Master's thesis

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

Ragnar Stene

Investigation of protection group exchange in late stage intermediates in the synthesis of 3-*O*-acylsulfoquinovosyl glycerols

Master's thesis in Chemical Engineering and Biotechnology
Supervisor: Nebojsa Simic
Co-supervisor: Sondre Nervik
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Preface

The work for this thesis has been conducted independently and in accordance with the exam regulations of the Norwegian University of Science and Technology (NTNU). The work was performed during the spring of 2021 at the Department of Chemistry at NTNU under the supervision of associate professor Nebojsa Simic, and co-supervised by Sondre Nervik. I would like to sincerely thank them both for all support, motivation and generosity, both professionally and mentally, over this past year.

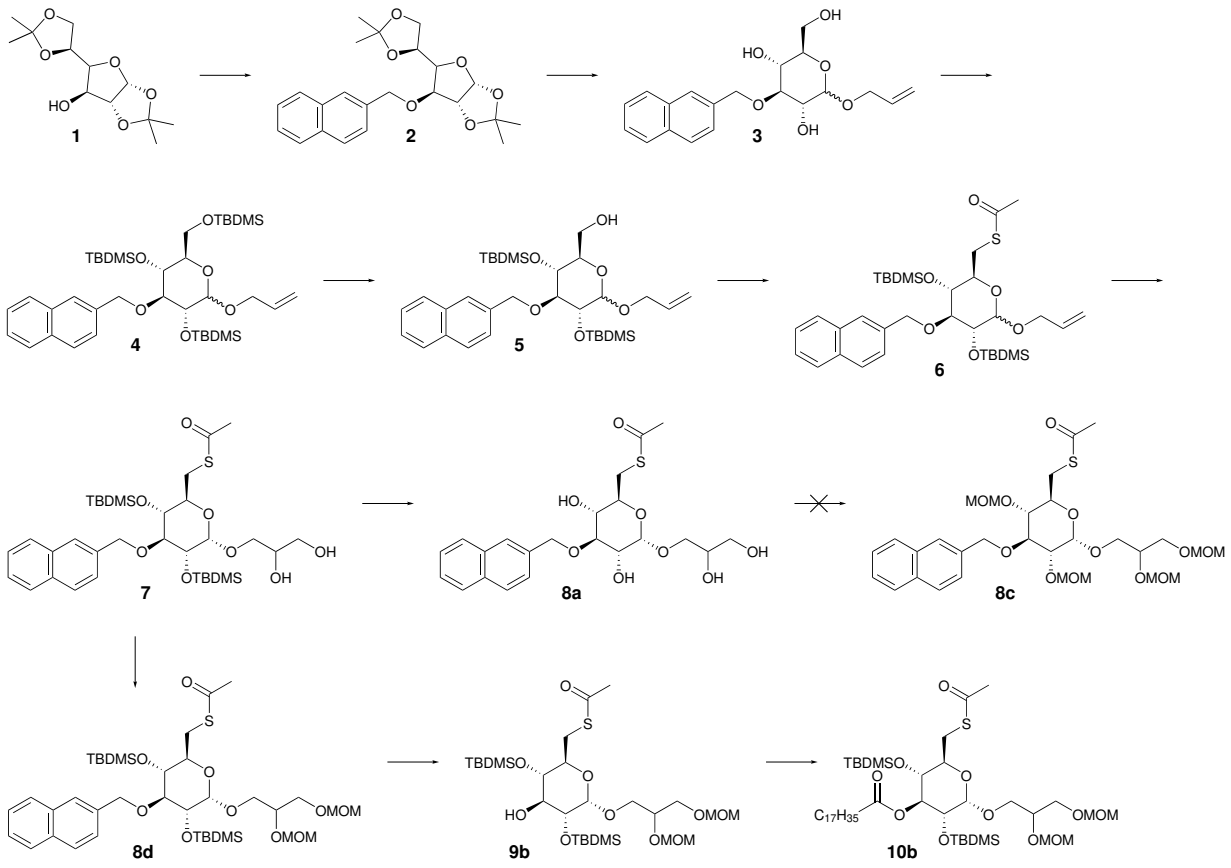
I would also like to thank my lab colleagues Petros Danielsen Siapkaras, Johannes Tveit, Wojtek Swiergon and my co-supervisor Sondre Nervik for creating a great working environment at the lab in addition to all the help and discussion they have contributed in this time we have worked together. Thanks also to Susana Villa Gonzales for running MS samples and Roger Aarvik and Julie Asmussen for the technical support.

Finally, a huge thank you to my family and friends. This thesis could never have been completed without you.

Abstract

The work presented herein was carried out as part of an attempt to total synthesise 3-*O*-acylsulfoquinovosyl glycerols, based on a natural product extracted from *Schlerochloa dura*. Previous work by the research group revealed that acetyl esters were unsuitable as permanent protection groups as the final global deprotection failed. New, more suitable, protection groups were therefore sought after.

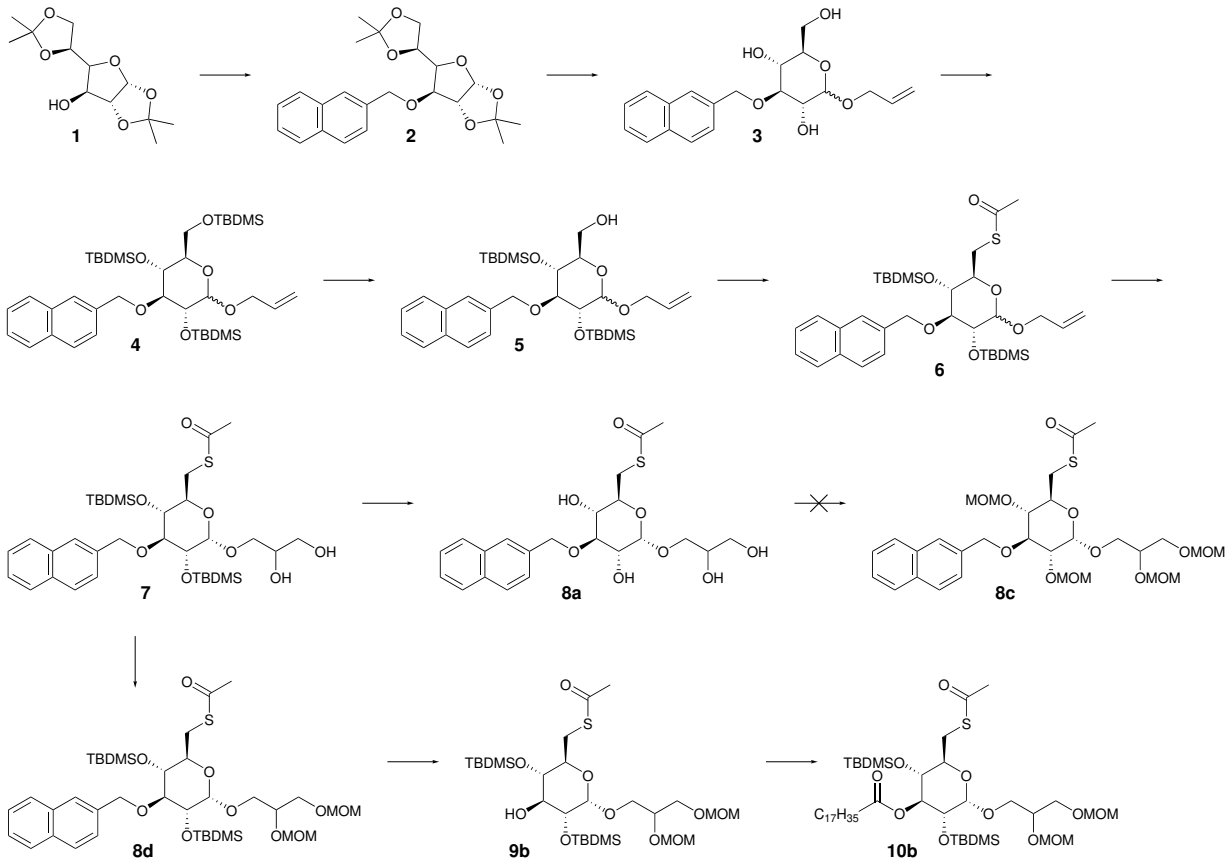
A key 3-*O*-NAP protected intermediate **7** was successfully produced in sufficient yields by a shortened route and used as a starting point for new reactions. Three pathways based on MOM-protection of hydroxyl groups were investigated for further functionalization, of which two were based on protection group exchange. Deprotection of the 3-*O*-NAP functionality proceeded smoothly in the presence of silyl ethers on the sugar ring and MOM groups on the glycerol moiety, however, subsequent esterification of the liberated 3-hydroxyl failed. Direct protection group exchange on the key intermediate towards a fully MOM-protected derivative could not be achieved. Though the removal of silyl ethers was successful, the conditions for insertion of MOM groups were too harsh, indicating a stability issue with the key intermediate. In an effort to circumvent this problem, protection group exchange was performed on an earlier intermediate, but similar incompatibility with the MOM-protection conditions was encountered. Based on the results, silyl ethers are exchangeable after the oxidation of the allylic double bond, but MOM-protection groups are either unsuitable or must be introduced under much milder conditions. Due to unexpectedly low yields in the formation of additional **7**, it was regrettably not feasible to test introduction of MOM under milder conditions.



Sammendrag

Arbeidet presentert i denne masteroppgaven ble utført som en del av et forskningsprosjekt hvor målet er å totalsyntetisere 3-*O*-acylsulfokinovosyl glyseroler, basert på et naturlig stoff ekstrahert fra *Schlerochloa dura*. Tidligere arbeid av forskningsgruppen har avdekket at acetyler er uegnet som beskyttelsesgrupper under syntesen, ettersom de førte til problemer under det siste avbeskyttelsestrinnet. For denne oppgaven var det derfor ønskelig å finne nye, mer passende, beskyttelsesgrupper.

Et sentralt 3-*O*-NAP beskyttet intermediat **7** ble syntetisert vellykket i tilstrekkelig utbytte ved en forkortet synteserute og deretter brukt som utgangspunkt for nye reaksjoner. Tre synteseveier basert på MOM-beskyttelse av hydroksylgrupper ble undersøkt for videre funksjonalisering, hvorav to var basert på bytte av beskyttelsesgrupper. Avbeskyttelse av 3-*O*-NAP-funksjonaliteten var vellykket i nærvær av silyletere på sukkerringen og MOM-grupper på glyseroldelen, men påfølgende esterifisering av den frigjorte 3-hydroksylen var mislykket. Direkte utveksling av silylgruppene på **7** til et fullt MOM-beskyttet intermediat var ikke vellykket. Selv om det var mulig å fjerne silyleterne, var betingelsene for innføring av MOM-grupper for tøffe, noe som indikerer et stabilitetsproblem med nøkkelintermediatet. I et forsøk på å omgå dette problemet ble beskyttelsesgruppene prøvd byttet på et tidligere mellomprodukt, men lignende uforenligheter med MOM-beskyttelsesbetingelsene ble påvist. Basert på resultatene kan silyletere byttes ut etter oksidasjon av den allyliske dobbeltbindingen, men MOM-beskyttelsesgrupper er enten uegnet eller må innføres under mye mildere forhold enn det som ble gjort i denne oppgaven. På grunn av uventet lavt utbytte i dannelsen av mer **7**, var det dessverre ikke mulig å teste innføring av MOM under mildere betingelser.



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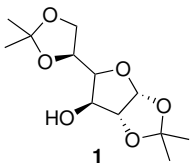
Symbols and abbreviations

Abbreviation	Explanation
AcSH	thioacetic acid
AD-mix-β	asymmetric dihydroxylation mixture β
All-OH	allylic alcohol
COSY	correlation spectroscopy
CSA	camphorsulfonic acidz
DCC	*N,N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMM	dimethoxymethane
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate
HCl	hydrochloric acid
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HSQC	heteronuclear single quantum coherence
IR	infrared spectroscopy
MeCN	acetonitrile
MEM	2-methoxyethoxymethyl
MEM-Cl	2-methoxyethoxymethyl chloride
MeOH	methanol
MOM	methoxymethyl
MOM-Br	methoxymethyl bromide
MOM-Cl	methoxymethyl chloride
MS	mass spectrometry
NAP	2-naphthylmethyl
NAP-Br	2-(bromomethyl)naphthalene
NMR	nuclear magnetic resonance
R_f	retention factor
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDMS-OTf	*tert*-butyldimethylsilyl triflate
TBDPS	*tert*-butyldiphenylsilyl
t-BuOH	*tert*-butanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSBr	bromotrimethylsilane
TFA	trifluoroacetic acid

UV	ultraviolet

Synthesised and isolated compounds



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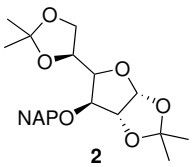

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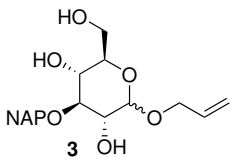

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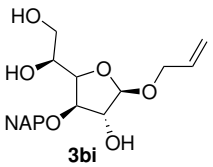

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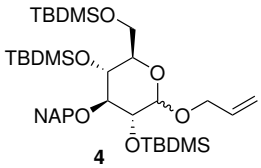

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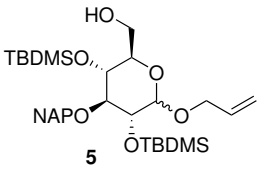

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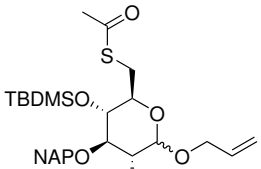

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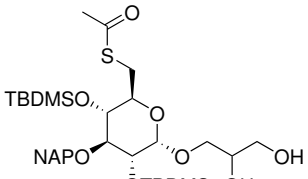

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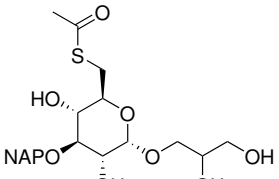

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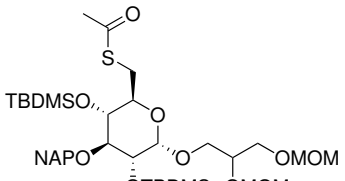

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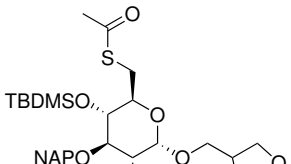

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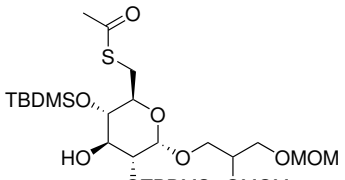

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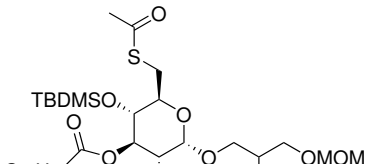

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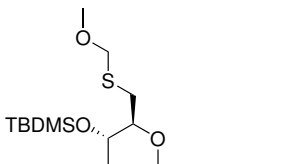

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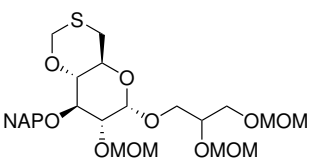

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1 Introduction

The work presented in this master thesis was carried out in relation to a research project at the Department of Chemistry at the Norwegian University of Science and Technology (NTNU). It is concerned with the total synthesis of 3-*O*-acylsulfoquinovosyl glycerols (Figure 1.1) and employs chemistry which has been extensively studied by the research group over the past 6 years.

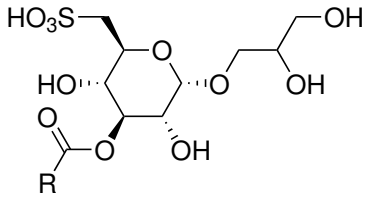


Figure 1.1: 3-*O*-acylsulfoquinovosyl glycerol.

The specific target molecule for this project is 1-*O*-glycerol-3-*O*-stearoyl-6-deoxy-6-sulfo-α-D-glucopyranoside (**12**, Figure 1.2) where the goal is to probe reaction conditions with the aim to solve previously experienced problems in the synthetic sequence. A similar compound, with a linolenoyl group at 3-*O* instead of stearoyl, was previously extracted from *Schlerochloa dura*. It is a plant which traditionally have been used to treat menstrual disorders in South-East Serbia and has been shown to exhibit anti inflammatory properties.[1,2]

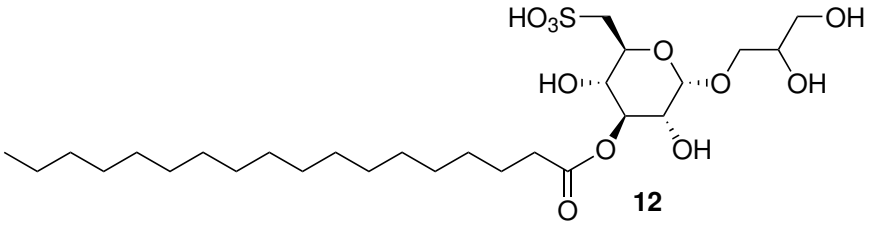
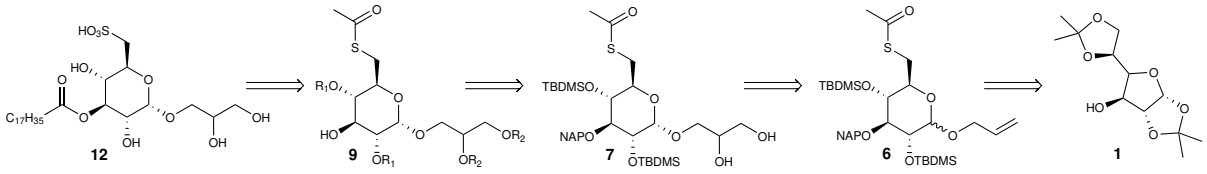


Figure 1.2: 1-*O*-glycerol-3-*O*-stearoyl-6-deoxy-6-sulfo-α-D-glucopyranoside (**12**).

Reaction conditions for synthesis of a fully protected intermediate (**6**) from commercial chemicals, have previously been found by the research group. The intermediate is orthogonally protected on 2-, 3-, and 4-*O*, this is expected to open up for selective esterification on 3-*O*. It also has precursor moieties for the glycerol unit and the sulfonic acid. The research group found **6** promising as it was relatively easy to clean, and because diastereoselective oxidation of the anomeric chain, into the corresponding glycerol compound **7**, seemed to be possible through the use of AD-mix-β. The discovered reaction conditions could make it possible to synthesise **7** in less reaction steps than had been utilized earlier. Therefore, in order to produce **7** as a starting point for new experiments, which in the end could synthesise **12**, the work previously done by the research group will be taken advantage of. Most of the known reactions are expected to be completed without complications and can be run in as large scale as manageable in order to produce as much of **7** as possible. These, known, reactions will be more thoroughly introduced in Section 1.2.

Besides a shortened synthetic route towards **7**, the introduction of previously untried protection groups on the glycerol moiety, exchange of protection groups in 2- and 4-position,

deprotection and subsequent esterification of the 3-position are the primary avenues of interest for this thesis. The rationale for the novel protection groups and the protection group exchange is to facilitate both the esterification and global deprotection steps, which have proved problematic in previous work.[3,4] Since **6** is orthogonally protected, i.e. 3-*O* protected by a different protection group from the rest of the hydroxyl groups, it is expected that the fatty acid can be selectively introduced by optimizing reaction conditions. For the esterification reaction, research have been done by Stenset, in an earlier master thesis for the research group, on finding reaction conditions which works for the insertion of the fatty acid.[4] These conditions are to be utilized under the fatty acid introduction in this project as well. A complete introduction to the thought process and plan for synthesis of **12** from **7** will be given in Section 1.3. See Scheme 1 for a retrosynthetic overview for the whole project.



Scheme 1: Retrosynthetic scheme for synthesis of **12** from **1**, via fully protected **6**, key intermediate **7** and 3-*O* deprotected intermediate **9**.

1.1 Carbohydrate chemistry

Before diving into the reactions, a short introduction to carbohydrate chemistry is necessary. A quick coverage on representation of configuration and nomenclature for especially monosaccharides, in addition to some other relevant subjects will be given. Monosaccharides are polyhydroxy aldehydes or ketones, with carbon chains of four to nine carbon atoms which can exist both in open-chain and cyclic form.[5] Cyclic monosaccharides can be represented in multiple ways. Fischer and Haworth projections[6] might be the most commonly known, this report will however use the representation proposed by Mills.[7] See Figure 1.3 for the different representations.

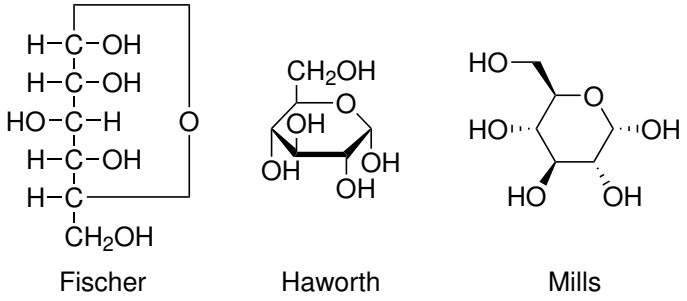


Figure 1.3: Fischer, Haworth and Mills representation of α-D-glucopyranose.

The compound shown in Figure 1.3, α-D-glucopyranose, is named with three prefixes, α, D and *gluco*. The D-prefix is commonly used when naming sugars, originating from the same Fischer as above, which used D and L to separate enantiomers of sugars.[8] Prefixes such as *gluco*-, *galacto*- and *manno*- is then used as common names to describe the stereocenters

in the rest of the chain, such that D- and L-glucopyranose compounds are enantiomers since every stereocenter are oppositely oriented, making them mirror images of each other. Together they work as a simple way of naming sugars, making the usual way of describing stereocenters with R- and S-prefixes redundant. When looking at Fischer projections, it is straightforward to determine if the compound is D- or L-configurated. If the oxygen on the stereocenter nearest the bottom points to the right, it is D-configurated, and if it points left it is L-configurated.

The numbering of cyclic monosaccharides are given in such a way that the anomeric carbon has as low value as possible, and then follows the ring around. The anomeric carbon is the only carbon which is bound to two oxygens. An oxygen connected to carbon n (C-n), is then named as n-O. Normally, new substituents on sugar rings are introduced at the hydroxyl group, not on the carbon. When a substituent is attached to the oxygen on C-n, it is n-O-substituted. The α-prefix is used to show that 1-O (the hydroxyl group on the anomeric carbon in Figure 1.3) is pointing the opposite way as the group in position 5. For the opposite situation, the prefix would be β. Since the prefixes are used to show different configuration at the anomeric carbons, α- and β-isomers are often called anomers. When the proton on the anomeric hydroxyl group is replaced by another group, the end of the name changes from *-nose* to *-noside*. Lastly, on the nomenclature of sugars, 5-membered rings are named as furanose, while 6-membered rings are named as pyranose.[6]

Carbohydrates consists of multiple hydroxyl groups and when they are used in synthetic chemistry, it is often desired to be able to selectively alter these hydroxyl groups. When looking at the α-D-glucopyranose compound in Figure 1.3, two hydroxyl groups differ from the rest, the anomeric and the primary group at C-6. The anomeric hydroxyl group is bounded to a carbon bounded to another oxygen, with the general formula $R_2C(OH)OR'$, meaning it is a hemiacetal.[9] A hemiacetal can be converted into an acetal, i.e. a new group is attached to the anomeric hydroxyl group, forming an ether and thereby an acetal. It is often easier to form an acetal than an ether, such that the rest of the hydroxyl groups will remain unchanged, due to electronic effects when using optimized conditions. Since the anomeric carbon is highly electrophilic, it opens up for nucleophilic attacks by alkoxides. The primary group will, often, be more reactive than the secondary groups in the rest of the compound, due to less steric hindrance. By using very bulky reagents, it is possible to selectively alter it. Low equivalents of the new substituent could in some cases give the desired result as well.

Steric hindrance will affect the relative reactivities of the secondary hydroxyl groups, especially when considering if they are axially or equatorially configurated. An axial hydroxyl group is generally more reactive than an equatorial, due to more space being available around it. However, to selectively alter the three secondary hydroxyl groups at C-2, C-3 and C-4 is often a difficult task, as they are very alike. It might in some cases be possible to selectively protect two of them, often those who are *syn*, as cyclic 1,2- or 1,3-diethers, leaving the last group open for reaction. The hydroxyl group on C-2 is also slightly affected of its proximity to the anomeric carbon, which by carefully choosing conditions can open for selective reaction.[5] Lastly, the anomeric effect should be mentioned. It is an effect which describes why the anomeric group is oriented in the sterically unfavoured axial position in unexpectedly large fractions. The equatorially oriented position is the sterically favoured position, but for sugar rings the axially oriented position is more present than in for example the corresponding substituted cyclohexane

compounds. The reason for this unexpected preference is proposed to be due to two contributing factors. Firstly, hyperconjugation between one of the electron lone pairs at the endocyclic oxygen and the empty antibonding molecular orbital between C-1 and 1-*O* stabilizes the molecule by delocalizing the electron lone pair. This hyperconjugation is not possible if the group is equatorially bonded. Secondly, if the anomeric oxygen is equatorially oriented, its dipole would be aligned with the dipole of the endocyclic oxygen atom. This interaction is destabilizing and does not occur if the oxygen is axially oriented.[10]

Carbohydrates are used in a broad variety of industries today. The research group is interested in the pharmaceutical potential of the target molecule, some attention to the use of carbohydrates in pharmaceuticals are therefore given. It has been discovered that many carbohydrates, especially polysaccharides, i.e. multiple monosaccharides coupled together, found in fungus, plants, algae and so on, have properties which are interesting for use in the pharmaceutical industry when extracted and isolated.[11] One example is the drug digoxin (Figure 1.4) which is extracted from the leaf of *Digitalis lanata*.[12] It has historically been used to treat heart failure, however, recent studies suggests that there might be better alternatives out there with concerns to unwanted side-effects.[13]

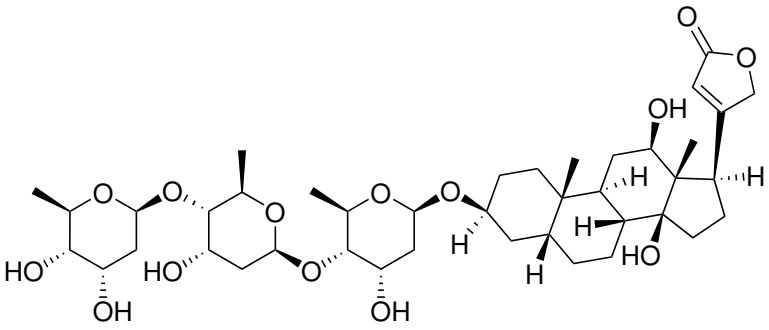
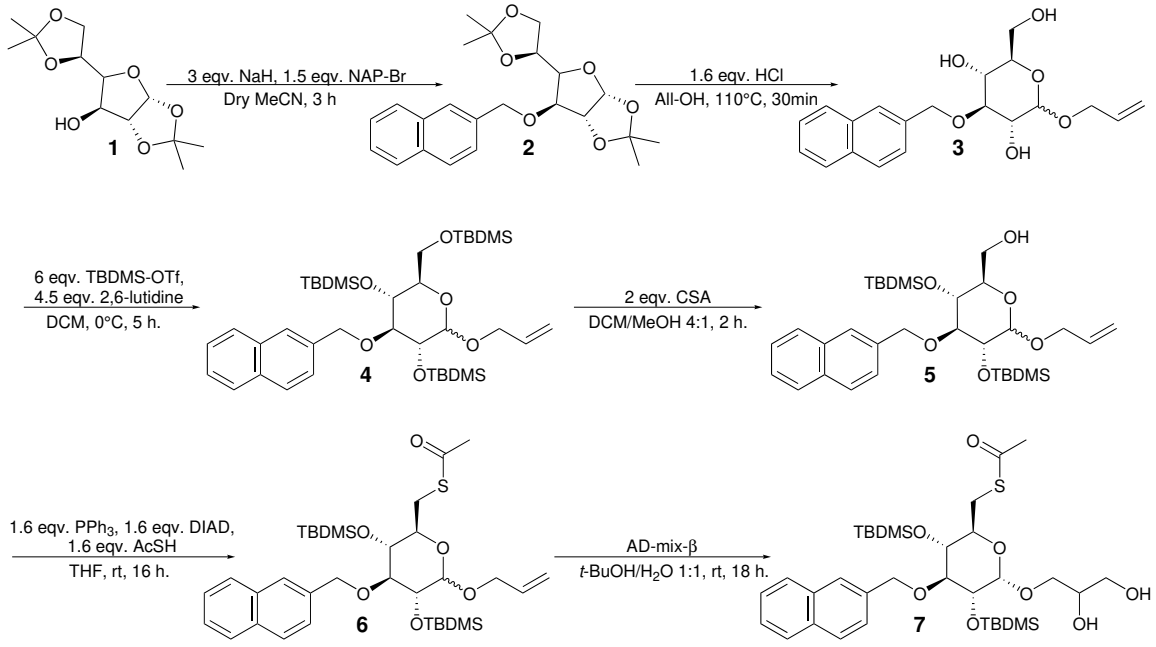


Figure 1.4: Digoxin.

Extraction and isolation of drugs from plants can be a tedious process, challenges of obtaining enough compound compared to the costs of growing and extracting the plants are also present. There might therefore in some cases be desired to produce the carbohydrates synthetically, instead. But, for this to be a viable option, the synthetic route needs to be as simple and cheap as possible. A well known, successful example of this is the pain-relieving medicine aspirin, where a precursor, salicin, was originally found in willow leaves which people used to chew on if they were in pain. In the 19th century a chemist named Charles Gerhardt produced aspirin by reacting sodium salicylate with acetyl chloride. Later work have improved the synthesis to the point of today, where it can be bought at a very reasonable price due to its low production costs.[14] Hopefully the work presented herein can contribute to a simpler synthesis of the previously mentioned compound from *Schlerochloa dura*.

1.2 Knowledge foundation - Synthesis of key intermediate 7

Scheme 2 gives an overview of the reactions which are mostly known and have been tested, at least with similar compounds, by the research group previously.

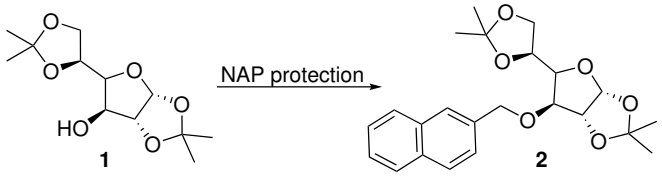


Scheme 2: Reactions which will be performed in order to produce **7** from starting material **1**.

In the first step a Williamson ether synthesis between **1** and 2-(bromomethyl)naphthalene (NAP-Br) occurs. The alcohol on **1** is first deprotonated, making a good nucleophile which then attacks NAP-Br in a S_N2-reaction, forming an ether and thereby 1,2;5,6-di-*O*-isopropylidene-3-*O*-NAP-α-D-glucofuranose (**2**). The rearrangement from the furanose to the pyranose form occurs under Fischer glycosylation conditions, forming both the α- and β-anomer of 1-*O*-allyl-3-*O*-NAP-D-glucopyranoside (**3**). Further functionalization of the compound is carried out by protection of all free hydroxyls as *tert*-butyldimethylsilyl (TBDMS) ethers, forming 1-*O*-allyl-2,4,6-tri-*O*-TBDMS-3-*O*-NAP-D-glucopyranoside (**4**). Selective deprotection of the primary 6-*O* via a camphorsulfonic acid (CSA) mediated hydrolysis forms 1-*O*-allyl-3-*O*-NAP-2,4-di-*O*-TBDMS-D-glucopyranoside (**5**). Previous work has identified this as the optimal point in the synthetic route for anomeric resolution by chromatographic means.

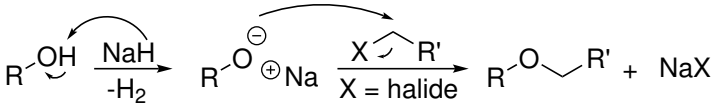
The research group has previously inserted the thioacetate moiety via a two-step process involving tosylation prior to substitution with potassium thioacetate. Due to the presence of silyl ethers, the substitution requires the use of hexamethylphosphoramide (HMPA) or dimethylformamide (DMF) for satisfactory conversion.[15] Seeking to shorten the route and avoid the use of high boiling-point solvents, a Mitsunobu-type reaction will instead be attempted forming 1-*O*-allyl-2,4-di-*O*-TBDMS-3-*O*-NAP-6-*S*-acetyl-D-glucopyranoside (**6**). AD-mix-β is then used to dihydroxylate the double bond on the anomeric chain into the glycerol. AD-mix-β is highly selective and oxidises the α-anomer much faster than the β-anomer, making it possible to remove eventual residues of the β-anomer.[3] The product 1-*O*-glycerol-2,4-di-*O*-TBDMS-3-*O*-NAP-6-*S*-acetyl-α-D-glucopyranoside (**7**) will therefore mostly consist of the desired α-anomer. The AD-mix-β is also diasteroselective, but which of the diastereomers that is formed is not known.

1.2.1 2-Naphthylmethyl protection



Scheme 3: NAP protection of **1** gives **2**.

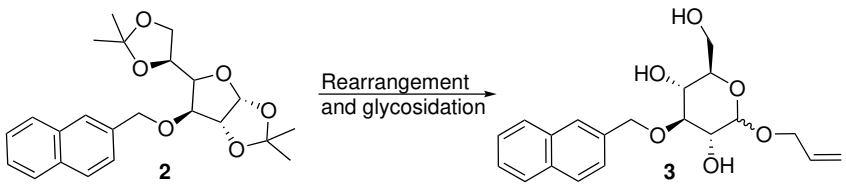
The starting material **1** has one free hydroxyl group, while the rest are protected as acetals in the form of isopropylidene groups. The 2-naphthylmethyl (NAP) protection group is more stable towards acid than the isopropylidene protection group. This makes it possible to protect 3-*O* with NAP (Scheme 3), before selectively removing the isopropylidene protection groups on the rest of the hydroxyl groups in acidic conditions. There are multiple ways to form a NAP ether based on, for example, which reagents one wants to use, or which compound is going to be protected. As the bromide on NAP-Br, used here, is in a primary position, the Williamson ether formation is a valid alternative for the introduction of NAP at 3-*O*. The Williamson ether synthesis works by treating the desired alcohol compound with a primary alkyl halide in a basic environment. Polar, aprotic solvents gives the fastest reaction rates. The alcohol will be deprotonated by the base, making it a good nucleophile which then can attack the electrophilic carbon the halogen is connected to. An ether is formed as the halogen leaves by a S_N2-reaction. The mechanism for a general Williamson ether synthesis with an alkyl halide and sodium hydride (NaH) as base is shown in Scheme 4.[16]



Scheme 4: Williamson ether formation mechanism.[16]

As such, NAP-Br and NaH together with **1** in a suitable solvent such as acetonitrile (MeCN), will give the desired product **2**. Wennekes *et al.* have performed a similar NAP protection reaction as the one shown in Scheme 2, only with DMF instead of MeCN, with a reported yield of 98%.[17] Both solvents are polar and aprotic, so the reaction is probably not influenced much by using MeCN instead.

1.2.2 Rearrangement - furanose to pyranose



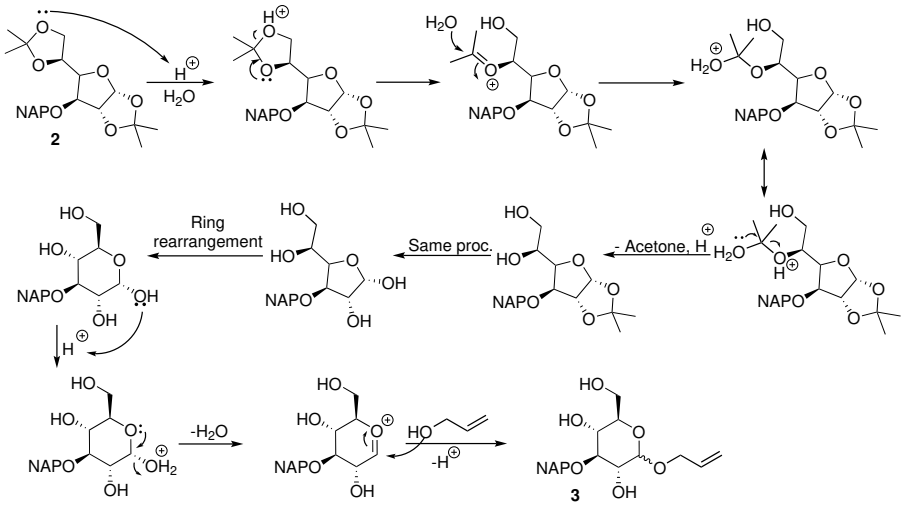
Scheme 5: Rearrangement and glycosidation of **2** gives **3**.

The rearrangement from the furanose form **2** to the pyranose form **3** is carried out in an excess of allylic alcohol (All−OH) together with aqueous hydrochloric acid (HCl). The

starting material is selectively deprotected by removal of the isopropylidene groups, allylic alcohol is simultaneously inserted on 1-*O* through a Fischer glycosidation reaction. This reaction is previously reported with a yield of 50% and an anomeric ratio of 2:1, though with Amberlyte resin (IR-120 H^+-form) as acid catalyst at 102 °C for 20 hours.[17] The research group has previosly employed the conditions reported by Fukase *et al.*, in which a 3-*O*-benzylated intermediate was refluxed in All-OH with HCl for 30 min, giving the corresponding allyl-3-*O*-benzyl-D-glucopyranoside in 89% yield (α:β 3:1).[18]

The isopropylidene groups are removed by hydrolysis with the aqueous acid, converting the groups back into the original diols. Literature suggests the 5,6-diols on furanose rings hydrolyses much faster than the 1,2-diols, making it likely that the 5,6-diols is deprotected first.[5] After the first deprotection, it is less known what happens. It might undergo further deprotection before anything else occurs, or be deprotected in a concerted glycosidation reaction. Due to greater stability, the ring will inevitably expand to the pyranoid form when the 1,2-*O*-isopropylidene acetal is cleaved, but if this occurs before or after insertion of the allylic alcohol is not known. Another possibility is that it happens in a concerted fashion, with ring expansion and glycosidation in one step. According to Miljković[5] direct glycosidation on the pyranose is very slow, which suggests the ring might not expand to the pyranoside-form until after the glycosidation. Bochkov and Zaikov[19] discuss this further, using methanolysis of α-L-arabinofuranose as an example. They concluded that it was impossible to make a definite conclusion on the mechanism based on what was known at the moment. The number of isomers, both α- and β-anomers of the furanose, pyranose, furanoside and pyranoside compounds, makes it difficult to follow the reaction good enough to conclude on anything.

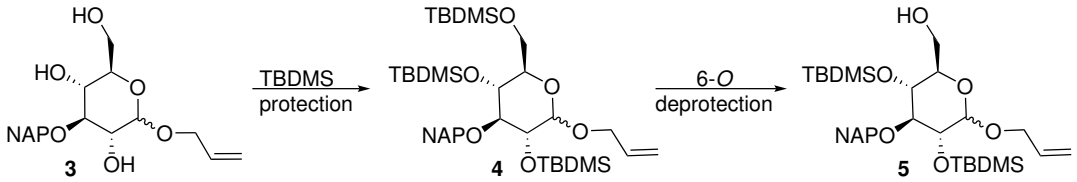
The research group have previously investigated this mechanism, confirming Miljković in that glycosylation on the furanose seems to be kinetically favoured. However, both the furanoside and the pyranose compound have been isolated by the group, so no conclusion on the reaction mechanism could be drawn.[20] Also, in the transformation from **2** to **3** (Scheme 5), the temperature is high, meaning that the thermodynamically favoured pyranose form will probably be the main form, and the ring rearrangement could possibly occur before glycosidation. A simplified mechanism for the reaction is proposed (Scheme 6), and, as mentioned, the steps after the first deprotection is probably not accurate.



Scheme 6: Simplified mechanism proposed for the rearrangement and glycosidation of **2** to give **3**.[5]

Since the reaction can take place in an S_N1 like reaction pathway, both the α- and β-anomer of **3** will be present. The ratio between the two anomers will depend on multiple factors, such as solvent and ring-substitutes, and also the anomeric effect. Even though axial addition (yielding α) at first glance seems like the most unstable option of the two when considering steric factors, it is in fact the most stable conformation due to the anomeric effect the α-anomer introduces. However, as mentioned, the other ring-substitutes will also affect the ratio, and steric factors clearly favour the β-anomer, so a mix of the two anomers is expected.

1.2.3 TBDMS protection and selective deprotection

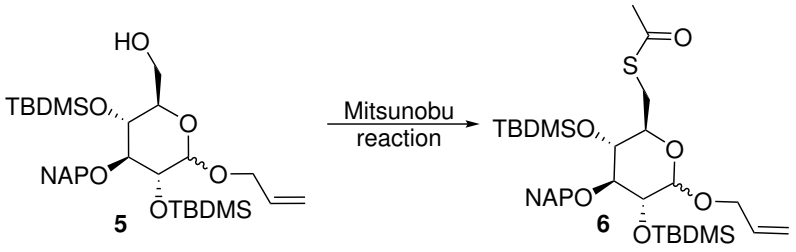


Scheme 7: TBDMS protection of **3** gives **4** and subsequent deprotection of 6-*O* affords **5**.

TBDMS ether is a well known and used protection group in organic chemistry. It is quite stable toward basic conditions, but sensitive towards acid. Because of its steric voluminosity, it is also often more stable as a secondary or tertiary ether, than as a primary ether.[21] Conditions for introduction largely depend on the alcohol substrate and how many hydroxyl groups are to be protected. The standard conditions involve the use of TBDMS chloride and imidazole as base in DMF or tetrahydrofuran (THF), where yields up to 96% have been reported.[22] In cases where steric crowding is a concern, the more reactive TBDMS triflate (TBDMS-OTf) often performs better, usually at lower temperatures, with 2,6-lutidine as base and dichloromethane (DCM) as solvent. Yields of 70-90% have been reported.[23] The latter method is utilized for protection of **3** in this project (Scheme 7). The research group has attempted the first method as well, but was not able to protect all of the hydroxyls simultaneously, with the 2,6-di-*O*-protected compound being the major product.

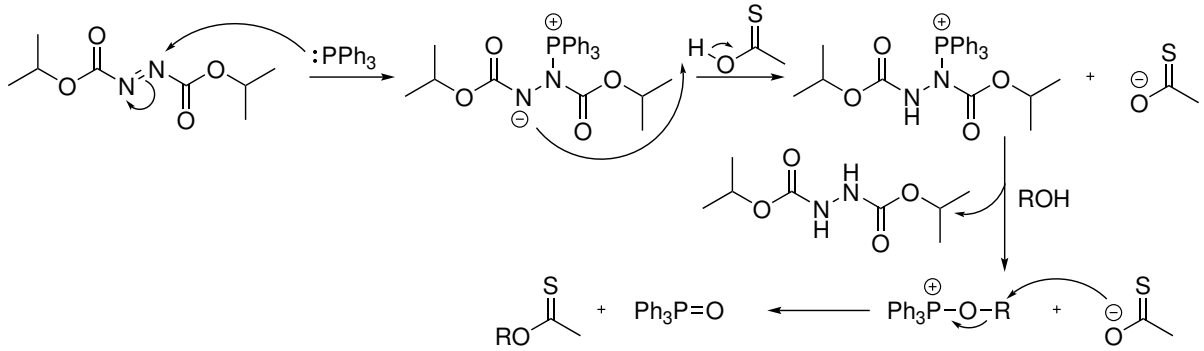
Deprotection of TBDMS can be executed in a multitude of ways, though nucleophilic attack by fluoride anions or acidic hydrolysis are most common.[24] Some possible reagents for deprotection are boron trifluoride, tetra-*n*-butylammonium fluoride (TBAF) or highly sulphated cellulose.[25] Another possible reagent is CSA. Since the TBDMS-group on 6-*O* on **4** is in a primary position, while the rest of the TBDMS protected oxygens are secondary, it can be selectively deprotected by carefully choosing conditions (Scheme 7). Selective deprotection of other primary TBDMS ethers in the presence of secondary TBDMS ethers with CSA have been performed with reported yields of 86%.[26] Previously the research group used ammonium fluoride to selectively deprotect 6-*O* in a kinetically controlled reaction. However, more recent work showed that CSA in a similarly kinetically controlled reaction made the reaction easier to control and thus better yields could be obtained. CSA will therefore be used for selective deprotection of 6-*O* on **4** as well. Further introduction into the removal of TBDMS will be given in Section 1.3.1.

1.2.4 Mitsunobu reaction



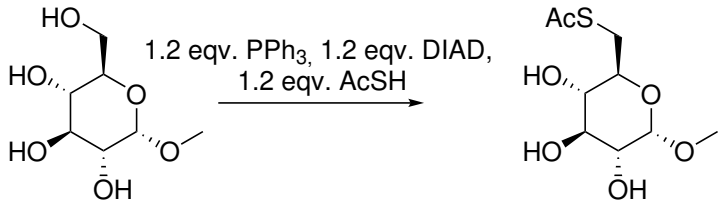
Scheme 8: Mitsunobu reaction with **5** inserts the thioacetate moiety at C-6, forming **6**.

The Mitsunobu reaction was discovered, and named after, Oyo Mitsunobu. It is a coupling reaction which utilizes diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh_3) to transform primary and secondary alcohols into other functional groups.[27,28] Other azodicarboxylate compounds than DEAD are sometimes used, for example when a more hindered or less toxic reagent is desired. Diisopropyl azodicarboxylate (DIAD) is used for this project. The Mitsunobu reaction will only take place if the nucleophile is acidic enough. Acids, such as thioacetic acid (AcSH), work well.[29] The reason for this is that the azodicarboxylate compound needs to be protonated, such that side reactions do not ensue. The reaction is initiated by PPh_3 attacking DIAD, forming a quaternary phosphonium salt. The salt will deprotonate the desired acid, making it a good nucleophile. Further reaction between the new salt and the alcohol will reduce DIAD into diisopropyl hydrazinedicarboxylate and form an oxyphosphonium ion. The R-group from the alcohol on this ion is electrophilic, it will thus react with the previously made nucleophile. The product, together with triphenylphosphine oxide, is formed through an S_N2 type reaction (Scheme 9).[30]



Scheme 9: Mitsunobu reaction mechanism with AcSH as the nucleophile and DIAD instead of DEAD which Mitsunobu originally used.[30]

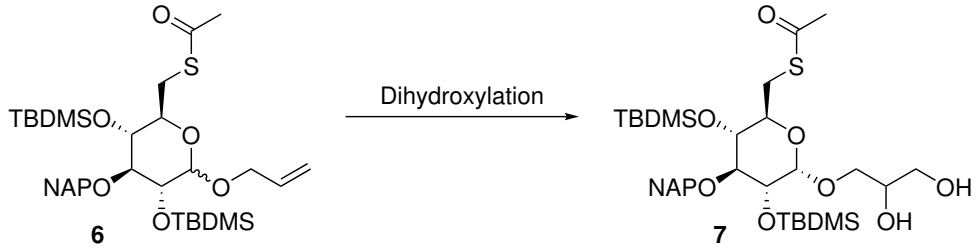
Reactions with insertion of thioacetate in 6-position when the other hydroxyl groups were protected with TBDMS and NAP (Scheme 8), have not been found in the literature. However, the reaction shown below (Scheme 10), was performed with a similar compound, methyl-α-D-glucopyranoside. The main difference being that the hydroxyls in 2-, 3- and 4-position were unprotected and slightly smaller equivalents of reagents (1.2 equivalents PPh_3, DIAD and AcSH compared to 1.6 equivalents used in this project) were used. The product was formed with a yield of 38%.[31]



Scheme 10: Mitsunobu reaction with thioacetate acid as the nucleophile, on an unprotected methyl-α-D-glucopyranoside.[31]

In a synthesis towards sulfoquinovose and sulfoquinovosyl diacylglycerides, a thioacetate was introduced at 6-position through a Mitsunobu reaction. It was carried out on a compound where 2-, 3-, 4- and 6-*O* were unprotected with reported yields from 73 to 86%. Only 1.1 equivalents AcSH were used, but 3.5 equivalents DIAD and PPh_3.[32] Jervis *et al.* have previously carried out a Mitsunobu reaction on trimethylsilyl protected α-D-glucopyranose, where only 6-*O* was unprotected. Insertion of azide in 6-position was performed successfully with diphenylphosphoryl azide as the nucleophile, yield of 83% was reported.[33]

1.2.5 Sharpless dihydroxylation

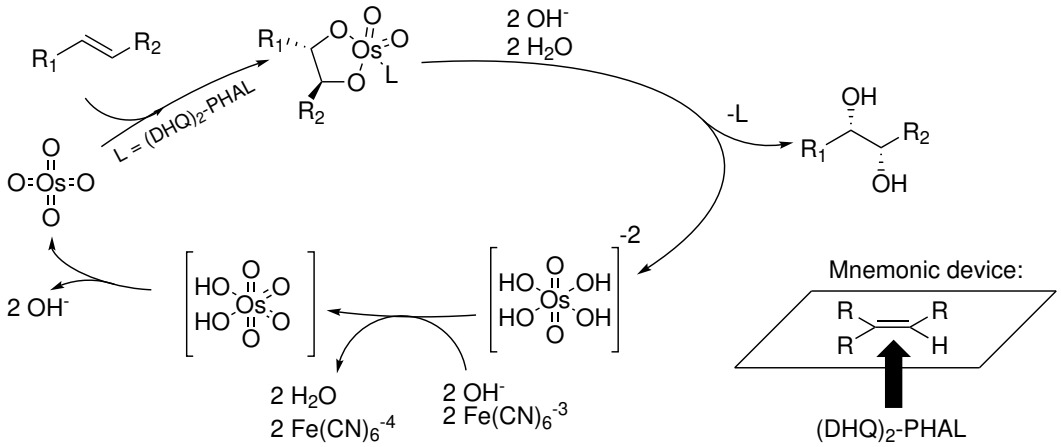


Scheme 11: Dihydroxylation of the allyl moiety on **6** gives the glycerol product **7**.

For oxidation of **6** to afford **7**, the Sharpless dihydroxylation reaction will be utilized (Scheme 11). It is a reaction used for converting alkenes into 1,2-diols. Originally alkenes were mixed with a stoichiometric amount of osmium tetroxide (OsO_4) and then hydrolysed with a reductive agent such as lithium aluminium hydride ($LiAlH_4$) to form racemic 1,2-diols. Sharpless and Hentges did, however, figure out that stoichiometric addition of tertiary alkyl bridgehead amines, which could form stable complexes with the stoichiometric amount of OsO_4, gave diols with high enantiomeric excess.[34]

Through further optimization, two phthalazine ligands were found, $(DHQ)_2$–PHAL and $(DHQD)_2$–PHAL, which respectively are the basis of the commercially available reagents AD-mix-α and -β today. These ligands made it possible to achieve very high enantiomeric excess when performing asymmetric dihydroxylation on many different olefin classes. It also meant that only a catalytic amount of OsO_4 and ligand were needed, whereas earlier one had to use stoichiometric amounts. The AD-mix chemicals consist mainly of ferricyanide and carbonate (99.4%), where the ferricyanide acts as a reoxidant for the osmium-complex after hydroxylation of the alkene has taken place, making it renewable and ready for another hydroxylation reaction.[35]

The asymmetric dihydroxylation does either take place from below with AD-mix-α or from above with AD-mix-β, see the mnemonic device in Scheme 12 which also includes a mechanism for the reaction.[36,37] The first step of the reaction is most likely a [3+2] cycloaddition which is then followed by a hydrolysis reaction and in the end reoxidation of the osmium-complex to OsO_4.[38]



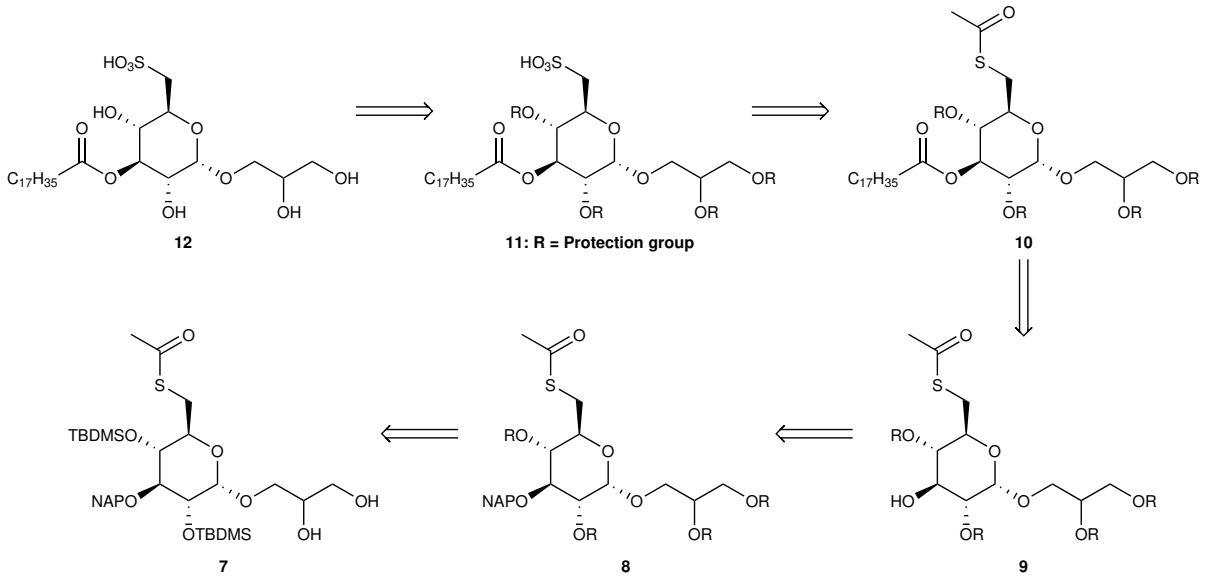
Scheme 12: Sharpless asymmetric dihydroxylation reaction mechanism and mnemonic device.[36,37]

Synthesis of a similar compound to **7**, only with benzyl as protection groups on 2-, 3- and 4-*O*, instead of TBDMS and NAP, have been carried out from the α, benzyl protected version of **6**. Conditions were similar to the ones used in this reaction. The reaction took place at room temperature and used *tert*-butanol (*t*-BuOH):water (1:1) as solvent, but with AD-mix-α instead of -β, 61% yield (diastereomeric ratio 8.1:1).[39] The same starting material have also been reacted in the same solvent and temperature, but with OsO_4 and trimethylamine *N*-oxide instead of AD-mix-β with 57% yield.[15] The reasoning for using OsO_4 instead of an AD-mix in the last reaction, was that the already chiral anomeric bond made it unnecessary to control the racemity as it did not matter whether or not the secondary alcohol formed was R- or S-configurated. They had previously synthesised diasteromeric pure compounds, which had insignificant differences in bioactivity.

Literature search for what effect OsO_4, AD-mix-α or AD-mix-β had if one has an anomeric mix of the α- and β-anomer yielded no results. However, work previously performed by the research group suggests that when one has an anomeric mix of **6** and desire the α-anomer of **7**, AD-mix-β gives the best anomeric selectivity. It reacts much faster with the α-anomer than the β, at least this is the case for 2,4-silylated and 2,4-acetylated compounds. It is also more selective towards one of the diastereomers, though at this stage it is not known which one.[40] It is thus possible to synthesise nearly pure **7**, as the β-anomer of **6** will react much slower than the α-anomer.

1.3 Novel chemistry

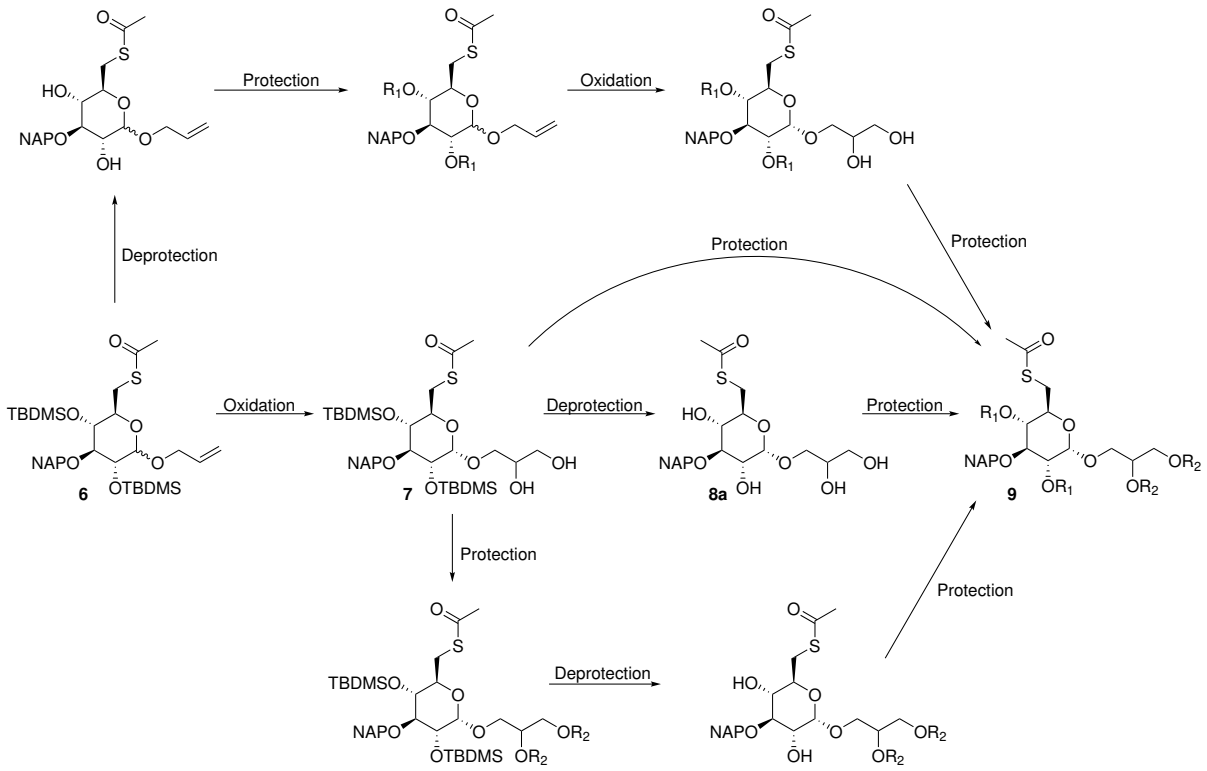
So, the intermediate **7** should be readily synthesised, but how do one proceed towards target molecule **12**? A retrosynthetic analysis for generation of target molecule **12** from the intermediate **7** gives an overview of what types of reactions are needed for the project (Scheme 13).



Scheme 13: Retrosynthetic analysis for generation of **12** from **7**.

The first step involves either protection of **7** with a new protection group on the glycerol diol, or deprotection of TBDMS and then global protection with a new protection group on the whole molecule. There are multiple concerns to take into consideration regarding the removal of TBDMS. First of all, it is not known whether NAP can be removed selectively with TBDMS on the ring. Secondly, earlier work performed by the research group does indicate that the subsequent esterification reaction is hampered by silyl ethers at neighbouring positions. Lastly, global deprotection of silyl have previously been reported to be problematic due to acyl migration and selectivity. For formation of **9** the NAP group will have to be cleaved off, such that esterification can take place to form **10**. Afterwards, oxidation of the thioacetate into sulfonic acid (SO_3H) will take place before the target molecule **12** is formed by removing all of the protection groups, simultaneously or in stages, depending on whether the hydroxyl groups are uniformly protected or not.

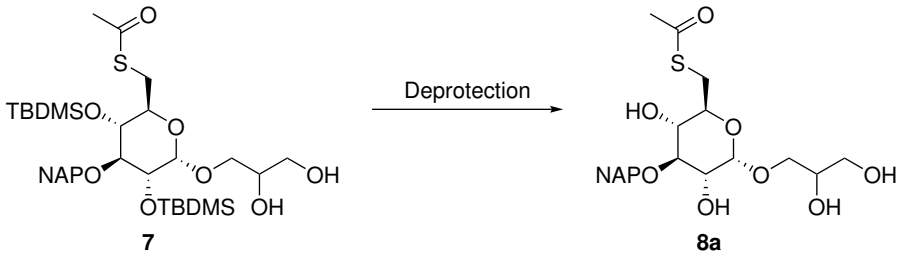
Formation of the intermediate **8** shown above, can occur through multiple reaction pathways from **6** (Scheme 14). Since there are some concerns about the usage of TBDMS, they could be cleaved off, either before or after oxidation. However, dihydroxylation of the allyl with TBDMS protected 2- and 4-*O* has been reported to be highly diastereomeric selective.[3] So, for this project at least, it is not desired to cleave them before oxidation. If the TBDMS groups are cleaved off after oxidation, new protection groups can be globally introduced at all free hydroxyl groups. Another possibility is to protect the glycerol first, and then selectively remove TBDMS before 2- and 4-*O* is protected by new protection groups. The most efficient reaction pathway would be to leave the TBDMS groups alone, and only protect the glycerol diols with new protection groups after oxidation of the anomeric chain, this way the amount of reaction steps are kept to a minimum.



Scheme 14: Possible reaction pathways for synthesis from **6** to the intermediate **9** which is the starting material for the NAP deprotection step.

1.3.1 Silyl deprotection

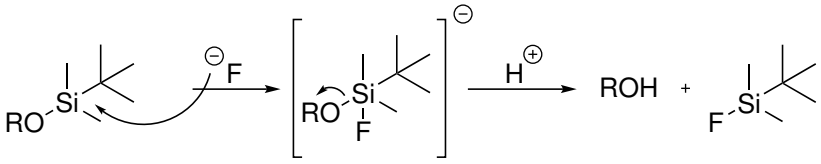
2- and 4-*O* on starting material **7** is protected with TBDMS ethers. If new protection groups on the ring are wanted, it would be desirable to cleave off these TBDMS ethers first, forming 1-*O*-glycerol-3-*O*-NAP-6-*S*-acetyl-α-D-glucopyranoside (**8a**) (Scheme 15). Deprotection has been reported in multiple ways depending on the starting material and which functional groups the compound consists of, and also if a selective deprotection is desired or not. Both acidic and basic conditions can be utilized, making the deprotection of TBDMS quite flexible.[21]



Scheme 15: Deprotection of TBDMS groups on 7 produces 8a.

For the deprotection of TBDMS ethers, three possible methods were deemed potentially suitable for the present intermediate - fluoride anion, Brønsted acid and Lewis acid. Corey and Venkateswarlu originally reported that treatment of a TBDMS protected lactone with 3 equivalents of TBAF in THF at 25 °C for 40 minutes gave the corresponding alcohol in over 99% yield.[41] The compound they deprotected only had one TBDMS protected

hydroxyl group and the other hydroxyl group were protected as a benzyl ether, which was not affected by the reaction. Benzyl and NAP ethers are quite similar, so it is assumed that the NAP ether is stable if reacted with TBAF as well. Later reports have suggested that one equivalent TBAF per desired TBDMS group to be cleaved off is sufficient.[42] The mechanism for deprotection of TBDMS with fluoride from TBAF is shown in Scheme 16.[43] The fluoride anion is small enough to be able to attack the silicon atom, forming a negative charge on the molecule. Workup then produces the alcohol.



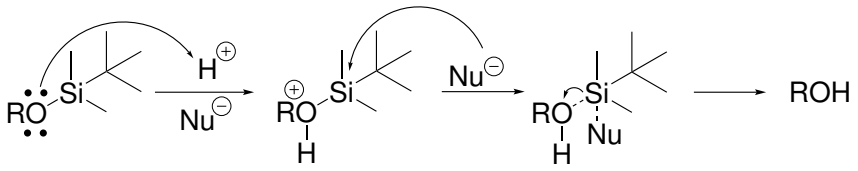
Scheme 16: Deprotection of TBDMS with fluoride.[43]

A possible challenge with fluoride deprotection is that the thioacetate group in 6-position could be converted to the corresponding thiol group, as TBAF is a highly nucleophilic compound.[44] While no examples of thioacetate deprotection with TBAF was found in the literature, there were found examples for the similar reduction of esters to alcohols.[45] Though the thiol can be directly oxidised to a sulfonic acid,[46] as is the desired moiety at 6-position, it is preferable to retain the acetyl functionality to prevent undesirable reactions in the intermittent steps before the final oxidation reaction. For example, thiols are known to react under Steglich esterification-like reaction conditions, forming a thioester group with the carboxylic acid.[47] Since Steglich's reaction conditions will be used for the insertion of the fatty acid, it could conceivably cause problems having a thiol instead of a thioacetate in the compound. Especially since it also would be a primary thiol, whereas the alcohol would be secondary, making it less sterically hindered and thus probably more reactive than the alcohol. In itself, the larger chain at 6-position might not prove a problem, as the acetyl functional group to be cleaved is the same no matter if it is a thioacetate or a larger thioester at 6-position. However, it would mean that the esterification of 3-*O* is challenged by another reaction and as will be discussed later, it is already expected to give low yields (Section 1.3.4). Instead of TBAF, milder fluoride reagents such as hydrogen fluoride pyridine could be used if thioacetate proves to be reduced by TBAF. However, hydrogen fluoride is known to be highly toxic[48] and a healthier option would probably be to probe acidic conditions instead, should TBAF prove unsuitable.

Acid-catalyzed deprotection of secondary TBDMS ethers have been reported by using a wide variety of acids.[21] Kawahara *et al.* used both formic acid at 30 °C and acetic acid at 30 and 50 °C to deprotect various TBDMS protected compounds with the goal of finding the optimal conditions with regards to reaction rate. The group found that the cleavage rate was fastest when using around 30% formic acid.[49] 30% formic acid will therefore also be attempted to deprotect the TBDMS groups on **7** for this project. Since an acid is used, there are not expected problems with regards to the thioacetate group in this case. The NAP group at 3-*O* is also reported to be quite stable under acidic conditions,[50] so it is expected that the TBDMS ethers can be cleaved off effectively and selectively in acidic conditions.

No literature was found on the acidic deprotection mechanism, other than that it would

depend on steric and electronic effects.[26] A probable mechanism is given in Scheme 17, based on reasonable assumptions. Trivalent silicon, i.e. TBDMS, leaving before the attack from the corresponding base or another nucleophile such as water (S_N1 mechanism) is a possibility. A concerted cleavage, similar to a S_N2 reaction, is also a possibility, with the alcohol leaving the silicon at the same time as the nucleophile attacks. TBDMS is though a pretty bulky group, and since both TBDMS groups on **7** are secondary, it might be most likely that trivalent silica leaves before nucleophilic attack, as there is limited space for attack at the molecule.



Scheme 17: Probable mechanism for deprotection of TBDMS under acidic conditions.

Since the deprotected product **8a** contains four hydroxyl groups, there are some concerns about purificating and isolating it, due to its high polarity. It would also mean the necessity for an extra step in the reaction pathway, just to insert new protection groups where TBDMS ethers are already present. Another possible pathway to reach the target compound **12** was therefore designed, as shown previously in Scheme 14. By protecting the glycerol diol on **7** first, it would be possible to either selectively deprotect TBDMS, or to cleave the NAP group off directly afterwards, at least if conditions which leave all of the other protection groups intact are found. In addition, there are multiple examples in the literature for converting TBDMS ethers into other protection groups, such as acetate or benzoate.[51,52] Such reactions would reduce the number of steps in the synthesis and would have to be looked into if the chosen protection group for the further reactions could be introduced by converting TBDMS.

1.3.2 Global protection

Protection groups are a vital part of syntheses which involves introduction of new groups on sugar rings. By manipulating the different hydroxyl groups with protection groups, it is possible, albeit often difficult, to selectively introduce new functional groups at different positions on the ring. When choosing which protection group to use in which situation, several conditions must be taken into account. The group needs to be easily introduced and cleaved at the appropriate stages of the synthetic pathway, while simultaneously remain inert in intermediate steps. The protection groups will also most likely affect further reactions, either directly or indirectly due to steric or electronic effects they introduce to the molecule. This is not always as easy to predict, but needs to be taken into consideration. If, for example, a reaction is desired at a sterically hindered position, it is most likely not wise to introduce bulky protection groups at the neighbouring positions since chances are big that they will reduce the reactivity.

There are two main ways of protecting hydroxyl groups on sugar rings, as ethers or as esters. For both variants there are extensive literature on both formation and removal of a wide variety of groups. A third possibility is as dioxolanes or dioxanes, i.e. acetals, when 1,2- or 1,3-diols are to be protected. Ethers are very flexible and can vary from simple

and stable methyl ethers, to much larger and more or less stable ethers, such as trityl and TBDMS ethers.[21] Ethers are commonly utilized when a protection group needs to be stable towards both acidic and basic conditions, or if the protection group is meant to be a permanent one. Esters are often both easily and mildly introduced and removed. Most esters are base-labile, because of the possibility of a nucleophilic attack at the carbonyl carbon, which in some situations might be desirable. However, esters have a tendency to migrate around the ring, which might lead to problems in selectivity.[53]

Before cleavage of the NAP-group and further esterification of 3-*O*, all of the free hydroxyl groups have to be protected. New protection groups for both 2- and 4-*O*, together with the two hydroxyl groups on the glycerol chain, were therefore desired. The protection group needs to be compatible with the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) catalyzed cleavage of the NAP protection group on 3-*O*, as well as the *N,N'*-dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) catalyzed esterification at the same position. The possibility of global deprotection at the same time as the oxidation of the thioacetate, either simultaneously or one-pot, could possibly be an opportunity by choosing an oxidatively removable group. However, it would have to be tolerant towards DDQ. Alternatively, an acid-labile protection group could be used, as the sulphur oxidation is often performed under acidic conditions. Ideally, the chosen protection group should also be introduceable under a broad range of conditions. This would give flexibility with respect to avoiding undesired side reactions with other functionalities present in the molecule, as well as providing multiple options in case the most common methods for introduction proves fruitless.

The research group has earlier protected the glucopyranoside compound with acetyl groups (Figure 1.5). However, due to the similarities between the acetyl and the inserted fatty acid, i.e. both having an ester functional group, conditions which allowed for selective cleavage of the acetyl groups while retaining the long chain acyl functionality in 3-position could not be established.[3]

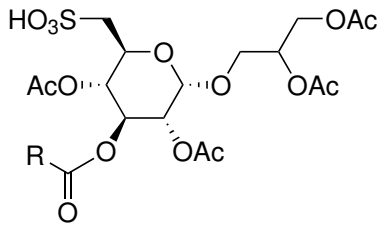


Figure 1.5: Similar compound to **11**, synthesised by the research group, with acetyl as protection groups.

From the literature it has been found that Wehrli and Pomeranz used hydrozinolysis to selectively remove acetyl groups on the sugar ring, while leaving esters on the glycerol chain intact. It was speculated that the glycerol esters aggregated into micelles with a hydrophobic center, which in turn exposed the polar acetyls on the sugar ring to the solvent, making a hydrophilic coat. This way only the acetyls could be attacked by hydrazine and the glycerol esters were protected from reaction.[54] More recent research by Manzo *et al.* confirms that sugar ring acetyls can be cleaved selectively while using a variety of fatty acids at the glycerol, as well as optimizing the reaction conditions.[55] The research group has found that these conditions, and others, does not work when

the fatty acid is on the ring instead of the glycerol. What happens is not completely clear, but none of the desired product is in any case formed.[3] It might be as Wehrli and Pomeranz hypothesised, meaning that the same phenomenon does not occur with fatty acid esters on the ring, as very similar conditions to theirs were attempted. Regardless, a new protection group which has different properties from acetyl is desired. The hope is that another protection group can be used to synthesise the precursor to **12** in sufficient yields, and also be properly removed without affecting the acyl group at 3-*O*.

Since previous work has indicated that esters might not be the way to go, an ether protection group is sought after. TBDMS, a silyl ether, is used for synthesis of **7**. Silyl ethers have been used as protection groups for alcohols for multiple decades and continues to be relevant today. Since the substituents at the silicon atom can be altered to give a wide variety of properties, silyl ethers can be very flexible even though they share the same functional group. By altering the substituents, one can for example protect a compound with different silyl ethers which then again can be selectively cleaved off. Other silyl ethers than TBDMS, which have seen much use, are for example trimethylsilyl (TMS) ether and *tert*-butyldiphenylsilyl (TBDPS) ether.[56]

Besides silyl ethers, there are many other types of ethers which could be considered suitable. Greene's book on protection groups in organic synthesis describes most of them with examples of both when they work and when they might not, together with examples on how to introduce and remove the groups.[21] By utilizing Greene's book, a couple of possible groups stands out, especially methoxymethyl (MOM) and 2-methoxyethoxymethyl (MEM) (Figure 1.6).

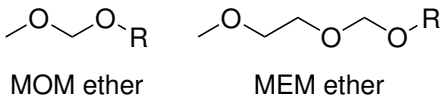


Figure 1.6: MOM and MEM ethers when used as protection groups for alcohols.

While MEM ethers looked quite promising for this project, there were not found any viable ways to introduce them without the use of MEM chloride (MEM-Cl). This reagent is carcinogenic[57] and it was therefore decided to focus on MOM instead. Also, earlier research by Stenset suggests that the esterification reaction is likely limited by sterically large protection groups at neighbouring positions.[4] Thus, the smaller MOM group could give better results than the slightly larger MEM group. However, both are pretty small compared to, for instance, TBDMS and TBDPS, so it might not have an impact.

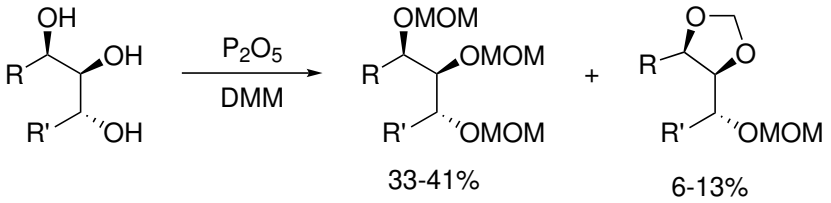
MOM has seen wide use as a protection group in organic chemistry. Many different methods have been used for insertion of the protection group. The most commonly used method is with MOM chloride (MOM-Cl) and *N,N*-diisopropylethylamine (DIPEA) in DCM.[21] This has for example been utilized by Stork and Takahashi, producing a MOM ether in 86% yield.[58] Instead of MOM-Cl, MOM bromide (MOM-Br) have also been used with success, Askin *et al.* introduced a primary MOM ether with MOM-Br and DIPEA in DCM with 72% yield.[59] Another possibility for insertion of the MOM groups is by dissolving the to-be protected alcohol in an excess of dimethoxymethane (DMM) together with phosphorus pentoxide (P_2O_5). This method was first reported by Fuji *et al.*, who applied it on multiple types of alcohols, with yields from 94% and upwards.[60] More recently, the same method has been utilized to protect 2- and 4-*O* on a

mannopyranoside compound with 94% yield. The other oxygens were already protected with other groups.[61] This is indicative of suitability for protection of **7** and **8a** through the same procedure. There are other ways to introduce MOM with DMM as well, such as *p*-toluenesulfonic acid or triflic acid instead of P_2O_5.[21]

The chosen protection group had to be, as previously mentioned, compatible with DDQ, DCC and EDCI catalyzed reactions. It was therefore desired to find examples from the literature where MOM ethers were unaffected by those kinds of reaction. While examples were scarce, at least one was found for each of DDQ and DCC. Matsushima *et al.* used DDQ in an oxidative acetalization of a compound with three MOM ethers, none of them were altered.[62] Grieco *et al.* used DCC to couple two compounds, where one of them had a MOM ether which remained unchanged during the reaction.[63] Since DCC and EDCI are fairly similar carbodiimide compounds, it was thought likely that if MOM was not affected by DCC, it would not be affected by EDCI either. By looking at the reaction mechanism for Steglich esterification in Scheme 21, it seems very unlikely that MOM will react with EDCI as well. Based on all of this, it was decided that MOM could be a viable protection group under the NAP deprotection and subsequent esterification.

The reported carcinogenic properties of MEM-Cl has also been reported for MOM-Cl.[64] Therefore, due to safety concerns, it is decided to primarily investigate the insertion of the MOM moiety from DMM. From the methods mentioned above, Fuji's method with P_2O_5 looked most promising, so it is chosen as the preferred way of inserting MOM ethers for this project. The aforementioned acids can be tested together with DMM before eventually MOM-Cl and DIPEA are used, if nothing else works.

A possible byproduct which could occur from protecting the compounds through the use of DMM and P_2O_5 is the formation of a methylene acetal from the 1,2-diol on the glycerol chain. This happened to Chen *et al.*, who obtained a product mix which contained from 15 to 25% of the methylene acetal protected compound, instead of the purely MOM protected compound (Scheme 18).[65] These acetals are very stable and therefore difficult to remove, needing very acidic conditions to cleave.[21] This is not a desired property for this project. However, if later work requires selective deprotection of 2- and 4-*O*, this method for a combined MOM and methylene protection could prove useful, and conditions which optimised the desired output could probably be found through research.



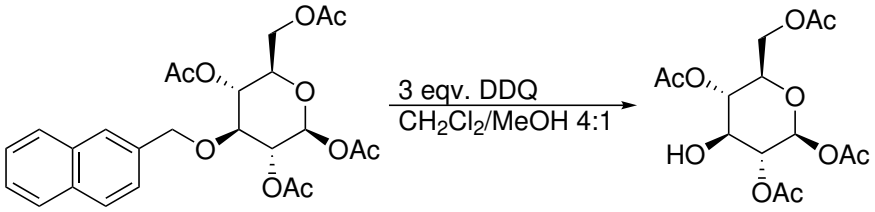
Scheme 18: Results from Chen *et al.*'s introduction of MOM. Yields, which varied with the R group, are given below the products.[65]

As mentioned in Section 1.3.1, a method for converting TBDMS ethers straight into MOM ethers would be interesting to explore. Sharma *et al.* have reported a simple method for MOM protection which included conversion of TBDMS to MOM. They carried out reactions with 10% zirconium(IV) chloride ($ZrCl_4$) together with the desired alcohol or TBDMS protected compound in DMM, and let the solution stir until no starting material

was left. The corresponding MOM ether was formed with reported yields from 93 to 97%.[66] While only one hydroxyl group was protected in their report, it was considered a promising starting point for experimentation on intermediate **7**. $ZrCl_4$ had a catalytic role in the reaction, so it could probably be kept at the same amount, and by increasing the amount of DMM the desired result could possibly be obtained. During their work, they also found that other groups, such as an anomeric methoxy group or isopropylidene groups, were stable under the reaction conditions. Since the NAP and thioester group on **7** are relatively stable, it was presumed that they would be unaffected during the $ZrCl_4$ reaction.

1.3.3 Naphthylmethyl deprotection

The NAP group is oxidatively removed by treating it with DDQ, as discovered by Xia *et al.*[67] Originally 3 equivalents DDQ in a 4:1 DCM:methanol (MeOH) system was used to remove NAP from pyranoside compounds (Scheme 19), with yields from 80 to 87%. Similar yields, 84-87%, have later been reported by Szabó *et al.*[68] They worked with somewhat more complicated benzyl protected disaccharides, but used the same reaction conditions to achieve the desired product.



Scheme 19: Original deprotection of NAP with DDQ as performed by Xia *et al.*[67]

While the NAP protected molecule originally was dissolved in DCM and MeOH, together with DDQ, it has later been shown that simply dissolving them in chloroform performs the reaction just as well. It has also been reported to give cleaner reaction profiles and lead to a facile purification process. A yield of at least 75% have been reported with the use of chloroform instead of a system of DCM and MeOH. This was, however, after three steps, so the actual yield for the NAP deprotection step would probably be even higher.[69]

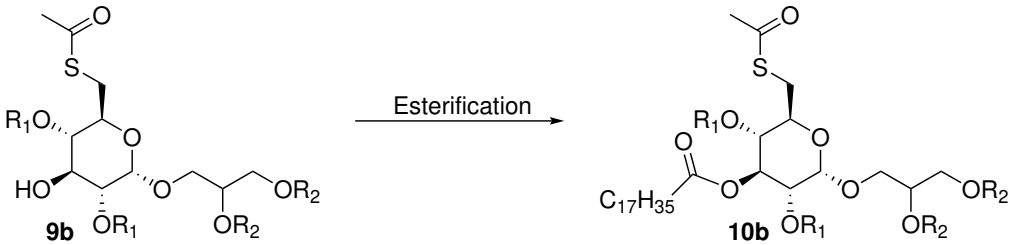
DDQ has been reported to cleave off TBDMS protection groups, which could pose a problem when wanting to selectively remove NAP on TBDMS protected **8d**. However, it has only been reported to do so when dissolved in wet, slightly polar solvents such as MeCN, THF and ethyl acetate (EtOAc). The use of still wet, but less polar solvents such as DCM and hexane led to low to no deprotection.[70,71] By changing the solvent to a less polar one, such as dry chloroform, it is believed that the TBDMS groups will remain untouched. Boeckman *et al.* have previously selectively deprotected NAP in the presence of TBDMS with the original conditions proposed by Xia *et al.* as mentioned above, with yields from 46% to 89%.[72] Since MeOH and DCM are more polar than chloroform, and the polarity of the solvent seems to heavily influence the cleavage ratio, it is expected that TBDMS protected **8d** should be readily converted to the 3-OH liberated product **9b** without the risk of cleaving off the silyl protection groups as well.

Another common method for deprotection of NAP are palladium catalysed hydrogenolysis. It was originally reported by Spencer *et al.* with high yields (above 85%) on a multiple of

compounds.[73] As a method it is not found to cause any complications with either MOM or TBDMS groups by choosing conditions carefully. However, lone electron pairs on 6-*S* are reported to coordinate with palladium, which poisons the catalyst.[74]

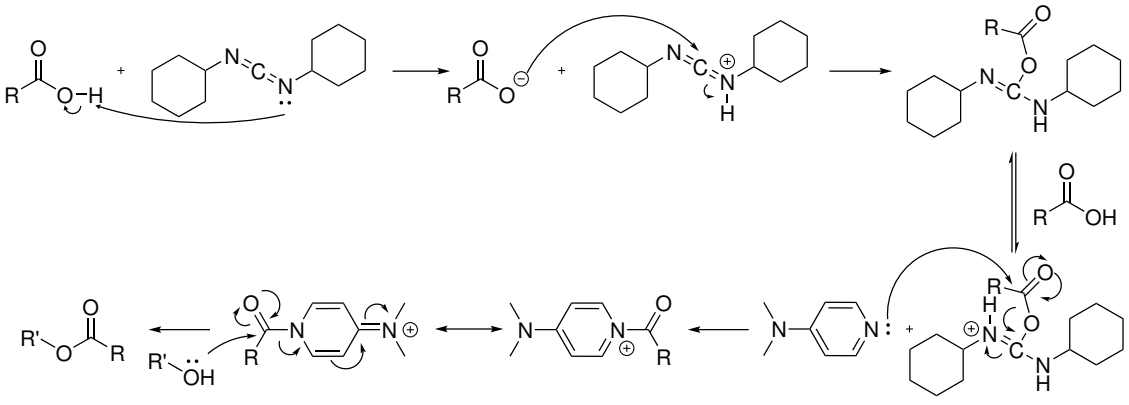
1.3.4 Esterification

Insertion of the fatty acid on 3-*O* is catalyzed by DCC and 4-dimethylaminopyridine (DMAP) (Scheme 20). While it would be preferable to insert linolenic acid, as is the goal for the main total synthesis project for the research group, only stearic acid is tested for this thesis as the work herein is mostly proof of concept. As stearic acid has a saturated chain, it is expected open up for acidic removal of TBDMS and MOM groups after the thioacetate is oxidized, without having to consider the possibility of an acid, such as HCl, performing hydrohalogenation on an unsaturated fatty acid chain.



Scheme 20: Esterification of 3-*O* on **9** with stearic acid gives **10**.

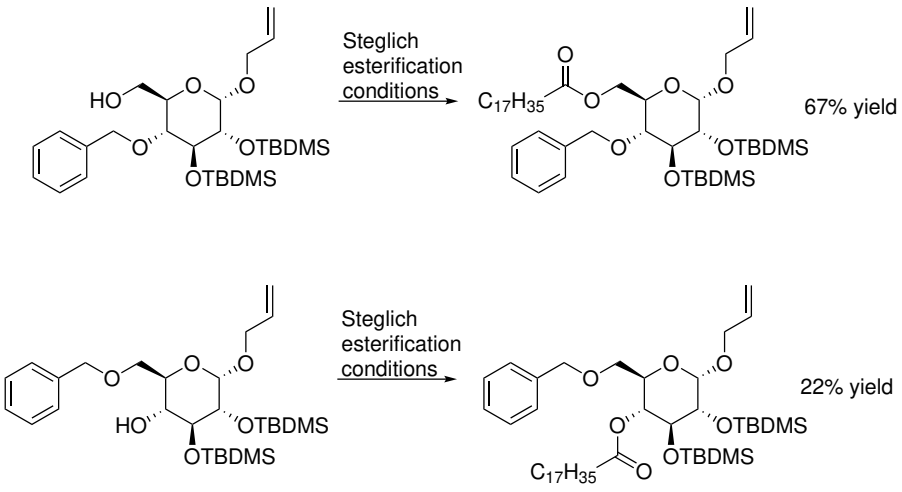
Esterification with DCC and DMAP as catalysts was first described by Steglich and Neises and is appropriately named the Steglich esterification.[75] It is a coupling reaction which forms an ester from an alcohol and a carboxylic acid. It can also produce thioesters from thiols,[76] which is one of the reason for having a thioester in 6-position, instead of a thiol as mentioned earlier. As shown by Steglich and Neises, the reaction can be carried out without DMAP, but at a much lower rate and yield. The DMAP acceleration also suppresses side reactions and makes it possible to produce sterically large esters.[77] This is especially important considering the relatively large protection groups in 2- and 4-position in TBDMS protected **9b**. The general reaction mechanism for Steglich esterification is shown in Scheme 21.[78,79]



Scheme 21: Steglich esterification reaction mechanism.[78,79]

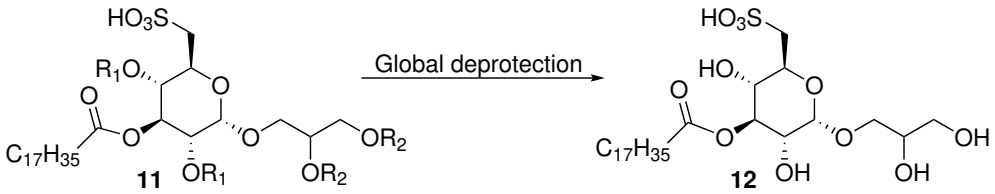
The urea byproduct when using DCC as coupling reagent is not water-soluble and will therefore not be removed by water extraction. This means it instead will have to be removed by chromatography. Luckily, there are other coupling reagents, which can be substituted for DCC without further altering the reaction conditions. One such reagent is the earlier mentioned EDCI, which originally was synthesised by Sheehan *et al.* as an alternative to non-water soluble carbodiimides.[80] It is often preferred to DCC exactly because its urea byproduct is water soluble, which most of the time means that cleaning of the reaction mixture will be less complicated.[81] There are, of course, many other ways of doing esterification reactions which are not mentioned here. Both by using Steglich-like conditions, but with different coupling reagents or other adjustments, such as altering the activation agent. Another well known method for esterification is the Fischer esterification reaction. However, slightly adjusted Steglich esterification conditions with DCC and EDCI is what the research group has utilized before, with varying success, and so it will also be used for this project. Also, since Fischer esterification is catalyzed by an acid,[82] it could potentially prove incompatible with other protection groups present in the molecule.

Work performed by Stenset in an earlier master thesis at NTNU shows the need for large equivalents of both fatty acid, promotor and catalyst to obtain sufficient yields when inserting a fatty acid at the 4-position. He also found that EDCI works much better (22% yield) than DCC (5% yield), while having else-wise similar conditions when introducing esters at 4-*O*. He also discusses the problems large neighbouring groups seems to inflict when doing the esterification reaction. He did esterification on both 4- and 6-*O*, where much higher yields were obtained for esterification of 6-*O* (Scheme 22).[4] The main difference between the two reactions were steric crowding around the hydroxyl group. For the most crowded hydroxyl group, the one at C-4, he only had one TBDMS ether in neighbouring positions, while at the other neighbour he had the benzyl methyl ether. For this project, **9b** will instead have neighbouring TBDMS ethers at both 2- and 4-*O*. The silyl ethers are relatively bulky, and two of them might hinder reaction even more. It is therefore presumed that exchanging the TBDMS groups with MOM instead, will make it possible to do the esterification in a more rewarding way.



Scheme 22: Results from Stenset's esterification with stearic acid on both 4- and 6-*O* in otherwise similar compounds.[4]

1.3.5 Global deprotection



Scheme 23: Global deprotection of **11** gives the target compound **12**.

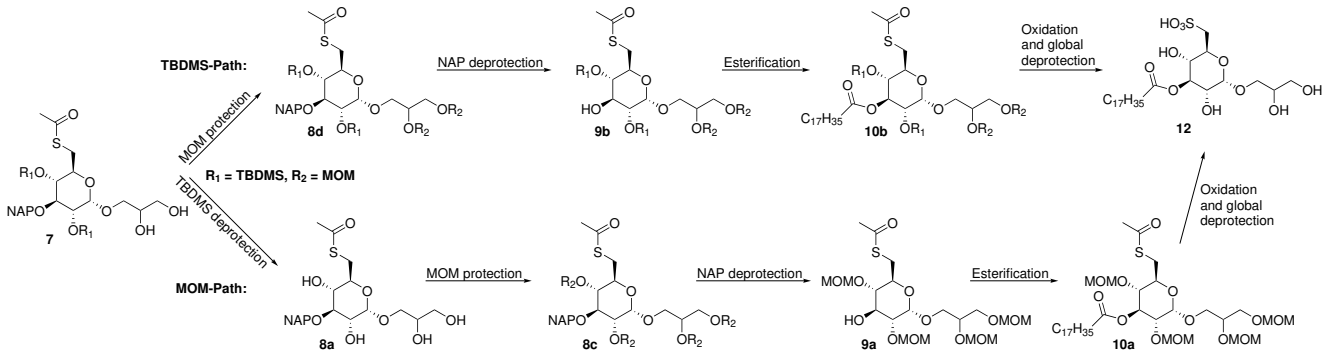
The target compound **12** is formed by globally deprotecting the thio oxidised intermediate **11** (Scheme 23). It is therefore desired to find conditions which can deprotect both MOM and TBDMS groups simultaneously, without affecting the acyl group. Esters are usually cleaved by either nucleophiles in aprotic solvents, or by base- or acid-catalysed hydrolysis.[83] Such conditions are therefore unwanted. Both protection groups are acid-sensitive, and these conditions will probably be attempted if any examples are found. The sulfonic acid moiety is in itself quite acidic and would probably not be affected by acidic conditions. Hanashima *et al.* have previously used trifluoroacetic acid (TFA) and acetic acid to deprotect TBDMS ethers on the sugar ring of sulfoquinovosyl compounds, with moderate yields (35-39%).[15] Their fatty acid ester was, unlike in **11**, attached to the terminal oxygen at the glycerol chain. Migration of the fatty acid around the ring is therefore expected to cause more problems in the deprotection of **11**, than it was for them. Since both protection groups on **11** protect secondary alcohols, and primary alcohols often are easier to deprotect than secondary, examples from the literature with secondary cleavage of both groups were desired. Examples with cleavage of primary groups might not work. For example, it was mentioned in Section 1.2.3 that two equivalents of CSA can be used to cleave the primary TBDMS group on **4**, without affecting the secondary ones.

Lin *et al.* dissolved their starting compound, which consisted of both a secondary TBDMS ether and a secondary MOM ether, in THF and added 6 equivalents of aqueous HCl before letting the reaction stir for 40 minutes at 40 °C. This gave the unprotected product in 55% yield.[84] Harsher conditions and/or longer reaction time could possibly be used to deprotect **11**, but as mentioned, it could affect the ester on C-3 as well. Another acid which have been reported to cleave secondary MOM and TBDMS ethers simultaneously is TFA. Prasad and Pawar used it to obtain the desired product in 93% yield by stirring the starting material in DCM and TFA at room temperature for four hours.[85]

Milder conditions might also be possible to use. Hanessian *et al.* used bromotrimethylsilane (TMSBr) in DCM at −30 °C to deprotect a secondary MOM ether and a secondary TBDMS ether simultaneously. Esters are reported to be stable under the same conditions,[86] which is essential for retaining the 3-*O*-acyl moiety. This is confirmed by other studies, which have found some esters to even be stable when dissolved in boiling TMSBr.[87] TMSBr or another Lewis acid might therefore be the best choice, as it is very unlikely to react with the ester, while Brønsted acids can donate protons to the ester functional group and in worst case hydrolyse it back into an alcohol and a carboxylic acid.

1.3.6 Synthetic plan for synthesis of 12 from 7

The synthetic plan for synthesis of **12** from **7** is shown in Scheme 24. It involves two separate routes which employs much of the same chemistry, but differs in the choice of protection group on the sugar ring.



Scheme 24: Two alternative routes are proposed for the synthesis of **12** from **7**, the TBDMS- and MOM-path.

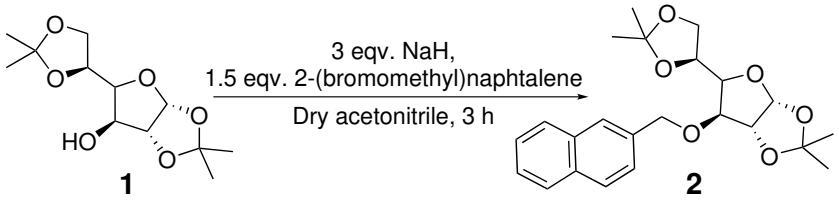
As discussed, the first step involves either protection of **7** with MOM at the glycerol diol, or deprotection of TBDMS and then global protection with MOM on every free hydroxyl group in the molecule. For these steps no previous research from the group are available. Time to find suitable conditions for the deprotection of TBDMS ethers and introduction of MOM ethers will therefore be allocated. When either tetra-*O*-MOM protected **8c** or 2',3'-di-*O*-MOM-2,4-di-*O*-TBDMS protected **8d** is formed, the NAP group will be cleaved in order to facilitate for esterification of 3-*O*. This will be done by dissolving the compound in chloroform and adding 3 equivalents DDQ, before stirring until the starting material is gone. If proven unsuitable, other methods can be attempted if found. Esterification will be done following the results from previous work by the research group. Large equivalents of reagents were needed for reaction. By protecting the hydroxyls on the ring with MOM instead of TBDMS, it is expected that milder conditions can be used, potentially simplifying purification.

Due to the lengthy synthesis of intermediate **7** and the amount of experimentation required to pinpoint the appropriate method for protection group manipulation, it is difficult to gauge how much time can be allotted to investigate thio oxidation and global deprotection. It would be highly desirable to verify whether the fully MOM-protected or TBDMS-MOM-protection combination are suited for thio oxidation and/or global deprotection. As previously mentioned, there are multiple aspects to investigate regarding these two steps, but as the global deprotection step was identified as the main challenge in previous work by the research group, experimental work on these intermediates should focus on global deprotection and the propensity for acyl migration. Regardless, two synthetic routes were planned with hope that **12** could be synthesised from at least one of them. The TBDMS route with **8d** as starting material before the cleavage of NAP, and the MOM route where TBDMS is replaced by MOM, forming **8c**, before the cleavage of NAP.

2 Results and discussion

2.1 Synthesis of key intermediate 7

2.1.1 Williamson ether synthesis



Scheme 25: 2-Naphthylmethyl (NAP) protection of the free hydroxyl group in compound 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**).

The initial protection of the 3-hydroxyl was carried out in accordance with previous work conducted by the research group (Section 1.2.1), and after 3 hours the reaction was quenched with water, acetonitrile (MeCN) evaporated and the solution extracted with dichloromethane (DCM). The reaction was performed in 4 parallels, of which neither were fully purified, results are summarized in Table 2.1.

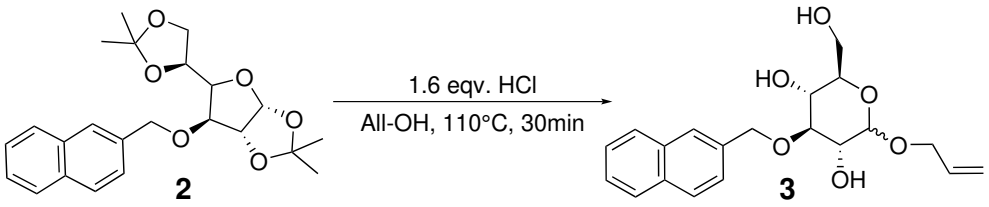
Table 2.1: Williamson ether synthesis reaction results.

Parallel	Starting material [mmol, g]	Unpurified product [g]	Yield [%]
1	11.526, 3.000	6.041	98.7
2	15.600, 4.061	8.247	-
3	16.291, 4.241	8.597	-
4	15.706, 4.088	8.712	-

In parallel 1, a small sample (310 mg) was purified by column chromatography, and the isolated yield was used to calculate the total yield. The calculated yield of 98.7% verified the viability of the reaction and was in accordance with previously reported results, where a similar Williamson ether reaction has been reported with a yield of 98%.[17] This made it unnecessary to perform further purification or yield calculations for the other parallels.

2.1.2 Rearrangement and glycosylation

The rearrangement into 1-*O*-allyl-3-*O*-NAP-D-glucopyranoside (**3**) was carried out using the conditions reported by Fukase *et al.*[18] After 30 minutes the reaction was terminated with triethylamine (NEt_3), evaporated and purified by silica gel chromatography with ethyl acetate (EtOAc):*n*-pentane (1:1) as eluent. Results are summarized in Table 2.2. The yield was calculated based on the amount of **1** used in the preceding reaction, as no intermediary purification of **2** was performed. No yield was calculated for parallel 1 as the product was later shown to be impure.



Scheme 26: Rearrangement and glycosylation of **2**.

Table 2.2: Rearrangement and glycosylation reaction results.

Parallel	Starting material [mmol, g]	Product [mmol, g]	Yield [%]
1[1]	10.598, 4.244	8.621, 3.107	-
2	15.600, 4.061	12.944, 4.665	83.0
3	16.291, 4.241	13.560, 4.887	83.2
4	15.706, 4.088	11.886, 4.284	75.7

When analyzing what was thought to be an anomeric mix of **3** from parallel 1, it was evident that at least four compounds were present in the mixture. Further purification on a silica gel column with EtOAc:*n*-pentane (3:1) allowed partial separation of the compounds. Based on NMR analysis a likely structure was found for the separated byproduct, 1-*O*-allyl-3-*O*-NAP-β-glucofuranoside (**3bi**, Figure 2.1).

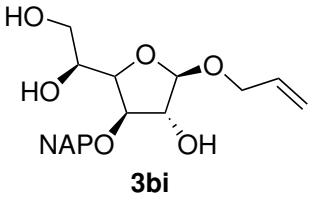


Figure 2.1: Likely byproduct 1-*O*-allyl-3-*O*-NAP-β-glucofuranoside (**3bi**) from the rearrangement and glycosylation reaction.

A compound similar to **3bi**, with benzyl protected 3-*O* instead of NAP protected, have earlier been synthesised by the research group with similar conditions (56% yield). The only differences being that the reaction was carried out at room temperature for 36 hours.[20] Since both the α- and β-anomer of **3**, the pyranoside product, were identified as well, it was likely that the last compound in the mix was the α-anomer of the furanose product **3bi**. Comparison of ^{1}H NMR spectra for the product, after purification, for each of the first three parallels, shows that product from parallel 1 contained more signals than the spectra for the last two parallels, which likely means there were more byproduct in the first parallel (Figure 2.2).

While it is not possible to reject the possibility of byproducts in parallel 2 and 3 from Figure 2.2, it is evidently more prominent in parallel 1, indicating a procedural error

[1] **2** as reported starting material

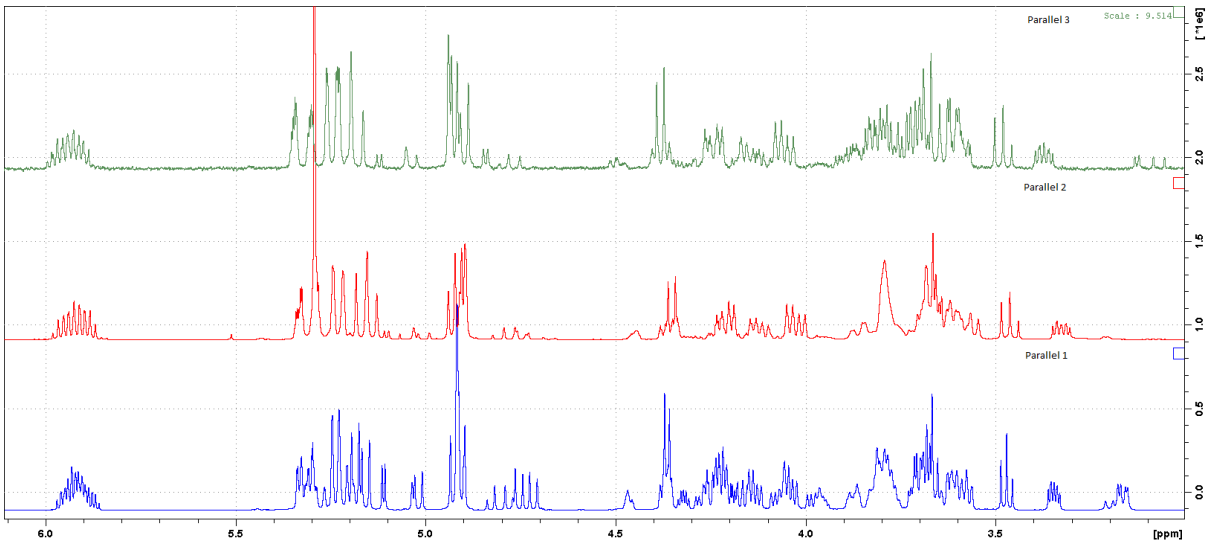
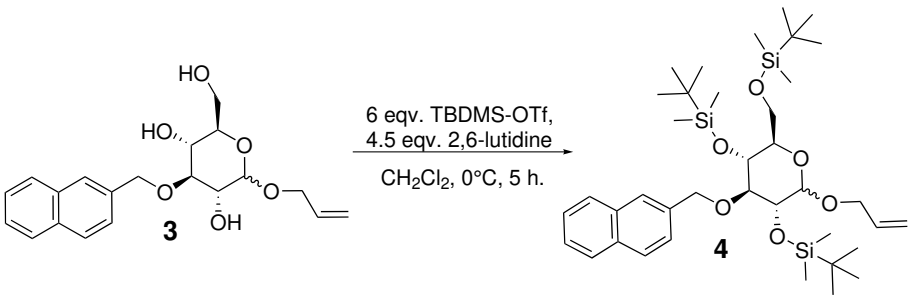


Figure 2.2: ^{1}H NMR spectrum comparison between the product from the rearrangement and glycosylation reaction of parallels 1 (blue), 2 (red) and 3 (green).

rather than unexpected reactivity. The most likely explanations are insufficient addition of acid or low temperature, which would both enable larger formation of the furanoside byproduct by kinetic control.

2.1.3 Silyl protection



Scheme 27: TBDMS protection of hydroxyls on **3**, with *tert*-butyldimethylsilyl triflate (TBDMS-OTf) and 2,6-lutidine as reagents.

As mentioned in Section 1.2.3, TBDMS-OTf reagent and corresponding conditions were employed to make sure the compound was fully silylated. Results for the silyl protections are summarized in Table 2.3. By assuming full conversion to the 2,4,6-tri-*O*-TBDMS protected derivative **4**, it was first assumed that purification could be done by simply eluting the compound through a short silica gel plug with a weak eluent to remove traces of 2,6-lutidine. However, when performing the subsequent selective deprotection of 6-*O* (Section 2.1.4) it was discovered that disilylated products had coeluted with the target product. Thus a calculated yield for parallel 1 is not presented. A silica gel column with DCM:*n*-pentane (1:1) as eluent was later used for purification of **4**.

Table 2.3: TBDMS protection results.

Parallel	Starting material [mmol, g]	Product [mmol, g]	Yield [%]
1	7.858, 2.832	-, 6.163	-
2	12.944, 4.665	4.306, 3.028	33.3
3	13.560, 4.887	1.807, 1.271	13.3
4	11.886, 4.284	10.401, 7.314	87.5

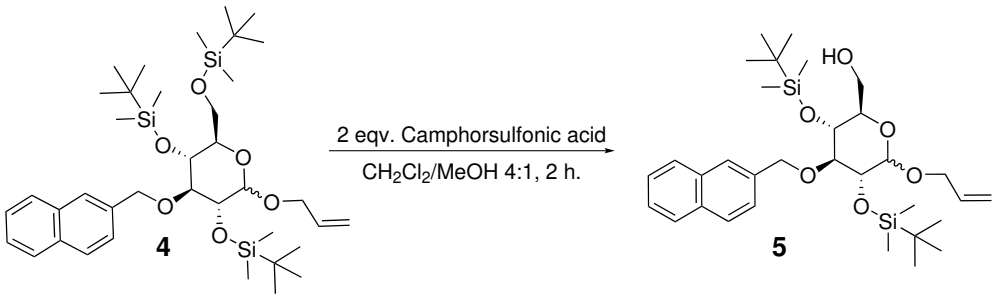
The aforementioned result for parallel 1 indicates that scaling up the reaction might present problems. However, this is inconclusive, as the starting material also contained the furanoside byproduct, **3bi**, and probably its α-anomer as well, as discussed above (Section 2.1.2). While the product from the last parallels was a yellow oil, the first parallel gave a pink, somewhat solid, product. As mentioned in the introduction (Section 1.2.3), good yields for TBDMS protection with TBDMS-OTf have been achieved earlier.[23] However, that was with molecules less complex than **3**, such as *tert*-butyl alcohol (*t*-BuOH), so the increased complexity might have affected the yield.

The research group has previously synthesised the 3-*O*-benzylated derivative of **4** in 76% yield, but at a much smaller scale.[88] The reaction was carried out in dry DCM to avoid unwanted reaction between water and TBDMS-OTf. 2,6-lutidine was stored in the fridge, and although it is dry when coming from the supplier, it might have become less dry over time upon opening and closing of the bottle. Allylic alcohol (All-OH) or water residues in the starting material might also have been a source for unwanted side reactions.

After purification of parallel 2, the low yield of 33% gave cause for concern. It was thought that the yield probably could be increased by letting the reaction reach room temperature before being terminated. For parallel 3 the reaction was allowed to do just this, in an attempt to get better yields. Purification did however show the complete opposite. The yield was much lower. It was thought unlikely that the increase in temperature after 4 hours would lower the yield so much. Instead it was hypothesised that something went amiss at the start of the reaction.

TBDMS-OTf was in parallel 4 added dropwise at a much slower rate than before, approximately 0.33 mL/ min versus 3 mL/ min, to avoid temperature increase. The reaction time was also increased to 24 hours, instead of 5 hours as originally proposed. For the first 10 hours, the reaction was kept at 0 °C, before it was allowed to rise to room temperature over night. After purification, **4** was obtained in 88% yield.

2.1.4 Selective deprotection of 6-*O*



Scheme 28: Selective deprotection of 6-*O* on **4**.

The selective deprotection of the primary TBDMS ether was carried out with camphorsulfonic acid (CSA) catalysed hydrolysis. After termination of the reaction, elution on silica gel with a weak eluent, EtOAc:*n*-pentane (1:20), allowed for partial separation of the α- and β-anomers of intermediate 1-*O*-allyl-2,4-di-*O*-TBDMS-3-*O*-NAP-D-glucopyranoside (**5**). The β-anomer eluted slightly earlier than the alpha, and fractions containing at least 80% α-anomer were collected and used in subsequent reactions. Results are shown in Table 2.4.

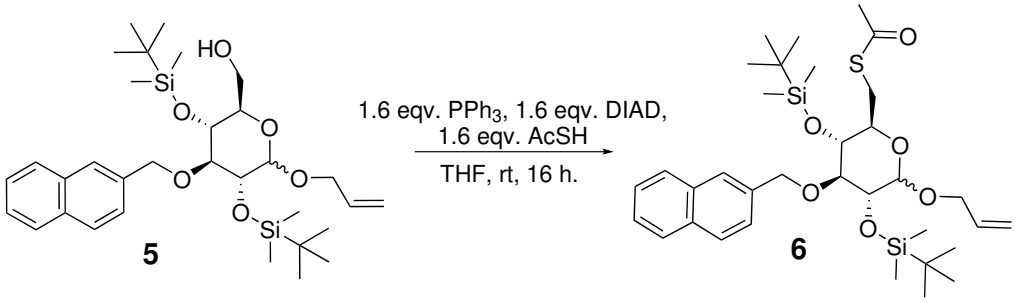
Table 2.4: 6-*O* deprotection results.

Parallel	Starting material [mmol, g]	Product [mmol, g]	Yield [%]
1	-, 5.870	0.931, 0.548	-
2	3.894, 2.738	0.474, 0.279	12.2
3	1.807, 1.271	0.890, 0.524	49.2
4	10.401, 7.314	3.038, 1.789	29.2 (69.1)

The yields reported for parallel 2 and 3 were calculated from the fractions which were gathered for further use. For parallel 4 the total yield was calculated to be 69.1%, but only 29.2% for the fractions collected for subsequent reactions. The large amount of material made it difficult to get satisfactory separation of the anomers. For parallel 3 separation was performed with small procedural errors, which could explain the unusual high yield after separation. The yield for parallel 1 was not calculated due to previously explained problems regarding impurities from the two preceding steps. The low yield in parallel 2 was a result of inadequate temperature control, as the reaction was started at room temperature. Despite lowering the temperature to 0 °C after 10 minutes, ^{1}H NMR clearly showed that some secondary TBDMS ethers had been deprotected, illustrating the importance of temperature for kinetic control.

Nearing the end of the project, it became clear that more intermediate **7** was needed for further reactions. Instead of starting from **1**, it was instead tried to separate the α- and β-residues of **5** that had not been separated from parallel 1 to 4. By utilizing a new eluent system, which started with *n*-pentane:DCM 2:1 and changed ratio every 500 mL to 1:1, 1:2 and lastly pure DCM, 1.29 g of the pure α-anomer of **5** was isolated for use in subsequent reactions.

2.1.5 Mitsunobu reaction



Scheme 29: Mitsunobu reaction on **5** with insertion of thioacetate.

Thioacetate was successfully introduced at position 6 through a Mitsunobu-type reaction, without the need to go via a tosyl derivative. Thus, **7** could be synthesised by a one step shorter reaction route than the research group had previously been able to. After termination of the reaction with water, the thioacetate product **6** was isolated by silica gel chromatography, EtOAc:*n*-pentane (1:15) as eluent. Results are summarized in Table 2.5.

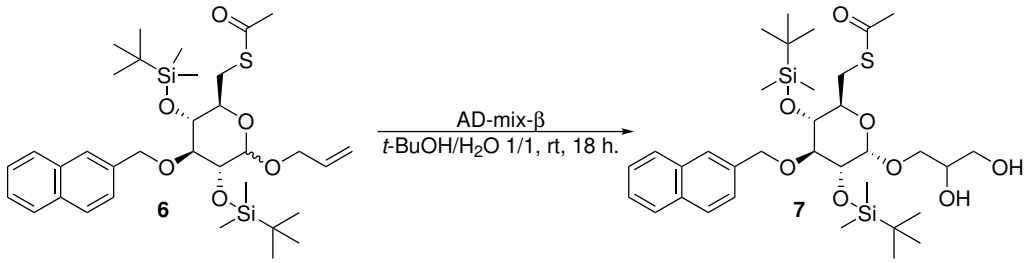
Table 2.5: Mitsunobu reaction results.

Parallel	Starting material [mmol, g]	Product [mmol, g]	Yield [%]
1	0.931, 0.548	0.769, 0.497	82.6
2	0.474, 0.281	0.434, 0.279	91.6
3	0.890, 0.524	0.844, 0.546	94.8
4	3.038, 1.789	2.168, 1.403	71.4
5	2.182, 1.285	0.264, 0.171	12.1
6	1.453, 0.856	0.182, 0.118	12.5

As expected from Mitsunobu reactions on other 2-, 3- and 4-protected α-D-glucopyranoside compounds, the yields were high in the first three parallels. All three parallels used reagents from new, unopened bottles. By the time parallel 4 were run, three weeks had passed since the reagents were opened for the first time. For parallel 5 and 6, four months had passed since the bottles first was opened. The lowered yields imply that the freshness of the reagents plays a major role for how well the reaction proceeds.

Since the yield in parallel 5 was very low, it was tried to increase the reagent equivalents to 3, instead of 1.6, in parallel 6. However, by looking at the results from parallel 6, it did not seem to help. It should also be mentioned that the NMR spectra of compound **6** are taken from unreacted **6** isolated after a subsequent dihydroxylation reaction, thus the low α:β ratio in the spectra (Appendix A.6).

2.1.6 Oxidative dihydroxylation



Scheme 30: Sharpless dihydroxylation reaction with **6** and AD-mix-β.

Selective oxidation of the anomeric chain was done by a Sharpless dihydroxylation reaction, with AD-mix-β as the oxidant. After stirring the reaction for 18 hours, sodium sulfite (Na_2SO_3) was added and the solution allowed to stir for another hour. The solution was then extracted with EtOAc and purified on a silica gel column with EtOAc:*n*-pentane (1:5) to yield 1-*O*-glycerol-2,4-di-*O*-TBDMS-3-*O*-NAP-6-*S*-acetyl-α-D-glucopyranoside (**7**). Results are shown in Table 2.6.

Table 2.6: Dihydroxylation results.

Parallel	Starting material [mmol, g]	Product [mmol, g]	Yield [%]
1	0.769, 0.497	0.526, 0.358	68.4
2	0.474, 0.281	0.279, 0.190	58.9
3	0.890, 0.524	0.380, 0.259	42.7
4	1.864, 1.206	1.438, 0.979	77.1
5	0.447, 0.289	0.214, 0.146	47.9

By comparing the relative integrals of one of the C-10 (see Figure 2.17 for carbon numbering) proton signals in the ^{1}H NMR spectra of starting material **6** and product **7**, it is possible to conclude that previous observations regarding difference in reaction kinetics between the two anomers seems to be correct.[40] When using a starting material with an α:β-ratio of approximately 4:1, the isolated dihydroxylated product had an α:β-ratio of around 25:1 (Figure 2.3).

In Section 2.1.4 it was shortly discussed that the differences in reported yields, for the selective deprotection, could be explained by how accurately the anomer separation was performed. As seen in Table 2.4, a yield of 49.2% for parallel 3 was reported, while in parallel 4 it was 29.2%. For the dihydroxylation reaction (Table 2.6) the reported yield in parallel 4 was 77.1%, while in parallel 3 it was 42.7%. Since reaction conditions otherwise were equal, it once again seems to confirm the difference in reaction kinetics between the two anomers, as the difference in yield can probably be attributed to the differences in α:β-ratio in the starting material **6**.

Having obtained the key intermediate **7**, work on completely novel chemistry could commence. Subsequent results are presented in two main sections, with one line of inquiry

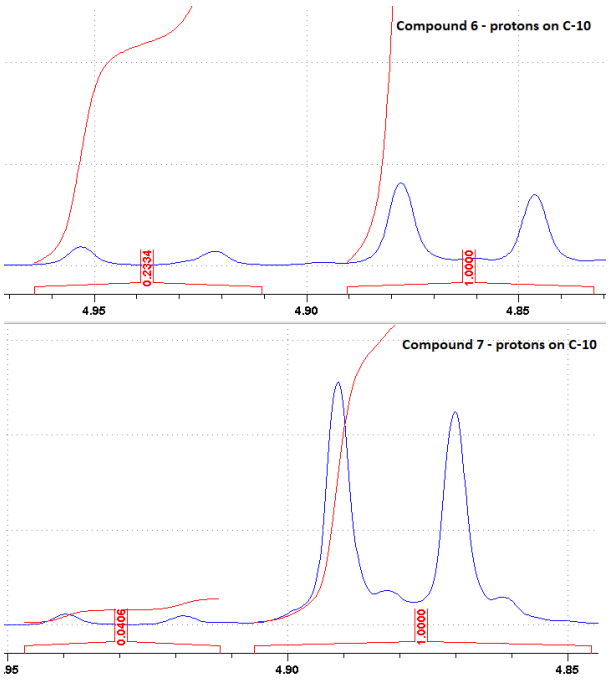


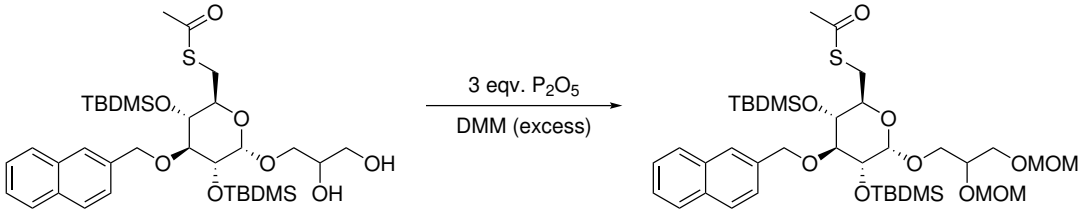
Figure 2.3: ^{1}H NMR spectrum comparison between starting material **6** and product **7** for parallel 2 which shows the difference in reactivity for the anomers.

based on intermediates with TBDMS ethers on the sugar ring and the other line of inquiry focused on protection group exchange.

2.2 TBDMS-path

2.2.1 MOM protection of 7

In the TBDMS-path, the silyl ethers on the sugar ring were retained while the glycerol moiety was protected as methoxymethyl (MOM) ethers. The main objective was to gauge whether the silyl ethers were compatible with cleavage of the 3-*O*-NAP group and subsequent esterification of the 3-position. It was also considered that the two different protection groups could allow selective deprotection, giving some flexibility in continuation of the investigations. If successful, it would mean that protection group exchange was unnecessary and the reaction pathway would become shorter, which of course was desired. The reaction conditions employed were an adaption of those described by Fuji *et al.*[60] (Scheme 31). Results summarized in Table 2.7.



Scheme 31: MOM protection of **7** with phosphorous pentoxide (P_2O_5) in dimethoxymethane (DMM).

By following the reaction on TLC it was found that the mixture only consisted of one UV

active compound after three hours for parallel 1 and 2 (Table 2.7). The starting material was fully converted after two hours, however, two compounds of higher polarity than the target product were still present. This was presumed to be partially MOM-protected derivatives. The reaction was left until only a single, highly non-polar compound was visible on TLC, after which the mixture was poured into an ice-cooled solution of sodium carbonate (Na_2CO_3), extracted with EtOAc, dried over $MgSO_4$ and purified by silica gel chromatography with EtOAc:*n*-pentane (1:5) as eluent. This gave the product 1-*O*-(2',3'-di-*O*-MOM)glycerol-2,4-di-*O*-TBDMS-3-*O*-NAP-6-*S*-acetyl-α-D-glucopyranoside (**8d**) as a faintly yellow oil.

Table 2.7: Results from MOM protection of **7** to **8d**.

Parallel	Starting material [mmol, g]	Product [mmol, g]	Yield [%]
1	0.071, 0.049	0.069, 0.053	97.1
2	0.111, 0.075	0.108, 0.083	97.6
3	0.386, 0.263	0.213, 0.164	55.2
4	1.101, 0.750	0.838, 0.644	76.1

The yield was much higher in the first two parallels than in the two last parallels. The last parallels also had a byproduct which was structurally clarified by NMR and MS analysis (Spectra in Appendix A.12) to be 1-*O*-(2',3'-di-*O*-methylene)glycerol-2,4-di-*O*-TBDMS-3-*O*-NAP-6-*S*-acetyl-α-D-glucopyranoside (**8ox**, Figure 2.4). **8ox** was produced in a yield of 13.8% (0.037 g, 0.053 mmol) from parallel 3, no yield for **8ox** was calculated for parallel 4.

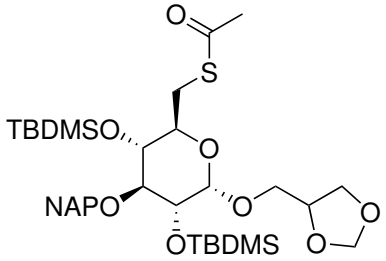
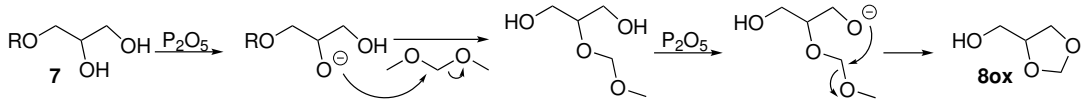


Figure 2.4: 1-*O*-(2',3'-di-*O*-methylene)glycerol-2,4-di-*O*-TBDMS-3-*O*-NAP-6-*S*-acetyl-α-D-glucopyranoside (**8ox**).

For parallel 3 the starting material was not completely evaporated, as ^{1}H NMR analysis showed presence of DCM residues. For the other parallels the starting material had been dried thoroughly. While P_2O_5 was dissolved slowly in DMM, likely at the rate it was consumed, a qualitative experiment revealed that DCM was much more effective in solubilizing P_2O_5. This meant that the concentration of P_2O_5 could have been slightly higher at any given time in parallel 3 than in the others. Parallel 1 and 2 were ran within a week of each other, where parallel 1 used DMM and P_2O_5 from brand new bottles. Parallel 3 and 4 were ran around a month later and for them TLC revealed that there were still starting material and partly protected material left after 3 hours. It also showed two faint spots around where the product was expected to be. All P_2O_5 had disappeared,

while for the first two parallels some P_2O_5 had still not been dissolved when the reaction was finished. Thus, more P_2O_5 (3 eqv.) were added to parallel 3 after three hours and the reaction was allowed to run for two more hours, before being terminated. For parallel 4 only one equivalent of P_2O_5 was added after all the initial P_2O_5 had disappeared and the reaction was instead left overnight. **8ox** was present in both parallel 3 and 4, but probably at a lower rate in parallel 4 as evidenced by the difference in reported yields for **8d** (Table 2.7). A possible mechanism is proposed for the formation of **8ox** in Scheme 32.



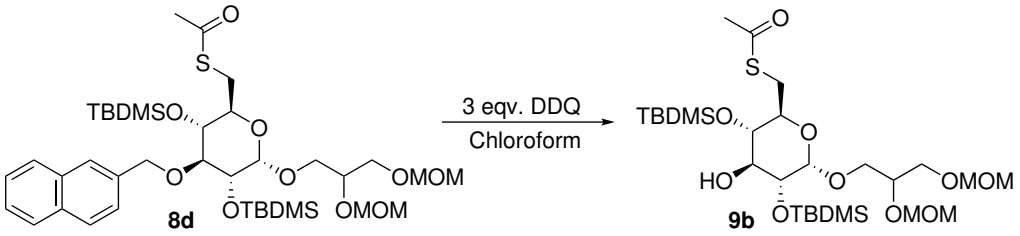
Scheme 32: Proposed mechanism for formation of **8ox** from **7**.

While the presence of DCM in parallel 3 could have influenced the reaction, it is more likely, given that the same byproduct was found in parallel 4, that the increased amount of P_2O_5 and/or the increase in reaction time contributes to the reduced yield and formation of byproduct. Niwa *et al.* produced the similarly pure acetal product in 85% yield by dissolving their starting material, a syn 1,2-diol, in DCM and adding 100 eqv. P_2O_5 together with 15 eqv. DMM and letting the solution stir for 1.5 hours at 50 °C.[89] From this as well, it is likely that larger equivalents of P_2O_5 is what causes the acetal formation, which also seems probable based on the lower yield in parallel 3 compared to parallel 4 (3 extra equivalents of P_2O_5 compared to 1 extra).

It seems clear that the disappearance of P_2O_5 and reduced reaction rate in parallel 3 and 4 are caused by the age of the chemicals which somehow altered the reaction progress. Most probable through absorption of water from the air over time, which in turn could have reduced their reactivity. In any case it became necessary to introduce harsher conditions, which in turn formed small amounts of unwanted by-product **8ox**. This was investigated more under the global MOM protection in Section 2.3, in which similar side reactions were observed.

2.2.2 NAP deprotection of 8d

The NAP deprotection of **8d** was carried out in accordance with the reaction conditions proposed by Xia *et al.*[67], but with chloroform ($CHCl_3$) instead of methanol (MeOH) and water as proposed by Verpalen *et al.*[69] (Scheme 33).



Scheme 33: NAP deprotection of **8d** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in $CHCl_3$ to form **9b**.

Analysis by ^{1}H NMR showed that all starting material was consumed after 10 hours, and the reaction was terminated by washing the solution through a short silica pad with EtOAc. Further evaporation of the filtrate under reduced pressure and purification by silica gel chromatography with EtOAc:*n*-pentane (1:12) yielded 1-*O*-(2',3'-di-*O*-MOM)glycerol-2,4-di-*O*-TBDMS-6-*S*-acetyl-α-D-glucopyranoside (**9b**) as a yellow oil. Results are shown in Table 2.8.

Table 2.8: Results from NAP deprotection of **8d**.

Parallel	Starting material [mmol, g]	Product [mmol, g]	Reaction time [h]	Yield [%]
1	0.093, 0.071	0.052, 0.033	24	56.6
2	0.130, 0.100	0.121, 0.076	12	92.3
3	0.831, 0.639	0.653, 0.411	10	78.7

For parallel 1 and 2 a slightly less polar eluent was used (EtOAc:*n*-pentane (1:10)) and some cleaved NAP residues coeluted with the target product. Thus, the recorded yields for these two parallels are likely slightly inaccurate. In parallel 3, in which the product was eluted with EtOAc:*n*-pentane (1:12), little coelution occured and the yield is more accurate. This is corroborated by ^{1}H NMR spectra (Figure 2.5), which clearly show the presence of aromatic protons (shifts between 8.1 and 7.5 ppm) in the product from parallel 2. The product in parallel 2 was also slightly miscoloured, with a yellow colour that had a more red hint than the product in parallel 3, probably because some DDQ residues coeluted as well. DDQ has an orange colour and no protons, which means it was not possible to conclude if it was present from the ^{1}H NMR spectrum.

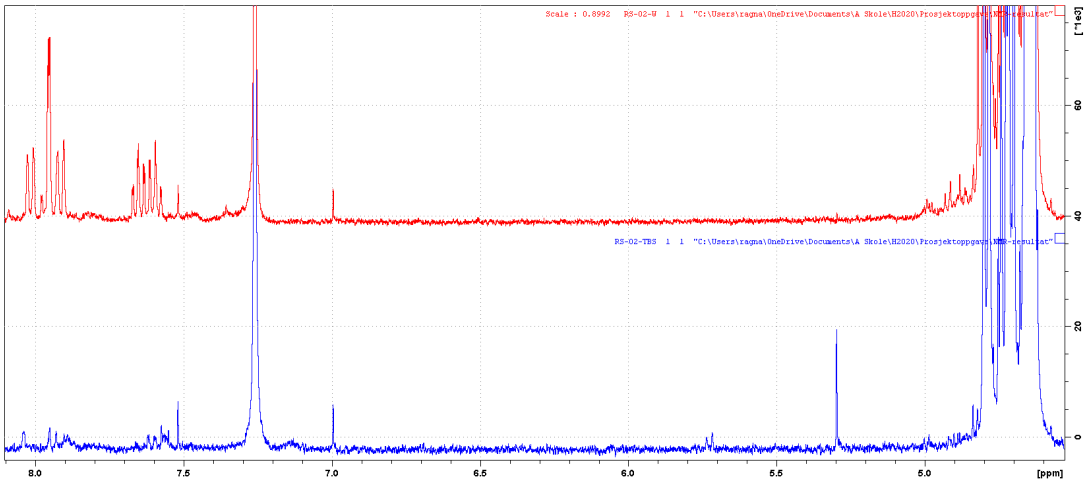


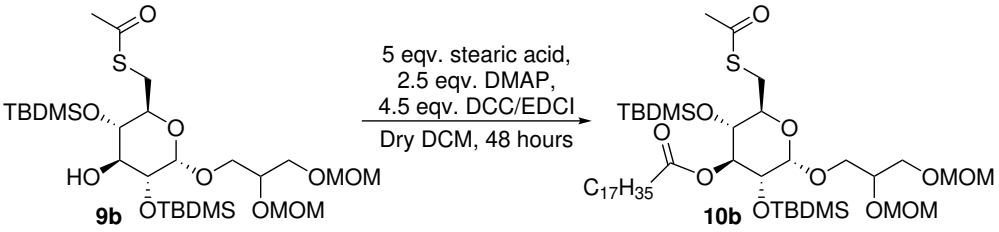
Figure 2.5: Comparison of ^{1}H NMR spectra for products from parallel 2 (red) and 3 (blue) in Table 2.8. Aromatic peaks between 8.1 and 7.5 ppm.

As expected from the literature, the TBDMS groups seemed to be intact. However, in the first parallel the reaction time was approximately twice as long as in the others, and gave a much lower yield. Since everything else was identical, it was presumed that the prolonged reaction time was the cause for the reduced yield, even though no final explanation could

be concluded from NMR analysis. If TBDMS ethers were cleaved off, as discussed in Section 1.3.3, the corresponding triol product would elute very slowly and probably be stuck on the silica gel with the weak eluent utilized here, which might be why NMR analysis did not provide any explanation. In any case, for the two last reactions, the NAP peaks were observed by ^{1}H NMR analysis. Since protons on the cleaved off aromatic rings had slightly higher shifts than those on **8d**, it was easy to see when to terminate the reaction.

2.2.3 Esterification

With the 3-OH functionality liberated (**9b**), Steglich esterification was attempted with both 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and *N,N*'-dicyclohexylcarbodiimide (DCC) as promotors. Reaction conditions were as described by Stenset,[4] who again based his conditions on the original article on Steglich esterification[75] (Scheme 34).



Scheme 34: Esterification on 3-*O* in **9b** formed **10b**.

Stenset originally stirred the reaction for 12 to 24 hours before termination. However, by monitoring the reactions by TLC, no conversion was observed. Nevertheless, after 48 hours it was decided to terminate the reaction and perform silica gel column chromatography, EtOAc:*n*-pentane (1:25) as eluent, in an attempt to verify whether any reaction had occured by either NMR or MS analysis. Results are summarized in Table 2.9.

Table 2.9: Results from the esterification of *3-O* on **9b**.

Promotor	Starting material [mmol, g]	Product [mmol, g]	Yield [%]
DCC	0.121, 0.076	0, 0	0
EDCI[2]	0.280, 0.176	0.022, 0.017	8.0

As seen in the table, no product was found for the reaction with DCC, neither by NMR or MS analysis. For the reaction with EDCI as promotor, there seemed to be some product which coeluted with stearic acid. NMR analysis was inconclusive, but MS indicated that trace residues of the product were present (Figure A.92). Due to coelution with stearic acid, the reported yield is inaccurate. In any case, even with the high reagent conditions, as well as prolonged reaction times (Scheme 34), Steglich esterification conditions are clearly unsuitable for 2,4-di-*O*-TBDMS protected intermediates. The findings corroborate Stensets observations regarding steric effects hampering this reaction. The small amount of

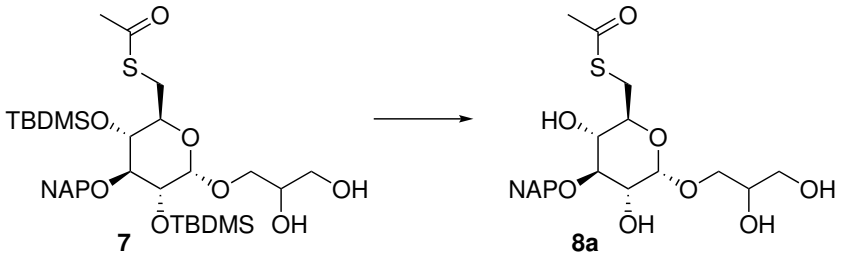
[2]Stearic acid residues in product sample.

product did also mean that no further reaction could be carried out for the TBDMS-path. Instead focus was shifted towards the MOM-path.

2.3 MOM-path

2.3.1 Silyl deprotection of 7

The MOM-path was initiated by cleavage of the silyl ethers in intermediate **7** to procure tetra-OH derivative **8a** (Scheme 35). As mentioned in Section 1.3.1, there are several literature methods available for silyl cleavage. Tetra-*n*-butylammonium fluoride (TBAF) was successfully used by Stenset,[4] though it should be noted that in that case there were no thioacetate groups present. Nevertheless, an excess (1.5 equivalents per TBDMS group) of TBAF in tetrahydrofuran (THF) at 0 °C was used as a starting point for experimentation.



Scheme 35: Deprotecting TBDMS groups on **7** would yield **8a**.

TLC monitoring (EtOAc:*n*-pentane (1:1)) indicated full conversion of the starting material after 1 hour, with one compound close to baseline (presumed product) and one compound close to the mobile phase front (presumed cleaved TBDMS). The reaction was quenched with water, THF evaporated, followed by extraction with EtOAc. ^{1}H NMR analysis of the crude product clearly indicated an impure product mix, and from the missing integral at around 2.34 ppm it was evident that the thioacetate moiety in 6-position had been cleaved. In an attempt to isolate the main components of the product mixture, silica gel column chromatography was conducted, starting with EtOAc:*n*-pentane (1:1) and gradually increasing the polarity by phasing out *n*-pentane and adding MeOH up to 10%. Fractions were analysed by TLC and gathered accordingly, however, further analysis by HPLC evinced significant coelution, with two main products present in the purest fraction (Figure 2.6).

Since it proved difficult to separate the compounds, an acetylation reaction was carried out, to see if the fully acetylated compound **8ac** (Figure 2.7) was formed. As the thioacetate methyl peak was missing it was presumed that the thioacetate had been reduced to a thiol by TBAF, in which case acetylation should have recovered it.

The partially purified product was acetylated by stirring in acetic anhydride:pyridine (1:1) overnight. The product from the acetylation reaction was compared with a ^{1}H NMR spectrum of **8ac**, which had previously been synthesised by the research group with the same reaction conditions for acetylation as used here.[3] By comparing the NMR spectra it seemed like **8ac** had not been formed (Figure 2.8).

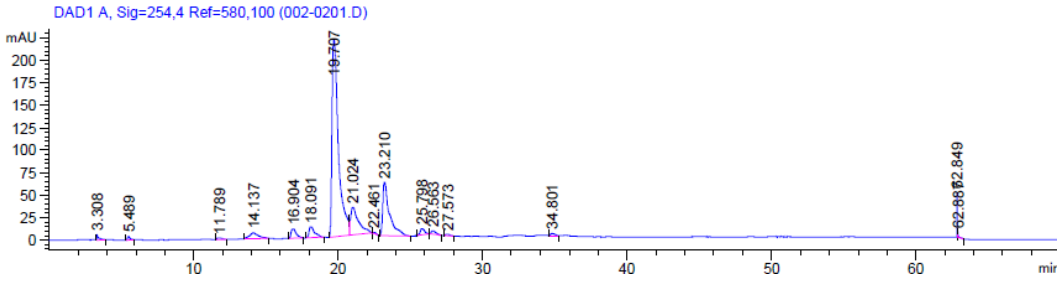


Figure 2.6: HPLC (Method Nico, 254nm) chromatogram of product mix after deprotection of **7** with TBAF.

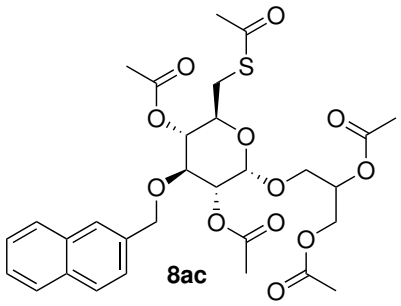


Figure 2.7: Acetylated compound **8ac**.

As mentioned, no previous literature of thioester cleavage with TBAF have been found. However, previous research on TBAF-catalysed deacylation of cellulose esters indicates that deacylation occurs rapidly by an E1cB mechanism on 2- and 3-*O*, while at the primary 6-*O* position it occurs at a much slower rate by a general base-catalysed mechanism.[90] The same research group did also report results which implied that a primary acetate group on cellulose esters were cleaved faster with TBAF than a secondary silyl ether (thexyldimethylsilyl ether).[91] While it is not directly transferable to the TBDMS deprotection of **7**, their results are still interesting when trying to figure out what happened with the thioester moiety.

In an effort to minimize cleavage of the thioester moiety, the reaction was run with exactly 1 equivalent of TBAF per TBDMS group. Assuming that the fluoride would be more selective for the silyl functionality than the carbonyl, it was hypothesized that lowering the TBAF concentration could minimize the cleavage of the thioacetate. However, the methyl peak around 2.33 ppm was once again absent in the ^{1}H NMR spectrum of the crude product, and it seemed like the thioacetate group indeed was cleaved faster than the TBDMS ethers. As the lowered amounts of TBAF still failed to provide the desired desilylated product and combined with the difficulties in purification and isolation of the product mixture, further experimentation with this desilylation method was discouraged. Slow addition of TBAF over time could have proved a possible solution to the problem, as thioacetate, based on the earlier mentioned mechanistic study, seemed to be cleaved by a general base-catalysed reaction. Slow addition would then possibly open up for fluoride attack on the silyl, while still maintaining a low enough pH level to prevent thioacetate cleavage.

Either way, it was instead decided to shift to silyl cleavage by hydrolytic means, which is also very commonly used. Trifluoroacetic acid (TFA) is often utilized, however, it is

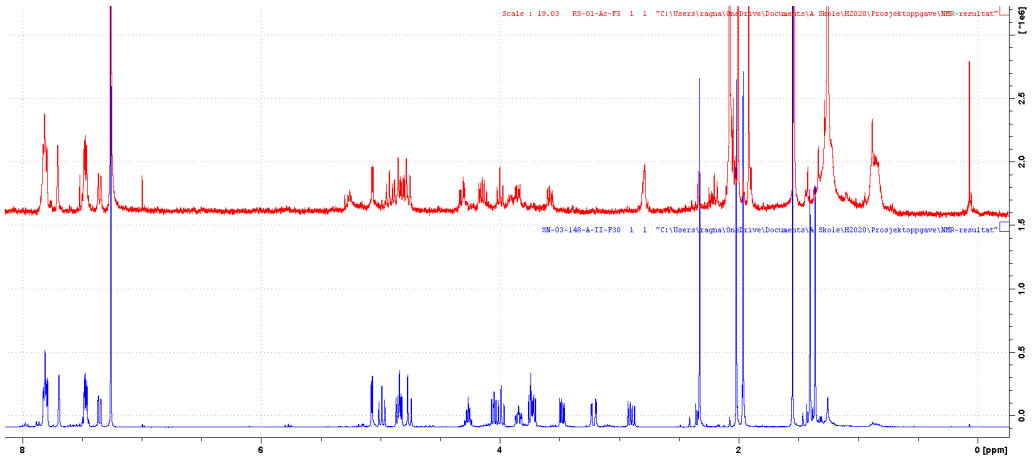
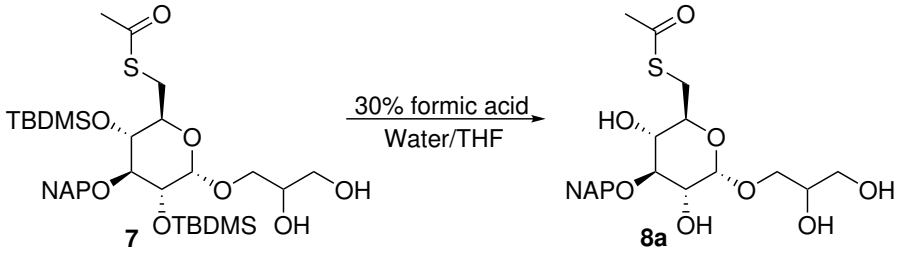


Figure 2.8: Comparison of the ^{1}H NMR spectra for **8ac** (blue) and the acetylated product mix from TBAF deprotection of **7** (red).

known to also hydrolyze NAP ethers,[92] rendering it unsuitable here. Instead, the formic acid deprotection of silyl ethers proposed by Kawahara *et al.*[49] seemed promising as a starting point (Scheme 36). Due to solubility problems, some THF was added to aid solvation of the somewhat non-polar **7**. Additional formic acid was added to maintain the desired concentration.



Scheme 36: Deprotection of **7** to **8a** with 30% formic acid.

Monitoring the reaction by TLC indicated very slow kinetics, and it was left over night before terminating it by addition of Na_2CO_3. The mixture was then extracted with EtOAc, dried over magnesium sulfate ($MgSO_4$) and purified by silica gel chromatography with EtOAc:*n*-pentane (1:2) as eluent, which gradually changed to pure EtOAc. This gave 1-*O*-glycerol-3-*O*-NAP-6-*S*-acetyl-α-D-glucopyranoside (**8a**) as a white oil. Results shown in Table 2.10.

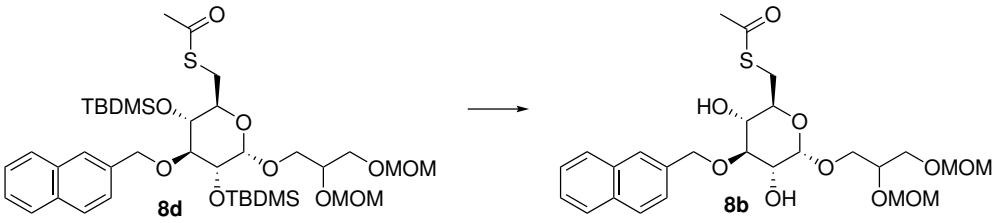
Table 2.10: Formic acid deprotection of **7** results.

Parallel	Starting material [mmol, g]	Product [mmol, g]	Yield [%]
1	0.108, 0.074	0.068, 0.031	62.7
2	0.382, 0.260	0.301, 0.136	78.7

For parallel 2 it should be noted that some of the product coeluted with partly deprotected **7**, so the reported yield is inaccurate. ^{1}H NMR analysis (Figure A.51) reveals the presence

of three compounds in the reaction mixture, which is seen by three methyl peaks in the range 2.34-2.39 ppm, corresponding to three individual thioacetate groups. None of the methyl peaks corresponds with the methyl peak in the ^{1}H NMR spectra of **7**. It did therefore seem likely that the mix contained the fully desilylated product **8a** as well as both of the partly desilylated 2-OH-4-*O*-TBDMS and 2-*O*-TBDMS-4-OH products. This implies a possibility of selective cleavage of one of the two TBDMS-protected hydroxyls, and consequently, the possibility of producing an intermediate with one MOM group and one TBDMS group on the sugar ring. Such an intermediate could possibly alleviate the steric constraints hampering conversion in the Steglich esterification step. No further attempt at separating the compounds was carried out, as it was assumed that eventual differences in reaction rates in the subsequent reactions could be seen by comparing the spectra of the products with the starting materials.

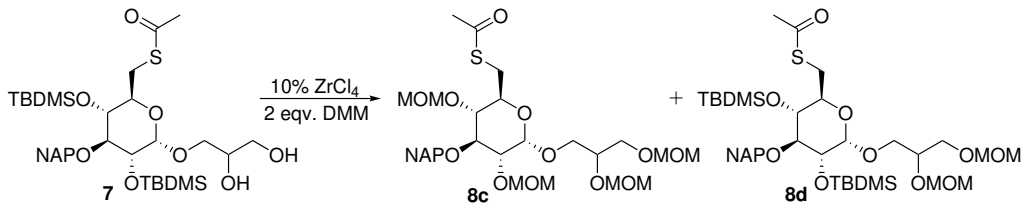
A selective TBDMS deprotection of **8d** into the ring unprotected compound **8b** was attempted (Scheme 37). Since MOM has been reported to be deprotected by formic acid,[93] only an attempt with 2 equivalents TBAF were tested. Based on the results from the TBAF deprotection of **8a** hopes were not high. As expected, the thioester methyl peak disappeared during reaction this time as well. Because **7** was more readily desilylated than **8d**, selective cleavage of silyl ethers in presence of MOM groups was not further investigated.



Scheme 37: Selective TBDMS deprotection of **8d** would have yielded **8b**.

2.3.2 Simultaneous silyl deprotection and MOM protection of 7

An interesting method for one-pot exchange of silyl ethers with MOM ethers has been published by Sharma *et al.*[66] The proposed conditions were employed in an effort to procure MOM-protected intermediate **8c** (Scheme 29). In this reaction, zirconium(IV) chloride (ZrCl4) appears to have a dual function as a catalyst for both silyl ether cleavage and MOM-protection. It was anticipated that even if the silyl exchange failed, the partially MOM-protected intermediate **8d** would be obtained as a side product (Scheme 38).



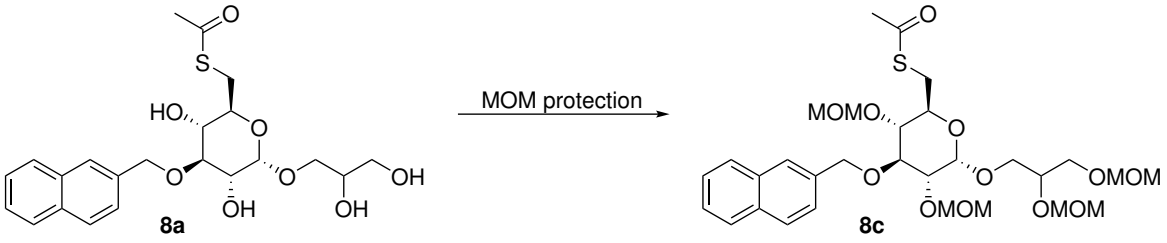
Scheme 38: Protection group exchange towards MOM-protected intermediate **8c** with partially MOM-protected **8d** as expected byproduct.

The reaction was allowed to stir for 48 hours, at which point TLC and ^{1}H NMR analysis showed that the solution only consisted of **7**, thus no reaction had taken place at all. Addition of more $ZrCl_4$ had no impact on the reaction. It was therefore carried out a new reaction with the same conditions, but with **8d** from the TBDMS path as starting material. The goal of the reaction was to see if the MOM ethers instead were cleaved off by $ZrCl_4$, in order to assess why the reaction had not taken place. This was reported as a possibility by Sharma *et al.* as well, but with higher concentration of $ZrCl_4$ in isopropanol. Due to the absence of nucleophilic solvent in this experiment, it was not thought likely that the ethers would be cleaved off. Again, no reaction occured, and as it seemed like these intermediates were not fit for this type of exchange reaction, the $ZrCl_4$ method was abandoned.

2.3.3 MOM protection of 8a

At this point it became evident that more **7** was needed, and this was the reason for the previously mentioned separation of **5** from anomerically impure obtained after column chromatography (Section 2.1.4). However, through subsequent reactions, only 150 mg of **7** was obtained. Due to delays in delivery of new chemicals, producing more intermediate from scratch was not an option. This meant that the limited amount of **7** synthesised, along with some small residues left from the TBDMS-path, were the only available for further reactions in the MOM-path.

As a consequence of the limited amount of starting material, only the product from the formic acid deprotection reaction (Table 2.10) was available for further reactions, i.e. 122 mg after samples for analysis were collected. It was assumed that **8a** could be protected with MOM by the same conditions employed in the MOM protection of glycerol hydroxyls in key intermediate **7** (Section 2.2.1). Due to the doubled amount of hydroxyls to be deprotonated, the addition of P_2O_5 was doubled to six equivalents, assuming that eliminating solvent residues and using neat DMM would keep the P_2O_5 concentration consistently low by limiting solubility, and thus preventing the formation of byproducts.



Scheme 39: Global MOM protection of **8a** would yield **8c**.

After 5 hours all P_2O_5 had disappeared and TLC with EtOAc:*n*-pentane (1:5) showed that at least two, quite polar compounds were present ($R_f < 0.15$). **8c** was expected to have a higher R_f-value than 0.15. **8d** sat very close to the solvent line with the same eluent, and while MOM groups were expected to be more polar than TBDMS groups, the difference in R_f-value was deemed to large to indicate formation of **8c**. Thus, three more equivalents P_2O_5 were added and the solution allowed to stir overnight before being terminated. However, after column chromatography, ^{1}H NMR analysis of product fractions again revealed the absence of the characteristic thioester methyl peak (Figure 2.9).

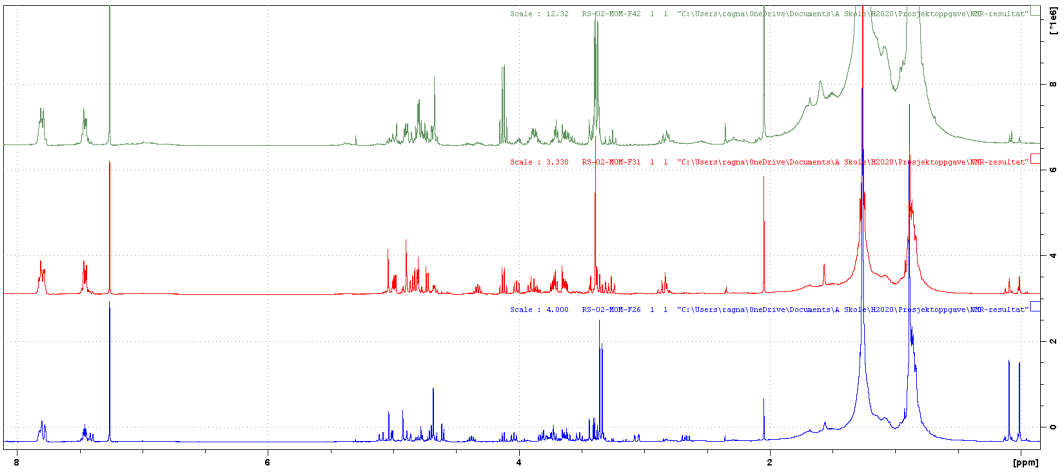


Figure 2.9: ^{1}H NMR spectra of fraction 26, 31 and 42. Thioester methyl peak expected as a tall singlet around 2.35 ppm, but no such peak was found.

The products eluted over a total of 17 fractions (30 mL each) with a total mass of 102 mg. Flushing the column with more polar eluent (EtOAc:*n*-pentane (1:1)) eluted a second product mixture with a mass of 43 mg. The ^{1}H NMR spectrum of this second product mixture clearly contains the thioester methyl peak, however, at only 20% of the expected integral (Figure 2.10). It became obvious that the reaction had failed, and with it the hopes of continuing the MOM path.

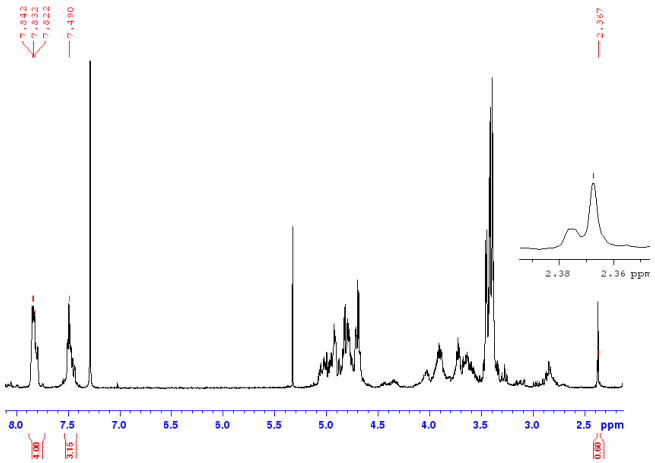


Figure 2.10: ^{1}H NMR spectrum of the fractions collected after fraction 42 which contained UV active compounds. Integrals of the aromatic protons and the relative integral of the thioester methyl protons are included.

From TLC it could be seen that all fractions from 26 to 42 contained various products. Since most of the fractions consisted of coeluted mixtures, which in turn made them difficult to analyse and identify, only the first and last fractions, 26 and 42, were fully characterised by the use of NMR, MS and IR analysis. See Appendix A.9 and A.10 for spectra. Analysis of fraction 26 seemed to imply it mostly consisted of 1-*O*-(2',3'-di-*O*-MOM)glycerol-2-*O*-MOM-3-*O*-NAP-4-*O*-TBDMS-6-*S*-MOM-α-D-glucopyranoside (**F26**, Figure 2.11).

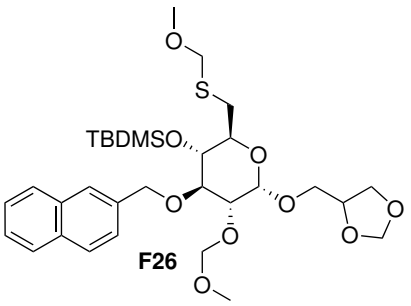


Figure 2.11: 1-*O*-(2',3'-di-*O*-MOM)glycerol-2-*O*-MOM-3-*O*-NAP-4-*O*-TBDMS-6-*S*-MOM-α-D-glucopyranoside (**F26**).

Similar to the previously discussed formic acid catalysed deprotection of **7** (Section 2.3.1), the 4-*O*-TBDMS ether moieties had survived the reaction. However, a previously unseen side reaction had occured on the 6-thio moiety. The ^{1}H NMR spectrum of the starting material clearly showed that the thioacetate methyl peak was present (Figure A.51), while here the thiol had been protected by a MOM group, forming a sulfide. No similar reaction has been found in the literature. The closest example are hydrolysis of a thioacetate into the thiol by reacting it with ammonia in ethanol and further reaction with MOM bromide and 1,8-diazabicyclo[5.4.0]undec-7-ene in DCM.[94] As P_2O_5 is a base, it was thought probable that it had formed the thiol through a similar base-catalysed hydrolysis of the thioacetate and then protected it with MOM through reaction with DMM.

For fraction 42, analysis suggested that the main compound in the fraction was the 4,6-methylene-bridged derivative **F42** (Figure 2.12). Structural characterisation of both **F26** and **F42** is elaborated in Section 2.4. 4-*O* and 6-*S* had, in similar fashion to the acetal formation described earlier for **8ox**, formed a 6-membered ring, probably through a similar mechanism to the one proposed in Scheme 32. The hydroxyl groups on the glycerol is protected by MOM, instead of as an acetal as they were in fraction 26. However, the acetal is slightly less polar than the MOM-groups, as discovered under the purification of **8d**, where **8ox** eluted first. Therefore, the corresponding glycerol acetal product with no 4,6-ring formation, as well as the corresponding tricyclic derivative, are probably present in the fractions in-between fraction 26 and 42 as well.

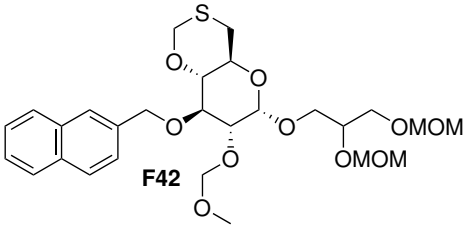
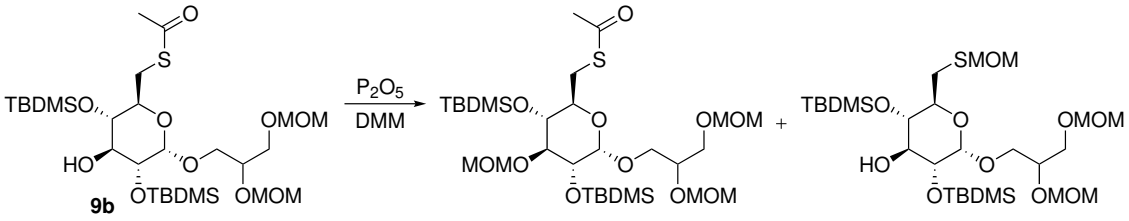


Figure 2.12: 4,6-methylene-bridged derivative **F42**.

From the formation of **F26** and **F42** one main question arise. Why did the thioacetate on **7** remain unchanged during the MOM protection of the hydroxyl groups on the glycerol, while it did not when the hydroxyl groups on the ring were to be protected? To gain a better understanding of this, the differences between the two reactions were examined. Three factors stood out: The starting material, the amount of P_2O_5 and the reaction time. Since only very small amounts of **7** and **8a** were left, saved for analysis, it was difficult

to conduct any similar experiments between them. Instead, the amount of P_2O_5 as well as reaction time could be tested. As the only compound with enough material to run two reactions with was product from the NAP deprotection reaction in the TBDMS path (**9b**), test reactions which aimed to see if MOM protection of 3-*O* on **9b** occured before or after modification of the thioacetate moiety was carried out. 120 mg of **9b** were dissolved in DMM and separated into two round bottomed flask, approximately 60 mg **9b** in each. P_2O_5, respectively 1 and 4 equivalents, were added to the stirred solutions (Scheme 40). Both reactions were followed on ^{1}H NMR with sampling after 1, 2, 3, 4 and 24 hours. After 24 hours, approximately 10 more equivalents P_2O_5 were added to the reaction with 4 equivalents from before and a new ^{1}H NMR sample was taken after further 24 hours.



Scheme 40: MOM protection of **9b** was carried out in order to see if 3-*O* or the 6-thio moiety were protected first.

In both reactions, the thioacetate group was intact after 24 hours (Figure 2.13 and 2.14), but from Figure 2.14 it can be seen that the thioacetate methyl peak is absent after 48 hours (see the orange line compared to the rest) after the addition of more P_2O_5.

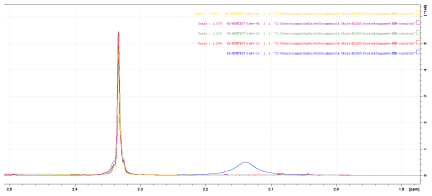


Figure 2.13: Comparison of ^{1}H NMR spectra for the reaction with 1 equivalent P_2O_5.

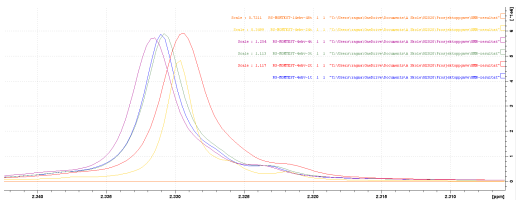


Figure 2.14: Comparison of ^{1}H NMR spectra for the reaction with 4-14 equivalents P_2O_5.

It is also worth noting that after 48 hours the TBDMS peaks, in the range of 0 and 0.18 ppm as well as between 0.8 and 0.9 ppm, had disappeared, while a new peak at 12.63 ppm was present (Figure 2.15). Peaks with shifts these high indicates that a highly acidic proton is probably present in the sample.[95]

P_2O_5 is known to react with water and form phosphoric acid (H_3PO_4).[96] H_3PO_4 have been reported to both cleave TBDMS ethers[97] and in addition, it can probably reduce thioacetate into a thiol as it has been reported to do the same with acetates to alcohols.[98] It was therefore hypothesised that H_3PO_4 had been formed due to water in the system, which again could explain why both the thioacetate was likely reduced and also why the TBDMS ether signals vanished. Examples of MOM protection on thiols are abundant in the literature.[99,100] To check whether water indeed was in the system, a ^{1}H NMR spectrum of DMM was acquired. However, no water peak at the expected chemical shift of 1.56 ppm[101] could be observed (Figure 2.16).

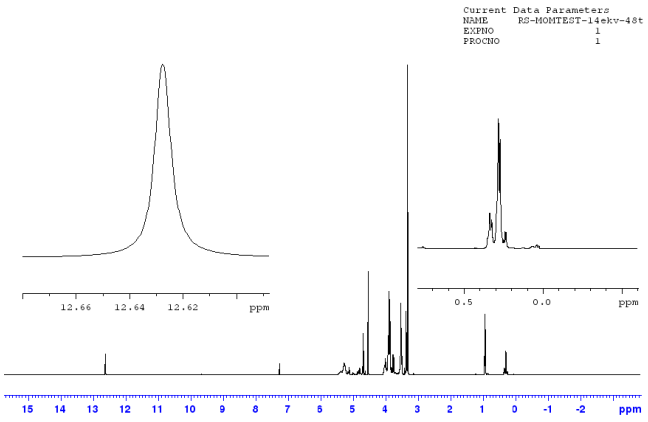


Figure 2.15: ^{1}H NMR spectrum of the reaction with **9b** and 14 equivalents P_2O_5 after 48 hours.

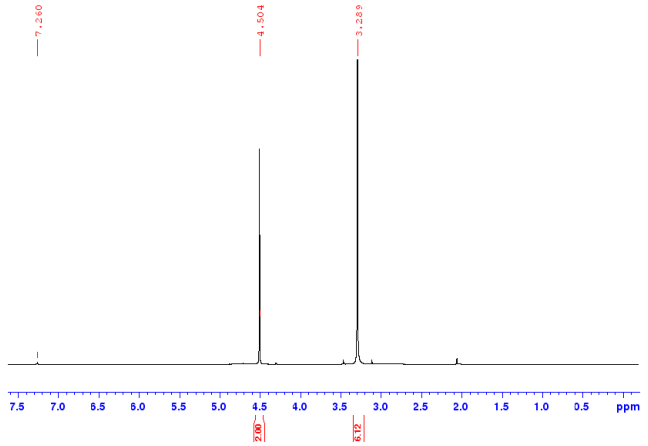


Figure 2.16: ^{1}H NMR spectrum of DMM used in reactions for this project.

As no water was found in the system, it did not seem likely that formation of H_3PO_4 was the problem. A more thorough investigation into the reaction and its conditions are probably needed in order to gain an understanding of what went wrong. It does in any case seem like the high concentration of P_2O_5 is the cause for the formation of byproducts and that formation of globally MOM-protected **8c** from **8a** could have been performed in good yields by using milder conditions. Byproducts also only seem to be formed when additional P_2O_5 are added after the reaction have been allowed to go for a while. However, this is most likely because of the higher concentration of P_2O_5 in the reaction, not because it is added at a later stage. As such, the lack of more suitable intermediate is regrettable, as more investigation could have clarified these issues.

2.4 Spectroscopic characterisation

Since most compounds synthesised in this project are novel, detailed spectroscopic data for each novel compound are listed herein. For compound **2** and **3**, NMR corresponded with previously reported spectra.[102] For most compounds ^{1}H NMR, ^{13}C NMR, COSY, HSQC and HMBC experiments were enough to elucidate the structure, with the exception of the TBDMS and some of the aromatic shifts. MS and IR analysis were used to confirm the results found from NMR analysis.

2.4.1 NMR

Since the products obtained in this project are structurally similar, a general structure with numbered positions is shown in Figure 2.17 to simplify understanding of the reported shifts and coupling constants. For compounds **F26** and **F42** numbering of the carbons are given in Figure 2.18, due to their somewhat different nature compared to the rest of the compounds. Their characterisation will also be further elaborated to explain the thought process in the elucidation of their somewhat unexpected structures. Solvent impurities are present in most spectra, these signals were identified using the tables provided by Fulmer *et al.* and thereafter ignored during the characterisation.[101] For **8a** it was not possible to accurately interpret the spectra as the product mix consisted of products in approximately equal concentrations, making it difficult to distinguish signals in the 2D NMR spectra.

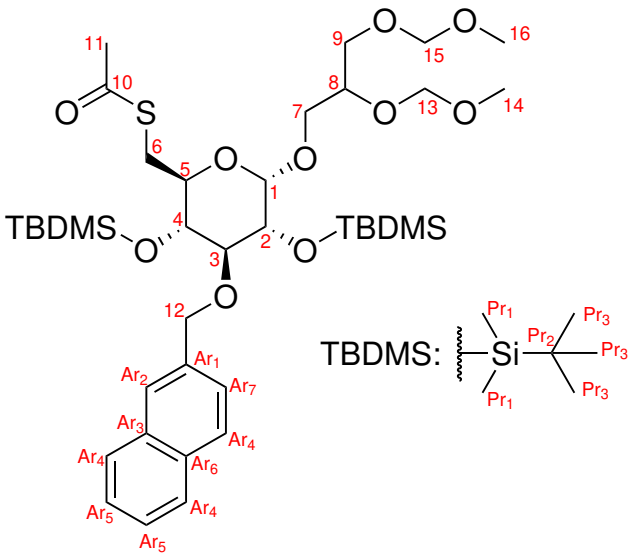


Figure 2.17: General structure for synthesised compounds in this project, with numbered positions.

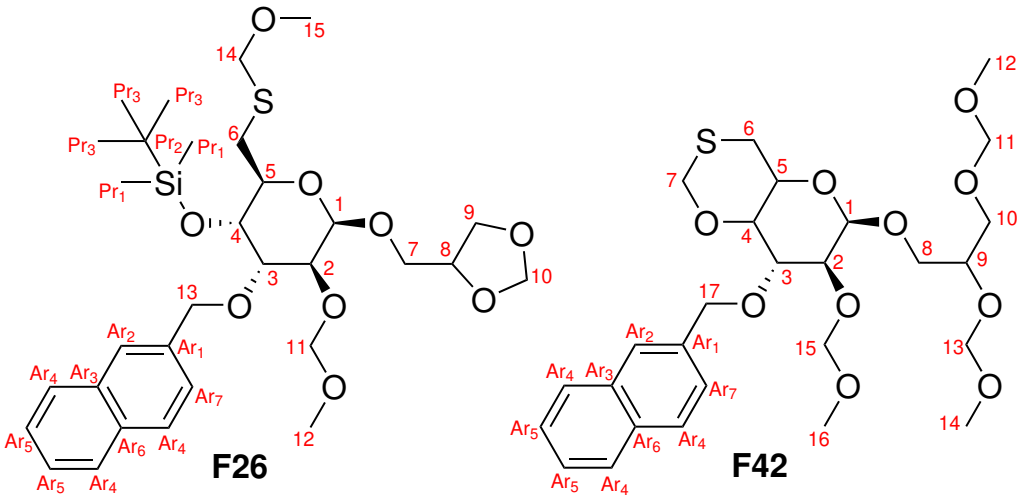


Figure 2.18: Byproducts **F26** and **F42** with numbered positions.

Proton chemical shifts are given in Table 2.11.

Table 2.11: Hydrogen shifts in ppm for synthesised compounds, relative to TMS in $CDCl_3$. For **8ox** the acetal atoms are given number 13. For hydrogens which are coupled to the same carbon, but with different shifts, subscripts a and b are added to separate them. For TBDMS protons an average shift value is given to save space, as they are not of much interest. For **10b** the carbonyl carbon is numbered as number 12.

H	**3bi**	**4α**	**4β**	**5β**	**6α**	**6β**	**7**	**8d**	**8ox**	**9b**	**10b**	**F26**	**F42**
1	4.93	4.78	4.31	4.37	4.75	4.28	4.72	4.69	4.76	4.66	4.72	5.00	4.91
2	4.39	3.77	3.59	3.61	3.80	3.62	3.79	3.77	3.77	3.49	3.70	3.64	3.62
3	4.22	3.75	3.40	3.43	3.71	3.38	3.64	3.66	3.65	3.68	5.35	3.74	3.89
4	4.26	3.57	3.64	3.36	3.46	3.50	3.46	3.45	3.45	3.33	3.55	3.52	3.25
5	4.07	3.65	3.27	3.66	3.74	3.31	3.72	3.70	3.71	3.66	3.75	3.79	3.88
6a	3.71	3.72	3.73	3.68	2.81	2.73	2.80	2.80	2.78	2.86	2.87	2.67	2.80
6b	3.82	3.89	3.87	3.86	3.65	3.72	3.64	3.64	3.65	3.58	3.58	3.07	2.85
7a	3.99	4.03	4.08	4.13	4.00	4.09	3.46	3.48	3.57	3.45	3.44	3.62	4.80
7b	4.24	4.24	4.36	4.34	4.24	4.35	3.94	3.90	3.73	3.86	3.89	3.82	4.80
8	5.90	5.98	5.98	5.98	5.96	5.96	3.94	4.00	4.29	3.94	3.96	4.39	3.74
9a	5.20	5.23	5.23	5.22	5.22	5.22	3.72	3.70	3.76	3.66	3.69	3.72	4.00
9b	5.30	5.35	5.35	5.31	5.36	5.31	3.79	3.70	4.01	3.66	3.69	4.04	4.00
10	7.46	-	-	-	-	-	-	-	-	-	-	4.98	3.71
11	-	-	-	-	2.36	2.35	2.36	2.35	2.36	2.33	2.35	4.65	4.75
12a	4.74	4.86	4.92	4.94	4.86	4.93	4.88	4.84	4.85	-	-	3.34	3.39
12b	4.93	5.25	5.16	5.15	5.22	5.13	5.16	5.18	5.20	-	-	-	-
13a	-	-	-	-	-	-	-	4.75	4.92	4.72	4.75	4.88	4.76
13b	-	-	-	-	-	-	-	4.84	5.03	4.79	4.75	5.10	4.76
14	-	-	-	-	-	-	-	3.44	-	3.40	3.42	4.68	3.40
15	-	-	-	-	-	-	-	4.67	-	4.64	4.66	3.36	4.67
16	-	-	-	-	-	-	-	3.40	-	3.37	3.38	-	3.37
Ar_1	-	-	-	-	-	-	-	-	-	-	-	-	-
Ar_2	7.79	7.80	7.80	7.80	7.80	7.80	7.80	7.79	7.80	-	-	7.78	7.79
Ar_3	-	-	-	-	-	-	-	-	-	-	-	-	-
Ar_4	7.80	7.80	7.80	7.80	7.80	7.80	7.80	7.80	7.80	-	-	7.81	7.81
Ar_5	7.48	7.44	7.44	7.44	7.45	7.45	7.46	7.45	7.45	-	-	7.46	7.46
Ar_6	-	-	-	-	-	-	-	-	-	-	-	-	-
Ar_7	7.46	7.39	7.39	7.36	7.37	7.37	7.36	7.38	7.37	-	-	7.41	7.45
Pr_1	-	-0.02	-0.02	-0.02	-0.01	-0.01	0.01	0.00	0.00	0.12	0.04	0.06	-
Pr_2	-	-	-	-	-	-	-	-	-	-	-	-	-
Pr_3	-	0.86	0.86	0.81	0.83	0.83	0.84	0.84	0.84	0.91	0.85	0.90	-

Carbon chemical shifts are given in Table 2.12.

Table 2.12: Carbon shifts in ppm for synthesised compounds, relative to TMS in $CDCl_3$. For 8ox the dioxolane atoms are given number 13. For TBDMS carbons, an average shift value is given to save space, as they are not of much interest.

C	**3bi**	**4α**	**4β**	**5β**	**6α**	**6β**	**7**	**8d**	**8ox**	**9b**	**10b**	**F26**	**F42**
1	107.7	97.8	102.3	103.0	97.8	102.4	100.0	99.3	99.2	98.9	98.6	98.3	99.1
2	79.4	74.7	75.9	75.6	74.5	75.7	74.3	74.5	74.4	73.8	72.3	80.3	78.4
3	84.6	82.6	86.6	86.3	82.2	86.2	82.2	82.0	82.1	74.1	75.9	81.2	78.5
4	79.5	71.1	70.9	76.7	74.7	74.7	74.5	74.6	74.5	74.8	73.4	74.1	84.5
5	71.2	73.3	77.5	71.0	71.2	75.8	71.6	71.2	71.4	70.9	70.6	72.9	65.5
6	64.3	63.0	62.8	62.4	32.0	32.2	31.8	31.9	31.9	31.6	31.7	32.3	31.5
7	69.0	68.3	70.2	71.1	68.5	70.6	71.2	68.2	68.1	68.3	67.8	68.4	70.5
8	134.0	134.3	134.4	134.3	134.0	134.1	70.3	74.4	74.3	74.4	74.5	74.5	68.4
9	117.6	118.0	117.7	118.0	118.3	118.2	64.2	67.9	67.4	67.8	67.8	67.4	74.6
10	-	-	-	-	195.1	195.2	195.1	195.1	195.1	195.0	194.9	95.5	67.6
11	-	-	-	-	30.7	30.6	30.7	30.6	30.7	30.6	30.6	97.9	97.7
12	72.7	74.8	75.0	75.1	74.8	75.1	75.0	74.8	74.8	-	166.0	55.6	55.6
13	-	-	-	-	-	-	-	96.2	95.5	96.3	96.3	75.0	96.3
14	-	-	-	-	-	-	-	55.7	-	55.6	55.7	76.1	55.6
15	-	-	-	-	-	-	-	96.9	-	96.9	96.9	56.0	97.0
16	-	-	-	-	-	-	-	55.5	-	55.4	55.5	-	55.6
17	-	-	-	-	-	-	-	-	-	-	-	-	75.7
Ar_1	134.7	137.2	136.9	136.7	137.0	136.7	136.7	136.9	136.9	-	-	136.8	136.5
Ar_2	127.0	124.7	124.5	124.6	124.7	124.7	124.7	124.8	124.7	-	-	125.4	126.0
Ar_3	133.4	133.5	133.5	133.4	133.5	133.4	133.4	133.4	133.4	-	-	133.5	133.5
Ar_4	128.3	127.8	127.8	127.8	127.8	127.8	127.8	127.8	127.8	-	-	127.9	128.0
Ar_5	126.5	125.7	125.7	125.7	125.7	125.7	125.8	125.7	125.7	-	-	125.7	126.1
Ar_6	133.3	132.7	132.6	132.6	132.6	132.7	132.7	132.7	132.7	-	-	132.9	133.1
Ar_7	125.7	124.8	124.6	124.4	124.7	124.5	124.6	124.7	124.7	-	-	125.3	125.6
Pr_1	-	-4.5	-4.2	-4.0	-4.0	-4.0	-4.2	-4.2	-4.2	-4.3	-4.1	-3.9	-
Pr_2	-	18.3	18.2	18.2	18.1	18.1	18.2	18.1	18.1	18.3	18.1	18.2	-
Pr_3	-	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	26.0	25.9	26.1	-

Coupling constants, where found, for the sugar ring protons are given in Table 2.13.

Table 2.13: Coupling constants in Hz, for sugar ring protons where they could be resolved.

	$J_{\mathrm{H1,H2}}$	$J_{\mathrm{H2,H3}}$	$J_{\mathrm{H3,H4}}$	$J_{\mathrm{H4,H5}}$	$J_{\mathrm{H5,H6a}}$	$J_{\mathrm{H5,H6b}}$
2	3.6	0.0	3.1	7.8	5.8	6.0
3bi	1.7	3.1	6.4	8.8	5.5	3.3
4α	3.4	9.3	8.0	9.5	6.6	5.3
4β	7.5	8.7	8.7	9.2	5.8	2.2
5β	7.5	8.8	8.8	9.0	6.0	2.8
6α	3.7	9.3	9.0	9.0	9.5	2.6
6β	7.6	8.7	8.7	8.9	10.1	2.6
7	3.7	9.3	UR	UR	9.5	UR
8d	3.6	9.3	UR	UR	9.5	UR
9b	3.7	9.3	UR	UR	8.9	2.8
10b	UR	UR	UR	UR	9.3	UR
8ox	3.7	UR	UR	UR	9.4	UR
F26	3.7	UR	UR	UR	8.7	UR
F42	UR	UR	UR	UR	UR	UR

As mentioned, the structural characterisation of **F26** and **F42** requires further explanation. The structure of **F42** was particularly unexpected, and thorough investigation into the NMR spectra was needed to find the correct structure. For both compounds analysis of the HMBC spectra were very important. By looking at which protons the carbons on the sugar ring had long-range couplings, it was possible to localise which positions the substitution groups were attached to. For **F42** it became clear that the compound had formed a new ring as both C-4 and C-6 coupled to the same protons on C-7. By similar logic it was determined that 2-*O* was MOM protected, while 4-*O* was TBDMS protected in **F26**. The original ring carbons and protons could be determined from the COSY and HSQC spectra, as the anomeric proton had a higher shift than the rest of the ring protons, due to it being part of an acetal.

2.4.2 Mass spectroscopy

The structure of compounds **8a** and **10b** were not possible to confirm by NMR alone. In liaison with mass spectroscopy they were, however, both confirmed. For **10b**, a peak at $m/z = 917.5634$ was found, as expected. The sample of **8a** found the expected peak at $m/z = 589.2275$, alongside the mass of partially deprotected **7**, where only one of the TBDMS groups was cleaved off, at $m/z = 589.2275$.

2.4.3 Infrared spectroscopy

The IR spectra, presented in Appendix A, were compatible with the results from NMR and MS. Alcohol groups showed as broad peaks around $3400\,\mathrm{cm}^{-1}$, C-H stretching typical

for alkenes and aromatic compounds was found around 3000 cm^{-1} and other typical signals from 1100 to 700 cm^{-1} for functional groups such as ethers, alcohols, alkenes and substituted aromatic compounds were also observed. After insertion of the thioacetate ester on C-6, a sharp peak at around 1696 cm^{-1} occurred, which fits well with the expected signal for the carbonyl.[95] As seen in the IR spectra for **F26** and **F42**, the thioacetate peak is gone (Figure A.63 and A.70).

2.4.4 Optical rotation

The specific rotation values for **7** and the compounds synthesised from it were all in the range from 28 to 80° at 20 °C. See Section 4 for specific values for each compound. While no literature reference values were found, the research group has earlier found that pure α-glucopyranosides seems to have positive specific optical rotation values in the same range.[4]

3 Conclusion and further work

The work presented herein was performed as part of an investigation into the total synthesis of 3-*O*-acylsulfoquinovosyl glycerols. Synthesis of intermediate **7** was performed through a new, shortened route in acceptable yields, and two paths were tested for further functionalization. The TBDMS path showed that TBDMS protection groups are not a viable option on 2- and 4-*O* under the esterification reaction as only a minimal yield of under 8% was obtained, likely due to steric hindrance. However, the TBDMS path proved that the NAP group could be cleaved in good yields by the use of DDQ in chloroform and it also indicated a viable option for MOM protection of the glycerol hydroxyls, which could possibly work for the whole ring as well. The MOM path experienced some difficulties. Deprotection with TBAF was unsuccessful due to side reaction at the thioacetate position. Deprotection with formic acid was successful, however, optimization is required in order to get pure **8a**. MOM protection of desilylated intermediates failed, probably due to inappropriately high basicity. However, test reactions indicated that this can be achieved by further experimentation with milder conditions. As such, the protection group exchange from silyl to MOM ether could still be a viable option in further synthesis work towards the target 3-*O*-acylsulfoquinovosyl glycerols.

For future work it would definitely be interesting to see if the MOM path indeed works as hoped. Optimization in the formation of **8a** and **8c** would mean that the NAP group could be cleaved off in probably around the same yields as reported in the formation of **9b**. The lower steric crowding of corresponding MOM protected intermediates could potentially be better suited for Steglich esterification under the same conditions employed in this project, or milder. The reported literature procedure for deprotection of MOM groups with TMSBr are highly interesting, as this could potentially enable the synthesis of unsaturated 3-*O*-acylsulfoquinovosyl glycerols, such as the linolenoyl group which was originally found in the natural product extracted from *Schlerochloa dura*. It would also be interesting to see if it is possible to introduce MOM ethers as protection groups from the start, however, this could potentially affect the diastereomeric selectivity of the allylic double bond as TBDMS ethers at the sugar ring seems to be nearly completely selective when dihydroxylating the allylic chain with AD-mix-β. In any case, it would mean that a method for removal of a primary MOM group in presence of secondary ones will need to be found, such that the thioacetate can be introduced at C-6. If the dihydroxylation persists to be diastereoselective with MOM ethers, it would remove the need for deprotection of TBDMS as well as probably reduce the difficulties found under the MOM protection of **8a**, as only the glycerol would need to be protected after the dihydroxylation reaction. This has already been done in good yields from **7** to **8d**.

4 Experimental

4.1 General info about chemicals and methods

Chemicals were purchased from commercial vendors and used without further purification. Solvent evaporation was performed with a rotary evaporator in a water bath at 40 °C. All reactions were carried out in oven-dried glassware (80 °C). Dry solvents were collected from a *Braun* MB SPS-800 Solvent Purification System.

4.1.1 Thin-layer chromatography (TLC)

TLC was used to monitor reactions, check eluent systems before column chromatography and to confirm which fractions contained product after purification on column chromatography. Silica gel on aluminium (60 Å, F_{254}, *Merck*) was used. Visualisation was achieved by UV light (254 nm) for aromatic compounds and staining with $KMnO_4$ for non-aromatic compounds.

4.1.2 High-performance liquid chromatography (HPLC)

Analytical HPLC analysis was performed using an *Agilent Technology* 1290 Infinity instrument with a G4220B binary pump, G4226A autosampler, G1316A column compartment and G1315D diode array detector. A Zorbax Eclipse XDB-C18 column (150 mm x 21.2 mm, 5 µm particle size) was used.

Agilent Technologies ChemStation for LC and CE systems software (version: B.04.03 SPI[87]) was used for automation and processing. Solvents were analytical (HPLC) grade, and the water *Milli-Q* purified. A flow of 1 mL/ min and a column temperature of 25 °C were used.

Method Nico: Gradient from MeCN:H_2O 80:20 to 100% MeCN over 50 minutes. Ending with isocratic elution at 100% MeCN for 10 minutes.

4.1.3 Column chromatography

Column chromatography was performed using silica gel from *Sigma Aldrich* (40 - 63 µm).

4.1.4 NMR spectroscopy

NMR spectra for analysis were recorded using a *Bruker* 600 MHz Avance III, operating at 600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR. A *Bruker* 400 MHz Avance II operating at 400 MHz for ^{1}H NMR was used for checking fractions from column chromatography. For all NMR spectra, chemical shifts are expressed as δ (ppm), relative to TMS, and coupling constants (J) are in Hertz. All spectra were processed using *Bruker* TopSpin 3.6.2. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

4.1.5 MS spectroscopy

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

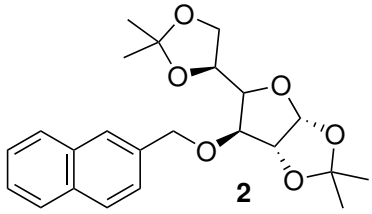
4.1.6 IR spectroscopy

IR spectra were recorded as a thin film, using a *Bruker* Alpha FTIR ECO-ATR spectrometer with OPUS software.

4.1.7 Optical rotation

Optical rotation was recorded using an *Anton Paar* MCP 5100 polarimeter, with a 2.5 mm or a 10 mm stainless steel sample holder, using the sodium D-line (589 nm) and temperatures at 20 or 25 °C.

4.2 Synthesis of 1,2;5,6-di-*O*-isopropylidene-3-*O*-NAP-α-D-glucofuranose (2)



2

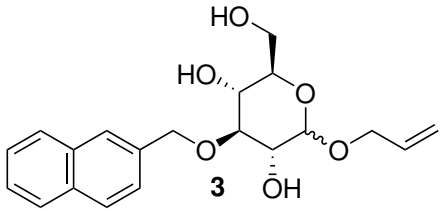
1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**) (3.000 g, 11.526 mmol) was dissolved in dry MeCN at 0 °C. NaH (3 eqv.) and 2-(bromomethyl)naphthalene (1.5 eqv.) was added and the solution was allowed to rise to room temperature. After 3 hours the reaction was quenched by addition of water and extracted three times with DCM (50 mL) before the organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2) gave **2** as a yellow oil (4.556 g, 11.376 mmol, 98.7%).

HRMS (ESI+) *m/z*: [M+Na] calcd. for $C_{23}H_{28}O_6Na$ 423.1784, found 423.1788; IR (cm^{-1}): 2928, 1371, 1214, 1165, 1062, 1020, 849, 817, 751, 476.

^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.86 – 7.79 (*m*, 4H), 7.50 - 7.45 (*m*, 3H), 5.93 (*d*, *J* = 3.6 Hz, 1H), 4.83 (*d*, *J* = 12.0 Hz, 2H), 4.80 (*d*, *J* = 12.0 Hz, 1H), 4.64 (*d*, *J* = 3.6 Hz, 1H), 4.42 (*m*, 1H), 4.19 – 4.10 (*m*, 2H), 4.09 (*d*, *J* = 3.1 Hz, 1H), 4.04 (*dd*, *J* = 8.6, 5.8 Hz, 1H), 1.50 (*s*, 3H), 1.44 (*s*, 3H), 1.40 (*s*, 3H), 1.32 (*s*, 3H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 135.2, 133.4, 133.2, 128.4, 128.0, 127.8, 126.6, 126.3, 126.1, 125.8, 112.0, 109.2, 105.5, 82.9, 81.8, 81.5, 72.7, 72.6, 67.6, 27.0, 27.0, 26.4, 25.6. NMR corresponds with previously reported spectra.[102]

4.3 Synthesis of 1-*O*-allyl-3-*O*-NAP-D-glucopyranoside (3)



2 (4.061 g, 15.600 mmol) was dissolved in All-OH (100 mL). HCl (1.6 eqv.) added and the solution warmed to 110 °C with reflux for 30 minutes. The reaction was terminated with Et_3N, evaporated under reduced pressure and purified by column chromatography (SiO_2, *n*-pentane:EtOAc 1:1). The product **3** was obtained as a yellow oil (4.665 g, 12.944 mmol, 83.0%).

m/z: [M+Na] calcd. for $C_{20}H_{24}O_6Na$ 383.1471, found 383.1476; IR (cm^{-1}): 3415, 2921, 1034, 819, 476.

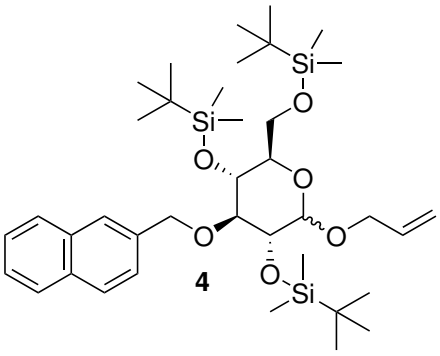
3α: ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.87 - 7.81 (*m*, 4H), 7.54 - 7.52 (*m*, 3H), 5.93 (*m*, 1H), 5.32 (*m*, 1H), 5.25 (*m*, 1H), 5.21 (*d*, J = 11.7 Hz, 1H), 4.93 (*d*, J = 3.8, 4.90 (*t*, J = 11.8 Hz, 1H)), 4.24 (*m*, 1H), 4.06 (*m*, 1H), 3.84 (*ddd*, J = 11.7, 5.3, 3.7 Hz, 1H), 3.78 (*ddd*, J = 7.1, 4.7 Hz, 1H), 3.73 (*td*, J = 9.3, 3.9 Hz, 1H), 3.70 (*m*, 1H), 3.67 (*t*, J = 8.9 Hz, 1H), 3.61 (*ddd*, J = 9.1, 6.1, 2.2, 1H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 135.8, 133.4, 133.1, 128.5, 128.0, 126.7, 126.3, 126.1, 125.8, 118.3, 97.7, 82.9, 75.0, 73.0, 71.1, 70.3, 68.7, 62.6. NMR corresponds with previously reported spectra.[102]

3β: ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.88 - 7.80 (*m*, 4H), 7.54 -7.45 (*m*, 3H), 5.94 (*m*, 1H), 5.32 (*m*, 1H), 5.24 (*m*, 1H), 5.17 (*d*, J = 11.8 Hz, 1H), 4.93 (*d*, J = 11.8 Hz, 1H), 4.37 (*d*, J = 7.7 Hz, H-1), 4.37 (*m*, 1H), 4.14 (*m*, 1H), 3.88 (*dd*, J = 12.0, 3.6 Hz, 1H), 3.78 (*dd*, J = 11.8, 5.0 Hz, 1H), 3.63 (*m*, 1H), 3.58 (*dd*, J = 9.2, 7.8 Hz, 1H), 3.48 (*m*, 1H), 3.36 (*ddd*, J = 9.6, 5.0, 3.6 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 135.9, 133.6, 133.3, 133.1, 128.6, 128.0, 127.8, 126.9, 126.3, 126.3, 126.1, 125.8, 118.2, 102.0, 83.5, 75.2, 74.8, 74.6, 70.6, 70.3, 62.6. NMR corresponds with previously reported spectra.[102]

4.4 Synthesis of 1-*O*-allyl-2,4,6-tri-*O*-TBDMS-3-*O*-NAP-D-glucopyranoside (4)



4

3 (4.284 g, 11.886 mmol) was dissolved in dry DCM and cooled to 0 °C. 2,6-lutidine (4.5 eqv.) and TBDMS-OTf (6 eqv.) was then added dropwise. After stirring for 10 hours at 0 °C the reaction was allowed to rise to room temperatuer over night before being quenched by addition of water, extracted three times with DCM (100 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, DCM:*n*-pentane 1:1) gave **4** as a yellow oil (7.314 g, 10.401 mmol, 87.5%).

m/z: [M+NH_4] calcd. for $C_{38}H_{70}NO_6Si_3$ 720.4511, found 720.4512; IR (cm^{-1}): 2929, 2857, 2173, 1254, 1081, 836, 778, 481, 418.

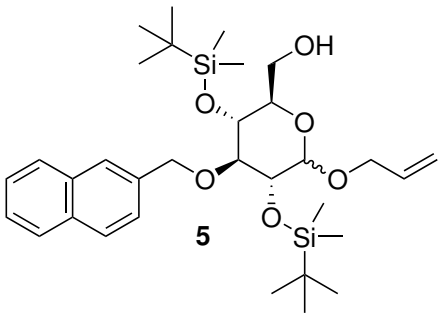
4α: ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.83 - 7.76 (*m*, 4H), 7.48 - 7.36 (*m*, 3H), 6.01 – 5.93 (*m*, 1H), 5.35 (*dq*, *J* = 17.1, 1.7 Hz, 1H), 5.26 – 5.20 (*m*, 2H), 4.86 (*d*, *J* = 12.5 Hz, 1H), 4.78 (*d*, *J* = 3.4 Hz, 1H), 4.24 (*ddt*, *J* = 12.8, 5.3, 1.5 Hz, 1H), 4.03 (*ddt*, *J* = 12.8, 6.6, 1.3 Hz, 1H), 3.88 (*dd*, *J* = 11.1, 1.9 Hz, 1H), 3.77 (*dd*, *J* = 9.3, 3.5 Hz, 1H), 3.76 – 3.68 (*m*, 2H), 3.64 (*ddd*, *J* = 9.7, 6.0, 2.0 Hz, 1H), 3.57 (*dd*, *J* = 9.5, 8.0 Hz, 1H), 0.93 - 0.80 (*m*, 27H), 0.09 - -0.13 (*m*, 18H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 137.2, 134.3, 133.5, 132.7, 128.0, 127.8, 127.5, 125.9, 125.4, 124.8, 124.7, 118.0, 97.8, 82.6, 74.8, 74.7, 73.3, 71.1, 68.3, 63.0, 26.1, 25.9, 18.6, 18.2, 18.1, -3.7, -4.4, -4.5, -4.6, -4.8, -5.2.

4β: ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.84 – 7.77 (*m*, 4H), 7.44 (*pd*, *J* = 6.8, 1.4 Hz, 2H), 7.39 (*dd*, *J* = 8.4, 1.6 Hz, 1H), 5.98 (*dddd*, *J* = 17.2, 10.3, 6.7, 5.5 Hz, 1H), 5.35 (*dt*, *J* = 17.3, 1.6 Hz, 1H), 5.26 – 5.14 (*m*, 2H), 4.92 (*d*, *J* = 12.6 Hz, 1H), 4.36 (*ddt*, *J* = 12.3, 5.5, 1.5 Hz, 1H), 4.31 (*d*, *J* = 7.5 Hz, 1H), 4.11 – 4.06 (*m*, 1H), 3.89 (*dd*, *J* = 11.1, 2.2 Hz, 1H), 3.73 (*dd*, *J* = 11.2, 5.8 Hz, 1H), 3.66 – 3.56 (*m*, 2H), 3.40 (*t*, *J* = 8.7 Hz, 1H), 3.27 (*ddd*, *J* = 9.2, 5.8, 2.2 Hz, 1H), 0.92 - 0.79 (*m*, 27H), 0.09 – -0.14 (*m*, 18H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 136.9, 134.4, 133.5, 132.6, 128.0, 127.8, 127.5, 125.9, 125.4, 124.6, 124.5, 117.7, 102.3, 86.6, 77.5, 75.9, 75.0, 70.9, 70.2, 62.8, 26.1, 18.6, 18.3, 18.2, -2.9, -3.8, -4.2, -4.6, -4.9, -5.2.

4.5 Synthesis of 1-*O*-allyl-2,4-di-*O*-TBDMS-3-*O*-NAP-D-glucopyranoside (5)



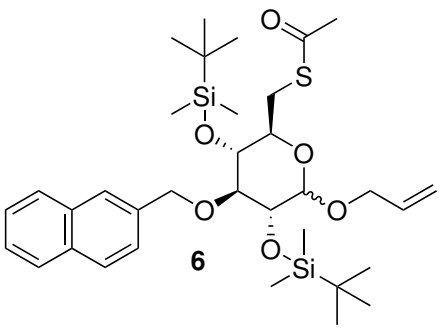
4 (7.314 g, 10.401 mmol) was dissolved in a DCM:MeOH 4:1 system at 0 °C. CSA (2 eqv.) was added and the solution stirred for 2 hours before being terminated by addition of aqueous $NaHCO_3$ and then extracted three times with DCM (100 mL). Purification by column chromatography (SiO_2) with eluent fractions of 500 mL consisting of *n*-pentante:DCM 2:1, 1:1, 1:2 followed by pure DCM gave **5** as a yellow oil (4.232 g, 7.187 mmol, 69.1%, α:β 17:3).

m/z: [M+Na] calcd. for $C_{32}H_{52}O_6NaSi_2$ 611.3200, found 611.3200; IR (cm^{-1}): 2856, 1252, 1073, 834, 778.

5β: ^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.84 – 7.76 (*m*, 4H), 7.45 (*pd*, J = 6.8, 1.4 Hz, 2H), 7.36 (*dd*, J = 8.5, 1.6 Hz, 1H), 5.98 (*ddt*, J = 16.6, 10.4, 6.1 Hz, 1H), 5.31 (*dq*, J = 17.2, 1.6 Hz, 1H), 5.22 (*dq*, J = 10.5, 1.3 Hz, 1H), 5.15 (*dd*, J = 12.6, 1.2 Hz, 1H), 4.94 (*d*, J = 12.5 Hz, 1H), 4.38 – 4.32 (*m*, 2H), 4.16 – 4.10 (*m*, 1H), 3.86 (*ddd*, J = 11.7, 7.1, 2.8 Hz, 1H), 3.71 – 3.59 (*m*, 3H), 3.43 (*t*, J = 8.8 Hz, 1H), 3.36 (*ddd*, J = 9.0, 6.0, 2.8 Hz, 1H), 0.83 – 0.79 (*m*, 18H), 0.10 – -0.13 (m, 12H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 136.7, 134.3, 133.4, 132.6, 128.0, 127.8, 127.6, 125.9, 125.5, 124.6, 124.4, 118.0, 103.0, 86.3, 76.7, 75.6, 75.1, 71.1, 71.0, 62.4, 26.0, 26.0, 18.2, 18.1, -3.7, -3.8, -4.2, -4.6.

4.6 Synthesis of 1-*O*-allyl-2,4-di-*O*-TBDMS-3-*O*-NAP-6-*S*-acetyl-D-glucopyranoside (6)



5 (0.524 g, 0.890 mmol) was dissolved in THF and cooled to 0 °C before PPh_3 (1.6 eqv.), DIAD (1.6 eqv.) and AcSH (1.6 eqv.) was added and the reaction stirred for 16 hours before being quenched with water and extracted three times by DCM (20 mL). Evaporation and purification by column chromatography (SiO_2, *n*-pentane:EtOAc 15:1) afforded **6** as a yellow oil (0.546 g, 0.844 mmol, 94.8%).

m/z: [M+NH_4] calcd. for $C_{34}H_{58}NO_6Si_2S$ 664.3523, found 664.3522; IR (cm^{-1}): 2927, 2856, 1697, 1463, 1253, 1082, 835, 779.

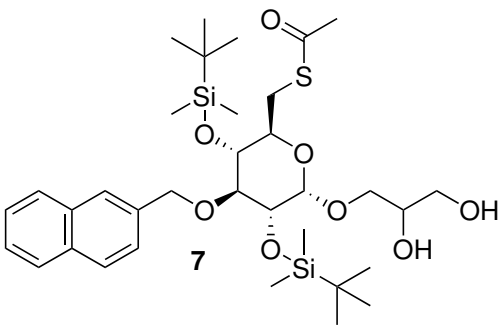
6α: ^{1}H NMR (600 MHz, $CDCl_3$,δ ppm): 7.84 – 7.76 (*m*, 4H), 7.49 – 7.41 (*m*, 2H), 7.37 (*m*, 1H), 5.96 (*dddd*, *J* = 17.1, 10.3, 6.7, 5.4 Hz, 1H), 5.39 - 5.34 (*m*, 1H), 5.26 – 5.20 (*m*, 2H), 4.86 (*d*, *J* = 12.5 Hz, 1H), 4.75 (*d*, *J* = 3.7 Hz, 1H), 4.24 (*ddt*, *J* = 12.7, 5.3, 1.3 Hz, 1H), 4.00 (*ddt*, *J* = 12.7, 6.6, 1.2 Hz, 1H), 3.80 (*dd*, 9.3, 3.7 Hz, 1H), 3.77 – 3.68 (*m*, 2H), 3.66 - 3.63 (*m*, 1H), 3.46 (*t*, *J* = 9.0 Hz, 1H), 2.81 (*dd*, *J* = 13.4, 9.5 Hz, 1H), 2.36 (*s*, 3H), 0.87 - 0.79 (*m*, 18H), 0.12 – -0,11 (*m*, 12H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 195.1, 137.0, 134.0, 133.5, 132.6, 128.0, 127.8, 127.6, 125.9, 125.5, 124.7, 124.7, 118.3, 97.8, 82.2, 74.8, 74.7, 74.5, 71.2, 68.5, 32.0, 30.7, 26.0, 25.9, 18.2, 18.1, -3.6, -4.2, -4.4, -4.5.

6β: ^{1}H NMR (600 MHz, $CDCl_3$): 7.84 – 7.76 (*m*, 4H), 7.49 – 7.41 (*m*, 2H), 7.37 (*m*, 1H), 5.96 (*dddd*, *J* = 17.1, 10.3, 6.7, 5.4 Hz, 1H), 5.34 - 5.29 (*m*, 1H), 5.24 – 5.20 (*m*, 1H), 5.13 (*dd*, *J* = 12.5, 1.3 Hz, 1H), 4.93 (*d*, *J* = 12.5 Hz, 1H), 4.35 (*ddt*, *J* = 12.3, 5.5, 1.4 Hz, 1H), 4.28 (*d*, *J* = 7.6 Hz, 1H), 4.11 – 4.07 (*m*, 1H), 3.77 – 3.68 (*m*, 1H), 3.62 (*dd*, *J* = 8.7, 7.6 Hz, 1H), 3.50 (*t*, *J* = 8.9 Hz, 1H), 3.38 (*t*, *J* = 8.7 Hz, 1H), 3.31 (*m*, 1H), 2.73 (*dd*, *J* = 13.5, 10.1 Hz, 1H), 2.35 (*s*, 3H), 0.87 - 0.79 (*m*, 18H), 0.11 – -0,13 (*m*, 12H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 195.2, 136.7, 134.1, 133.4, 132.6, 128.0, 127.8, 127.6, 125.9, 125.5, 124.7, 124.5, 118.2, 102.4, 86.2, 75.8, 75.7, 75.1, 74.7, 70.6, 32.2, 30.6, 26.0, 18.2, 18.1, -3.7, -3.8, -4.0, -4.2.

4.7 Synthesis of 1-*O*-glycerol-2,4-di-*O*-TBDMS-3-*O*-NAP-6-*S*-acetyl-α-D-glucopyranoside (7)



7

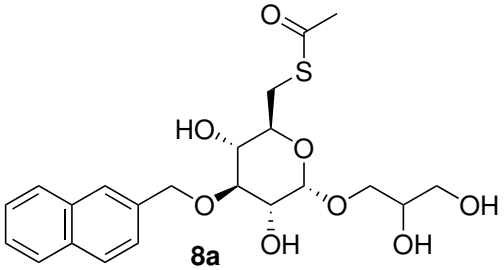
6 (1.206 g, 1.864 mmol) was dissolved in *t*-BuOH:H_2O 1:1 before addition of AD-mix-β (2.60 g). The reaction was stirred for 18 hours before addition of Na_2SO_3 (2.88 g) and then stirred for another hour before being extracted three times with EtOAc (40 mL), dried over $MgSO_4$ and purification by column chromatography (SiO_2, *n*-pentane:EtOAc 5:1) gave **7** as a yellow oil (0.979 g, 1.438 mmol, 77.1%).

m/z: [M+NH_4] calcd. for $C_{34}H_{60}NO_8Si_2S$ 698.3578, found 698.3579; IR (cm^{-1}): 2927, 1696, 1252, 1086, 834, 777, 627, 475. $[\alpha]_D^{25} = 71.4°$(*c* 0.0021, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.84 – 7.76 (*m*, 4H), 7.50 – 7.41 (*m*, 2H), 7.36 (*dd*, *J* = 8.5, 1.7 Hz, 1H), 5.16 (*m*, 1H), 4.91 – 4.85 (*m*, 1H), 4.72 (*d*, *J* = 3.7 Hz, 1H), 3.94 (*m*, 2H), 3.84 – 3.76 (*m*, 2H), 3.76 – 3.68 (*m*, 2H), 3.68 – 3.60 (*m*, 2H), 3.49 – 3.43 (*m*, 2H), 2.85 (*d*, *J* = 5.0 Hz, 1H), 2.80 (*dd*, *J* = 13.4, 9.5 Hz, 1H), 2.36 (*s*, 3H), 2.30 (*dd*, *J* = 7.6, 5.2 Hz, 1H), 0.90 – 0.78 (*m*, 18H), 0.14 – -0.13 (*m*, 12H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 195.1, 136.7, 133.4, 132.7, 128.0, 127.8, 127.6, 126.0, 125.5, 124.7, 124.6, 100.0, 82.2, 75.0, 74.5, 74.3, 71.6, 71.2, 70.3, 64.2, 31.8, 30.7, 26.1, 25.9, 18.2, 18.0, -3.6, -4.2, -4.3, -4.7.

4.8 Synthesis of 1-*O*-glycerol-3-*O*-NAP-6-*S*-acetyl-α-D-glucopyranoside (8a)

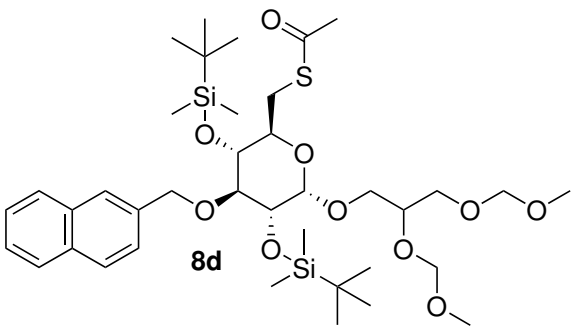


8a

7 (74 mg, 0.108 mmol) was dissolved in aqueous formic acid (30%, H_2O:THF (2:1), 10 mL). The reaction was allowed to stir overnight, before being terminated with aqueous sodium bicarbonate. The solution was extracted three times with EtOAc (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, *n*-pentane:EtOAc 2:1) afforded **8a** as a white oil (31 mg, 0.068 mmol, 62.7%).

m/z: [M+Na] calcd. for $C_{22}H_{28}O_8SNa$ 475.1410, found 475.1403; IR (cm^{-1}): 3375, 2925, 1692, 1355, 1125, 1036, 819, 780, 630. $[\alpha]_D^{25} = 53.6°$(*c* 0.0082, CH_2Cl_2).

4.9 Synthesis of 1-*O*-(2',3'-di-*O*-MOM)glycerol-2,4-di-*O*-TBDMS–3-*O*-NAP-6-*S*-acetyl-α-D-glucopyranoside (8d)



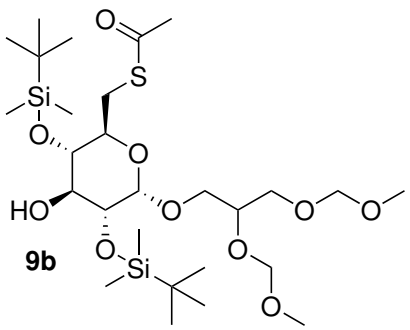
P_2O_5 (47 mg, 0.33 mmol) was added to a stirred solution of **7** (75 mg, 0.111 mmol) in DMM (10 mL). After 3 hours the solution was poured into ice-cooled aqueous Na_2CO_3 (35 mg, 0.330 mmol). The solution was extracted three times with EtOAc (15 mL), the combined organic layers dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, *n*-pentane:EtOAc 5:1) gave **8d** as a faintly yellow oil (83 mg, 0.108 mmol, 97.6%).

m/z: [M+NH_4] calcd. for $C_{38}H_{68}NO_{10}SSi_2$ 786.4102, found 786.4099; IR (cm^{-1}): 2926, 1696, 1462, 1252, 1035, 835, 778. $[\alpha]_D^{20} = 49.0°$(*c* 0.0049, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 7.84 – 7.75 (*m*, 4H), 7.49 – 7.41 (*m*, 2H), 7.38 (*dd*, *J* = 8.4, 1.6 Hz, 1H), 5.18 (*d*, *J* = 12.5, 1H), 4.86 – 4.80 (*m*, 2H), 4.75 (*m*, 1H), 4.72 – 4.65 (*m*, 1H), 4.67 (*s*, 2H), 4.04 – 3.97 (*m*, 1H), 3.90 (*dd*, *J* = 10.0, 4.9 Hz, 1H), 3.77 (*dd*, *J* = 9.3, 3.6 Hz, 1H), 3.75 – 3.60 (*m*, 5H), 3.52 – 3.42 (*m*, 2H), 3.44 (*s*, 3H), 3.40 (*s*, 3H), 2.80 (*dd*, *J* = 13.3, 9.5 Hz, 1H), 2.35 (*s*, 3H), 0.86 (*s*, 9H), 0.80 (*s*, 9H), 0.11 (*s*, 3H), 0.05 (*s*, 3H), -0.08 (*s*, 3H), -0.10 (*s*, 3H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 195.1, 136.9, 133.4, 132.7, 128.0, 127.8, 127.6, 125.9, 125.5, 124.8, 124.7, 99.3, 96.9, 96.2, 82.0, 74.8, 74.6, 74.5, 74.4, 71.2, 68.2, 67.9, 55.7, 55.5, 31.9, 30.6, 26.1, 25.8, 18.2, 18.0, -3.6, -4.3, -4.6.

4.10 Synthesis of 1-*O*-(2',3'-di-*O*-MOM)glycerol-2,4-di-*O*-TBDMS-6-*S*-acetyl-α-D-glucopyranoside (9b)



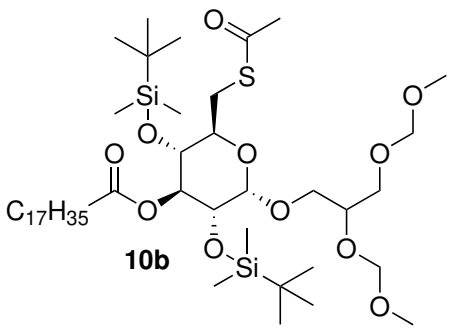
DDQ (566 mg, 2.45 mmol) was added to a stirred solution of **8d** (639 mg, 0.831 mmol) in $CHCl_3$ (20 mL). The solution was allowed to stir for 10 hours before being terminated by washing the mixture through a short silica pad with EtOAc. The filtrate was then evaporated and purified by column chromatography (SiO_2, *n*-pentane:EtOAc 12:1) which gave **9b** as a yellow oil (411 mg, 0.653 mmol, 78.7%).

m/z: [M+NH_4] calcd. for $C_{38}H_{68}NO_{10}SSi_2$ 786.4102, found 786.4099; IR (cm^{-1}): 2929, 1696, 1472, 1250, 1030, 834, 777, 627. $[\alpha]_D^{20} = 80.2°$(*c* 0.0334, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 4.79 (*d*, J = 6.8 Hz, 1H), 4.74 – 4.69 (*m*, 1H), 4.66 (*d*, J = 3.7 Hz, 1H), 4.64 (*s*, 2H), 3.94 (*m*, 1H), 3.86 (*dd*, J = 10.1, 4.9 Hz, 1H), 3.71 - 3.61 (*m*, 4H), 3.61 – 3.55 (*m*, 1H), 3.52 – 3.43 (*m*, 2H), 3.46 – 3.30 (*m*, 7H), 2.88 – 2.83 (*m*, 1H), 2.33 (*s*, 3H), 2.07 (1H, 3-OH), 0.93 – 0.88 (*m*, 18H), 0.15 (*s*, 3H), 0.15 (*s*, 3H), 0.09 (*s*, 3H), 0.07 (*s*, 3H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 195.0, 98.9, 96.9, 96.3, 74.8, 74.4, 74.1, 73.8, 70.9, 68.3, 67.8, 55.6, 55.4, 31.6, 30.6, 26.1, 25.9, 18.4, 18.2, -3.6, -4.3, -4.6, -4.7.

4.11 Synthesis of 1-*O*-(2',3'-di-*O*-MOM)-2,4-di-*O*-TBDMS-3-*O*-stearaoyl-6-*S*-acetyl-α-D-glucopyranoside (10b)



9b (176 mg, 0.280 mmol), stearic acid (398 mg, 1.39 mmol) and DMAP (85 mg, 0.70 mmol) was dissolved in dry DCM (11 mL). An inert atmosphere (N_2) was facilitated before EDCI (22 mL, 1.26 mmol) was added to the stirred solution. The reaction was quenched with water after 48 hours, extracted three times with DCM (20 mL), dried over $MgSO_4$, evaporated under reduced pressure and purified by column chromatography (SiO_2, *n*-pentane:EtOAc 25:1). The product, **10b**, coeluted with stearic acid as a blank oil (17 mg, 0.022 mmol, 8.0%).

m/z: [M+Na] calcd. for $C_{45}H_{90}O_{11}SNaSi_2$ 917.5640, found 917.5634; IR (cm^{-1}): 2921, 2852, 1457, 1036, 835. $[\alpha]_D^{20} = 25.8°$(*c* 0.0062, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$, δ ppm): 5.40 - 5.28 (*m*, 1H), 4.78 - 4.62 (*m*, 5H), 4.00 - 3.93 (*m*, 1H), 3.91 - 3.84 (*m*, 1H), 3.78 - 3.72 (*m*, 1H), 3.72 - 3.50 (*m*, 5H), 3.48 - 3.32 (*m*, 7H), 2.91 - 2.83 (*m*, 1H), 2.35 (*s*, 3H), 2.42 (*m*, 2H), 1.66 - 0.88 (*m*, 33H), 0.91 - 0.78 (*m*, 18H), 0.13 - -0.04 (*m*, 12H).

^{13}C NMR (150 MHz, $CDCl_3$, δ ppm): 194.4, 166.0, 98.6, 96.9, 96.3, 75.9, 74.5, 73.4, 72.3, 70.6, 67.8, 55.7, 55.5, 34.0 - 14.0 (17C), 31.7, 30.6, 26.0, 25.7, 18.2, 17.9, -3.6, -3.6, -4.2, -4.9.

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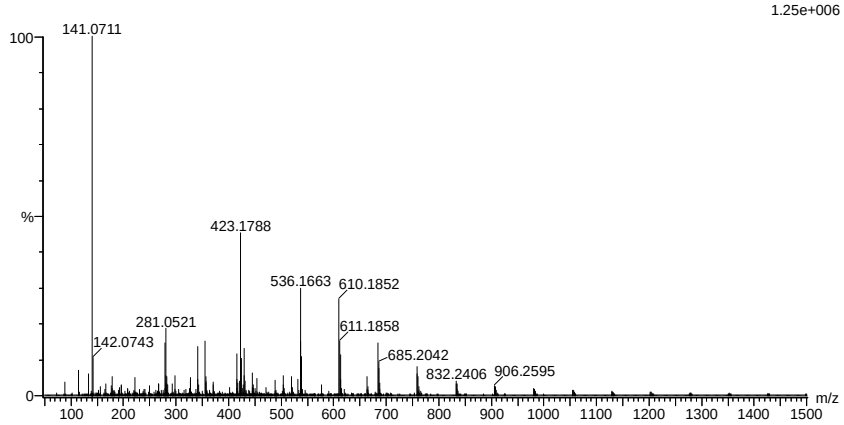
A Spectroscopic data

A.1 Spectroscopic data for compound 2

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
551 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-1 O: 0-15 Na: 0-1
2020_499 69 (0.657) AM2 (Ar,35000.0,0.00,0.00); Cm (68:71)
1: TOF MS ES+



Minimum:				-50.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
423.1788	423.1784	0.4	0.9	9.5	2310.7	n/a	n/a	C23 H28 O6 Na

Figure A.1: HRMS (ESI+) spectrum of compound **2**.

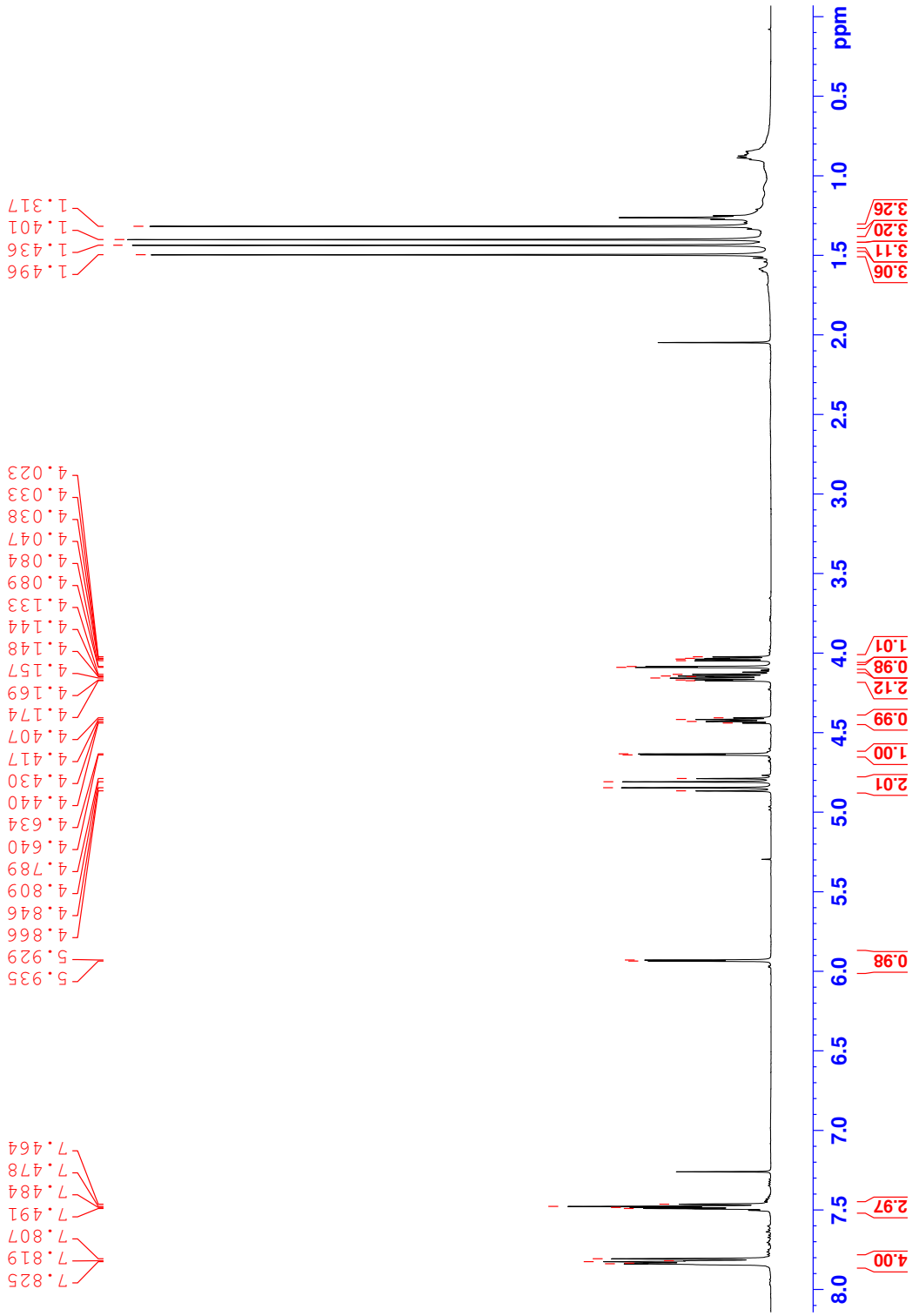


Figure A.2: ^{1}H NMR spectrum of compound **2**.

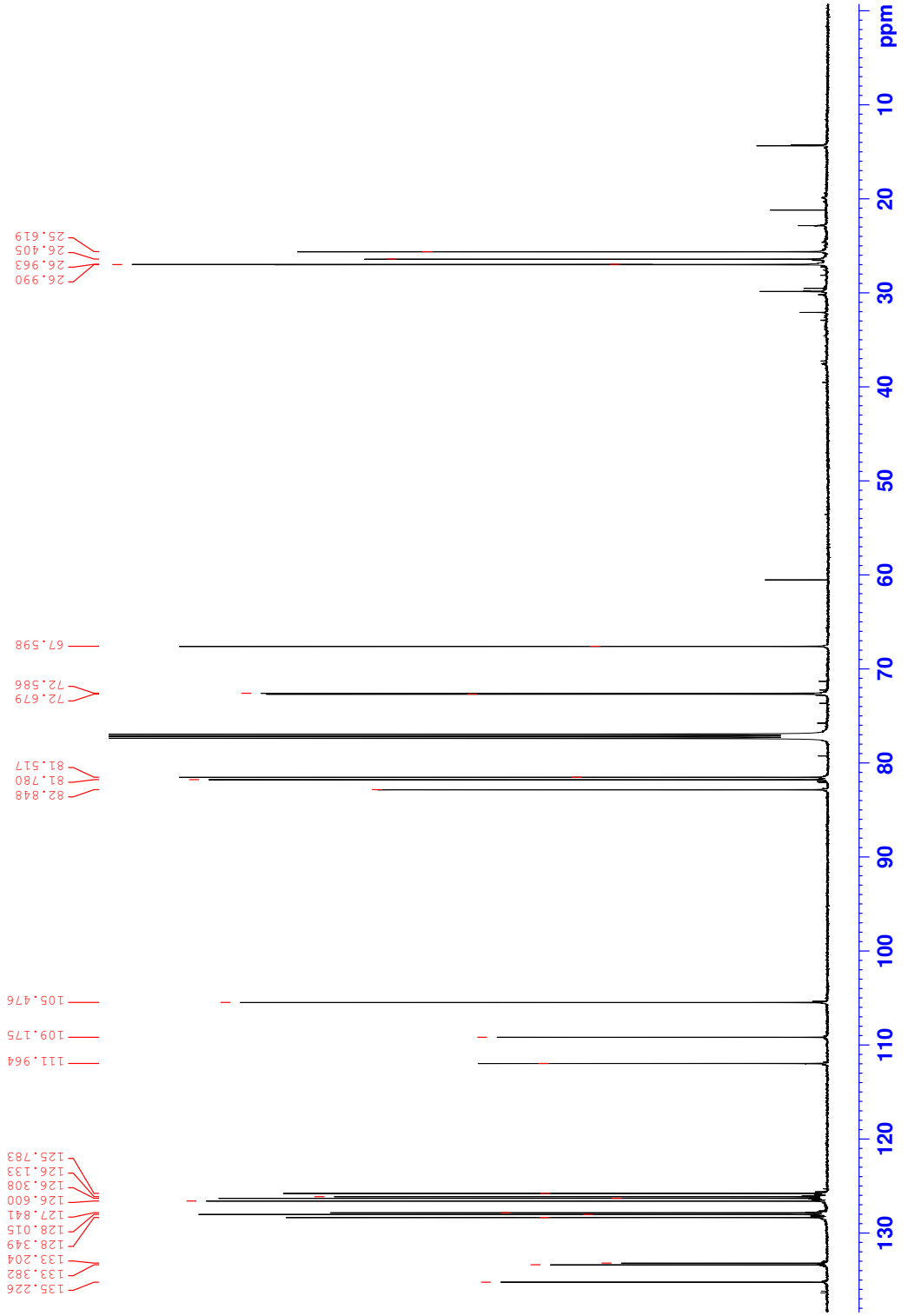


Figure A.3: ^{13}C NMR spectrum of compound **2**.

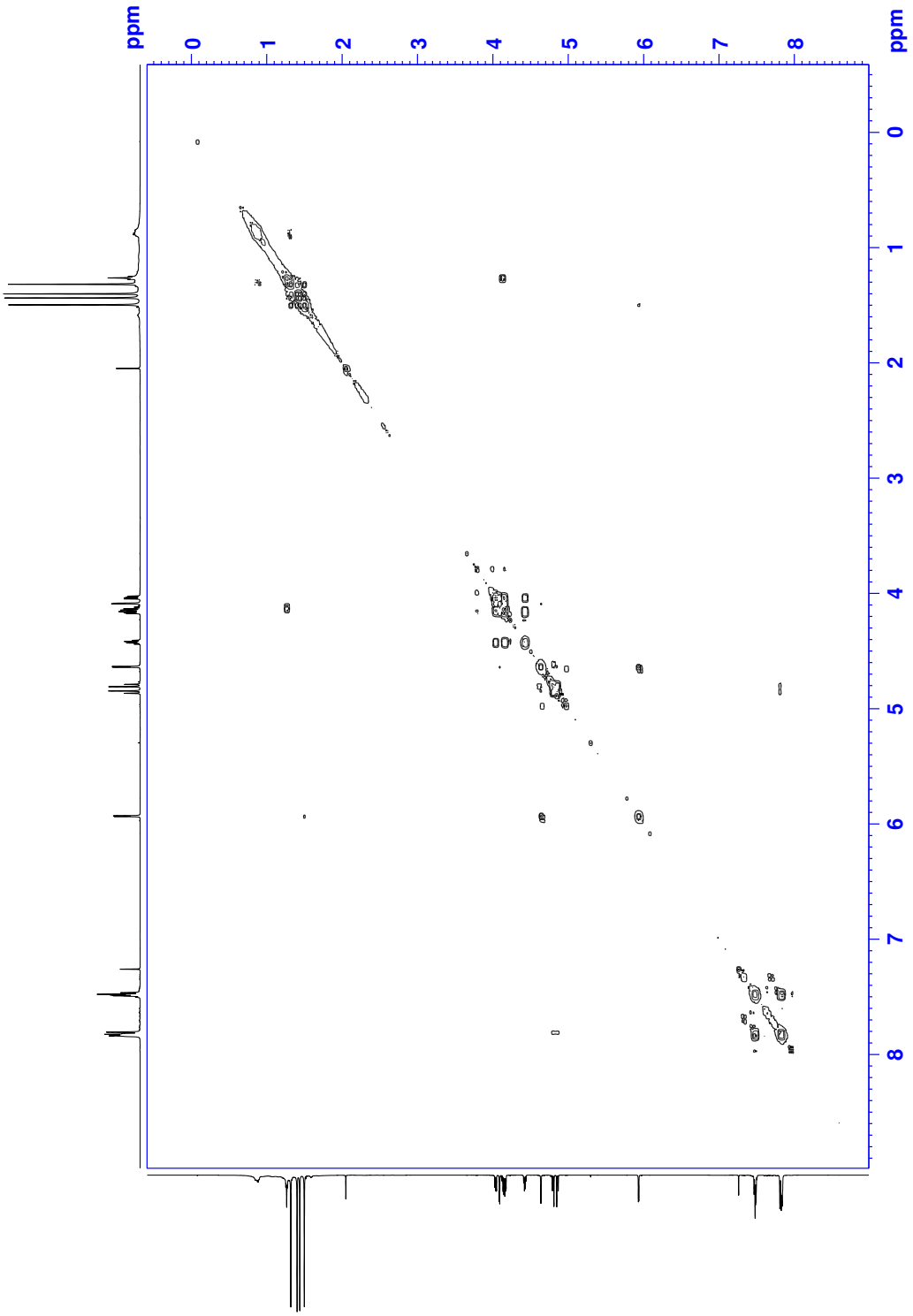


Figure A.4: COSY spectrum of compound **2**.

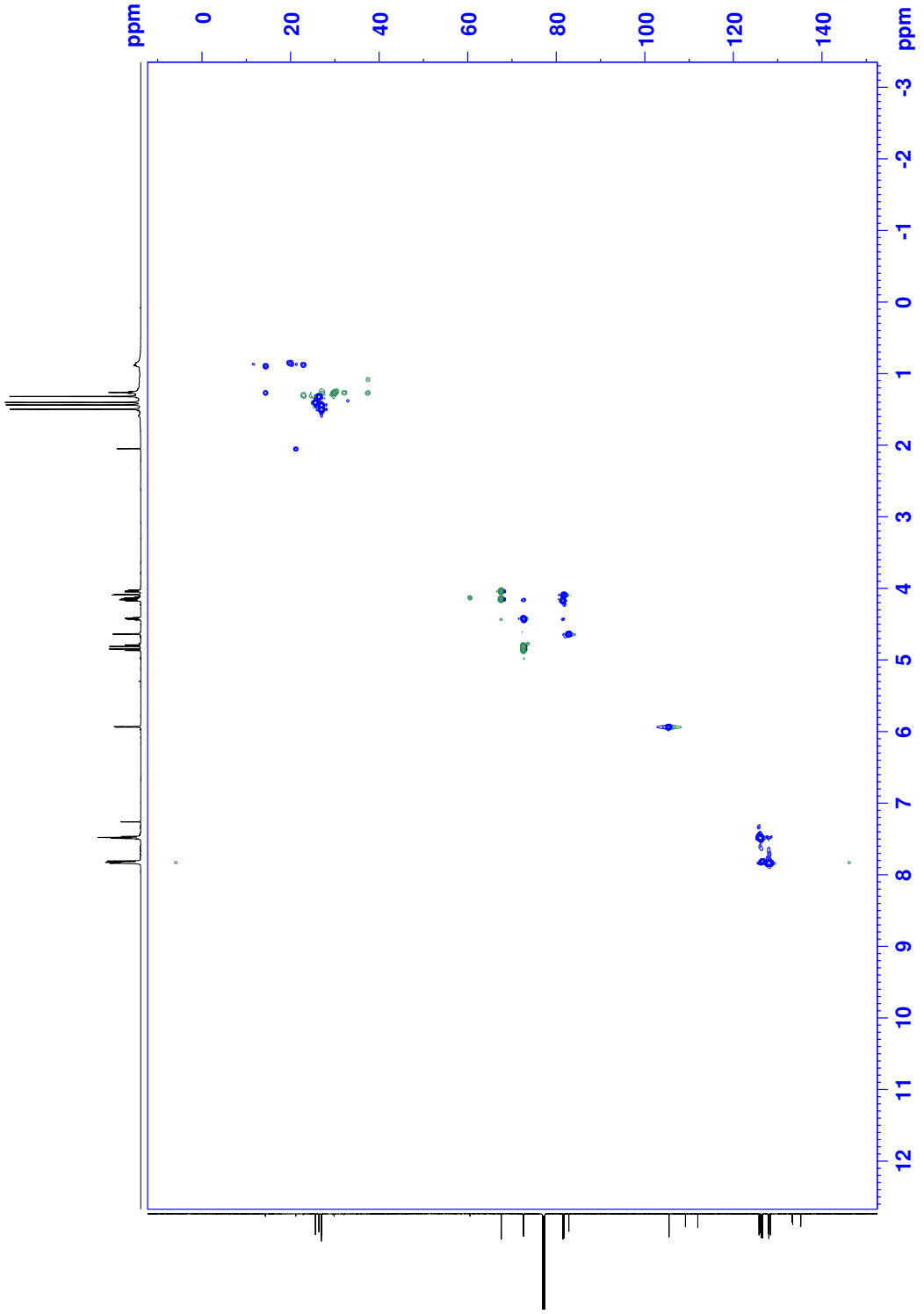


Figure A.5: HSQC spectrum of compound **2**.

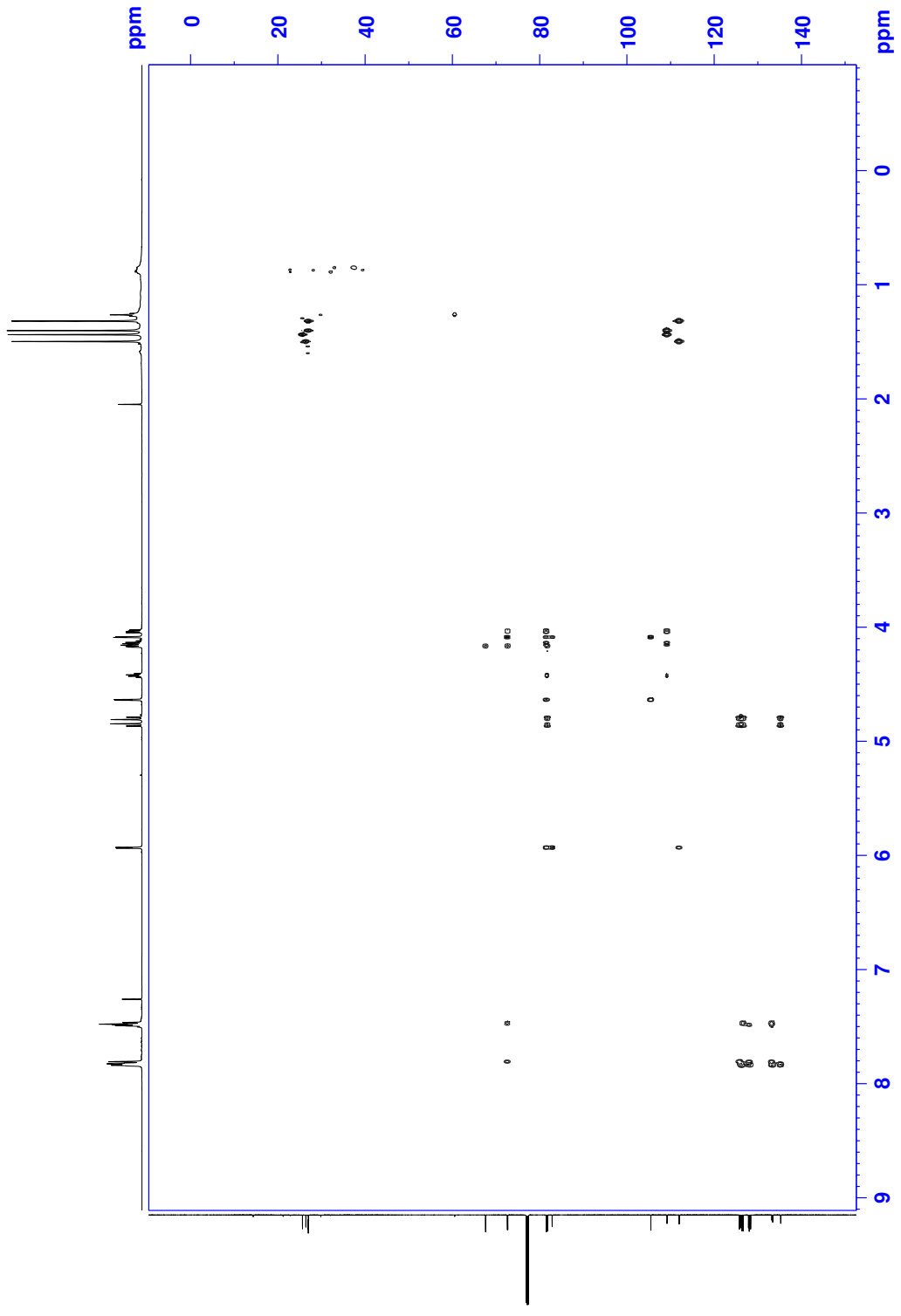


Figure A.6: HMBC spectrum of compound **2**.

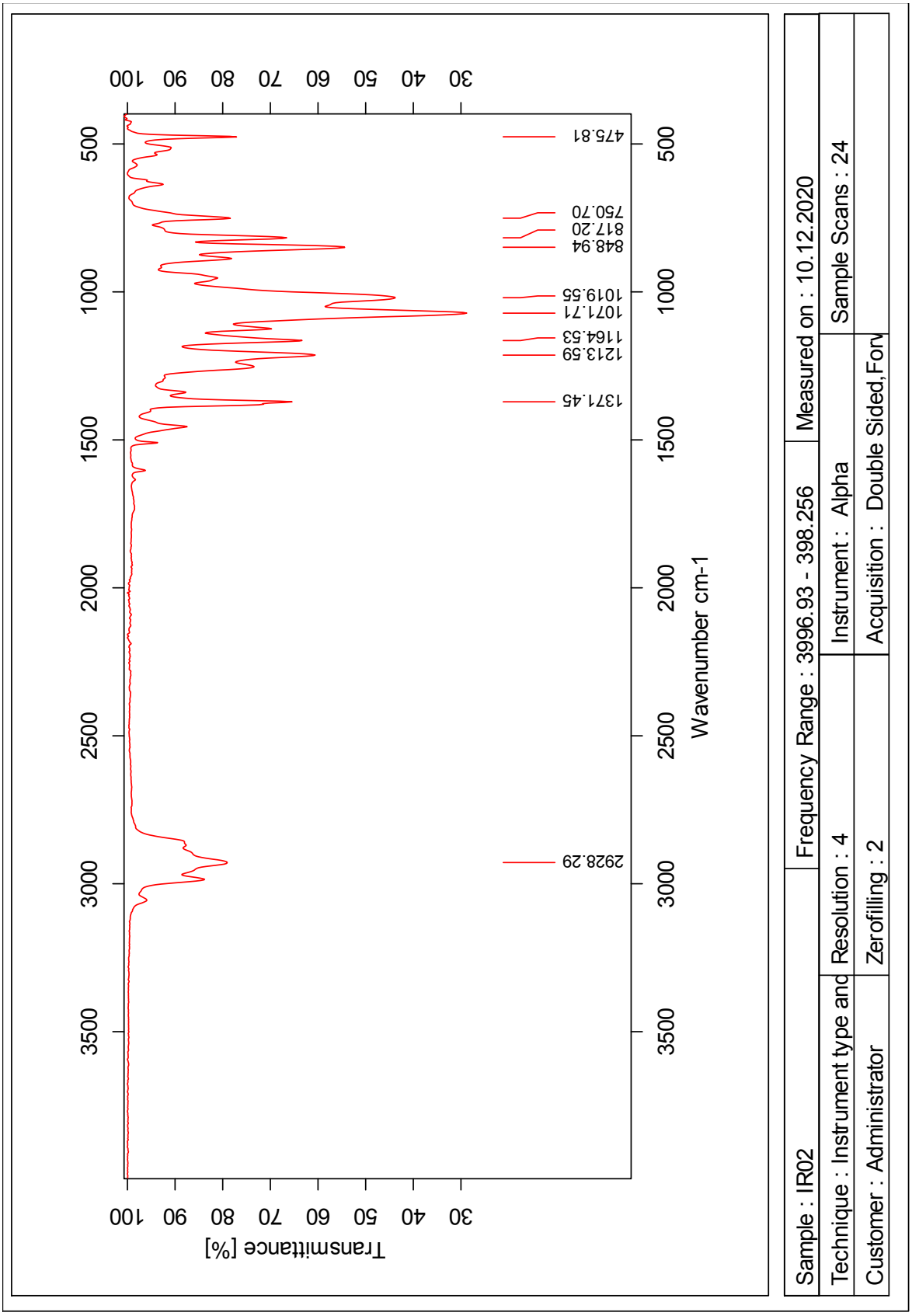


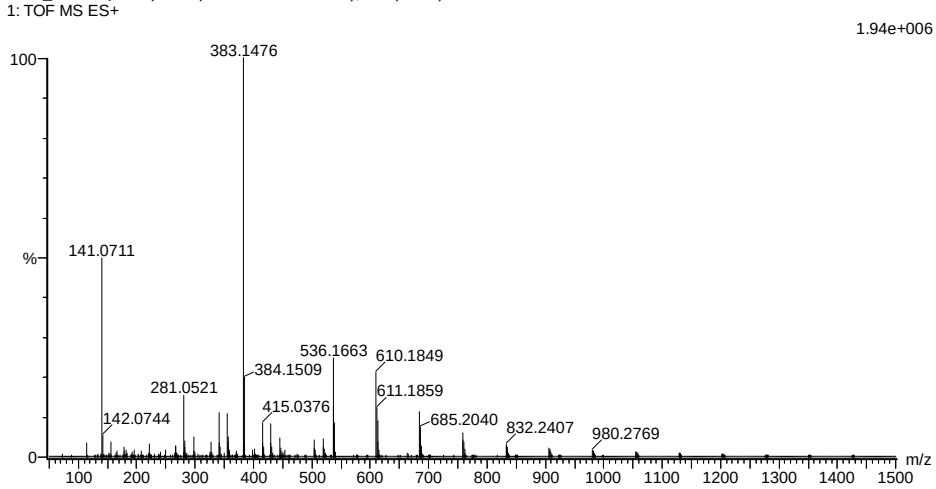
Figure A.7: IR spectrum of compound **2**.

A.2 Spectroscopic data for compound 3

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
549 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-1 O: 0-15 Na: 0-1
2020_500 71 (0.674) AM2 (Ar,35000.0,0.00,0.00); Cm (71:73)
1: TOF MS ES+



Minimum:				-50.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
383.1476	383.1471	0.5	1.3	8.5	2413.6	n/a	n/a	C20 H24 O6 Na

Figure A.8: HRMS (ESI+) spectrum of compound **3**.

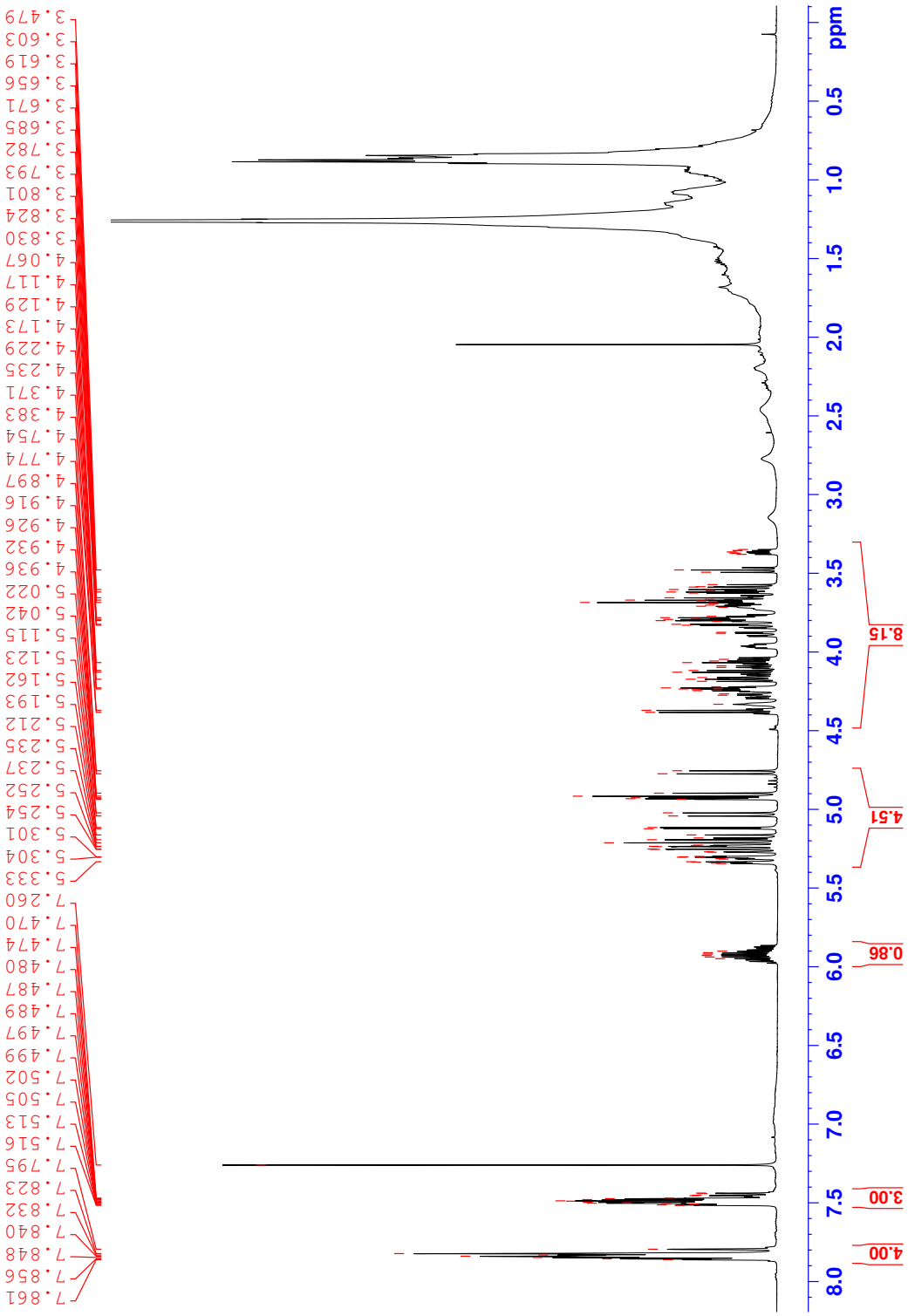


Figure A.9: ^{1}H NMR spectrum of compound **3**.

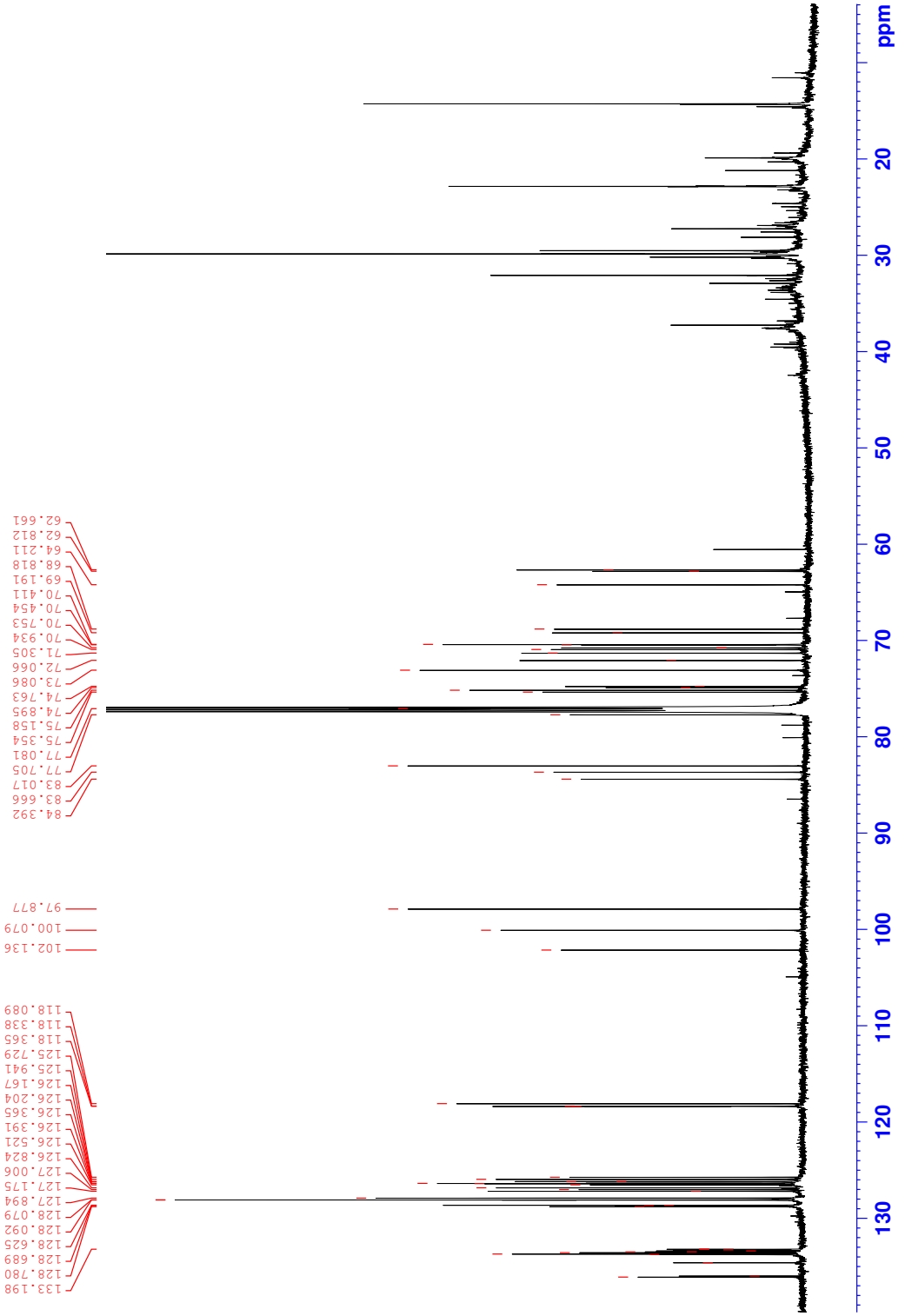


Figure A.10: ^{13}C NMR spectrum of compound **3**.

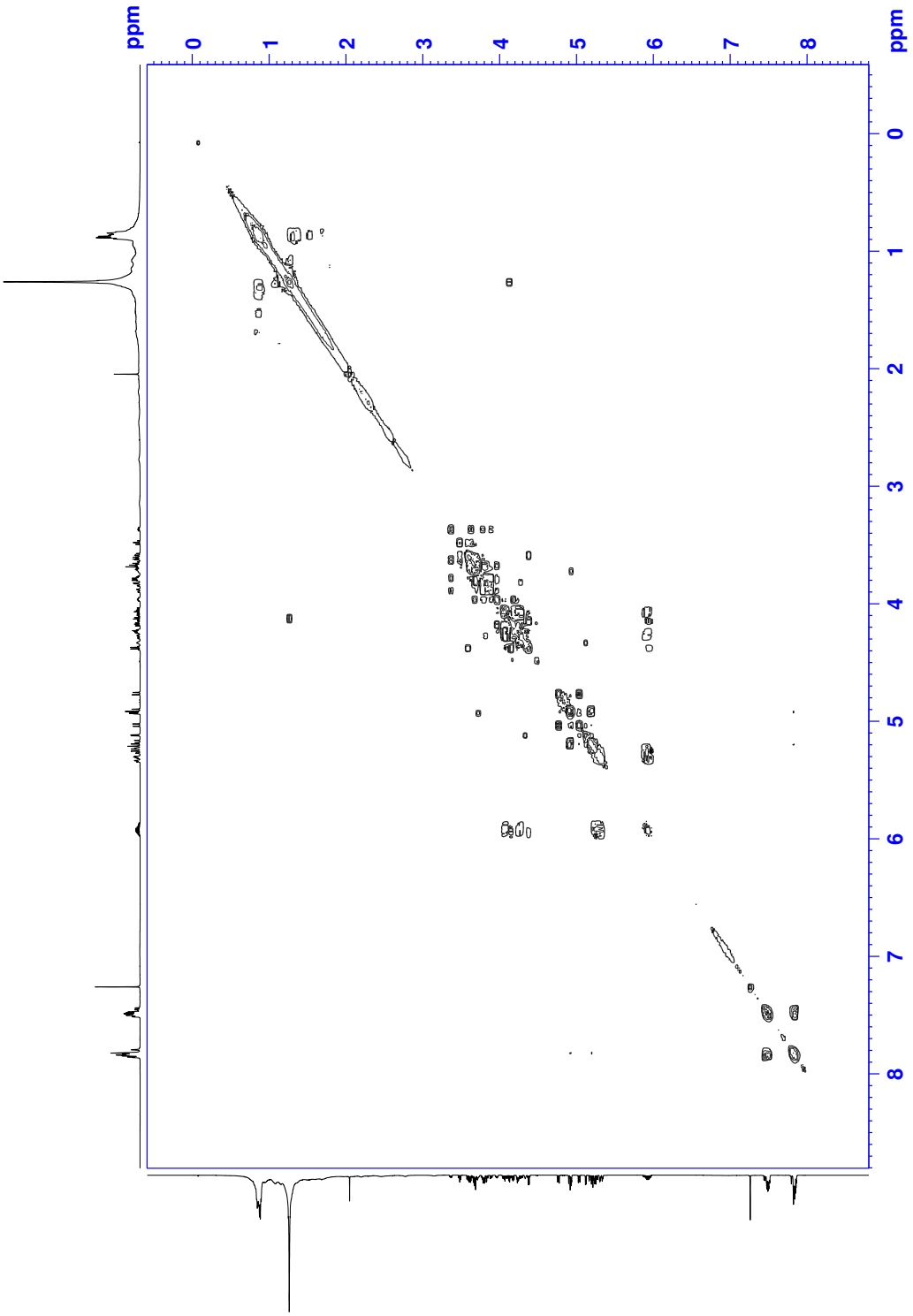


Figure A.11: COSY spectrum of compound **3**.

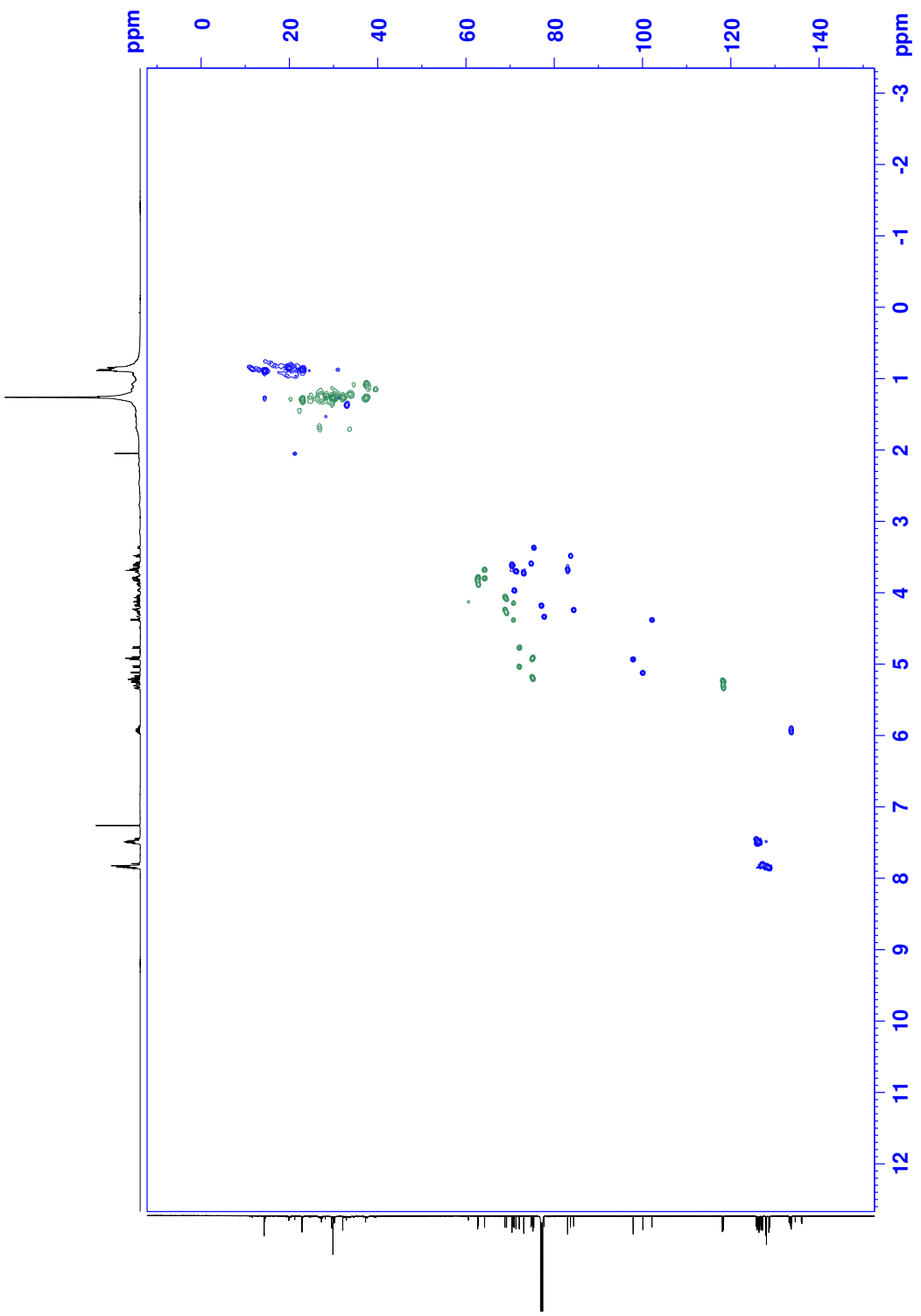


Figure A.12: HSQC spectrum of compound **3**.

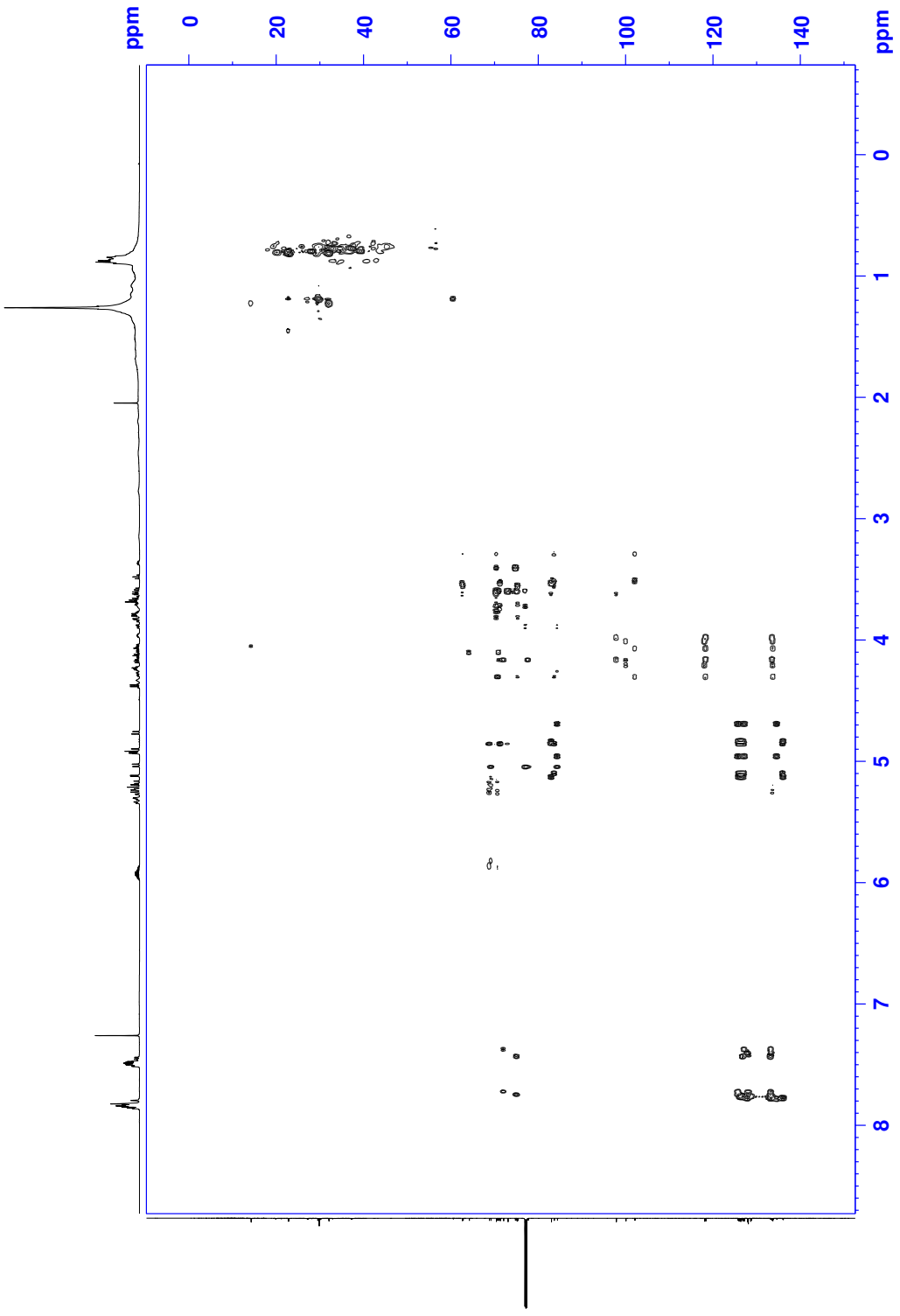


Figure A.13: HMBC spectrum of compound **3**.

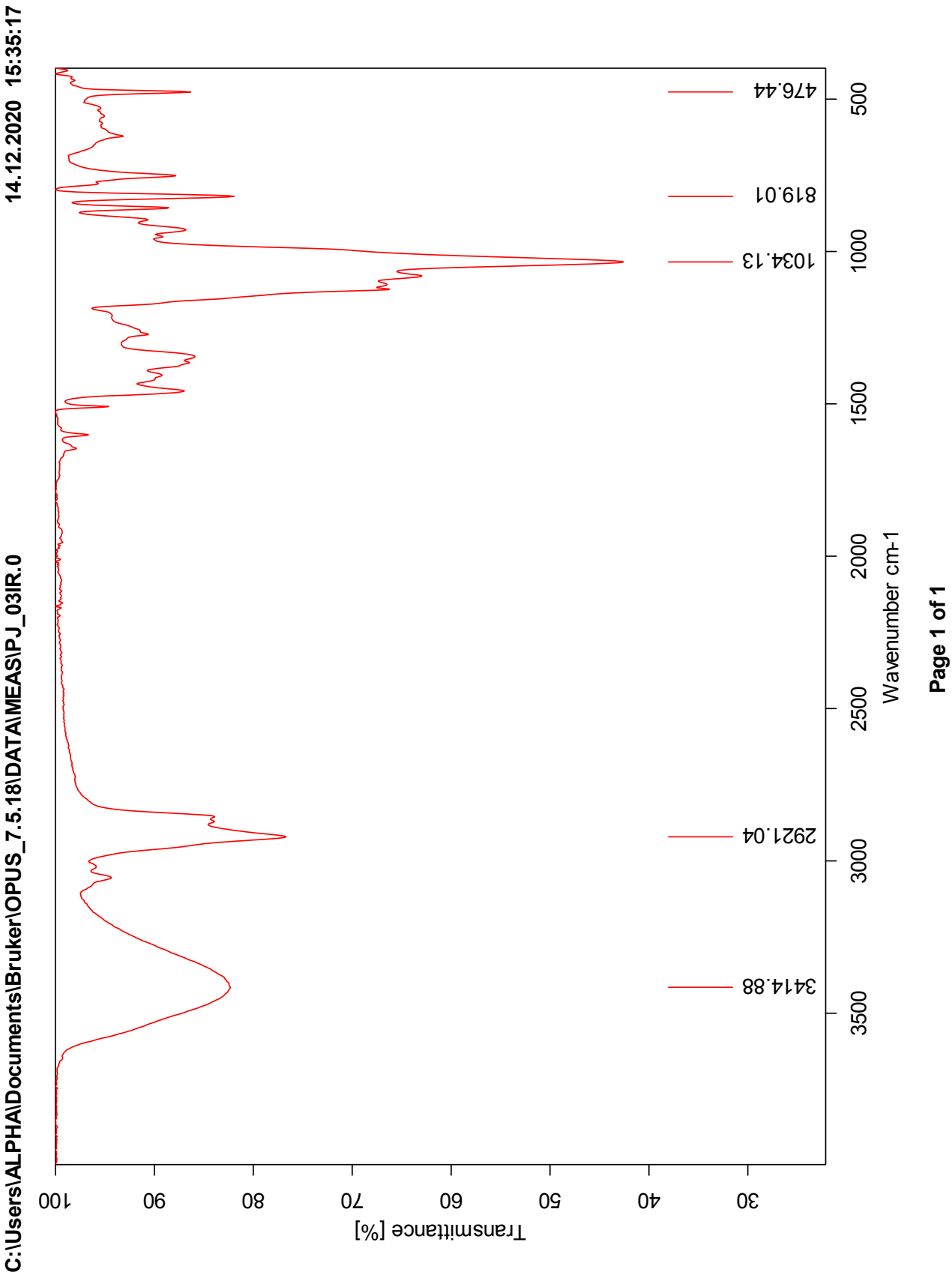


Figure A.14: IR spectrum of compound **3**.

A.3 Spectroscopic data for compound 3bi

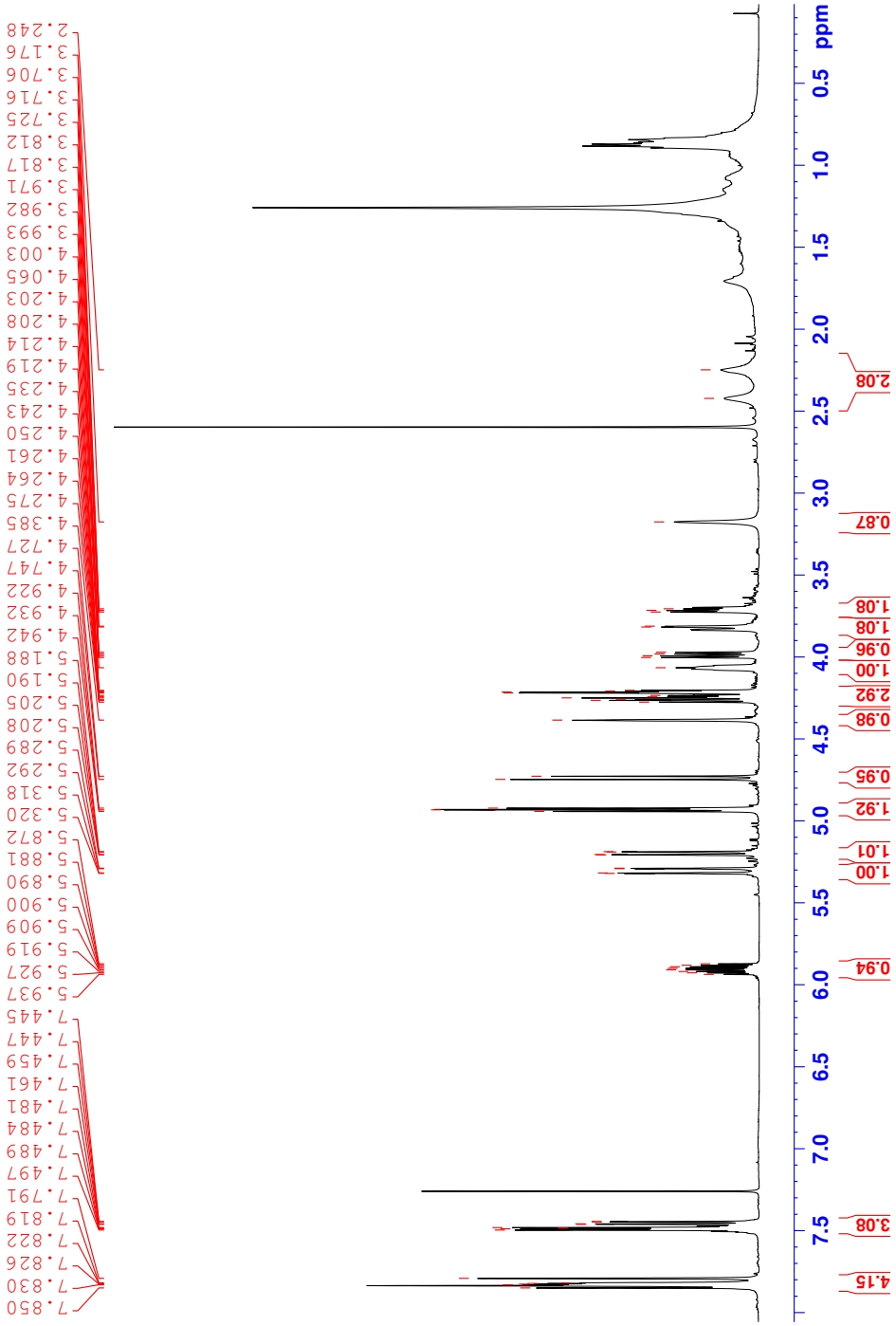


Figure A.15: ^{1}H NMR spectrum of compound **3bi**.

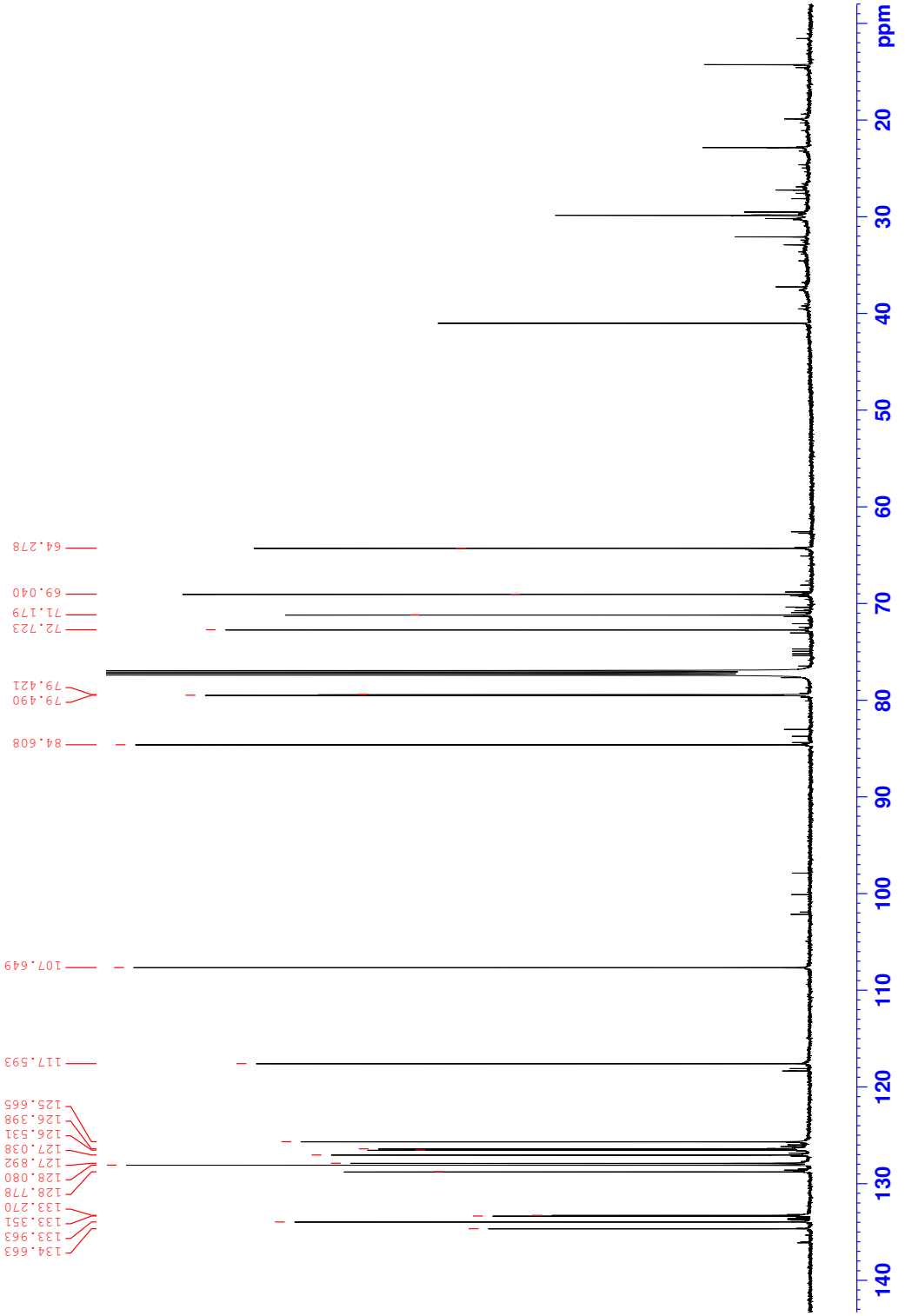


Figure A.16: ^{13}C NMR spectrum of compound **3bi**.

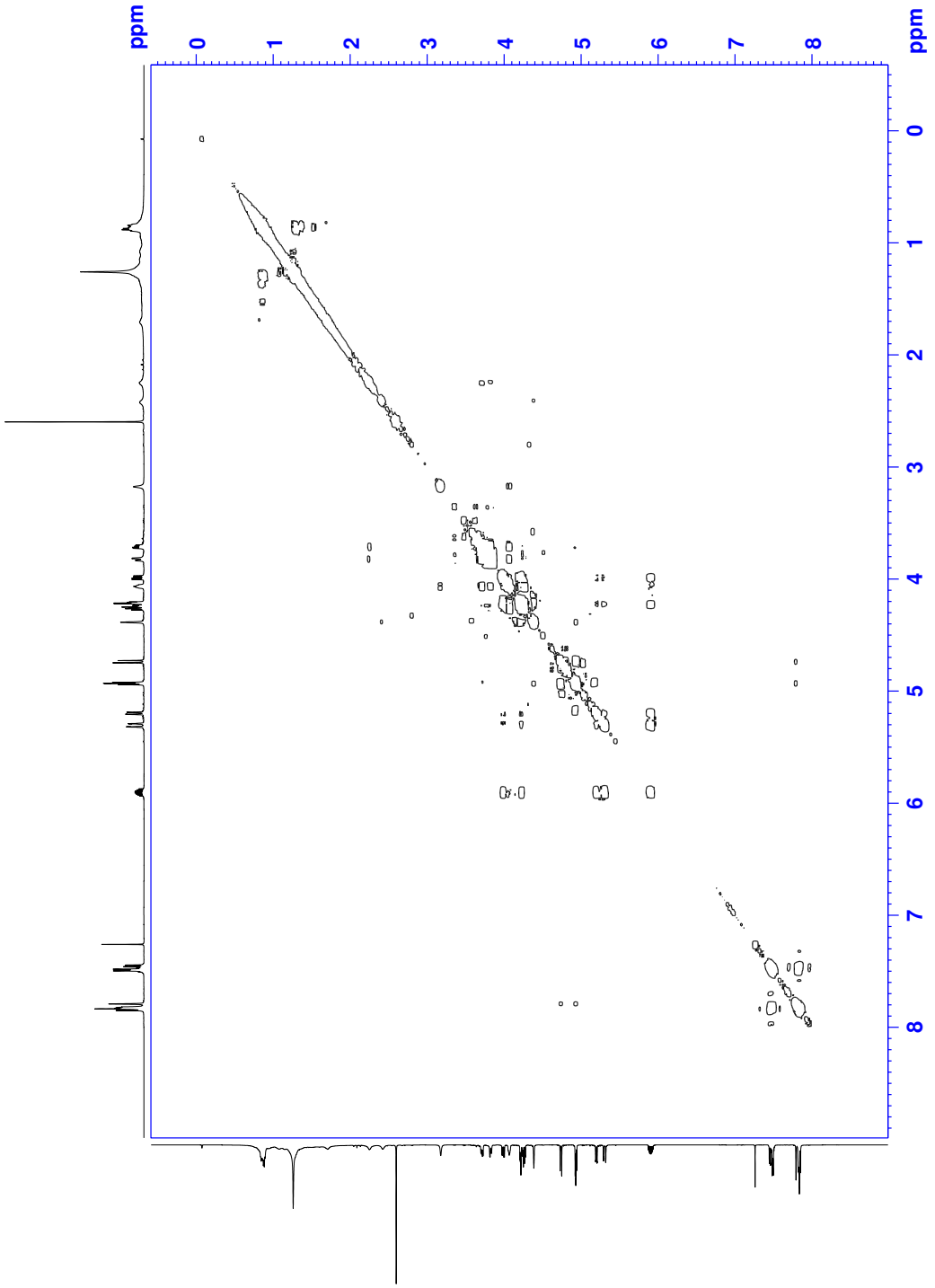


Figure A.17: COSY spectrum of compound **3bi**.

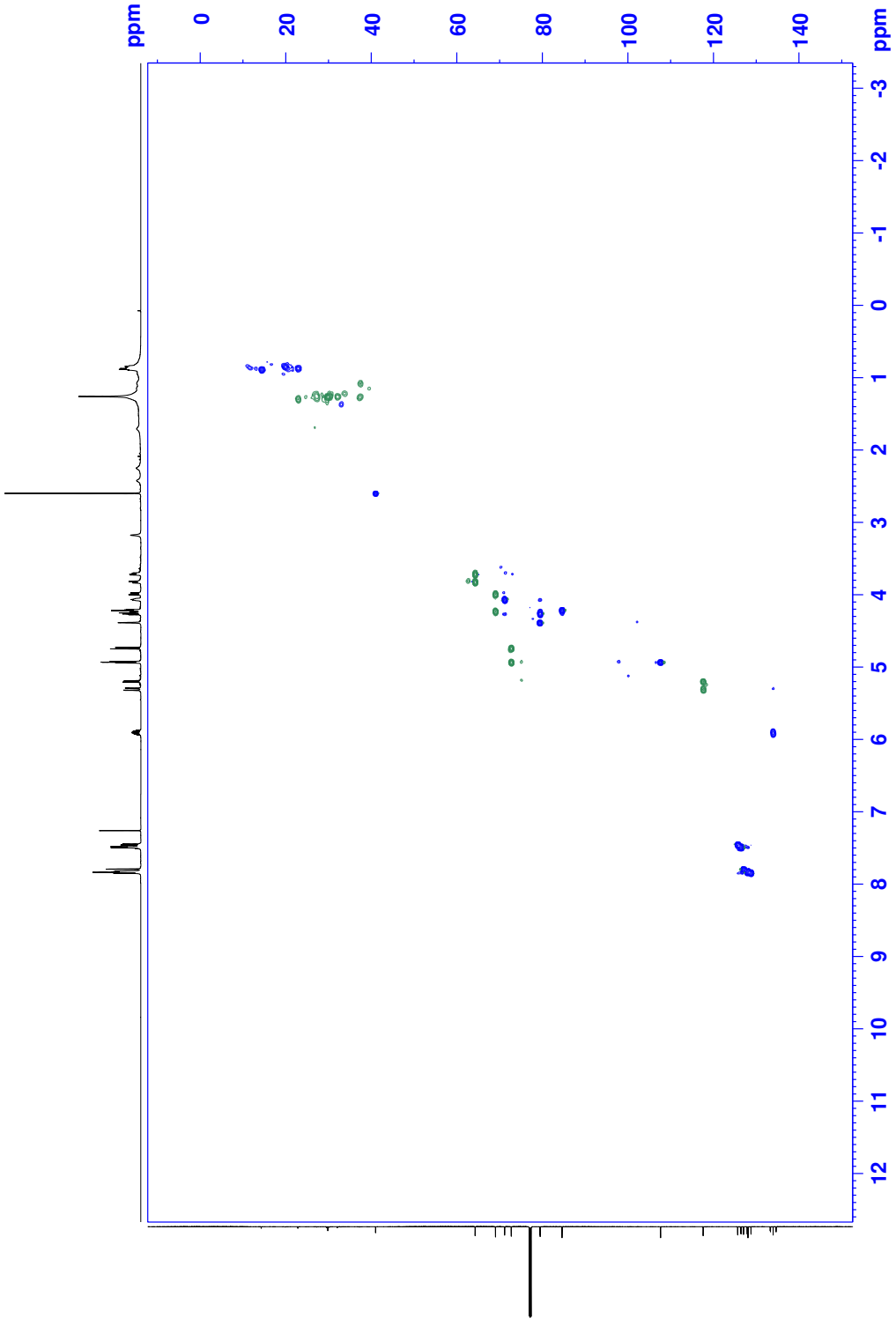


Figure A.18: HSQC spectrum of compound **3bi**.

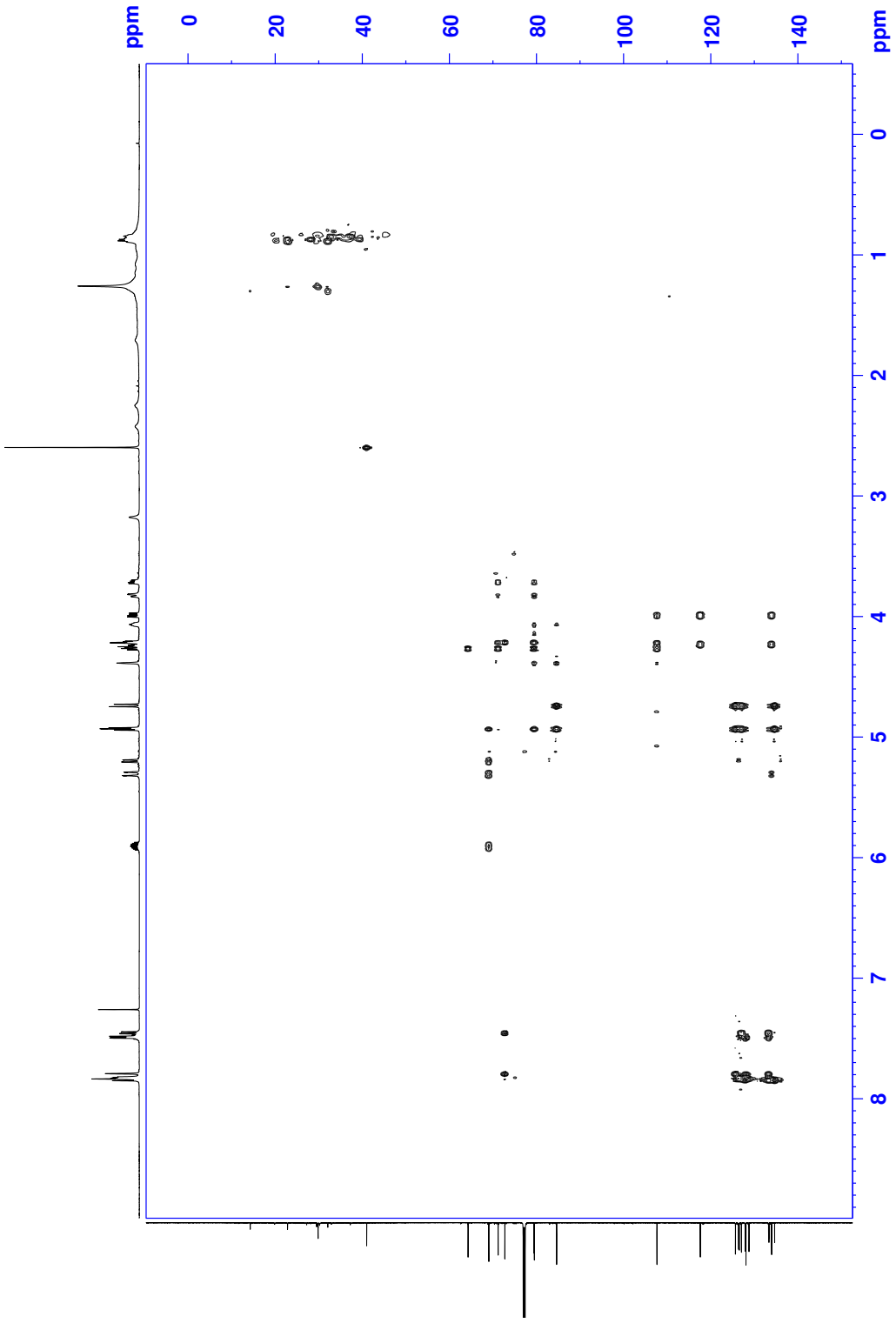


Figure A.19: HMBC spectrum of compound **3bi**.

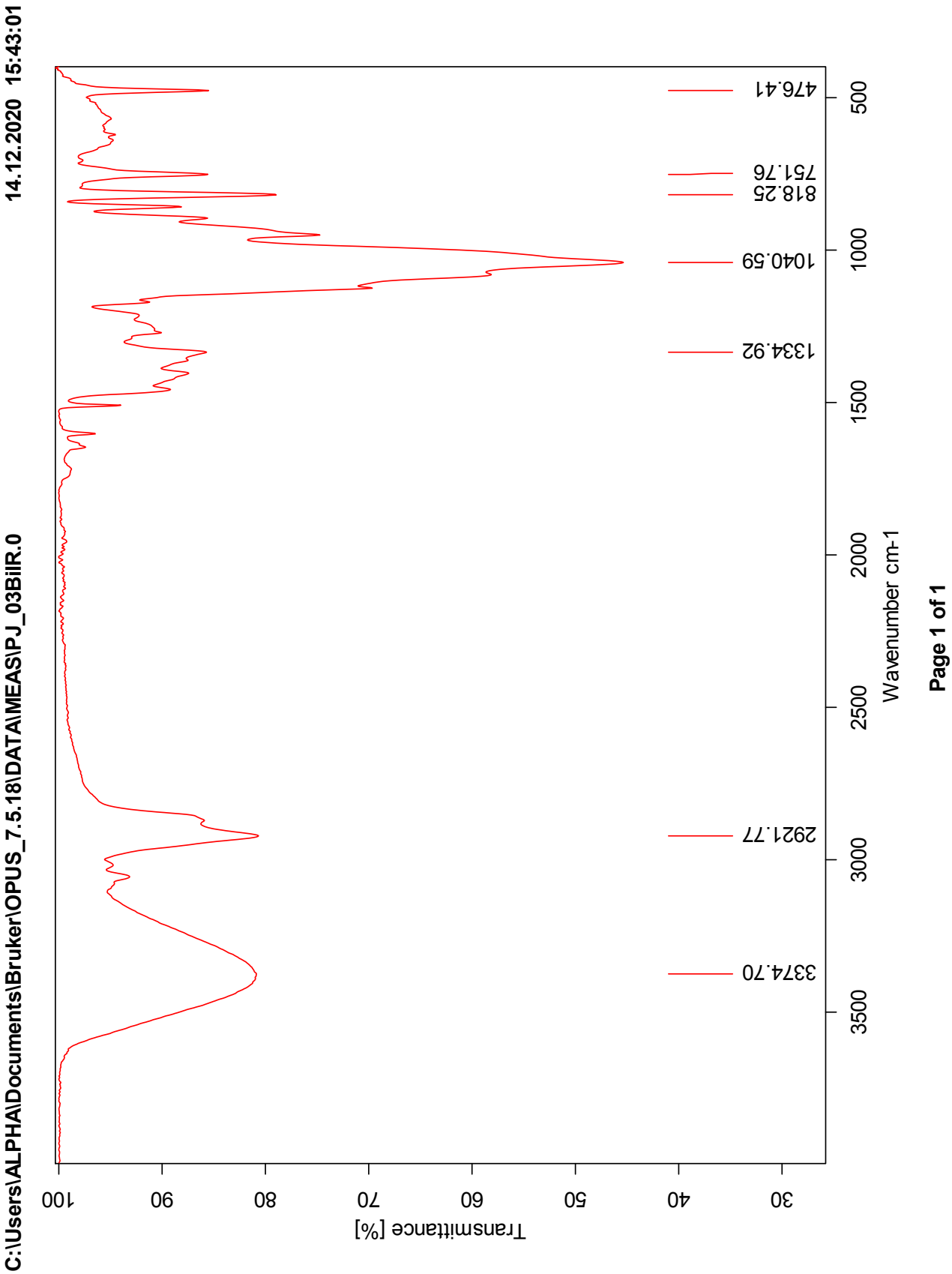


Figure A.20: IR spectrum of compound **3bi**.

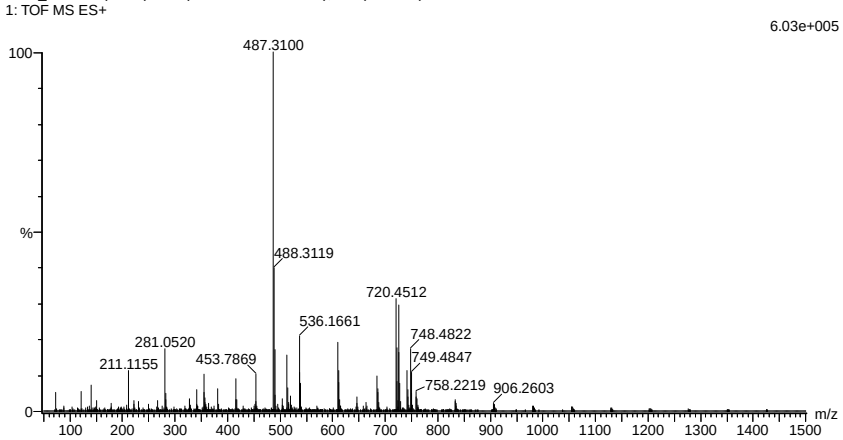
A.4 Spectroscopic data for compound 4

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
2195 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-1 O: 0-15 Na: 0-1 Si: 0-3

2020_501 130 (1.223) AM2 (Ar,35000.0,0.00,0.00); Cm (130:133)
1: TOF MS ES+



Minimum:				-50.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
720.4512	720.4511	0.1	0.1	7.5	1312.7	0.048	95.35	C38 H70 N O6 Si3
	720.4510	0.2	0.3	1.5	1321.0	8.361	0.02	C34 H67 N O13 Na
	720.4514	-0.2	-0.3	0.5	1315.9	3.271	3.80	C33 H71 N O10 Na Si2
	720.4507	0.5	0.7	8.5	1317.4	4.786	0.83	C39 H66 N O9 Si

Figure A.21: HRMS (ESI+) spectrum of compound **4**.

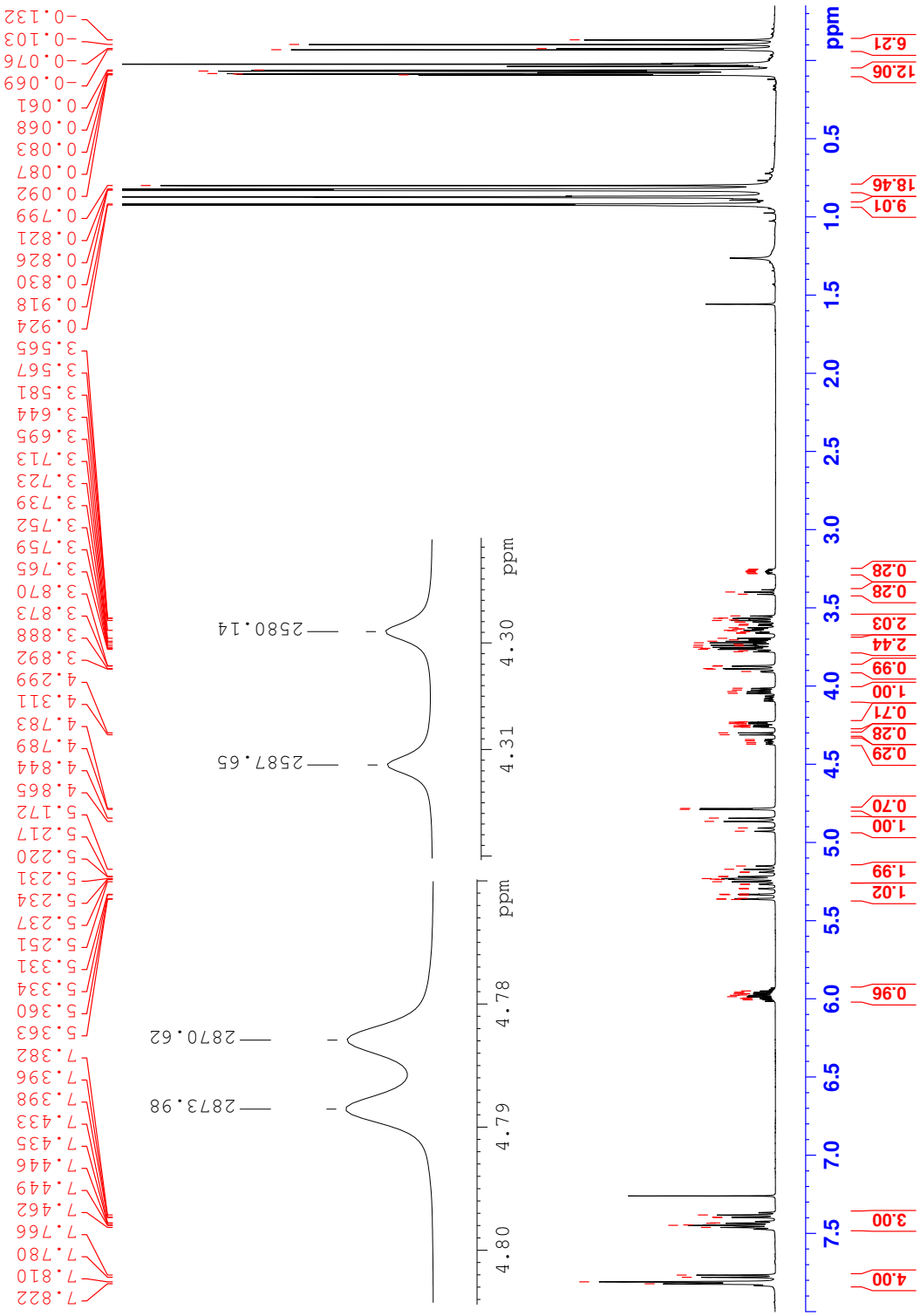


Figure A.22: ^{1}H NMR spectrum of compound **4**.

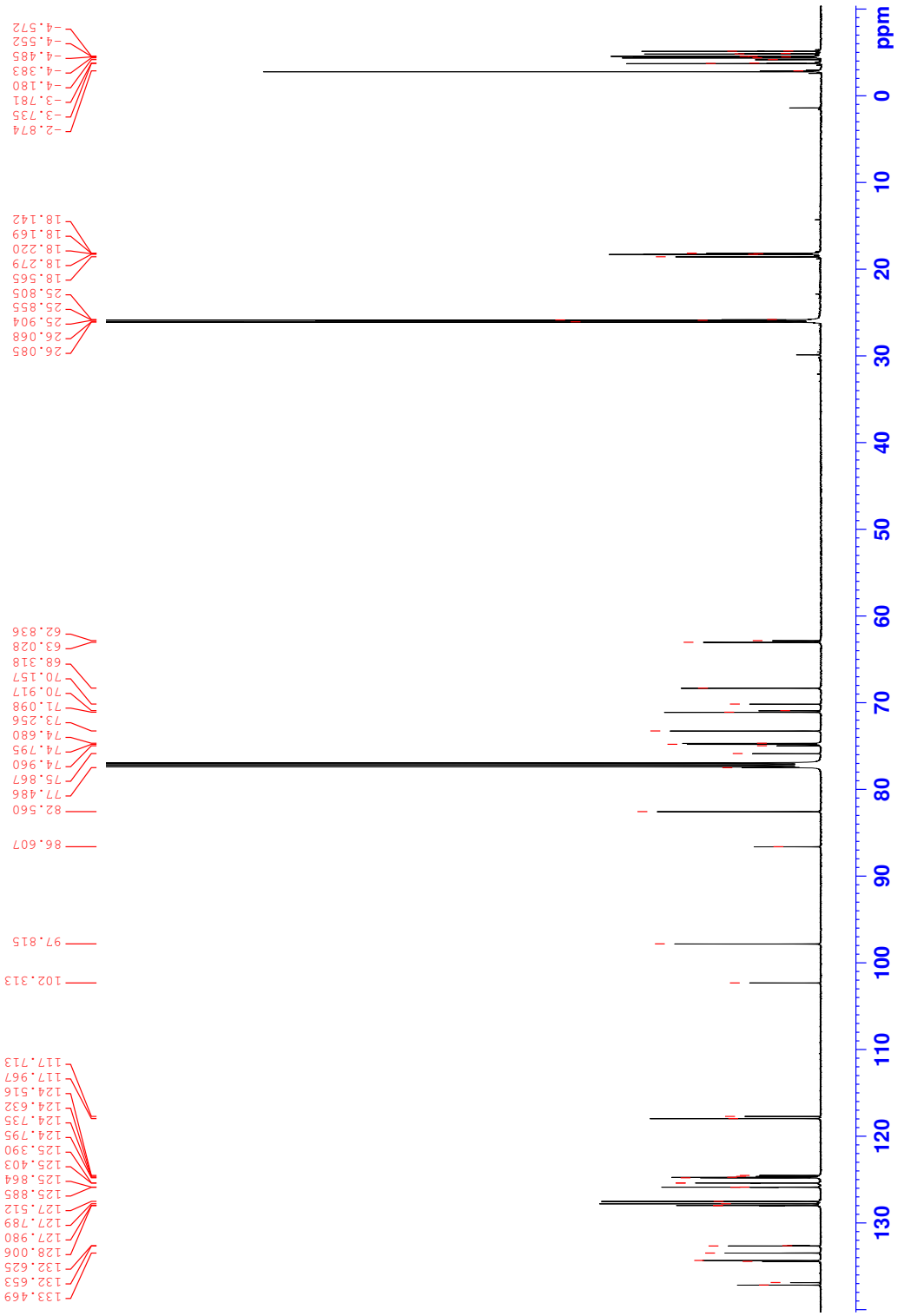


Figure A.23: ^{13}C NMR spectrum of compound **4**.

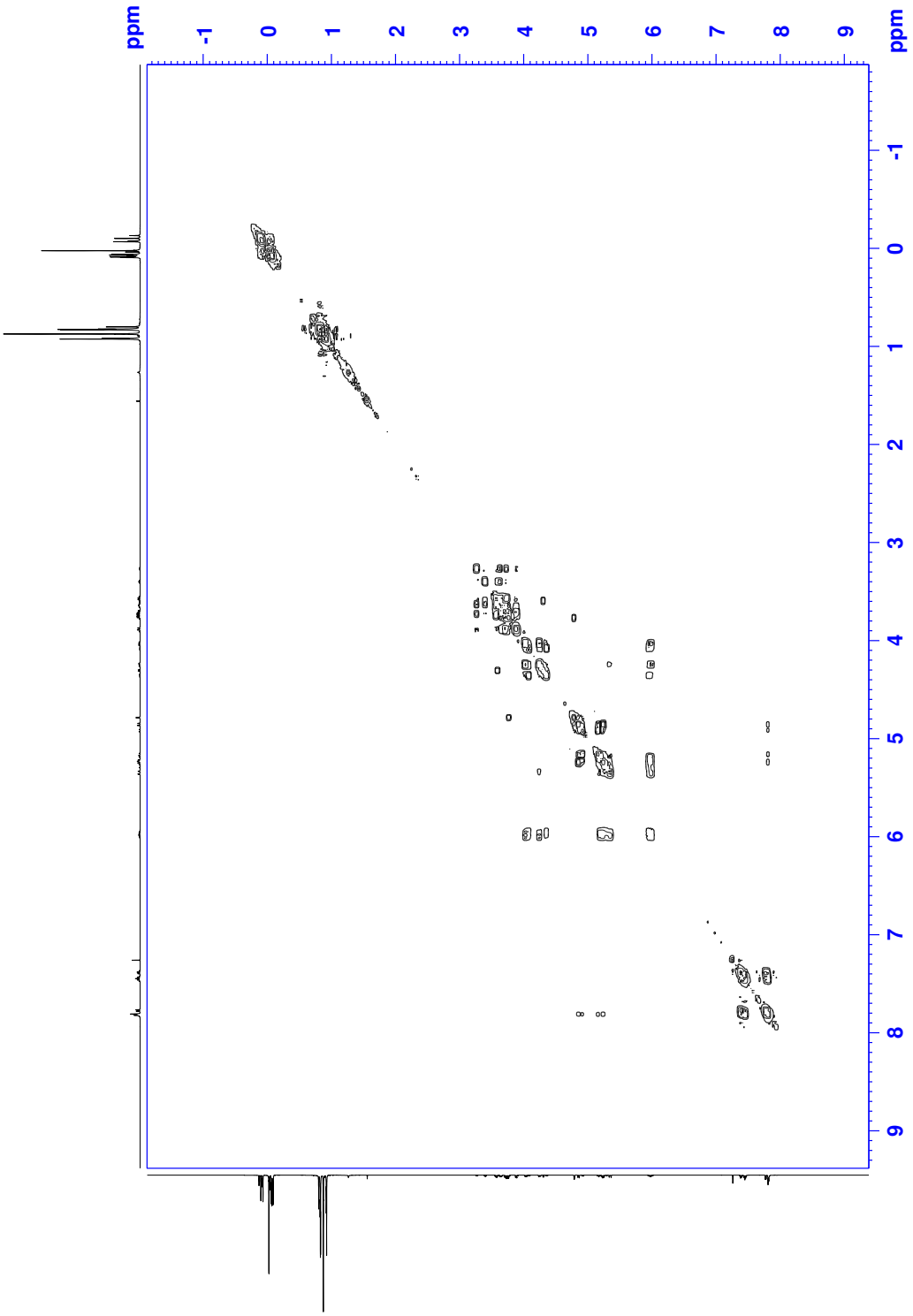


Figure A.24: COSY spectrum of compound **4**.

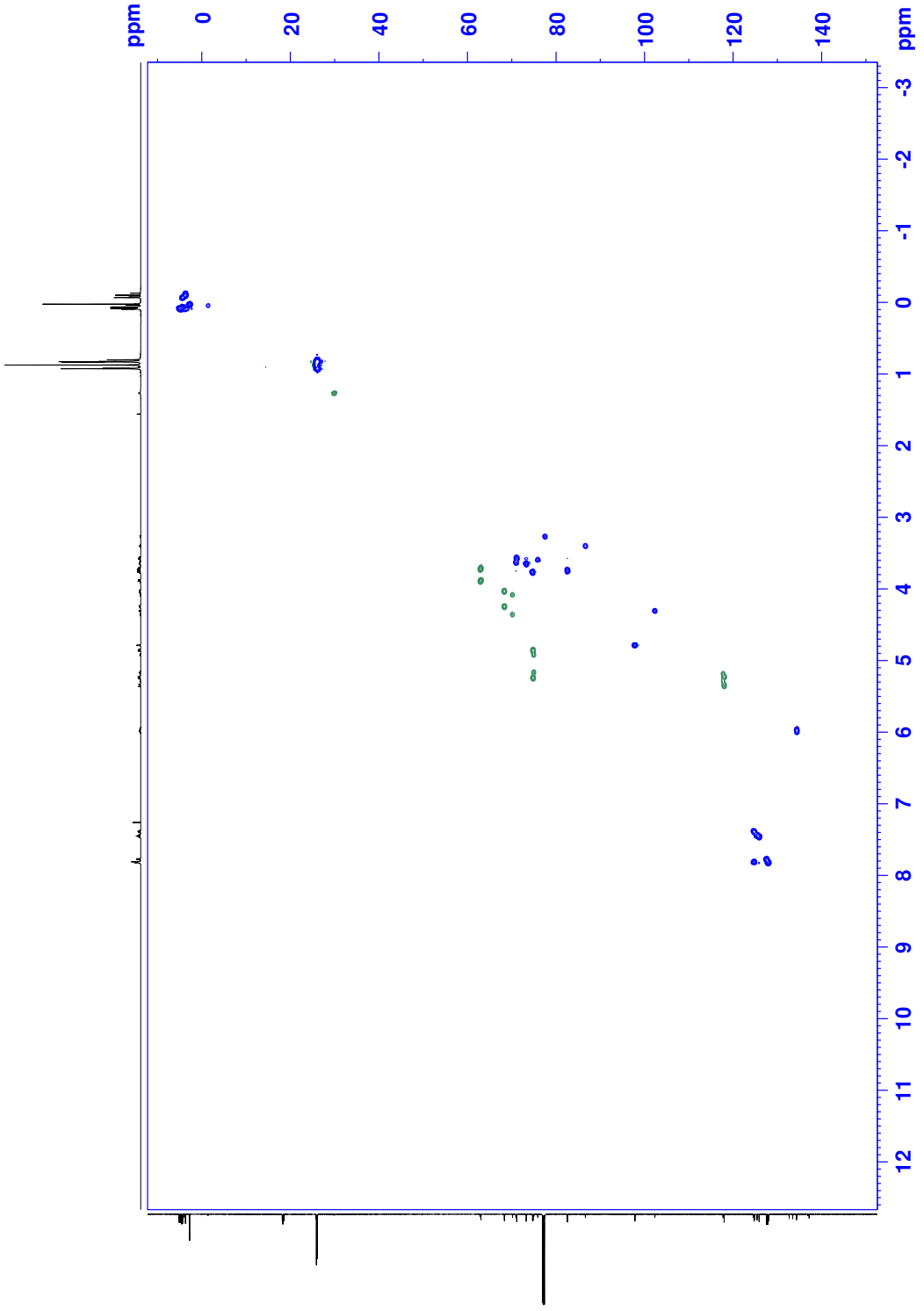


Figure A.25: HSQC spectrum of compound **4**.

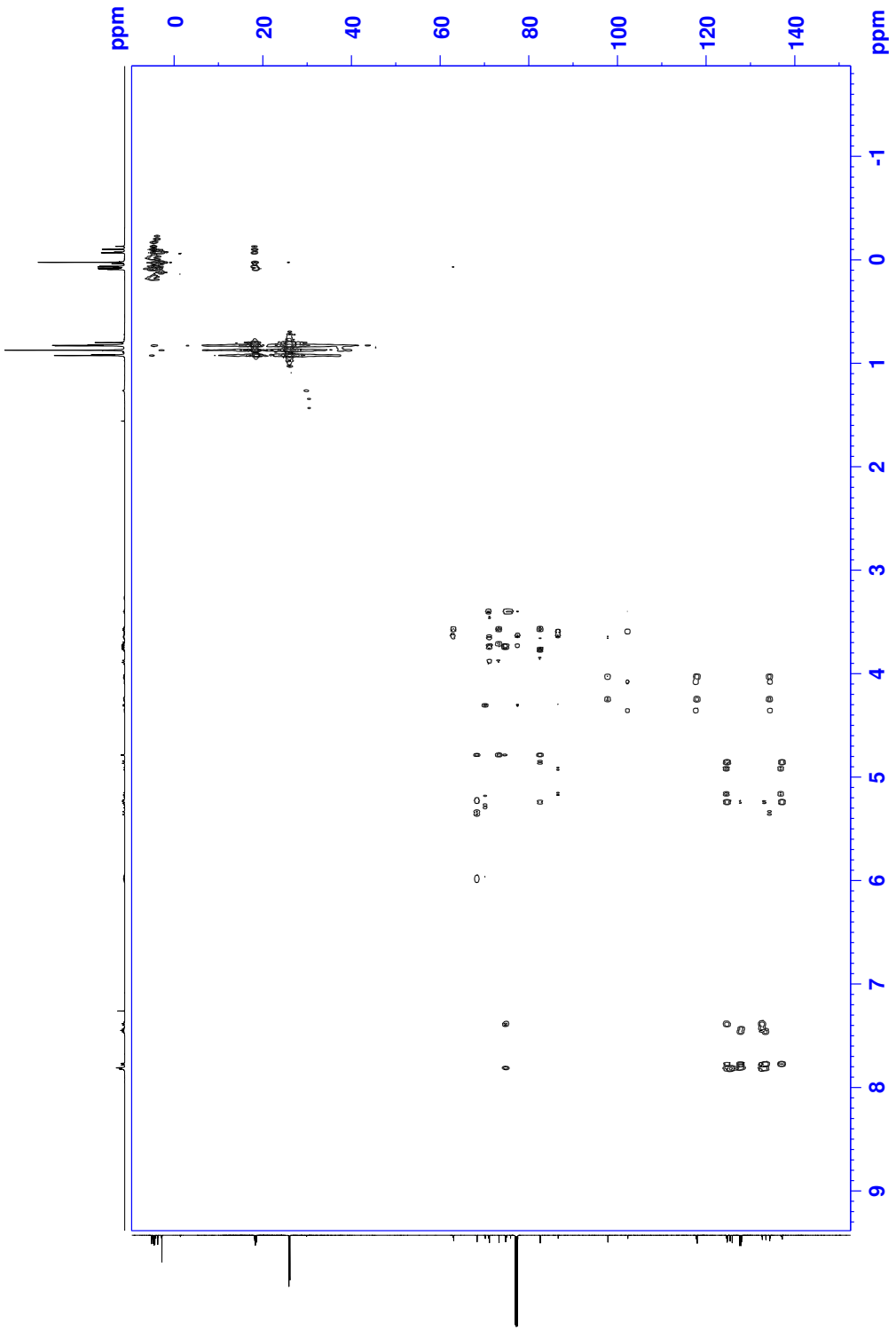


Figure A.26: HMBC spectrum of compound **4**.

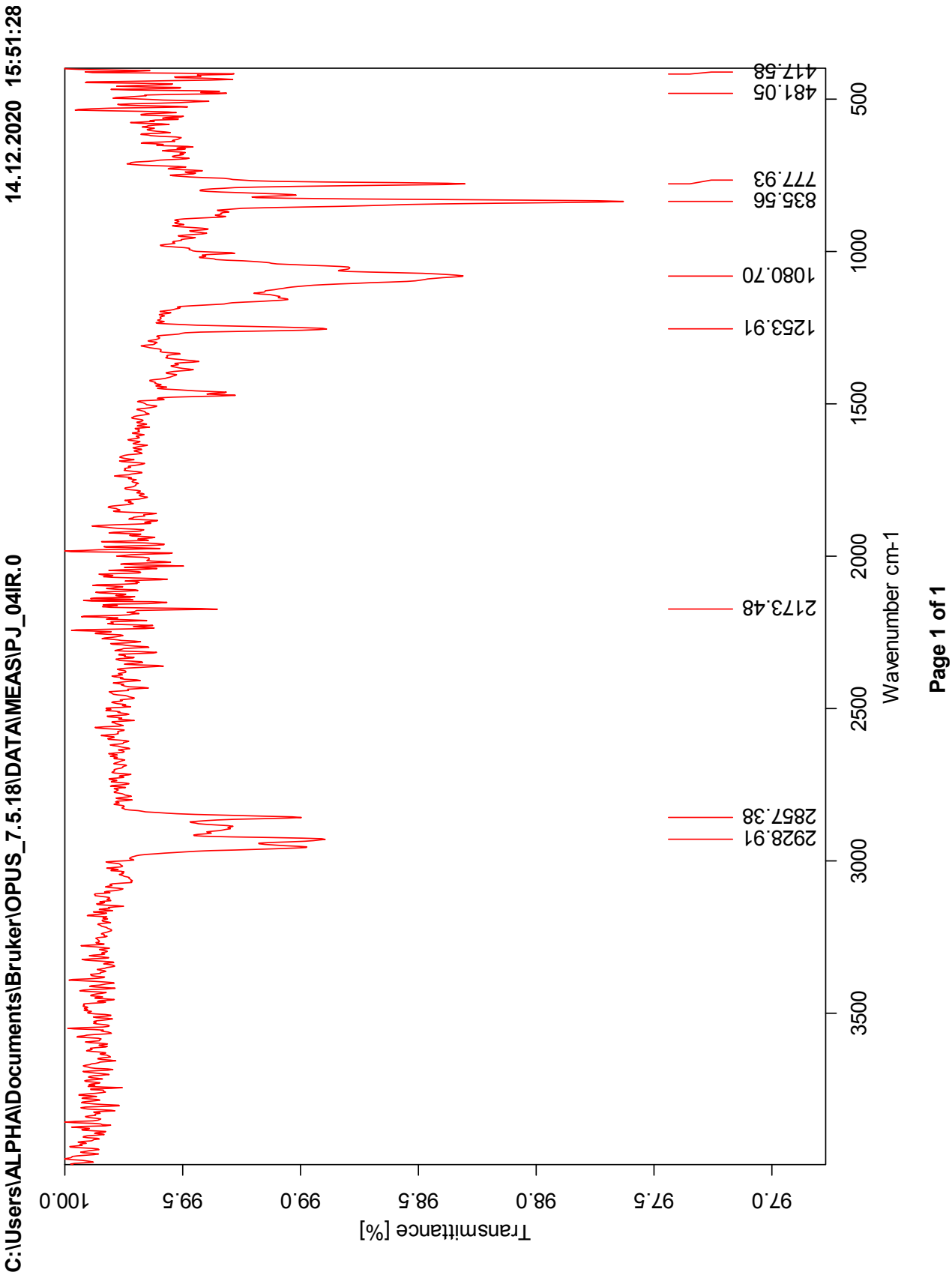


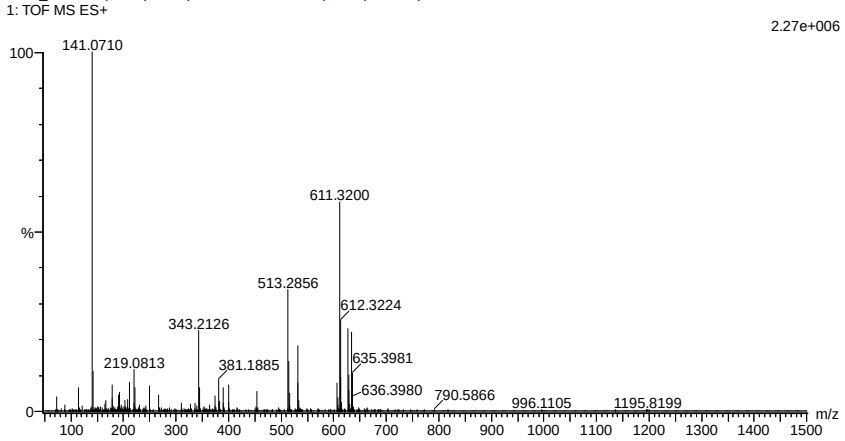
Figure A.27: IR spectrum of compound **4**.

A.5 Spectroscopic data for compound 5

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
2176 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-1 O: 0-15 Na: 0-1 Si: 0-3
2020_502 112 (1.057) AM2 (Ar,35000.0,0.00,0.00); Cm (110:120)
1: TOF MS ES+



Minimum:				-50.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
611.3200	611.3200	0.0	0.0	8.5	1541.4	0.014	98.63	C32 H52 O6 Na Si2
	611.3197	0.3	0.5	15.5	1555.4	13.984	0.00	C37 H51 O2 Si3
	611.3196	0.4	0.7	9.5	1559.9	18.489	0.00	C33 H48 O9 Na
	611.3193	0.7	1.1	16.5	1545.7	4.288	1.37	C38 H47 O5 Si

Figure A.28: HRMS (ESI+) spectrum of compound **5**.

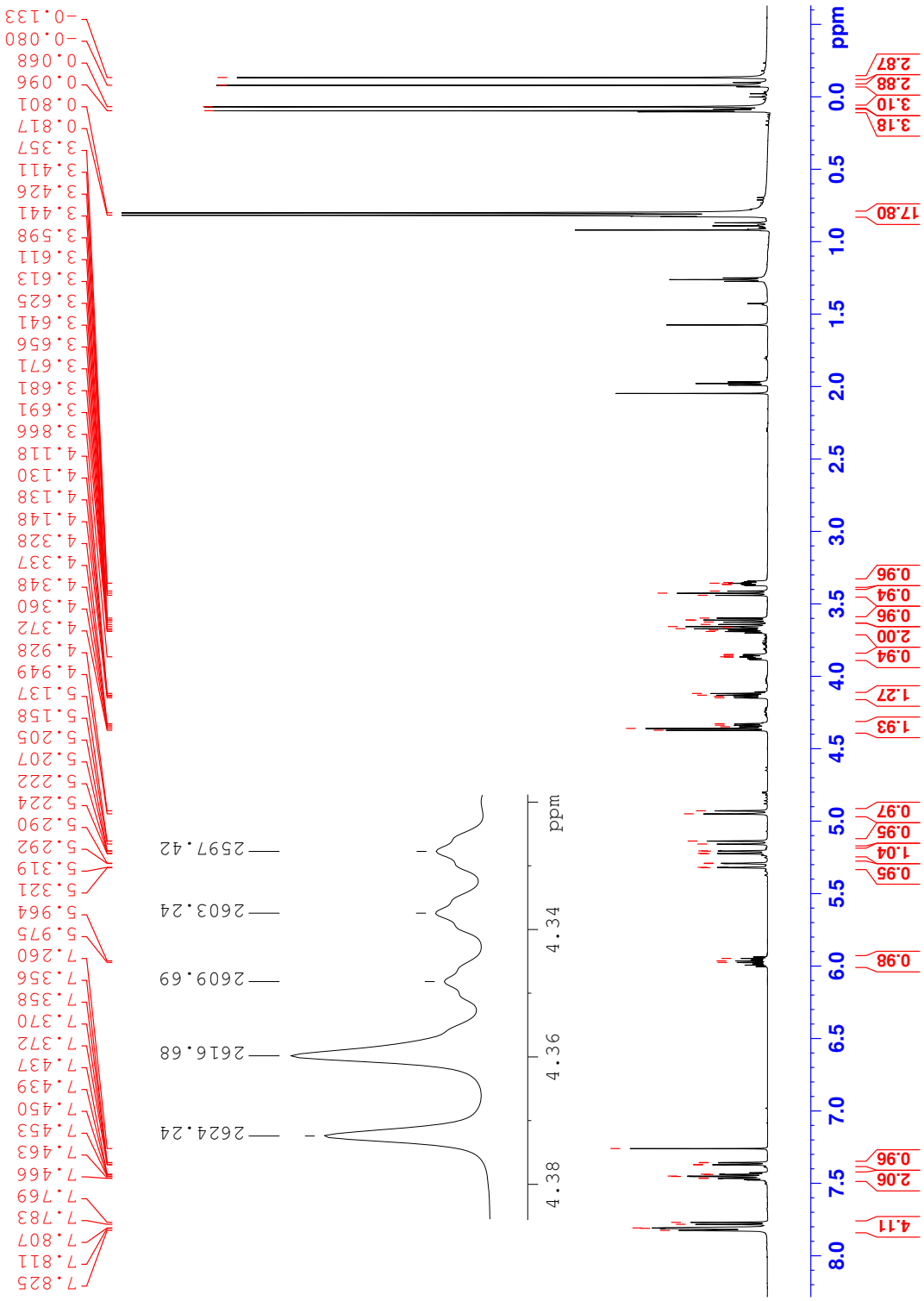


Figure A.29: ^{1}H NMR spectrum of compound **5**.

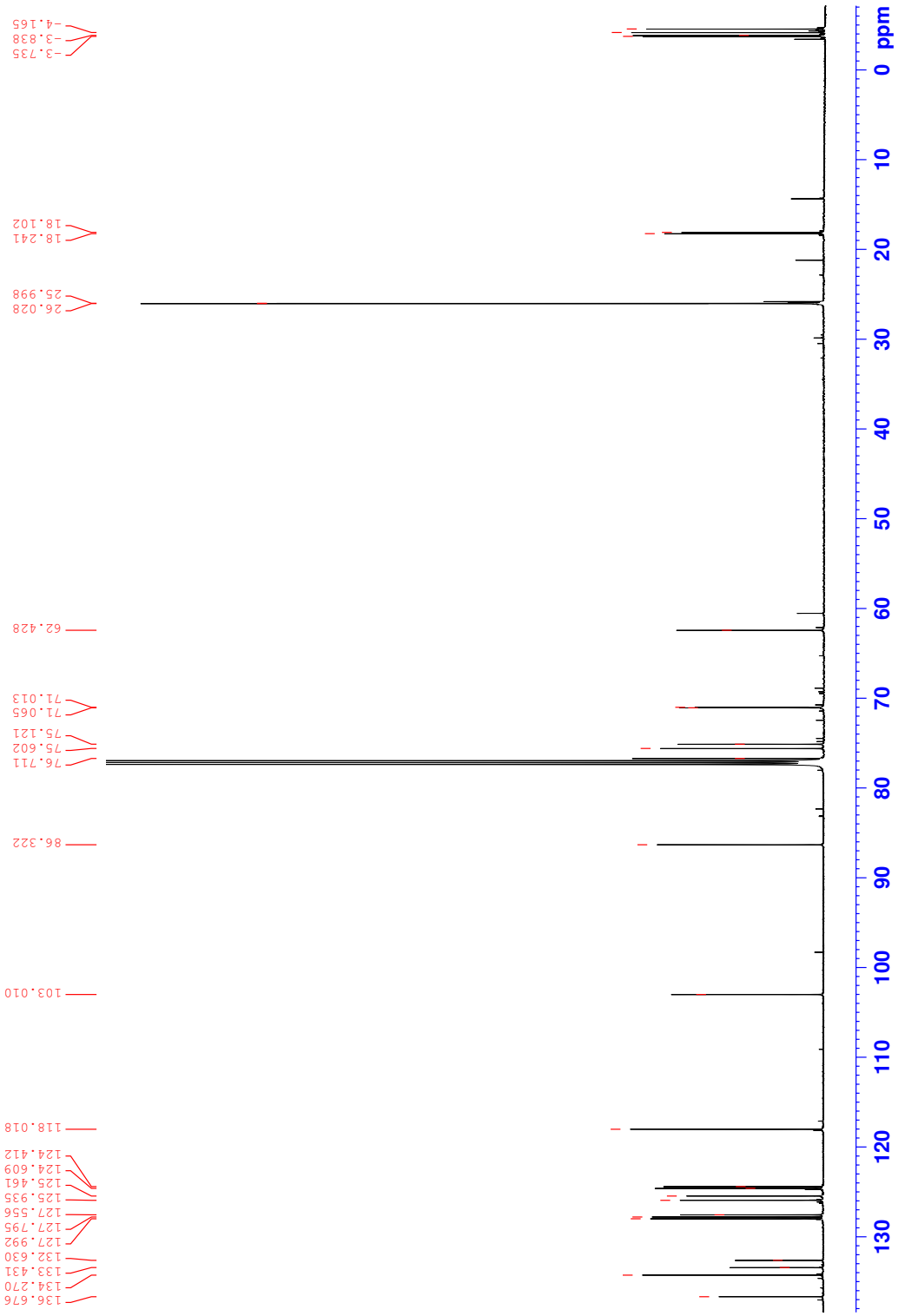


Figure A.30: ^{13}C NMR spectrum of compound **5**.

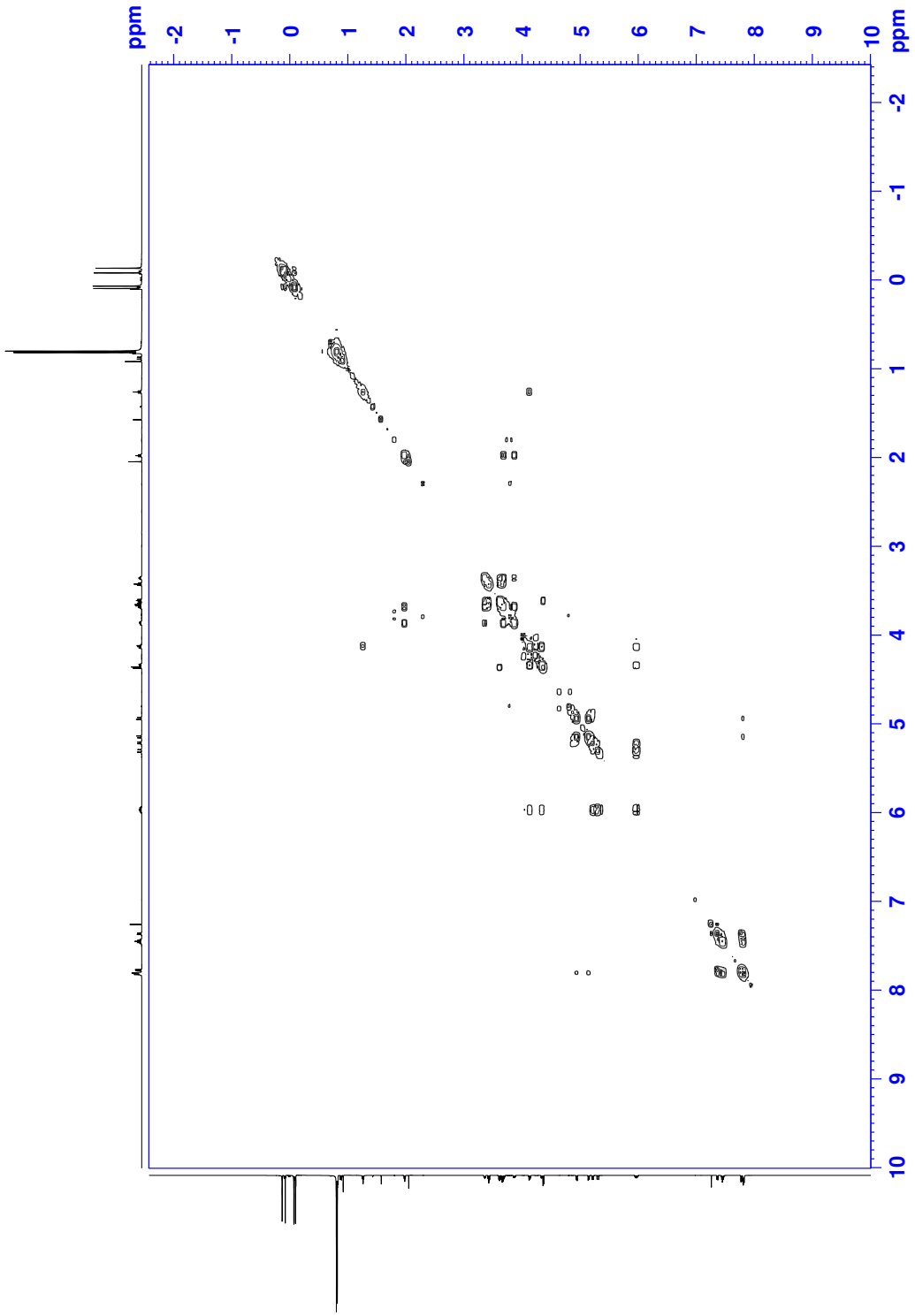


Figure A.31: COSY spectrum of compound **5**.

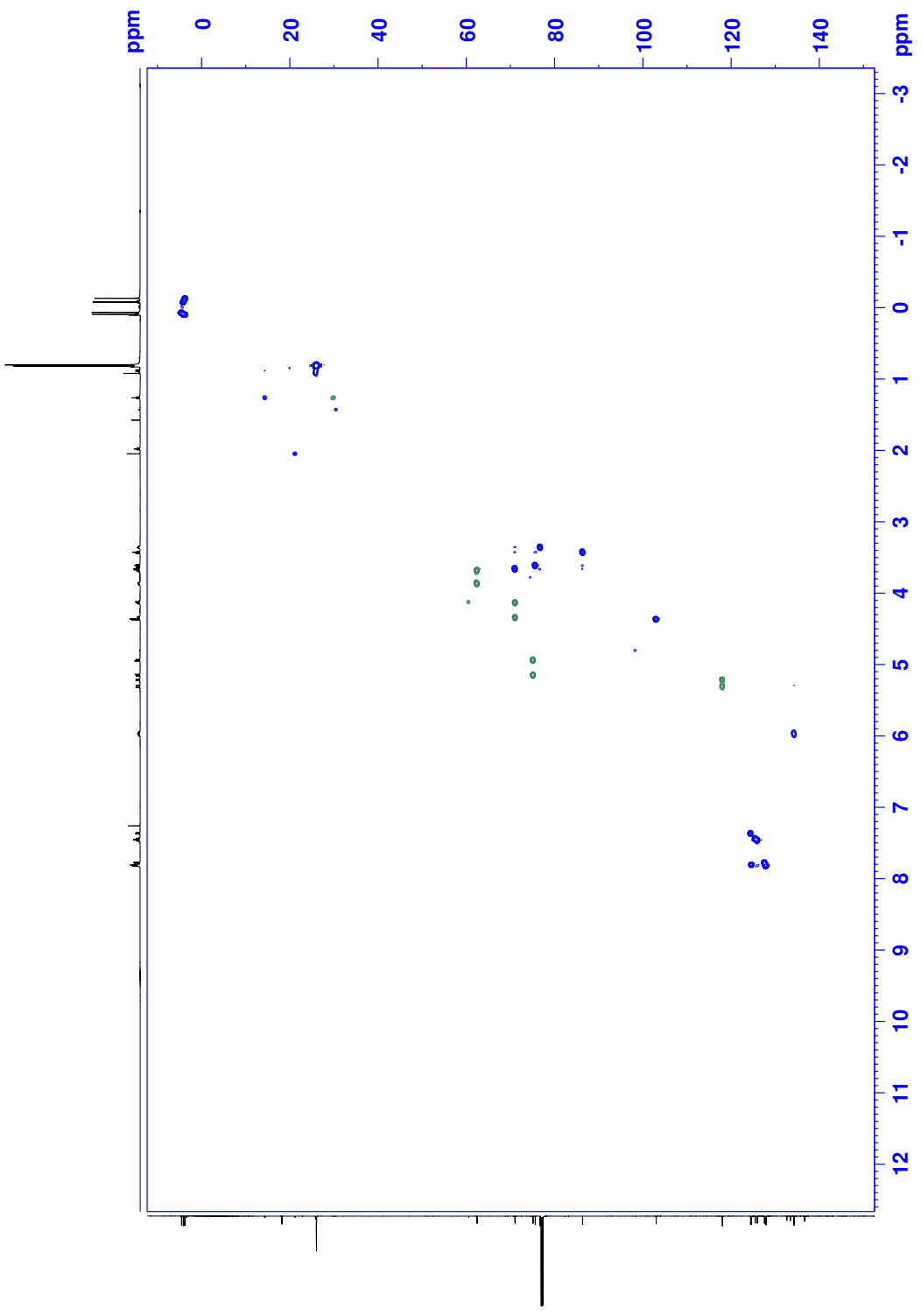


Figure A.32: HSQC spectrum of compound **5**.

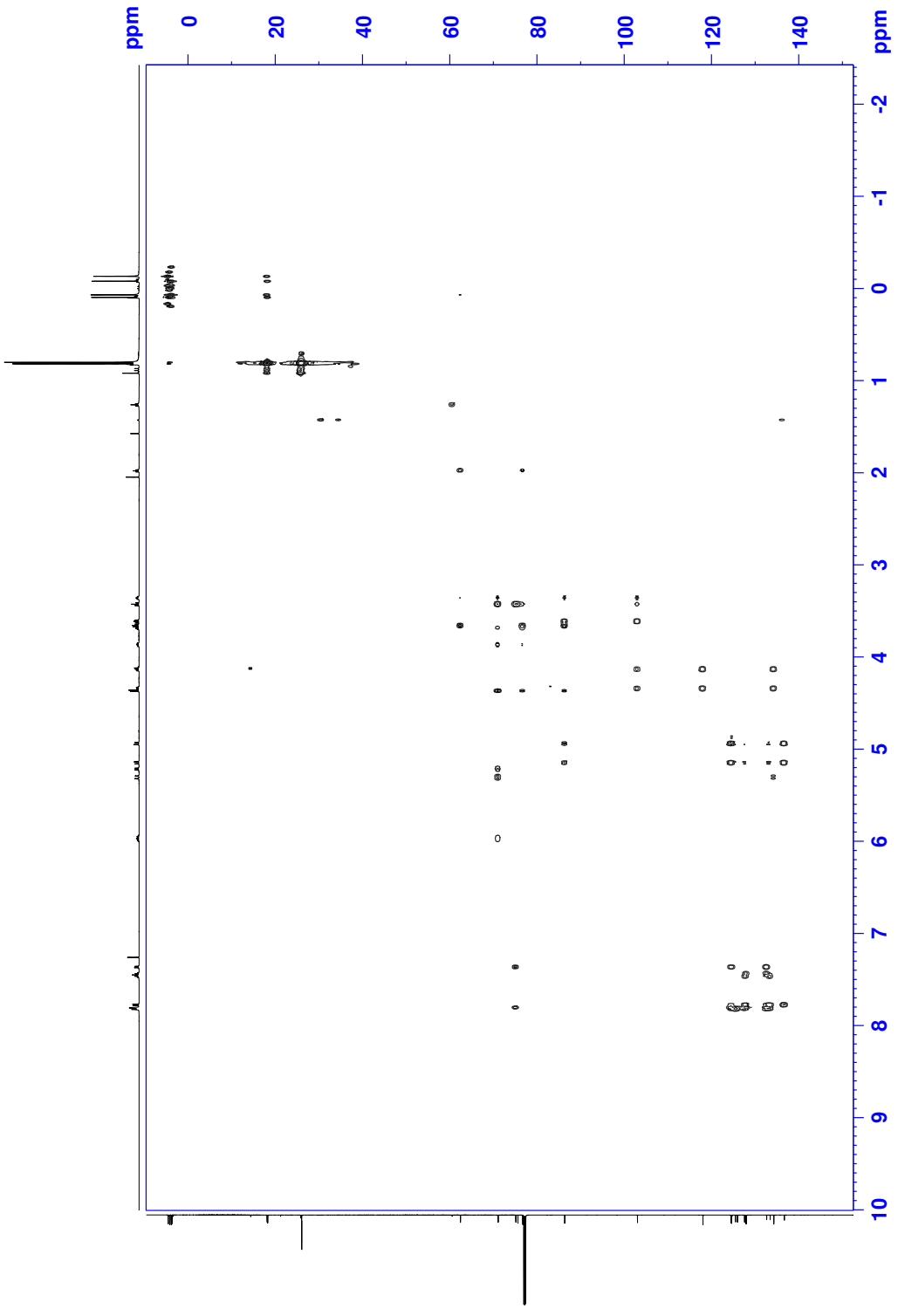


Figure A.33: HMBC spectrum of compound **5**.

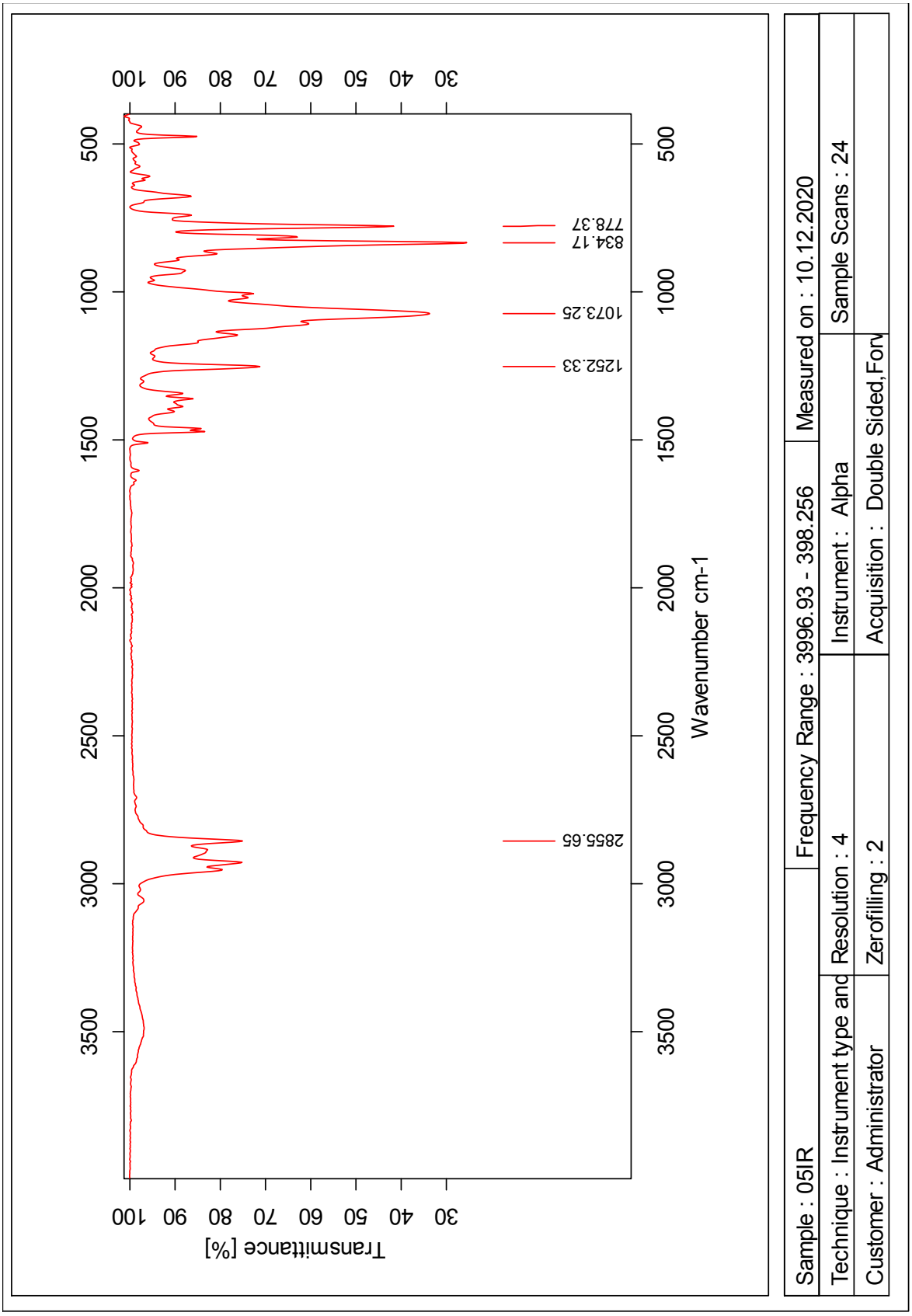


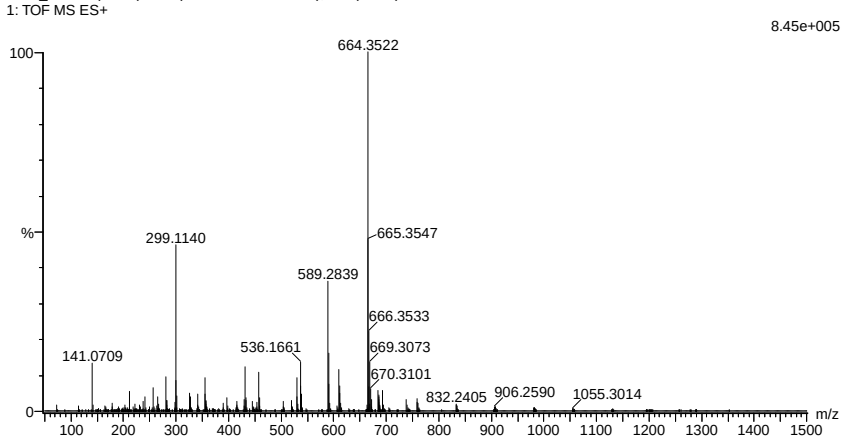
Figure A.34: IR spectrum of compound **5**.

A.6 Spectroscopic data for compound 6

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
2179 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-1 O: 0-15 Si: 0-3 S: 0-1
2020_503 87 (0.823) AM2 (Ar,35000.0,0.00,0.00); Cm (87:88)
1: TOF MS ES+



Minimum:				-50.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
664.3522	664.3523	-0.1	-0.2	8.5	1443.1	0.763	46.62	C34 H58 N O6 Si2 S
	664.3521	0.1	0.2	8.5	1443.3	0.953	38.54	C33 H58 N O7 Si3
	664.3519	0.3	0.5	9.5	1444.9	2.546	7.84	C35 H54 N O9 S
	664.3517	0.5	0.8	9.5	1445.0	2.658	7.01	C34 H54 N O10 Si

Figure A.35: HRMS (ESI+) spectrum of compound **6**.

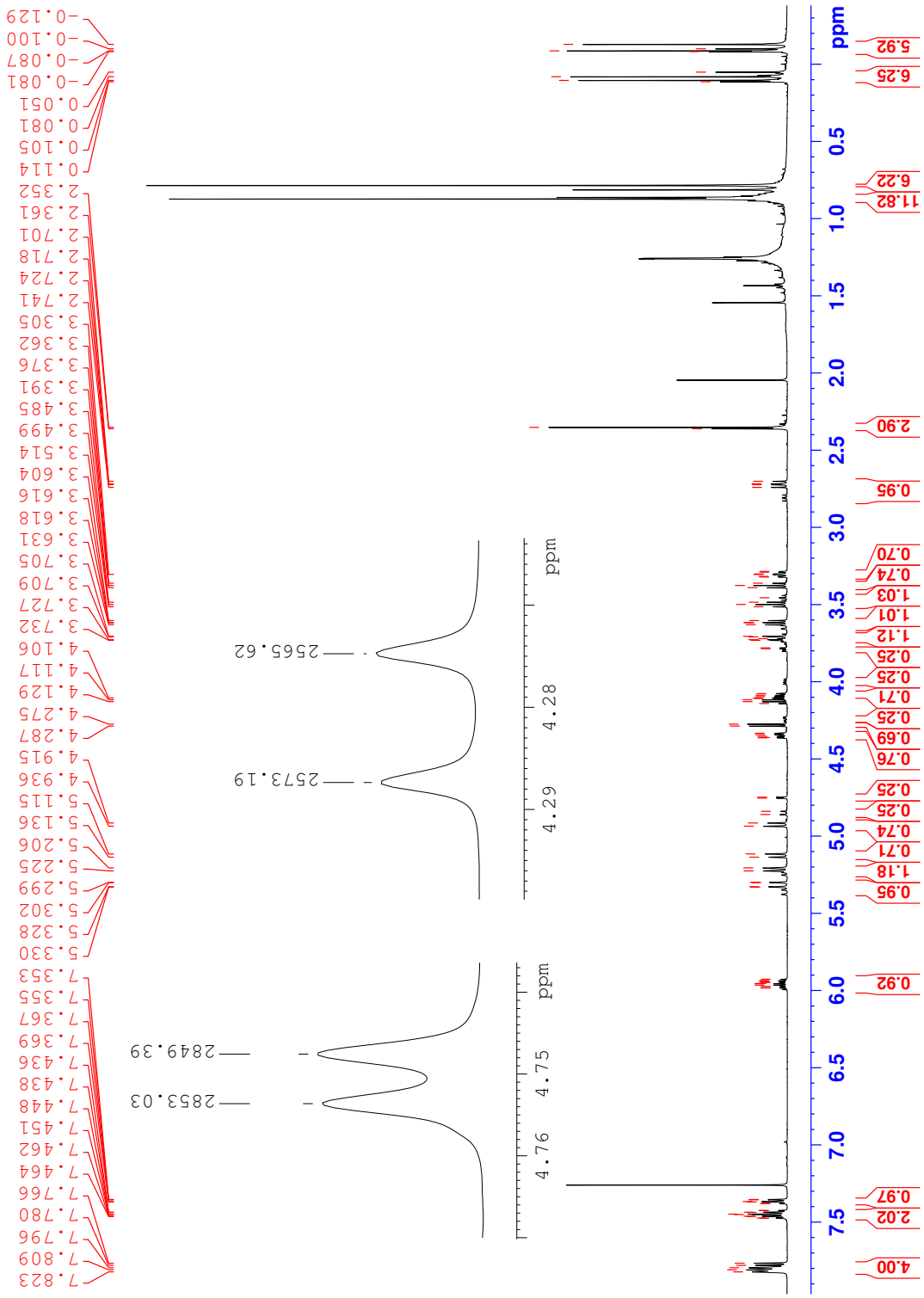


Figure A.36: ^{1}H NMR spectrum of compound **6**.

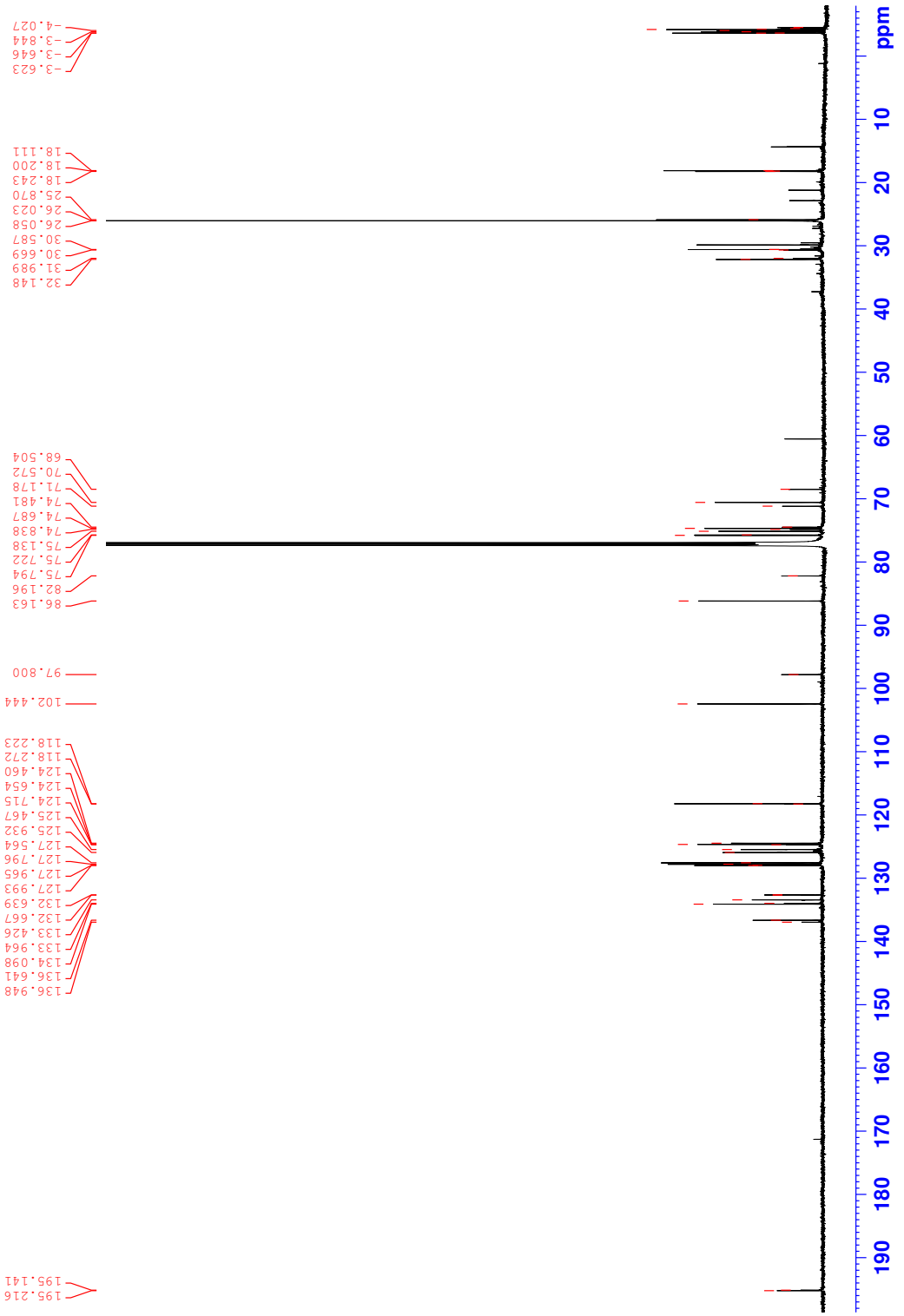


Figure A.37: ^{13}C NMR spectrum of compound **6**.

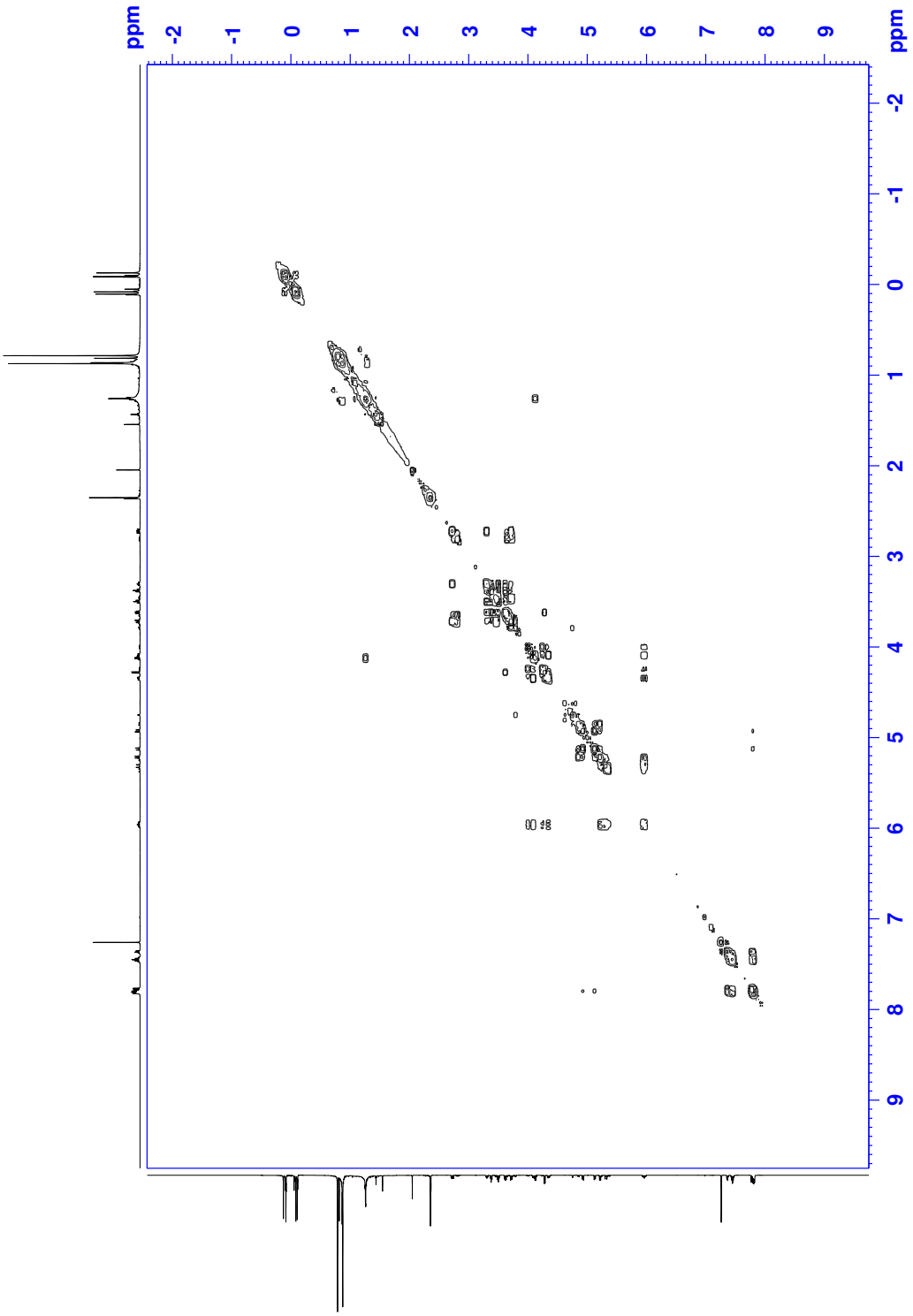


Figure A.38: COSY spectrum of compound **6**.

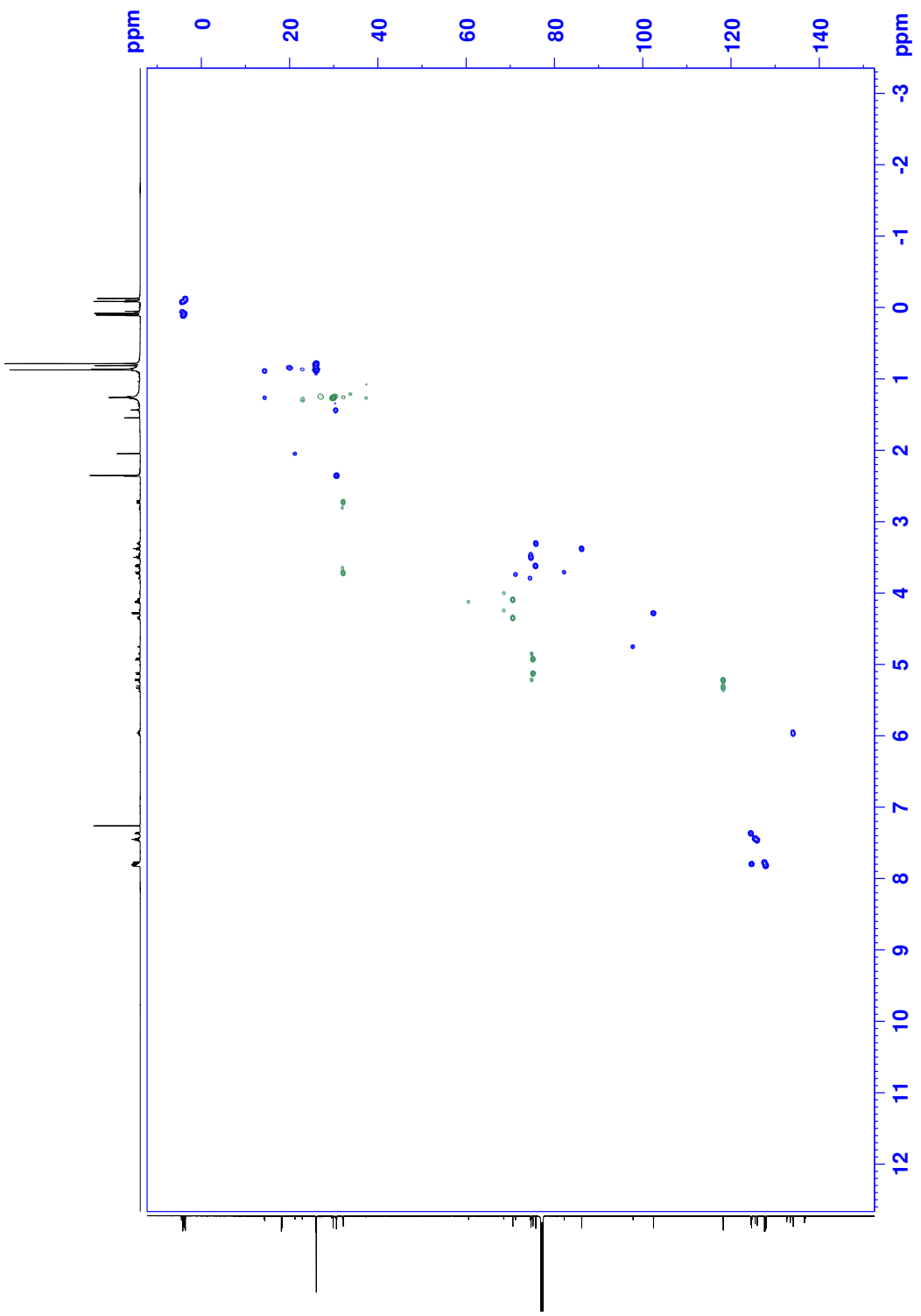


Figure A.39: HSQC spectrum of compound **6**.

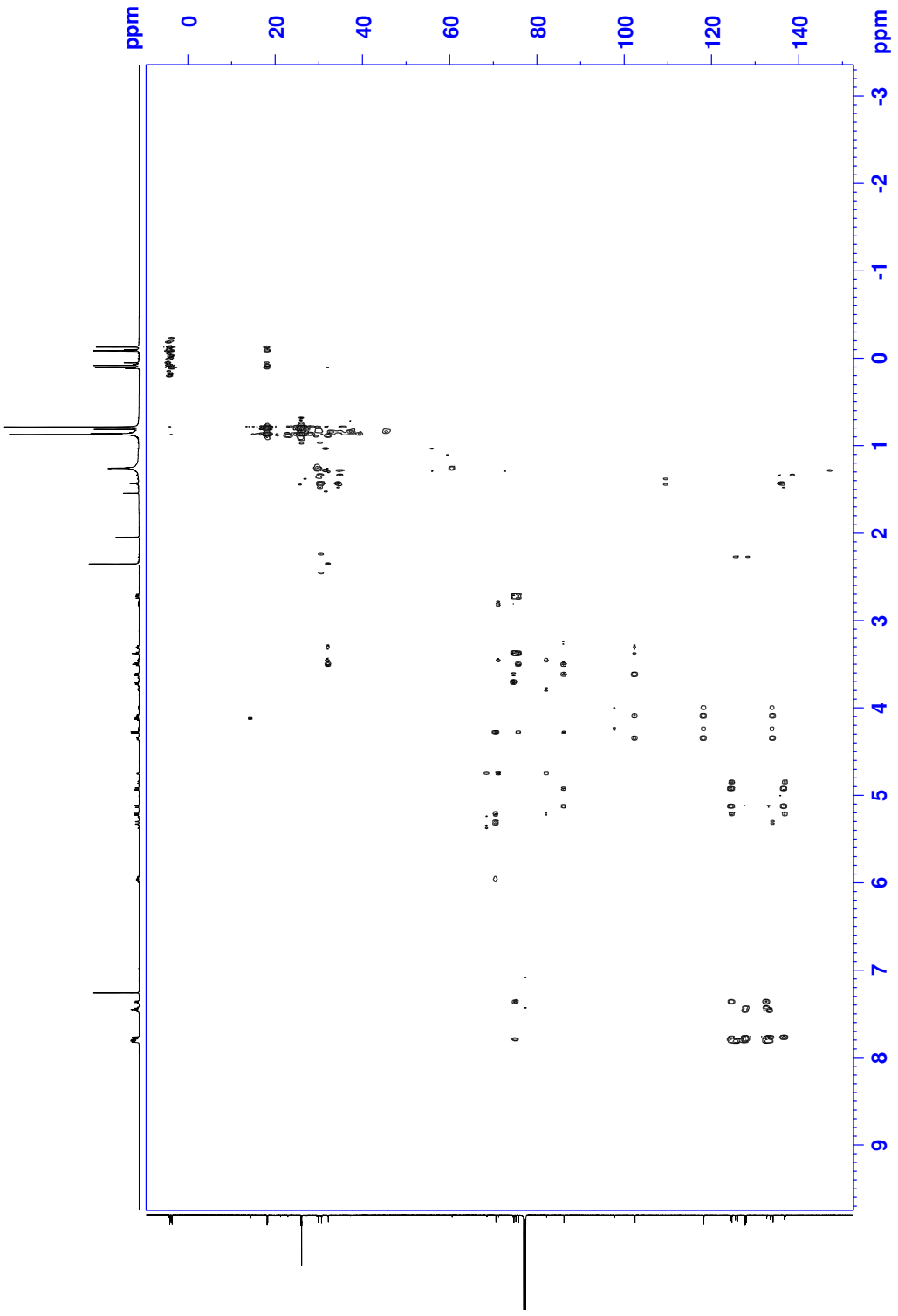


Figure A.40: HMBC spectrum of compound **6**.

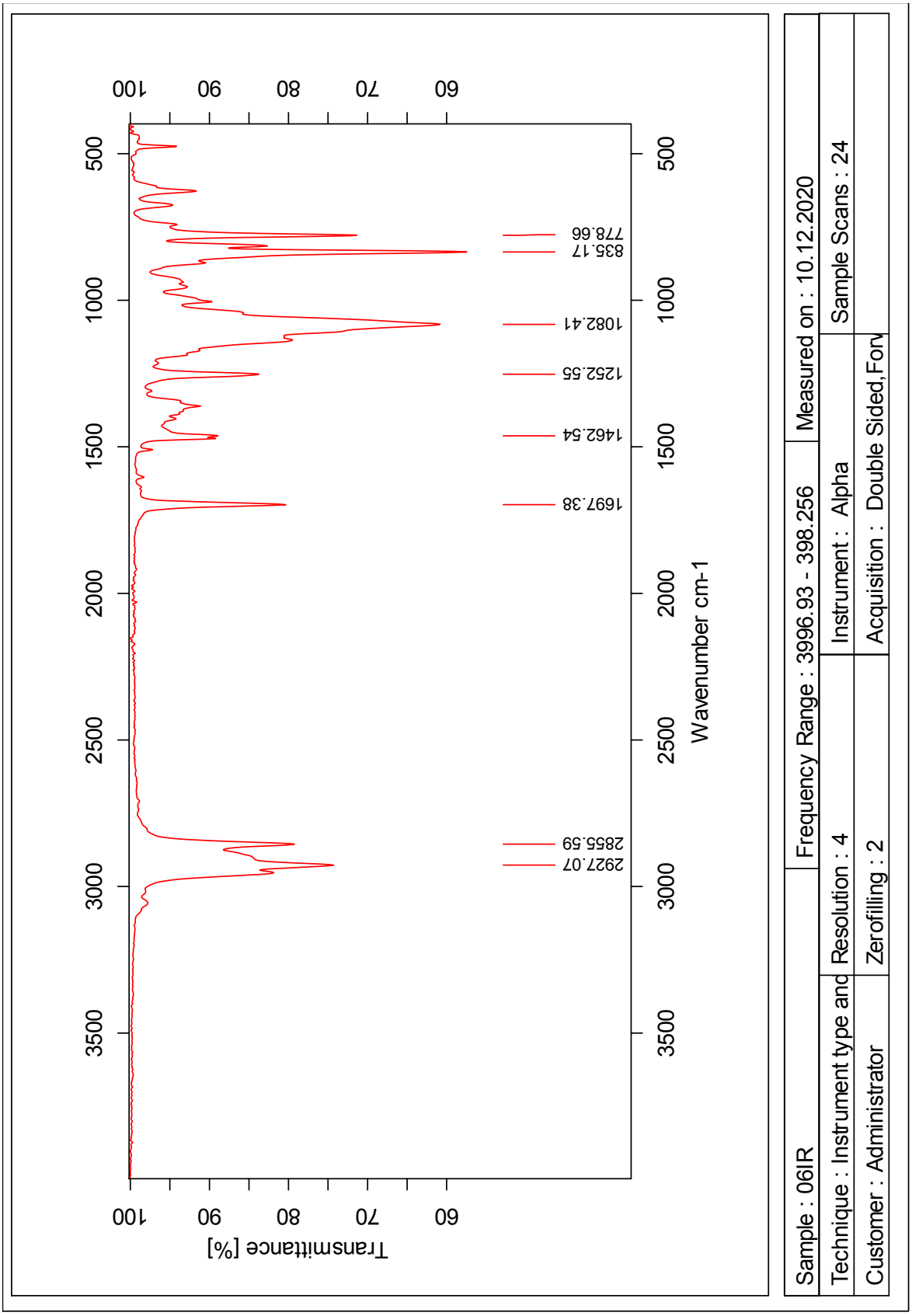


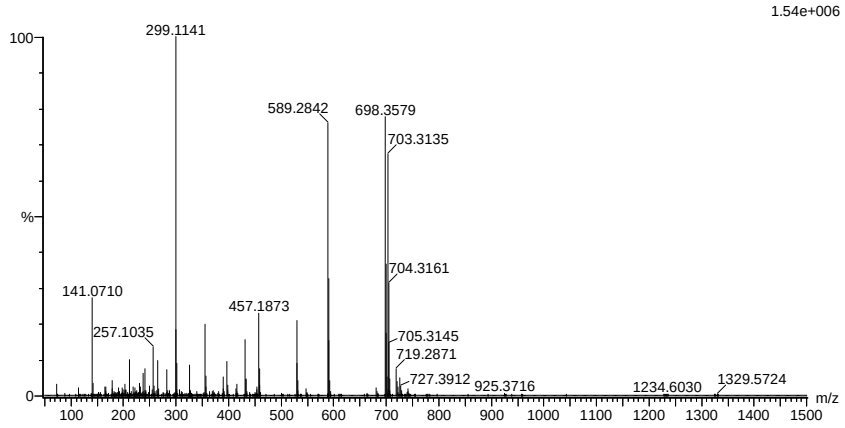
Figure A.41: IR spectrum of compound **6**.

A.7 Spectroscopic data for compound 7

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
2183 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-1 O: 0-15 Si: 0-3 S: 0-1
2020 504 87 (0.822) AM2 (Ar,35000.0,0.00,0.00); Cm (87:91)
1: TOF MS ES+



Minimum:				-50.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
698.3579	698.3578	0.1	0.1	7.5	1625.8	0.637	52.87	C34 H60 N O8 Si2 S
	698.3576	0.3	0.4	7.5	1626.0	0.903	40.54	C33 H60 N O9 Si3
	698.3574	0.5	0.7	8.5	1628.5	3.329	3.58	C35 H56 N O11 S
	698.3572	0.7	1.0	8.5	1628.6	3.502	3.01	C34 H56 N O12 Si

Figure A.42: HRMS (ESI+) spectrum of compound **7**.

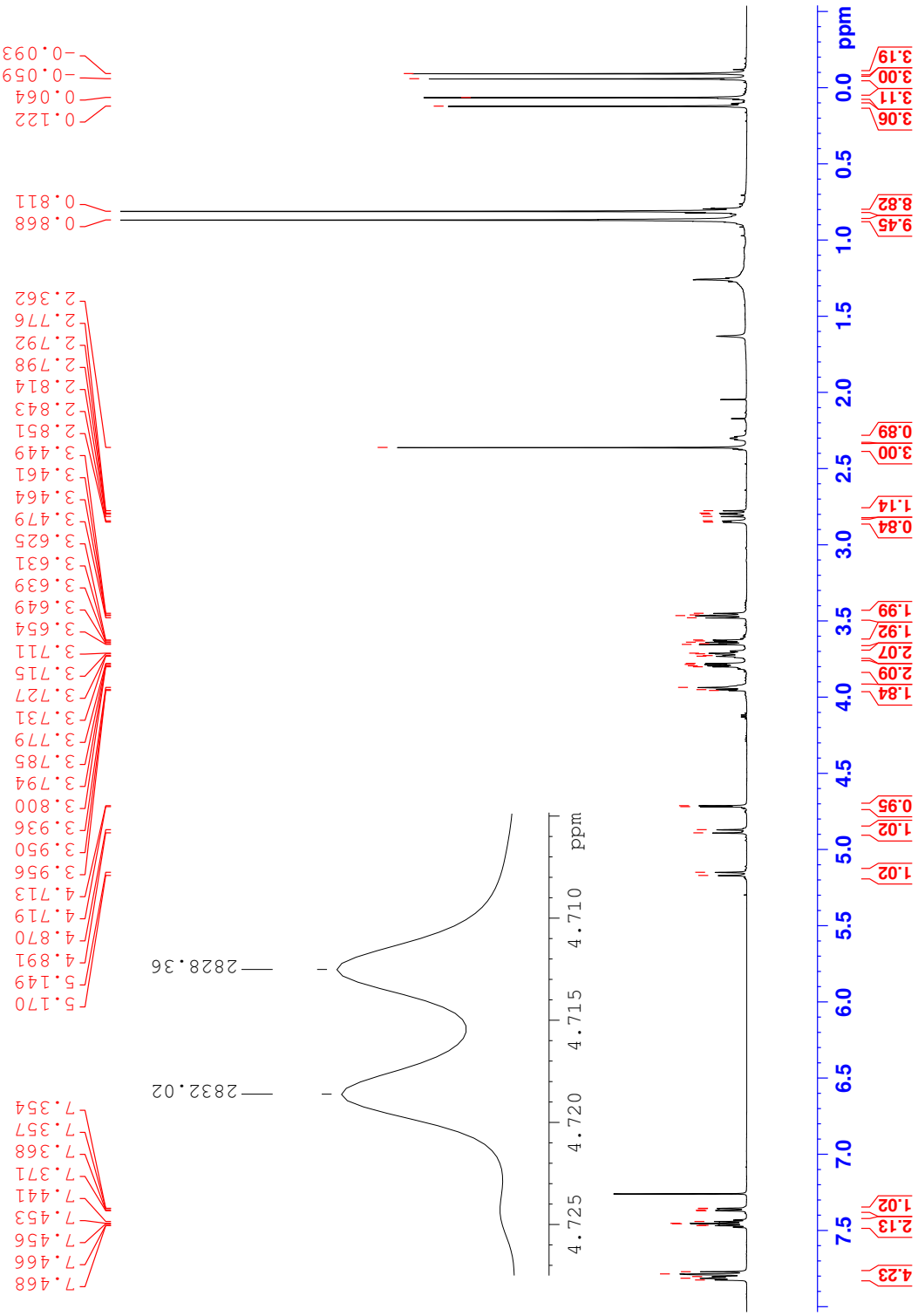


Figure A.43: ^{1}H NMR spectrum of compound **7**.

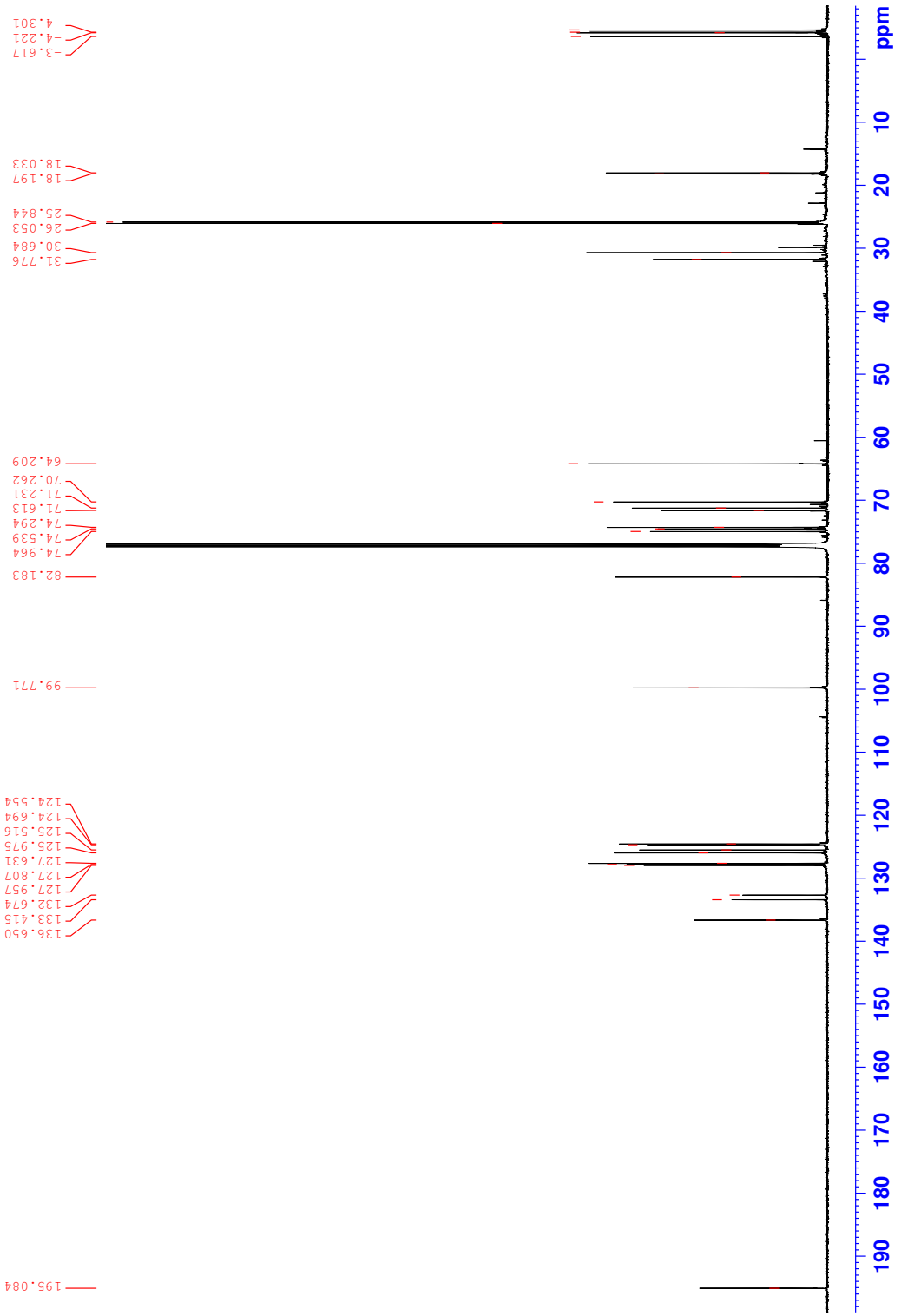


Figure A.44: ^{13}C NMR spectrum of compound **7**.

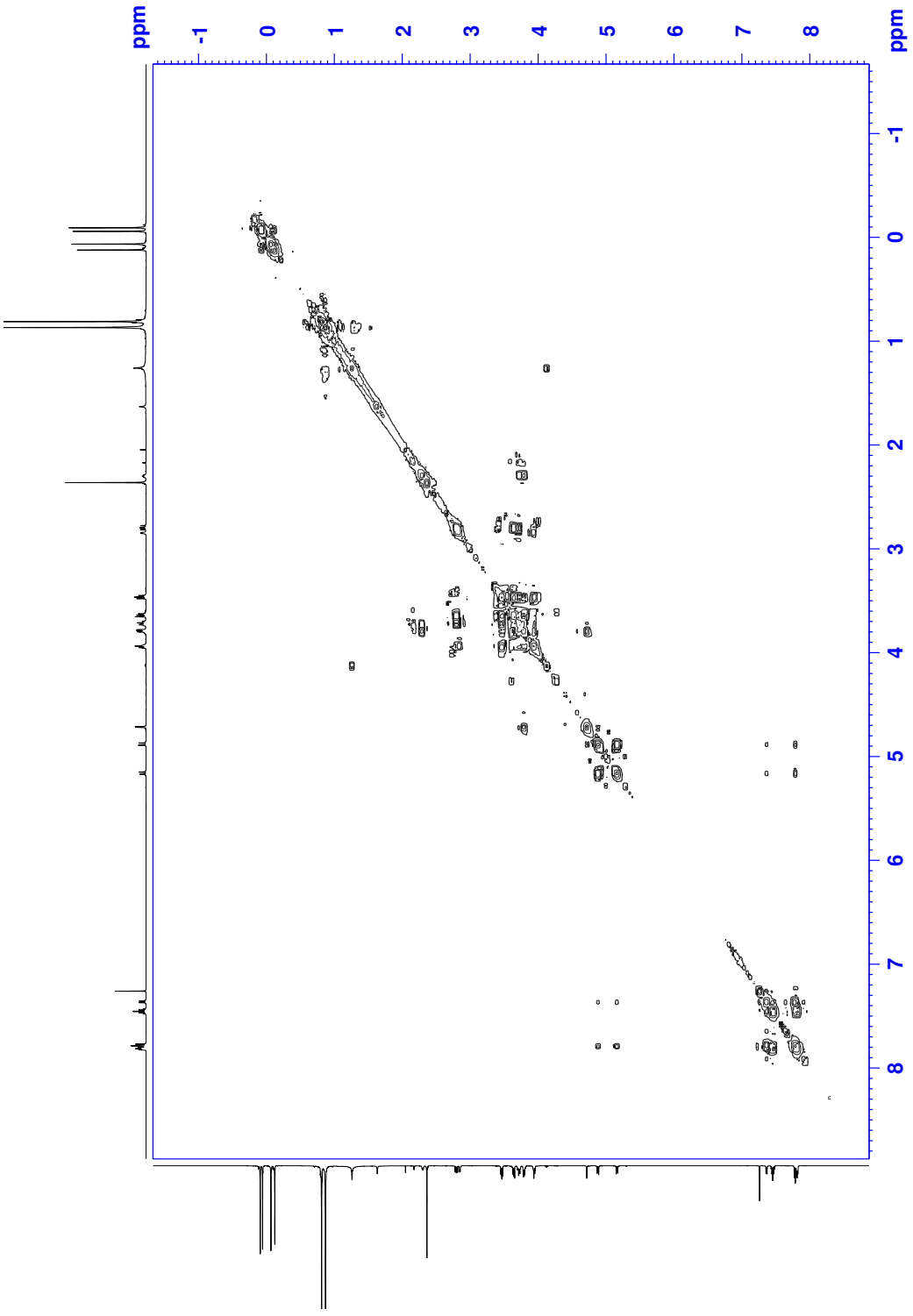


Figure A.45: COSY spectrum of compound **7**.

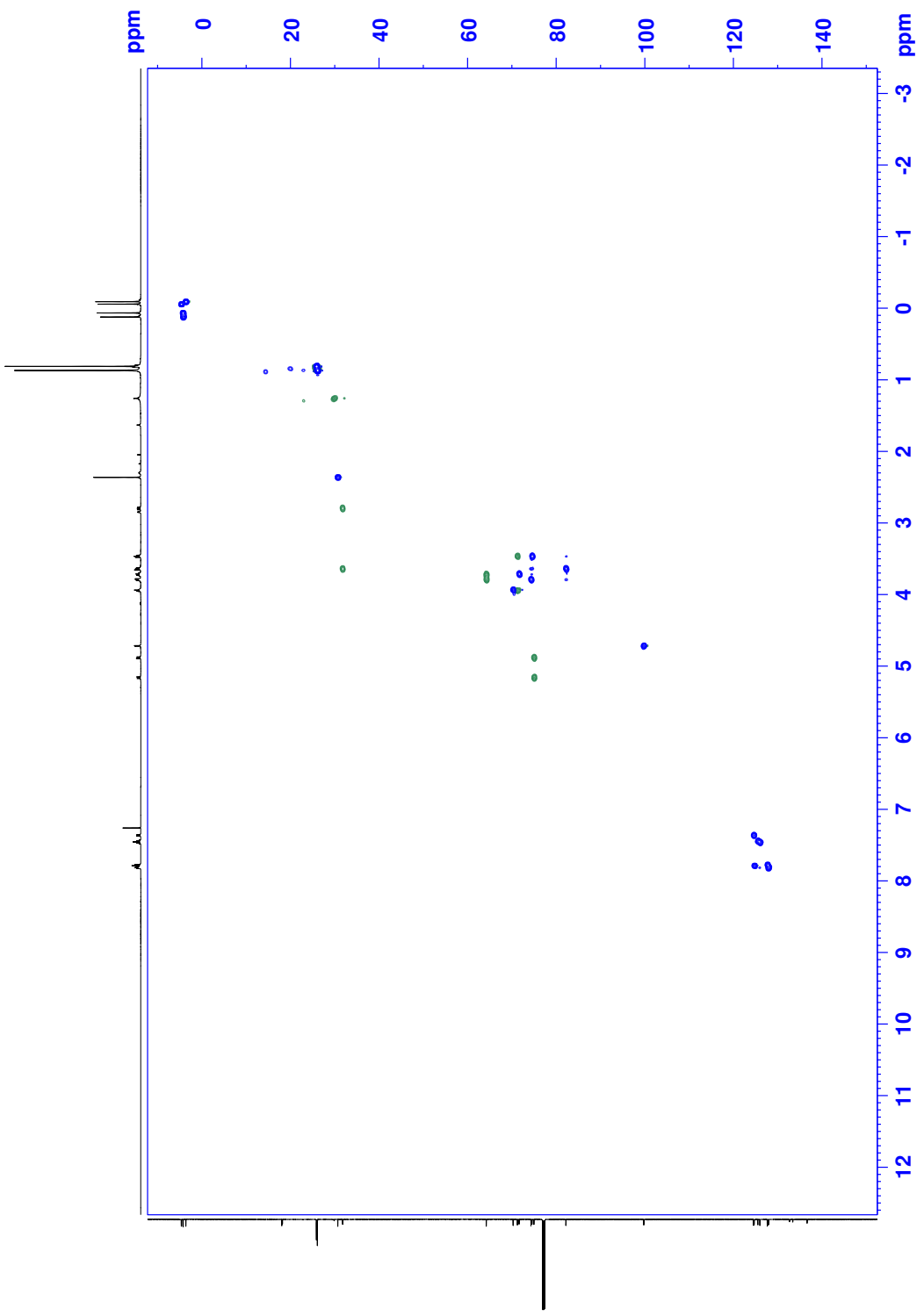


Figure A.46: HSQC spectrum of compound **7**.

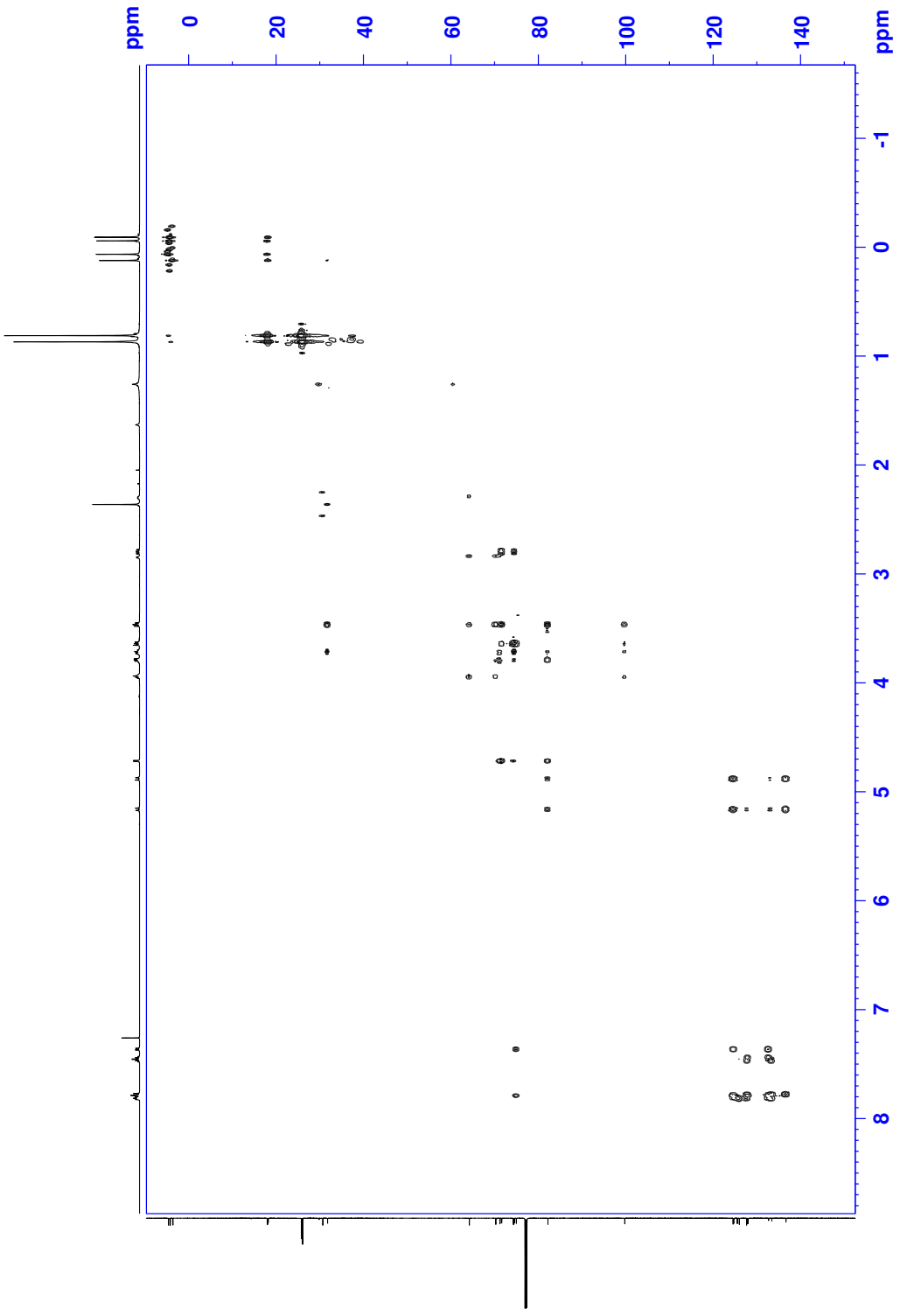


Figure A.47: HMBC spectrum of compound **7**.

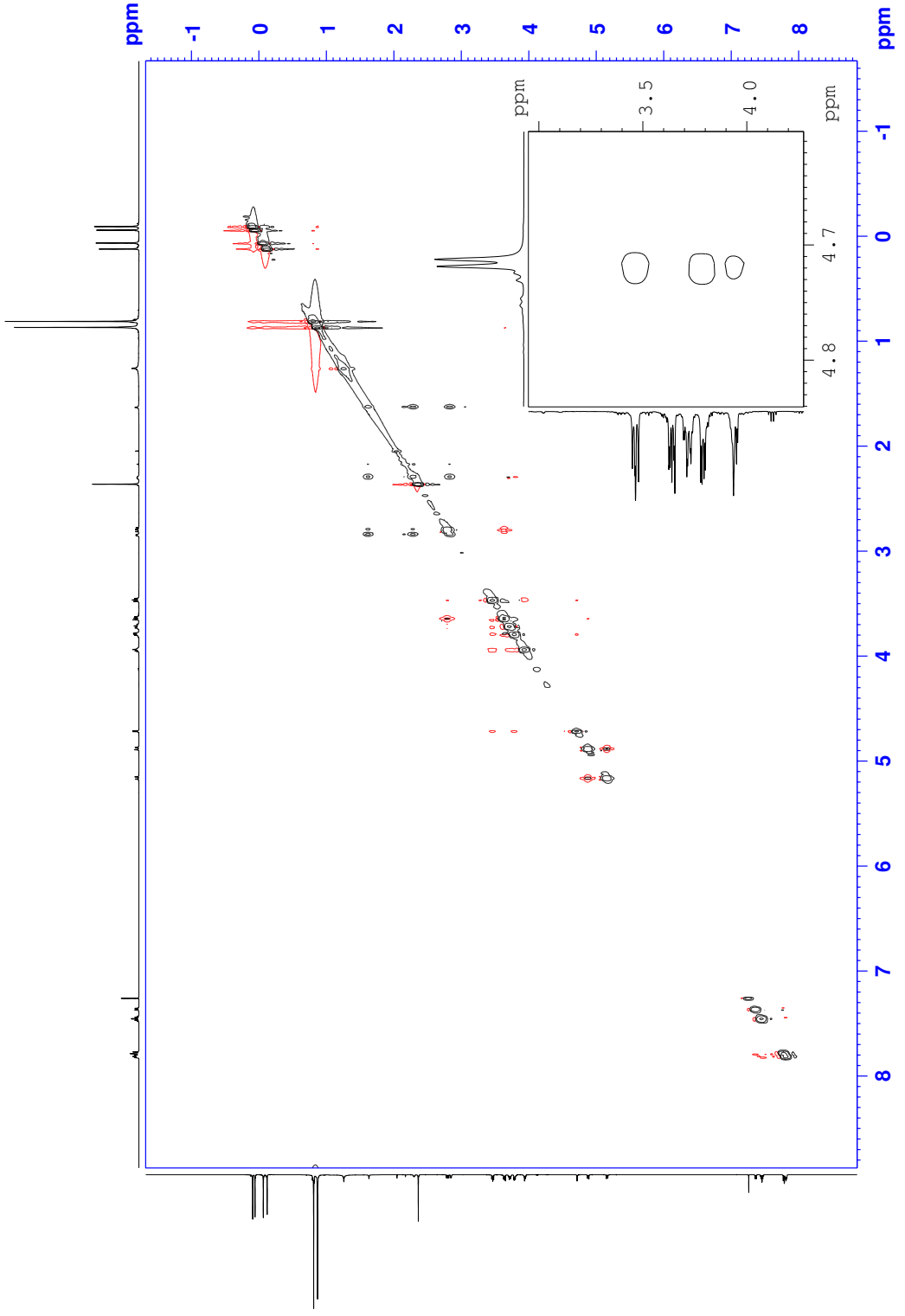


Figure A.48: NOESY spectrum of compound **7**.

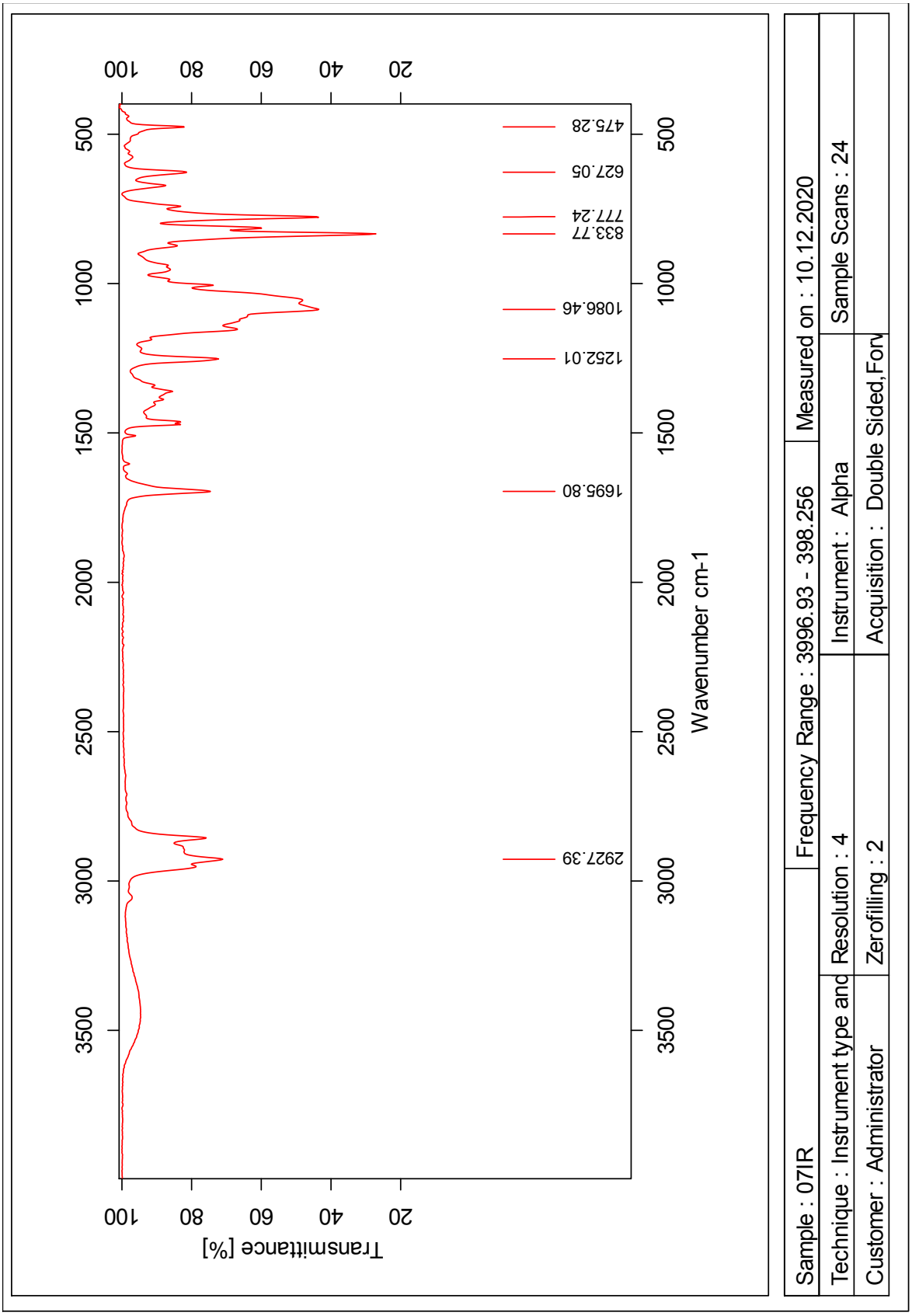


Figure A.49: IR spectrum of compound **7**.

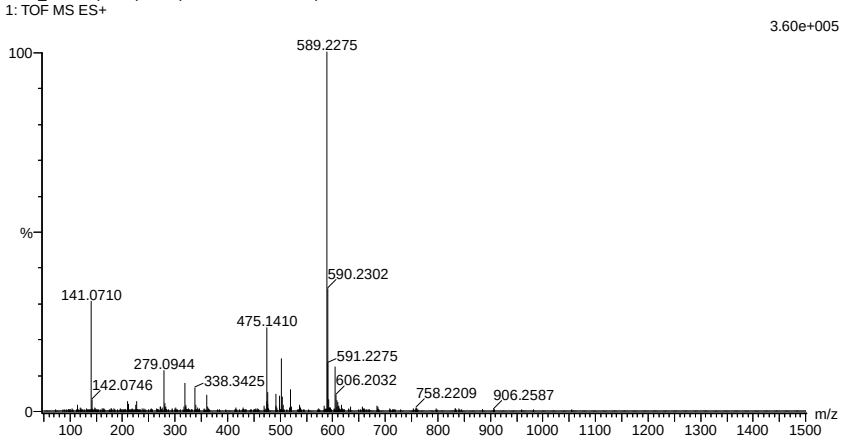
A.8 Spectroscopic data for compound 8a

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
1044 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-3 O: 0-9 S: 0-1 Na: 0-1

2021_324 52 (0.500) AM2 (Ar,35000.0,0.00,0.00)
1: TOF MS ES+



Minimum:				-10.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
475.1410	475.1403	0.7	1.5	8.5	1344.7	n/a	n/a	C22 H28 O8 S Na

Figure A.50: HRMS (ESI+) spectrum of compound **8a**.

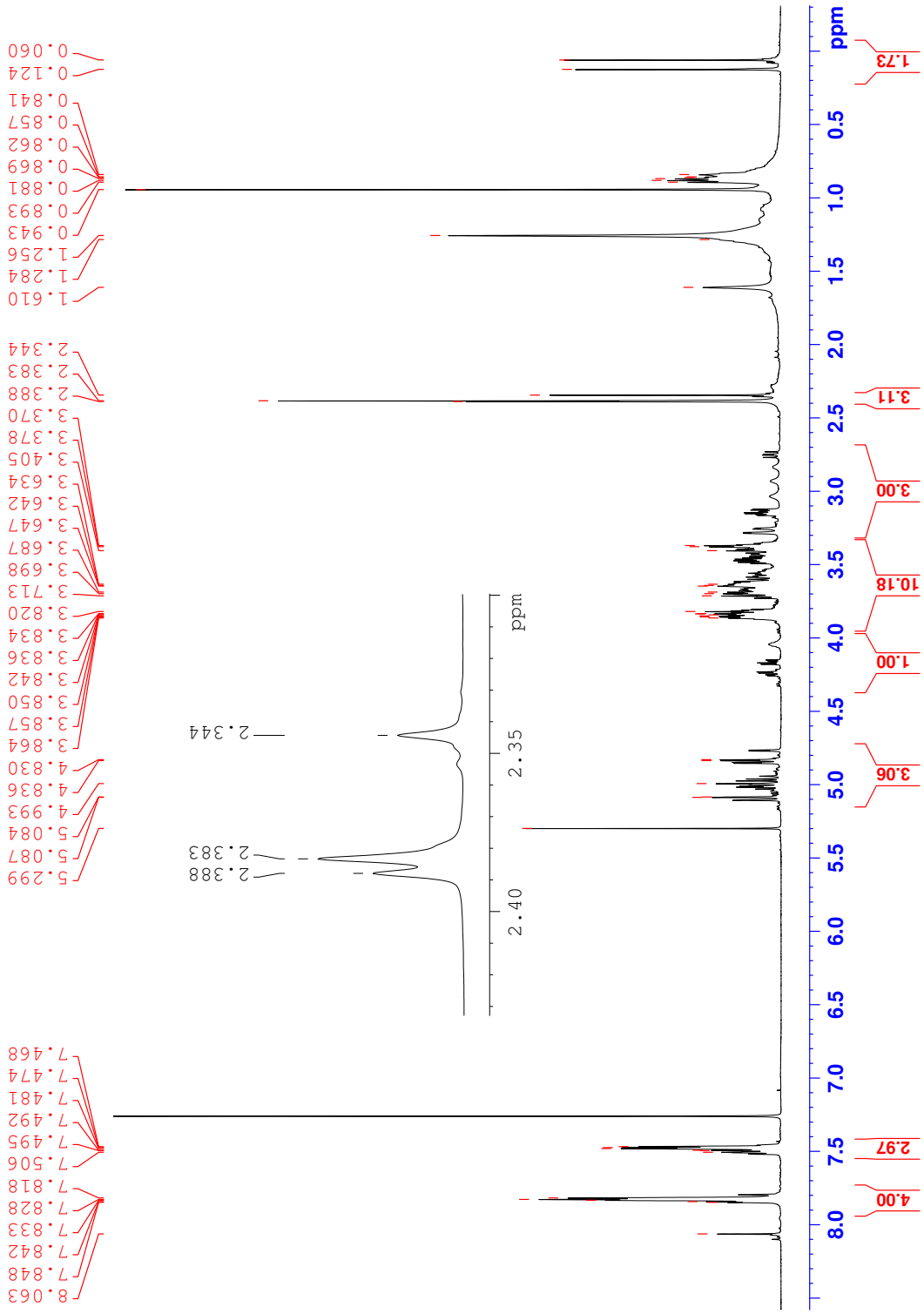


Figure A.51: ^{1}H NMR spectrum of compound **8a**.

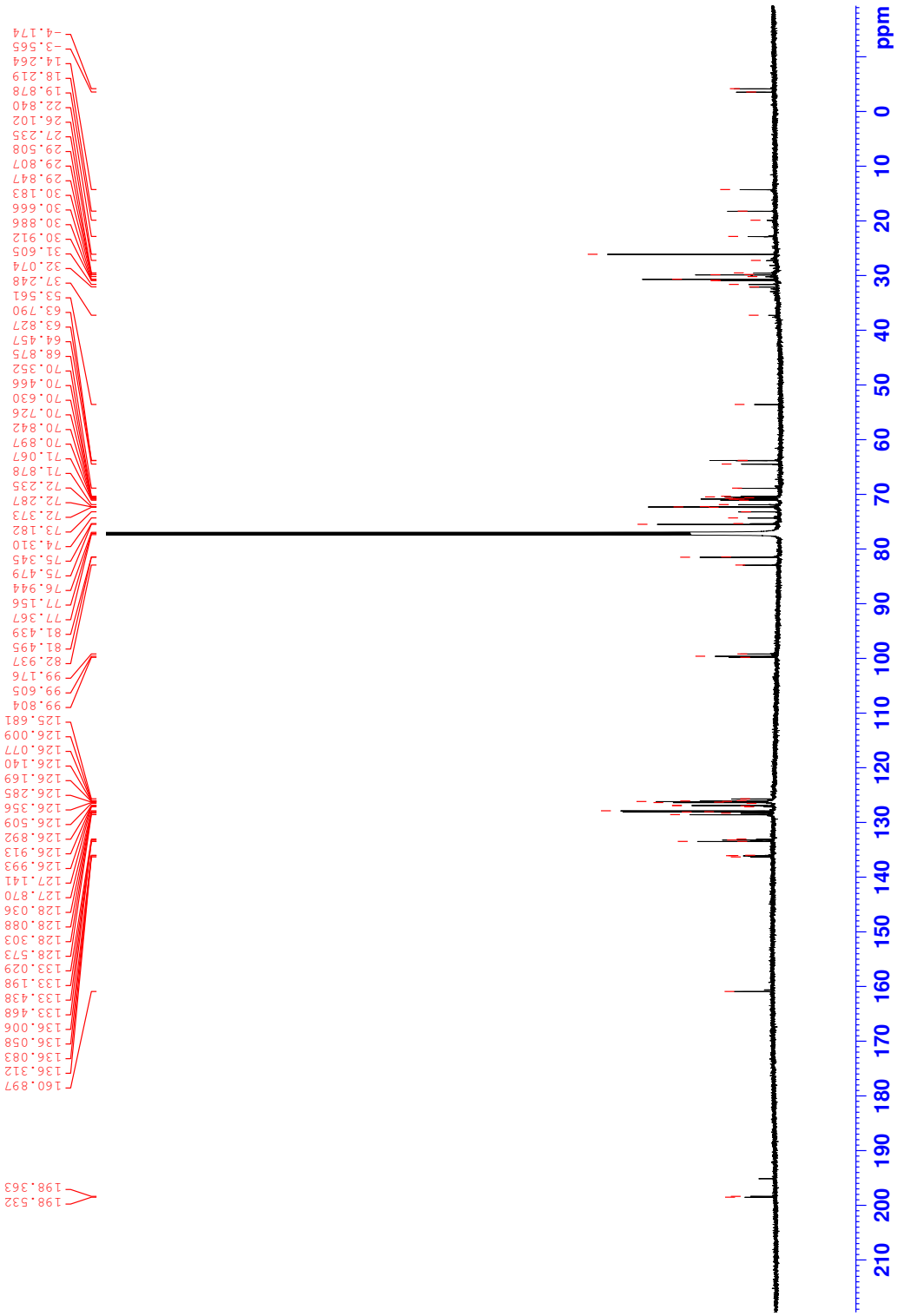


Figure A.52: ^{13}C NMR spectrum of compound **8a**.

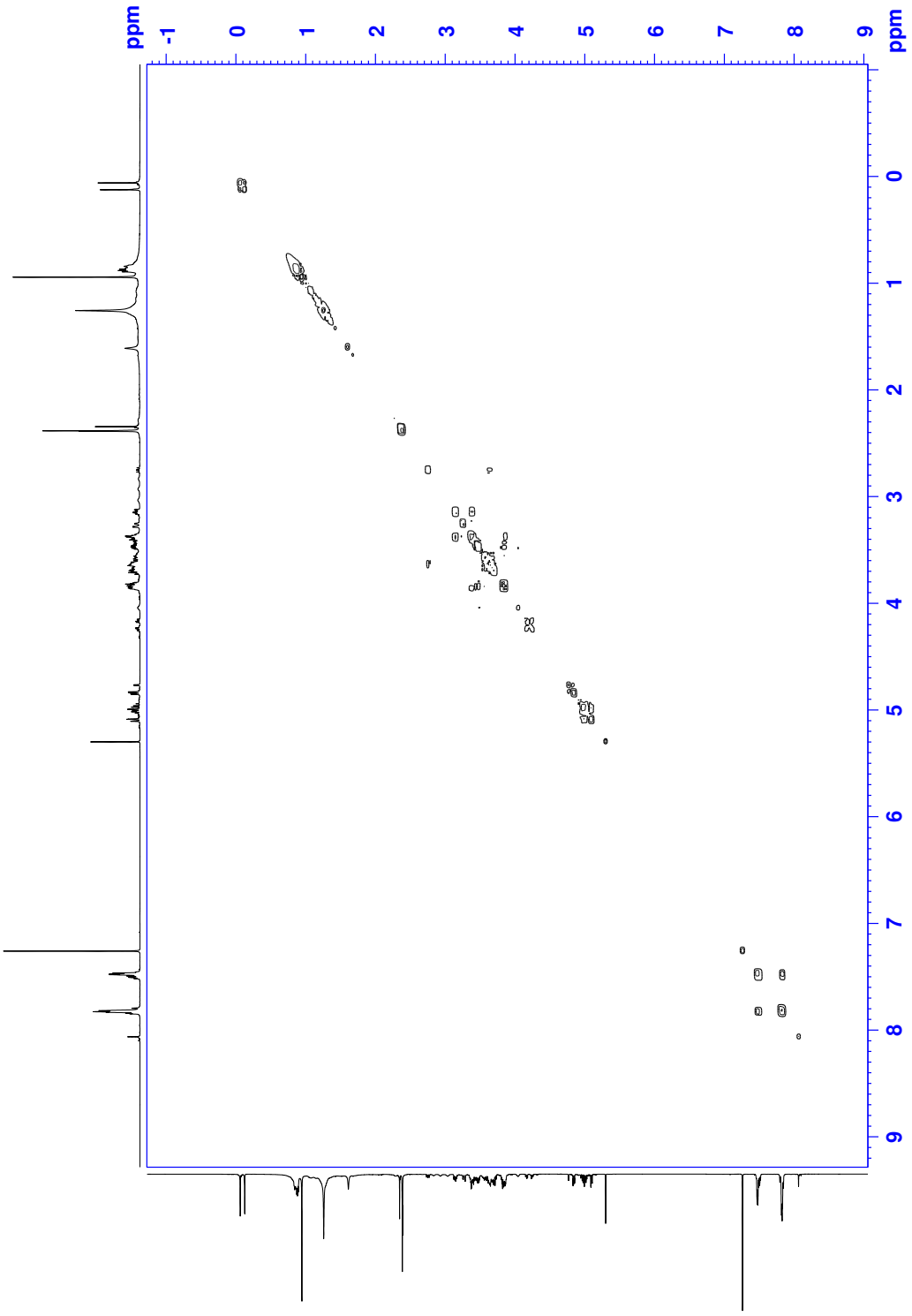


Figure A.53: COSY spectrum of compound **8a**.

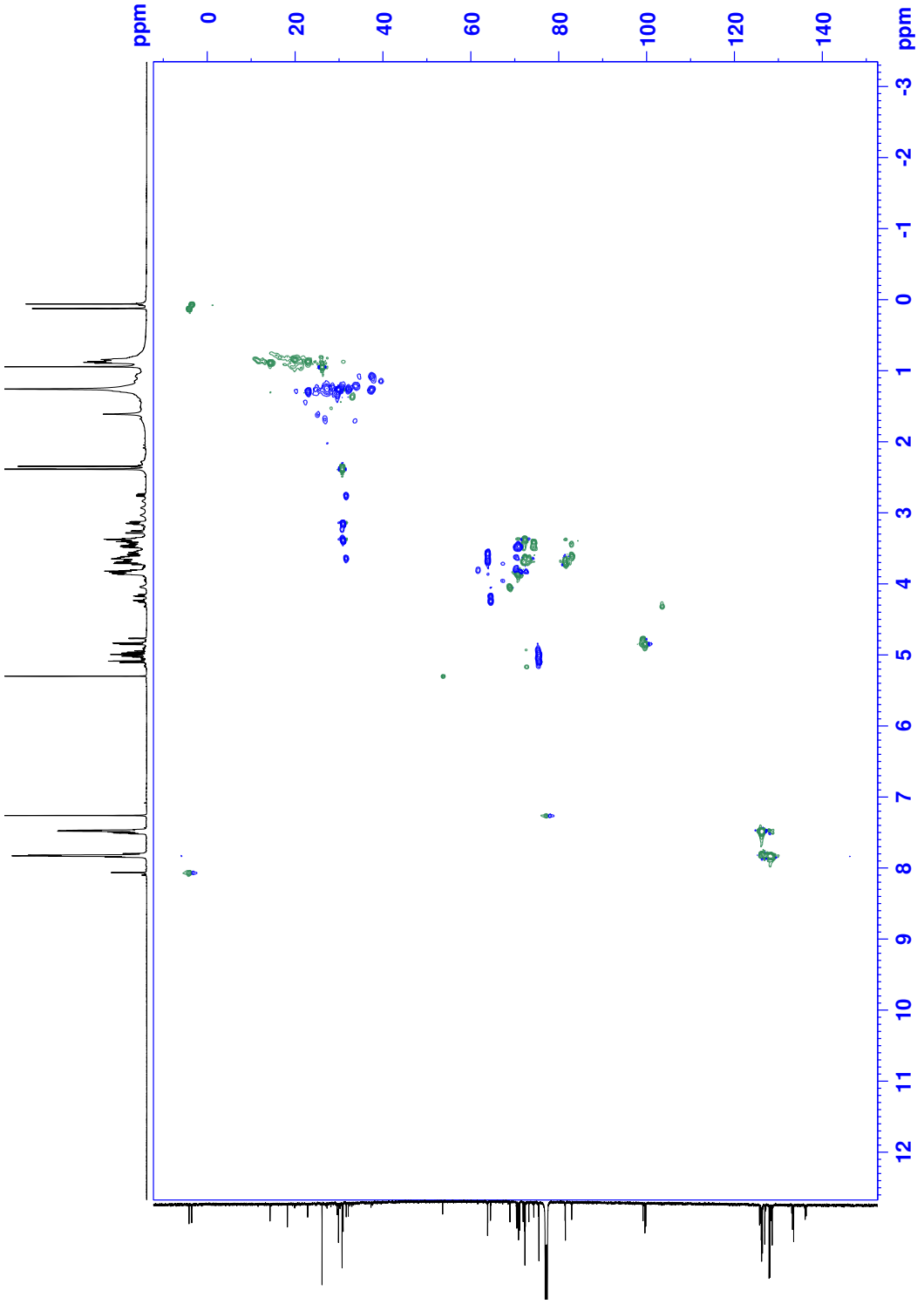


Figure A.54: HSQC spectrum of compound **8a**.

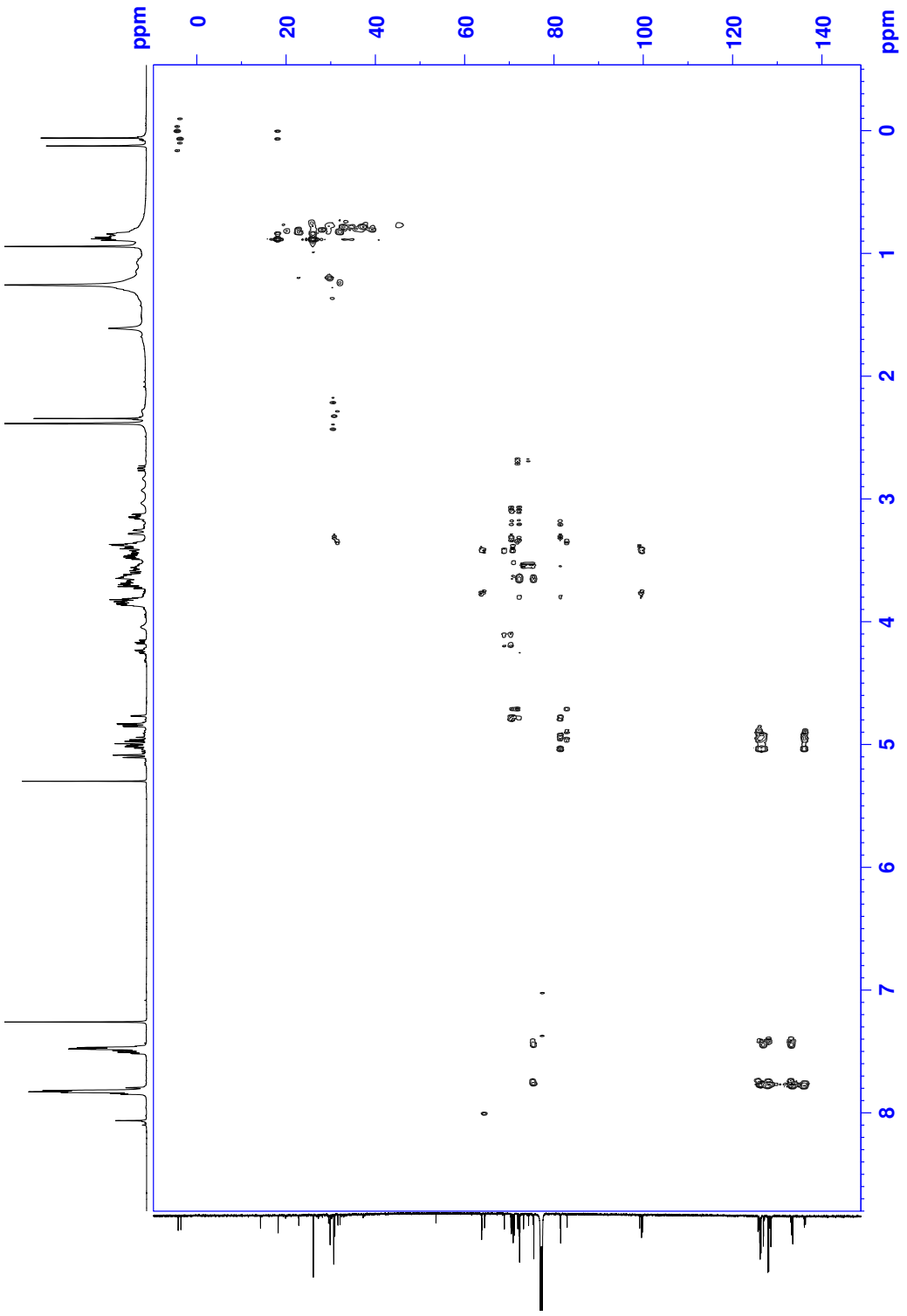


Figure A.55: HMBC spectrum of compound **8a**.

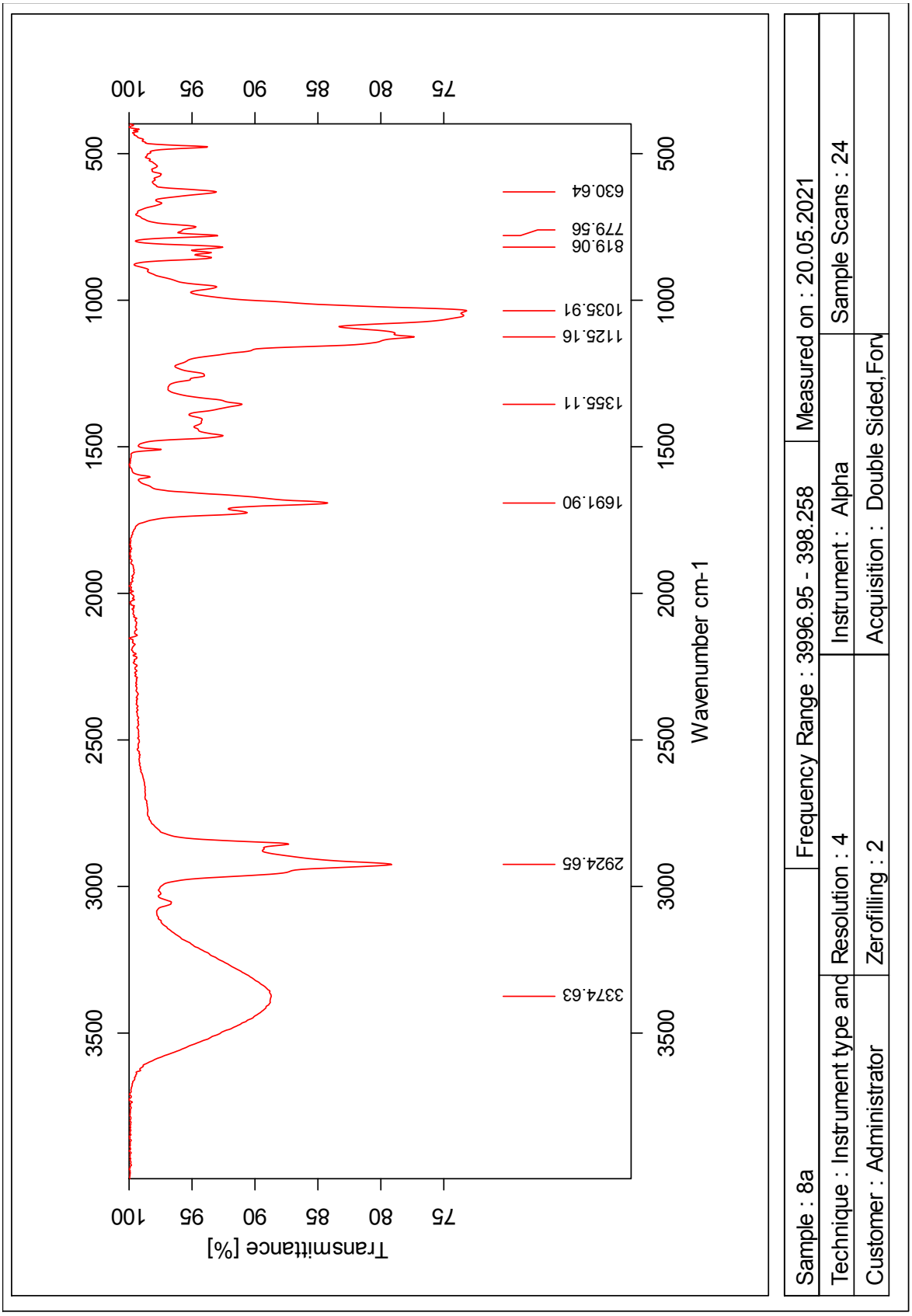


Figure A.56: IR spectrum of compound **8a**.

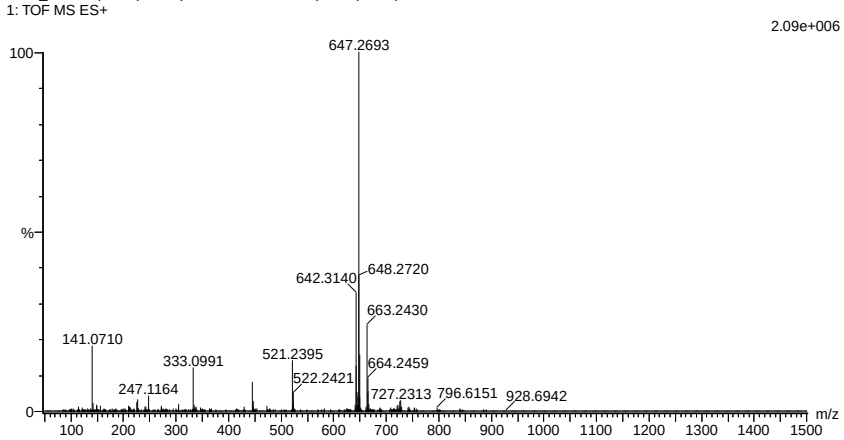
A.9 Spectroscopic data for compound F26

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
3935 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-3 O: 0-9 S: 0-1 Na: 0-1 Si: 0-2

2021_325 55 (0.526) AM2 (Ar,35000.0,0.00,0.00); Cm (55:61)
1: TOF MS ES+



Minimum:				-10.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
647.2693	647.2686	0.7	1.1	8.5	1524.8	0.000	99.96	C31 H48 O9 S Na Si
	647.2706	-1.3	-2.0	22.5	1533.2	8.428	0.02	C40 H40 N2 O3 Na Si
	647.2683	1.0	1.5	15.5	1533.5	8.643	0.02	C36 H47 O5 S Si2
	647.2699	-0.6	-0.9	30.5	1537.6	12.747	0.00	C46 H35 N2 O2

Figure A.57: HRMS (ESI+) spectrum of compound **F26**.

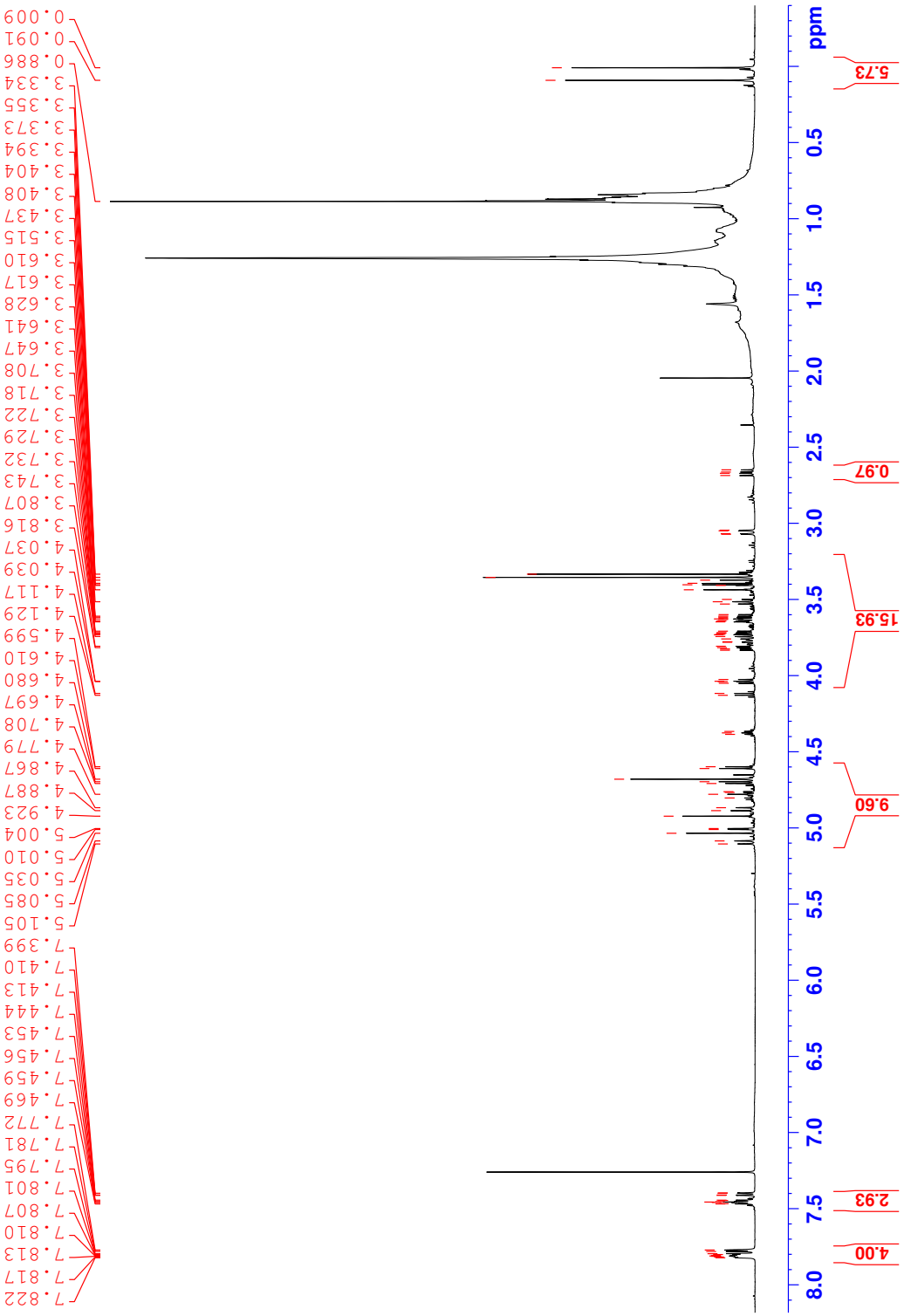


Figure A.58: ^{1}H NMR spectrum of compound **F26**.

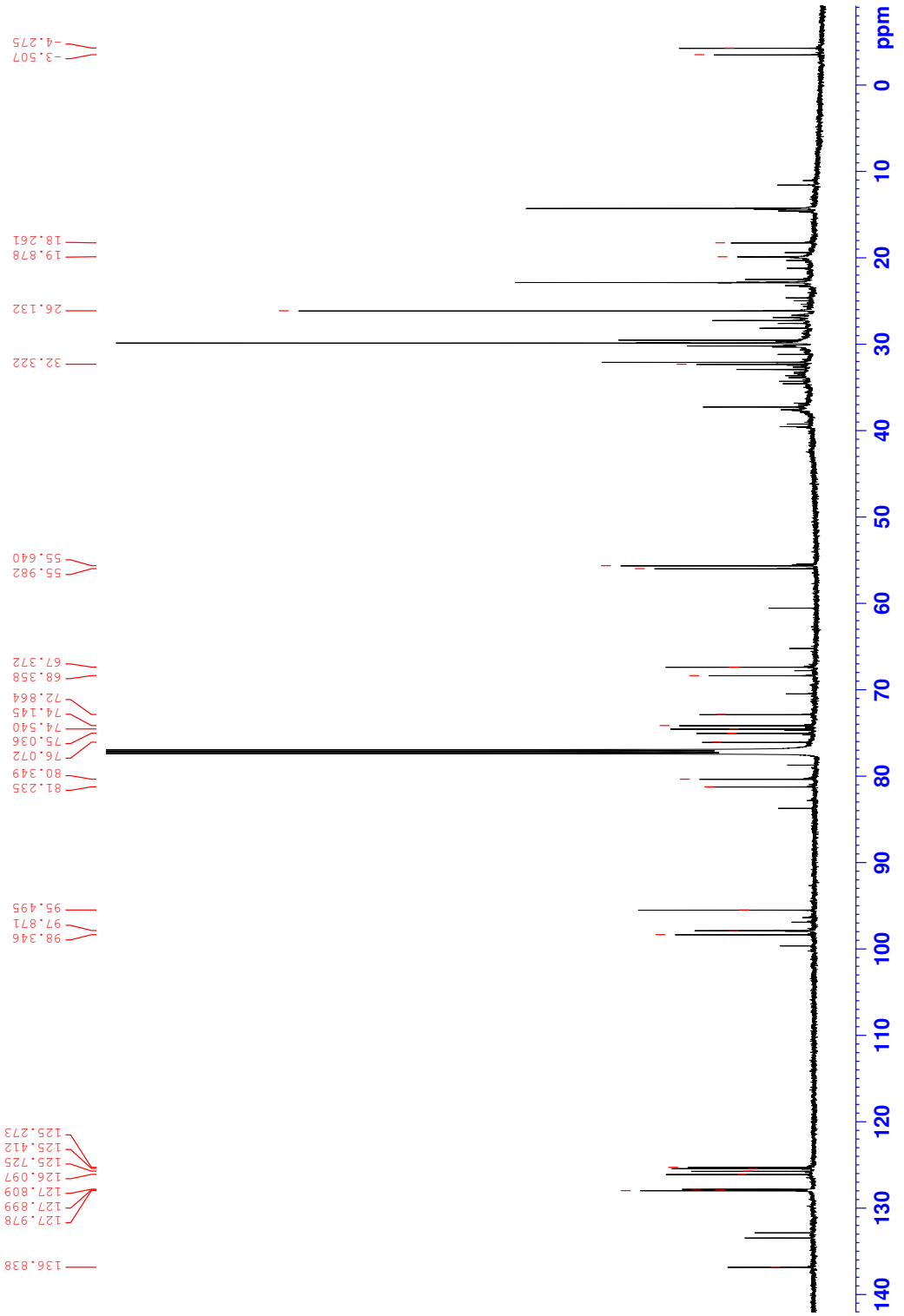


Figure A.59: ^{13}C NMR spectrum of compound **F26**.

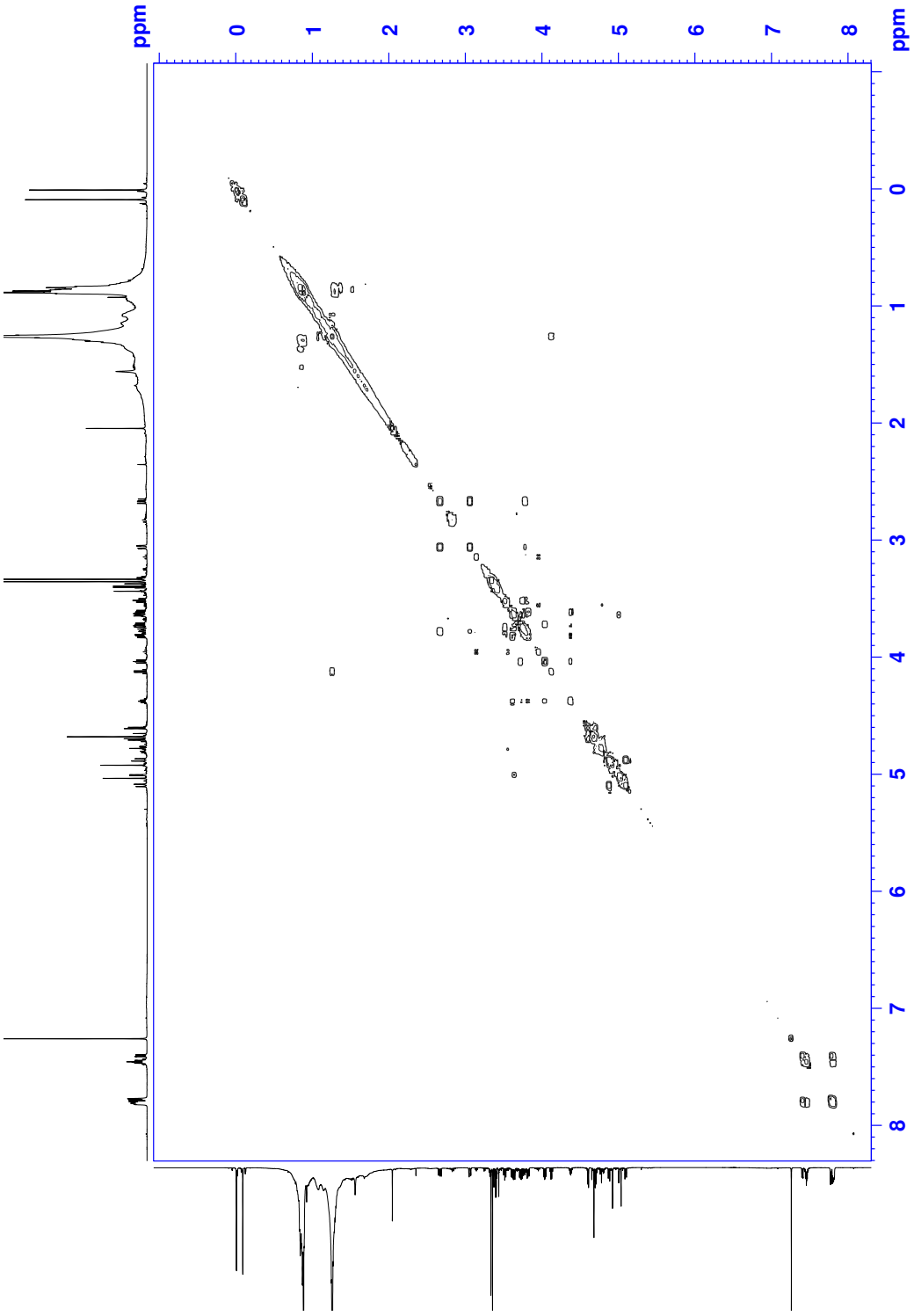


Figure A.60: COSY spectrum of compound **F26**.

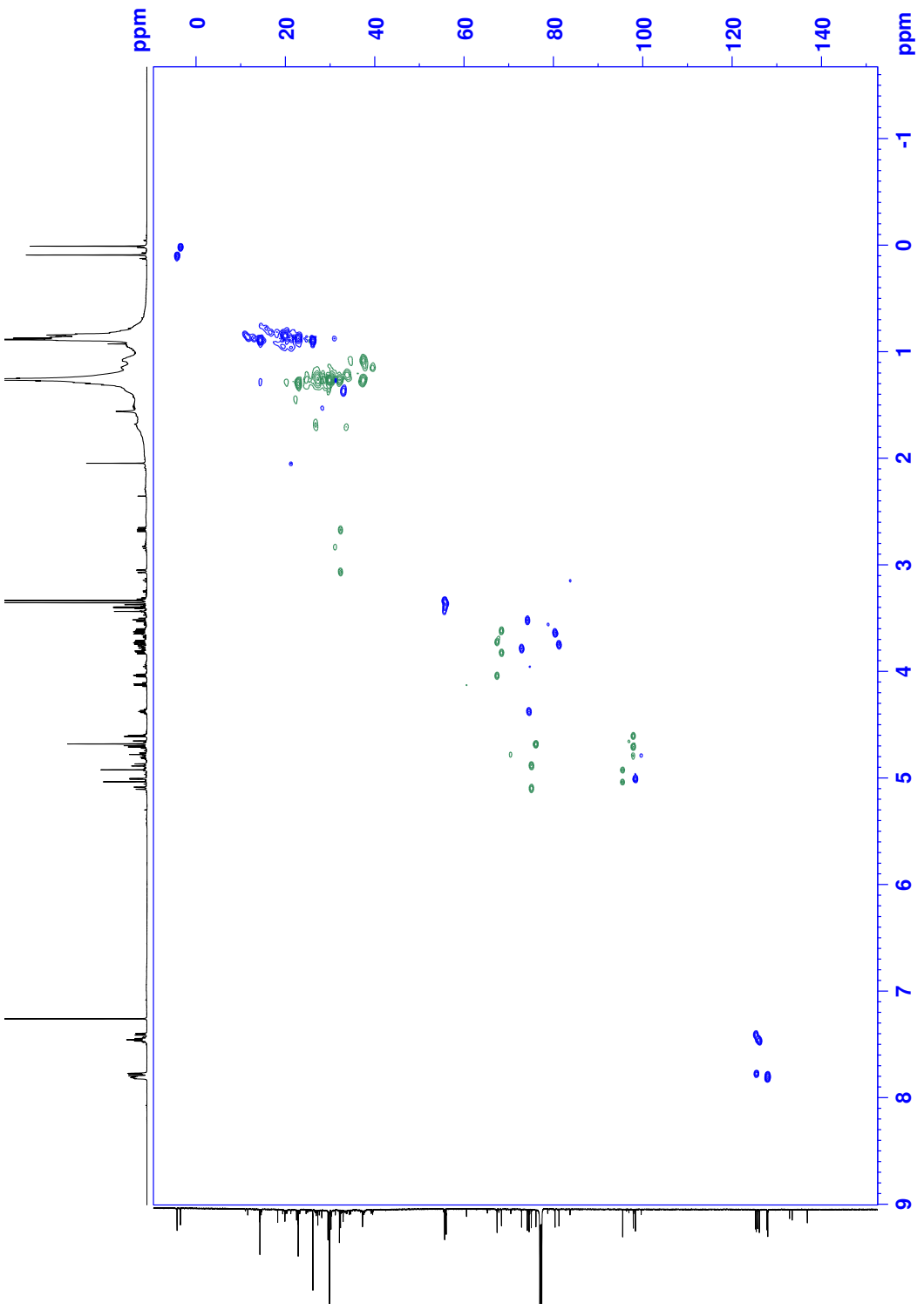


Figure A.61: HSQC spectrum of compound **F26**.

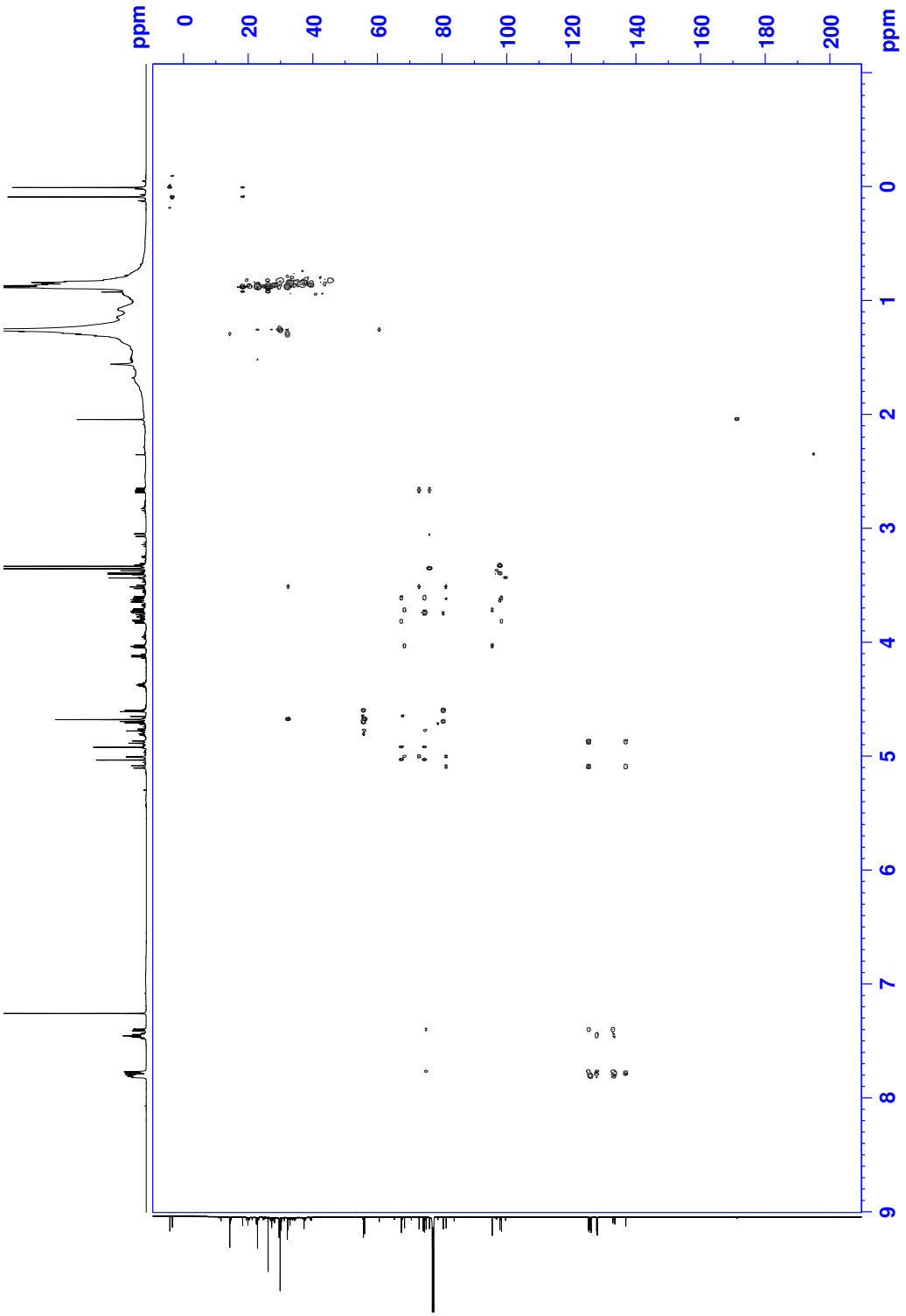


Figure A.62: HMBC spectrum of compound **F26**.

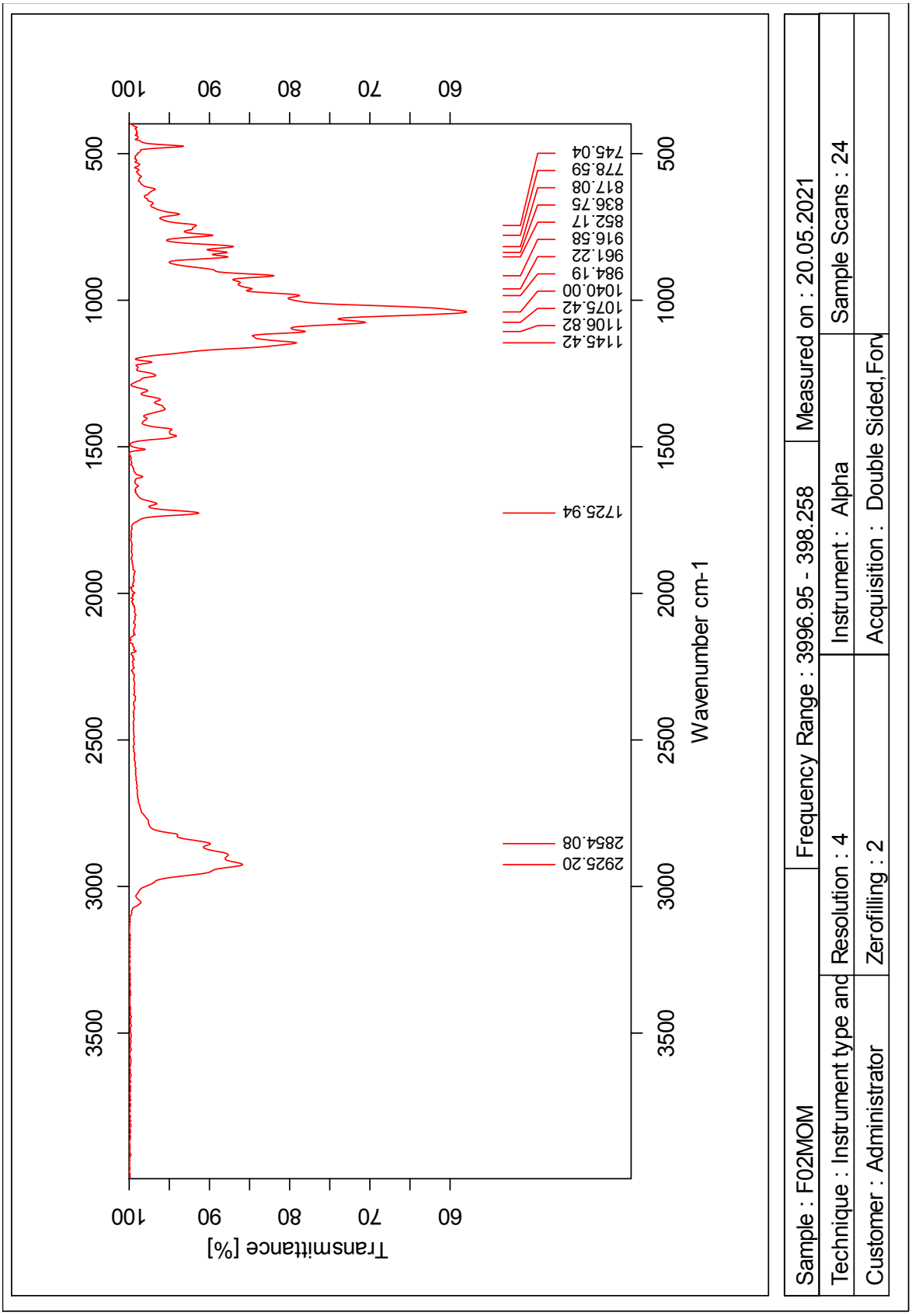


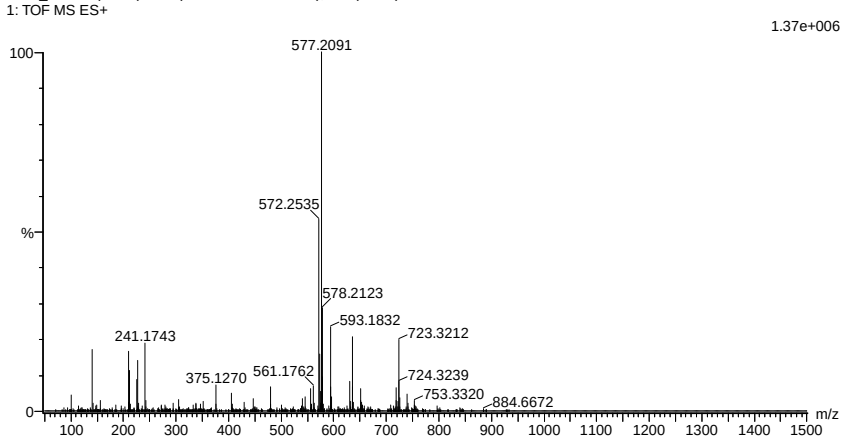
Figure A.63: IR spectrum of compound **F26**.

A.10 Spectroscopic data for compound F42

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
1342 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-3 O: 0-10 Na: 0-1 S: 0-1
2021_326 55 (0.526) AM2 (Ar,35000.0,0.00,0.00); Cm (55:60)
1: TOF MS ES+



Minimum:				-10.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
577.2091	577.2083	0.8	1.4	8.5	1583.6	n/a	n/a	C27 H38 O10 Na S

Figure A.64: HRMS (ESI+) spectrum of compound **F42**.

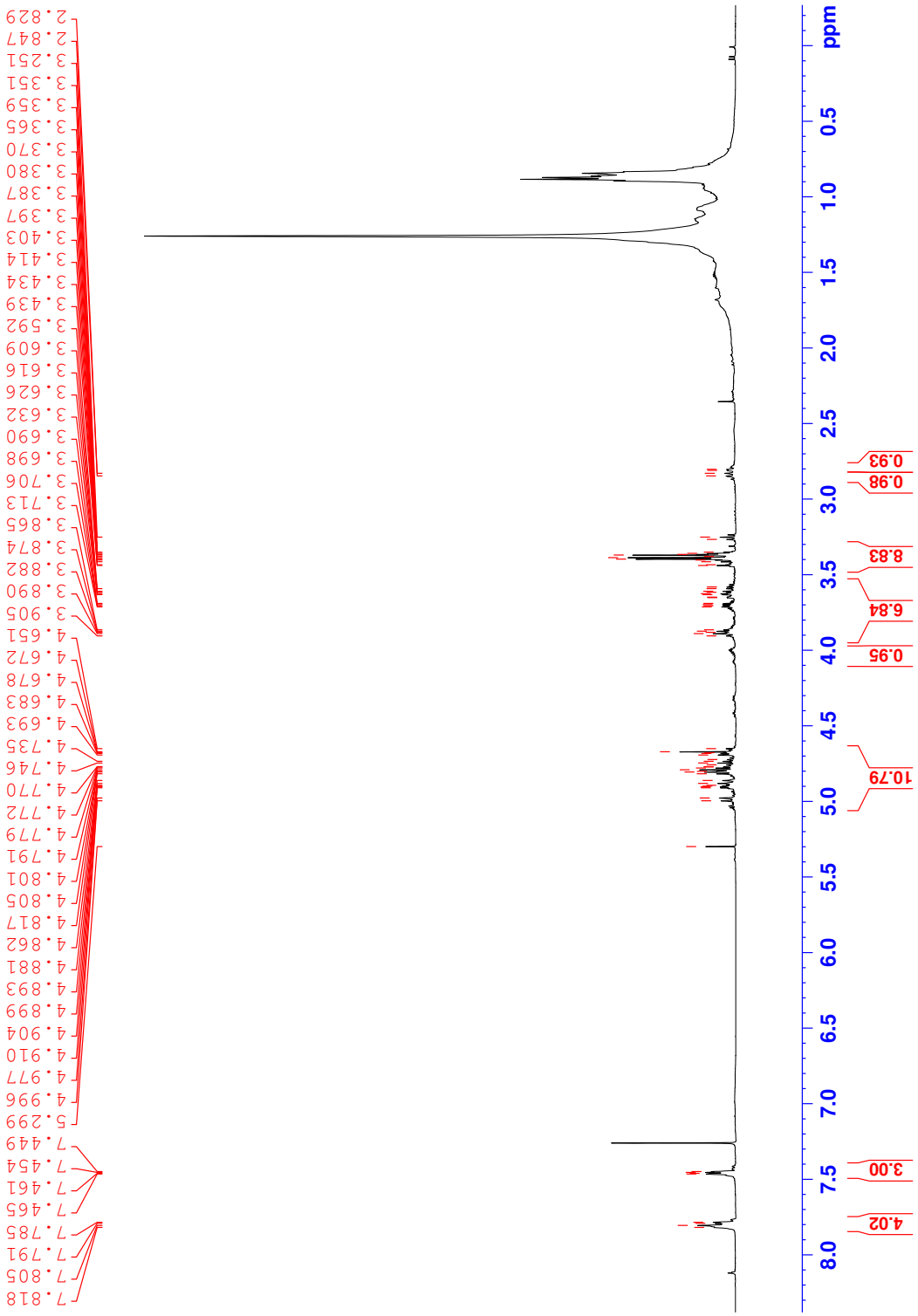


Figure A.65: ^{1}H NMR spectrum of compound **F42**.

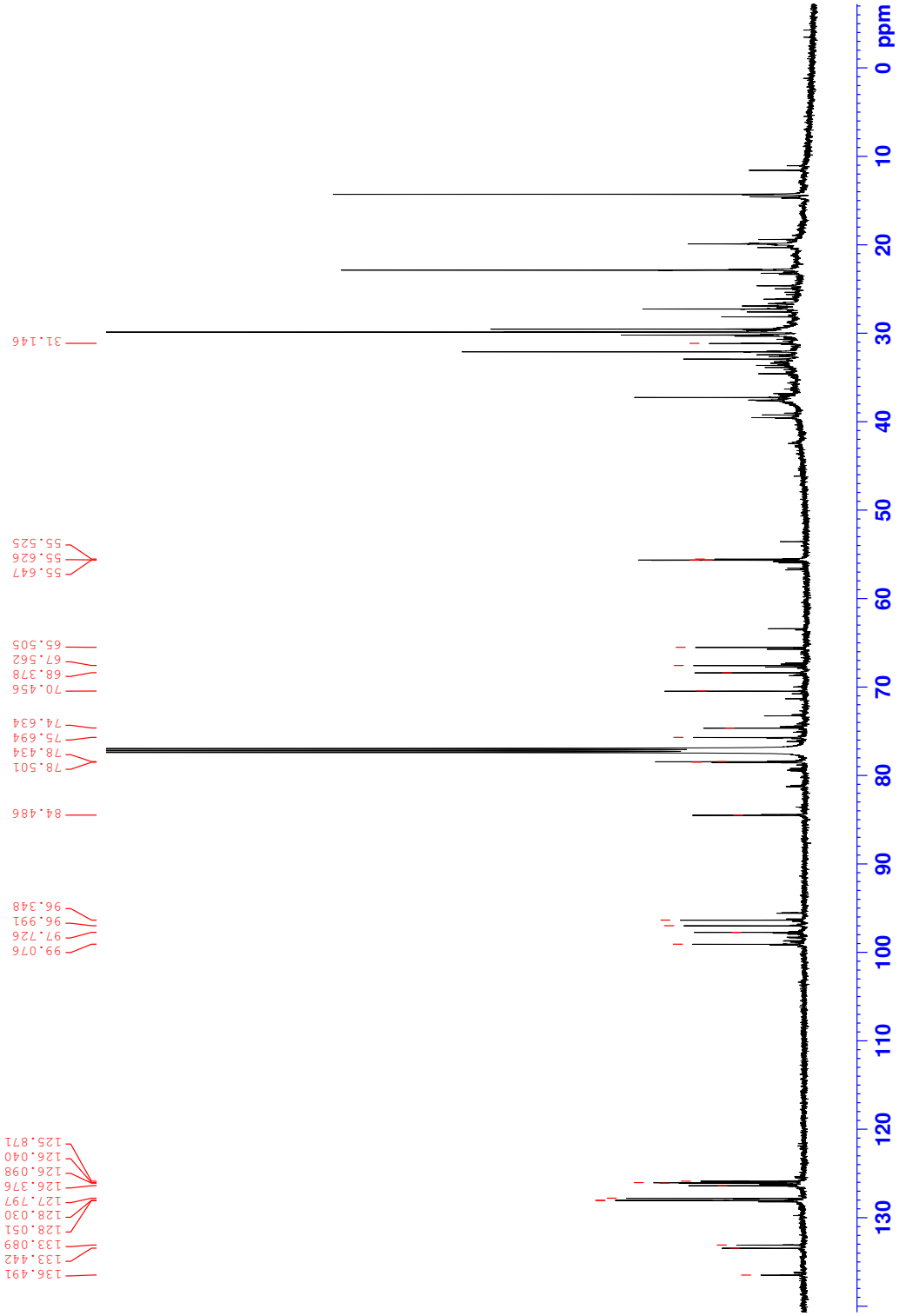


Figure A.66: ^{13}C NMR spectrum of compound **F42**.

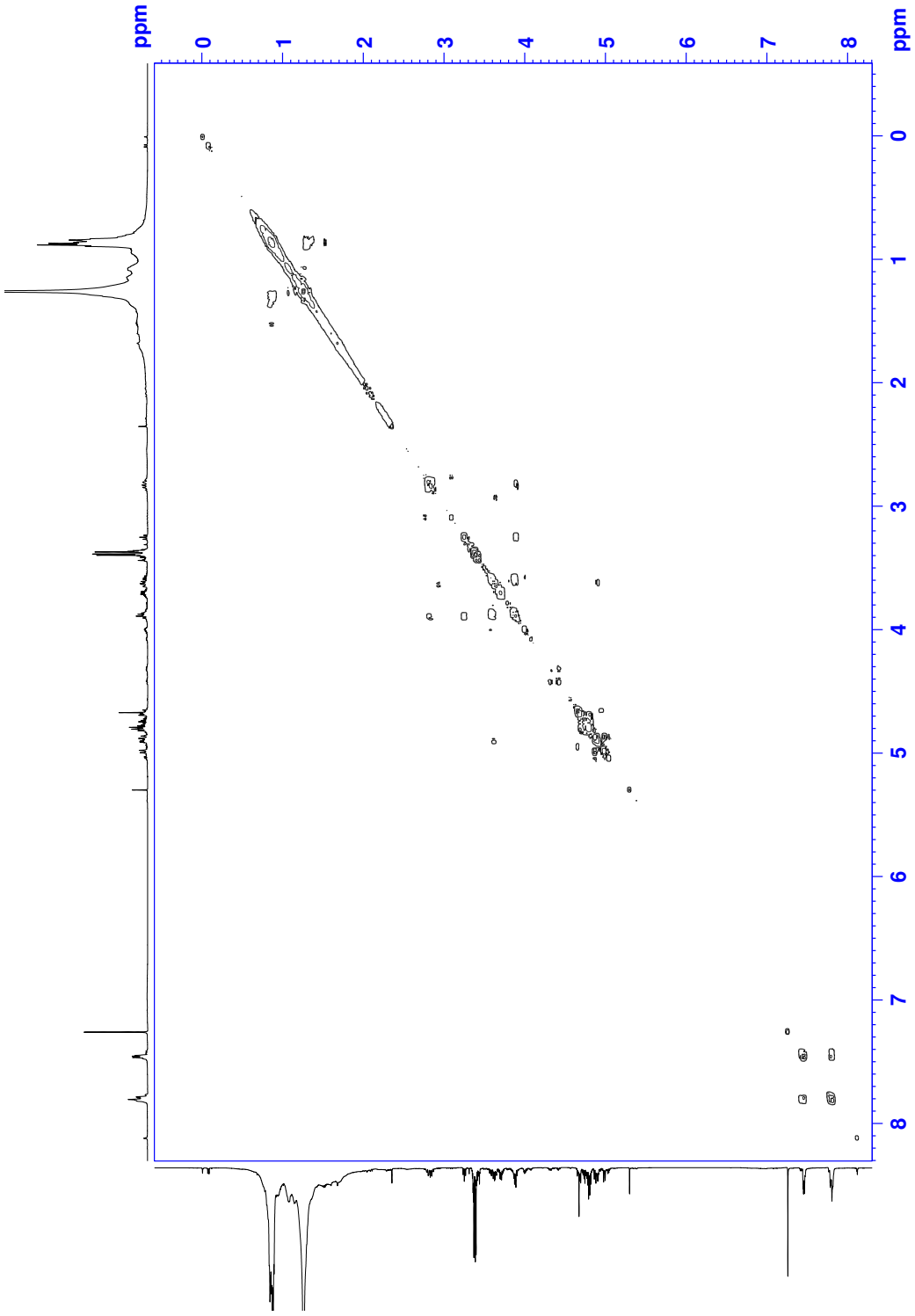


Figure A.67: COSY spectrum of compound **F42**.

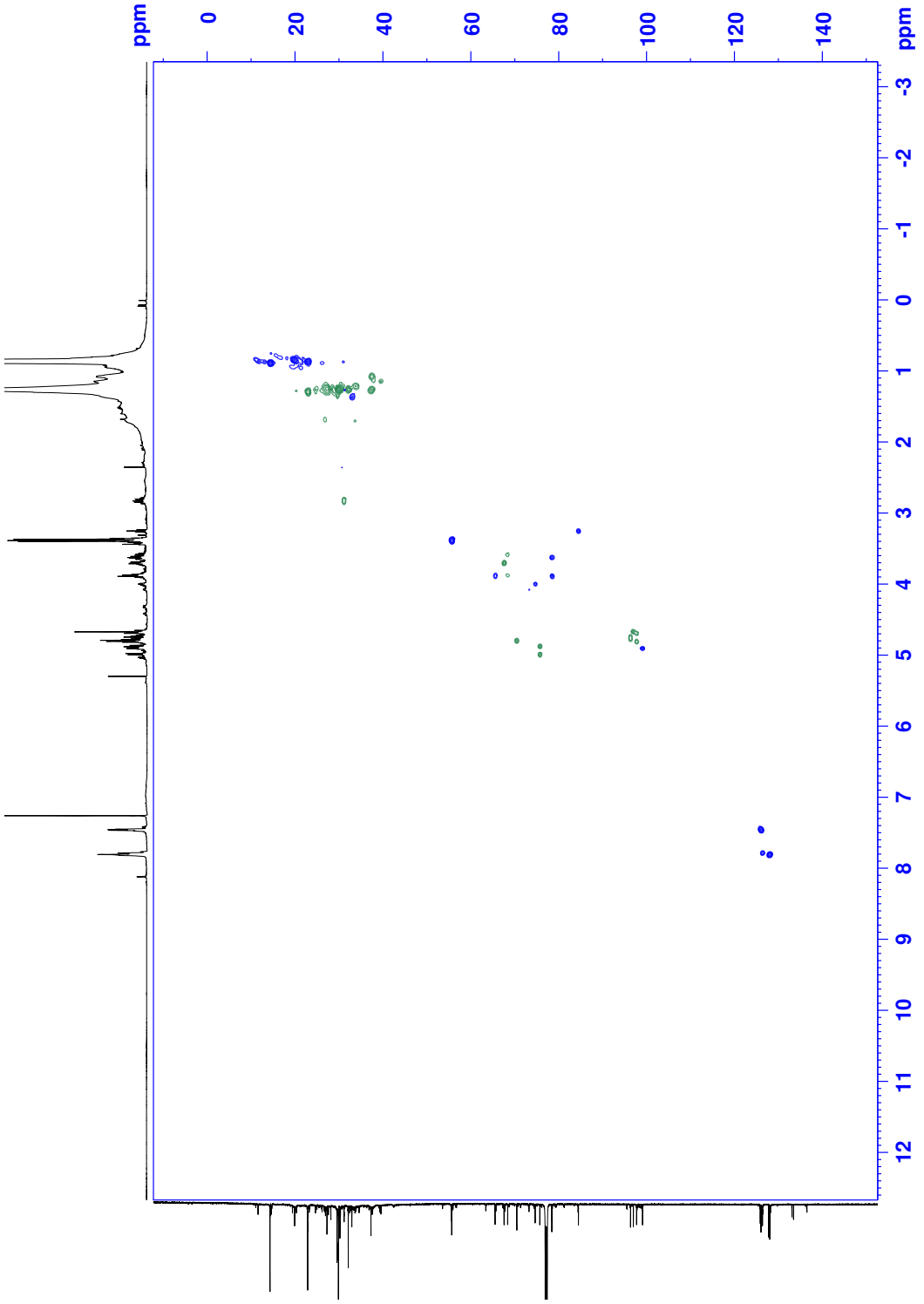


Figure A.68: HSQC spectrum of compound **F42**.

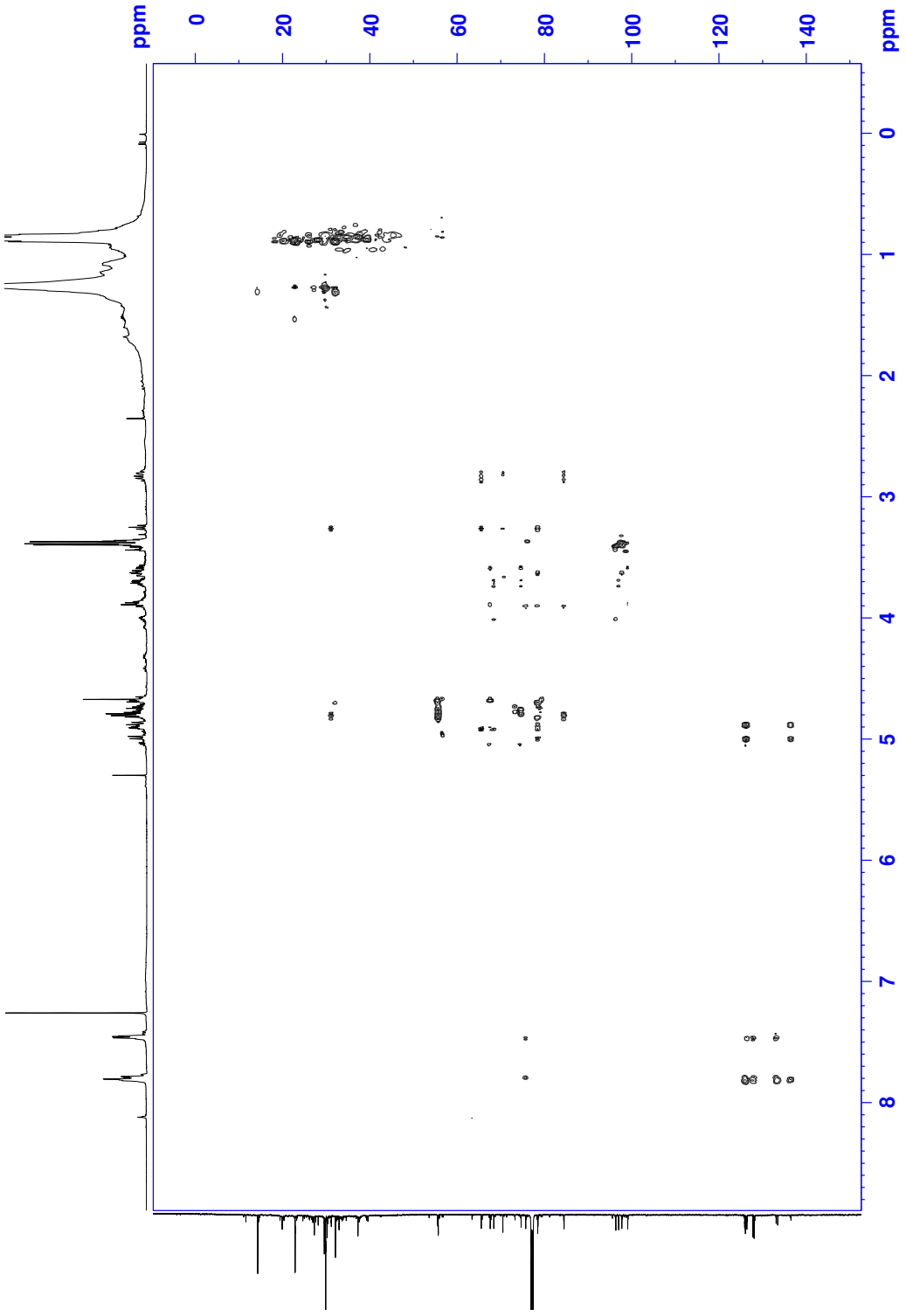


Figure A.69: HMBC spectrum of compound **F42**.

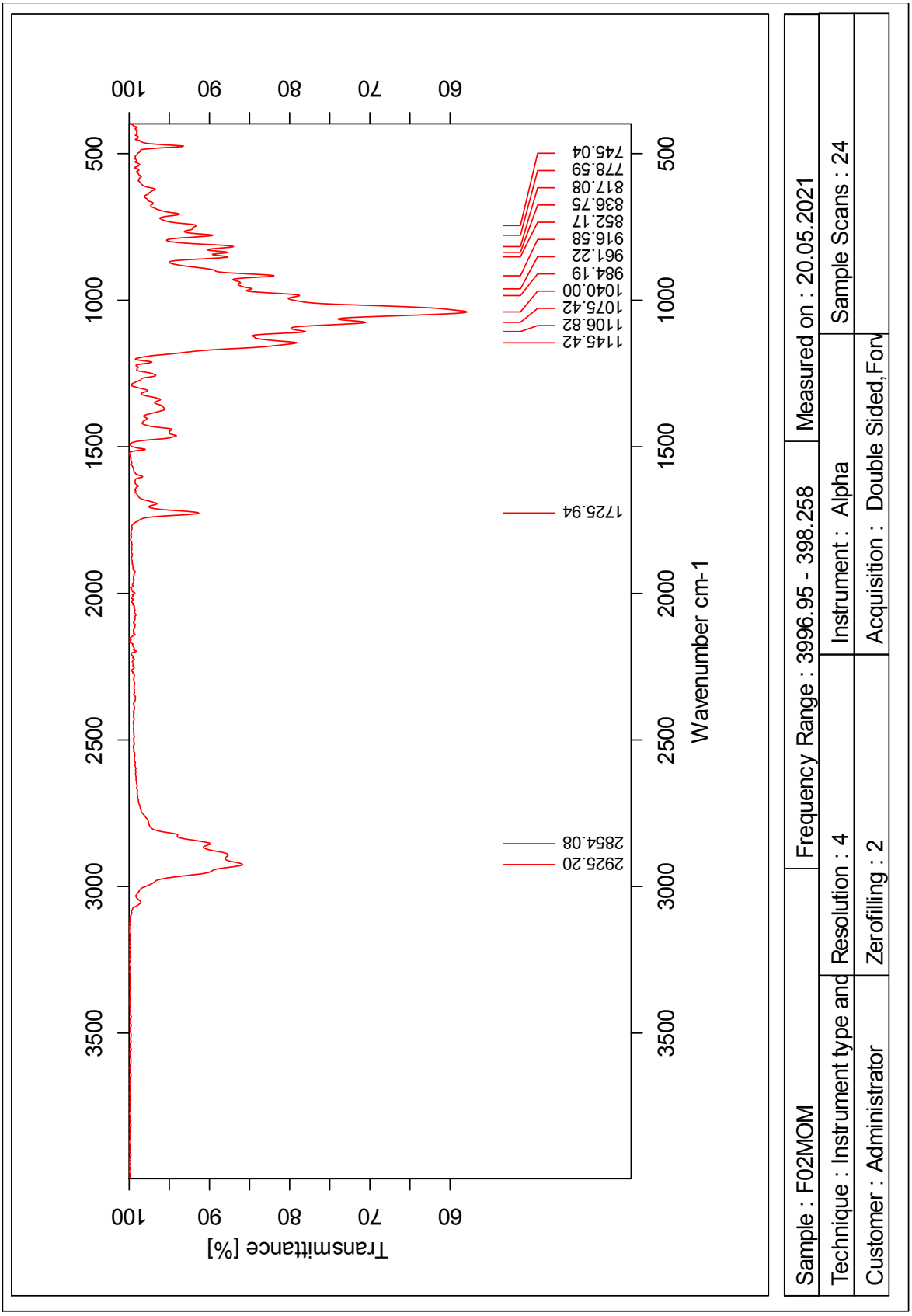


Figure A.70: IR spectrum of compound **F42**.

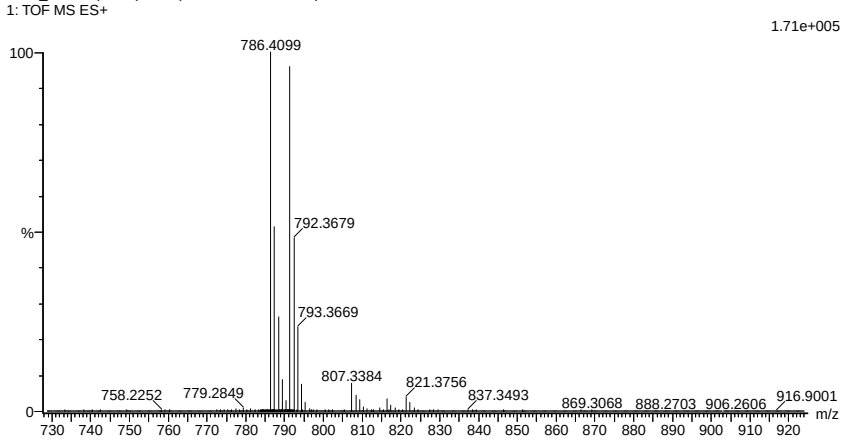
A.11 Spectroscopic data for compound 8d

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 2.1 PPM / DBE: min = -10.0, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 6

Monoisotopic Mass, Even Electron Ions
3545 formula(e) evaluated with 6 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 N: 0-1 O: 0-12 Na: 0-1 S: 0-1 Si: 0-3

2021_110 78 (0.743) AM2 (Ar,35000.0,0.00,0.00)
1: TOF MS ES+



Minimum:				-10.0				
Maximum:		5.0	2.1	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
786.4099	786.4100	-0.1	-0.1	35.5	1075.6	9.195	0.01	C60 H52 N
	786.4100	-0.1	-0.1	7.5	1068.1	1.606	20.06	C37 H68 N O11 Si3
	786.4102	-0.3	-0.4	7.5	1066.7	0.237	78.87	C38 H68 N O10 S Si2
	786.4107	-0.8	-1.0	27.5	1073.9	7.453	0.06	C54 H57 N O Na Si
	786.4109	-1.0	-1.3	27.5	1073.2	6.789	0.11	C55 H57 N Na S
	786.4110	-1.1	-1.4	-0.5	1071.2	4.723	0.89	C32 H73 N O11 Na S Si3

Figure A.71: HRMS (ESI+) spectrum of compound **8d**.

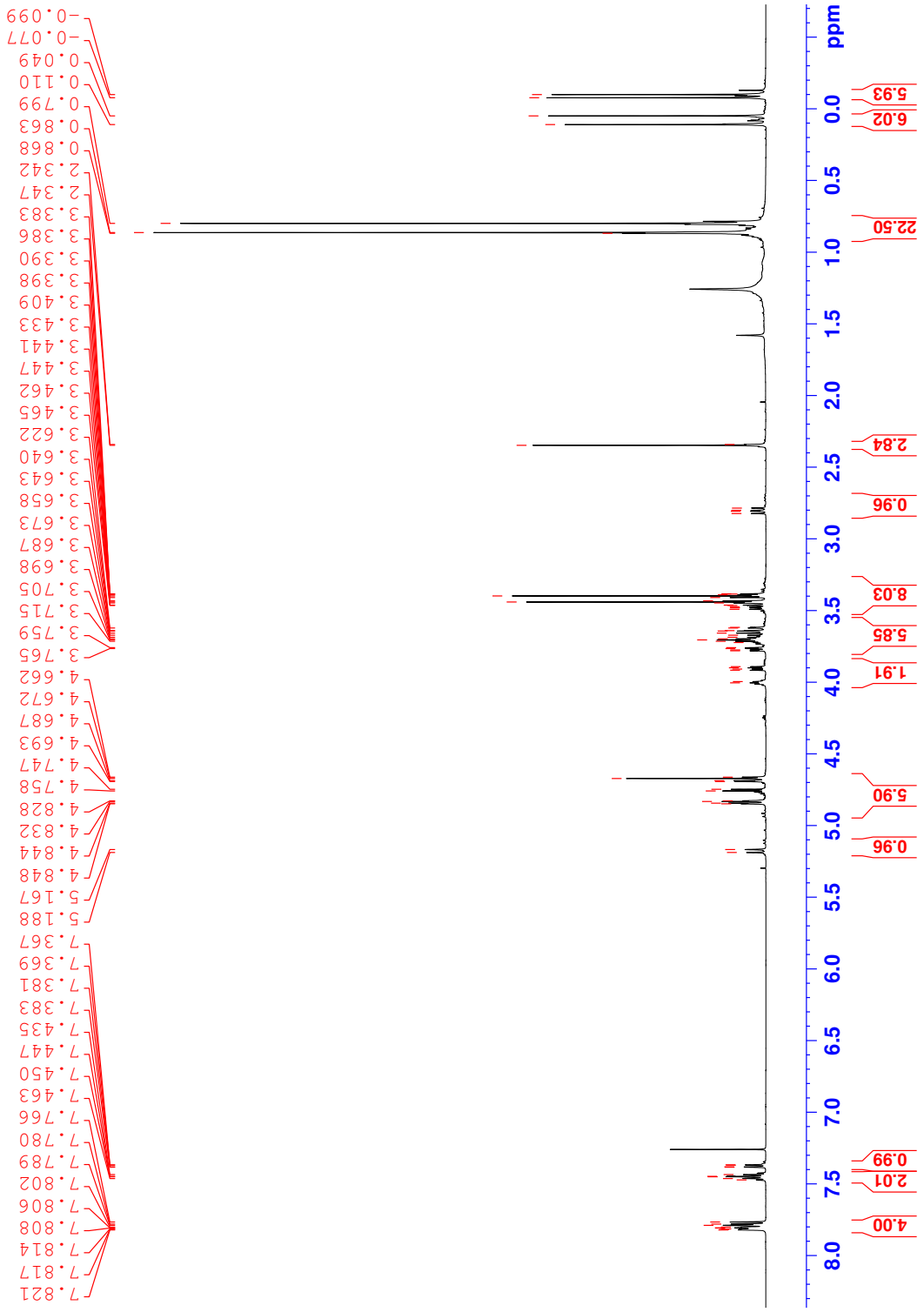


Figure A.72: ^{1}H NMR spectrum of compound **8d**.

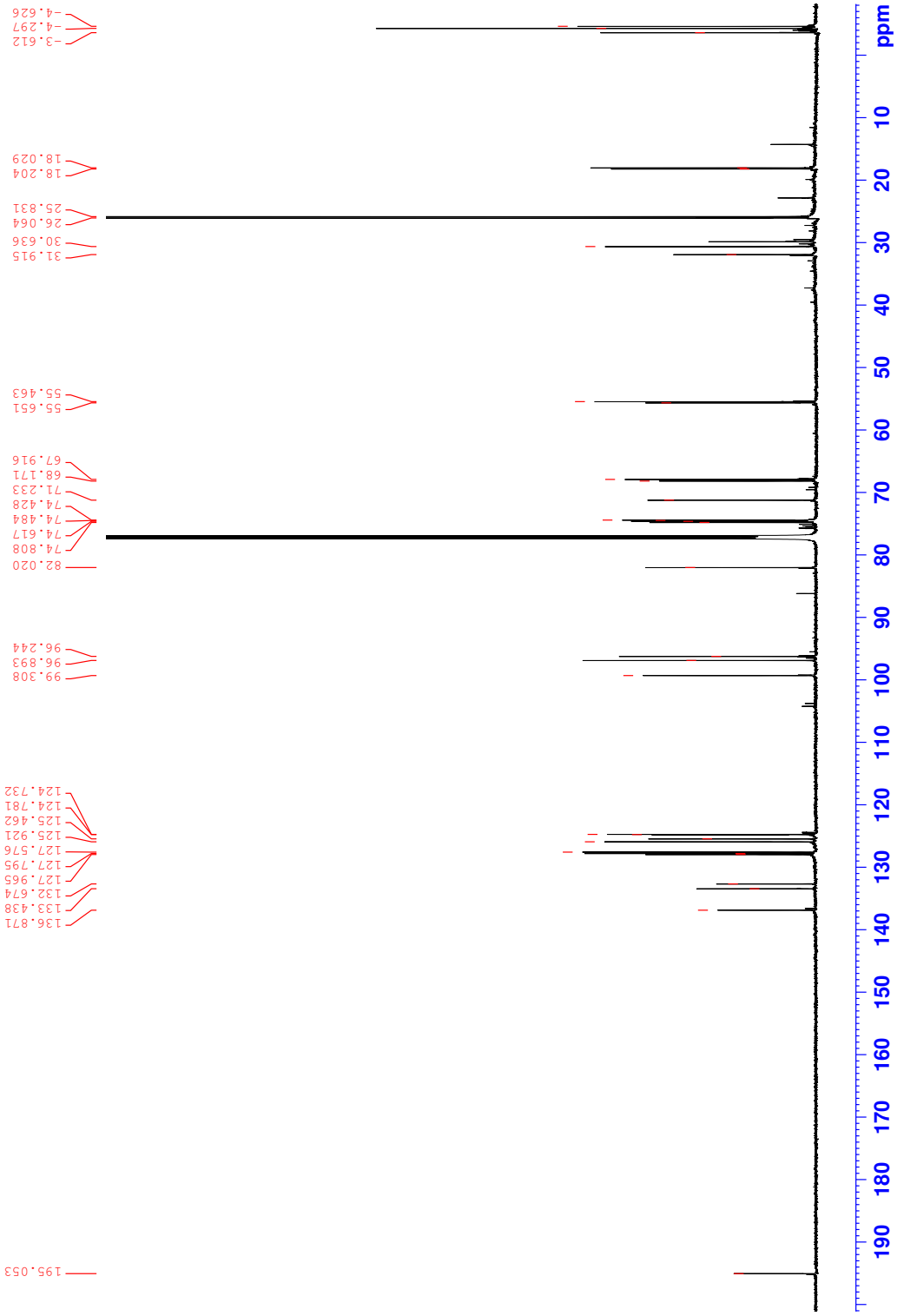


Figure A.73: ^{13}C NMR spectrum of compound **8d**.

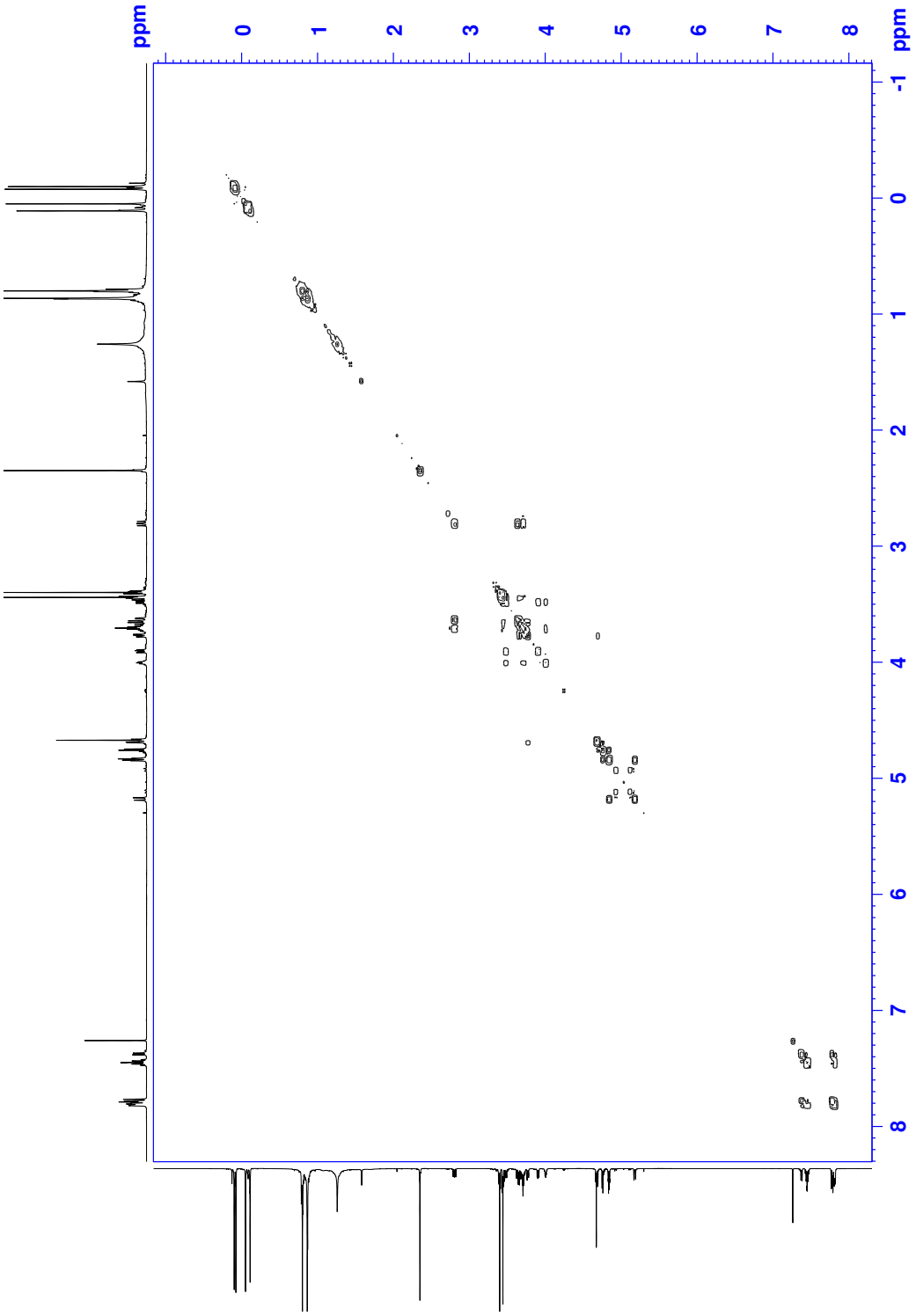


Figure A.74: COSY spectrum of compound **8d**.

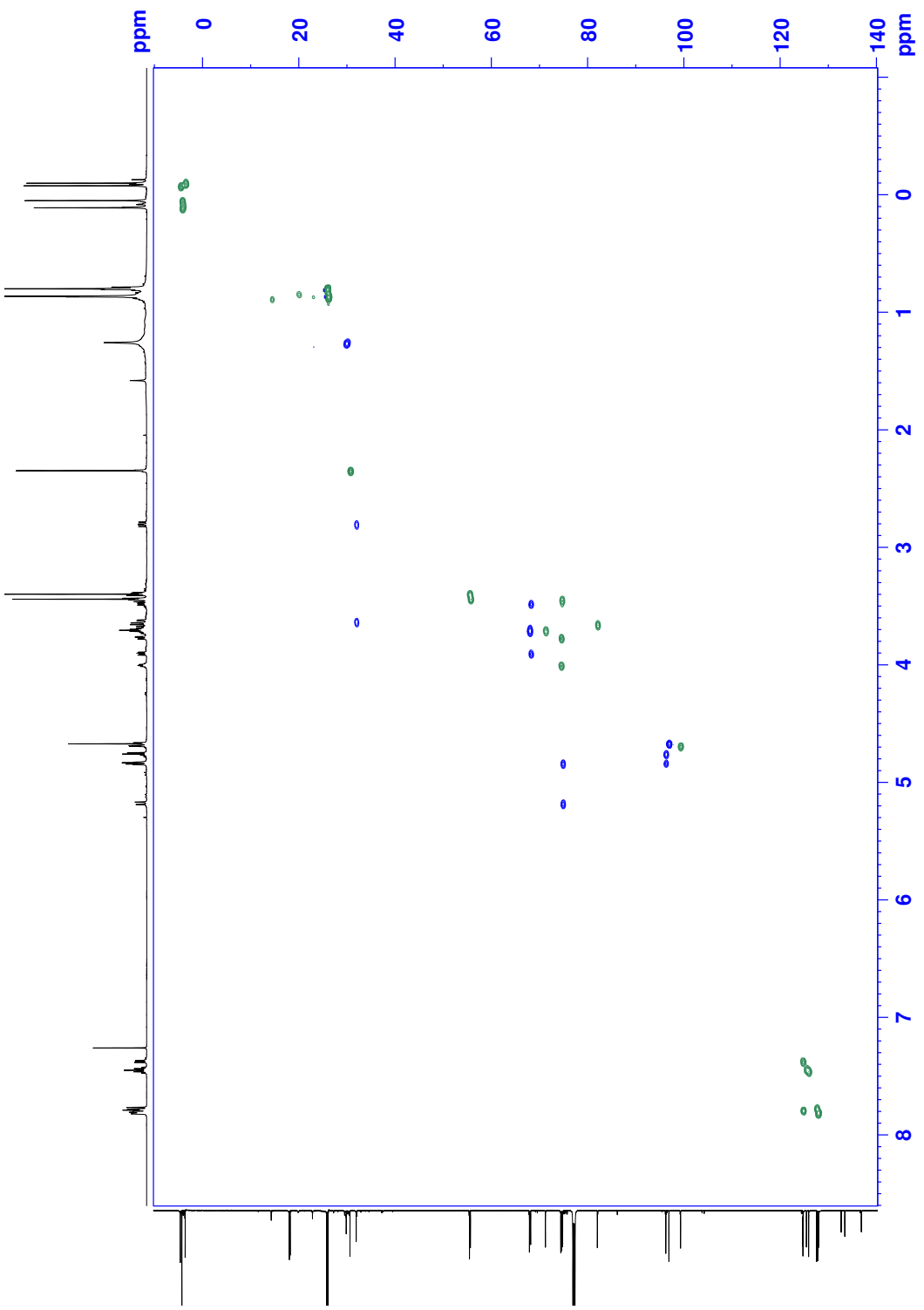


Figure A.75: HSQC spectrum of compound **8d**.

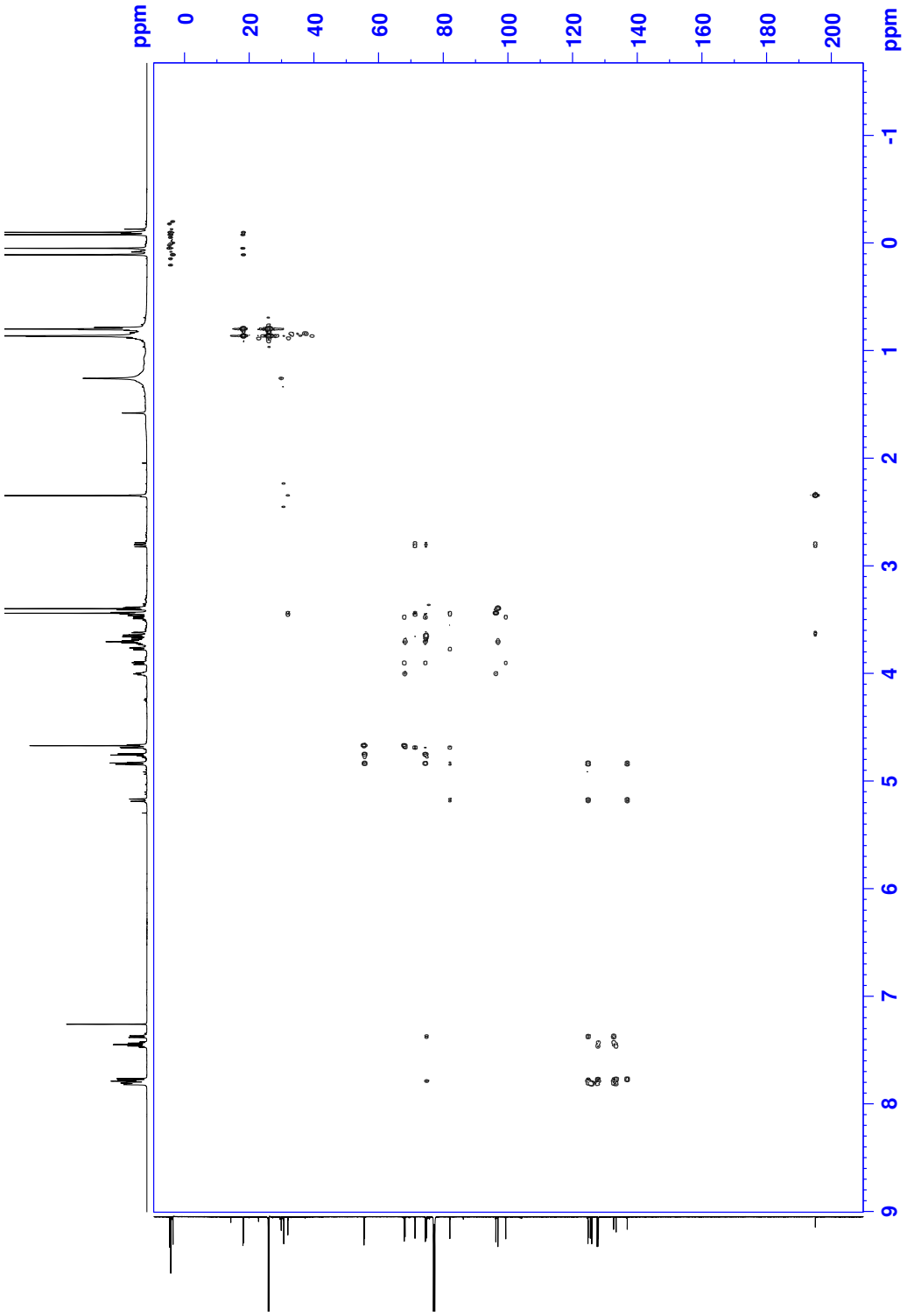


Figure A.76: HMBC spectrum of compound **8d**.

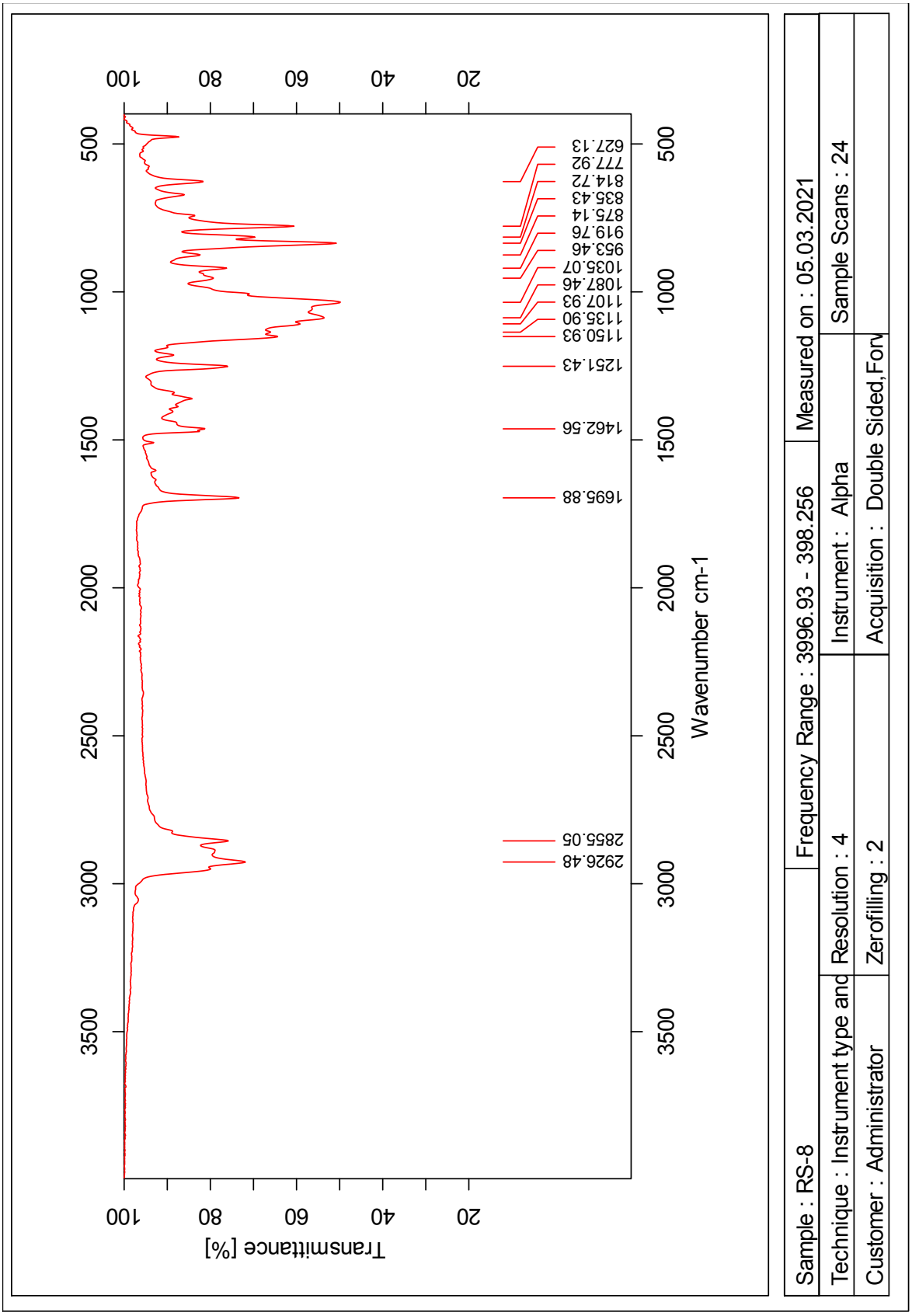


Figure A.77: IR spectrum of compound **8d**.

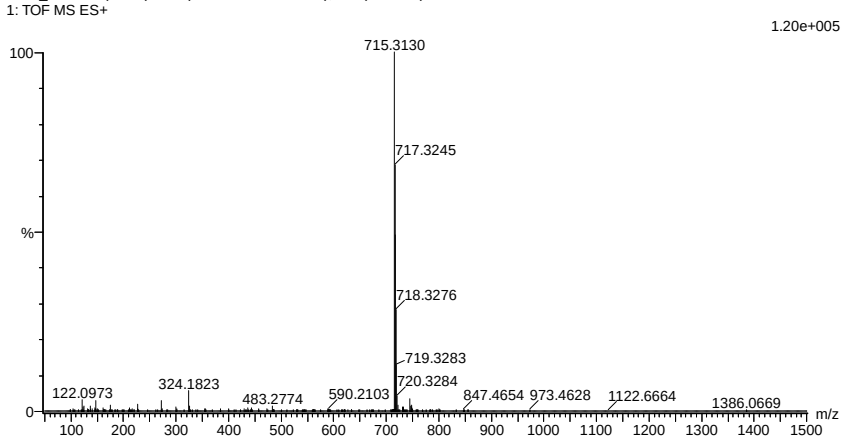
A.12 Spectroscopic data for compound 8ox

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
1333 formula(e) evaluated with 6 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 O: 0-12 S: 0-1 Si: 0-2 Na: 0-1

2021_129 100 (0.945) AM2 (Ar,35000.0,0.00,0.00); Cm (100:103)
1: TOF MS ES+



Minimum:				-10.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
715.3130	715.3132	-0.2	-0.3	9.5	975.0	4.246	1.43	C35 H56 O8 S Si2 Na
	715.3128	0.2	0.3	10.5	974.6	3.852	2.12	C36 H52 O11 S Na
	715.3126	0.4	0.6	10.5	973.6	2.857	5.74	C35 H52 O12 Si Na
	715.3125	0.5	0.7	17.5	974.7	3.945	1.94	C41 H51 O7 S Si
	715.3122	0.8	1.1	17.5	974.2	3.405	3.32	C40 H51 O8 Si2
	715.3118	1.2	1.7	18.5	970.9	0.157	85.44	C41 H47 O11

Figure A.78: HRMS (ESI+) spectrum of compound **8ox**.

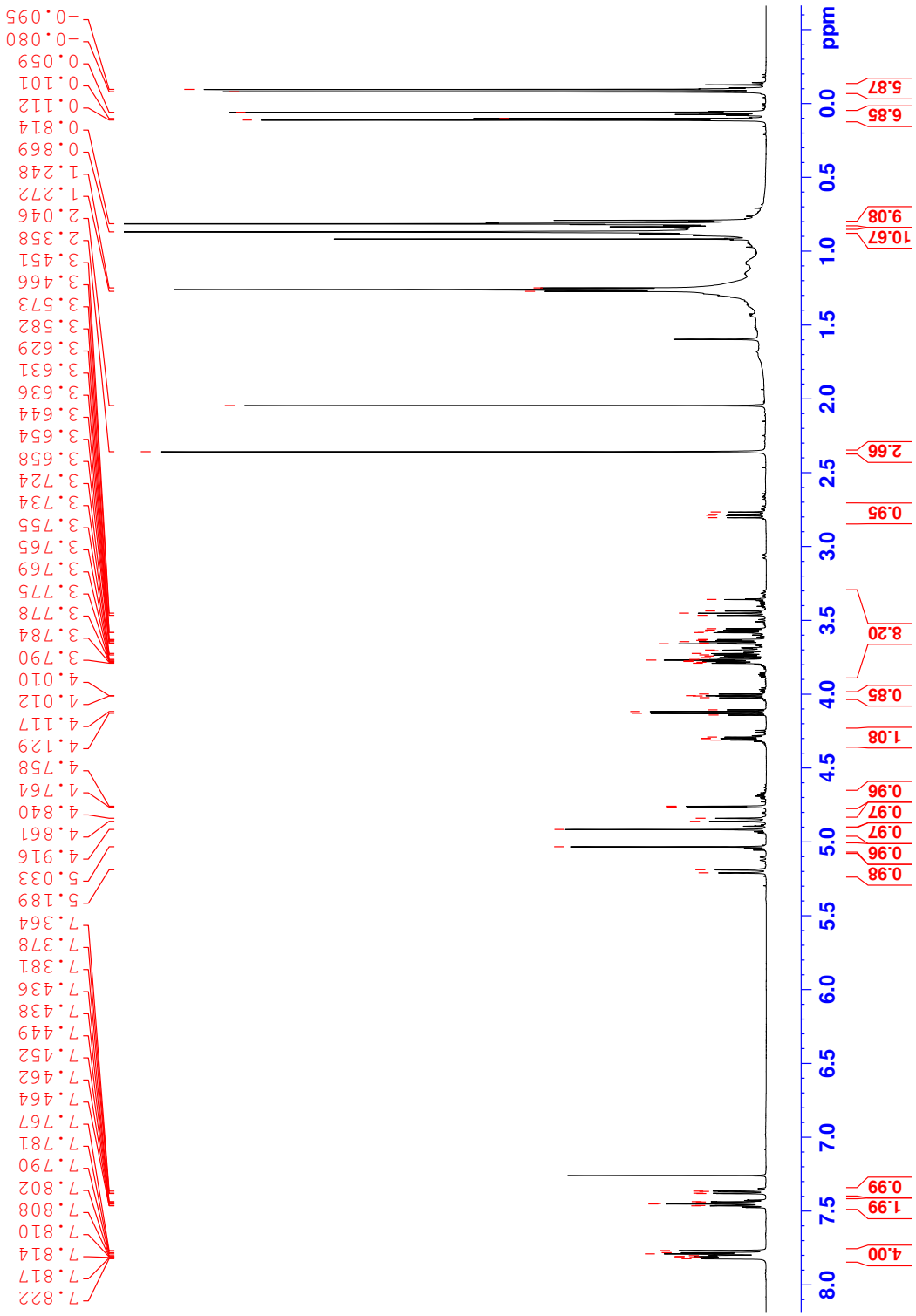


Figure A.79: ^{1}H NMR spectrum of compound **8ox**.

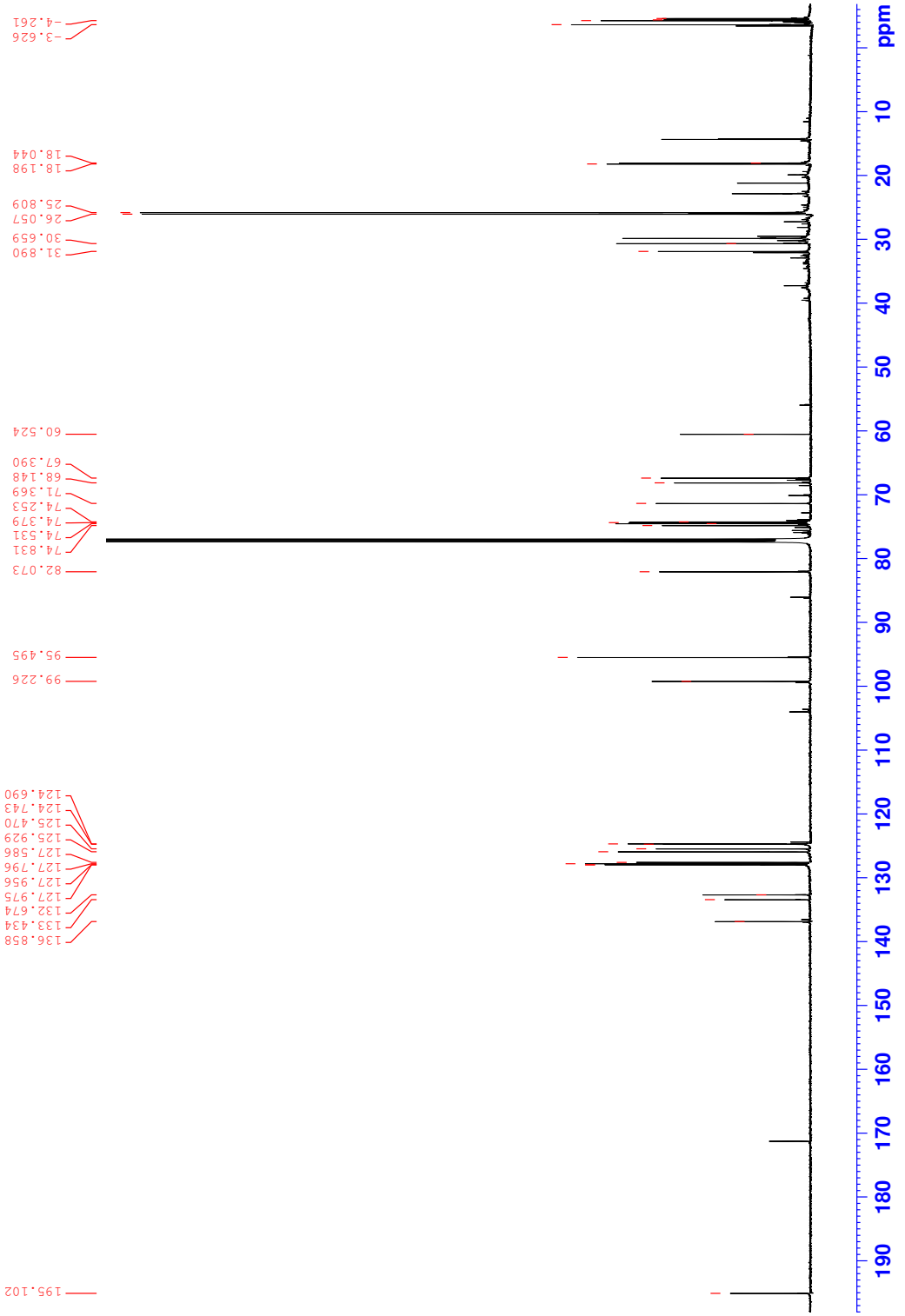


Figure A.80: ^{13}C NMR spectrum of compound **8ox**.

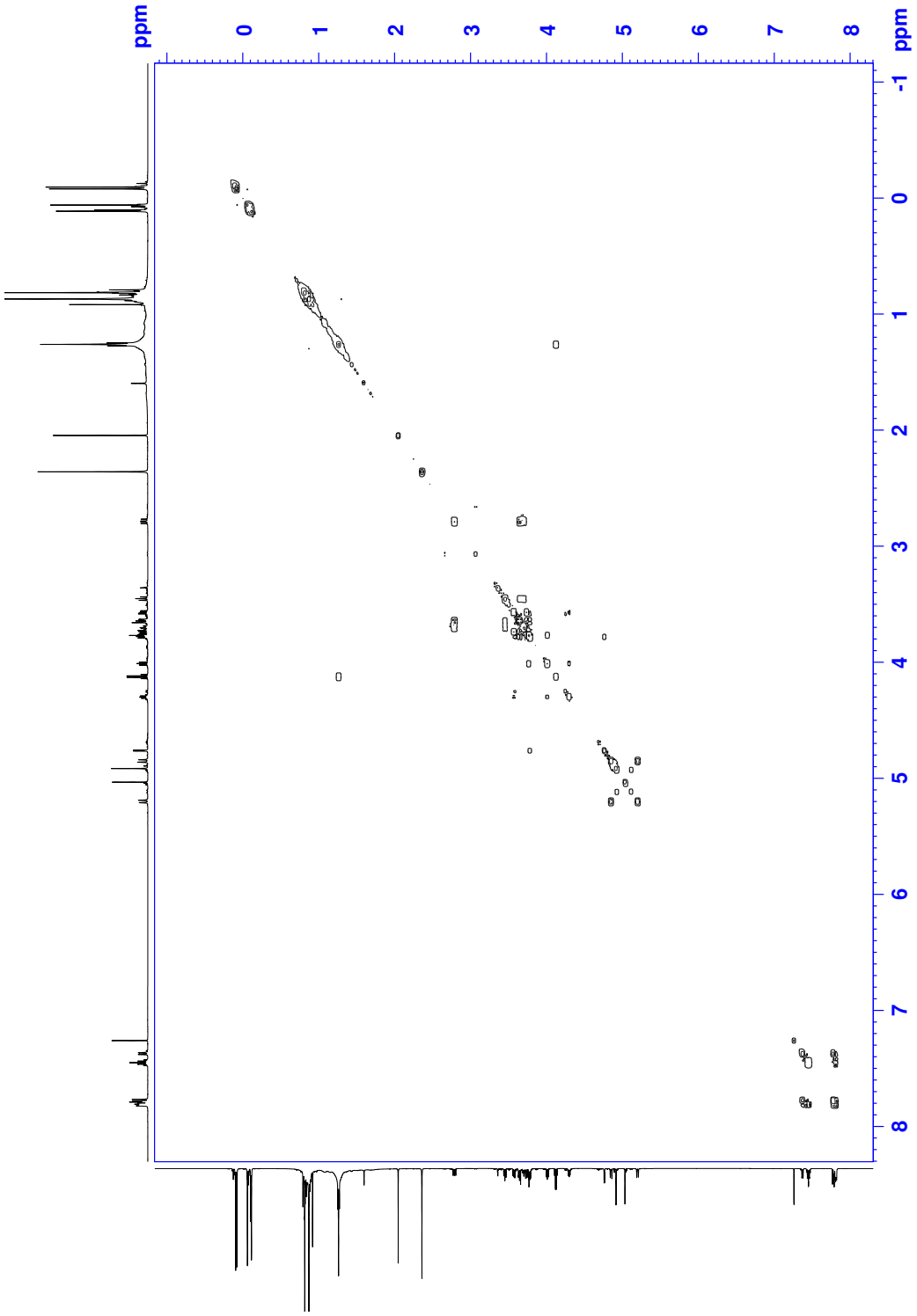


Figure A.81: COSY spectrum of compound **8ox**.

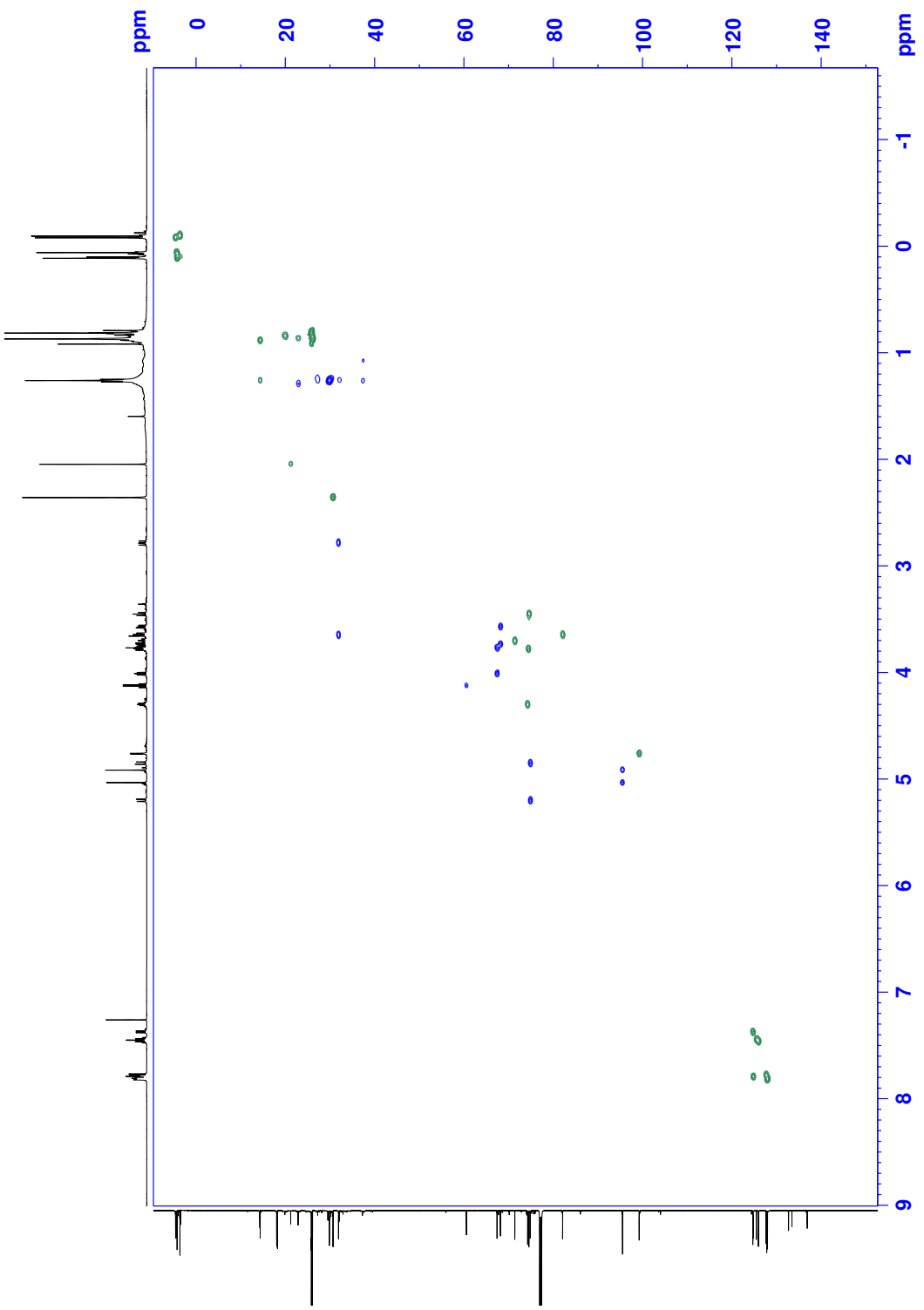


Figure A.82: HSQC spectrum of compound **8ox**.

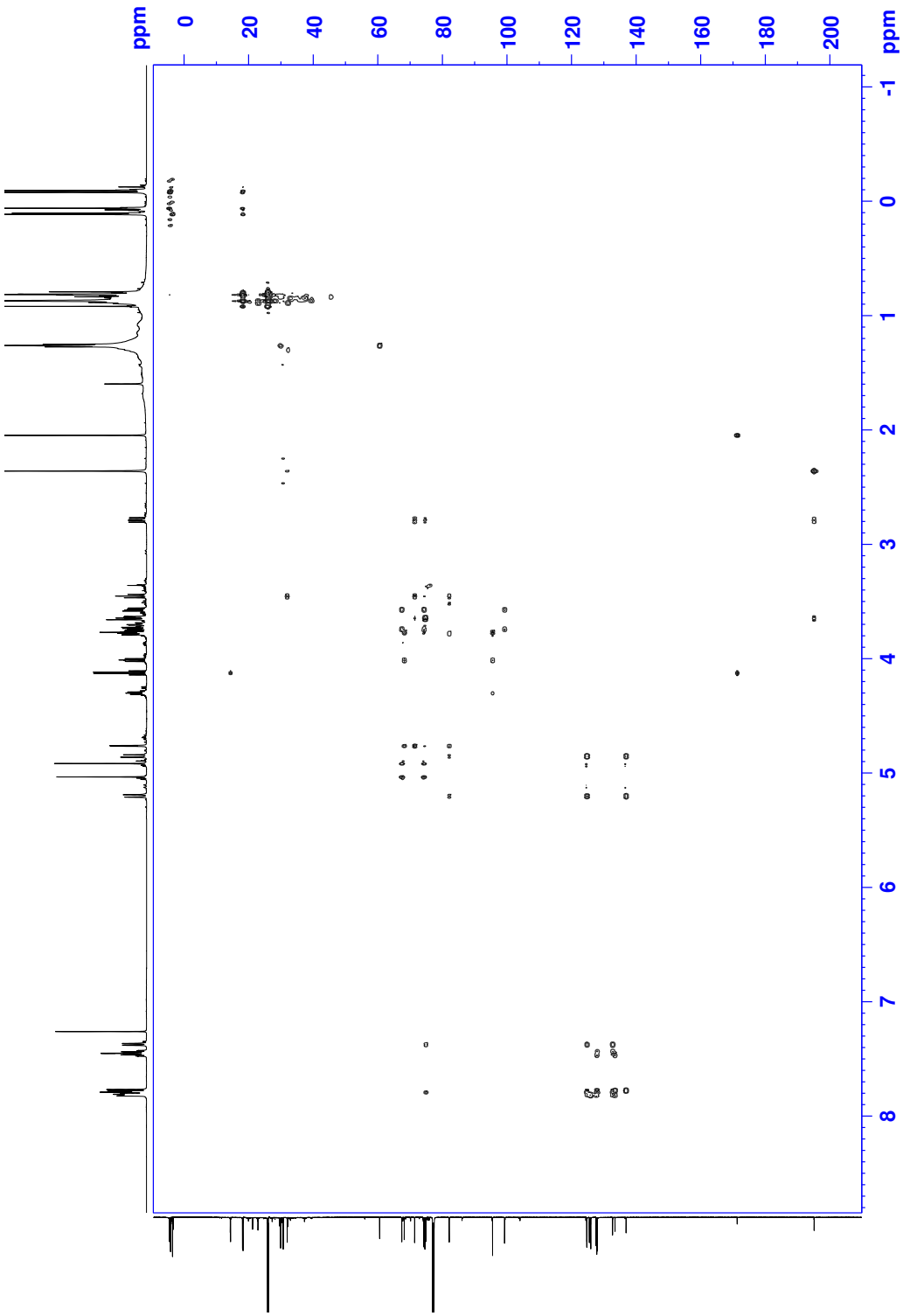


Figure A.83: HMBC spectrum of compound **8ox**.

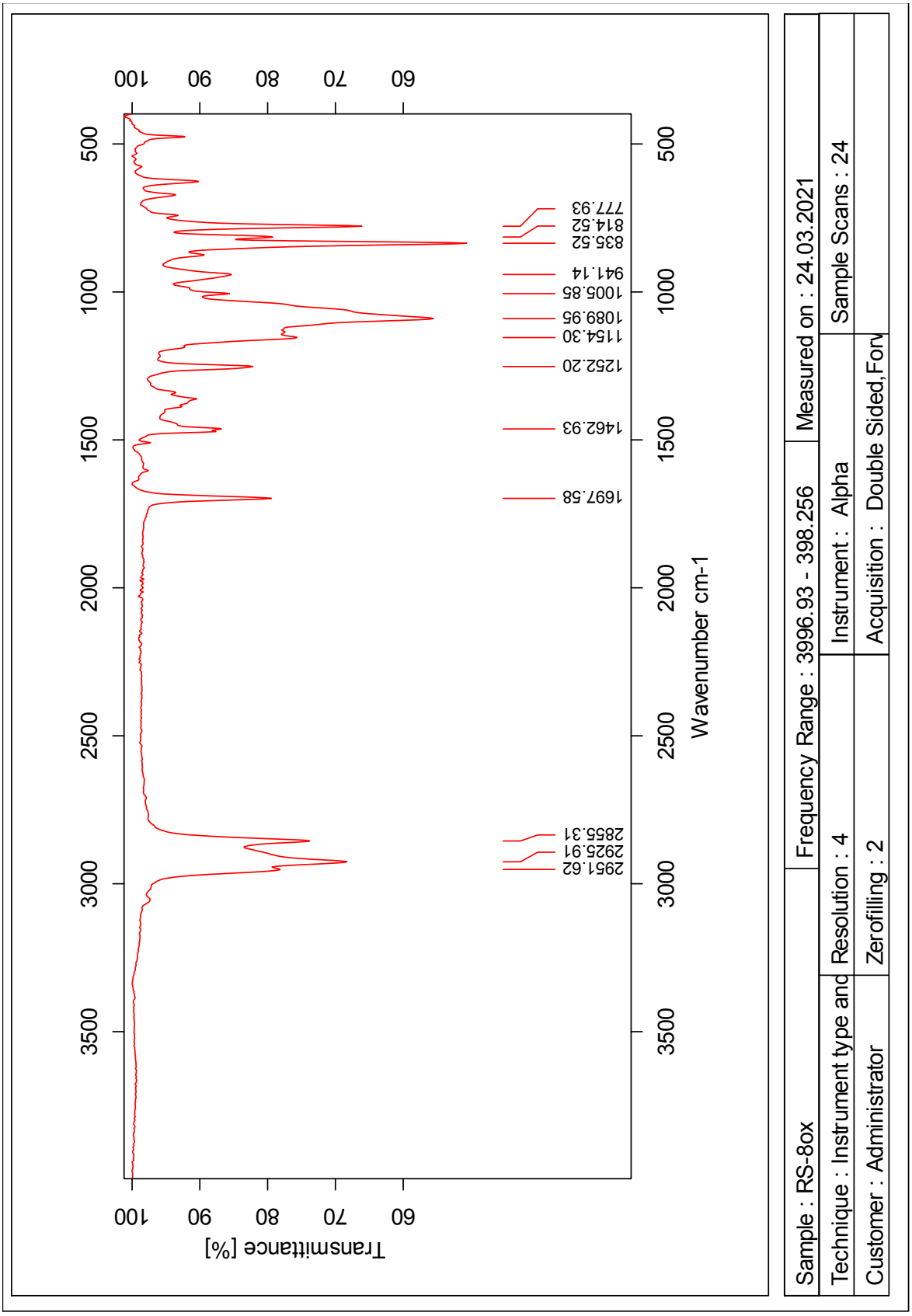


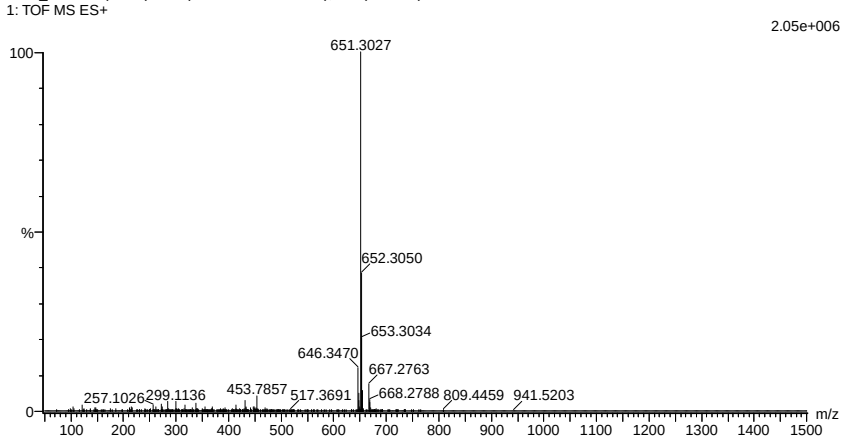
Figure A.84: IR spectrum of compound **8ox**.

A.13 Spectroscopic data for compound 9b

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
1527 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 O: 0-15 Na: 0-1 Si: 0-2 S: 0-1
2021_239 121 (1.144) AM2 (Ar,35000.0,0.00,0.00); Cm (111:121)
1: TOF MS ES+



Minimum:				-10.0				
Maximum:		5.0	2.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
651.3027	651.3030	-0.3	-0.5	1.5	1498.8	0.266	76.64	C27 H56 O10 Na Si2 S
	651.3023	0.4	0.6	9.5	1500.1	1.565	20.91	C33 H51 O9 Si S
	651.3021	0.6	0.9	9.5	1502.3	3.713	2.44	C32 H51 O10 Si2
	651.3026	0.1	0.2	2.5	1509.0	10.436	0.00	C28 H52 O13 Na S
	651.3024	0.3	0.5	2.5	1512.5	13.917	0.00	C27 H52 O14 Na Si
	651.3017	1.0	1.5	10.5	1520.2	21.655	0.00	C33 H47 O13
	651.3028	-0.1	-0.2	29.5	1522.3	23.733	0.00	C49 H40 Na

Figure A.85: HRMS (ESI+) spectrum of compound **9b**.

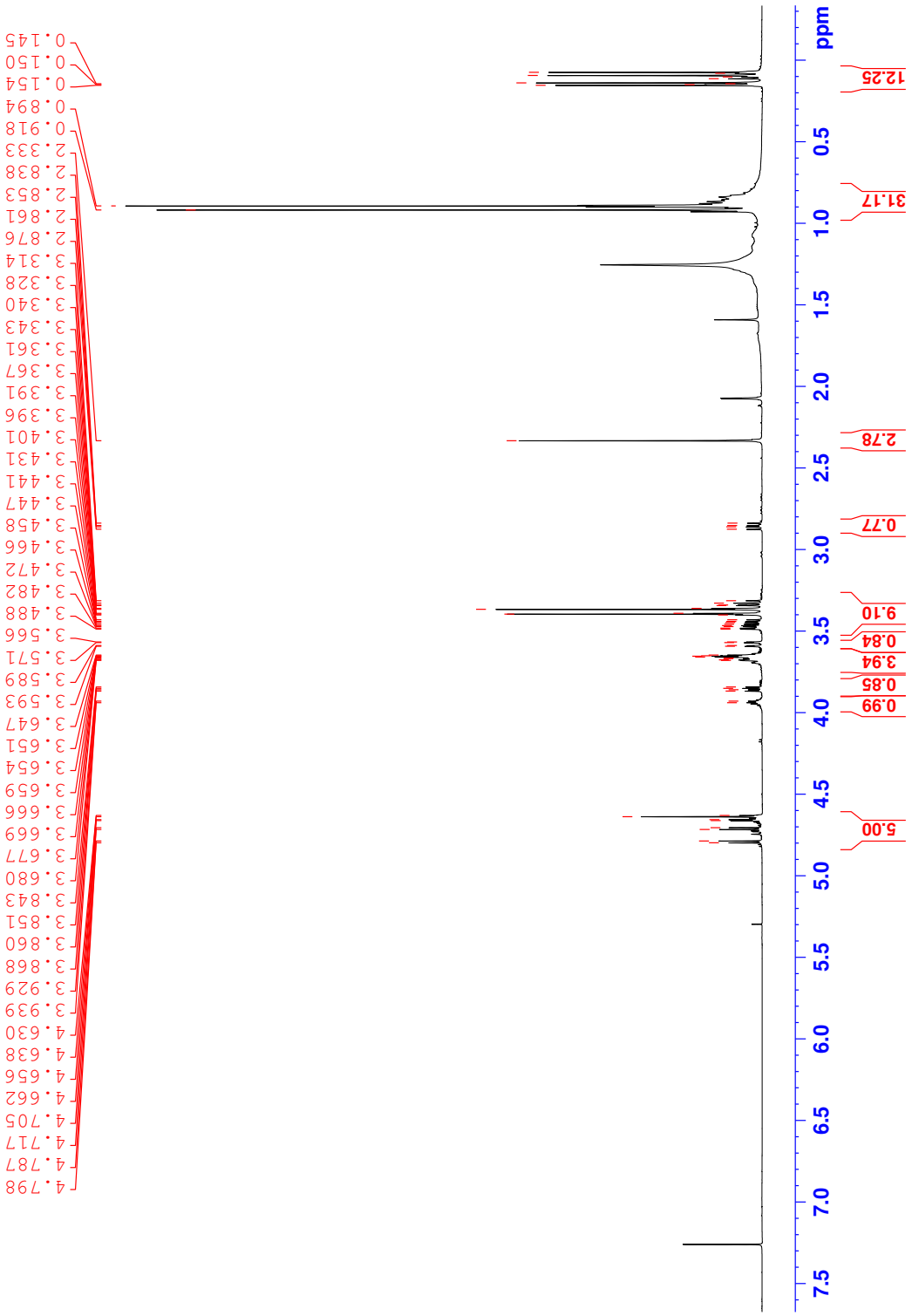


Figure A.86: ^{1}H NMR spectrum of compound **9b**.

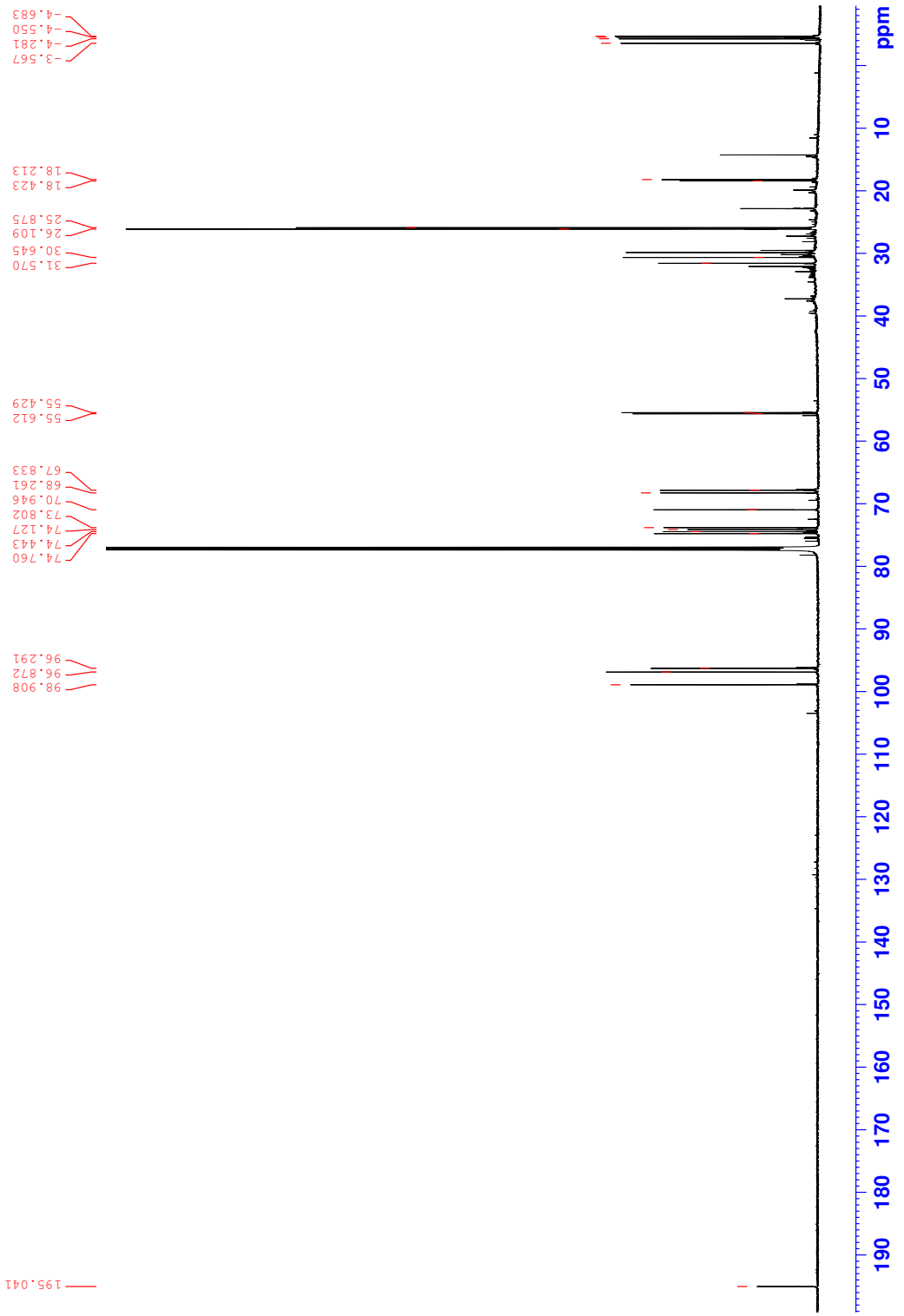


Figure A.87: ^{13}C NMR spectrum of compound **9b**.

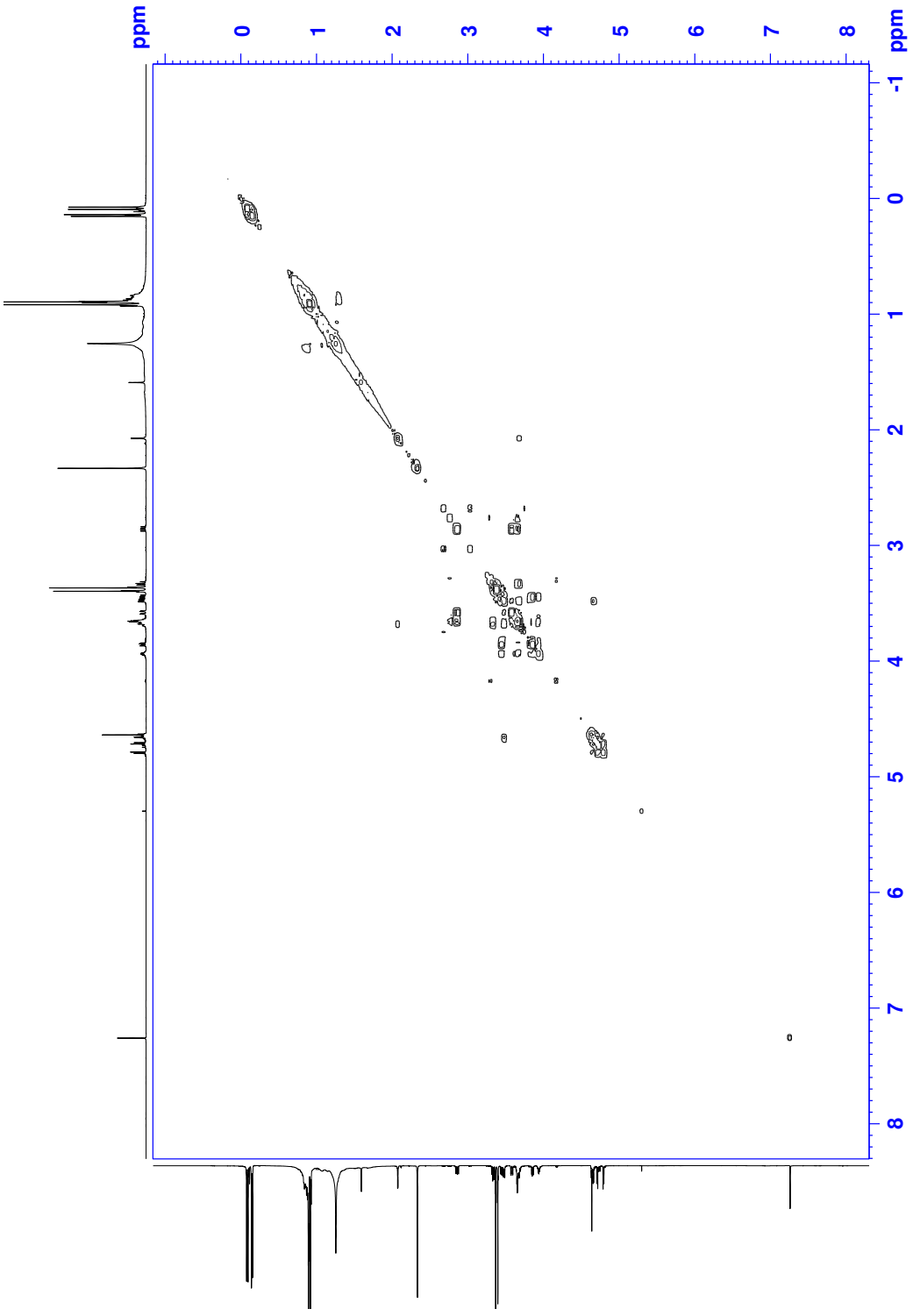


Figure A.88: COSY spectrum of compound **9b**.

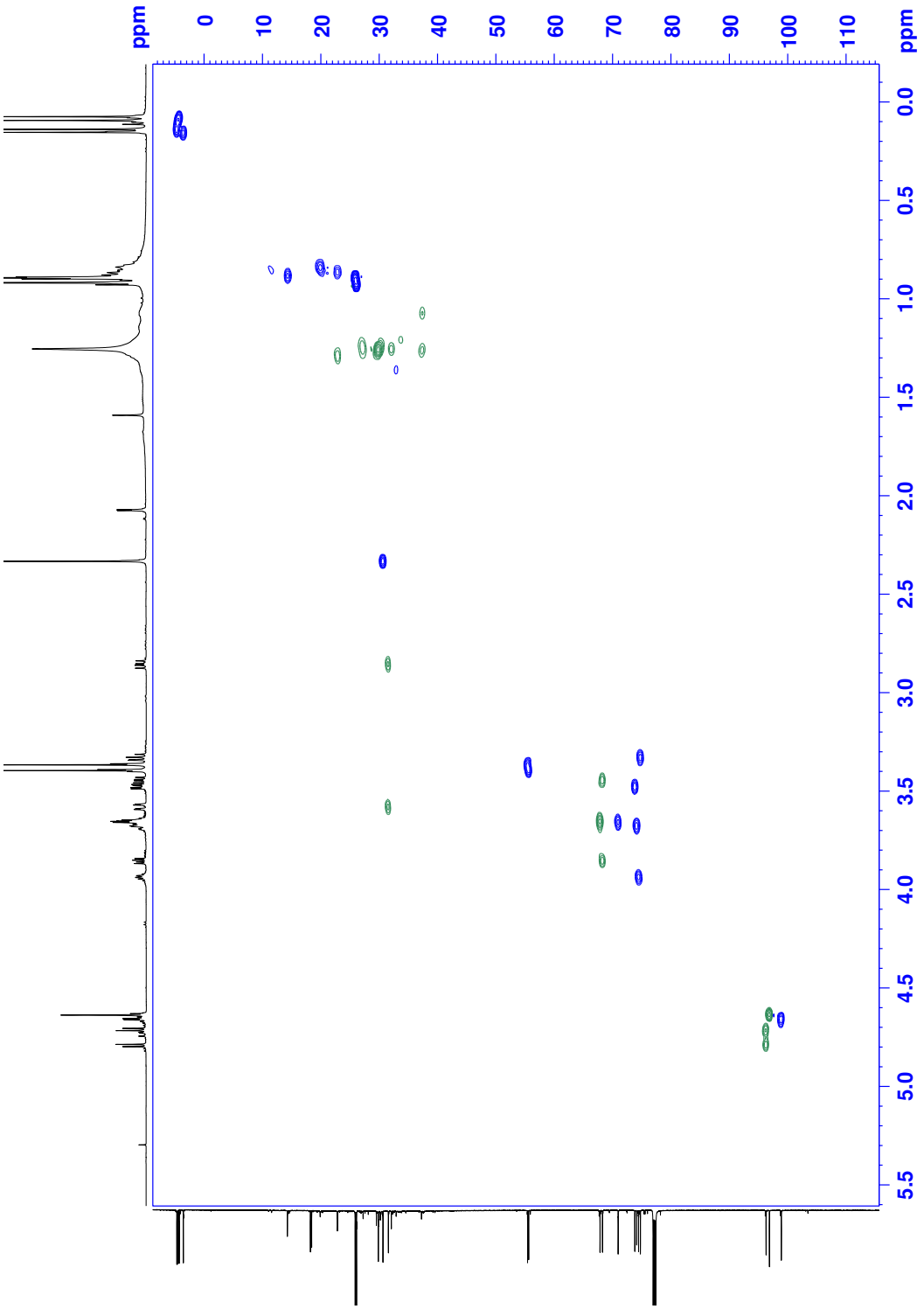


Figure A.89: HSQC spectrum of compound **9b**.

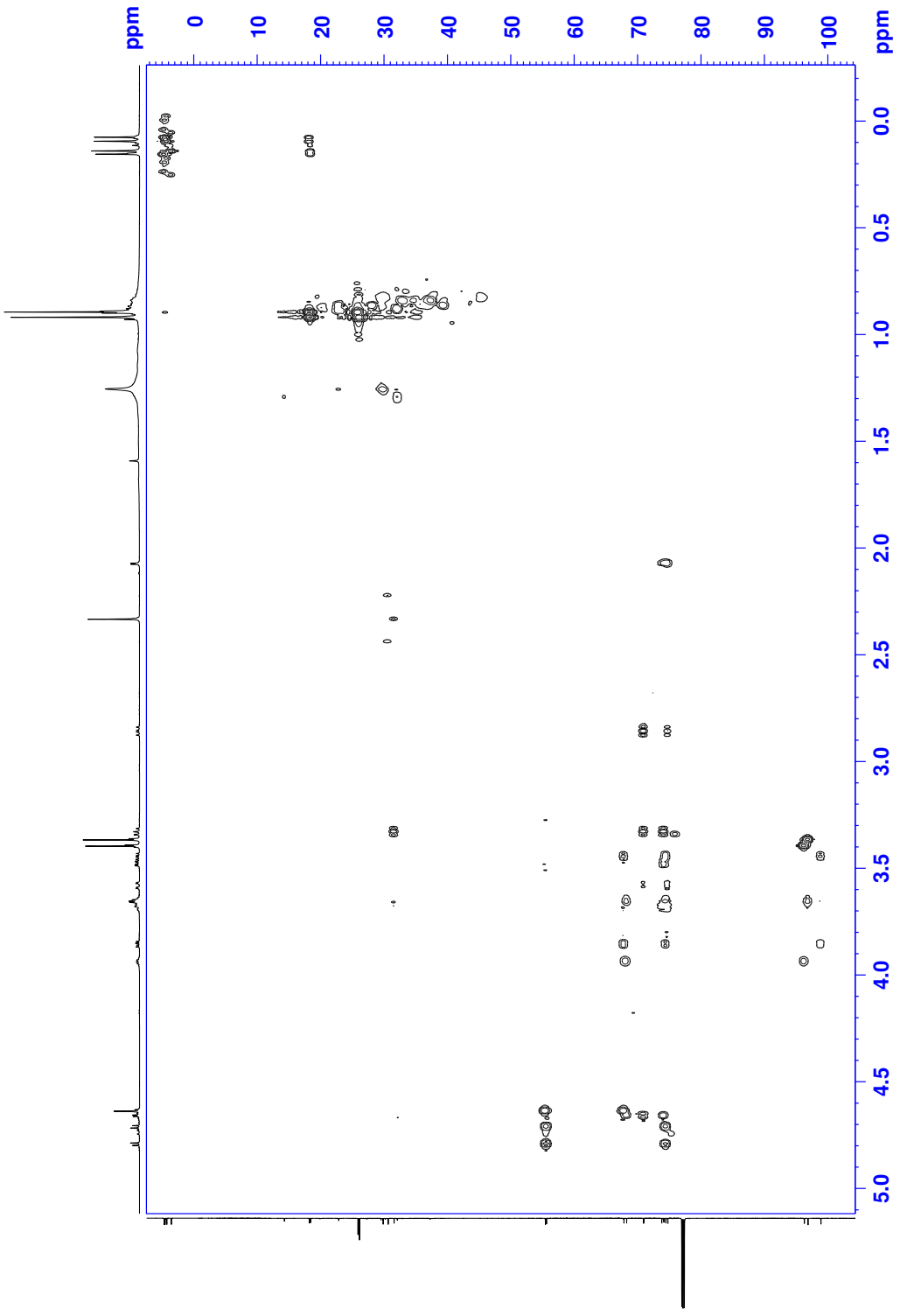


Figure A.90: HMBC spectrum of compound **9b**.

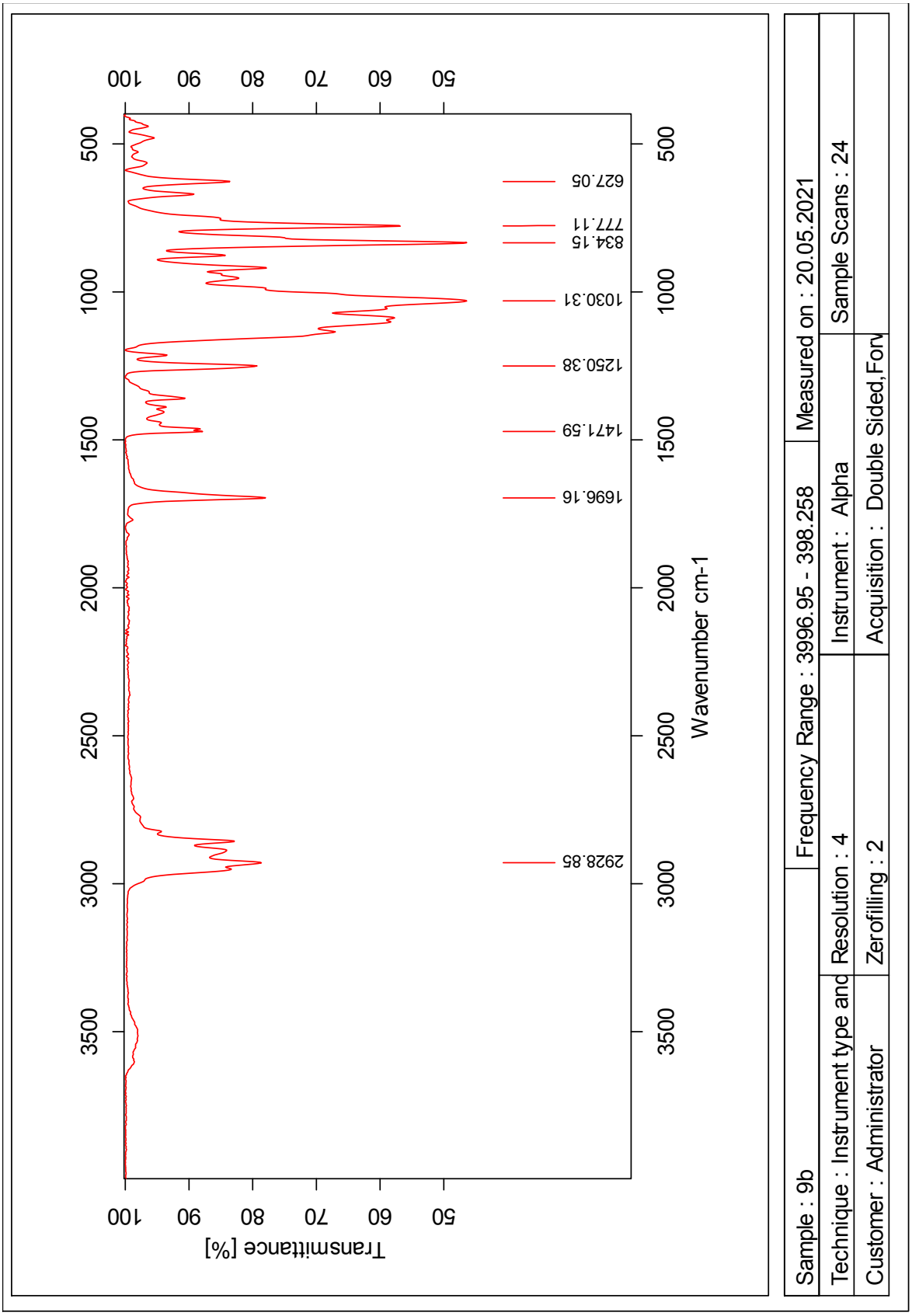


Figure A.91: IR spectrum of compound **9b**.

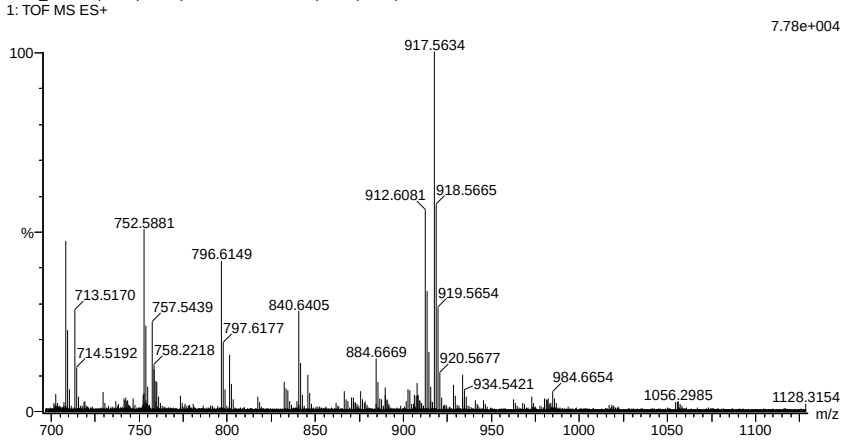
A.14 Spectroscopic data for compound 10b

Elemental Composition Report **Page 1**

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

Monoisotopic Mass, Even Electron Ions
1632 formula(e) evaluated with 7 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100 H: 0-100 O: 0-15 S: 0-1 Na: 0-1 Si: 0-2

2021_322 42 (0.404) AM2 (Ar,35000.0,0.00,0.00); Cm (40:43)
1: TOF MS ES+



Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
Minimum:				-10.0				
Maximum:		5.0	2.0	50.0				
917.5634	917.5640	-0.6	-0.7	2.5	926.2	0.030	97.00	C45 H90 O11 S Na Si2
	917.5633	0.1	0.1	10.5	929.8	3.607	2.71	C51 H85 O10 S Si
	917.5630	0.4	0.4	10.5	932.1	5.861	0.28	C50 H85 O11 Si2
	917.5636	-0.2	-0.2	3.5	937.4	11.144	0.00	C46 H86 O14 S Na
	917.5634	0.0	0.0	3.5	938.1	11.891	0.00	C45 H86 O15 Na Si
	917.5626	0.8	0.9	11.5	942.1	15.911	0.00	C51 H81 O14
	917.5637	-0.3	-0.3	30.5	942.4	16.144	0.00	C67 H74 O Na

Figure A.92: HRMS (ESI+) spectrum of compound **10b**.

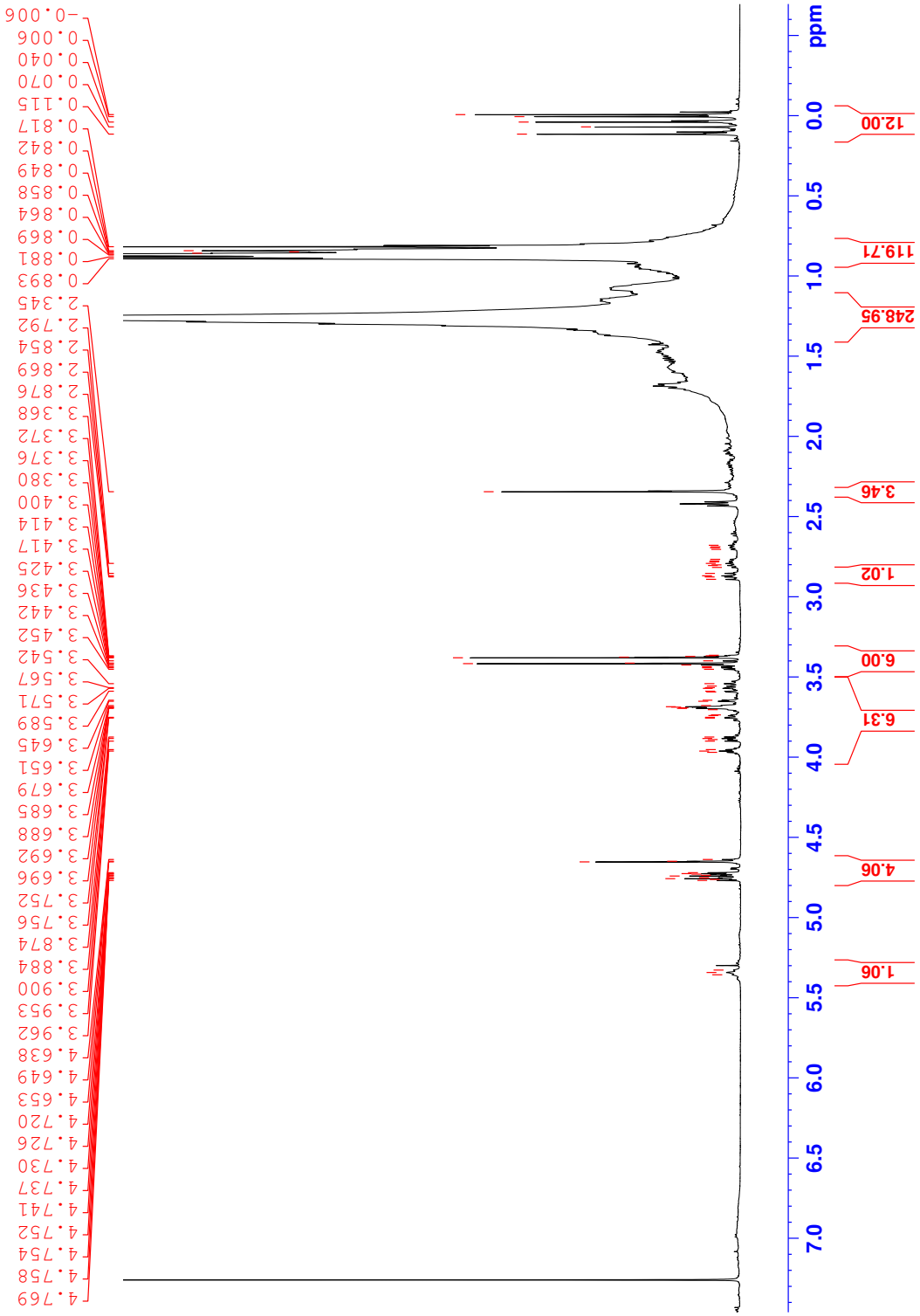


Figure A.93: ^{1}H NMR spectrum of compound **10b**.

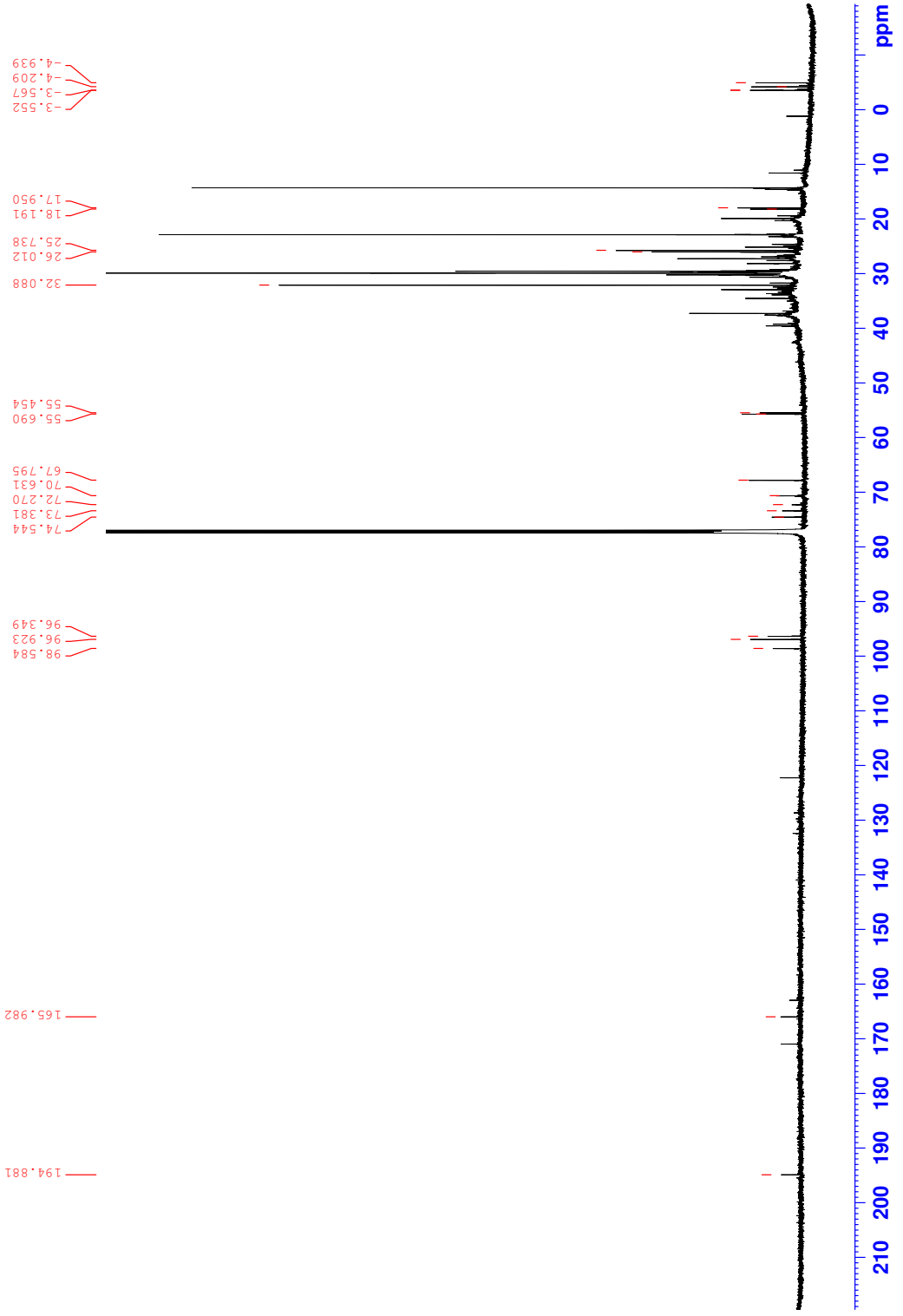


Figure A.94: ^{13}C NMR spectrum of compound **10b**.

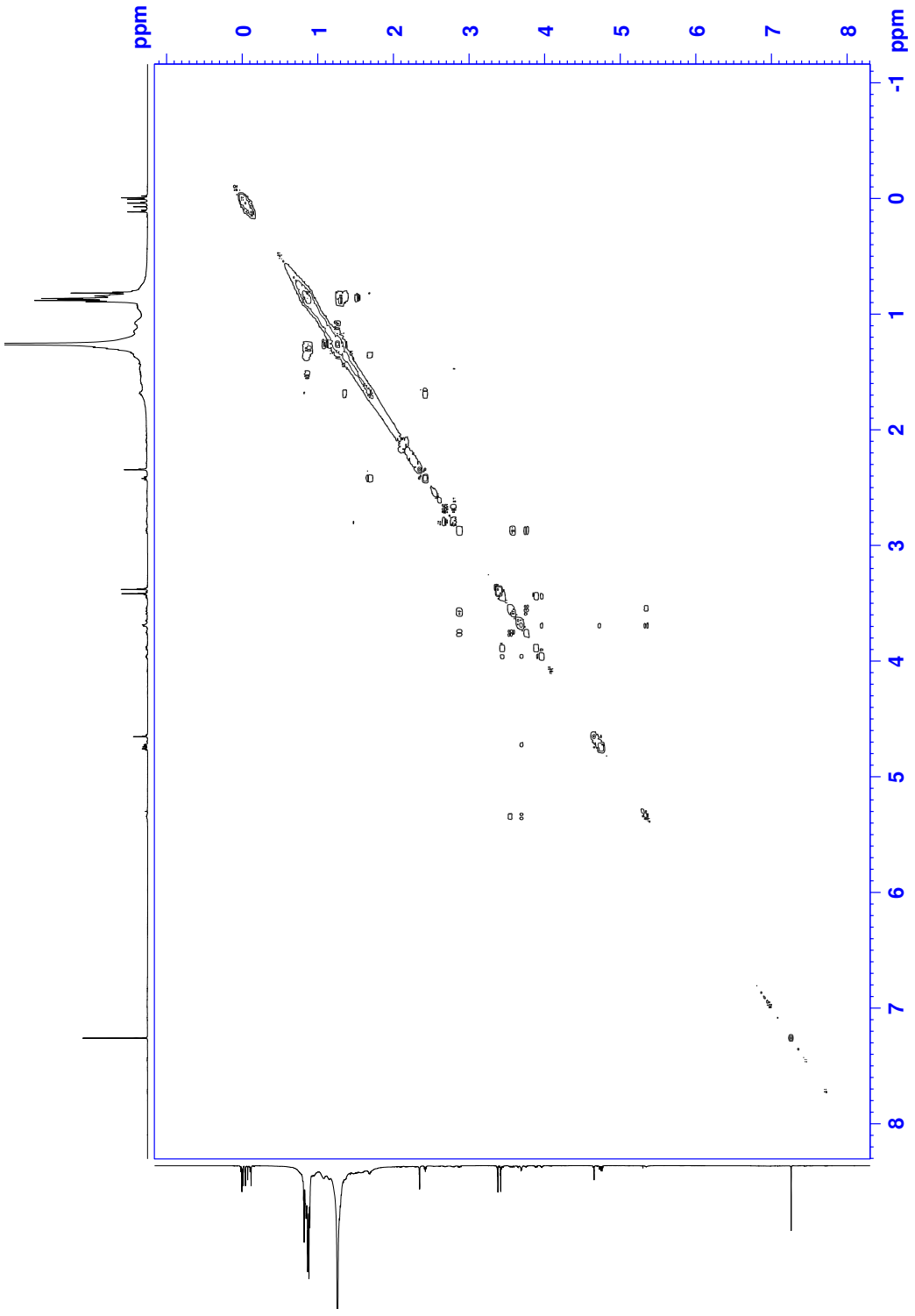


Figure A.95: COSY spectrum of compound **10b**.

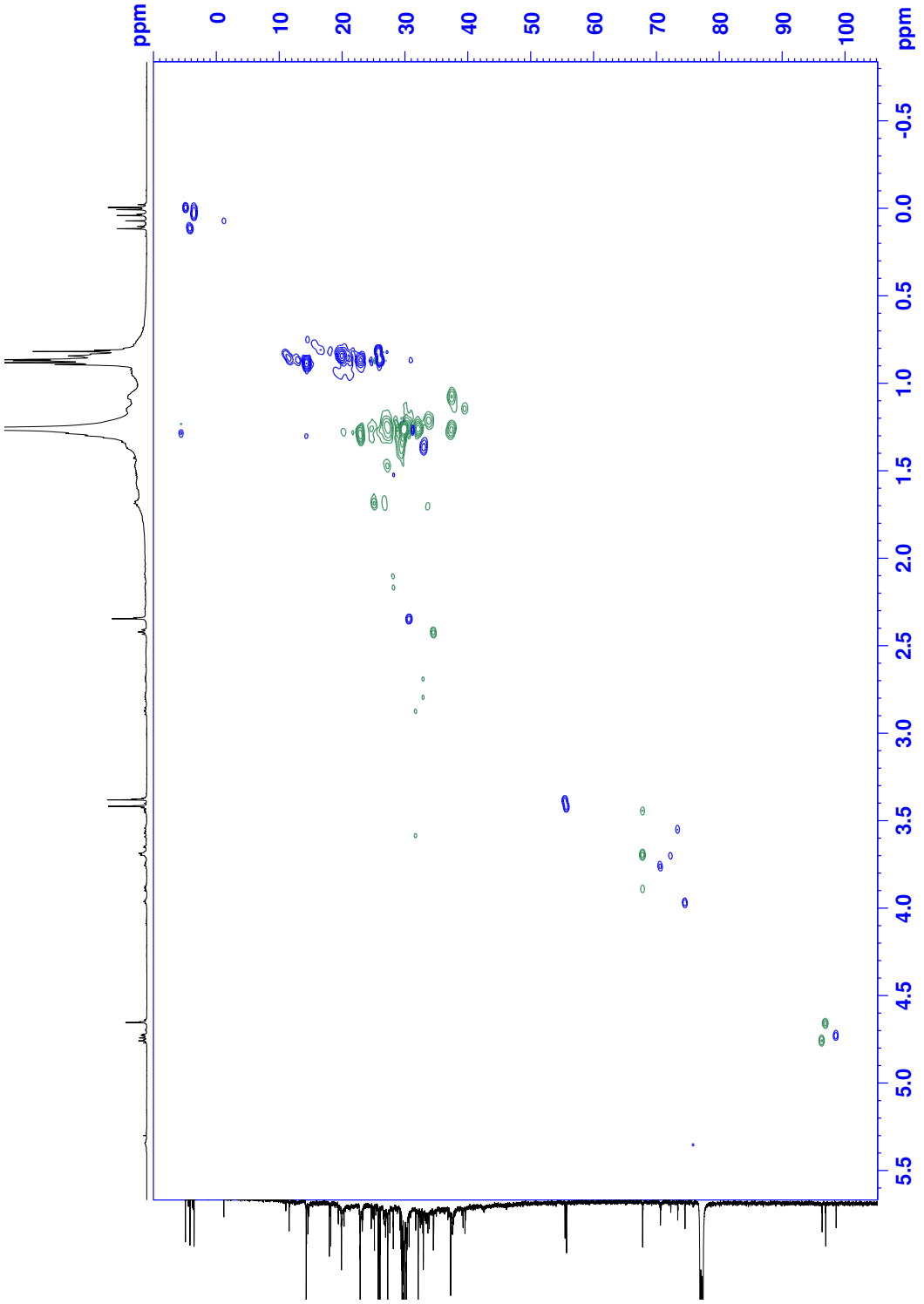


Figure A.96: HSQC spectrum of compound **10b**.

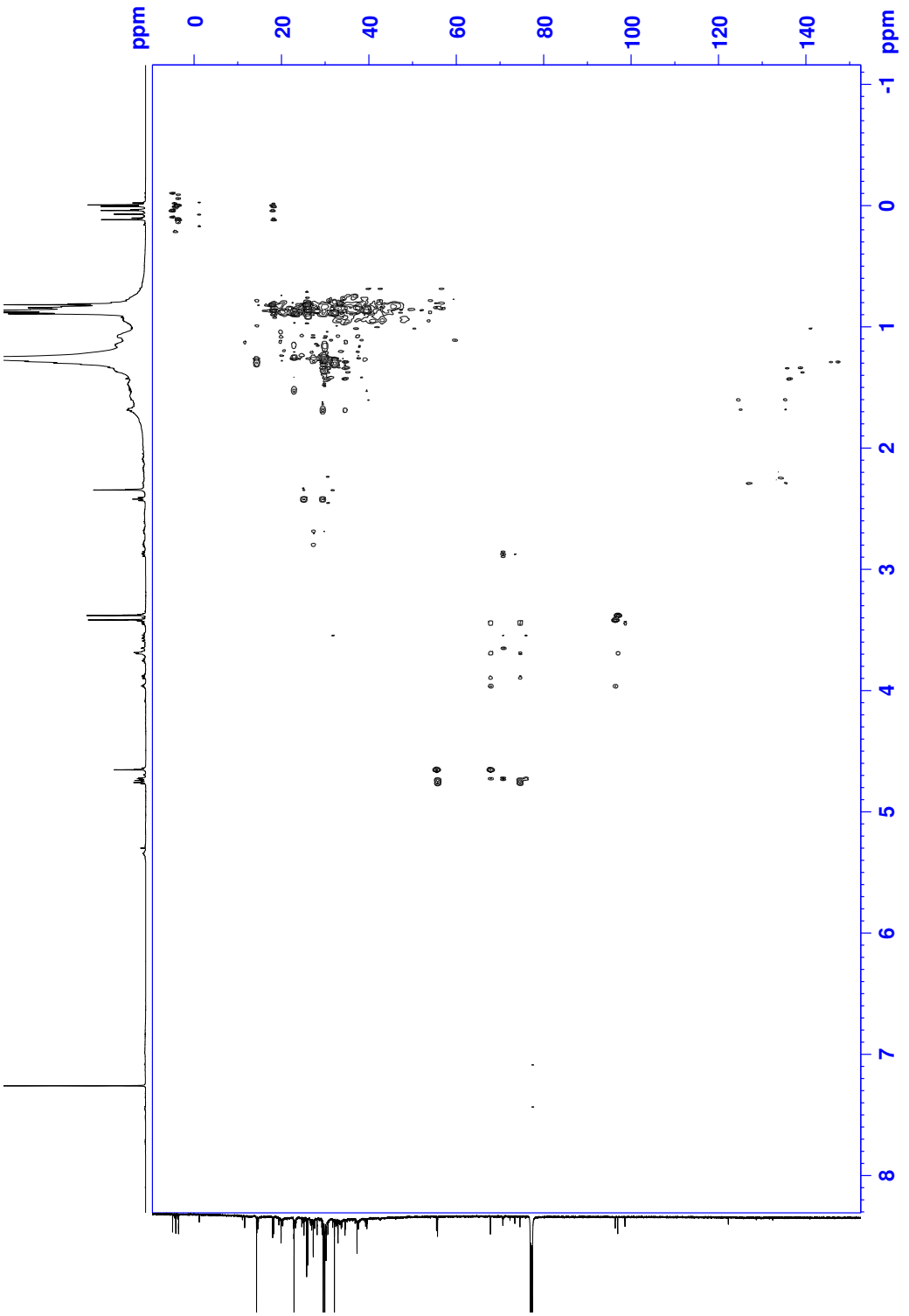


Figure A.97: HMBC spectrum of compound **10b**.

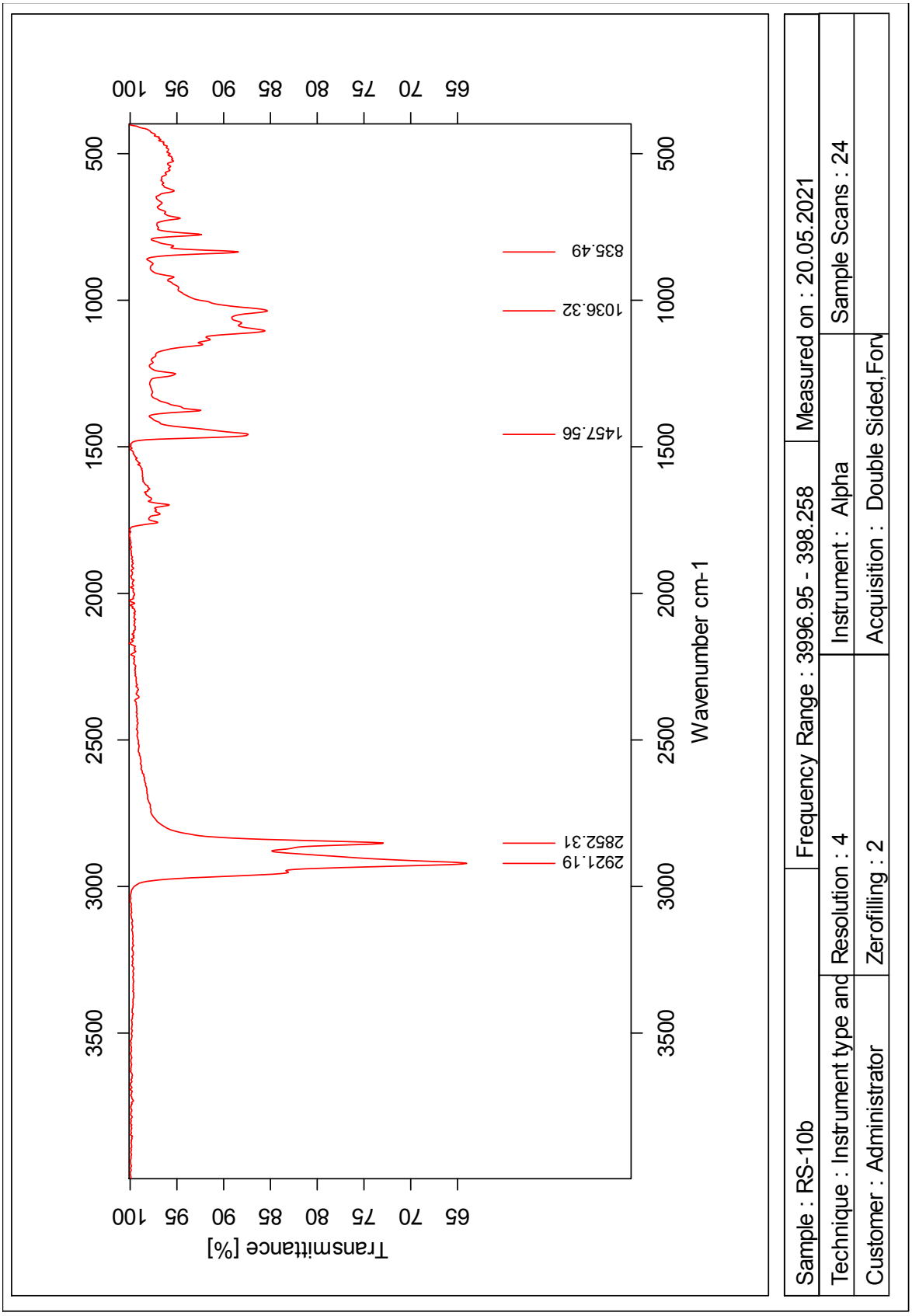


Figure A.98: IR spectrum of compound **10b**.

Ragnar Stene

Investigation of protection group exchange in late stage intermediates in the synthesis of 3-*O*-acylsulfoquinovosyl

NTNU
Norwegian University of
Science and Technology