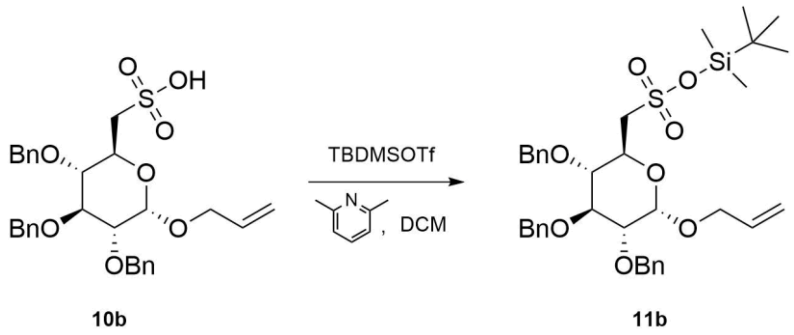
Due to the extensive use of silyl ethers as protection groups in other work on the project,[38,56] the possibility of protecting the introduced sulfonic acid moiety as a silyl sulfonate was of great interest to the project.

3.2.3 Protection of the sulfonic acid moiety

While TMS has previously used as a temporary protection group of sulfones,[70] protection of sulfoquinovose derivates and sulfonic acids as permanent silyl ethers are, to the best of our knowledge, not described in literature. In theory,[50,51] the sulfoquinovose derivate **10a/b** can be stirred with a silylation agent in basic conditions, to protect the acid moiety as a silyl ether. Due to the extensive use of TBDMS ethers elsewhere in the project, and due to its relative ease of introduction on alcohols, the introduction of TBDMS on the sulfate group was explored.

The silylation was attempted on the crude mixture of allyl sulfoquinovose derivative **10b** after acidic workup. Other work in the project, experimenting with introduction of silyl ethers found TBDMS triflates as superior reagents for introducing the TBDMS protection group

onto both primary and secondary hydroxyl groups.[38] For this reason, TBDMSOTf was chosen as silylation agent for the initial reaction. The results are displayed in Table 10.



Scheme 28: Protection of the sulfonic acid moiety on **10b** using TBDMSOTf, lutidine in DCM.

Table 10: Result from the silylation of the sulfonic acid moiety on compound **10b**. The reaction is performed in Pyridine.

Entry	**Scale**	**R**	**TBDMSOTf [Eq]**	**Lutidine [Eq]**	**Conditions**	**Yield [%]**
1	100mg	$CH_2CH{=}CH_2$	1.4	2	8h at 0°C	0%

Due to time constraints and the consumption of substrate **9b,** only one reaction as a proof of concept was attempted.

Pyridine was chosen as a solvent, together with lutidine to deprotonate the sulfonic acid. The findings from NMR were, however, non-conclusive, showing a mixture of compounds, including the substrate 10b. Shifts from the silyl group were observed in the spectrum, but could not be assigned without further purification. Assuming the protected compound would have properties allowing for HPLC separation, a method preparative HPLC was employed in an attempt to isolate the product. The instrument and method used, is listed in the experimental section. The results revealed several peaks, too scant for analysis, with one larger peak at t_R = 11.23 min. NMR analysis revealed this peak to be a degradation product. Further analysis on NMR and confirmation by MS proved this compound to be the Allyl 4,6-*O*-benzylidene-*α*-*D*-glucopyranoside (**5b**).

It seems most probably that somehow either the oxidation, the acidic workup, or the following reaction with TBDMSOTf caused the degradation. The by-product could not be observed on HPLC of **10b** on its salt or acid form, nor in its NMR spectrum. This indicates that the unwanted reaction occurred as a side reaction in the attempted silylation. However, this is

uncertain due to the problems in HPLC analysis of these compounds, as described in section 3.2.2. The sulfonic acid moiety is a strong acid, and is known to potentially cause side reactions.[92] A possible explanation for the observed results is intermolecular reactions between the sulfonic acid and the benzyl ethers on adjacent molecules, known to be liable to some strong acids.[39] Through what mechanism, is, however, not known, and would need further research to verify. The findings do, however, indicate that it may not be favourable to convert the compounds to their acid form for analysis or further work.

Compound **11b** could not be isolated from the reaction mixture, indicating that the reaction was either unsuccessful, or that the yield was too low to be observed. As mentioned in section 2.5, several protection groups have been developed and shown to be efficient in protecting sulfonic acid moietyes. These groups would all likely better suited for our purposes, but as explained above, protecting all moieties on the molecule as silyl ethers would allow for simultaneous deprotection of several sites, therefore being of great interest to the research group.

The results from the attempted protection of the sulfonic acid moiety with TBDMS, may be explained by the character of a potentially formed Si-O-S bond. Sulfur is in itself considerably more electronegative than silicon, with a value of 2.58 on the Pauling scale in comparison to silicone with 1.90.[93] This will in effect shorten the O-S bond, and lengthen the Si-O bond. This is supported by the frequent use of reagents such as dimethyl sulfate[94] and methane sulfonate[95] as potent alkylation agents. While the driving force behind the alkylating properties of these compounds is the difference in strength in the S-O and the C-O bond, the difference is even larger in the case of silicone, strengthening the theory that silyl ethers are unfit protection groups for the sulfonic acid moiety. This corresponds well to the known trend in silyl ether stability; more electronegative and bulky substituents on the silicone, strengthen the Si-O bond. Protection groups such as trichloroethyl (TCE)[92] and trifluoroethanol (TFE)[69] are likely more effective, due to the presence of highly electronegative groups on the carbon, in effect strengthening the C-O bond. Based on these assumptions, the sulfoquinovose derivates **10a/b** will likely have to be protected with one such group. This will be discussed further in section 5.

3.2.4 Stability testing of silyl ethers

Benzyl ethers were observed as suited protection groups working with Oxone, being resilient to the acidic conditions employed in the oxidation as well as the oxidant itself. The proposed

strategy towards the total synthesis project entails working with both silyl and benzyl ethers. Thus, the stability of silyl ethers in the same conditions are of great interest.

Silyl ethers stability in acidic conditions are, as covered in section 2.4.2, dependent on the size, and electronegative nature of the substituents on the silicone. TBDMS has been shown to liable to low pH >1 in aqueous conditions at room temperature,[39] and may therefore be labile to the acidic conditions used in the oxidation, in addition to the oxidation reagent used itself. Although no water is present, and therefore the exact pH of the conditions is hard to predict, the conditions are undoubtfully highly acidic.

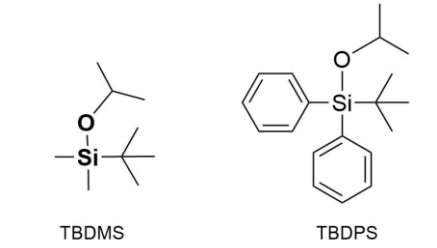
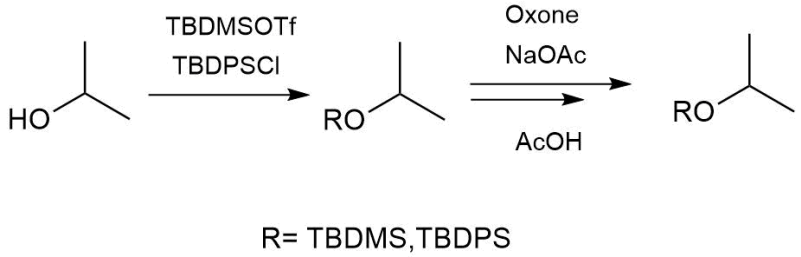


Figure 7: TBDMS and TBDPS model substrates employed.

For this reason, model substrates of two different silyl ethers (Figure 7) were prepared from isopropanol using known procedures (Scheme 29).[50,51,56] TBDMS was chosen for obvious reasons, while the second more bulky silyl ether, tert-butyl diphenyl silane (TBDPS) was tested due to its proven stability.[50] Quenching of the reaction mixtures was performed in the exact same way as in the oxidation of **9a/b**, but due to the compounds being highly soluble in DCM, extraction was sufficient as means of workup. The results are displayed in Table 11.



Scheme 29: Generation of silyl ether protected model substrates using isopropanol. 1.5 equivalents of the silyl ether and 2.5 Eq lutidine was employed. Oxidation conditions are displayed in Table 11.

Table 11: Results from the stability testing reaction of TBDMS and TBDPS protected isopropanol. The reactions were run using the same conditions as for **9a/b** employing AcOH as solvent.

Silyl ether	**Oxone [Eq]**	**NaOAC [Eq]**	**Conditions**	**Stability**
TBDMS	5	20	20h, r.t	Stable
TBDPS	5	20	20h, r.t	Stable

Both compounds were purified on silica and analyzed by NMR to verify their structures before being subjected to the conditions listed in Table 11. In addition, HPLC chromatograms

of the compounds were compared. HPLC results recorded before and after being subjected to the oxidation conditions, are displayed in Figure 8. In addition, ^{1}H-NMR was used to verify the integrity of the structures.

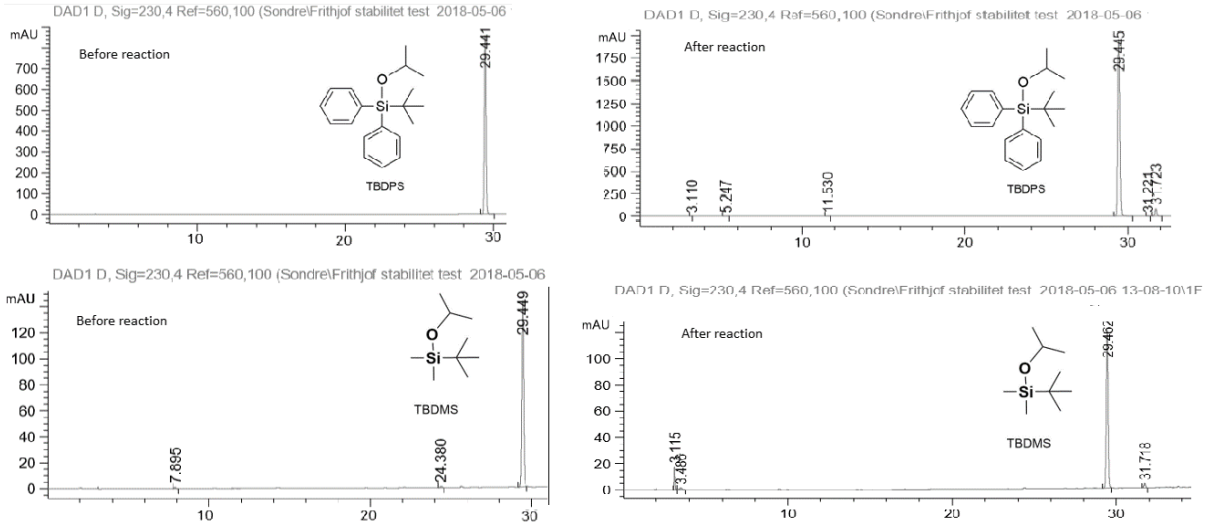


Figure 8: HPLC analysis of the TBDMS and TBDPS protected model substrates before and after being subjected to the oxidation conditions.

The silyl ethers were found to be robust enough to withstand the conditions employed in oxidation of **9a/b**, verified by HPLC results and ^{1}H-NMR. Being model substrates, this is in itself not enough to with full confidence predict the stability of these protection groups when employed on a sugar backbone, but is a strong indication of their compatibility with Oxone and concentrated acetic acid, as well as addition of the aqueous buffer system employed in the quench. Allyl and methyl 2,3-di-*O*-TBDMS-4,6-benzylidene glucopyranoside derivates are, during the writing of this thesis, being synthesised elsewhere in the project for further testing of the TBDMS group when on the sugar backbone.

In summary, working with methyl glucosides employing benzyl ether protecting groups were observed to withstand the conditions employed in oxidation of the thioester moiety. Trial stability testing of TBDMS and TBDPS were observed to withstand the conditions on model substrates.

Lastly, difficulties in the purification, as well as observed by-products indicate that the allyl substituent may be unsuited for reactions involving Oxone. For this reason, the order of functionalization may entail oxidation and protection of the allyl group, before oxidation of

the thioester to its corresponding sulfoquinovose. Oxidation of the allyl substituent, prior to functionalisation of C-6 has been reported in literature.[4] This will be discussed further in the Future work part of the thesis.

3.3 Compound Characterization

In this section characterization of compounds **5-10a** and **5-10b** will be presented. In addition, the results will be compared to values available in literature, and outliers will be discussed.

Compounds were analyzed with ^{1}H-NMR, ^{13}C-NMR and with necessary 2-D experiments to assign all carbons and protons where possible. On some compounds HSQC-TOCSY methods and HSQC with increased resolution was employed for characterization of benzylic protons and ^{13}C atoms. This was, however, not possible for all compounds, due to overlapping signals in the benzylic region. This is denoted as n.r (not resolved). The results from the characterization of the methyl glucosides are presented in section 3.3.1, while the allyl glycosides are presented in section 3.3.2.

NMR data for the intermediates **3-4a/b** are not given in this section, due to factors discussed in section 3.1.2 and comprehensive NMR data available in literature for the relevant compounds.[28,32,96,7]

3.3.1 NMR data for compounds **5**-1**0a**

An overview of spectroscopic data available in literature for compounds **5-10a** is displayed in Table 12. Though several sources have been found for most compounds, only those judged to be of high quality and detail have been included. A check mark indicates the data to be found in literature assigned to specific positions, while the cross indicates only shifts are given without assignment. Check with a following minus indicates that the data is either incomplete, or differ from the assignment done in this thesis.

Table 12: Overview of NMR data on compounds 5-10a in literature. A checkmark indicates full assignment and the cross incomplete or non-existent. Check followed by a minus denotes incomplete data or deviation from assignment done in the thesis.

	Found in literature		
Compound	^{1}H shifts	^{13}C shifts	Assignment
5a[73]	✓	✓	✓-
6a[73]	✓	✓	✓-
7a[3]	✓	✓	✓-
8a[84]	✓	✓	✓-
9a[85]	✓	✓	✓-
10a[9]	×	×	×

^{13}C shifts for methyl glucosides **5a-10a** are displayed in in Table 13, and corresponding proton shifts are given in Table 14. The molecules' structures and the numbering of the sugar skeleton as well as substituents are shown in Figure 10. Observed coupling constants between protons in the sugar ring are displayed in Figure 9. Resolved coupling constants can be found in the experimental section and will not be discussed in length here. Each spectrum, as well as MS and IR results are to be found in the appendix section.

For all compounds but **7a**, structure elucidation yielded the same assignment as that found in literature. Some improvements were, however, accomplished in some cases resolving multiplicities of the protons on C-5 and C-6, missing in several sources, due to overlapping signals. In addition, assignment of shifts and multiplicities for H-2 and H-4 for compound **8a** could not be found. The same overlap was observed using a 400 MHz proton channel, but both signals were distinguishable in a higher resolution spectrum obtained from using a 600 MHz instrument.

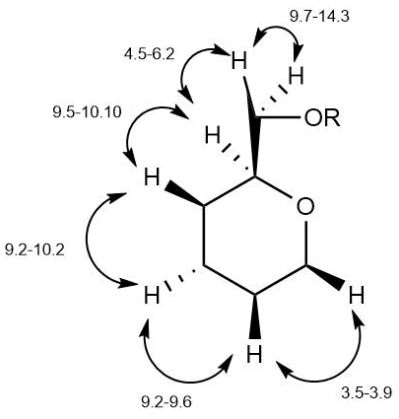


Figure 9. Observed coupling constants between protons in the sugar backbone

One inconsistency was found in the assignment of shifts of compound **7a**. The only source found to fully assign all proton and carbon shifts[3] reported H-4 as the triplet observed at 4.01 ppm in the spectrum (Appendix C, Figure C.2), while assignment done in this thesis placed this shift as H-3. Clear correlation was observed in COSY (Appendix C, Figure C.3) between H-2 at 3.49 ppm and the triplet at 4.01 ppm, while no such correlation could be seen from 3.49 ppm to 3.52 ppm. Due to this observation, reported assignment for **7a** differs from that in literature on this point.

Lastly, all compounds except **8a** were lacking assignments of the benzylic CH_2 groups, as well as placement of carbons and protons in the benzyl ether protection groups. Benzylic protons, as well as quaternary carbons on the benzyl ring could be assigned from standard HSQC and HMBC experiments. Full characterization of protons and carbons in the benzylic region was successful for **6a** and **7a**, using HSQC-TOCSY experiments along with increased resolution HSQC (shortened spectral width). For compounds **8a**,**9a**,**10a** shifts could not be assigned in this region due to overlapping signals.

^{13}C and proton shifts for compound **10a** were found in literature[6,9], but no full characterization exists to the best of our knowledge. Due to the ionic character of the compound, NMR experiments could not be done in $CDCl_3$, but were instead analyzed in CD_3OD. The water peak observed at 4.87[97] was used to calibrate the spectrum, enabling full characterization.

Table 13: ^{13}C-NMR chemical shifts (δ, ppm) of 5a-10a in $CDCl_3$ using TMS as an internal standard. Compound 10a was recorded in CD_3DO. Shifts denoted n.r could not be determined due to overlap in the benzylic region.

	5a	**6a**	**7a**	**8a**	**9a**	**10a**
Carbon						
1	99.7	99.3	98.2	98.0	97.9	98.5
2	72.9	79.2	77.5	76.8	80.0	81.6
3	71.8	78.6	82.0	81.8	81.9	83.1
4	80.9	82.1	80.0	79.7	80.5	81.7
5	62.4	62.3	70.8	68.5	69.4	68.5
6	68.9	69.1	61.8	68.6	30.9	53.9
7	55.6	55.3	55.2	55.4	55.2	55.9
4-OBn						
1^1	101.9	101.3	75.1	75.0	75.2	75.8
2^1	137.0	137.4	138.1	137.8	137.9	139.6
3^1	129.3	126.0	128.1	128.1	128.1	128.9
4^1	128.3	128.2	128.5	128.5	128.1	128.9
5^1	126.3	128.9	128.0	127.9	127.6	128.6
2-OBn						
1^2		73.8	73.4	73.5	73.4	73.9
2^2		138.2	138.2	137.9	138.0	139.6
3^2		128.1	128.1	n.r	n.r	n.r
4^2		128.6	128.5	n.r	n.r	n.r
5^2		127.9	127.9	n.r	n.r	n.r
3-OBn						
1^3		75.34	75.7	75.7	75.8	76.4
2^3		138.7	138.7	138.5	138.6	140.1
3^3		128.	128.0	n.r	n.r	n.r
4^3		128.3	128.4	n.r	n.r	n.r
5^3		127.6	127.6	n.r	n.r	n.r
TsO/SAc						
1^4				144.8	194.9	
2^4				129.8	30.6	
3^4				127.9		
4^4				132.9		
5^4				21.3		

Tabell 14: ^{1}H NMR chemical shifts (δ, ppm) of 5a-10a in $CDCl_3$ using TMS as an internal standard. Compound 10a was recorded in CD_3OD calibrated to the water peak. Where a range is indicated, individual protons could not be determined due to overlap in the benzylic region. Multiplicity are given for protons in the sugar skeleton and anomeric substituent.

	5a	**6a**	**7a**	**8a**	**9a**	**10a**
Hydrogen						
1	4.79 (d)	4.59 (d)	4.56 (d)	4.51 (d)	4.53 (d)	4.73 (d)
2	3.63 (dd)	3.55 (dd)	3.49 (dd)	3.47 (dd)	3.50 (dd)	3.57 (dd)
3	3.93 (t)	4.04 (t)	4.01 (t)	3.94 (t)	3.96 (t)	3.80 (t)
4	3.49 (t)	3.60 (t)	3.52 (t)	3.40 (t)	3.30 (t)	3.24-3.31 (m)
5	3.81 (td)	3.82 (td)	3.70 (m)	3.76 (ddd)	3.75 (td)	4.16 (td)
6a	4.29 (dd)	4.26 (dd)	3.75 (dd)	4.18 (m)	3.42 (dd)	3.24-3.31 (m)
6b	3.75 (dd)	3.70 (t)	3.65 (m)	4.12 (dd)	3.02 (dd)	2.91 (dd)
OMe	3.46 (s)	3.40 (s)	3.34 (s)	3.30 (s)	3.35 (s)	3.37 (s)
4-OBn						
C-1a^{1}	5.53	5.49	4.86	4.81	4.88	4.87
C-1b^{1}	-	-	4.62	4.43	4.61	4.64
C-2^{1},6^{1}	7.47-7.49	7.50	7.34	7.32	7.35	7.37
C-3^{1},5^{1}	7.31-7-41	7.40	7.38	7.38	7.36	7.36
C-4^{1}	7.31-7-41	7.39	7.32	7.34	7.30	7.28
2-OBn						
C-1a^{2}		4.85	4.77	4.77	4.78	4.69
C-1b^{2}		4.69	4.46	4.62	4.67	4.67
C-2^{2},6^{2}		7.39	7.40	7.27-7.36	7.29-7.35	7.24-7.40
C-3^{2},5^{2}		7.35	7.37	7.27-7.36	7.29-7.35	7.24-7.40
C-4^{2}		7.38	7.34	7.27-7.36	7.29-7.35	7.24-7.40
3-OBn						
C-1a^{3}		4.83	4.97	4.96	4.96	4.93
C-1b^{3}		4.51	4.82	4.79	4.80	4.75
C-2^{3},6^{3}		7.41	7.41	7.27-7.36	7.29-7.35	7.24-7.40
C-3^{3},5^{3}		7.32	7.37	7.27-7.36	7.29-7.35	7.24-7.40
C-4^{3}		7.29	7.33	7.27-7.36	7.29-7.35	7.24-7.40
TsO/SAc						
1^{4}				-	2.32	
2^{4}				7.76		
3^{4}				7.16		
4^{4}				-		
5^{4}				2.39		

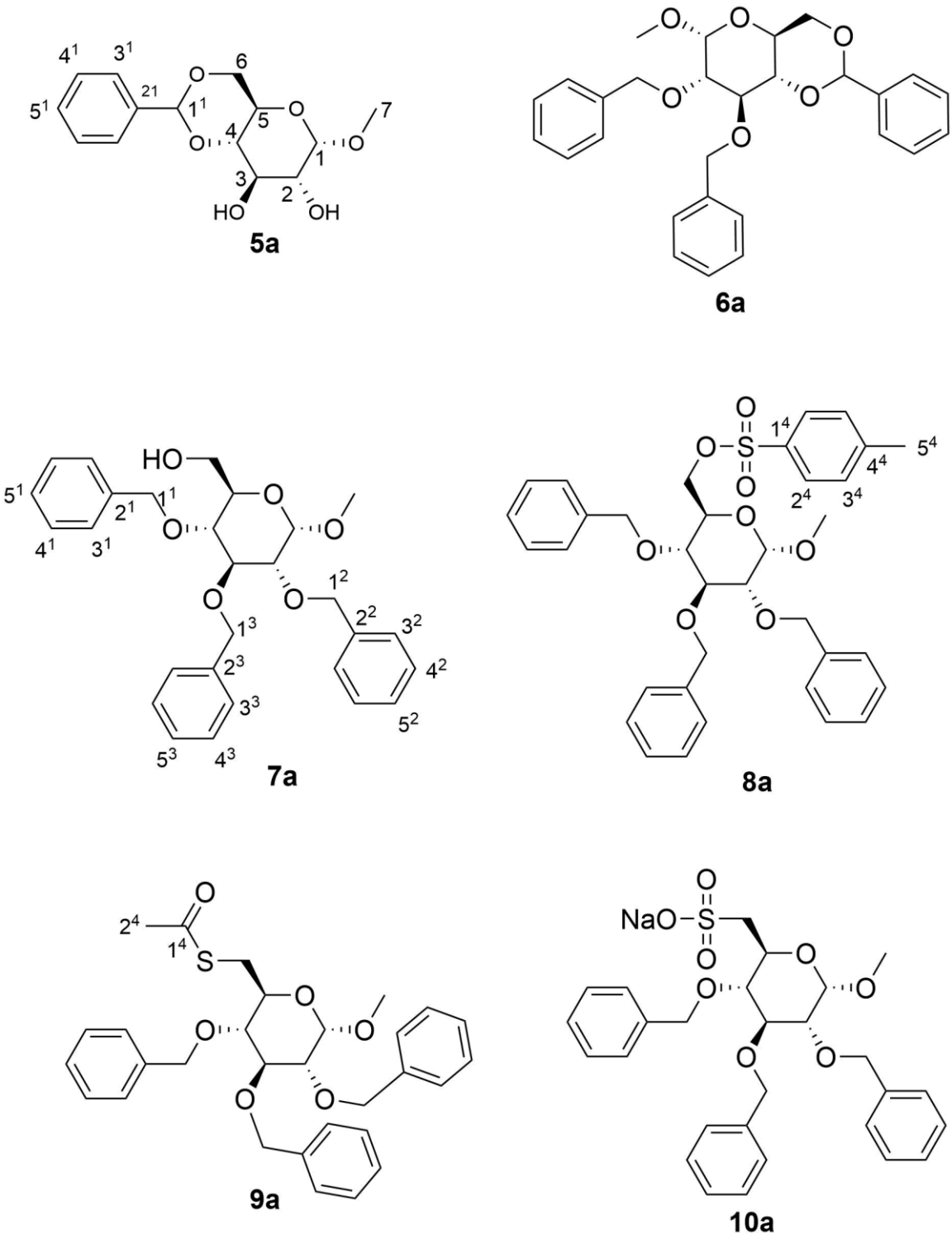


Figure 10. Compounds **5-10a** with numbering of carbon skeleton and substituents. NMR data for the compounds are given in table 13 and 14.

3.3.2 NMR data for compounds **5-10b**

An overview of spectroscopic data available of compounds **5-10b** in literature is displayed in Table 15. Though several sources have been found for most compounds, only those judged of high quality and detail have been included. A check mark indicates the data to be found in literature, assigned to specific positions while the cross indicates only shifts are given, without assignment. Check with a following minus indicates that the data is either incomplete, or differ from the assignment done in this thesis.

Table 15. Overview of NMR data on compounds 5-10a in literature. A checkmark indicates full assignment and the cross incomplete or non-existent. Check followed by a minus denotes incomplete data or deviation from assignment done in the thesis.

	Found in literature		
Compound	^{1}H shifts	^{13}C shifts	Assignment
5b[74]	✓	✓	✓-
6b[58]	✓	✓	✓-
7b[4]	✓	✓	✓
8b[4]	✓	✓	✓
9b[98]	✓	×	✓-
10b	×	×	×

The ^{13}C shifts for methyl glucosides **5-10b** are displayed in in Table 16, and corresponding proton shifts are given in Table 17. The molecules' structures and the numbering of the sugar skeleton as well as substituents are shown in Figure 12. Observed coupling constants between protons in the sugar ring are displayed in Figure 11. Resolved coupling constants can be found in the experimental section and will not be discussed in length here. Each spectrum, as well as MS and IR results, are to be found in the appendix section.

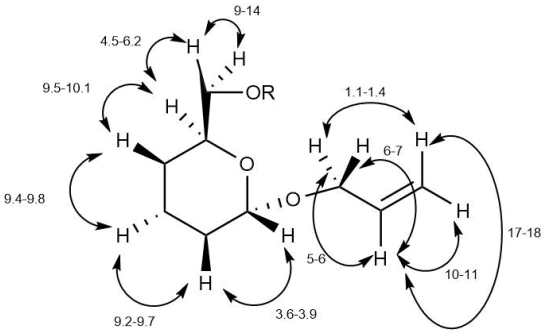


Figure 11. Observed coupling constants between protons in the sugar backbone and in the anomeric substituent.

In general, NMR data available for the allyl derivates were of higher detail than that of the corresponding methyl derivates. For compound **5b** and **6b** proper multiplicity and coupling details between the allylic protons could not be found in literature. This thesis provides more details about shift and multiplicity of the allylic protons, so they could be discerned. For compound **5-10b**, the multiplicity of the terminal allylic CH_2 could not be determined. Though observed as a possible doublet of quartets (dq), or as doublet of doublets of triplets (ddt), the shifts are for this reason reported as multiplets. The

same problem was encountered for the allylic O-CH_2 group. Although resembling a doublet of doublets of triplets (ddt), the multiplicity could not with certainty be determined. The O-CH_2 and terminal CH_2 shifts are in literature reported respectively as ddt and dq.[4] Employing experiments such as *J*RES may have allowed for better resolving of these shifts, but were not deemed a priority in this thesis.

In addition, as for the methyl derivates, for most compounds, assignment of benzylic protons could not be located in literature. Assignment of these shifts, as well as quaternary carbons on the benzyl substituents, were resolved by conventional HSQC and HMBC experiments, and were observed as similar to those in the corresponding methyl derivates, in terms of shifts. Full assignment of protons and carbons in the benzylic region was successful for **6b** and **7b**, using HSQC-TOCSY experiments together with increased resolution HSQC (with a reduced spectral width). For compounds **8b** and **9b**, shifts could not be assigned (as for the methyl derivates) in this region, due to overlapping signals. Full assignment of carbon shifts could not be found for compound **9b** in literature, but were successfully assigned in this work.

As discussed in section 3.2.2, compound **10b** could not be purified. ^{1}H-NMR assignment was however possible, even in a mixture of by-products due to sufficient correlation observed for crucial shifts. MS confirmed the structure, and where uncertain, the shifts were assigned by comparison to those in **10a**. The assignment should, however, be viewed as tentative. Due to overlap in the ^{13}C spectra, carbon assignment could not be performed.

Tabell 16: ^{13}C-NMR chemical shifts (δ, ppm) of 5b-10b in $CDCl_3$ using TMS as an internal standard. Compound 10b was recorded in CD_3DO. Shifts denoted n.r could not be determined due to overlap in the benzylic region.

	5b	**6b**	**7b**	**8b**	**9b**
Carbon					
1	97.9	96.8	95.6	95.5	95.2
2	72.9	79.3	80.0	79.7	79.9
3	71.8	78.6	81.9	81.8	81.8
4	80.9	82.2	77.4	77.3	80.6
5	62.6	62.5	70.9	68.7	69.5
6	69.9	69.0	61.9	68.6	30.9
7	69.8	68.5	68.3	68.3	68.1
8	133.3	133.6	133.7	133.5	133.5
9	118.3	118.4	119.2	118.4	118.4
4-OBn					
1^1	101.9	101.3	75.1	75.03	75.2
2^1	137.1	137.4	138.1	137.9	133.9
3^1	126.3	126.0	127.8	n.r	127.8
4^1	128.3	128.2	128.5	n.r	128.2
5^1	129.3	128.9	127.6	n.r	127.9
2-OBn					
1^2		73.6	73.3	73.3	73.2
2^2		138.2	138.2	138.0	138.1
3^2		128.1	128.1	n.r	n.r
4^2		128.4	128.4	n.r	n.r
5^2		127.9	127.9	n.r	n.r
3-OBn					
1^3		75.4	75.7	75.7	75.7
2^3		138.8	138.8	138.6	138.7
3^3		128.0	127.9	n.r	n.r
4^3		128.3	128.5	n.r	n.r
5^3		127.6	127.6	n.r	n.r
TsO/SAc					
1^4				144.8	194.9
2^4				128.0	30.5
3^4				127.9	
4^4				132.9	
5^4				21.6	

Tabell 17: ^{1}H NMR chemical shifts (δ, ppm) of 5b-10b in $CDCl_3$ using TMS as an internal standard. Compound 10b was recorded in CD_3OD. Where a range is indicated, individual protons could not be determined due to overlap in the benzylic region. . Multiplicity are given for protons in the sugar skeleton and anomeric substituent.

	5b	**6b**	**7b**	**8b**	**9b**	**10b**
Hydrogen						
1	4.94 (d)	4.80 (d)	4.78 (d)	4.70 (d)	4.73 (d)	4.88 (n.r)
2	3.63 (td)	3.56 (dd)	3.50 (dd)	3.47 (dd)	3.51 (dd)	3.59 (dd)
3	3.95 (t)	4.07 (t)	4.03 (t)	3.97 (t)	3.99 (t)	3.97 (t)
4	3.49 (t)	3.61 (t)	3.53 (t)	3.45 (dd)	3.31 (t)	3.33 (m)
5	3.84 (td)	3.88 (td)	3.70 (m)	3,81 (ddd)	3.81(ddd)	4.22 (td)
6a	4.26 (dd)	4.25 (dd)	3.76 (dd)	4.22 (dd)	3.42 (dd)	2.90 (dd)
6b	3.73 (t)	3.70 (t)	3.70 (m)	3.93 (m)	3.00 (dd)	3.33 (m)
7a	4.26 (m)	4.18 (m)	4.13 (m)	4.07 (m)	4.15 (m)	4.36 (m)
7b	4.05 (m)	4.03 (m)	4.00 (m)	3.93 (m)	3.97(m)	4.04 (m)
8	5.92 (dddd)	5.90 (dddd)	5.90 (dddd)	5.90 (dddd)	5.91(dddd)	5.95 (dddd)
9a	5.33 (m)	5.33 (m)	5.21 (m)	5.27 (m)	5.31 (m)	5.43 (m)
9b	5.25 (m)	5.23 (m)	5.30 (m)	5.19 (m)	5.22 (m)	5.21 (m)
4-OBn						
C-1a^{1}	5.53	5.56	4.88	4.82	4.88	4.88
C-1b^{1}	-	-	4.64	4.42	4.61	4.71
C-2^{1},6^{1}	7.49	7.49	7.39	7.28-7.36	7.35	7.20-7.34
C-3^{1},5^{1}	7.36	7.40	7.37	7.28-7.36	7.36	7.20-7.34
C-4^{1}	7.36	7.39	7.31	7.28-7.36	7.32	7.20-7.34
2-OBn						
C-1a^{2}		4.83	4.77	4.73	7.74	4.61
C-1b^{2}		4.68	4.66	4.61	4.62	4.64
C-2^{2},6^{2}		7.39	7.39	7.28-7.36	7.27-7.34	7.20-7.34
C-3^{2},5^{2}		7.35	7.38	7.28-7.36	7.27-7.34	7.20-7.34
C-4^{2}		7.36	7.32	7.28-7.36	7.27-7.34	7.20-7.34
3-OBn						
C-1a^{3}		4.96	5.00	4.98	4.99	4.94
C-1b^{3}		4.84	4.83	4.77	4.80	4.84
C-2^{3},6^{3}		7.41	7.36	7.28-7.36	7.27-7.34	7.20-7.34
C-3^{3},5^{3}		7.32	7.35	7.28-7.36	7.27-7.34	7.20-7.34
C-4^{3}		7.29	7.32	7.28-7.36	7.27-7.34	7.20-7.34
TsO/SAc						
1^{4}				-	-	
2^{4}				7.79	2.39	
3^{4}				7.17		
4^{4}				-		
5^{4}				2.38		

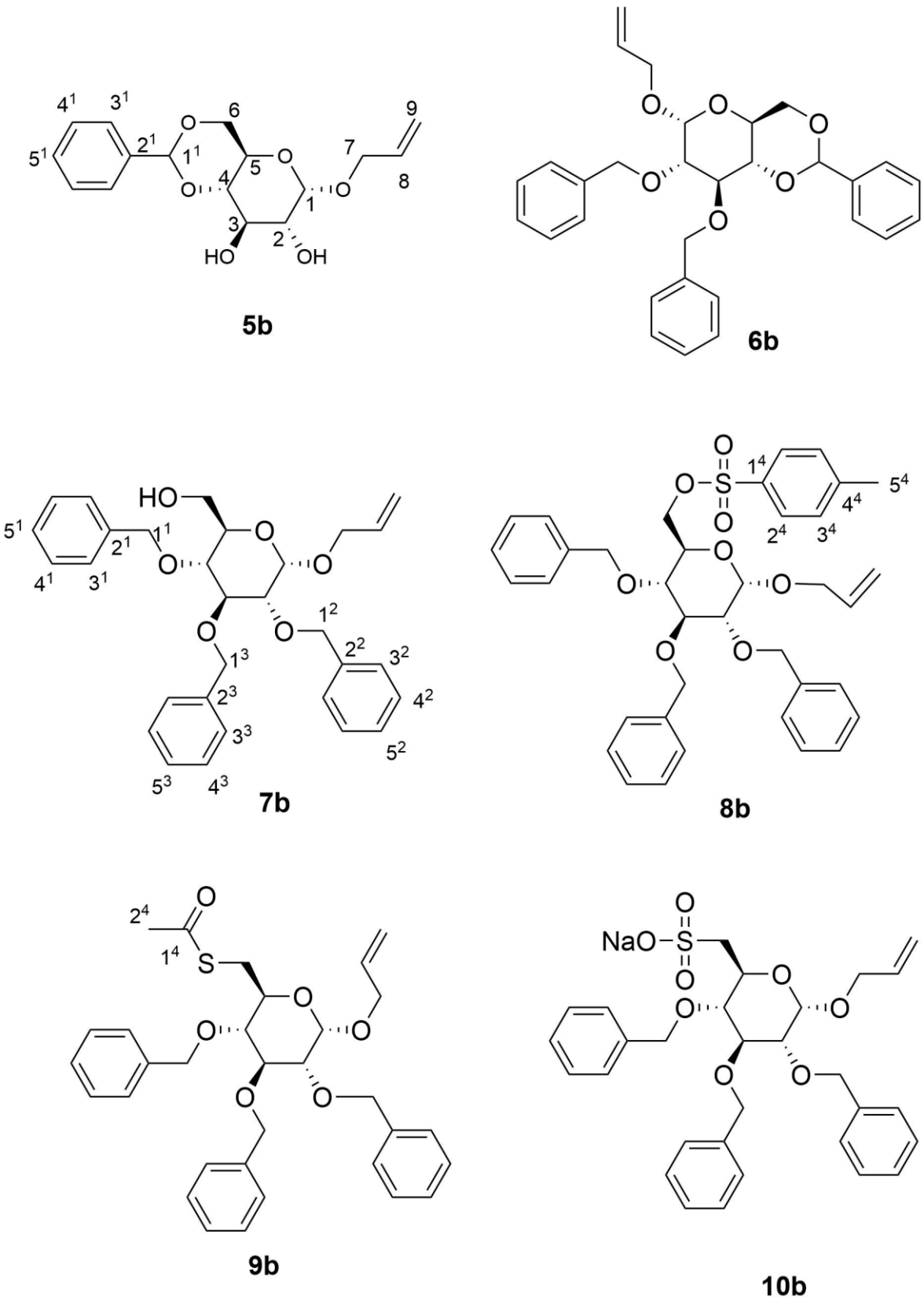


Figure 12. Compounds **5**-**10b** with numbering of carbon skeleton and substituents. NMR data for these compounds are given in table 16 and 17.

3.3.3 Infrared Spectroscopy

In itself, infrared spectroscopy is not well suited for monitoring most of the reactions performed in this thesis, due to the similarity and therefore overlap of the absorption frequencies. However, some new functionalities, such as the strong C=O stretch from the thioester group on **9a/b** at around 1700 cm^{-1} and the broad O-H stretch from free alcohols at around 3400 cm^{-1}, are easily identified.

4. Conclusion

In this master thesis, two strategies for selective protection of allyl and methyl glucopyranosides to procure 3,4,5-tri-*O*-benzylated *α*-*D*-glucopyranose derivatives have been explored and compared. In addition, functionalization of C-6 with a sulfonic acid moiety was investigated. For each step of the synthesis the conditions have been optimized to some extent, and where possible, detailed spectroscopic data have been recorded for intermediates of interest.

In comparing the two protection methodologies in question, initial protection of O-4 and O-6 as a benzylidene before benzylation and subsequent liberation of O-6 was found to be superior to the approach involving initial mono-protection of O-6, with triphenylmethyl as a protection group. Each step in synthetic pathway 1 was successfully optimized to give satisfactory yields, working in scales over 1 gram. A total yield of the linear synthesis of 55% for the methyl 3,4,5-tri-O-benzylated *α*-*D*-glucopyranose (**7a**) and 42% for the allyl 3,4,5-tri-O-benzylated *α*-*D*-glucopyranose (**7b**) was reached, with the intermediates being fully characterized by NMR. Effects of the anomeric substituents were observed in the initial protection of the hydroxyl groups, where the allyl glucosides were reached in 10-20 % less than the corresponding methyl glucoside.

The anomeric ratio of the compounds was monitored, and by altering the method of purification of early intermediates, the ratio of *β*-anomer was observed below 1:20. For compound **7a/b** and further in the synthesis, no *β*-anome*r* could be observed by NMR. Separation of the anomers was not attempted, but HPLC of an anomeric mixture of compound **7b** indicated anomers of the intermediate as potentially separable on silica, using a gradient eluent systems.

The second protection route was deemed inferior, with initial yields of tritylation and benzylations far below that of pathway 1. Although substantially better yields have been reported in literature, the results could not be reproduced.[7,28] In addition, issues were observed in working with the trityl group together with the allyl substituent, and no pure samples of **3b** and **4b** could be obtained for analysis.

Functionalization of the primary alcohol to a thioacetate was performed in accordance with literature.[6,8,9,90] The reactions were observed as repeatable, giving each intermediate in yields above 80% for the allyl and methyl glucosides, with only slight optimization needed. Further oxidation of the thioacetates **9a/b** was conducted using Oxone. Some problematic aspects of

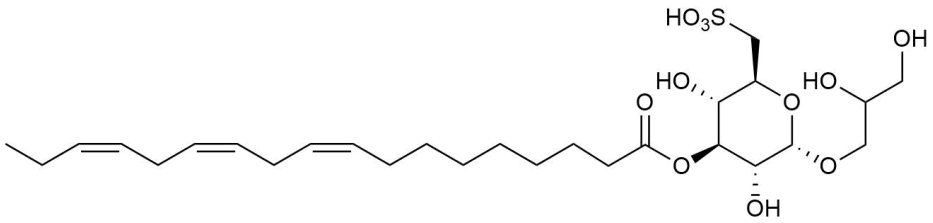
the workup were addressed, yielding sulfoquinovose derivate **10a** in 80%. Oxidation of allyl thioester **9b** was only partly successful, yielding the desired sulfoquinovose derivative **10b** in a mixture of by-products, not separable by conventional flash chromatography. Experimentation in developing a HPLC method was not successful. Severe challenges were encountered in the chromatographic analysis of sulfoquinovose derivates **10a/b**, and a suitable method for HPLC could not be found. This further complicated the identification of by-products observed in the synthesis of **10b**. Further experimentation was highly desired, but could not be conducted due to consumption of starting material **9a/b** and time restraints. Thus, the findings from this work on oxidations of **10a/b** suggest that further protection of the sulfoquinovose intermediates may be needed for successful purification and characterization. For this reason, a trial reaction attempting to protect the sulfoquinovose **10b** as a silyl ether was attempted employing conditions previously described to give high yields in protecting both primary and secondary alcohols. The reaction resulted in several by-products, with the main product being identified as the degradation product **5b**, likely as a result of intermolecular reactions in the reaction mixture. For reasons covered in section 3.2.3, TBDMS protection of the sulfonic acid was unsuccessful, indicating that other protection groups might be more suited.

Due to the extensive use of silyl ethers as protection groups elsewhere in the research project, the compatibility of the protection group with conditions employed in the oxidation of **9b/a** were explored. Model substrates of TBDMS and TBDPS protected isopropanol were subjected to the same conditions employed in the oxidation of **9a/9b**, and were observed as resilient to the acidic conditions employed.

The total yields from the synthesis of the sulfoquinovose derivates **10a** and **10b,** starting from methyl *α-D*-glucopyranoside and *α-D*-glucose respectively, were calculated to 32% (**10a)** and ~24% (**10b**).

5. Future work

The findings in this thesis aims to contribute to the research project working towards the total synthesis compound **1c** (Figure 13).



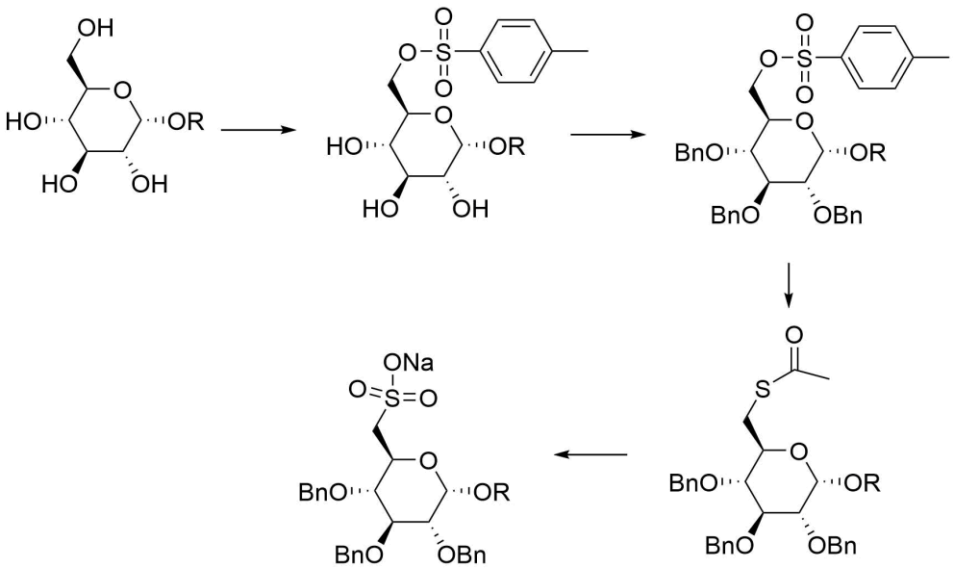
1c

Figure 13: The target compound of the research project **1c.**

As mentioned in the introduction, the functionalization of several sites of the glucopyranoside is required to reach the target molecule, as well as protection patterns allowing modifications without affecting other moieties on the molecule. The protection pattern achieved in the work performed in this thesis was purposely designed to allow for modification of carbon C-6 and would not in itself allow for esterification of O-3 without selective mono-deprotection.

Although not likely to be the chosen protection strategy in the total synthesis towards compound **1c**, understanding the effects of the protection groups, compatibility to reagents as well as efficiency in purification and workup will be of importance for the future work on the project.

Triphenylmethyl was deemed an unsuited protection group for the chemistry performed in this thesis due to severe complications in purification and analysis. Although further experimentation likely could improve the yields, other protection groups may be of greater interest for mono-protection of the primary alcohol. Due to the relative ease and high yields observed in the tosylations of 6-hydroxyl compounds, it seems logical to modify this route by substituting trityl for tosyl in the initial protection of 6-OH. Although the tosyl group's selectivity towards the primary alcohol has seen little experimentation,[4,99] novel reactions indicate some selectivity when using few equivalents over long reaction times. Initial protection of the O-6 as a tosyl would, in effect, shorten the synthetic route explored in this thesis with one step, reaching the sulfonic acid derivates **10a/10b** as illustrated in Scheme 30. This might however require adjusting the benzylation conditions, seeing the tosyl groups stability to sodium hydride is uncertain.[100]



Scheme 30: Alternative route to the sulfoquinovose derivates.

Insertion of sulfur into the C-6 primary position and its subsequent oxidation was, in part, successful. Findings indicated benzyl ethers, the sugar ring, as well as the methyl substituent as compatible with the conditions employed in Oxone oxidations. In addition, trial stability tests employing model substrates indicate TBDMS as stable in the conditions used in the oxidation reactions. Due to the observed problematic nature of the allyl substituents in these reactions, further work may entail preliminary oxidation and protection of the allyl substituent before oxidation of the thioester. This has previously been achieved using conventional oxidants such as OsO_4.[101] Oxidation of the allyl substituent may also be achieved by employing Oxone in a Shi epoxidation[89], indicating a potential tandem oxidation of the allyl and thioester groups. The resulting alcohol could further be protected as silyl esters by procedures established by other research group members.[56]

Findings in working with the unprotected sulfonic acid moieties are in line with literature, in that its polar nature complicates purification and analysis of the compounds.[69,92] For this reason, effectively protecting the sulfonic acid with suitable groups would be a logical next step in working with the sulfoquinovose derivates. Initial attempts of protecting the sulfonic acid moiety as a silyl ether using TBDMS was unsuccessful, but further experimentation using different substituents on the silicone may yield better result. A more promising path would likely be, as covered in section 3.2.3, experimentation with proven protection groups such as TEC and TFE.[68,69,92]

Oxidation of the thioester on C-6 has previously been done with unprotected 1,2 diols on the anomeric position using Oxone, reporting high yields, indicating that the 1,2 diols may be less problematic than the allyl substituent when employing Oxone.[4,90] Obvious problematic aspects of this approach are stereochemical control of the oxidation products, separation of enantiomer mixtures as well as selectivity issues in introducing different protecting groups on the sulfonate and the diol.

A possible strategy to obtain the desired functionalization on C-1 without employing the allyl group is glycosylation of C-1 with a chirally pure protected glycerol. This would likely take place early in the synthetic pathway, as this would lower the polarity of the early intermediates, potentially allowing for more facile purification. An added benefit of this approach is the effect it may have on the anomeric ratio of the compound. Although bulky groups have been shown to have little impact on the anomeric effect, more experimentation into the effect of electronegative substituents as protection groups on glycerol, is of interest.

6. Experimental

6.1 General considerations

Starting materials and reagents employed herein were all purchased from Sigma Aldrich and have been used without further purification unless otherwise specified. Dry solvents were collected from a Braun MB SPS-800 Solvent Purification system. Temperatures above 25°C were regulated using oil immersion. Freeze drying of samples were done using a LABCONO Freezone 1.

6.6.1 Thin Layer Chromatography and flash column chromatography

All reactions were monitored using thin layer chromatography with silica gel on aluminium plates; 60, F254, Merck and were visualized by UV-light and a solution of 1% $KMnO_4$ and K_2CO_3 in water. Column chromatography was performed using Merck and Sigma-Aldrich silica gel 60Å (40-64nm).

6.6.2 High-Performance Liquid Chromatography

HPLC analysis was performed on an Agilent UHPLC system using: Agilent 1290 Infinity Bin-Pump VL, G4220B binary pump, Agilent 1290 infinity, G4226A autosampler, Agilent 1260 TCAA, G1316A degasser and a 1260 DAD, G4212-60007 diode array detector. Agilent UHPLC for LC-3D systems was used to analyze the HPLC data.

A Zorbax Bonus-RP-250x 4.6mm with a Zorbax Bonus-RP 12.5x4.6mm guard column was used as the stationary phase. The eluent was a gradient increasing from 80:20 ACN:water to 100% Acetonitrile over 40 minutes with 5 minutes at 100%. Flow: 1ml/min.

Preparative HPLC was performed on an Agilent preparative HPLC system using: Agilent 1260 Infinity Bin-Pump VL, G1361A., Agilent 1260 Prep, ALS G2260A autosampler, Agilent 1260 TCC, G1316A degasser, Agilent 1260 FC-PS, G1364B sample collector and a Agilent 126, G1315D diode array detector. Agilent Chemstation Open LAB was used to analyse the data.

An Agilent Prep. 5, C-18 150x 21.2 mm, PN-443405-102 was used as a stationary phase. The eluent was a gradient increasing from 80:20 ACN:water to 100% Acetonitrile over 40 minutes with 5 minutes at 100%. Flow: 20ml/min

6.6.3 Melting point analysis

Melting points for crystalline products were recorded using a Stuart SMP40 automatic melting point apparatus.

6.6.4 Mass Spectroscopy

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 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.

6.6.5 Infrared Spectroscopy

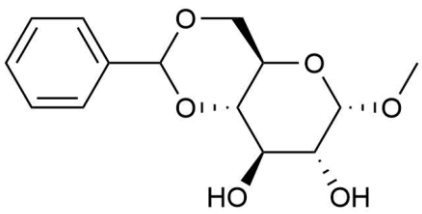
Infrared absorption spectra were acquired using a Bruker ALPHA ECO-ATR instrument. Results were processed and analyzed using OPUS 7.5 software.

6.6.6 NMR spectroscopy

^{1}H- and ^{13}C-NMR 1D as well as 2D spectra were recorded using a Bruker 600 MHz Avance III HD equipped with a 5-mm cryogenic CP-TCI z-gradient probe and SampleCase and a Bruker 400 MHz Avance III HD equipped with a 5-mm SmartProbe z-gradient probe and SampleCase. Spectra are presented with acquisition parameters in the appendix section. Chemical shifts are reported as ppm (parts per million)(δ) using TMS as internal standard. All compounds, except **10a/b,** were run in deuterated chloroform as a solvent. **10a** and **10b** were run in deuterated methanol and were calibrated using either the water or solvent residual peak. Coupling constants (*J*) are given in Hertz (Hz). Chemical shifts displayed in section 3.3 were determined using 1D ^{1}H- and ^{13}C-NMR, COSY, HSQC, HMBC and HSQC-TOCSY NMR experiments.

6.2 Synthesis methyl glucosides **5**-**10a**

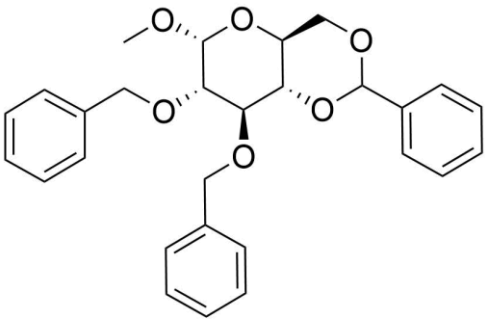
6.2.1 Methyl 4,6-*O*-benzylidene-*α*-*D*-glucopyranoside (**5a**)



5a

To a solution of methyl*α*-*D*-glucopyranoside (5.07 g, 26 mmol) in CH_3CN (30 ml), DMAc (4 ml) and DMF (4 ml), benzaldehyde dimethyl acetal (8 ml, 52 mmol) and *p*-toluene sulfonic acid (0.494 g, 2.6 mmol) were added while stirring at room temperature. The mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure, and the product was recrystallized in EtOH using water as an anti-solvent. This yielded **5a** (6.24 g, 22 mmol, 85%) as a white solid. R_f= 0.6 (1:5 EtOAc:*n*-pentane),t_R (HPLC) = 12.67 min, Mp: 157-162 °C **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.49 (m, 2H, *o*-Ar-CH), 7,36 (m, 3H, *p,m*-Ar-CH), 5.53 (s, 1H, O-Bn-CH), 3.93 (d,1H, *J*= 3.92, H-1), 4.29 (dd, 1H, *J*= 9.7, 4.28, H-6a), 3.93 (t, 1H, *J*= 9.24, H-3), 3.81 (td, 1H, *J*= 9.42, 4.62, H-5), 3.75 (dd, 1H, *J*= 9.7, 5.52, H-6b), 3.63 (dd, 1H, *J*= 9.14, 3.83, H-2), 3.49 (t, 1H, *J*= 9.25, H-4), 3.46 (s, 3H, OMe), 3.0 (s, 1H, OH), 2.94 (s, 1H, OH), **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 137.0 (Cq-Ar), 129.38 (C-Ar), 128.3 (C-Ar), 126.3(C-Ar), 101.96 (Ar-CH), 99.77 (C-1), 80.91 (C-4), 72.90(C-2), 71.81(C-3), 68.94(C-6), 62.37(C-5), 55.60(OMe). HRMS (ESI+) m/z: 305.1004, $[M+Na]^+$calc. for $C_{14}H_{18}O_6Na$ 305.1001, IR(cm^{-1}): 3360 (br), 2969 (m), 2936 (m), 2863 (m), 1373 (m), 1069 (s), 1025 (s), 996 (s),749 (s), 696 (s), Spectroscopic data corresponds with previously reported values.[73]

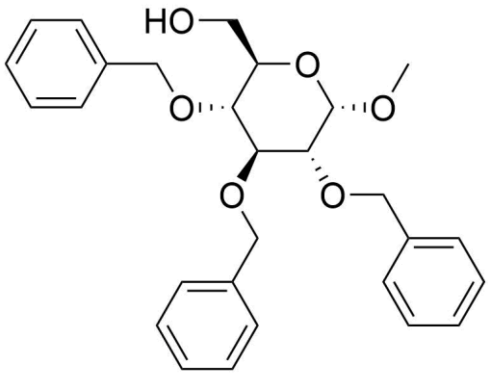
6.2.2 Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-*α*-*D*-glucopyranoside (**6a**)



6a

Compound **5a** (1.01 g, 3.5 mmol), NaH (0.429 g, 17.0 mmol) and TBAI (0.170 g, 0.5 mmol) was dissolved in dry THF (25 ml) and the mixture was added benzyl bromide (1.31 ml, 11.0 mmol) while stirring at room temperature. The mixture was heated to 60 °C and stirred for 2 hours. The reaction was terminated by the addition of water (20 ml) and was then extracted with EtOAc (3x40 ml). The combined organic layer was then washed with brine (3x40 ml) and dried over $MgSO_4$ before solvent removal under reduced pressure. The residue was purified on silica (1:10 EtOAc:*n*-pentane) to yield **6a** (0.9771g, 2.5mmol, 71%) as a white waxy solid, R_f = 0.4 (1:10 EtOAc:*n*-pentane), t_R (HPLC) = 36.16 min, MP = 87-94 °C, **^{1}H-NMR** (400 Mhz, $CDCl_3$) δ: 7.48 (m, 2H, *o*-CH-OBn), 7.26-7.41 (m, 13H, Ar-CH) 5.49 (s, 1H) 4.91 (d, 1H, *J*= 11.29, Ar-CH_2), 4.85 (d, 1H, 11.06, Ar-CH_2), 4.83 (d, 1H, *J*= 11.2, Ar-CH_2), 4.69 (s, 1H, *J*= 12.20, Ar-CH_2), 4.59 (d, 1H, *J*= 3.70, H-1), 4.26 (dd, 1H, *J*= 10.34, 4.8, H-6a), 4.04 (t, 1H *J*= 9.26, H-3), 3.82 (td, 1H, *J*= 9.26, 4.7, H-5), 3.70 (t, 1H, *J*= 10.35, H-6b), 3.60 (t, 1H, *J*= 9.34, H-4), 3.55 (dd, 1H, *J*= 9.3, 3.7. H-2), 3.40 (s, 3H, OMe). **^{13}C-NMR**(100 MHz, $CDCl_3$):138.7 (Ar-Cq),138.17 (Ar-Cq), 137.41 (Ar-Cq), 128.90 (Ar-CH), 128.45 (Ar-CH), 128.30 (Ar-CH), 128.21 (Ar-CH), 128.12 (Ar-CH), 128.03 (Ar-CH), 127.91 (Ar-CH), 127.58 (Ar-CH), 126.03 (Ar-CH), 101.27 (CH-Ar), 99.25 (C-1), 82.14 (C-4), 79.17 (C-2), 78.60 (C-3), 75.34 (Ar-CH_2), 73.79 (Ar-CH_2), 69.07 (C-6), 62.32 (C-5), 55.34 (OMe). HRMS (ESI+) m/z: 485.1946 $[M+Na]^+$calc. for $C_{28}H_{30}O_6Na$ 485.1940, IR(cm^{-1}): 3032 (w), 2923 (w), 2866 (w), 1496 (m), 1449 (m), 1367 (m), 1083 (s), 1048 (s) Spectroscopic data corresponds with previously reported values.[102]

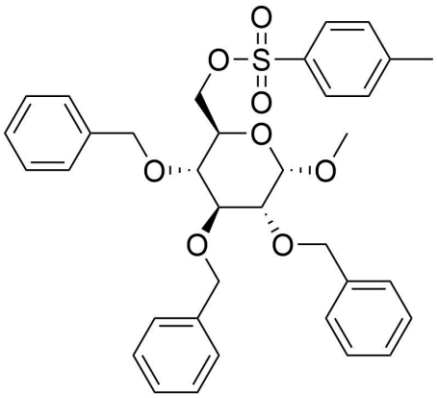
6.2.3 Methyl 2,3,4-tri-*O*-benzyl-*α*-*D*-glucopyranoside (**7a**)



7a

In a solution of compound **6a** (2.98 g, 6.7 mmol) in CH_2Cl_2/diethyl ether (7:4) (60 ml), $LiAlH_4$ (0.67 g, 26.7 mmol) was added in two portions wile stirring. The mixture was heated to reflux and $AlCl_3$ (2.36 g, 30.0 mmol) solved in dry diethyl ether (10 ml) was added dropwise. The mixture was then stirred at reflux for one hour before being quenched with EtOAc (20 ml) and water (20 ml). The product was extracted with EtOAc (3x100 ml). The combined organic layer was then dried with $MgSO_4$ and the solvent removed under reduced pressure. The resulting residue was purified on silica (1:20 EtOAc:*n*-pentane) to yield **7a** (2.75 g, 5.9 mmol, 88%) as a colorless oil, R_f = 0.7 (1:20 EtOAc:*n*-pentane), t_R (HPLC) = 31.03 min, **^{1}H-NMR** (600 MHz, $CDCl_3$) δ: 7.30 (m, 15H, H-Ar), 4.97 (d, 1H, *J*= 10.9, CH_2-Ar), 4.86 (d, 1H, *J*= 10.98, CH_2-Ar), 4.82 (d, 1H, *J*= 10.75, CH_2-Ar), 4.77 (d, 1H, *J*= 12.15, CH_2-Ar), 4.64 (d, 1H, *J*= 11.93, CH_2-Ar), 4.62 (d, 1H, *J*= 11.01, CH_2-Ar), 4.56 (d, 1H, *J*= 3.64, H-1), 4.01 (t, 1H, *J*= 9.4, H-3), 3.75 (dd, 1H, *J*= 9.6, 2.6, H-6a), 3.70 (m, 1H, H-5), 3.65 (m,1H, H-6b), 3.52 (t, 1H, *J*= 9.5, H-4), 3.49 (dd, 1H, *J*= 9.30, 3.7, H-2), 3.34 (s, 3H, OMe) **^{13}C-NMR**(150 MHz, $CDCl_3$) δ: 138.80 (Ar-Cq), 138.21 (Ar-Cq), 138.17 (Ar-Cq), 128.63 (Ar-CH), 128.52 (Ar-CH), 128.45 (Ar-CH), 128.16 (Ar-CH), 128.06 (Ar-CH), 128.01 (Ar-CH), 127.99 (Ar-CH), 127.91 (Ar-CH), 127.67 (Ar-CH), 98.20 (C-1), 81.99 (C-3), 80.03 (C-4), 77.51 (C-2), 75.78 (CH_2-Ar), 75.07 (CH_2-Ar), 73.44 (CH_2-Ar), 70.80 (C-5), 61.81 (C-6), 55.23 (OMe). HRMS (ESI+) m/z: 487.2100 $[M+Na]^+$calc. for $C_{28}H_{32}O_6Na$ 487.2097, IR(cm^{-1}): 3470 (br), 3029 (w), 2919 (w), 1496 (m), 1453 (m), 1360 (m), 1047 (s), 733 (s), 694 (s), Spectroscopic data corresponds with previously reported values.[3]

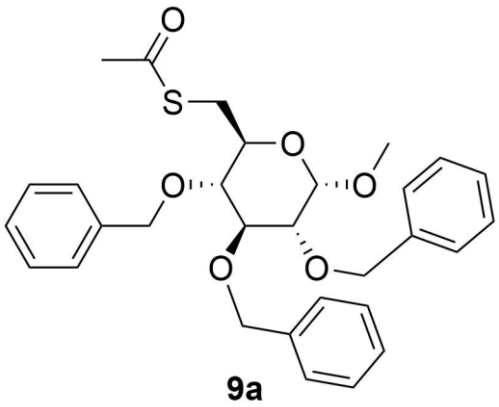
6.2.4 Methyl 2,3,4-tri-*O*-benzyl-6-O-tosyl-*α*-*D*-glucopyranoside (**8a**)



8a

To a solution of compound **7a** (2.75g, 5.9mmol) in pyridine (50ml), tosyl chloride (2.65g, 14.8mmol) was added while stirring. The mixture was stirred at room temperature for 24 hours. The reaction was terminated by the addition of water (20 ml) and the aqueous phase was extracted with EtOAc (4x30 ml). The combined organic layer was washed with brine (3x40 ml) and dried over $MgSO_4$ before the solvents were removed under reduced pressure. The resulting residue was purified on silica (1:4 EtOAc:*n*-pentane) to yield **8a** (2.63 g, 42 mmol, 71%) as a yellow thick oil, R_f = 0.7 (1:4 EtOAc:*n*-pentane), t_R (HPLC) = 33.69 min, **^{1}H-NMR** (600 MHz, $CDCl_3$) δ: 7.76 (d, 2H, *J*= 8.09, Ts-CH), 7.26-7.35 (m, 15H, Ar-CH), 7.14 (m, 2H, Ts-CH), 4.96 (d, 1H, *J*= 10.89, CH_2-Ar), 4.81 (d, 1H, *J*= 10.61, CH_2-Ar), 4.79 (d, 1H, *J*= 10.25, CH_2-Ar), 4.77 (d, 1H, *J*= 10.94 CH_2-Ar), 4.75 (d, 1H, *J*= 12.17, CH_2-Ar), 4.62 (d, 1H, *J*= 11.96, CH_2-Ar), 4.51 (d, 1H, *J*= 3.65, H-1), 4.42 (d, 1H, *J*= 10.57, CH_2-Ar), 4.18 (m, 1H, H-6a), 4.12 (dd, 1H, *J*= 13.14, 7.29, H-6b), 3.94 (t, 1H, *J*= 9.43, H-3), 3.76 (ddd, 1H, J = 9.44, 3.9, 2.1, H-5), 3.47 (dd, 1H, *J*= 9.43, 3.65, H-2), 3.40 (t, 1H, *J*= 9.43, H-4), 3.30 (s, 3H, OMe), 2.39 (s, 3H, Me). **^{13}C-NMR**(150 MHz, $CDCl_3$) δ: 144.84 (Ar-Cq), 138.56 (Ar-Cq), 137.98 (Ar-Cq), 137.78 (Ar-Cq), 132.89 (Ar-CH), 129.81 (Ar-CH), 129.81 (Ar-CH), 128.51 (Ar-CH), 128.42 (Ar-CH), 128.12 (Ar-CH), 128.00 (Ar-CH), 127.93 (Ar-CH), 127.90 (Ar-CH), 127.85 (Ar-CH), 127.67 (Ar-CH), 98.05 (C-1), 81.86 (C-3), 79.69 (C-4), 76.84 (C-2), 75.73 (CH_2-Ar), 74.99 (CH_2-Ar), 73.45 (CH_2-Ar), 68.60 (C-6), 68.50 (C-5), 55.35 (OMe), 21.64 (Me), HRMS (ESI+) m/z: 641.2187 $[M+Na]^+$calc. for $C_{35}H_{38}O_8SNa$ 641.2185, IR(cm^{-1}): 2985 (w), 2926 (w), 1449 (m), 1372 (m), 1238 (s), 1072 (s), 1044 (s), 698 (m), Spectroscopic data corresponds with previously reported values.[84]

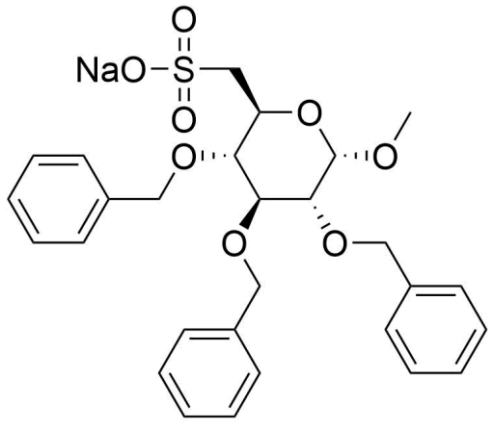
6.2.5 Methyl 2,3,4-tri-*O*-benzyl-6-thioacetate-*α*-*D*-glucopyranoside (**9a**)



9a

Compound **8a** (1.23 g, 1.98 mmol) was dissolved in ethanol (25 ml, 98.9%). While stirring, potassium thioacetate (0.54 g, 5.1 mmol) was added. The solution was stirred for 2 hours at reflux. At the end of the reaction period, the mixture was added distilled water (20 ml) and the aqueous phase was extracted with EtOAc (4x50 ml). The combined organic layer was washed with brine (3x 40ml) and dried over $MgSO_4$ before the solvents were removed under reduced pressure. The resulting residue was purified on silica (1:10 EtOAc:*n*-pentane) to yield compound **9a** (0.832g, 1.6mmol, 84%) as a light orange solid, R_f = 0.8 (1:10 EtOAc:*n*-pentane), t_R (HPLC) = 32.650 min, **^{1}H-NMR** (600 Mhz, $CDCl_3$) δ: 7.26-7.38 (m, 15H, Ar-CH), 4.97 (d , 1H, *J*= 11.08, CH_2-Ar), 4.88 (d, 1H, *J*= 11.08, CH_2-Ar), 4.80 (d, 1H, *J*= 9.85, CH_2-Ar), 4.77 (d, 1H, *J*= 11.08, CH_2-Ar), 4.64(d, 1H, *J*= 12.03, CH_2-Ar), 4.61(d, 1H, *J*= 12.20, CH_2-Ar), 4.53(d, H, *J*= 3.54, H-1), 3.96 (t, 1H, *J*= 9.18, H-3), 3.75 (td, 1H, *J*= 7.9, 3.16, H-5), 3.50 (dd, 1H, *J*= 9.44, 3.56, H-2), 3.42 (dd, 1H, *J*= 13.6, 3.17. H-6a), 3.35 (s, 3H, OMe), 3.30 (t, 1H, *J*= 9.34, H-4), 3.02 (dd,1H, *J*= 13.7, 8.0, H-6b), 2.32 (s, 3H, Me), **^{13}C-NMR**(150 MHz, $CDCl_3$) δ: 194.90 (CO), 138.62 (Ar-Cq), 138.07 (Ar-Cq), 137.94 (Ar-Cq), 128.49 (Ar-CH), 128.45 (Ar-CH), 128.19 (Ar-CH), 128.11 (Ar-CH), 128.01 (Ar-CH), 127.97 (Ar-CH), 127.89 (Ar-CH), 127.69 (Ar-CH), 97.90 (C-1, 81.86 (C-3), 80.54 (C-4), 79.93 (C-2), 75.81 (CH_2-Ar), 75.21 (CH_2-Ar), 73.40 (CH_2-Ar), 69.35 (C-5), 55.18 (OMe), 30.89 (OMe), 30.55 (Me).HRMS (ESI+) m/z: 545.1981 $[M+Na]^+$calc. for $C_{30}H_{34}O_6SNa$ 545.1974, IR(cm^{-1}): 3030 (w), 2910 (w), 1693 (s), 1453 (m), 1357 (m), 1048 (s), 907 (m), 734 (s), 692 (s), 626 (s), Spectroscopic data corresponds with previously reported values.[85]

6.2.6 Methyl 2,3,4-tri-*O*-benzyl-6-sulfo-monosodium-*α*-*D*-glucopyranoside (**10a**)

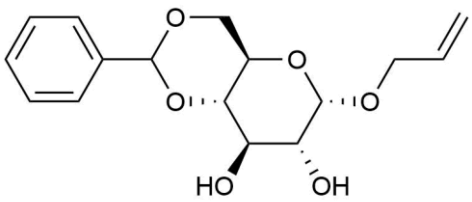


10a

Compound **9a (**125 mg, 0.24 mmol) was dissolved in glacial AcOH (5 ml) to which NaOAC (392 mg, 4.7 mmol) and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 368 mg, 1.2 mmol) was added while stirring at room temperature. After stirring for 12h, saturated aqueous $NaHCO_3$ (10 ml), saturated aqueous Na_2CO_3 (10 ml) and H_2O (5 ml) were carefully added to the mixture. The solvents were removed under reduced pressure, and the resulting residue was freeze dried over 72 hours. CH_3CN (20 ml) was added to the crude product, stirred for 20 min, cooled in an ice bath, and filtered off. The filtrate was washed with CH_3CN (20 ml) and filtered two more times. The collected CH_3CN-solution was evaporated under reduced pressure, and the resulting oily crude product was purified on silica column, by eluting with a gradient, starting with 1:10 EtOAc:*n*-pentane and followed by 1:5 EtOAc:*n*-pentane. The product eluted after flushing with 1:5 MeOH: EtOAc yieding **10a (**110mg, 0.2mmol, 84%) as a clear oil. R_f = 0.5 (1:5 MeOH: EtOAc), **^{1}H-NMR** (600 MHz, CD_3OD)δ: 7.24-7.40 (m, 15H, CH-Ar), 4.93(d, 1H, *J*= 10.72, CH_2-Ar), 4.87 (d, 1H, *J*= 10.94, CH_2-Ar) 4.75 (d, 1H, *J*= 11.44, CH_2-Ar),4.73 (d, 1H, *J*= 3.68, H-1) 4.69 (d, 1H, *J*= 12.02, CH_2-Ar), 4.67 (d, 1H, *J*= 12.34), 4.64 (d, 1H, *J*= 11.12, CH_2-Ar), 4.16 (td, 1H, *J*= 9.92, 1.23, H-5), 3.80 (t, 1H, *J*= 9.29, H-3), 3.57 (dd, 1H, *J*= 9.46, 3.73, H-2), 3.37 (s, 3H, OMe), 3.24-3.31 (m, 2H, H-6a, H-4), 2.91 (dd, 1H, *J*= 13.99, 9.46, H-6b) **^{13}C-NMR** (150 MHz, CD_3OD) δ: 140.11 (Ar-Cq), 139.64 (Ar-Cq), 129.42 (Ar-CH), 129.34 (Ar-CH), 128.31 (Ar-CH), 129.20 (Ar-CH), 128.96 (Ar-CH), 128.91 (Ar-CH), 128.88 (Ar-CH), 128.67 (Ar-CH), 128.58 (Ar-CH), 98.54 (C-1), 83.03 (C-3), 81.70 (C-4), 81.60 (C.2), 76.45 (CH_2-Ar), 75.83 (CH_2-Ar), 73.88 (CH_2-Ar), 68.52 (C-5), 55.94 (OMe), 53.95 (C-6), HRMS (ESI-) m/z: 527.1740 [M+Na]calc. for $C_{28}H_{31}O_8SNa$ 527.1740, IR(cm^{-1}): 3444 (br), 3063 (w), 3031 (w), 2922 (w), 1453 (m), 1360 (m), 1196 (s), 1175 (s), 1089 (s), 1049 (s), 995 (s), 734 (s), 695 (s), Spectroscopic data corresponds with previously reported values.[6]

6.3 Synthesis of Allyl glucosides **5-10b**

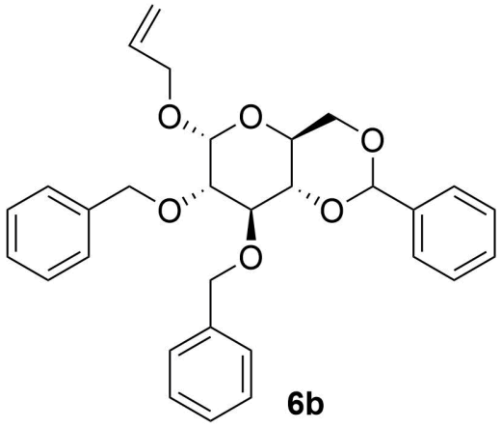
6.3.1 Allyl 4,6-*O*-benzylidene-*α*-*D*-glucopyranoside (**5b**)



5b

To a solution of *D*-*α*-Glucose (21.69 g, 120 mmol) solved in allyl alcohol (80 ml), TMSCl (80 ml, 600 mmol) was added while stirring. The mixture was stirred for 3 days at room temperature before the solvents were removed under reduced pressure. The resulting brown oil was dissolved in acetonitrile (80 ml) added DMF (10 ml). Benzaldehyde dimethyl acetal (25 ml, 190 mol) and para-toluene sulfonic acid (2.01 g, 11 mmol) were added. The mixture was stirred at room temperature for five hours before being poured onto cold brine (200 ml). The resulting precipitate was recrystalized in ethanol and water before drying in vacuo to yield compound **5b** (14.153 g, 45 mmol, 37%) as a white solid, R_f = 0.6 (1:5 EtOAc:*n*-pentane), t_R (HPLC) = 12.28 min, Mp: 157-162, °C **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 7.44-7.53 (m, 2H, Ar-CH), 7.31-7.41 (m, 3H, Ar-CH), 5.92 (dddd, 1H, *J*=17.3, 10.21, 6.52, 5.27, H-8), 5.53 (s,1H, CH-Ar), 5.33 (m, 1H, *J*= 17.34, 1.75, H-9a),5.25 (m, 1H, *J*= 10.26, 1.43, H-9b), 4.96 (d, 1H, *J*= 3.89, H-1), 4.27 (dd, 1H, *J*= 10.20, 4.77, H-6a), 4.26 (m, 1H, *J*= 12.73, 5.28, 1.33, H-7a), 4.06 (m, 1H, *J*= 12.79, 6.32, 1.21, H-7b), 3.94 (td, 1H, *J*= 9.41, 2.1, H-3), 3.84 (td, 1H, *J*= 9.83, 4.78, H-5), 3.74 (t, 1H, *J*= 10.25, H6-b), 3.63 (dd, 1H, J = 9.69, 3.93, H-2), 3.49 (t, 1H, *J*= 9.40, H-4), 2.71 (d, 1H, *J*= 2.26, OH), 2.23 (d, 1H, *J*= 9.6, OH).**^{13}C-NMR**(100 MHz, $CDCl_3$) δ: 137.03 (Ar-Cq), 133.29 (C-8), 129.27 (Ar-CH), 128.35 (Ar-CH), 126.31 (Ar-CH), 118.35 (C-9), 101.92 (CH-Ar), 97.85 (C-1), 80.93 (C-4, 72.84 (C-2), 71.80 (C-3), 68.88 (C-6), 62.59 (C-5), HRMS (ESI+) m/z: 331.1158 $[M+Na]^+$calc. for $C_{16}H_{20}O_6Na$ 331.1161, IR(cm^{-1}): 3371 (br), 3016 (w), 2969 (w), 2942 (w), 2865 (w), 1451 (m), 1371 (s), 1073 (s), 1011 (s), 748 (s), 698 (s), 657 (s). Spectroscopic data corresponds with previously reported values.[74]

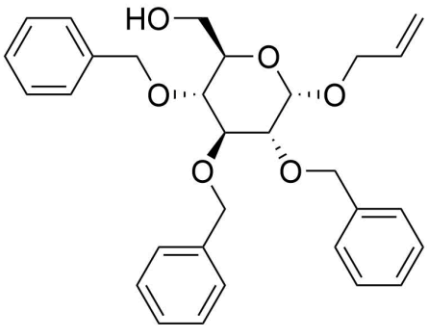
6.3.2 Allyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-*α*-*D*-glucopyranoside (**6b**)



6b

Compound **6a** (1.09 g, 3.5 mmol), NaH (0.42 g, 17 mmol) and TBAI (190 mg, 0.5 mmol) were dissolved in dry THF (25 ml) and benzyl bromide (2.0ml, 17 mmol) was added to the mixture while stirring at room temperature. The mixture was heated to 60° C and stirred for two hours. The reaction was terminated with the addition of water (20 ml) and was then extracted with EtOAc (3x40 ml). The combined organic layer was washed with brine (3x40 ml), dried over $MgSO_4$, before the solvent was removed under reduced pressure. The residue was purified on silica (1:20 EtOAc:*n*-pentane) to yield **6b** (1.26 g, 2.59 mmol, 74%) as a white solid, R_f = 0.76 (1:20 EtOAc:*n*-pentane), t_R (HPLC) = 34.47 min, ^{1}**H-NMR** (600 MHz, $CDCl_3$) δ: 7.47-7.51 (m, 2H, CH-Ar), 7.26-7.39 (m, 13H, CH-Ar), 5.94 (dddd, 1H, *J*=17.32, 10.26, 6.62, 5.24, H-8), 5.55 (s, 1H, CH-Ar), 5.33 (m, 1H, *J*= 17.34, 1.57, H-9a), 5.23(m, 1H, *J*= 10.26, 1.28, H-9b), 4.9 (d, 1H, *J*= 11.44, CH_2-Ar), 4.84 (d, 1H, *J*= 11.26, CH_2-Ar), 4.83 (d, 1H, *J*= 12.15, CH_2-Ar), 4.80 (d, 1H, *J*= 3.74, H-1), 4.68 (d, 1H, *J*= 12.32, CH_2-Ar), 4.25 (dd, 1H, *J*= 10.33, 4.83, H-6a), 4.18 (m, 1H, *J*= 12.80, 5.24, 1.26, H-7a), 4.07 (t, 1H, *J*= 9.28, H-3), 4.03 (m, 1H, *J*= 12.90, 6.67, 1.37, H-7b), 3.88 (td, 1H, *J*= 9.52, 4.91, H-5), 3.70 (t, 1H, *J*= 10.24, H-6b), 3.61 (t, 1H, *J*= 9.26, H-4), 3.56 (dd, 1H, *J*= 9.26, 3.72, H-2), ^{13}**C-NMR**(150 MHz, $CDCl_3$) δ: 138.81 (Ar-Cq), 138.22 (Ar-Cq), 137.43 (Ar-Cq), 133.64 (C-8), 128.90 (Ar-CH), 128.42 (Ar-CH) 128.30 (Ar-CH), 128.23 (Ar-CH), 128.06 (Ar-CH), 128.00 (Ar-CH), 127.87 (Ar-CH), 127.57 (Ar-CH), 126.03 (Ar-CH),118.37 (C-9), 101.25 (CH-Ar), 96.79 (C-1), 82.22 (C-4), 79.25 (C-2), 78.64 (C-3), 75.36 (CH_2-Ar), 73.61 (CH_2-Ar), 69.04 (C-6), 62.59 (C-5), HRMS (ESI+) 511.2105 (calc. $C_{30}H_{32}O_6Na$, 511.2097). HRMS (ESI+) m/z: 511.2105 $[M+Na]^+$calc. for $C_{30}H_{32}O_6Na$ 511.2097, IR(cm^{-1}): 3063 (w), 3032 (w), 2917 (w), 2867(w), 1452 (m), 1365 (m), 1083 (s), 992 (s), 925 (s), 735 (s), 694 (s). Spectroscopic data corresponds with previously reported values.[58]

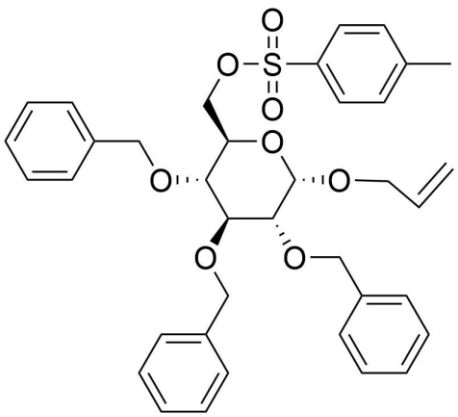
6.3.3 Allyl 2,3,4-tri-*O*-benzyl-*α*-*D*-glucopyranoside (**7b**)



7b

To a solution of Compound **6b** (750 mg, 1.55 mmol) in a mixture of CH_2Cl_2/diethyl ether (7:4) (60 ml) was added $LiAlH_4$ (148 mg, 3.9 mmol) in two portions while stirring. The mixture was heated to reflux and was added $AlCl_3$ (520mg, 3.9mmol) dissolved in dry diethyl ether (10 ml) dropwise. The mixture was then stirred at reflux for one hour before being quenched with EtOAc (20 ml) and water (20 ml) before being extracted with EtOAc (3x100 ml). The combined organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The resulting residue was purified on silica (1:20 EtOAc:*n*-pentane) to yield **7a** (637mg, 1.30mmol, 84%) as a colourless oil, R_f = 0.6 (1:20 EtOAc:*n*-pentane), t_R (HPLC) = 29.047 min, ^{1}**H-NMR** (600 MHz, $CDCl_3$) δ: 7.25-7.39 (m, 15H. CH-Ar), 5.9 (dddd, 1H, *J*=17.22, 10.29, 6.59, 5.27, H-8) 5.3 (m, 1H, *J*= 17.23, 1.42, H-9a), 5.21 (m, 1H, *J*= 10.28, 1.42, H-9b) 5.00 (d, 1H, 10.82, CH_2-Ar), 4.88 (d, 1H, *J*= 11.01, CH_2-Ar), 4.83 (d, 1H, *J*= 10.82, CH_2-Ar), 4.77 (d, 1H, *J*= 12.0, CH_2-Ar), 4.78 (d, 1H, *J*= 3.64, H-1), 4.66 (d, 1H, *J*= 11.85, CH_2-Ar), 4.64 (d, 1H, *J*= 11.29, CH_2-Ar), 4.13 (m, 1H, *J*= 11.38 , 5.36, 1.39 H-7a), 4.03 (t, 1H, *J*= 9.24, H-3), 4.00 (m, 1H, *J*= 11.59, 6.60, 1.40, H-7b) 3.76 (dd, 1H, *J*= 9.14, 5.06, H-6a) 3.70 (m, 1H, H-5), 3.70 (m, 1H, H-6b), 5.53 (t, 1H, *J*= 9.25, H-4), 3.50 (dd, 1H, *J*= 9.37, 3.59, H-2).**^{13}C-NMR**(150 MHz, $CDCl_3$) δ: 138.81 (Ar-Cq), 138.17 (Ar-Cq), 138.14 (Ar-Cq), 133.70 (C-8), 128.51 (Ar-CH), 128.46 (Ar-CH), 128.41 (Ar-CH), 128.09 (Ar-CH), 127.96 (Ar-CH), 127.91 (Ar-CH), 127.80 (Ar-CH), 127.61 (Ar-CH), 127.60 (Ar-CH), 119.29 (C-8), 95.67 (C-1), 81.94 (C-3), 80.02 (C-1), 77.41 (C-4), 75.74 (CH_2-Ar), 75.09 (CH_2-Ar), 73.27 (CH_2-Ar), 70.86 (C-5), 68.31 (C-7), 61.88 (C-6). HRMS (ESI+) m/z: 513.2257 $[M+Na]^+$calc. for $C_{30}H_{34}O_6Na$ 513.2253, IR(cm^{-1}): 3479 (br), 3030 (w), 2922 (w), 2868 (w), 1496 (m), 1453 (m), 1359 (m), 1069 (s), 1027 (s), 926 (s), 734 (s), 695 (s), Spectroscopic data corresponds with previously reported values.[4]

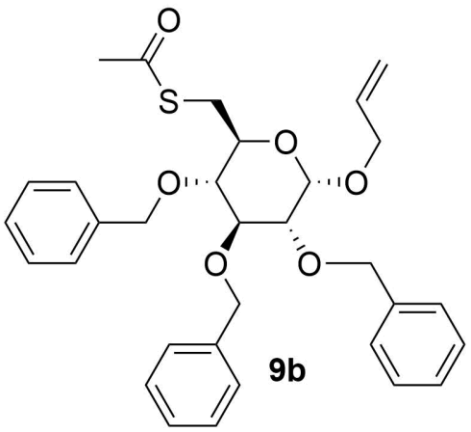
6.3.4 Allyl 2,3,4-tri-*O*-benzyl-6-O-tosyl-*α*-*D*-glucopyranoside (**8b**)



8b

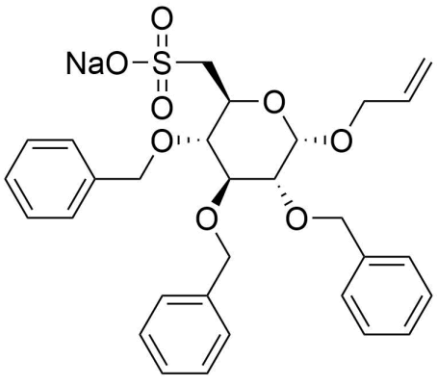
To a solution of compound **7b** (500 mg, 1 mmol) in pyridine (50 ml), tosyl chloride (470 mg, 2.5 mmol) was added while stirring. The mixture was stirred at room temperature for 24 hours. At the end of the reaction period, water (20 ml)was added to the mixture and the aqueous phase was extracted with EtOAc (4x30 ml). The combined organic layer was washed with brine (3x40 ml) and dried over $MgSO_4$, before the solvents were removed under reduced pressure. The resulting residue was purified on silica (1:4 EtOAc:*n*-pentane) to yield **8a** (550 mg, 0.86 mmol, 86%) as a yellow oil, R_f = 0.8 (EtOAc:*n*-pentane 1:4), t_R (HPLC) = 31.65 min, **^{1}H-NMR** (600 MHz, $CDCl_3$) δ: 7.76 (d, 2H, *J*= 8.38, CH-ArTs), 7.25-7.36 (m, 15H, Ar-CH), 7.14 (m, 2H, CH-ArTs) 5.88 (dddd, 1H, *J*=17.24, 10.51, 6.64, 5.27, H-8), 5.27 (m, 1H, *J*= 17.21, 1.39, H-9a), 5.19 (m, 1H, *J*= 10.51, 1.91, H-9b), 4.98 (d, 1H, *J*= 11.05, CH_2-Ar), 4.82 (d, 1H, *J*= 10.77, CH_2-Ar), 4.77 (d, 1H, *J*= 10.90, CH_2-Ar), 4.73 (d, 1H, *J*= 11.86, CH_2-Ar), 4.7 (d, 1H, *J*= 3.76, H-1), 4.61 (d, 1H, *J*= 11.96m CH_2-Ar), 4.42 (d, 1H, *J*= 10.99, CH_2-Ar), 4.22 (dd, 1H, *J*= 10.62, 4.33, H-6a), 4.16 (dd, 1H *J*= 10.48, 4.23, H-6b), 4.07 (m, 1H, *J*= 12.6, 5.32, 1.67, H-7a), 3.97 (t, 1H, 9.41, H-3), 3.93 (m, 1H, *J*= 12.7, 6.54, 1.81, H-7b), 3.81 (m, 1H, *J*= 9.63, 4.21, 2.16, H-5), 3.47 (dd, 1H, *J*= 9.43, 3.78, H-2), 3.45 (dd, 1H, *J*= 9.47, 8.45, H-4), 2.38 (s, 3H, Me), **^{13}C-NMR** (150 MHz, $CDCl_3$) δ: 144.84 (Ar-Cq), 138.63 (Ar-Cq), 138.03 (Ar-Cq), 137.88 (Ar-Cq), 133.47 (C-8), 132.91 (Ar-CH), 129.81 (Ar-CH), 128.47 (Ar-CH), 128.42 (Ar-CH), 128.07 (Ar-CH), 128.01 (Ar-CH), 127.97 (Ar-CH), 127.95 (Ar-CH), 127.87 (Ar-CH), 127.65 (Ar-CH), 118.43 (C-9), 95.53 (C-1), 81.82 (C-3), 79.72 (C-2), 77.22 (C-4), 75.70 (CH_2-Ar), 75.03 (CH_2-Ar), 73.26 (CH_2-Ar), 68.70 (C-5), 68.59 (C-6), 68.37 (C-7), 21.63 (Me). HRMS (ESI+) m/z: 667.2346 $[M+Na]^+$calc. for $C_{37}H_{40}O_8SNa$ 667.2342, IR(cm^{-1}): 3030 (w), 2923 (w), 2869 (w), 1453 (m), 1362 (s), 1176 (s), 1089 (s), 1071 (s), 1027 (s), 976 (s), 930 (s), 813 (s), 736 (s), 696 (s). Spectroscopic data corresponds with previously reported values.[4]

6.3.5 Allyl 2,3,4-*tri*-*O*-benzyl-6-thioacetate-*α*-*D*-glucopyranoside (**9b**)



Compound **8b** (600 mg, 0.93 mmol) was dissolved in ethanol (25 ml, 98.9%). While stirring potassium thioacetate (276 mg, 2.4 mmol) was added. The solution was stirred for three hours at reflux. At the end of the reaction period, water (20ml) was added to the reaction mixture and the aqueous phase was extracted with EtOAc (4x50 ml). The combined organic layer was washed with brine (3x40 ml) and dried over $MgSO_4$, before the solvents were removed under reduced pressure. The resulting residue was purified on silica (1:10 EtOAc:*n*-pentane) to yield compound **9a** (427 mg, 0.78 mmol, 84%) as a light yellow oil, R_f = 0.7 (EtOAc:*n*-pentane 1:10), t_R (HPLC) = 32.17 min, ^{1}**H-NMR** (600 MHz, $CDCl_3$) δ: 7.26-7.38 (m, 15H, CH-Ar) 5.91 (dddd, 1H, *J*=17.21, 10.34, 6.62, 5.24, H-8), 5.31 (m, 1H, *J*= 17.21, 1.39, H-9a), 5.22 (m, 1H, *J*= 10.41, 1.41, H-9b), 4.99 (d, 1H, *J*= 10.77, CH_2-Ar), 4.88 (d, 1H, *J*= 10.64, CH_2-Ar), 4.80 (d, 1H, *J*= 11.03, CH_2-Ar), 4.75 (d, 1H, *J*= 12.03, CH_2-Ar), 4.73 (d, 1H, *J*= 3.62, H-1), 4.63 (d, 1H, *J*= 12.21, CH_2-Ar), 4.61 (d, 1H, *J*= 10.49, CH_2-Ar) 4.15 (m, 1H, *J*= 12.7, 6.52, 1.40, H-7a), 3.99 (t, 1H, *J*= 9.65, H-3), 3.97 (m, 1H, *J*= 12.7, 5.53, 1.39, H-7b), 3.81 (ddd, 1H, *J*= 9.73, 4.22, 2.17, H-5), 3.51 (dd, 1H, *J*= 9.69, 3.60, H-2), 3.42 (dd, 1H, *J*= 13.5, 4.23, H-6b), 3.31 (t, 1H, *J*= 9.57, H-4) 3.0 (dd, 1H, *J*= 13.55, 4.62, H-6b), 2.39 (d, 3H, Me), ^{13}**C-NMR**(150 MHz, $CDCl_3$) δ: 194.92 (CO), 138.72 (Ar-CH), 138.13 (Ar-Cq), 138.13 (Ar-Cq), 137.96 (Ar-Cq), 133.54 (C-8), 128.51 (Ar-CH), 128.47 (Ar-CH), 128.45 (Ar-CH), 128.43 (Ar-CH), 128.22 (Ar-CH), 128.08 (Ar-CH), 128.02 (Ar-CH), 128.00 (Ar-CH). 127.90 (Ar-CH), 127.79 (Ar-CH), 127.67 (Ar-CH), 127.66 (Ar-CH), 118.41 (C-9), 95.24 (C-1), 81.82 (C-3), 80.59 (C-4), 79.96 (C-2), 75.75 (CH_2-Ar), 75.23 (CH_2-Ar), 73.18 (CH_2-Ar), 69.47 (C-5), 68.07 (C-7), 30.93 (C-6), 30.53 (Me). HRMS (ESI+) m/z: 571.2130 $[M+Na]^+$calc. for $C_{32}H_{36}O_6SNa$ 571.2130, IR(cm^{-1}): 3030 (w), 2921 (w), 2867 (w), 1694 (s), 1496 (m), 1354 (m), 1359 (m), 1092 (s), 1071 (s), 1028 (s), 737 (s), 697 (s), 629 (s).

6.3.6 Allyl 2,3,4-tri-*O*-benzyl-6-sulfo-monosodium-*α*-*D*-glucopyranoside (**10b**)

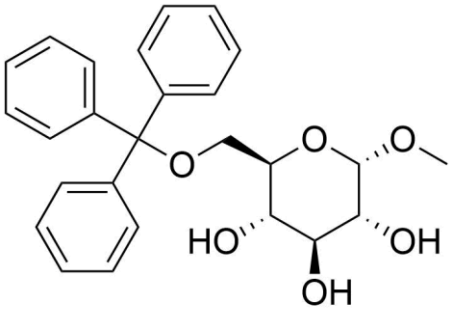


10b

Compound **9b (**500 mg, 0.91 mmol) was dissolved in glacial AcOH (10 ml) to which NaOAC (1.51 g, 18 mmol) and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 1.42 g, 18 mmol) were added while stirring at room temperature. After stirring for 12h, saturated aqueous $NaHCO_3$ (20 ml), saturated aqueous Na_2CO_3 (20 ml) and water (10 ml) were carefully added to the mixture. The solvents were removed under reduced pressure, and the resulting residue was freeze dried over 72 hours. CH_3CN (20 ml) was added to the crude product, stirred for 20 minutes, cooled in an ice bath, and filtered off. This procedure was repeated 3 times. The collected CH_3CN was removed under reduced pressure. The resulting crude product was eluting on silica column with a gradient starting with 1:10 (EtOAc:*n*-pentane) and followed by 1:3 MeOH:EtOAc to yield **10b (**403mg, 0.7mmol, 77%) as a white solid. **^{1}H-NMR** (600 MHz, CD_3OD) δ: 7.20-7.34 (m, 15H, CH-Ar), 5.95 (dddd, 1H, *J*=17.10, 10.34, 6.61, 5.23, H-8), 5.43 (m, 1H, *J*= 17.06, 1.32, H-9a), 5.21 (m, 1H, J = 10.42, 1.21, H-9b), 4.94 (d, 1H, *J*= 10.32, CH_2-Ar), 4.88(d, 1H, *J*= 3.78, H-1), 4.84(d, 1H, *J*= 11.24, CH_2-Ar), 4.72(d, 1H, *J*= 10.99, CH_2-Ar), 4.71(d, 1H, *J*= 10.86, CH_2-Ar), 4.68(d, 1H, *J*= 11.07), 4.61 (d, 1H, *J*= 11.27, CH_2-Ar), 4.36(m, 1H, *J*= 13.01, 5.21, 1.21, H-7a), 4.22 (1H, J = 9.37, H-5), 4.04(m, 1H, *J*= 13.05, 6.53, 1.28, H-7b) 3.97 (t, 1H, *J*= 9.34, H-3), 3.59(dd, 1H, *J*= 9.48, 3.68. H-2), 3.33 (m, 2H, H-4, H-6b), 2.90 (dd, 1H, *J*= 14.08, 9.47, H-6a)**^{13}C-NMR**(150MHz,CD_3OD) δ: Not resolved. See section 3.2.2. HRMS (ESI-) m/z: 553.1899 [M]calc. for $C_{30}H_{33}O_8S$ 553.1896, IR(cm^{-1}): 2986 (w), 2934 (w), 2893 (w), 1568 (m), 1454 (m), 1231 (s), 1164 (m), 1070 (s), 1017 (s), 846 (s), 736 (s), 696 (s).

6.4 Synthesis of 6-*O*-trityll derivates

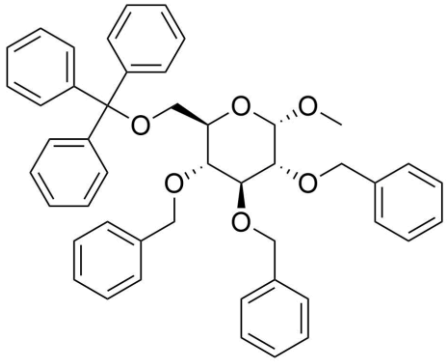
6.4.1 Methyl 6-*O*-trityl-*α*-*D*-glucopyranoside (**3a**)



3a

To methyl *α*-*D*-glucopyranoside (10.16 g, 52 mmol) solved in pyridine (100 ml), TrCl (triphenylmethyl chloride) (16.04 g, 57 mmol) and DMAP (635 mg, 5.2 mmol) were added while stirring. The mixture was stirred at 110°C for 8 hours before the reaction was terminated by the addition of water (40 ml).The mixture was extracted with EtOAc (3x100 ml). The combined organic layer was washed with brine (3x100 ml) and dried over anhydrous $MgSO_4$ before solvents were removed under reduced pressure. The resulting crude product was recrystalized using isopropanol to yield **3a** (14.5 g, 33.28 mmol, 64%) as white crystals. t_R (analytical HPLC) = 8.43 min, Mp: 143-151°C **^{1}H-NMR** (600 MHz, $CDCl_3$) δ: 7.45 (m, 6H, Ar-CH), 7.31 (m, 6H, Ar-CH), 7.24 (m, 3H), 4.77 (d, 1H, *J*= 3.75, H-1) 3.67 (m, 1H, H-3), 3.65 (dd, 1H, *J*= 9.23, 4.35, H-5), 3.50-3.55 (m, 2H,), 3.43 (s, 3H, OMe), 3.41 (dd, 1H, *J*= 9.82, 4.43, H-6a), 3.38 (dd, 1H, *J*= 10.13, 5.54, H-6b). **^{13}C-NMR**(150 MHz, $CDCl_3$) δ:143.66 (Ar-Cq),129.06 (Ar-CH), 127.95 (Ar-CH), 127.20 (Ar-CH), 99.06 (C-1), 74.77 (C-3), 72.27 (C-2), 71.91 (C-4), 69.76 (C-5), 64.04(C-6), 55.31 (OMe), 2.7 (bs, 1H, OH), 2.56 (d, 1H, *J*= 2.16, OH), 2.13 (d, 1H, *J*= 9.41, IH), HRMS (ESI+) m/z: 459.1784 $[M+Na]^+$calc. for $C_{26}H_{28}O_6Na$ 459.1784, IR(cm^{-1}): 3370 (br), 2969 (w), 2929 (w), 1447 (m), 1370 (m), 1148 (m), 1034 (s), 1000 (s), 951 (m), 700 (s), 634 (m). Spectroscopic data corresponds with literature values.[79]

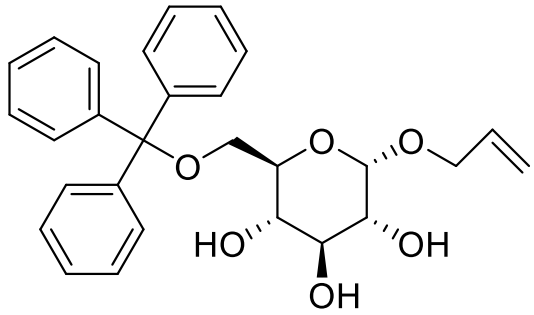
6.4.2 Methyl 2,3,4-*tri*-*O*-benzyl-6-O-trityl-*α*-*D*-glucopyranoside (**4a**)



4a

Compound **3a** (500 mg, 1.2 mmol), NaH (124 mg, 5.1 mmol) and TBAI (32 mg, 0.1 mmol) were dissolved in dry THF (20 ml) and benzyl bromide (0.61 ml, 5.1 mmol) was added to the mixture, while stirring at room temperature. The mixture was stirred for 24 hours at room temparature. The reaction was terminated with the addition of water (10 ml) and was then extracted with EtOAc (3x40 ml). The combined organic layer was then washed with brine (3x40 ml) and dried over $MgSO_4$. The solvent was then removed under reduced pressure. The residue was purified on silica column with a gradient starting with 1:40 EtOAc:*n*-pentane increasing to 1:20 and lastly 1:10 to yield **4a** (636 mg, 0.9 mmol, 76%) as a glassy solid, R_f = 0.8(1:10 EtOAc:*n*-pentane) t_R (HPLC) = 39.01 min, **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 6.83-7.51 (m, 30H, CH-Ar), 4.94 (d, 1H, *J*= 10.74, O-3-CH_2-Ar), 4.83 (d, 1H, *J*= 12.18, O-2-CH_2-Ar), 4.80 (d, 1H, *J*= 10.81, O-3-CH_2-Ar), 7.76(d, 1H, *J*= 3.69. H-1), 4.72 (d, 1H, *J*= 12.12, O-2-CH_2-Ar), 4.68 (d, 1H, *J*= 10.47, O-4-CH_2-Ar), 4.28 (d, 1H, *J*= 10.47, O-4-CH_2-Ar), 3.96 (t, 1H, *J*= 9.35, H-3), 3.80 (bdd, 1H, *J*= 10.21, 3.20, 1.63, H-5), 3.58- 3.64 (m, 2H, *J*= 3.67, 9.43, 9.82, H-2, H-4), 3.49 (dd, 1H, *J*= 10.12, 1.74, H-6a), 3.44 (s, 3H, OMe), 3.18, (dd, 1H, *J*= 9.97, 4.72, H-6b) **^{13}C-NMR**(100 MHz, $CDCl_3$) δ: 143.98 (Ar-Cq), 138.74 (Ar-Cq), 138.35 (Ar-Cq), 137.95 (Ar-Cq), 129.82 (Ar-CH), 128.49 (Ar-CH), 128.46 (Ar-CH), 128. 21 (Ar-CH), 128.18 (Ar-CH), 128.07 (Ar-CH), 128.04 (Ar-CH), 127.88 (Ar-CH), 127.70 (Ar-CH), 127.58 (Ar-CH), 126.95 (Ar-CH), 97.93 (C-1), 82.32 (C-3), 80.26 (C-2), 78.12 (C-4), 76.01 (O-3-CH_2-Ar), 75.01 (O-4-CH_2-Ar), 73.38 (O-2-CH_2-Ar), 70.29 (C-5), 62.66 (C-6), 54.97 (CH_3), HRMS (ESI+) m/z: 729.3193 $[M+Na]^+$calc. for $C_{47}H_{46}O_6Na$ 729.3192, IR(cm^{-1}): 3028 (w), 2922 (m), 2853 (m), 1494 (m), 1452 (s), 1090 (m), 1056 (m), 1027 (m), 999 (m), 967 (m), 732 (s). Spectroscopic data corresponds with literature values.[7]

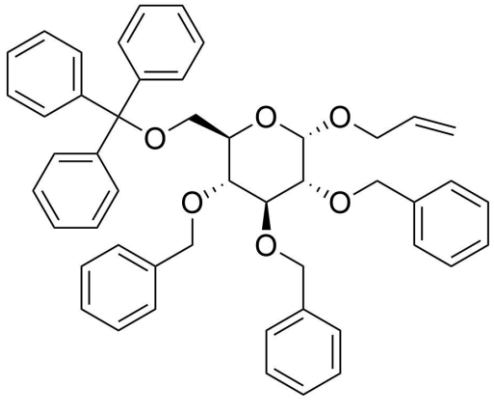
6.4.3 Allyl 6-*O*-trityl-*α*-*D*-glucopyranoside (**3b**)



3b

To a solution of *D*-*α*-glucose (1.81g, 10mmol) solved in allyl alcohol (30ml), TMSCl (6ml, 50mmol) was added while stirring. The mixture was stirred for 3 days at room temperature before the mixture was evaporated under reduced pressure. The resulting brown oil was dissolved in pyridine (30ml) and TrCl (3.0g, 12mmol) and DMAP (122mg, 1mmol) were added. The mixture was heated to 110°C and stirred for 8 hours before water (10ml) was added. The mixture was extracted with EtOAc (100ml x3). The resulting combined organic layer was washed with brine (100ml x3) and dried over anhydrous $MgSO_4$ before solvents were removed under reduced pressure to yield a yellow oil. A pure sample of the product could not be procured for analysis. See section 3.1.2

6.4.3 Allyl2,3,4-tri-*O*-benzyl-6-O-trityl-*α*-*D*-glucopyranoside (**4b**)



4b

The crude reaction mixture of **3b** (1.2 g, 3 mmol), NaH (432 mg, 15mmol) and TBAI (96 mg, 0.3 mmol) were dissolved in dry THF (25 ml) and benzyl bromide (1.43 ml, 15 mmol) was added to the mixture while stirring at room temperature. The mixture was heated to 60° C and stirred for 2 hours. The reaction was stopped with the addition of water (20ml) and was then extracted with EtOAc (3x40ml). The combined organic layer was then washed with brine (3x40ml) and dried over $MgSO_4$, before the solvent was removed under reduced pressure. A pure sample of the product could not be procured for analysis. See section 3.1.2

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Appendix

Appendix A. Spectroscopic data for **5a**

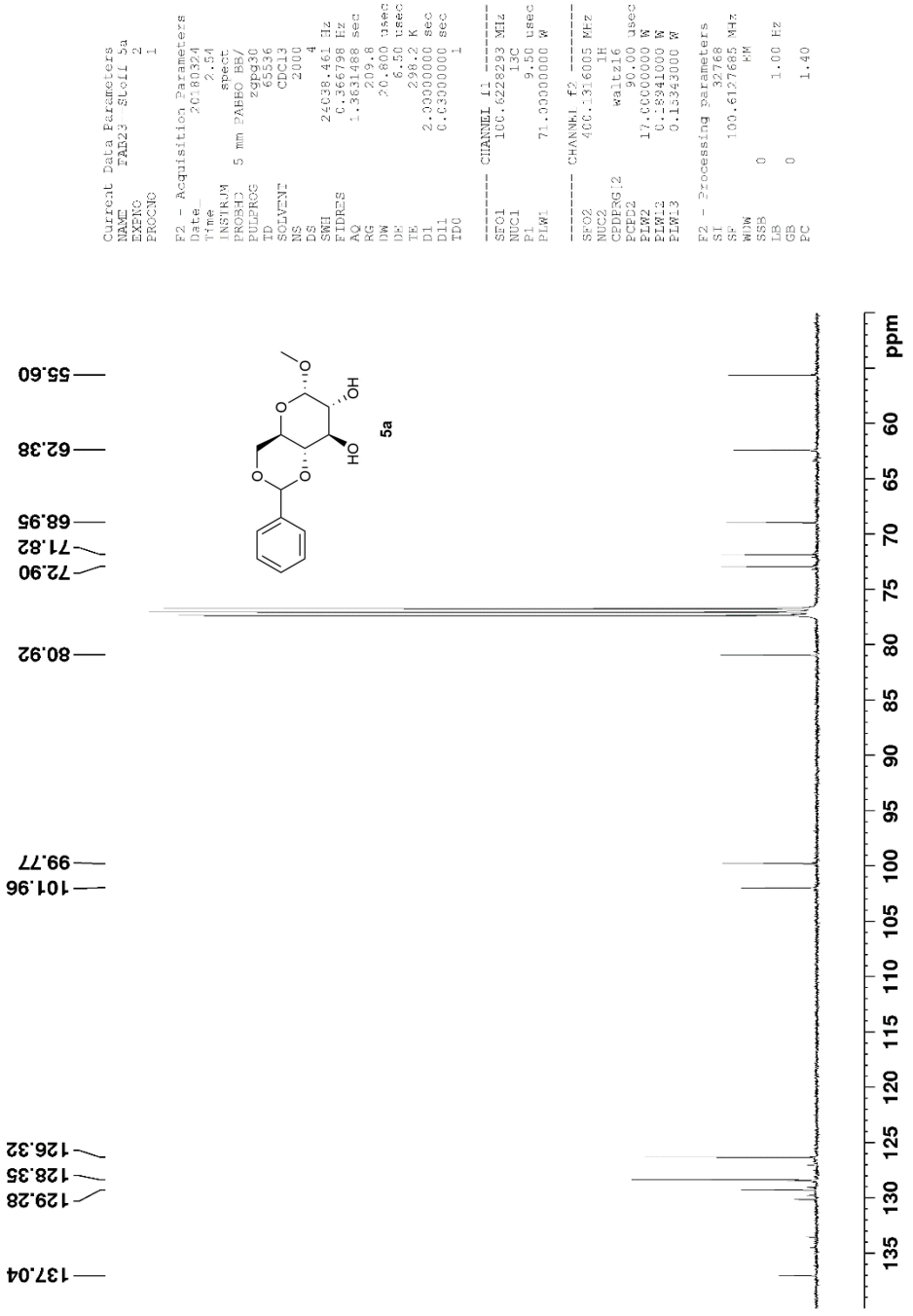


Figure A.1. ^{13}C-NMR spectrum of compound **5a.**

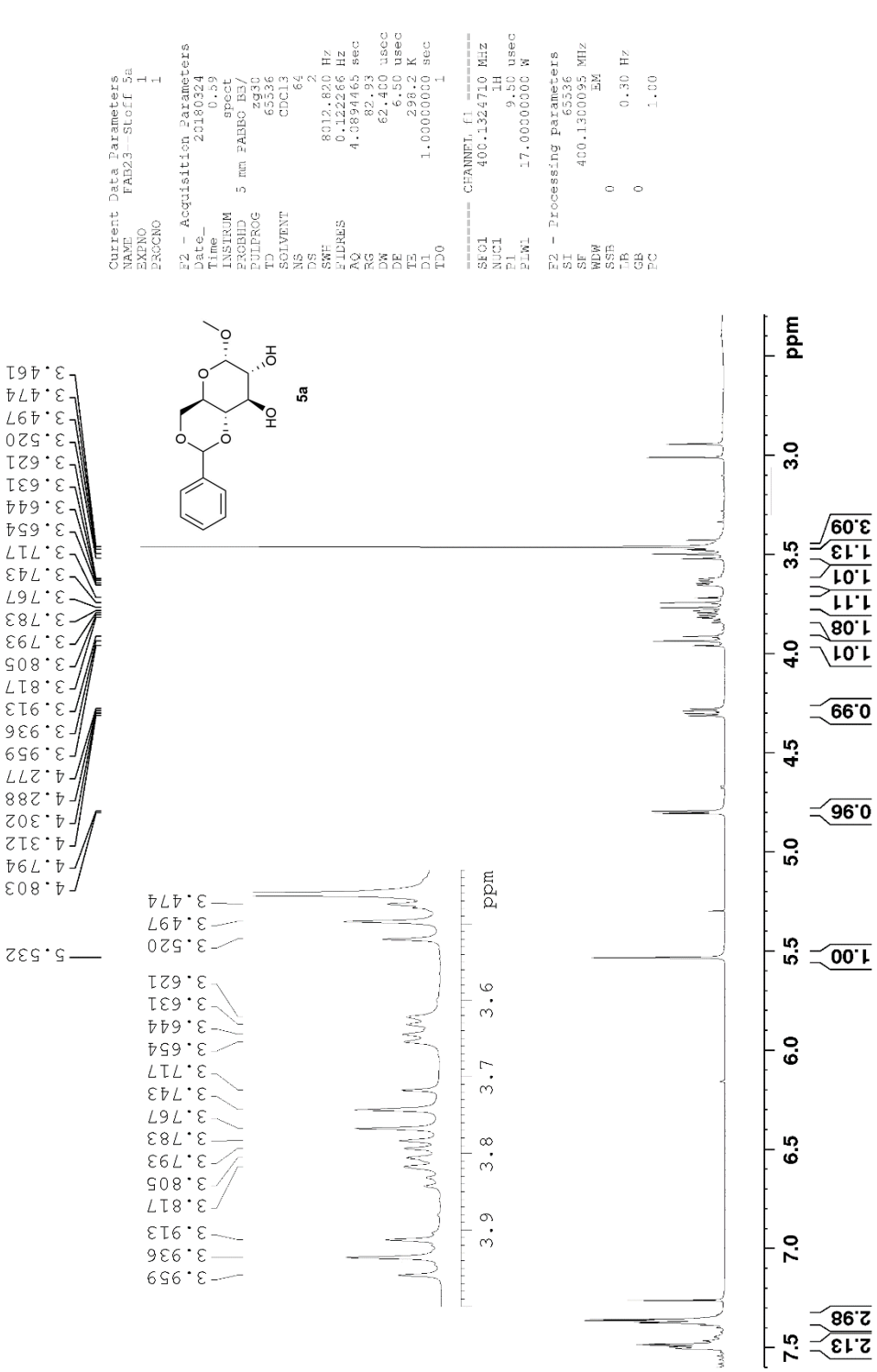


Figure A.2. [1]H-NMR spectrum of compound **5a.**

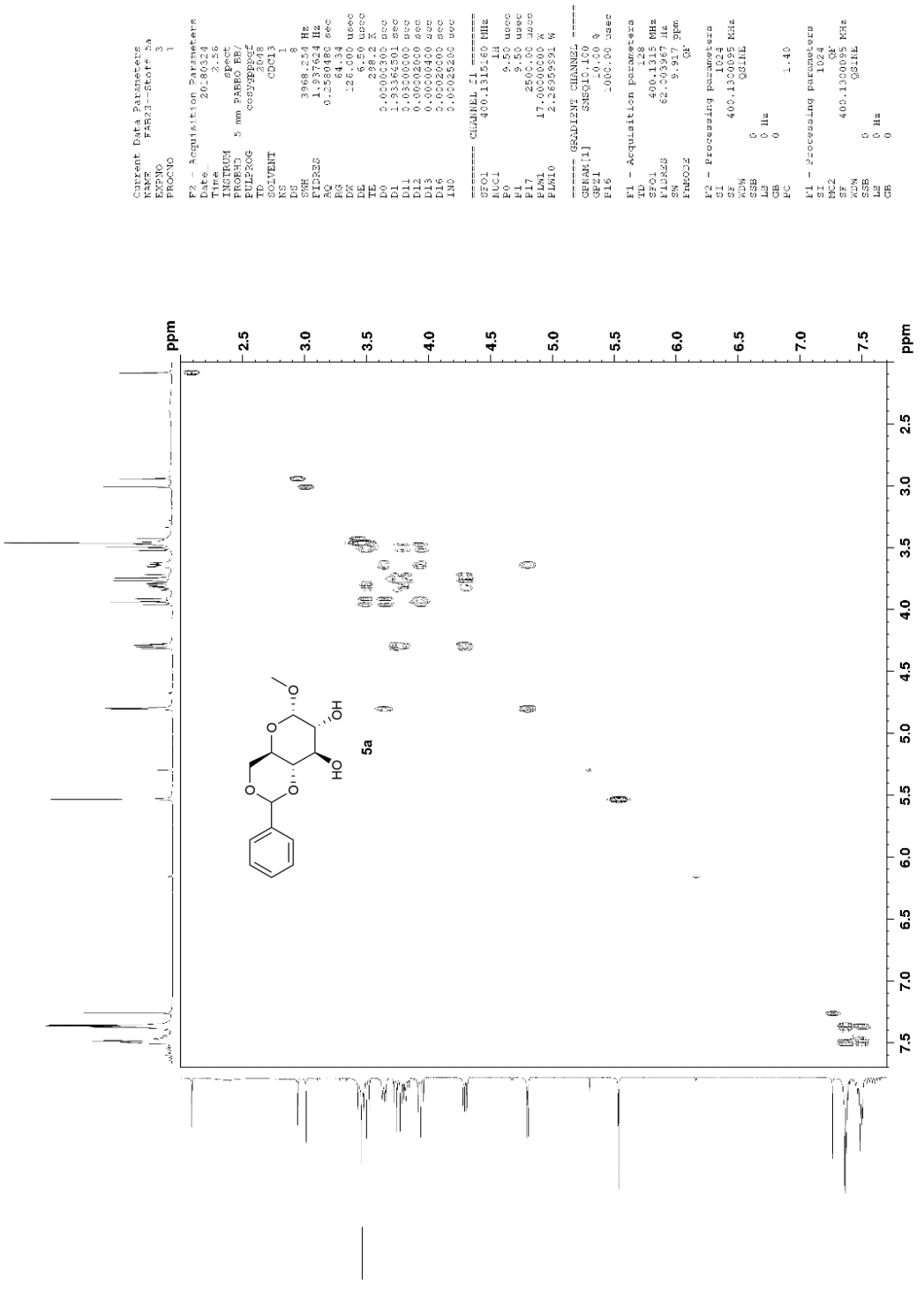


Figure A.3. COSY spectrum of compound **5a**.

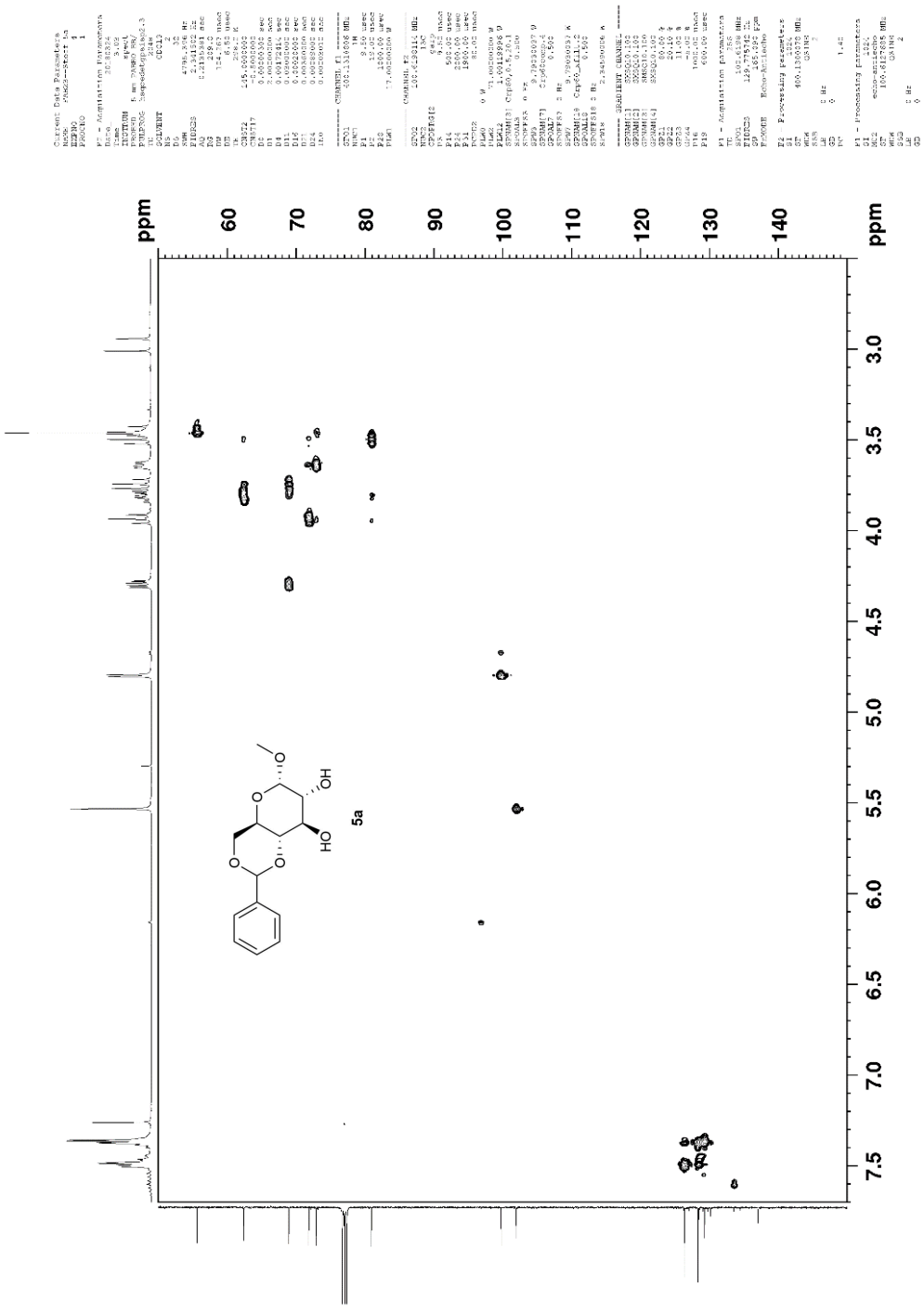


Figure A.4. HSQC spectrum of compound **5a**.

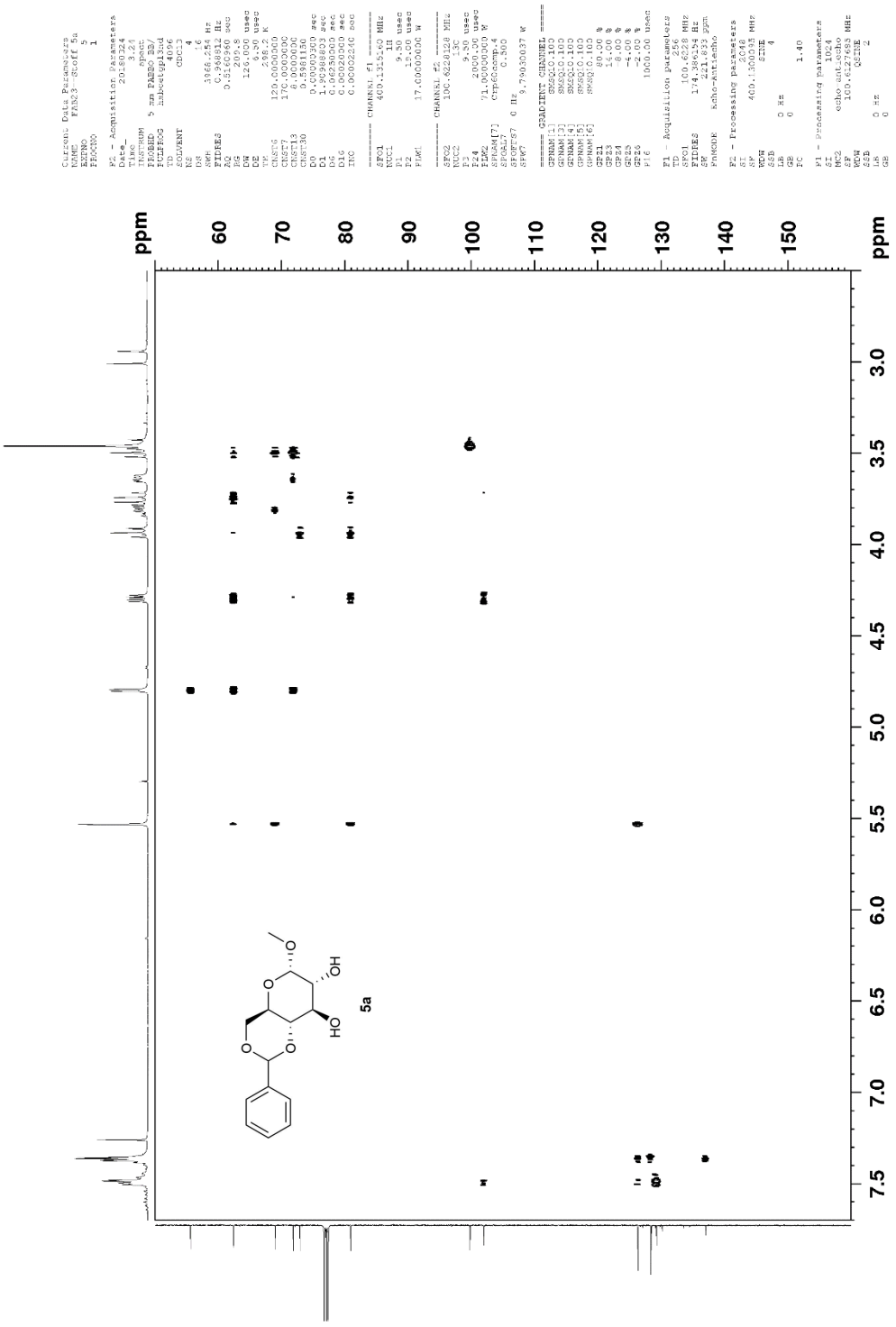


Figure A.5. HMBC spectrum of compound **5a**.

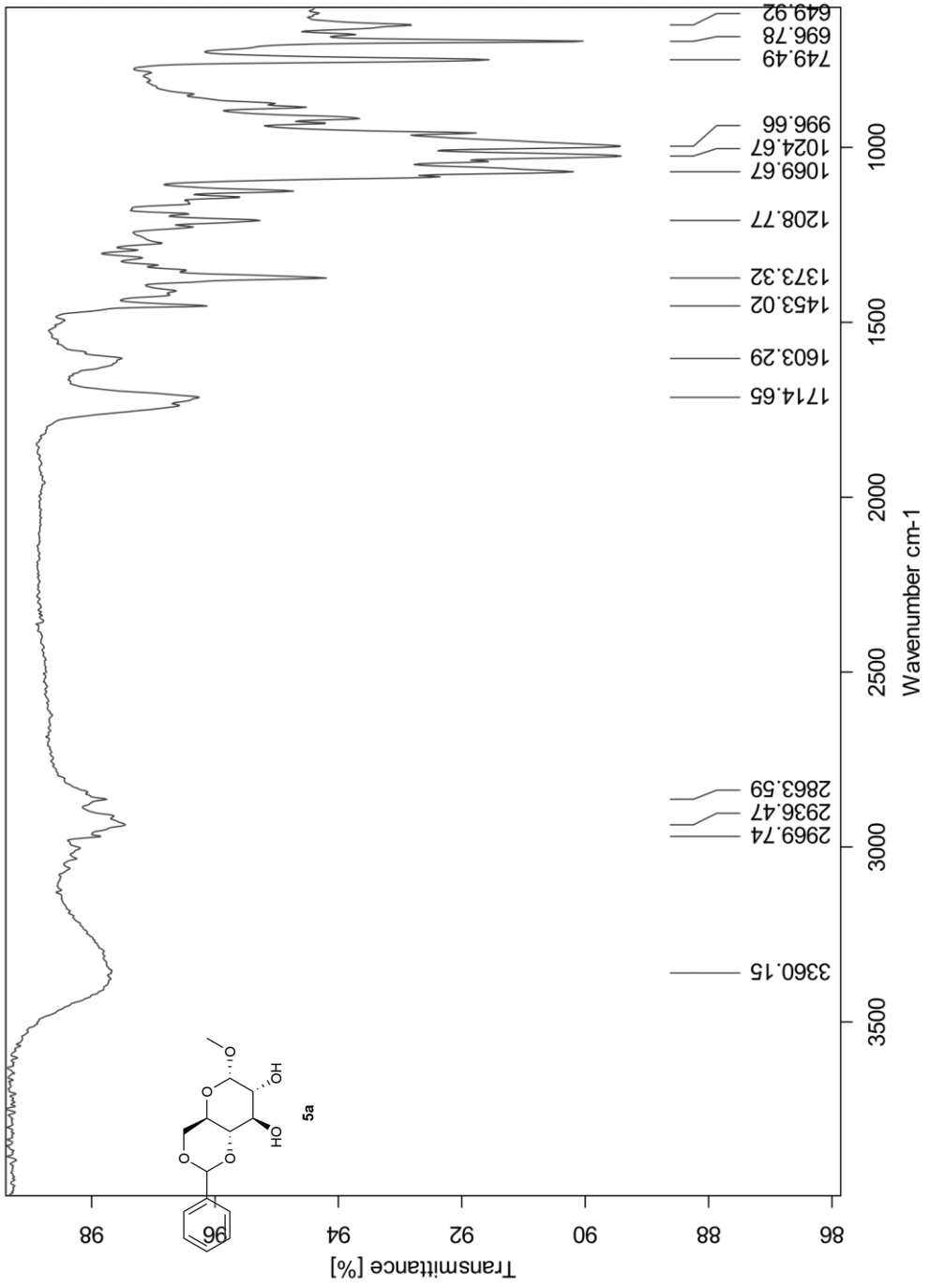
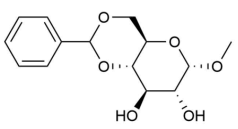


Figure A.6. IR spectrum of compound **5a**.

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

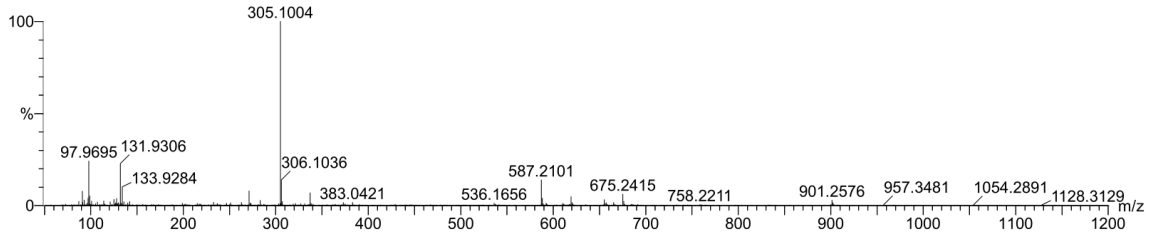


5a

Monoisotopic Mass, Even Electron Ions
819 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-10 Na: 0-1 Au: 0-1

2018-146 48 (0.900) AM2 (Ar,35000.0,0.00,0.00); Cm (47:49)
1: TOF MS ES+

5.99e+005



Minimum:				-1.5				
Maximum:		5000.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
305.1004	305.1001	0.3	1.0	5.5	1157.0	0.243	78.42	C14 H18 O6 Na
	305.0998	0.6	2.0	9.5	1158.3	1.533	21.58	C12 H13 N6 O4

Figure A.7. MS results for compound **5a**.

Appendix B. Spectroscopic data for compound **6a**

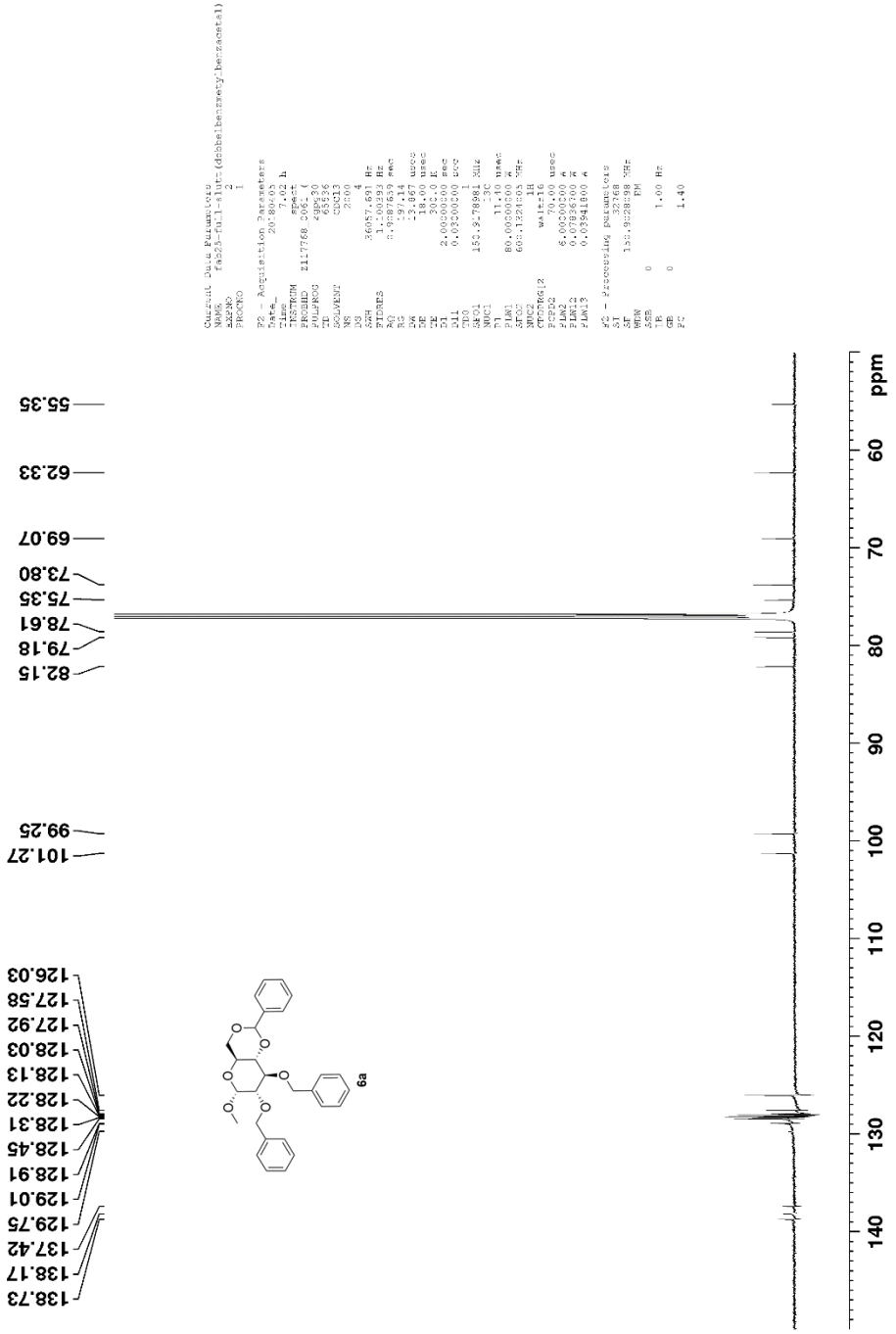


Figure B.1. ^{13}C.NMR spectrum of compound **6a**.

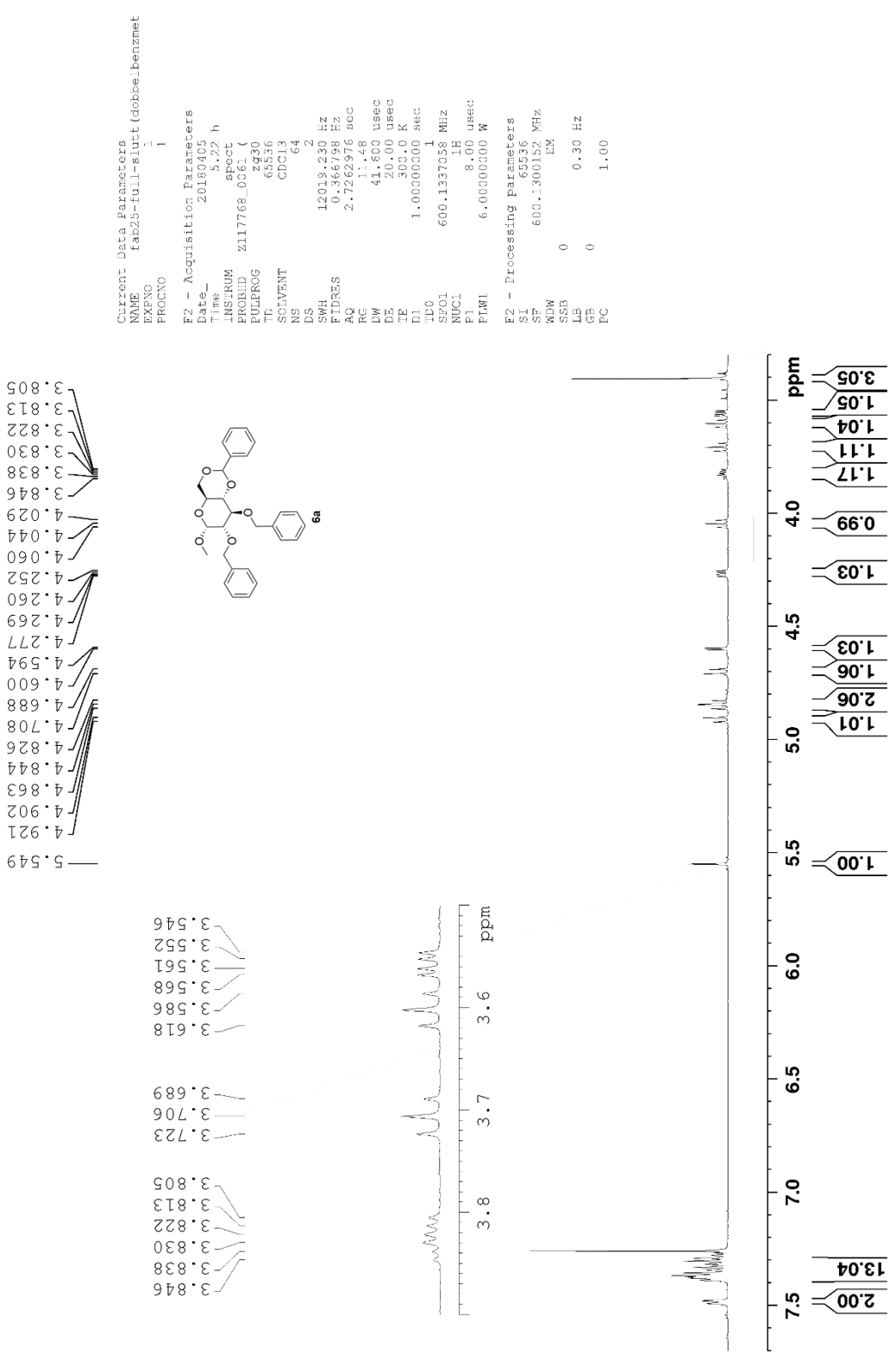


Figure B.2 ^{1}H-NMR spectrum of compound **6a**.

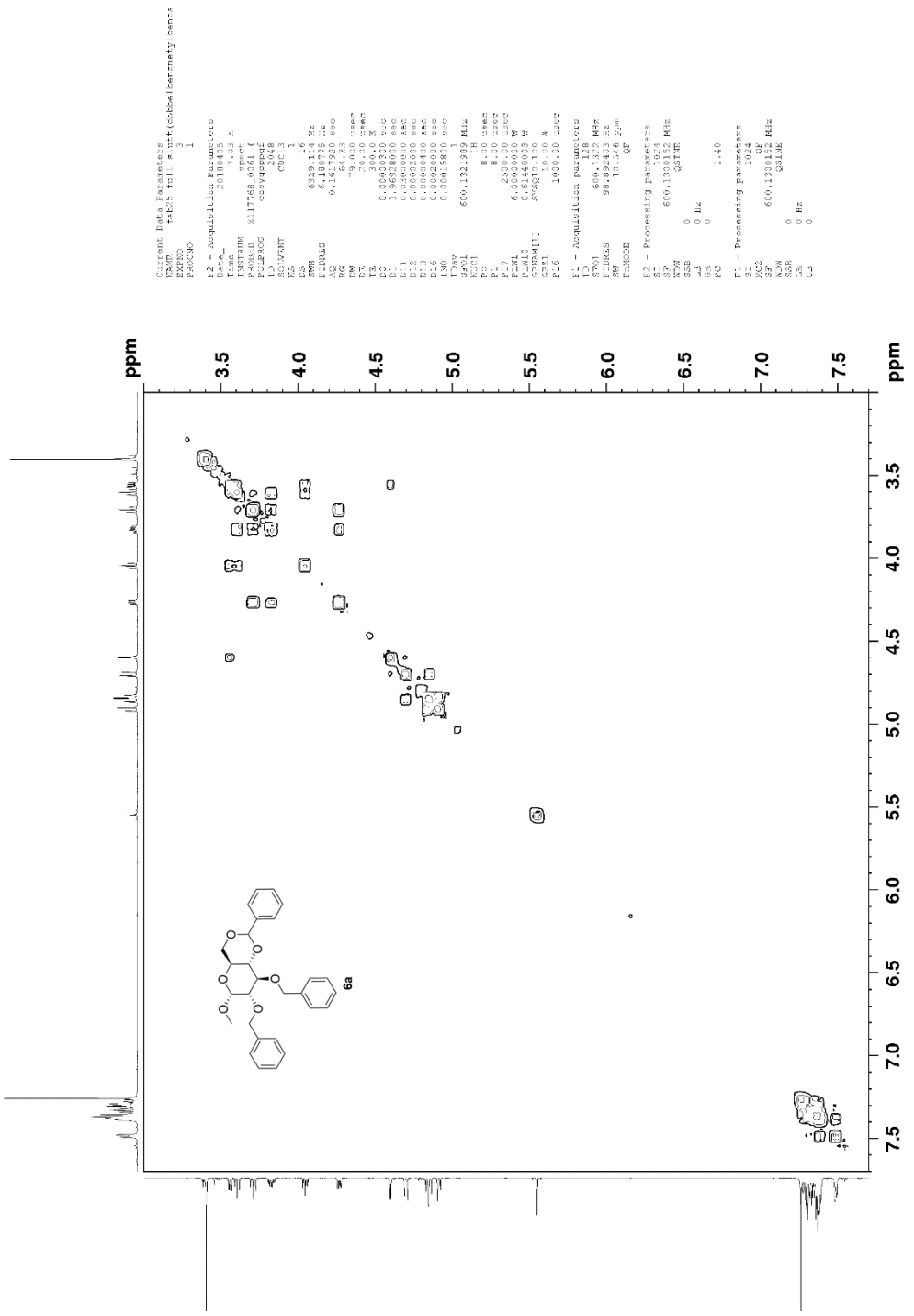


Figure B.3. COSY spectrum of compound **6a**.

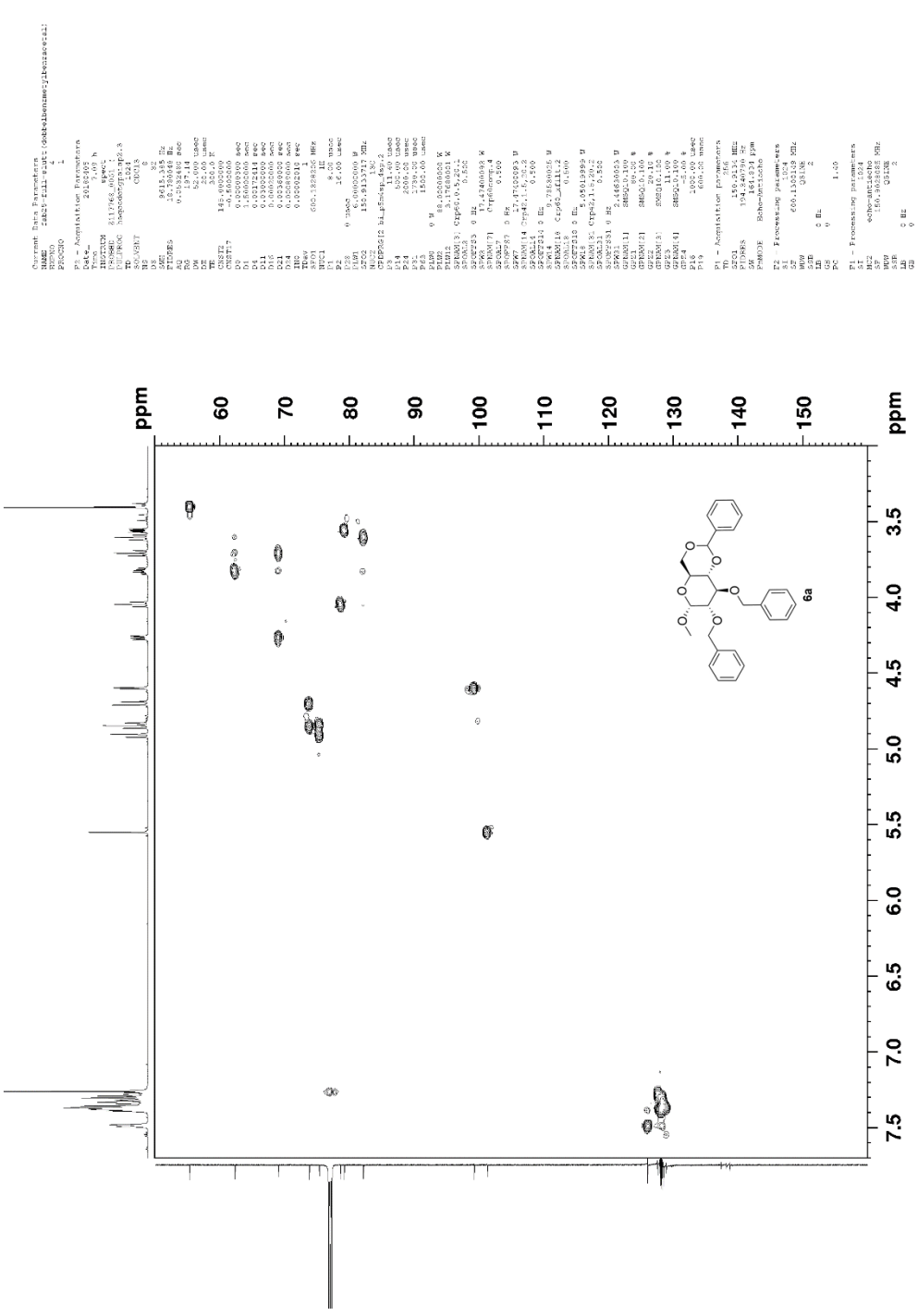


Figure B.4. HSQC spectrum of compound **6a**.

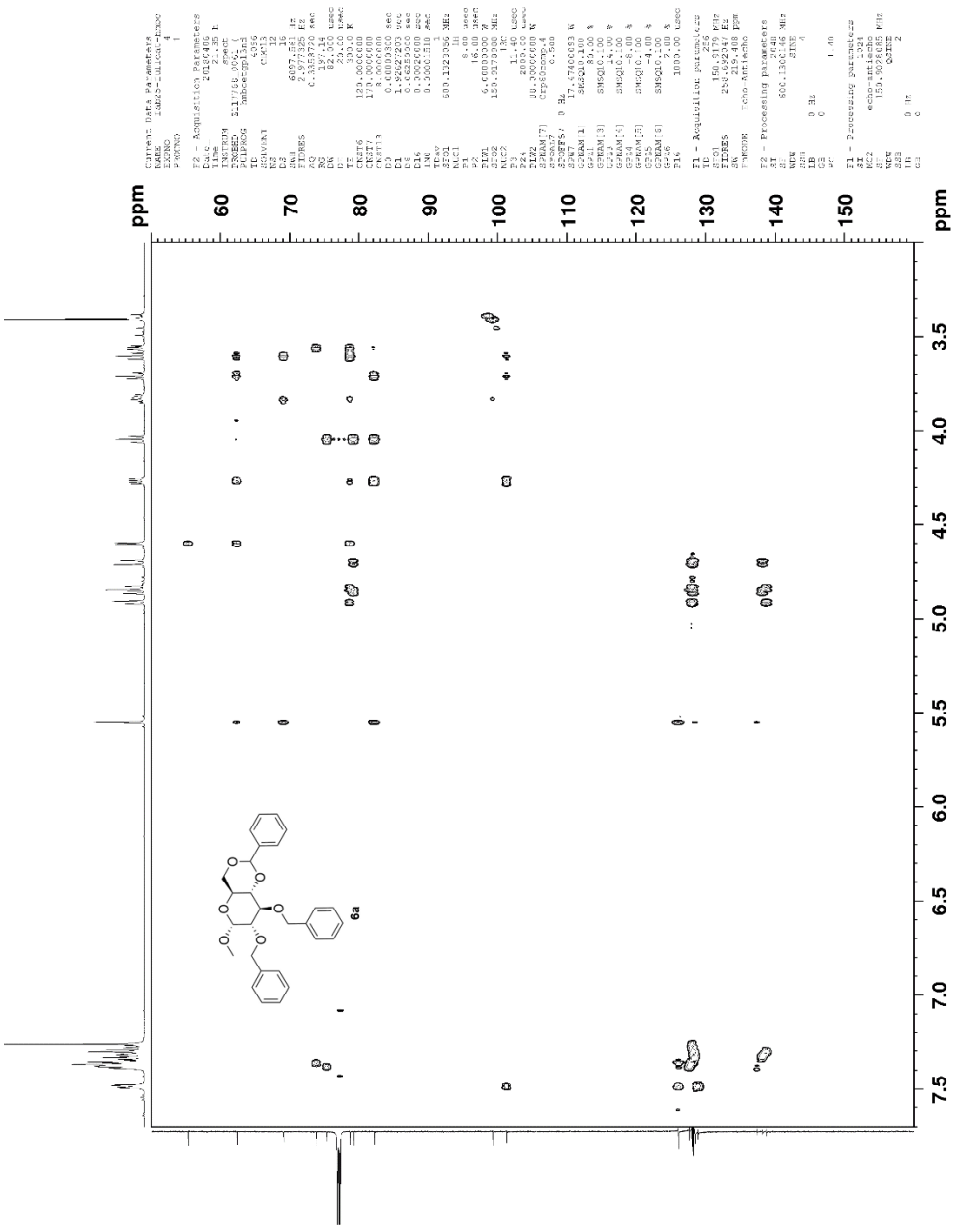


Figure B.5. HMBC spectrum of compound **6a**.

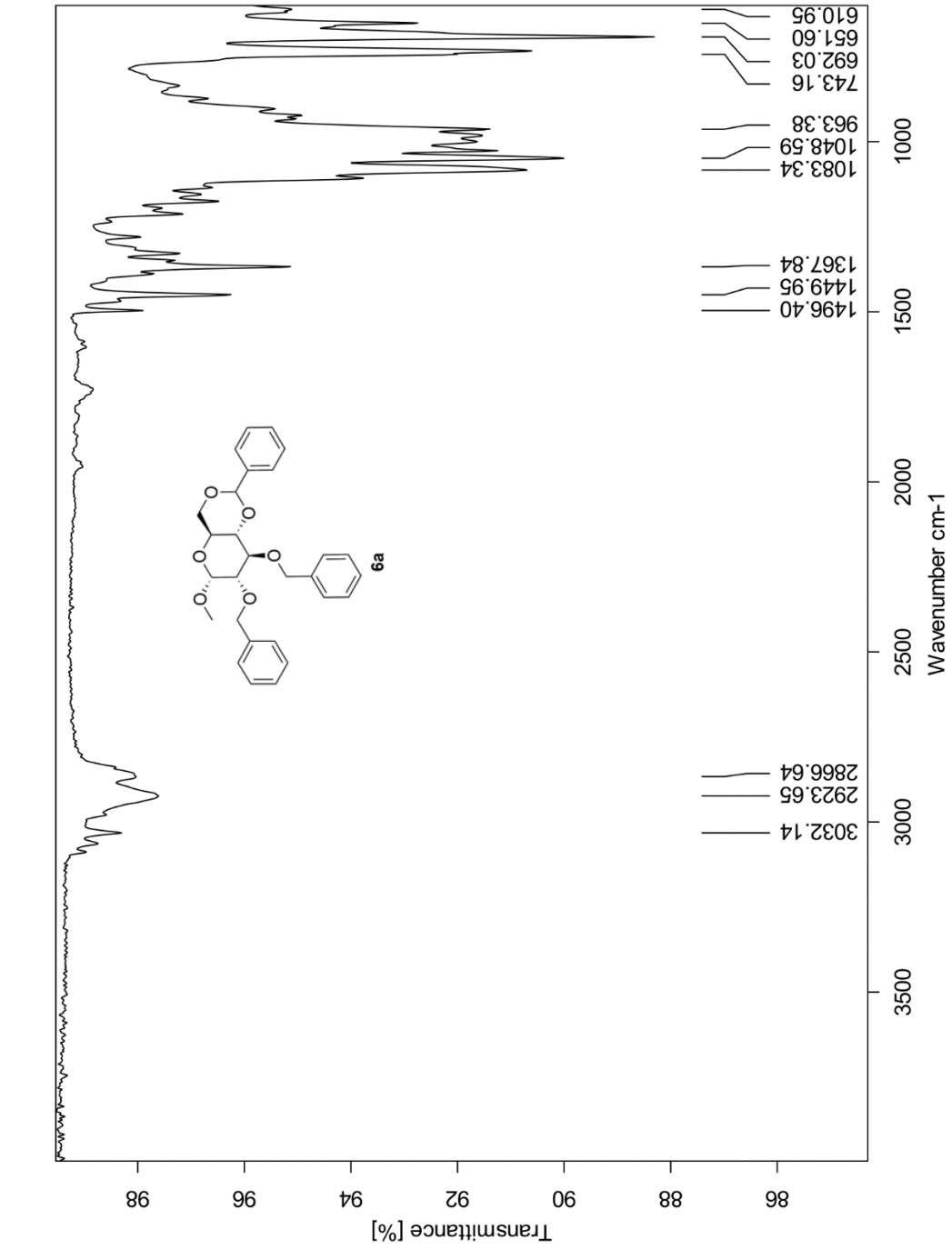


Figure B.6. IR spectrum of compound **6a.**

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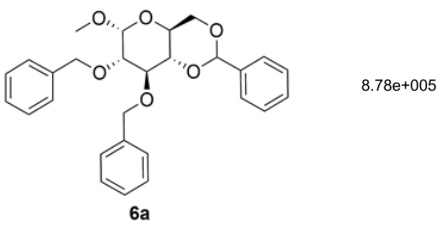
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 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
1253 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-10 Na: 0-1
2018-154 56 (1.048) AM2 (Ar,35000.0,0.00,0.00); Cm (53:56)
1: TOF MS ES+



8.78e+005

Minimum:				-1.5				
Maximum:		5000.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
485.1946	485.1951	-0.5	-1.0	22.5	988.9	2.524	8.01	C27 H21 N10
	485.1940	0.6	1.2	13.5	986.8	0.404	66.79	C28 H30 O6 Na
	485.1953	-0.7	-1.4	18.5	989.4	3.011	4.93	C29 H26 N4 O2 Na
	485.1937	0.9	1.9	17.5	988.0	1.596	20.27	C26 H25 N6 O4

Figure B.7. MS results for compound **6a.**

Appendix C. Spectroscopic data for compound **7a**

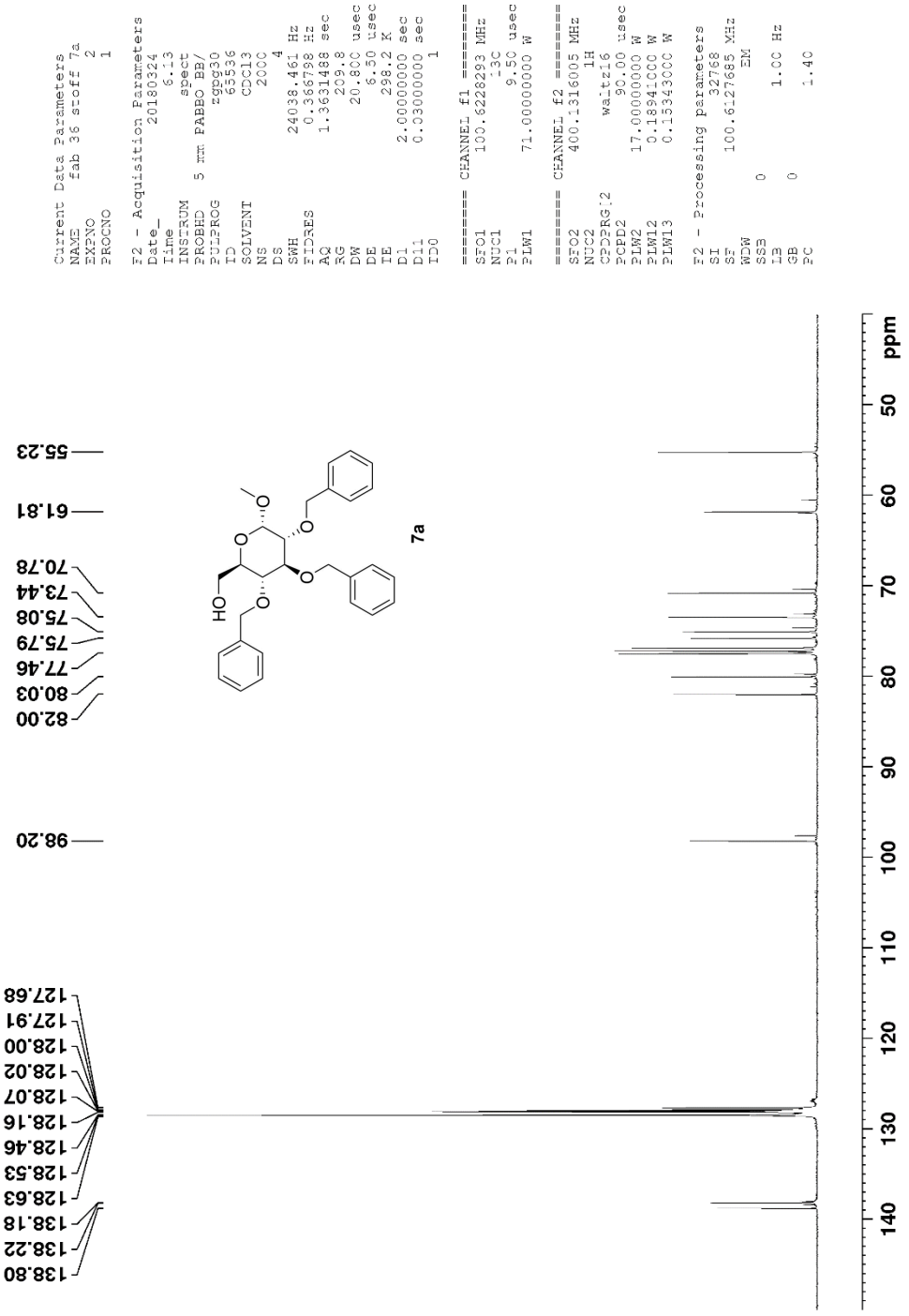


Figure C.1. ^{13}C-NMR spectrum of compound **7a**.

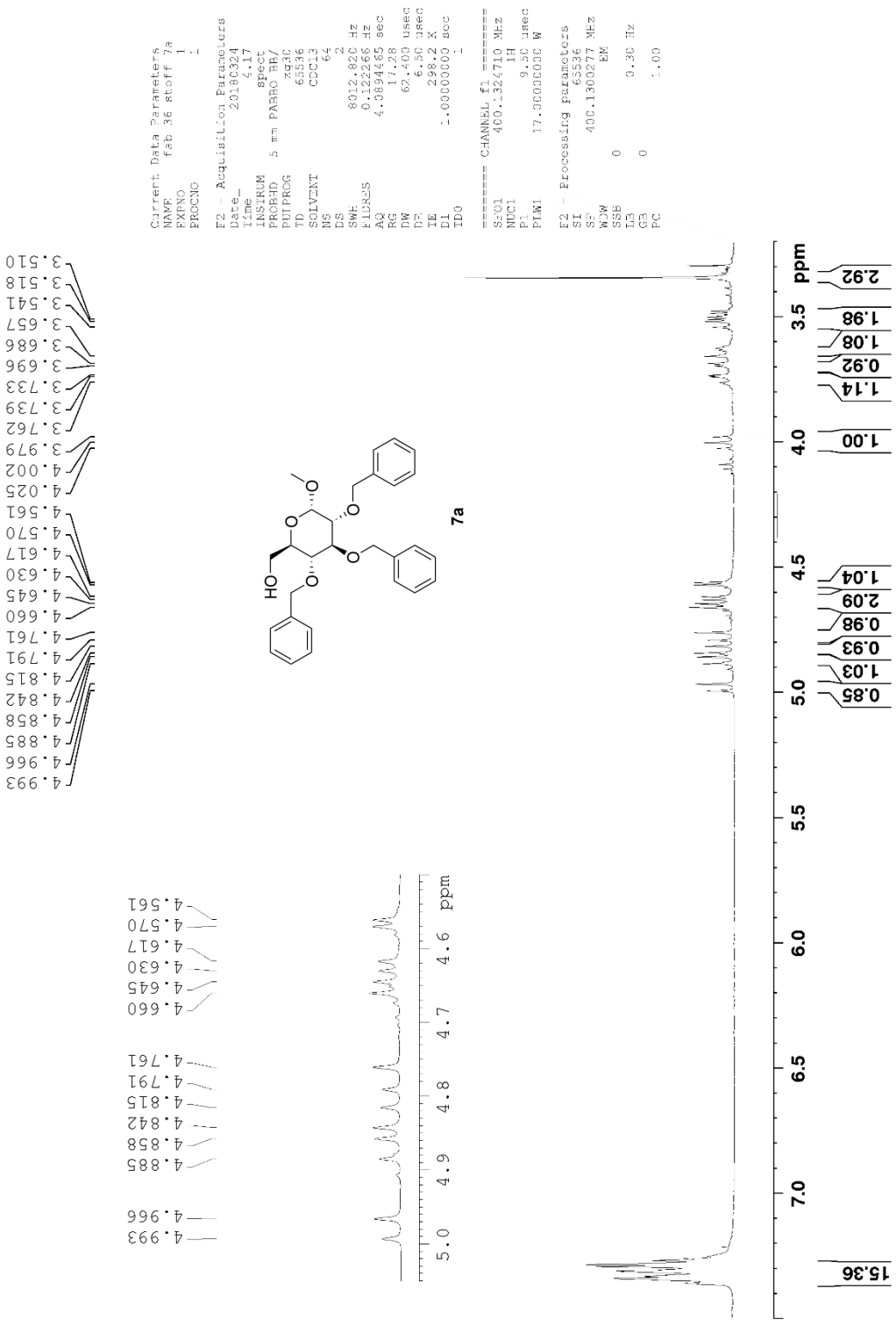


Figure C.2. [1]H-NMR spectrum of compound **7a**.

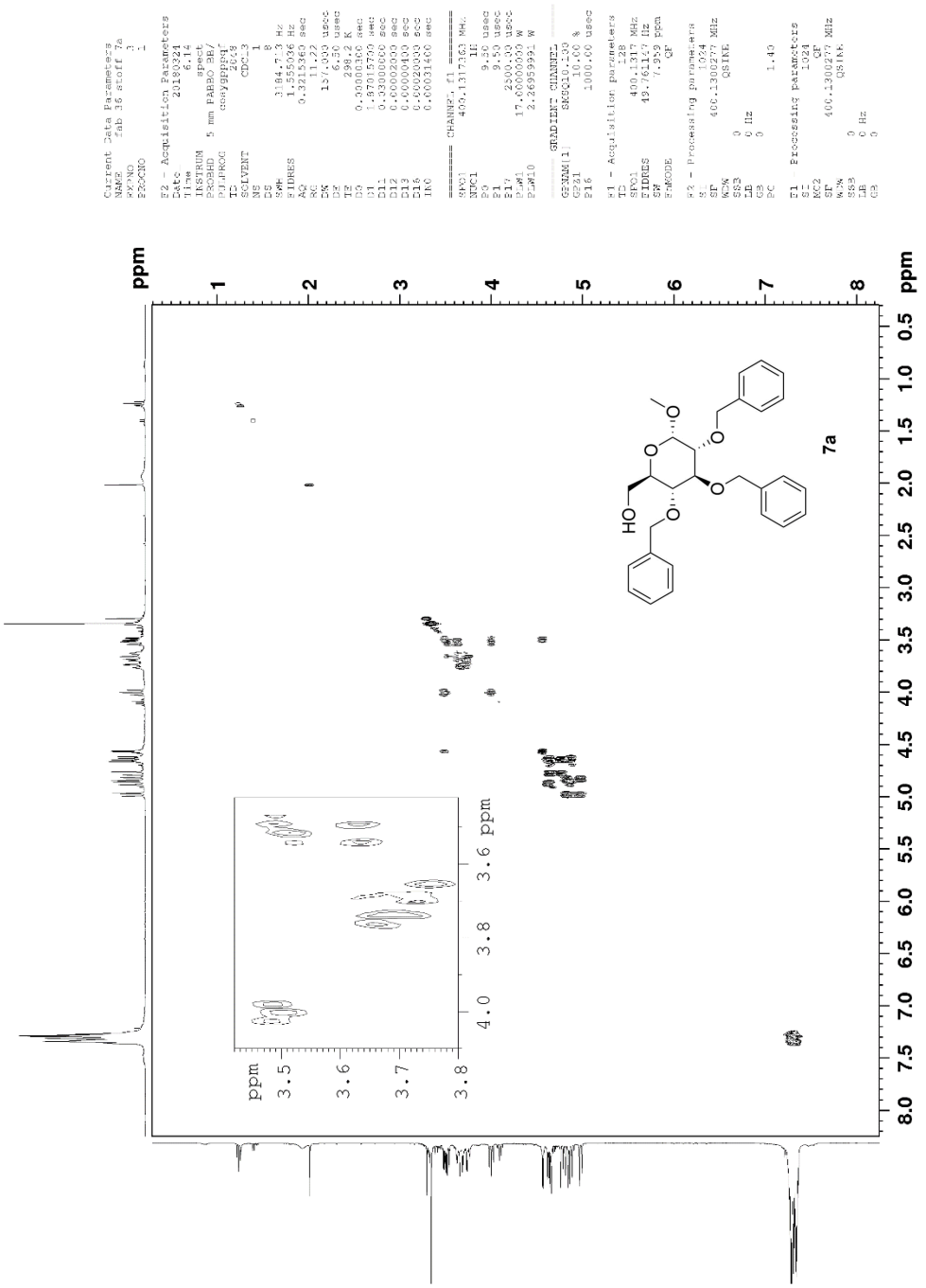


Figure C.3. COSY spectrum of compound **7a**.

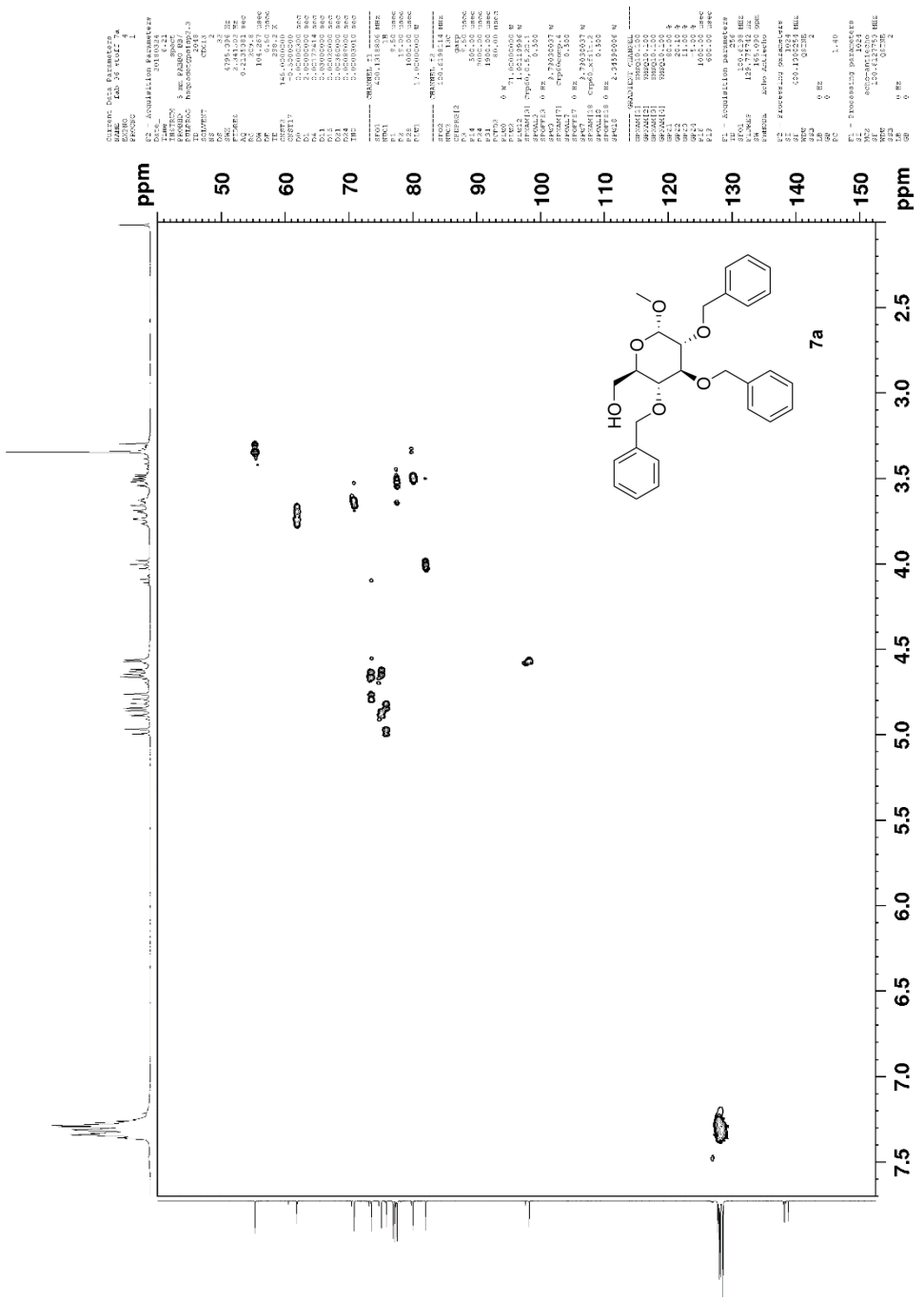


Figure C.4. HSQC spectrum of compound **7a**.

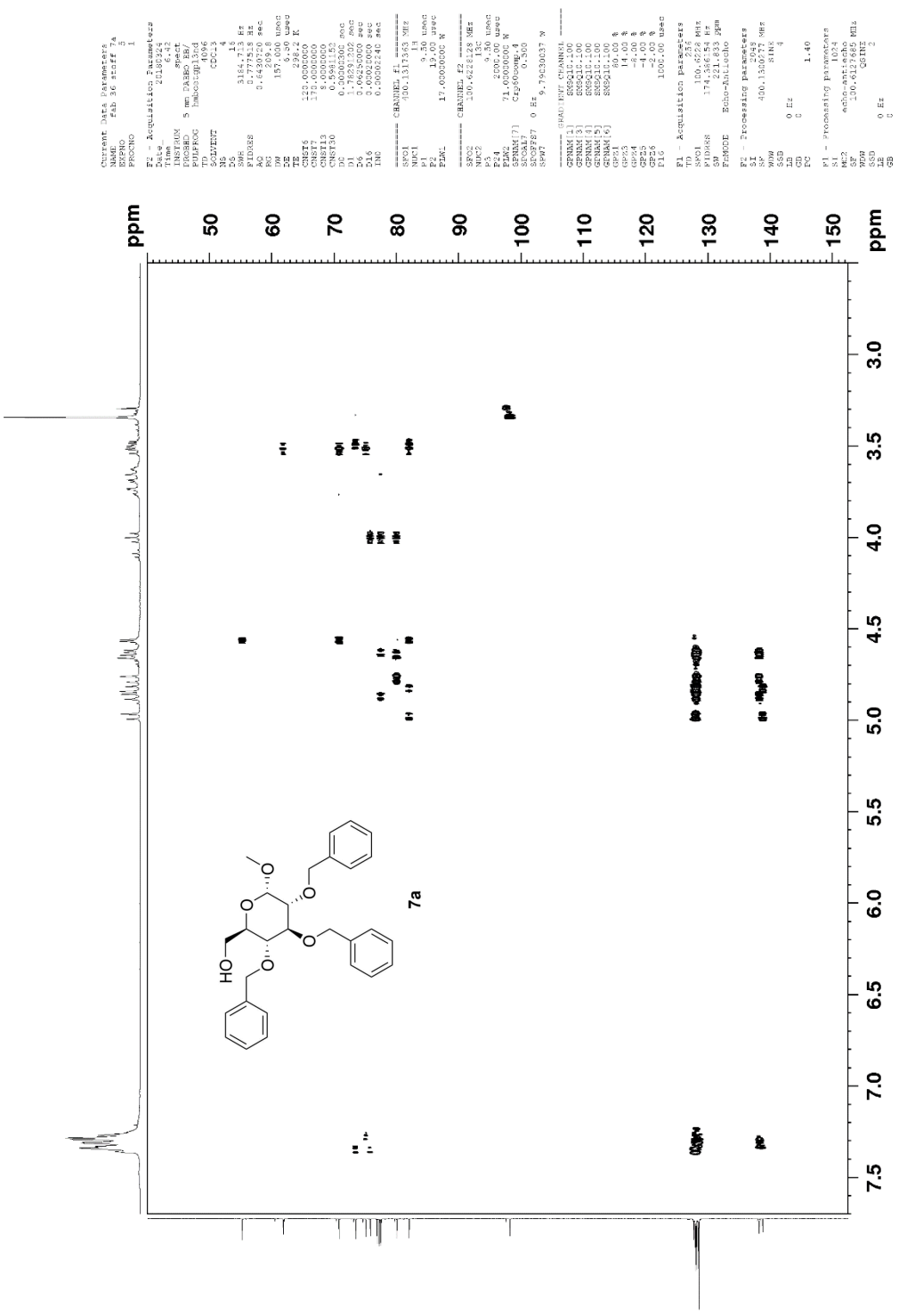


Figure C.5. HMBC spectrum of compound **7a**.

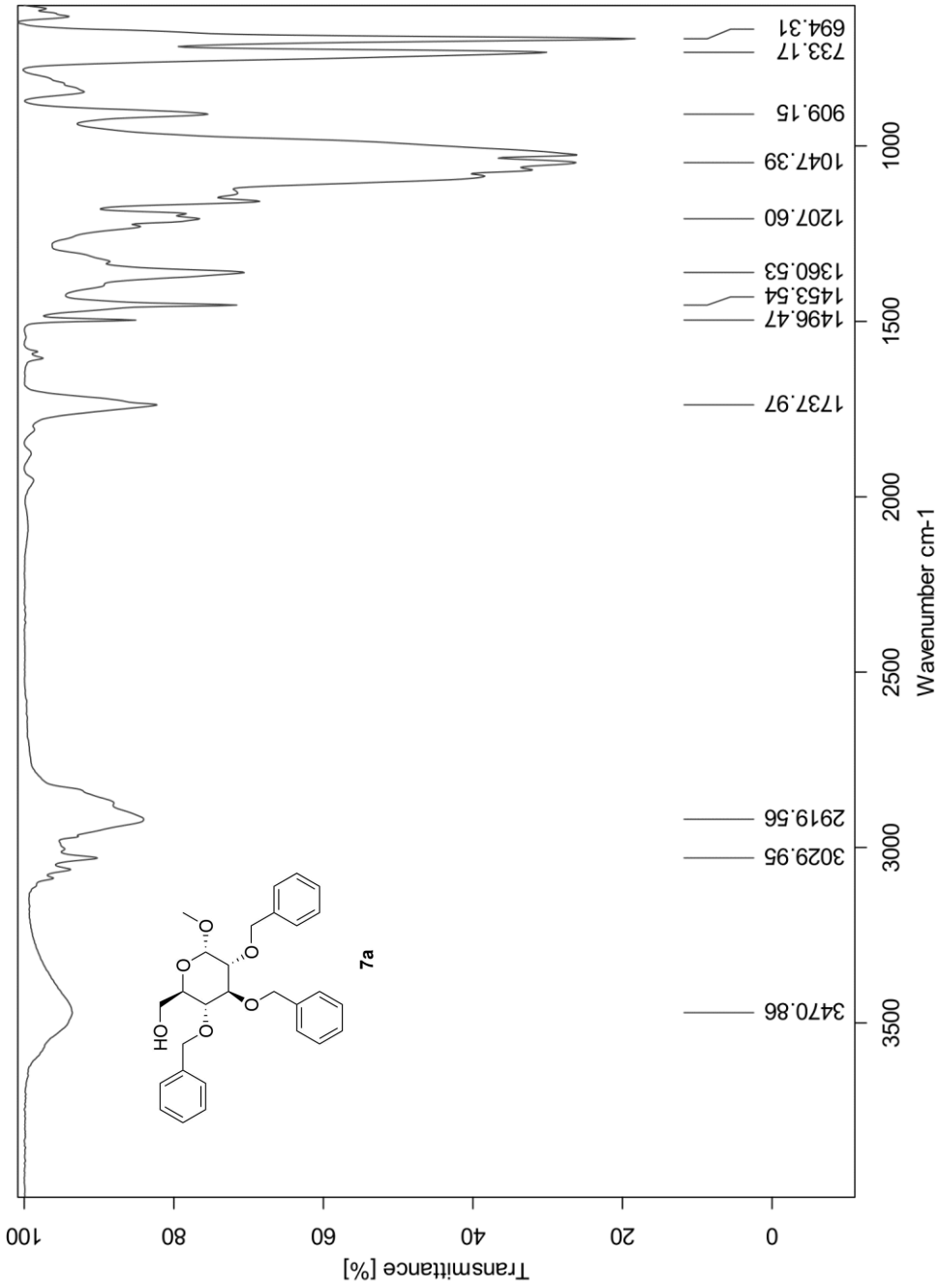
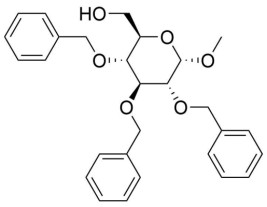


Figure C.6. IR spectrum of compound **7a**.

Elemental Composition Report **Page 1**

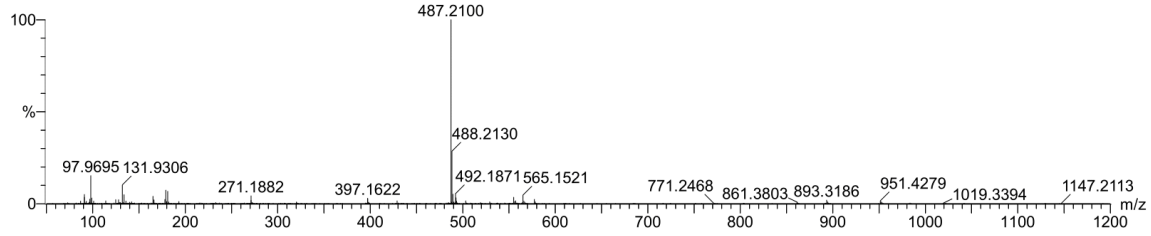


7a

Single Mass Analysis
Tolerance = 5.0 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
632 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 O: 0-10 Na: 0-1 S: 0-5
2018-159 53 (0.985) AM2 (Ar,35000.0,0.00,0.00); Cm (53:54)
1: TOF MS ES+

8.07e+005



Minimum:				-1.5				
Maximum:		5000.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
487.2100	487.2097	0.3	0.6	12.5	942.5	0.004	99.56	C28 H32 O6 Na
	487.2096	0.4	0.8	19.5	955.7	13.154	0.00	C34 H31 O S
	487.2105	-0.5	-1.0	11.5	958.8	16.331	0.00	C29 H36 O Na S2
	487.2121	-2.1	-4.3	15.5	947.9	5.415	0.44	C30 H31 O6

Figure D.6. MS results for compound **7a**.

Appendix D. Spectroscopic data for compound **8a**

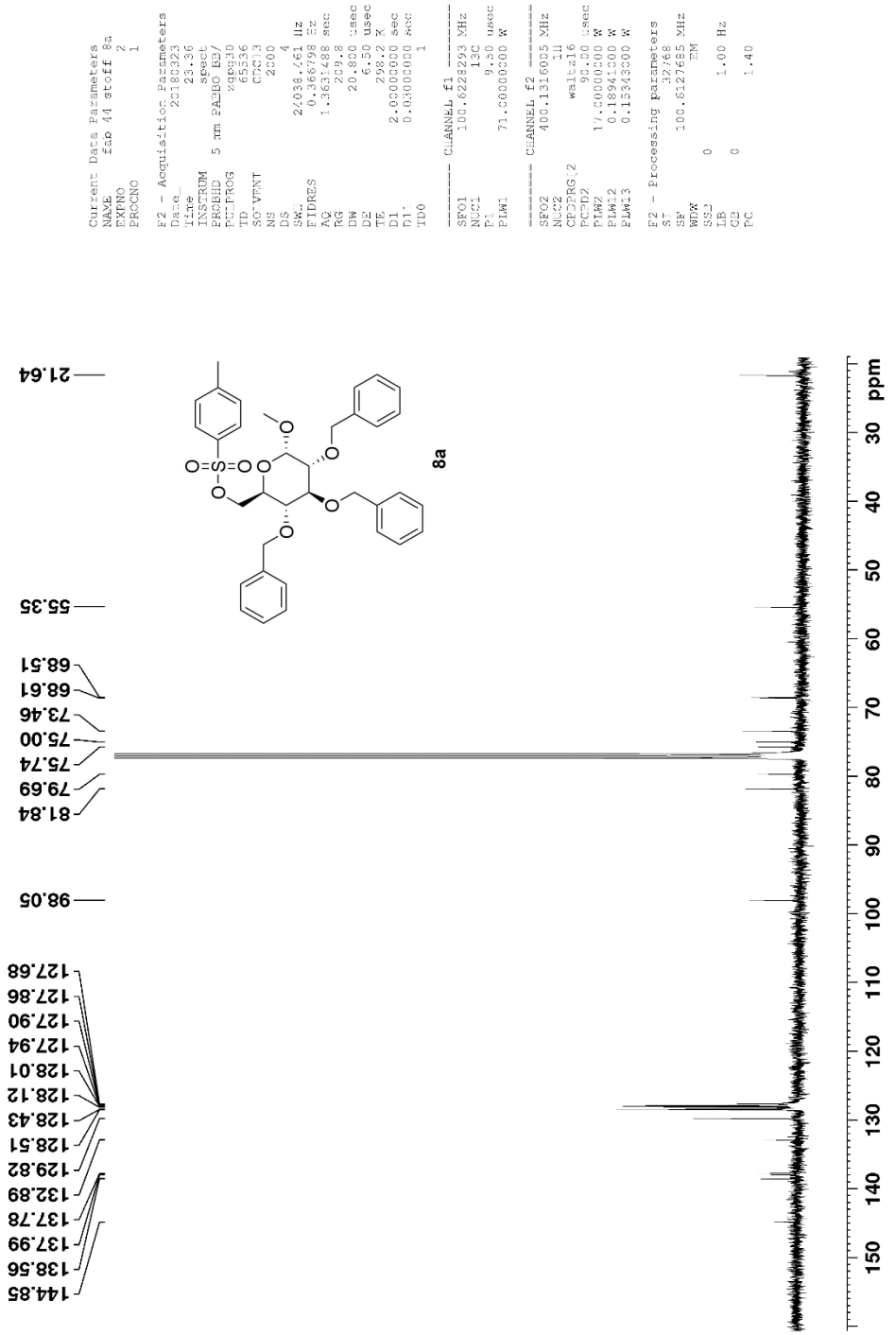


Figure D.1. ^{13}C-NMR spectrum for compound **8a**.

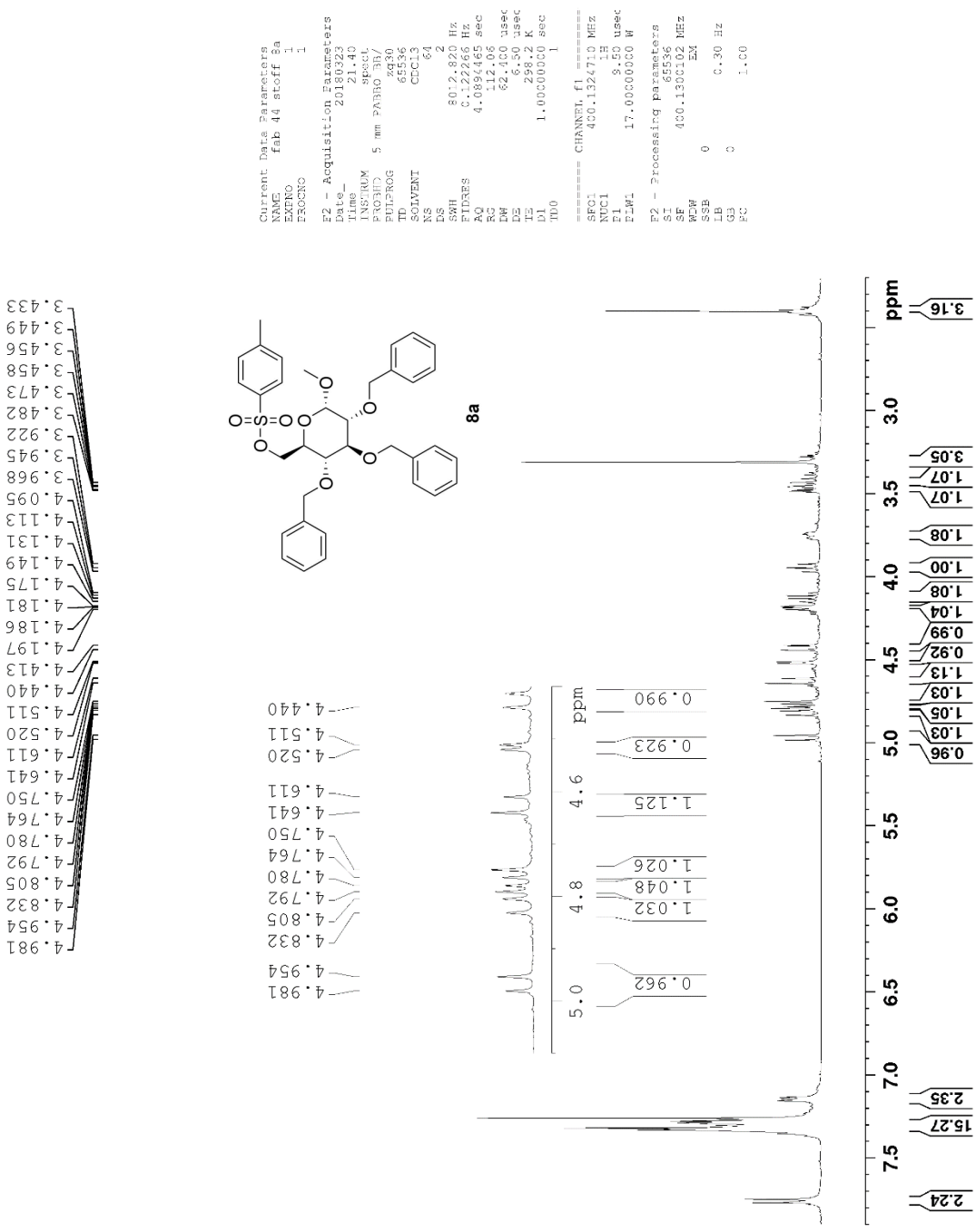


Figure D.2. [1]H-NMR spectrum of compound **8a**.

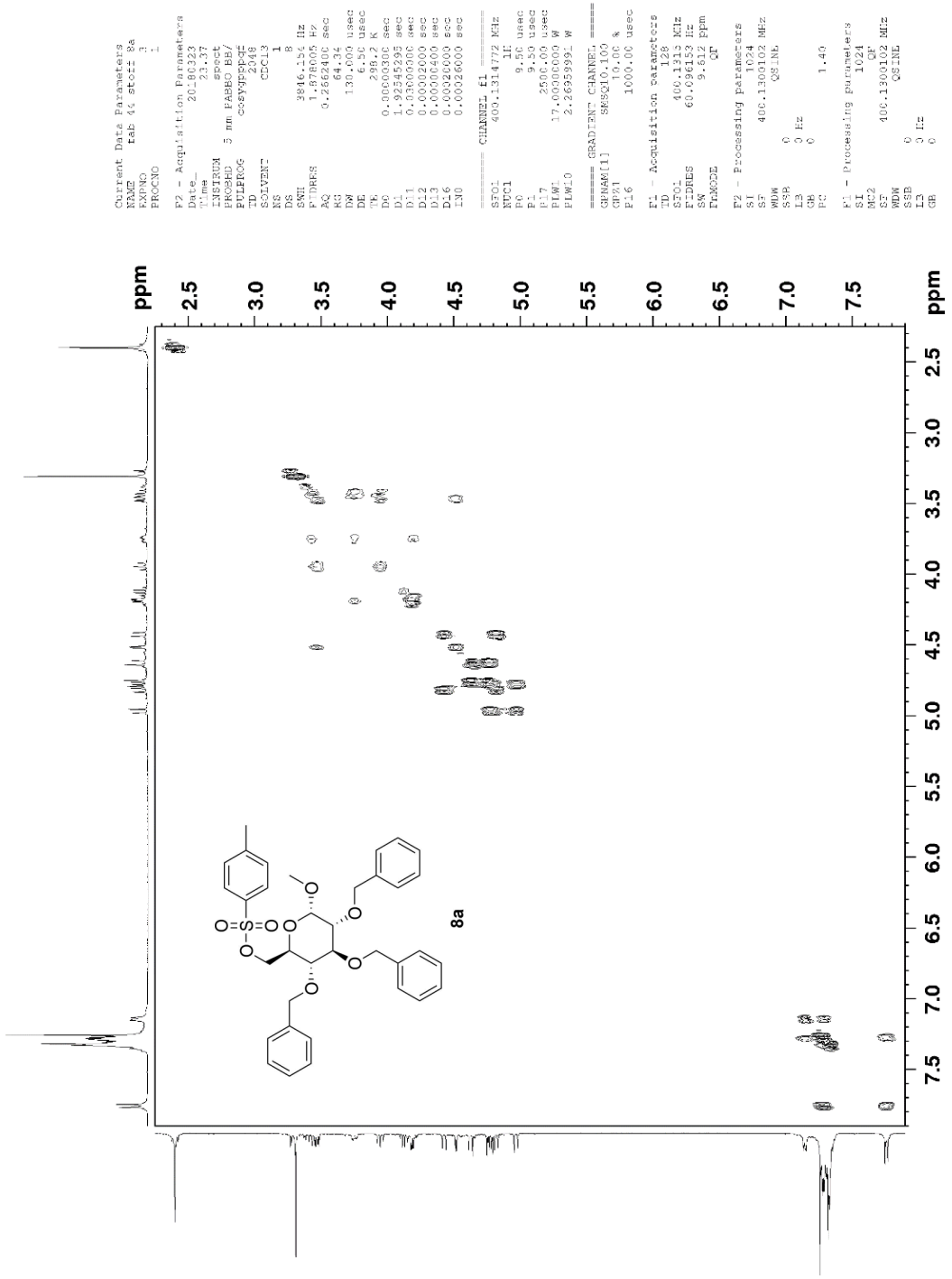


Figure D.3. COSY spectrum of compound **8a.**

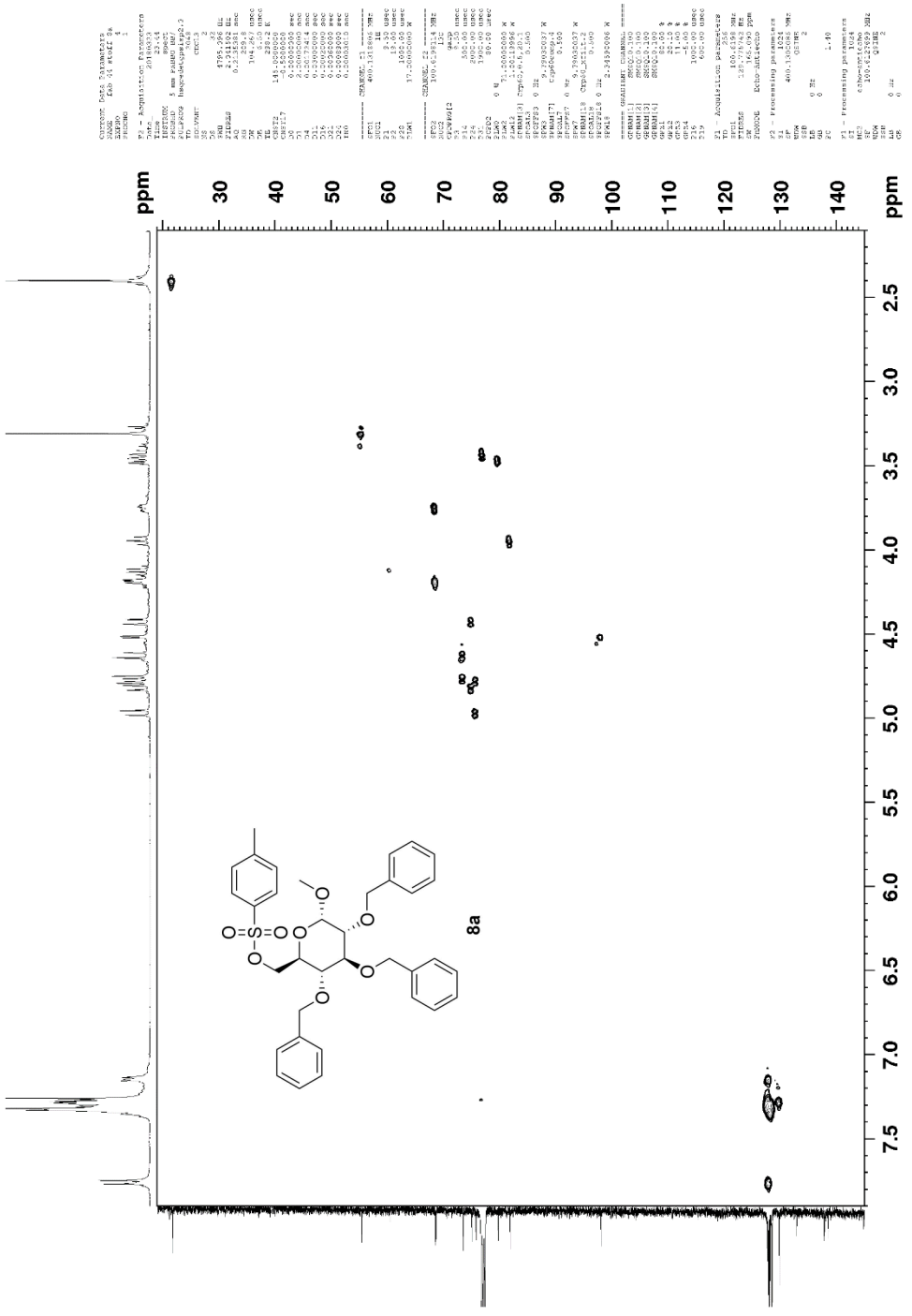


Figure D.4. HSQC spectrum of compound **8a**.

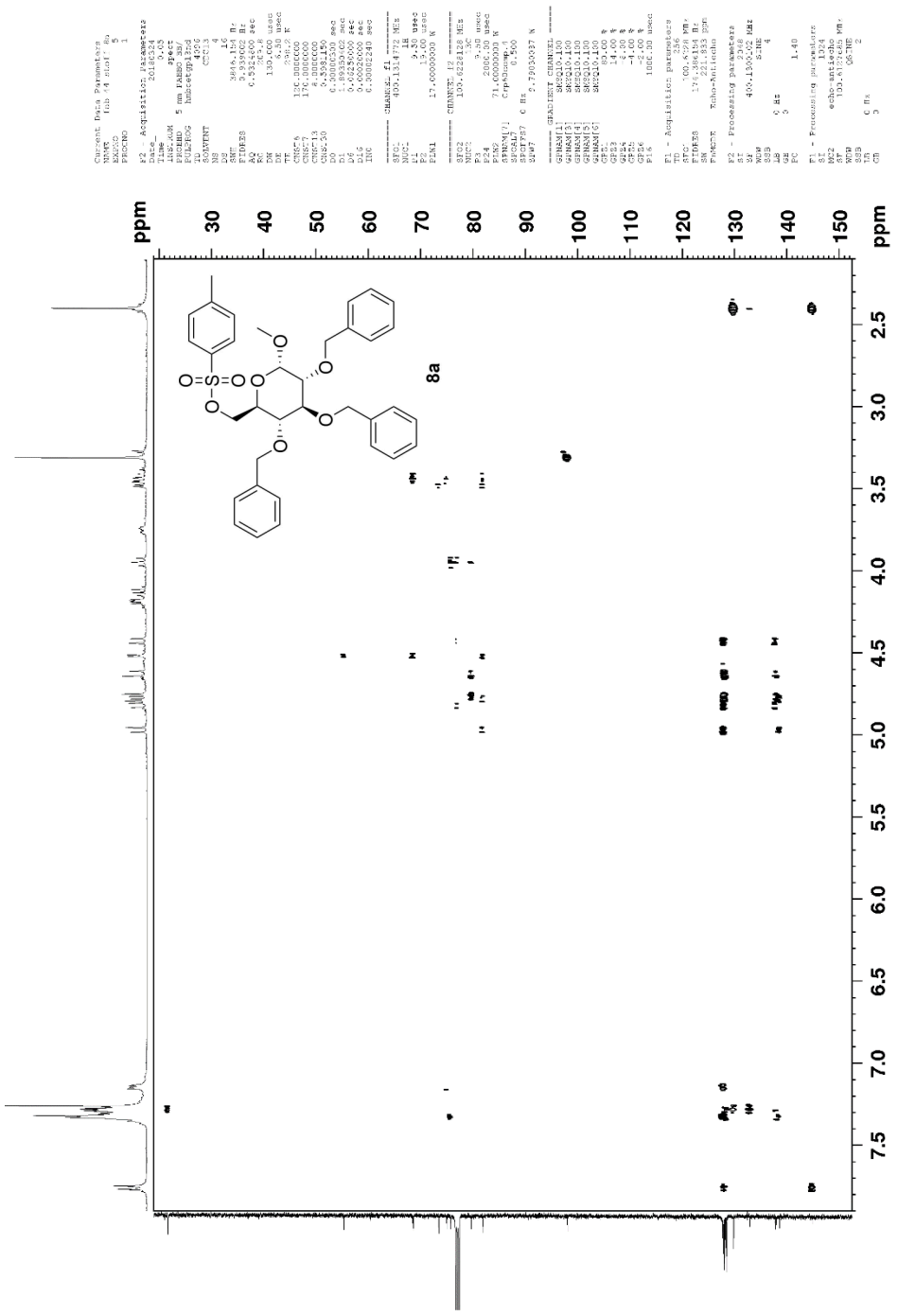


Figure D.5. HMBC spectrum of compound **8a.**

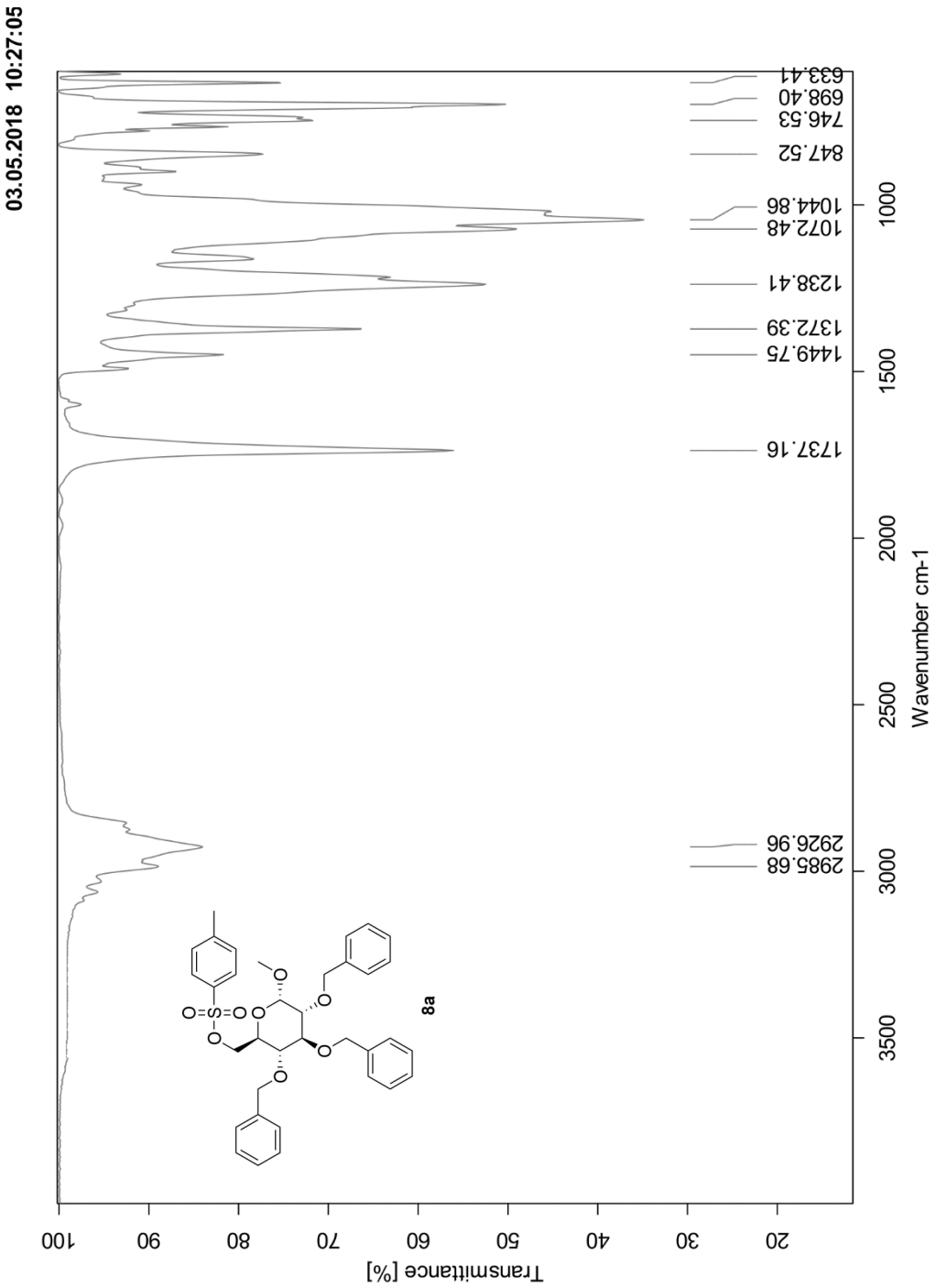
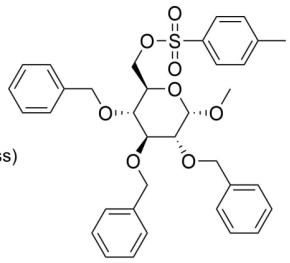


Figure D.6. IR spectrum of compound **8a**.

Elemental Composition Report **Page 1**

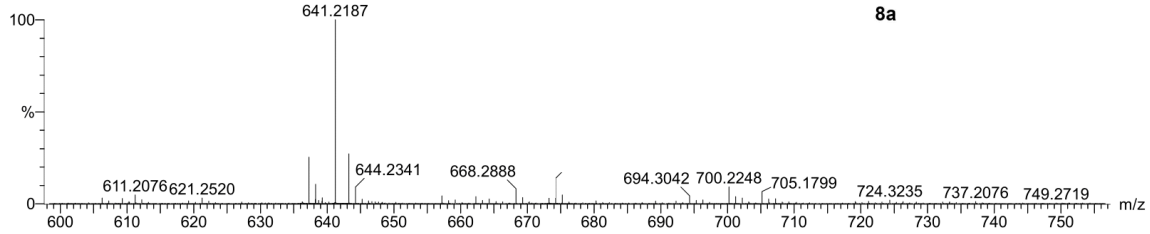
Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
765 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 O: 0-20 Na: 0-1 S: 0-2
2018_230pos 47 (0.882) AM2 (Ar,35000.0,0.00,0.00); Cm (45:47)
1: TOF MS ES+



8a

2.81e+005



Minimum:				-1.5				
Maximum:		5000.0	2.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
641.2187	641.2185	0.2	0.3	16.5	707.6	1.671	18.80	C35 H38 O8 Na S
	641.2184	0.3	0.5	23.5	707.1	1.244	28.81	C41 H37 O3 S2
	641.2175	1.2	1.9	24.5	706.5	0.646	52.39	C40 H33 O8

Figure D.7 MS results for compound **8a**.

Appendix E. Spectroscopic data for compound **9a**

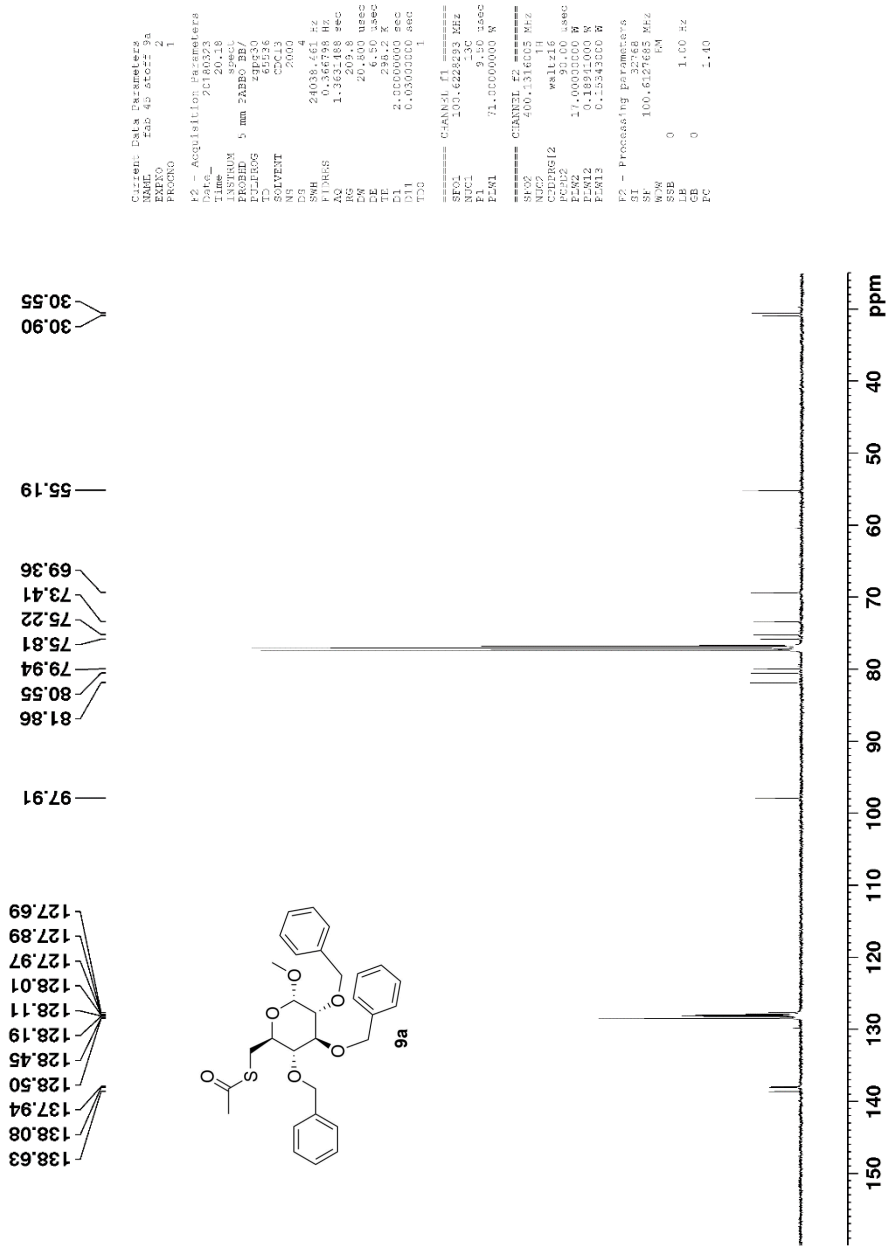


Figure E.1. ^{13}C-NMR spectrum of compound **9a**.

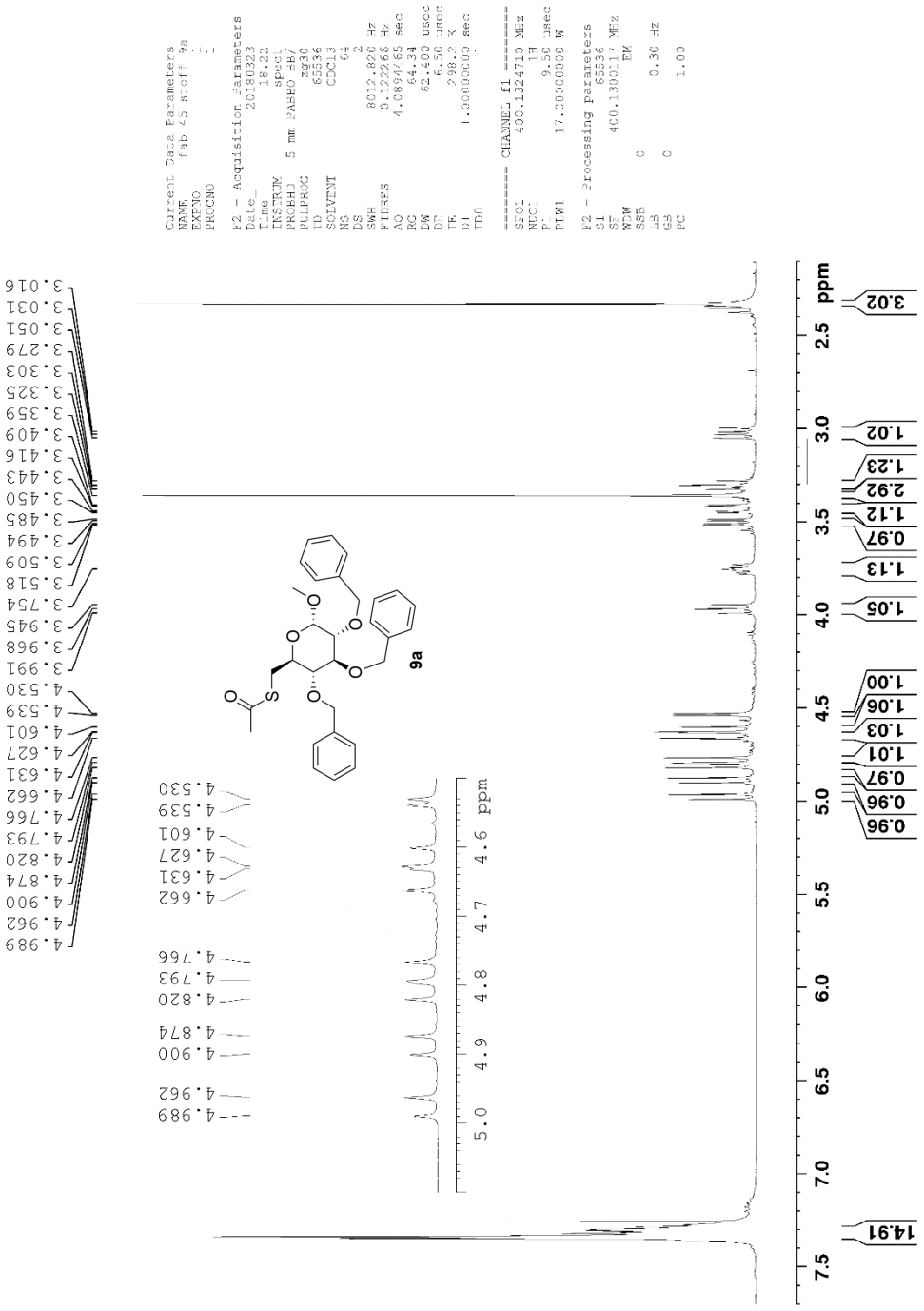


Figure E.2. ^{1H}-NMR spectrum of compound **9a.**

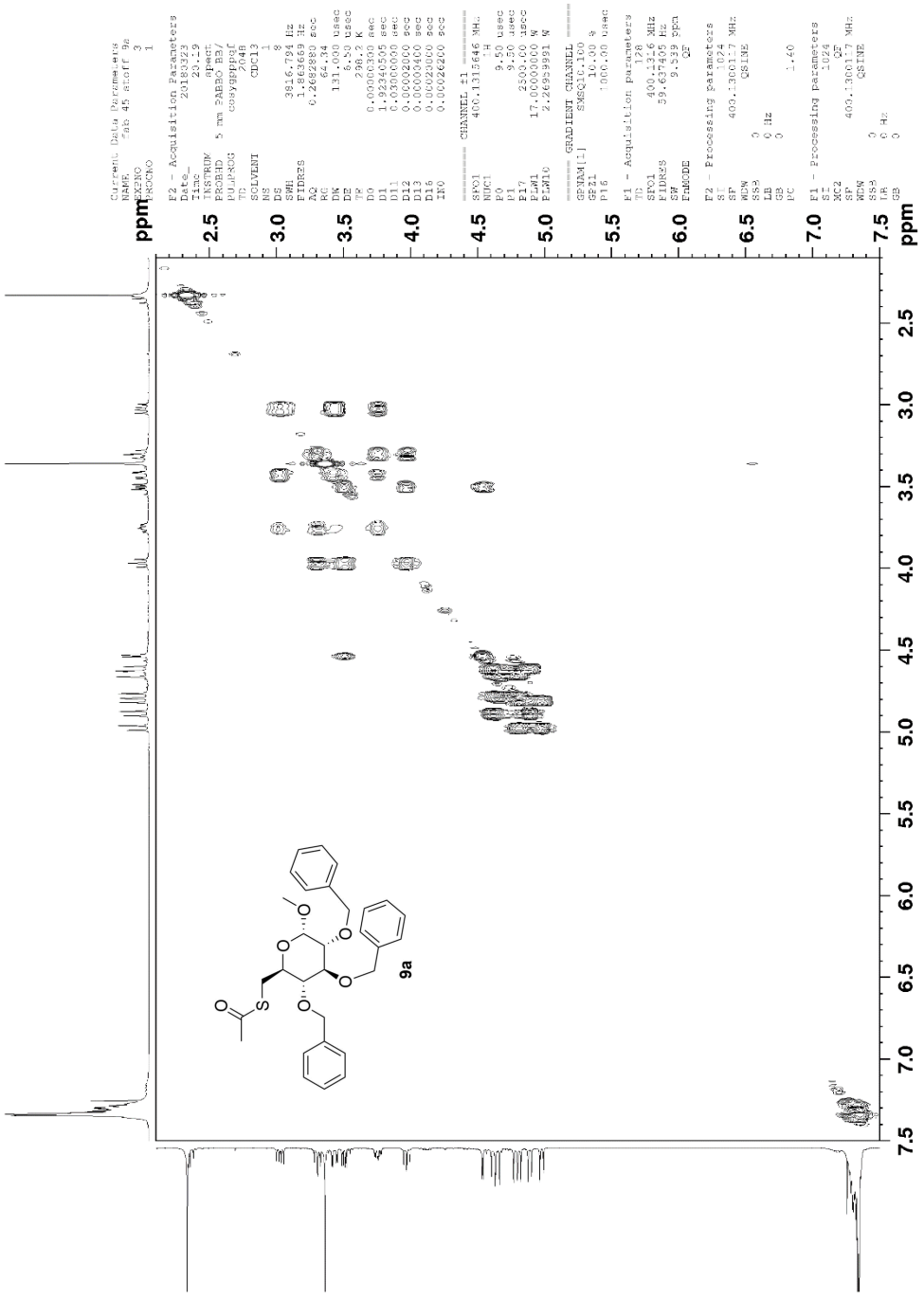


Figure E.4. COSY spectrum of compound **9a**.

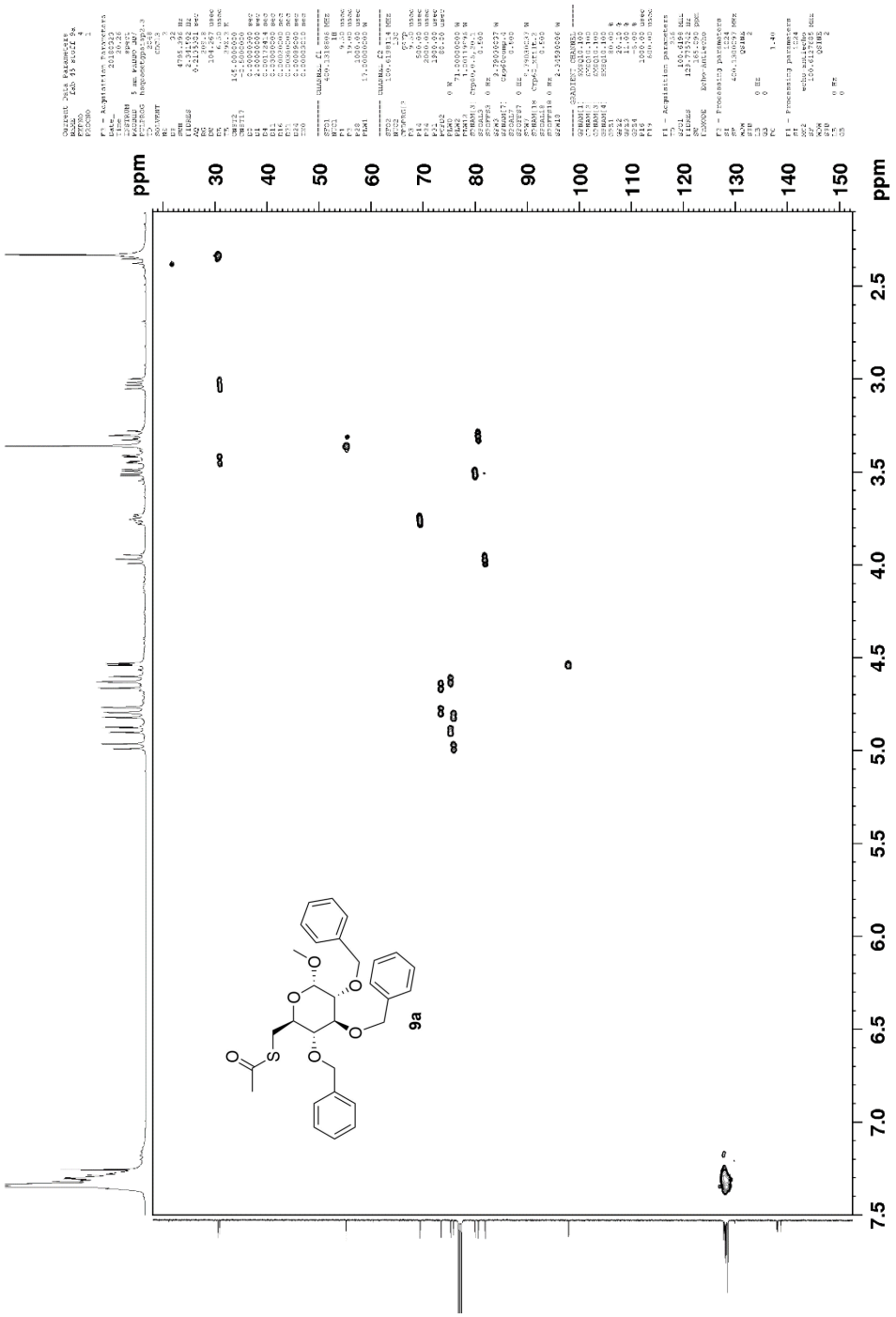


Figure E.5 HSQC spectrum of compound **9a**.

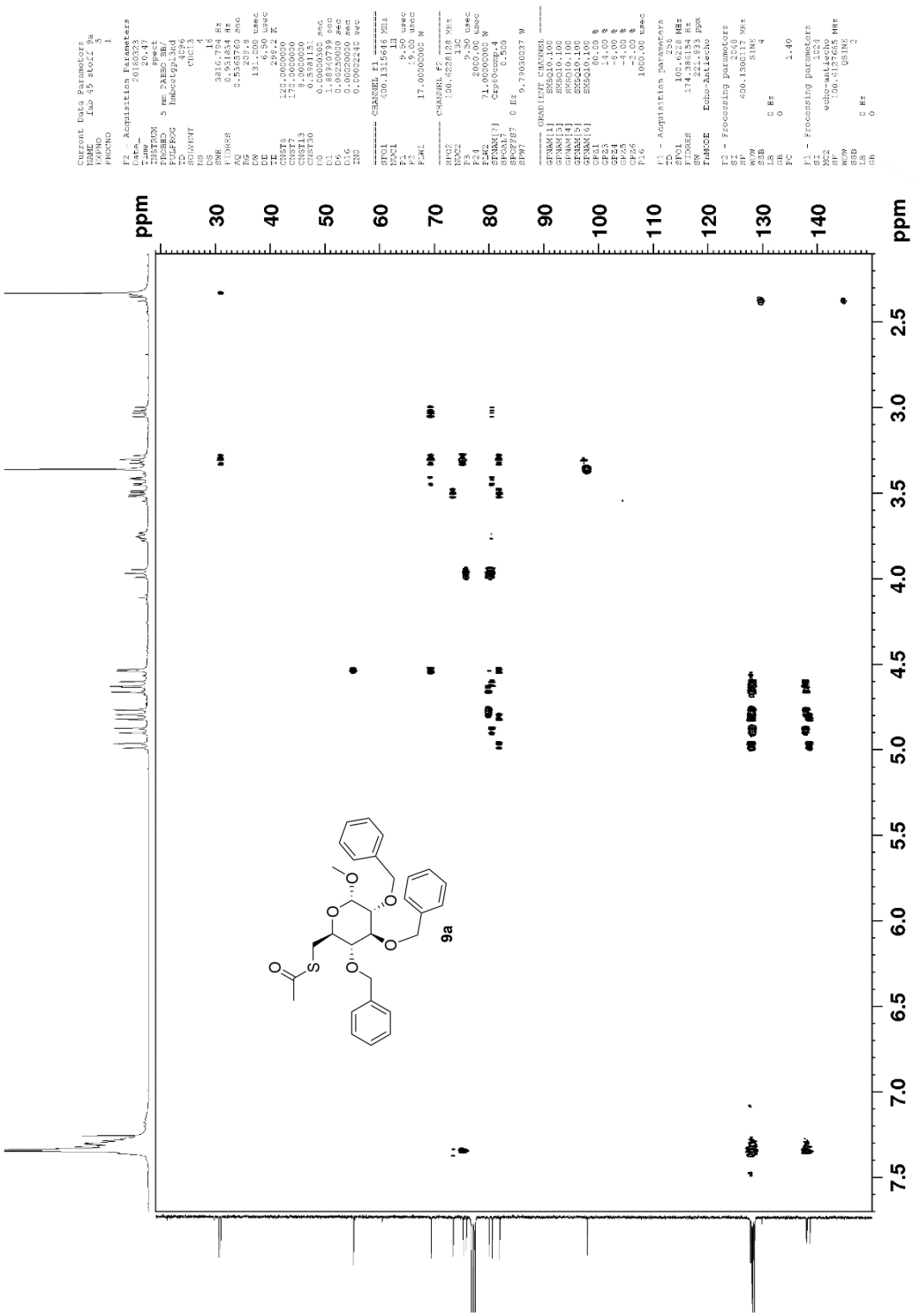


Figure E.6 HMBC spectrum of compound **9a**.

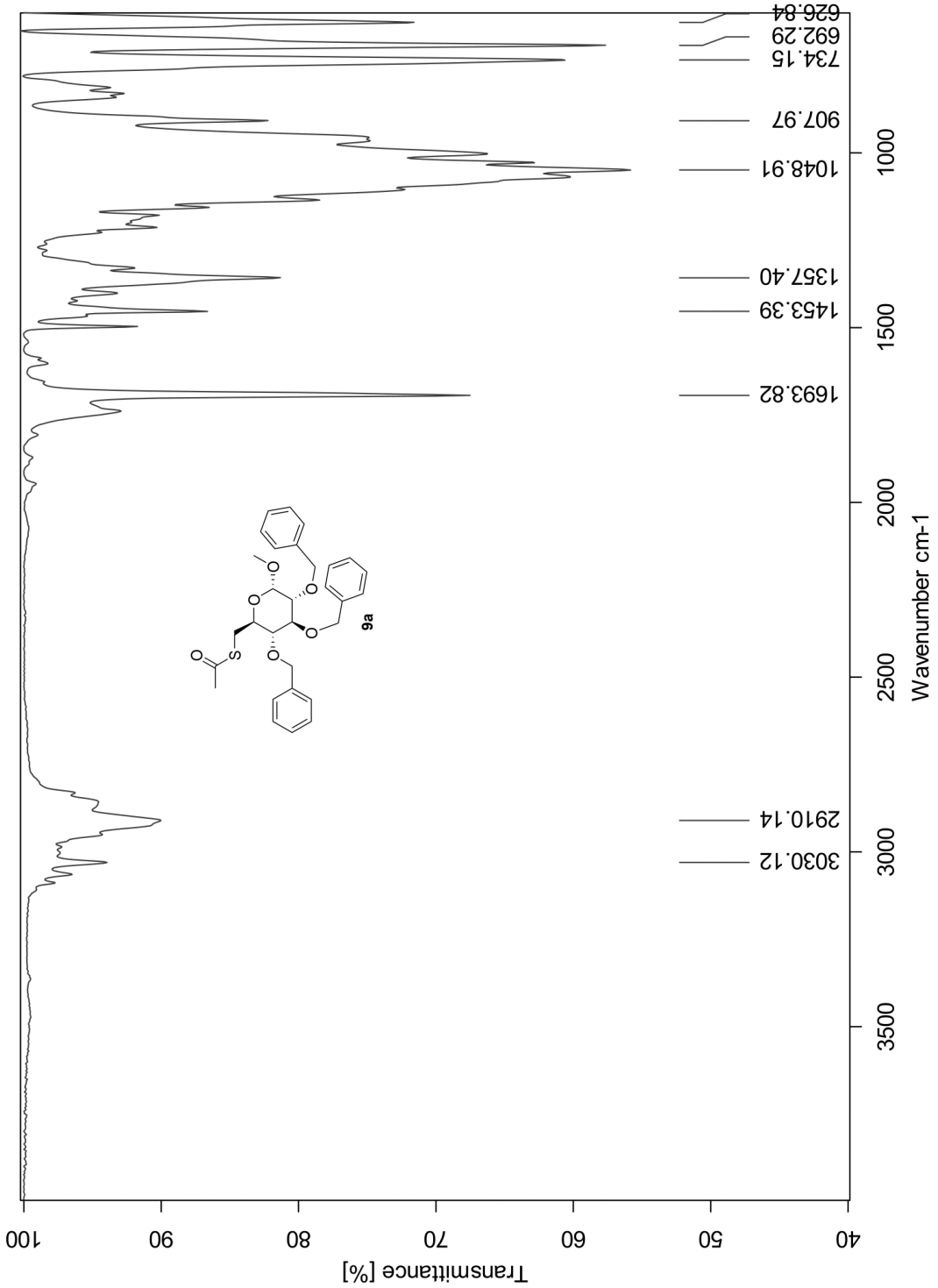
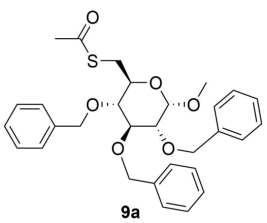


Figure E.6. IR spectrum of compound **9a.**

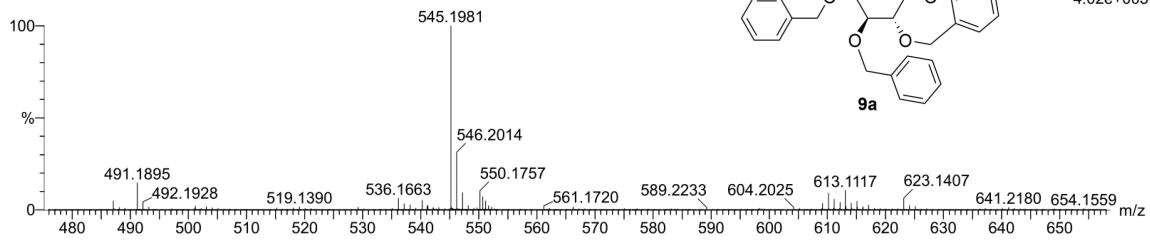
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 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
701 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 O: 0-10 Na: 0-1 S: 0-5
2018-158 47 (0.883) AM2 (Ar,35000.0,0.00,0.00); Cm (47:48)
1: TOF MS ES+



4.02e+005



Minimum:				-1.5				
Maximum:		5000.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
545.1981	545.1982	-0.1	-0.2	12.5	821.4	10.207	0.00	C31 H38 O Na S3
	545.1974	0.7	1.3	13.5	811.2	0.001	99.93	C30 H34 O6 Na S
	545.1973	0.8	1.5	20.5	818.6	7.360	0.06	C36 H33 O S2

Figure E.7. MS results for compound **9a**.

Appendix F. Spectroscopic data for compound **10a**

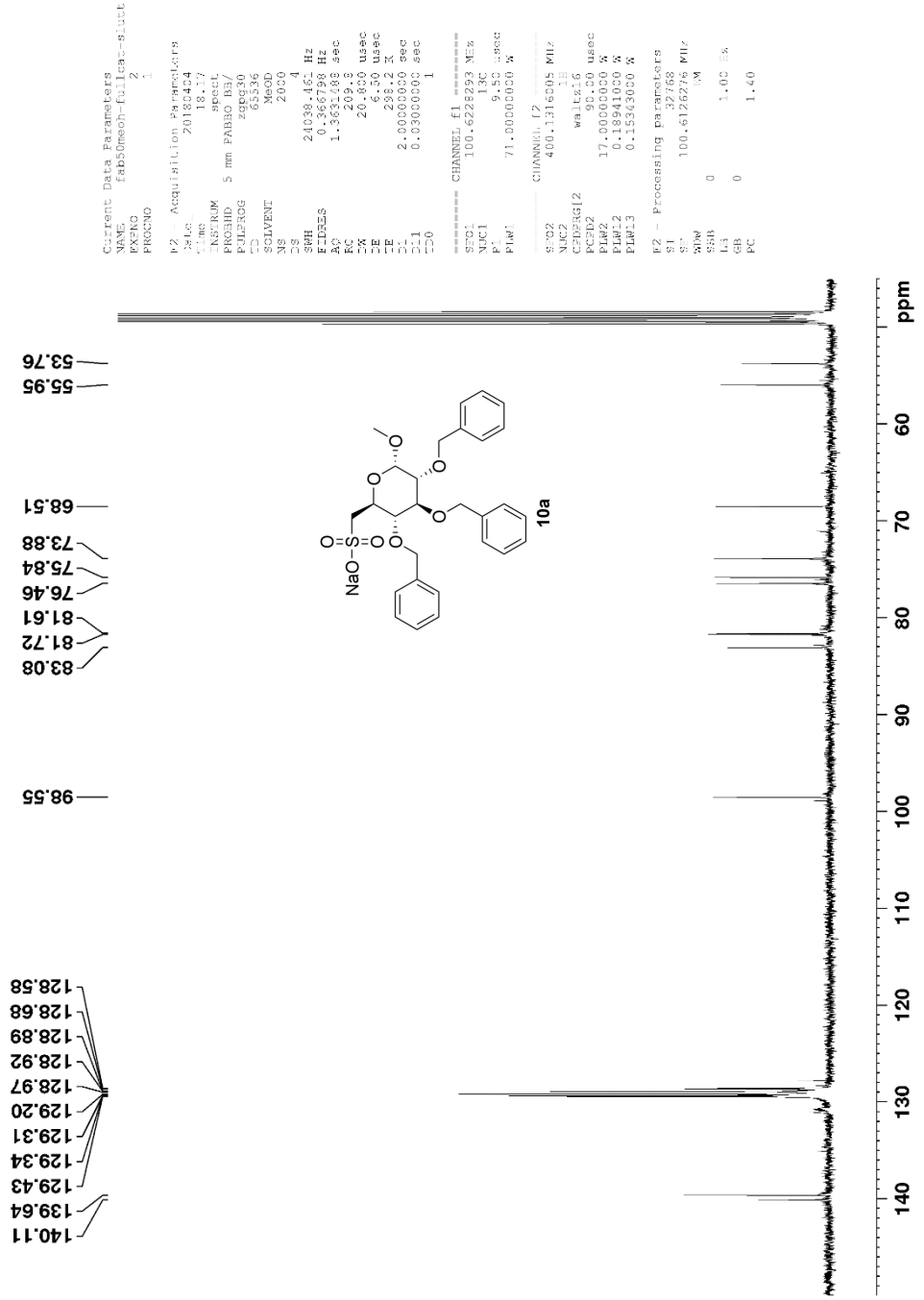


Figure F.1. ^{13}C-NMR spectrum of compound **10a**.

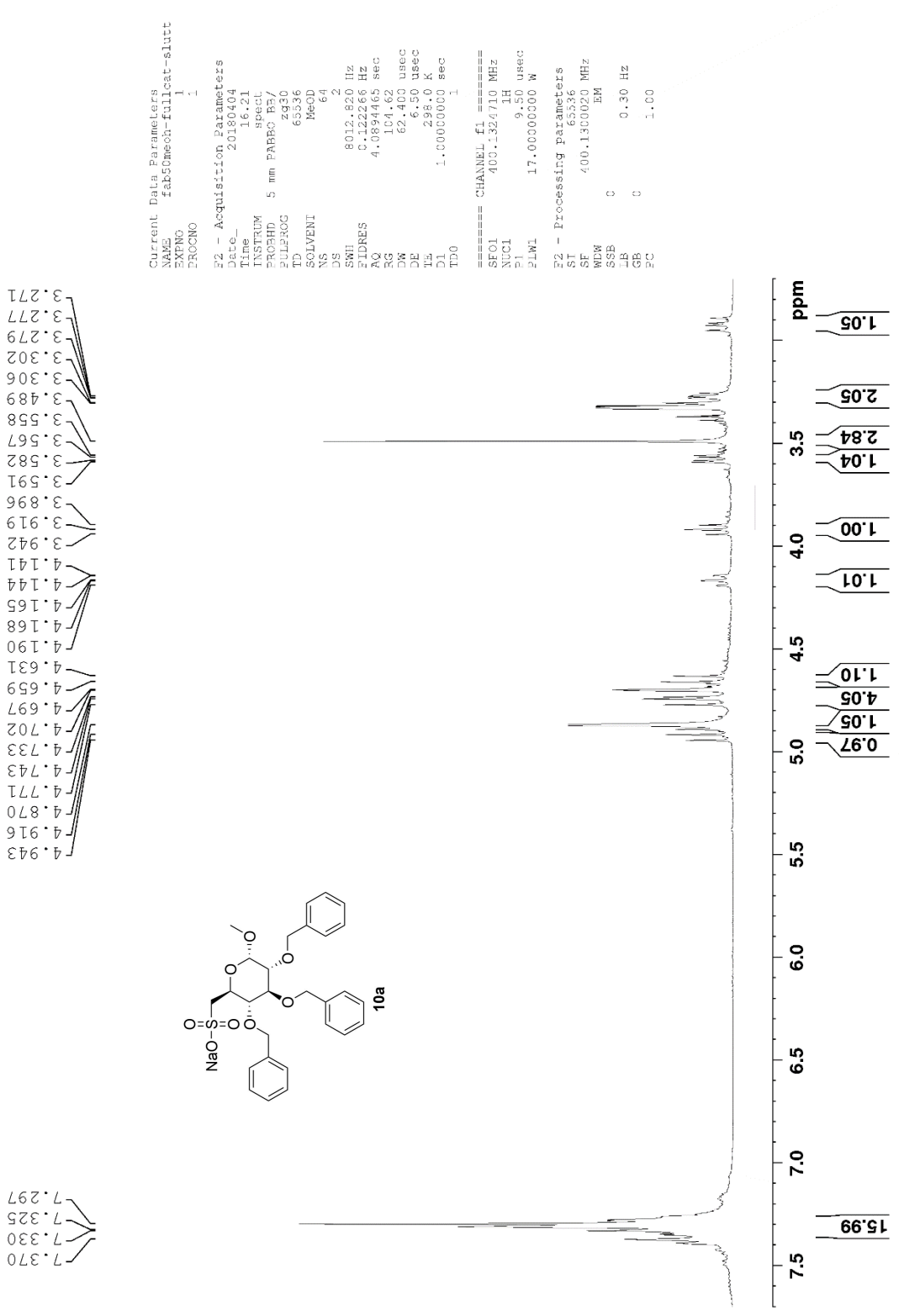


Figure F.2. ^{1}H-NMR spectrum of compound **10a**.

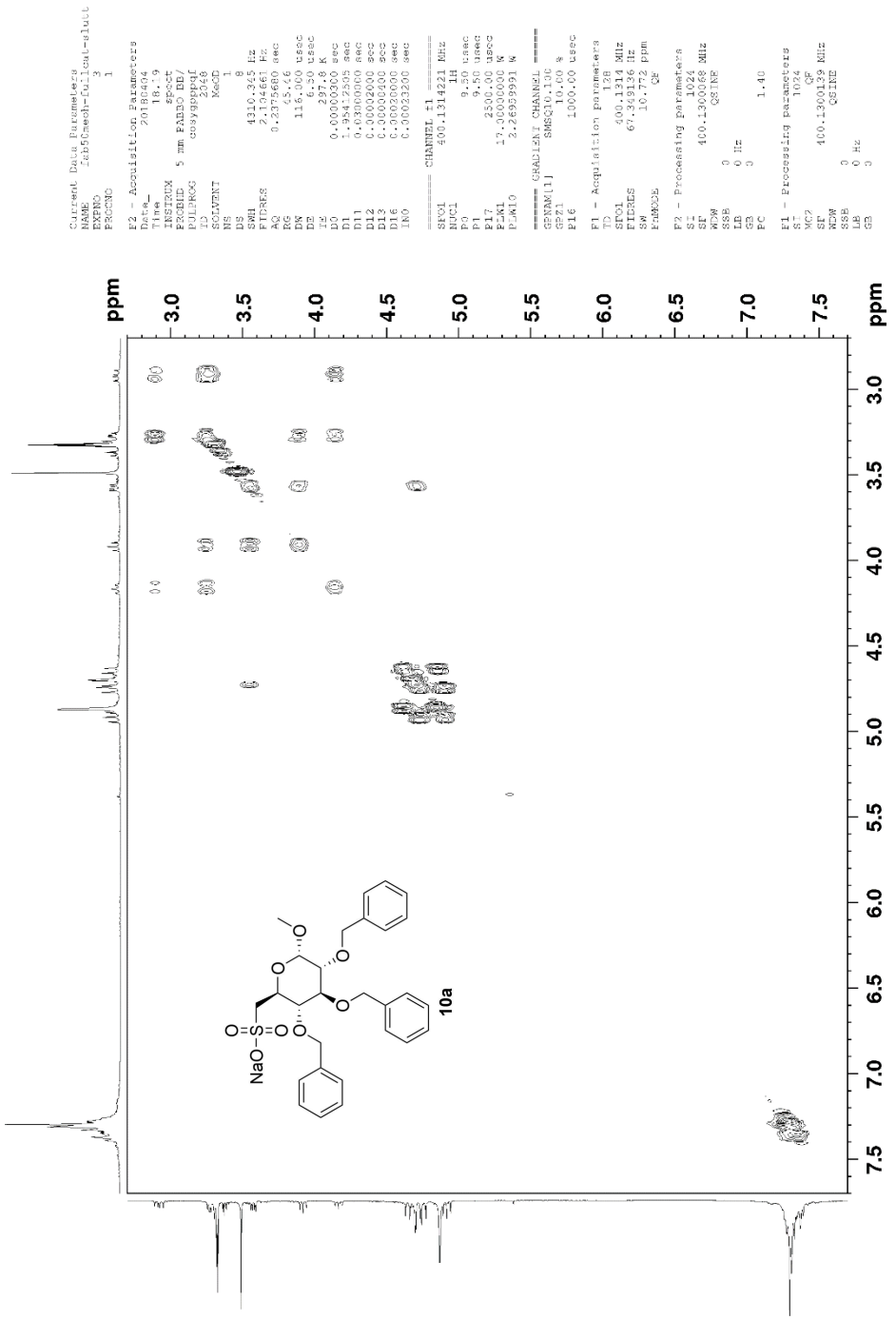


Figure F.3. COSY spectrum of compound **10a**.

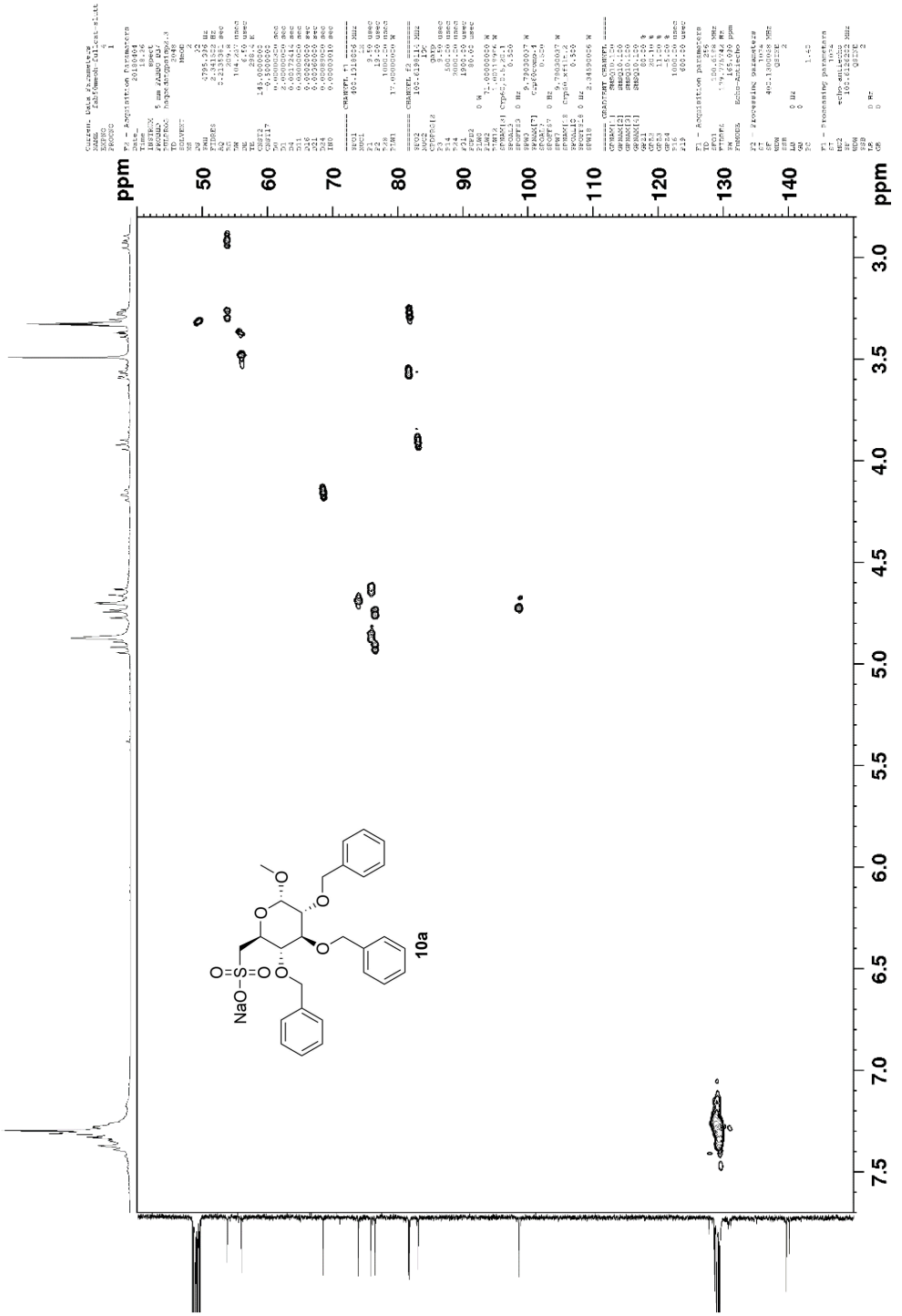


Figure F.4. HSQC spectrum of compound **10a**

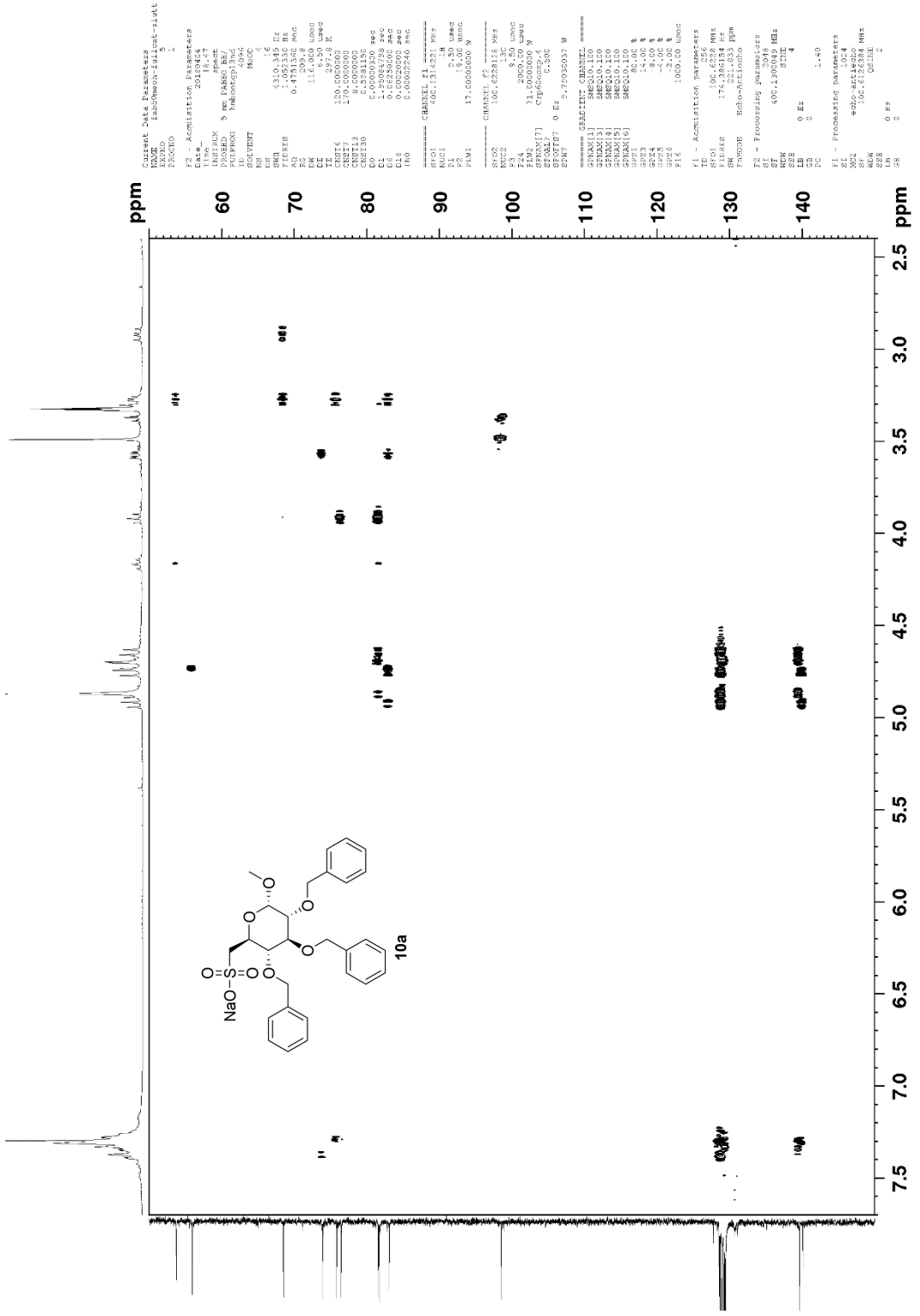


Figure F.5. HMBC spectrum of compound **10a**

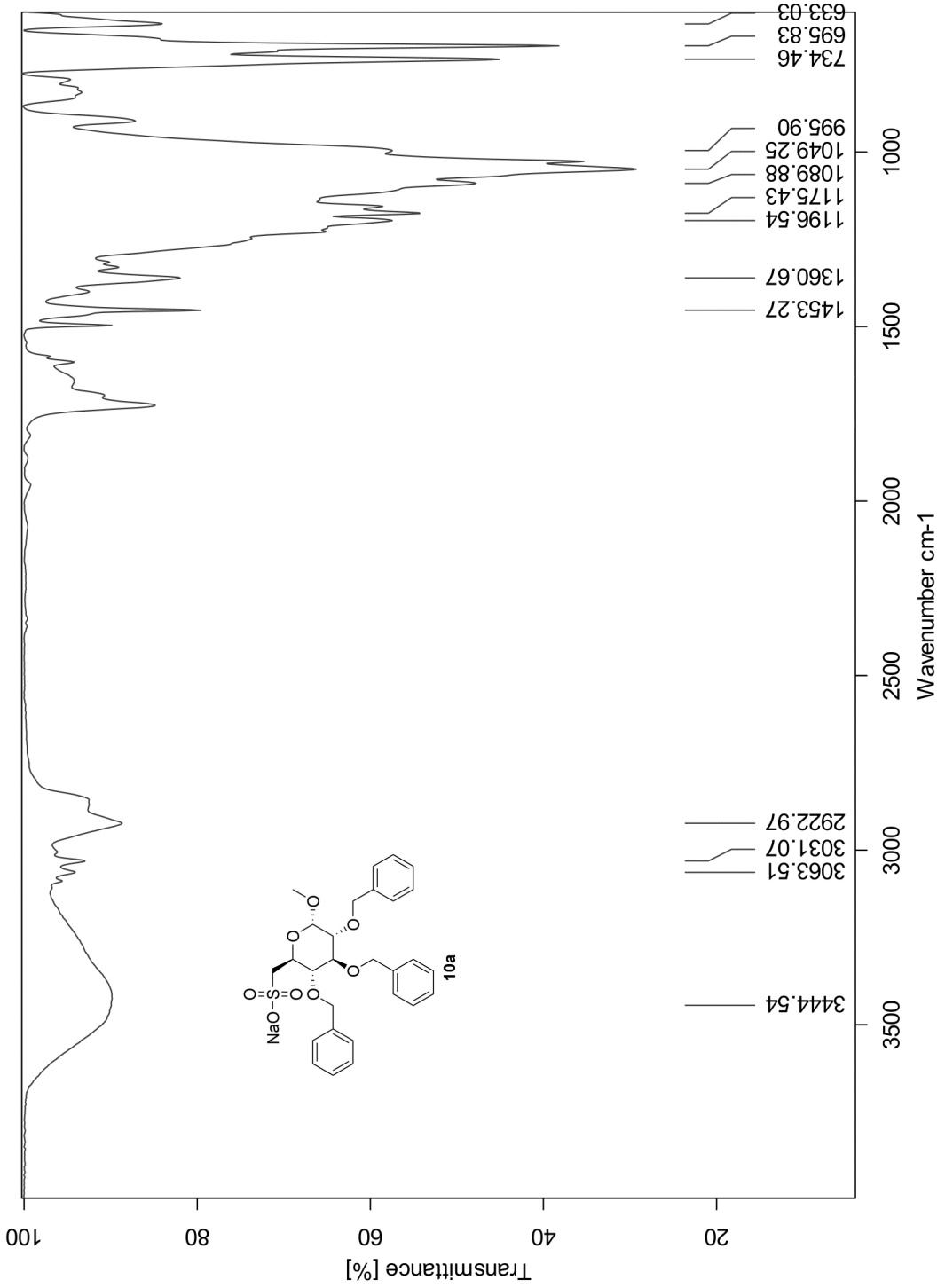
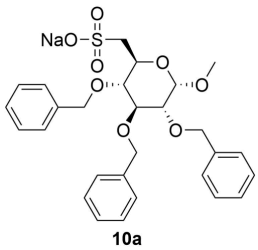


Figure F.6. IR spectrum of compound **10a**.

Elemental Composition Report **Page 1**

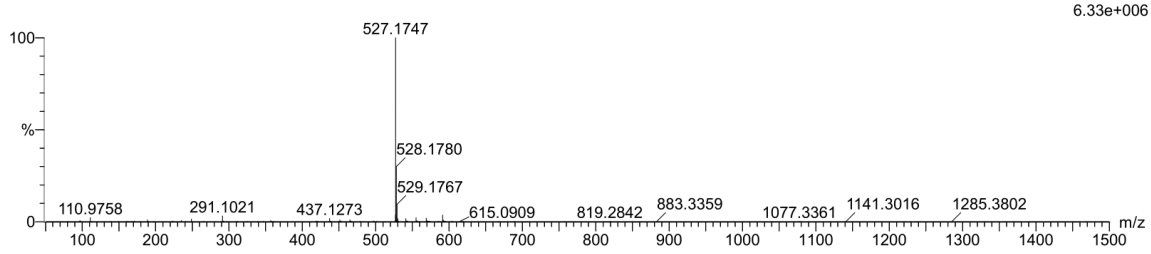


10a

Single Mass Analysis
Tolerance = 2.0 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
385 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 O: 0-10 Na: 0-1 S: 0-2
2018-160negZ 3 (0.087) AM2 (Ar,35000.0,0.00,0.00); Cm (3:4)
1: TOF MS ES-

6.33e+006



Minimum:				-1.5				
Maximum:		5000.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
527.1747	527.1740	0.7	1.3	13.5	973.6	0.000	99.97	C28 H31 O8 S
	527.1749	-0.2	-0.4	5.5	981.7	8.100	0.03	C23 H36 O8 Na S2

Figure F.6. MS results for compound **10a**.

Appendix G. Spectroscopic data for compound **5b**

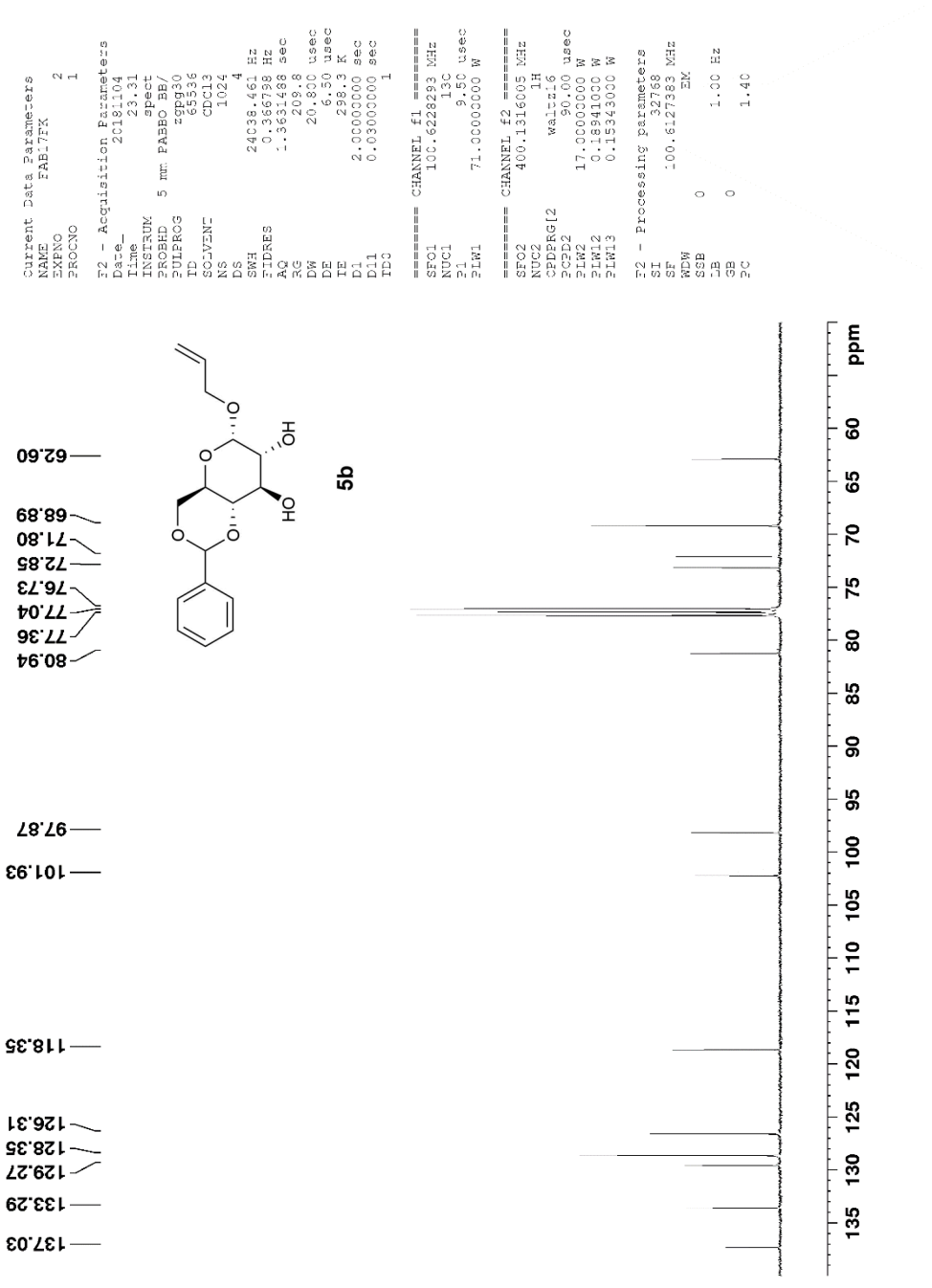


Figure G.1. ^{13}C-NMR spectrum of compound **5b**.

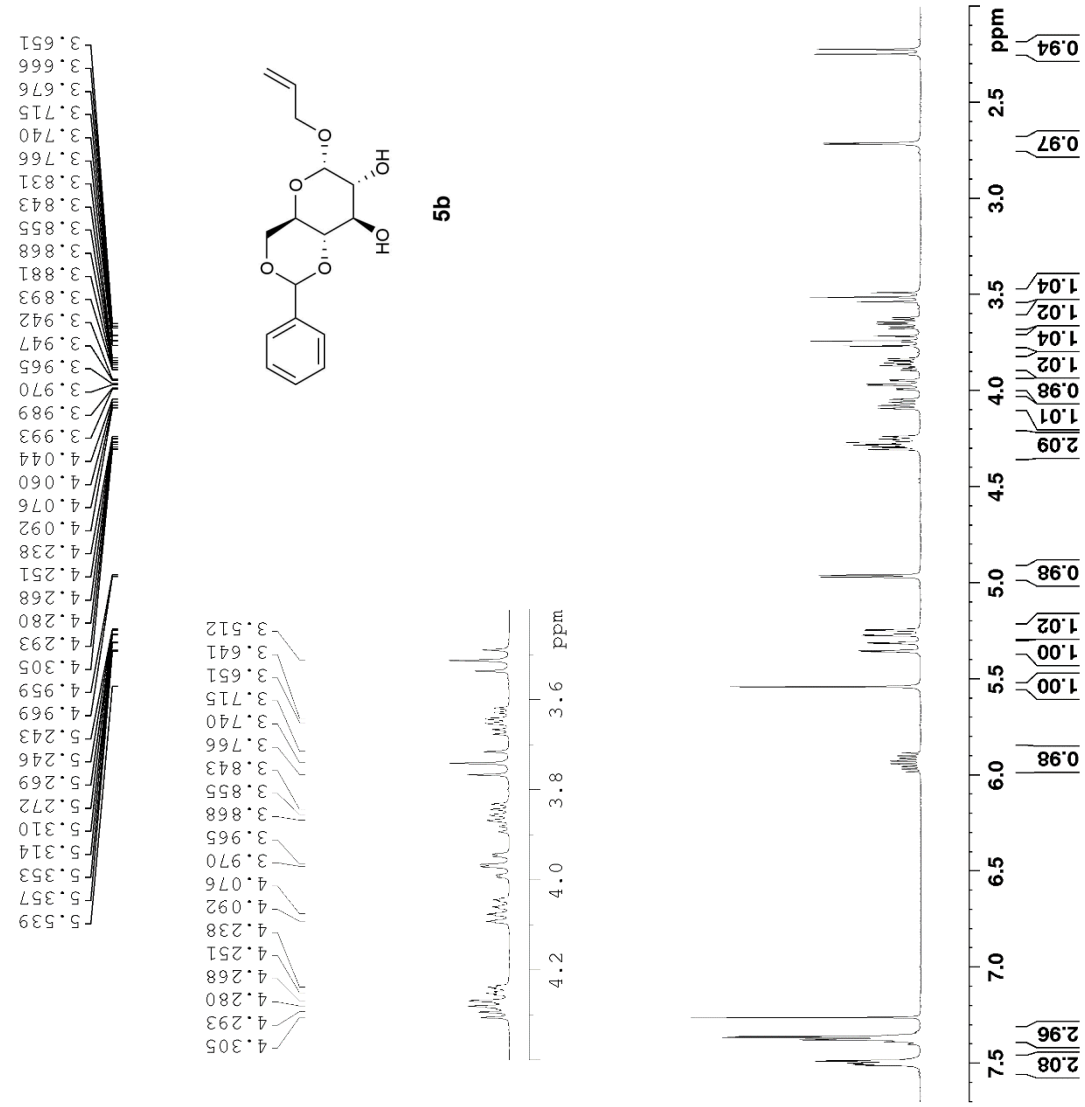


Figure G.2. ^{1}H-NMR spectrum of compound **5b**

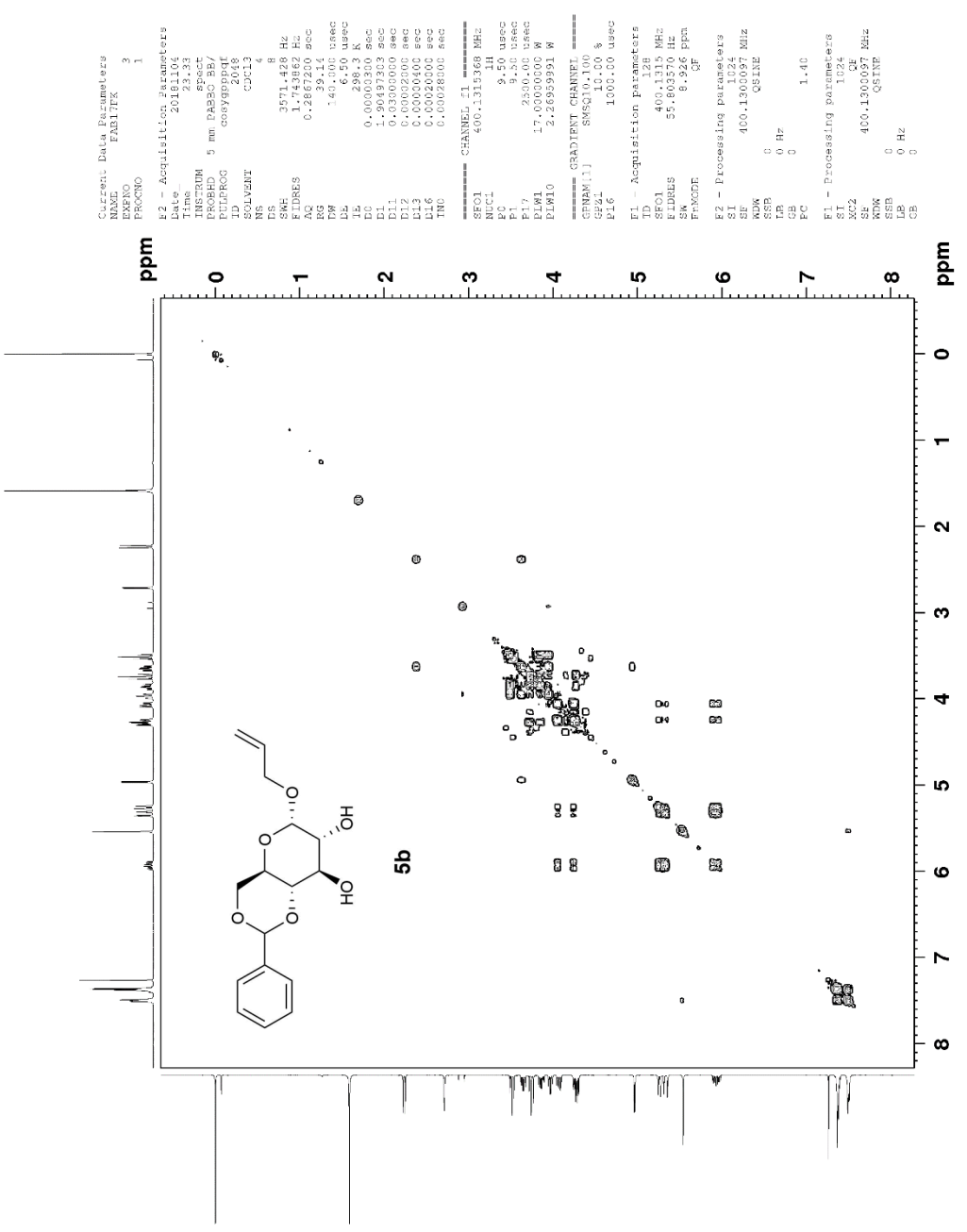


Figure G.3. COSY spectrum of compound **5b**.

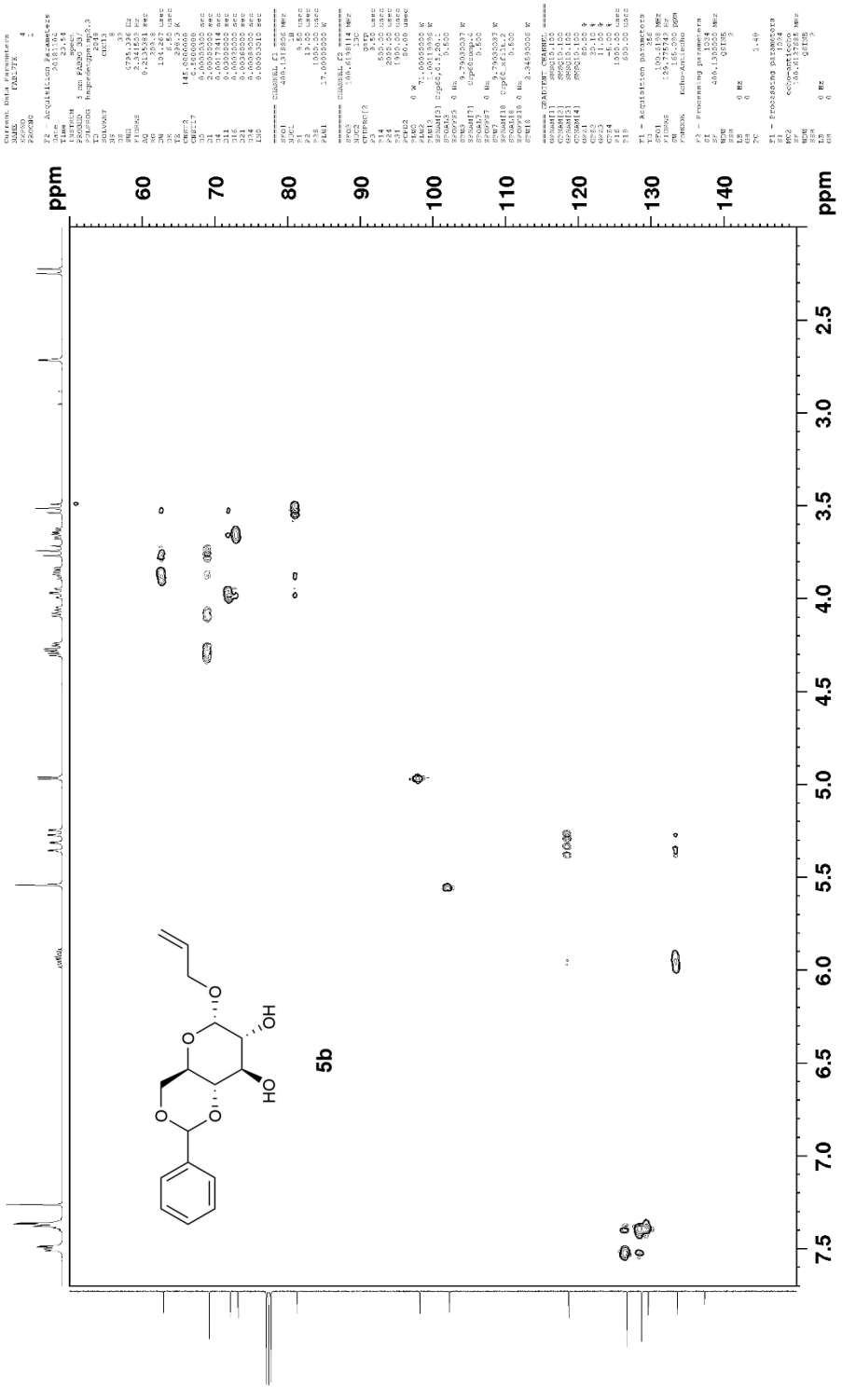


Figure G.4. HSQC spectrum of compound **5b**.

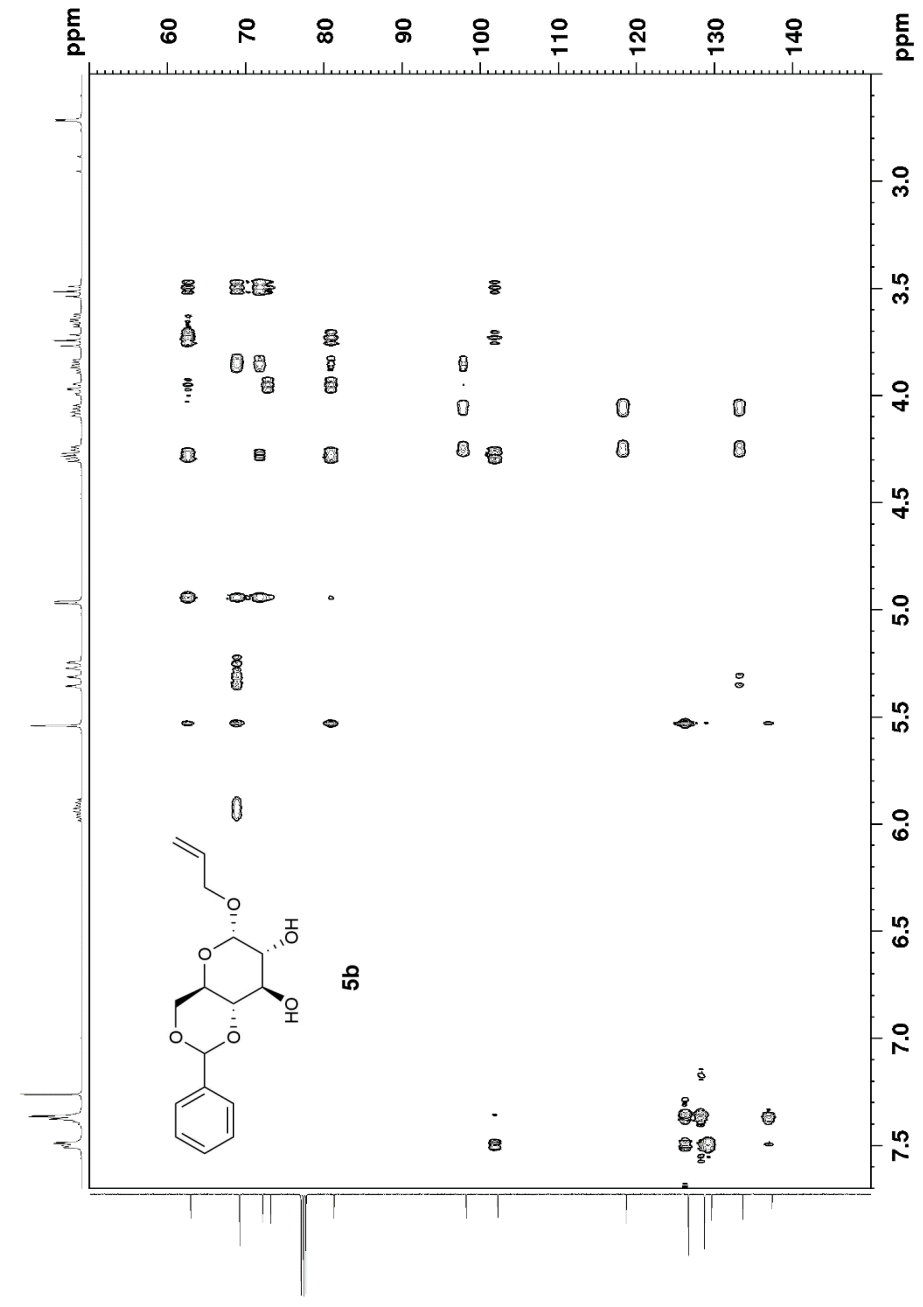


Figure G.5. HMBC spectrum of compound **5b**.

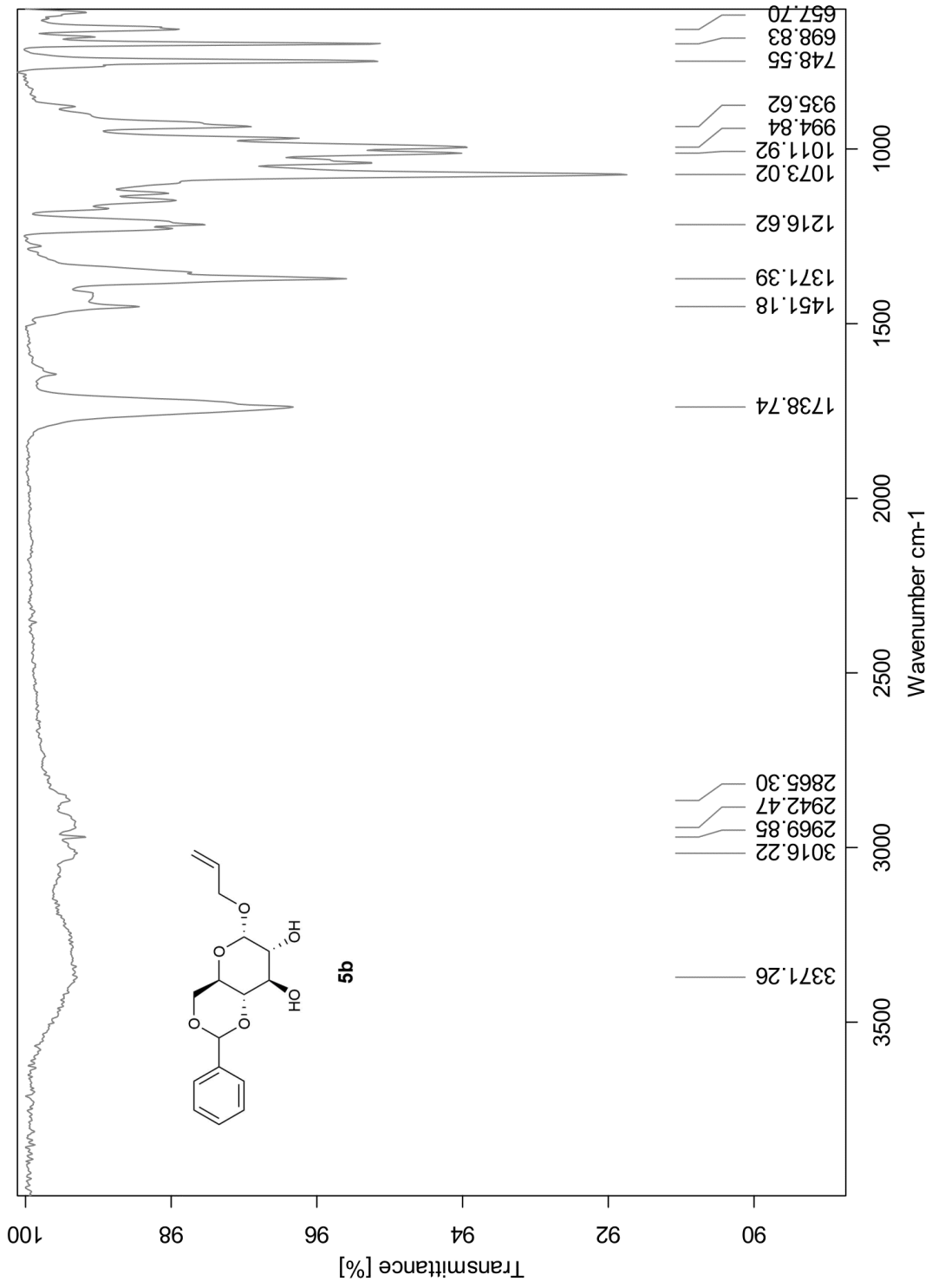


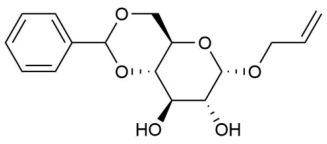
Figure G.6. IR spectrum of compound **5b**.

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 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
958 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-10 Na: 0-1 Au: 0-1

2018-147 47 (0.883) AM2 (Ar,35000.0,0.00,0.00); Cm (47:48)
1: TOF MS ES+



5b

Minimum:				-1.5				
Maximum:		5000.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
331.1161	331.1158	0.3	0.9	6.5	1162.1	0.135	87.34	C16 H20 O6 Na
	331.1155	0.6	1.8	10.5	1164.0	2.067	12.66	C14 H15 N6 O4

Figure G.7. MS results for **5b**.

Appendix H. Spectroscopic data for compound **6b**

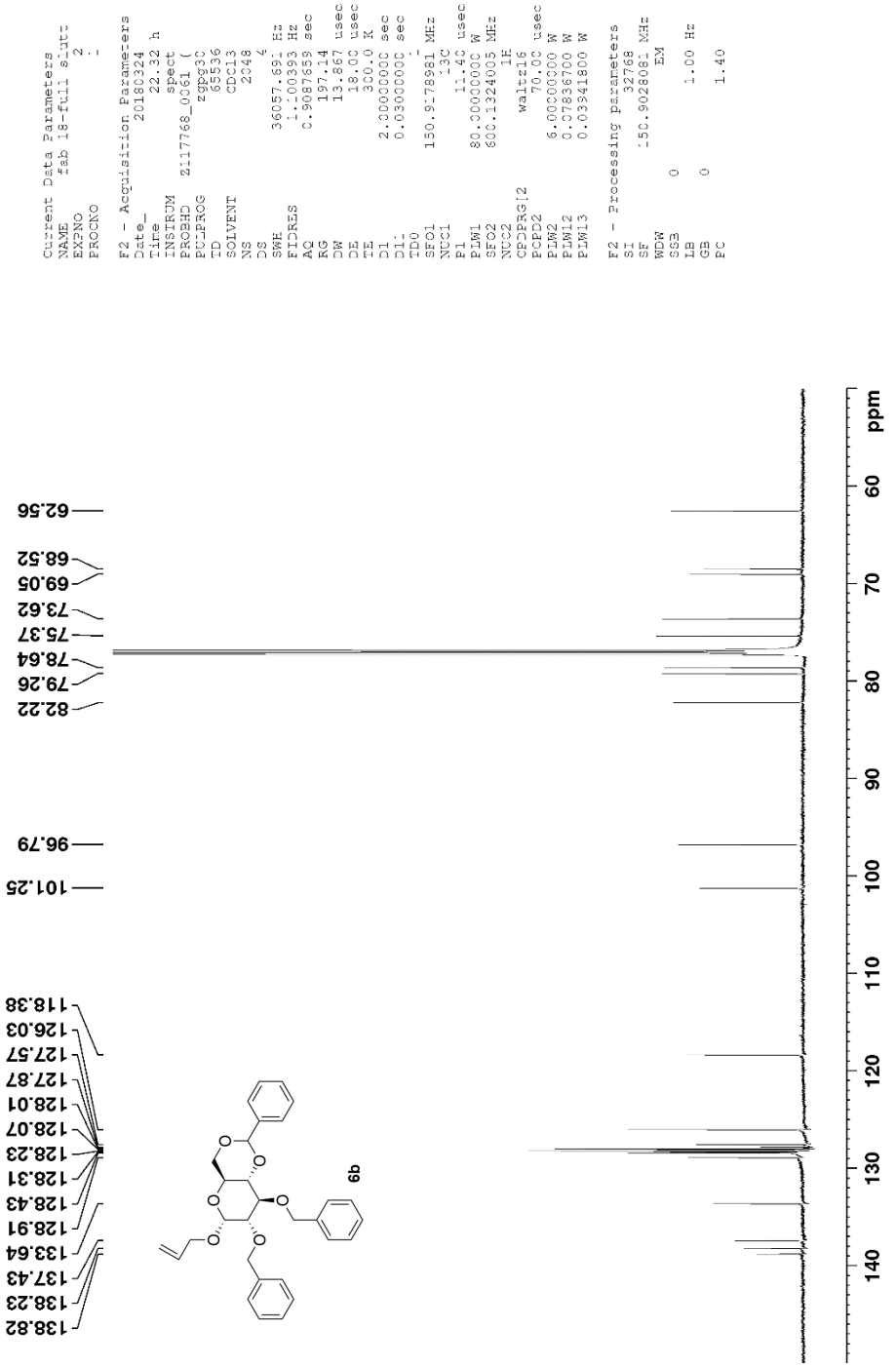


Figure H.1. ^{13}C-NMR spectrum of compound **6b**.

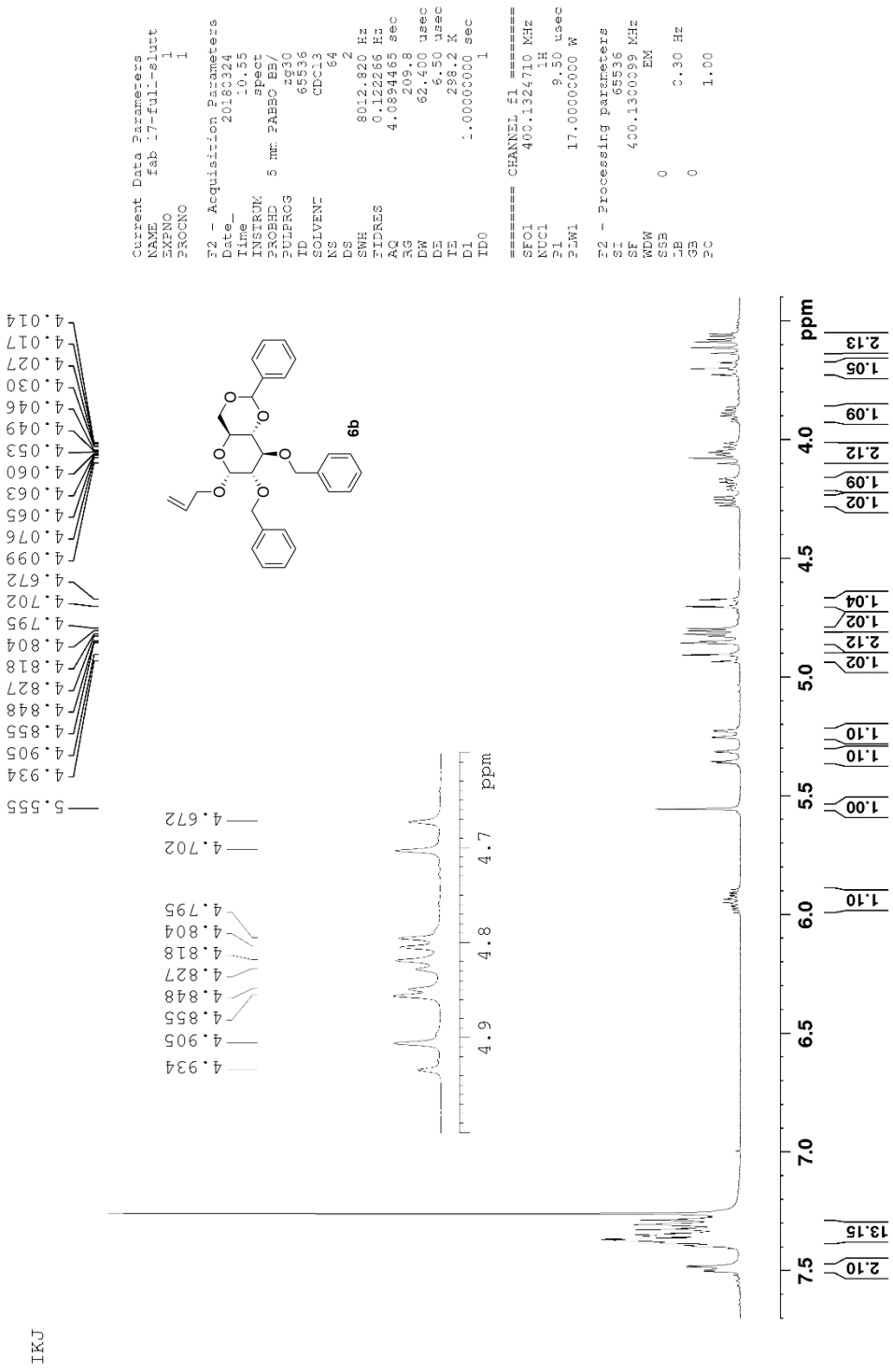


Figure H.2. [1]H-NMR spectrum of compound **6b**.

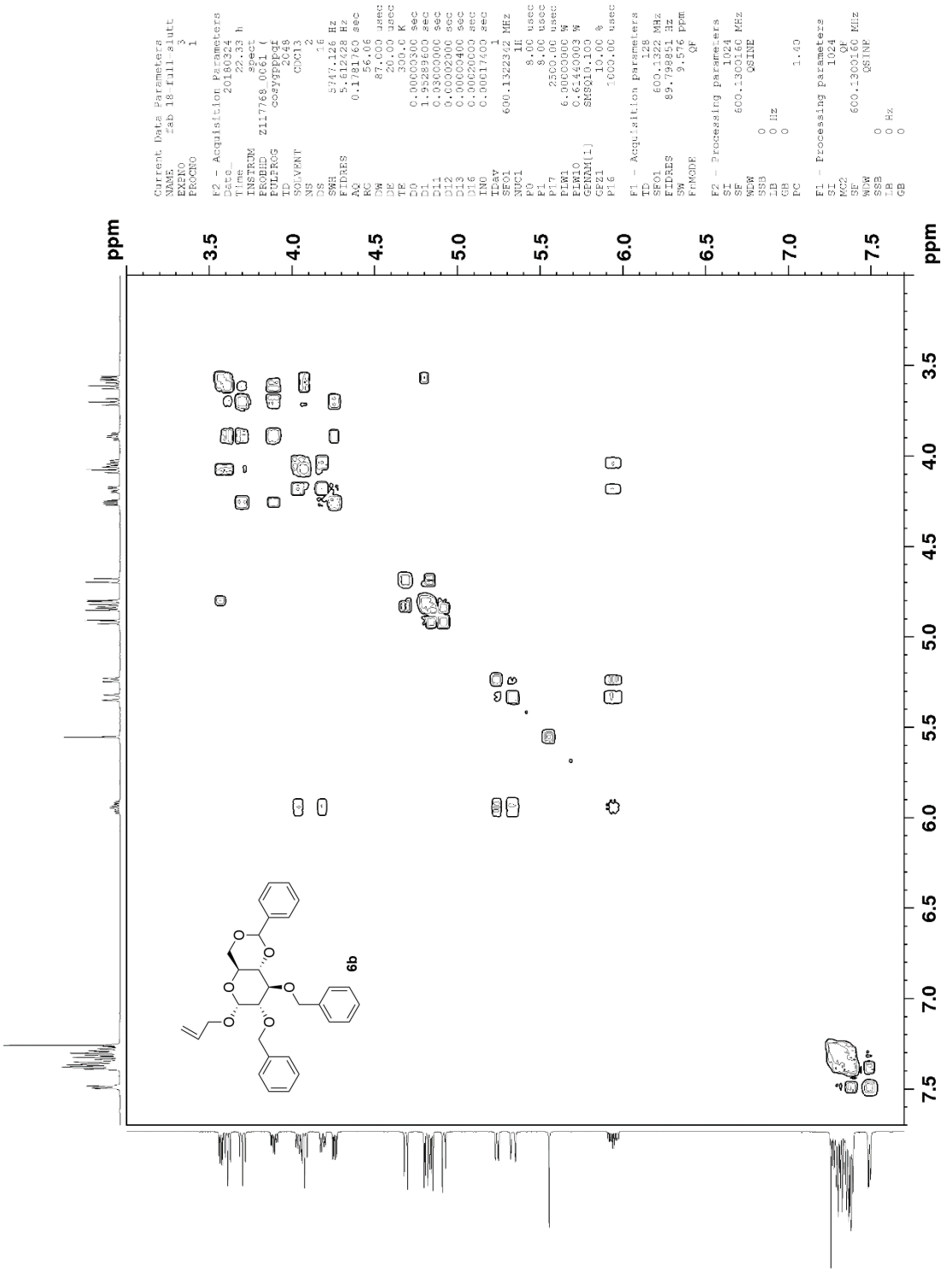


Figure H.3. COSY spectrum of compound **6b**.

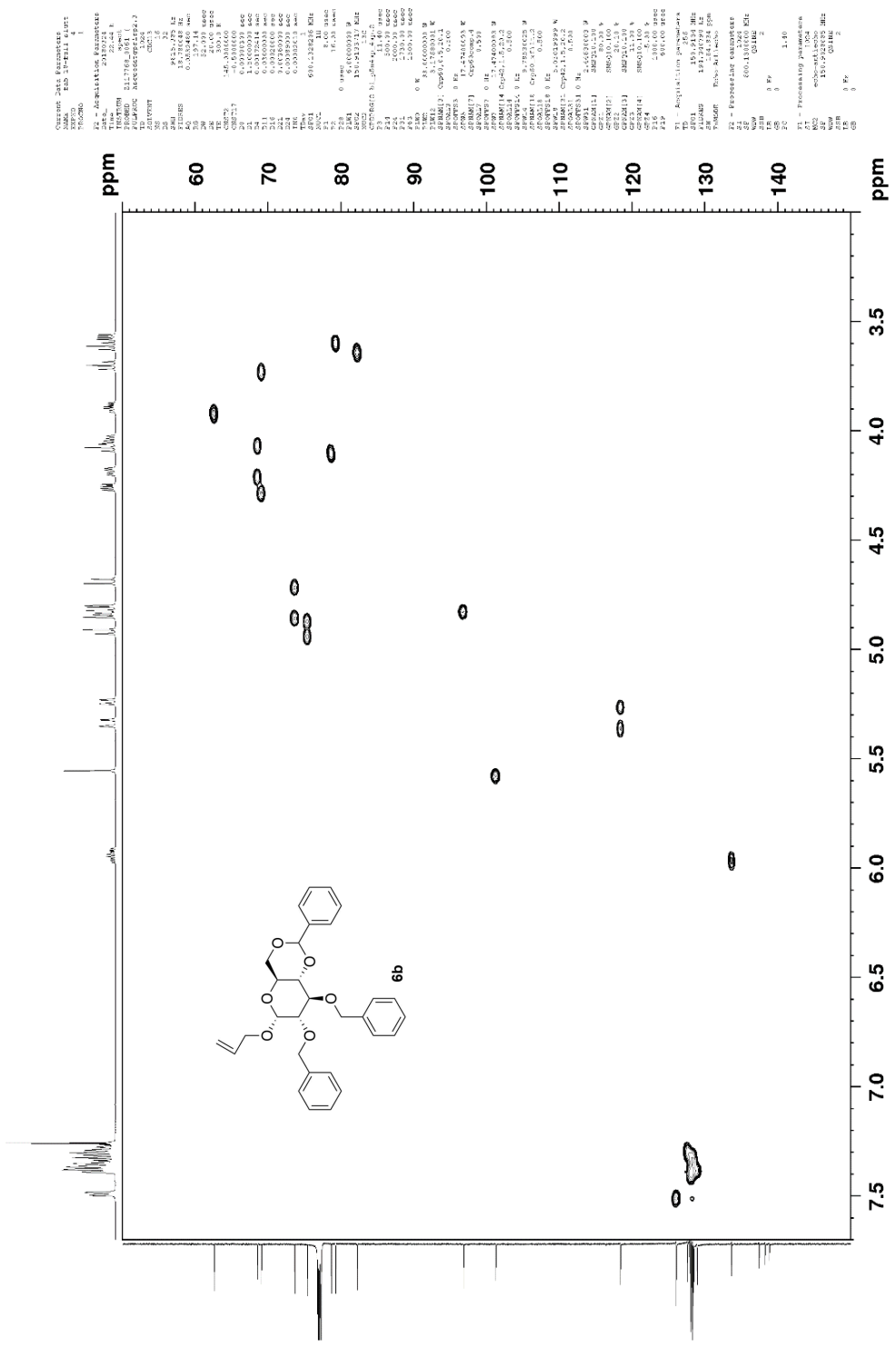


Figure H.4. HSQC spectrum of compound **6b**.

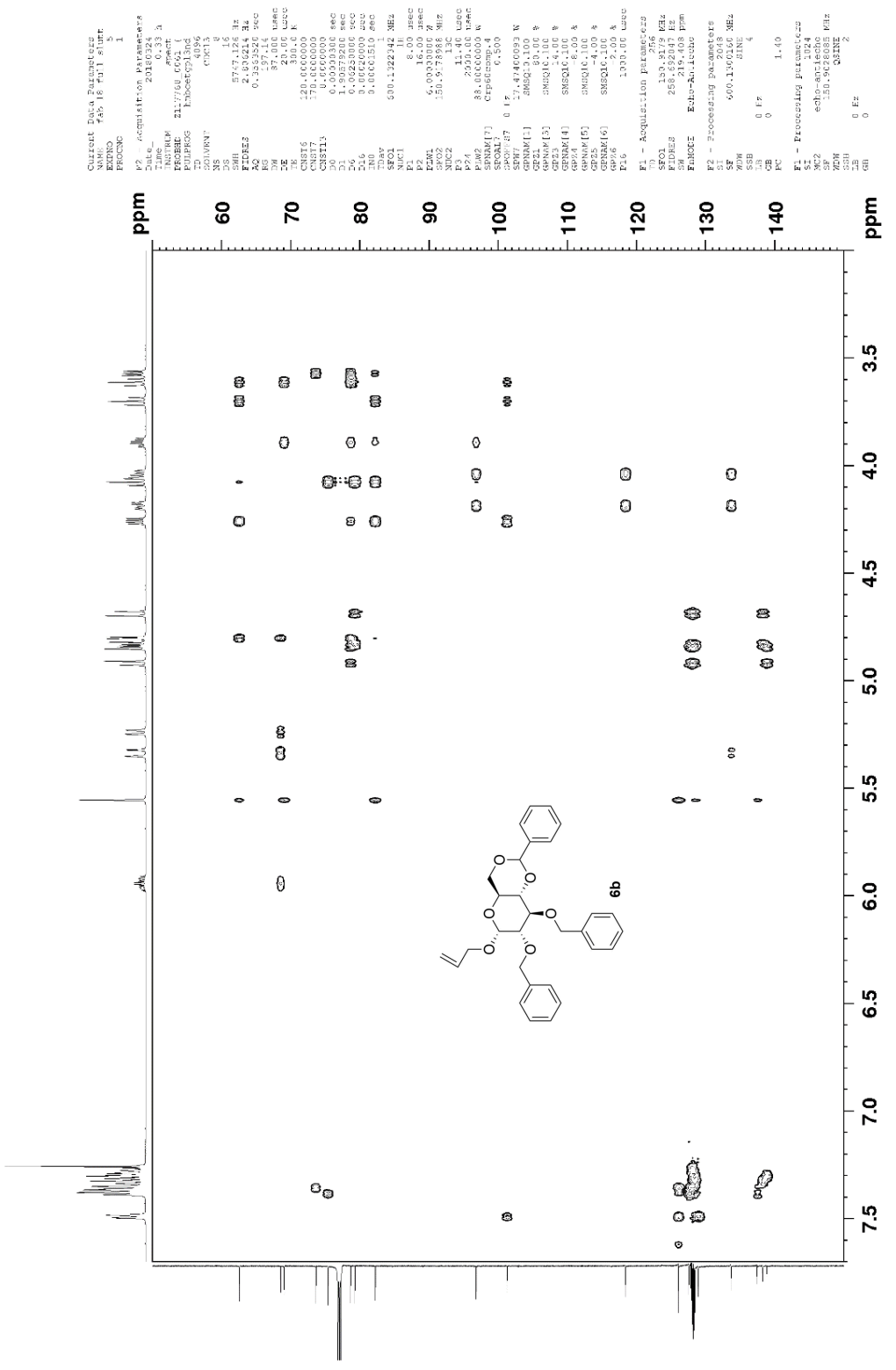


Figure H.5. HMBC spectrum of compound **6b**.

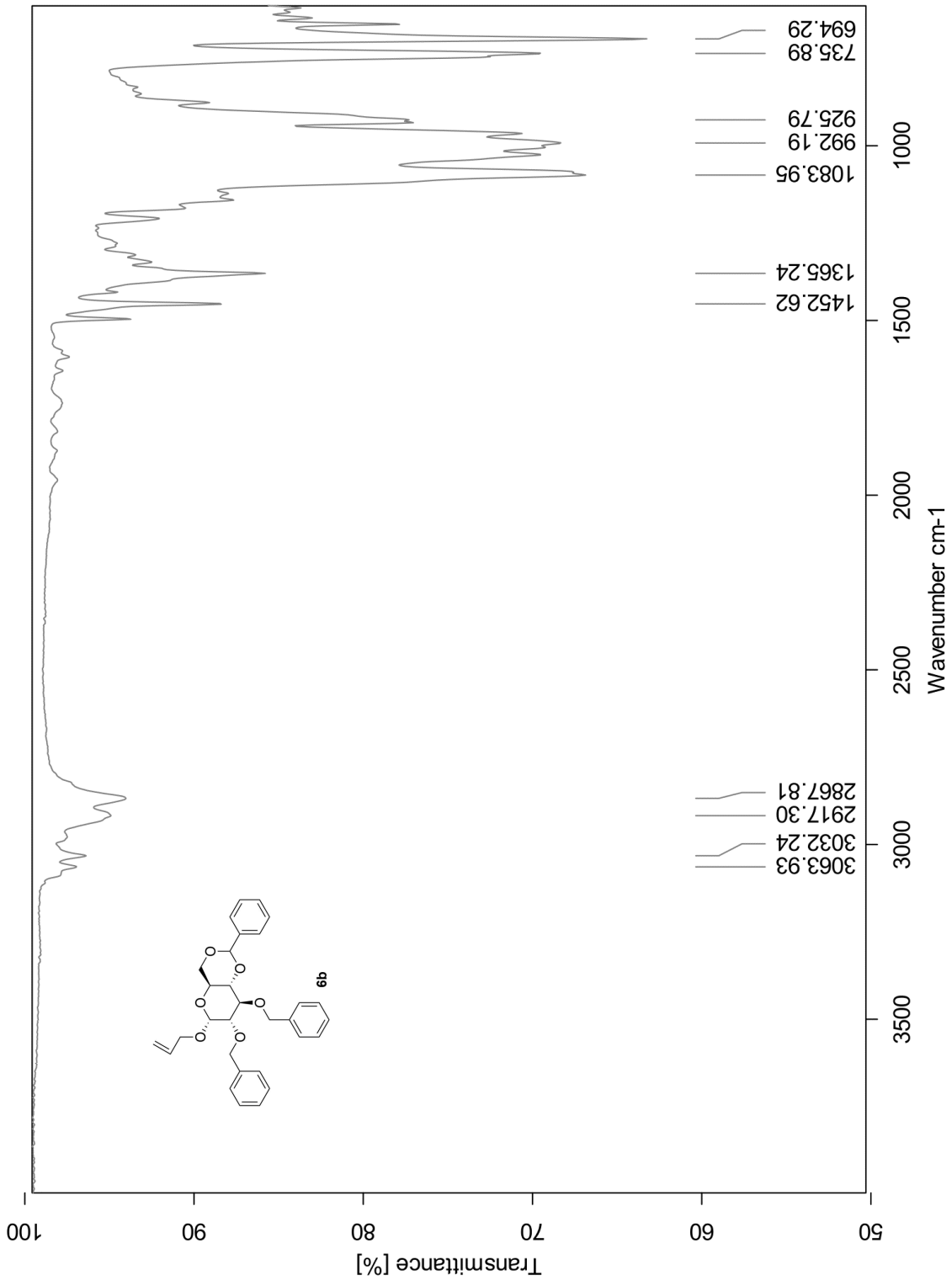
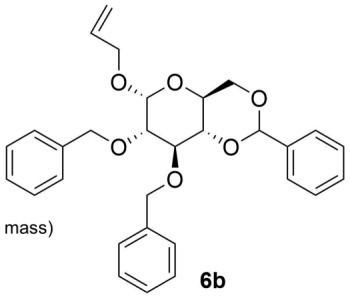


Figure H.6. IR spectrum of compound **6b**.

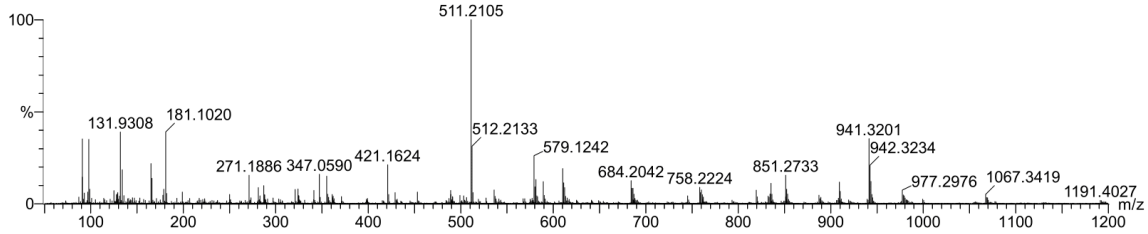
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 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
1332 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-10 Na: 0-1
2018-148 45 (0.837) AM2 (Ar,35000.0,0.00,0.00); Cm (44:45)
1: TOF MS ES+

2.29e+005



Minimum:				-1.5				
Maximum:		5000.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
511.2105	511.2107	-0.2	-0.4	23.5	825.1	2.287	10.15	C29 H23 N10
	511.2110	-0.5	-1.0	19.5	825.3	2.502	8.19	C31 H28 N4 O2 Na
	511.2097	0.8	1.6	14.5	823.0	0.203	81.66	C30 H32 O6 Na

Figure H.7. MS results for compound **6b**.

Appendix I. Spectroscopic data for compound **7b**

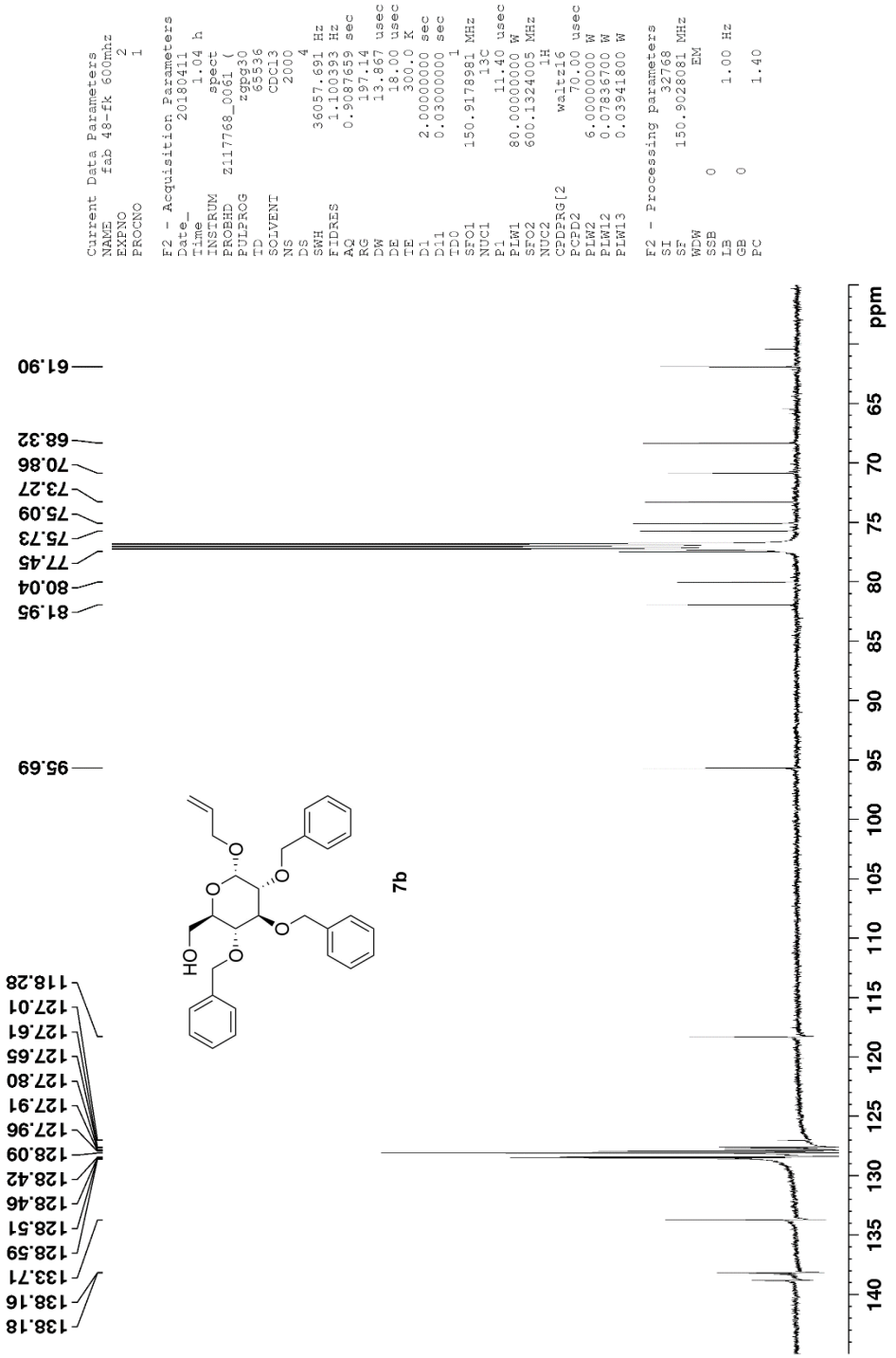


Figure I.1. ^{13}C-NMR spectrum of compound **7b**.

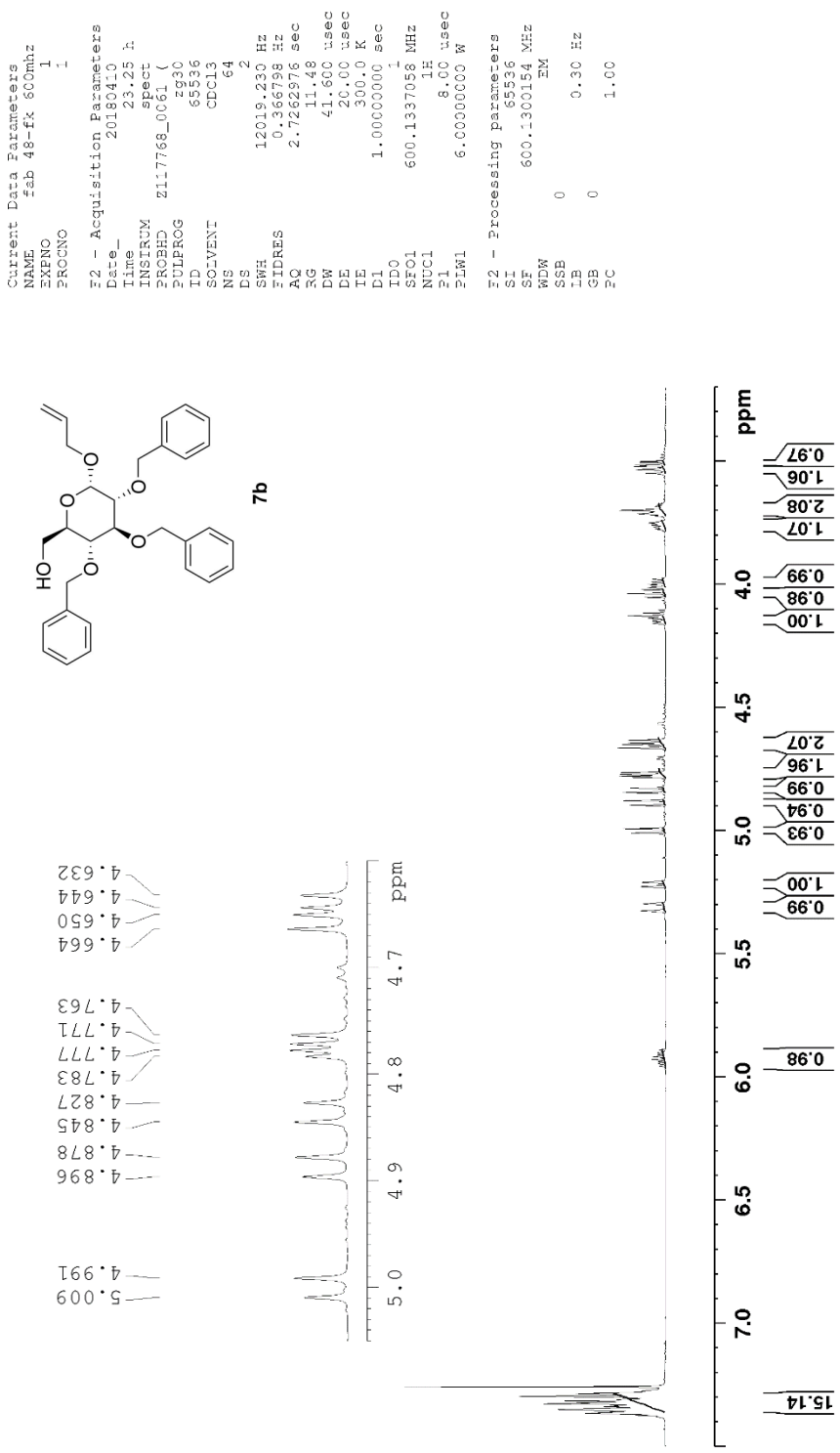


Figure I.2. ^{1}H-NMR spectrum of compound **7b**.

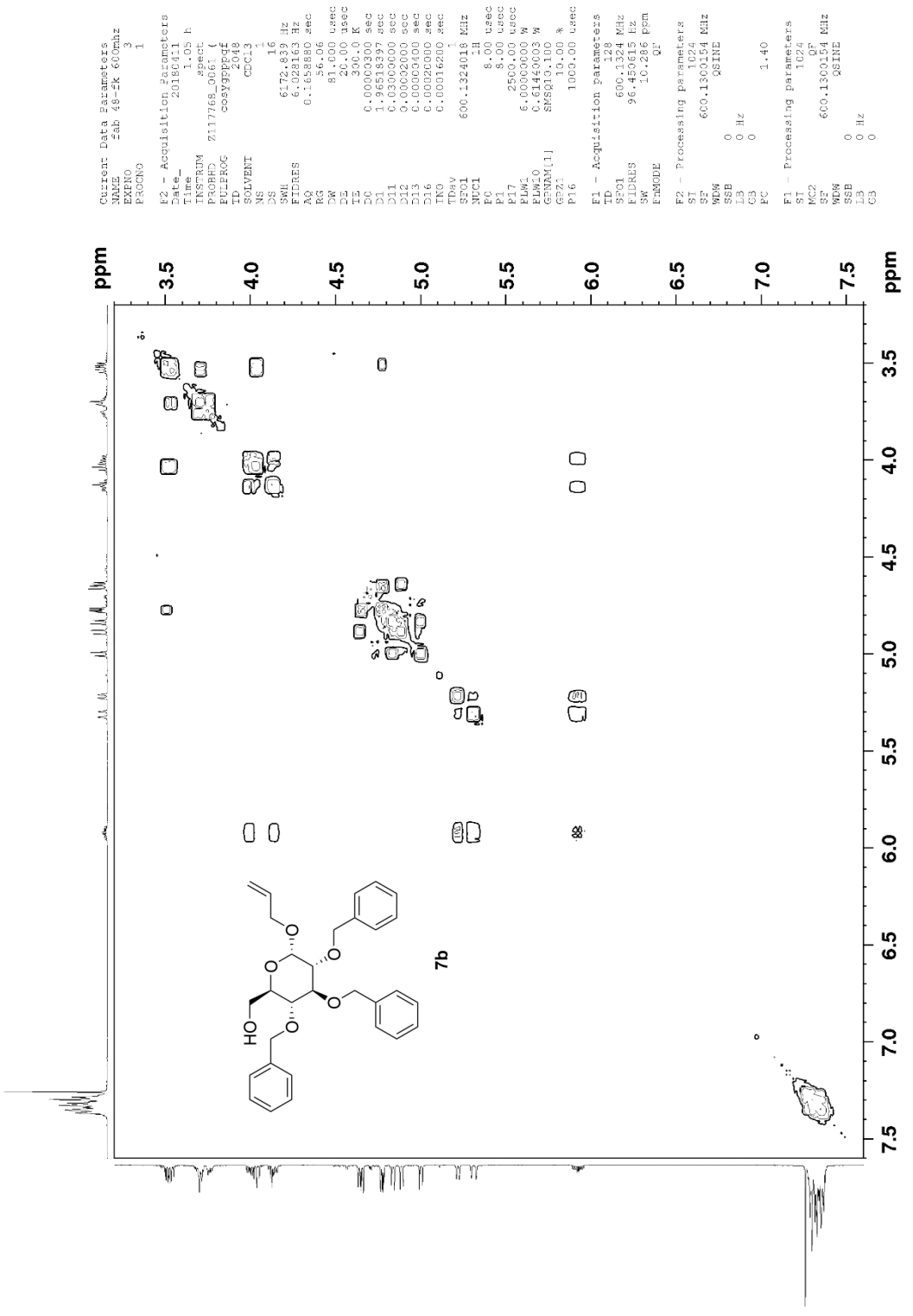


Figure I.3.COSY spectrum of compound **7b**.

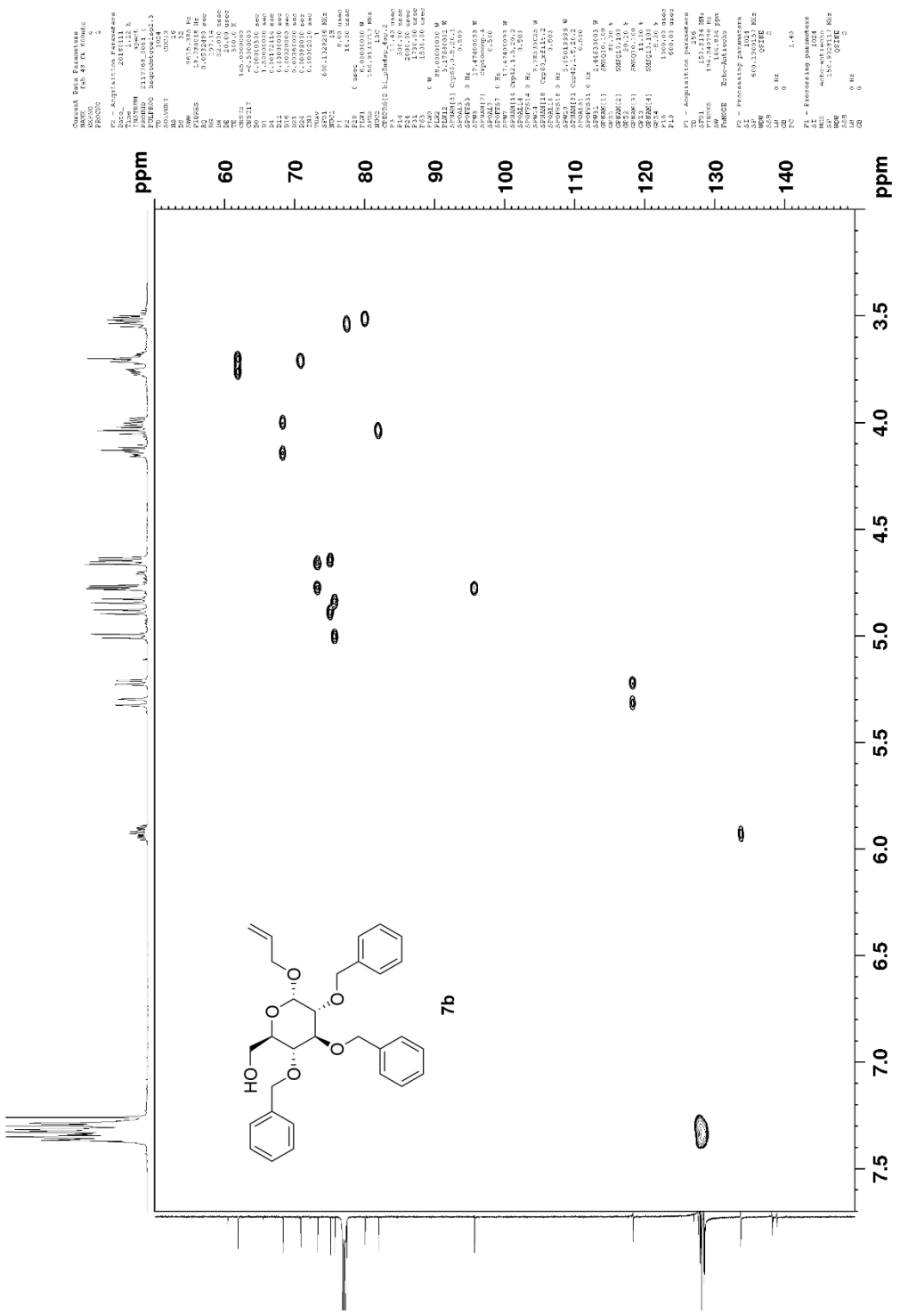


Figure I.4.HSQC spectrum of compound **7b**.

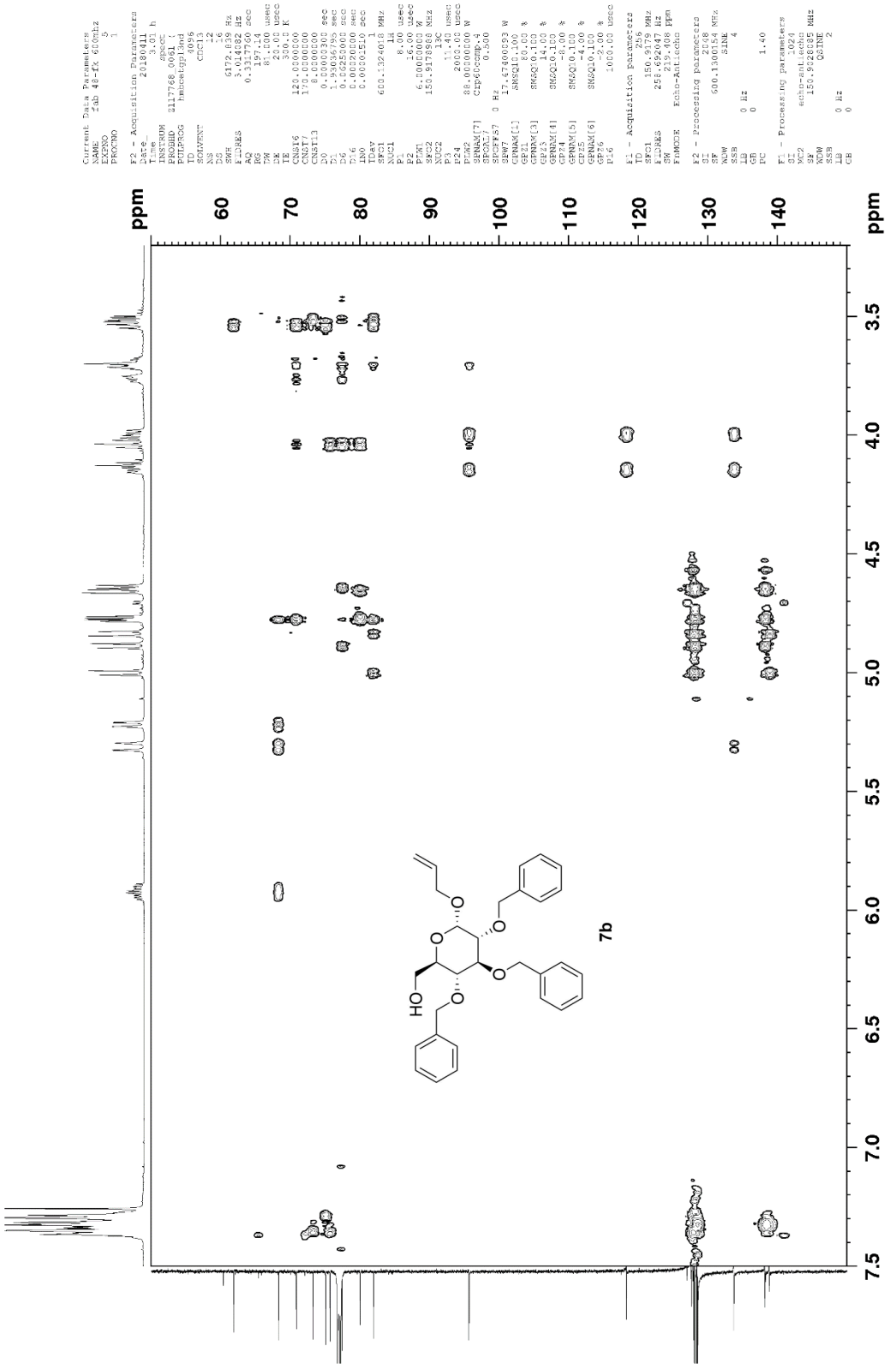


Figure I.5.HMBC spectrum of compound **7b**.

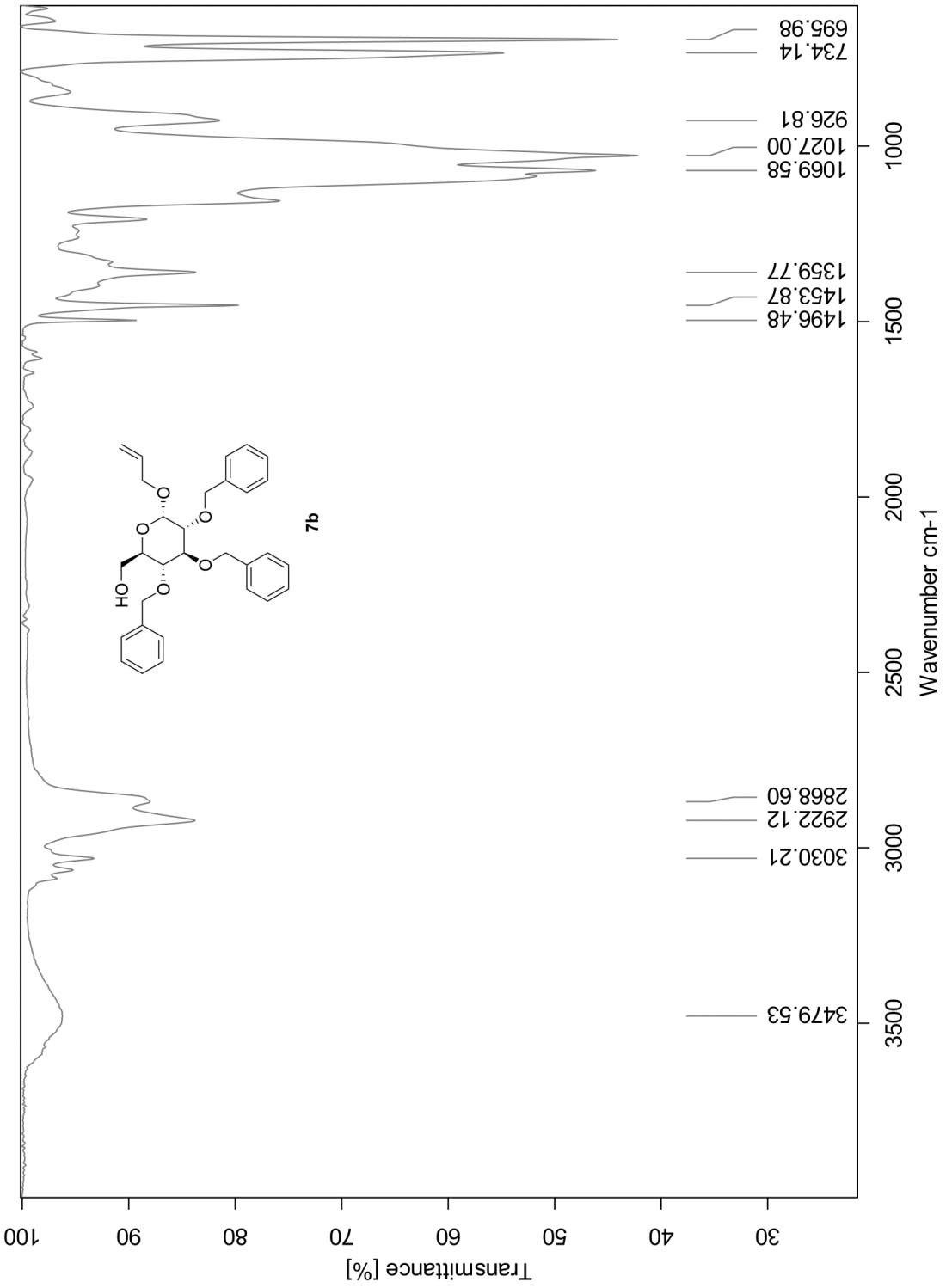
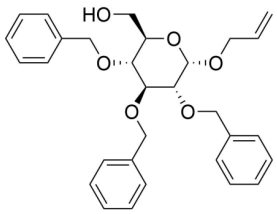


Figure I.6. IR spectrum of compound **7b**.

Elemental Composition Report **Page 1**

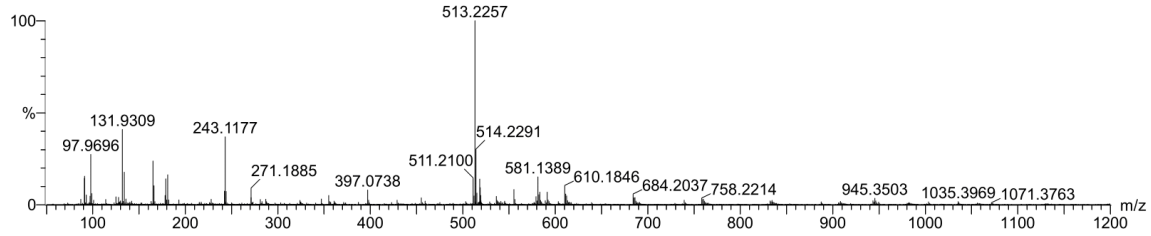


7b

Single Mass Analysis
Tolerance = 2.0 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
1333 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-10 Na: 0-1
2018-155 46 (0.866) AM2 (Ar,35000.0,0.00,0.00); Cm (46:48)
1: TOF MS ES+

5.12e+005



Minimum:				-1.5				
Maximum:		5000.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
513.2257	513.2253	0.4	0.8	13.5	921.5	0.185	83.08	C30 H34 O6 Na
	513.2264	-0.7	-1.4	22.5	924.9	3.593	2.75	C29 H25 N10
	513.2250	0.7	1.4	17.5	923.8	2.514	8.10	C28 H29 N6 O4
	513.2266	-0.9	-1.8	18.5	924.1	2.801	6.08	C31 H30 N4 O2 Na

Figure I.7. MS results for compound **7b**.

Appendix J. Spectroscopic data for compound **8b**

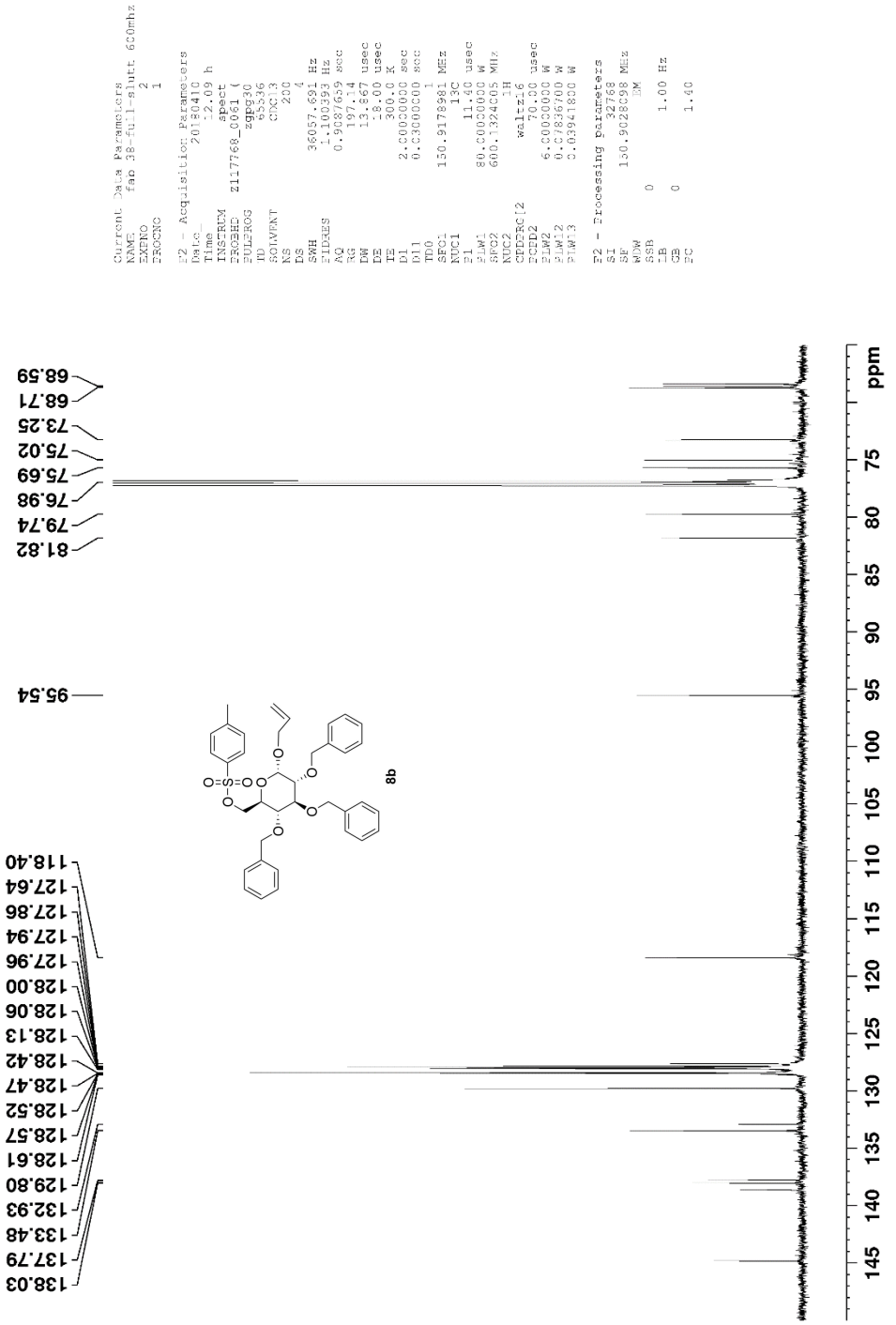


Figure J.1. ^{13}C-NMR spectrum of compound **8b**.

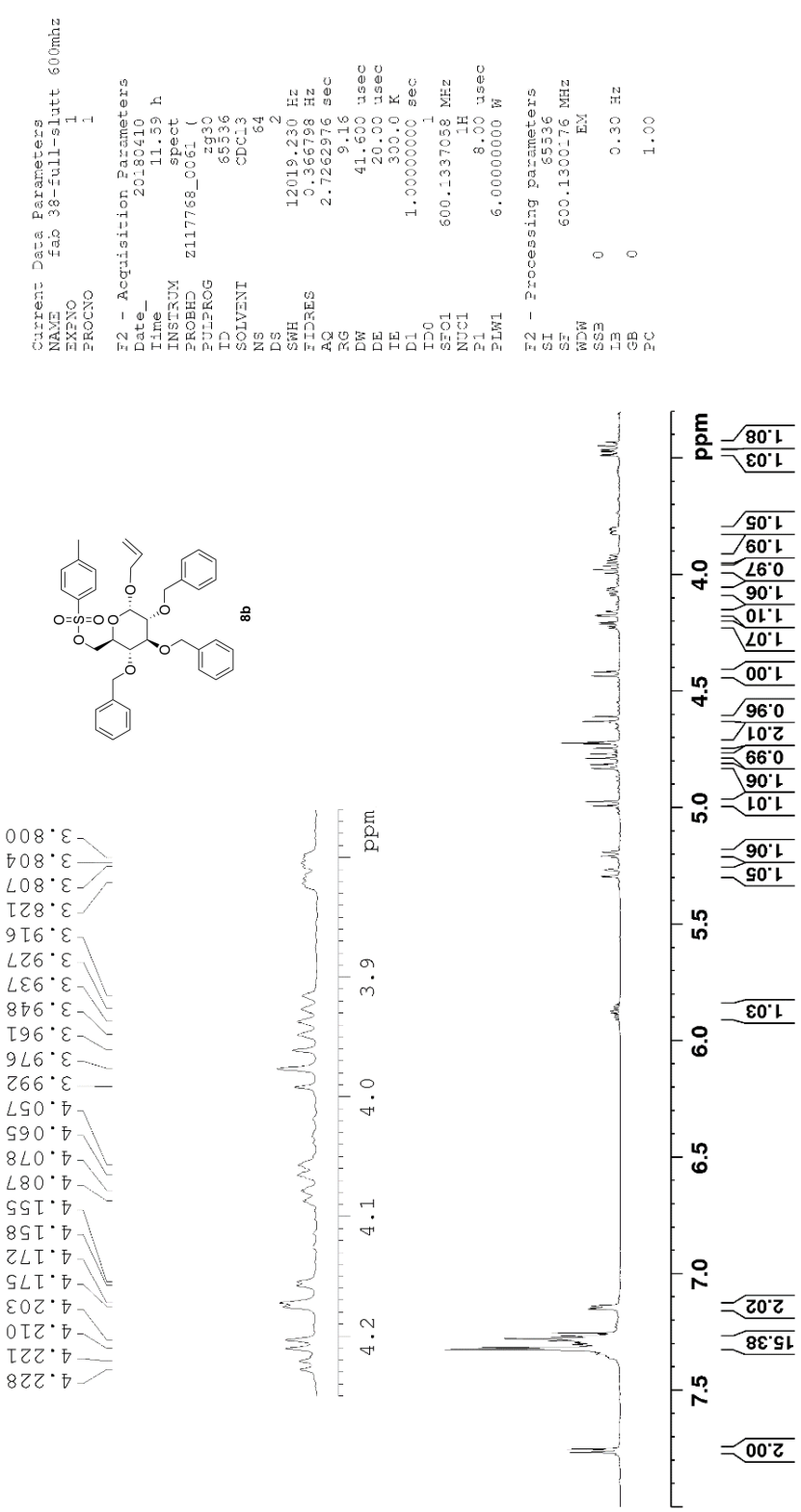


Figure J.2. [1]H-NMR spectrum of compound **8b**.

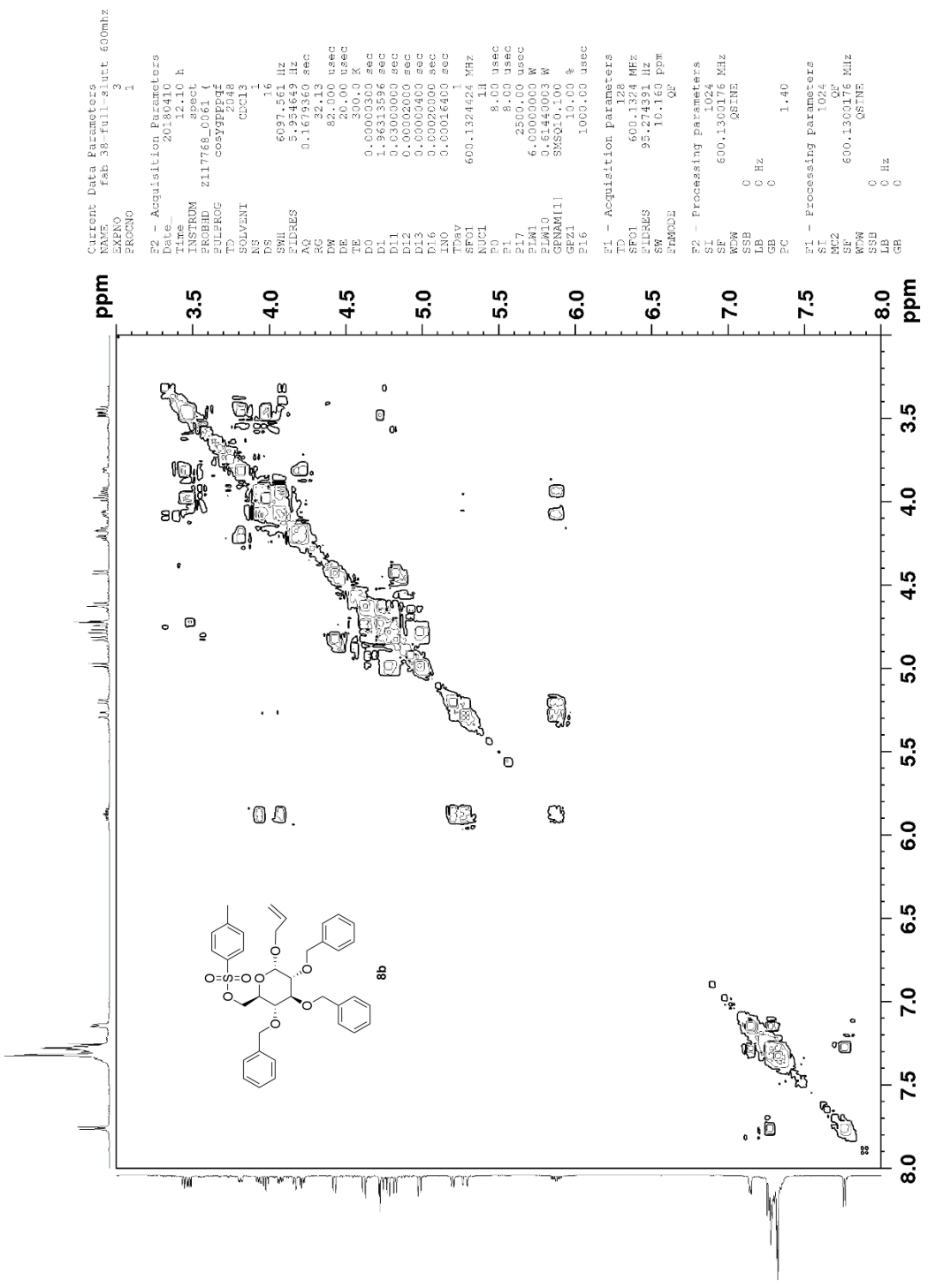


Figure J.3.COSY spectrum of compound **8b**.

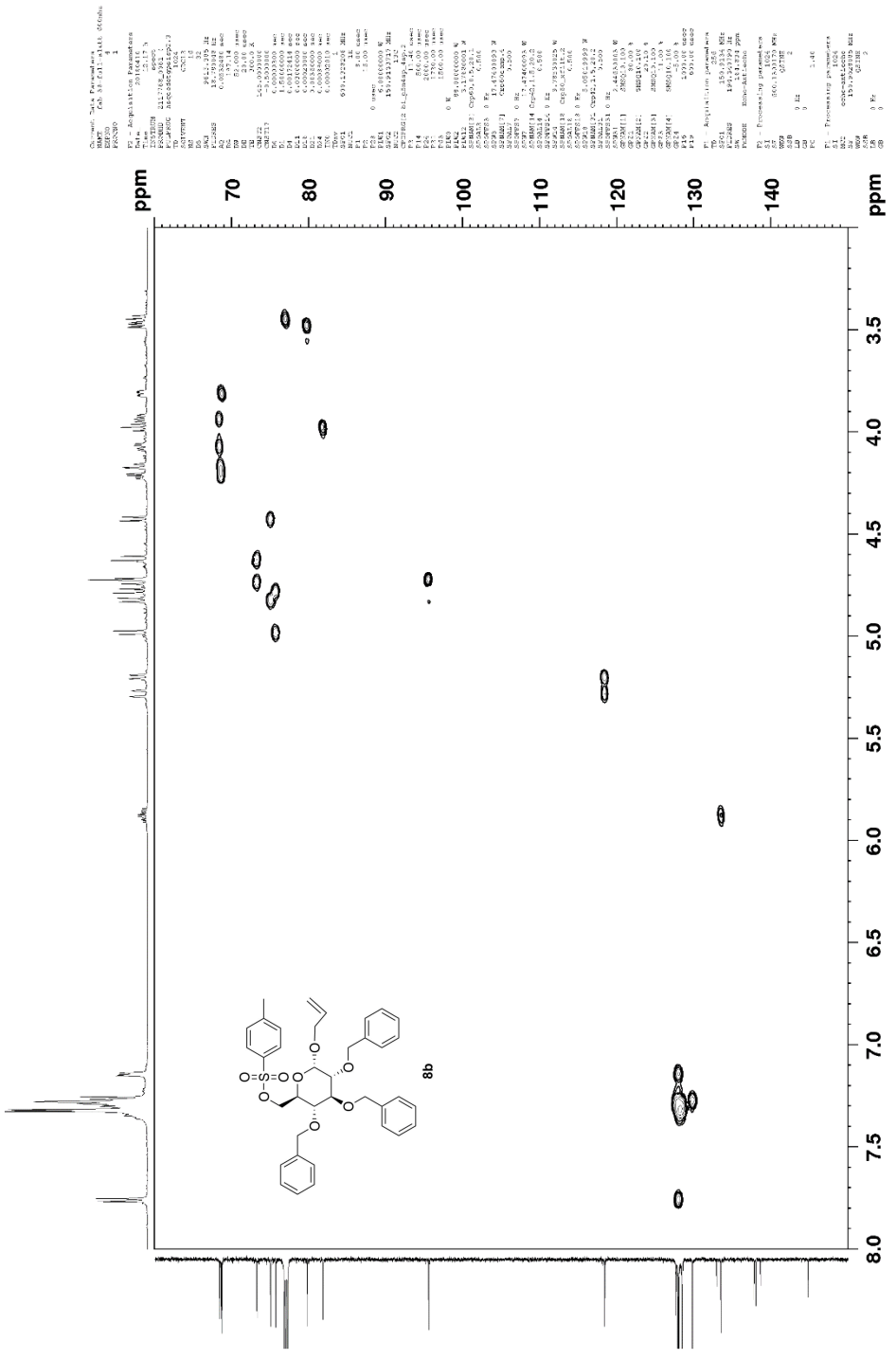


Figure J.4.HSQC spectrum of compound **8b**.

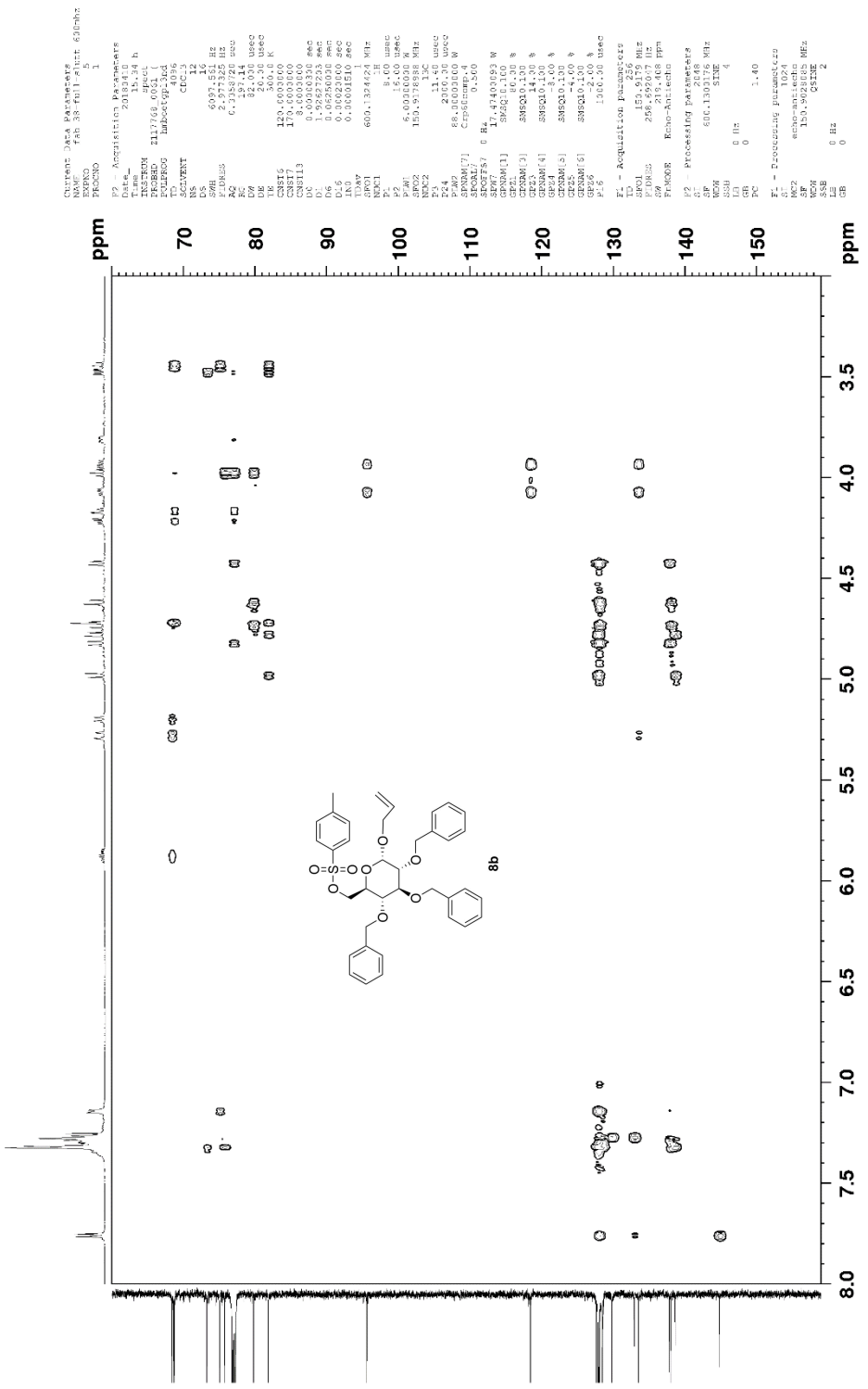


Figure J.5 HMBC spectrum of compound **8b**.

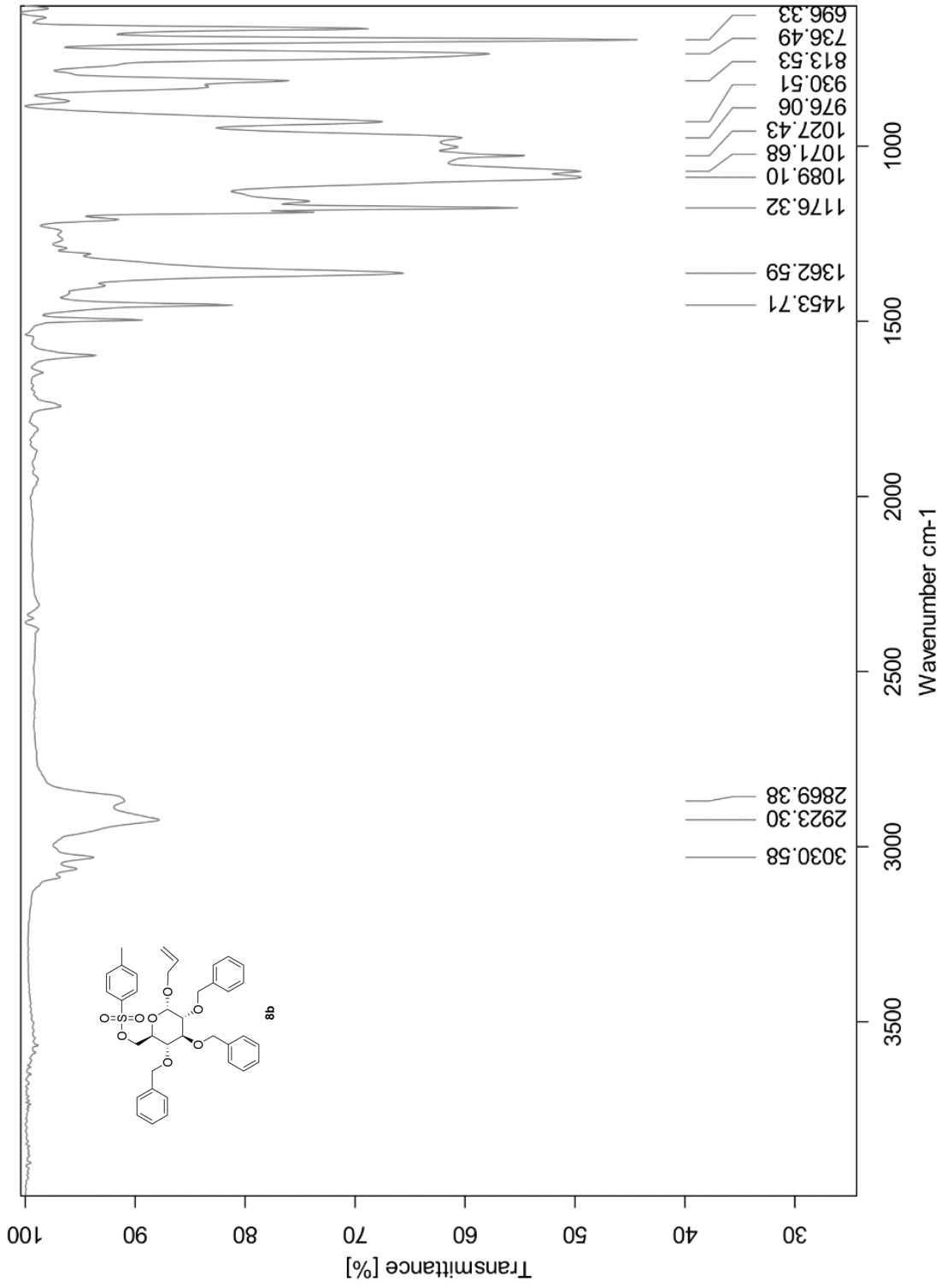
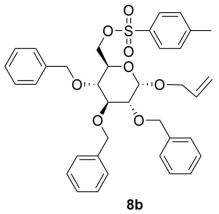


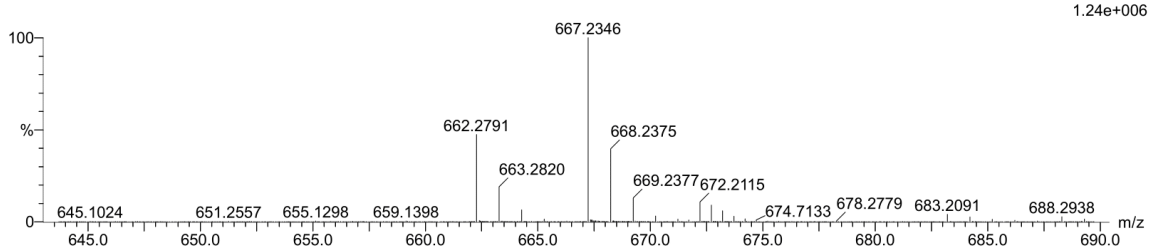
Figure J.6.IR spectrum of compound **8b**.

Elemental Composition Report **Page 1**



Single Mass Analysis
Tolerance = 2.0 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
915 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 O: 0-10 Na: 0-1 S: 0-5
2018-156 62 (1.151) AM2 (Ar,35000.0,0.00,0.00); Cm (58:62)
1: TOF MS ES+



Minimum:				-1.5				
Maximum:		5000.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
667.2346	667.2342	0.4	0.6	17.5	859.5	0.000	99.95	C37 H40 O8 Na S
	667.2350	-0.4	-0.6	16.5	870.4	10.886	0.00	C38 H44 O3 Na S3
	667.2341	0.5	0.7	24.5	867.3	7.732	0.04	C43 H39 O3 S2

Figure J.7 MS results for compound **8b**.

Appendix K. Spectroscopic data for compound **9b**

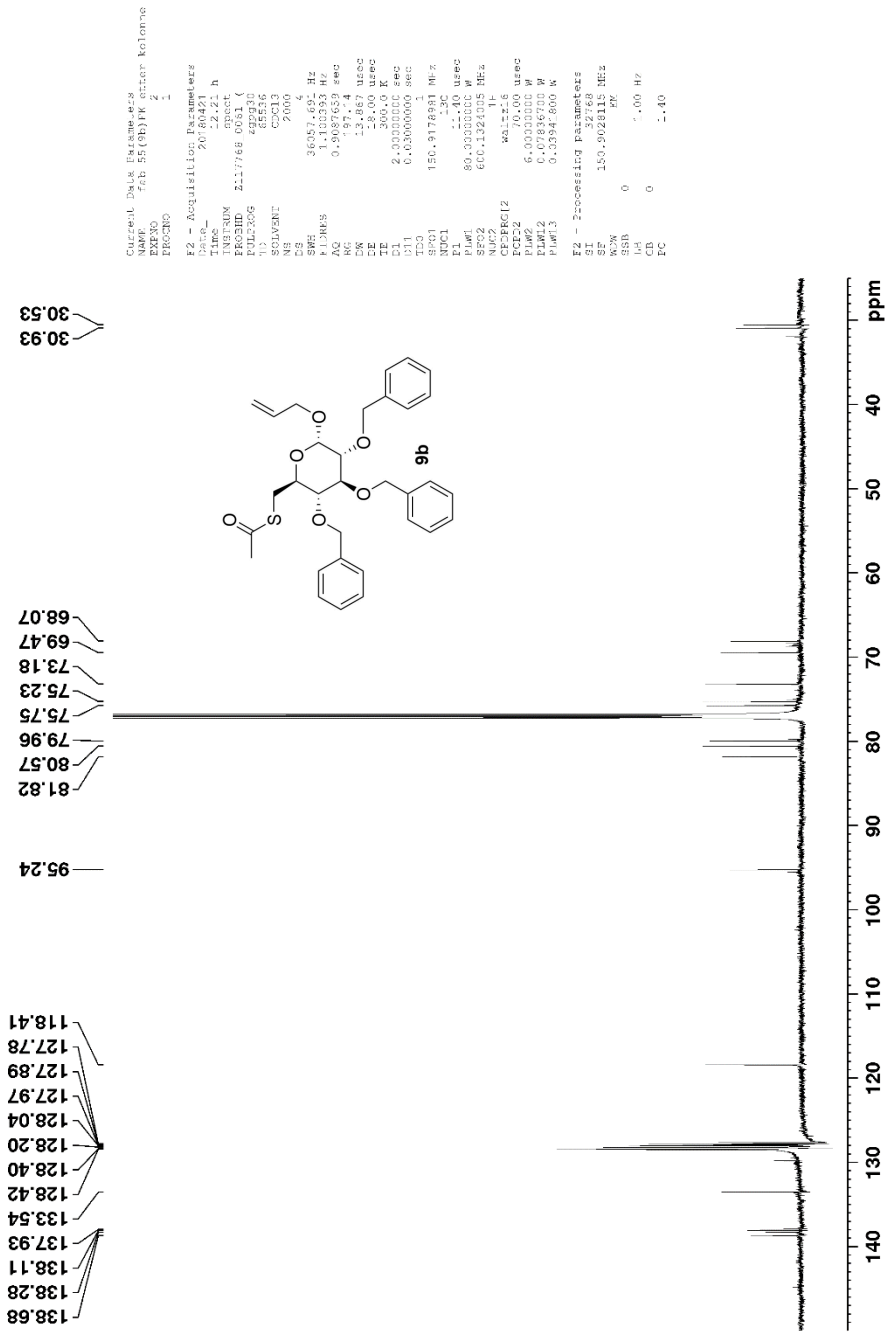


Figure K.1. ^{13}C-NMR spectrum of compound **9b**.

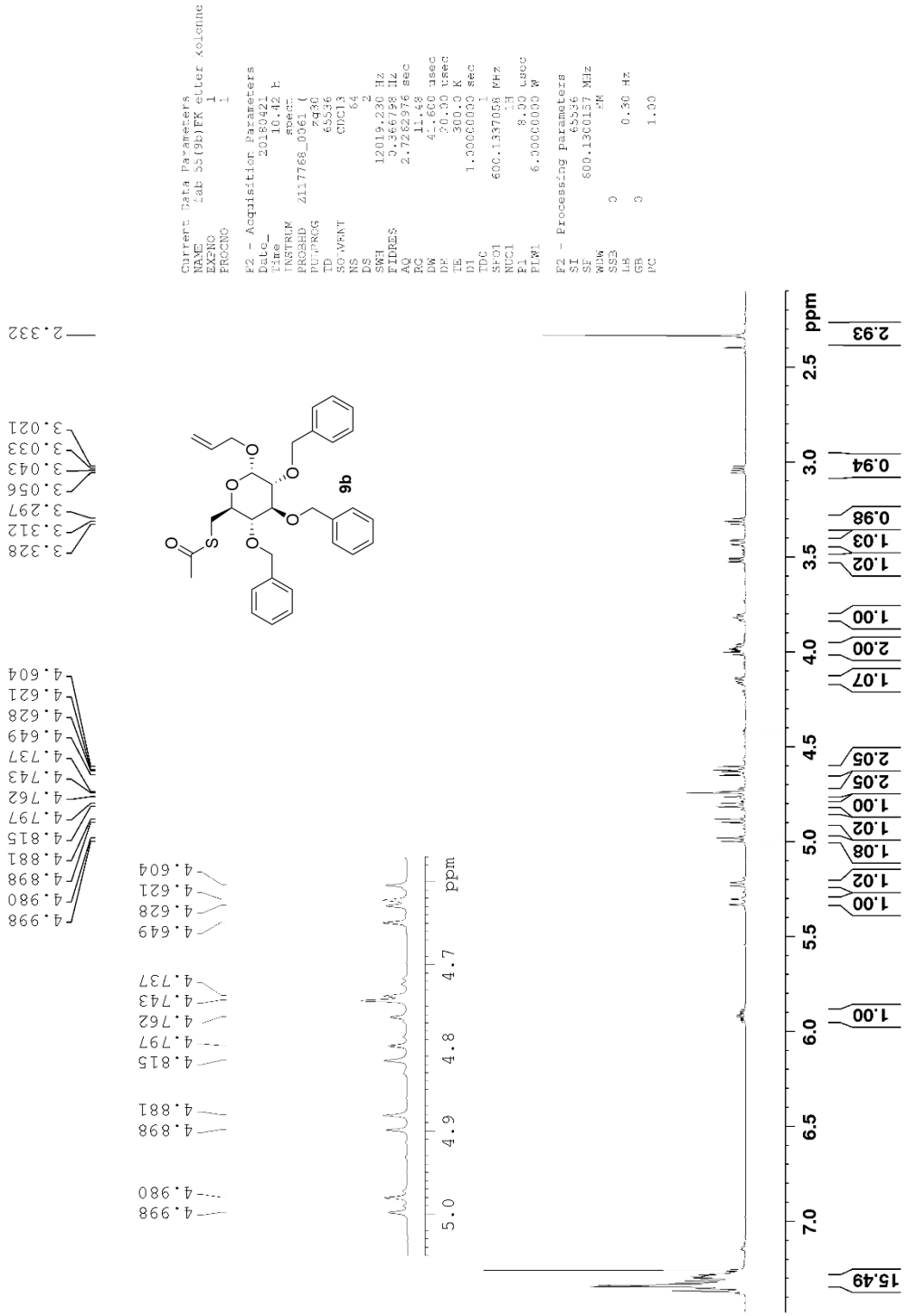


Figure K.2. ^{1}H-NMR spectrum of compound **9b**.

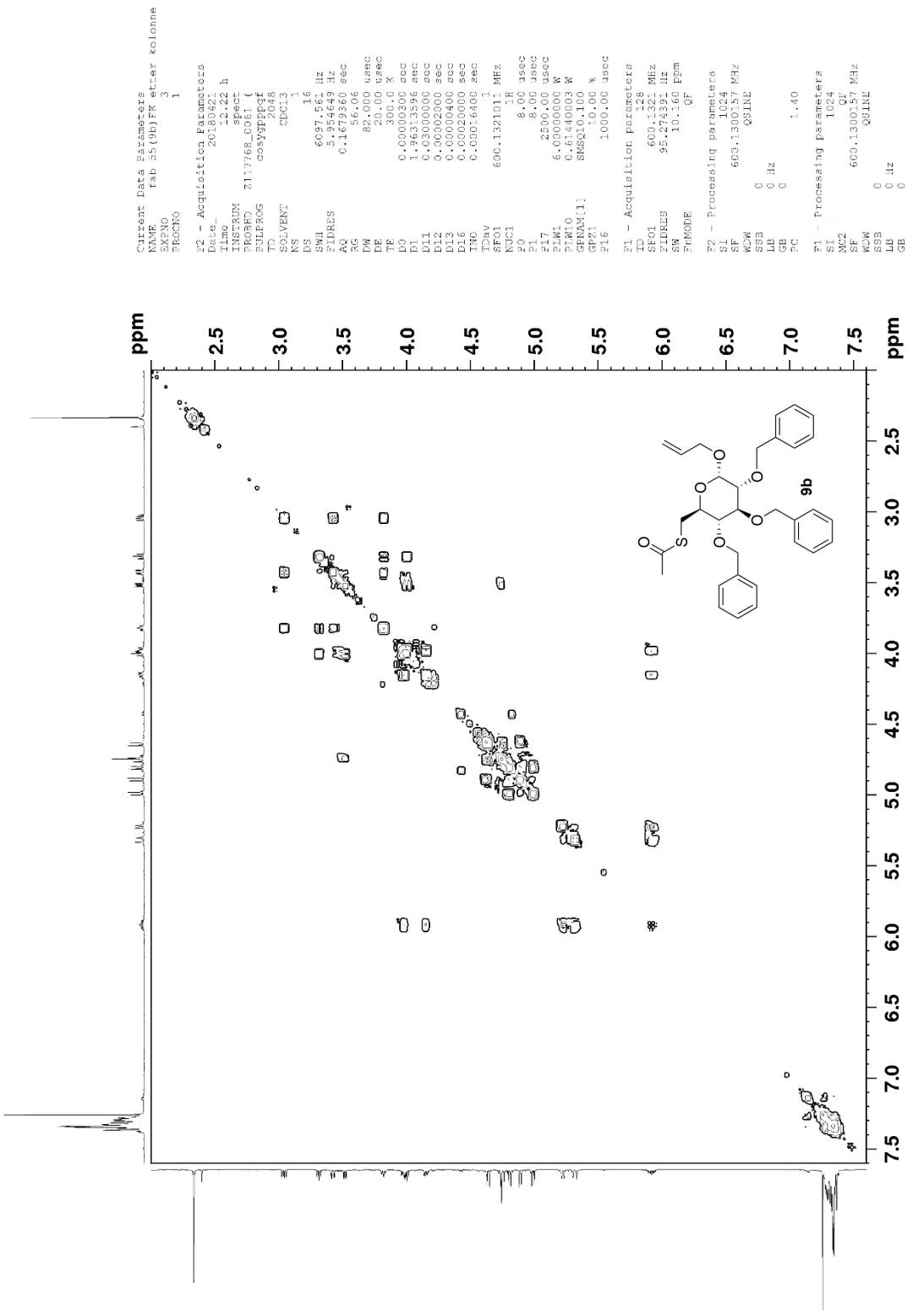


Figure K.3. COSY spectrum of compound **9b**.

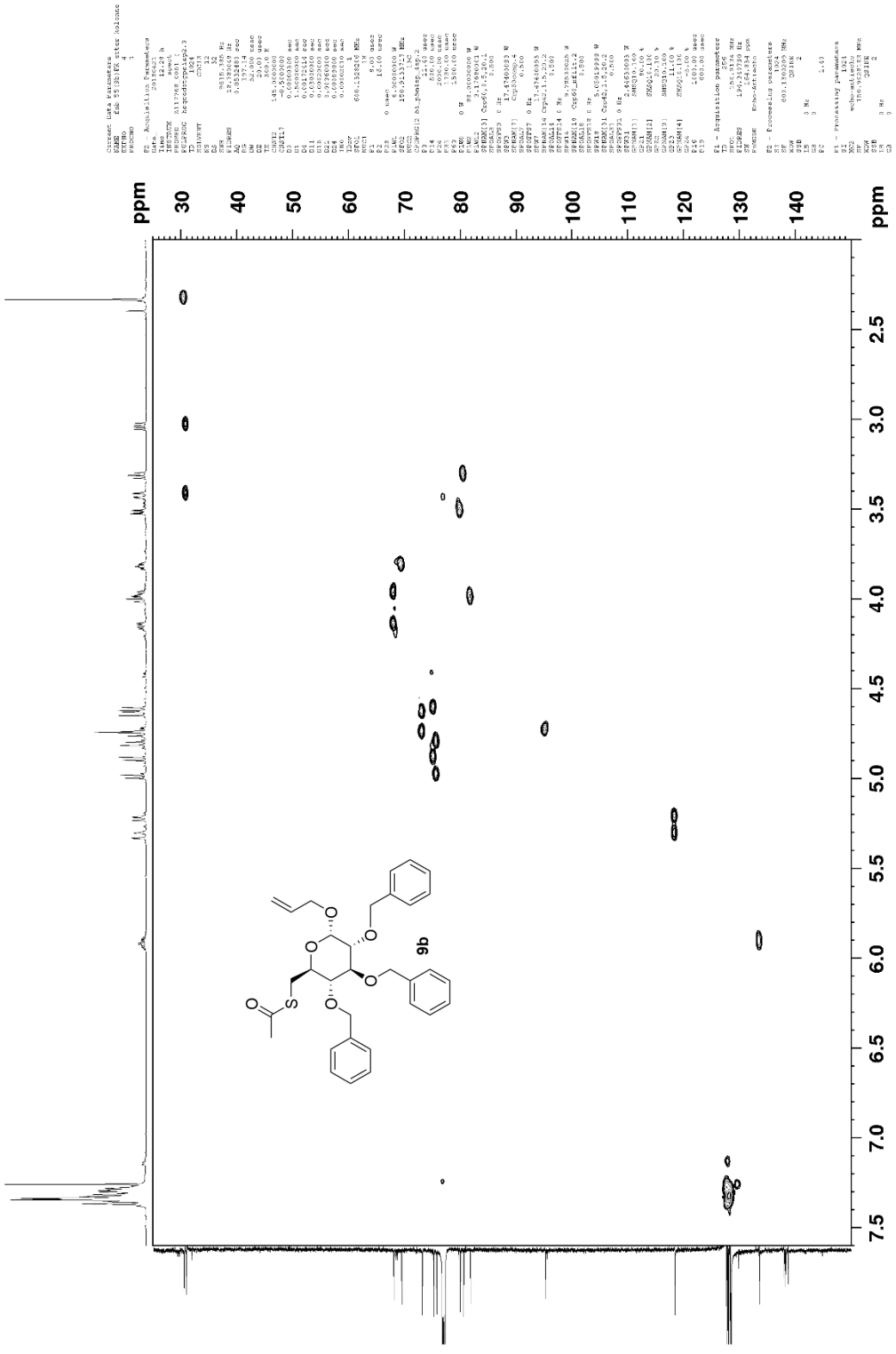


Figure K.4. HSQC spectrum of compound **9b**.

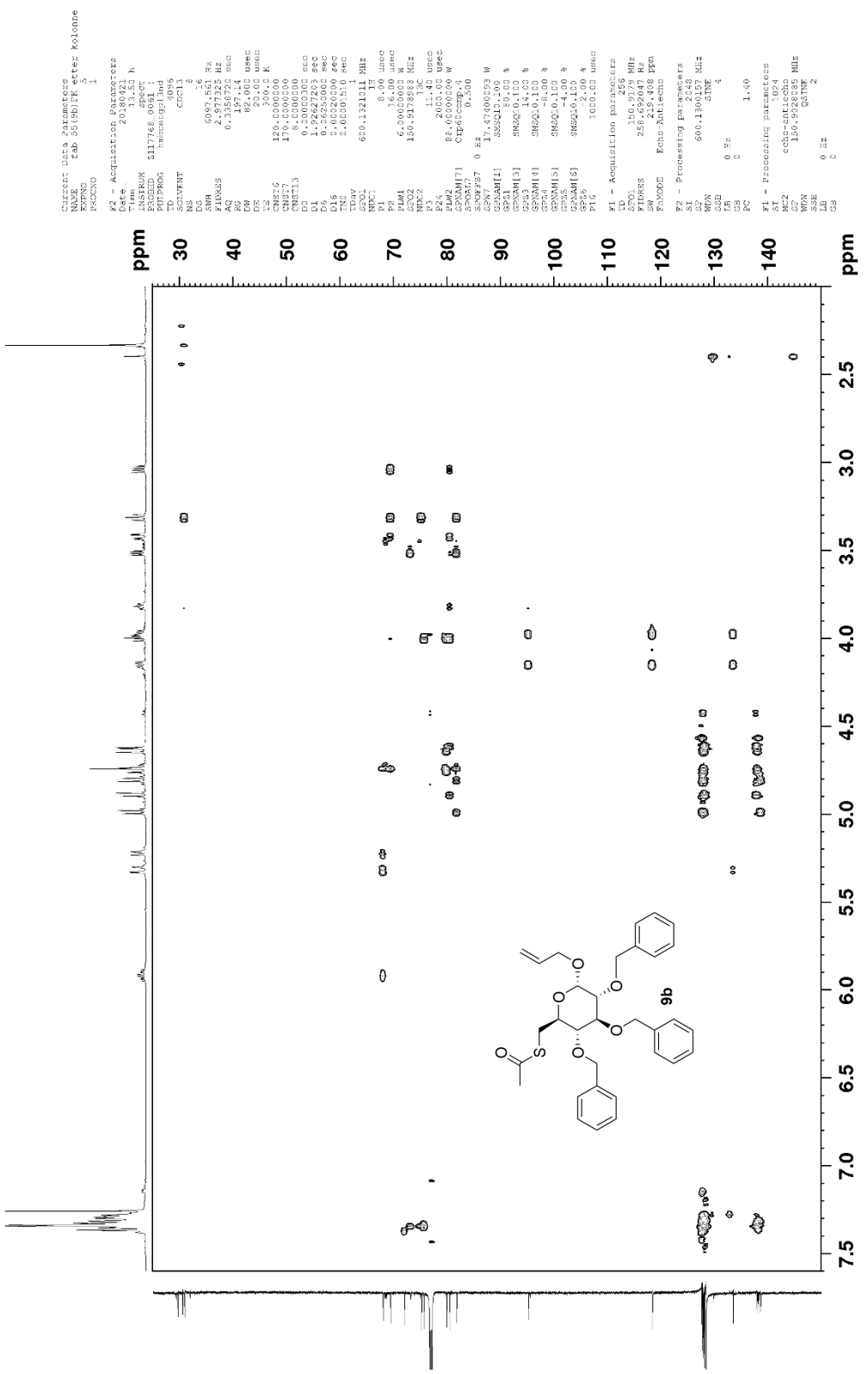


Figure K.5. HMBC spectrum of compound **9b**.

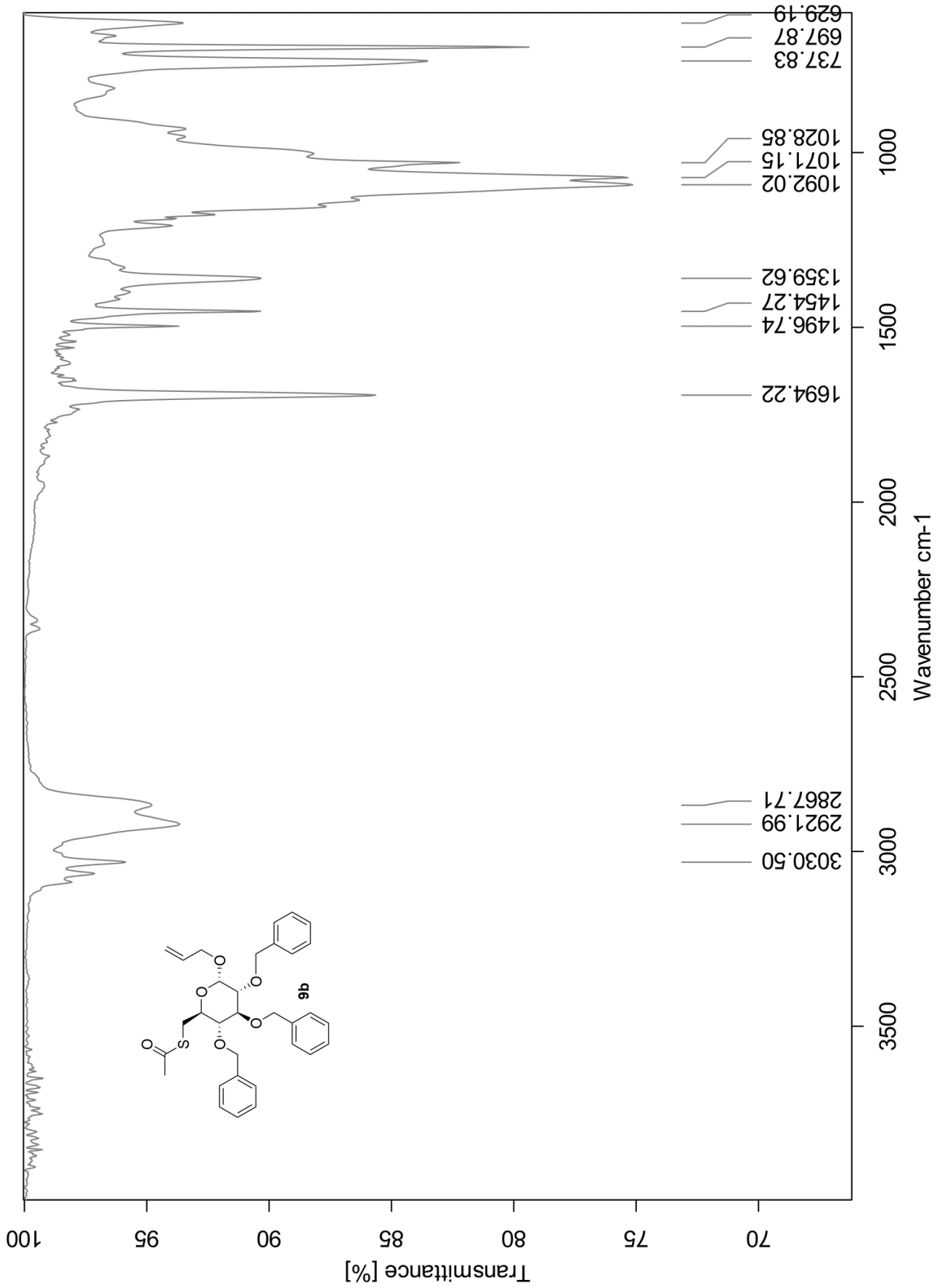
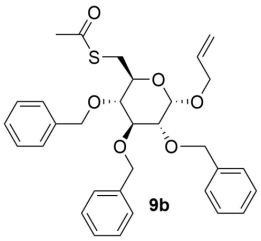


Figure K.6. IR spectrum of compound **9b**.

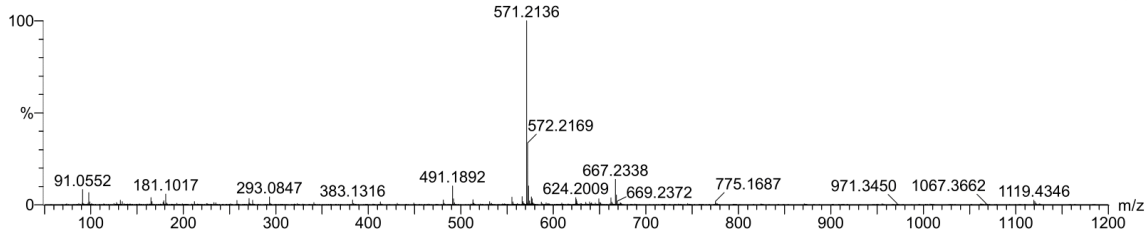
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 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
764 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 O: 0-10 Na: 0-1 S: 0-5
2018-161 58 (1.083) AM2 (Ar,35000.0,0.00,0.00); Cm (56:58)
1: TOF MS ES+

1.57e+006



Minimum:				-1.5				
Maximum:		5000.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
571.2136	571.2139	-0.3	-0.5	13.5	932.4	10.723	0.00	C33 H40 O Na S3
	571.2130	0.6	1.1	14.5	921.7	0.000	99.95	C32 H36 O6 Na S
	571.2129	0.7	1.2	21.5	929.3	7.655	0.05	C38 H35 O S2

Figure K.7. MS results for compound **9b**.

Appendix L. Spectroscopic data for compound **10b**

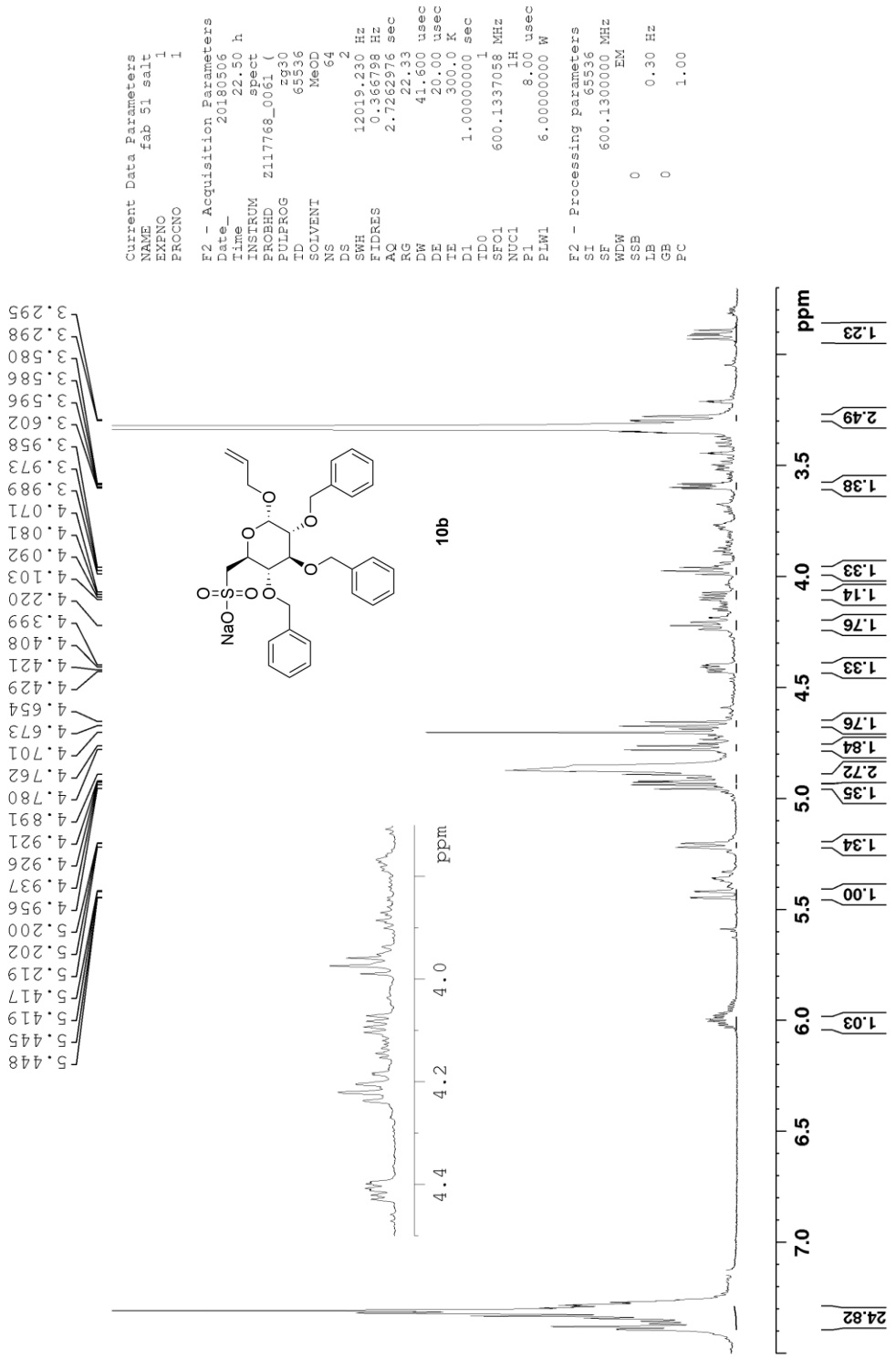


Figure L.1. ^{13}C-NMR spectrum of compound **10b**.

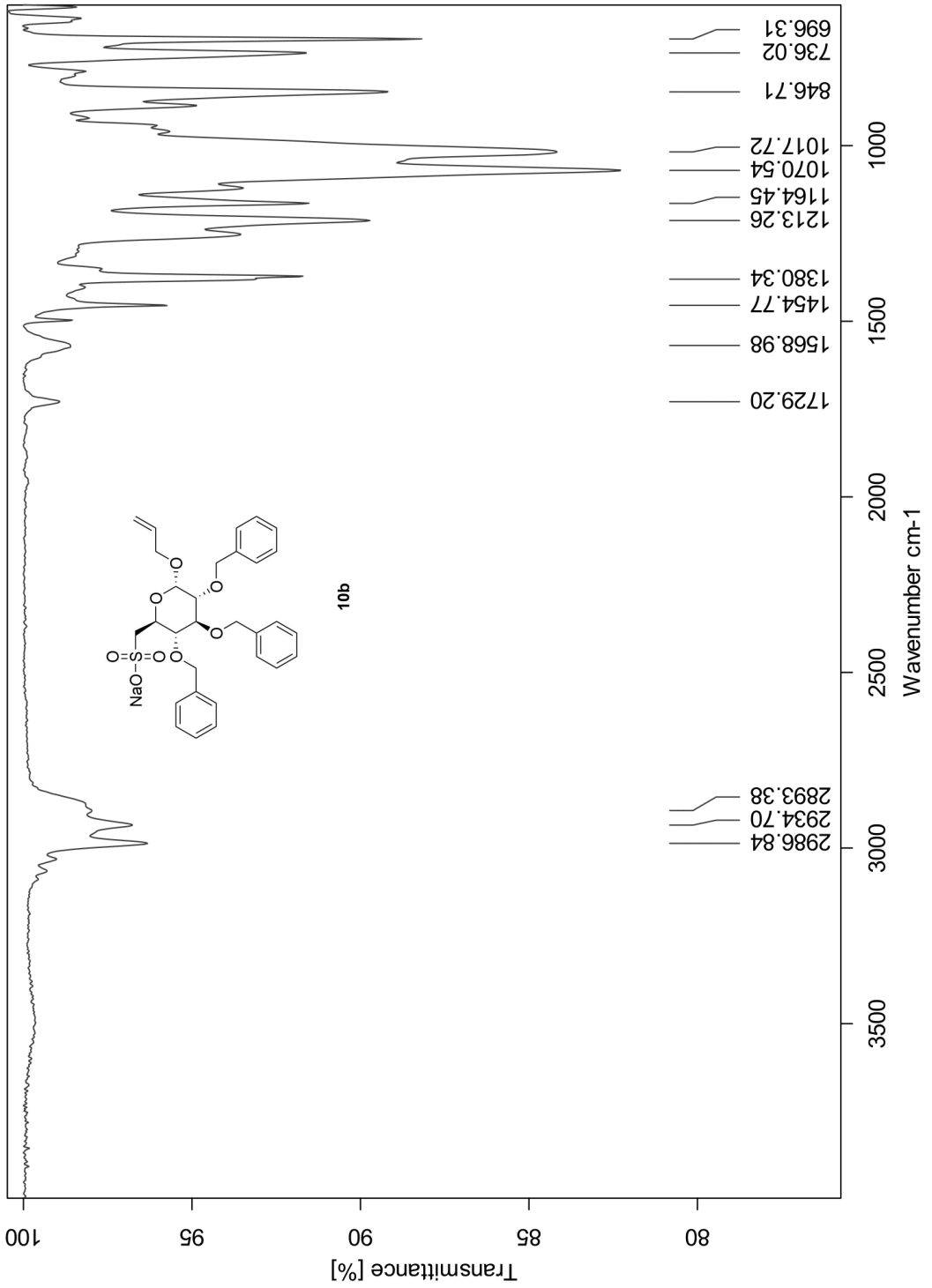
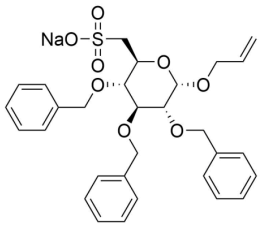


Figure L.2. IR spectrum of compound **10b**.

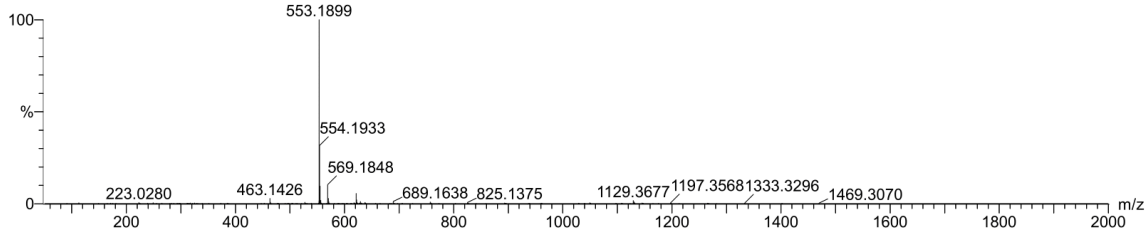
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



Monoisotopic Mass, Even Electron Ions
3369 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-20 S: 0-2
2018_223NEG_FIA 34 (0.637) AM2 (Ar,35000.0,0.00,0.00); Cm (32:34)
1: TOF MS ES-

10b 1.33e+006



Minimum:				-1.5				
Maximum:		5000.0	2.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
553.1899	553.1896	0.3	0.5	14.5	818.8	0.132	87.65	C30 H33 O8 S
	553.1903	-0.4	-0.7	10.5	827.1	8.518	0.02	C23 H33 N6 O6 S2
	553.1894	0.5	0.9	11.5	826.7	8.114	0.03	C22 H29 N6 O11
	553.1890	0.9	1.6	5.5	828.3	9.721	0.01	C22 H37 N2 O10 S2
	553.1908	-0.9	-1.6	16.5	826.9	8.266	0.03	C23 H25 N10 O7
	553.1889	1.0	1.8	29.5	827.9	9.236	0.01	C35 H21 N8
	553.1910	-1.1	-2.0	19.5	820.7	2.099	12.25	C31 H29 N4 O4 S

Figure L.3. Ms results for compound **10b**.

Appendix M. Spectroscopic data for compound **3a**

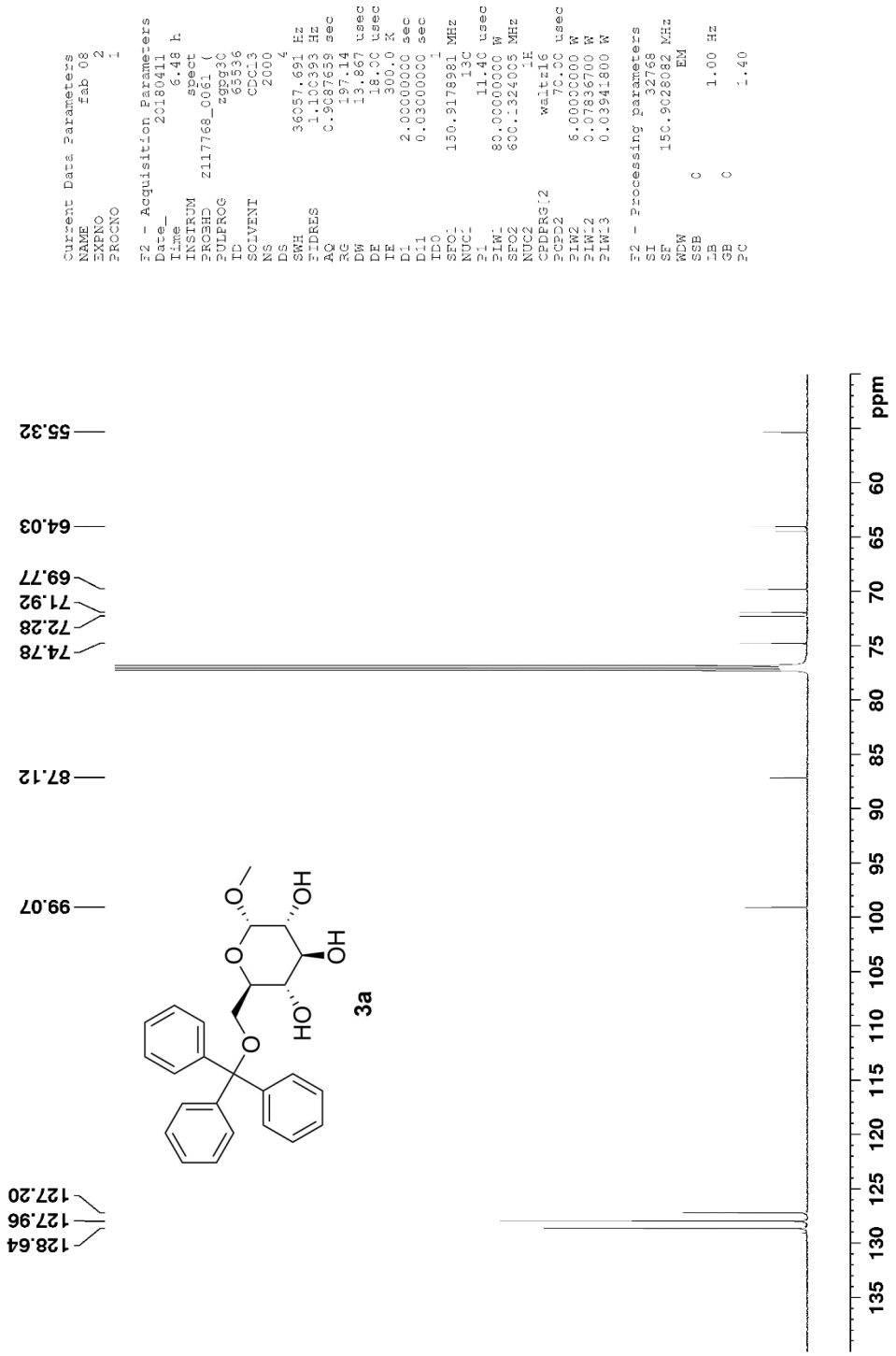


Figure M.1 ^{13}C-NMR spectrum of compound **3a**.

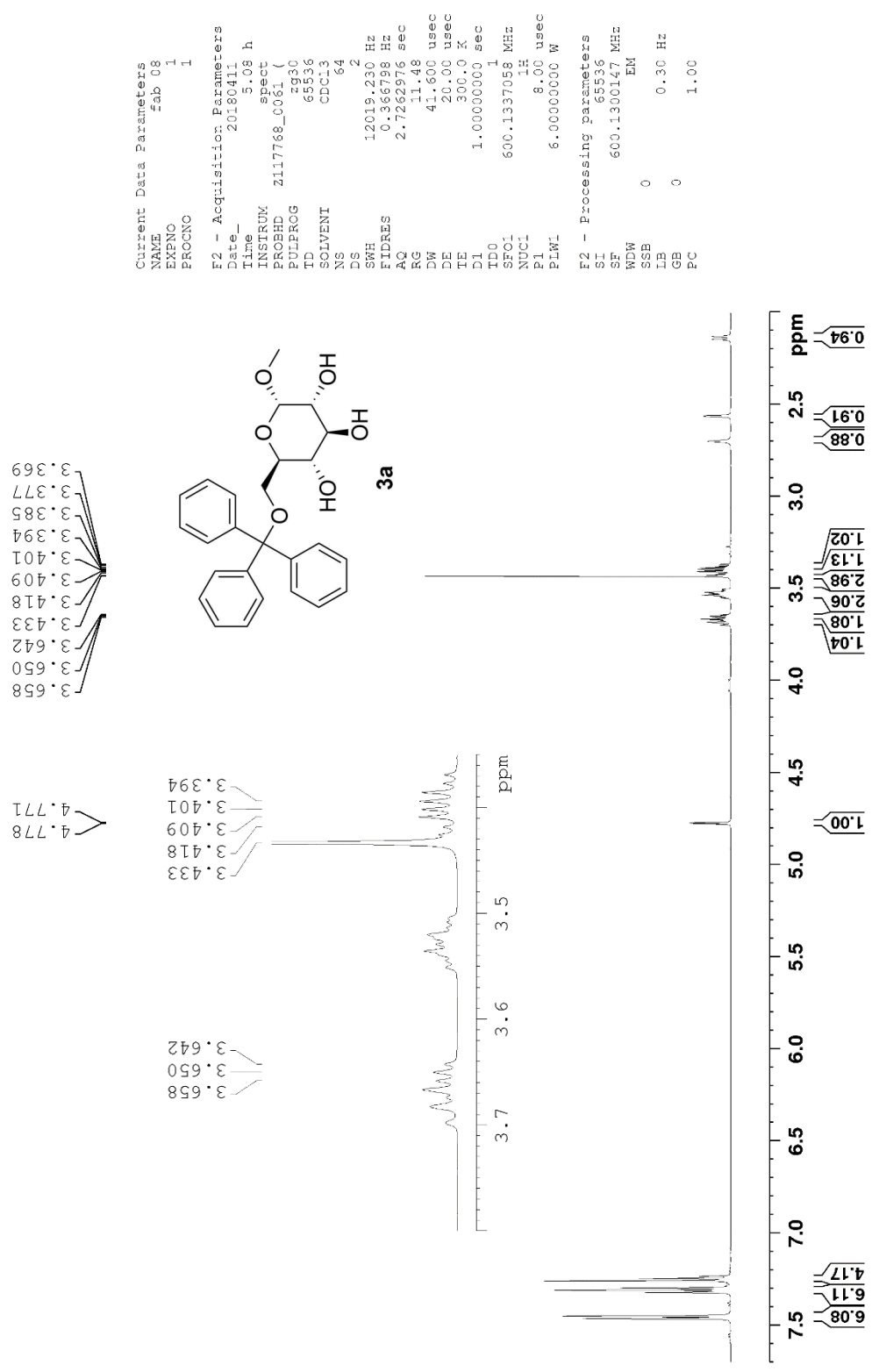


Figure M.2 [1]H-NMR spectrum of compound **3a**.

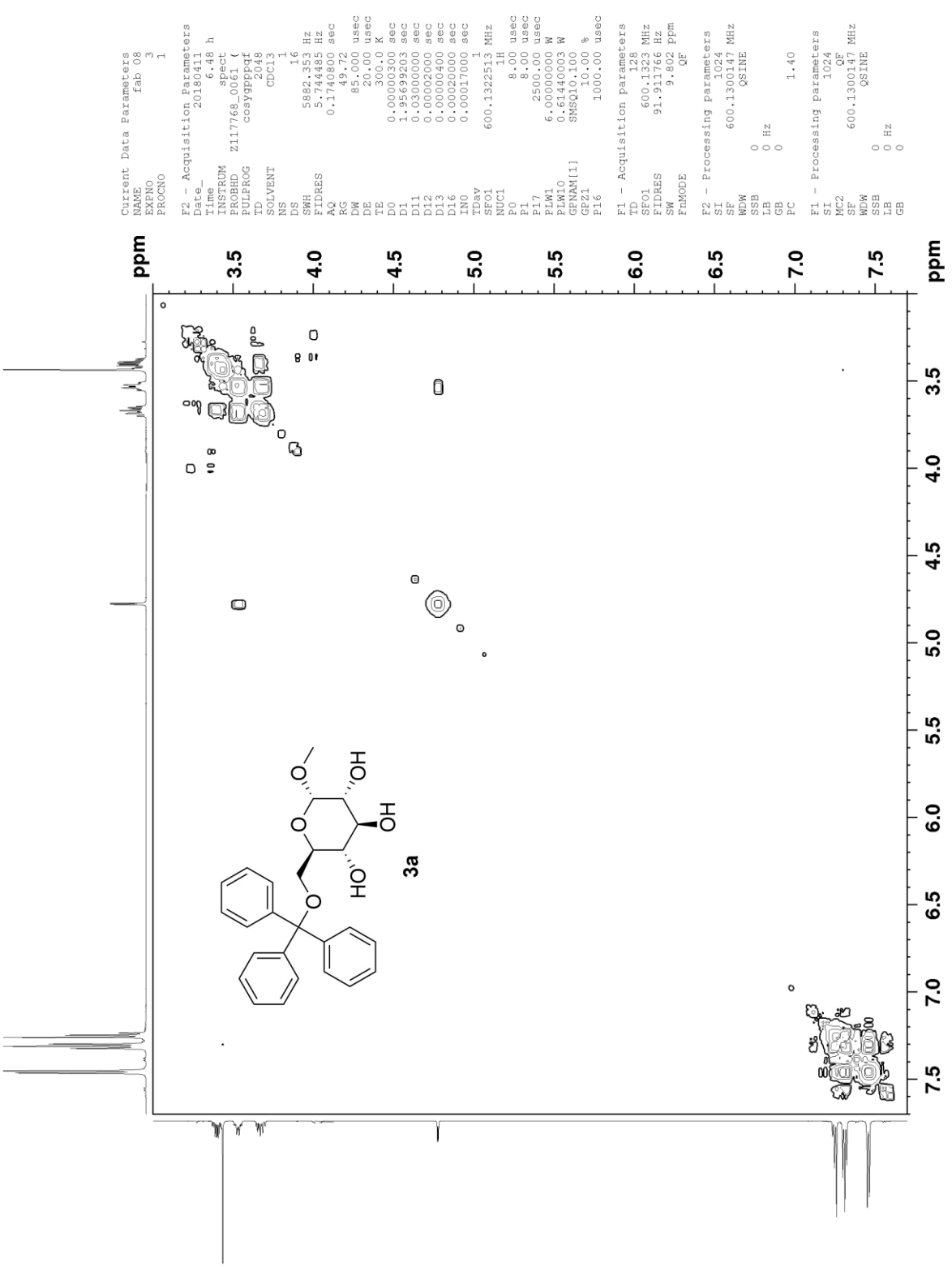


Figure M.3 **COSY** spectrum of compound **3a**.

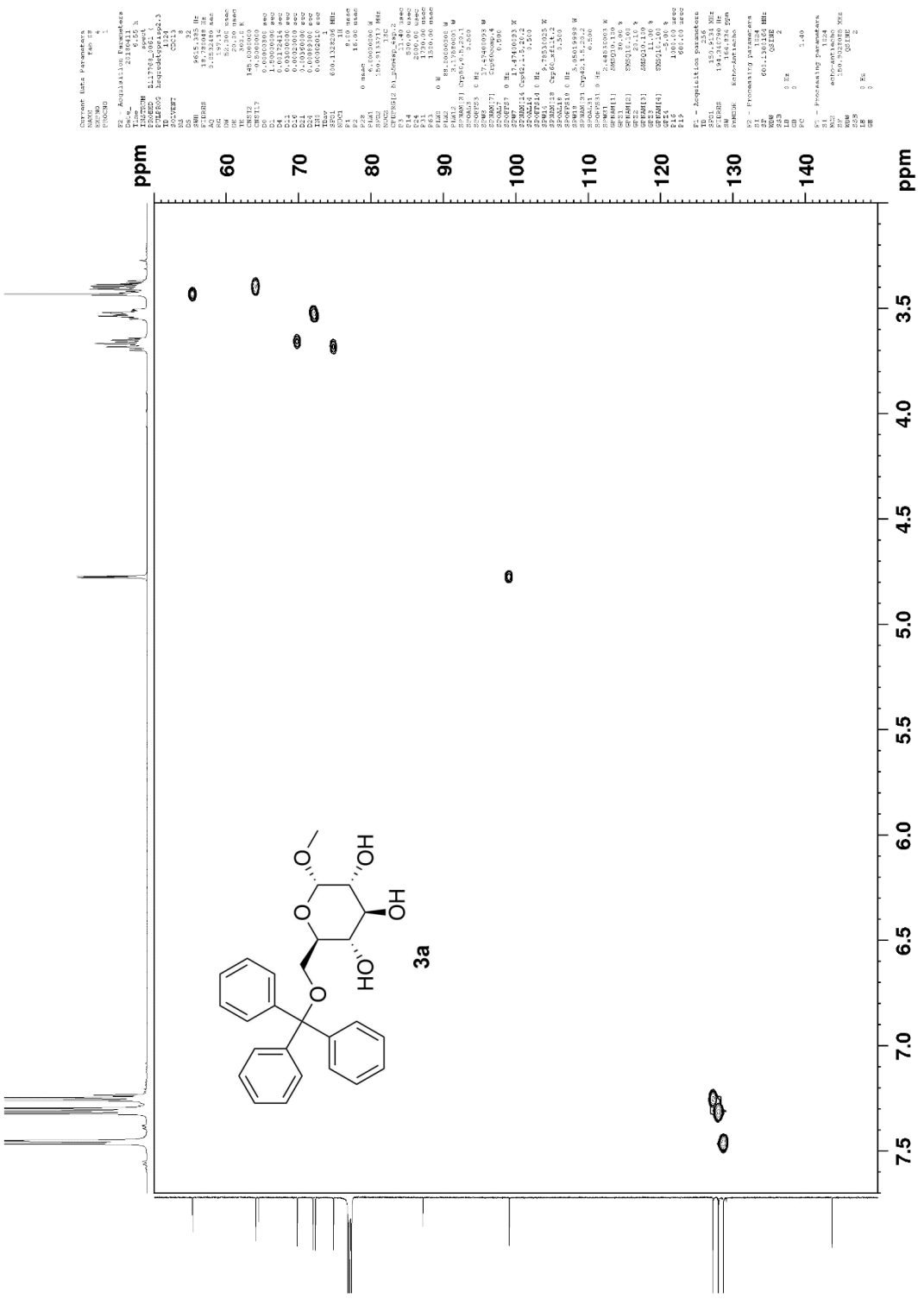


Figure M.4 HSQC spectrum of compound **3a**.

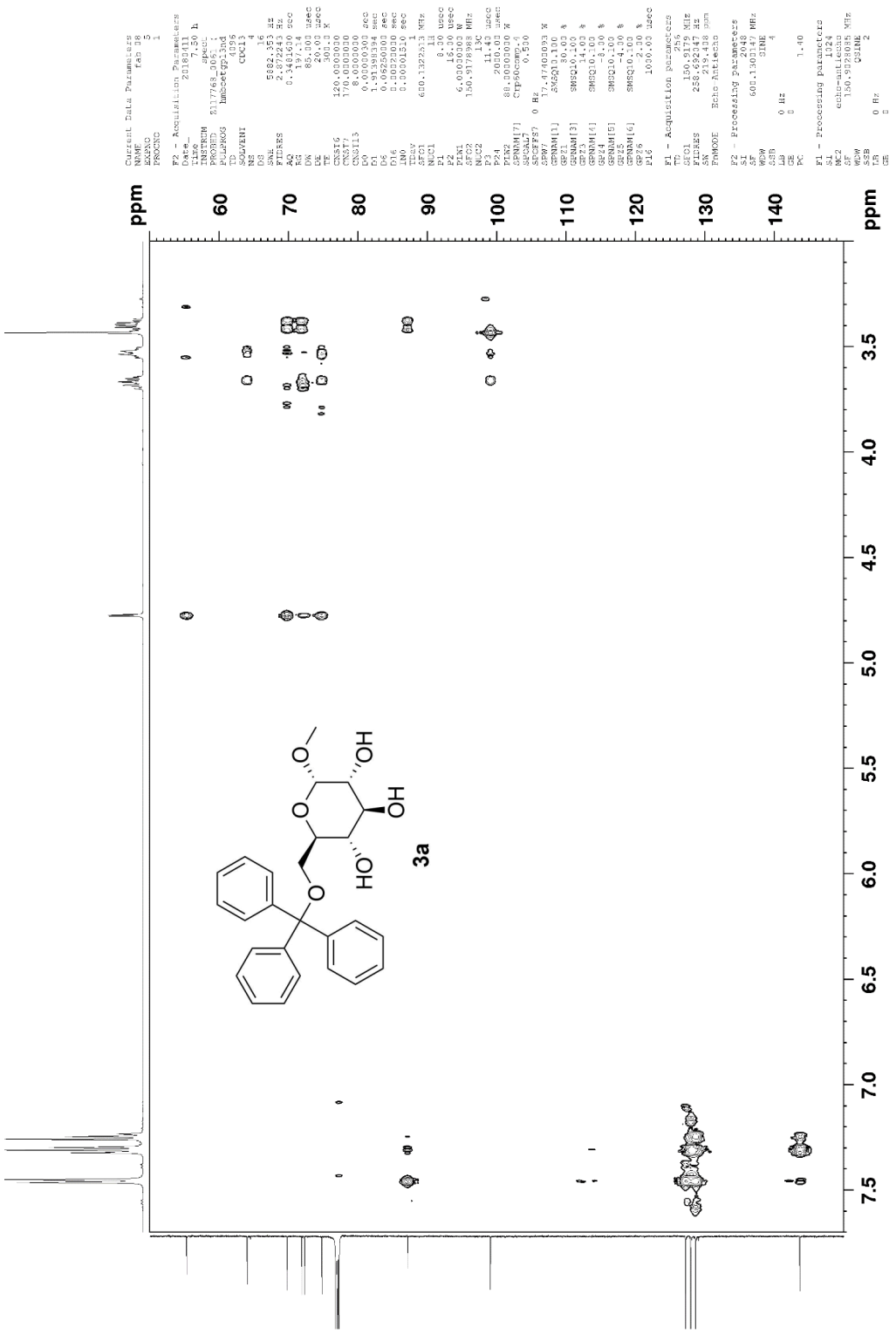


Figure M.5 HMBC spectrum of compound **3a**.

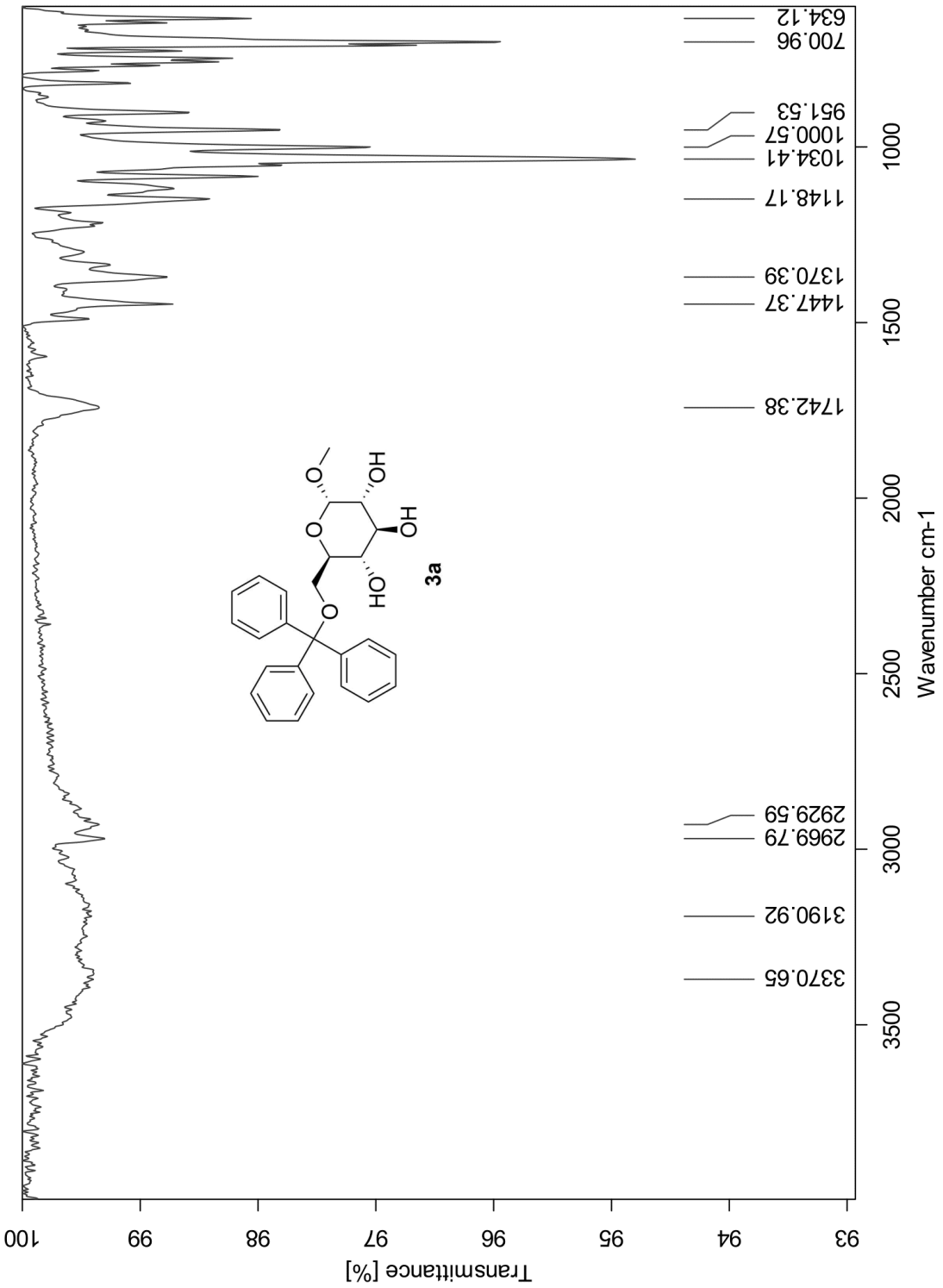
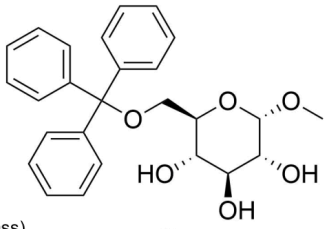


Figure M.6 IR spectrum of compound **3a**.

Elemental Composition Report **Page 1**

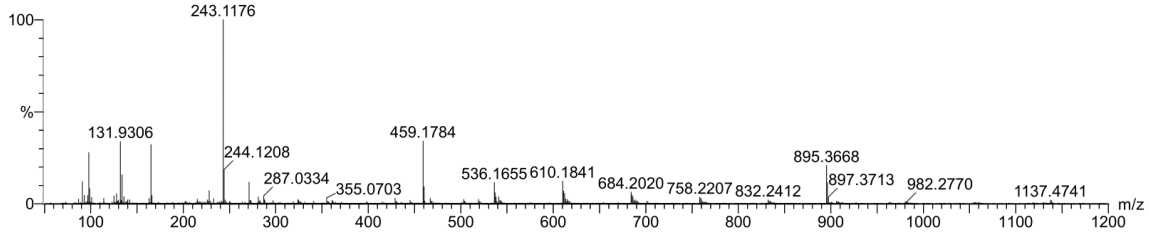
Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3



3a

Monoisotopic Mass, Even Electron Ions
1182 formula(e) evaluated with 2 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-10 Na: 0-1
2018-151 49 (0.917) AM2 (Ar,35000.0,0.00,0.00); Cm (49:50)
1: TOF MS ES+

2.99e+005



Minimum:				-1.5				
Maximum:		5000.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
459.1784	459.1784	0.0	0.0	12.5	781.2	3.017	4.89	C26 H28 O6 Na
	459.1781	0.3	0.7	16.5	778.3	0.050	95.11	C24 H23 N6 O4

Figure M.7. MS results for compound **3a**.

Appendix N. Spectroscopic data for compound **4a**

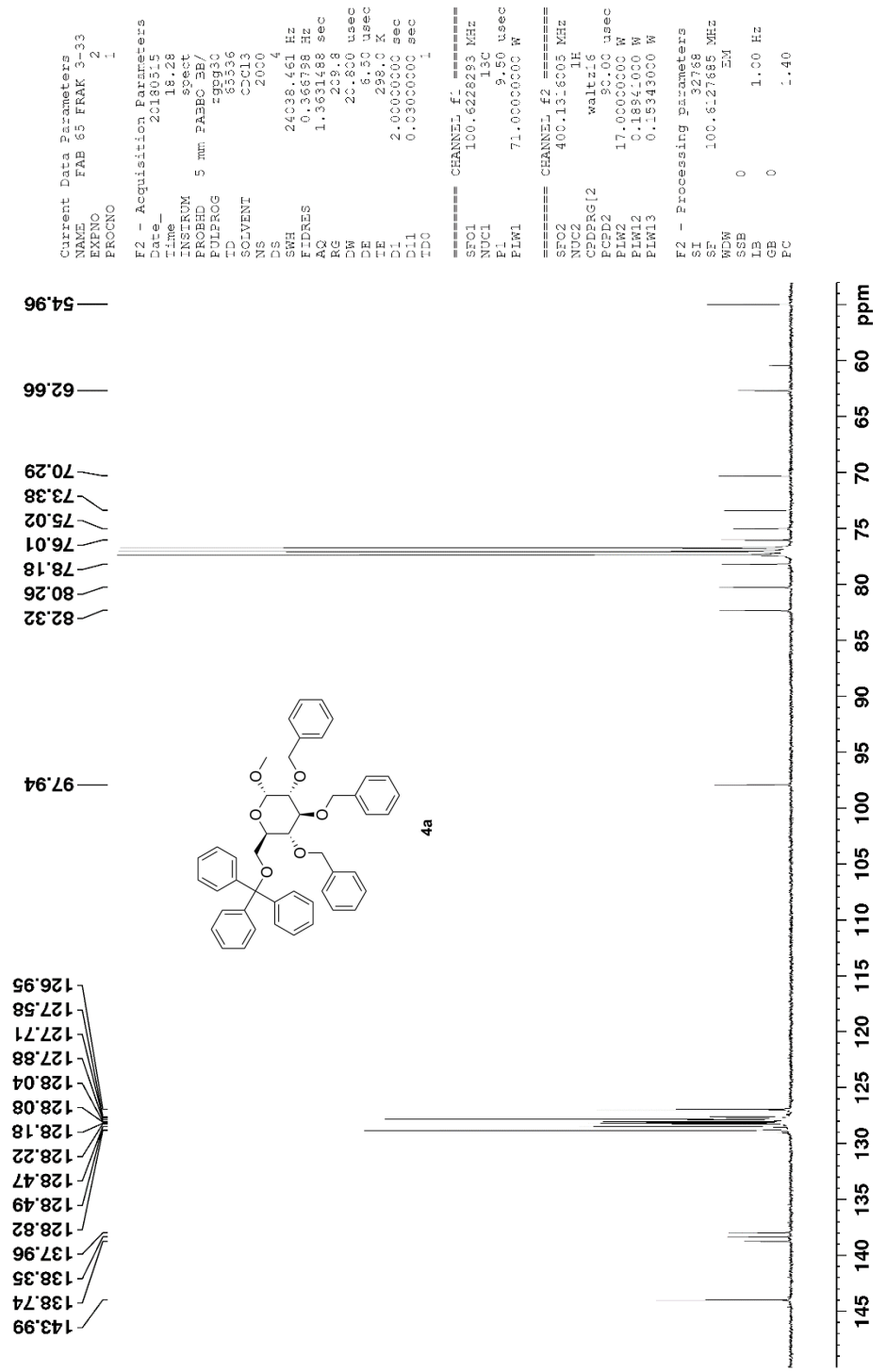


Figure N.1 ^{13}C-NMR spectrum of compound **4a**.

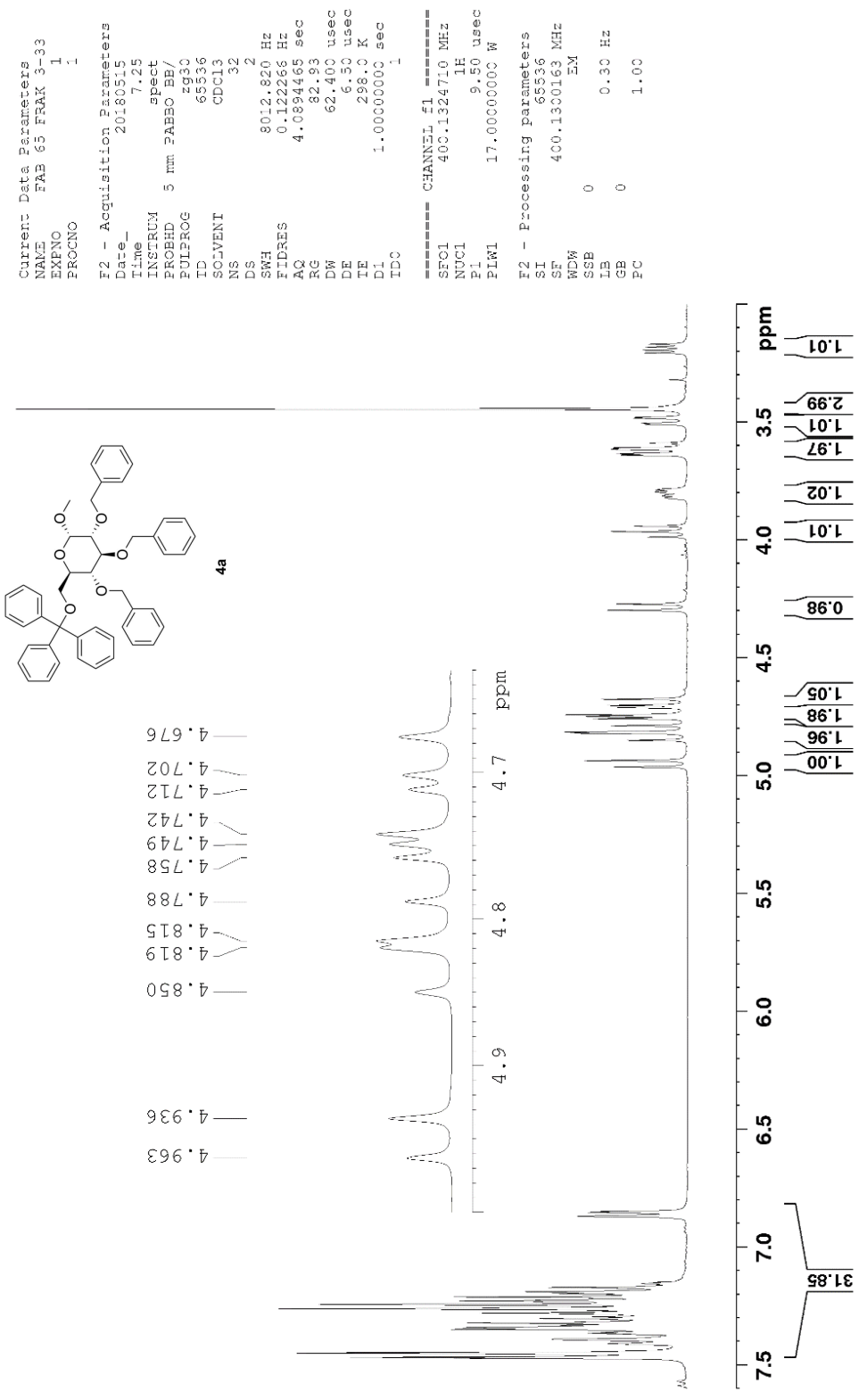


Figure N.2 ^{1}H-NMR spectrum of compound **4a**.

‘

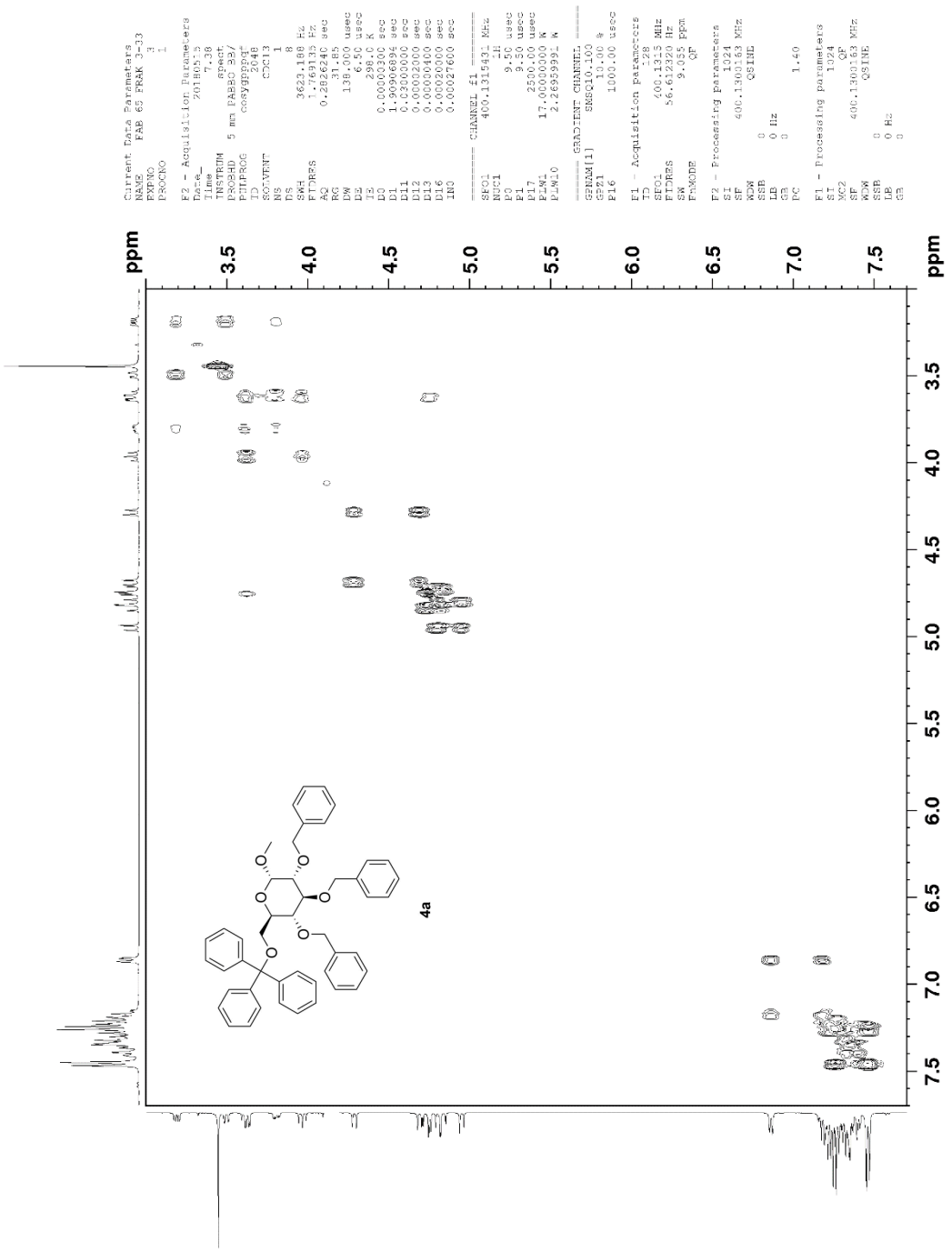


Figure N.3 COSY spectrum of compound **4a**.

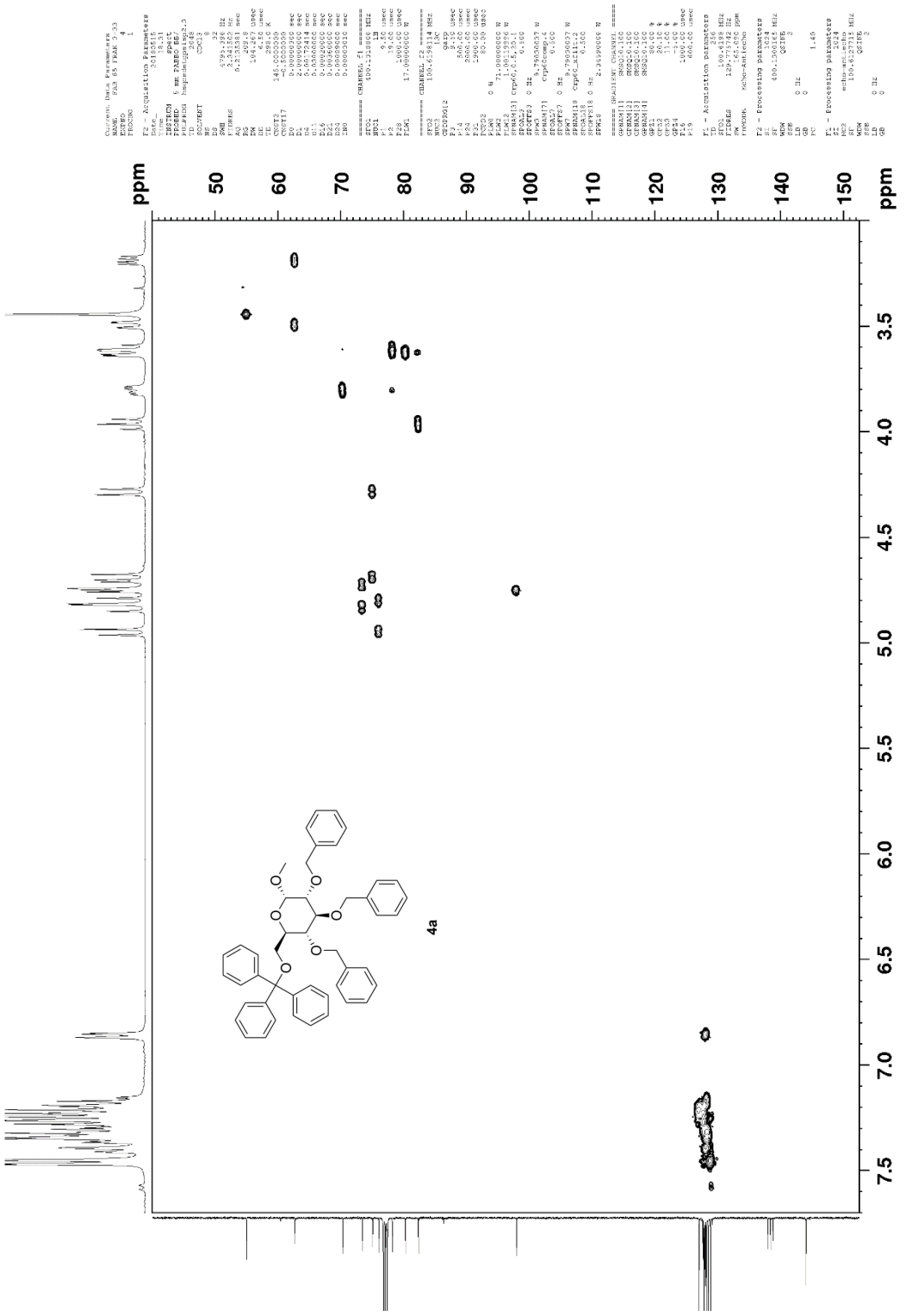


Figure N.4 HSQC spectrum of compound **4a**.

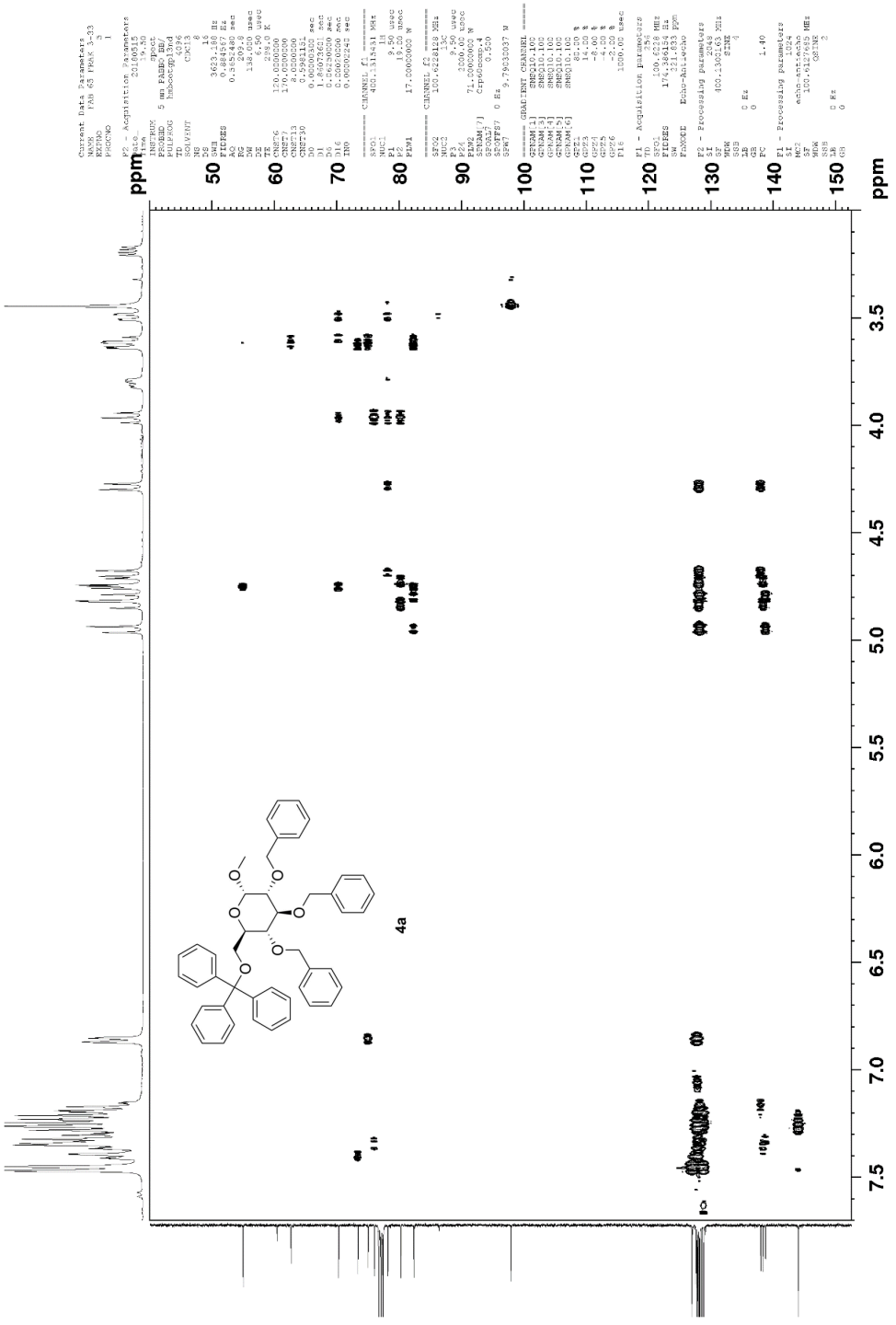


Figure N.5 HMBC spectrum of compound **4a**.

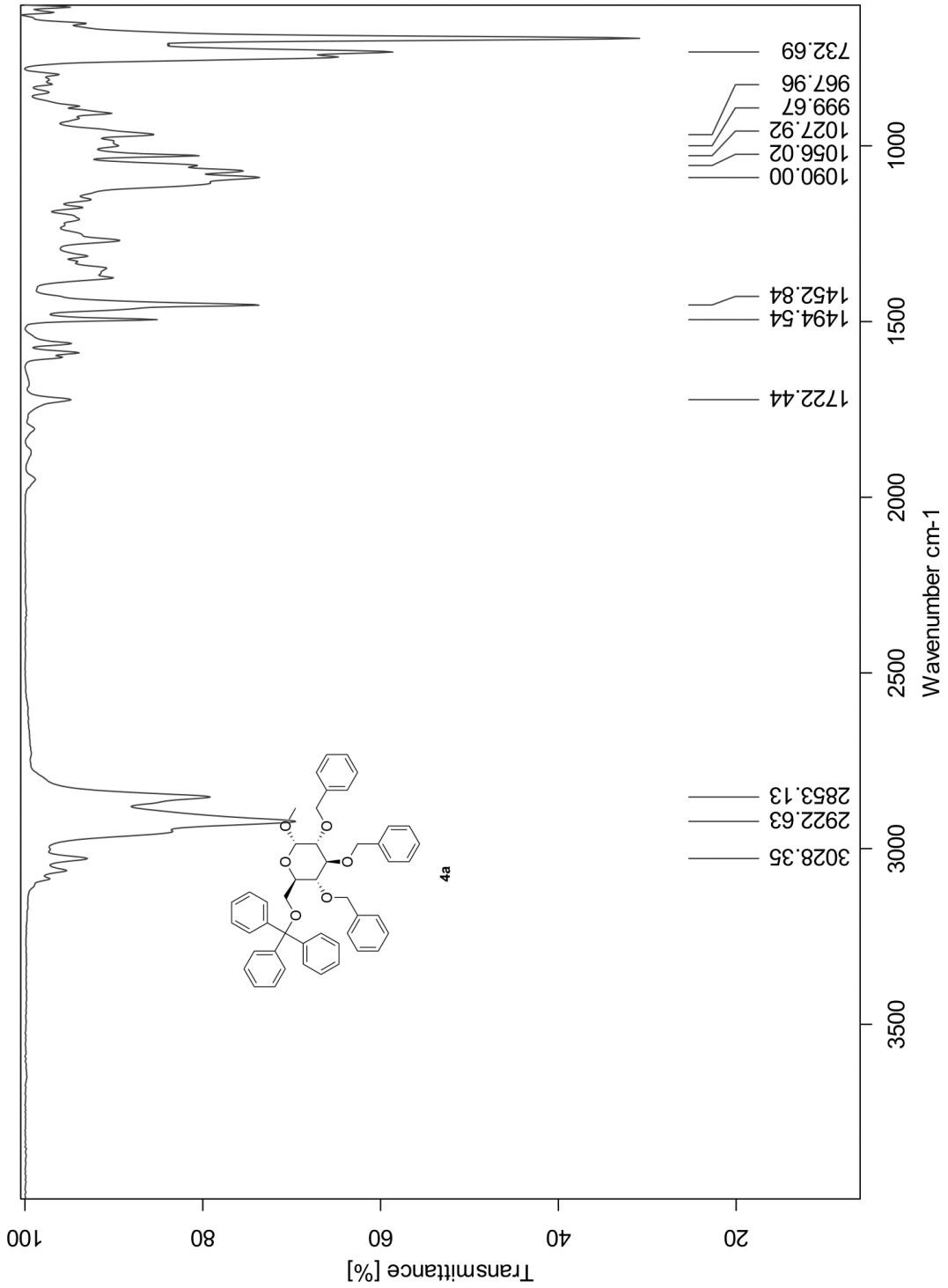
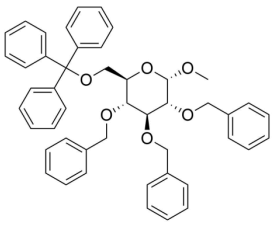


Figure N.6 IR spectrum of compound **4a**.

Elemental Composition Report **Page 1**

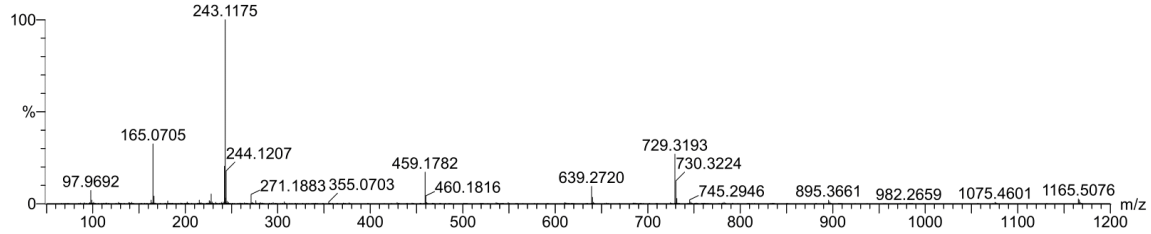


4a

Single Mass Analysis
Tolerance = 2.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
3295 formula(e) evaluated with 9 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-500 H: 0-1000 N: 0-10 O: 0-20 Na: 0-1
2018_240pos 47 (0.882) AM2 (Ar,35000.0,0.00,0.00); Cm (47:58)
1: TOF MS ES+

4.17e+006



Minimum:				-1.5				
Maximum:		5000.0	2.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
729.3193	729.3189	0.4	0.5	28.5	748.9	1.239	28.97	C45 H41 N6 O4
	729.3194	-0.1	-0.1	10.5	749.0	1.312	26.94	C32 H49 N4 O15
	729.3192	0.1	0.1	24.5	749.3	1.621	19.78	C47 H46 O6 Na
	729.3203	-1.0	-1.4	33.5	750.3	2.616	7.31	C46 H37 N10
	729.3179	1.4	1.9	30.5	750.5	2.763	6.31	C44 H38 N10 Na
	729.3184	0.9	1.2	12.5	750.5	2.800	6.08	C31 H46 N8 O11 Na
	729.3181	1.2	1.6	5.5	751.4	3.696	2.48	C31 H53 O19
	729.3205	-1.2	-1.6	29.5	751.6	3.913	2.00	C48 H42 N4 O2 Na
	729.3202	-0.9	-1.2	-0.5	754.4	6.664	0.13	C19 H50 N10 O18 Na

Figure N.7 MS results of compound **4a**.