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Total Synthesis of Farnesyl Lipid I/II Analogues

and

Contributions to the Total Synthesis of Neaumycin B

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Eidesstaatliche Erklärung

Hiermit versichere ich an Eides statt, dass ich die vorliegende Arbeit unter Einhaltung der Regeln guter wissenschaftlicher Praxis selbstständig verfasst, keine anderen als die angegebenen Quellen und Hilfsmittel benutzt und die Zitate kenntlich gemacht habe.

Bonn, den 18.02.2025

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Christina Braun

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List of Abbreviations

(*S*)-2-Me-CBS	(*S*)-2-methyl-*Corey-Bakshi-Shibata* oxazaborolidine catalyst
2-CTC	2-chlorotrityl chloride
9-BBN	9-borabicyclo(3.3.1)nonane
Ac_2O	acetic anhydride
AcOH	acetic acid
AgOTf	silver triflate
Ala	alanine
AT	acyl transferase
BDMS	bromodimethylsulfonium bromide
BINAP	2,2´–bis(diphenylphosphino)–1,1´–binaphthyl
Cbz	benzyloxycarbonyl
CDI	1,1-carbonyldiimidazol
CoA	coenzyme A
cod	cycloocta-1,5-diene
CPME	cyclopentylmethylether
CSA	camphorsulfonic acid
dba	dibenzylideneacetone
DCC	N,N'-dicyclohexyl carbodiimide
DCE	1,2-dichlorethane
DCM	dichloromethane
DDQ	2,3-dichlor-5,6-dicyano-1,4-benzochinone
DH	dehydratase
DIBAL-H	diisobutyl aluminium hydride
DIPEA	diisopropylethylamine
DIPT	diisopropyltartrate
DMAP	dimethylaminopyridine
DMB	3,4-dimethoxybenzyl
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMI	1,3-dimethyl-2-imidazolidione
DMP	Dess-Martin periodane
DMSO	dimethylsulfoxide
DNA	desoxyribonucleic acid
dtbbpy	4,4'-di-*tert*-butyl-2,2'-dipyridyl
E.faecalis	*Enterococcus faecalis*
ee	enantiomeric excess
ER	enoyl reductase
Et_2O	Diethyl ether
Et_3SiH	triethylsilane
EtOH	ethanol
Fmoc	fluorenylmethylenoxycarbonyl
GlcNAc	*N*-acetylglucosamine
Glu	glutamic acid
HBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-hexafluorophosphate
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HGT	horizontal genetic tranfer
HMBA-PEG	4-hydroxymethylbenzoic acid PEG resin
HMPA	hexamethylphosphoramide

HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenztriazol hydrate
HPLC	high performance liquid chromatography
HWE	*Horner-Wadsworth-Emmons*
KHMDS	potassium bis(trimethylsilyl)amide
KR	keto reductase
LAH	lithium aluminium hydride
LD	lethal dosis
LDA	lithiumdiisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidine
LLS	longest linear sequence
Lys	lysine
mCPBA	*meta*-chlorperbenzoic acid
MeOH	methanol
MeOTf	methyltrifluormethylsulfonate
MIC	minimum inhibitory concentration
MOM	methoxy methyl
MS	molecular sieves
MTBE	methyltertbutyl ether
MurNAc	*N*-acetyl muramic acid
$NaHCO_3$	sodium bicarbonate
NaHMDS	sodium bis(trimethylsilyl)amide
NaOMe	sodium methanolate
NBS	*N*-bromosuccinimide
***n*BuLi**	*n*-butyl lithium
NHK	Nozaki-Hiyama-Kishi
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
o.n.	overnight
PGN	Peptidoglycan network
Phth	phthalimide
PivCl	pivaloyl chloride
PK	polyketide
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
PMB-TCAI	*para*-methoxybenzyltrichloracetimidate
PPTS	pyridinium *para*-toluenesulfonic acid
p-TsOH	*para*-toluenesulfonic acid
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium-hexafluorophosphate
PyOAP	(7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
RNA	ribonucleic acid
rt	room temperature
S.pneumoniae	*Streptococcus pneumoniae*
SAE	*Sharpless* asymmetric epoxidation
SEE	silyl enol ether
S_N	nucleophilic substitution

SPPS	solid-phase peptide synthesis
TBAF	tetrabutylammonium fluoride
TBAP	tetrabutylammonium phosphate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCA	trichloracetonitrile
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidinyloxyl
TES	triethylsilyl
Tf_2O	triflic acid anhydride
TFA	trifluoracetic acid
TFE	trifluorethanol
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSE	trimethylsilylethyl
Troc	trichloroethoxycarbonyl
TS	transition state
UDP-MurNAc	UDP-*N*-acetyl muramic acid
VMA	vinylogous *Mukaiyama* aldol

Abstract

Abstract Part I

One of the big challenges of our time is the antibiotic crisis that humanity is facing. The rapidly increasing resistance of bacteria against common used antibiotics presents a threat to human health.[1] In combination with the rise of multiresistant strains there is an urge for new targets as well as the invention of efficient drugs to fight this development.[2] As the main building block of the cell wall of *Gram* positive bacteria, lipid II presents a readily available target on the outside of the cell.[3] Additionally, the availability of lipid II is crucial for the cell's survival. Moreover, across investigated bacterial strains basically no changes of the glycosylphosphate moiety of lipid II are found. The latter pledges for the motif to be highly conserved and therefore less prone to mutations which could potentially cause antibiotic resistance.[3]

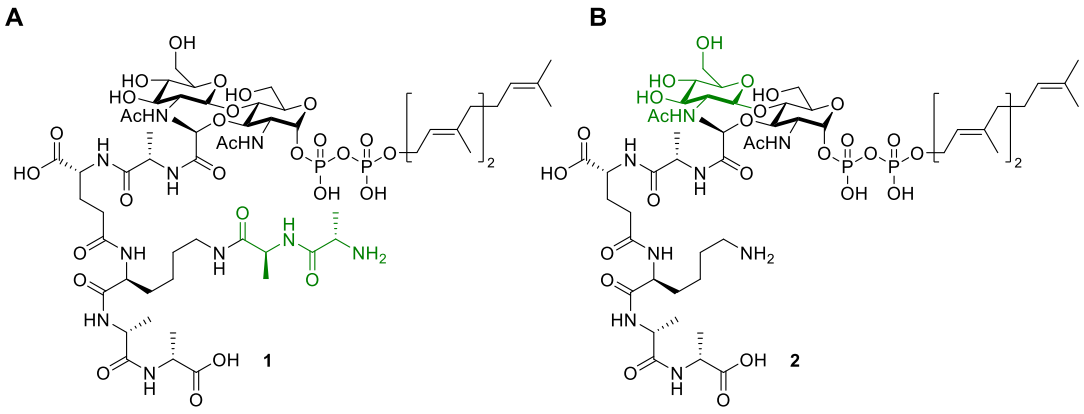
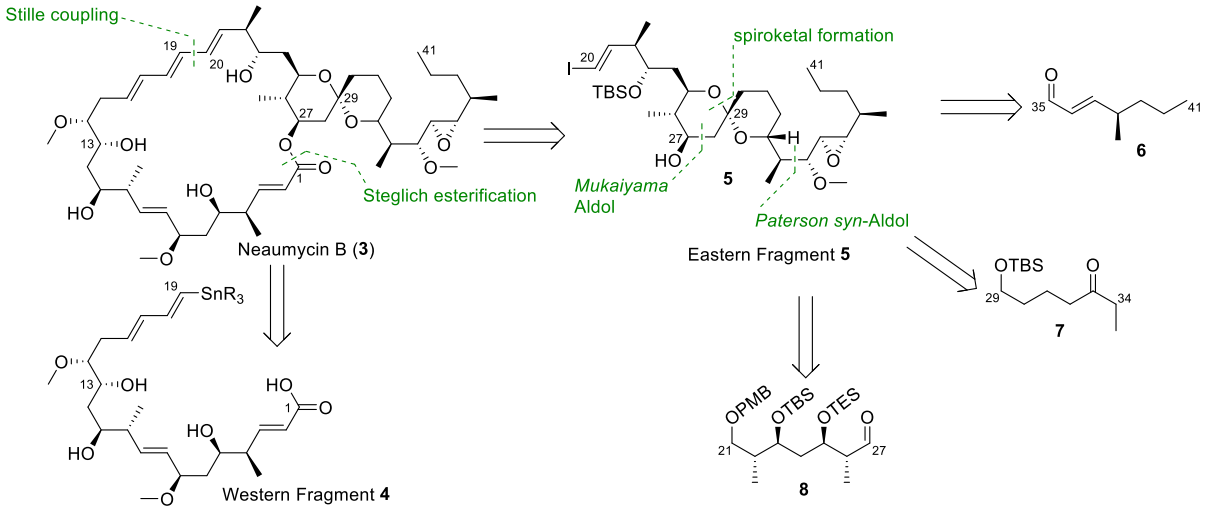


*Figure 1: **A**: Chemical structure of farnesyl lipid II containing side chain modification found in S. pneumoniae and E. faecalis (**1**). **B**: Structure of farnesyl lipid II (**2**).*

In the first part of this study the focus was on finishing the synthesis of farnesyl lipid II analogue **1** containing a side chain modification that is commonly found in *Streptococcus pneumoniae* (*S. pneumoniae*) and *Enterococcus faecalis* (*E. faecalis*) (Figure 1). Herein, the solid-phase peptide synthesis (SPPS) method established in the group by *L. Wingen* to introduce a side chain modification was verified to be widely applicable.[4] Since the chemoenzymatic conversion as the last step of the established synthesis of farnesyl lipid II (**2**) gave low yields and required a tedious purification process to obtain pure product, the investigation towards a fully chemical route towards farnesyl lipid II (**2**) was commenced.

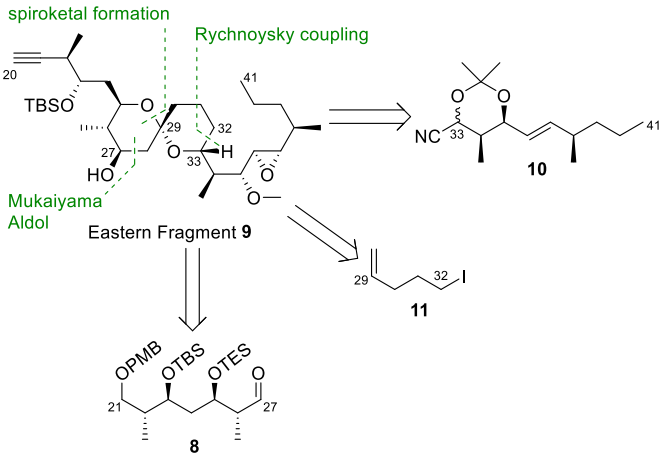
Abstract Part II

In the second part of this thesis the focus was placed on the synthesis of the newly isolated macrolide neaumycin B (**3**, Scheme 1), which was first isolated in 2012 from a soil actinomycete strain. Its structure and relative stereochemistry was proposed based on comprehensive mass and nuclear magnetic resonance (NMR) spectroscopy interpretation.[5] However, in 2018, *Jensen* and *Fenical et al.* published a different structure of neaumycin B (**3**) containing a full stereochemical assignment using NMR spectroscopy and bioinformatic analysis of the biosynthetic gene cluster.[7] Moreover, "significant potency and selectivity towards U87 human glioblastoma"[7] was found.



*Scheme 1: Retrosynthesis of the originally proposed structure of neaumycin B (**3**).*[8]

Since neaumycin B (**3**) resembled an interesting target structure combined with a high biological activity, a retrosynthetic analysis was conducted (Scheme 1). This study focused on the synthesis of the eastern fragment **5** while the western fragment **4** was part of the PhD thesis of *R. Wagner*. The first retrosynthetic approach towards spiroketal **5** relied on a *Paterson* aldol reaction between aldehyde **6** and ketone **7**. However, the reaction did not work as intended and the desired product was not formed under the screened conditions. Therefore, to obtain the linear precursor of spiroketal **5**, the synthetic strategy was changed to a *Rychnovsky* coupling between cyanohydrin **10** and iodide **11** (Scheme 2). Meanwhile, aldehyde **8** and the corresponding envisioned *Mukaiyama* aldol reaction were not changed. The synthesis of cyanohydrin **10** was not concluded due to the publication of the total synthesis of the proposed structure of neaumycin B (**3**) by *Smith et al.* as well as *Zhang et al.*,[8] which showed that the original structural proposal was incorrect.



*Scheme 2: Adapted retrosynthetic strategy towards eastern fragment **9** of neaumycin B (**3**).*

Thereafter, the focus shifted from pursuing a total synthesis towards revising the stereochemistry of neaumycin B. Both groups stated that the NMR data they obtained from their synthetic compound **3** did not match the data published for the isolated natural product.[8] In collaboration with *M. Adamek* (University of Tübingen) the stereochemistry was revised. To prove the proposed stereochemistry olefin **12** and triol **13** were synthesised to perform a comparative NMR study. Meanwhile, NMR data comparison suggests that the revised structure **12** may present the correct stereochemistry while the NMR data for compound **13** still displayed deviations from the natural product.

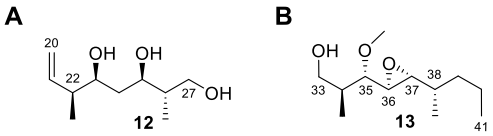


*Figure 2: **A**: C_{20}-C_{27} fragment **12** with revised stereochemistry for NMR study. **B**: C_{33}-C_{41} fragment **13** with adapted stereochemistry for NMR study.*

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1 Part I: Total Synthesis of Lipid I/II Analogues

1.1 Introduction

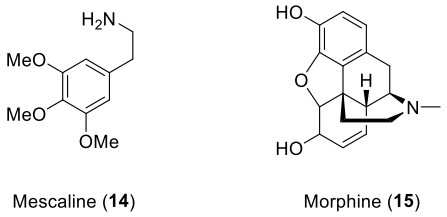
1.1.1 History of Natural Products

A natural product is defined as an organic compound from natural sources like microbes, plants, fungi or animals.[1] It is a product of the secondary metabolism therefore it is not crucial for the survival of the organism.[2] However, as many secondary metabolites are cytotoxic they can provide protection for the producer organism from predators or confer some other evolutionary advantage.[3,4] Although the number of building blocks for secondary metabolites is limited, the variety in structure of the latter seems to be infinite.[4]

The interest in treatments found in natural remedies as well as in hallucinogens goes back to the dawn of humanity.[1,5] Thus, the roots of natural product chemistry can be found in the curiosity of mankind about sensory perceptions like odour, taste, colour or cure for diseases.[1] That is why medicine and natural products have been tightly intertwined for thousands of years due to traditional medicines and poisons.[6,7] The earliest records of natural products being used as a cure for health complaints was found on clay tablets in cuneiform from Mesopotamia that dated back to 2600 BC.[8]

In respect thereof, China is also well known for their naturopathy.[1] An ancient popular folk drug which still finds use nowadays is the extract from the Ginkgo tree (*Ginkgo biloba* L.) which is meant to improve memory and sharpen mental alertness. The main component found to be responsible for the effects of the Gingko extracts is nowadays known to be ginkgolide B.[1]

Likewise, in ancient Egypt the residents had a profound pharmacological and surgical knowledge, captured in two scripts which lasted throughout centuries. The first of the two is the *Ebers* papyrus dating back to 2900 BC and the other one is the *Edwin Smith* Surgical papyrus which allows insights into ancient pharmacy.[1,8] Various psychodelic plants have been used since ancient times for example American Indians used the peyote cactus for thousands of years which contains mescaline (**15**) and other alkaloids or Sumerians using opium (morphine (**16**)) for pain relief being documented as early as 4000 BC (Figure 3).[1]

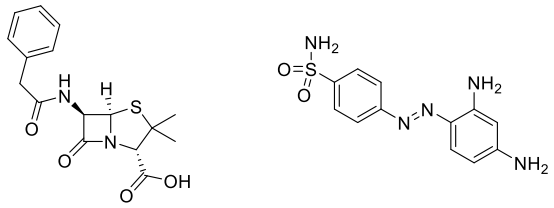


Mescaline (**14**) Morphine (**15**)

*Figure 3: Chemical structure of mescaline (**14**) and morphine (**15**).*[1]

All of these traditional healing approaches and the use of naturally occuring substances have layed the foundation for early medicines as well as ensuing modern clinical, pharmaceutical and chemical studies.[6] Though the role of chemistry in medicine has not been established until the work of the German-Swiss physician and alchemist *Paracelsus* (1493 – 1541).[1]

A major breakthrough in natural product chemistry and drug discovery was made with the discovery of penicillin G (**16**) by *Fleming* in 1928 (Figure 4) as well as the re-isolation and clinical studies in the 1940s by *Chain*, *Florey* and co-workers. Those resulted in commercialisation of synthetic penicillins and the revolution of drug discovery research.[6]



Penicillin G (**16**) Prontosil (**17**)

*Figure 4: Chemical structure of penicillin G (**16**) and prontosil (**17**).*[6]

However, it should be noted that the use of synthetic antibacterials was introduced with Prontosil® (**17**) even before WWII (Figure 5). Including the first clinical efficacy report in 1933 resulting in *Domagk* being awarded with the Nobel prize in 1938.[9]

In general, the second half of the twentieth century can be depicted as a "golden era" for total synthesis and isolation of natural products relating thereto the drugs derived from or inspired by the latter.[10] With the rise of combinatorial chemistry it was believed that all needed drugs could be discovered following this new approach rather than rational drug design or natural product leads.[10] Nevertheless, until today natural products remain as the most successful source of potential drug leads.[5,8,11]

1.1.2 Natural Product Chemistry and Total Synthesis

In the beginning of the nineteenth century, the Swedish chemist *J. J. Berzelius* coined the term „organic compound“ (1807).[1] But it was not until the coincidental discovery of *F. Wöhler* in 1828 that the beginning of organic chemistry was marked. While he was hoping to obtain “ammonium cyanate” upon heating of potassium cyanate with ammonium sulfate, he observed the formation of colourless urea crystals being identical to the ones isolated from urine. Thereby he accomplished the first conscious total synthesis.[1,12,13]

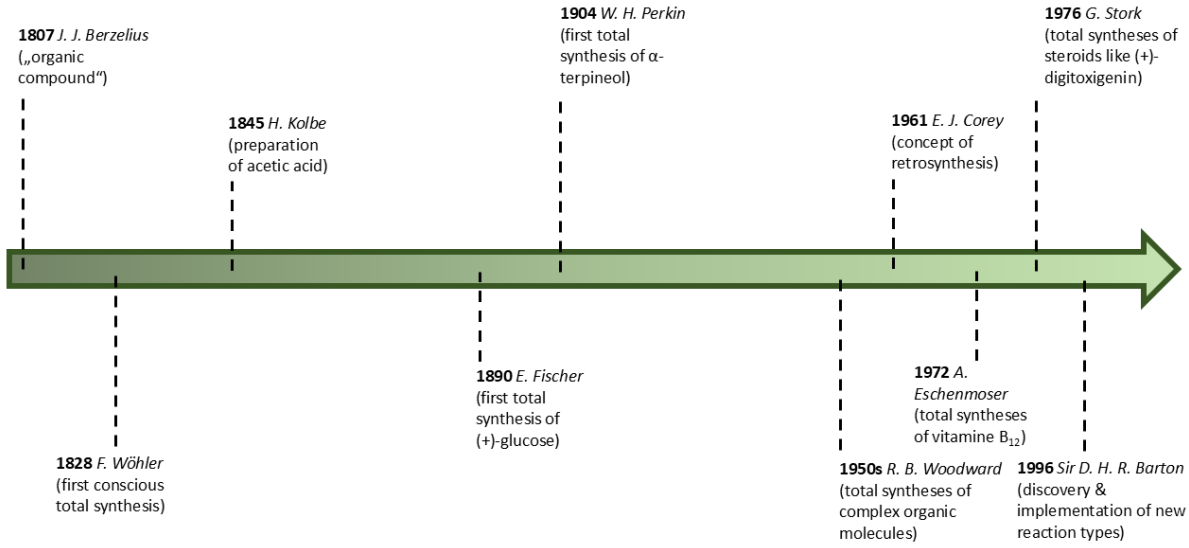


Figure 5: Timeline representing fundamental dates and discoveries regarding natural product total synthesis.

It was not until another 17 years later that the myth surrounding the term “organic compound” needing to be related to any kind of vitalism was resolved. Due to the preparation of acetic acid from inorganic material in 1845 by *H. Kolbe*, organic chemistry became the chemistry of carbon compounds.[1,14] In this context the term “synthesis” for the description of assembling an organic compound from other substances was used for the first time (Figure 5).[14] Besides, *Kolbe* has also been involved in the development of aspirin an analgetikum derived from salicylic acid which was formerly isolated from leafs of wintergreen plants. But with the invention of the inexpensive synthesis of salicylic acid from sodium phenolate and carbon dioxide in 1859 by *Kolbe*, the way for the industrial production of aspirin was paved. Aspirin was first commercially produced in 1893 by the *Bayer Company* and still being one of the most popular drugs.[1]

Another milestone within the nineteenth century marks the first total synthesis of (+)-glucose by *E. Fischer* in 1890. Since this was the first total synthesis of a compound containing stereochemistry[15] and he was awarded the Nobel Prize in 1902 for his contributions to the field of organic chemistry and total synthesis. With the transition into the twentieth century the field of total synthesis picked up momentum striving for more complex structures and elaborate strategy design.[12] Examples for the achievements of these times are the total synthesis of α-terpineol by *W. H. Perkin* in 1904[16] and the total synthesis of camphor by *G. Komppa* in 1903 and *W. H. Perkin* in 1904.[12] Towards the middle of this century *R. B. Woodward* began to have an outstanding impact on total synthesis of complex organic molecules. Some of his prominent targets being cortisone (**18**, 1951),[17] strychnine (**19**, 1954)[18] and lysergic acid (**20**, 1954) (Figure 6).[19][12]

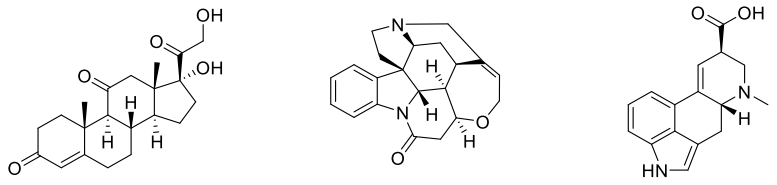


*Figure 6: Chemical structure of cortisone (**18**), strychnine (**19**) and lysergic acid (**20**).[12]*

Moving along the timeline *E. J. Corey* started to further shape total synthesis by introducing the concept of retrosynthesis[20] with his total synthesis of longifolene in 1961.[21] Between 1950 and 1990 the field of total synthesis in general experienced a massive growth with some famous chemists from these times like *G. Stork* who is known for his total syntheses of steroids like (+)-digitoxigenin,[22] prostaglandins like (+)-15-(*S*)-prostaglandin A_2[23] and tetracyclines like 12a-deoxytetracycline.[24]

A. Eschenmoser had a lasting effect on the community of total synthesis. One of his most famous targets being vitamine B_{12}.[25] Furthermore, *Sir D. H. R. Barton* shaped organic chemistry with his discoveries like the photocleavage of nitrite esters or deoxygenation reactions broadening the range of reactions that can be implemented to build up new structures.[26] The shift into the new millenium continuously challenged the field of total synthesis by the discovery of new structural motifs in isolated compounds, which now can be sufficiently analysed as analytical tools evolved drastically since the beginnings of the field. As a result thereof, the focus was shifted from structure elucidation towards exploration, discovery and implementation of new chemistry.[12]

1.1.3 Targets for Antibiotics

Nowadays bioinformatics represent a powerful tool for identifying the spectrum of organisms in which a target is present.[27] Therefore, ensuring a wide range of use cases for newly invented drugs. There are a few criteria that should be taken into account when searching for new targets. A very important factor to keep in mind is the selectivity of the drug for the pathogen over the host. Here the use of bioinformatics proves to come in handy again to see differences in mammalian and bacterial homologous proteins.[27]

As another crucial requirement poses the essentiality of the target for growth and survival of the bacterium.[27] Besides that, the issue of resistance has been an increasingly important consideration as the number of bacteria with resistance to commonly used drugs is on the rise.[28,29] Additionally, due to excessive or wrong use of antimicrobial agents in health care and the food industry, the rise of multidrug resistant strains has been hastened.[28–30] Lastly, after a lot of new antibiotics have been discovered and approved for use between 1940 and 1960, a stagnation in antibiotic discovery can be observed following those years.[31] All of the beforementioned factors contribute to the antibiotic resistance crisis which is currently faced.[28,29]

Understanding of how resistance arises includes the comprehension of the resitome, the totality of genes contributing to resistance to antibiotics.[32] But how do insights into these mechanisms affect drug discovery and target choice? The adumbration of inevitable resistance to any newly designed drug is discouraging in this current era of antibiotic crisis. Hence, it is important to keep in mind that as opposed to the population of viruses containing preexisting mutations conferring resistance to small molecule drugs[33] antimicrobial drug resistance in bacteria is thought to arise slowly by stepwise changes due to adaptive epigenetic mechanisms, gene amplification and mutations in pathogens and by horizontal genetic transfer (HGT) leading to incremental increase of the minimum inhibitory concentration (MIC).[34] Widely used antibiotics have indeed faced increased resistance but the latter usually does not rise rapidly to clinical significance. This is due to the fact that almost all of the antimicrobial drugs used today are “multitargeted” as multiple genes encode the target or the protein producing the target. Therefore, they can be thought of targeting at a genetic level.[27] Lastly, cell entry is another indispensible prerequisite. The need of getting the inhibitor to its site of action in most cases means permeating the bacterial cell wall. This can

be an especially challenging hurdle in the case of *Gram*-negative bacteria since they possess two cell membranes with orthogonal sieving properties. In general, conceiving a drug that meets this requirement is problematic as there are no existing rules for cell entry.[27]

Most current bactericidal antimicrobials inhibit DNA, RNA, the cell wall or protein biosynthesis.[35] Inhibition of DNA replication for example is achieved with quinolones, which are derivatives of nalidixic acid and have been discovered as a byproduct of the synthesis of chloroquine. One example are fluoroquinolones targeting DNA-topoisomerase complexes.[36] Rifamycins, a group of semi-synthetic bactericidal antimicrobials, have first been isolated from *Amycolatopsis mediterranei* in the 1950s and inhibit the RNA synthesis.[37] Thus, compounds belonging to this class of bactericidals are having a catastrophic effect on prokaryotic nucleic acid metabolism by inhibiting the DNA-dependent transcription.[35]

Disruption of the bacterial cell wall synthesis mainly leads to lytic cell death upon treatment with cell wall synthesis inhibitors like β-lactams and glycopeptides. These antibacterial agents induce changes in the cell shape and size, provoking cell stress responses and ultimately lead to cell lysis.[38] As the only target being readily available on the outside of the cell interfering with the cell wall biosynthesis is the only target circumventing the issues of cell entry.[39] At last, the inhibition of protein biosynthesis can be achieved by either targeting the 50S subunit of the ribosome with an antimicobial like erythromycin (**21**)[40] or the 30S subunit can be addressed by antibiotics like tetracyclines (**22**) (Figure 7).[41, 42] Both of the latter being among the broadest classes of antibiotics.[35]

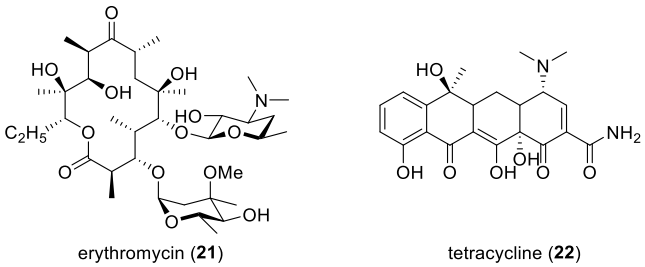


*Figure 7: Chemical structure of erythromycin (**21**) and tetracycline (**22**).[42–44]*

1.1.4 Bacterial Cell Wall and its Biosynthesis

As opposed to eukaryotic cells prokaryotic cells are surrounded by a cell wall consisting of a peptidoglycan network (PGN).[43] Its main task is ensuring cell integrity, withstand the turgor of the cell and protect it from osmotic lysis.[39] Besides that, the PGN is a crucial component for cell growth and division. It is based on the universal building block lipid II (**23**) which is

composed of three main structural subunits.[43] The hydrophilic disaccharide moiety is build up by alternating monosaccharides GlcNAc and MurNAc which are linked by a β-1,4 glycosidic bond. Attached to its D-lactyl group every MurNAc unit carries the peptide part of lipid II (**23**) which is responsible for cross-linkage between the glycan strands.[43] In contrast to the sugar part, a strain dependent variety of the peptide stem can be observed.[44] Also attached to the MurNAc *via* a pyrophosphate moiety is the last component of the PGN building block namely the hydrophobic bactoprenol linker (Figure 8).[43] Given the fact, that an intact cell wall is crucial to the survival and replication of bacteria its biosynthesis needs to be strictly regulated.[45] Especially as it takes place in three different places within the prokaryotic cell. In the cytoplasm, where the synthesis of the nucleotide precursor UDP-MurNAc-pentapeptide is carried out, on the inner side of the cytoplasmic membrane, where the bactoprenol linker gets attached to the precursor, as well as on the outer side of the cytoplasmic membrane where the polymerization of the building block to the PGN takes place.[46]

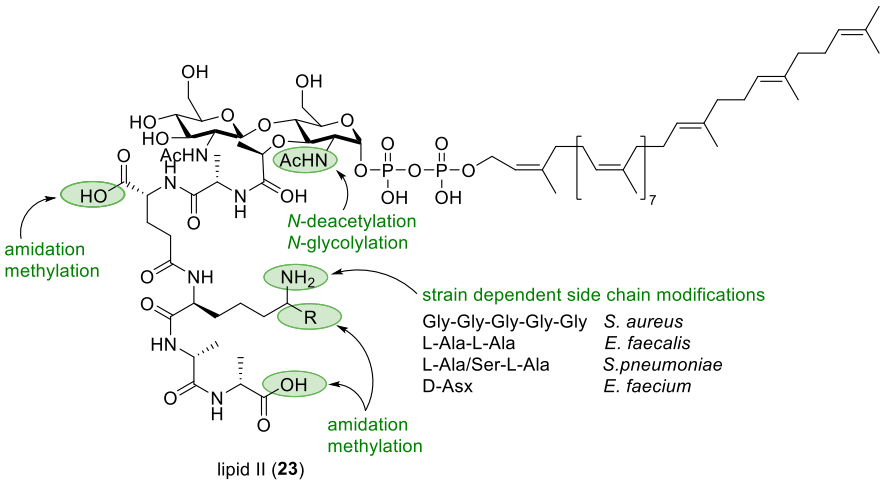
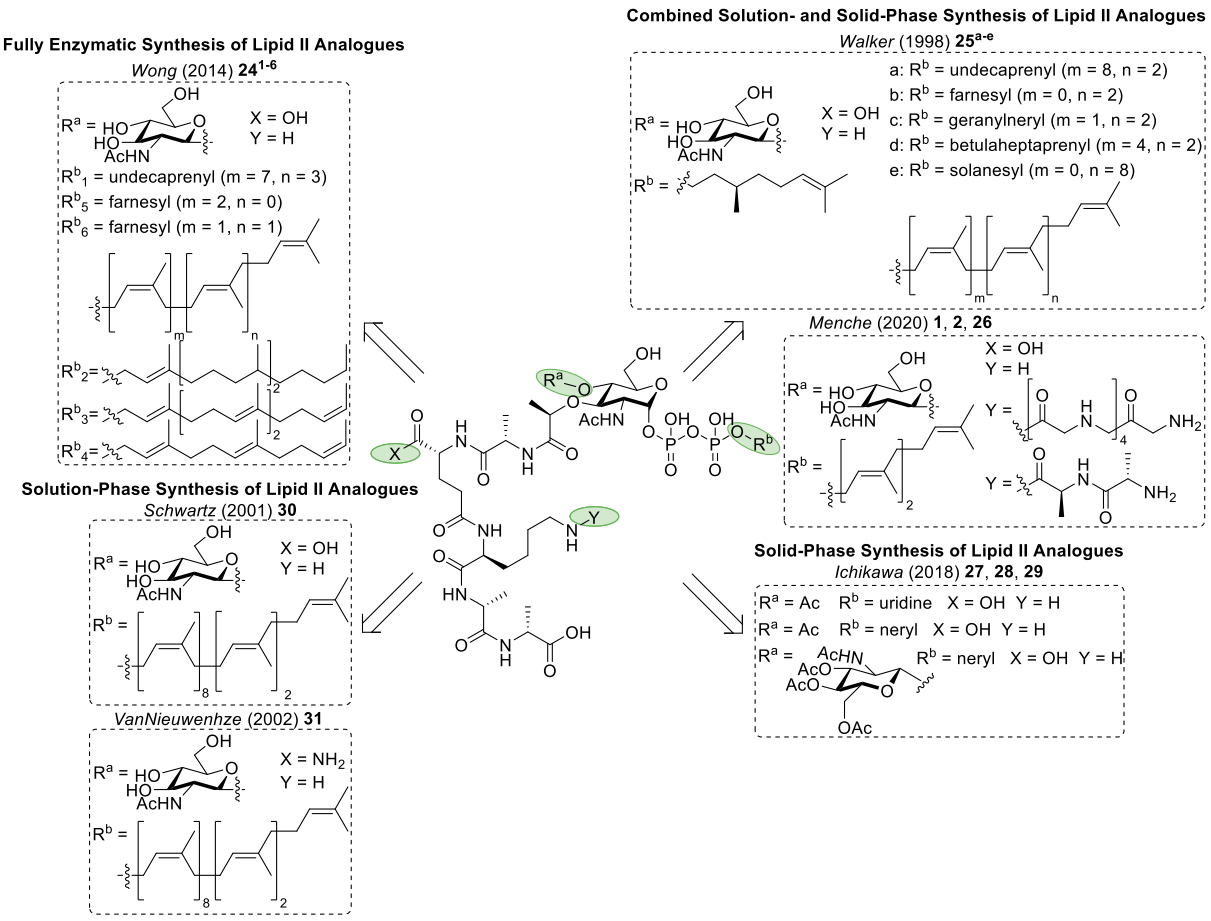


*Figure 8: Chemical structure of lipid II (**23**). Positions for most frequently found alterations highlighted in green.*[47]

Bearing the pivotal role of the prokaryotic cell wall in bacterial survival in mind, it has grown to become one of the most important, as well as most easily accessible antimicrobial targets.[48] Therefore, the interest in functional studies with the key precursor of PGN lipid II (**23**) has grown from the point of view of antibacterial research and medicinal chemistry.[49]

1.2 State of Knowledge

Between the years of 1998 and 2020, several different synthetic approaches towards the naturally occuring bacterial cell wall building block lipid II (**23**) and analogues thereof were published (Scheme 3). In the following, the various total syntheses are presented and the differences highlighted.

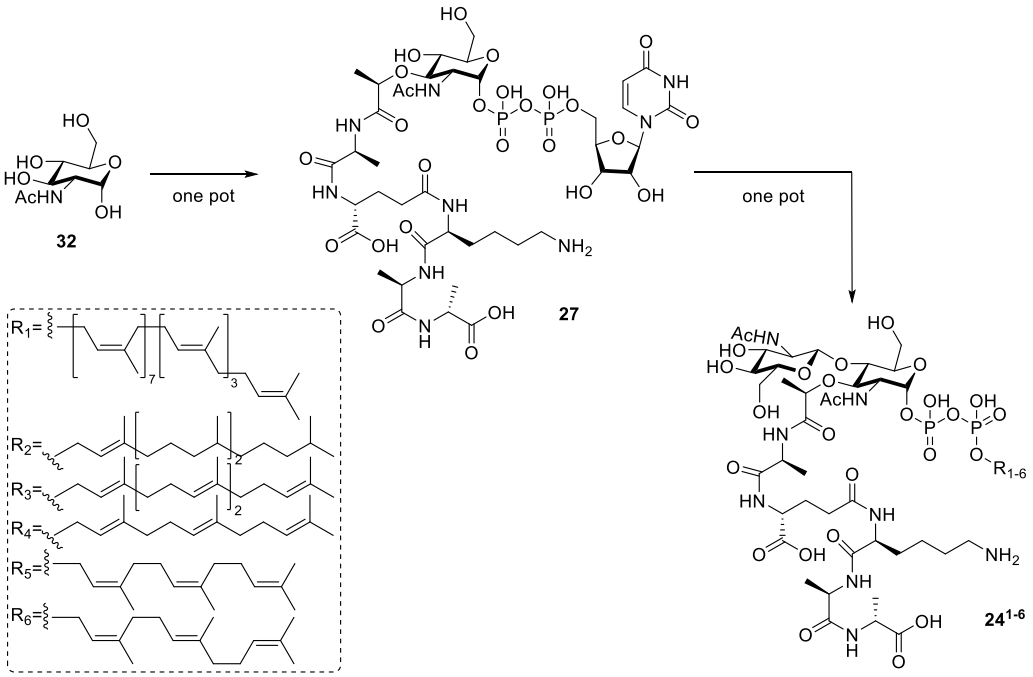


Scheme 3: Overview of published total syntheses towards lipid II and analogues thereof. Areas containing differences in between the different syntheses highlighted in green.[44,50–56]

1.2.1 Fully Enzymatic Synthesis of Lipid II Derivatives

A novel synthetic strategy towards natural lipid II and analogues has been published by *Wong et al.* in 2014 (Scheme 4).[52] It is completely based on the corresponding enzymes found in cell wall biosynthesis, therefore mimicking the pathway in bacterial cells. Starting the synthesis with the preparation of UDP-MurNAc pentapeptide (**27**) from *N*-acetyl glucosamine (**32**) using GlmU/NahK and then MurA – MurF in one pot. The application of a finely tuned system of enzymes for the synthesis as well as enzymes required for regeneration is needed yielding 60% to 80% in this step.[52] Lastly, incubation of the respective lipid alcohol

and UDP-MurNAc pentapeptide (**27**) with three recombinant enzymes (UK, MraY and MurG) yielded lipid II analogues (**24$^{1-6}$**) in another one pot reaction in 50% to 70%.[52]

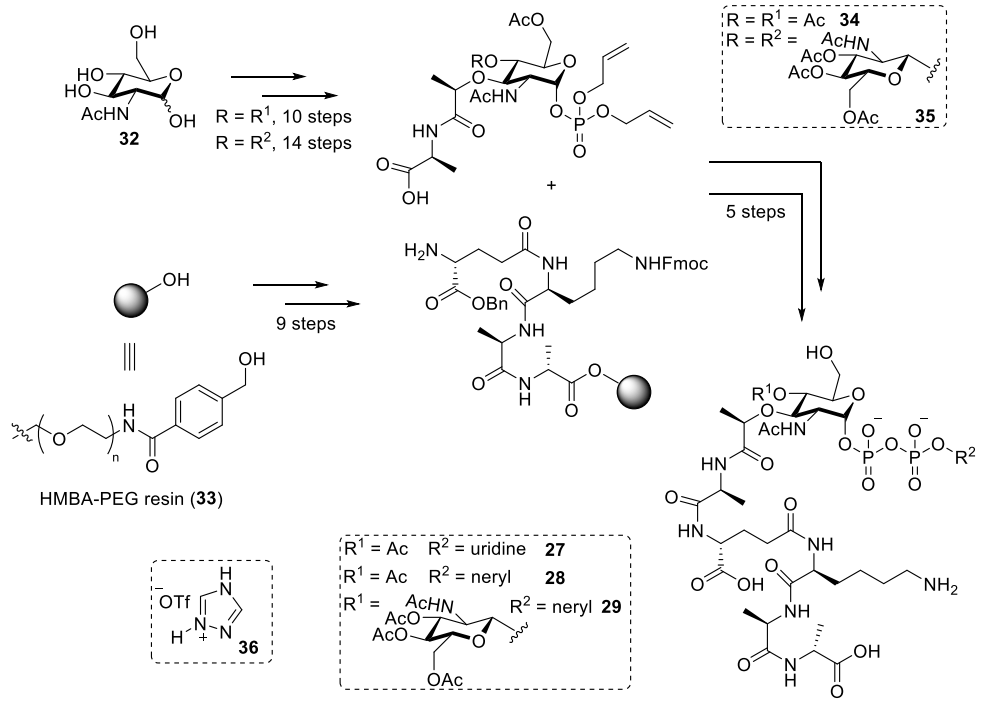


Scheme 4: Fully enzymatic synthesis of lipid II derivatives by Wong et al.[52]

1.2.2 Fully Solid-Phase Based Synthesis of Lipid II Analogues

The group of *Ichikawa* has invented a modular solid-phase approach towards Park's nucleotide (UDP-MurNAc pentapeptide, **27**), lipid I (**28**) and II (**29**) analogues in 2018 (Scheme 5).[53] It allows for the conduction of multiple steps in a short amount of time, including just one classical purification step after cleavage from the solid-phase.[53]

The beginning of their approach is marked by the immobilisation of the *C*-terminus of Fmoc-D-Ala onto the solid support (HMBA-PEG resin (**33**)). Base labile protecting groups, as well as a resin allowing for basic cleavage, were chosen as the diphosphate moiety is known to be labile under acidic conditions.[57] The synthesis of the mono- (**34**) and disaccharide (**35**) building block was performed over ten or respectively 14 steps starting from *N*-acetyl D-glucosamine (**32**), following a known procedure.[55] Afterwards, the particular building block was attached to the solid-phase coupled tetrapeptide composed of D-Ala-D-Ala-L-Lys-D-Glu carrying suitable protecting groups. To suppress isomerisation during the coupling procedure PyOAP and HOAt in DMF/DCM was used instead of standard conditions (PyBOP/HOBt).



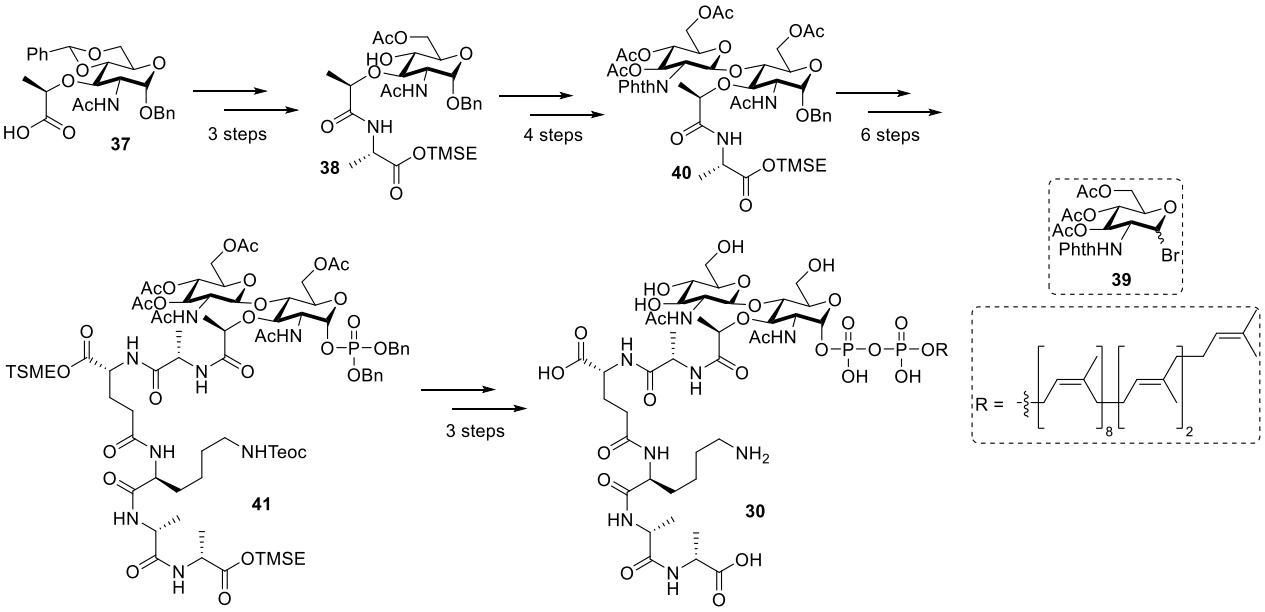
Scheme 5: Solid-phase synthesis of lipid II analogues by Ichikawa et al.[53]

Considering the investigation of the key diphosphate formation on the solid-phase, the use of the triflate salt of 1*H*-triazole (**36**) led to the best conversion.[58] As the last two steps, concluding the total synthesis, the cleavage from the resin followed by global deprotection were performed yielding neryl lipid II (**29**) in 20% over twelve steps starting from resin bound D-Ala (Scheme 5).[53]

1.2.3 Solution-Phase Based Total Synthesis of Lipid II and Analogues

A solely solution-phase based approach towards lipid II was first published by *Schwartz et al*.[51] in July 2001 and shortly afterwards by *VanNieuwenhze et al*.[59] in March 2002 (Schemes 6 and 7). The synthesis of *Schwartz et al.* started from commercially available carbohydrate (**37**), which was transformed into glycosyl acceptor (**38**) in three steps with a yield of 58%. Adjacently, one of the key steps of this synthetic approach, the formation of the β-1,4 glycosidic bond between glycosyl acceptor (**38**) and glycosyl donor (**39**), using *Koenigs-Knorr* conditions (AgOTf)[60] was performed with a yield of 60% (Scheme 6).[51] Afterwards, the protecting groups of the former glycosyl donor needed to be changed to acetyl protecting groups, allowing for a late stage global deprotection step. To prepare the disaccharide moiety for coupling to the peptide part, the phosphate group was introduced to the anomeric position of MurNAc and the silyl group from the acid function of the L-Ala was cleaved. Thereafter, the truncated disaccharide can be merged with the tetrapeptide unit, which was acquired from a

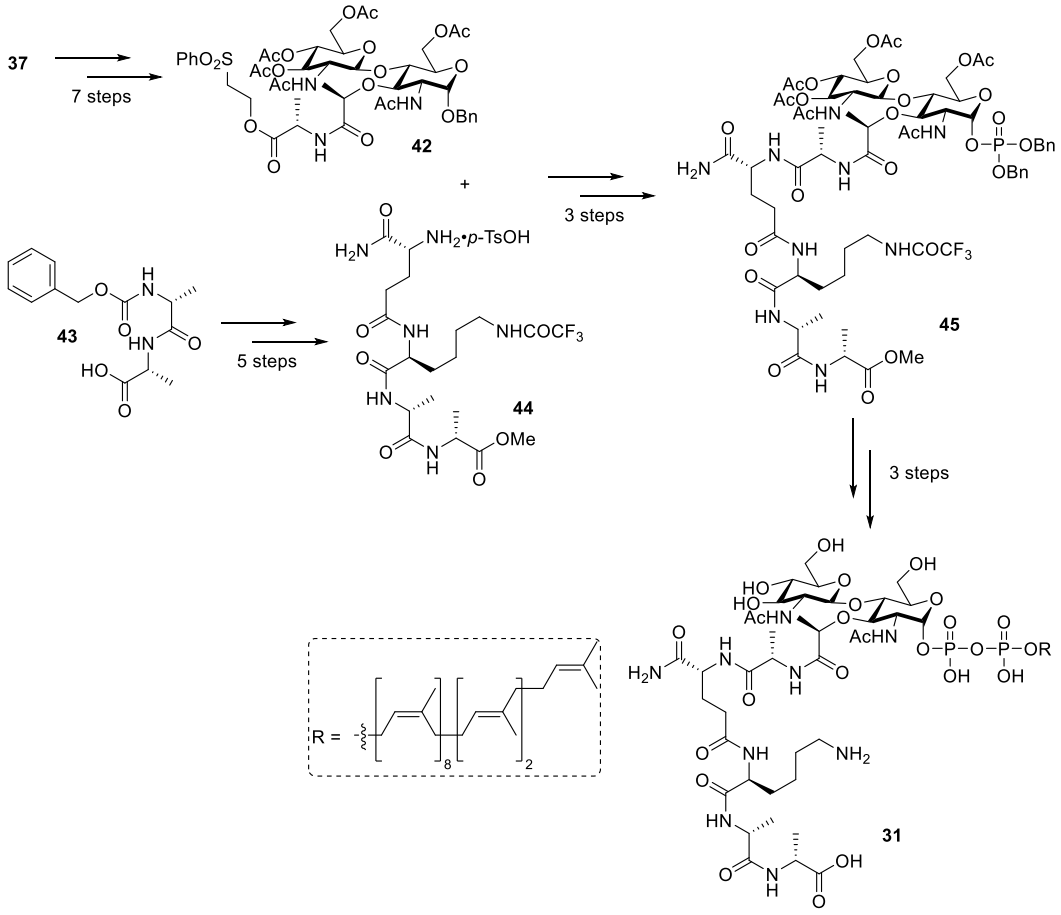
supplier, using standard coupling conditions (PyBOP/HOBt) yielding 15% of compound **41** over six steps.[51] Late stage formation of the diphosphate moiety introduced the natural C_{55} bactoprenol chain and global deprotection led to lipid II (**30**) in 14 steps starting from carbohydrate **50** with an overall yield of 0.7%.[51]



*Scheme 6: Schematic representation of the solution-phase synthesis of lipid II (**30**) by Schwartz et al.[51]*

In the approach by *VanNieuwenhze et al.*, the same commercially available carbohydrate **37** was utilised as the starting material. However, a different protecting group approach was followed, while the key reaction (*Koenigs-Knorr* coupling to the disaccharide)[59,61] remained the same, yielding disaccharide **42** in seven steps with a yield of 21%. For the creation of the tetrapeptide building block, the group of *VanNieuwenhze* chose a five step synthetic route starting from commercially available Cbz-D-Ala-D-Ala (**43**) overall yielding 46% of compound **44** (Scheme 7).[56]

Following the synthesis of the building blocks **42** and **44**, a three-step conversion strategy was conducted resulting in amino sugar **45** in 46%. Finally, a series of coupling and deprotection steps were performed, installing the diphosphate moiety as late as possible in the synthesis. After those final steps, the amine derivative of natural lipid II (**31**) was observed in a total yield of 2% over 13 consecutive steps starting from carbohydrate **37**.[59]



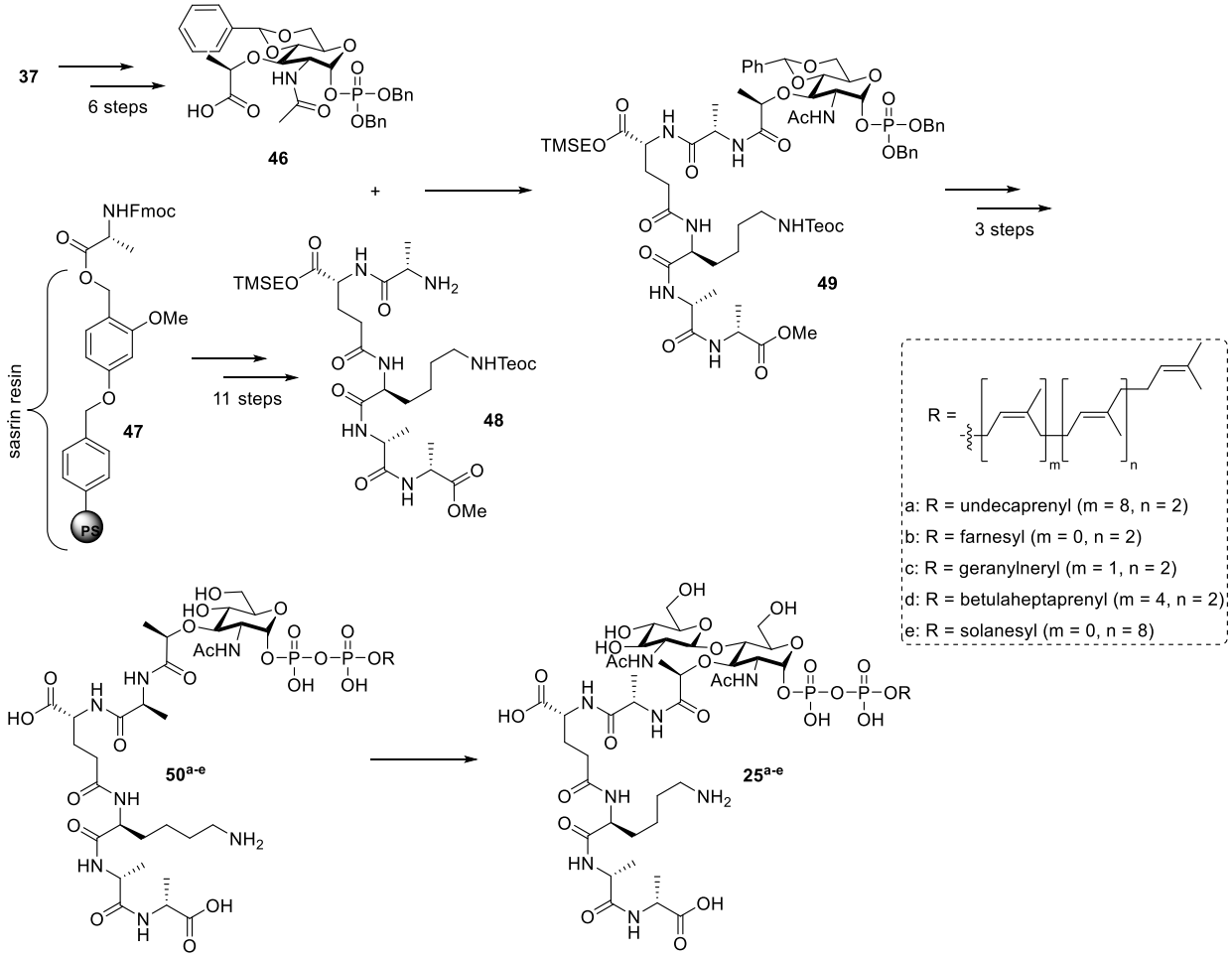
*Scheme 7: Overview of the solution-phase synthesis of lipid II (**31**) by VanNieuwenhze et al.[55,56]*

1.2.4 Combined Solution- and Solid-Phase Based Approaches Towards Lipid II Analogues

After all, the first synthesis of lipid II derivatives was published by *Walker et al*. in 1998, replacing the natural C_{55} carbon chain with a C_{10} citronellol chain. Proving the value of those shortened lipid analogues, as due to the replacement of the natural bactoprenol chain with citronellol the solubility of the resulting analogue could be increased. Besides that, the analysis was simplified and the known instability of allylic diphosphates could be circumvented.[50] Despite those distinctive advantages of the shortened lipid I analogues, the group of *Walker* could still demonstrate the conversion of the latter to the respective shortened lipid II analogues in an essay using isolated MurG. It was proven, that the unnatural analogues were still recognised as substrates of the natural enzyme. They implemented the chemoenzymatic conversion of lipid I (**50**$^{a-e}$) to lipid II (**25**$^{a-e}$) as a key step of their synthetic route (Scheme 8).[47] Besides utilising the chemoenzymatic conversion, their approach comprised of solution- as well as solid-phase based chemistry.

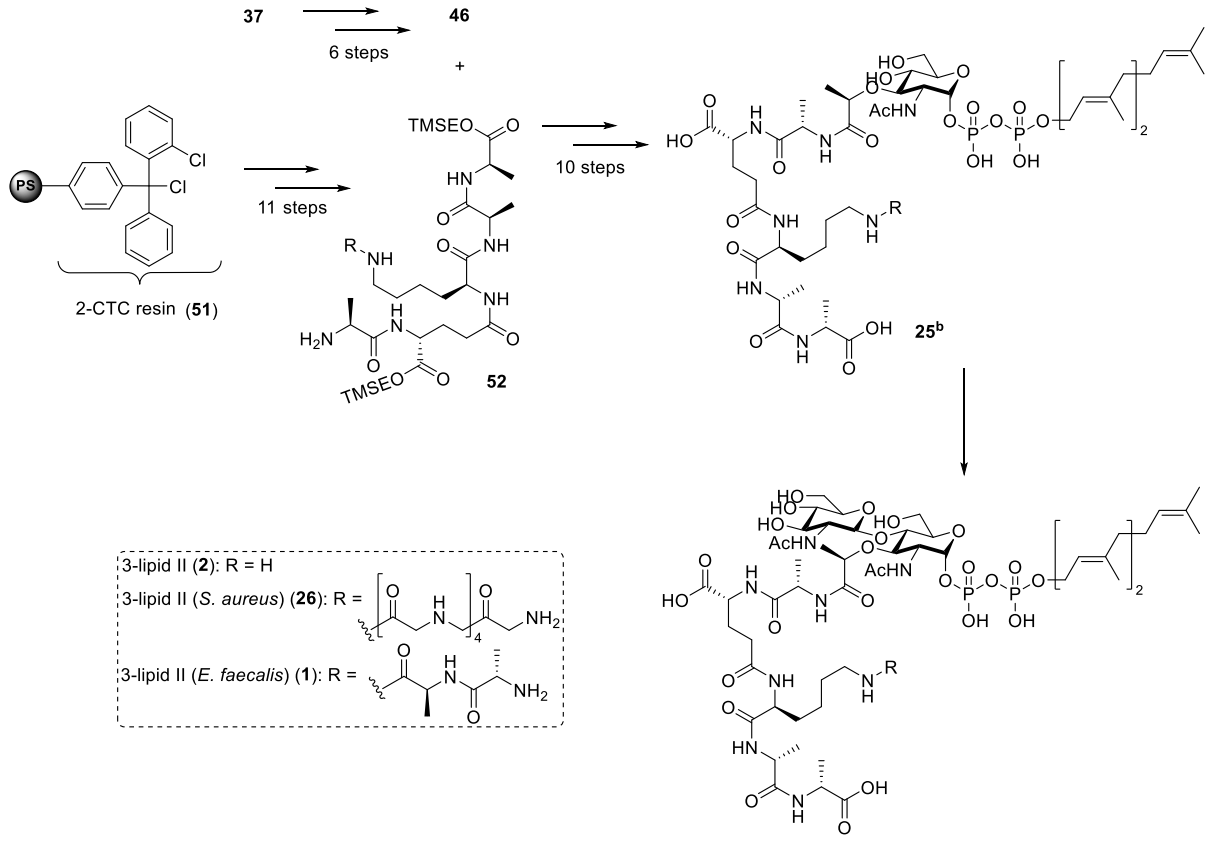
Starting the total synthesis, as seen before, from commercially available carbohydrate (**37**) truncating it in six steps with a yield of 44%. Thereafter, the prepared monosaccharide **46** was

implemented in the amide coupling to the pentapeptide **48**. The latter was observed following a solid-phase approach starting from sasrin-D-Ala-Fmoc (**47**). Within eleven steps the desired pentapeptide building block **48** was obtained in a total yield of 15%. With both components in hand the *Walker* group proceeded with the coupling using standard conditions (PyBOP/HOBt) to observe the respective amino sugar **49** in 92% yield (Scheme 8).[47]



*Scheme 8: Synthetic approach towards lipid II analogues (**25**$^{a-e}$) combining solution-phase and solid-phase chemistry with chemoenzymatic conversion by Walker et al.[47]*

In their first attempt, the citronellol side chain was directly introduced as the diphopshate[50] whereas their approach changed to the phosphate coupling in their second publication on that topic a year later.[47] The last step of the synthesis was the global deprotection to obtain lipid I analogue **50** in an overall yield of 7% starting from carbohydrate **37** (Scheme 8).[47] The total synthesis of natural lipid II (**38**$^{a-e}$) and other analogues was published by *Walker et al.* in 2001 using the chemoenzymatic conversion with MurG as well as implementing slight improvements to their original route.[62]



*Scheme 9: Modular combined approach towards shortened lipid II analogues (**1**, **2**, **26**) by our group.[44]*

Based on the published results, our group adapted a synthetic route towards farnesyl lipid I (**25^{b}**) and II (**2**) and analogues **26** and **1** thereof in 2020, utilising the beforementioned key steps (mixture of solution- and solid-phase chemistry, chemoenzymatic conversion).[44] In this approach, the SPPS was improved by changing the used resin. In addition, there was a change in the choice of the shortened side chain towards farnesol and the observed yields in the synthesis of the monosaccharide building block **46** were increased (Scheme 9).[44]

Once again, starting from commercially available carbohydrate **37**, it was transformed into compound **46** over six steps with a yield of 60%. Preparing the amide coupling between monosaccharide **46** and pentapeptide **52** the latter was obtained *via* a mixed approach of SPPS and solution-phase synthesis. In this case, a 2-chlorotrityl chloride (2-CTC) resin (**51**) was chosen for SPPS, since it allows for the use of Fmoc/silyl protecting groups and mild cleavage conditions (HFIP). Combining the synthesis of the tetrapeptide *via* solid-phase with classic solution-phase coupling of the previously protected last amino acid (L-Ala) to prevent epimerisation during the protection of the pentapeptide yielded compound **52** in 59% over eleven steps (Scheme 9).[44]

Following the strategy of a late stage introduction of the diphosphate moiety and global deprotection, farnesyl lipid I (**25^{b}**) was obtained. Adjacently, monosaccharide **25^{b}** was subjected to chemoenzymatic conversion (MurG), yielding farnesyl lipid II (**2**). The desired product **2** was obtained in a LLS of 17 steps with an overall yield of 11% after HPLC purification, allowing for unprecedented high purity of the observed compounds (Scheme 9).[44]

1.3 Aims of this Study

The aim of this study was to further validate our published modular synthetic approach towards shortened lipid analogue **1** (Figure 9).[44] The applicability of the latter to various strain specific side chain modifications should be proven. Thereofore, the synthesis of farnesyl lipid II analogue **1**, carrying the side chain modification found in *S. pneumoniae* as well as *E. faecalis*, should be furnished.

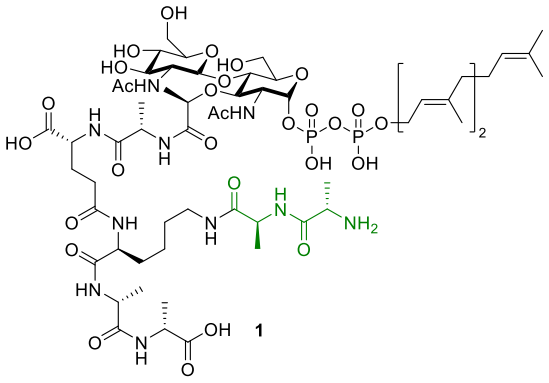


*Figure 9: Shortened lipid II analogue **1** containing side chain modification found in S. pneumoniae and E. faecalis highlighted in green.[47]*

Alongside the approach combining the chemical synthesis of shortened lipid I (**25^{b}**) and its chemoenzymatic conversion to shortened lipid II (**2**) allowing for alterations regarding the implementation of the second sugar unit during the chemoenzymatic conversion, a fully chemical approach towards the respective shortened lipid II analogue **2** should be initiated. The latter should circumvent the problem of a low yield in the final step of the total synthesis, hopefully simplifying the purification of the final product (Scheme 9).

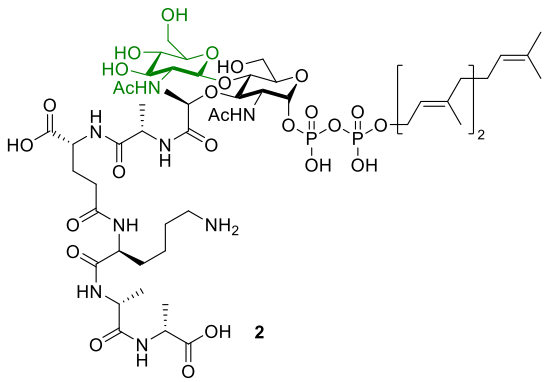
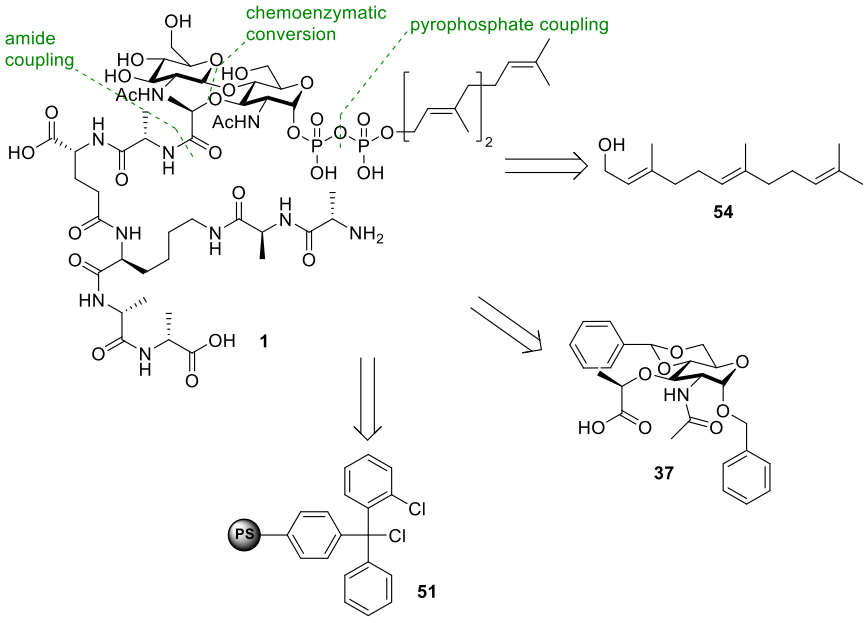


*Figure 10: Structure of shortened lipid II (**2**). GlcNAc (highlighted in green) should be introduced via chemical synthesis rather than by chemoenzymatic conversion.*

1.4 Results and Discussion

1.4.1 Retrosynthetic Analysis of Farnesyl Lipid II Containing Side Chain Modification Found in *S. pneumoniae* and *E. faecalis* (1)

In accordance with the previously established route towards farnesyl lipid II (**2**, Figure 10),[44] the retrosynthetic analysis of compound **1** resulted in the disassembly of the latter into three main building blocks.

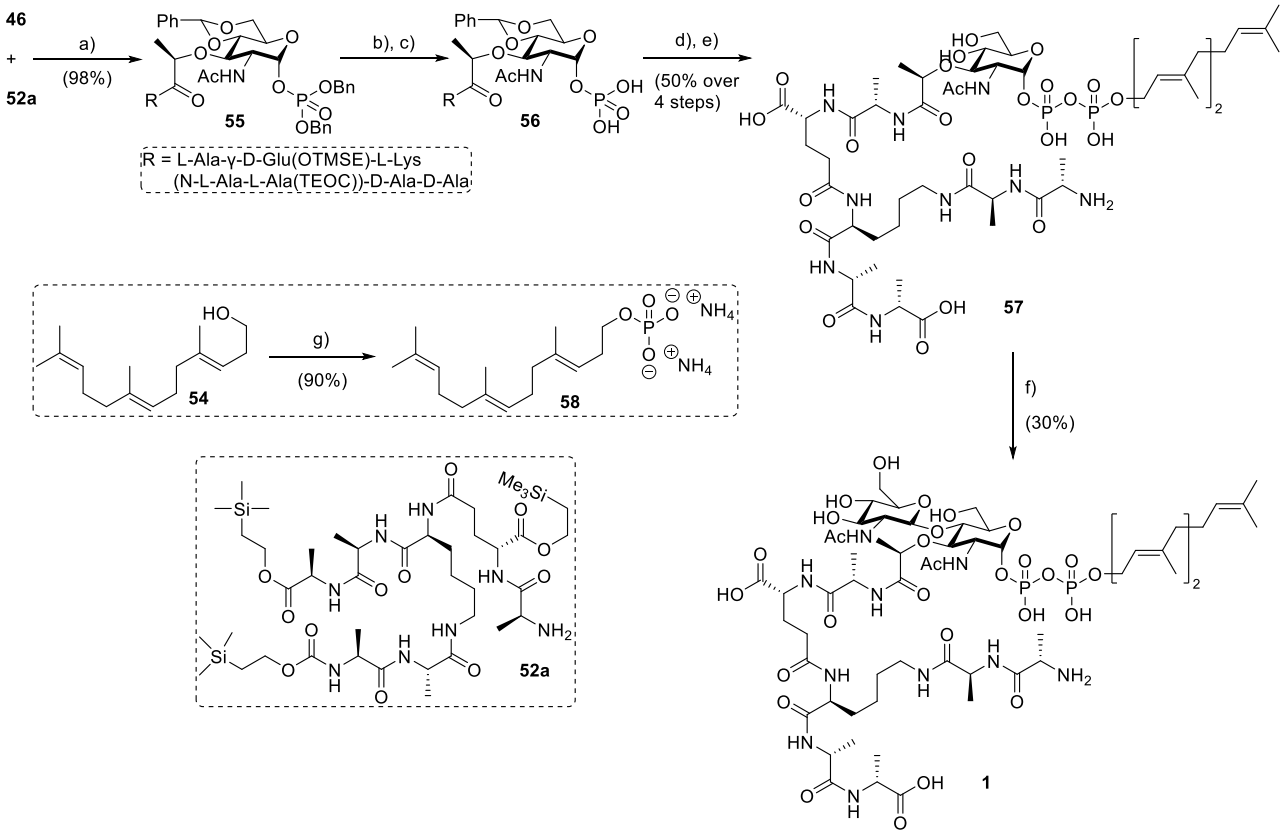


*Scheme 10: Retrosynthetic analysis of farnesyl lipid II analogue **1** containing side chain modification found in S. pneumoniae and E. faecalis.[44,54]*

The carbohydrate moiety should be synthesised from commercially available muramic acid derivative **37**. As the last step of the synthesis, farnesyl lipid I (**25^{b}**) could be chemoenzymatically converted to the disaccharide found in lipid II (**1**) by the group of *T. Schneider* (University of Bonn). Lastly, the peptide part of compound **1** will be constructed in an approach using solid-phase and solution-phase peptide synthesis starting from 2-CTC resin **51**, exploiting an orthogonal protecting group strategy to implement the side chain modification during the solid-phase synthesis. Afterwards, the peptide will be linked to the prepared carbohydrate *via* an amide bond formation.

1.4.2 Synthesis of Farnesyl Lipid II from *S. pneumoniae* and *E. faecalis* (1)

During my preceding master thesis in our group the synthesis of all required building blocks **46**, **52a** and **58** has been performed as well as the first coupling step of carbohydrate **46** and peptide **52a** (Scheme 11).[54,63]



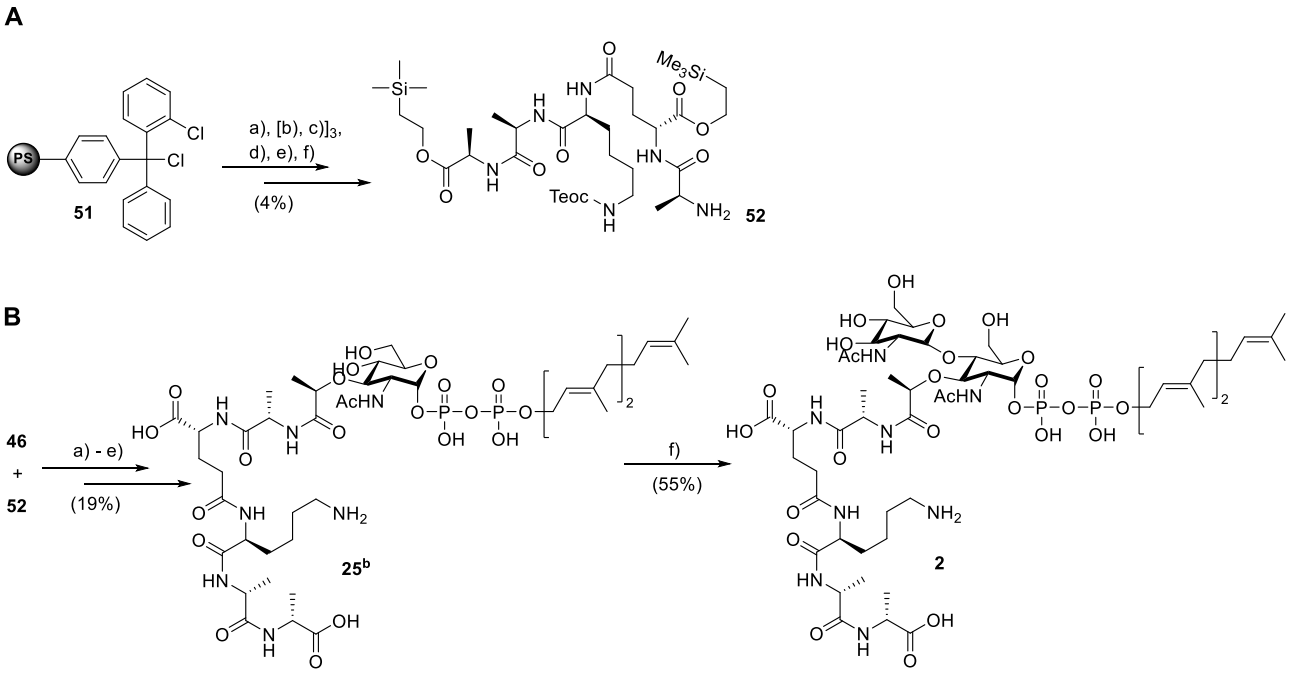
*Scheme 11: Synthesis of farnesyl lipid II analogue **1** containing the side chain modification found in S. pneumoniae and E. faecalis **1**. Reaction conditions: a) PyBOP, HOBt, DIPEA, DMF, rt, 45 min, **98%**;[63] b) 10% Pd/C, H_2, MeOH, rt, 30 min; c) 80% AcOH/water, rt, 2 d; d) **58**, CDI, 1:1 DMF/THF, rt, 2 h; then MeOH, rt, 45 min; then DMF, then **56**, DMF, rt, 3 d; e) TBAF, DMF, rt, 2 d, **50%** over four steps;[54]; f) MurG, **30%**; g) TCA, TBAP over 1 h, ACN, rt, 7 h, **90%**.*

Following up on the previously gained results,[44] the carbohydrate portion of amino sugar **55** was deprotected in a two-step procedure. First, the benzyl groups were cleaved under hydrogenolytic conditions followed by an acidic cleavage of the acetal yielding compound **56** (Scheme 11). After that, farnesyl phosphate **58** was activated *in situ*, using CDI, to conduct the pyrophosphate coupling. Subsequent to the conjunction of all fragments, the silyl protecting groups, which were present in the peptide portion, were cleaved with TBAF, to obtain farnesyl lipid I (**57**) in a yield of 50% over four steps. In the final step, farnesyl lipid I (**57**) was converted to farnesyl lipid II (**1**) in a chemoenzymatic conversion following the previously established protocol[44] in cooperation with the group of *T. Schneider* (University of Bonn). In summary, farnesyl lipid II analogue **1** was prepared in a LLS of 20 steps starting from 2-CTC resin **51** with an overall yield of 2%. Parts of this synthetic route have already been published.[54]

1.4.3 Finalising the Synthesis of Farnesyl Lipid II (2)

The synthesis of farnesyl lipid II without a side chain modification **2** was also continued from the previous master thesis.[63] The synthesis of carbohydrate **46** and farnesyl phosphate **58**

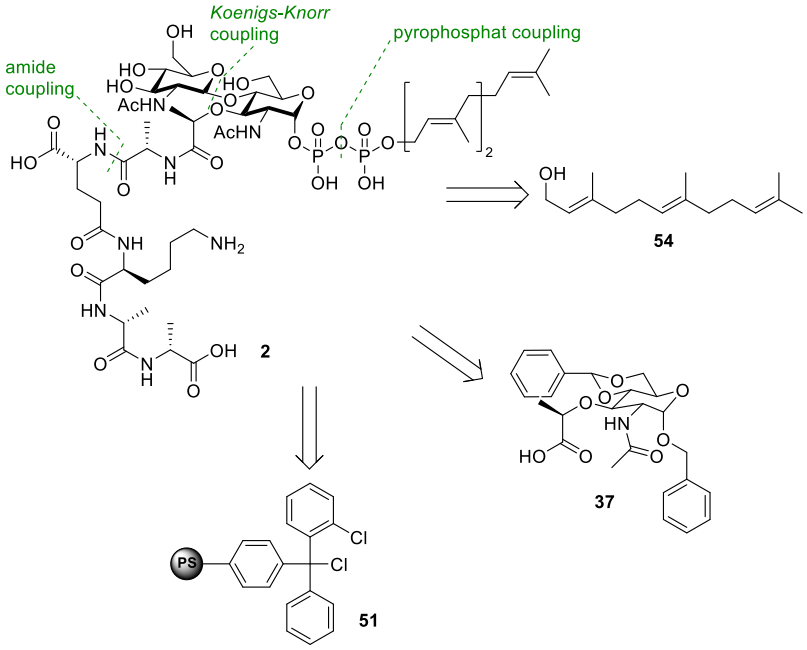
was equivalent to the one shown in Scheme 11. Herein, the stem peptide **52**, consisting of five amino acid residues, was prepared, following the already described approach of solid-phase and solution-phase peptide synthesis.[44] Preparation of farnesyl lipid I (**25^{b}**) proceeded in five steps from the coupling of monosaccharide **46** and peptide **52** (Scheme 12, **B**). Thereafter, the conversion of farnesyl lipid I (**25^{b}**) to lipid II (**2**) has not been conducted during the previous study, due to time constraints. Thus, in cooperation with the group of *T. Schneider* (University of Bonn) the chemoenzymatic conversion was conducted followed by HPLC purification.



*Scheme 12: Furnishing of the synthesis of farnesyl lipid II (**2**). **A**: Synthesis of pentapeptide **52**. Reaction conditions: a) CH_2Cl_2, rt, 20 min; b) 20% piperidine/DMF, rt, 5 min; then 20% piperidine/DMF, rt, 15 min; c) HBTU, HOBt, DIPEA, DMF, respective amino acid, rt, 30 min; then HBTU, HOBt, DIPEA, DMF, respective amino acid, rt, 30 min; d) 20% HFIP/CH_2Cl_2, rt, 3 h, **39%**; e) PyBOP, HOBt, DIPEA, D-Ala-OTMSE, DMF, rt, 40 min, **19%**; f) 20% piperidine/DMF, rt, 30 min, **50%**. **B**: Final steps towards farnesyl lipid II (**2**). Reaction conditions: a) PyBOP, HOBt, DIPEA, DMF, rt, 45 min, **98%**; b) 10% Pd/C, H_2, MeOH, rt, 30 min; c) 80% AcOH/water, rt, 2 d; d) **58**, CDI, 1:1 DMF/THF, rt, 2 h; then MeOH, rt, 45 min; then DMF, then **57**, DMF, rt, 3 d, **20%** over four steps; e) TBAF, DMF, rt, 2 d, **95%**;[63]; f) MurG, **55%**.*

Afterwards, the gained substrate **2** was given to the group of *T. Schneider* (University of Bonn) again, to be used for the elucidation of structure-activity relationships and modes of action of investigated potential antibiotics.

1.4.4 Retrosynthetic Analysis of Farnesyl Lipid II (2) (Solely Chemical Approach)



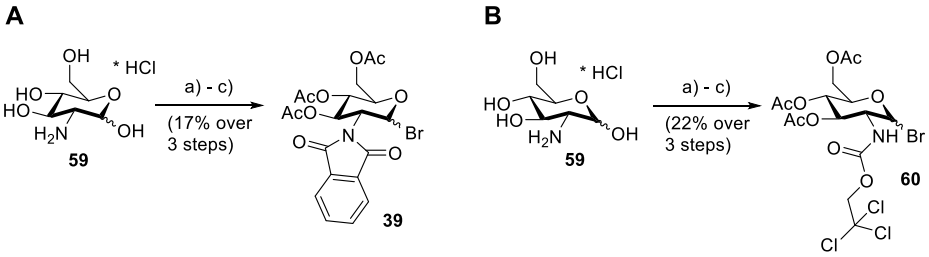
*Scheme 13: Retrosynthetic analysis of farnesyl lipid II (**2**) via solely chemical synthesis.*

As also previously discussed in chapter 1.4.1, the retrosynthetic analysis of farnesyl lipid II analogues **1** and **2** generally led to three building blocks. The starting materials for the solely chemical synthesis of farnesyl lipid II (**2**) are depicted in Scheme 13 and are the same as for compound **1**. The general synthetic strategy to prepare compound **2** is similar to the one described above. In this case, the disaccharide building block will be obtained from muramic acid derivative **37**, which will be coupled to a suitable glycosyl donor in a *Koenigs-Knorr* reaction furnishing the disaccharide motif. During the carbohydrate synthesis, the first amino acid of the pentapeptide will already be introduced as a protecting group for the lactyl group of carbohydrate **37**. Therefore, the respective tetrapeptide will need to be obtained by the established combined SPPS and solution-phase approach, starting from the 2-CTC resin **51**.[44,54] The farnesyl phosphate will be prepared from farnesol (**54**) as described above (Scheme 11).

1.4.5 Solely Chemical Synthesis of Farnesyl Lipid II

For the planned *Koenigs-Knorr* reaction, two different literature known glycosyl donors **39** and **60** (Scheme 14, **A** & **B**) should be tested, to see which would give the best results in conjunction with the respective glycosyl acceptor. The synthesis of both glycosyl donors started from commercially available D-glucosamine hydrochloride (**59**), which first underwent protection of the primary amine. In the first case, compound **59** was treated with phthalic

anhydride to transform the amine to the phthalimide (not shown) with a yield of 68%.[64] Afterwards, the hydroxy groups were acetylated using standard conditions (acetic anhydride in pyridine)[64] and the anomeric center was brominated using hydrogen bromide in acetic acid[65] to obtain compound **52** in 17% over three steps (Scheme 14, **A**). In the other case, D-glucosamine hydrochloride (**59**) was first treated with 2,2,2-trichloroethyl chloroformate to protect the amine.[66] Acetylation of the hydroxy groups was performed using the same conditions as before (54%).[64] While bromination of the anomeric center and the anomeric center was carried out,[65] yielding compound **60** in a yield of 22% over three steps (Scheme 14, **B**). Thus, both potential glycosyl donors **39** and **60** were synthesised in three steps respectively, starting from the common precursor D-glucosamine hydrochloride (**59**) and only differing in the C_2 protecting group of the amine.

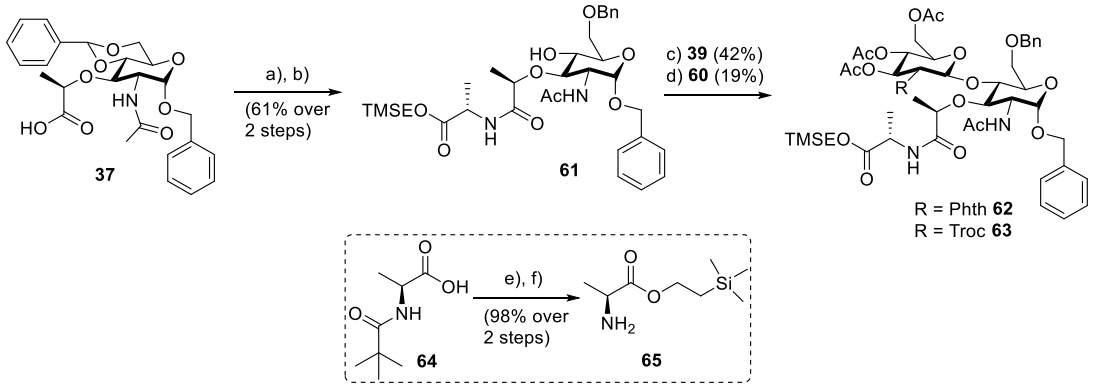


Scheme 14: Synthesis of two different glycosyl donors to test in Koenigs-Knorr reaction. ***A****: Synthesis of glycosyl donor* ***39*** *carrying Phth protecting group. Reaction conditions: a) phthalic anhydride, $NaHCO_3$, H_2O, rt, 4 h,* ***68%****;[64] b) Ac_2O, pyridine, rt, 16 h,* ***40%****;[64] c) 33% HBr/AcOH, rt, 1.5 h,* ***61%****.[65]* ***B****: Synthesis of glycosyl donor* ***60*** *carrying Troc protecting group. Reaction conditions: a) $NaHCO_3$, 2,2,2-trichloroethyl chloroformate, H_2O, rt, 3 h,* ***82%****;[66] b) Ac_2O, pyridine, rt, 4 h,* ***54%****;[64] c) 33% HBr/AcOH, rt, 1.5 h,* ***50%****.[65]*

As there already are several publications on the total synthesis of lipid II and analogues thereof,[67] the herein presented synthesis of glycosyl acceptor **61** (Scheme 15) is inspired by those.[44,50,51,55,56] Like in the approach discussed before where the disaccharide is installed in a chemoenzymatic conversion, synthesis of the saccharide moiety started with muramic acid derivative **37**. This time, the free acid of compound **37** was subjected to an amide coupling with L-Ala-OTMSE (**65**), which itself was obtained from protected L-alanine **64** in two steps (98%). Thus, there was no need for the use of a classical protecting group for the lactyl moiety, saving two steps in the synthesis.

On this account, the early introduction of suitably protected L-alanine **65** could also solve some of the issues, that have been encountered during the synthesis of the sugar moiety used in the chemoenzymatic approach.[63] Firstly, as mentioned, the use of L-Ala-OTMSE (**65**) opposed to a classical protecting group saved two steps within the synthesis. Especially as in

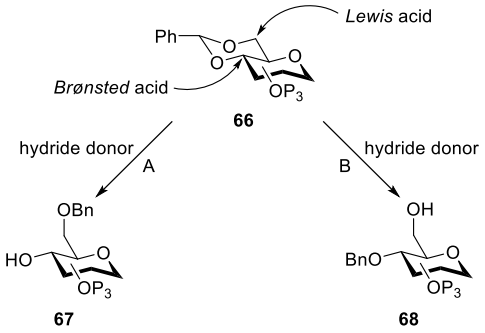
this case the introduction and cleavage of the trichloroethanol has caused some troubles,[63,68] leading to low yields (1%). On the other hand, the L-alanine residue could potentially provide enough steric bulk to prevent the unwanted cleavage of the acetal protecting group during the hydrogenolytic cleavage of the benzyl group of the anomeric center, making the re-protection step unnecessary.[63]



*Scheme 15: Synthesis of suitably protected L-Ala **65**, glycosyl acceptor **61** and Koenigs-Knorr reaction to obtain disaccharide **62** or **63** respectively. Reaction conditions: a) N-methylmorpholine (NMM), 2-chloro-4,6-dimethoxy-1,3,5-triazine, DCM, 0 °C, 45 min, then NMM, L-Ala-OTMSE (**65**), DCM, rt, 3 days, **98%**; b) Et_3SiH, DCM, TFA, 0 °C, 5 h, then TFA, 0 °C, o.n., **62%**;[55] c) AgOTf, DCM, -40 °C, 3 h, then -40 °C, o.n., then warm to rt, **42%**;[51] d) 4 Å MS, AgOTf, DCM, rt, o.n., **19%**.[55]*

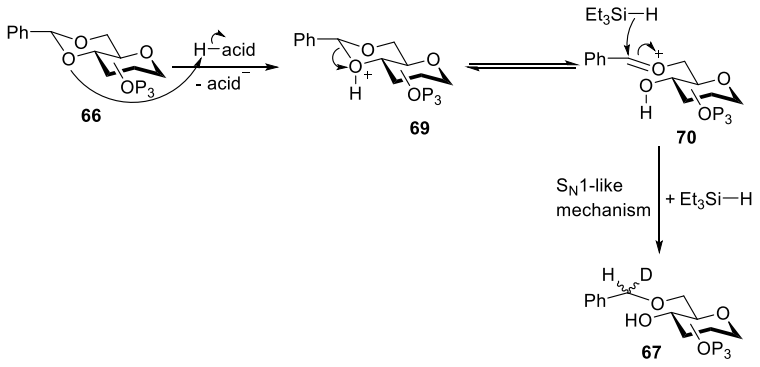
Two different conditions for the amide coupling of monosaccharide **37** and amino acid **65** have been tested, either using classic coupling reagents (DIPEA, HOBt, PyBOP)[51] or *N*-methylmorpholine and 2-chloro-4,6-dimethoxy-1,3,5-triazine (Scheme 15).[55] As the purification of the reaction using classical coupling reagents has shown to be rather tedious, due to similar polarities of the product and some byproducts, the obtained yield was rather low (33%). Therefore, the coupling conditions used by *VanNieuwenhze et al.* were applied which gave the desired aminosugar in good yields (98%).[55]

After the introduction of the amide bond, the acetal group needed to either be fully removed or regioselectively opened, to free the C_4-hydroxy group for the planned *Koenigs-Knorr* reaction (Scheme 15). To test both potential pathways, the obtained amide was treated with *p*-TsOH, cleanly cleaving the acetal yielding the C_4, C_6 diol in 82%. Then, the respective diol was planned to be selectively acetylated at the primary C_6-OH group. Unfortunately, only double acetylated product was obtained, making the two hydroxy functions indistinguishable. Alternatively, the formed amide was subjected to reductive conditions (Et_3SiH, TFA), leading to the regioselective opening of the acetal and therefore releasing the C_4 hydroxy function as intended (**61**).



Scheme 16: Mechanistic explanation of regioselectivity for the reductive opening of acetals in carbohydrate chemistry by Garegg et al.[69]

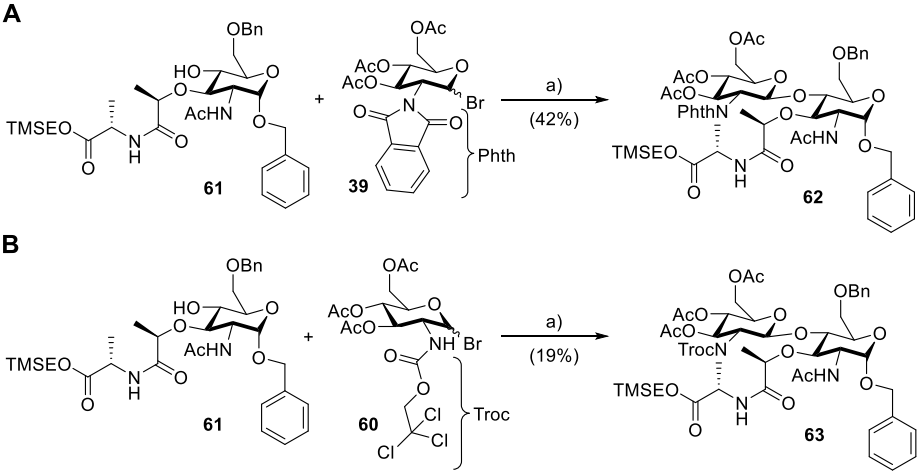
In general, the regioselectivity of a reductive acetal opening can be influenced by structural-, steric- and electronic-factors, as well as by the nature of the hydride donor, acid promoter, the solvent and the respective reaction conditions.[70] In 1974, the group of *Mukaiyama* reported their investigations on acid-mediated additions of *C*-nucleophiles to acetals which is a comparable reaction to the one considered here.[71] Additional mechanistic investigations were performed by *Denmark et al.,*[72] using low temperature nuclear magnetic resonance (NMR) spectroscopy. Herein, the formation of an initial complex between the *Lewis* acid and the acetal was unveiled[73] which was not the reactive intermediate of the investigated reaction.[74] Those preliminary results from the use of triethylsilane and TFA to reduce acetals and ketals in the 1970s[75] were conveyed to carbohydrate chemistry in 1995.[76] On the basis of the previously gained knowledge, *Garegg et al.*[69] made a mechanistic proposal on the regioselectivity of reductive acetal opening. Depending on the steric bulk of the employed *Lewis* or rather *Brønsted* acid, the attack of the latter would take place on the more or the less accessible oxygen of the acetal **66**. According to *Garegg et al.*, a sterically more demanding *Lewis* acid would therefore attack at the less hindered C_6 oxygen leading to the benzyl ether ending up at the C_4 hydroxy function (**67**, Scheme 16, pathway B), whereas a sterically undemanding proton would attack at the C_4 oxygen forming the more stabilised C_6 oxocarbenium ion **70** (Scheme 17).[69] Thereafter, the activated acetal **69** is in an equilibrium with the respective oxocarbenium ion **70** and will be reduced to compounds **67** and **68**.[77]



Scheme 17: Proposed mechanism for regioselective reductive acetal opening.[77]

The use of silanes in combination with either a *Bronsted* acid like TFA or a *Lewis* acid offers mild reaction conditions, tolerating a wide scope of functional groups.[78] Furthermore, by applying these conditions a selective formation of C_6 benzyl ethers from the reductive opening of cyclic acetals was observed.[78] As no effect of the configuration of the anomeric center on the regioselective outcome of the reaction was found,[76] the proposed mechanism of the performed reductive acetal opening is presented in Scheme 17. The previously discussed factors were applied to the specific system, explaining the observed regioselectivity of the reaction. With regard to the stereoselectivity of the hydride transfer, the obtained activated acetal **69** or rather oxocarbenium ion **70** will be reduced following a S_N1-like mechanism.[79] With both glycosyl acceptor **61** and glycosyl donors **39** and **60** in hand, the formation of the disaccharide was approached.

As the key step of this synthetic route, a *Koenigs-Knorr* reaction between the free C_4 hydroxy function of glycosyl acceptor **61** and either glycosyl donor **39** or **60** was planned. With regard to the *Koenigs-Knorr* reaction shown in part **A** of Scheme 18, the conditions used by the group of *Schwartz* were exactly replicated.[51] Silver triflate was used to activate the glycosyl bromide **52** at -40 °C.[60] Therefore, the formation of the β-1,4 linkage was controlled by the neighbouring group effect of the phthalimido group on C_2 of glycosyl donor **52** as intended.[80,81] Comparing the results *Schwartz et al.* reported a yield of 60%[51] which was not quite matched in this study (42%, Scheme 18, **A**).

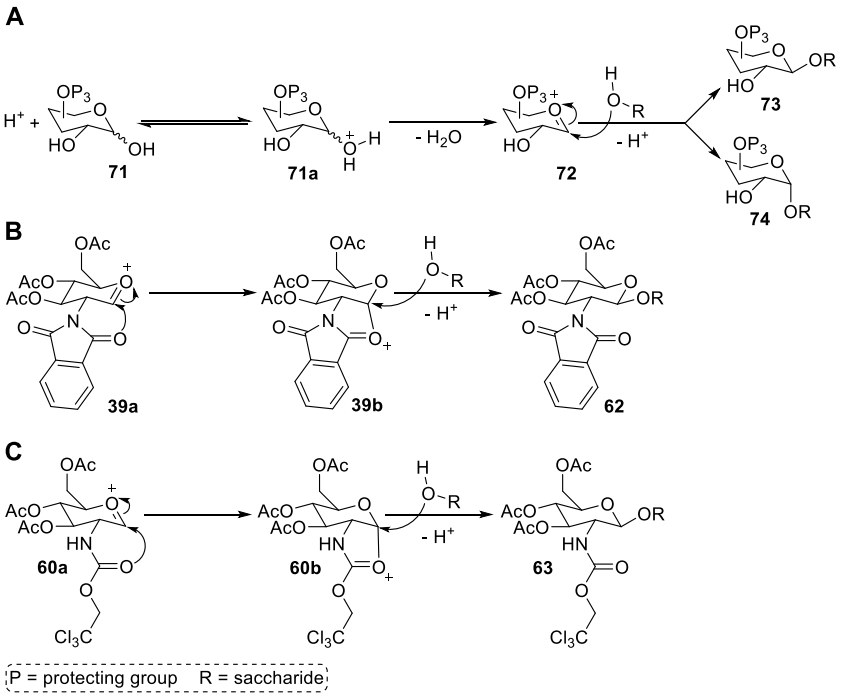


Scheme 18: Comparison of conducted Koenigs-Knorr reactions. ***A****: Following procedure by Schwartz et al. Reaction conditions: a)* ***39****, AgOTf, DCM, -40 °C, 3 h, then -40 °C, o.n., then warm to rt,* ***42%****.*[51] ***B****: Following procedure by VanNieuwenhze et al. Reaction conditions: a)* ***60****, 4Å MS, AgOTf, DCM, rt, o.n.,* ***19%****.*[56]

Based on the work of *Wong et al.* on glycosyl donors,[61] in the approach published by *VanNieuwenhze et al.*[59] Troc-protected glycosyl donor **60** was used. As seen before, the glycosyl bromide **60** was activated by the use of silver triflate. Afterwards, the desired β-1,4 linkage between glycosyl acceptor **61** and glycosyl donor **60** was formed due to the directing effect of the C_2-Troc group of the glycosyl donor **60**. In this case, the reaction was conducted at room temperature and a literature yield of 74% was reported,[59] which could not be replicated in this case (19%, Scheme 18, **B**). Comparing the two reactions, the use of the Phth protected glycosyl donor **39** gave better results even though *Wong et al.*[61] stated a Troc protected glycosyl donor like compound **60** should be beneficial. In their study from 1999, the group observed that the reactivity of 2-aminoglycosides is influenced by the protecting group installed at the nitrogen.[61] It was found that in comparison to the *N*-Phth group the *N*-Troc group had a large activating effect.[61] Considering the yields, the overall conditions have to be taken into account as well. The reaction following the procedure by *Schwartz* was performed at -40 °C,[51] whereas the reaction following the conditions given by *VanNieuwenhze* was carried out at room temperature.[59] To optimise the conditions for the *Koenigs-Knorr* reaction further experiments needed to be executed, which was done as a part of the master thesis of *S. Morgenschweis*[82] and afterwards in the master thesis of *E. Nikolajev*[83] who also took over the topic for his PhD thesis. Therefore, herein no further studies have been conducted.

In both cases (Scheme 18, **A** & **B**) the desired β-1,4 linked disaccharide was observed as only diastereomer. The stereoselectivity of this reaction can be explained by considering the mechanism. Generally, the course of the transformation of the hemi-acetal starting

material **71** to the acetal **73** or **74** is depicted in Scheme 19 (**A**). First, the anomeric hydroxy group of the glycosyl donor **71** is activated by an acid, forming cation **71a**. The latter then forms the oxocarbenium ion **72** by elimination of water. The oxocarbenium ion is then attacked by the hydroxy group of the glycosyl acceptor in a S_N1 reaction, forming both anomers **73** and **74**. In this case, no stereocontrol is given.[69]



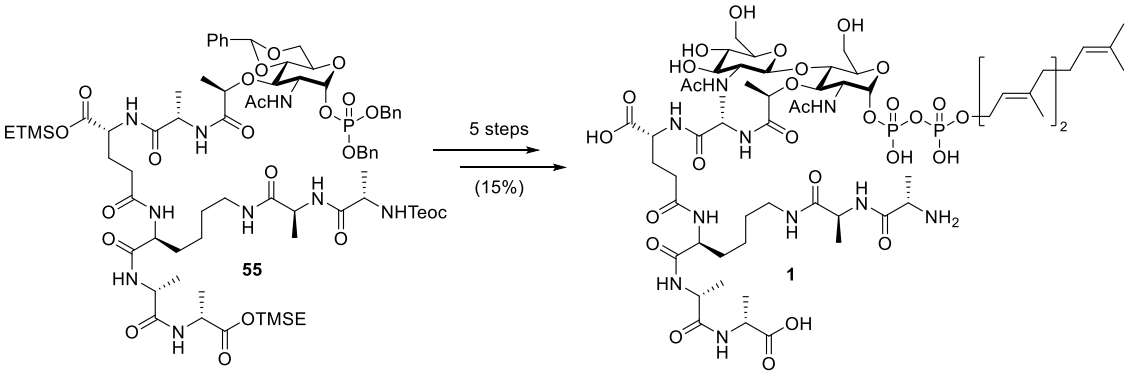
*Scheme 19: **A**: General mechanism of a glycosylation.[69] **B**: Mechanism of the Koenigs-Knorr reaction performed with glycosyl donor **52**. **C**: Mechanism of the Koenigs-Knorr reaction carried out with glycosyl donor **72**.[80]*

In 1901, *Koenigs* and *Knorr* published a procedure which selectively gave rise to β-glycosides of glucose.[81] Herein, the respective oxocarbenium ions **39a** and **60a** (Scheme 19, **B** & **C**) were formed from glycosyl donors **39** and **60** by the addition of silver triflate, leading to the formation of poorly soluble silver bromide. But in general, the formation of the oxocarbenium ions **39a** and **60a** follows a similar mechanism as depicted in Scheme 19 (**A**).[69] The latter can then undergo an intramolecular attack by the lone pair of the C_2 amine protecting group, forming a dioxolanium ring (**39b** and **60b**). As the amine group is located below the ring, the attack also takes place from below. This observation is known as anchimetric assistance.[80] The formed oxocarbenium ions **39b** and **60b** then undergo a nucleophilic attack (S_N2) by the alcohol of the glycosyl acceptor. Inversion of the configuration of C_1 leads to the β-anomer, showing a C_1-C_2 *trans* stereochemistry.[80] Deprotonation of the formed acetal leads to glycosides **62** and **63**.[80] Per-*O*-acylated glycosyl bromides **52** and **72** were used as they commonly react faster than the corresponding chlorides.[84]

1.5 Conclusion and Outlook

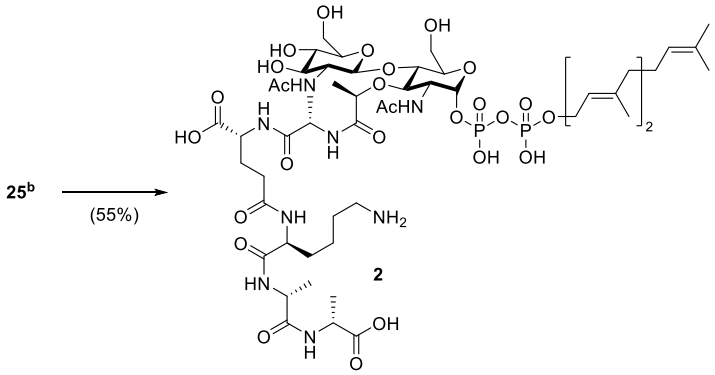
1.5.1 Conclusion

In summary, lipid II derivative **1** was synthesised in a LLS of 20 steps starting from commercially available 2-CTC resin (**51**) with an overall yield of 2% finishing the work presented in a previous study.[63] The established combined approach of solid-phase and solution-phase peptide synthesis exploiting a orthogonal protecting group concept has been proven to also be applicable to various strain specific side chains. The last remaining five steps of the synthesis were conducted within this study with a yield of 15% to furnish farnesyl lipid II derivative **1** (Scheme 20). Parts of these results have already been published.[54]



*Scheme 20: Synthesis of lipid II analogue **1**.*

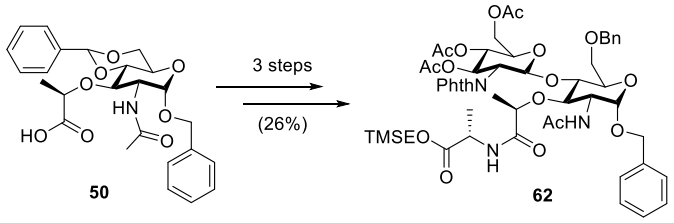
Additionally, the chemoenzymatic conversion of farnesyl lipid I (**25^{b}**) to farnesyl lipid II (**2**) was conducted in cooperation with the group of *T. Schneider* (University of Bonn) (Scheme 21), furnishing the latter compound in a LLS of 18 steps starting from 2-CTC resin (**51**) with a total yield of 2%. The precursor **25^{b}** has also been obtained during a previous study.[63]



*Scheme 21: Synthesis of farnesyl lipid II (**2**).*

Both lipid II analogues **1** and **2** were given to the group of *T. Schneider* (University of Bonn) for further studies on structure activity relationships as well as modes of action of potential antibiotics.

As the yields of the chemoenzymatic conversion of lipid I (**25^{b}**) to lipid II (**2**) with MurG were rather low (30% - 55%) and inconsistent, a solely chemical route towards farnesyl lipid II (**2**) should be established in the group. Thus, a sufficient supply for further studies, as well as very pure compounds without a tedious HPLC purification in the end of the synthetic route will be ensured. Herein, the same carbohydrate precursor **37** was transformed to the disaccharide **62** in three steps with a yield of 26% (Scheme 22). The key step of the new synthetic route being the *Koenigs-Knorr* reaction. The latter yielded the desired disaccharide with two different glycosyl donors (**39** and **60**).

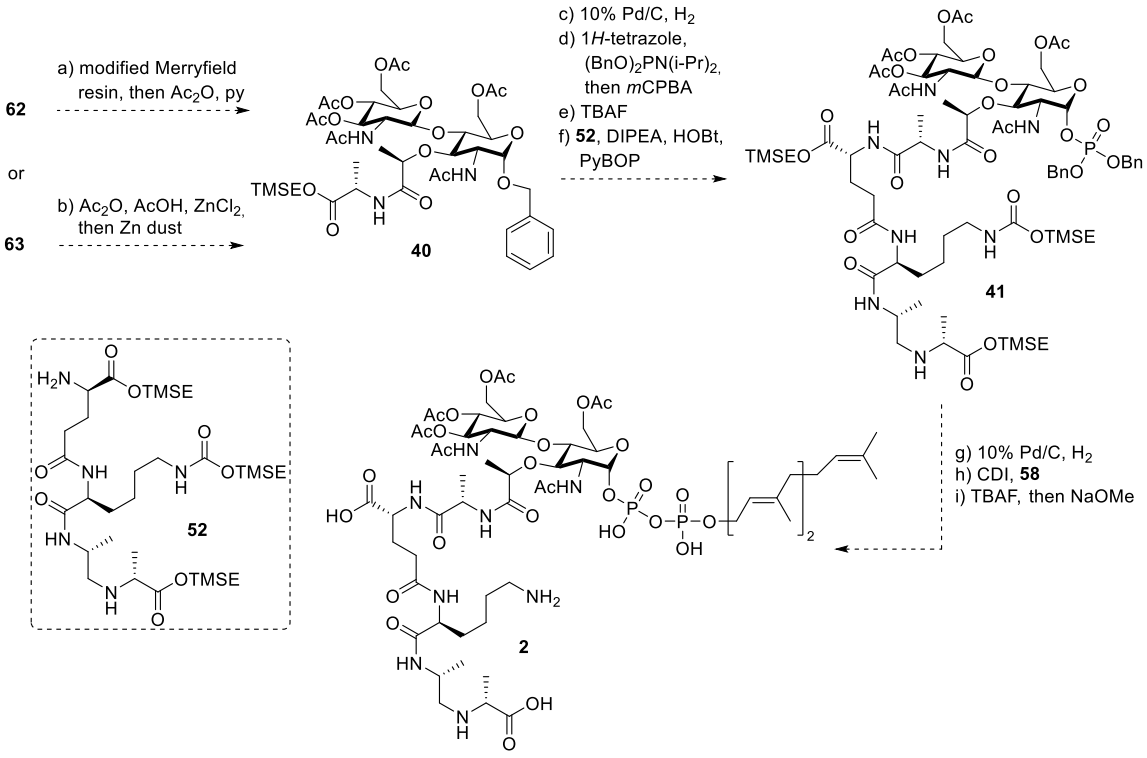


*Scheme 22: Synthetis of the disaccharide motif **62** for the solely chemical synthesis of farnesyl lipid II (**2**).*

1.5.2 Outlook

Considering the solely chemical synthesis of farnesyl lipid II (**2**) the amine protecting group (either *N*-Phth or *N*-Troc), which was introduced for its anchimeric assistance during the *Koenigs-Knorr* coupling needs to be changed to an acetyl group yielding compound **40**. Afterwards, the phosphate as well as the remaining tetrapeptide will be introduced within four steps yielding amino sugar **54**. Lastly, the labile pyrophosphate moiety will need to be installed and the finalised compound globally deprotected to obtain farnesyl lipid II (**2**, Scheme 23). The remaining studies were taken up by *S. Morgenschweis* during his master thesis[82] followed by *E. Nikolajev*[83] during his master thesis, who is also taking over this topic for his PhD in our group.

After furnishing lipid II analogues **1** and **2**, both were supplied to the biologists to conduct several tests. However, the results thereof are still pending.



*Scheme 23: Remaining synthetic steps towards solely chemically synthesised farnesyl lipid II (**2**).*

2 Part II: Contributions to the Total Synthesis of Neaumycin B (3)

2.1 Introduction

2.1.1 Polyketides

In the 1890s, *J. N. Collie* proposed a mechanism for the formation of aromatic natural products.[85,86] They belong to the class of natural products which is named polyketides as the related compounds contain many carbonyls and alcohols which are separated by methylene groups. But it was not until the 1950s when *Birch* proposed that polyketones could be build up from acetate units.[87,88] He verified his idea by feeding isotopically-labelled (^{14}C) acetate to a polyketide-producing organism followed by laborious investigations of the incorporated radioactivity. Thereby, *Birch* was able to prove the biosynthetic pathway building up polyketides.[87,88] Nowadays, this group of natural products is known for its structural and functional diversity as well as the pharmacological activity of its members.[85,87]

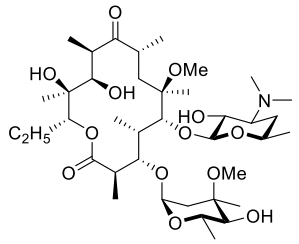
As the availability of radioactive isotopes of carbon and hydrogen was spreading, a broader understanding of the biosynthesis of these natural products first became possible. The pace at which the knowledge about this topic grew, vastly increased with the introduction of NMR studies in the early 1970s.[85] Within the next ten to 15 years, fundamental results regarding the identification of precursors as well as detailed insights into the assembly and subsequent modification were gained. Until the late 1980s, evidence had proven that the assembly of aromatic and reduced polyketides was mechanistically closely related to the, by then well understood, formation of saturated fatty acids.[85]

Polyketides are build up by polyketide synthases (PKS) by repetitive *Claisen* condensation of an activated starter unit (or respectively the growing chain), with malonyl CoA elongation units. Therefore, the analysis of the respective gene cluster can allow some insights into the linear structure.[89,90]

2.1.2 Macrolides

Macrolides are a subgroup of the polyketide family, being produced by type I polyketide synthases. They resemble complex metabolites, showing the characteristic macrocyclic lactone ring being decorated with multiple stereogenic centers. One or more sugar moieties can be attached to the backbone *via* a glycosidic bond.[91,92]

Some of the most successful natural products being used in the treatment of infectious and immune diseases belong to this class. Classic macrolides, like erythromycin A (**21**) and clarithromycin (**75**), are drugs used for the treatment of *Gram*-positive bacterial infections (Figure 11).[89]



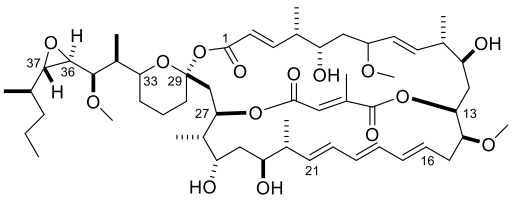
clarithromycin (**75**)

*Figure 11: Chemical structure of clarithromycin (**75**).[89,91]*

In addition to the classic application areas of macrolides, like antimicrobials or immunosuppressants, recent studies suggest an unrecognised potential of newly discovered marine-derived, as well as classic macrolides, in the treatment of cancer.[93]

2.1.3 Neaumycin

In 2012, the group of *Shen* isolated a new macrolide (**76**, Figure 12) from the soil actinomycete strain *Streptomyces* sp NEAU-x211 which was found in HunLunbuir, Inner Mongolia, China. The white solid was investigated by comprehensive mass and NMR spectroscopy to elucidate its structure.[94]



76

*Figure 12: Proposed structure of neaumycin (**76**) by Shen et al.[94,95]*

Due to the interpretation of the acquired data of neaumycin (**76**), it was believed to consist of a 30-membered macrolide, containing a diester bridge between C_{13} and C_{27} as a unique structural motif, as well as 19 stereogenic centers (Figure 12).[94] On the basis of the chosen analytical methods, a relative configuration for most of the stereocenters was given. In addition to the isolation and structure elucidation, neaumycin (**76**) was tested for its toxicity. Throughout the experiments with selected cancer cell lines, no activity was observed at a concentration of 1 μM under the tested conditions.[94]

Three years later, in 2015, *Simone et al.* were investigating the ramoplanin producing strain *Actinoplanes* sp. ATCC 33076. Meanwhile they found unrelated lipophilic compounds during their HPLC purification.[96] They were able to isolate and characterise three of the five observed compounds, when they realised that one of them seemed to be identical to neaumycin (**76**, Figure 12) reported by *Shen*.[94] On the basis of the retention times of the compounds during the HPLC purification they were named neaumycin A – E while the identical compound was labelled neaumycin A (**77a**, Figure 13).

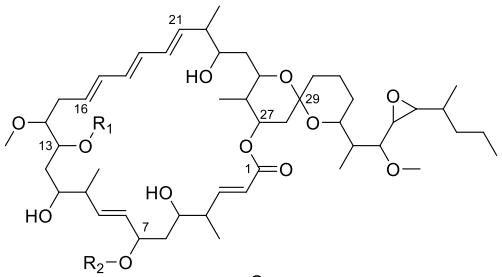
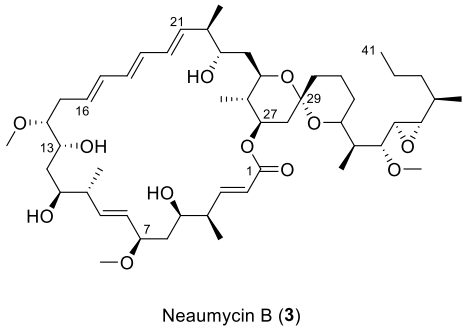


*Figure 13: Revised structure of neaumycin (**77a**) without assigned stereochemistry by Simone et al.[96]*

During the structural elucidation experiments of the structure of the observed congeners, *Simone et al.* assigned a "zone of low flexibilty" to C_{24}, C_{28}, C_{30}, C_{31} and C_{32}.[96] But, as opposed to the proposal of the diesterification of 3-methylfumaric acid by *Shen et al.*,[94] they justified this observation with the presence of a spiroketal motif.[96] This suggestion is based on the rigidity of this region being found in both investigated congeners neaumycin A (**77a**) and neaumycin B (**77b**). Although the latter is lacking the 3-methylfumaric acid residue. Therefore, the originally proposed structure of neaumycin A (**76**, Figure 12) by *Shen et al.* was revised to be a 28-membered spiroketal-containing macrolide carrying a 3-methylfumaric acid residue at C_{13} as depicted in Figure 13.[96] Due to its structure, neaumycin B (**77b**) is related to the class of cytovaricin-ossamycin-oligomycin macrolides.[92] Furthermore, little cytotoxicity against several bacterial strains for neaumycin A (**77a**) and B (**77b**) themselves was found. Though, as the compounds have been found in ramoplanin producing strains, a combination of both compounds was tested for biological activity.[96] Over the course of these experiments an enhancement of the activity of ramoplanin against a methicillin-resistant *Staphylococcus aureus* strain was discovered, decreasing the MIC of ramoplanin by two orders of magnitude in the presence of neaumycin A (**77a**) or B (**77b**).[96]

Another three years later, in 2018, *Jensen* and *Fenical et al.* published a structure proposal of neaumycin B (**3**, Figure 22) with a full assignment of all 19 stereocenters.[89] In their case, the compound was isolated from a marine-derived actinomycete bacterium (*Micromonospora* CNY-010), which itself was isolated from the surface of the tropical brown alga *Stypopodium zonale* collected in the Bahamas Islands.[89]



Neaumycin B (**3**)

*Figure 14: Proposed 3D structure of neaumycin B (**3**) with assigned stereochemistry by Jensen and Fenical et al.[89]*

Within this study, a combined approach of bioinformatic analysis of the producing gene cluster and thorough NMR spectroscopy was chosen. Subsequently, the proposed 28-membered spiroketal-containing macrolide core structure was confirmed and the missing stereoinformation was added to the 19 chiral centers (Figure 14).[89]

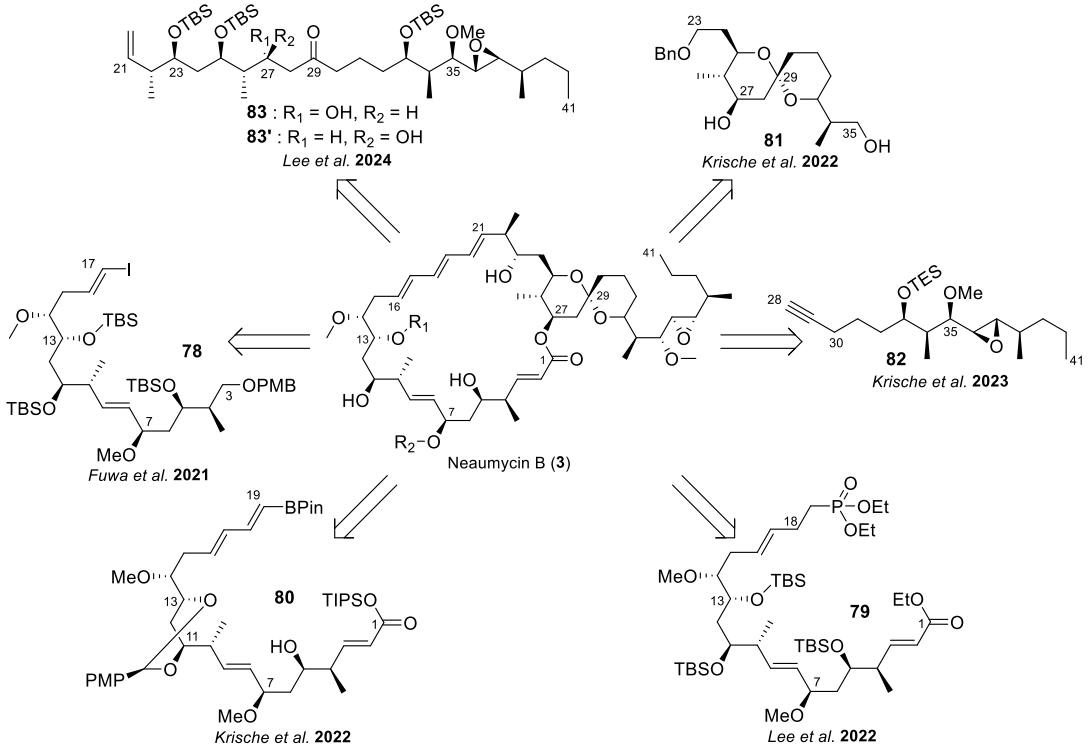
The obtained cultural extract showed modest *in vitro* growth inhibition against HCT-116 colon carcinome (IC_{50} = 1 µM), whereas for isolated and purified neaumycin B (**3**) a significant activity and selectivity against RPMI-8226, a major plasma cancer cell type, was observed. In addition to these observations, a significant potency and selectivity towards U87 human glioblastoma, a highly difficult cancer type to treat, was found in ancillary testing.[89]

Glioblastoma are perceived as lethal neoplasms showing a poor probability of survival, even with extensive treatment like surgery, radiotherapy, chemotherapy and immunotherapy.[97] Thus, they are known to be the most malignant type of glioma. On this note, the results of this study showing the lethal dosis (LD_{50}) of neaumycin B (**3**) to be 5.6×10^{-5} µg/mL (6.4×10^{-8} µM). In combination with its high level of selectivity, those results may further indicate its potential to serve as a lead structure for the design of drugs in glyoblastoma treatment.[89]

2.2 State of Knowledge

2.2.1 Published Syntheses of Fragments of Neaumycin B (3)

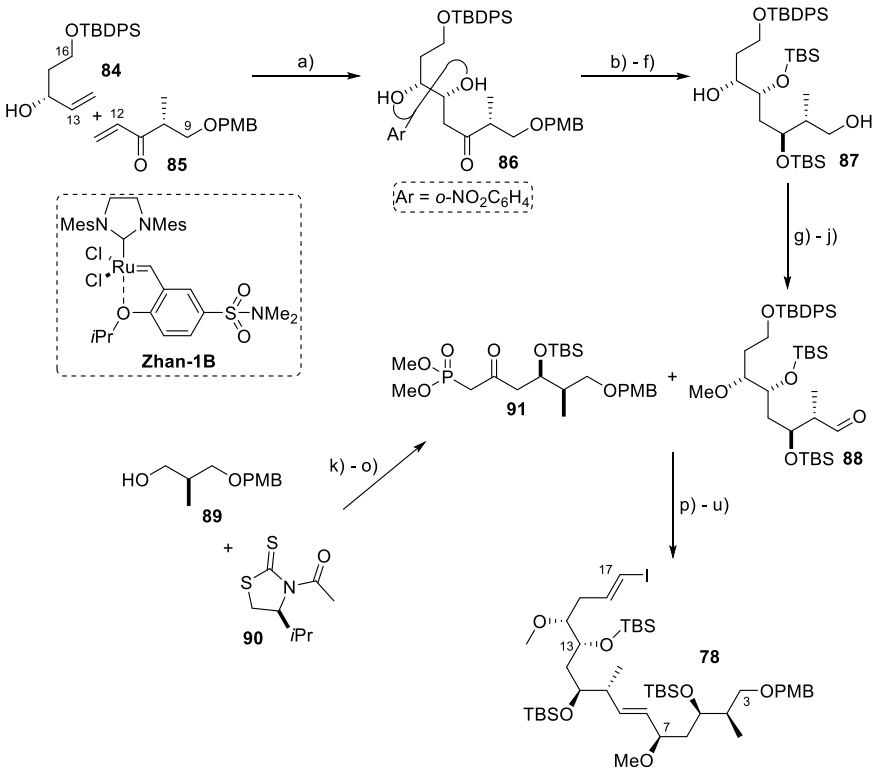
Between the years 2021 to 2024, five syntheses towards fragments of neaumycin B (**3**) have been published. Within these syntheses all parts/stereogenic centers of the desired natural product were addresed. The first synthesis of a fragment of neaumycin B (**3**) was published in 2021 by the group of *Fuwa*.[98] This publication covers the southern hemisphere of neaumycin B (**3**), namely the acyclic domain from C_3-C_{17} (**78**, Scheme 24).



*Scheme 24: Overview of published fragment syntheses towards the proposed structure of neaumycin B (**3**) up until 2024.*

In order to prepare the aldehyde portion **88** for the *HWE* reaction, the synthesis started from known allylic alcohol **84** [99] and α,β-unsaturated ketone **85** (Scheme 25).[100] These two compounds were linked *via* an olefin cross-metathesis,[101] followed by a hemiacetalization/intramolecular oxa-*Michael* addition.[102] Adjacently, the tandem approach of olefin metathesis/hemiacetalisation/intramolecular oxa-*Micheal* addition is conducted using the *Zhan*-1B catalyst, *ortho*-nitrobenzaldehyde and camphorsulfonic acid (CSA) yielding 59% of a product as a diastereomeric mixture at the acetal carbon (**86**). Afterwards, the C_{11} carbonyl group was stereoselectively reduced[103] and the acetal group protecting the C_{13} and C_{14} hydroxy functions was meant to be opened regioselectively under reductive conditions. To allow the use of mild conditions for the acetal opening, the nitro group was

reduced, increasing the reactivity by reversing the effect of the substituent from electron withdrawal (NO_2-group) to electron donation (NH_2-group). Therefore, the C_{11} hydroxy-directed regioselective reduction yielded the desired diol after thorough screening of the reaction conditions.[98]



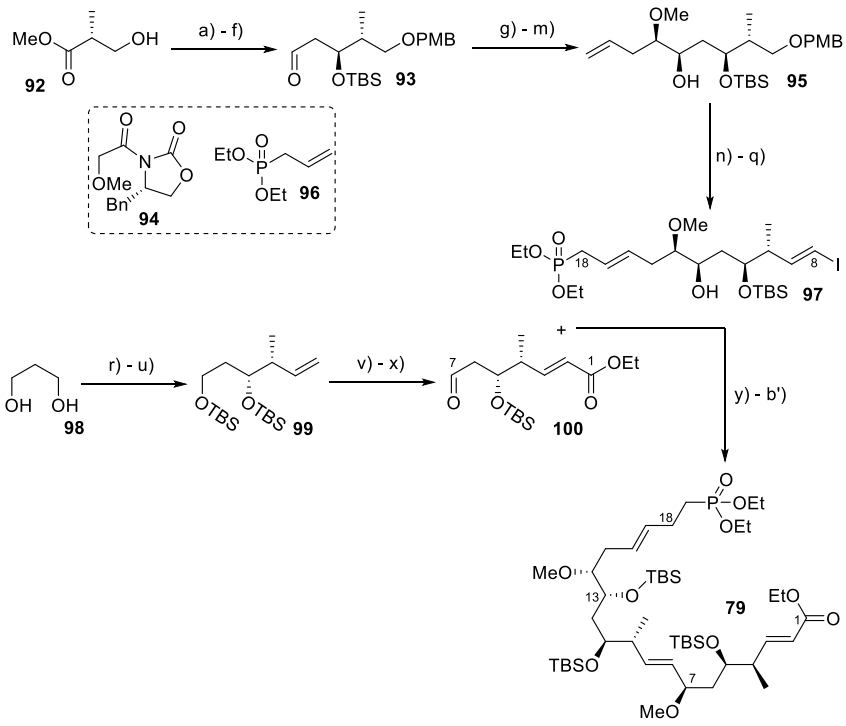
*Scheme 25: Synthesis of C_3–C_{17} fragment **78** of neaumycin B (**3**) by Fuwa et al. Reaction conditions: a) Zhan-1B, o-$NO_2C_6H_4CHO$, CSA, Et_2O, rt, **59%** (dr 1.3:1 at acetal carbon); b) $LiAlH_4$, LiI, Et_2O, -95 °C, **95%** (dr > 20:1); c) H_2, Pd/C, aq. HCHO, EtOH, **95%**; d) $LiAlH_4$, $AlCl_3$, CPME, -65 °C, **71%**; e) TBSCl, imidazole, DMF, 60 °C, **99%**; f) Li naphthalenide, THF, -20 °C, **92%**; g) PivCl, pyridine, 0 °C, **94%**; h) Me_3OBF_4, proton sponge, CH_2Cl_2, **95%**; i) DIBAL-H, THF, -78 °C to rt, **84%**; j) DMP, $NaHCO_3$, CH_2Cl_2, **99%**; k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 0 °C; l) $TiCl_4$, iPr_2NEt, CH_2Cl_2, -78 °C, **quant** (two steps, dr 8:1); m) MeONHMe*HCl, imidazole, CH_2Cl_2, **95%**; n) TBSCl, imidazole, DMF, 50 °C, **quant**; o) $MeP(O)(OMe)_2$, nBuLi, THF, -78 °C, **98%**; p) NaHMDS, THF, -78 °C to 0 °C, **97%** (E/Z > 20:1); q) (S)-2-Me-CBS, BH_3*THF, THF, -20 °C, **quant** (dr 12:1); r) MeI, Ag_2O, Et_2O, rt, **91%**; s) NH_4F, MeOH, 50 °C, **51%** (**93% brsm**); t) DMP, $NaHCO_3$, CH_2Cl_2, rt, **94%**; u) $CrCl_2$, CHI_3, THF/1,4-dioxane, **84%** (E/Z 8:1).[98]*

Tert-butyldimethylsilyl (TBS) protection of the observed diol followed by reductive cleavage of the PMB-protecting group as well as the residual acetal protecting group using lithium naphthalenide gave rise to compound **87** (Scheme 25). To obtain aldehyde **88** the primary alcohol was protected using pivaloyl chloride followed by the methylation of the remaining C_{14} hydroxy group and subsequent formation of the aldehyde by DIBAl-H reduction and DMP oxidation.[98] Preparation of the phosphonate fragment **91** was achieved starting from known alcohol **89**.[104] *Swern* oxidation[105] to the respective aldehyde followed by *Nagao* asymmetric acetate aldol reaction[106] with thiazolidinethione **90** gave rise to the aldol adduct. The latter was transformed into the *Weinreb* amide and the secondary alcohol was TBS protected.

Treatment of the respective TBS-ether with dimethyl methylphosphonate and *n*BuLi resulted in the phosphonate **91**.[98] After conduction of the envisioned *HWE* reaction, the α,β unsaturated ketone was obtained. Subsequent asymmetric reduction utilising (*S*)-2-methyl-CBS oxazoborolidine lead to the desired allylic alcohol along with its C_7 epimer.[98] After that, the C_7 hydroxy function was methylated and the *tert*-butyldiphenylsilyl (TBDPS) ether was selectively cleaved using NH_4F in MeOH.[107] Lastly, *Dess-Martin* oxidation followed by *Takai* olefination[108] revealed vinyl iodide **78** (Scheme 25).[98]

Following the first synthetic approach towards the southern hemisphere of neaumycin B (**78**) by *Fuwa et al.*, the group of *Lee et al*. published a stereoselective synthetic route towards the C_1-C_{18} fragment of neaumycin B (**79**) in August 2022 (Scheme 24).[109] Key steps within their synthetic approach towards vinyl iodide **97** were the diastereoselective allylation, *Evans syn*-aldol and olefin metathesis (Scheme 26).[109] Starting from commercially available (*R*)-*Roche* ester (**92**) a PMB protection followed by $LiAlH_4$ reduction and DMP oxidation to obtain the aldhyde[110] were conducted. The latter was used for the *anti*-selective allylation affording the homoallylic alcohol.[111] Thereafter, the newly formed secondary alcohol was TBS protected and the olefin was cleaved oxidatively by dihydroxylation and subsequent glycol cleavage.[109] Then, the prepared aldehyde **93** was conducted to an *Evans syn*-aldol reaction using oxazolidinone **94** ensued by TBS protection.[112] Reductive cleavage of the *Evans* auxiliary was followed by a three step sequence starting with the triflation of the primary alcohol, followed by S_N2 substitution of the triflate with TMS-acetylene anion and lastly, the removal of TMS under basic conditions to obtain the terminal alkyne.[113] Hereafter, the terminal olefin **95** which was to be subjected to olefin metathesis with phosphonate **96**. The latter was obtained by using the *Schwartz* reagent.[114] After conducting the olefin metathesis,[115] PMB deprotection was achieved using DDQ. Finally, DMP oxidation to the aldehyde and subsequent *Takai* olefination gave rise to the desired vinyl iodide **97** (Scheme 26).[116] To prepare aldehyde **100** the synthesis started from 1,3-propanediol (**98**), which was conducted towards a mono TBS protection followed by *Swern* oxidation and *Brown syn*-crotylation.[117] Subsequent TBS protection proceeded with quantitative yield obtaining compound **99**. Afterwards, the primary TBS-ether was selectively cleaved. Lastly, the olefin metathesis using *Hoveyda-Grubbs* II catalyst and ethyl acrylate was performed followed by DMP oxidation to furnish aldehyde **100**.[118] Fragment coupling was first envisioned *via* a diastereoselective

addition reaction with vinyl iodide **97** derived organometallic reagents (M = Li or MgX), but all efforts remained unsuccessful.[109]



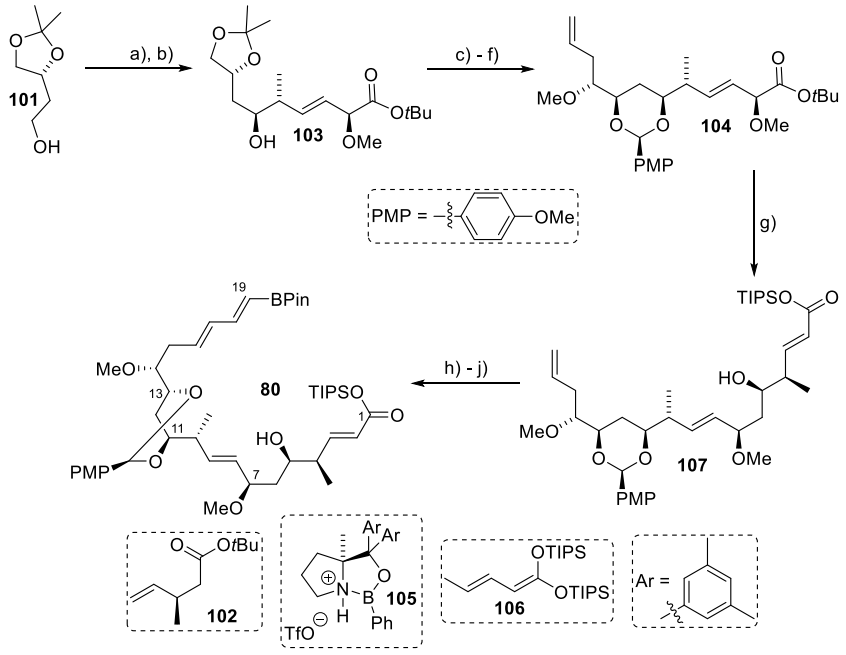
*Scheme 26: Synthesis of C_1–C_{18} fragment **79** of neaumycin B (**3**) by Lee et al. Reaction conditions: a) PMB acetimidate, PPTS, CH_2Cl_2, rt, **95%**; b) $LiAlH_4$, THF, 0 °C, **77%**; c) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt; d) $SnCl_4$, allylSnBu_3, CH_2Cl_2, -78 °C, **70%** (two steps); e) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, **88%**; f) $NaIO_4$, OsO_4, 2,6-lutidine, dioxane/H_2O (3:1), rt, **87%**; g) **93**, nBu_2BOTf, Et_3N, CH_2Cl_2, -78 °C; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, **86%** (two steps); i) $LiBH_4$, H_2O, Et_2O, rt, **84%**; j) Tf_2O, Et_3N, CH_2Cl_2, -78 °C; k) TMS-acetylene, nBuLi, HMPA, THF, 0 °C; l) K_2CO_3, MeOH, rt, **74%** (three steps); m) Cp_2ZrHCl, THF, rt, **75%**; n) **95**, Grubbs II, CH_2Cl_2, reflux; o) DDQ, CH_2Cl_2/pH 7 buffer, **61%** (two steps); p) DMP, $NaHCO_3$, CH_2Cl_2, rt; q) $CrCl_2$, CHI_3, THF, 0 °C, **50%** (two steps); r) TBSCl, imidazole, THF, -78 °C, **77%**; s) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; t) nBuLi, KOtBu, BF_3*OEt_2, (Z)-but-2-ene, (-)-(Ipc)$_2$BOMe, THF, -78 °C, **50%** (two steps); u) TBSOTf, DIPEA, CH_2Cl_2, 0 °C, **quant.**; v) CSA, MeOH, -30 °C, **75%**; w) ethyl acrylate, Hoveyda-Grubbs II, CH_2Cl_2, reflux, **73%**; x) DMP, $NaHCO_3$, CH_2Cl_2, rt, **81%**; y) $NiCl_2$, $CrCl_2$, DMF, rt, **74%** (dr 1.8:1); z) DMP, $NaHCO_3$, CH_2Cl_2, rt, **86%**; a') (S)-CBS, BH_3*DMS, THF, 0 °C, **83%**; b') MeOTf, 2,6-di-tert-butylpyridine, $CHCl_3$, rt, **44% brsm**.[119]*

Therefore, the approach was changed to a three-step sequence, comprising a *Nozaki-Hiyama-Kishi* reaction between vinyl iodide **97** and aldehyde **100** (Scheme 26), resulting in a 1.8:1 mixture of C_7 alcohols[120] followed by DMP oxidation to the respective α,β-unsaturated ketone and a stereoselective reduction using a *Corey-Bakshi-Shibata* reduction.[121] Lastly, the secondary alcohol was methylated to obtain compound **79**.[109] In conclusion, the C_1–C_{18} fragment **79** was obtained within a total of 28 steps (0.2%), whereas the vinyl iodide **97** was prepared in 17 steps (5%) and aldehyde **100** in seven steps (17%) respectively.[109]

In November 2022, the group of *Krische* published a synthesis towards the C_1–C_{19} fragment **80** as well as C_{23}–C_{35} fragment **81** of neaumycin B (**3**) (Scheme 24).[122] Within their fragment synthesis the group applied their newly developed *anti*-diastereoselective ruthenium-

JOSIPHOS-catalysed butadiene-mediated crotylation of primary alcohol proelectrophiles *via* a hydrogen auto-transfer[122] as well as a novel variant of the catalytic asymmetric vinologous *Mukaiyama* aldol reaction (VMA).[122]

Their synthesis of the C_1–C_{19} substructure **80** started from from (*R*)-malic acid derived alcohol **101**, which was transformed in a butadiene-mediated crotylation.[123] A ruthenium-based catalyst was utilised, instead of a catalyst based on the less abundant iridium, as well as butadiene, which also has a significantly higher abundance than the commonly used α-methyl allyl acetate.[122] Subsequently, the product of the reaction was implemented in a cross-metathesis with (*R*)-3-methoxy-4-pentenoic acid tert-butyl ester (**102**)[124] using a *Hoveyda-Grubbs* II catalyst to build up the C_5-C_{14} motif (Scheme 27). After that, the compound was converted to the primary alcohol *via* an acid-catalysed 1,2-ketal-1,3-acetal exchange.[125]

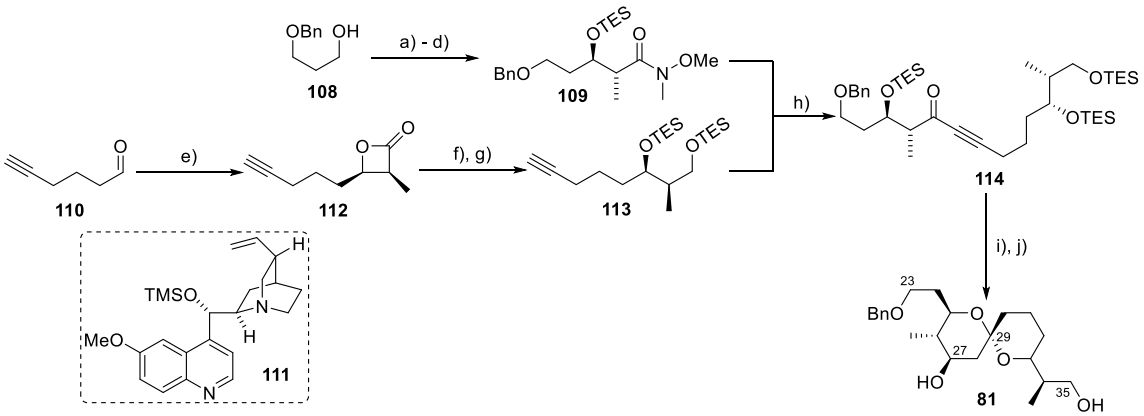


*Scheme 27: Synthesis of C_1-C_{19} fragment **80** of neaumycin B (**3**) by Krische et al. Reaction conditions: a) $RuI(CO)_3(\eta^3\text{-}C_3H_5)$, SL-J502-2, TFE, MTBE, syn-1,3-butadiene, 100 °C, **86%**; b) HG II cat., **102**, PhMe, 70 °C, **47%**; c) CSA, $PMPCH(OMe)_2$, DCM, rt, **83%**; d) Ir-BINAP cat., K_2CO_3, H_2O, 4-Cl-3-NO_2BzOH, 3-methylbutan-2-ol, allylacetate, dioxane, 120 °C, **60%**; e) MeI, Ag_2O, Et_2O, rt, **72%**; f) DIBAl-H, Et_2O, -78 °C, **86%**; g) **105**, **106**, 2-PrOH, DCM, -78 °C, **70%**; h) TBSOTf, 2,6-lutidine, DCM, -78 °C to -10 °C, **76%**; i) HG II, Ar PhMe, acrolein, rt, **68%**; j) LiTMP, $CH_2(Bpin)_2$, THF, -78 °C, **83%**.[122]*

Hereafter, the product of the preceding reaction was utilised in an asymmetric allyl acetate-mediated iridium-catalysed allylation.[126,127] Then, the product of the latter was converted to the C_5 aldehyde, by first conducting an *Irvine-Purdie* methylation[128] at the C_{14}-OH, followed by DIBAL-H reduction to the aldehyde, which is then employed in an oxazaborolidine-catalysed VMA reaction.[129] This was the most precise way of transforming the aldehyde into the desired C_1–C_{17} substructure.[122] The latter was then further developed to the C_1–C_{19}

fragment **80** *via* cross-metathesis with acrolein leading to the respective enal compound and a boron-*Wittig* olefination[130] of the latter, following the prorocol of the *Morken* group.[130] Within this approach, a twelve step LLS to the C_1–C_{19} fragment **80** of neaumycin B (**3**)[122] has been presented overall yielding 4% of the desired compound. Additionally, the route was significantly shorter than the previously published twenty steps to the C_3–C_{17} fragment **78** by *Fuwa et al.* (Scheme 25).[98]

Regarding synthesis of the C_{23}–C_{35} subunit **81**, commercially available 1,3-propanediol monobenzyl ether (**108**) was chosen as starting material. It was first subjected to a ruthenium-JOSIPHOS-catalysed butadiene-mediated crotylation to obtain the homoallylic alcohol (Scheme 28).[123] After that, the terminal olefin was transformed into the methyl ester by ozonolytic cleavage,[131] ensued by TES protection of the secondary alcohol and installation of the *Weinreb* amide **109** spanning the C_{23}–C_{27} motif.[132] Alkyne **110** was subjected to a *Lewis* base catalysed ketene [2 + 2] cycloaddition using compound **111** to obtain the respective β-lactone **112**. Subsequently, the latter was reduced to the diol, which was then transformed into the bis-TES ether **114** clasping C_{28}–C_{35}.[122] Coupling of *Weinreb* amide **109** and alkyne **113** was conducted *via* acyl substitution to furnish the envisioned acetylenic ketone **114**, which was exposed to methanol containing an acid catalyst to cleave the TES ethers contained in the molecule.[122]

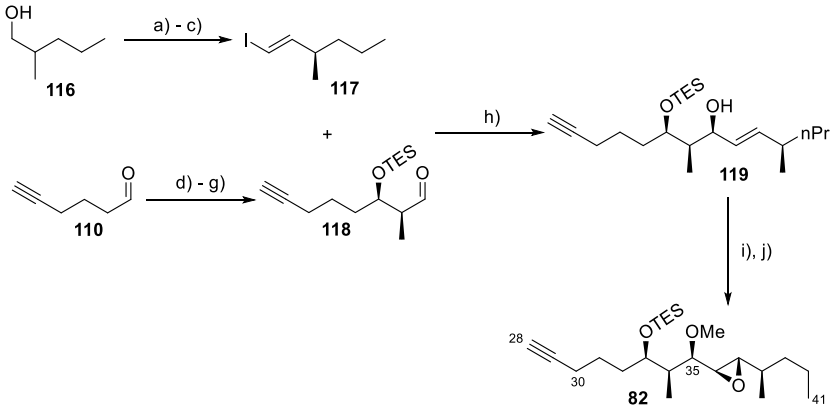


*Scheme 28: Synthesis of C_{23}-C_{35} fragment **81** of neaumycin B (**3**) by Krische et al. Reaction conditions: a) $RuI(CO)_3(\eta^3\text{-}C_3H_5)$., SL-J502-2, TFE, MTBE, syn-butadi-1,3-ene, 100 °C, **85%**; b) O_3, NaOH, MeOH, DCM, -78 °C, **64%**; c) TESCl, imidazole, DMF, rt, **72%**; d) (MeO)NHMe*HCl, iPrMgBr, THF, 0 °C, **83%**; e) EtCOCl, **111** cat, DIPA, $LiClO_4$, DCM:Et_2O, -65 °C, **99%**; f) $LiAlH_4$, Et_2O, 0 °C, **92%**; g) TESCl, imidazole, DMF, rt, **98%**; h) nBuLi, **114**, THF, -78 °C to rt, **92%**; i) TsOH*H_2O, DCM:MeOH, rt; j) DCM, rt, then $NaBH_4$, MeOH, rt, **64%** (two steps).[122]*

In addition to the deprotection, the cyclisation to the spiroketal also took place under these conditions. Thereafter, the carbonyl group at C_{27} needed to be reduced to the respective hydroxy function as it caused instability to the newly formed spiroketal. As a result, after

reduction with methanolic $NaBH_4$, a single epimer was observed. In summary, the C_{23}–C_{35} subunit **81** was obtained over seven steps (LLS) as a 4:1 mixture of diastereomers, in regard of the C_{27} alcohol, with an overall yield of 17% (Scheme 28).[122]

In September 2023, the group of *Krische* published a route towards the north-eastern C_{28}–C_{41} subunit **82** of neaumycin B (**3**) within eight steps (2% overall yield) starting from 2-methylpentanol (**116**) and aldehyde **110**.[133] Commencing the synthesis towards vinyl iodide **117** with lipase catalysed racemic resolution of 2-methylpentanol (**116**), enantiomerically enriching the (*R*)-isomer.[134] *Swern* oxidation gave rise to the respective volatile aldehyde which was immediately used in the *Takai* olefination[135] furnishing the desired vinyl iodide **117** (Scheme 29).[133]

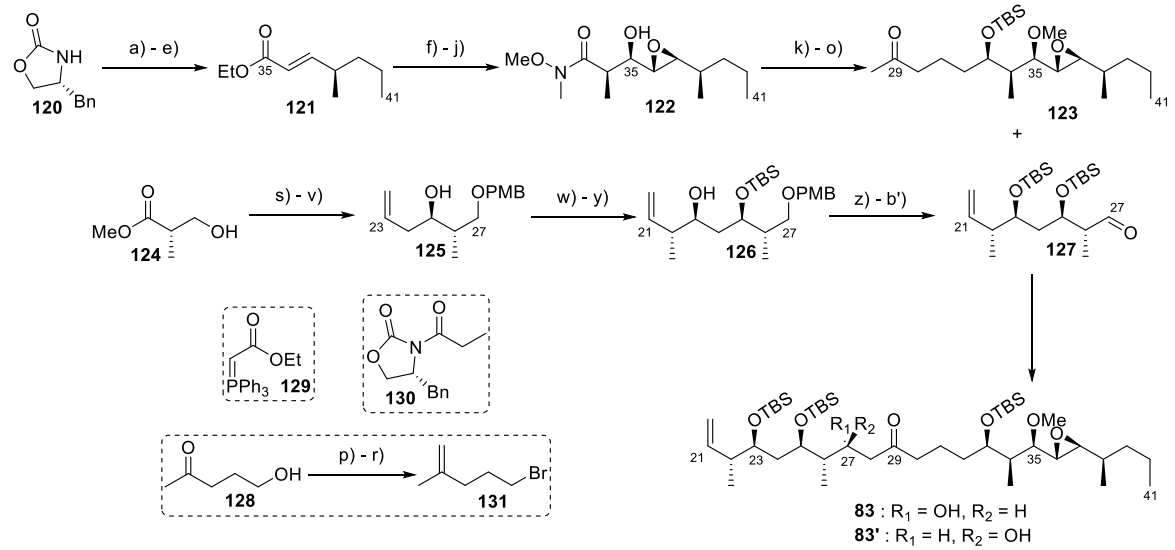


*Scheme 29: Synthesis of C_{28}-C_{41} motif **82** of neaumycin B (**3**) by Krische et al. Reaction conditions: a) H_2C=CHOAc, amano lipase, DCM, rt, **44%**; b) $(COCl)_2$, DMSO, TEA, DCM, -78 °C; c) $CrCl_3$, Zn, NaI, CHI_3, THF, rt, **27%** (two steps); d) EtCOCl, O-TMS-quinidine, $(2\text{-}Pr)_2NEt$, $LiClO_4$, DCM:Et_2O (2:1), -65 °C, **40%**; e) $LiAlH_4$, Et_2O, 0 °C, **92%**; f) TESCl, imidazole, DMF, rt, **98%**; g) $(COCl)_2$, DMSO, TEA, DCM, -78 °C to rt, **70%**; h) tBuLi, Me_2Zn, THF, -78 °C, **94%**; i) m-CPBA, MeOH, **80%**; j) NaH, MeI, DMAP, THF, rt, **80%**.[133]*

Aldehyde **118** was obtained starting with the previously described organocatalytic β-lactonisation[136] of aldehyde **110**.[122] Afterwards, the β-lactone **113** was reduced to the diol, which was protected as bis-silyl ether before *Swern* oxidation conditions[137] cleaved the primary TES group with subsequent oxidation to the desired C_{28}–C_{35} aldehyde **118**.[133] Thereafter, substrate-directed asymmetric carbonyl vinylation of vinyl iodide **117** and aldehyde **118** proofed to be difficult. *Williams'* vinyl-substituted triorganozincates, which are used for addition to α,β-stereogenic aldehydes were used as a precedent.[138] It was assumed, that under the influence of THF as a *Lewis* basic solvent the β-siloxy group would react *via Felkin-Anh* addition.[139] In fact, the desired *syn*-1,3 allylic alcohol **119** was obtained as a 12:1 mixture.[133] Subsequent to the successful coupling, the diastereoselective epoxidation of the C_{36}–C_{37} double bond was missing to complete the synthesis of compound **82** (Scheme 29).

Thus, several epoxidation protocols were tested, but all of them were lacking a satisfactory *syn* to *anti* selectivity.[140] As it was assumed that the dissatisfying selectivity of the epoxidation was caused by hydrogen bonds forming between the peracid and the hydroxy group of the allylic alcohol, the solvent was changed from DCM to methanol, improving the *syn* to *anti* ratio to 4:1 in an "*anti-Henbest*"[133] peracid epoxidation. Lastly, methylation of C_{35}-OH gave rise to the north-eastern fragment **119**.[133]

Finally, in January 2024, the group of *Lee et al.* published the synthesis towards the north-eastern C_{21}–C_{41} subunit **83**/**83'** of neaumycin B (**3**).[141] Compound **83**/**83'** was build up from the C_{21}–C_{27} fragment **127** coupled to C_{28}–C_{41} ketone **123**. To build up the C_{21}–C_{27} aldehyde, the synthesis started from (*S*)-*Roche* ester (**124**) using a well-established protocol[110,111,142] to gain the desired homoallylic alcohol **125**. Hereafter, TBS protection followed by oxidative cleavage of the terminal olefin resulted in the respective aldehyde.[141]



*Scheme 30: Synthesis of C_{21}-C_{41} motif **83/83'** of neaumycin B (**3**) by Lee et al. Reaction conditions: a) nBuLi, pentanoyl chloride, THF, -78 °C, **98%**; b) NaHMDS, MeI, THF, -78 °C, **83%**; c) $LiBH_4$, EtOH, Et_2O, -10 °C, **83%**; d) $(COCl)_2$, DMSO, TEA, DCM, -78 °C; e) **129**, DCM, reflux, **91%** (two steps); f) DIBAL-H, DCM, -78 °C, **83%**; g) DMP, $NaHCO_3$, DCM, 0 °C to rt, **84%**; h) **130**, $TiCl_4$, DIPEA, NMP, DCM, 0 °C, **85%**; i) $AlMe_3$, NH(Me)OMe*HCl, THF, -10 °C to 0 °C, **70%**; j) m-CPBA, 2,6-di-tert-butylpyridine, DCM, -20 °C; k) NaH, MeI, THF, -10 °C; l) **131**, tBuLi, THF, -78 °C, **55%** (three steps); m) (S)-CBS, BH_3*$SSMe_2$, THF, -78 °C to -40 °C, **86%**; n) TBSOTf, 2,6-lutidine, DCM, -78 °C, **82%**; o) $NaIO_4$, OsO_4, 2,6-lutidine, dioxane/H_2O (3:1), rt, **89%**; p) $MePPh_3Br$, tBuOK, THF, rt, **55%**; q) p-TsCl, TEA, DCM, 0 °C to rt, **88%** (two steps); r) LiBr, acetone, reflux; s) 4-methoxybenzyl-2,2,2-trichloroacetimidate, PPTS, DCM, 0 °C to rt, **95%** (two steps); t) $LiAlH_4$, THF, 0 °C, **71%**; u) DMP, $NaHCO_3$, DCM, 0 °C to rt, **85%**; v) $SnCl_4$, allyl-$SnBu_3$, DCM, -78 °C, **93%**; w) TBSOTf, 2,6-lutidine, DCM, -78 °C, **95%**; x) $NaIO_4$, OsO_4, 2,6-lutidine, dioxane/H_2O (3:1), rt, **81%**; y) (E)-but-2-ene, nBuLi, KotBu, (+)-$(Ipc)_2$BOMe, BF_3*OEt_2, THF, -78 °C, **71%**; z)TBSOTf, 2,6-lutidine, DCM, -78 °C, **95%** ; a') DDQ, DCM, pH 7 buffer, **81%**; b') $(COCl)_2$, DMSO, TEA, DCM, -78 °C.[141]*

The latter was then subjected to a *re*-face *anti*-selective *Brown* crotylation,[143] followed by a three step sequence to furnish olefin **126**. Starting with the silyl protection of C_{23}-OH ensued by PMB deprotection and *Swern* oxidation of the primary alcohol furnishing compound **127** in

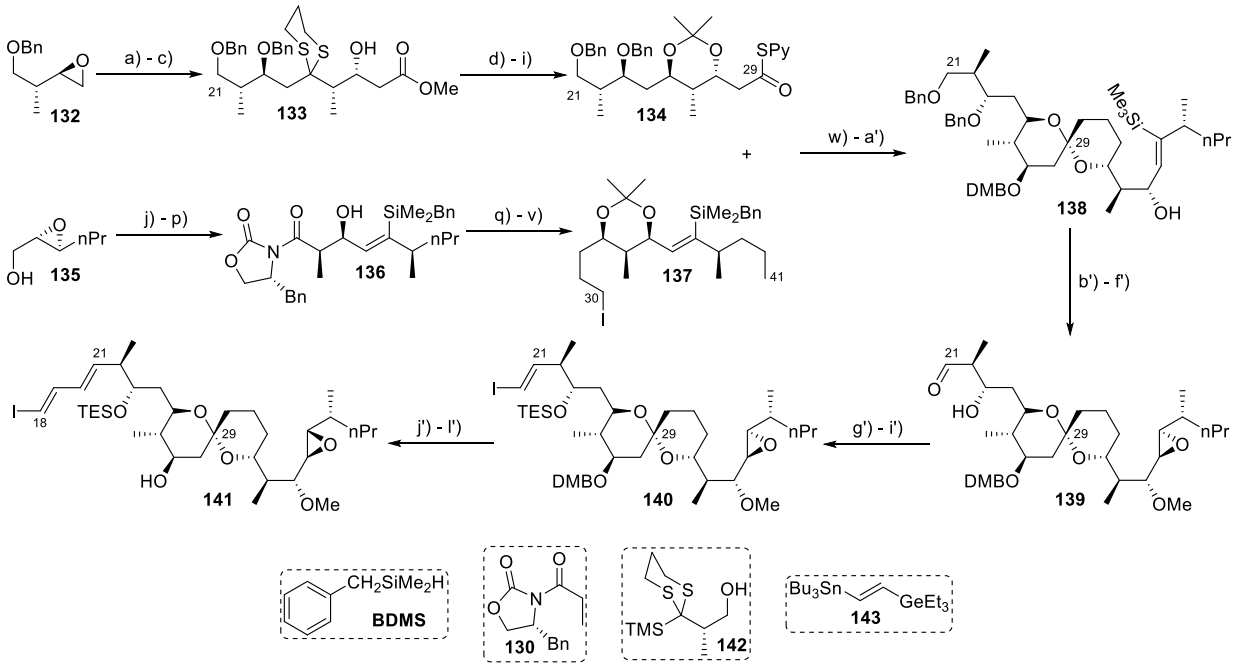
ten steps (Scheme 30).[141] Synthesis of ketone **123** started with acylation of oxazolidinone **130** with pentanoyl chloride and subsequent stereoselective alkylation. Reductive cleavage of the auxiliary yielded the primary alcohol.[141] The latter was transformed to the (*E*)-α,β-unsaturated ethyl ester **121** by *Swern* oxidation succeeded by *Wittig* olefination.[144] After that, DIBAL-H reduction followed by DMP oxidation gave rise to the respective aldehyde, which was subjected to *Evans syn*-aldol with oxazolidinone **130**.[145] Hereafter, the oxazolidinone was transformed into the *Weinreb* amide, followed by hydroxy directed epoxidation yielding compound **122**.[146] The C_{35}-OH function of epoxide **122** was methylated under standard conditions, before compound **131**[119,147] was lithiated and added to the *Weinreb* amide. The synthesis of bromide **131** started from ketone **128**, which was first transformed to the olefin in a *Wittig* reaction prior to the tosylation of the primary alcohol. Lastly, the tosylated compound was subjected to a bromination reaction yielding compound **131**. Stereoselective reduction of C_{33} was conducted by *Corey-Bakshi-Shibata* reduction[148] and the obtained hydroxy function was silyl protected. Finally, oxidative cleavage of the olefin revealed ketone **123** (Scheme 30).[141] With both fragments in hand the group of *Lee* proceeded to investigate the conditions for the envisioned acetate aldol reaction between aldehyde **127** and ketone **123** setting the (*R*) configuration at C_{27}-OH. However, due to the meanwhile published total synthesis of neaumycin B (**3**) the investigations of *Lee et al.* were concluded.[141]

2.2.2 Published Total Syntheses of Neaumycin B (3)

In August 2023, the group of *Smith* published the first total synthesis of the proposed structure of neaumycin B (**3**) (Scheme 33).[149] The 28-membered macrolactone was build up by the connection of two major fragments being the C_1–C_{17} southern hemisphere **151** and the C_{18}–C_{41} northern hemisphere **141**.[149]

The synthesis of the C_{21}–C_{29} north-western fragment **134** started with a *Brook* rearrangement/epoxide ring opening sequence[150,151] of epoxide **132** and dithiane **142**.[151] Afterwards, benzyl protection, silyl deprotection and Cu/TEMPO-catalysed oxidation were conducted yielding the aldehyde. The latter was reacted with a methyl acetate derived enolate in a *Felkin-Anh* selective aldol reaction ensued by dithioacetal hydrolysis.[152] Then, *Evans-Saksena* reduction[153] and 1,3-diol protection were followed by the saponification of the methyl ester. Finally, thioesterification furnished compound **134**.[149] Next, the north-eastern

C_{30}–C_{41} fragment was addressed, starting with regioselective ring-opening of epoxide **135** (Scheme 31).[154] Biphasic periodate cleavage and dibromo-olefination[155] resulted in the dibromo-alkene, which was treated with *n*BuLi and formaldehyde to obtain the respective propargylic alcohol. Hydroxyl-directed Ru-catalysed *trans*-hydrosilylation[156] gave rise to the primary allylic alcohol, which was subsequently oxidised with MnO_2.

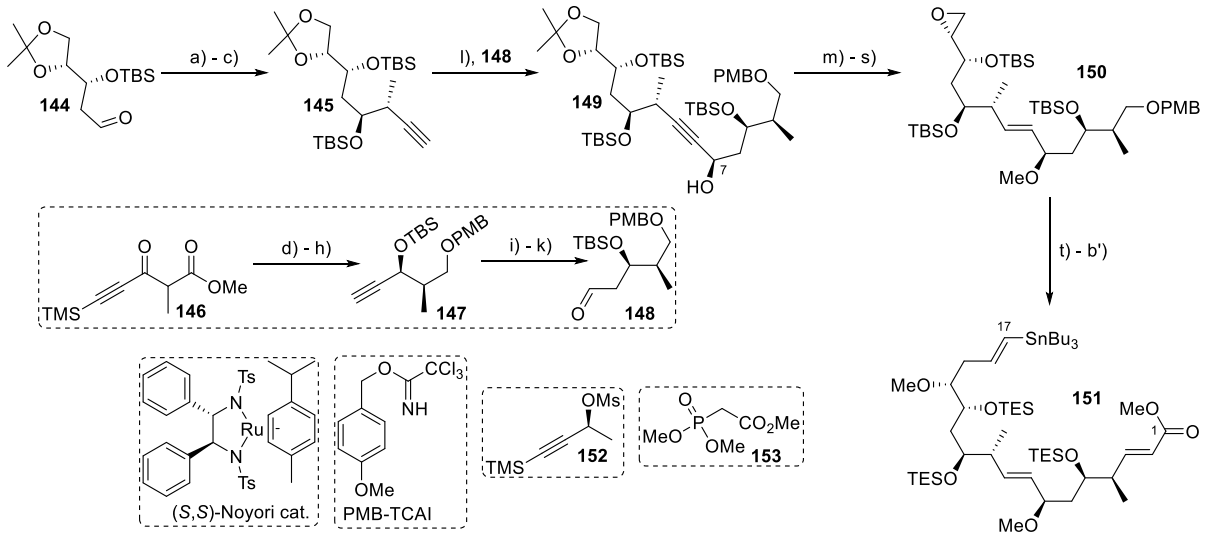


*Scheme 31: Synthesis of the C_{18}-C_{41} northern hemisphere **141** of neaumycin B (**3**) by Smith et al. Reaction conditions: a) **142**, nBuLi, Et_2O, then **132**, HMPA, -78 °C to 0 °C, **82%**; b) BnBr, KHMDS, then 1 N HCl; c) Stahl's [O], **87%** (two steps); d) acetic acid methylester, LDA, THF, -78 °C, **>95%**; e) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O; f) $NMe_4BH(OAc)_3$, **73%** (two steps); g) 2-methoxypropene, PPTS, **96%**; h) LiOH, THF/H_2O; i) $(Spy)_2$, PPh_3, **95%** (two steps); j) $AlMe_3$, **95%**; k) $NaIO_4$, Bu_4NIO_4; l) PPh_3, CBr_4, **84%** (two steps); m) nBuLi, $(CH_2O)_n$, **84%**; n) BDMS, Cp*Ru(MeCN)$_3PF_6$, **91%**; o) MnO_2, **>95%**; p) **130**, Bu_2BOTf, NEt_3, DCM, -78 °C; q) $MeNH_2OMe^+Cl^-$, $AlMe_3$, **82%** (two steps); r) allylMgBr; s) $NaBH_4$, Et_2BOMe; t) 2-methoxypropene, PPTS, **72%** (three steps); u) 9-BBN, H_2O_2; v) PPh_3, I_2, imidazole, **95%** (two steps); w) $NiBr_2$(dtbbpy), Cp_2ZrCl_2, Zn, DMI, **76%**; x) PTSA, DCM/MeOH, **67%**; y) TBAF; z) KHMDS, DMB-Br; a') MeLi, **88%** (three steps); b') TBHP, $VO(acac)_2$, **83%**; c') TBAF, **96%**; d') Ag_2O, MeI, **84%**; e') H_2, Pd/C, **62%**; f') TEMPO, PIDA; g') TESCl, NEt_3, 4-DMAP, Et_2O, **84%**; h') Bu_3SnCHI_2, $CrCl_2$, DMF; i') NIS, THF, **78%** (two steps); j') DDQ, **90%**; k') **143**, CuTC, $Pd(PPh_3)_4$, **63%**; l') NIS, **89%**.[149]*

The respective aldehyde was subjected to an *Evans* aldol[157] reaction yielding compound **136** and adjacently the auxiliary was transformed to the *Weinreb* amide. The β-hydroxy ketone was obtained after addition of allyl bromide, followed by *Narasaka-Prasad* reduction[158] and acetal protection. The north-eastern fragment **137** was furnished by hydroboration/oxidation and *Appel* reaction.[159] Thereafter, coupling of the north-western **134** and north-eastern fragment **137** was examined, leading to the use of recently developed nickel-catalysed reductive cross-coupling.[160] The obtained ketone was converted to the spiroketal by exposing it to acidic conditions.[149] Hereafter, the prepared compound was treated with a catalytic amount of TBAF ensuring the closure of C_{35}–C_{37} five-membered siloxane ring[161] before the

C_{27}-OH was DMB protected. Unmasking of C_{35}-OH to give compound **152** was achieved by treatment with methyllithium. Its directing properties were used in the following stereoselective epoxidation.[162] Silyl deprotection with TBAF,[163] methylation of C_{35}-OH and hydrogenolysis of benzyl ethers yielded the respective diol. The (*E*)-olefin clasping C_{20}–C_{41} was obtained after oxidation of the primary alcohol at C_{21} to the aldehyde **139**. After TES protection the *Takai-Utimoto*[164] was conducted obtaining (*E*)-selective vinyl-stannane, which was transformed to the respective iodide **140**. PMB deprotection was followed by *Stille* cross-coupling[165] between the prepared iodide **140** and germylstannane **143**.[165,166] The observed dienyl germane was transformed to the desired vinyl iodide **141** by treatment with *N*-iodosuccinimide (Scheme 31).

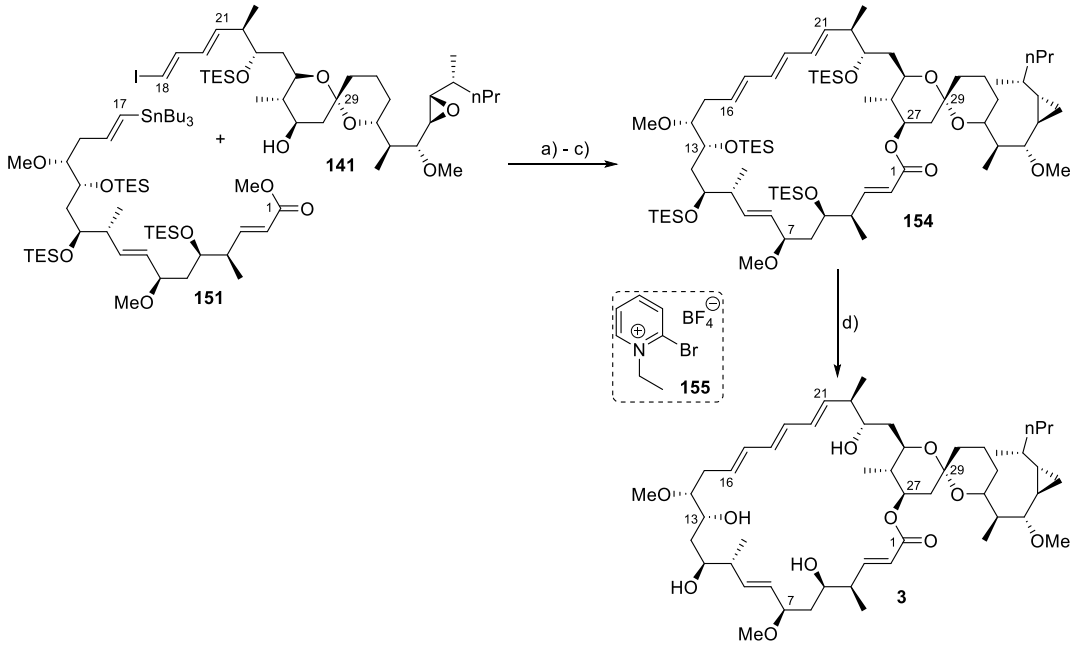
Subsequently, the south-western fragment **145** was approached by starting from the known aldehyde **144**[167] subjected to *Marshall* asymmetric propargylation.[168] After treatment with TBAF the respective diol was observed. This was then silyl protected to furnish compound **145** (Scheme 32).[149]



*Scheme 32: Synthesis of the C_1-C_{17} southern fragment **151** of neaumycin B (**3**) by Smith et al. Reaction conditions: a) **152**, $Pd(OAc)_2$, PPh_3, $ZnEt_2$; THF, -20 °C; b) TBAF, **71%** (two steps); c) TBSOTf, **93%**; d) (S,S)-Noyori cat., HCO_2H:NEt_3 (5:2), DCM, rt, **83%**; e) TBSCl; f) DIBAl-H, **80%** (two steps); g) PMB-TCAI, CSA, DCM; h) K_2CO_3, MeOH, **80%** (two steps); i) H_2, Lindlar cat.; j) 9-BBN, H_2O_2, **72%** (two steps); k) Stahl's [O], **87%**; l) (+)-N-methylephedrine, $Zn(OTf)_2$, Et_3N, PhMe, rt, **90%**; m) $[Cp^*RuCl]_4$, Bu_3SnH, DCM, **72%**; n) $Bu_4N^+Ph_2PO_2^-$, CuTC, DMF, **99%**; o) $Me_3O^+BF_4^-$, proton sponge, **87%**; p) TFA, DCM, 0 °C, **87%**; q) TsCl, NEt_3, nBu_2SnO; r) NaH, THF, rt; s) TBSCl, imidazole, DCM, **92%** (three steps); t) TMS acetylene, nBuLi, BF_3*OEt_2, THF, -78 °C, **97%**; u) $Me_3O^+BF_4^-$, **90%**; v) TBAF, THF; w) Et_3SiCl, **90%** (two steps); x) DDQ; y) DMP; z) **153**, LiCl, iPrNEt, ACN, **71%** (three steps); a') NBS, AgOAc; b') $Pd(PPh_3)_4$, Bu_3SnH, **87%**.[149]*

To synthesise the south-eastern fragment **148**, β-keto ester **146** was conducted to *Noyoris'* catalytic asymmetric dynamic kinetic resolution[169] to obtain the respective alcohol. TBS-protection was followed by DIBAL-H reduction of the ester and PMB-protection of the primary

alcohol. Exposure of the compound to mild basic conditions yielded the TMS-deprotected alkyne **147**.[149] Reduction of the terminal olefine ensued by hydroboration/oxidation and Cu/TEMPO catalysed oxidation[170] furnished compound **148**.[149] Aldehyde **148** and alkyne **145** were coupled in a *Carreira* asymmetric alkynylation[171] succeeded by *trans*-reduction of the triple bond using a ruthenium-catalysed hydrostannation/destannation procedure.[172] Methylation of the alcohol **149** was conducted before treatment with TBAF produced the respective triol. After that, selective tosylation of the primary hydroxy group and epoxide ring closure were followed by silyl protection of the remaining hydroxy groups yielding compound **150** (Scheme 32). Opening of the installed epoxide was conducted by subjecting it to BF_3-assisted nucleophilic ring opening with lithium trimethylsilyl (TMS) acetylide.[149] Methylation of C_{14}-OH was ensued by global removal of the silyl groups with TBAF and reprotection of the latter as TES ethers. Afterwards, the PMB group was removed and the corresponding alcohol was oxidised using DMP[173], which was succeeded by HWE olefination.[174] Lastly, bromination of the alkyne function and hydrostannation[175] furnished vinyl stannane **151**.[149]

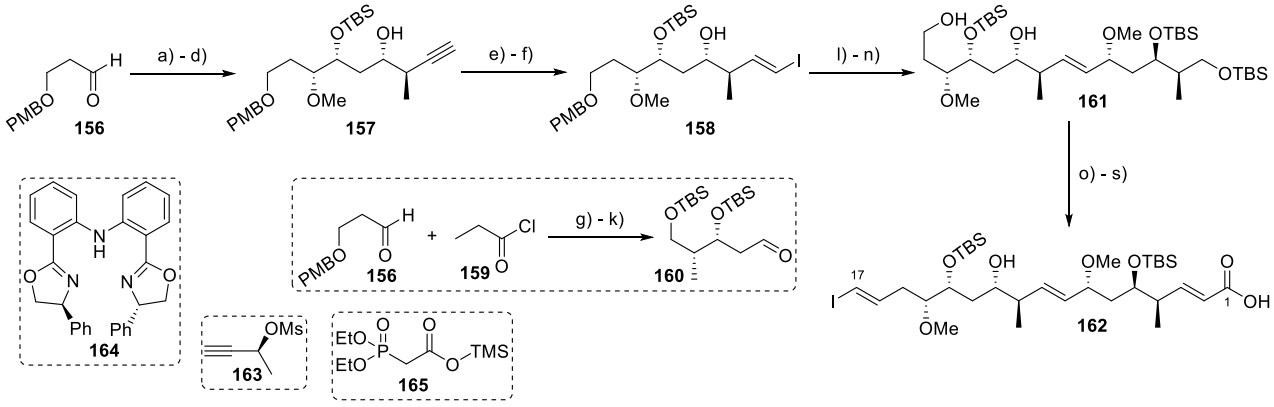


*Scheme 33: Synthesis of the proposed structure of neaumycin B (**3**) by Smith et al. Reaction conditions: a) $Pd_2(dba)_3$, $AsPh_3$, $Bu_4N^+Ph_2PO_2^-$, DMF, rt, **89%**; b) Me_3SnOH, **86%**; c) **155**, DCM, $NaHCO_3$, rt, **80%**; d) TBAF, HOAc, **80-90%**.[149]*

Having the northern **141** (Scheme 31) and southern hemisphere **151** (Scheme 32) prepared the coupling first proceeded *via* a *Stille* reaction[176], successfully creating the (*E,E,E*)-1,3,5-triene. Afterwards, hydrolysis of the methyl ester[177] followed by *Mukaiyama* macrolactonisation[178] furnished the 28-membered macrolactone. Lastly, global deprotection

was carried out under mild conditions revealing neaumycin B (**3**) with its proposed stereochemistry (Scheme 33).[89,149] Upon comparison of the ^{1}H-NMR data of the isolated neaumycin B (**3**) and the synthesised structure **3** by *Smith et al.*, deviations between the two compounds were discovered.[89,149] Additionally, no activity against human glioblastoma cells of the synthetic compound **3** was detected.[149]

In October 2023, *Zhang et al.* published their successful total synthesis of neaumycin B (**3**).[179] The group planned to build up the 28-membered macrolactone from the C_1–C_{17} western fragment **162** (Scheme 34) and the C_{18}–C_{41} eastern fragment **173** (Scheme 35) using *Yamaguchi* conditions for the esterification of C_1 and C_{27}-OH and a *Suzuki* coupling[180–183] furnishing the (*E,E,E*)-1,3,5-triene to close the macrolactone.

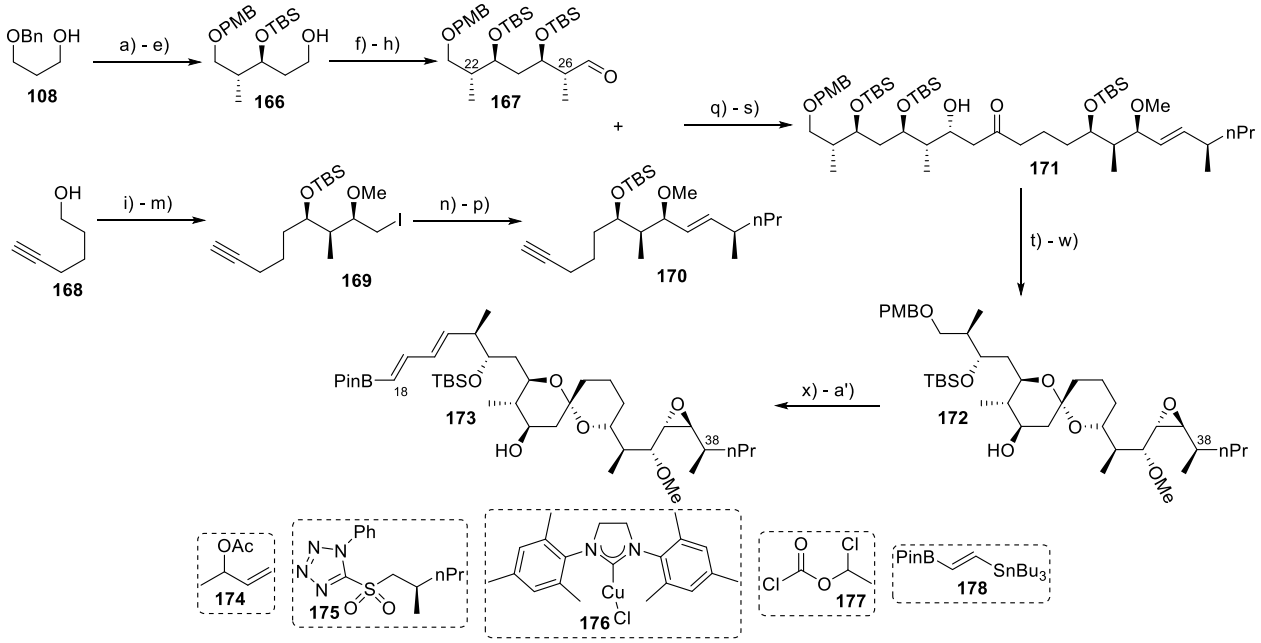


*Scheme 34: Synthesis of the C_1-C_{17} fragment **162** of neaumycin B (**3**) by Zhang et al. Reaction conditions: a) (S)-VAPhos-NEt$_2$, Ni(COD)$_2$, BEt$_3$, (Z)-silyloxidiene, toluene, **67%**; b) Me$_3$O$^+$BF$_4^-$, proton sponge, DCM, 0 °C, **89%**; c) O$_3$, DCM, -78 °C, **76%**; d) **163**, Pd(dppf)Cl$_2$, PPh$_3$, InI, THF/HMPA, 0 °C, **85%**; e) TBSOTf, 2,6-lutidine, DCM, 0 °C, **88%**; f) Cp$_2$ZrHCl, then I$_2$, THF, 0 °C to rt, **84%**; g) LiClO$_4$, DIPEA, O-TMS-quinidine, Et$_2$O/DCM, -78 °C, **53%**; h) LiAlH$_4$, THF; i) TBSOTf, 2,6-lutidine, DCM, **71%** (two steps); j) DDQ, DCM/buffer; k) DMP, NaHCO$_3$, DCM, **68%** (two steps); l) **164**, CrCl$_2$, NiCl$_2$, DMSO, 0 °C, **65%**; m) Me$_3$O$^+$BF$_4^-$, proton sponge, DCM, 0 °C, **94%**; n) DDQ, DCM/buffer, 0 °C, **78%**; o) DMP, NaHCO$_3$, DCM, **90%**; p) CrCl$_2$, CHI$_3$, 1,4-dioxane/THF, 0 °C, **80%**; q) CSA, MeOH/DCM, -30 °C; r) DMP, NaHCO$_3$, DCM; s) **165**, nBuLi, THF, -78 °C to 40 °C, **44%** (three steps).[179]*

As the first step of the shown synthetic approach towards C_1–C_{17} western fragment **162** a nickel-catalysed vicinal diol formation following the protocol by *Fürstner*[184] was conducted with aldehyde **156** and (*Z*)-silyloxydiene. Afterwards, methylation of the C_{14}-OH group was achieved using *Meerwein's* salt[185] succeeded by oxidative cleavage, yielding the respective aldehyde, which was utilised in a *Marshall* propargylation with **163** to yield compound **157**.[186] After protecting C_{11}-OH as silyl ether the alkyne was transformed into vinyl iodide **158** by hydrozirconation with the *Schwartz'* reagent[187] and subsequent iodination.

To follow the envisioned route of building up western fragment **173** from vinyl iodide **158** and aldehyde **160** *via* NHK, the synthesis of aldehyde **160** remained to be performed. Starting from

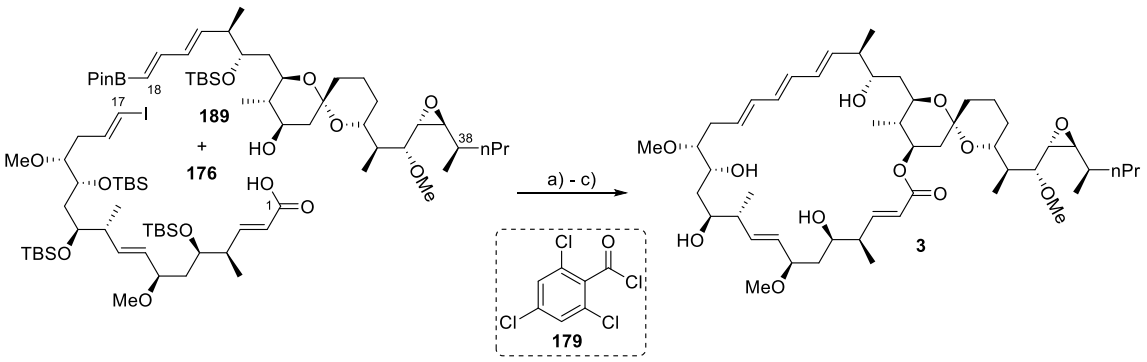
propionyl chloride (**159**) and aldehyde **156** a base-catalysed asymmetric ketene [2 + 2] cycloaddition[95,122,136] was executed ensued by β-lactone reduction and silyl protection of the diol. Thereafter, the primary PMB-group was removed and the alcohol oxidised to obtain the desired aldehyde **160** (Scheme 34).[179] The *Nozaki-Hiyama-Kishi*[188] coupling was carried out implementing the best conditions identified through a thorough screening progress. Subsequently, C_7-OH was methylated and the primary PMB-group removed acquiring compound **161**. Subsequent DMP oxidation of the alcohol to the respective aldehyde was followed by a HWE olefination with phosphonate **165** to complete compound **162**.



*Scheme 35: Synthesis of the C_{18}-C_{41} fragment **173** of neaumycin B (**3**) by Zhang et al. Reaction conditions: a) **174**, K_3PO_4, (R)-SEGPHOS-Ir, THF/H_2O, 70 °C, **82%**; b) TBSCl, imidazole, DCM, **90%**; c) O_3, DCM/MeOH, -78 °C, $NaBH_4$, rt, **70%**; d) PMBCAT, CSA, DCM, **75%**; e) 10% Pd/C, 1-methylcyclohexa-1,3-diene, 2,6-lutidine, MeOH, 50 °C, **80%**; f) **174**, K_3PO_4, (S)-SEGPHOS-Ir, THF/H_2O, 70 °C, **78%**; g) TBSCl, imidazole, DCM, **90%**; h) O_3, then PPh_3, DCM, -78 °C, **56%**; i) DMP, $NaHCO_3$, DCM, **84%** crude; j) $(-)$-$(Ipc)_2BOMe$, tBuOK, BF_3*OEt_2, nBuLi, cis-2-butene, THF, -78 °C, **76%**; k) MOMCl, DIPEA, DCM, **72%**; l) IBr, -80 °C, toluene, then DIPA, H_2O, rt; m) TBSOTf, 2,6-lutidine, DCM, **56%**; n) AIBN, nBu_3SnH, hv, O_2, toluene, then $NaBH_4$, EtOH, **65%**; o) DMP, $NaHCO_3$, DCM, **73%**; p) **175**, KHMDS, DME, -78 °C, **69%**; q) nBuLi, THF, -78 °C, **51%**; r) **176**, MesCuCl, $B_2(pin)_2$, NaOtBu, $P(Cy)_3$, MeOH/THF, 0 °C; s) $NaBO_3$*$4H_2O$, THF/H_2O, 0 °C to rt, **81%** (two steps); t) BzOTf, pyridine, DCM, -78 °C, **77%**; u) **177**, MeOH/DCM, rt, then TBSOTf, 2,6-lutidine, DCM, -78 °C, **70%**; v) K_2CO_3, MeOH, **91%**; w) CF_3CO_3H, Na_2HPO_4, DCE/THF, -10 °C to 0 °C, **53%**; x) DMDO, acetone, **88%**; y) NaClO, KBr, TEMPO, DCM/$NaHCO_3$, **89%**; z $CrCl_2$, CHI_3, THF, -10 °C to 0 °C, **71%**; a') **178**, $Pd(CH_3CN)Cl_2$, DMF, 35 °C, **87%**.[179]*

The synthesis of the C_{18}–C_{41} eastern fragment **173** started from 1,3-propanediolmonobenzylether (**108**) converting it to its branched homoallylic alcohol *via Krische's* (*R*)-SEGPHOS-modified iridium catalysed crotylation with but-3-en-2-yl acetate (**174**).[189–196] Silyl protection was succeeded by a reductive ozonolysis yielding the respective primary alcohol, which was PMB protected. After that, the benzyl group was cleaved hydrogenolytically and the primary alcohol converted in another *Krische* transfer

hydrogenative crotylation using the (*S*)-enantiomer of the SEGPHOS ligand in this case.[189–196] The obtained homoallylic alcohol was converted into the desired aldehyde **167** *via* silyl protection ensued by oxidative cleavage of the olefin (Scheme 35). Alkyne **170** was synthesised from commercially available 5-hexyn-1-ol (**168**) by oxidation of the latter to the aldehyde which was conducted to *Brown's* assymmetric butene-mediated crotylation.[197,198] The observed branched homoallylic alcohol was MOM-protected before it underwent electrophilic activation with iodmonobromide, initiating *Taylor's* ether transfer process.[199] Subsequently, C_{33}-OH was silyl protected and the iodine exchanged for a hydroxy group,[200] which was then oxidised to the respective aldehyde. Then, the latter was subjected to a *Julia-Kocienski* olefination[201] with compound **175** completing the synthesis of alkyne **170**. Coupling of aldehyde **167** and alkyne **170** was pursued leading to the internal alkynyl product. To allow for the installation of the spiroketal *via* acid-catalysed [6,6]-spiroketalization of the respective ketone,[202] the coupling product was further elaborated. First, the alkynyl compound was subjected to a borylcupration[203] to obtain the respective vinyl boronate (Scheme 35). Then, the latter was oxidised to the ketone and the free hydroxy group at C_{27} was protected as benzyl ether. To transform the linear precursor **171** to the desired spiroketal, it was treated with 1-chloroethyl chloroformat (**177**), which ensured the required acidic conditions by *in situ* formation of HCl.[204] Thereafter, silyl protection of C_{23}-OH and debenzoylation were succeeded by epoxidation to compound **172** using CF_3CO_3H.[205] The latter was then conducted to a four-step reaction sequence, completing the synthesis of boronate **173**. PMB deprotection of compound **172** was succeeded by *Anelli* oxidation[206] yielding the respective aldehyde which was subjected to a *Takai-Utimoto* olefination obtaining the vinyl iodide. Finally, the latter was transformed to boronate **173** in a *Stille* coupling with compound **178**.



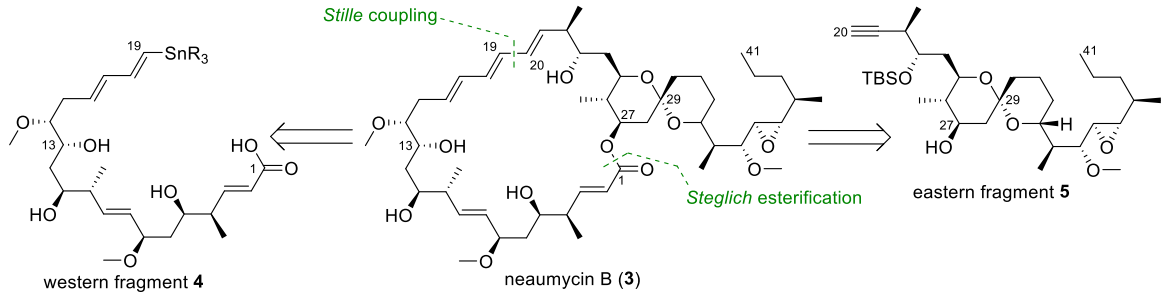
*Scheme 36: Synthesis of neaumycin B (**3**) by Zhang et al. Reaction conditions: a) DMAP, NEt_3, **179**, toluene, rt to -20 °C, **68%**; b) Tl_2CO_3, $Pd(PPh_3)_4$, THF/H_2O, **44%**; c) 3HF*NEt_3, NEt_3, MeCN, **35%**.[179]*

Having synthesised the eastern **173** (Scheme 35) and the western fragment **162** (Scheme 34), the synthesis proceeded towards the final steps. First, a *Yamaguchi* esterification[207] was performed linking the eastern **173** and western fragment **162**. Afterwards, the macrolactone was closed in a *Suzuki* coupling[180–183] leaving a global deprotection under mild conditions as the last step revealing neaumycin B (**3**) (Scheme 36). In summary, the group of *Zhang* synthesised neaumycin B (**3**) in a LLS of 22 steps obtaining the same ^{1}H-NMR data as *Smith et al.* The deviations between the data for the isolated neaumycin B (**3**) and synthesised neaumycin B (**3**) have been analysed, suggesting a wrong stereochemical assignment in the areas of bigger discrepancies.[179]

2.3 Aims of this Study

2.3.1 Synthesis of the Eastern Fragment 5 of Neaumycin B (3)

The aim of this study was to develop a total synthesis towards the structure of neaumycin B (**3**) proposed by *Jensen* and *Fenical et al*.[89] Therefore, a retrosynthetic analysis of compound **3** was conducted splitting the 28-membered macrocyclic structure into two substructures. The western and eastern fragments **4** and **5** thus obtained are to be connected *via* a *Stille* coupling between C_{19} and C_{20}, as well as a *Steglich* esterification between C_{27}-OH and the C_1-carboxylic acid (Scheme 37).



*Scheme 37: Retrosynthetic analysis of the proposed structure of neaumycin B (**3**).*

Herein, the focus was on synthesising the eastern fragment **5**, while at the same time the synthesis of the western fragment **4** was handled by *R. Wagner*.

2.3.2 Structural Revision of Neaumycin

As described in chapter 2.2, fragment syntheses and two independent total syntheses were published by other groups during our work on the total synthesis presented in this study. Based on the results of *Smith*[149] and *Zhang*[179] it became apparent, that the proposed structure[89] of neaumycin B (**3**, Scheme 37) does not represent the correct stereochemistry of the isolated natural product. Deviations in the NMR data of the natural product and the synthetic compounds,[179] as well as no activity of the synthetic neaumycin against glioblastoma cells[149] were observed. Therefore, a new bioinformatic analysis of the gene cluster responsible for the biosynthesis of neaumycin B (**3**) was performed by *M. Adamek* (*Ziemert* group, University of Tübingen). The results thereof are presented in Figure 15.

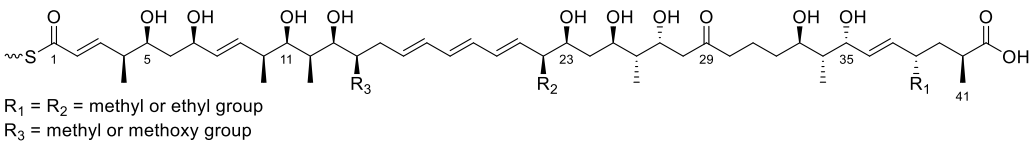


Figure 15: Resulting linear structure of the new bioinformatic analysis of the gene cluster of neaumycin by M. Adamek.

On the account of these results a revised structure of the eastern fragment of neaumycin B (**180**) was proposed (Figure 16).

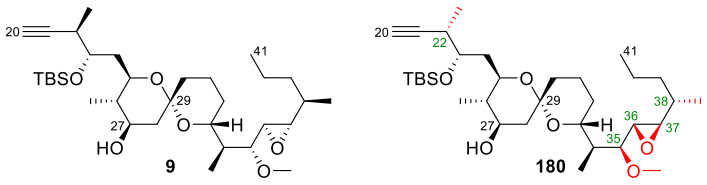


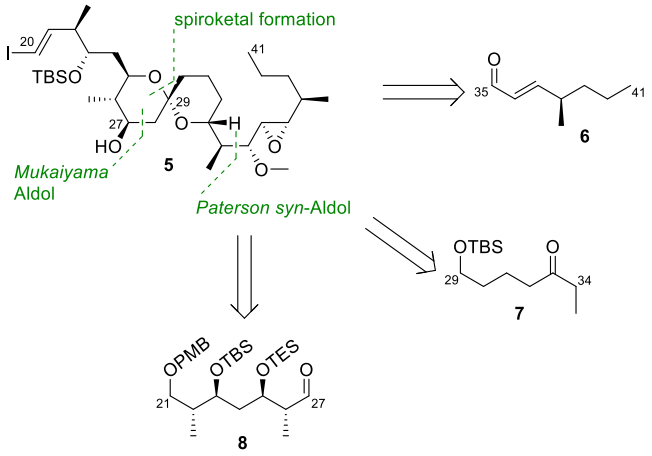
*Figure 16: Comparison of the proposed stereochemistry of the eastern fragment of neaumycin B (**9**) and the revised stereochemistry of the eastern fragment of neaumycin B (**180**).*

Thus, the fragments representing the revised stereochemistry by *Adamek* should be synthesised to allow for a NMR comparison with the data of the natural product.

2.4 Results and Discussion

2.4.1 First Retrosynthetic Analysis (Aldol Approach) of the originally proposed structure

Based on the retrosynthesis of neaumycin B (**3**) presented in Scheme 38, the eastern moiety **5** will be further disassembled into the smaller fragments **6**, **7** and **8**. Besides the syntheses thereof key steps of the assembly of eastern fragment **5** were planned to be a *Paterson syn*-aldol reaction between aldehyde **6** and ketone **7**, as well as a *Mukaiyama* aldol reaction establishing the connection of C_{27} and C_{28}. Then, the prepared linear precursor was meant to undergo a spiroketal formation yielding the scaffold of vinyl iodide **5**.



*Scheme 38: Retrosynthetic analysis of the eastern fragment **5** of the proposed structure of neaumycin B (**3**).*

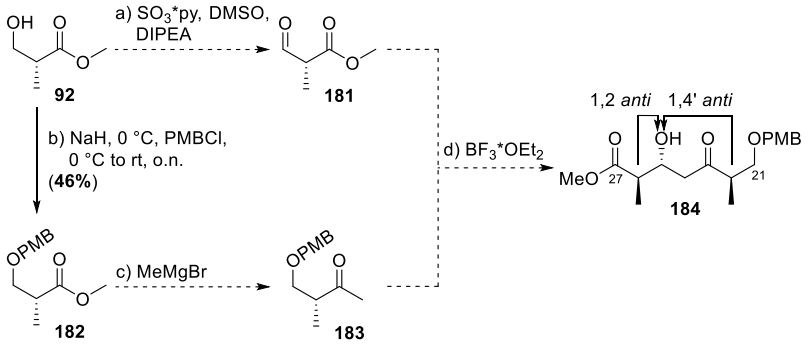
2.4.2 Fragment Syntheses of the Proposed Structure of Neaumycin B (3)

In the following, the established synthetic routes towards the presented fragments (Scheme 38) will be discussed.

2.4.2.1 Synthesis of Aldehyde 8

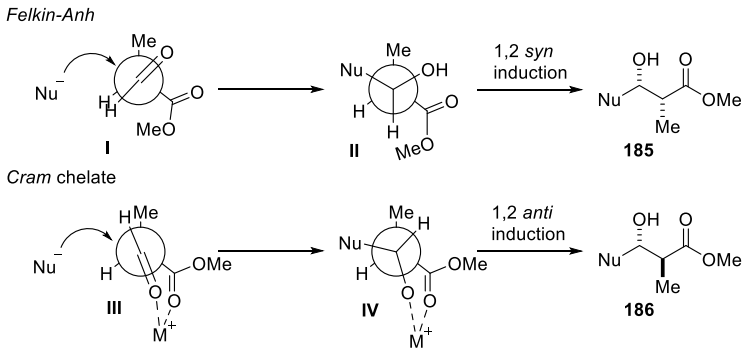
Commencing with the first synthetic approach towards the C_{21}-C_{27} fragment **8**, a modular route was chosen relying on a *Mukaiyama* aldol reaction as the key step. Both required reactants, aldehyde **181** and ketone **183**, were planned to be obtained from (*S*)-*Roche* ester (**92**). Researching conditions for the planned *Mukaiyama* aldol led to the dissertation of *M. Dieckmann,* who performed extensive studies on aldol systems containing one component obtained from one of the *Roche* esters.[208] In the course of these extensive experiments, low yields with bad diastereoselectivities were achieved. Furthermore, only limited reproducibility of the yield and stereoselectivity was found. It was also stated, that the obtained mixtures of diastereomers were only seperable by HPLC in a few cases. Otherwise, the diastereomers

were impossible to separate.[208] A possible explanation for the low yield might be the instability of the TMS silyl enol ether obtained from PMB-protected methyl ketone **183** (Scheme 39). Changing the aldehyde and ketone functionalities between the fragments might be an option to overcome the observed instability issues. Unfortunately, in this case that strategy would not work as both fragments are derived from (*R*)-*Roche* ester (**92**).



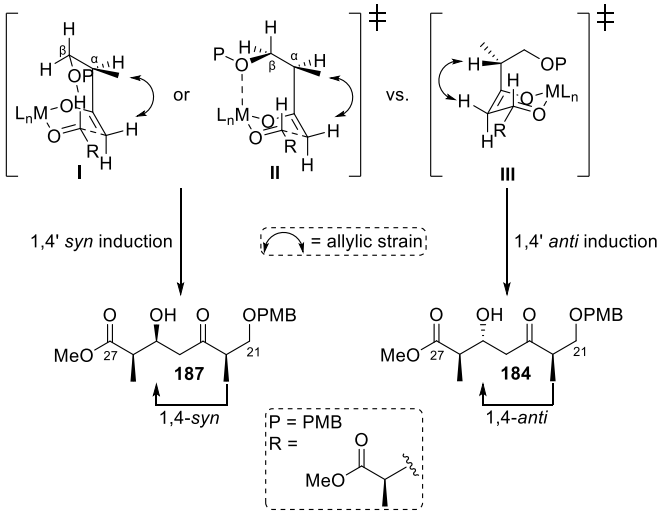
*Scheme 39: Modular approach towards aldol fragment **184**.*

Regarding the stereochemistry a 1,2 *anti* as well as a 1,4' *anti* induction are needed to obtain the desired aldol product **184** from aldehyde **180** and ketone **183** (Scheme 39). The desired 1,2 *anti*-induction of the α-chiral aldehyde **180** would correspond to the *anti-Felkin* or *Cram* chelate product (Scheme 40). In most cases the *Felkin-Anh* induction of an α-chiral aldehyde is weak and could therefore be overruled if the 1,4' *anti* induction is strong. As part of the total synthesis of caliculin, *Evans* found a preferred 1,2 *anti* induction using a similar system.[209] But, while studying chiral aldehydes in a *Mukaiyama* aldol reactions, a 1,2-*syn* induction was found by *Evans et al.* using a benzyl protected *Roche* ester derived aldehyde.[210,211] Additionally, a 1,2 *anti* induction can be observed in aldol reactions utilising Li bases or $TiCl_4$ in combination with a PMB-protecting group.[210,211] On the basis of these conflicting results, a final prediction of stereo induction did not seem reliable.



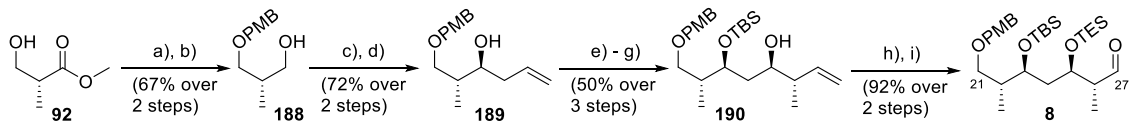
*Scheme 40: Schematic depiction of the Felkin-Anh transition state (**I**) leading to a 1,2 syn induction (**II** and **185**) as well as the Cram chelate transition state (**III**) leading to a 1,2 anti induction (**IV** and **186**) during a Mukaiyama aldol addition.[208,209]*

Additionally in this case, a 1,4' *anti* induction is desired as opposed to the study of *Dieckmann,* who observed a preference towards the 1,4' *syn* stereoinduction using either PMB-protected *Roche* ester derived methyl ketone or the TBS-protected derivative.[208] As the methyl ketone **183** carries a PMB-group in β-position, which is known to coordinate metals, the reaction would most likely proceed *via* TS **I** or **II** which both lead to a 1,4' *syn* induction according to the model of *Paterson* and *Paton* (Scheme 41).[212,213] If there is no β-chiral center in the methyl ketone, within this model the TS is either stabilised *via* a hydrogen bond between the coordinating β-substituent and the aldehyde hydrogen (TS **I**) or *via* the coordination of the latter to the metal center (TS **II**). Additionally, the allylic strain of the α-methyl chiral center stabilises the preferred conformation of the TS.[212,213] The preference for a 1,4' *syn* induction could theoretically be overruled if a bulky, non-coordinating protecting group is used for the β-alkoxy substituent of the methyl ketone (TS **III**).[214,215] In this case, an open transition state **III** would minimise the allylic strain leading to the 1,4' *anti* product **184**. However, during *Dieckmann's* studies a contradictory 1,4' *syn* induction was found, even with the non-coordinating TBS protecting group.[208,216]



*Scheme 41: Explanation of a 1,4' syn induction during a Mukaiyama aldol reaction via closed transition state **I** or **II** explained by the model of Paterson and Paton[212,217] versus a 1,4' anti induction during a Mukaiyama aldol via an open transition state **III**.[214,215]*

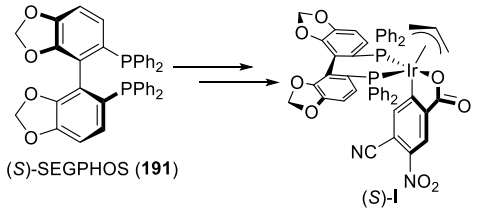
Overall, the results of these studies argue for a difficult prediction of stereoinduction combined with low yields. Therefore, a new synthetic route towards compound **8** was developed. Herein, the synthesis was planned to be linear instead of modular, still starting from (*R*)-*Roche* ester (**92**) but relying on iterative allylation and crotylation reactions rather than aldol chemistry (Scheme 42).



*Scheme 42: Revised linear approach towards the aldehyde fragment **8**. Reaction conditions: a) PMBOC(NH)CCl$_3$, CSA, DCM, rt, 19 h, **74%**; b) DIBAL-H, THF, -78 °C to rt, 1 h, **90%**; c) SO$_3$*py, DMSO, DIPEA, DCM, 0 °C, 1 h, **quant**; d) (-)-(Ipc)$_2$BOMe, allylMgBr, Et$_2$O, 0 °C to rt, 1 h, then aldehyde, -78 °C, 1.5 h, **72%**, dr 20:1; e) TBSCl, imidazole, DCM, rt, 75 min, **quant**; f) O$_3$, DCM/MeOH (14:1), Sudan III (0.1% solution in DCM), PPh$_3$, rt, 3 h, **98%**; g) KO^{t}Bu, trans-2-butene, n-BuLi, THF, -78 °C, 30 min, then warm to -45 °C, 10 min, then cool to -78 °C, (-)-(Ipc)$_2$BOMe, THF, 2 h, BF$_3$*OEt$_2$, aldehyde, THF, 5 h, **51%**, dr 20:1; h) TESCl, imidazole, DCM, rt, 75 min, **95%**; i) OsO$_4$, NMO*H$_2$O, acetone/H$_2$O, rt, 42 h, then Pb(OAc)$_4$, toluene, rt, 1 h, **97%**.*

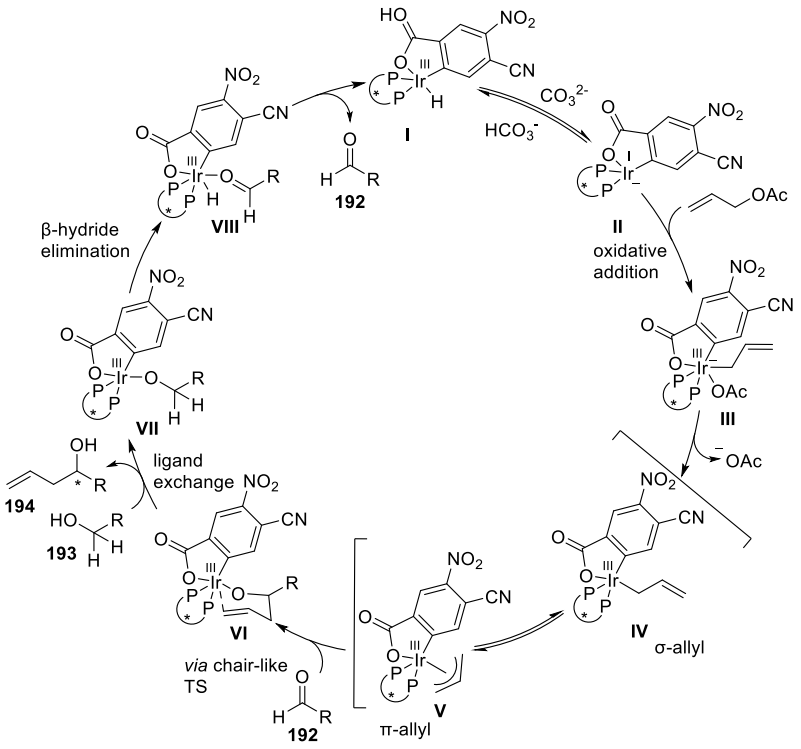
Firstly, (*R*)-*Roche* ester (**92**) was protected as a PMB-ether using PMB-acetimidate and CSA rather than PMB chloride and sodium hydride. Change of the reagents facilitated the purification of the obtained PMB-ether and raised the yield of the reaction from 46% (Scheme 39) to 74% (Scheme 42). Thereafter, the ester was reduced to the primary alcohol **188** (DIBAL-H, 90%), which was first tried to be converted to compound **189** in a *Krische* allylation.[127,218] The reaction proceeded with a yield of 65% but a diastereomeric ratio of only 1.4:1.

In general, the *Krische* allylation is a stereoselective, catalytic transfer hydrogenative carbonyl allylation, which does not require the previous formation of organometallic reagents. The required iridium catalyst can be obtained from [Ir(cod)Cl]$_2$, a chiral triarylphosphine ligand like (*S*)-SEGPHOS (**191**), additives like Cs$_2$CO$_3$ and substituted nitrobenzoic acid. It is either formed *in situ* like (*S*)-**I** (Scheme 43) or it can be prepared, isolated and stored.[218]



*Scheme 43: In situ preparation of (S)-**I** from (S)-SEGPHOS (**191**).[218]*

By using different non-metallic allyl donors various structural motifs can be accessed *via* the *Krische* allylation. All accessible products contain a chiral homoallylic alcohol as common structural moiety, which will be obtained following the schematic catalytic cycle of the *Krische* allylation shown in Scheme 44.[127]



Scheme 44: Schematic depiction of the mechanism of the Krische allylation.[127]

In the presence of Cs_2CO_3 the initial *ortho*-cyclometalated Ir (III) complex **I** is in equilibrium with the anionic Ir (I) complex **II**. The anionic complex **II** is stabilised by the electron withdrawing effect of the *ortho*-carboxy and *para*-nitro groups of the benzoate, therefore facilitating the deprotonation of complex **I** to **II**. Thereafter, the oxidative addition of allyl acetate to **II** yields the anionic Ir (III) complex **III** which then forms the neutral σ-allyl complex **IV** by expulsion of acetate. Complex **IV** quickly equilibrates with the π-allyl haptomer **V**. Generally, allylation reactions proceeding *via* a chair-like *Zimmermann-Traxler* transition state belong to the type I allylation reactions. In contrast to this, type II allylation reactions proceed through an open transition state.[219,220] Herein, the allyl transfer takes place through a closed *Zimmermann-Traxler* transition state (Scheme 44), yielding homoallyl iridium alkoxid **VI**.[219,220] Since, the free coordination side of the iridium (III) complex **VI** is taken by the terminal olefin of the homoallylic alcohol a β-hydride elimination is prevented. Therefore, the conformational stability of the homoallylic alcohol is ensured. A ligand exchange between the formed homoallylic alcohol **194** and substrate alcohol **193** frees a coordination side of the iridium (III) complex **VII**. Hence, in this case a β-hydride elimination is possible, which leads to complex **VIII**. Lastly, the aldehyde **192**, formed in this way, dissociates regenerating the *ortho*-cyclometalated Ir (III) complex **I** and closing the catalytic cycle.

Due to the specifics of the reaction mechanism of the *Krische* allylation, both the alcohol and the aldehyde are suitable substrates. If instead of the alcohol the aldehyde is used as starting material, isopropanol is added as a hydrogen donor. Thus, the formation of complexes **VIII** and **I** is facilitated.[218] The stereochemical course of the *Krische* allylation can be explained by the coordination mode of the six-membered closed transition state between σ-allyl haptomer **IV** and complex **VI**. The sterically less demanding allyl is located between the sterically demanding chiral aromatic and the phenyl moieties of the ligand. If the aldehyde faces towards the front, it resides in a more open environment and the aldehyde C-H bond can interact with the phenyl ring, leading to weak CH-π interactions (Figure 17, **A**).

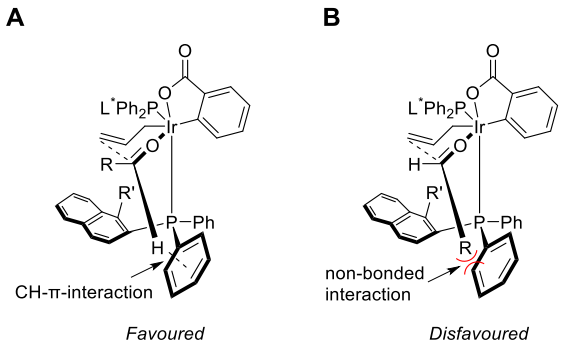
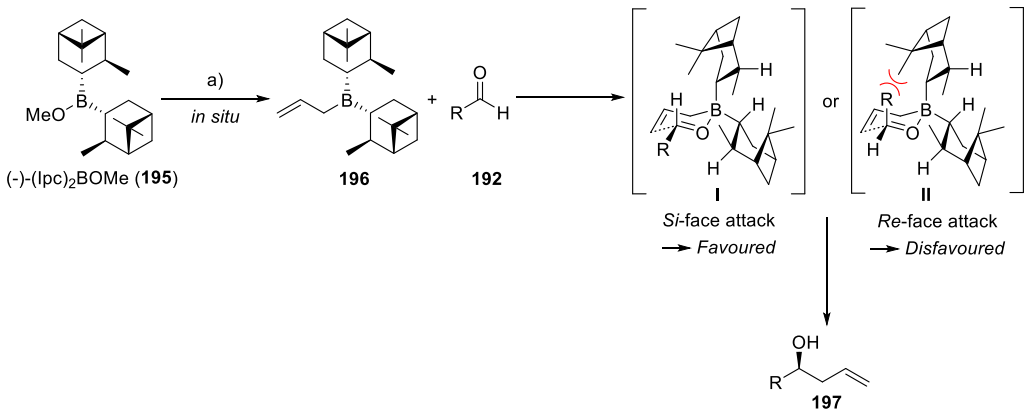


Figure 17: Explanation of the stereochemical course of the Krische allylation by the coordination mode of the six-membered closed transition state. ***A****: aldehyde establishes weak CH-π interactions.* ***B****: steric clash between aldehyde residue and phenyl ring.*[127]

If the aldehyde is aligned in the other possible way, there is steric clash between the aldehyde residue and the phenyl ring. As a result, the other possible binding mode is barely present, leading to a high stereoselectivity of the reaction (Figure 17, **B**).[127] Generally speaking, the possibility of either using the alcohol or the aldehyde as a substrate is an advantage of the *Krische* allylation over the otherwise commonly used *Brown* allylation, which needs to be conducted with the aldehyde. In most cases, starting the allylation from the alcohol instead of the aldehyde will save one step within an anyways lengthy total synthesis. Additionally, the catalytic course of the *Krische* allylation prevents the stoichiometric formation of byproducts, facilitating the workup and purification process. But, as the *Krische* allylation requires high temperatures (90 °C to 120 °C) in combination with long reaction times (48 h), it is only really feasible for thermically stable substrates. In this case, the lack of thermal stability of the intermediary formed aldehyde **192** was most likely the reason for the unsatisfactory yield and diastereomeric ratio of the performed *Krische* allylation as product **189** was obtained in 65% yield and a diastereomeric ratio of only 1.4:1 (Scheme 44).

Consequently, instead of a *Krische* allylation from alcohol **188**, the latter was converted to the aldehyde in a *Parikh-Doering* oxidation and then subjected to *Brown* allylation conditions. In this case, homoallylic alcohol **189** was obtained in a satisfactory yield of 72% with a diastereomeric ratio of 20:1 (Scheme 42). In general, the *Brown* allylation is a condensation between an aldehyde and a chiral *B*-allyl reagent forming a chiral homoallylic alcohol. The *B*-allyl reagent is formed *in situ* from commercially available (+)-$(Ipc)_2$BOMe or (-)-$(Ipc)_2$BOMe and allylMgBr.[143,221,222] This allylation reaction is commonly performed at low temperatures like -78 °C, as higher temperatures decrease the stereoselectivity. Classically, polar aprotic solvents like THF or Et_2O are used as they show the best results regarding reactivity and stereoselectivity.[223] Like the previously discussed *Krische* allylation, the *Brown* allylation proceeds *via* a closed chair-like *Zimmermann-Traxler* transition state. Therefore, it also classes as a type I allylation reaction (Scheme 45).[219,220]



*Scheme 45: In situ preparation of allylating agent from (-)-$(Ipc)_2$BOMe (**195**) and subsequent allylation of aldehyde **192**. Reaction conditions: a) allylMgBr, -78 °C. Brown allylation of an aldehyde **192** with the freshly prepared B-allyl reagent **196** proceeds via two possible transition states (**I** and **II**). Due to the 1,3-diaxial interaction in TS **II**, TS **I** is favoured, leading to the homoallylic alcohol **197**.*[219,220]

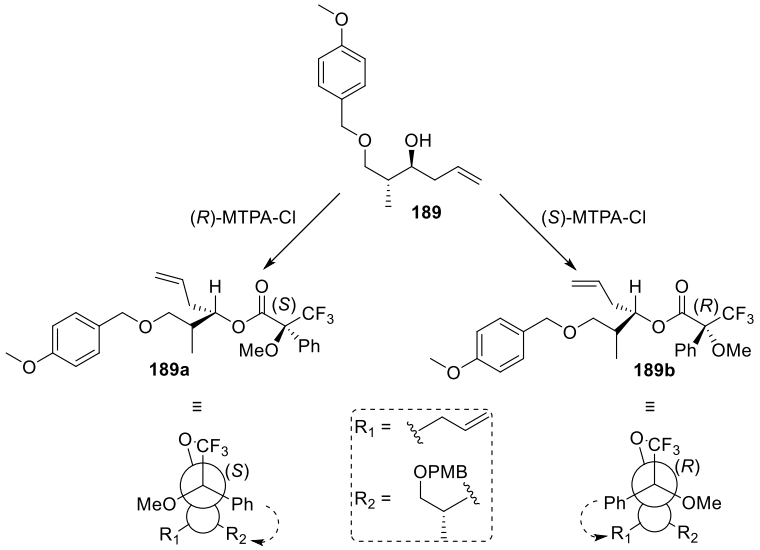
Firstly, as described above, the commercially available (-)-$(Ipc)_2$BOMe (**195**) was transformed to the chiral *B*-allyl reagent **196** *in situ* by treating compound **195** with allylMgBr. Afterwards, aldehyde **192** was added to the reaction and was activated by the boron reagent, forming either transition state **I** or **II**. The adjacent nucleophilic attack will take place in such a way, that the 1,3-diaxial interactions will be prevented. Thus, the residue of the aldehyde will rather occupy the equatorial position, like in the favoured TS **I**, than the axial position as in disfavoured TS **II** (Scheme 45).[143,197,222] As opposed to the *Krische* allylation, in this case, solely the aldehyde represents a suitable substrate for the allylation.[218] Due to the low temperatures (-78 °C), at which the *Brown* allylation is conducted, as well as the short reaction

times (1 h), it is suitable for less stable substrates, which tend to decompose under *Krische* conditions. Hence, it was chosen here, as the *Krische* allylation did not give satisfactory results.

In order to proof the stereochemical outcome of the allylation reaction, a *Mosher* ester analysis was performed.[224] The *Mosher* ester (or amide) analysis is the most frequently used method within the various NMR based methods to deduce the stereochemistry of secondary alcohols (or amines).[225] It was first reported in 1973 by *Dale* and *Mosher*,[226] who used chiral, enantiomerically pure carboxylic acids to derivatise secondary carbinols or α-chiral amines[226,227] with unknown configuration. Their study included various acids,[225] but herein the focus will be on the most widely used α-methoxy-α-trifluoromethylphenylacetic acid (MTPA-OH) also known as *Mosher's* acid.[224] Firstly, two diastereomeric esters are prepared from the secondary carbinol, of which the configuration should be deduced, with either (*S*)-MTPA-OH or (*R*)-MTPA-OH. Therefore, either MTPA-OH can be used in combination with DCC as coupling agent or MTPA-Cl is employed, which is reactive enough by itself.[228] The synthesis of the two diastereomeric MTPA esters can be conducted in a small scale (up to < 1 µmol) as the following ^{1}H NMR analysis displays a high sensitivity. Since diastereomers differ in their physical and spectroscopic properties, *Dale* and *Mosher* found that the prepared MTPA esters show different arrays of chemical shifts in their ^{1}H NMR spectra.[224]

Thus, a comparative $\Delta\delta^{SR}$ analysis of the ^{1}H NMR spectral data of both diastereomeric esters is conducted adjacent to the synthesis. Thereby, the sign of the difference in chemical shift of several analogous pairs of protons in the diastereomeric esters is investigated. Herein, the calculated $\Delta\delta^{SR}$ values are determined as $\Delta\delta^{SR} = \delta^S - \delta^R$ by convention.[224] Comparing the differences in chemical shift of the protons residing within substituents R_1 and R_2 enables the deduction of the absolute configuration of the original carbinol. The latter is based on the empirically identified conformational picture shown in Scheme 46. Herein, the important conformations of the dominating rotamer in spectroscopic features, distinguishing the diastereomers, is shown. Within compound **189a** and **189b**, the ester adopts the usual *s-trans* arrangement about its O-CO bond, while the CF_3-group and methine proton of the MTPA moiety are *syn*-coplanar with the carbonyl group.[224] Thus, the aryl residue, which is known to impose an anisotropic, magnetic shielding effect on protons above and below the plane of the aryl ring is able to affect either the protons residing in R_2 (**189a**) or R_1 (**189b**). As a result thereof, the respective protons undergo an upfield shift in ^{1}H NMR. In the case of **189a**, the

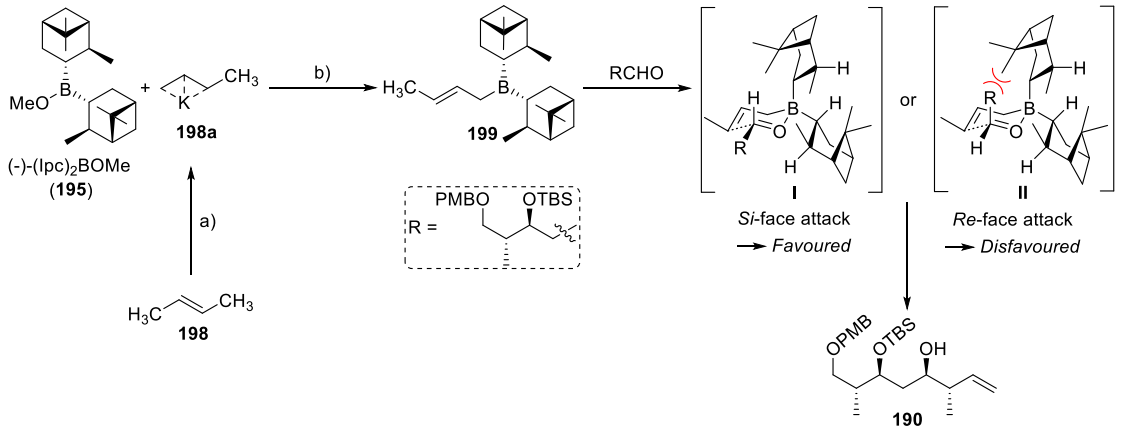
protons located within R_2 are more shielded than protons of R_1 and vice versa for **189b**.[226,229] Consequently, the signs of the $\Delta\delta^{SR}$ values for protons of R_1 will be positive whereas R_2 protons will display a negative sign. This knowledge can be directly translated to the substructure of R_1 and R_2 and thereby the absolute configuration of the original carbinol **189** can be deduced.[224]



*Scheme 46: Mosher ester analysis to determine the absolute configuration of the secondary alcohol **189**. Transformation of compound **189** with either (R)- or (S)-MTPA-Cl forming (S)-ester **189a** or (R)-ester **189b** respectively. Furthermore, the Newman projection of compounds **189a** and **189b** is shown to visualise the shielding of either R_2 in **189a** or R_1 in **189b** by the phenyl group.*

Afterwards, the hydroxy group was protected as a TBS-ether using standard conditions (TBSCl, imidazole, quant) prior to the oxidative cleavage of the terminal olefin *via* ozonolysis (Scheme 42). Since the PMB-ether can be cleaved under oxidative conditions, a redox indicator was used, in order to prevent undesired PMB cleavage. Herein, Sudan III, an ozonisable dye, was used as internal standard.[230] In the study of *Veysoglu et al*. from 1980, a relative reactivity of various commercially available dyes was emperically determined. Herein, Sudan III has shown to work best for isolated double bonds among the tested dyes.[230]

Thereafter, a *Brown* crotylation was conducted using (-)-$(Ipc)_2$BOMe, to obtain compound **190** in 51% and a diastereomeric ratio of 20:1. In general, the *Brown* crotylation follows the same reaction mechanism as the *Brown* allylation, which was described above (Scheme 45). Instead of allylMgBr, *trans*-butene (**198**) was used, in order to introduce the methyl group in a stereoselective *anti* fashion.[143,197] The crotylation proceeds *via* a closed six-membered transition state. Due to the minimisation of the 1,3-diaxial interactions found in TS **II** the *Si*-face attack *via* TS **I** is favoured leading to the desired product **190** (Scheme 47).[223]

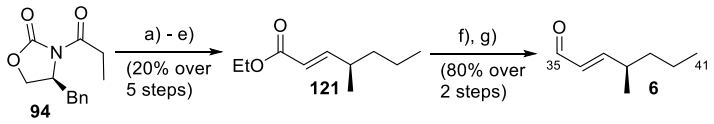


*Scheme 47: Mechanism of the Brown crotylation reaction. Reaction conditions: a) n-BuLi, KO^{t}Bu, -45 °C; b) BF_3*OEt_2, -78 °C.*[143,223]

Subsequently, the newly formed hydroxy function was protected as TES-ether under standard conditions (TESCl, imidazole, 95%) prior to oxidative cleavage of the terminal double bond to obtain the desired aldehyde **8** (Scheme 42). Unlike before, instead of an ozonolysis, a two-step one-pot *Lemieux-Johnson* oxidation was performed using osmium(IV) oxide, to introduce the 1,2-diol, and lead(IV) acetate, to cleave the gained glycol. The change in strategy was caused by the fact, that the ozonolysis machine could not be used at that time. Nevertheless, aldehyde **8** was obtained in a LLS of ten steps with an overall yield of 22% starting from (*R*)-*Roche* ester (**92**).

2.4.2.2 Synthesis of Aldehyde 6

Starting with the synthesis of aldehyde moiety **6** the first approach towards the latter was inspired by *Terrell et al.*[231]

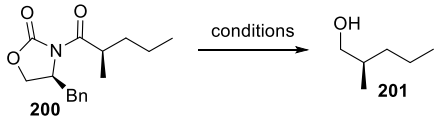


*Scheme 48: First synthetic approach towards aldehyde fragment **6** inspired by Terrell et al.*[231] *Reaction conditions: a) NaHMDS, THF, -78 °C, 30 min, then allyl bromide, -78 °C, 3 h; b) Pd/C, H_2, THF, rt, 5 h, **51%** (two steps), dr 20:1; c) $LiBH_4$, Et_2O, 0 °C to rt, 1 h, **73%**; d) $(COCl)_2$, DMSO, DCM, -60 °C, 25 min, then NEt_3, -60 °C to 0 °C; e) $Ph_3PCHO_2CH_3$, DCM, 0 °C to rt, 1 h, **54%** (two steps), dr 20:1; f) DIBAL-H, THF, -78 °C to rt, 1 h, **80%**; g) SO_3*py, DMSO, DIPEA, DCM, 0 °C to rt, 30 min, **quant**.*

As depicted in Scheme 48, the first step of the synthetic route was the stereoselective *Evans* alkylation of (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (**94**) with allyl bromide, followed by a one-pot reduction of the terminal olefin of the coupling product using palladium on charcoal under a hydrogen atmosphere to obtain the saturated compound. The synthesis of the enantiomeric alcohol and aldehyde was literature known and proceeded with a good diastereomeric ratio of 20:1.[231,232] In accordance with *Evans et al.*, the assymmetric induction

during the reaction can be interpreted by assuming the formation of a metal-chelated (*Z*)-enolate. The diastereofacial selection of the following alkylation is dictated by the C_4-substituent of the oxazolidinone ring.[233] The purification of the obtained product has shown to be rather tedious as multiple rounds of flash column chromatography were required. Therefore, the rather low yield of the reaction (51%) was not surprising. Nevertheless, a good diastereoselectivity (20:1) was obtained.

Afterwards, the *Evans* auxiliary was meant to be cleaved under reductive conditions giving rise to the respective alcohol. Initially, the conditions published by *Penning et al.* and also used by *Terrell et al.* were applied to reductively cleave the *Evans* auxiliary (Table 1, entry 1).[231,234] However, the moderate to good yields suffered from poor reproducability in this study. As it was believed, that the addition of water could inhibit the reaction rather than enhancing it, the reaction was conducted under the same conditions, but leaving out the water (Table 1, entry 2). In this case, a good yield was obtained in some reactions, but the range of observed yields was very broad. Therefore, the reducing agent was changed to lithium aluminium hydride instead.[235] Under these conditions, a more consistent and reliable yield was obtained (Table 1, entry 3). Even though, the general conditions seemed to be more suitable for the system, variations in the yield were obtained. These findings can potentially be explained by the rather high volatility of the prepared alcohol **201** (Scheme 49).



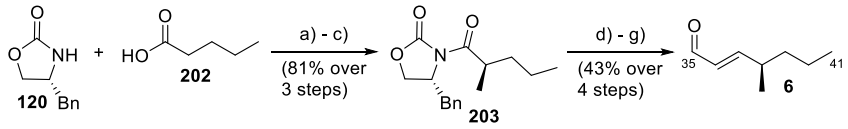
*Scheme 49: Reductive cleavage of the Evans auxiliary towards alcohol **201**.*

*Table 1: Different reaction conditions for the reductive cleavage of the Evans auxiliary to the respective alcohol **201**.*

entry	reducing agent	temperature and solvent	isolated yield
1	$LiBH_4$	rt, Et_2O (0.05 M)/H_2O (1.10 equiv)	17%
2	$LiBH_4$	rt, Et_2O (0.05 M)	5 – 73%
3	$LiAlH_4$	0 °C, Et_2O (0.05 M)	46 – 96%

Apart from reductively cleaving the auxiliary, the direct transformation to the respective aldehyde was tried using the *Schwartz* reagent (Cp_2ZrHCl). However, no product was obtained. In addition to the direct conversion to the aldehyde, the transformation to the *Weinreb* amide was also investigated.[236] Because of the unsatisfactory yields (35%), the initial plan to convert the *Evans* auxiliary to the respective alcohol was retained.

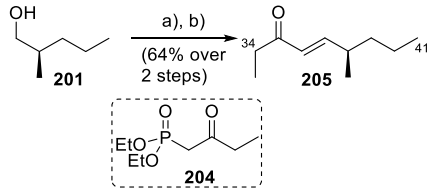
Thereafter, a one-pot *Swern* oxidation *Wittig* reaction was conducted.[231] Use of a stabilised ylide ($Ph_3PCHO_2CH_3$) during the *Wittig* reaction gave rise to the desired (*E*)-configured double bond with a diastereomeric ratio of 20:1. Adjacently, the obtained α,β-unsaturated ester was reduced to the alcohol using DIBAL-H, before the latter was oxidised under *Parikh-Doering* conditions, yielding the desired α,β-unsaturated aldehyde **6** (80%, Scheme 48). The synthesis was conducted in a LLS of seven steps yielding 16%.



*Scheme 50: Adapted synthesis of aldehyde fragment **6**. Reaction conditions: a) NEt_3, PivCl, THF, -30 °C, 75 min; b) LiCl, **120**, -30 °C to rt, 5 h, **quant** (two steps); c) NaHMDS, THF, -78 °C, 1 h, then MeI, -78 °C to -50 °C, 3 h, **81%**, dr 20:1; d) $LiAlH_4$, Et_2O, 0 °C, to rt, 1 h, **96%**; e) $(COCl)_2$, DCM, DMSO, -60 °C, 25 min, then NEt_3, -60 °C to 0 °C, then $Ph_3PCHO_2CH_3$, 0 °C to rt, 1 h, **54%** (two steps), dr 20:1; f) .DIBAL-H, THF, -78 °C to rt, 1 h, **80%**; g) SO_3*py, DMSO, DIPEA, DCM, 0 °C, 30 min, **quant**.*

Due to the low yield and tedious purification process of the first step of this route (Scheme 48), an alternative approach was developed (Scheme 50). Herein, the first step consisted of the coupling of valeric acid (**202**) to (*R*)-4-benzyl-2-oxazolidinone (**120**). Therefore, the acid was first treated with pivaloyl chloride and triethylamine to form the mixed anhydride, which then formed the amide bond after the addition of the *Evans* auxiliary **120**. Afterwards, the *Evans* alkylation proceeded using NaHMDS and methyl iodide cleanly providing compound **203** in 81% over those three steps and a diastereomeric ratio of 20:1. As seen before, the diastereofacial selectivity of the *Evans* alkylation can be explained by the C_4-substituent of the oxazolidinone ring dictating the attack of the metal-chelated (*Z*)-enolate.[233] The remaining step of this synthetic route were the same as in the one presented above (Scheme 48). The LLS of this synthesis consisted of seven steps with an overall yield of 35%. Based on these results the first route was replaced.

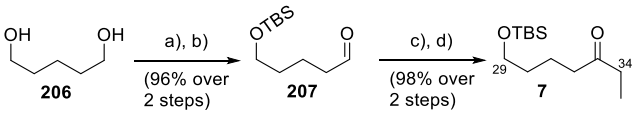
In order to test the best conditions for the envisioned *Paterson syn*-aldol reaction, the two fragments were also synthesised with interchanged functionalities. Hence, alcohol **201**, which was gained from the cleavage of the *Evans* auxiliary, was oxidised to the respective aldehyde under *Swern* conditions ($(COCl)_2$, DMSO, DIPEA) prior to subjecting it to a HWE reaction using compound **204** (Scheme 51). The α,β-unsaturated ketone **205** was gained in a LLS of six steps starting from valeric acid (**202**) with a yield of 38%.



*Scheme 51: Synthesis of ketone fragment **205** for the Paterson syn-aldol reaction with swapped functionalities. Reaction conditions: a) $(COCl)_2$, DIPEA, DCM, DMSO, -60 °C, 25 min; b) LiCl, MeCN, **204**, DIPEA, then aldehyde, rt, 12 h, **64%** (two steps).*

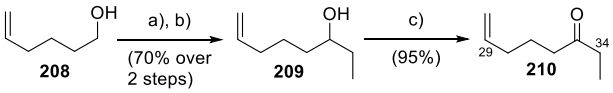
2.4.2.3 Synthesis of Ketone 7

The first synthetic approach towards the C_{29}-C_{34} fragment **7** is shown in Scheme 52. Starting the synthesis from 1,5-pentandiol (**206**) performing a statistical protection of only one of the two hydroxy functions followed by a *Parikh-Doering* oxidation yielded aldehyde **207** in 50% over two steps. Then, the latter was treated with ethyl magnesium bromide in a *Grignard* reaction to form the racemic secondary alcohol, which then was oxidised to ketone **7** in another *Parikh-Doering* oxidation. The synthesis proceeded in a LLS of four steps with a yield of 94%.



*Scheme 52: Synthetic route towards ketone fragment **7**. Reaction conditions: a) TBSCl, imidazole, DCM, rt, 75 min, **50%**; b) SO_3*py, DMSO, DIPEA, DCM, 0 °C to rt, 30 min, **quant**; c) EtMgBr, THF, 0 °C, 30 min, **98%**; d) SO_3*py, DMSO, DIPEA, DCM, 0 °C to rt, 30 min, **quant**.*

Compound **7** was intended to be coupled in a *Paterson syn*-aldol reaction to aldehyde **6**, forming the new C_{34}-C_{35} bond. Later on, the TBS-ether was meant to be cleaved giving rise to the primary alcohol. The latter should be transformed to a methyl ketone, needed for the planned *Mukaiyama* aldol reaction. Therefore, the alcohol was intended to be oxidised to the aldehyde, subjected to another *Grignard* reaction, using methyl magnesium bromide in this case, and then oxidised to the ketone under *Parikh-Doering* conditions.

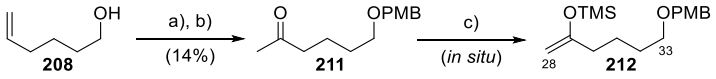


*Scheme 53: Synthetic route towards revised ketone fragment **210**. Reaction conditions: a) SO_3*py, DMSO, DIPEA, DCM, 0 °C, 1 h, **quant**; b) EtMgBr, THF, 0 °C, 30 min, **70%**; c) SO_3*py, DMSO, DIPEA, DCM, 0 °C, 1 h, **95%**.*

As the described sequence to prepare the fragment for the *Mukaiyama* aldol reaction only contained well-established reactions, but consisted of many steps, fragment **7** was slightly

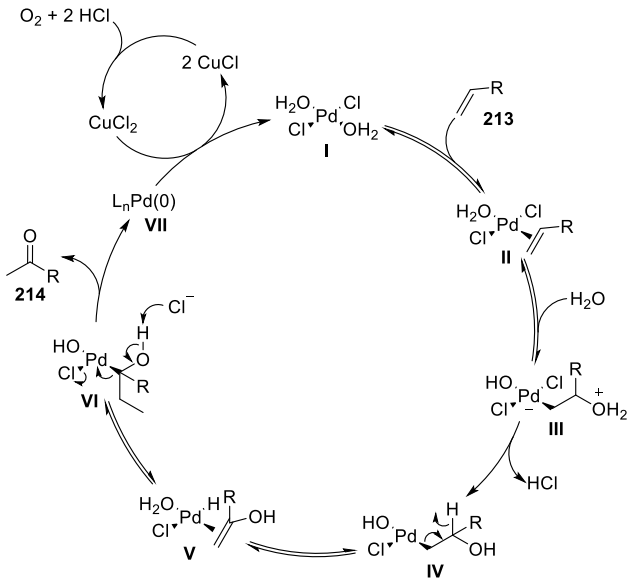
adapted (Scheme 53). In this case, 5-hexen-1-ol (**208**) was used as starting material, first being oxidised to the aldehyde using *Parikh-Doering* conditions. Afterwards, the ethyl group was introduced in a *Grignard* reaction yielding racemic alcohol **209**. Another *Parikh-Doering* oxidation finalised the synthesis of compound **210** in a LLS of three steps with a yield of 67%.

Apart from shortening the fragment synthesis by one step, implementing the olefin instead of a protected alcohol might also be beneficial for the preparation of the methyl ketone for the *Mukaiyama* aldol reaction. Instead of having to perform a four-step sequence, the terminal olefin can be converted to the methyl ketone *via* a *Wacker* oxidation. Thus, changing the second hydroxy function to a terminal olefin saves four steps within the synthesis of the linear precursor of eastern fragment **5**. In order to test reaction conditions for the planned *Wacker* oxidation, as well as for the *Mukaiyama* aldol reaction with aldehyde **8**, compound **212** was synthesised (Scheme 54). Theoretically, the order of aldol reactions to prepare the linear precursor from fragments **8**, **6** and **210** would be interchangable depending on what would be more promising to give better overall yields.



*Scheme 54: Synthesis of test fragment **212** for Mukaiyama aldol. Reaction conditions: a) PMBCl, NaH, THF, 0 °C, 2 h, then rt, o.n., **68%**; b) $PdCl_2$, CuCl, DMF/H_2O (7:1), O_2, rt, o.n., **20%**; c) DIPEA, nBuLi, THF, -78 °C, 30 min, then **211**, -78 °C, 45 min, then TMSCl, -78 °C to 10 °C, 3 h.*

Preparation of silyl enol ether **212** started from 5-hexen-1-ol (**208**) as well, first performing a PMB protection (PMBCl, NaH, 68%). The compound was meant to subsequently undergo a *Wacker* oxidation, hence a protecting group which was stable under acidic conditions needed to be chosen (Scheme 54). For the standard *Wacker* oxidation, a catalytic Pd(II) source and a co-oxidant are used under acidic, aqueous, aerobic conditions to access methyl ketones from terminal olefins (Scheme 55).[237,238] As most organic compounds are poorly soluble in water DMF can be used as a co-solvent.[239] This "*Clement* modification" was the foundation for the nowadays commonly applied *Tsuji-Wacker* conditions ($PdCl_2$ (cat), CuCl, O_2 (balloon pressure), DMF/H_2O 7:1).[240] Starting the catalytic cycle from $PdCl_2$ aqua complex **I**, which coordinates alkene **213** to form complex **II**. Thereafter, water is added to the coordinated alkene in a hydroxypalladation, forming compound **III**. Most sources claim this step to be rate determining.[241,242] Adjacently, a β-hydride elimination is proposed yielding compound **V**, in which the newly formed alkene is still coordinated.[242]



Scheme 55: Proposed mechanism of the Wacker oxidation.[237]

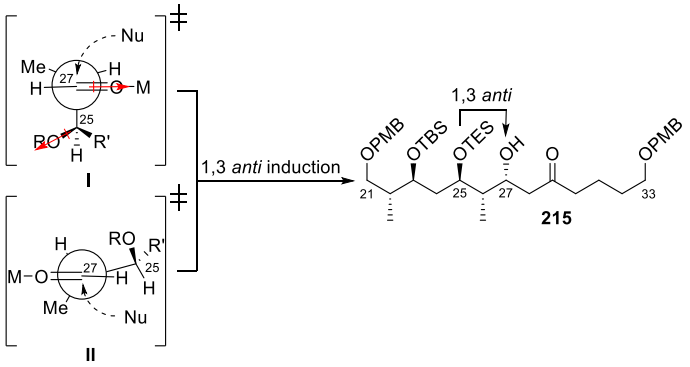
This organometallic step is proposed due to studies using deuterated starting materials showing that substrate hydrogens are conserved in the process.[238,243] The coordinated enol reinserts into the Pd-H bond forming the isomeric Pd-alkyl **VI**. Lastly, another β-hydride elimination of the hydroxy group's hydrogen was proposed to yield product **214**, but computational studies suggested a chloride assisted deprotonation, that leads to elimination and reduction of Pd(II) (**VI**) to Pd(0) (**VII**).[244] Closing the catalytic cycle, Pd(0) needed to be reoxidised to Pd(II). Copper salts facilitate this process *via* the rapid oxidation of Cu(I) with HCl and molecular oxygen, although bimetallic complexes have also been implicated as potential catalytic species.[245]

In this case, the *Wacker* oxidation was conducted implementing standard conditions ($PdCl_2$, CuCl, O_2 atmosphere) yielding methyl ketone **211** in 20% (Scheme 54). The latter was *in situ* transformed to the silyl enol ether needed for the plannend *Mukaiyama* aldol.

2.4.2.4 *Mukaiyama* Aldol Reaction

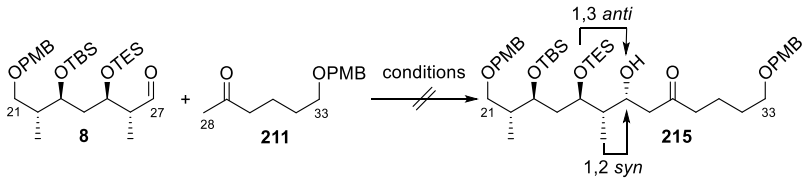
To install the C_{27}-C_{28} bond, a methyl ketone *Mukaiyama* aldol reaction between aldehyde fragment **8** and ketone fragment **211** was planned. Herein, ketone fragment **211** was used as a test system to first investigate reaction conditions. Since ketone **211** was achiral the stereochemical course of the aldol reaction was planned to be induced by the α-chiral aldehyde **8**. As previously explained, the desired 1,2 *syn* induction corresponds to the *Felkin-Anh* product and therefore should be favoured. Besides, the β-alkoxy group of the aldehyde **8** exerts a moderate 1,3 *anti* induction, also preferring the desired stereochemical outcome of

the reaction. The assumed stereoinduction can be explained by either the *Evans* polar model[246] (TS **I**) or the *Reetz/Cram*[247] model (TS **II**, Scheme 56).



*Scheme 56: Evans polar model (**I**) and Reetz/Cram model (**II**) explaining 1,3 anti induction during Mukaiyama aldol reaction.[246,247]*

Regarding the *Evans* polar model, the dipole interactions within TS **I** can be minimised by arranging the biggest substituent to be in a 90 ° angle towards the carbonyl group, which is in accordance to the *Felkin-Anh* model. Thus, the nucleophile attacks *via* the *Bürgi-Dunitz* trajectory, leading to the 1,3 *anti* product.[246] Alternatively, the *Reetz/Cram* model, which is shown in TS **II**, can be used to explain the exerted stereo induction of the β-alkoxy substituent (Scheme 56). This model has been invented to explain the 1,3 *anti* induction of BF_3 mediated of *Sakurai* allylations.[247] As the *Lewis* acidic BF_3 is a monodentate ligand, the classical *Cram* chelate model failed to explain the formation of the favoured product. Hence, *Reetz* proposed a transition state, in which the electrostatical interaction of the dipoles lead to an antiperiplanar conformation of the carbonyl group regarding to the σ-sceleton of the carbon chain. Then, the nucleophile attacks from the less hindered diastereofacial side of the carbonyl resulting in the 1,3 *anti* product as well.[247] In theory, silyl groups are considered to be voluminous and non-coordinating. However, due to the results of *M. Dieckmann's* PhD thesis, it can be assumed that silyl groups tend to have a certain potential to coordinate metals after all.[208] Otherwise, the just discussed stereo models could not be applied to the system. For the preparation of the respective silyl enol ether (SEE) the procedure by *Zhang et al*.[248] was used while for the adjacent *Mukaiyama* aldol conditions published by *Anderl et al*.[249] were applied.



*Scheme 57: Mukaiyma aldol reaction between aldehyde **8** and ketone **211**. Reaction conditions in Table 2.*

Table 2: Investigated reaction conditions for Mukaiyama aldol depicted in Scheme 57.

entry	conditions	yield
1	1.00 equiv **211**, 1.20 equiv LDA[a], 2.00 equiv TMSCl[b], 0.85 equiv **8**, 1.00 equiv CaH_2, 1.30 equiv BF_3*OEt_2	-
2	1.00 equiv **211**, 1.20 equiv LDA[a], 2.00 equiv TMSCl[c], 0.85 equiv **8**, 1.00 equiv CaH_2, 1.30 equiv BF_3*OEt_2	-

[a]: prepared *in situ*

[b]: from previously opend bottle

[c]: from freshly opened bottle

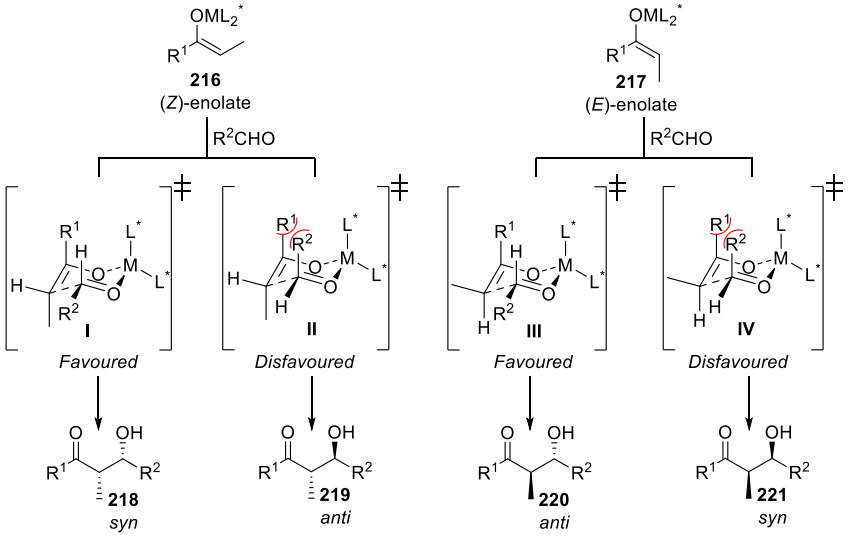
Even though the desired product **215** should reassemble a matched case of reagent induced stereochemistry, no product formation was observed. As the aldehyde **8** was obtained in high purity, the formation of the silyl enol ether (SEE) from ketone **211** was assumed to cause problems. In the first reaction (Table 2, entry 1), only the aldehyde was reisolated, pleading for a relatively high stability of the latter. However, the SEE could not be reisolated. This led to the assumption that it might had deteriorated. Therefore, within the second attempt of the reaction (Table 2, entry 2), freshly opened TMSCl was used, as it was hoped to ensure the formation of the SEE. Nevertheless, no product could be isolated and the starting materials were regained. However, in this case the ketone **211** was regained as well. This either meant, that the SEE had not been formed in the first place, or it might had deteriorated during the work up. Further investigations of the reaction conditions will need to be performed in future studies, as the focus of this study shifted with the publication of the total syntheses of neaumycin by *Smith et al.*[149] and *Zhang et al.*[179]

2.4.2.5 *Paterson syn*-Aldol Reaction

In order to install the C_{34}-C_{35} carbon bond, compounds **6** and **210** were obtained. If the ketone and aldehyde functionalities were swapped, the C_{33}-C_{34} carbon bond was installed. Herein, a *Paterson* aldol reaction, using an ethyl ketone was chosen to install the 1,3-diol, 2-methyl

motif in a *syn*-stereoselective fashion. Within this study, the main focus was on screening for conditions for the aldol addition between ketone **210** and aldehyde **6** (Scheme 59, Table 3).

In 1990, *Paterson et al.* published their full[217,250] results on the use of boron reagents for the enantio- and diastereoselective aldol addition of achiral methyl and ethyl ketones to aldehydes.[217] Under the assumption, that the ethyl ketone aldol addition would proceed through a chair-like transition state, the group established suitable conditions to selectively form either the (*Z*)- or (*E*)-enolate (**216** and **217**).[217] The depicted transition states show a high degree of π-face selectivity during the aldol addition of the aldehyde (Scheme 58).

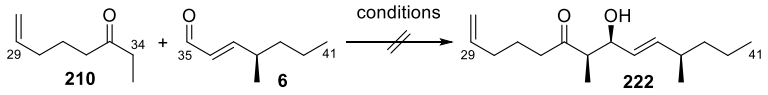


*Scheme 58: Stereochemical course of Paterson aldol addition of ethyl ketones applying the underlying assumption of a chair-like transition state (**I, II, III, IV**).[217,251]*

Chiral isopinocampheyl (Ipc) ligands on boron reagents were utilised by the group of *Brown* for assymmetric hydroboration[252,253] and later on used in diastereoselective allylation and crotylation reactions.[197,254] In addition, the group of *Meyers* used Ipc ligands for enantioselective azaenolate additions to aldehydes.[255,256] Furthermore, (+)- and (-)-$(Ipc)_2BH$ can easily be prepared from inexpensive (+)- or (-)-α-pinene respectively, following the procedure by *Brown et al*.[253] For these reasons, diisopinocampheyl boron triflate is widely used in assymmetric syntheses.[257] The latter can be prepared *in situ* from (+)- or (-)-$(Ipc)_2BH$ treating it with triflic acid in hexane.[255,256,258]

In this study it was found, that $(Ipc)_2BOTf$ selectively forms the (*Z*)-enolate **216** leading to the *syn* aldol product **218**, while $(Ipc)_2BCl$ forms the (*E*)-enolate **217** and adjacently the *anti* aldol product **220** (Scheme 58).[217] Based on previous studies,[259] the formation of (*Z*)-enolate borinates is additionally reinforced by maximising the kinetic selectivity during the

deprotonation of the ketone-reagent complex by the use of a sterically demanding base. The combination of $(n\text{Bu})_2$BOTf and DIPEA in this step has shown good selectivities (*Z*:*E* > 99:1).[217] Moreover, using DCM as the solvent in the reaction, the best yields in combination with the highest enantiomeric excess (*ee*) were observed, while the use of Et_2O lead to moderate results. Excessive amounts of hexane lowered the enantioselectivity of the aldol addition. Therefore, it was found that the ratio of DCM to hexane in the reaction should not exceed a ratio of 8:1.[217] Since the desired product **222** contained a 1,2 *syn* motif with the hydroxy group being (*S*)- and the methyl group being (*R*)-configured, freshly prepared (+)-$(Ipc)_2$BOTf in dry hexane was used (Scheme 59, Table 3).[255,256,258] The used general procedure of the reaction was from *Menche et al.*,[260] as their system was similar to this problem.



Scheme 59: Investigated Paterson syn aldol system. Reaction conditions in Table 3.

Table 3: Investigated reaction conditions for the Paterson syn aldol reaction depicted in Scheme 59.

entry	ketone	aldehyde	solvent	base	B-reagent	yield
1	1.00 equiv	2.10 equiv	DCM	DIPEA	(+)-$(Ipc)_2$BOTf	-
	(0.02 M)[a]	(0.04 M)[a]		(2.55 equiv)	(2.05 equiv)[b]	
2	1.00 equiv	1.65 equiv	DCM	DIPEA	(+)-$(Ipc)_2$BOTf	-
	(0.29 M)[a]	(0.29 M)[a]		(2.55 equiv)	(2.05 equiv)[b]	
3	1.00 equiv	1.30 equiv	Et_2O	DIPEA	(+)-$(Ipc)_2$BOTf	-
	(0.29 M)[a]	(0.29 M)[a]		(2.55 equiv)	(2.05 equiv)[b]	
4	1.00 equiv	1.00 equiv	Et_2O	DIPEA	(+)-$(Ipc)_2$BOTf	-
	(0.29 M)[a]	(0.29 M)[a]		(2.55 equiv)	(2.05 equiv)[b]	
5	1.00 equiv	1.30 equiv	Et_2O	DIPEA	(+)-$(Ipc)_2$BOTf	-
	(0.50 M)[a]	(0.48 M)[a]		(2.10 equiv)	(1.30 equiv)[b]	
6	1.00 equiv	1.20 equiv	Et_2O	DIPEA	(+)-$(Ipc)_2$BOTf	-
	(0.42 M)[a]	(0.51 M)[a]		(2.10 equiv)	(1.00 equiv)[b]	

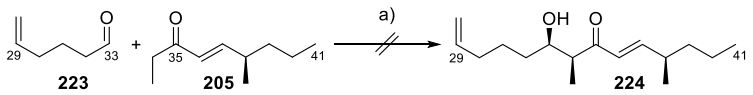
[a]: stock solution prepared in same solvent as the reaction was carried out in, dried over 3 Å MS at -15 °C, o.n.

[b]: freshly prepared from (+)-$(Ipc)_2$BOMe and triflic acid[217]

Therefore, entry 1 of Table 3 resembles the exact conditions reported by *Menche et al.* for a very similar system.[260] However, no product formation was observed. Since both stock

solutions were pretty diluted, the concentration was increased to 0.29 M, while the excess of aldehyde was decreased (Table 3, entry 2). Even though the use of DCM was meant to give the best yields and selectivities,[217] the solvent was swapped for Et_2O. This decision was based on observations made for a very similar problem within the group. Regarding that *Paterson* aldol reaction the yields could be improved using Et_2O instead of DCM, while the selectivities remained good (Table 3, entries 3 and 4). In entry 4 equimolar amounts of ketone and aldehyde were used, but still no product was isolated. Thereafter, the concentration of the respective stock solutions was further increased and the aldehyde was used in a slight excess (Table 3, entries 5 and 6). Although several different conditions were tested, no product formation was obtained.

In analogy to fragment **210**, the C_{29}-C_{33} moiety **223** was prepared carrying the aldehyde. Therefore, only the first step of the fragment synthesis was performed and the obtained aldehyde **223** subjected to a *Paterson syn*-aldol reaction with ketone **205**.



*Scheme 60: Paterson syn aldol reaction between aldehyde **223** and ketone **205**. Reaction conditions: a) (-)-$(Ipc)_2$BOMe, DIPEA, Et_2O, -78 °C to -15 °C, o.n.*

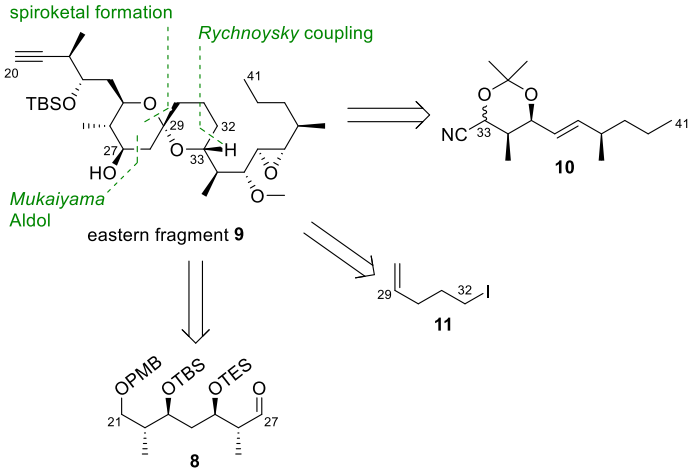
Since the functionalities of the aldehyde and ketone were interchanged, the *syn* aldol reaction was carried out with enantiomeric (-)-$(Ipc)_2$BOTf. As presumed, no product formation was obtained either. Within the PhD studies of *L. M. Wingen*[261] a fairly similar system was investigated and no product formation was observed. In that case, it was assumed that the enolisation of the enone fragment **205** caused problems. Even when KHMDS was used as a base, no reaction took place. Therefore, the functionalities were chosen as depicted in Scheme 59 in the first place.

However, in this study none of the systems led to the formation of the desired *syn* aldol product. Since screening for suitable aldol conditions can be rather laborious, the approach to obtain the C_{33}-C_{34} bond formation by aldol reaction was changed.

2.4.3 Revised Retrosynthetic Analysis of the originally proposed structure

As the planned *Paterson syn*-aldol reaction between aldehyde **6** and ketone **210** was unsuccessful (Table 3), the retrosynthesis of eastern fragment **9** of neaumycin B (**3**) was changed (Scheme 61). Besides the change of the two fragments **10** and iodide **11**, making up

the C_{29}-C_{41} moiety of the eastern fragment, the vinyl iodide at C_{19} was changed to an alkyne due to stability reasons.



*Scheme 61: Revised retrosynthetic analysis of eastern fragment **5** of the originally proposed structure of neaumycin B (**3**).*

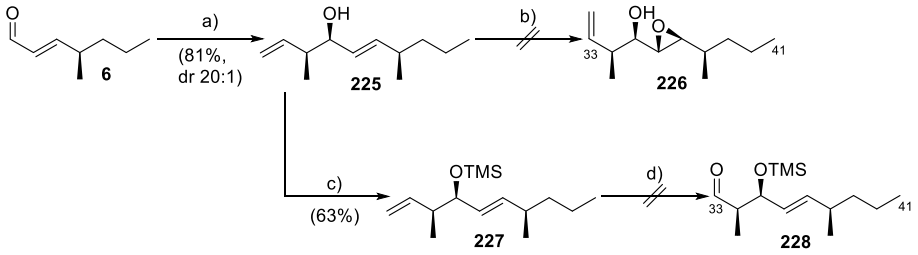
The C_{20}-C_{27} fragment **8** and its synthesis will stay the same as presented above, still allowing for a *Mukaiyama* aldol reaction between C_{27} and C_{28}. Alongside the just mentioned aldol reaction the second key step building up the linear precursor is a *Rychnovsky* coupling of cyanohydrin **10** and iodide **11**. Afterwards, a spiroketal formation was planned to finalise the scaffold of the eastern fragment **9** (Scheme 61).

2.4.4 Synthesis of the Revised Fragments

Henceforth, the syntheses of cyanohydrin **10** and iodide **11** will be presented. This coupling approach was inspired by the synthesis of the polyol motif of pentamycin by *A. Babczyk*.[262]

2.4.4.1 Synthesis of Cyanohydrin 10

Starting the synthesis of cyanohydrin **10**, the already prepared aldehyde **6** was transformed to diene **225** *via* a *Brown syn*-crotylation with a satisfying yield (81%) and diastereomeric ratio of 20:1 (Scheme 62). The mechanism and the consequential diastereoselectivity of the reaction were discussed above. Afterwards, the newly formed hydroxy group was protected as a TMS-ether **227**, preparing the compound for the upcoming reactions. The yield has been rather low (63%) due to the instability of compound **227** towards the slightly acidic conditions of standard flash column chromatography on silica gel. Therefore, the purification needed to be performed as quickly as possible to avoid a major loss of material. Then, the terminal olefin of **227** was meant to be cleaved in a *Lemieux-Johnson* reaction. Osmium(VIII) oxide was used to gain the 1,2-diol, which should subsequently be cleaved using lead(IV) acetate.



*Scheme 62: Synthesis of cyanohydrin fragment **10** starting from aldehyde **6**. Reaction conditions: a) KO^{t}Bu, cis-2-butene, n-BuLi, THF, -78 °C, 25 min, then, (+)-(Ipc)$_2$BOMe, Et$_2$O, -78 °C, 75 min, then BF$_3$*OEt$_2$, **6**, THF, -78 °C, 3 h, **81%**, dr 20:1; b) conditions see Table 4; c) TMSCl, DIPEA, DCM, rt, 2 h, **63%**; d) OsO$_4$, NMO*H$_2$O, acetone/H$_2$O, rt, 20 h, then Pb(OAc)$_4$, toluene, rt, 20 min.*

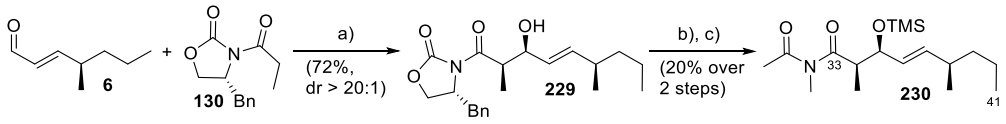
Instead of the desired compound **228**, decomposition of the starting material was observed. Since TMS-ether **227** contained two double bonds, the attack of the used osmium(VIII) oxide must have been unselective. In contrast to previous assumptions, the better accessibility of the terminal double bond compared to the higher electron density of the internal double bond did not lead to a significant regioselectivity of the reaction. Thus, an over-oxidation of the reactant probably took place, resulting in decomposition. These experiments were carried out as part of *S. Güvenc's* bachelor's thesis.[263]

Another way to chemically distinguish the two double bonds was to first perform a *Sharpless* epoxidation of the allylic alcohol **225** to the respective epoxide and adjacently perform the oxidative cleavage of the terminal double bond. As depicted in Scheme 62 this approach did not lead to the desired epoxide **226** either. In this case only starting material was reisolated. The investigated conditions for the *Sharpless* epoxidation are depicted in Table 4. Since the reaction is sensitive to water crushed 3 Å molecular sieves were employed in the reaction (entries 2 and 3). Even after 18 hours no reaction took place (Table 4, entry 3).

*Table 4: Investigated conditions for the Sharpless epoxidation of compound **225**.*

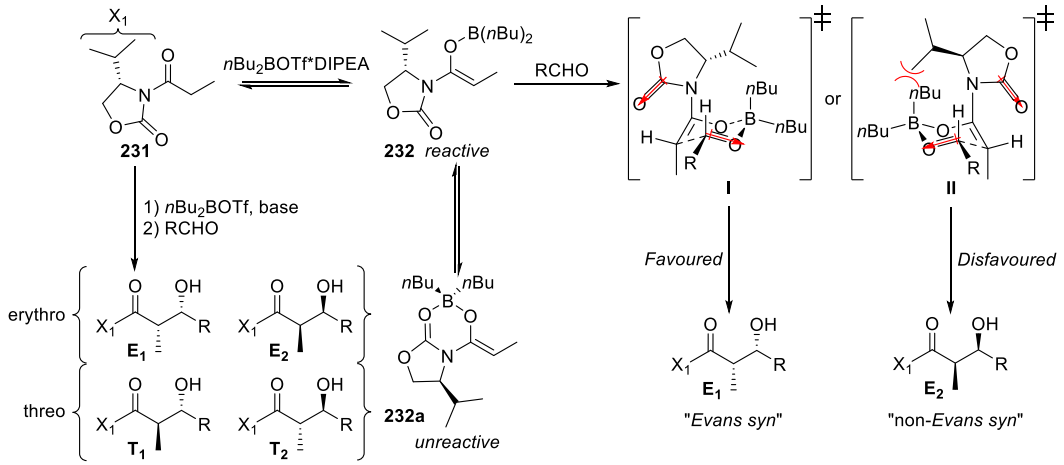
entry	conditions	yield
1	Ti(^{i}OPr)$_4$, (-)-DIPT, ^{t}BuOOH, DCM, -20 °C, 20 min	-
2	Ti(^{i}OPr)$_4$, (-)-DIPT, ^{t}BuOOH, DCM, 3 Å MS, -20 °C, 2 h	-
3	Ti(^{i}OPr)$_4$, (-)-DIPT, ^{t}BuOOH, DCM, 3 Å MS, -20 °C, 18 h	-

Consequently, the approach towards cyanohydrin **10** *via* a *Brown syn*-crotylation (Scheme 62) was discarded and a new synthetic route was developed. Again, the synthesis was based on aldehyde **6**, which was first conducted to an *Evans syn*-aldol yielding allylic alcohol **229** in 72% with a diastereomeric ratio of 20:1 (Scheme 63).



*Scheme 63: Revised synthesis of cyanohydrine fragment **10** starting from aldehyde **6**. Reaction conditions: a) nBu_2BOTf, DIPEA, DCM, 0 °C, 1 h, then aldehyde, -78 °C, 2 h, **72%**, dr 20:1; b) Me(MeO)NH*HCl, $AlMe_3$, THF, 0 °C, 30 min, then -40 °C, **229**, then rt, 2 h, **28%**; c) NEt_3, TMSCl, DCM, rt, 2 h, **71%**.*

In 1981, *Evans et al*. reported on an aldol condensation using chiral enolates to ensure for a highly stereoregulated course of the reaction.[157] Controlling the diastereoselection (**E_1** and **E_2** versus **T_1** and **T_2**) as well as the enantioselection (**E_1** versus **E_2** and **T_1** versus **T_2**) of the reaction proved to be challenging. However, it was reported that the use of chiral oxazolidin-2-one reagents in a *n*Bu_2BOTf mediated aldol reaction[259,264,265] resulted in a highly stereoselective formation of the (*Z*)-enolate **232**.[157] Thereafter, the aldol condensation proceeded with observed diastereomeric ratios of 99.4:0.2:0.2:0.2 (**E_1** : **E_2** : **T_1** : **T_2**, Scheme 64).[157] Furthermore, the assymmetric induction during the reaction seemed to stem from the C_4 substituent of the used oxazolidinone, favouring the transition *via* **I** rather than **II**, minimising steric interference. Therefore, the formation of **E_1** or the "*Evans syn*" product is favoured over **E_2**. Additionally, it was mentioned that, the observed asymmetric induction using methyl ketones was way lower than for corresponding (*Z*)-ketone enolates.[266]

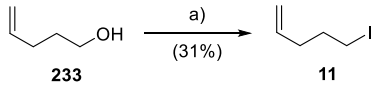


Scheme 64: Mechanism of the Evans aldol reaction. Red arrows mark dipole moments.[157,232,251,265]

Introducing the 1,2-*syn* motif of the methyl and hydroxyl group stereoselectively in this way avoided distinguishing between two different double bonds within the molecule. The absolute configuration of the hydroxy group was confirmed to be (*S*) by *Mosher* ester analysis as described before. Thereafter, the *Evans* auxiliary was converted to the *Weinreb* amide in 28% yield, using the *Weinreb* salt Me(MeO)NH*HCl and $AlMe_3$,[263] followed by the formation of

the TMS-ether **230** in 71% (Scheme 63). Up until this point, the LLS towards compound **230** starting from valeric acid (**202**) consists of ten steps with an overall yield of 5%.

2.4.4.2 Synthesis of Compound 11



*Scheme 65: Synthesis of alkyl iodide **11** for envisioned Rychnovsky coupling. Reaction conditions: a) PPh_3, imidazole, I_2, benzene, rt, 90 min, **31%**.*

Finally, the alkyl iodide **11** was obtained from pent-4-en-1-ol (**233**) in an *Appel* reaction (Scheme 65). However, due to the publication of the total syntheses of neaumycin B (**3**) by *Smith et al.*[149] and *Zhang et al.*[179] and the associated realisation of the incorrect stereochemistry of the proposed structure by *Jensen* and *Fenical et al.*,[89] the synthesis was aborted at this point.

2.4.5 Development of Revised Stereochemistry (*M. Adamek*, *N. Ziemert* University of Tübingen)

As a result of the observations of *Smith et al.*[149] and *Zhang et al.*[179] a new stereochemical proposal of the structure of neaumycin B (**3**) should be developed. Therefore, *M. Adamek* (*Ziemert* group, University of Tübingen) performed a bioinformatic study of the biosynthetic gene cluster of neaumycin once again.[267] Thus, a step-by-step analysis of the type I PKS assembly line responsible for the formation of the backbone of neaumycin B (**3**) was conducted. The prediction of the respective starter- or extender-units is based on the acyl transferase (AT) domain signature while the chirality of hydroxy and methyl groups is determined by the keto reductase (KR) domain.[267] Herein, the predictions are based on the presence or absence of certain amino acid residues at the active site of the KR domain. Furthermore, the predictions have been done by antiSMASH[268] and *via* HMM models by *Kitsche and Kalesse*.[269] Validation of the obtained results has been carried out by manual inspection of the alignments according to the rules determined by *Keatinge-Clay*.[270] Introduction of a double bond to the polyketide (PK) backbone is executed by the dehydratase (DH) domain which dehydrates β-hydroxy carbonyls to olefins. Moreover, the reduction of the introduced double bond to the alkane is undertaken by the enoyl reductase (ER) domain. During this reductive step the chirality of a present methyl group is set.[271]

Based on these predictions the PK backbone of neaumycin B was assembled (**B**, Figure 18)[267] and compared to the results of the bioinformatic and NMR analysis by *Jensen and Fenical* (**A**,

Figure 18).[89] Regarding the C_4-C_5, C_{10}-C_{11} and C_{34}-C_{35} connections a double bond was predicted by the bioinformatic analysis of both *Jensen* and *Fenical*[89] and *Adamek*.[267] However, due to the NMR studies by *Jensen* and *Fenical* hydroxy groups were placed at C_5, C_{11} and C_{35} (**C**, Figure 18). In addition to the conclusive NMR data *Jensen* and *Fenical* identified specific amino acid alterations within the respective DH domains possibly leading to the deactivation of the latter.[89] During the bioinformatic analysis by *Adamek* this explanation was validated to be plausible. Hence, the corresponding DH domains in modules 4, 16 and 19 were assumed to be inactive.[267] The respective chirality predictions were based on the KR domain type in the regarding modules. Besides these unanimous results, there were also some deviations of the predictions by *Adamek*[267] towards the interpretation of the NMR data by *Jensen* and *Fenical*.[89] Specifically, the carbon centers C_4, C_5, C_{10}, C_{22} and C_{35} were affected.

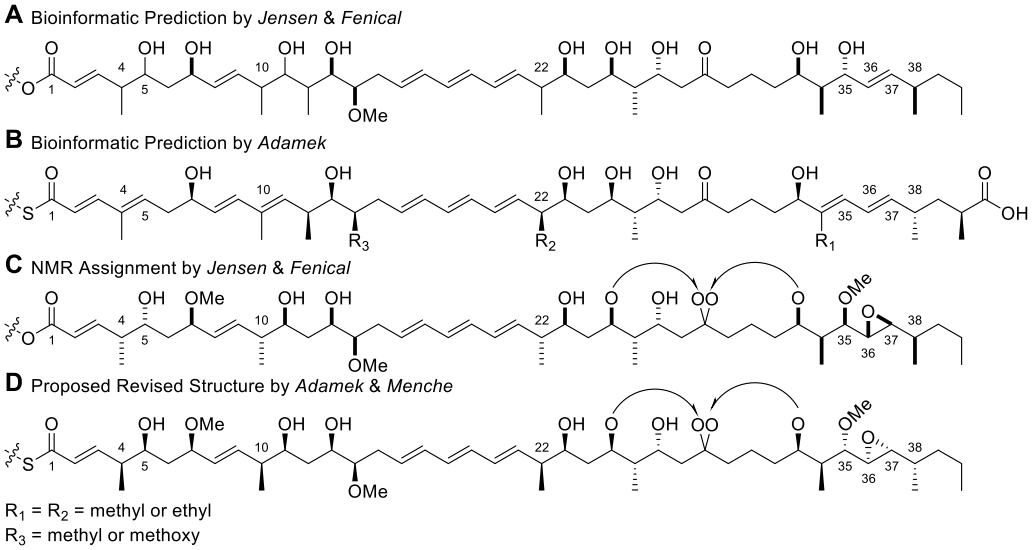


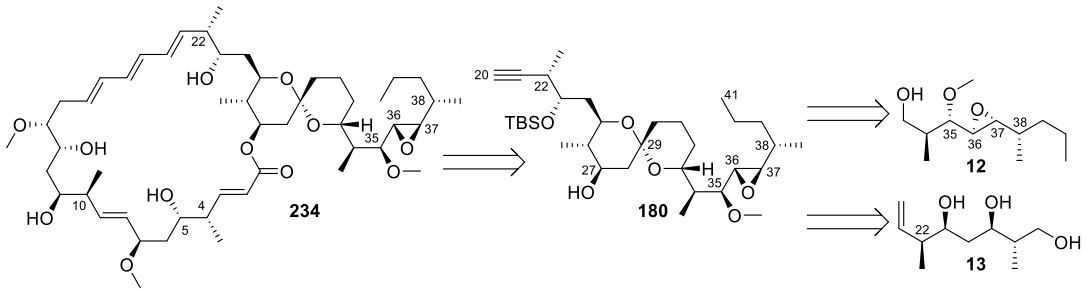
*Figure 18: **A**: Bioinformatic prediction of the backbone of neaumycin B by Jensen and Fenical.[89] **B**: Bioinformatic prediction of the backbone of neaumycin B by Adamek. **C**: NMR based structure proposal of neaumycin B by Jensen and Fenical.[89] **D**: Revised stereochemical proposal of neaumycin B by Adamek and Menche.*

Since the KR domain in module 16 (C_{10}) seemed to be unusual, no reliable bioinformatic prediction was possible. However, the NMR comparison of the synthetic proposed structure of neaumycin B (**3**) with the data for the isolated natural product by *Zhang et al*.[179] showed rather big differences of the NMR chemical shifts of C_{10} and the adjacent methyl group C_{43}. Thence, changing the stereochemistry of the C_{10} chiral center was suggested (**D**, Figure 18).[267] Both bioinformatic analyses predicted a methyl group at C_{12} (**A** and **B**, Figure 18), the NMR data did not show methylation at this center though (**C** and **D**, Figure 18).[89] Apart from that, *Jensen* and *Fenical* predicted the chiral center at C_{38} to be (*S*) configured in the text, but a (*R*) configuration was shown in the figure, which was also deduced from the NMR data.[89] The

bioinformatic analysis by *Adamek* suggested a (*S*) configuration at C_{38}, which was further supported by the NMR data by *Zhang et al.*[179] showing a deviation of NMR chemical shifts for this center once again. The starter unit of the PKS was predicted as propionyl CoA by *Jensen* and *Fenical*, while antiSMASH[268] predicted malonyl CoA.[267] Since the NMR data of *Jensen* and *Fenical*[89] as well as *Zhang et al.*[179] suggested a propionyl CoA starter unit this motif was maintained.[267] The formation of the spiroketal (indicated with half arrows in **C** and **D**, Figure 18), as well as the epoxidation of the C_{36}-C_{37} olefinic bond, occured after the PK synthesis by the PKS. Therefore, no bioinformatic prediction was possible. Thus, the proposed stereochemistry of the epoxide (**D**, Figure 18) was based on the NMR data by *Jensen* and *Fenical*[89] as well as *Zhang et al*.[179] A NMR chemical shift difference was stated for C_{36} as well as C_{37},[179] suggesting the stereochemistry to not be correct. Since it was thought that an all *syn* configuration of C_{35}, C_{36} and C_{37} seemed plausible, the stereochemistry of C_{36} and C_{37} was switched according to the C_{35} hydroxy group (**D**, Figure 18).[267]

2.4.6 Retrosynthetic Analysis of the Revised Structure

If the bioinformatic predictions from the linear structure of the PKS[267] are transferred to the cyclic structure of neaumycin B (**234**), the stereochemistry shown in Scheme 66 is obtained for the eastern fragment **180**.



*Scheme 66: Retrosynthetic analysis of revised eastern fragment **180** obtaining fragments **12** and **13** for the following NMR study.*

Considering the retrosynthesis of eastern fragment **180**, epoxide **12** and triol **13** were obtained containing all revised chiral centers. As the fragment coupling was not aimed at, the alkyl linker (C_{28}-C_{32}) was neglected.

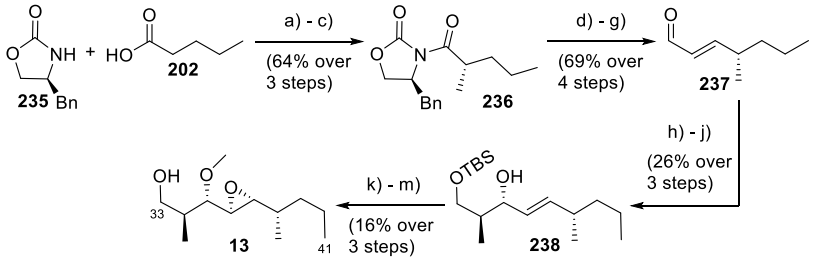
2.4.7 Synthesis of the Fragments for the Comparative NMR Study

According to the retrosynthetic analysis, the fragments **12** and **13** should be prepared. Considering the C_{20}-C_{27} moiety **12**, only one stereocenter needed to be changed compared to aldehyde **8**, leading to the use of the enantiomeric starting material. Otherwise, the previously

developed synthetic strategy should be adopted. In the case of the C_{33}-C_{41} fragment **13**, the previously established synthesis had to be adapted to a greater extend.

2.4.7.1 Synthesis of Compound 13

Modifying the already described synthesis led to the use of enantiomeric (*S*)-4-benzyl oxazolidinone (**235**) in the first step. Hence, after the coupling of valeric acid (**202**) to the auxiliary **235** (quant) the following methylation could occur with opposing stereochemistry resulting in compound **236** (64%, dr 20:1, Scheme 67).



*Scheme 67: Synthesis of revised fragment **13**. Reaction conditions: a) NEt_3, PivCl, THF, -30 °C, 75 min; b) LiCl, (S)-4-benzyl-2-oxazolidinone, THF, -30 °C to rt, 5 h, **quant** (two steps); c) NaHMDS, THF, -78 °C, 1 h, then MeI, -78 °C, 3 h, **64%**; d) $LiAlH_4$, Et_2O, 0 °C to rt, 1 h, **76%**; e) $(COCl)_2$, DMSO, DCM, -60 °C, 25 min, then NEt_3, -60 °C to 0 °C, then $Ph_3PCHO_2CH_3$, 0 °C to rt, 10 min, **quant**; f) DIBAL-H, THF, -78 °C to rt, 1 h, **91%**; g) SO_3*py, DMSO, DIPEA, DCM, 0 °C to rt, 30 min, **quant**; h) (1R,2S)-2-[N-benzyl-N-(mesitylenesulfonyl)amino]-1-phenyl-1-propyl propionate, NEt_3; $(cyhex)_2BOTf$, DCM, -78 °C, 2 h, then **237**, -78 °C, 1 h, then slowly warm to rt over 2 h, **55%**, dr 20:1; i) $LiAlH_4$, THF, 0 °C, 1 h, **78%**; j) imidazole, TBSCl, DCM, 0 °C, 25 min, **61%**; k) $Ti(^iOPr)_4$, (+)-DIPT, ^{t}BuOOH, DCM, 4 Å MS, -30 °C, 44 h, **quant**, dr 20:1; l) NaH, DMAP, MeI, THF, 0 °C to rt, 16 h, **50%**; m) TBAF, THF, 0 °C to rt, 4 h, **34%**.*

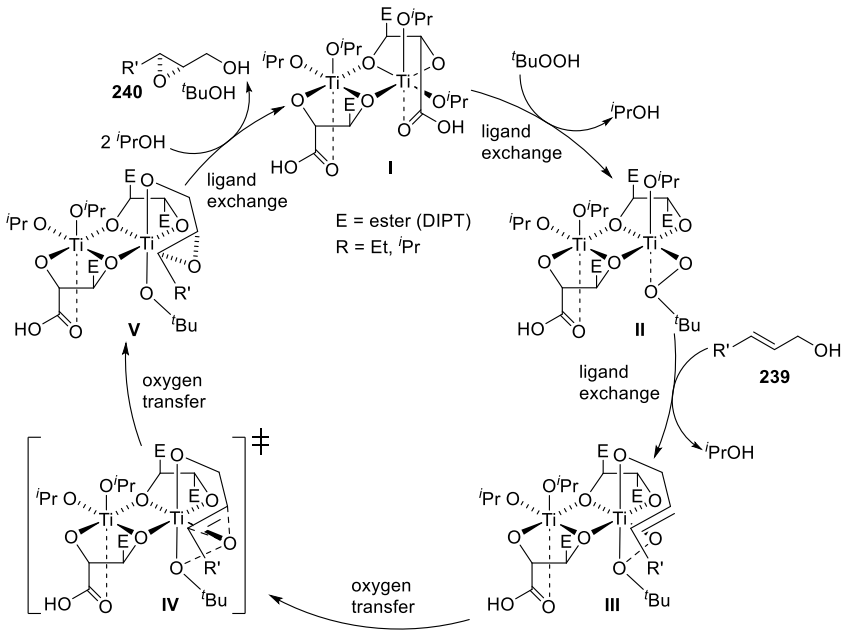
After that, the auxiliary was reductively cleaved using $LiAlH_4$ to obtain the respective alcohol in 76% yield. The following one-pot oxidation *Wittig* reaction procedure gave rise to the α,β-unsaturated ester in a good yield. Adjacently, the ester was reduced to α,β-unsaturated alcohol with DIBAL-H (91%), which was then oxidised to aldehyde **237** under *Parikh-Doering* conditions (quant, Scheme 67). In the following, the aldehyde **237** was subjected to a *Masamune anti*-aldol reaction to set the stereoinformation of the C_{34} methyl group as well as the C_{35} hydroxy function. The reaction proceeded with a satisfying yield of 55% and a diatereomeric ratio of 20:1.

Propionate aldol reactions utilising norephedrin-derived auxiliaries were first introduced by *Abiko* and *Masamune*.[272] Depending on the conditions selected for the enolisation of the auxiliary, either the (*E*)- or (*Z*)-enolate is selectively formed.[251] While the (*E*)-configured enolate leads to the *anti* aldol product, the (*Z*)-configured enolate forms the *syn* product respectively with high selectivities and yields.[273] In general, propionate aldol reactions with

norephedrin-derived auxiliaries have a broad substrate scope. However, within syntheses the latter was mainly used to selectively obtain the *anti* product.[274]

Subsequently, the *Masamune* auxiliary was cleaved ($LiAlH_4$) resulting in a 1,3-diol (78%). Since the allylic alcohol was required for the intended *Sharpless* epoxidation of the olefin, the primary alcohol was selectively protected as TBS-ether, using imidazole and a solution of TBSCl in DCM yielding compound **238** (61%). Thereafter, the *Mosher* ester analysis of the absolute configuration of the hydroxy function was conducted. In this case, the *Mosher* ester analysis was only performed after the cleavage of the auxiliary. Since the steric demand of the norephedrin-derived auxiliary was anticipated to be relatively big, a low yield was expected performing the esterification adjacently to the aldol reaction. Thus, the analysis of the absolute configuration of C_{35} was carried out with compound **238** (Scheme 67). The evaluation of the results confirmed the C_{35} stereocenter to be (*R*)-configured. Afterwards, the latter was treated with Ti(IV) isopropoxide and (+)-diisopropyltatrate (DIPT) giving rise to the desired epoxide in a diastereomeric ratio of 20:1.

The *Sharpless* assymmetric epoxidation is a catalytic method to stereoselectively create epoxides.[275] It uses an active titanium-tartrate catalyst for the asymmetric epoxidation of allylic alcohols. Therefore, the catalyst is formed from titanium isopropoxide ($Ti(^iOPr)_4$) and tartrate derivatives, like in this case DIPT. *Tert*-butyl hydroperoxide (^{t}BuOOH) functions as the oxygen donating species.[275] The mechanism of the oxygen transfer during the epoxidation reaction is depicted in Scheme 68. Herein, the active catalyst is believed to be a bimetallic complex of two Ti-centers being bridged by two tartrate ligands (DIPT). Firstly, the Ti source ($Ti(^iOPr)_4$) needs to be transformed to complex **I** *via* a ligand exchange. Thus, the Ti is coordinated by chelating tartrate ligands in addition to the isopropoxide ligands. Another ligand exchange takes place to form complex **II**. Therefore, ^{t}BuOOH replaces the equatorial isopropoxide ligand forming a bidentate, triangular dioxametallacycle complex **II**. Then, the allylic alcohol **239** substitutes the remaining isopropoxide ligand in a subsequent ligand exchange, occupying the axial position of Ti-complex **III**.[276] After that, an oxygen transfer from the lower face of TS **IV** forms complex **V**. The latter then undergoes another ligand exchange releasing the epoxide **240** and *tert*-butanol which are replaced by two isopropanol ligands.[277] As depicted in Scheme 68, the epoxidation is believed to take place at one Ti-center, whereas the other Ti-atom may have a cooperative effect.[277]

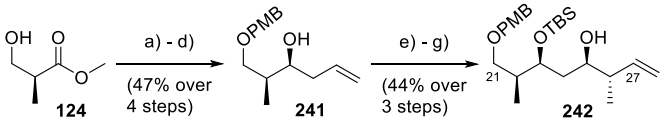


Scheme 68: Mechanism of the Sharpless asymmetric epoxidation.[275,276]

Lastly, the C_{35} hydroxy function was methylated using sodium hydride, catalytic amounts of *N,N'*-dimethylaminopyridine and methyliodide, as reporteded by *Krische et al.*[133] for a similar system. Subsequent global deprotection of the TBS-ether using TBAF concluded the synthesis of fragment **13**. In summary, the desired compound was obtained in a LLS of 13 steps starting from valeric acid (**202**) with an overall yield of 2%.

2.4.7.2 Synthesis of Compound 12

Herein, the already gained experience from assembling compound **8** was exploited to give access to fragment **12**.

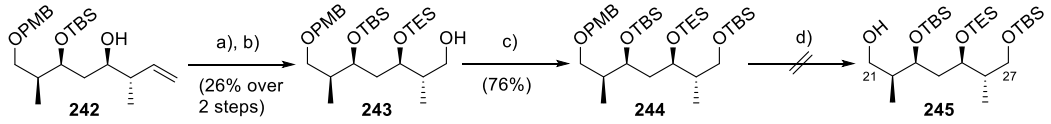


*Scheme 69: Synthesis of compound **242**. Reaction conditions: a) PMBOC(NH)CCl$_3$, CSA, DCM, rt, 19 h, **74%**; b) DIBAL-H, THF, -78 °C to rt, 1 h, **90%**; c) SO$_3$*py, DIPEA, DMSO, DCM, 0 °C, 45 min, **quant**; d) (-)-(Ipc)$_2$BOMe, Et$_2$O, allylMgBr, 0 °C, 75 min, then cool to -78 °C, aldehyde, -78 °C, 3 h, **71%**, dr 20:1; e) TBSOTf, 2,6-lutidine, DCM, 0 °C, 2 h, **68%**; f) O$_3$, 0.1% Sudan III, DCM, PPh$_3$, -78 °C to rt, 90 min, **75%**; g) KO^{t}Bu, trans-2-butene, nBuLi, THF, -78 °C to -45 °C, then cool to -78 °C, (-)-(Ipc)$_2$BOMe, -78 °C, 1 h, then BF$_3$*OEt$_2$, aldehyde, -78 °C, 4 h **75%**, dr 20:1.*

Because of the changed stereochemistry at C_{22} the synthesis started from (*S*)-*Roche* ester (**124**), which was first protected as PMB-ether (PMB-trichloracetimidate, CSA, 74%), followed by the reduction of the ester to the respective alcohol (DIBAL-H, 90%) and oxidation under *Parikh-Doering* conditions to obtain the aldehyde (quant). The latter was then subjected to a

Brown syn-crotylation yielding compound **241** in 71% with a diastereomeric ration of 20:1 (Scheme 69). The stereochemical outcome of the allylation reaction was proven by *Mosher* ester analysis to be (*S*)-configured. Thereafter, the newly formed alcohol was protected as a TBS-ether using TBSOTf and 2,6-lutidine in this case (68%). Thereafter, the oxidative cleavage of the terminal olefin was performed by ozonolysis using Sudan III as a redox indicator, to prevent over-oxidation and therefore the cleavage of the PMB-ether (75%). The respective aldehyde was used in the subsequent *Brown anti*-crotylation resulting in olefin **242** (75%, dr 20:1, Scheme 69). Instead of performing another *Mosher* ester analysis the 1,3 diol can be transformed to the acetonide. Since the absolute stereochemistry of the C_{23} chiral center was determined by *Mosher* ester analysis, the absolute stereochemistry of C_{25} can be deduced in this way.[278] Analysis of the formed acetonide confirmed a 1,3 *syn* configuration of the C_{23} and C_{25} hydroxy function. Therefore, the C_{25} chiral center was proven to be (*R*) configured.

Following the synthetic strategy developed for compound **8** the C_{25} hydroxy group was protected as TES-ether (TESCl, imidazole, 50%). Subsequently, the terminal olefin was meant to be cleaved oxidatively yielding the primary alcohol **243**. Firstly, a *Lemieux-Johnson* oxidation was performed, as it gave good results during the synthesis of compound **8**.

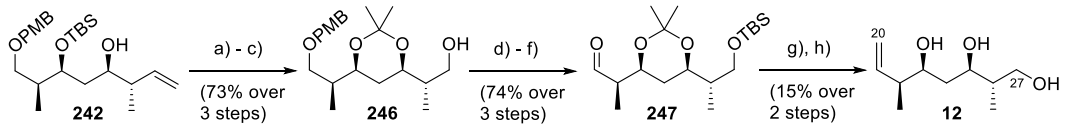


*Scheme 70: Synthetic route to compound **245**. Reaction conditions: a) TESCl, imidazole, DCM, rt, o.n., **50%**; b) O_3, 0.1% Sudan III, $NaBH_4$, DCM/MeOH, -78 °C to rt, 1 h, **51%**; c) TBSOTf, 2,6-lutidine, DCM, 0 °C, 4 h, **76%**; d) DDQ, pH 7 buffer, DCM, rt, 90 min.*

In this case, the desired aldehyde was received with a yield of 82%. Adjacently, the aldehyde was reduced with DIBAL-H yielding alcohol **243** (69%). Additionally, reductive ozonolysis conditions were tested by quenching the reaction with sodium borohydride instead of triphenylphosphine. In this case, the alcohol **243** was accessible in one step with a yield of 51%. Hereafter, the primary alcohol was converted to the TBS-ether **244** (TBSOTf, 2,6-lutidine, 76%). Then, the PMB-ether needed to be cleaved by using DDQ. In this case, only decomposition of the reactant was observed (Scheme 70). Since the TES-ether might be labile to the employed conditions, it was assumed that the PMB-ether deprotection could be affected thereby. Within the total synthesis approach the C_{23}- and C_{25}-hydroxy functions need to be distinguishable. Therefore, milder deprotection conditions ($MgBr_2$*OEt_2 and Me_2S) will

need to be implemented. Herein, the distinguishability of the two secondary alcohols did not matter. Hence, the protecting group approach was changed.

The acetonide was planned to be synthesised anyways, to proof the stereochemical outcome of the *Brown anti*-crotylation. Thus, the stereochemistry could be confirmed without loosing material, while also circumventing the instability issues of the TES-ether observed before. The TBS-ether was cleaved (TBAF, 89%) enabling an acetonide formation (quant). Hereafter, a reductive ozonolysis, implementing Sudan III as redox indicator, was performed giving rise to primary alcohol **246** (82%, Scheme 71). Transformation of the latter to aldehyde **247** started with TBS protection under standard conditions (TBSCl, imidazole, quant), followed by cleavage of the PMB-ether using DDQ in pH 7 buffer, cleanly providing the desired alcohol in 74% in this case.



*Scheme 71: Synthesis of compound **12**. Reaction conditions: a) TBAF, THF, 0 °C to rt, 3.5 h, **89%**; b) 2,2-DMP, p-TsOH, DCM, rt, 2 h, **quant**; c) O_3, 0.1% Sudan III, $NaBH_4$, -78 °C to rt, 2 h, **82%**; d) TBSCl, imidazole, DCM, 0 °C to rt, 6 h, **quant**; e) DDQ, pH 7 buffer, DCM, rt, 90 min, **74%**; f) IBX, DMSO, rt, 90 min, **quant**; g) KO^tBu, Ph_3PCH_3Br, THF, 0 °C to rt, 1 h, **51%**; h) CSA, THF/MeOH, 0 °C to rt, 3 h, **30%**.*

Lastly, the obtained alcohol was oxidised to aldehyde **247** utilising 2-iodoxybenzoic acid (IBX) (quant). Then, the terminal olefin was introduced *via* a *Wittig* reaction using methyltriphenylphosphonium bromide (KO^tBu, Ph_3PCH_3Br, 51%). The last step of the synthetic route was the global deprotection of the C_{23}-C_{25} acetonide, as well as the C_{27} TBS-ether. As both groups are known to be labile to acidic conditions, the protected olefin was treated with camphorsulfonic acid in a mixture of THF and methanol, resulting in the desired compound **12** (30%).[279]

Recapitulatory, the synthesis of **12** was performed in a LLS of 15 steps starting from (*S*)-*Roche* ester (**124**) in an overall yield of 2%. In comparison to the initially envisioned route, the sequence using the acetonide protecting group was one step longer. However, the yield of the reductive ozonolysis could be improved from 51% to 82%. Additionally, the yield of the TBS protection of the primary C_{27} hydroxy function was increased from 76% to a quantitative yield. Moreover, within the original protecting group approach the deprotection of the PMB group failed under the employed conditions, while it was possible to be conducted with a satisfactory yield (74%) in the second approach. Since the yields of the adjacent reactions

could be increased in combination with enabling the synthesis of the desired compound **12** lengthening the route by one step seemed reasonable.

2.4.8 Comparative NMR Analysis

In order to proof the proposed revised stereochemistry of neaumycin B (**234**, Figure 19), the triol fragment **12** and epoxide **13** were synthesised to perform a comparative NMR study. With both fragments in hand the NMR data were obtained and compared with the data published for the isolated natural product,[89] as well as with the data for the synthetic neaumycin B (**3**) by *Zhang et al*.[179] The procedure of first conducting a bioinformatic analysis of the biosynthetic gene cluster, proposing the stereochemistry of the respective natural product, followed by a NMR comparison of small fragments with the natural product has already proven to be valuable in the assignment of all stereocenters of vancoresmycin.[260] Therefore, the same approach was followed herein to revise the stereochemistry of neaumycin B (**3**).

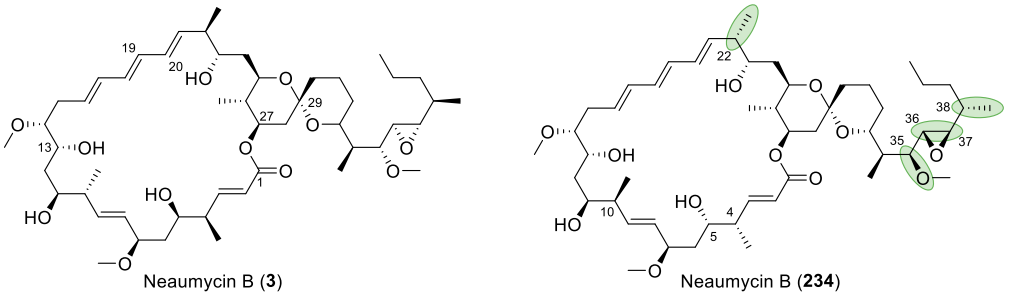


*Figure 19: Depiction of the proposed structure of neaumycin B (**3**) by Jensen and Fenical et al.[89] compared to the proposed revised structure of neaumycin B (**234**) by Adamek and Menche.[267] Changed stereocenters, that were part of this study are highlighted in green.*

2.4.8.1 Comparison of C_{20}-C_{27} Fragment 12

The results of the NMR comparison for the synthesised fragment **12** with the already published NMR data for neaumycin B[89] (**3**) are shown in Table 5 for the ^{1}H-NMR data and in Table 6 for the ^{13}C-NMR data.

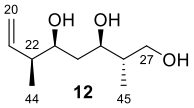


*Figure 20: Chemical structure of compound **12**.*

Table 5 contains the assigned ^{1}H-NMR signals for the C_{20}-C_{27} region of isolated and synthesised neaumycin B, corresponding to the herein synthesised fragment **12**. The last two columns of the table contain the differences of either the synthesised proposed structure of neaumycin B (**3**) to the isolated product or of the fragment **12** to the natural product. If the stereochemistry of either of the synthesised molecules matches the natural product, the difference of the NMR signals should be fairly small.

*Table 5: Comparison of the ^{1}H-NMR data of the isolated neaumycin B with the synthetic neaumycin B (**3**) by Zhang et al. and the data gained from fragment **12**. All data were obtained in $CDCl_3$.*

#H	δ NP[a][89]	δ *Zhang*[a][179]	δ *Menche*[a]	$\Delta(\delta_{NP} - \delta_{Zhang})$	$\Delta(\delta_{NP} - \delta_{Menche})$
20	6.02	6.03	5.11	-0.01	0.91
21	5.47	5.72	5.79	-0.25	-0.32
22	2.16	2.38)	2.31	-0.22	-0.15
44	1.11	1.10	1.05	0.01	0.06
23	3.45	3.89	3.78	-0.44	-0.33
24a	1.96	1.66	1.73	-0.30	0.23
24b	1.23	1.41	1.51	-0.18	-0.28
25	3.85	3.95	3.78	-0.10	0.07
26	1.47	1.55	1.73	-0.08	-0.26
45	0.66	0.78	0.89	-0.12	-0.23
27a	4.84	4.70	3.64	0.14	1.06
27b	4.84	4.70	3.78	0.14	1.2

[a]: chemical shift in [ppm], multiplicity and coupling constant in [Hz] neglected due to better clarity

The values for the differential of the edges of the small comparative fragments **12** and **13** will be high. As the chemical surrounding of the respective hydrogen or carbon atoms differs quite a lot from the structure of the macrocycle of neaumycin B, these results can be explained. Nevertheless, a comparison of the data of the stereocenters in question was still expected to be representative, as they would never be located too close to the edges of the comparative compounds.

Considering the higher differences for the ^{1}H data of the C_{21}-C_{24} region of the synthetic product by the group of *Zhang* and the natural product, an incorrect stereochemical assignment seemed likely.

*Table 6: Comparison of the ^{13}C-NMR data of the isolated neaumycin B with the synthetic neaumycin B (**3**) by Zhang et al. and the data gained from compound **12**. All data were obtained in $CDCl_3$.*

#C	δ NP[a][89]	δ *Zhang*[a][179]	δ *Menche*[a]	$\Delta(\delta_{NP} - \delta_{Zhang})$	$\Delta(\delta_{NP} - \delta_{Menche})$
20	131.1	130.7	116.1	0.4	15.0
21	137.3	136.4	140.4	0.9	-3.1
22	45.2	42.4	44.3	2.8	0.9
44	17.2	14.8	14.4	2.4	2.8
23	76.5	74.7	76.5	1.8	0.0
24	37.5	36.8	38.0	0.7	-0.5
25	76.3	75.5	79.0	0.8	-2.7
26	41.8	41.3	40.7	0.5	1.1
45	13.7	13.8	14.1	-0.1	-0.4
27	71.2	72.1	67.7	-0.9	3.5

[a]: chemical shift in [ppm]

The same analysis was conducted for the ^{13}C-NMR data of the respective C_{20}-C_{27} region (Table 6). Again, relatively large deviations between the data of the C_{22}-C_{23} region of the isolated and synthetic product **3** by *Zhang et al.* were observed, further reinforcing the stereochemistry had to be revised.

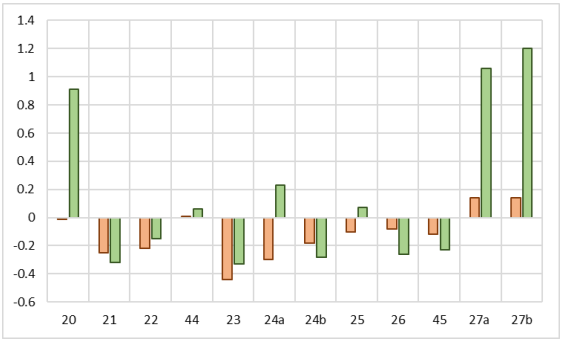


*Figure 21: ^{1}H chemical shift differences between isolated neaumycin B[89] and C_{20}-C_{27} fragment **12**. $\Delta(\delta_{NP} - \delta_{Zhang})$ shown in orange and $\Delta(\delta_{NP} - \delta_{Menche})$ shown in green.*

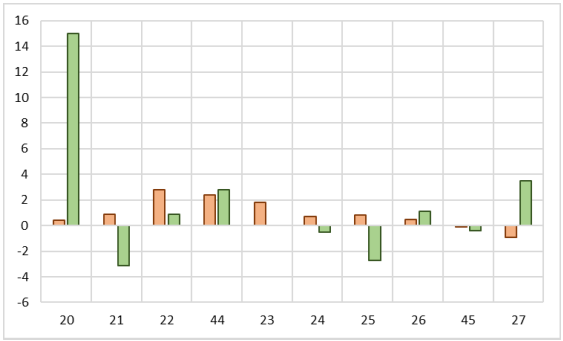


*Figure 22: ^{13}C chemical shift differences between isolated neaumycin B[89] and C_{20} to C_{27} fragment **12**. $\Delta(\delta_{NP} - \delta_{Zhang})$ shown in orange and $\Delta(\delta_{NP} - \delta_{Menche})$ shown in green.*

Since the *de novo* conducted bioinformatic analysis suggested a different stereochemistry as well, C_{22} center was changed in compound **12**. Thus, the deviations of the gained NMR data could be minimised for both ^{1}H and ^{13}C NMR data. The results of Tables 5 and 6 were further visualised as bar diagrams (Figures 21 and 22).

The depicted bars represent the values of $\Delta(\delta_{NP} - \delta_{Zhang})$ in orange and $\Delta(\delta_{NP} - \delta_{Menche})$ in green respectively. In coherence with the results explained above, the green bars tend to be smaller in respect to the C_{22}-C_{24} region for Figure 21 and the C_{22}-C_{23} region for Figure 22.The only stereocenter within this fragment of the structure, that should be changed according to the revised stereochemical prediction, was the C_{22} methyl group. As it can be seen in the Tables 5 and 6 as well as in the Figures 21 and 22 the deviation of the NMR data was minimised compared to the previous results.[179] In combination the data may suggest that the (*R*) configuration of C_{22} has to be revised to (*S*) instead.

2.4.8.2 Comparison of C_{33}-C_{41} Fragment 13

Similarly, the ^{1}H- and ^{13}C-NMR data of compound **13** were compared to the data of the isolated[89] and synthesised product **3** (Tables 7 and 8).[179]

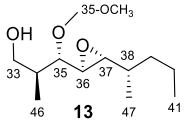


*Figure 23: Chemical structure of compound **13**.*

As opposed to the results presented above, in the case of compound **13** no conclusive results were obtained based on the conducted NMR study. The regions showing larger deviations of the synthesised compound **3** towards the isolated neaumycin B were C_{34}-C_{35} and C_{36}-C_{38} (Tables 7 and 8). Unfortunately, after revision of the stereochemistry the obtained values for compound **13** were not significantly smaller (H_{35}, H_{38} and H_{46}) or even bigger (H_{34}, H_{36}, H_{37} and H_{47}) than before. Hence, the proposed stereochemistry of compound **13** or the C_{33}-C_{41} region of neaumycin B could not be confirmed.

While conducting the comparative NMR study with epoxide **13**, it became apparent, that the spiroketal moiety had a greater influence than expected. In consequence of the missing spiroketal motif, the electronic characteristics influencing the C_{33}-C_{41} region of neaumycin were not displayed. Additionally, the spiroketal potentially forces the side chain into a favoured conformation, further influencing the observed chemical shifts.

*Table 7: Comparison of the ^{1}H-NMR data of the isolated neaumycin B with the synthetic neaumycin B (**3**) by Zhang et al. and the data gained from fragment **13**. All data were obtained in $CDCl_3$.*

#H	δ NP[a][89]	δ *Zhang*[a][179]	δ *Menche*[a]	$\Delta(\delta_{NP} - \delta_{Zhang})$	$\Delta(\delta_{NP} - \delta_{Menche})$
33a	3.50	3.59	3.72	-0.09	-0.20
33b	3.50	3.59	3.62	-0.09	-0.12
34	1.61	1.70	2.00	-0.09	-0.39
46	0.93	1.11	1.04	-0.18	-0.11
35	3.19	2.92	2.95	0.27	0.24
35-OCH_3	3.54	3.43	3.43	0.11	0.11
36	2.94	2.98	2.76	-0.04	0.18
37	2.47	2.47	2.75	0.00	-0.28
38	1.36	1.40	1.37	-0.04	-0.01
47	1.02	1.02	0.98	0.00	0.04
39a	1.40	1.39	1.52	0.01	-0.12
39b	1.26	1.24	1.37	0.02	-0.11
40a	1.39	1.40	1.37	-0.01	0.02
40b	1.34	1.33	1.37	0.01	-0.03
41	0.91	0.92	0.91	-0.01	0.00

[a]: chemical shift in [ppm], multiplicity and coupling constant in [Hz] neglected due to better clarity

By comparing the ^{13}C-NMR data (Table 8) a similar picture emerged. In this case, none of the obtained differences were smaller, but the deviation for C_{34}, C_{46}, C_{35}, $C_{35\text{-}OCH3}$, C_{36}, C_{37}, C_{47} and C_{39} were actually larger. In order to visualise the results, the following diagrams (Figures 24 and 25) were created from the data in Tables 7 and 8 once again. Within the C_{33}-C_{41} fragment **13**, the chiral centers at C_{35}, C_{36}, C_{37} and C_{38} were proposed to have to be changed. Looking at Figures 24 and 25 it became quite apparent, that the aquired data for compound **13** did not match the natural product as well.

*Table 8: Comparison of the ^{13}C-NMR data of the isolated neaumycin B with the synthetic neaumycin B (**3**) by Zhang et al. and the data gained from compound **13**. All data were obtained in $CDCl_3$.*

#C	δ NP[a][89]	δ *Zhang*[a][179]	δ *Menche*[a]	$\Delta(\delta_{NP} - \delta_{Zhang})$	$\Delta(\delta_{NP} - \delta_{Menche})$
33	73.1	75.0	66.2	-1.9	6.9
34	43.3	42.2	38.8	1.1	4.5
46	10.4	11.1	13.3	-0.7	-2.9
35	80.5	82.2	85.5	-1.7	-5.0
35-OCH_3	58.1	58.0	58.9	0.1	-0.8
36	61.2	60.3	56.5	0.9	4.7
37	58.8	59.3	62.5	-0.5	-3.7
38	35.5	35.7	35.7	-0.2	-0.2
47	17.1	16.9	16.0	0.2	1.1
39	35.7	35.7	36.9	0.0	-1.2
40	20.3	20.3	20.2	0.0	0.1
41	14.1	14.4	14.4	-0.3	-0.3

[a]: chemical shift in [ppm]

Apart from the possibility that the predicted stereochemistry for the C_{33}-C_{41} region was incorrect, the already mentioned influence of the neighbouring spiroketal group within the natural product might be greater than expected. Since the extend of the influence of the latter can not be assumed, further studies will need to be performed.

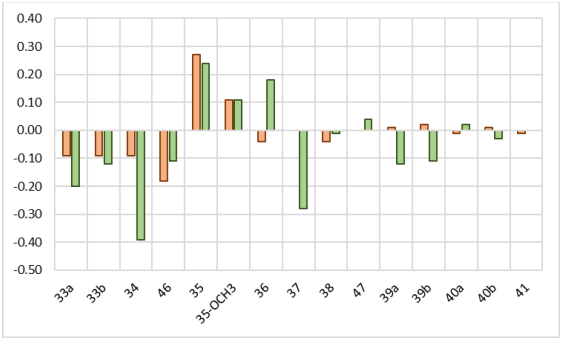


*Figure 24: ^{1}H chemical shift differences between isolated neaumycin B[89] and C_{33} to C_{41} fragment **13**. $\Delta(\delta_{NP} - \delta_{Zhang})$ shown in orange and $\Delta(\delta_{NP} - \delta_{Menche})$ shown in green.*

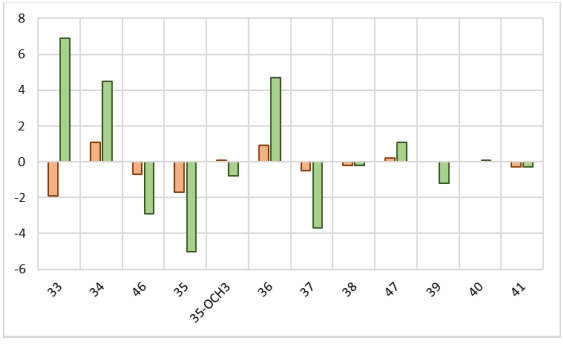


*Figure 25: ^{13}C chemical shift differences between isolated neaumycin B[89] and C_{33} to C_{41} fragment **13**. $\Delta(\delta_{NP} - \delta_{Zhang})$ in orange and $\Delta(\delta_{NP} - \delta_{Menche})$ shown in green.*

2.5 Conclusion and Outlook

2.5.1 Conclusion

In summary, two different retrosynthetic approaches were developed to accomplish the total synthesis of the proposed structure of neaumycin B (**3**). Following the plan of the first retrosynthetic analysis compound **8** was prepared from (*R*)-*Roche* ester (**92**) in a LLS of ten steps with a yield of 22% (Scheme 72). Key steps of the fragment synthesis were the consecutive *Brown* allylation and crotylation in combination with the ozonolysis of terminal olefins using Sudan III as redox indicator.



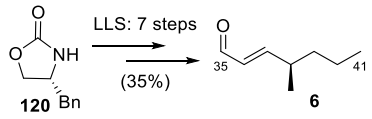
*Scheme 72: Synthesis of aldehyde **8** for the planned Mukaiyama aldol reaction.*

The α,β-unsaturated aldehyde **6** was prepared from (*S*)-4-benzyl-3-propionyloxazolidin-2-one (**94**) in a LLS of seven steps with an overall yield of 16%. Herein, the stereochemistry of the C_{38} methyl group was set in an *Evans* alkylation while the (*E*)-configured double bond was introduced in a one-pot *Swern* oxidation *Wittig* reaction (Scheme 73).



*Scheme 73: First synthetic route towards aldehyde **6** for the envisioned Paterson aldol reaction.*

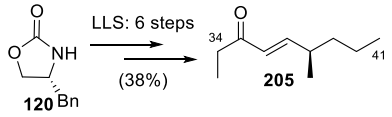
Since the conversion of the commercially available (*S*)-4-benzyl-3-propionyloxazolidin-2-one (**94**) in an *Evans* alkylation gave low yields and resulted in a tedious purification process the synthesis of aldehyde **6** was revised. Starting the synthesis from (*R*)-4-benzyl-2-oxazolidinone (**120**) gave rise to compound **6** in a LLS of seven steps, as well increasing the overall yield to 35% while the key steps of the synthesis remained the same (Scheme 74).



*Scheme 74: Second synthesis of aldehyde **6** for the planned Paterson aldol.*

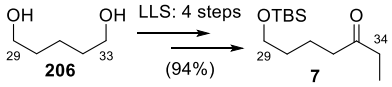
In order to test both possibilities of the fragment coupling in the envisioned *Paterson* aldol reaction, the alcohol obtained from the reductive cleavage of the auxiliary was converted to the α,β-unsaturated ketone **205** in a one-pot *Swern* oxidation, HWE reaction. Thus,

compound **205** was obtained in six linear steps starting from (*R*)-4-benzyloxazolidin-2-one (**120**) with an overall yield of 38% (Scheme 75).



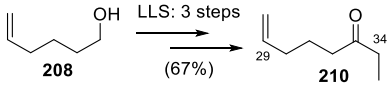
*Scheme 75: Synthetic route towards ketone **205** for the Paterson aldol reaction with swapped functionalities.*

Firstly, the ketone fragment **7** was planned to be used in the *Paterson* aldol reaction with aldehyde **6**. Hence, 1,5-pentandiol was converted to the respective ketone in a four-step sequence with a yield of 94% (Scheme 76).



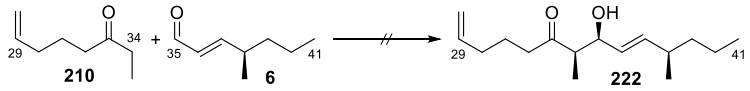
*Scheme 76: First synthetic approach of ethyl ketone **7** for the Paterson aldol reaction.*

However, using the protected alcohol as synthon for a methyl ketone that should be installed in the late stage synthesis of eastern fragment **9** would add four extra steps to the overall synthesis. Therefore, the protected alcohol was exchanged for a double bond, which can be transferred to a methyl ketone in a *Wacker* oxidation. Starting from pent-5-en-1-ol (**208**) the respective ketone **210** was obtained within three steps in a yield of 67% (Scheme 77).



*Scheme 77: Synthesis of adapted ethyl ketone **210** for the Paterson aldol reaction.*

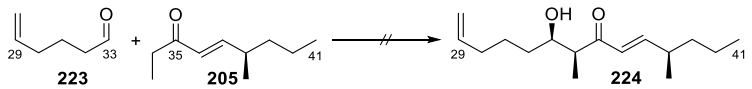
Initially, the *Paterson* aldol reaction between ketone **210** and aldehyde **6** was investigated with different screened conditions listed in Table 3. However, none of the applied conditions led to the desired product **222** (Scheme 78). Thereafter, the functionalities of ketone and aldehyde were swapped to investigate, if that would facilitate the desired reaction in this case.



*Scheme 78: Paterson aldol between aldehyde **6** and ketone **210**.*

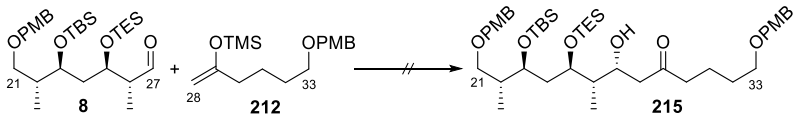
Freshly prepared aldehyde **223** was obtained from pent-5-en-1-ol (**208**) using *Parikh-Doering* conditions. Then, it was conducted to a *Paterson* aldol reaction with enolised ketone **205** (Scheme 79). Since the *Paterson* aldol reaction depeicted in Scheme 78 did not lead to the

desired product the functionalities of the two components were swapped. But unfortunately,[261] no conversion took place either and both starting materials were reisolated. As all tested aldol conditions did not lead to the desired product, the approach to install the C-C bond was changed.



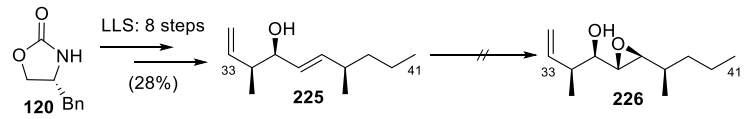
Scheme 79: Failed Paterson aldol reaction with swapped functionalities.

Unfortunately, the envisioned *Mukaiyama* aldol reaction between aldehyde **8** and ketone **211** was not successful under the tested conditions either. Therefore, compound **215** could not be obtained within this study (Scheme 80).

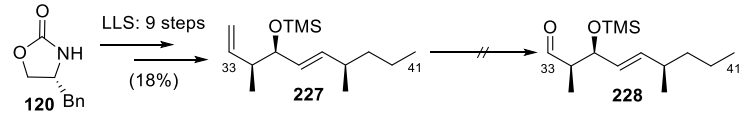


*Scheme 80: Failed Mukaiyama aldol of aldehyde **8** and in situ generated SEE **212** from ketone **211**.*

Since the planed *Paterson syn* aldol reaction was not successful, the retrosynthesis of the eastern fragment **9** was adapted. Instead of setting the stereochemistry of the C_{34} methyl group as well as the C_{35} hydroxy group within the fragment coupling, a *Brown* crotylation was performed yielding compound **225** in a LLS of eight steps with an overall yield of 28% (Scheme 80). Thereafter, the fragment coupling should proceed *via* a *Rychnovsky* coupling, installing the C_{32}-C_{33} bond. To prepare the desired cyanohydrin, either the epoxide should be introduced first or a selective oxidative cleavage of the terminal olefin should be performed. But neither of the two approaches worked as intended.



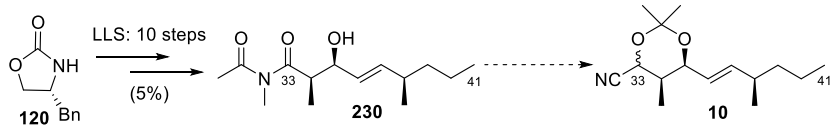
*Scheme 81: First failed synthetic approach towards cyanohydrin **10**.*



*Scheme 82: Second failed approach towards cyanohydrin **10**.*

Therefore, the synthesis of cyanohydrin **10** was slightly adapted. In this case, the stereochemistry of the C_{34} methyl group and the C_{35} hydroxy group was set in an *Evans* aldol

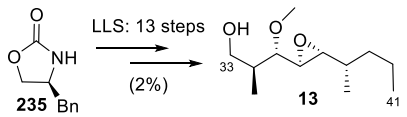
reaction. After the transformation of the auxiliary to the *Weinreb* amide, compound **230** was obtained in 5% over a LLS of ten steps. To furnish the synthesis of compound **10**, the *Weinreb* amide **230** would need to be transferred to the aldehyde, followed by the three-step one-pot conversion of the latter to the desired cyanohydrin **10**. Due to the confirmation of the wrongly assigned stereochemistry of the isolated neaumycin B (**3**)[149,179] this approach was not further pursued (Scheme 83).



*Scheme 83: Successful synthesis of Weinreb amide **230**.*

Based on the results published by *Smith et al*.[149] and *Zhang et al*.,[179] the stereochemistry of the natural product neaumycin B (**3**) needed to be revised. Therefore, *M. Adamek* (*Ziemert* group, Eberhard Karls university of Tübingen) performed a bioinformatic analysis of the biosynthetic gene cluster producing neaumycin B once again.[267] In combination with a careful re-evaluation of the published NMR assignment by *Jensen* and *Fenical et al*.,[89] a revised stereochemistry of neaumycin B (**234**) was proposed.[267] In order to prove the suggested stereochemistry, compounds **12** and **13** (Scheme 84) were synthesised. As the general structure of the fragments remained the same, their synthesis was closely related to the ones presented above.

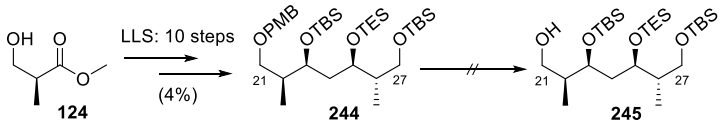
Hence, the synthesis of alcohol **13** commenced with the addition of valeric acid (**202**) to (*S*)-4-benzyloxazolidin-2-one (**235**). However, to introduce the *anti* motif of the C_{34} methyl group and the C_{35} methoxy group a *Masamune anti* aldol reaction was conducted. The epoxide was established in a *syn* fashion using *Sharpless* conditions. In summary, compound **13** was obtained in a LLS of 13 steps starting from (*S*)-4-benzyloxazolidin-2-one (**235**) in an overall yield of 2% (Scheme 84).



*Scheme 84: Synthesis of the adapted C_{33}-C_{41} fragment **13** of neaumycin B (**234**) for NMR comparison with the natural product.*

The synthesis of the C_{20}-C_{27} compound **12** (Scheme 85) was initially performed in analogy to the presented approach towards aldehyde **8**. However, in this case the starting material was the enantiomeric (*S*)-*Roche* ester (**124**). As seen before, a *Brown* allylation followed by a *Brown*

crotylation allowed to build up the carbon backbone of compound **231**. Unfortunately, decomposition took place during the deprotection of the PMB-ether, due to the instability of the TES-ether to the employed conditions.



*Scheme 85: Failed approach towards the revised C_{20}-C_{27} fragment **12** of neaumycin B (**234**).*

Thence, the protecting group strategy was revised, utilising an 1,3-acetonide instead of the silyl groups. The latter simultaneously confirmed the 1,3-*syn* arrangement of the diol. Herein, the deprotection of the PMB-ether proceeded smoothly, giving rise to the primary alcohol. Subsequently, an IBX oxidation followed by a *Wittig* reaction were performed. After the global deprotection using acidic conditions compound **12** was obtained in a LLS of 15 steps starting from compound **124** with an overall yield of 2% (Scheme 86).



*Scheme 86: Successful synthesis of the adapted C_{20} to C_{27} fragment **12** of neaumycin B (**234**).*

With both compounds **12** and **13** in hand, the proposed stereochemistry should be confirmed in a NMR study. Thus, the NMR data of fragments **12** and **13** were compared with the data of the isolated neaumycin B, as well as the prepared neaumycin B (**3**).[89] During the analysis of the obtained data it became apparent, that the suggested stereochemistry of the C_{20}-C_{27} fragment **12** (Figure 26, **A**) matched the data of the natural product, while the data for the C_{33}-C_{41} fragment **13** (Figure 26, **B**) was not conclusive.

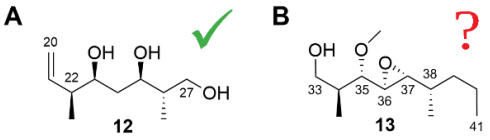
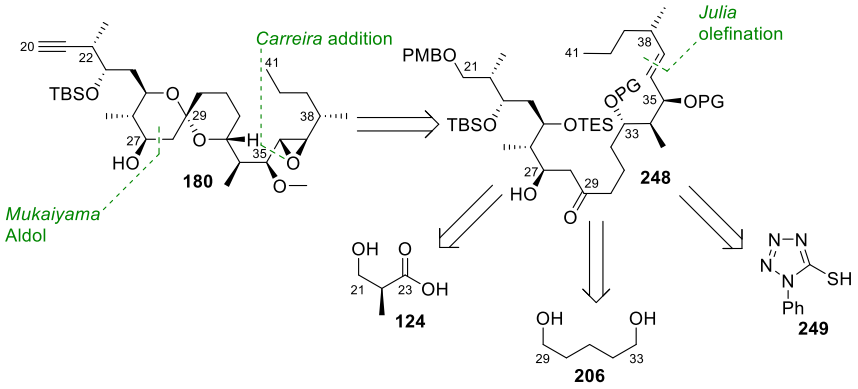


*Figure 26: Results of the conducted NMR comparison. **A**: Revised stereochemistry of C_{22} of **12** matched the data for the natural product suggesting to represent the correct stereochemistry. **B**: NMR data of comparative fragment **13** did not match the data of the natural product, therefore leaving the correct stereochemistry of this part of the molecule unresolved.*

2.5.2 Outlook

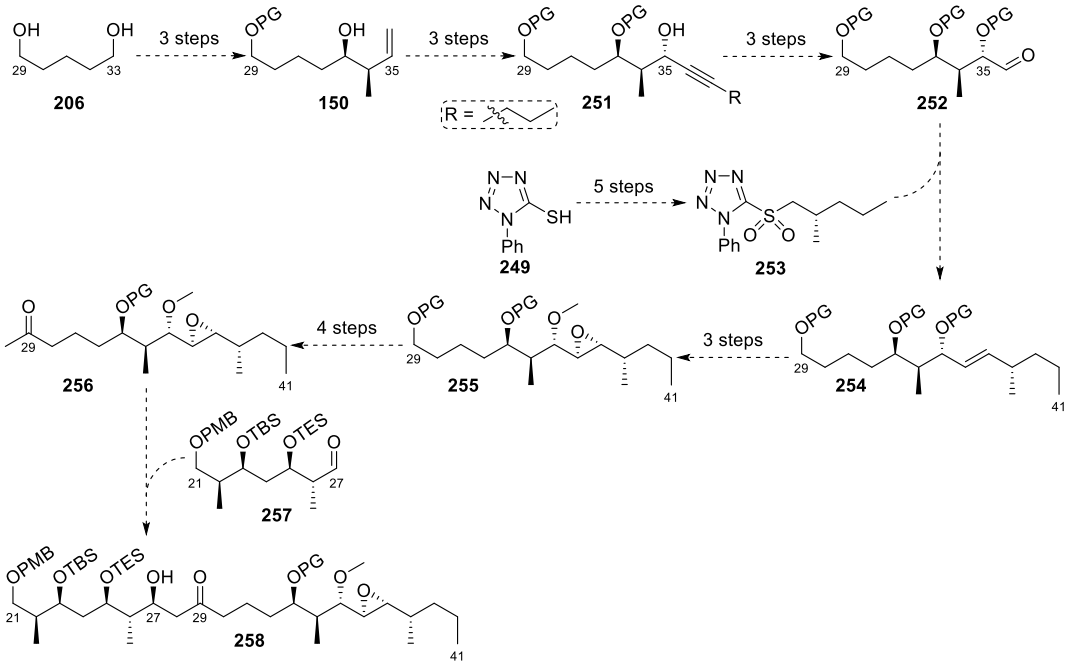
With the insights gained while working on this project and studying related literature, a third retrosynthetic analysis of the eastern fragment **180** of neaumycin B (**234**) was developed (Scheme 87).[280] Herein, a linear synthesis of the C_{28}-C_{36} part of the linear precursor of the

eastern fragment **180** of neaumycin B (**234**) is planned while the C_{36}-C_{37} olefin will be introduced following a literature known *Julia* olefination.[281,282]



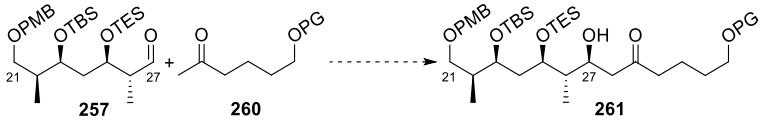
*Scheme 87: Revised retrosynthetic analysis of eastern fragment **180** of neaumycin B (**234**).*

Furthermore, the stereochemistry of the C_{33}-C_{41} fragment will need to be corrected. Currently, a different promising diastereomer is being synthesised as part of the master thesis of *T. Treu*. Regardless of the results thereof, the proposed synthetic route would be adaptable. As the stereochemistry of the C_{33} and C_{34} chiral centers will be established in a *Brown* crotylation, all four diastereomers would be accessible. The same will apply for the planned *Carreira* addition of the *in situ* generated pentynylzinc compound to the aldehyde obtained from compound **250**. Herein, the use of either (+)- or (-)-*N*-methyl ephedrine will determine the stereochemical outcome of the addition (Scheme 88). Moreover, both C_{38} enantiomers are accessible following a known procedure.[281,282] Lastly, there are multiple well known procedures to establish the epoxide in the desired configuration. Besides the adaptability of the proposed synthetic route it would also reduce the number of linear steps to obtain the C_{29} to C_{41} fragment **254** from 16 to ten. Since the C_{36}-C_{37} double bond will be installed in a *Julia* olefination the one-pot *Swern* oxidation *Wittig* reaction will be circumvented which posed as the bottle neck of the herein presented syntheses of this motif.



*Scheme 88: Proposed synthesis towards linear precursor **258** of spiroketal **180**.*

Since the proposed revision of the stereochemistry of the C_{20}-C_{27} fragment **12** of neaumycin B (**234**) was confirmed, the intended *Mukaiyama* aldol reaction between the respective aldehyde **257** and methyl ketone **260** should be further investigated (Scheme 88). Especially as it would represent the final coupling step in the adapted synthesis of the spiroketal compound **180** (Scheme 87). Hence, establishing suitable conditions for this key step in future studies will be crucial.



Scheme 89: Test system for the investigation of suitable conditions for the key Mukaiyama aldol addition.

3 Experimental Part

3.1 Materials and Methods

3.1.1 Reaction Conditions

All used reagents were purchased from commercial suppliers (*Sigma Aldrich*, *TCI*, *Acros*, *Alfa Aesar*, *abcr*, *Carbolution*, *BLDpharm*) in the highest available purity grade and used without further purification. Anhydrous solvents (THF, toluene, CH_2Cl_2, MeCN, Et_2O, *n*-hexane, DMF, DMSO, acetone) were obtained from a solvent drying system MB SPS-800 (*MBraun*) and stored over molecular sieves (3 Å or 4 Å). The employed starting materials for the herein presented synthesis of lipid I and II analogues have been prepared during the preceding master thesis, according to published procedures.[63]

Unless stated otherwise, all reactions were performed in dry solvents under an argon atmosphere in flame-dried glassware, which had been flushed with argon. The reactants were handled using standard *Schlenk* techniques. Temperatures above rt (23 °C) refer to oil bath temperatures, which were controlled by a temperature modulator. Cooling of reactions was carried out by using the following baths: acetone/dry ice (−78 °C), water/ice (0 °C). For cooling overnight or to different temperatures an immersion cooler was used (*Huber*, TC100E-F).

TLC monitoring was performed using silica gel 60F254 pre-coated polyester sheets (0.2 mm silica gel, *Macherey-Nagel*) and for reversed phase TLC silica gel 60 RP-18 F254S pre-coated aluminum sheets (*Merck*). The spots were detected by using UV light (365 nm, 254 nm) and staining with one of the following staining solutions and subsequent heating. Used staining solutions being CAM (1.0 g $Ce(SO_4)_2$) , 2.5 g $(NH_4)_6Mo_7O_{24}$, 8.0 mL conc. H_2SO_4 in 100.0 mL H_2O), PMA (10.0 g $H_3[P(Mo_3O_{10})_4]$*x H_2O, 200.0 mL), potassium permanganat (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL 10% NaOH, 200 mL H_2O), sulfuric acid (10% conc. H_2SO_4/abs. methanol).

3.1.2 Purification Methods

Flash column chromatography was performed using silica gel (pore size 60 Å; 40-63 µm) purchased from *MerckMillipore* or *Sigma Aldrich.* For reversed phase column chromatography C18-reversed phase silica gel (pore size 90 Å) from *Sigma Aldrich* or *Carl Roth* was used. Elution of the compounds was executed using the stated solvent mixtures under a positive pressure of air. Solvents for column chromatography were either purchased in HPLC grade or distilled prior to use. Semi-preparative and analytical HPLC analyses were performed on *Knauer*

Wissenschaftliche Geräte GmbH systems by *A. J. Schneider*. All solvents used for HPLC were purchased in HPLC grade. The chromatograms were recorded by UV-detection. Given yields refer to the purified products.

3.1.3 Analytical Methods

All NMR spectra were recorded in deuterated solvents obtained from *Deutero*, *Carl Roth* or *Sigma Aldrich* on *Bruker* spectrometers at the *University Bonn* under supervision of *Dr. S. Nozinovic*. Operating frequencies being 100 (**^{13}C**), 125 (**^{13}C**), 175 (**^{13}C**), 400 (**^{1}H**), 500 (**^{1}H**), and 700 MHz (**^{1}H**). Spectra were measured at room temperature (298 K) unless stated otherwise and chemical shifts are reported in ppm relative to $(Me)_4Si$ (δ = 0.00 ppm) and were calibrated to the residual signal of undeuterated solvents. Obtained data for **^{1}H** NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens, assignment). Abbreviations used are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

Mass spectra (**MS**) and high-resolution-mass spectra (**HRMS**) were recorded on the documented systems in Table 9 at the *University Bonn* under supervision of *Dr. M. Engeser*.

*Table 9: Used MS systems for **MS** and **HRMS**.*

System	Manufacturer	Measurements
micrOTOF-Q	*Bruker Daltonik*	ESI, APCI, nano-ESI, MS-MS
Orbitrap XL	*Thermo Fischer Scientific*	ESI, APCI, APPI, nano-ESI
Apex IV FT-ICR	*Bruker Daltonic*	ESI, nano-ESI, MALDI, EI, CI

Optical Rotation

Data were recorded on *Anton Paar* MCP 150 at 20 °C with a 10.00 mm cuvette using a LED (589 nm) as light source. The optical rotation was measured three times and the specific rotation was calculated. $[\alpha]\lambda T = \alpha\lambda T l \cdot c$

$$[\alpha]_\lambda^T = \frac{\alpha_\lambda^T}{l \cdot c}$$

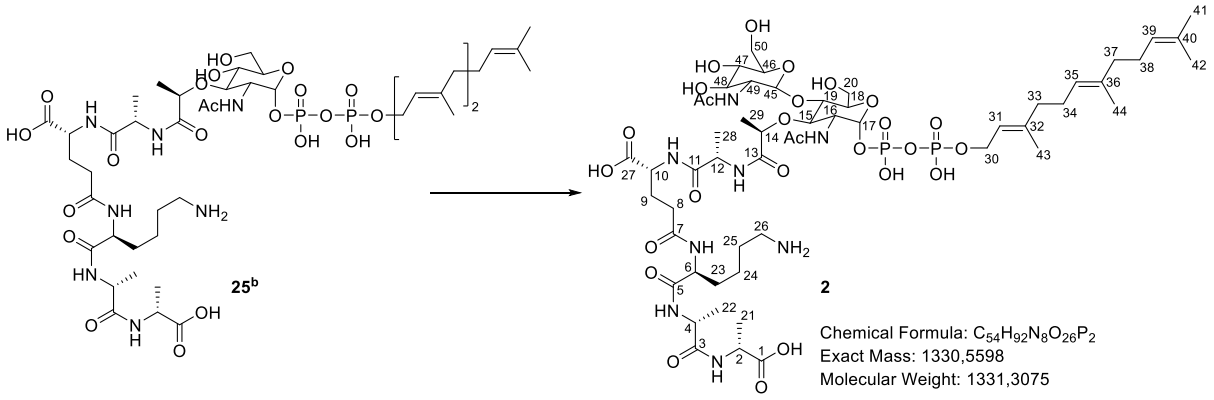
[α]: specific rotation [°·mL·dm^{-1}·g^{-1}], λ = wave length of light source [nm], *T* = temperature [°C], α = optical rotation [°], *l* = length of cuvette [dm], *c* = concentration [g·mL^{-1}].

The concentration (*c* = 1.00 ≡ 10 mg/mL) and the solvent are indicated in the parenthesis.

3.2 Synthesis of Lipid I/II and Analogues Thereof

Synthesis of Compound 2

N^2-(((2*R*)-2-(((2*R*,3*R*,4*R*,5*S*,6*R*)-3-Acetamido-5-(((2*S*,3*R*,4*R*,5*S*,6*R*)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-2-((hydroxy((hydroxy(((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)phosphoryl)oxy)phosphoryl)oxy)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yl)oxy)propanoyl)-L-alanyl)-N^5- ((*S*)-6-amino-1-(((*R*)-1-(((*R*)-1-carboxyethyl)amino)-1-oxopropan-2-yl)amino)-1- oxohexan-2-yl)-D-glutamine



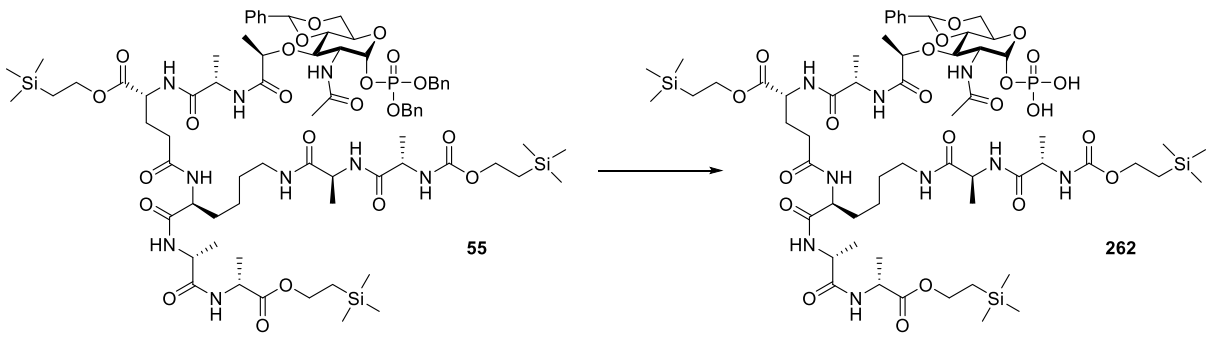
The chemoenzymatic conversion of compound **25^b** was performed *in vitro* in a total volume of 4.5 mL containing 1.50 mg (1.33 mmol) compound **25^b**, 2 mM UDP–D-GlcNAc, 50 mM NaP_i and 0.5 mM $MgCl_2$, pH 6.5. The reaction was initiated by the addition of 300 mg of MurG– His_6. Subsequent to the incubation of the mixture for 4 h at 30 °C it was quenched by the addition of 9 mL MeOH and evaporated to dryness. The dried samples were dissolved in distilled water for mass spectrometric analysis. The crude product was purified by HPLC (35 – 50% NH_4HCO_3 (0.1% aq.)/methanol, retention time 8.0 min, using a KNAUER Eurospher II 100-5 C8; 5 mm; 250 – 16 mm + precolumn 30 – 16 mm, 205 nm) yielding 0.98 mg (0.73 mmol, 55%) of a white, amorphous solid. Recombinant MurG–His_6 enzyme was overexpressed and purified as described for MurG[39] and dialysed against 10 mM NaP_i buffer, pH 7.0.

α_D^{25} = +11 ° (c = 0.18 in H_2O). **^{1}H** NMR (D_2O, 700 MHz) δ = 5.50 – 5.47 (m, 1H, H-17), 5.46 (t, *J* = 6.9 Hz, 1H, H-31), 5.23 (t, *J* = 6.4 Hz, 1H, H-35), 5.20 (t, *J* = 6.4 Hz, 1H, H-39), 4.63 (d, *J* = 8.3 Hz, 1H, H-45), 4.51 – 4.49 (m, 2H, H-30), 4.35 (q, *J* = 7.1 Hz, 1H, H-4), 4.32 – 4.27 (m, 2H, H-12, H-14), 4.24 – 4.20 (m, 2H, H-6, H-10), 4.15 – 4.12 (m, 3H, H-2, H-16), 3.98 – 3.89 (m, 4H, H-18, H-19, H-20, H-50), 3.86 – 3.81 (m (pt), 1H, H-15), 3.79 – 3.74 (m, 3H, H-20, H-49, H-50), 3.58 (pt (dd), *J* = 8.6 Hz, 1H, H-48), 3.46 – 3.91 (m, 2H, H-46, H-47), 2.97 (t, *J* = 7.0 Hz, 2H, H-26),

2.34 – 2.33 (m, 2H, H-8), 2.19 – 2.17 (m, 3H, H-9, H-34), 2.14 – 2.11 (m, 4H, H-33, H-38), 2.07 (s, 3H, CH_3–NHAc), 2.05 (t, *J* = 7.7 Hz, 2H, H-37), 2.01 (s, 3H, CH_3–NHAc), 1.93 – 1.89 (m, 1H, H-90), 1.86 – 1.82 (m, 1H, H-23), 1.81 – 1.79 (m, 1H, H-23), 1.74 (s, 3H, H-43), 1.71 (s, 3H, H-42), 1.69 – 1.66 (m, 2H, H-25), 1.64 (s, 6H, H-41, H-44), 1.47 (d, *J* = 6.9 Hz, H-28), 1.46 (d, *J* = 6.8 Hz, 3H, H-29), 1.45 – 1.39 (m, 2H, H-24), 1.40 (d, *J* = 7.2 Hz, 3H, H-22), 1.35 (d, *J* =7.2 Hz, 3H, H-21). **^{13}C** NMR (D_2O, 176 MHz) δ = 179.8 (C-1), 177.6 (C-27), 175.7 (C-11), 175.7 (C-7), 174.4 (NHAc–C=O), 174.2 (NHAc–C=O), 174.1 (C-5), 174.0 (C-3), 173.6 (C-13), 143.2 (C-32), 136.7 (C-36), 133.5 (C-40), 124.4 (C-39), 124.2 (C-35), 119.3 (C-31), 100.1 (C-45), 94.2 (C-17), 78.4 (C-14), 77.9 (C-15), 75.9 (C-46), 74.0 (C-48), 73.8 (C-18), 72.4 (C-19), 70.3 (C-47), 63.1 (C-30), 61.1 (C-50/C-20), 59.7 (C-50/C-20), 56.1 (C-49), 54.3 (C-6), 53.7 (C-10), 53.5 (C-16), 51.0 (C-2), 50.0 (C-12), 49.6 (C-4), 39.2 (C-26), 38.8 (C-33), 38.8 (C-37), 31.8 (C-8), 30.5 (C-23), 28.2 (C-9), 26.5 (C-25), 25.8 (C-38), 25.6 (C-34), 24.9 (C-42), 22.2 (C-24), 22.2 (NHAc–CH_3), 22.1 (NHAc–CH_3), 18.7 (C-22), 17.4 (C-21), 17.0 (C-41), 16.9 (C-28), 16.5 (C-29), 15.7 (C-43), 15.3 (C-44). ^{31}P NMR (D_2O, 284 MHz) δ = - 10.9 (d, *J* = 20.7 Hz), - 13.4 (d, *J* = 19.2 Hz). **HRMS (ESI)** m/z: calcd for $C_{54}H_{90}N_8O_{26}P_2$ $[M - 2H]^{2-}$: 664.2726, found: 664.2719, calcd for $C_{54}H_{89}N_8O_{26}P_2$ $[M - 3H]^{3-}$: 442.5127, found: 442.5117. The spectroscopic data were in agreement with those previously reported.[44]

Synthesis of Compound 262

2-(Trimethylsilyl)ethyl N^2-(((*R*)-2-(((2*R*,4a*R*,6*R*,7*R*,8*R*,8a*S*)-7-acetamido-2-phenyl-6-(phosphonooxy)hexahydropyrano[3,2-d][1,3]dioxin-8-yl)oxy)propanoyl)-L-alanyl)-N^5-((*S*)-1-oxo-1-(((*R*)-1-oxo-1-(((*R*)-1-oxo-1-(2-(trimethylsilyl)ethoxy)propan-2-yl)amino)propan-2-yl)amino)-6-((*S*)-2-((*S*)-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)propanamido)propanamido)hexan-2-yl)-D-glutaminate



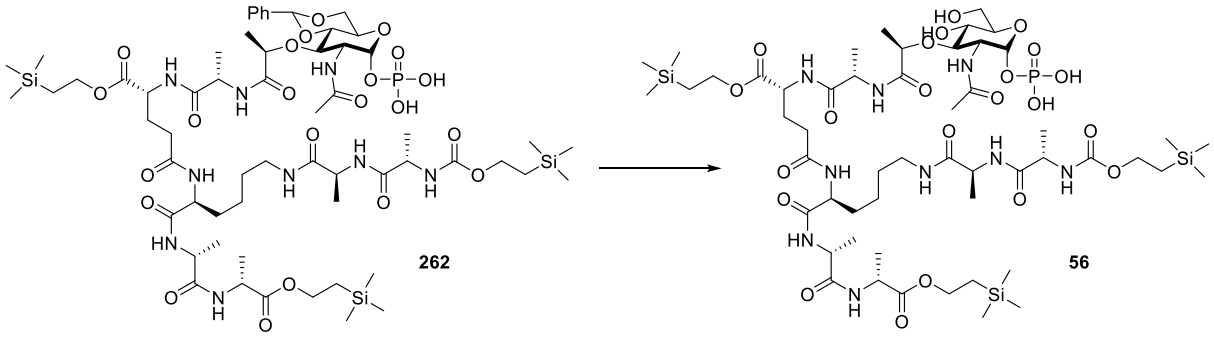
Chemical Formula: $C_{60}H_{104}N_9O_{22}PSi_3$
Exact Mass: 1417,6341
Molecular Weight: 1418,7618

Compound **55** (61.6 mg, 38.5 µmol, 1.00 eq) was dissolved in MeOH (3.85 mL) and Pd/C (62.8 mg, Pd-10%) was added. The flask was flooded with H_2 and was stirred at room temperature overnight until full conversion to compound **262** was detected by mass spectrometry. The reaction mixture was filtered over Celite® and the residue was washed with methanol. The solvent was removed under reduced pressure to yield 44.4 mg (31.3 µmol, 81%) of a colourless, crystalline solid which was used without further purification or analysis.

HRMS (ESI) *m/z*: calcd for $C_{60}H_{103}N_9O_{22}PSi_3$ $[M - H]^-$: 1416.6269, found: 1416.6289.[54]

Synthesis of Compound 56

2-(Trimethylsilyl)ethyl N²-(((*R*)-2-(((2*R*,3*R*,4*R*,5*S*,6*R*)-3-acetamido-5-hydroxy-6-(hydroxymethyl)-2-(phosphonooxy)tetrahydro-2H-pyran-4-yl)oxy)propanoyl)-L-alanyl)-N⁵-((*S*)-1-oxo-1-(((*R*)-1-oxo-1-(((*R*)-1-oxo-1-(2-(trimethylsilyl)ethoxy)propan-2-yl)amino)propan-2-yl)amino)-6-((*S*)-2-((*S*)-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)propanamido)propanamido)hexan-2-yl)-D-glutaminate



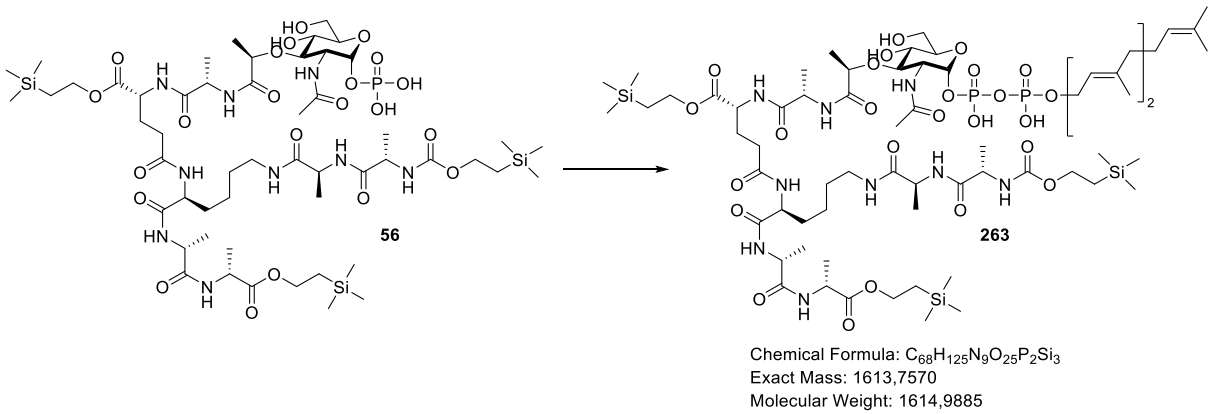
Chemical Formula: $C_{53}H_{100}N_9O_{22}PSi_3$
Exact Mass: 1329,6028
Molecular Weight: 1330,6528

Acetal **262** (44.4 mg, 31.3 µmol) was dissolved in 80% AcOH/water (3.13 mL) and the reaction was stirred 2 d at room temperature. Mass spectrometry showed full conversion at this point, toluene (21 mL) was added and the solvent was removed under reduced pressure to yield 37.1 mg of a colourless, crystalline solid (27.9 µmol, 89%) which was used without further purification or analysis.

HRMS (ESI) *m/z*: calcd for $C_{53}H_{98}N_9O_{22}Psi_3$ $[M - 2H]^{2-}$: 663.2965, found: 663.2962.[54]

Synthesis of Compound 263

2-(Trimethylsilyl)ethyl N^2-(((2*R*)-2-(((2*R*,3*R*,4*R*,5*S*,6*R*)-3-acetamido-5-hydroxy-2-((hydroxy((hydroxy(((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)phosphoryl)oxy)phosphoryl)oxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)oxy)propanoyl)-L-alanyl)-N^5-((*S*)-1-oxo-1-(((*R*)-1-oxo-1-(((*R*)-1-oxo-1-(2-(trimethylsilyl)ethoxy)propan-2-yl)amino)propan-2-yl)amino)-6-((*S*)-2-((*S*)-2-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)propanamido)propanamido)hexan-2-yl)-D-glutaminate



Farnesolphosphate **58** (78.6 mg, 266.1 µmol) was coevaporated from toluene (2 mL) two times and dissolved in 50% DMF/THF (3.82 mL). Carbonyldiimidazole (CDI, 170.2 mg, 1.06 mmol) was dissolved in 50% DMF/THF (3.82 mL) and added to the farnesolphosphate solution. The reaction was stirred for 2 hours at room temperature and MeOH (76.3 µL) was added before stirring further 45 minutes at room temperature. The solvents were removed under reduced pressure and the synthesised phosphoimidazole intermediate was coevaporated from toluene (2 mL) twice before the addition of DMF (3.1 mL). Mass spectrometry showed the successfully synthesised **58a**.

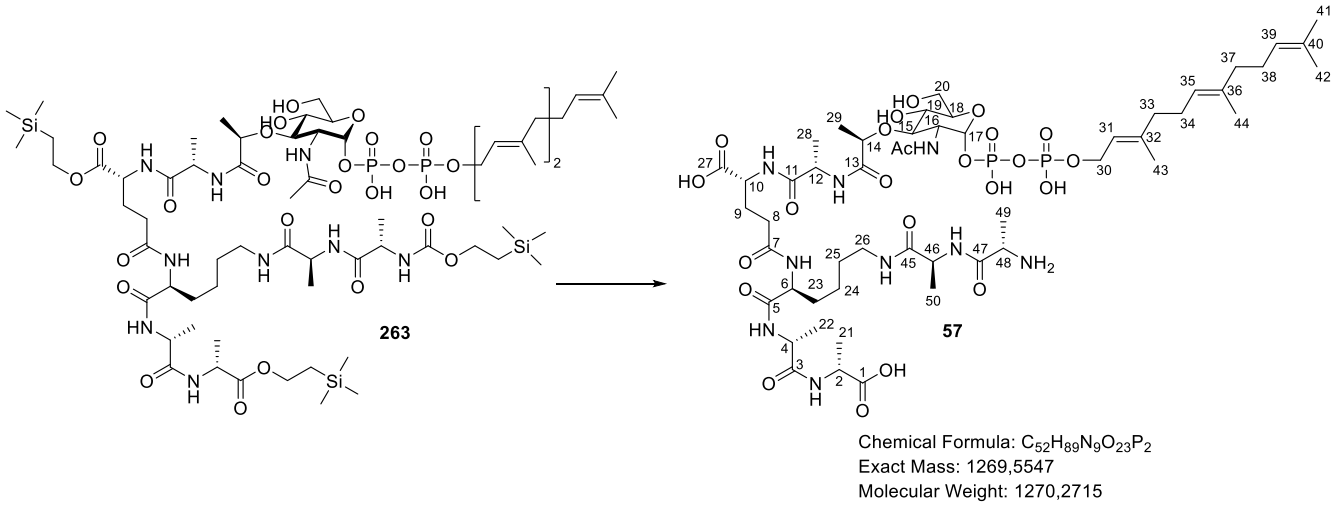
HRMS(ESI) *m/z*: calcd for $C_{18}H_{28}N_2O_3P$ $[M - H]^-$: 351.1843, found: 351.1835.

In the meantime phosphate **56** (37.1 mg, 27.9 µmol) was coevaporated first from 0.4 mL pyridine and then twice from 2 mL toluene under argon. DMF (3.1 mL) and the freshly prepared phosphoimidazole solution were added and the reaction was stirred for 3 days at room temperature. The solvent was removed under reduced pressure and the crude product was semi-purified by gel permeation chromatography (Sephadex® LH-20, GE Healthcare, 260 x 20 mm, methanol) to yield 53.9 mg (33.4 µmol, 90%) of a colourless, amorphous solid, which was used for the next reaction without further purification or analysis.

R_f = 0.78 (4 MeOH/2 $CHCl_3$/0.5 water). **HRMS (ESI)** *m/z*: calcd for $C_{68}H_{123}N_9O_{24}P_2Si_3$ $[M - 2H]^{2-}$: 791.8737, found: 791.8740.[54]

Synthesis of Compound 57

N^2-(((2*R*)-2-(((2*R*,3*R*,4*R*,5*S*,6*R*)-3-Acetamido-5-hydroxy-2-((hydroxy((hydroxy(((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)phosphoryl)oxy)phosphoryl)oxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)oxy)propanoyl)-L-alanyl)-N^5-((*S*)-6-((*S*)-2-((*S*)-2-aminopropanamido)propanamido)-1-(((*R*)-1-(((*R*)-1-carboxyethyl)amino)-1-oxopropan-2-yl)amino)-1-oxohexan-2-yl)-D-glutamine



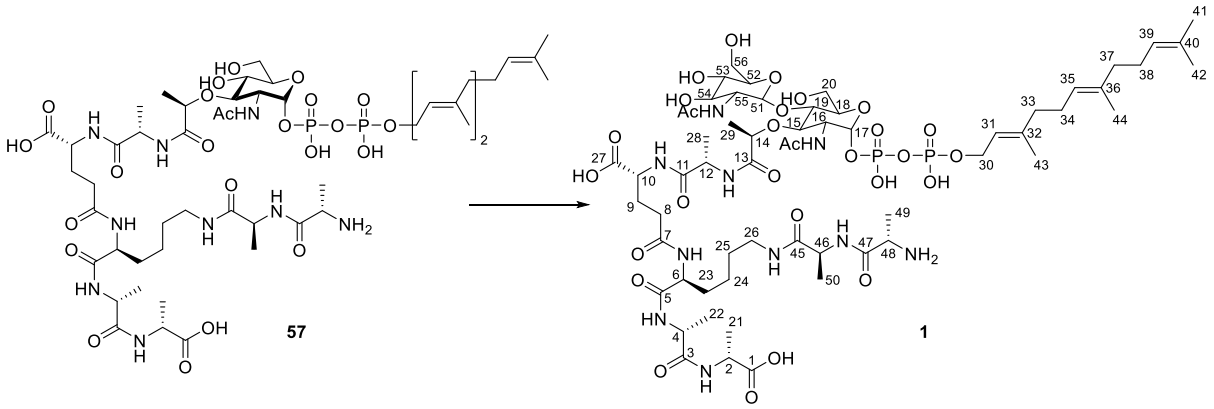
Protected, semi-pure **263** (53.9 mg, 33.4 µmol) was coevaporated twice from 1 mL toluene under argon and dissolved in DMF (0.5 mL). The solution was cooled to 0 °C and a 1 M solution of tetrabutylammonium fluoride in THF (TBAF, 0.70 mL, 701 µmol) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 2 days at room temperature before removing the solvent under reduced pressure. The crude product was purified by gel permeation chromatography (Sephadex® LH-20, GE Healthcare, 260 x 20 mm, methanol) and the tetrabutylammonium counterions were exchanged to ammonium using percolation through Dowex® 50WX8 with a 0.02 M NH_4HCO_3 solution. Dowex® 50WX8 was washed before usage with 3:1 NH_3/water and 0.02 M NH_4HCO_3 solution until pH of the eluent turned 8. The solvent was removed by lyophilisation to yield 21.9 mg (16.7 µmol, 50% over four steps) of compound **57** as a colourless, amorphous solid, which may be further purified by HPLC (25% – 50 % NH_4HCO_3 (0.1% aq.)/methanol, retention time 8.1 min, using a KNAUER Eurospher II 100-5 C8; 5 µm; 250 x 16 mm + precolumn 30 x 16 mm, 205 nm).

R_f = 0.87 (3 MeOH/ 3 CH_2Cl_2/ 1 water). **α_D^{25}** = +33 ° (*c* = 0.34 in MeOH). **^{1}H** NMR (D_2O, 500 MHz) δ = 5.50 – 5.46 (m, 1H, H-17), 5.46 (t, *J* = 6.8 Hz, 1H, H-37), 5.23 (t, *J* = 6.8 Hz, 1H, H-41), 5.21 –

5.16 (m, 1H, H-45), 4.52 4.47 (m, 2H, H-36), 4.36 (q, *J* = 7.2 Hz, 1H, H-14), 4.31 – 4.29 (m, 1H, H-4), 4.29 – 4.24 (m, 3H, H-6, H-10, H-12), 4.23 – 4.21 (m, 11H, H-28), 4.21 – 4.19 (m, 1H, H-30), 4.19 – 4.14 (m, 2H, H-2, H-16), 3.99 – 3.94 (m, 1H, H-18), 3.91 – 3.85 (m, 2H, H-20), 3.80 (dd, *J* = 9.7 Hz, *J* = 9.7 Hz, 1H, H-15), 3.64 (pt, *J* = 9.7 Hz, 1H, H-19), 3.26 – 3.23 (m, 2H, H-26), 2.33 – 2.28 (m, 2H, H-8), 2.20 – 2.14 (m, 3H, H-9, H-40), 2.15 – 2.11 (m, 4H, H-39, H-44), 2.02 (t, *J* = 7.5 Hz, 2H, H-43), 2.00 (s, 3H, CH_3-NHAc), 1.93 – 1.88 (m, 1H, H-9), 1.83 – 1.76 (m, 2H, H-23), 1.73 (s, 3H, H-50), 1.72 – 1.70 (m, 2H, H-25), 1.70 (s, 3H, H-48), 1.64 (s, 3H, H-47), 1.63 (s, 3H, H-49), 1.55 (d, *J* = 7.1 Hz, 3H, H-32), 1.53 – 1.50 (m, 2H, H-24), 1.45 (d, *J* = 7.2 Hz, 3H, H-22), 1.42 (d, *J* = 6.9 Hz, 3H, H-34), 1.38 (d, *J* = 7.1 Hz, 3H, H-35), 1.37 (d, *J* = 7.2 Hz, 3H, H-31), 1.34 (d, *J* = 7.1 Hz, 3H, H-21). **^{13}C** NMR (D_2O, 176 MHz) δ = 181.4 (C-1), 177.9 (C-33), 175.9 (C-11), 175.8 (C-7), 174.8 (C-5), 174.1 (NHAc-C=O), 174.1 (C-3), 173.7 (C-13), 172.1 (C-27), 172.0 (C-29), 143.2 (C-38), 136.8 (C-42), 133.4 (C-46), 124.5 (C-45), 124.4 (C-41), 119.3 (C-37), 94.8 (C-17), 79.9 (C-15), 78.2 (C-12), 73.1 (C-18), 68.2 (C-19), 63.2 (C-36), 58.2 (C-20), 54.3 (C-10), 54.3 (C-6), 53.3 (C-16), 52.2 (C-28), 51.1 (C-2), 50.2 (C-4), 49.9 (C-30), 49.5 (C-14), 38.9 (C-26), 38.9 (C-39), 38.9 (C-43), 31.9 (C-8), 30.7 (C-23), 28.2 (C-9), 27.7 (C-25), 25.9 (C-44), 25.5 (C-40), 25.0 (C-48), 22.5 (NHAc-CH_3), 22.2 (C-24), 19.2 (C-32), 18.7 (C-34), 17.5 (C-21), 17.0 (C-47), 17.0 (C-22), 16.7 (C-35), 16.6 (C-31), 15.7 (C-50), 15.3 (C-49). **^{31}P** NMR (D_2O, 284 MHz) δ = -10.8 (d, *J* = 14.8 Hz), -13.4 (d, *J* = 14.8 Hz). **HRMS (ESI)** *m/z*: calcd for $C_{53}H_{87}N_9O_{25}P_2$ $[M - 2H]^{2-}$: 655.7650, found: 655.7651, calcd for $C_{53}H_{88}N_9O_{25}P_2$ $[M - H]^-$: 1312.5372, found: 1312.5381, calcd for $C_{53}H_{87}DN_9O_{25}P_2$ [M – 2H + D]: 1313.5435, found: 1313.5421.[54]

Synthesis of Compound 1

N^2-(((2*R*)-2-(((2*R*,3*R*,4*R*,5*S*,6*R*)-3-Acetamido-5-(((2*R*,3*R*,4*R*,5*S*,6*R*)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-2-((hydroxy((hydroxy(((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)oxy)phosphoryl)oxy)phosphoryl)oxy)-6-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)oxy)propanoyl)-L-alanyl)-N^5-((*S*)-6-((*S*)-2-((*S*)-2-aminopropanamido)propanamido)-1-(((*R*)-1-(((*R*)-1-carboxyethyl)amino)-1-oxopropan-2-yl)amino)-1-oxohexan-2-yl)-D-glutamine



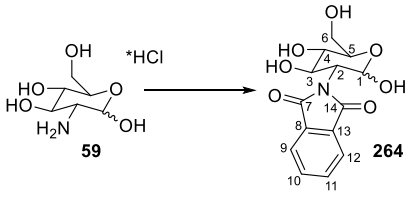
The chemoenzymatic conversion of monosccharide **57** was performed *in vitro* in a total volume of 8.5 mL containing 3.00 mg (2.50 µmol) compound **57**, 2 mM UDP–D-GlcNAc, 50 mM NaP_i and 0.5 mM $MgCl_2$, pH 6.5. The reaction was initiated by the addition of 300 mg of MurG–His_6. Subsequent to the incubation of the mixture for 4 hours at 30 °C it was quenched by the addition of 17 mL MeOH and evaporated to dryness. The dried samples were dissolved in distilled water for mass spectrometric analysis. The crude product was purified by HPLC (25 – 50% NH_4HCO_3 (0.1% aq.)/methanol, retention time 7.5 min, using a KNAUER Eurospher II 100-5 C8; 5 µm; 250 x 16 mm + precolumn 30 x 16 mm, 205 nm) yielding 1.10 mg (0.75 µmol, 30%) of a white, amorphous solid. Recombinant MurG–His_6 enzyme was overexpressed and purified as described for MurG[39] and dialysed against 10 mM NaP_i buffer, pH 7.0.

R_f = 0.59 (RP C18, 3:1 MeCN/H_2O). **α_D^{20}** = +15 ° (c = 0.11 in H_2O). **^{1}H** NMR (D_2O, 700 MHz) δ = 5.50 – 5.46 (m, 1H, H-17), 5.46 (t, *J* = 6.8 Hz, 1H, H-37), 5.23 (t, *J* = 6.8 Hz, 1H, H-41), 5.21 – 5.16 (m, 1H, H-45), 4.63 (d, *J* = 8.2 Hz, 1H, H-51), 4.52 - 4.47 (m, 2H, H-36), 4.36 (q, *J* = 7.2 Hz, 1H, H-14), 4.31 – 4.29 (m, 1H, H-4), 4.29 – 4.24 (m, 3H, H-6, H-10, H-12), 4.23 – 4.21 (m, 1H, H-28), 4.21 – 4.19 (m, 1H, H-30), 4.19 – 4.14 (m, 2H, H-2, H-16), 3.99 – 3.94 (m, 2H, H-18, H-56), 3.91 – 3.85 (m, 2H, H-20), 3.80 (dd, *J* = 9.7 Hz, *J* = 9.7 Hz, 1H, H-15), 3.79 – 3.74 (m, 2H, H-

55, H-56'), 3.64 (pt, *J* = 9.7 Hz, 1H, H-19), 3.58 (pt, *J* = 8.6, 8.6 Hz, 1H, H-54), 3.46 – 3.41 (m, 2H, H-52, H-53), 3.26 – 3.23 (m, 2H, H-26), 2.33 – 2.28 (m, 2H, H-8), 2.20 – 2.14 (m, 3H, H-9, H-40), 2.15 – 2.11 (m, 4H, H-39, H-44), 2.07 (s, 3H, NHAc-CH_3), 2.02 (t, *J* = 7.5 Hz, 2H, H-43), 2.01 (s, 3H, CH_3-NHAc), 1.93 – 1.88 (m, 1H, H-9), 1.83 – 1.76 (m, 2H, H-23), 1.73 (s, 3H, H-50), 1.72 – 1.70 (m, 2H, H-25), 1.70 (s, 3H, H-48), 1.64 (s, 3H, H-47), 1.63 (s, 3H, H-49), 1.55 (d, *J* = 7.1 Hz, 3H, H-32), 1.53 – 1.50 (m, 2H, H-24), 1.45 (d, *J* = 7.2 Hz, 3H, H-22), 1.42 (d, *J* = 6.9 Hz, 3H, H-34), 1.38 (d, *J* = 7.1 Hz, 3H, H-35), 1.37 (d, *J* = 7.2 Hz, 3H, H-31), 1.34 (d, *J* = 7.1 Hz, 3H, H-21). **^{13}C** NMR (D_2O, 176 MHz) δ = 181.4 (C-1), 177.9 (C-33), 175.9 (C-11, HMBC), 175.8 (C-7, HMBC), 174.8 (C-5), 174.2 (NHAc-C=O, HMBC), 174.1 (NHAc-C=O, HMBC), 174.1 (C-3, HMBC), 173.7 (C-13, HMBC), 172.1 (C-27, HMBC), 172.0 (C-29, HMBC), 143.2 (C-38, HMBC), 136.8 (C-42), 133.4 (C-46, HMBC), 124.5 (C-45, HMBC), 124.4 (C-41), 119.3 (C-37, HMBC), 100.1 (C-51, HMBC), 94.8 (C-17, HMBC), 79.9 (C-15), 78.0 (C-12), 75.9 (C-52, HMBC), 74.0 (C-54, HMBC), 73.1 (C-18), 70.3 (C-53, HMBC), 68.1 (C-19), 63.2 (C-36, HMBC), 61.1 (C-56, HMBC), 58.2 (C-20), 56.1 (C-55, HMBC), 54.3 (C-10), 54.3 (C-6), 53.3 (C-16, HMBC), 52.2 (C-28, HMBC), 51.1 (C-2), 50.2 (C-4), 49.5 (C-30), 48.9 (C-14), 38.9 (C-26), 38.9 (C-39), 38.9 (C-43), 31.9 (C-8), 30.7 (C-23), 28.2 (C-9, HMBC), 27.8 (C-25), 25.9 (C-44, HMBC), 25.5 (C-40), 25.0 (C-48), 22.5 (NHAc-CH_3), 22.2 (C-24), 22.1 (NHAc-CH_3), 19.2 (C-32), 18.7 (C-34), 17.5 (C-21), 17.0 (C-47), 17.0 (C-22), 16.7 (C-35), 16.7 (C-31), 15.7 (C-50), 15.3 (C-49, HMBC). **^{31}P** NMR (D_2O, 284 MHz) δ = -10.8 (d, *J* = 14.8 Hz), -13.4 (d, *J* = 14.8 Hz). **HRMS (ESI)** *m/z*: calcd for $C_{60}H_{101}N_{10}O_{28}P_2$ $[M-H]^-$: 1471.627, found: 1471.628.

Synthesis of Compound 264

2-(2,4,5-Trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3-yl)isoindolin-1,3-diketon



Chemical Formula: $C_{14}H_{15}NO_7$
Exact Mass: 309,0849
Molecular Weight: 309,2740

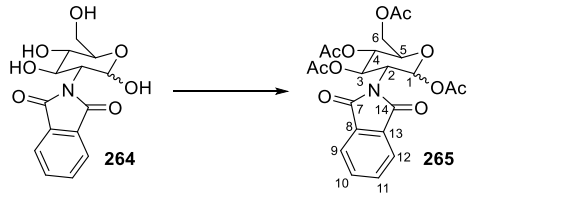
To a stirred solution of 10.00 g D-glucosamine hydrochlorid (**59**) (46.50 mmol, 1.00 equiv) in 50.00 mL water were added 3.90 g $NaHCO_3$ (46.40 mmol, 2.00 equiv) and powdered phthalic anhydride (6.80 g, 46.50 mmol, 1.00 equiv). The solution was stirred for 2 hours at room temperature before more $NaHCO_3$ (3.90 g) was added to the suspension which was stirred for additional 2 hours. After 4 hours in total the homogenous solution was acidified with 2 M HCl

(40 mL), toluene (40 mL) was added and the mixture concentrated in vacuo. The flask was cooled in an ice bath before the precipitate was filtered off and washed with small amounts of cold water. The filtrate was lyophilised to obtain a colourless amorphous solid (10.01 g, 32.40 mmol, 70%) which was used for the next reaction without further purification.

R_f = 0.02 (9:1 EE/MeOH). **α_D^{20}** = +30 ° (c = 1.00 in MeOH). **^{1}H** NMR (D_2O, 500 MHz) δ = 7.69 - 7.61 (m, 2H, H-10, H-11), 7.57 (t, *J* = 7.2 Hz, 2H, H-9, H-12), 5.37 (d, *J* = 3.5 Hz, 1H, H-1), 4.10 (dd, *J* = 10.7 , 3.5 Hz, 1H, H-2), 3.95 - 3.89 (m, 2H, H-6), 3.84 (dd, *J* = 5.2, 3.3 Hz, 1H, H-3), 3.81 (t, *J* = 5.3 Hz, 1H, H-4), 3.68 (td, *J* = 8.3, 3.6 Hz, 1H, H-5). **^{13}C** NMR (D_2O, 125 MHz) δ = 173.3 (C-7, C-14), 132.6 (C-8, C-13), 128.8 (C-10, C-11), 127.6 (C-9, C-12), 90.8 (C-1), 71.7 (C-5), 70.7 (C-3), 70.2 (C-4), 60.7 (C-6), 54.7 (C-2). **HRMS (ESI)** *m/z*: calcd for $C_{14}H_{16}NO_7$ $[M + H]^+$: 489.1715, found: 489.1717.

Synthesis of Compound 265

6-(Acetoxymethyl)-3-(1,3-dioxoisoindolin-2-yl)tetrahydro-2*H*-pyran-2,4,5-triyltriacetat



Chemical Formula: $C_{22}H_{23}NO_{11}$
Exact Mass: 477,1271
Molecular Weight: 477,4220

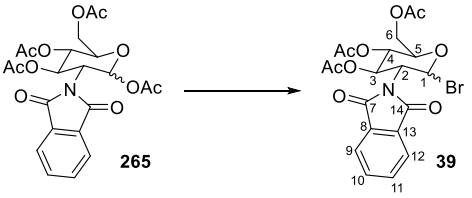
10.01 g of the obtained product **264** (32.40 mmol, 1.00 equiv) was dissolved in 50 mL pyridine and treated with 25 mL Ac_2O (264.40 mmol, 8.20 equiv) for 18 hours at room temperature. The mixture was diluted with 50 mL ethyl acetate and the organic layer washed with $CuSO_4$ solution (1 x 50 mL, aq, sat) as well as brine (1 x 50 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure to obtain a foamie colourless solid (7.72 g,16.20 mmol, 34%) as a mixture of α- and β-anomers.

R_f = 0.48 and 0.55 (2:3 EE:benzene). **α_D^{20}** = +71 ° (c = 1.30 in MeOH). **^{1}H** NMR ($CDCl_3$, 500 MHz) δ = 7.85 (dd, *J* = 5.5, 2.7 Hz, 2H, H-10, H-11), 7.75 (dd, *J* = 5.1, 3.0 Hz, 2H, H-9, H-12), 6.29 (d, *J* = 3.4 Hz, 1H, H-1), 5.16 (dd, *J* = 10.2, 9.2 Hz, 1H, H-3), 4.72 (dd, *J* = 11.6, 3.4 Hz, 1H, H-4), 4.37 (dd, *J* = 12.3, 4.0 Hz, 1H, H-2), 4.32 (ddd, *J* = 10.3, 3.9, 2.0 Hz, 1H, H-6), 4.19 - 4.13 (m, 1H, H-6'), 4.13 - 4.09 (m, 1H, H-5), 2.12 (s, 3H, H-Ac), 2.09 (s, 3H, H-Ac), 2.06 (s, 3H, H-Ac), 1.87 (s, 3H, H-Ac). **^{13}C** NMR ($CDCl_3$, 125 MHz) δ = 170.8 (C-7, C-14), 170.2 (C-21), 169.9 (C-19), 169.7 (C-17), 169.5 (C-15), 136.2 (C-8, C-13), 134.6 (C-10, C-11), 123.6 (C-9, C-12), 90.7 (C-1), 20.6 (C-16), 70.3 (C-5), 69.5

(C-3), 67.2 (C-4), 61.7 (C-6), 53.0 (C-2), 21.2 (C-22), 20.9 (C-20), 20.8 (C-18), 20.6 (C-16). **HRMS (ESI)** *m/z*: calcd for $C_{22}H_{23}NO_{11}Na$ $[M + Na]^+$: 500.1163, found: 500.1157.

Synthesis of Compound 39

2-(Acetoxymethyl)-6-brom-5-(1,3-dioxoisoindolin-2-yl)tetrahydro-2*H*-pyran-3,4-diyldiacetat



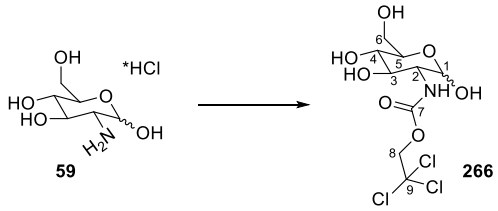
Chemical Formula: $C_{20}H_{20}BrNO_9$
Exact Mass: 497,0321
Molecular Weight: 498,2820

A solution of 1.00 g of the previously obtained product **265** (2.10 mmol, 1.00 equiv) in a 33% w/w solution of hydrogen bromide in glacial acetic acid (12.00 mL, 44.10 mmol, 21.00 equiv) was prepared. This solution was stirred for 1.5 hours at room temperature. Then, the solution was diluted with DCM (20 mL) and poured into an aqueous saturated ice-cold $NaHCO_3$ solution. The pH was adjusted with solid $NaHCO_3$ until no more CO_2 evolution was observed and the aqueous layer extracted with DCM (2 x 20 mL) before the combined organic layers were dried over Na_2SO_4 The solvent was evaporated under reduced pressure and the crude product obtained as a slightly brownish amorphous solid (1.00 g, 2.10 mmol, 96%) which was used in the next reaction without any further purification.

R_f = 0.67 (7:3 CH/EE). **α_D^{20}** = +57.3 ° (c = 1.10 in $CHCl_3$). **^{1}H** NMR ($CDCl_3$, 500 MHz) δ = 7.86 (dd, *J* = 5.6 , 3.0 Hz, 2H, H-10, H-11), 7.75 (dd, *J* = 5.8, 3.2 Hz, 2H, H-9, H-12), 6.51 (d, *J* = 8.9 Hz, 1H, H-1), 5.88 (dd, *J* = 10.6 , 9.1 Hz, 1H, H-2), 5.21 (m, 1H, H-5), 4.47 (dd, *J* = 10.6 , 8.9 Hz, 1H, H-3), 4.36 (dd, *J* = 12.4 , 4.4 Hz, 1H, H-6), 4.15 (dd, *J* = 12.4 , 2.1 Hz, 1H, H-6'), 4.02 (ddd, *J* = 10.2 , 4.4 , 2.2 Hz, 1H, H-4), 2.03 (s, 3H, H-Ac), 1.99 (s, 3H, H-Ac), 1.86 (s, 3H, H-Ac). **^{13}C** NMR ($CDCl_3$, 125 MHz) δ =177.1 (C-7, C-14), 170.2 (C-19),169.7 (C-17), 168.8 (C-15), 127.3 (C-8, C-13), 125.8 (C-10, C-11), 123.9 (C-9, C-12), 89.9 (C-1), 72.8 (C-5), 70.7 (C-3), 68.5 (C-4), 61.7 (C-6), 53.6 (C-2), 20.9 (C-20), 20.8 (C-18), 20.5 (C-16). **HRMS (ESI)** *m/z*: calcd for $C_{20}H_{20}BrNO_9Na$ $[M + Na]^+$: 520.0214, found: 520.0215.

Synthesis of Compound 266

2,2,2-Trichloroethyl ((3*R*,4*R*,5*S*,6*R*)-2,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3-yl)carbamate



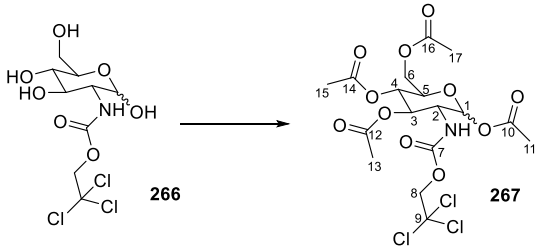
Chemical Formula: $C_9H_{14}Cl_3NO_7$
Exact Mass: 352,9836
Molecular Weight: 354,5610

To a suspension of 0.50 g D-(+)-glucosamine hydrochloride (**59**) (2.32 mmol, 1.00 equiv) in H_2O (5.00 mL) was added 0.59 g $NaHCO_3$ (7.07 mmol, 3.05 equiv) at room temperature and the resulting mixture was stirred 1 hour. Then 1.60 mL 2,2,2-trichloroethyl chloroformate (11.59 mmol, 5.00 equiv) was added dropwise over 20 minutes. The reaction was stirred an additional 3 hours after which a white solid had formed. The reaction was filtered, and the residue washed with H_2O (40 mL). Afterwards the solid was redissolved in a mixture of methanol and DCM (1:1) and the solvent evaporated under reduced pressure. The formed colourless foam was dried in HV o.n. (0.68 g, 1.91 mmol, 82%).

R_f = .0.47 (1:9 MeOH/EE). **α_D^{20}** = +10.2 ° (c = 1.50 in $CHCl_3$). **^{1}H** NMR (CD_3OD, 700 MHz) δ = 5.14 (d, *J* = 3.5 Hz, 1H, H-1), 4.83 (s, 1H, H-8), 4.72 (d, *J* = 12.1 Hz, 1H, H-8'), 3.82 – 3.77 (m, 2H, H-4, H-6), 3.73 – 3.65 (m, 2H, H-3, H-6'), 3.58 (dd, *J* = 10.6, 3.5 Hz, 1H, H-2), 3.39 – 3.34 (m, 1H, H-5). **^{13}C** NMR (CD_3OD, 175 MHz) δ = 156.9 (C-7), 97.2 (C-9), 92.8 (C-1), 75.6 (C-8), 73.1 (C-4), 72.7 (C-3), 72.4 (C-5), 62.8 (C-6), 57.9 (C-2). **HRMS (ESI)** *m/z*: calcd for $C_9H_{15}Cl_3NO_7$ $[M + H]^+$: 353.9909, found: 353.9906.

Synthesis of Compound 267

(3*R*,4*R*,5*S*,6*R*)-6-(Acetoxymethyl)-3-(((2,2,2-trichloroethoxy)carbonyl)amino)tetrahydro-2*H*-pyran-2,4,5-triyl triacetate



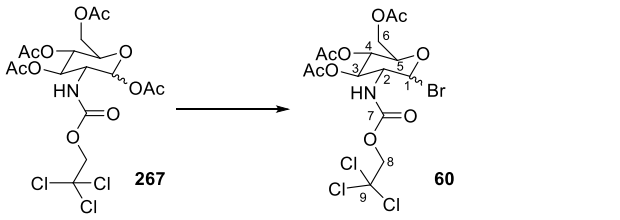
Chemical Formula: $C_{17}H_{22}Cl_3NO_{11}$
Exact Mass: 521,0258
Molecular Weight: 522,7090

The crude Troc-protected glucosamine **266** (0.68 g, 1.91 mmol, 1.00 equiv) was dissolved in 17.85 mL pyridine and 0.90 mL acetic anhydride (9.54 mmol, 5.00 equiv) was added dropwise over 5 minutes. The resulting solution was stirred for 5 hours at room temperature before it was diluted with 40 mL EtOAc, washed with 2 N HCl (6 x 15 mL) and brine (1 x 15 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to yield a pale yellow foam constituted of the α- and β-anomer (0.97 g, 1.86 mmol, 97%).

R_f = 0.72 and 0.68 (EE). **α_D^{20}** = +15 ° (c = 3.20 in $CHCl_3$). **^{1}H** NMR (CD_3OD, 500 MHz) δ = 6.16 (d, *J* = 2.4 Hz, 1H, H-1), 5.32 (dd, *J* = 11.1, 9.4 Hz, 1H, H-3), 5.10 (t, *J* = 9.8 Hz, 1H, H-4), 4.77 – 4.69 (m, 2H, H-8), 4.29 (dd, *J* = 12.5, 4.1 Hz, 1H, H-6), 4.13 (dt, *J* = 9.9, 2.6 Hz, 2H, H-2, H-5), 4.06 (dd, *J* = 12.4, 2.3 Hz, 1H, H-6'), 2.18 (s, 3H, H-11), 2.05 (s, 3H, H-17), 2.01 (d, *J* = 1.7 Hz, 6H, H-13, H-15). **^{13}C** NMR (CD_3OD, 125 MHz) δ = 172.3 (C-10), 171.8 (C-12), 171.2 (C-14), 170.8 (C-16), 156.8 (C-7), 97.1 (C-9), 91.6 (C-1), 71.9 (C-3), 71.0 (C-5), 69.9 (C-4), 63.0 (C-6), 54.5 (C-2), 20.7 (C-11), 20.7 (C-15), 20.6 (C-13), 20.6 (C-17). **HRMS (ESI)** *m/z*: calcd for $C_{17}H_{23}Cl_3NO_{11}$ $[M + H]^+$: 522.0331, found: 522.0333.

Synthesis of Compound 60

(2*R*,3*S*,5*R*)-2-(Acetoxymethyl)-6-bromo-5-(((2,2,2-trichloroethoxy)carbonyl)amino)-tetrahydro-2*H*-pyran-3,4-diyl diacetate



Chemical Formula: $C_{15}H_{19}BrCl_3NO_9$
Exact Mass: 540,9309
Molecular Weight: 543,5690

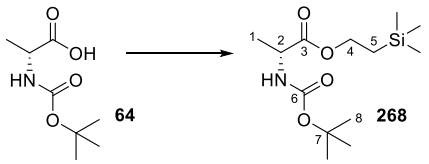
Fully protected **267** (95.70 mg, 183.08 µmol, 1.00 equiv) was dissolved in 33% w/w hydrogen bromide in acetic acid and stirred for 1.5 hours at room temperature. Afterwards, the mixture was diluted with DCM (2.5 mL) and poured into ice cold $NaHCO_3$ solution (aq, sat) before the pH value was adjusted with solid $NaHCO_3$ until no CO_2 formation was observed upon the addition. The organic layer was seperated and dried over Na_2SO_4 after that the mixture was concentrated in vacuo. Lastly, the crude product was purified by column chromatography (SiO_2, 7:3 CH/EE) yielding 49.30 mg of the desired product as a yellow oil (90.70 µmol, 50%).

R_f = 0.24 (CH/EE 7:3). **α_D^{20}** = +70.0 ° (c = 1.00, CH_2Cl_2). **^{1}H** NMR (CD_3OD, 500 MHz) δ = 5.22 (ddd, *J* = 10.5, 9.2, 5.5 Hz, 1H, H-4), 4.97 (q, *J* = 9.3 Hz, 1H, H-5), 4.83 (s, 1H, H-8), 4.69 (dd, *J* = 12.1,

1.5 Hz, 1H, H-8), 4.52 (t, *J* = 8.8 Hz, 1H, H-1), 4.32 – 4.11 (m, 1H), 3.71 – 3.58 (m, 2H, H-6), 3.58 – 3.53 (m, 2H, H-2, H-3), 2.02 (s, 3H), 2.00 (d, *J* = 2.1 Hz, 3H), 1.96 (d, *J* = 1.6 Hz, 3H). **^{13}C** NMR (CD_3OD, 125 MHz) δ= 172.4 (C=O Ac), 171.4 (C=O Ac), 171.3 (C=O Ac), 156.7 (C-7), 103.1 (C-1), 97.2 (C-9), 75.5 (C-3), 75.4 (C-8), 74.1 (C-4), 70.3 (C-5), 61.9 (C-6), 57.3 (C-2), 20.6 (CH3-Ac), 20.6 (CH3-Ac), 20.6 (CH3-Ac). **HRMS (ESI)** calcd for $C_{15}H_{19}Cl_3NO_9$ $[M - Br^-]^+$: 462.012, found: 462.012.

Synthesis of Compound 268

2-(Trimethylsilyl)ethyl (tert-butoxycarbonyl)-D-alaninate



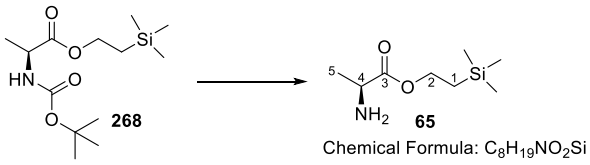
Chemical Formula: $C_{13}H_{27}NO_4Si$
Exact Mass: 289,1709
Molecular Weight: 289,4470

1.50 g of Boc-L-Ala-OH (**64**) (7.93 mmol, 1.00 equiv) and 194.00 mg DMAP (1.59 mmol, 0.20 equiv) were preloaded into a flame dried Schlenk flask and dried in HV for 10 minutes. Afterwards 40 mL of ethyl acetate (dried over 3 Å MS o.n.) were added and the solution cooled to 0 °C. Then 1.70 mL 2-(trimethylsilyl)ethanol (11.90 mmol, 1.50 equiv) and 9.51 mL DCC (1 M solution in DCM, 9.51 mmol, 1.20 equiv) were added and the solution was warmed to room temperature and stirred for 2 hours. The reaction mixture was subsequently filtered through Celite® and the residue washed with ethyl acetate (2 x 20 mL). The solvent was removed under reduced pressure and the crude product purified by column chromatography (SiO_2, 9:1 CH/EE) to observe the product as a slightly yellow oil (2.26 g, 7.79 mmol, 98%).

R_f = 0.18 (CH/EE 9:1). **α_D^{20}** = +10.5 ° (c = 1.14, CH_2Cl_2). **^{1}H** NMR (DMSO-d_6, 500 MHz): δ = 7.22 (d, *J* = 7.4 Hz, 1H, NH), 4.17 – 4.04 (m, 2H, H-4), 3.96 (t, *J* = 7.4 Hz, 1H, H-2), 1.37 (s, 9H, H-8), 1.22 (d, *J* = 7.3 Hz, 3H, H-1), 0.93 (t, *J* = 8.3 Hz, 2H, H-5), 0.03 (s, 9H, 3 x CH_3-Si); **^{13}C** NMR (DMSO-d_6, 126 MHz): δ = 173.1 (C-3), 155.2 (C-6), 78.1 (C-7), 62.4 (C-4), 49.1 (C-2), 28.2 (C-8), 16.8 (C-5), 16.8 (C-1), -1.5 (CH_3-Si). **HRMS(ESI)** *m/z*: calcd for $C_{13}H_{28}NO_4Si^+$ $[M + H]^+$:290.1782, found: 290.1784.

Synthesis of Compound 65

2-(Trimethylsilyl)ethyl L-alaninate



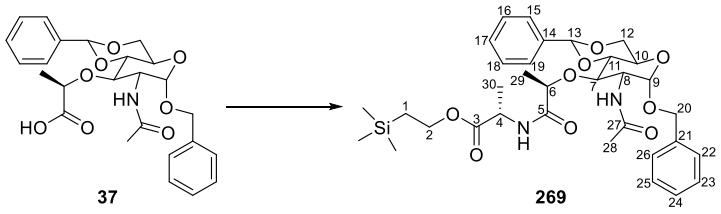
Chemical Formula: $C_8H_{19}NO_2Si$
Exact Mass: 189,1185
Molecular Weight: 189,3300

Double protected L-alanine **268** (2.26 g, 7.79 mmol, 1.00 equiv) was dissolved in 46.1 mL 20% TFA/DCM and stirred at room temperature for 1 hour. Toluene was added to the mixture to coevaporate the TFA under reduced pressure. The product was obtained as a yellow, viscous oil (2.24 g, 11.81 mmol, quant) which was used for the next reaction without further purification.

$\mathbf{R_f}$ = 0.18 (DCM/MeOH 9:1). $\boldsymbol{\alpha_D^{20}}$ = +0.9 ° (c = 1.14, CH_2Cl_2). **^{1}H** NMR (CD_3OD, 500 MHz) δ = 4.38 – 4.32 (m, 2H, H-2), 4.06 (q, *J* = 7.2 Hz, 1H, H-4), 1.54 (d, *J* = 7.3 Hz, 3H, H-5), 1.11 – 1.07 (m, 2H, H-1), 0.09 (s, 9H, 3 x CH_3-Si). **^{13}C** NMR (CD_3OD, 125 MHz) δ = 171.1 (C-3), 66.0 (C-2), 49.9 (C-4), 18.3 (C-1), 16.2 (C-5), -1.6 (3 x CH_3-Si). **HRMS (ESI)**: *m/z*: calcd for $C_8H_{19}NO_2SiNa^+$ $[M + Na]^+$: 212.1077, found: 212.1076.

Synthesis of Compound 269

2-(Trimethylsilyl)ethyl ((*R*)-2-(((2*R*,4a*R*,6*S*,7*R*,8*R*,8a*S*)-7-acetamido-6-(benzyloxy)-2-phenylhexahydropyrano[3,2-D][1,3]dioxin-8-yl)oxy)propanoyl)-L-alaninate



Chemical Formula: $C_{33}H_{46}N_2O_9Si$
Exact Mass: 642,2973
Molecular Weight: 642,8210

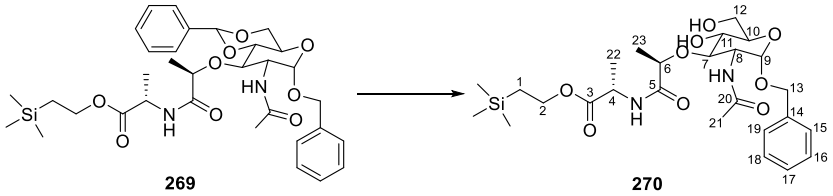
Benzyl *N*-acetyl-4,6-benzylidene muramic acid (**37**) (100.00 mg, 212.09 µmol, 1.00 equiv) was dispersed in 1.51 mL DCM and cooled to 0 °C before the addition of 23.57 µL *N*-methylmorpholine (212.09 µmol, 1.00 equiv) and 44.68 mg 2-chloro-4,6-dimethoxy-1,3,5-triazine (254.50 µmol, 1.20 equiv). After the solution has been stirred at 0 °C for 45 minutes the mixture was diluted with 1.51 mL DCM. Then another 23.57 µL NMM (212.09 µmol, 1.00 equiv) as well as 48.19 mg L-alanine-OTMSE (254.50 µmol, 1.20 equiv) were added. Subsequently, the reaction mixture was slowly warmed to room temperature and stirred for 3 days before the mixture was filtered. The filtrate was washed with 1 N HCl (1 x 3 mL) and

brine (1 x 3 mL) before the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was coevaporated from toluene twice and dried in HV o.n. to obtain a colourless crystalline solid (133.10 mg, 201.06 µmol, 98%).

R_f = 0.30 (2:1 CH/EE). **α_D^{20}** = +56.3 ° (c = 1.12, CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.49 – 7.44 (m, 2H, H-15, H-19), 7.40 – 7.31 (m, 8H, H-16, H-17, H-18, H-22, H-23, H-24, H-25, H-26), 6.88 (d, *J* = 7.3 Hz, 1H, NH-Ala), 6.23 (d, *J* = 8.8 Hz, 1H, NH-Ac), 5.59 (s, 1H, H-13), 4.97 (d, *J* = 3.8 Hz, 1H, H-9), 4.74 (d, *J* = 11.9 Hz, 1H, H-20), 4.51 (d, *J* = 11.8 Hz, 1H, H-20'), 4.39 (p, *J* = 7.3 Hz, 1H, H-4), 4.26 (ddd, *J* = 9.9, 8.8, 3.9 Hz, 1H, H-8), 4.23 (dd, *J* = 10.2, 4.8 Hz, 1H, H-12), 4.21 – 4.18 (m, 2H, H-2), 4.11 (q, *J* = 6.8 Hz, 1H, H-6), 3.88 (td, *J* = 9.7, 4.8 Hz, 1H, H-10), 3.77 (t, *J* = 10.3 Hz, 1H, H-12'), 3.74 – 3.71 (m, 1H, H-7), 3.69 (t, *J* = 9.2 Hz, 1H, H-11), 1.91 (s, 3H, H-28), 1.38 (d, *J* = 7.2 Hz, 3H, H-30), 1.35 (d, *J* = 6.8 Hz, 3H, H-29), 1.01 – 0.98 (m, 2H, H-1), 0.04 (s, 9H, 3 x CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 175 MHz) δ = 173.3 (C-3 [HMBC]), 173.0 (C-5 [HMBC]), 170.8 (C-27 [HMBC]),132.3 (C-14 [HMBC]), 131.6 (C-21 [HMBC]), 129.0 (C-22, C-26), 128.6 (C-16, C-18), 128.6 (C-23, C-25), 128.5 (C-17, C-24), 126.4 (C-15, C-19), 101.8 (C-13), 98.1 (C-9), 82.2 (C-11), 78.5 (C-6), 77.9 (C-7), 70.4 (C-20), 69.3 (C-12), 64.0 (C-2), 63.5 (C-10), 53.5 (C-8 [HSQC]), 48.5 (C-4), 23.6 (C-28), 19.5 (C-29), 18.1 (C-30), 17.6 (C-1), -1.5 (3 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{33}H_{47}N_2O_9Si$ $[M + H]^+$: 643.3045, found: 643.3051. Data was in agreement with previously published results.[51]

Synthesis of Compound 270

2-(Trimethylsilyl)ethyl ((*R*)-2-(((2*S*,3*R*,4*R*,5*S*,6*R*)-3-acetamido-2-(benzyloxy)-5-hydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)oxy)propanoyl)-L-alaninate



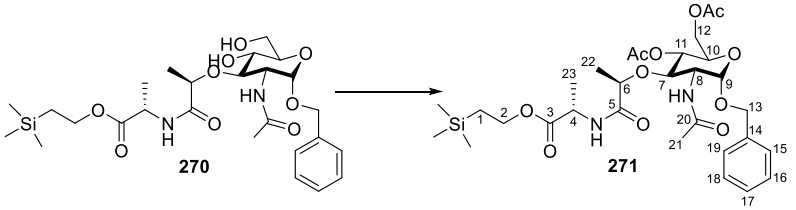
Chemical Formula: $C_{26}H_{42}N_2O_9Si$
Exact Mass: 554,2660
Molecular Weight: 554,7120

44.8 mg of **269** (0.07 mmol, 1.00 equiv) were dissolved in 1.13 mL MeOH and 1.53 mg *p*-TsOH (8.40 µmol, 0.12 equiv) were added before the mixture was warmed to 75 °C and stirred for 30 minutes. Afterwards the solvent was removed under reduced pressure and the crude product was purified using column chromatography (SiO_2, 5:1 EE/MeOH) to obtain a colourless crystalline solid (31.70 mg, 0.06 mmol, 82%).

$\mathbf{R_f}$ = 0.58 (5:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +53.5 ° (c = 1.05 in CH_2Cl_2). **^{1}H** NMR (CD_3OD, 700 MHz) δ = 7.42 – 7.39 (m, 2H, H-16, H-18), 7.39 – 7.34 (m, 2H, H-15, H-19), 7.32 – 7.28 (m, 1H, H-17), 4.90 (m, 1H, H-9), 4.77 (d, *J* = 12.1 Hz, 1H, H-13), 4.53 (d, *J* = 12.1 Hz, 1H, H-13‘), 4.35 (p, *J* = 7.1 Hz, 2H, H-4), 4.26 – 4.21 (m, 2H, H-8, H-12), 3.98 (dd, *J* = 10.7, 3.6 Hz, 1H, H-6), 3.87 – 3.83 (m, 1H, H-10), 3.74 (dd, *J* = 11.8, 5.5 Hz, 1H, H-12‘), 3.71 – 3.65 (m, 2H, H-2), 3.52 (dd, *J* = 10.0, 8.7 Hz, 1H, H-7), 1.92 (s, 3H, H-21), 1.42 (d, *J* = 7.3 Hz, 3H, H-23), 1.40 (d, *J* = 6.8 Hz, 3H, H-22), 1.06 – 1.00 (m, 2H, H-1), 0.07 (s, 9H, 3 x CH_3-Si). **^{13}C** NMR (CD_3OD, 176 MHz) δ = 176.1 (C-3), 174.2 (C-5), 173.4 (C-20), 138.9 (C-14), 129.4 (C-15, C-19), 129.2 (C-16, C-18), 128.8 (C-17), 97.5 (C-9), 80.9 (C-11), 78.6 (C-6), 74.3 (C-7), 71.5 (C-13), 70.2 (C-12), 64.7 (C-2), 62.6 (C-10), 54.8 (C-8), 49.5 (C-4), 22.8 (C-21), 19.6 (C-22), 18.2 (C-1), 17.4 (C-23), -1.5 (3 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{26}H_{43}N_2O_9Si$ $[M + H]^+$: 555.2732, found: 555.2736. The data was in agreement with previously published results.[57]

Synthesis of Compound 271

2-(Trimethylsilyl)ethyl ((*R*)-2-(((2*S*,3*R*,4*R*,5*S*,6*R*)-3-acetamido-5-acetoxy-6-(acetoxymethyl)-2-(benzyloxy)tetrahydro-2H-pyran-4-yl)oxy)propanoyl)-L-alaninate



Chemical Formula: $C_{30}H_{46}N_2O_{11}Si$
Exact Mass: 638,2871
Molecular Weight: 638,7860

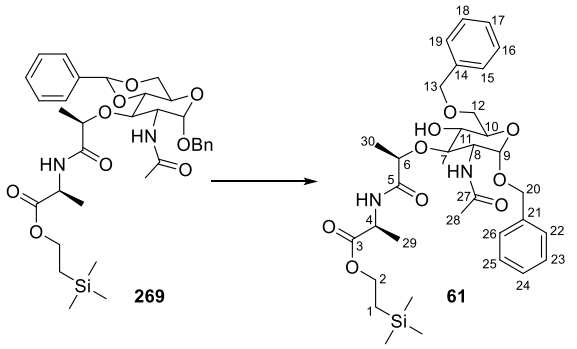
Diol **270** (43.70 mg, 78.00 µmol, 1.00 equiv) was dissolved in DCM (1.24 mL) and the resulting solution cooled to -30 °C. Pyridine (12.70 µL, 169.00 µmol, 2.14 equiv) was added dropwise. Then acetyl chloride (5.10 µL, 78.00 µmol, 1.00 equiv) was dissolved in DCM (0.40 mL) and added to the reaction mixture at -30 °C over 15 minutes. The solution was slowly warmed to 0 °C before it was diluted with DCM (2.00 mL) and the organic layer was washed with 0.01 M HCl (2 x 2 mL) and brine (1 x 2 mL). Afterwards, it was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, EE) to obtain 38.70 mg of compound **271** (60.58 µmol, 78%) as a colourless crystalline solid.

$\mathbf{R_f}$ = 0.47 (EE). $\boldsymbol{\alpha_D^{20}}$ = +58.7 ° (c = 0.98 in CH_2Cl_2). **^{1}H** NMR (CD_3OD, 700 MHz) δ = 7.41 – 7.37 (m, 2H, H-15, H-19), 7.38 – 7.33 (m, 2H, H-16, H-18), 7.33 – 7.29 (m, 1H, H-17), 5.01 (dd, *J* = 10.3, 9.1 Hz, 1H, H-9), 4.72 (d, *J* = 12.0 Hz, 1H, H-13), 4.55 (d, *J* = 12.0 Hz, 1H, H-13‘), 4.29 (q, *J* = 7.3

Hz, 1H, H-4), 4.24 – 4.19 (m, 3H, H-2, H-12), 4.14 (q, *J* = 6.9 Hz, 1H, H-6), 4.13 – 4.08 (m, 2H, H-8, H-10), 4.04 (dd, *J* = 12.2, 2.5 Hz, 1H, H-12‘), 3.98 (ddd, *J* = 10.3, 4.6, 2.5 Hz, 1H, H-7), 3.83 (dd, *J* = 10.6, 9.1 Hz, 1H, H-11), 2.06 (s, 3H, CH_3-OAc), 1.88 (s, 3H, CH_3-OAc), 1.40 (d, *J* = 7.4 Hz, 3H, H-23), 1.28 (d, *J* = 6.8 Hz, 3H, H-22), 1.03 – 0.99 (m, 2H, H-1), 0.05 (s, 9H, 3 x CH_3-Si). **^{13}C** NMR (CD_3OD, 176 MHz) δ = 175.2 (C-5), 174.1 (C-3), 173.3 (C=O-OAc), 172.5 (C=O-OAc), 138.5 (C-14), 129.5 (C-16, C-18), 129.4 (C-15, C-19), 129.1 (C-17), 78.9 (C-6), 78.5 (C-11), 71.5 (C-9), 70.8 (C-13), 69.4 (C-7), 64.7 (C-2), 63.6 (C-12), 54.9 (C-8, C-10), 49.6 (C-4), 22.8 (CH_3-OAc), 20.7 (CH_3-OAc), 19.4 (C-22), 18.1 (C-1), 17.2 (C-23), -1.5 (3 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{30}H_{47}N_2O_{11}Si$ $[M + H]^+$: 639.2944, found: 639.2949.

Synthesis of Compound 61

2-(Trimethylsilyl)ethyl ((*R*)-2-(((2*S*,3*R*,4*R*,5*S*,6*R*)-3-acetamido-2-(benzyloxy)-6-((benzyloxy)methyl)-5-hydroxytetrahydro-2*H*-pyran-4-yl)oxy)propanoyl)-L-alaninate



Chemical Formula: $C_{33}H_{48}N_2O_9Si$
Exact Mass: 644,3129
Molecular Weight: 644,8370

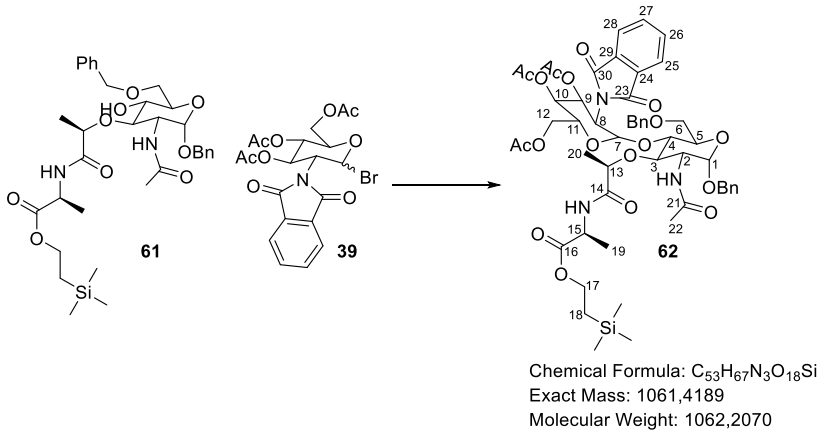
163.50 µL Triethylsilane (1.02 mmol, 5.00 equiv) was added to a dispersion of 131.60 mg compound **269** (204.72 µmol, 1.00 equiv) in 1.49 mL DCM at 0 °C. Then, 78.33 µL TFA (1.02 mmol, 5.00 equiv) was added dropwise and the reaction stirred for 5 hours at 0 °C before a second addition of 47.00 µL TFA (0.61 mmol, 3.00 equiv). After that the mixture continued stirring at 0 °C overnight before the mixture was diluted with DCM (1.50 mL) and slowly neutralised with $NaHCO_3$ solution (aq, sat). The aqueous layer was extracted with DCM (3 x 2 mL) and the combined organic layers washed with brine (2 x 8 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified by column chromatography (SiO_2, packed with 7:3 EE/CH, eluted with EE) yielding 81.30 mg of a colourless amorphous solid (126.08 µmol, 62%).

R_f = 0.21 (CH/EE 1:2). **α_D^{20}** = +79.1 ° (c = 0.86, CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.37 – 7.31 (m, 10H, H-15 – H-19, H-22 – H-26), 6.87 (d, *J* = 7.4 Hz, 1H, NH-Ala), 6.10 (d, *J* = 8.9 Hz,

1H, NH-Ac), 4.89 (d, *J* = 3.6 Hz, 1H, H-9), 4.77 – 4.66 (m, 1H, H-20), 4.62 – 4.52 (m, 2H, H-13), 4.51 – 4.43 (m, 1H, H-20'), 4.39 (p, *J* = 7.3 Hz, 1H, H-4), 4.23 – 4.12 (m, 4H, H-2, H-6, H-8), 3.84 – 3.78 (m, 1H, H-7), 3.78 – 3.72 (m, 1H, H-12), 3.72 – 3.66 (m, 2H, H-11, H-12'), 3.56 (dd, *J* = 10.5, 8.7 Hz, 1H, H-10), 2.91 (d, *J* = 2.9 Hz, 1H, OH), 1.88 (s, 3H, H-28), 1.39 (d, *J* = Hz, 3H, H-29), 1.37 (d, *J* = Hz, 3H, H-30), 1.03 – 0.97 (m, 2H, H-1), 0.05 (s, 9H, 3 x CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 173.2 (C-3), 172.9 (C-5), 170.4 (C-27), 138.5 (C-arom), 137.7 (C-arom), 128.9 (C-arom), 128.8 (C-arom), 128.6 (C-arom), 128.1 (C-arom), 97.5 (C-9), 80.7 (C-10), 78.1 (C-6), 74.0 (C-13), 72.3 (C-11), 70.9 (C-12), 70.8 (C-7), 70.1 (C-20), 64.0 (C-2), 52.8 (C-8), 48.5 (C-4), 23.5 (C-28), 19.3 (C-30), 18.0 (C-29), 17.6 (C-1), -1.5 (3 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{33}H_{48}N_2O_9SiNa$ $[M + Na]^+$: 667.3021, found: 667.3025. The spectroscopic data were in agreement with those previously reported.[56]

Synthesis of Compound 62

(2*R*,3*S*,5*R*)-6-(((2*R*,3*S*,4*R*,5*R*,6*S*)-5-Acetamido-6-(benzyloxy)-2-((benzyloxy)methyl)-4-(((*R*)-1-oxo-1-(((*S*)-1-oxo-1-(2-(trimethylsilyl)ethoxy)propan-2-yl)amino)propan-2-yl)oxy)tetrahydro-2H-pyran-3-yl)oxy)-2-(acetoxymethyl)-5-(1,3-dioxoisoindolin-2-yl)tetrahydro-2H-pyran-3,4-diyl diacetate



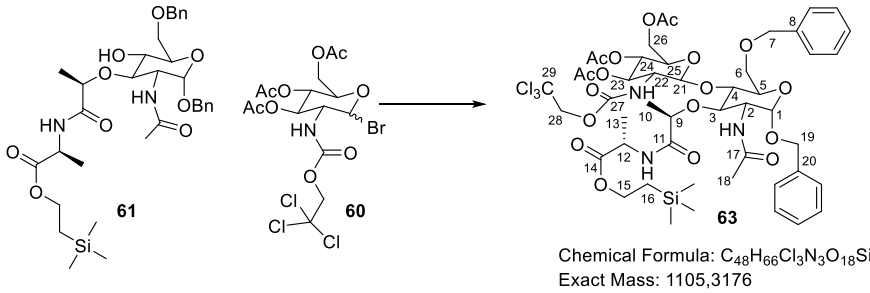
Glycosyl acceptor **61** (8.90 mg, 13.80 µmol, 1.00 equiv) was dissolved in DCM (66.0 µL) and added to a *Schlenk* tube containing flame dried 3 Å MS. The mixture was stirred at room temperature for 20 minutes before it was cooled to -40 °C. Subsequently, silver triflate (10.64 mg, 41.41 µmol, 3.00 equiv)) was added followed by glycosyl donor **39** (13.75 mg, 27.60 µmol, 2.00 equiv) dissolved in DCM (0.1 mL) which was added over 3 hours. After the addition the mixture was stirred at -40 °C overnight and then allowed to slowly warm to room temperature. The reaction was filtered over Celite and washed with DCM. The organic layer was washed with $NaHCO_3$ (2 x 1 mL) and brine (1 x 1 mL) before it was dried over Na_2SO_4 and

the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, packed in 1:1 CH/EE, eluted with, 1:1 CH/EE, then 25% CH/EE and 15% CH/EE) to obtain the desired product as a colourless crystalline solid (6.1 mg, 5.74 µmol, 42%).

R_f = 0.17 (1:1 CH/EE). **α_D^{20}** = +27 ° (c = 0.67 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 400 MHz) δ = 7.75 (dd, *J* = 5.5, 3.0 Hz, 4H, H_{arom} Phth), 7.37 – 7.33 (m, 10H, H_{arom} Bn), 6.87 (d, *J* = 7.3 Hz, 1H, NH-Ala), 6.12 (d, *J* = 8.9 Hz, 1H, NH-Ac), 4.97 (d, *J* = 3.7 Hz, 1H, H-7), 4.92 – 4.85 (m, 4H, 2 x CH_2-Bn), 4.89 (d, *J* = 3.8 Hz, 1H, H-1), 4.54 – 4.43 (m, 1H, H-15), 4.42 – 4.36 (m, 1H, H-13), 4.24 – 4.18 (m, 2H, H-17), 4.14 (d, *J* = 8.6 Hz, 1H, H-8), 3.94 (dd, *J* = 12.0, 4.8 Hz, 3H, H-4, H-9, H-10), 3.83 – 3.76 (m, 4H, H-2, H-3, H-6, H-12), 3.76 – 3.69 (m, 3H,H-5, H-6', H-12'), 3.59 – 3.53 (m, 1H, H-11), 1.95 (s, 9H, 3 x CH_3-OAc), 1.88 (s, 3H, H-22), 1.41 – 1.36 (m, 6H, H-19, H-20), 1.04 – 0.97 (m, 2H, H-18), 0.04 (s, 9H, 3 x CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 173.5 (C-14), 172.1 (C-16), 169.8 (C-21), 169.6 (C=O Ac), 169.6 (C=O Ac), 169.3 (C=O Ac), 169.2 (C-23, C-30), 137.4 (C-24), 135.0 (C-29), 129.3 ($C_{arom.}$), 129.1 ($C_{arom.}$), 129.0 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.7 ($C_{arom.}$), 128.2 ($C_{arom.}$), 128.2 ($C_{arom.}$), 128.0 ($C_{arom.}$), 128.0 ($C_{arom.}$), 128.0 (C-28), 127.3 (C-25), 127.1 (C-27), 123.6 (C-26), 96.8 (C-1), 95.6 (C-7), 76.3 (C-13), 76.0 (C-3), 75.1 (C-4), 73.9 (CH_2-Bn), 70.5 (C-5), 70.1 (CH_2-Bn), 68.5 (C-9), 68.4 (C-10), 68.1 (C-6), 62.6 (C-17), 62.1 (C-11), 61.4 (C-12), 54.7 (C-8), 53.5 (C-2), 47.5 (C-15), 22.5 (C-22), 20.3 (CH_3-OAc), 20.3 (CH_3-OAc), 19.9 (CH_3-OAc), 18.6 (C-20), 17.0 (C-19), 16.5 (C-18), −1.65 (3 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{53}H_{68}N_3O_{18}Si$ $[M + H]^+$: 1062.4262, found: 1062.4266.

Synthesis of Compound 63

(2*R*,3*S*,4*R*,5*R*)-6-(((2*R*,3*S*,4*R*,5*R*,6*S*)-5-Acetamido-6-(benzyloxy)-2-((benzyloxy)methyl)-4-(((*R*)-1-oxo-1-(((*S*)-1-oxo-1-(2-(trimethylsilyl)ethoxy)propan-2-yl)amino)propan-2-yl)oxy)tetrahydro-2*H*-pyran-3-yl)oxy)-2-(acetoxymethyl)-5-(((2,2,2-trichloroethoxy)carbonyl)amino)tetrahydro-2*H*-pyran-3,4-diyl diacetate



Chemical Formula: $C_{48}H_{66}Cl_3N_3O_{18}Si$
Exact Mass: 1105,3176
Molecular Weight: 1107,4940

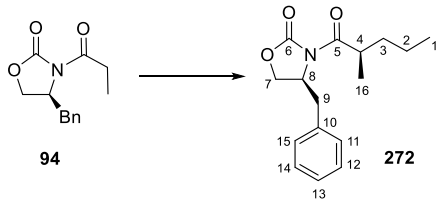
Glycosyl acceptor **61** (9.70 mg, 15.04 µmol, 1.00 equiv) was dissolved in DCM (56.0 µL) and added to a Schlenk tube containing flame dried 3 Å MS. To this solution silver triflate (11.59 mg, 45.13 µmol, 3.00 equiv) was added at room temperature. Afterwards a solution of glycosyl donor **60** (10.22 mg, 18.80 µmol, 1.25 equiv) in DCM (0.20 mL) was added to the mixture over 1 hour. Subsequently, the reaction mixture was stirred at room temperature for 20 hours before it was filtered through Celite® and washed with DCM. The organic layer was washed with $NaHCO_3$ (1 x 1 mL) and brine (1 x 1 mL), dried over Na_2SO_4 and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (SiO_2, packed in 1:1 CH/EE, then eluted with a gradient 15% CH/EE, EE, 5% MeOH/EE) to observe the desired product as a slightly yellow viscous oil (3.20 mg, 2.89 µmol, 19%).

R_f = 0.22 (CH/EE 1:2). **α_D^{20}** = +25.0 ° (c = 0.56, CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz): δ = 7.36 – 7.34 (m, 10H, $H_{arom.}$), 6.86 (d, 1H, *J* = 6.9 Hz, NH-OAc), 6.09 (d, 1H, *J* = 7.3 Hz, NH-Ala), 5.64 (d, 1H, *J* = 9.5 Hz, NH-Troc), 5.06 (d, 1H, *J* = 3.6 Hz, H-1), 5.00 (t, 1H, *J* = 9.7 Hz, H-24), 4.97 (d, 1H, *J* = 3.7 Hz, H-21α), 4.85 (t, 1H, *J* = 10.0 Hz, H-23), 4.79 (d, 1H, *J* = 12.0 Hz, H-7), 4.75 (d, 1H, *J* = 12.1 Hz, H-28), 4.68 (d, 1H, *J* = 12.4 Hz, H-28'), 4.66 – 4.61 (m, 1H, H-19), 4.47 (d, 1H, *J* = 12.0 Hz, H-19'), 4.44 – 4.41 (m, 1H, H-12), 4.40 (d, 1H, *J* = 12.0 Hz, H-7'), 4.39 – 4.36 (m, 1H, H-9), 4.33 (d, 1H, *J* = 8.4 Hz, H-21β), 4.29 (ddd, *J* = 10.5, 9.4, 3.8 Hz, 1H, H-26), 4.22 – 4.19 (m, 2H, H-15), 4.05 – 3.97 (m, 1H, H-26'), 3.95 (ddd, *J* = 10.0, 4.2, 2.1 Hz, 1H, H-4), 3.96 – 3.93 (m, 1H, H-22), 3.91 – 3.88 (m, 1H, H-2), 3.68 (dd, 1H, *J* = 11.0, 2.7 Hz, H-6), 3.63 (d, 1H, *J* = 10.4 Hz, H-5), 3.56 (dd, *J* = 10.5, 8.7 Hz, 1H, H-6'), 3.50 – 3.38 (m, 1H, H-25), 2.01 (s, 3H, OAc-CH_3), 1.98 (s, 3H, OAc-CH_3), 1.93 (s, 3H, OAc-CH_3), 1.89 (s, 3H, C-18), 1.47 (d, 3H, *J* = 7.0 Hz, H-13), 1.38 (d, 3H, *J* = 7.0 Hz, H-10), 1.04 – 0.98 (m, 2H, H-16), 0.04 (s, 9H, 3 x CH_3-Si).; **^{13}C** NMR (CD_2Cl_2, 176 Hz): δ = 174.0 (C-11), 173.2 (C-14), 170.8 (OAc-C=O), 170.6 (C-17), 170.0 (OAc-C=O), 169.9 (OAc-C=O), 169.8 (OAc-C=O), 154.6 (C-27), 138.1 (C-8), 137.4 (C-20), 129.3 ($C_{arom.}$), 129.1 ($C_{arom.}$), 129.0 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.7 ($C_{arom.}$), 128.2 ($C_{arom.}$), 128.2 ($C_{arom.}$), 128.0 ($C_{arom.}$), 128.0 ($C_{arom.}$), 100.3 (C-21β), 97.5 (C-21α), 97.2 (C-1), 77.5 (C-9), 76.6 (C-3), 76.5 (C-4), 74.8 (C-28), 73.9 (C-7), 72.6 (C-23), 71.9 (C-25), 70.8 (C-5), 70.3 (C-19), 68.6 (C-24), 68.1 (C-6), 64.1 (C-15), 61.8 (C-26), 54.0 (C-2), 51.3 (C-22), 48.5 (C-12), 23.3 (C-18), 20.9 (OAc-CH_3), 20.8 (OAc-CH_3), 20.8 (OAc-CH_3), 18.1 (C-10), 18.0 (C-13), 17.6 (C-16), -1.5 (3 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{48}H_{67}Cl_3N_3O_{18}Si$ $[M + H]^+$: 1108.3236, found: 1108.3233

3.3 Contributions Towards the Total Synthesis of Neaumycin B

Synthesis of Compound 272

(*R*)-4-Benzyl-3-((*R*)-2-methylpentanoyl)oxazolidin-2-one



Chemical Formula: $C_{16}H_{21}NO_3$
Exact Mass: 275,1521
Molecular Weight: 275,3480

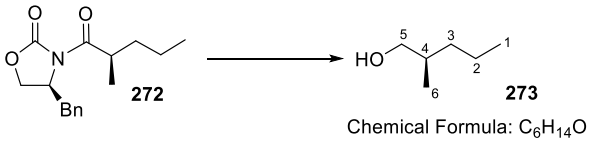
NaHMDS (1.0 M in THF, 12.96 mL, 12.96 mmol, 1.10 equiv) was precooled to -78 °C and a solution of compound **94** (2.50 g, 11.40mmol, 1.00 equiv) in THF (9.91 mL) was slowly added ensuring the temperature staying below -70 °C. The mixture was stirred for 30 minutes at -78 °C before allylbromide (5.77 mL, 34.34 mmol, 3.00 equiv) was added dropwise making sure the internal temperature of the reaction would stay below -70 °C. After that, the reaction mixture was stirred for three hours at -78 °C and then quenched with NH_4Cl (6 mL). The organic solvent was removed under reduced pressure prior to adding Et_2O (30 mL) to the residual aqueous layer. The layers were separated and the organic layer washed with H_2O (1 x 9 mL), 1 N $NaHSO_4$ (1 x 9 mL) and brine (1 x 9 mL). Then, the organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was redissolved in THF (11.4 mL) and transferred to a new reaction flask containing Pd/C (10%, 1.51 g, 5.70 mmol, 0.50 equiv). The argon atmosphere was exchanged for H_2 and the reaction stirred at room temperature for 5 hours. Thereafter, the mixture was filtered through Celite®, washed with EE (3 x 5 mL) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, 4:1 CH/EE) to observe the desired product as a colourless oil (1.60 g, 5.81 mmol, 51%).

R_f = 0.17 (4:1 CH/EE). **α_D^{20}** = +9.8 °(c = 0.5 in $CHCl_3$). **^{1}H** NMR ($CDCl_3$, 700 MHz) δ = 7.35 – 7.32 (m, 2H, H-12, H-14), 7.29 – 7.26 (m, 1H, H-13), 7.23 – 7.21 (m, 2H, H-11, H-15), 4.69 (ddt, *J* = 9.8, 7.6, 3.1 Hz, 1H, H-8), 4.19 (ddd, *J* = 8.6, 7.7, 0.8 Hz, 1H, H-9), 4.15 (dd, *J* = 9.1, 2.9 Hz, 1H, H-9'), 3.77 (h, *J* = 6.7 Hz, 1H, H-4), 3.31 (dd, *J* = 13.4, 3.4 Hz, 1H, H-7), 2.73 (dd, *J* = 13.3, 9.8 Hz, 1H, H-7'), 1.80 – 1.73 (m, 1H, H-3), 1.47 – 1.34 (m, 3H, H-2, H-3'), 1.17 (d, *J* = 6.8 Hz, 3H, H-16), 0.94 (t, *J* = 7.2 Hz, 3H, H-1). **^{13}C** NMR ($CDCl_3$, 176 MHz) δ = 177.6 (C-5), 153.3 (C-6), 135.5 (C-10), 129.6 (C-11, C-15), 129.1 (C-12, C-14), 127.5 (C-13), 66.1 (C-9), 55.5 (C-8), 38.3 (C-7), 37.5

(C-4), 36.2 (C-3), 20.4 (C-2), 16.9 (C-16), 14.2 (C-1). **HRMS (APCI)** *m/z*: calcd for $C_{16}H_{22}NO_3$ $[M + H]^+$: 276.1594, found: 276.1589.

Synthesis of Compound 273

(*R*)-2-Methylpentan-1-ol



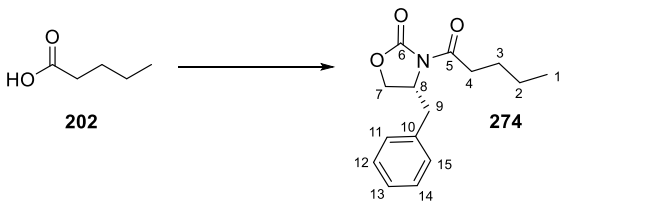
Chemical Formula: $C_6H_{14}O$
Exact Mass: 102,1045
Molecular Weight: 102,1770

Compound **272** (570.60 mg, 2.07 mmol, 1.00 equiv) was dissolved in Et_2O (41.31 mL) and cooled to 0 °C. The resulting solution was treated with $LiBH_4$ (1.15 mL, 2.28 mmol, 1.10 equiv), the cooling bath removed and the reaction stirred at room temperature for one hour. The reaction was quenched by the addition of 1 M NaOH (10 mL) and the biphasic mixture stirred until both layers appeared to be clear (15 minutes). The aqueous layer was diluted with H_2O (30 mL) prior to separating the layers and extracting the aqueous layer with Et_2O (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, the solvent removed under reduced pressure and the crude product purified by column chromatography (SiO_2, 1:1 CH/EE) yielding 153.90 mg (1.51 mmol, 73%) of the desired product as a colourless liquid.

$\mathbf{R_f}$ = 0.46 (1:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +2.1 °(c = 0.19 in CH_2Cl_2). **^{1}H** NMR ($CDCl_3$, 499 MHz) δ = 3.51 (dd, *J* = 10.5, 5.7 Hz, 1H, H-5), 3.42 (dd, *J* = 10.5, 6.6 Hz, 1H, H-5'), 1.68 – 1.58 (m, 1H, H-4), 1.45 – 1.22 (m, 3H, H-2, H-3), 1.18 – 1.03 (m, 1H, H-3'), 0.91 (d, *J* = 6.7 Hz, 3H, H-6), 0.90 (t, *J* =7.1 Hz, 3H, H-1). **^{13}C** NMR ($CDCl_3$, 126 MHz) δ = 68.6 (C-5), 35.6 (C-4), 35.6 (C-3), 20.2 (C-2), 16.7 (C-6), 14.5 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_6H_{14}OH$ $[M + H]^+$: 103.1117, found: 103.1113.

Synthesis of Compound 274

(*R*)-4-Benzyl-3-pentanoyloxazolidin-2-one



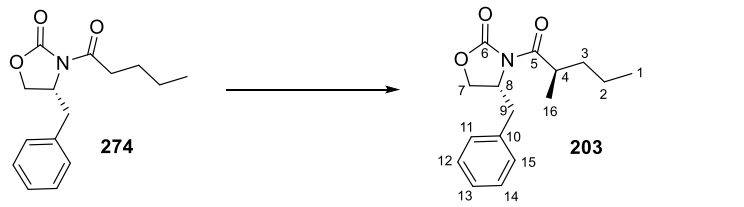
Chemical Formula: $C_{15}H_{19}NO_3$
Exact Mass: 261,1365
Molecular Weight: 261,3210

In a flame-dried *Schlenk* flask valeric acid (**202**) (750.00 mg, 7.34 mmol, 1.00 equiv) was dissolved in THF (41.3 mL) and the mixture was cooled to -20 °C to -30 °C. Then triethylamine (1.86 g, 18.36 mmol, 2.50 equiv) was added dropwise before the dropwise addition of pivaloyl chloride (973.98 mg, 8.08 mmol, 1.10 equiv) to the reaction mixture. The slurry mixture was stirred for 75 minutes at -20 °C to -30 °C. Afterwards LiCl (466.93 mg, 11.02 mmol, 1.50 equiv) and (*R*)-(+)-benzyl-2-oxazolidinone (**120**) (1.43 g, 8.08 mmol, 1.10 equiv) were added in THF (7.1mL). The mixture was allowed to warm to room temperature and continued stirring for 5 hours before saturated ammonium chloride solution was added. The aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was applied on Celite for column chromatography (SiO_2, 5:1 CH/EE). A colourless oil (1.92 g, 7.36 mmol, quant) was observed.

R_f = 0.18 (5:1 CH/EE). **α_D^{20}** = +4.5 ° (c =0.13 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.35 – 7.32 (m, 2H, H-12, H-14), 7.29 – 7.26 (m, 1H, H-13), 7.22 – 7.19 m, 2H, H-11, H-15), 4.67 (dddd, *J* = 9.1, 7.9, 3.4, 2.8 Hz, 1H, H-8), 4.20 (ddd, *J* = 8.7, 7.9, 0.7 Hz, 1H, H-7), 4.15 (dd, *J* = 9.0, 2.7 Hz, 1H, H-7), 3.22 (dd, *J* = 13.5, 3.4 Hz, 1H, H-9), 2.93 (ddd, *J* = 16.8, 8.5, 6.5 Hz, 1H, H-4), 2.89 – 2.85 (m, 1H, H-4), 2.83 (dd, *J* = 13.5, 9.1 Hz, 1H, H-9), 1.70 – 1.62 (m, 2H, H-3), 1.41 (h, *J* = 7.4 Hz, 2H, H-2), 0.95 (t, *J* = 7.4 Hz, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 700 MHz) δ = 173.6 (C-5), 153.9 (C-6), 136.0 (C-10), 129.9 (C-11, C-15), 129.2 (C-12, C-14), 127.6 (C-13), 66.6 (C-7), 55.4 (C-8), 38.2 (C-9), 35.6 (C-4), 26.8 (C-3), 22.7 (C-2), 14.1 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_{15}H_{19}NO_3H$ $[M + H]^+$: 262.1438, found: 262.1443.

Synthesis of Compound 203

(*R*)-4-Benzyl-3-((*R*)-2-methylpentanoyl)oxazolidin-2-one



Chemical Formula: $C_{16}H_{21}NO_3$
Exact Mass: 275,1521
Molecular Weight: 275,3480

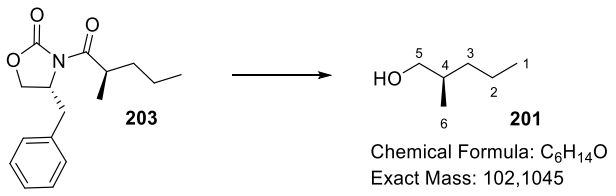
The derivatised oxazolidinone **274** (1.92 g, 7.35 mmol, 1.00 equiv) was dissolved in THF (26.3 mL) and the solution cooled to -78 °C. Afterwards, sodium bis(trimethylsilyl)amide

(5.51 mL, 11.02 mmol, 1.0 M in THF, 1.50 equiv) was added dropwise and the mixture was stirred for 1 hour at -78 °C. Then, methyl iodide (1.37 mL, 22.04 mmol, 3.00 equiv) was added dropwise to the solution and the stirring was continued at -78 °C for 4 hours. Next, saturated ammonium chloride solution was added and the aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 5:1 CH/EE) to yield a colourless oil (1.64 g, 5.95 mmol, 81%).

R_f = 0.27 (5:1 CH/EE). **α_D^{20}** = - 41.7 ° (c = 0.01 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.35 – 7.31 (m, 2H, H-12, H-14), 7.29 – 7.25 (m, 1H, H-13), 7.23 – 7.20 (m, 2H, H-11, H-15), 4.67 (dddd, *J* = 9.0, 7.7, 3.4, 2.7 Hz, 1H, H-8), 4.20 (ddd, *J* = 9.0, 7.7, 0.7 Hz, 1H, H-7), 4.15 (dd, *J* = 9.0, 2.7 Hz, 1H, H-7´), 3.69 (h, *J* = 6.8 Hz, 1H, H-4), 3.19 (dd, *J* = 13.5, 3.4 Hz, 1H, H-9), 2.83 (dd, *J* = 13.5, 9.0 Hz, 1H, H-9´), 1.70 (dddd, *J* = 12.6, 8.8, 6.9, 5.9 Hz, 1H, H-3), 1.42 – 1.28 (m, 3H, H-2, H3´), 1.19 (d, *J* = 6.8 Hz, 3H, H-16), 0.90 (t, *J* = 7.2 Hz, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 177.4 (C-5), 153.5 (C-6), 136.0 (C-10), 129.9 (C-11, C-15), 129.2 (C-12, C-14), 127.6 (C-13), 66.5 (C-7), 55.6 (C-8), 38.1 (C-9), 37.8 (C-4), 35.9 (C-3), 20.8 (C-2), 17.4 (C-16), 14.3 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_{16}H_{21}NO_3H$ $[M + H]^+$: 276.1594, found: 276.1597.

Synthesis of Compound 201

(*R*)-2-Methylpentan-1-ol



Chemical Formula: $C_6H_{14}O$
Exact Mass: 102,1045
Molecular Weight: 102,1770

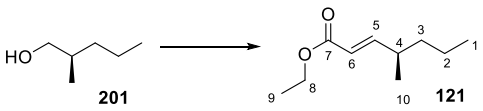
The starting material **203** (172.50 mg, 626.48 µmol, 1.00 equiv) was dissolved in diethylether (1.99 mL) and the solution cooled to 0 °C. Then, $LiAlH_4$ (438.54 µL, 877.07µmol, 2.0 M in Et2O, 1.40 equiv) was diluted with Et_2O (0.73 mL) and dropwise added to the reaction mixture over 10 minutes. The mixture was stirred for 2 hours at 0 °C before brine (5 mL) was added dropwise over 5 minutes and the bilayer mixture stirred for further 30 minutes at 0 °C. The aqueous layer was diluted with water (5 mL) and then extracted with Et2O (3 x 5 mL). Afterwards, the combined organic layers were dried over $MgSO_4$ and the solvent evaporated

under reduced pressure. The crude product was purified by column chromatography (SiO_2, 1:1 pentane/EE) to yield a colourless oil (64.38 mg, 630.12 µmol, quant).

R_f = 0.50 (1:1 CH/EE). **α_D^{20}** = +2.1 °(c = 0.19 in CH_2Cl_2). **^{1}H** NMR ($CDCl_3$, 500 MHz) δ = 3.54 – 3.38 (m, 2H, H-5), 1.68 – 1.59 (m, 1H, H-4), 1.44 – 1.33 (m, 2H, H-2, H-3), 1.33 – 1.24 (m, 1H, H-2), 1.14 – 1.06 (m, 1H, H-3), 0.92 – 0.90 (m, 3H, H-6), 0.90 (d, *J* = 7.0 Hz, 3H, H-1). **^{13}C** NMR ($CDCl_3$, 126 MHz) δ = 68.6 (C-5), 35.6 (C-4), 35.6 (C-3), 20.2 (C-2), 16.7 (C-6), 14.5 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_6H_{14}OH$ $[M + H]^+$: 103.1117, found: 103.1113.

Synthesis of Compound 121

Ethyl (*R*,*E*)-4-methylhept-2-enoate



Chemical Formula: $C_{10}H_{18}O_2$
Exact Mass: 170,1307
Molecular Weight: 170,2520

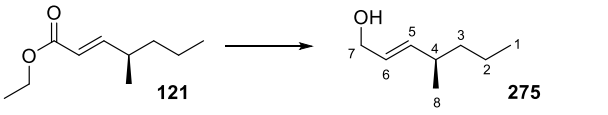
Oxalyl chloride (214.08 mmL, 2.50 mmol, 1.21 equiv) was dissoled in DCM (16.7 mmL) and cooled to -60 °C. Then, DMSO (351.68 µmL, 4.95 mmol, 2.40 equiv) was added and the solution stirred for 10 minutes at -60 °C. Afterwards the alcohol **201** (210.80 mg, 2.06 mmol, 1.00 equiv) was dissolved in DCM (12.3 mL) and dropwise added to the stirred solution which was continued stirring at -60 °C for 15 minutes. Lastly, triethylamine (1.42 mL, 10.21 mmol, 4.95 equiv) was added dropwise and the mixture was allowed to warm to 0 °C. After that methyl(triphenylphosphoranylidene)acetate (2.15 g, 6.18 mmol, 3.00 equiv) was added and the mixture warmed to room temperature and stirred for 10 more minutes at room temperature. The reaction mixture was poured into brine and the aqueous layer extracted with DCM (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was applied to Celite® and purified by column chromatography (SiO_2, 5:1 CH/EE) to yield a colourless oil (189.39 mg, 1.11 mmol, 54%).

R_f = 0.60 (5:1 CH/EE). **α_D^{20}** = - 3.6 °(c = 0.16 in CH_2Cl_2). **^{1}H-NMR** (CD_2Cl_2, 500 MHz) δ = 6.87 (dd, *J* = 15.7, 7.9 Hz, 1 H, H-5), 5.77 (dd, *J* = 15.7, 1.2 Hz, 1 H, H-6), 4.12 (q, *J* = 7.1 Hz, 2 H, H-8), 2.34 - 2.28 (m, 1 H, H-4), 1.35 - 1.29 (m, 4 H, H-2, H-3), 1.26 (t, *J* = 7.1 Hz, 3 H, H-9), 1.04 (d, *J* = 6.7 Hz, 3 H, H-10), 0.88 (t, *J* = 7.1 Hz, 3 H, H-1). **^{13}C-NMR** (CD_2Cl_2, 126 MHz) δ = 167.5 (C-7),

155.2 (C-5), 119.3 (C-6), 51.5 (C-8), 38.3 (C-3), 36.4 (C-4), 27.1 (C-10), 20.4 (C-2), 19.5 (C-9), 14.2 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_{10}H_{18}O_2H$ [M + H]$^+$: 171.2595, found: 171.2598.

Synthesis of Compound 275

(*R*,*E*)-4-Methylhept-2-en-1-ol



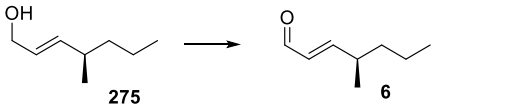
Chemical Formula: $C_8H_{16}O$
Exact Mass: 128,1201
Molecular Weight: 128,2150

The α,β-unsaturated ester **121** (37.1 mg, 217.91 µmol, 1.00 equiv) was dissolved in THF (1.45 mL) and the solution cooled to -78 °C. DIBAl-H (479.41 µL, 479.41 µmol, 1.0 M in CH, 2.20 equiv) was added dropwise before the reaction was continued stirring for 75 minutes at -78 °C. Sodium, potassium tartrate solution was added and the aqueous layer extracted with DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 5:1 CH/EE) to yield a colourless oil (22.35 mg, 174.32 µmol, 80%).

R_f = 0.15 (5:1 CH/EE). **α_D^{20}** = +1.3 °(c = 0.19 in CH_2Cl_2). **^{1}H** NMR ($CDCl_3$, 700 MHz) δ = 5.62 – 5.53 (m, 2H, H-5, H-6), 4.09 (d, *J* = 4.3 Hz, 2H, H-7), 2.15 (p, *J* = 6.6 Hz, 1H, H-4), 1.34 – 1.20 (m, 4H, H-2, H-3), 0.98 (d, *J* = 6.8 Hz, 3H, H-8), 0.88 (t, *J* = 7.0 Hz, 3H, H-1). **^{13}C** NMR ($CDCl_3$, 700 MHz) δ = 139.5 (C-5), 127.2 (C-6), 64.1 (C-7), 39.2 (C-3), 36.2 (C-4), 20.5 (C-2), 20.5 (C-8), 14.3 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_8H_{16}OH$ [M + H]$^+$: 129.1274, found: 129.1271.

Synthesis of Compound 6

(*R*,*E*)-4-Methylhept-2-enal



Chemical Formula: $C_8H_{14}O$
Exact Mass: 126,1045
Molecular Weight: 126,1990

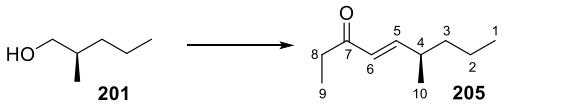
SO_3*pyridine complex (257.80 mg, 1.62 mmol, 3.25 equiv) and DMSO (2.50 mL, 35.14 mmol, 70.50 equiv) were preloaded in the flask and DIPEA (0.28 mL, 1.62 mmol, 3.25 equiv) was added. The mixture was stirred for 5 minutes at room temperature. Then the alcohol **275** (63.90 mg, 498.38 µmol, 1.00 equiv) was dissolved in DCM (2,56 mL) and added to the mixture

which was cooled to 0 °C. It was stirred 30 minutes at 0 °C before sodium bicarbonate solution was added. The aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were washed with $CuSO_4$ solution (2 x 15 mL), ammonium chloride solution (2 x 15 mL) and brine (1 x 15 mL). After washing the organic layer was dried over $MgSO_4$ and the solvent was evaporated. The crude product was used for the next reaction without further purification.

R_f = 0.39 (5:1 CH/EE). **^{1}H-NMR** (CD_2Cl_2, 300 MHz) δ = 9.48 (d, *J* = 7.8 Hz, 1H, H-7), 6.75 (dd, *J* = 15.7, 7.6 Hz, 1H, H-5), 6.04 (ddd, *J* = 15.6, 7.8, 1.2 Hz, 1H, H-6), 2.50 - 2.43 (m, 1H, H-4), 1.41 - 1.31 (m, 4H, H-2, H-3), 1.08 (d, *J* = 6.7 Hz, 3H, H-8), 0.90 (dd, *J* = 7.5, 6.6 Hz, 3H, H-1).

Synthesis of Compound 205

(*R*,*E*)-6-Methylnon-4-en-3-one



Chemical Formula: $C_{10}H_{18}O$
Exact Mass: 154,1358
Molecular Weight: 154,2530

Oxalylchloride (50.78 μL, 592.11 μmol, 1.21 equiv) was dissolved in DCM (7.9 mL) and cooled to -60 °C. Then, DMSO (83.42 μL, 1.17 mmol, 2.40 equiv) was added and the solution stirred for ten minutes at -60 °C. Afterwards, the alcohol **201** (50.00 mg, 489.35 μmol, 1.00 equiv) was dissolved in DCM (5.8 mL) and added dropwise to the stirred solution which was continued stirring at -60 °C for 15 minutes. Lastly, triethylamine (337.63 μL, 2.42 mmol, 4.95 equiv) was added dropwise and the mixture was allowed to warm to 0 °C and stirred for another 30 minutes. Afterwards, a saturated aqueous ammonium chloride solution was added and the layers separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with brine (40 mL). The latter were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was used for the next reaction without further purification or analysis. **R_f** = 0.64 (1:1 CH/EE).

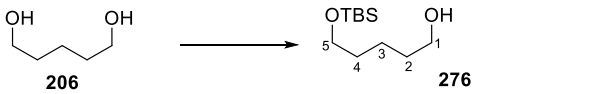
Subsequently, a flame dried *Schlenk* flask was equipped with a magnetic stirring bar and charged with lithium chloride (31.12 mg, 734.03 μmol, 1.50 equiv) and MeCN (2.37 mL). To the flask was added diethyl (2-oxobutyl)phosphonate (142.56 μL, 734.03 μmol) and *i*-Pr_2NEt (102.29 μL, 587.22 μmol, 1.20 equiv) in one portion. The *in situ* prepared aldehyde (49.01 mg,

489.35 μmol, 1.00 equiv) was dissolved in MeCN (2.33 mL) and added dropwise to the reaction mixture. The reaction was stirred at room temperature 12 hours. At this time all starting material was consumed, and the reaction mixture was poured into a separatory funnel containing brine (7 mL). The resulting biphasic mixture was shaken vigorously and the organic layer was separated. The aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (SiO_2, 5:1 CH/EE) to afford dienoate **205** (47.9 mg, 310.53 μmol, 64 %) as a yellow oil.

R_f = 0.47 (5:1 CH/EE). **α_D^{20}** = +5.0° (c = 1.00, $CHCl_3$). **^{1}H** NMR ($CDCl_3$, 500 MHz) δ = 6.71 (dd, *J* = 15.9, 7.9 Hz, 1H, H-5), 6.05 (dd, *J* = 16.0, 1.2 Hz, 1H, H-6), 2.57 (q, *J* = 7.3 Hz, 2H, H-8), 2.36 – 2.26 (m, 1H, H-4), 1.41 – 1.22 (m, 4H, H-2, H-3), 1.10 (t, *J* = 7.4 Hz, 3H, H-9), 1.05 (d, *J* = 6.7 Hz, 3H, H-2), 0.89 (t, *J* = 7.1 Hz, 3H, H-1). **^{13}C** NMR ($CDCl_3$, 125 MHz) δ = 201.7 (C-7), 152.6 (C-5), 128.4 (C-6), 38.5 (C-3), 36.6 (C-4), 33.4 (C-8), 20.5 (C-2), 19.6 (C-10), 14.2 (C-1), 8.4 (C-9). **HRMS (ESI)** m/z: calcd for $C_{10}H_{19}O$ $[M + H]^+$: 155.1430, found: 155.1430.

Synthesis of Compound 276

5-((*Tert*-butyldimethylsilyl)oxy)pentan-1-ol



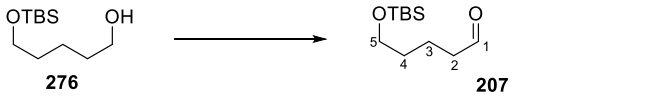
Chemical Formula: $C_{11}H_{26}O_2Si$
Exact Mass: 218,1702
Molecular Weight: 218,4120

In a flame dried flask pentanediol (**206**) (500.00 mg, 4.80 mmol, 1.00 equiv) was dissolved in DCM (48.0 mL) and imidazole (653.54 mg, 9.60 mmol, 2.00 equiv) was added. After addition of *tert*-butyldimethylsilyl chloride (180.86 mg, 1.20 mmol, 0.25 equiv) the reaction mixture was stirred at room temperature for 75 minutes. Then, saturated aqueous NH_4Cl solution (50 mL) was added and the layers were seperated. The aqueous layer was extracted with DCM (3 x 50 mL) and the combined organic layers were washed with water (1 x 150 mL) and brine (1 x 150 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product (251.50 mg, 1.15 mmol, 96%) was used for the next reaction without further purification.

R_f = 0.19 (4:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 3.60 (dt, *J* = 8.1, 6.4 Hz, 4H, H-1, H-5), 1.61 – 1.48 (m, 4H, H-2, H-4), 1.45 – 1.32 (m, 2H, H-3), 0.89 (s, 9H, $C(CH_3)_3$), 0.04 (s, 6H, 2 x CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 63.6 (C-1), 63.3 (C-5), 33.2 (C-4), 33.2 (C-2), 26.3 ($C(CH_3)_3$), 22.6 (C-3), -5.1 (2 x CH_3-Si). **HRMS(ESI)** *m/z*: calcd for $C_{11}H_{27}O_2Si$ $[M + H]^+$: 219.1775, found: 219.1776.

Synthesis of Compound 207

5-((*Tert*-butyldimethylsilyl)oxy)pentanal



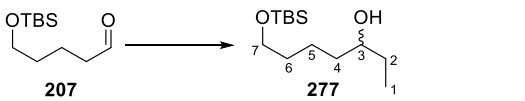
Chemical Formula: $C_{11}H_{24}O_2Si$
Exact Mass: 216,1546
Molecular Weight: 216,3960

The mono-protected alcohol **276** (30.00 mg, 0.14 mmol, 1.00 equiv) was dissolevd in DCM (0.7 mL) and added to a solution of SO_3*py (71.82 mg, 0.45 mmol, 3.25 equiv) and DIPEA (0.08 mL, 0.41 mmol, 3.00 equiv) in DMSO (0.7 mL) at 0 °C. The mixture was stirred at 0 °C for 30 minutes. Then saturated aqueous NH_4CO_3 solution was added and the phases separated. The aqueous layer was extracted with DCM (3 x 2 mL) and the combined organic layers washed with saturated aqueous $CuSO_4$ (2 x 10 mL), saturated aqueous NH_4Cl (2 x 10 mL) and brine (1 x 10 mL) before the combined organic layers were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product (31.6 mg, 0.15 mmol, quant.) used in the next reaction without further purification or analysis.

R_f = 0.48 (4:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 400 MHz) δ = 9.73 (s, 1H, H-1), 3.62 (t, *J* = 6.2 Hz, 2H, H-2), 2.47 – 2.39 (m, 2H, H-5), 1.74 – 1.61 (m, 2H, H-4), 1.57 – 1.48 (m, 2H, H-3), 0.89 (s, 9H, $C(CH_3)_3$), 0.04 (s, 6H, CH_3-Si).

Synthesis of Compound 277

7-((*Tert*-butyldimethylsilyl)oxy)heptan-3-ol



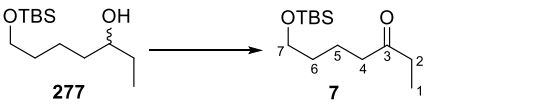
Chemical Formula: $C_{13}H_{30}O_2Si$
Exact Mass: 246,2015
Molecular Weight: 246,4660

Freshly prepared aldehyde **207** (30.1 mg, 0.14 mmol, 1.00 equiv) was dissolved in THF (1.4 mL) and ethyl magnesium bromide solution (1.0 M, 0.17 mL, 0.17 mmol, 1.20 equiv) was added dropwise at 0 °C. The reaction was stirred at 0 °C for 30 minutes before it was diluted with THF (0.7 mL) and saturated aqueous NH_4Cl solution was added. The aqueous phase was extracted with DCM (3 x 3 mL) and the combined organic layers were washed with brine (1 x 10 mL) and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, 4:1 CH/EE) yieldind a slightly yellow liquid (40.10 mg, 0.16 mmol, quant.).

R_f = 0.28 (4:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 3.61 (t, *J* = 6.3 Hz, 2H, H-7), 3.48 (tt, *J* = 8.6, 5.3 Hz, 1H, H-3), 1.52 – 1.34 (m, 6H, H-4, H-5, H-6), 0.92 (t, *J* = 7.5 Hz, 3H, H-1), 0.89 (s, 9H, $C(CH_3)_3$), 0.04 (s, 6H, 2 x CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 73.6 (C-3), 63.6 (C-7), 37.3 (C-2), 33.4 (C-4), 30.8 (C-6), 26.3 ($C(CH_3)_3$), 22.5 (C-5), 10.2 (C-1), -5.1 (2 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{13}H_{31}O_2Si$ $[M + H]^+$: 247.2088, found: 247.2091.

Synthesis of Compound 7

7-((*Tert*-butyldimethylsilyl)oxy)heptan-3-one



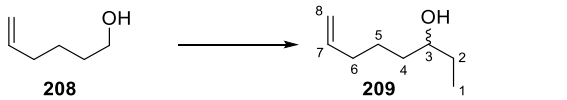
Chemical Formula: $C_{13}H_{28}O_2Si$
Exact Mass: 244,1859
Molecular Weight: 244,4500

In a flame dried *Schlenk* flask SO_3*py (62.24 mg, 0.39 mmol, 3.25 equiv) was dissolved in DMSO (0.6 mL) and DIPEA (0.07 mL, 0.37 mmol, 3.00 equiv) was added dropwise before the resulting solution was cooled to 0 °C. The racemic alcohol **277** (40.10 mg, 0.16 mmol, 1.00 equiv) was dissolved in DCM (0.6 mL) and added dropwise to the solution which was continued stirring at 0 °C for 30 minutes. Afterwards saturated aqueous NH_4CO_3 solution (3 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (3 x 5 mL) and the combined organic layers were washed with saturated aqueous $CuSO_4$ solution (2 x 10 mL), saturated aqueous NH_4Cl solution (2 x 10 mL) and brine (1 x 10 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, 4:1 CH/EE) yielding a slightly yellow liquid (48.70 mg, 0.20 mmol, quant.).

R_f = 0.47 (4:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 3.60 (t, *J* = 6.4 Hz, 2H, H-7), 2.43 – 2.36 (m, 4H, H-2, H-4), 1.62 – 1.57 (m, 2H, H-5), 1.50 – 1.46 (m, 2H, H-6), 1.01 (t, *J* = 7.4 Hz, 3H, H-1), 0.89 (s, 9H, $C(CH_3)_3$), 0.04 (s, 6H, 2 x CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 175 MHz) δ = 211.6 (C-3), 63.2 (C-7), 36.1 (C-2), 32.7 (C-6), 26.1 ($C(CH_3)_3$), 20.8 (C-4), 18.6 (C-5), 8.00 (C-1) -5.3 (2 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{13}H_{29}O_2Si$ $[M + H]^+$: 245.1931, found: 245.1932.

Synthesis of Compound 209

Oct-7-en-3-ol



Chemical Formula: $C_8H_{16}O$
Exact Mass: 128,1201
Molecular Weight: 128,2150

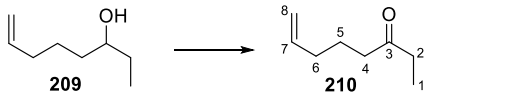
In a flame dried *Schlenk* flask SO_3*py (2.59 g, 16.22 mmol, 3.25 equiv) was dissolved in DMSO (25.0 mL) and DIPEA (2.53 mL, 14.98 mmol, 3.00 equiv) was added dropwise before the resulting solution was cooled to 0 °C. Hex-5-en-1-ol (**208**) (500.00 mg, 4.99 mmol, 1.00 equiv) was dissolved in DCM (25.0 mL) and added dropwise to the solution which was continued stirring at 0 °C for 30 minutes. Afterwards, saturated aqueous NH_4CO_3 solution (25 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (3 x 25 mL) and the combined organic layers were washed with saturated aqueous $CuSO_4$ solution (2 x 50 mL), saturated aqueous NH_4Cl solution (2 x 50 mL) and brine (1 x 50 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was used for the next reaction without further purification or analysis. **R_f** = 0.28 (5:1 CH/EE).

In situ prepared aldehyde (245.38 mg, 2.50 mmol, 1.00 equiv) was dissolved in THF (25.0 mL) and ethyl magnesium bromide solution (1.0 M, 3.00 mL, 3.00 mmol, 1.20 equiv) was added dropwise at 0 °C. The reaction was stirred at 0 °C for 30 minutes before it was diluted with THF (25 mL) and saturated aqueous NH_4Cl solution was added. The aqueous phase was extracted with DCM (3 x 40 mL) and the combined organic layers were washed with brine (1 x 130 mL) and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, 5:1 CH/EE) yieldind a colourless liquid (259.50 mg, 2.02 mmol, 81%).

R_f = 0.19 (4:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 5.83 (ddtd, *J* = 17.0, 10.2, 6.7, 1.5 Hz, 1H, H-7), 5.01 (dddt, *J* = 17.1, 6.8, 3.6, 1.7 Hz, 1H, H-8), 4.97 – 4.89 (m, 1H, H-8'), 3.49 (tq, *J* = 8.4, 4.3 Hz, 1H, H-3), 2.13 – 2.01 (m, 2H, H-6), 1.57 – 1.45 (m, 2H, H-5), 1.45 – 1.21 (m, 4H, H-2, H-4), 0.95 – 0.86 (m, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 175 MHz) δ = 139.4 (C-7), 114.6 (C-8), 73.4 (C-3), 36.8 (C-2), 34.2 (C-6), 30.7 (C-4), 25.4 (C-5), 10.1 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_8H_{17}O$ $[M + H]^+$: 129.1274, found: 129.1274.

Synthesis of Compound 210

Oct-7-en-3-one



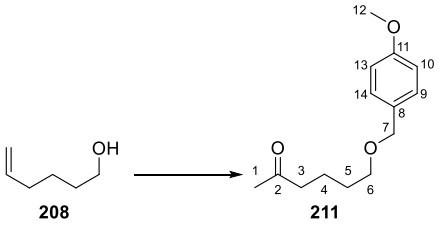
Chemical Formula: $C_8H_{14}O$
Exact Mass: 126,1045
Molecular Weight: 126,1990

In a flame dried *Schlenk* flask SO_3*py (316.30 mg, 1.98 mmol, 3.25 equiv) was dissolved in DMSO (3.1 mL) and DIPEA (0.32 mL, 1.83 mmol, 3.00 equiv) was added dropwise before the resulting solution was cooled to 0 °C. The racemic alcohol **209** (78.40 mg, 0.61 mmol, 1.00 equiv) was dissolved in DCM (3.1 mL) and added dropwise to the solution which was continued stirring at 0 °C for 30 minutes. Afterwards saturated aqueous NH_4CO_3 solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with saturated aqueous $CuSO_4$ solution (2 x 40 mL), saturated aqueous NH_4Cl solution (2 x 40 mL) and brine (1 x 40 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, 5:1 CH/EE) yielding a colourless liquid (53.80 mg, 0.87 mmol, 70%).

R_f = 0.48 (4:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 5.79 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, H-7), 5.01 (ddt, *J* = 17.1, 2.0, 1.6 Hz, 1H), 4.96 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 2.43 – 2.36 (m, 4H, H-2, H-4), 2.07 – 2.01 (m, 2H, H-6), 1.64 (p, *J* = 7.5 Hz, 2H, H-5), 1.01 (t, *J* = 7.3 Hz, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 700 MHz) δ = 211.5 (C-3), 138.7 (C-7), 115.1 (C-8), 41.8 (C-4), 36.2 (C-2), 33.6 (C-6), 23.3 (C-5), 8.0 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_8H_{15}O$ $[M + H]^+$: 127.1117, found: 127.1114.

Synthesis of Compound 211

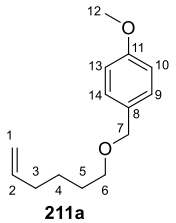
6-((*Para*-methoxybenzyl)oxy)-hex-2-one



208 **211**

Chemical Formula: $C_{14}H_{20}O_3$
Exact Mass: 236,1412
Molecular Weight: 236,3110

A flame dried *Schlenk* falsk was charged with sodium hydride (107.82 mg, 2.70 mmol, 2.70 equiv) and dry THF (2.0 mL). The suspension was cooled to 0 °C before alcohol **208** (100.00 mg, 998.39 µmol, 1.00 equiv) was added dropwise and the mixture stirred at 0 °C for one hour. Thereafter, PMBCl (162.45 µL, 1.20 mmol, 1.20 equiv) was added dropwise and the reaction continued stirring at 0 °C for one hour. Afterwards, the cooling bath was removed and the reaction left stirring at rt o.n.. Water (2.0 mL) was added before the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic layers were washed with brine (1 x 8 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, 20:1 CH/EE) to obtain 160.43 mg (678.91 µmol, 68%) of a colourless oil. Even though the PMB-alcohol was not fully removed the product was used in the next reaction.



211a

Chemical Formula: $C_{14}H_{20}O_2$
Exact Mass: 220,1463
Molecular Weight: 220,3120

R_f = 0.15 (20:1 CH/EE). **^{1}H** NMR (400 MHz, CD_2Cl_2) δ = 7.33 – 7.30 (m, 4H, H-9, H-10, H-13, H-14), 5.82 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, H-2), 5.00 (ddt, *J* = 17.1, 2.2, 1.6 Hz, 1H, H-1), 4.93 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H, H-1'), 4.39 (s, 2H, H-7), 3.79 (s, 3H, H-12), 3.43 (t, *J* = 6.5 Hz, 2H, H-6), 2.10 – 2.02 (m, 2H, H-3), 1.63 – 1.54 (m, 2H, H-5), 1.50 – 1.40 (m, 2H, H-4).

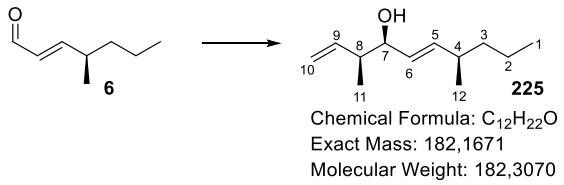
Palladium(II) chloride (4.02 mg, 22.70 µmol, 0.10 equiv) and copper(I) chloride (22.47 mg, 226.95 µmol, 1.00 equiv) were dissolved in DMF/H2O (7:1, 0.19 mL) and stirred under an

oxygen atmosphere at room temperature for one hour. Afterwards, freshly prepared PMB-protected alcohol (50.00 mg, 226.95 µmol, 1.00 equiv) was dissolved in DMF/H_2O (7:1, 180.0 µL) and added to the reaction mixture. The reaction was stirred at room temperature o.n. before water (0.5 mL) and NH_4Cl solution (0.5 mL) were added. The aqueous layer was extracted with Et_2O (3 x 1 mL). Adjacently, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, 10:1 CH/EE) to obtain 10.73 mg (45.39 µmol, 20%) of a colourless oil.

R_f = 0.46 (1:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.30 – 7.22 (m, 2H, H-9, H-14), 6.90 – 6.85 (m, 2H, H-10, H-13), 4.39 (s, 2H, H-7), 3.79 (d, *J* = 2.5 Hz, 3H, H-12), 3.43 (t, *J* = 6.1 Hz, 2H, H-6), 2.42 (t, *J* = 7.0 Hz, 2H, H-5), 2.08 (s, 3H, H-1), 1.65 – 1.51 (m, 4H, H-3, H-4). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 209.0 (C-2), 159.6 (C-11), 133.3 (C-8), 129.6 (C-9), 128.9 (C-14), 114.2 (C-10), 114.0 (C-13), 72.8 (C-7), 70.2 (C-6), 55.6 (C-12), 43.6 (C-5), 30.0 (C-1), 30.0 (C-3), 21.0 (C-4). **HRMS (ESI)** *m/z*: calcd for $C_{14}H_{21}O_3$ $[M + H]^+$: 237.1485, found: 237.1488.

Synthesis of Compound 225

(3*S*,4*S*,5*E*,7*R*)-3,7-Dimethyldeca-1,5-dien-4-ol



Chemical Formula: $C_{12}H_{22}O$
Exact Mass: 182,1671
Molecular Weight: 182,3070

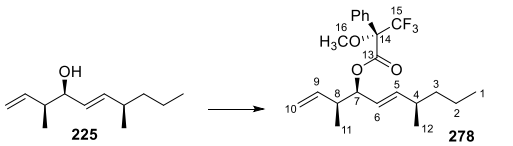
A stock solution of the aldehyde **6** (62.90 mg, 498.42 µmol, 0.30 M, 1.00 equiv) was prepared in THF and dried over molecular sieves overnight. Dry potassium *tert*-butoxide (69.19 mg, 598.10 µmol, 1.20 equiv) was dissolved in THF (0.35 M, 1.71 mL) and the mixture cooled to -78 °C. In a seperate *Schlenk* tube *cis*-butene (235.00 µL, 2.49 mmol, 5.00 equiv) was condensed at -78 °C and subsequently transferred to the reaction flask using a transfer cannula. Afterwards, *n*-BuLi (2.5 M in hexane, 239.24 µL, 598.10 µmol, 1.20 equiv) was added dropwise over 15 minutes yielding a yellow reaction mixture. The solution was warmed to -45 °C and stirred at this temperature for ten minutes before it was recooled to -78 °C. (+)-$(Ipc)_2$BOMe (197.08 mg, 623.02 µmol, 1.25 equiv) was dissolved in diethylether (0.5 M, 1.25 mL) and added to the reaction over 30 minutes revealing a colourless solution that was stirred for additional 45 minutes at -78 °C. Then BF_3*OEt_2 (78.25 µL, 622.99 µmol, 1.25 equiv) was added dropwise

immediatly followed by the addition of the prepared stock solution of the aldehyde over 75 minutes. The reaction was stirred for three hours at -78 °C before it was carefully treated with sodium hydroxide solution (3 M, 3.90 mL), methanol (1.2 mL) and hydrogen peroxide (35%, 1.2 mL) and warmed to room temperature. Then, it was stirred under reflux for one hour, cooled to room temperature and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 7 mL) prior to washing the combined organic layers with saturated sodium thiosulfate (1 x 25 mL), ammonium chloride (1 x 25 mL) and brine (1 x 25 mL). They were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 50:1 CH/EE to 10:1 CH/EE) yielding a colourless oil (54.52 mg, 299.05 µmol, 60%).

R_f = 0.23 (10:1 CH/EE). **α_D^{20}** = -0.5 ° (c = 0.11 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 5.85 – 5.74 (m, 1H, H-9), 5.51 – 5.44 (m, 1H, H-5), 5.39 (ddd, *J* = 15.4, 6.9, 0.8 Hz, 1H, H-6), 5.07 (ddd, *J* = 7.0, 1.9, 1.2 Hz, 1H, H-), 5.04 (d, *J* = 1.2 Hz, 1H, H-), 3.91 (t, *J* = 6.1 Hz, 1H, H-7), 2.36 – 2.27 (m, 1H, H-8), 2.13 (p, *J* = 6.7 Hz, 1H, H-4), 1.35 – 1.23 (m, 4H, H-2, H-3), 0.99 (d, *J* = 6.9 Hz, 3H, H-11), 0.97 (d, *J* = 6.7 Hz, 3H, H-12), 0.89 – 0.85 (m, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 140.9 (C-9), 139.2 (C-5), 129.2 (C-6), 115.4 (C-10), 76.5 (C-), 44.2 (C-8), 39.6 (C-3), 36.7 (C-4), 20.9 (C-2), 20.8 (C-12), 15.1 (C-11), 14.3 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_{12}H_{21}$ $[M - OH^-]^+$: 165.1638, found: 165.1638.

Synthesis of Compound 278

(3*S*,4*S*,7*R*,*E*)-3,7-Dimethyl deca-1,5-dien-4-((*S*)-α-methoxy-α-trifluoromethylphenyl) ethanoate



Chemical Formula: $C_{22}H_{29}F_3O_3$
Exact Mass: 398,21
Molecular Weight: 398,47

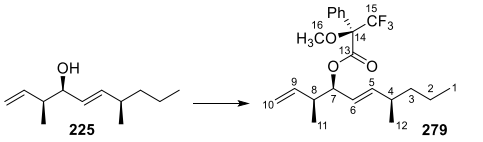
Compound **225** (4.40 mg, 24.14 mmol, 1.00 equiv) and pyridine (6.03 µL, 74.82 mmol, 3.10 equiv) were dissolved in DCM (0.6 mL). Then (*S*)-MTPA-Cl (8.58 mmL, 45.86 mmol, 1.90 equiv) was added to the mixture and it was stirred at room temperature overnight. The reaction was quenched by adding water (1 mL) and diethyl ether (2 mL). The aqueous layer was extracted with diethyl ether (3 x 2 mL) and the combined organic layers were dried over

$MgSO_4$. The solvent was evaporated under reduced pressure and a colourless oil was obtained (14.10 mg, 35.39 µmol, quant).

R_f = 0.40 (20:1 CH/EE). **α_D^{20}** = +6.8 ° (c = 0.15 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.58 - 7.37 (m, 5H, H-Ph), 5.73 - 5.62 (m, 2H, H-5,H-9), 5.41 (ddd, *J* = 1.0, 8.4, 14.9 Hz, 1H, H-6), 5.36 (dd, *J* = 5.8, 8.4 Hz, 1H, H-7), 5.02 - 4.96 (m, 2H, H-10), 3.41 (d, 1.4 Hz, 3H, H-16), 2.49 (tdt, *J* = 7.0, 5.8, 1.2 Hz, 1H, H-8), 2.19 - 2.14 (m, 1H, H-4), 1.33 - 1.21 (m, 4H, H-2, H-3), 0.97 (d, *J* = 2.3 Hz, 3H, H-12), 0.96 (d, *J* = 2.4 Hz, 3H, H-11), 0.87 (ddt, *J* = 7.0, 4.3, 2.3 Hz, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 166.0 (C-13), 144.2 (C-5), 139.1 (C-Ph), 133.1 (C-15), 130.6 (C-14), 129.2 (C-Ph), 128.7 (C-Ph), 128.7 (C-Ph), 127.3 (C-Ph), 123.8 (C-6), 116.0 (C-10), 81.4 (C-7), 56.3 (C-16), 41.8 (C-8), 39.2 (C-3), 36.8 (C-4), 20.8 (C-12), 20.6 (C-2), 15.2 (C-11), 14.2 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_{22}H_{29}F_3O_3Na$ $[M + Na]^+$: 421.1961, found: 421.1971.

Synthesis of Compound 279

(3*S*,4*S*,7*R*,*E*)-3,7-Dimethyl deca-1,5-dien-4-((*R*)-α-methoxy-α-trifluoromethylphenyl) ethanoate



Chemical Formula: $C_{22}H_{29}F_3O_3$
Exact Mass: 398,2069
Molecular Weight: 398,4662

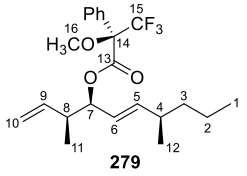
Compound **225** (4.20 mg, 32.04 mmol, 1.00 equiv) and pyridine (5.75 µL, 71.42 mmol, 3.10 equiv) were diluted in DCM (0.6 mL) and (*R*)-MTPA-Cl (8.19 µL, 43.77 mmol, 1.90 equiv) was then added to the mixture which stirred at room temperature overnight. Water (1 mL) and diethyl ether (2 mL) were poured into the reaction mixture. Afterwards the aqueous layer was extracted with diethyl ether (3 x 2 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The product was gained as a colourless oil (20.00 mg, 50.19 µmol, quant).

R_f = 0.28 (20:1 CH/EE). **α_D^{20}** = - 41.9 ° (c = 0.04 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.59 - 7.39 (m, 5 H, H-Ph), 5.79 (ddd, *J* = 17.8, 10.0, 7.0 Hz, 1 H, H-9), 5.62 (dd, J = 15.3, 8.0 Hz, 1 H, H-5), 5.37 - 5.26 (m, 1 H, H-7), 5.28 (ddd, *J* = 15.3, 8.0, 1.1 Hz, 1 H, H-6), 5.09 (q, *J* = 1.4 Hz, 1 H, H_{cis}-10), 5.06 (ddt, *J* = 1.4, 3.0, 6.1 Hz, 1 H, H_{trans}-10), 3.56 (d, *J* = 1.2 Hz, 3 H, H-16), 2.54 (tdt, *J* = 6.9, 5.6, 1.3 Hz, 1 H, H-8), 2.13 - 2.10 (m, 1 H, H-4), 1.38 - 1.23 (m, 4 H, H-2, H-3), 1.05

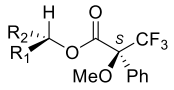
(d, *J* = 6.9 Hz, 3 H, H-11), 0.94 (d, *J* = 6.8 Hz, 3 H, H-12), 0.86 (d, *J* = 3.5 Hz, 3 H, H-1). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 166.0 (C-13), 143.6 (C-5), 139.4 (C-Ph), 132.9 (C-15), 130.0 (C-9), 130.0 (C-14), 128.8 (C-Ph), 128.7 (C-Ph), 127.9 (C-Ph), 123.6 (C-6), 116.0 (C-10), 81.4 (C-7), 55.8 (C-16), 41.7 (C-8), 39.2 (C-3), 36.8 (C-4), 20.8 (C-12), 20.5 (C-2), 16.7 (C-11), 14.5 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_{22}H_{29}F_3O_3Na$ $[M + Na]^+$: 421.1961, found: 421.1959.

*Table 10: Evaluation of ^{1}H-NMR of the achieved diastereomers. The difference in chemical shifts for each of the analogous pairs of protons for the S- and R-MTPA esters **278** and **279** were determined.*

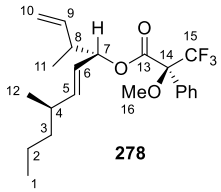
# H	δ *S*-ester [ppm]	δ *R*-ester [ppm]	$\Delta\delta^{S-R}$ [ppm]	$\Delta\delta^{S-R}$ [Hz]
6	5,41	5,28	0,13	65
5	5,7	5,62	0,08	40
4	2,17	2,12	0,05	25
12	0,97	0,94	0,03	15
8	2,49	2,54	- 0,05	- 25
10	4,99	5,07	- 0,08	- 40
9	5,7	5,79	- 0,09	- 45
11	0,96	1,05	- 0,09	- 45



279



278a

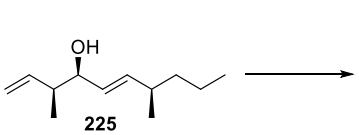


278

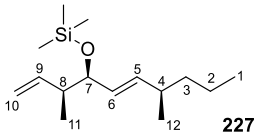
Protons (H-6, H-5, H-4, H-12) with a positive difference belong to R_1 and protons (H-8, H-10, H-9, H-11) with a negative difference appertain to R_2. This leads to the result that the secondary alcohol **225** has indeed a stereocenter with the configuration (*S*).

Synthesis of Compound 227

(((3*S*,4*S*,7*R*,*E*)-3,7-Dimethyldeca-1,5-dien-4-yl)oxy)trimethylsilane



225



227

Chemical Formula: $C_{15}H_{30}OSi$
Exact Mass: 254,2066
Molecular Weight: 254,4890

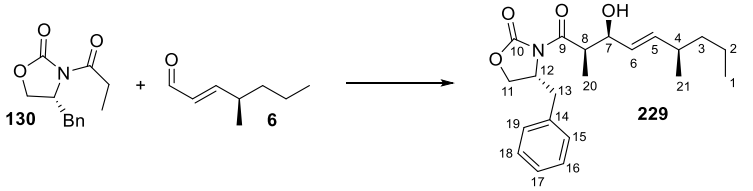
To a stirred solution of secondary alcohol **225** (79.90 mg, 0.44 mmol, 1.00 equiv) in DCM (4.38 mL) at 0 °C was added NEt_3 (0.24 mL, 1.75 mmol, 4 equiv) and TMSCl (0.17 mL, 1.31 mmol, 3.00 equiv). The mixture was stirred for 30 minutes at 0 °C before TMSCl (0.08 mL, 0.66 mmol, 1.50 equiv) was added again. The reaction was allowed to warm to room

temperature and continued stirring for 1.5 hours. Afterwards it was quenched with saturated $NaHCO_3$-solution. The organic phase was separated, and the aqueous phase was extracted with DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (SiO_2, CyHex:EtOAc = 40:1) and the pure product was obtained as a yellow liquid (70.54 mg, 277.20 µmol, 63%).

R_f = 0.4 (40:1 CH/EE). **α_D^{20}** = -0.4 ° (c = 0.12 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 5.83 – 5.76 (m, 1H, H-9), 5.37 – 5.33 (m, 2H, H-5, H-6), 4.99 – 4.95 (m, 2H, H-10), 3.86 (t, *J* = 6.3 Hz, 1H, H-7), 2.23 – 2.17 (m, 1H, H-8), 2.10 (dp, *J* = 13.8, 6.9 Hz, 1H, H-4), 1.34 – 1.18 (m, 4H, H-2, H-3), 0.97 (d, *J* = 6.7 Hz, 3H, H-12), 0.96 (d, *J* = 6.7 Hz, 3H, H-11), 0.86 (t *J* = 7.1 Hz, 3H, H-1), 0.08 (s, 9H, $(CH_3)_3$-Si). **^{13}C** NMR (CD_2Cl_2, 175 MHz) δ = 141.8 (C-9), 138.1 (C-5), 130.3 (C-6), 114.1 (C-10), 78.0 (C-7), 44.9 (C-8), 39.6 (C-3), 36.7 (C-4), 20.8 (C-2), 20.8 (C-11), 15.5 (C-12), 14.3 (C-1), 0.5 ($(CH_3)_3$-Si). **HRMS (ESI)** *m/z*: calcd for $C_{15}H_{30}OSiNa$ $[M + Na]^+$: 277.1964, found: 277.1961.

Synthesis of Compound 229

(*R*)-4-Benzyl-3-((2*R*,3*S*,6*R*,*E*)-3-hydroxy-2,6-dimethylnon-4-enoyl)oxazolidin-2-one



Chemical Formula: $C_{21}H_{29}NO_4$
Exact Mass: 359,2097
Molecular Weight: 359,4660

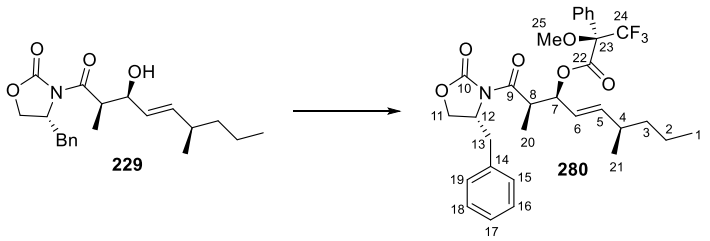
(*R*)-4-Benzyl-2-oxazolidinone (**130**) (85.00 mg, 364.69 µmol, 1.00 equiv) was preloaded into the reaction flask and dried in HV for five minutes. Afterwards, it was dissolved in DCM (5.52 mL) and cooled to 0 °C. Then, DIPEA (76.17 µL, 437.27 µmol, 1.20 equiv) was added dropwise followed by the addition of *n*Bu_2BOTf (1.0 M in Et_2O, 364.39 µL, 364.39 µmol, 1.00 equiv). The resulting mixture was stirred at 0 °C for one hour and then cooled to -78 °C. Hereafter, a solution of aldehyde **6** (45.99 mg, 364.39 µmol, 1.00 equiv) in DCM (2.43 mL) was added dropwise followed by stirring of the reaction mixture at -78 °C for two hours. Subsequently, the reaction was quenched with NH_4Cl (10 mL), the layers separated and the aqeous layer extracted with DCM (3 x 10 mL). The combined organic layers were washed with

water (1 x 30 mL) and brine (1 x 30 mL) before they were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 2:1 CH/EE) yielding 94.10 mg of the desired product as a colourless oil (261.78 µmol, 72%).

R_f = 0.27 (2:1 CH/EE). **α_D^{20}** = -53.2 °(c = 0.98 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.35 – 7.32 (m, 2H, H-16, H-18), 7.30 – 7.27 (m, 1H, H-17), 7.22 – 7.20 (m, 2H, H-15, H-19), 5.59 (ddd, J = 15.4, 7.8, 1.3 Hz, 1H, H-5), 5.42 (ddd, *J* = 15.5, 6.2, 1.1 Hz, 1H, H-6), 4.72 – 4.66 (m, 1H, H-12), 4.39 (dtd, *J* = 5.8, 3.6, 1.3 Hz, 1H, H-7), 4.22 (ddd, *J* = 9.1, 7.8, 0.6 Hz, 1H, H-13), 4.18 (dd, *J* = 9.1, 2.8 Hz, 1H, H-13'), 3.82 (qd, *J* = 7.0, 4.1 Hz, 1H, H-8), 3.19 (dd, *J* = 13.6, 3.4 Hz, 1H, H-11), 2.85 (dd, *J* = 13.6, 8.9 Hz, 1H, H-11'), 2.59 (d, *J* = 3.3 Hz, 1H, OH), 2.18 – 2.11 (m, 1H, H-4), 1.32 – 1.23 (m, 4H; H-2, H-3), 1.22 (d, *J* = 7.0 Hz, 3H, H-20), 0.98 (d, *J* = 6.8 Hz, 3H, H-21), 0.90 – 0.85 (m, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 176.9 (C-9), 153.5 (C-10), 139.4 (C-5), 135.8 (C-14), 129.9 (C-15, C-19), 129.2 (C-16, C-18), 128.0 (C-6), 127.7 (C-17), 73.2 (C-7), 66.7 (C-13), 55.5 (C-12), 43.4 (C-8), 39.5 (C-3), 38.1 (C-11), 36.6 (C-4), 20.8 (C-2), 20.7 (C-21), 14.2 (C-1), 11.6 (C-20). **HRMS (APCI)** *m/z*: calcd for $C_{21}H_{30}NO_4$ $[M + H]^+$: 360.2169, found: 360.2167.

Synthesis of Compound 280

(2*R*,3*S*,6*R*,*E*)-1-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-2,6-dimethyl-1-oxonon-4-en-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



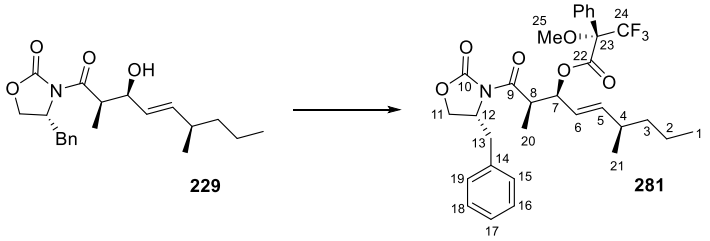
Secondary alcohol **229** (4.00 mg, 11.13 µmol, 1.00 equiv) was treated with dry pyridine (2.78 µL, 34.50 µmol, 3.10 equiv) and the mixture dissolved in DCM (0.28 mL). Subsequently, (*R*)-MTPA-Cl (3.96 µL, 21.14 µmol, 1.90 equiv) was added and the mixture stirred at room temperature overnight. Thereafter, water (0.5 mL) and Et_2O (0.5 mL) were added and the reaction mixture partitioned between the layers which were then separated. The aqueous

layer was extracted with Et_2O (3 x 0.5 mL) prior to drying the combined organic layers over $MgSO_4$ and evaporating the solvent under reduced pressure.

R_f = 0.34 (5:1 CH/EE). **α_D^{20}** = -5 ° (c = 0.78 in CH2Cl$_2$). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.46 – 7.45 (m, 5H, H_{arom}), 7.36 – 7.30 (m, 2H, H-16, H-18), 7.31 – 7.26 (m, 1H, H-17), 7.21 – 7.17 (m, 2H, H-15, H-19), 5.76 – 5.73 (m, 1H, H-5), 5.55 (ddd, *J* = 15.5, 7.7, 1.0 Hz, 1H, H-6), 4.58 (ddt, *J* = 9.0, 6.9, 3.5 Hz, 1H, H-12), 4.19 – 4.16 (m, 2H, H-7, H-13), 4.11 (dd, *J* = 7.0, 6.0 Hz, 1H, H-13'), 3.57 – 3.23 (m, 1H, H-8), 3.54 (s, 3H, OMe), 3.18 (dd, *J* = 13.5, 3.4 Hz, 1H, H-11), 2.83 (dd, *J* = 13.5, 9.0 Hz, 1H, H-11'), 2.23 – 2.13 (m, 1H, H-4), 1.27 (ddt, *J* = 5.9, 2.5, 1.6 Hz, 4H, H-2, H-3), 1.15 (d, *J* = 7.0 Hz, 3H, H-20), 0.97 (d, *J* = 6.7 Hz, 3H, H-21), 0.87 (t, *J* = 7.1 Hz, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 173.7 (C-9), 167.3 (C-22), 153.6 (C-10), 144.3 (C-5), 135.8 (C-14), 132.0 (C_{arom}), 130.3 (C-15, C-19), 129.9 (C_{arom}), 129.3 (C_{arom}), 129.1 (C-16, C-18), 128.0 (C-6), 127.8 (C_{arom}), 127.7 (C-17), 123.5 (C_{arom}), 78.3 (C-7), 66.8 (C-13), 55.8 (C-12), 42.2 (C-8), 39.2 (C-3), 38.1 (C-11), 36.8 (C-4), 20.8 (C-2), 20.5 (C-21), 14.3 (C-1), 12.5 (C-20). **HRMS (ESI)** *m/z*: calcd for $C_{31}H_{37}F_3NO_6$ $[M + H]^+$: 576.2567, found: 576.2565.

Synthesis of Compound 281

(2*R*,3*S*,6*R*,*E*)-1-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-2,6-dimethyl-1-oxonon-4-en-3-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

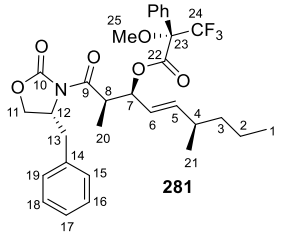


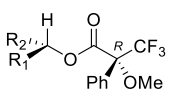
In a vial alcohol **229** (4.00 mg, 11.13 µmol, 1.00 equiv) and dry pyridine (2.78 µL, 34.50 µmol, 3.10 equiv) were mixed and then dissolved in DCM (0.28 mL) prior to the addition of (*S*)-MTPA-Cl (3.96 µL, 21.14 µmol, 1.90 equiv) and stirring of the reaction mixture at room temperature overnight. After that, the mixture was partitioned between water (0.5 mL) and Et_2O (0.5 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 0.5 mL). Afterwards, the combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo.

R_f = 0.38 (5:1 CH/EE). **α_D^{20}** = +7.8 (c = 0.89 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.44 (d, *J* = 2.0 Hz, 5H, H_{arom}), 7.34 (tt, *J* = 6.8, 1.1 Hz, 2H, H-16, H-18), 7.31 – 7.26 (m, 1H, H-17), 7.22 – 7.18 (m, 2H, H-15, H-19), 5.63 (ddd, *J* = 15.5, 7.9, 1.0 Hz, 1H, H-5), 5.40 – 5.35 (m, 1H, H-6), 4.58 (ddt, *J* = 9.1, 7.0, 3.4 Hz, 1H, H-12), 4.21 – 4.14 (m, 2H, H-7, H-13), 4.15 – 4.10 (m, 1H, H-13'), 4.08 – 3.85 (m, 1H, H-8), 3.57 (q, *J* = 1.3 Hz, 3H, OMe), 3.20 (dd, *J* = 13.5, 3.4 Hz, 1H, H-11), 2.85 (dd, *J* = 13.5, 8.9 Hz, 1H, H-11'), 2.15 – 2.07 (m, 1H, H-4), 1.37 – 1.17 (m, 4H, H-2, H-3), 1.25 (d, *J* = 7.0 Hz, 3H, H-20), 0.93 (d, *J* = 6.8 Hz, 3H, H-21), 0.86 (dtd, *J* = 7.2, 5.3, 2.0 Hz, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 173.8 (C-9), 167.7 (C-22), 146.5 (C-10), 143.5 (C-5), 140.3 (C-14), 132.3 (C_{arom}), 130.2 (C-15, C-19), 129.9 (C_{arom}), 129.3 (C_{arom}), 129.0 (C-16, C-18), 128.0 (C-6), 127.9 (C_{arom}), 125.6 (C-17), 123.2 (C_{arom}), 77.9 (C-7), 66.8 (C-13), 55.8 (C-12), 42.1 (C-8), 39.2 (C-3), 38.1 (C-11), 36.7 (C-4), 20.7 (C-2), 20.4 (C-21), 14.3 (C-1), 12.3 (C-20). **HRMS (ESI)** *m/z*: calcd for $C_{31}H_{37}F_3NO_6$ $[M + H]^+$: 576.2567, found: 576.2565.

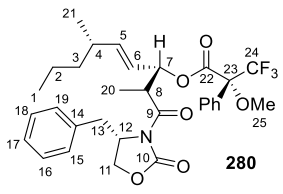
*Table 11: Evaluation of ^{1}H-NMR of the achieved diastereomers. The difference in chemical shifts for each of the analogous pairs of protons for the S- and R-MTPA esters **280** and **281** were determined.*

# H	δ *S*-ester [ppm]	δ *R*-ester [ppm]	$\Delta\delta^{S-R}$ [ppm]	$\Delta\delta^{S-R}$ [Hz]
H-11	3.20	3.18	0.02	10
H-11'	2.85	2.83	0.02	10
H-12	4.58	4.58	0	0
H-13	4.18	4.18	0	0
H-13'	4.13	4.11	0.02	10
H-20	1.25	1.15	0.1	50
H-6	5.38	5.55	-0.17	-85
H-5	5.63	5.75	-0.12	-60
H-4	2.11	2.18	-0.07	-35
H-21	0.93	0.97	-0.04	-20
H-3	1.27	1.27	0	0
H-2	1.27	1.27	0	0
H-1	0.86	0.87	-0.01	-5





281a

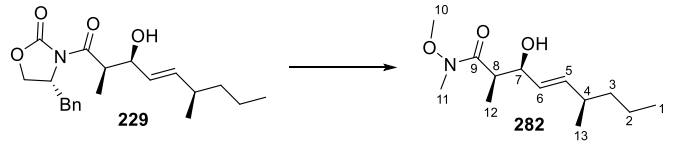


280

Protons (H-11, H-12, H-13, H-20) with a positive difference belong to R_1 and protons (H-6, H-5, H-4, H-3, H-2, H-1, H-21) with a negative difference go with R_2. This leads to the result that the secondary alcohol **229** indeed is (*S*) configured.

Synthesis of Compound 282

(2*R*,3*S*,6*R*,*E*)-3-Hydroxy-*N*-methoxy-*N*,2,6-trimethylnon-4-enamide



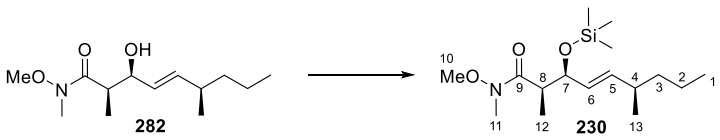
Chemical Formula: $C_{13}H_{25}NO_3$
Exact Mass: 243,1834
Molecular Weight: 243,3470

A stirred solution of Me(MeO)-NH*HCl (115.19 mg, 1.18 mmol, 5.00 equiv) in THF (3.63 mL) was cooled to 0 °C and subsequently treated with Me_3Al (2.0 M in toluene, 1.18 mL, 2.36 mmol, 10.00 equiv). The mixture was stirred at 0 °C for 30 minutes before it was cooled to -40 °C and compound **229** (84.90 mg, 236.18 µmol, 1.00 equiv) was dissolved in THF (2.72 mL) and added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for three hours. Afterwards, the reaction was quenched by the addition of saturated aqueous *Rochelle's* salt solution (10 mL) and continued stirring for 30 minutes. Thereafter, the layers were separated and the aqeous layer extracted with DCM (3 x 10 mL). The extract was washed with *Rochelle's* salt solution (1 x 10 mL), H_2O (1 x 10 mL) and brine (1 x 10 mL), dried over Na_2SO_4 and the solvent removed in vacuo. The crude product was purified by column chromatography (SiO_2, 2:1 CH/EE) yielding 15.90 mg of a slightly yellow oil (65.34 µmol, 28%).

R_f = 0.22 (2:1 CH/EE). **α_D^{20}** = -48.1 (c = 1.03 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 5.58 (ddd, *J* = 15.5, 7.9, 1.4 Hz, 1H, H-5), 5.38 (ddd, *J* = 15.5, 5.9, 1.1 Hz, 1H, H-6), 4.34 – 4.29 (m, 1H, H-7), 3.69 (s, 3H, H-10), 3.50 (s, 1H), 3.16 (s, 3H, H-11), 2.91 (s, 1H, H-8), 2.17 – 2.10 (m, 1H, H-4), 1.33 – 1.21 (m, 4H, H-2, H-3), 1.12 (d, *J* = 7.1 Hz, 3H, H-12), 0.98 (d, *J* = 6.7 Hz, 3H, H-13), 0.90 – 0.86 (m, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 175 MHz) δ = 138.5 (C-5), 128.4 (C-6), 72.8 (C-7), 62.0 (C-10, HSQC), 40.2 (C-8, HSQC), 39.6 (C-3), 36.7 (C-4), 32.1 (C-11, HSQC), 20.8 (C-2), 20.7 (C-13), 14.3 (C-1), 10.9 (C-12). **HRMS (ESI)** *m/z*: calcd for $C_{13}H_{26}NO_3$ $[M + H]^+$: 244.1907, found: 244.1910.

Synthesis of Compound 230

(2*R*,3*S*,6*R*,*E*)-*N*-Methoxy-*N*,2,6-trimethyl-3-((trimethylsilyl)oxy)non-4-enamide



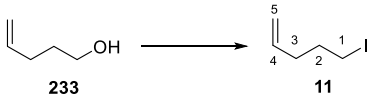
Chemical Formula: $C_{16}H_{33}NO_3Si$
Exact Mass: 315,2230
Molecular Weight: 315,5290

Secondary alcohol **282** (15.90 mg, 65.34 µmol, 1.00 equiv) was dissolved in DCM (0.65 mL). The resulting solution was cooled to 0 °C and NEt_3 (36.48 µL, 261.36 µmol, 4.00 equiv) was added followed by TMSCl (24.88 µL, 196.02 µmol, 3.00 equiv)). After that, the mixture was stirred at 0 °C for two hours before the addition of $NaHCO_3$ (1 mL). The layers were separated and the aqeous layer extracted with DCM (3 x 1 mL) prior to drying the combined organic layers over $MgSO_4$ and evaporating the solvent under reduced pressure. The crude product was purified by column chromatography (SiO_2, 5:1 CH/EE) yielding the desired product as a colourless oil (14.70 mg, 46.59 µmol, 71%).

$\mathbf{R_f}$ = 0.46 (5:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = -37 ° (c = 1.0 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 5.40 (dd, *J* = 15.3, 7.5 Hz, 1H, H-5), 5.36 – 5.33 (m, 1H, H-6), 4.12 (dd, *J* = 8.7, 6.8 Hz, 1H, H-7), 3.64 (s, 3H, H-10), 3.09 (s, 3H, H-11), 2.96 (s, 1H, H-8), 2.07 (q, *J* = 6.3 Hz, 1H, H-4), 1.30 – 1.17 (m, 4H, H-2, H-3), 1.11 (d, *J* = 6.8 Hz, 3H, H-12), 0.94 (d, *J* = 6.7 Hz, 3H, H-13), 0.88 – 0.83 (m, 3H, H-1), 0.09 (s, 9H, 3 x CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 138.5 (C-5), 130.1 (C-6), 76.2 (C-7), 61.9 (C-10, HSQC), 42.9 (C-8, HSQC), 39.5 (C-3), 36.7 (C-4), 32.0 (C-11, HSQC), 20.8 (C-2), 20.8 (C-13), 14.8 (C-12), 14.3 (C-1), 0.5 (3 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{16}H_{34}NO_3Si$ $[M + H]^+$: 316.2302, found: 316.2300.

Synthesis of Compound 11

5-Iododpenten



Chemical Formula: C_5H_9I
Exact Mass: 195,9749
Molecular Weight: 196,0315

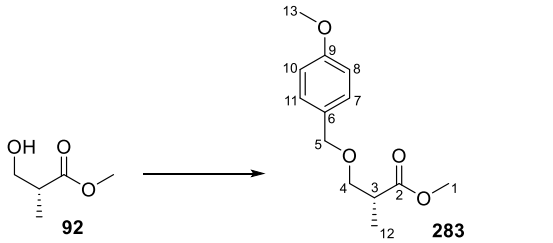
Triphenylphosphine (3.05 g, 11.61 mmol, 2.00 equiv) and imidazole (790.38 mg, 11.61 mmol, 2.00 equiv) were added to a stirred solution of compound **233** (0.50 g, 5.80 mmol, 1.00 equiv)

in benzene (20.0 mL). After the addition of iodine (2.21 g, 8.71 mmol, 1.50 equiv) to the reaction mixture the latter was stirred for 90 min at room temperature. Thereafter, the mixture was filtered over Celite and the solvent was removed under reduced pressure. Lastly, the crude product was purified by column chromatography (SiO_2, 70:1 CH/EE) to yield 355.30 mg of a yellow oil (1.81 mmol, 31%). The obtained product contained traces of PPh_3, which could not be removed by column chromatography.

R_f = 0.60 (70:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 400 MHz) δ = 5.78 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H, H-4), 5.08 (ddt, *J* = 17.2, 2.1, 1.6 Hz, 1H, H-5), 5.01 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H, H-5'), 3.21 (t, *J* = 7.0 Hz, 2H, H-1), 2.16 (dtt, *J* = 7.7, 6.4, 1.4 Hz, 2H, H-2), 1.91 (p, *J* = 6.9 Hz, 2H, H-3). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 137.2 (C-4), 115.9 (C-5), 34.7 (C-2), 33.0 (C-3), 6.9 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_5H_{10}I$ $[M + H]^+$: 196.9822, found: 196.9818.

Synthesis of Compound 283

Methyl (*R*)-3-((4-methoxybenzyl)oxy)-2-methylpropanoate



Chemical Formula: $C_{13}H_{18}O_4$
Exact Mass: 238,1205
Molecular Weight: 238,2830

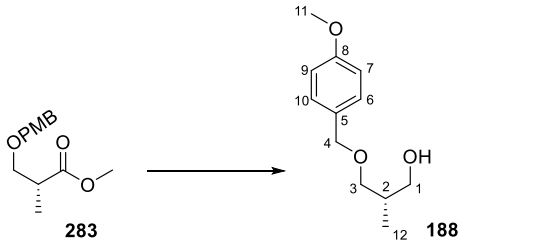
In a flame dried *Schlenk* flask (*R*)-*Roche* ester (**92**) (500.00 mg, 4.23 mmol, 1.00 equiv) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.20 g, 4.23 mmol, 1.00 equiv) were dissolved in DCM (8.46 mL). Camphorsulfonic acid (39.5 mg, 0.17 mmol, 0.04 equiv) was added and the reaction mixture stirred at room temperature for 19 hours. Afterwards 0.1 M NaOH (1.7 mL) was added. The aqueous layer was diluted with water, the layers were separated and the aqueous layer extracted with DCM (3 x 2 mL). The combined organic layers were washed with brine (1 x 8 mL) and dried over $MgSO_4$. Afterwards, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, 1:1 CH/EE) to obtain 745.87 mg (3.13 mmol, 74%) of a colourless oil.

R_f = 0.54 (1:1 CH/EE). **α_D^{20}** = - 7.0° (c = 1.00, in $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.24 – 7.20 (m, 2H, H-7, H-11), 6.89 – 6.84 (m, 2H, H-8, H-10), 4.41 (s, 2H, H-5), 3.79 (s, 3H, H-13),

3.65 (s, 3H, H-1), 3.60 (dd, *J* = 9.1, 7.2 Hz, 1H, H-4), 3.46 (dd, *J* = 9.1, 5.8 Hz, 1H, H-4'), 2.73 (pd, *J* = 7.1, 5.8 Hz, 1H, H-3), 1.14 (d, *J* = 7.1 Hz, 3H, H-12). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 175.5 (C-2), 159.7 (C-9), 130.9 (C-6), 129.6 (C-7, C-11), 114.0 (C-8, C-10), 73.1 (C-5), 72.2 (C-4), 55.6 (C-13), 51.9 (C-1), 40.6 (C-3), 14.1 (C-12). **HRMS (ESI)** *m/z*: calcd for $C_{13}H_{18}O_4Na$ $[M + Na]^+$: 261.1097, found: 261.1095.

Synthesis of Compound 188

(*S*)-3-((4-Methoxybenzyl)oxy)-2-methylpropan-1-ol



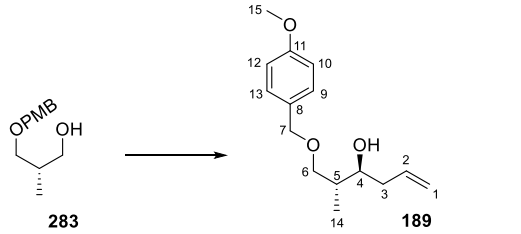
Chemical Formula: $C_{12}H_{18}O_3$
Exact Mass: 210,1256
Molecular Weight: 210,2730

PMB-protected (*R*)-*Roche* ester **283** (742.00 mg, 3.11 mmol, 1.00 equiv) was dissolved in THF (20.73 mL) and cooled to -78 °C. DIBAl-H (1.0 M in THF, 6.84 mL, 6.84 mmol, 2.20 equiv) was added dropwise to the cooled solution. After the addition the reaction mixture was allowed to warm to room temperature and stirred for an additional hour. Saturated aqueous potassium, sodium tartrate solution (20 mL) was added and the biphasic mixture stirred at room temperature for two hours until both layers appeared to be clear. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure before the crude product was purified by column chromatography (SiO_2, 1:1 CH/EE) to yield a slightly yellow liquid (588.55 mg, 2.80 mmol, 90%).

R_f = 0.31 (1:1 CH/EE). **α_D^{20}** = - 15.0° (c = 1.00 , in $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.27 – 7.22 (m, 2H, H-6, H-10), 6.89 – 6.85 (m, 2H, H-7, H-9), 4.42 (d, *J* = 1.4 Hz, 2H, H-4), 3.79 (s, 3H, H-11), 3.56 – 3.52 (m, 2H, H-1), 3.50 (ddd, *J* = 9.1, 4.8, 0.5 Hz, 1H, H-3), 3.39 (dd, *J* = 9.1, 7.8 Hz, 1H, H-3'), 2.03 – 1.96 (m, 1H, H-2), 0.86 (d, *J* = 7.0 Hz, 3H, H-12). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 159.7 (C-8), 130.9 (C-5), 129.6 (C-6, C-10), 114.1 (C-7, C-9), 75.4 (C-3), 73.3 (C-4), 67.9 (C-1), 55.6 (C-11), 36.2 (C-2), 13.7 (C-12). **HRMS (ESI)** *m/z*: calcd for $C_{12}H_{18}O_3Na$ $[M + Na]^+$: 233.1148, found: 233.1148.

Synthesis of Compound 189

(2*R*,3*S*)-1-((4-Methoxybenzyl)oxy)-2-methylhex-5-en-3-ol



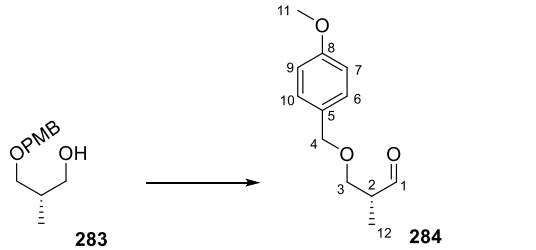
Chemical Formula: $C_{15}H_{22}O_3$
Exact Mass: 250,1569
Molecular Weight: 250,3380

In a pressure tube $[Ir(cod)Cl]_2$ (40.30mg, 0.06 mmol, 2.50 mol%), (*S*)-SEGPHOS (73.30 mg, 0.12 mmol, 0.05 equiv), Cs_2CO_3 (162.90 mg, 0.50 mmol, 0.20 equiv) and 3-nitrobenzoic acid (41.80 mg, 0.25 mmol, 0.10 equiv) were dissolved in THF (6.22 mL) followed by the addition of allyl acetate (2.69 mL, 24.90 mmol, 10.00 equiv) and the mixture was heated to 90 °C and stirred for 90 minutes. Thereafter, the mixture was cooled to room temperature and alcohol **283** (523.15 mg, 2.49 mmol, 1.00 equiv) dissolved in THF (6.22 mL) was added. Then, the reaction was heated to 120 °C and stirred for 48 hours. After that, the crude mixture was concentrated in vacuo and applied to Celite® to be purified by column chromatography (SiO_2, 3:1 CH/EE) yielding 406.80 mg of a slightly yellow oil (1.62 mmol, 65%, dr 1.3:1).

$\mathbf{R_f}$ = 0.31 (3:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = -3.2° (c = 0.97 , in CH_2Cl_2). ^{1}**H** NMR (CD_2Cl_2, 500 MHz) δ = 7.28 – 7.23 (m, 2H, H-9, H-13), 6.89 – 6.86 (m, 2H, H-10, H-12), 5.94 – 5.75 (m, 1H, H-2), 5.15 – 5.03 (m, 2H, H-1), 4.43 – 4.40 (m, 2H, H-7), 3.79 (d, *J* = 1.2 Hz, 3H, H-15), 3.57 – 3.49 (m, 2H, H-6), 3.49 – 3.43 (m, 1H, H-4), 2.47 (tq, *J* = 6.1, 1.1 Hz, 1H, H-3), 2.19 (tt, *J* = 7.3, 1.3 Hz, 1H, H-3'), 1.88 – 1.79 (m, 1H, H-5), 0.90 (d, *J* = 7.0 Hz, 3H, H-14). ^{13}**C** NMR (CD_2Cl_2, 126 MHz) δ = 159.7 (C-11), 136.1 (C-2), 130.7 (C-8), 129.7 (C-9, C13), 117.0 (C-1), 114.1 (C-10, C-12), 75.3 (C-6), 74.7 (C-4), 73.4 (C-7), 55.6 (C-15), 39.8 (C-3), 38.4 (C-5), 14.0 (C-14). **HRMS (ESI)** *m/z*: calcd for $C_{15}H_{23}O_3$ $[M + H]^+$: 251.1642, found: 251.1639.

Synthesis of Compound 284

(*R*)-3-((4-Methoxybenzyl)oxy)-2-methylpropanal



283 **284**

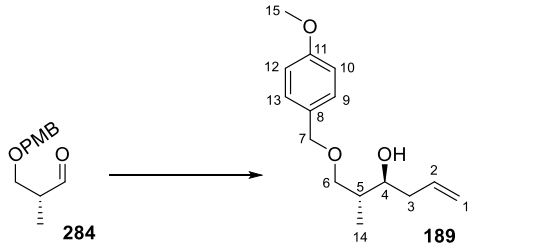
Chemical Formula: $C_{12}H_{16}O_3$
Exact Mass: 208,1099
Molecular Weight: 208,2570

SO_3*py complex (279.80 mg, 1.76 mmol, 3.25 equiv) was dissolved in DMSO (2.70 mL) and stirred at room temperature for 5 minutes before the solution was cooled to 0 °C and DIPEA (0.27 mL, 1.62 mmol, 3.00 equiv) was added dropwise. Afterwards, the alcohol **283** (114.2 mg, 0.54 mmol, 1.00 equiv) was dissolved in DCM (2.7 mL) and added to the cooled mixture. The reaction continued stirring at 0 °C for 30 minutes before $NaHCO_3$ solution (6 mL) was added. Subsequently, the layers were separated and the aqueous layer extracted with DCM (3 x 6 mL). Afterwards, the combinded organic layers were washed with $CuSO_4$ (2 x 20 mL), NH_4Cl (2 x 20 mL) and brine (1 x 20 mL) before they were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The crude product was used in the next reaction without further purification.

R_f = 0.30 (4:1 CH/EE). **α_D^{20}** = - 29.0° (c = 1.00 , in $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 9.67 (d, *J* = 1.6 Hz, 1H, H-1), 7.25 – 7.21 (m, 2H, H-6, H-10), 6.88 – 6.85 (m, 2H, H-7, H-9), 4.43 (s, 2H, H-4), 3.79 (s, 3H, H-11), 3.66 – 3.60 (m, 2H, H-3), 2.61 (dtdd, *J* = 14.0, 7.0, 5.3, 1.6 Hz, 1H, H-2), 1.09 (d, *J* = 7.1 Hz, 3H, H-12). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 204.1 (C-1), 159.7 (C-8), 130.7 (C-5), 129.6 (C-6, C-10), 114.1 (C-7, C-9), 73.3 (C-4), 70.3 (C-3), 55.6 (C-11) 47.3 (C-2), 10.8 (C-12). **HRMS (ESI)** *m/z*: calcd for $C_{12}H_{16}O_3Na$ $[M + Na]^+$: 231.0992, found: 231.0997.

Synthesis of Compound 189

(2*R*,3*S*)-1-((4-Methoxybenzyl)oxy)-2-methylhex-5-en-3-ol



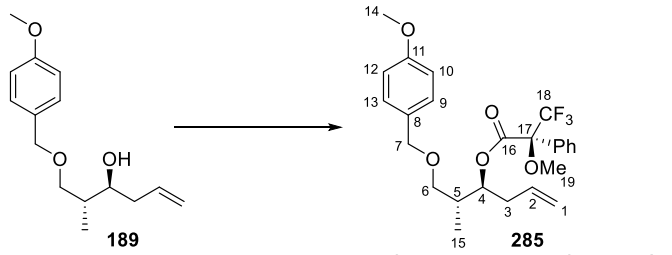
Chemical Formula: $C_{15}H_{22}O_3$
Exact Mass: 250,1569
Molecular Weight: 250,3380

(-)-*B*-methoxydiisopinocampheylborane (214.10 mg, 0.68 mmol, 1.25 equiv) was preloaded into a *Schlenk* flask and dissolved in Et_2O (0.67 mL). Then, the solution was cooled to 0 °C before allylMgBr (1.0 M in Et_2O, 0.65 mL, 0.65 mmol, 1.20 equiv) was added dropwise over 5 minutes. The ice bath was removed and the mixture stirred for 1 hour at room temperature. Afterwards, the latter was cooled to -78 °C and the aldehyde **284** (112.5 mg, 0.54 mmol, 1.00 equiv) was dissolved in Et_2O (0.40 mL) and dropwise added to the reaction. Stirring was continued for 1.5 hours at -78 °C before the reaction mixture was diluted with THF (2.0 mL) and 3 M NaOH (1.03 mL) and 35% H_2O_2 (1.00 mL) were added. Subsequently, the biphasic mixture was allowed to warm to room temperature and then refluxed at 70 °C for 1 hour. The mixture was cooled to room temperature before the layers were separated and the aqueous layer was extracted with Et_2O (3 x 2 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Purification of the crude product by column chromatography (SiO_2, 10:1 CH/EE) lead to the desired product as a clear colourless oil (122.57 mg, 0.49 mmol, 72%, dr > 20:1).

$\mathbf{R_f}$ = 0.09 (10:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = -3.2° (c = 0.97 , in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.26 – 7.23 (m, 2H, H-9, H-13), 6.89 – 6.86 (m, 2H, H-10, H-12), 5.89 (dddd, *J* = 16.9, 10.2, 7.6, 6.4 Hz, 1H, H-2), 5.11 – 5.04 (m, 2H, H-1), 4.43 (d, *J* = 0.8 Hz, 2H, H-7), 3.79 (s, 3H, H-15), 3.57 – 3.51 (m, 2H, H-6), 3.46 (dd, *J* = 9.2, 6.9 Hz, 1H, H-4), 2.39 – 2.28 (m, 1H, H-3), 2.14 (dtt, *J* = 14.1, 7.7, 1.2 Hz, 1H, H-3), 1.85 – 1.78 (m, 1H, H-5), 0.90 (d, *J* = 7.0 Hz, 3H, H-14). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 159.7 (C-11), 136.1 (C-2), 130.7 (C-8), 129.7 (C-9, C13), 117.0 (C-1), 114.1 (C-10, C-12), 75.3 (C-6), 74.7 (C-4), 73.4 (C-7), 55.6 (C-15), 39.8 (C-3), 38.4 (C-5), 14.0 (C-14). **HRMS (ESI)** *m/z*: calcd for $C_{15}H_{23}O_3$ $[M + H]^+$: 251.1642, found: 251.1637.

Synthesis of Compound 285

(2*R*,3*S*)-1-((4-Methoxybenzyl)oxy)-2-methylhex-5-en-3-yl-(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



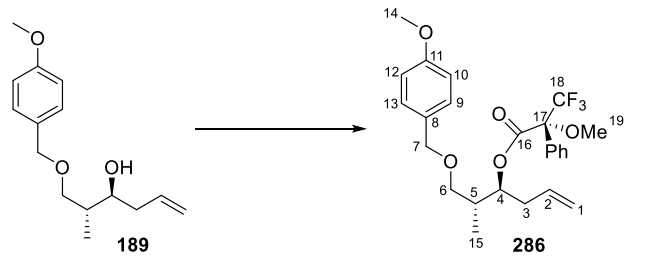
Chemical Formula: $C_{25}H_{29}F_3O_5$
Exact Mass: 466,1967
Molecular Weight: 466,4972

Alcohol **189** (4.7 mg, 18.77 µmol, 1.00 equiv) and dry pyridine (5.00 µL, 58.19 µmol, 3.10 equiv) were preloaded into the reaction vessel and dissolved in DCM (0.50 mL) before (*R*)-MTPA-Cl (7.7 µL, 35.66 µmol, 1.90 equiv) was added and the reaction was stirred at room temperature overnight Then, the mixture was partitioned between water (0.5 mL) and Et_2O (0.5 mL) and the layers separated before the aqueous layer was extracted with Et_2O (3 x 0.5 mL). The organic layers were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 10:1 CH/EE) to obtain a colourless oil (11.0 mg, 23.58 µmol, quant).

R_f = 0.26 (10:1 CH/EE). **α_D^{20}** = -13.6 (c = 1.27 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.54 – 7.49 (m, 2H, H-Ph), 7.46 – 7.36 (m, 3H, H-Ph), 7.26 – 7.20 (m, 2H, H-9, H-13), 6.89 – 6.84 (m, 2H, H-10, H-12), 5.64 (dddd, J = 16.7, 10.3, 7.8, 6.2 Hz, 1H, H-2), 5.24 (ddd, J = 7.8, 5.8, 4.2 Hz, 1H, H-?), 5.00 (dt, J = 7.1, 1.6 Hz, 1H, H-1), 4.96 (d, J = 1.4 Hz, 2H, H-1) 4.38 (q, J = 11.5 Hz, 1H, H-4), 3.79 (s, 3H, H-14), 3.48 (s, 3H, H-19), 3.44 – 3.29 (m, 2H, H-6), 2.45 – 2.36 (m, 1H, H-3), 2.36 – 2.27 (m, 1H, H-3), 2.21 – 2.13 (m, 1H, H-5), 0.97 (d, J = 7.0 Hz, 3H, H-15). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 171.2 (C-16), 166.3 (C-18), 159, 6 (C-11), 133.8 (C-2), 132.7 (C-Ph) 131.0 (C-8), 130.0 (C-Ph), 129.6 (C-9, C-13), 128.7 (C-Ph), 128.0 (C-Ph), 118.3 (C-1), 114.0 (C-10, C-12), 78.1 (C-4), 73.1 (C-7), 71.7 (C-6), 55.6 (C-14/19), 36.8 (C-5), 35.1 (C-3), 13.2 (C-15).**HRMS (ESI)** *m/z*: calcd for $C_{25}H_{29}F_3O_5Na$ $[M + Na]^+$: 489.1853, found: 489.1853.

Synthesis of Compound 286

(2*R*,3*S*)-1-((4-Methoxybenzyl)oxy)-2-methylhex-5-en-3-yl-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



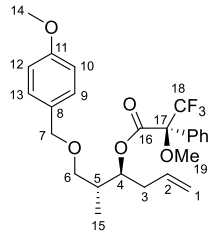
Chemical Formula: $C_{25}H_{29}F_3O_5$
Exact Mass: 466,1967
Molecular Weight: 466,4972

Alcohol **189** (4.3 mg, 15.97 µmol, 1.00 equiv) and dry pyridine (4.70 µL, 49.53 µmol, 3.10 equiv) were preloaded into the reaction vessel and dissolved in DCM (0.50 mL) before (*S*)-MTPA-Cl (7.3 µL, 30.36 µmol, 1.90 equiv) was added and the reaction was stirred at room temperature overnight. Then, the mixture was partitioned between water (0.5 mL) and Et_2O (0.5 mL) and the layers separated before the aqueous layer was extracted with Et_2O (3 x 0.5 mL). The organic layers were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 10:1 CH/EE) to obtain a colourless oil (8.10 mg, 17.36 µmol, quant).

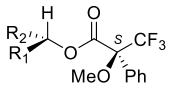
$\mathbf{R_f}$ = 0.21 (10:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +4.7 ° (c = 1.0 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.48 – 7.36 (m, 7H, H-Ph), 7.24 – 7.19 (m, 2H, H-9, H-13), 6.89 – 6.84 (m, 2H, H-10, H-12), 5.79 (dddd, *J* = 16.6, 10.3, 7.8, 6.1 Hz, 1H, H-2), 5.25 (ddd, *J* = 7.8, 5.7, 4.2 Hz, 1H, H-4), 5.14 – 5.07 (m, 2H, H-1), 4.38 – 4.25 (m, 2H, H-7), 3.79 (s, 3H, H-14), 3.52 (q, *J* = 1.3 Hz, 3H, H-14/19?), 3.40 (q, *J* = 1.3 Hz, 2H, H-14/19?), 3.32 – 3.18 (m, 2H, H-6), 2.47 (dddt, *J* = 13.5, 5.9, 4.2, 1.6 Hz, 1H, H-3), 2.43 – 2.33 (m, 1H, H-3), 2.19 – 2.08 (m, 1H, H-5), 0.85 (d, *J* = 7.0 Hz, 3H, H-15). **^{13}C** NMR (V, 176 MHz) δ = 166.3 (C-16?), 161.0 (C-18?), 159.6 (C-11), 134.2 (C-2), 132.9 (C-Ph), 131.0 (C-Ph), 130.6 (C-8), 130.0 (C-), 129.5 (C-9, C-13), 129.2 (C-Ph), 128.7 (C-Ph), 127.8 (C-Ph), 127.3 (C-), 118.4 (C-1), 114.0 (C-10, C-12), 78.2 (C-4), 73.0 (C-7), 71.6 (C-6), 56.3 (C-19?), 56.0 (C-19?), 55.6 (C-14), 36.7 (C-5), 35.2 (C-3), 13.0 (C-15). **HRMS (ESI)** *m/z*: calcd for $C_{25}H_{29}F_3O_5Na$ $[M + Na]^+$: 489.1853, found: 489.1859.

*Table 12: Evaluation of ^{1}H-NMR of the achieved diastereomers. The difference in chemical shifts for each of the analogous pairs of protons for the S- and R-MTPA esters **285** and **286** were determined.*

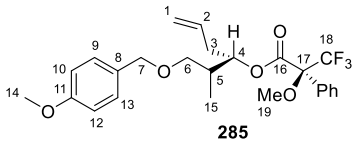
# H	δ *S*-ester [ppm]	δ *R*-ester [ppm]	$\Delta\delta^{S-R}$ [ppm]	$\Delta\delta^{S-R}$ [Hz]
6	3.37	3.25	0.12	84
15	0.97	0.85	0.12	84
5	2.17	2.14	0.03	21
9, 13	7.23	7.22	0.01	7
10, 12	6.87	6.86	0.01	7
3	2.41	2.47	- 0.06	- 42
3'	2.32	2.38	- 0.06	- 42
1	4.98	5.10	- 0.12	- 84
2	5.64	5.79	- 0.15	- 105



285



285a

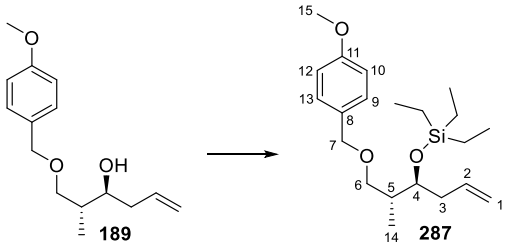


285

Protons (H-6, H-15, H-5, H-9, H-13, H-10, H-12) with a positive difference belong to R_1 and protons (H-3, H-3', H-1, H-2) with a negative difference appertain to R_2. This leads to the result that the secondary alcohol **189** has indeed a stereocenter with the configuration (*S*).

Synthesis of Compound 287

Triethyl(((2*R*,3*S*)-1-((4-methoxybenzyl)oxy)-2-methylhex-5-en-3-yl)oxy)silane



Chemical Formula: $C_{21}H_{36}O_3Si$
Exact Mass: 364,2434
Molecular Weight: 364,6010

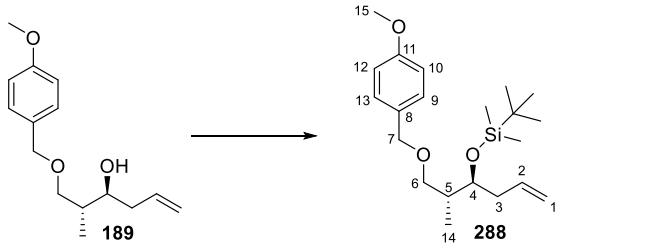
Alcohol **189** (96.5 mg, 0.39 mmol, 1.00 equiv) was dissolved in DCM (3.9 mL) and imidazole (212.40 mg, 3.12 mmol, 8.00 equiv) was added. The mixture was stirred 5 minutes at room temperature to allow the imidazole to dissolve before triethylsilyl chloride (0.10 mL, 0.56 mmol, 1.50 equiv) was added. After the addition the reaction was stirred at room temperature for 35 minutes. NH_4Cl (5 mL) was added and the layers were separated. Then, the aqueous layer was extracted with DCM (3 x 5 mL) prior to drying the combined organic

layers over $MgSO_4$. Hereafter, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, 20:1 CH/EE) to observe 100.3 mg of the desired product as a colourless oil (275.10 µmol, 71%).

R_f = 0.29 (20:1 CH/EE). **α_D^{20}** = -15.4 ° (c = 0.77 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.26 – 7.22 (m, 2H, H-9, H-13), 6.88 – 6.84 (m, 2H, H-10, H-12), 5.86 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H, H-2), 5.07 – 4.99 (m, 2H, H-1), 4.42 – 4.34 (m, 2H, H-7), 3.79 (s, 3H, H-15), 3.75 (dt, *J* = 6.2, 5.2 Hz, 1H, H-4), 3.46 (dd, *J* = 9.2, 5.6 Hz, 1H, H-6), 3.29 (dd, *J* = 9.1, 6.8 Hz, 1H, H-6'), 2.26 – 2.14 (m, 2H, H-3), 1.91 (pt, *J* = 6.8, 5.5 Hz, 1H, H-5), 0.95 (t, *J* = 7.9 Hz, 9H, 3 x CH_3-TES), 0.91 (d, *J* = 6.9 Hz, 3H, H-14), 0.62 – 0.55 (m, 6H, 3 x CH_2-Si). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 159.5 (C-11), 136.2 (C-2), 131.5 (C-8), 129.4 (C-9), 116.7 (C-1), 114.0 (C-10), 73.9 (C-4), 73.0 (C-7), 72.6 (C-6), 55.6 (C-15), 39.2 (C-5), 38.7 (C-3), 13.4 (C-14), 7.1 (3 x CH_3-TES), 5.5 (3 x CH_2-Si). **HRMS (ESI)** *m/z*: calcd for $C_{21}H_{37}O_3Si$: 365.2506, found: 365.2505.

Synthesis of Compound 288

***Tert*-butyl(((2*R*,3*S*)-1-((4-methoxybenzyl)oxy)-2-methylhex-5-en-3-yl)oxy)dimethylsilane**



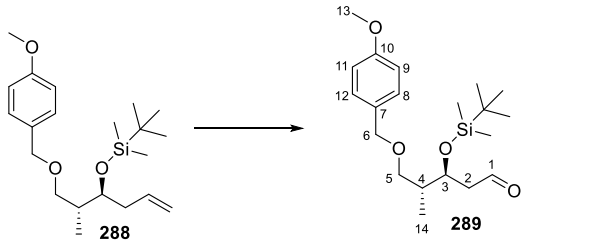
Chemical Formula: $C_{21}H_{36}O_3Si$
Exact Mass: 364,2434
Molecular Weight: 364,6010

Alcohol **189** (330.00 mg, 1.32 mmol, 1.00 equiv) was dissolved in DCM (4.0 mL) and treated with 2,6-lutidine (0.31 mL, 2.64 mmol, 2.00 equiv). Thereafter, the mixture was cooled to 0 °C and *tert*-butyldimethylsilyl triflate (0.45 mL, 1.98 mmol, 1.50 equiv) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 2 hours at room temperture. After that, water (5.0 mL) and DCM (5.0 mL) were added and the layers separated. The aqueous layer was extracted with DCM (3 x 5 mL) before the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. Lastly, the crude product was purified by column chromatography (SiO_2, packed in CH, eluted with 20:1 CH/EE) to observe the desired product as a colourless oil (492.21 mg, 1.35 mmol, quant.).

R_f = 0.28 (10:1 CH/EE). **α_D^{20}** = -17 ° (c = 0.95 in CH_2Cl_2). **^{1}H** (CD_2Cl_2, 500 MHz) δ = 7.26 – 7.22 (m, 2H, H-9, H-13), 6.88 – 6.84 (m, 2H, H-10, H-12), 5.85 (dddd, *J* = 17.0, 10.2, 7.4, 6.7 Hz, 1H, H-2), 5.08 – 4.98 (m, 2H, H-1), 4.38 (q, *J* = 11.5 Hz, 2H, H-7), 3.79 (s, 3H, H-15), 3.73 (q, *J* = 5.5 Hz, 1H, H-6), 3.47 (dd, *J* = 9.2, 5.6 Hz, 1H, H-6'), 3.29 (dd, *J* = 9.2, 6.8 Hz, 1H, H-4), 2.28 – 2.14 (m, 2H, H-3), 1.98 – 1.86 (m, 1H, H-5), 0.91 (d, *J* = 8.0 Hz, 3H, H-14), 0.88 (s, 9H, $C(CH_3)_3$), 0.04 (d, *J* = 4.2 Hz, 6H, 2 x CH_3-Si).**^{13}C** (CD_2Cl_2, 126 MHz) δ = 159.5, (C-11), 136.1 (C-2), 131.5 (C-8), 129.4 (C-9, C-13), 116.7 (C-1), 114.0 (C-10, C-12), 73.8 (C-4), 72.9 (C-7), 72.6 (C-6), 55.6 (C-15), 38.9 (C-5), 38,6 (C-3), 26.1 (3 x CH3) 18.4 (C-Si), 13.5 (C-14), -4.1 (CH3-Si), -4.6 (CH3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{21}H_{37}O_3Si$ $[M + H]^+$: 365.2506, found: 365.2506.

Synthesis of Compound 289

(3*S*,4*R*)-3-((*Tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-4-methylpentanal

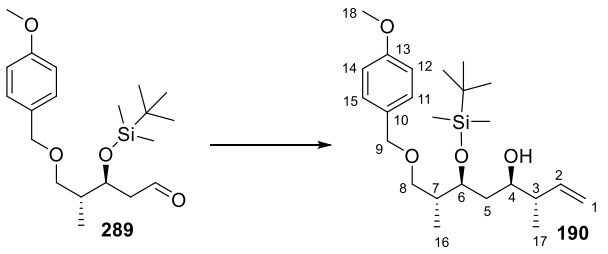


Olefin **288** (106.10 mg, 291.00 mmol, 1.00 equiv) was dissolved in DCM/MeOH (14:1, 6.61 mL) and 5 drops of a 0.1% Sudan III solution were added prior to cooling the reaction mixture to -78 °C. A stream of ozone was lead through the reaction solution until it turned colourless and the residual ozone was purged with Argon before PPh_3 (114.49 mg, 436.50 mmol, 1.50 equiv) was added and the mixture allowed to warm to room temperature. After that, it was continued stirring at room temperature for 3 hours followed by the evaporation of the solvent under reduced pressure. Afterwards, the crude product was purified by column chromatography (SiO_2, packed in CH, eluted with 10:1 CH/EE) to yield a colourless oil (104.54 mg, 285.18 mmol, 98%).

R_f = 0.22 (10:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 400 MHz) δ = 9.75 (t, *J* = 2.4 Hz, 1H; H-1), 7.26 – 7.21 (m, 2H, H-8, H-12), 6.89 – 6.84 (m, 2H, H-9, H-11), 4.44 – 4.34 (m, 2H, H-6), 3.79 (s, 3H, H-13), 3.40 – 3.27 (m, 2H, H-5), 2.50 – 2.43 (m, 2H, H-2), 2.09 – 1.99 (m, 1H, H-4), 0.91 – 0.89 (m, 3H, H-14), 0.87 (s, 9H, $C(CH_3)_3$), 0.09 – 0.02 (m, 6H, 2 x CH_3-Si).

Synthesis of Compound 190

(3*S*,4*R*,6*S*,7*R*)-6-((*Tert*-butyldimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-3,7-dimethyloct-1-en-4-ol



Chemical Formula: $C_{24}H_{42}O_4Si$
Exact Mass: 422,2852
Molecular Weight: 422,6810

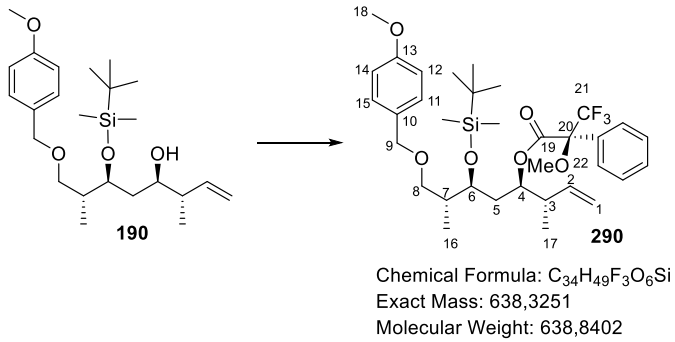
Potassium *tert*-butoxide (49.96 mg, 445.22 µmol, 1.53 equiv) was suspended in THF (0.39 mL) and subsequently cooled to -78 °C. In a separate flask *trans*-2-butene (16.33 mg, 290.99 µmol, 1.00 equiv) was condensed at -78 °C and transferred to the KO*t*Bu suspension using a transfer cannula. After the addition of *trans*-2-butene *n*-BuLi (2.5 M in hexanes, 167.61 µL, 419.03 µmol, 1.44 equiv) was added over 30 minutes and the resulting mixture warmed to -45 °C for 10 minutes before recooling to -78 °C. Afterwards, a solution of (-)-$(Ipc)_2BOMe$ (142.68 mg, 451.04 µmol, 1.55 equiv) in THF (0.46 mL) was slowly added within one hour. Stirring was continued at -78 °C for one hour before the mixture was treated with BF_3*OEt_2 (70.03 µL, 567.44 µmol, 1.95 equiv) followed by the addition of aldehyde **289** (106.67 mg, 290.00 µmol, 1.00 equiv) in THF (0.46 mL) within one hour. After that, the reaction mixture was stirred for four hours at -78 °C. Subsequently, the mixture was treated with 2 M NaOH (0.7 mL) followed by 35% H_2O_2 (0.13 mL) and the mixture was allowed to warm to room temperature and continued stirring overnight. The biphasic mixture was diluted with H_2O (1.0 mL) and Et_2O (1.0 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 1 mL). After that, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Lastly, the crude product was purified by column chromatography (SiO_2, packed with CH, eluted with 10:1 CH/EE) to observe the product as a colourless oil (62.20 mg, 147.16 µmol, 51%, dr: 20:1).

$\mathbf{R_f}$ = 0.12 (10:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = -73.2 ° (c = 0.49 in CH_2Cl_2). ^{1}**H** NMR (CD_2Cl_2, 700 MHz) δ = 7.24 - 7.22 (m, 2H, H-11, H-15), 6.88 - 6.85 (m, 2H, H-12, H-14), 5.80 (ddd, *J* = 17.1, 10.5, 7.7 Hz, 1H, H-2), 5.05 - 4.99 (m, 2H, H-1), 4.41 (d, *J* = 11.6 Hz, 1H, H-9), 4.34 (d, *J* = 11.6 Hz, 1H, H-9'), 4.07 (ddd, *J* = 8.5, 4.5, 3.7 Hz, 1H, H-6), 3.79 (s, 3H, H-18), 3.60 (ddt, *J* = 9.2, 4.7, 2.4 Hz, 1H, H-4),

3.30 (dd, *J* = 9.4, 7.8 Hz, 1H, H-8), 3.24 (dd, *J* = 9.4, 6.1 Hz, 1H, H-8'), 2.19 - 2.14 (m, 1H, H-3), 2.11 - 2.05 (m, 1H, H-7), 1.46 (dd, *J* = 4.5, 2.7 Hz, 1H, H-5), 1.42 - 1.39 (m, 1H, H-5'), 1.00 (d, *J* = 6.9 Hz, 3H, H-16), 0.90 (s, 9H, 3 x CH3), 0.88 (d, *J* = 7.0 Hz, 3H, H-17), 0.11 (s, 3H, CH3-Si), 0.10 (s, 3H, CH3-Si). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 159.6 (C-13), 141.1 (C-2), 132.3 (C-10), 129.5 (C-11, C-15), 115.1 (C-1), 114.0 (C-12, C-14), 74.2 (C-4, C-6), 73.0 (C-9), 72.6 (C-8), 55.6 (C-18), 44.3 (C-3), 39.4 (C-7), 35.4 (C-5), 26.0 (3 x CH3), 18.3 (C_q-Si), 16.0 (C-16), 11.7 (C-17), -4.1 (CH3-Si), -4.5 (CH3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{24}H_{42}O_4SiNa$ [M + Na]$^+$: 445.2745, found: 445.2739.

Synthesis of Compound 290

(3*S*,4*R*,6*S*,7*R*)-6-((*Tert*-butyldimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-3,7-dimethyloct-1-en-4-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



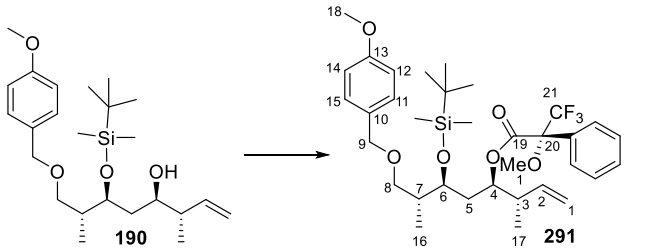
Secondary alcohol **190** (5.00 mg, 11.83 µmol, 1.00 equiv) and dry pyridine (2.95 µL, 36.67 µmol, 3.10 equiv) were placed in the reaction vessel and dissolved in DCM (0.18 mL) prior to the addition of (*R*)-MTPA-Cl (4.21 µL, 22.48 µmol, 1.90 equiv). The reaction was stirred at room temperature overnight. Then, H_2O (0.5 mL) as well as Et_2O (0.5 mL) were added and the reaction mixture partitioned between the phases. The layers were separated and the aqueous layer extracted with Et_2O (3 x 0.5 mL). Subsequently, the combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo. The crude product was used without further purification (7.30 mg, 11.43 µmol, 97%).

R_f = 0.35 (10:1 CH/EE). **α_D^{20}** = -23 ° (c = 0.77 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.43 – 7.37 (m, 5H, H_{arom}), 7.26 – 7.22 (m, 2H, H-11, H-15), 6.88 – 6.85 (m, 2H, H-12, H-14), 5.61 (ddd, *J* = 17.1, 10.4, 8.2 Hz, 1H, H-1), 5.08 – 4.95 (m, 2H, H-2), 4.45 – 4.41 (m, 1H, H-9), 4.35 (d, *J* = 11.6 Hz, 1H, H-9'), 4.10 (ddd, *J* = 8.6, 5.0, 3.7 Hz, 1H, H-6), 3.79 (s, 3H, H-16), 3.68 – 3.64 (m, 1H, H-4), 3.41 (s, 3H, OMe), 3.32 – 3.24 (m, 1H, H-8), 3.22 (dd, *J* = 9.5, 5.8 Hz, 1H, H-8'), 2.24 –

2.17 (m, 1H, H-3), 2.13 – 2.03 (m, 1H, H-7), 1.47 – 1.45 (m, 2H, H-5), 1.00 (d, *J* = 6.9 Hz, 3H, H-16), 0.90 (s, 9H, $C(CH_3)_3$-Si), 0.87 (d, *J* = 7.0 Hz, 3H, H-17), 0.04 (d, *J* = 10.6 Hz, 6H, CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 167.7 (C-19), 161.0 (C-13), 140.8 (C-2), 132.3 (C-10), 130.7 (C_{arom}), 130.3 (C_{arom}), 129.5 (C-11, C-15), 129.2 (C_{arom}), 129.0 (C_{arom}), 127.9 (C_{arom}), 127.3 (C_{arom}), 114.0 (C-1, C-12, C-14), 78.3 (C-21), 73.0 (C-4, C-6), 72.0 (C-9), 70.9 (C-8), 55.6 (C-18, OMe), 44.1 (C-3), 41.1 (C-20), 38.3 (C-7), 35.3 (C-5), 26.0 ($C(CH_3)_3$-Si), 18.3 (C_q-Si), 16.4 (C-16), 13.4 (C-17), -4.4 (CH_3-Si), -4.4 (CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{34}H_{53}F_3O_6SiN$ $[M + NH_4]^+$: 656.3589, found: 656.3590.

Synthesis of Compound 291

(3*S*,4*R*,6*S*,7*R*)-6-((*Tert*-butyldimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-3,7-dimethyloct-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



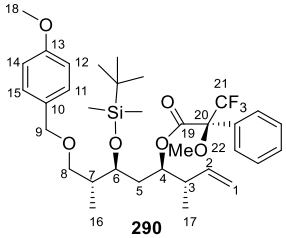
Alcohol **190** (5.00 mg, 11.83 µmol, 1.00 equiv) and dry pyridine (2.95 µL, 36.67 µmol, 3.10 equiv) were placed in the reaction vessel and dissolved in DCM (0.18 mL) prior to the addition of (*S*)-MTPA-Cl (4.21 µL, 22.48 µmol, 1.90 equiv). The reaction was stirred at room temperature overnight. Then, H_2O (0.5 mL) as well as Et_2O (0.5 mL) were added and the reaction mixture partitioned between the phases. The layers were separated and the aqueous layer extracted with Et_2O (3 x 0.5 mL). Subsequently, the combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo. The crude product was used without further purification (6.90 mg, 10.80 µmol, 91%).

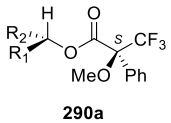
R_f = 0.33 (10:1 CH/EE). **α_D^{20}** = -42 ° (c = 0.99 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.48 – 7.37 (m, 5H, H_{arom}), 7.26 – 7.21 (m, 2H, H-11, H-15), 6.88 – 6.85 (m, 2H, H-12, H-14), 5.82 – 5.76 (m, 1H, H-1), 5.05 – 5.00 (m, 2H, H-2), 4.43 (d, *J* = 11.6 Hz, 1H, H-9), 4.35 (d, *J* = 11.6 Hz, 1H, H-9'), 4.10 (ddd, *J* = 8.6, 4.9, 3.7 Hz, 1H, H-6), 3.79 (s, 3H, H-18), 3.66 (ddd, *J* = 8.0, 4.6, 3.2 Hz, 1H, H-4), 3.41 (q, *J* = 1.3 Hz, 3H, OMe), 3.32 – 3.24 (m, 2H, H-8), 2.20 (ddddd, *J* = 13.8, 8.0,

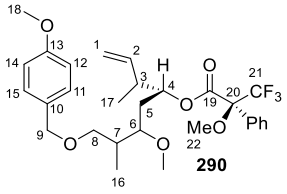
5.8, 4.0, 2.9 Hz, 1H, H-3), 2.12 – 2.07 (m, 1H, H-7), 1.49 – 1.39 (m, 2H, H-5), 1.00 (d, *J* = 6.9 Hz, 3H, H-16), 0.90 (s, 9H, $C(CH_3)_3$-Si), 0.88 (d, *J* = 7.1 Hz, 3H, H-17), 0.12 (d, *J* = 7.1 Hz, 6H, CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 167.6 (C-19), 159.6 (C-13), 140.8 (C-2), 132.0 (C-10), 131.1 (C_{arom}), 130.9 (C_{arom}), 129.5 (C-11, C-15), 129.2 (C_{arom}), 129.0 (C_{arom}), 128.8 (C_{arom}), 127.9 (C_{arom}), 115.3 (C-1), 114.0 (C-12, C-14), 74.7 (C-21), 74.3 (C-4, C-6), 73.0 (C-9), 72.6 (C-8), 55.6 (C-18, OMe), 44.1 (C-20), 39.4 (C-7), 34.9 (C-5), 26.0 ($C(CH_3)_3$-Si), 18.3 (C_q-Si), 15.9 (C-16), 11.5 (C-17), -4.1 (CH_3-Si), -4.5 (CH_3-Si). **HRMS (ESI)** m/z: calcd for $C_{34}H_{53}F_3O_6SiN$ $[M + NH_4]^+$: 656.3589, found: 656.3588.

*Table 13: Evaluation of ^{1}H-NMR of the achieved diastereomers. The difference in chemical shifts for each of the analogous pairs of protons for the S- and R-MTPA esters **290** and **291** were determined.*

# H	δ *S*-ester [ppm]	δ *R*-ester [ppm]	$\Delta\delta^{S-R}$ [ppm]	$\Delta\delta^{S-R}$ [Hz]
5	1.46	1.44	0.02	14
6	4.10	4.10	0	0
7	2.11	2.10	0.01	7
8	3.29	3.28	0.01	7
9	4.43	4.43	0	0
9'	4.35	4.35	0	0
11, 15	7.24	7.24	0	0
12, 14	6.87	6.87	0	0
16	1.00	0.99	0.01	7
17	0.87	0.88	-0.01	-7
3	2.20	2.21	-0.01	-7
2	5.02	5.03	-0.01	-7
1	5.68	5.73	-0.05	-35
18	3.79	3.79	0	0



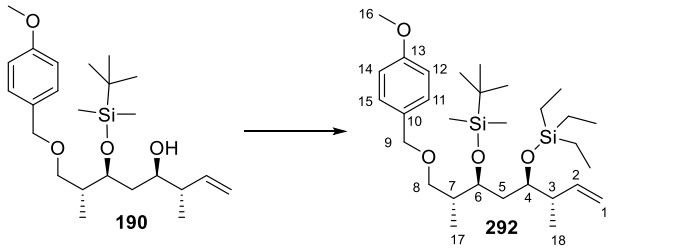




Since protons displaying a positive $\Delta\delta^{S-R}$ value belong to R_1, H-, .can be assigned to R_1. While H-, show negative $\Delta\delta^{S-R}$ values and are therefore assigned to belong to R_2. Therefore, the configuartion of the investigated stereocenter of the secondary alcohol **190** is proven to be (*R*).

Synthesis of Compound 292

(5*S*,7*R*)-7-((*S*)-But-3-en-2-yl)-9,9-diethyl-5-((*R*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,3,3-tetramethyl-4,8-dioxa-3,9-disilaundecane



Chemical Formula: $C_{30}H_{56}O_4Si_2$
Exact Mass: 536,3717
Molecular Weight: 536,9440

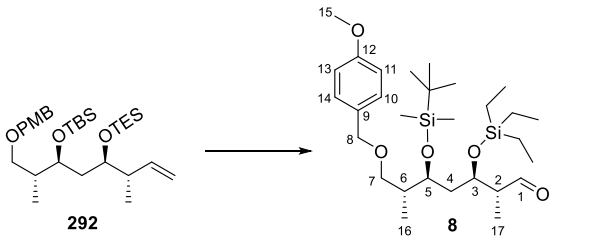
In a flame-dried *Schlenk* flask imidazole (19.07 mg, 280.12 µmol, 8.00 equiv) was dried in HV for 5 minutes prior to dissolving alcohol **190** (14.80 mg, 35.01 µmol, 1.00 equiv) in DCM (0.35 mL) and adding it to the reaction flask. The reaction was stirred for five minutes at room temperature until the imidazole was mostly dissolved before TES-Cl (8.82 µL, 52.52 µmol, 1.50 equiv) was added dropwise. The resulting mixture was stirred at room temperature for 1.5 hours before another portion of TES-Cl (8.82 µL, 52.52 µmol, 1.50 equiv) was added and the mixture stirred at room temperature overnight. Thereafter, NH_4Cl (0.5 mL) was added and the layers separated. The aqueous layer was extracted with DCM (3 x 0.5 mL) and the combined organic layers dried over $MgSO_4$. Afterwards the solvent was removed under reduced pressure and the crude product purified by column chromatography (SiO_2, packed in CH, eluted with 10:1 CH/EE) yielding 17.80 mg (33.15 µmol, 95%) of the desired product as colourless oil.

R_f = 0.51 (10:1 CH/EE). **α_D^{20}** = -51.6 ° (c = 1.02 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.25 – 7.22 (m, 2H, H-11, H-15), 6.87 – 6.85 (m, 2H, H-12, H-14), 5.76 (ddd, J = 17.3, 10.4, 8.2 Hz, 1H, H-2), 4.99 – 4.91 (m, 2H, H-1), 4.41 – 4.31 (m, 2H, H-9), 3.85 (ddd, J = 8.2, 4.6, 3.4 Hz, 1H, H-6), 3.81 (td, J = 5.6, 2.8 Hz, 1H, H-4), 3.79 (s, 3H, H-16), 3.36 – 3.17 (m, 2H, H-8), 2.33 – 2.25 (m, 1H, H-3), 1.98 (dtt, J = 10.2, 6.9, 3.4 Hz, 1H, H-7), 1.52 – 1.43 (m, 2H, H-5), 1.02 (d, J = 6.9 Hz, 3H, H-18), 0.89 (d, J = 7.0 Hz, 3H, H-17), 0.89 (s, 9H, $C(CH_3)_3$-TBS), 0.60 (q, J = 8.1 Hz, 6H, CH_2-TES), 0.06 (s, 3H, CH3-TBS), 0.05 (s, 3H, CH3-TBS). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 159.5 (C-13), 140.7 (C-2), 131.4 (C-10), 129.3 (C-11, C-15), 115.1 (C-1), 113.9 (C-12, C-14), 73.0 (C-4), 73.0 (C-9), 72.7 (C-8), 70.8 (C-6), 55.6 (C-16), 42.6 (C-3), 39.4 (C-7), 37.4 (C-5), 26.1 ($C(CH_3)_3$-TBS),

16.8 (C-18), 12.3 (C-17), 5.5 (CH_2-TES), -4.3 (CH_3-Si), -4,3 (CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{30}H_{57}O_4Si_2$ $[M + H]^+$: 537.3790, found: 537.3797.

Synthesis of Compound 8

(2*R*,3*R*,5*S*,6*R*)-5-((*Tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,6-dimethyl-3-((triethylsilyl)oxy)heptanal

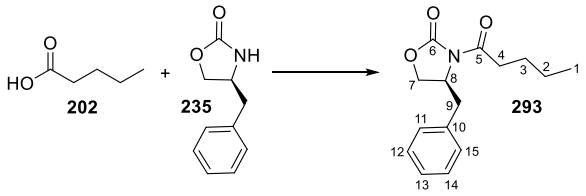


Olefin **292** (17.80 mg, 33.15 µmol, 1.00 equiv) was dissolved in acetone/H_2O (10:1, 0.41 mL) and NMO*H_2O (8.70 mg, 66.30 µmol, 2.00 equiv) was added followed by OsO_4 (4% in H_2O, 10.53 µL, 1.66 µmol, 0.05 equiv). The resulting reaction mixture was stirred for 41.5 hours at room temperature until TLC showed full conversion of the starting material. Afterwards, $Na_2S_2O_3$ (1.0 mL) was added and the mixture diluted with DCM (1.0 mL) before the layers were separated and the aqueous layer extracted with DCM (3 x 1.0 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue was redissolved in toluene (0.43 mL) and $Pb(OAc)_4$ (96%, 17.61 mg, 38.12 µmol, 1.15 equiv) was added. The reaction was stirred at room temperature for 1 hour and then filtered through a Celite plug and washed with DCM (3 x 1.0 mL). The solvent was removed under reduced pressure and the crude product purified by column chromatography (SiO_2, 10:1) to obtain the desired aldehyde as a colourless oil (17.30 mg, 32.10 µmol, 97%).

R_f = 0.21 (10:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 400 MHz) δ = 9.68 (d, *J* = 2.1 Hz, 1H, H-1), 7.24 (t, *J* = 7.6 Hz, 2H, H-10, H-14), 6.88 – 6.83 (m, 2H, H-11, H-13), 4.37 (s, 2H, H-8), 4.12 – 4.06 (m, 1H, H-5),3.95 – 3.89 (m, 1H, H-3), 3.79 (s, 3H, H-15), 3.39 – 3.20 (m, 2H, H-7), 2.48 – 2.42 (m, 1H, H-2), 2.11 – 1.99 (m, 1H, H-6), 1.68 (dt, *J* = 7.9, 4.9 Hz, 2H, H-4), 1.12 (d, *J* = 7.0 Hz, 3H, H-17), 0.95 (t, *J* = 7.9 Hz, 9H; 3 x CH_3-TES), 0.89 (d, *J* = 8.8 Hz, 3H, H-16), 0.89 (s, 9H, $C(CH_3)_3$), 0.65 – 0.57 (m, 6H, 3 x CH_2-Si), 0.05 (d, *J* = 8.6 Hz, 6H, 2 x CH_3-Si).

Synthesis of Compound 293

(*S*)-4-Benzyl-3-pentanoyloxazolidin-2-one



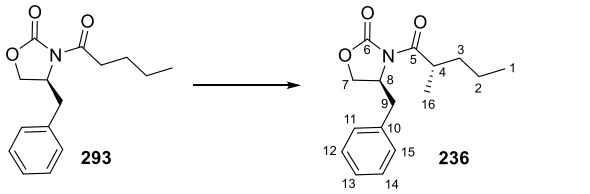
Chemical Formula: $C_{15}H_{19}NO_3$
Exact Mass: 261,1365
Molecular Weight: 261,3210

In a flame-dried *Schlenk* flask valeric acid (**202**) (500.00 mg, 4.90 mmol, 1.00 equiv) was dissolved in THF (27.5 mL) and the mixture was cooled to -20 °C to -30 °C. Then, triethylamine (1.71 mL, 12.24 mmol, 2.50 equiv) was added dropwise before the dropwise addition of pivaloyl chloride (0.66 mL, 5.39 mmol, 1.10 equiv) to the reaction mixture. The slurry mixture was stirred for 75 minutes at -20 °C to -30 °C. Afterwards, LiCl (311.29 mg, 7.34 mmol, 1.50 equiv) and (*S*)-(-)-benzyl-2-oxazolidinone (**235**) (954.26 mg, 5.39 mmol, 1.10 equiv) were added in THF (4.75 mL). The mixture was allowed to warm to room temperature and continued stirring for 5 hours before saturated ammonium chloride solution (30 mL) was added. The aqueous phase was extracted with DCM (3 x 30 mL) and the combined organic layers dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was applied on Celite for column chromatography (SiO_2, 5:1 CH/EE). A colourless oil (1.31 g, 5.01 mmol, quant) was observed.

$\mathbf{R_f}$ = 0.18 (5:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +58.0° (c = 1.00, $CHCl_3$). $^{\mathbf{1}}$**H** NMR (CD_2Cl_2, 700 MHz) δ = 7.35 – 7.32 (m, 2H, H-12, H-14), 7.29 – 7.26 (m, 1H, H-13), 7.22 – 7.19 m, 2H, H-11, H-15), 4.67 (dddd, *J* = 9.1, 7.9, 3.4, 2.8 Hz, 1H, H-8), 4.20 (ddd, *J* = 8.7, 7.9, 0.7 Hz, 1H, H-7), 4.15 (dd, *J* = 9.0, 2.7 Hz, 1H, H-7), 3.22 (dd, *J* = 13.5, 3.4 Hz, 1H, H-9), 2.93 (ddd, *J* = 16.8, 8.5, 6.5 Hz, 1H, H-4), 2.89 – 2.85 (m, 1H, H-4), 2.83 (dd, *J* = 13.5, 9.1 Hz, 1H, H-9), 1.70 – 1.62 (m, 2H, H-3), 1.41 (h, *J* = 7.4 Hz, 2H, H-2), 0.95 (t, *J* = 7.4 Hz, 3H, H-1). $^{\mathbf{13}}$**C** NMR (CD_2Cl_2, 700 MHz) δ = 173.6 (C-5), 153.9 (C-6), 136.0 (C-10), 129.9 (C-11, C-15), 129.2 (C-12, C-14), 127.6 (C-13), 66.6 (C-7), 55.4 (C-8), 38.2 (C-9), 35.6 (C-4), 26.8 (C-3), 22.7 (C-2), 14.1 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_{15}H_{19}NO_3H$ $[M + H]^+$: 262.1438, found: 262.1443.

Synthesis of Compound 236

(*S*)-4-Benzyl-3-((*S*)-2-methylpentanoyl)oxazolidin-2-one



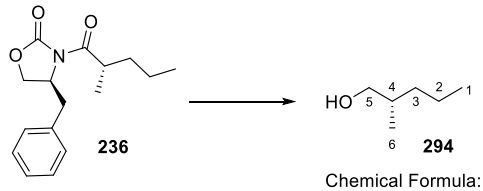
Chemical Formula: $C_{16}H_{21}NO_3$
Exact Mass: 275,1521
Molecular Weight: 275,3480

The derivatised oxazolidinone **293** (1.28 g, 4.90 mmol, 1.00 equiv) was dissolved in THF (17.5 mL) and cooled to -78 °C. Subsequently, NaHMDS (2.0 M in THF, 3.67 mL, 7.35 mmol, 1.50 equiv) was slowly added followed by the dropwise addition of methyl iodide (914.80 µL, 14.69 mmol, 3.00 equiv). The reaction mixture was stirred at -78 °C for 2 hours and then warmed to -50 °C and stirred additional 2 hours. Thereafter, a mixture of NH_4Cl and water (3:1, 20 mL) was added and the layers separated. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic layers dried over $MgSO_4$ prior to evaporating the solvent in vacuo. Lastly, the crude product was purified by column chromatography (SiO_2, 7:1 CH/EE) yielding 865.30 mg (3.14 mmol, 64%) of the desired product as a colourless oil.

R_f = 0.27 (5:1 CH/EE). **α_D^{20}** = +41.7 ° (c = 0.01 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.35 – 7.31 (m, 2H, H-12, H-14), 7.29 – 7.25 (m, 1H, H-13), 7.23 – 7.20 (m, 2H, H-11, H-15), 4.67 (dddd, *J* = 9.0, 7.7, 3.4, 2.7 Hz, 1H, H-8), 4.20 (ddd, *J* = 9.0, 7.7, 0.7 Hz, 1H, H-7), 4.15 (dd, *J* = 9.0, 2.7 Hz, 1H, H-7´), 3.69 (h, *J* = 6.8 Hz, 1H, H-4), 3.19 (dd, *J* = 13.5, 3.4 Hz, 1H, H-9), 2.83 (dd, *J* = 13.5, 9.0 Hz, 1H, H-9´), 1.70 (dddd, *J* = 12.6, 8.8, 6.9, 5.9 Hz, 1H, H-3), 1.42 – 1.28 (m, 3H, H-2, H3´), 1.19 (d, *J* = 6.8 Hz, 3H, H-16), 0.90 (t, *J* = 7.2 Hz, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 177.4 (C-5), 153.5 (C-6), 136.0 (C-10), 129.9 (C-11, C-15), 129.2 (C-12, C-14), 127.6 (C-13), 66.5 (C-7), 55.6 (C-8), 38.1 (C-9), 37.8 (C-4), 35.9 (C-3), 20.8 (C-2), 17.4 (C-16), 14.3 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_{16}H_{21}NO_3H$ $[M + H]^+$: 276.1594, found: 276.1597.

Synthesis of Compound 294

(*S*)-2-Methylpentan-1-ol



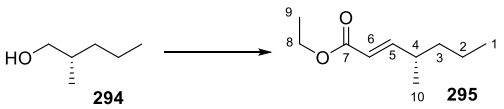
Chemical Formula: $C_6H_{14}O$
Exact Mass: 102,1045
Molecular Weight: 102,1770

To cleave the oxazolidinone auxiliary compound **236** (865.30 mg, 3.14 mmol, 1.00 equiv) was dissolved in Et_2O (10.0 mL) and cooled to 0 °C prior to the dropwise addition of $LiAlH_4$ (2.0 M in Et_2O, 2.20 mL, 4.40 mmol, 1.40 equiv) diluted with Et_2O (3.7 mL) over 15 minutes. The reaction mixture was stirred at 0 °C for 1.5 hours until brine (10.0 mL) was added over 5 minutes. Then, the bilayer mixture was warmed to room temperature and continued stirring for 30 minutes before the layers were separated. After that, the aqueous layer was extracted with Et_2O (3 x 10 mL), the combined organic layers dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Purification of the crude product was achieved by column chromatography (SiO_2, 1:1 pentane/EE) yielding a colourless liquid (244.30 mg, 2.39 mmol, 76%).

$\mathbf{R_f}$ = 0.50 (1:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = -12.0° (c = 1.00, $CHCl_3$). ^{1}**H** NMR ($CDCl_3$, 500 MHz) δ = 3.54 – 3.38 (m, 2H, H-5), 1.68 – 1.59 (m, 1H, H-4), 1.44 – 1.33 (m, 2H, H-2, H-3), 1.33 – 1.24 (m, 1H, H-2), 1.14 – 1.06 (m, 1H, H-3), 0.92 – 0.90 (m, 3H, H-6), 0.90 (d, *J* = 7.0 Hz, 3H, H-1). ^{13}**C** NMR ($CDCl_3$, 126 MHz) δ = 68.6 (C-5), 35.6 (C-4), 35.6 (C-3), 20.2 (C-2), 16.7 (C-6), 14.5 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_6H_{14}OH$ $[M + H]^+$: 103.1117, found: 103.1113.

Synthesis of Compound 295

Ethyl (*S*,*E*)-4-methylhept-2-enoate



Chemical Formula: $C_{10}H_{18}O_2$
Exact Mass: 170,1307
Molecular Weight: 170,2520

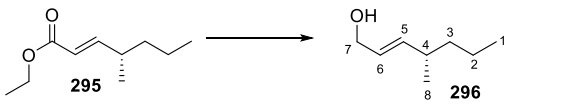
In a two step one-pot procedure the observed alcohol **294** was first oxidised to the respective aldehyde using *Swern* conditions. Therefore, oxalylchloride (from freshly openend glass

ampoule, 344.98 µL, 4.02 mmol, 1.20 equiv) was dissolved in DCM (27.2 mL) and the resulting solution cooled to -60 °C. Afterwards, DMSO (566.73 µL, 7.98 mmol, 2.40 equiv) was added dropwise and the solution stirred for 20 minutes at -60 °C before alcohol **307** (339.70 mg, 3.32 mmol, 1.00 equiv) was dissolved in DCM (20.4 mL) and added dropwise to the reaction mixture which continued stirring for 15 minutes at -60 °C. Hereafter, dropwise addition of triethylamine (2.29 mL, 16.46 mmol, 4.95 equiv) at -60 °C was followed by warming the reaction to 0 °C. Lastly, the *Wittig* reaction was performed by adding ethyl (triphenylphosphoranylidenephosphate)acetate (3.48 g, 9.97 mmol, 3.00 equiv) to the mixture at 0 °C. Thereafter, stirring was continued for 30 minutes at 0 °C and then the mixture was allowed to warm to room temperature and stirred for an additional hour. Finally, the reaction was stopped by the addition of brine (60 mL) followed by separating the layers and extraction of the aqueous layer with DCM (3 x 50 mL). Afterwards, the combined organic layers were dried over $MgSO_4$, the solvent evaporated under reduced pressure and the crude product applied to Celite and purified by column chromatography (SiO_2, 10:1 CH/EE) yielding the α,β-unsaturated methyl ester as a colourless oil (249.30 mg, 1.60 mmol, 48%).

$\mathbf{R_f}$ = 0.43 (10:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +3.6 °(c = 0.16 in CH_2Cl_2). **^{1}H-NMR** (CD_2Cl_2, 500 MHz) δ = 6.87 (dd, *J* = 15.7, 7.9 Hz, 1 H, H-5), 5.77 (dd, *J* = 15.7, 1.2 Hz, 1 H, H-6), 4.12 (q, *J* = 7.1 Hz, 2 H, H-8), 2.34 - 2.28 (m, 1 H, H-4), 1.35 - 1.29 (m, 4 H, H-2, H-3), 1.26 (t, *J* = 7.1 Hz, 3 H, H-9), 1.04 (d, *J* = 6.7 Hz, 3 H, H-10), 0.88 (t, *J* = 7.1 Hz, 3 H, H-1). **^{13}C-NMR** (CD_2Cl_2, 126 MHz) δ = 167.5 (C-7), 155.2 (C-5), 119.3 (C-6), 51.5 (C-8), 38.3 (C-3), 36.4 (C-4), 27.1 (C-10), 20.4 (C-2), 19.5 (C-9), 14.2 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_{10}H_{19}O_2$ $[M + H]^+$: 171.2595, found: 171.2598.

Synthesis of Compound 296

(*S*,*E*)-4-Methylhept-2-en-1-ol



Chemical Formula: $C_8H_{16}O$
Exact Mass: 128,1201
Molecular Weight: 128,2150

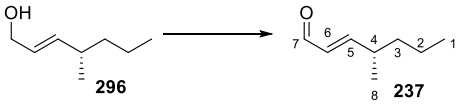
Reduction of the α,β-unsaturated ethyl ester **295** was conducted by DIBAl-H reduction. Therefore, compound **295** (272.40 mg, 1.60 mmol, 1.00 equiv) was dissolved in THF (10.7 mL) and the solution cooled to -78 °C. Then, DIBAl-H (1.0 M in CH, 3.51 mL, 3.51 mmol, 2.20 equiv) was added dropwise and the reaction kept stirring at -78 °C for 2.5 hours. After that,

potassium, sodium tatrate solution (10 mL) was added and the bilayer mixture warmed to room temperature and stirred at this temperature for 1.5 hours until both layers appeared to be clear. The layers were separated and the aqueous layer extracted with DCM (3 x 10 mL), washed with brine (1 x 30 mL), dried over $MgSO_4$ and the solvent evaporated in vacuo. As a last step the crude product was purified by column chromatography (SiO_2, 5:1 CH/EE) to yield 149.50 mg (1.17 mmol, 73%) of a colourless liquid.

R_f = 0.15 (5:1 CH/EE). **α_D^{20}** = -1.3 °(c = 0.19 in CH_2Cl_2). **^{1}H** NMR ($CDCl_3$, 700 MHz) δ = 5.62 – 5.53 (m, 2H, H-5, H-6), 4.09 (d, *J* = 4.3 Hz, 2H, H-7), 2.15 (p, *J* = 6.6 Hz, 1H, H-4), 1.34 – 1.20 (m, 4H, H-2, H-3), 0.98 (d, *J* = 6.8 Hz, 3H, H-8), 0.88 (t, *J* = 7.0 Hz, 3H, H-1). **^{13}C** NMR ($CDCl_3$, 700 MHz) δ = 139.5 (C-5), 127.2 (C-6), 64.1 (C-7), 39.2 (C-3), 36.2 (C-4), 20.5 (C-2), 20.5 (C-8), 14.3 (C-1). **HRMS (ESI)** *m/z*: calcd for $C_8H_{16}OH$ $[M + H]^+$: 129.1274, found: 129.1271.

Synthesis of Compound 237

(*S*,*E*)-4-Methylhept-2-enal



Chemical Formula: $C_8H_{14}O$
Exact Mass: 126,1045
Molecular Weight: 126,1990

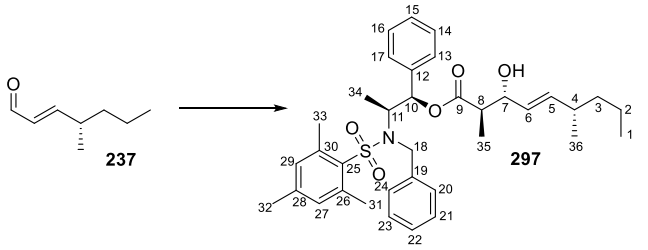
Oxidation of alcohol **296** to the α,β-unsaturated aldehyde **237** was performed under *Parikh-Doering* conditions. In respect thereof, SO_3*py complex (252.85 mg, 1.06 mmol, 3.25 equiv) was preloaded in the reaction flask and dissolved in DMSO (1.63 mL). The resulting solution was stirred at room temperature for 5 minutes prior to cooling it to 0 °C and adding DIPEA (179.76 µL, 1.06 mmol, 3.25 equiv) dropwise. Alcohol **309** (41.70 mg, 325.23 µmol, 1.00 equiv) was dissolved in DCM (1.63 mL) and added dropwise to the reaction which was stirred at 0 °C for 1 hour. Afterwards, $NaHCO_3$ (5 mL) was added, the layers were separated and the aqueous layer extracted with DCM (3 x 5 mL). The combined organic layers were washed with $CuSO_4$ (2 x 20 mL), NH_4Cl (2 x 20 mL) and brine (1 x 20 mL) before they were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product (38.10 mg, 301.90 µmol, 93%) was used for the next reaction without further purification.

R_f = 0.43 (5:1 CH/EE). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 9.48 (d, *J* = 7.9 Hz, 1H, H-7), 6.74 (dd, *J* = 15.7, 7.6 Hz, 1H, H-5), 6.04 (ddd, *J* = 15.7, 7.9, 1.2 Hz, 1H, H-6), 2.46 (dtt, *J* = 13.4, 6.8, 1.2 Hz,

1H, H-4), 1.45 – 1.37 (m, 2H, H-3), 1.37 – 1.29 (m, 2H, H-2), 1.08 (d, *J* = 6.7 Hz, 3H, H-8), 0.91 (t, *J* = 7.2 Hz, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 194.5 (C-7), 164.6 (C-5), 131.6 (C-6), 38.4 (C-4), 37.1 (C-3), 20.7 (C-2), 19.3 (C-8), 14.2 (C-1).

Synthesis of Compound 297

(1*R*,2*S*)-2-((*N*-Benzyl-2,4,6-trimethylphenyl)sulfonamido)-1-phenylpropyl (2*R*,3*R*,6*S*,*E*)-3-hydroxy-2,6-dimethylnon-4-enoate



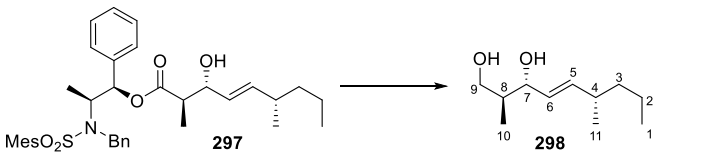
Chemical Formula: $C_{36}H_{47}NO_5S$
Exact Mass: 605,3175
Molecular Weight: 605,8340

Observed aldehyde **237** was transformed in a *Masamune* anti-Aldol reaction. For this purpose, (1*R*,2*S*)-2-(*N*-benzyl-*N*-mesitylenesulfonyl)amino-1-phenyl-1-propyl propionate (121.64 mg, 253.60 µmol, 0.84 equiv) was dissolved in DCM (2.37 mL) and triethylamine (stored over 3 Å MS o.n., 84.16 µL, 603.81 µmol, 2.00 equiv) was added dropwise prior to cooling the solution to -78 °C. Then, a pre-cooled solution of $(cyHex)_2BOTf$ (164.45 mg, 504.18 µmol, 1.67 equiv) in DCM (1.13 mL) was added using a transfer cannula. To insure full enolisation the reaction mixture was stirred for 2 hours at -78 °C. After that, aldehyde **250** (38.10 mg, 301.90 µmol, 1.00 equiv) was dissolved in DCM (1.30 mL) and dropwise added to the reaction which was stirred at -78 °C for an additional hour before it was slowly allowed to warm up over 2 hours. To stop the reaction pH 7 buffer (0.95 mL), MeOH (2.37 mL) and 35% H_2O_2 (0.24 mL) were added. After the mixture warmed to room temperature it was stirred vigorously overnight. Hereafter, the layers were separated and the aqueous layer extracted with Et_2O (3 x 3 mL) prior to washing the combined organic layers with brine (10 mL), drying them over Na_2SO_4 and removing the solvent under reduced pressure. Lastly, the crude product was purified by HPLC (85% MeCN, 15% H_2O, retention time 17.3 min, using a MACHEREY-NAGEL Nucleodur 100-5 C18ec; 5 µm; 250 x 16 mm + precolumn (N21112154), 205 nm) yielding 100.50 mg (165.89 µmol, 55%) of a colourless amorphous solid.

R_f = 0.04 (10:1 CH/EE). **α_D^{20}** = +14.7 ° (c = 0.63 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.32 – 7.29 (m, 2H, H-15, H-22), 7.26 – 7.17 (m, 6H, H-13, H-14, H-16, H-17, H-21, H-23), 6.91 (dd, *J* = 1.3, 0.7 Hz, 2H, H-27, H-29), 6.89 – 6.86 (m, 2H, H-20, H-24), 5.77 (d, *J* = 3.7 Hz, 1H, H-10), 5.58 (ddd, *J* = 15.4, 7.8, 0.9 Hz, 1H, H-5), 5.39 – 5.34 (m, 1H, H-6), 4.78 (d, *J* = 16.7 Hz, 1H, H-18), 4.61 (d, *J* = 16.7 Hz, 1H, H18'), 4.14 – 4.05 (m, 2H, H-7, H-11), 2.54 – 2.47 (m, 1H, H-8), 2.50 (d, *J* = 0.6 Hz, 6H, H-31, H-33), 2.29 (d, *J* = 0.7 Hz, 3H, H-32), 2.18 – 2.11 (m, 1H, H-4), 1.27 (dddd, *J* = 7.0, 4.0, 2.8, 1.6 Hz, 4H, H-2, H-3), 1.14 (d, *J* = 7.0 Hz, 3H; H-34), 1.05 (d, *J* = 7.2 Hz, 3H, H-35), 0.98 (d, *J* = 6.7 Hz, 3H, H-36), 0.90 – 0.85 (m, 3H, H-1). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 174.6 (C-9), 143.2 (C-25), 141.2 (C-5), 140.6 (C-26, C-30), 139.4 (C-19), 139.0 (C-12), 134.1 (C-28), 132.6 (C-27, C-29), 128.8 (C-13, C-17), 128.6 (C-14, C-16), 128.6 (C-6), 128.0 (C-15, C-22), 127.4 (C-21, C-23), 126.3 (C-20, C-24), 78.7 (C-10), 75.6 (C-7), 57.4 (C-11), 48.7 (C-18), 46.5 (C-8), 39.5 (C-3), 36.7 (C-4), 23.1 (C-31, C-33), 21.0 (C-32), 20.9 (C-2), 20.6 (C-36), 14.3 (C-1), 14.3 (C-35), 13.5 (C-34). **HRMS (ESI)** *m/z*: calcd for $C_{36}H_{47}NO_5SNa$ $[M + Na]^+$: 628.3067, found: 628.3068.

Synthesis of Compound 298

(2*S*,3*R*,6*S*,*E*)-2,6-Dimethylnon-4-ene-1,3-diol



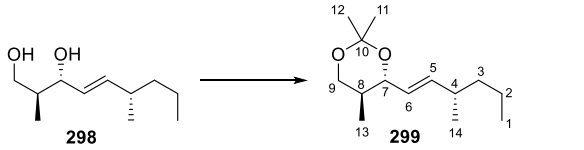
Chemical Formula: $C_{11}H_{22}O_2$
Exact Mass: 186,1620
Molecular Weight: 186,2950

Cleavage of the *Masamune* reagent was achieved by using reductive conditions. Therefore, compound **297** (15.00 mg, 24.76 µmol, 1.00 equiv) was dissolved in THF (0.25 mL) and cooled to 0 °C before $LiAlH_4$ (2.0 M in THF, 34.66 µL, 69.33 µmol, 2.80 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 1 hour. After that, brine (0.3 mL) was cautiously added over 5 minutes and the mixture was vigorously stirred for 2 hours. Then, the layers were separated and the aqueous layer was extracted with Et_2O (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, 1:1 CH/EE) to yield 3.60 mg of a colourless oil (19.31 µmol, 78%).

R_f = 0.18 (1:1 CH/EE). **α_D^{20}** = +24.3 ° (c = 1.12 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 5.54 – 5.50 (m, 1H, H-5), 5.45 – 5.41 (m, 1H, H-6), 3.94 – 3.91 (m, 1H, H-7), 3.66 (dd, *J* = 10.8, 3.9 Hz, 1H, H-9), 3.59 (dd, *J* = 10.8, 7.4 Hz, 1H, H-9'), 2.15 (dddd, *J* = 13.1, 7.6, 6.6, 1.0 Hz, 1H, H-4), 1.72 (ddtd, *J* = 14.2, 7.8, 7.0, 3.9 Hz, 1H, H-8), 1.35 – 1.24 (m, 4H, H-2, H-3), 0.99 (d, *J* = 6.7, 3H, H-11), 0.91 – 0.87 (m, 3H, H-1), 0.81 (d, *J* = 7.0 Hz, 3H, H-10). **^{13}C** NMR (CD_2Cl_2, 175 MHz) δ = 140.0 (C-5), 130.5 (C-6), 79.3 (C-7), 67.9 (C-9), 41.0 (C-8), 39.6 (C-3), 36.7 (C-4), 20.9 (C-2), 20.8 (C-11), 14.3 (C-1), 13.8 (C-10). **HRMS (ESI)** *m/z*: calcd for $C_{11}H_{23}O_3$ $[M + H]^+$: 187.1693, found: 187.1695.

Synthesis of Compound 299

(4*R*,5*S*)-2,2,5-Trimethyl-4-((*S*,*E*)-3-methylhex-1-en-1-yl)-1,3-dioxane



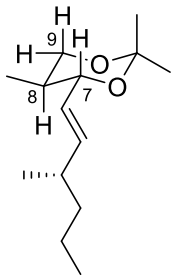
Chemical Formula: $C_{14}H_{26}O_2$
Exact Mass: 226,1933
Molecular Weight: 226,3600

Diol **298** (4.40 mg, 23.62 µmol, 1.00 equiv) was dissolved in DCM (0.34 mL) and 2,2-DMP (144.70 µL, 1.18 mmol, 50.00 equiv) was added followed by the addition of *para*-toluenesulfonic acid (406.71 µg, 2.36 µmol, 0.10 equiv) before the reaction was stirred at room temperature for 2 hours. Afterwards, $NaHCO_3$ (1 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (3 x 1 mL). The combined organic layers were dried over $MgSO_4$, the solvent evaporated in vacuo and the crude product purified by column chromatography (SiO_2, 10:1 CH/EE) yielding 4.12 mg (18.20 µmol, 77%) of a colourless oil.

R_f = 0.26 (10:1 CH/EE). **α_D^{20}** = +19 ° (c = 1.03 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 5.52 (ddd, *J* = 15.4, 7.9, 0.7 Hz, 1H, H-5), 5.29 – 5.24 (m, 1H, H-6), 3.82 (dd, *J* = 10.2, 7.7 Hz, H-7), 3.68 (ddd, *J* = 11.7, 5.2, 1.4 Hz, 1H, H-9), 3.51 (t, *J* = 11.5 Hz, 1H, H-9), 2.18 – 2.10 (m, 1H, H-4), 1.59 (ddqd, *J* = 11.8, 10.0, 6.7, 5.1 Hz, 1H, H-8), 1.44 (dd, *J* = 1.3, 0.7 Hz, 6H, H-11, H-12), 1.32 – 1.22 (m, 4H, H-2, H-3), 0.99 (d, *J* = 6.7 Hz, 3H, H-14), 0.88 (ddt, *J* = 7.9, 5.9, 1.2 Hz, 3H, H-1), 0.69 (dd, *J* = 6.7, 2.1 Hz, 3H, H-13). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 140.9 (C-5), 128.0 (C-6), 98.4 (C-10), 77.8 (C-7), 66.2 (C-9), 39.6 (C-3), 36.8 (C-4), 34.6 (C-8), 30.1 (C-11/C-12), 27.4 (C-), 20.9

(C-2), 20.7 (C-14), 19.4 (C-11/C-12), 14.3 (C-1), 12.8 (C-13). **HRMS (ESI)** m/z: calcd for $C_{14}H_{27}O_2$ $[M + H]^+$: 227.2006, found: 227.2004

Table 14: Confirmation of the given structure by the ^1H-^1H coupling constants.

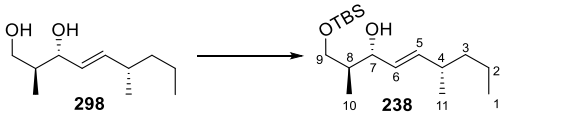


$^3J_{H\text{-}7,\ H\text{-}8}$ = 10.2 Hz

$^3J_{H\text{-}8,\ H\text{-}7}$ = 10.0 Hz

Synthesis of Compound 238

(2*S*,3*R*,6*S*,*E*)-1-((*Tert*-butyldimethylsilyl)oxy)-2,6-dimethylnon-4-en-3-ol



Chemical Formula: $C_{17}H_{36}O_2Si$
Exact Mass: 300,2485
Molecular Weight: 300,5580

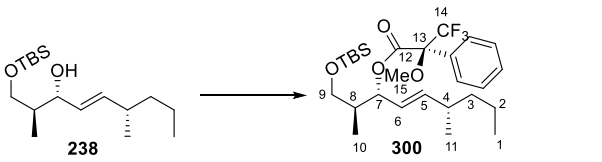
The obtained diol **298** (17.80 mg, 95.55 µmol, 1.00 equiv) was dissolved in DCM (0.32 mL) and cooled to 0 °C followed by the addition of imidazole (9.76 mg, 143.32 µmol, 1.50 equiv) and *tert*-butyldimethylsilyl chloride (12.96 mg, 85.99 µmol, 0.90 equiv) dissolved in DCM (0.19 mL) before the solution was stirred at 0 °C for 25 minutes. Hereafter, NH_4Cl (1 mL) was added, the layers separated and the aqueous layer extracted with DCM (3 x 1 mL). Subsequently, the combined organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, 10:1 CH/EE) to obtain a colourless oil (17.60 mg, 58.56 µmol, 61%).

$\mathbf{R_f}$ = 0.27 (10:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +33 ° (c = 1.0 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 5.49 (ddd, *J* = 15.2, 7.8, 0.9 Hz, 1H, H-5), 5.38 (ddd, *J* = 15.4, 7.1, 0.9 Hz, 1H, H-6), 3.92 (dt, *J* = 7.4, 3.8 Hz, 1H, H-7), 3.75 (dd, J = 10.0, 4.4 Hz, 1H, H-9), 3.57 (dd, *J* = 10.0, 7.1 Hz, 1H, H-9'), 3.24 (d, *J* = 3.3 Hz, 1H), 2.14 (p, *J* = 6.8 Hz, 1H, H-4), 1.74 – 1.64 (m, 1H, H-8), 1.31 – 1.23 (m, 4H, H-2, H-3), 0.98 (d, *J* = 6.7 Hz, 3H, H-11), 0.90 (s, 9H, $C(CH_3)_3$), 0.88 (t, *J* = 7.0 Hz, 3H, H-1), 0.82 (dd, *J* = 7.0, 1.8 Hz, 3H, H-10), 0.07 (s, 6H, 2 x CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 138.7 (C-5), 130.5 (C-6), 77.8 (C-7), 68.0 (C-9), 40.8 (C-8), 39.6 (C-3), 36.7 (C-4), 27.3 ($C(CH_3)_3$), 26.0 (2 x CH_3-Si),

20.9 (C-11, C-2), 14.3 (C-1), 13.6 (C-10). **HRMS (ESI)** *m/z*: calcd for $C_{17}H_{36}O_2SiNa$ $[M + Na]^+$: 323.2377, found: 323.2373.

Synthesis of Compound 300

(2*S*,3*R*,6*S*,*E*)-1-((*Tert*-butyldimethylsilyl)oxy)-2,6-dimethylnon-4-en-3-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

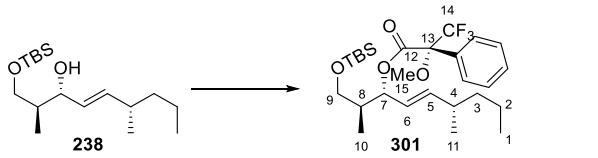


Mono-protected alcohol **238** (5.60 mg, 18.63 µmol, 1.00 equiv) was preloaded into a vial alongside dry pyridine (4.80 µL, 59.62 µmol, 3.20 equiv) and both substances were dissolved in DCM (0.29 mL). Then, (*R*)-MTPA-Cl (6.62 µL, 35.40 µmol, 1.90 equiv) was added and the reaction mixture stirred at room temperature overnight. The reaction was partitioned between water (0.5 mL) and Et_2O (0.5 mL) and the layers separated. Then, the aqueous layer was extracted with Et_2O (3 x 0.5 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The crude product was purified by column chromatography (SiO2, 10:1 CH/EE) to yield 3.20 mg (6.19 µmol, 33%) of a colourless oil.

$\mathbf{R_f}$ = 0.39 (10:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +11.3 ° (c = 0.46 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.41 – 7.39 (m, 5H, H_{arom}), 5.75 (dd, *J* = 15.1, 8.0 Hz, 1H, H-5), 5.55 – 5.37 (m, 1H, H-6), 3.52 (q, *J* = 1.2 Hz, 3H, OMe), 3.48 – 3.41 (m, 3H, H-7, H-9), 2.17 (d, *J* = 7.2 Hz, 1H, H-4), 1.95 (ddd, *J* = 12.7, 7.1, 5.9 Hz, 1H, H-8), 1.32 – 1.23 (m, 4H, H-2, H-3), 0.97 (d, *J* = 6.7 Hz, 3H, H-11), 0.89 (d, *J* = 1.0 Hz, 9H, $C(CH_3)_3$-Si), 0.88 – 0.86 (m, 3H, H-1), 0.83 (d, *J* = 6.9 Hz, 3H, H-10), 0.01 (dd, *J* = 3.7, 1.5 Hz, 6H, CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 166.8 (C-12), 144.6 (C-5), 130.7 (C-6), 129.9 (C_{arom}), 129.2 (C_{arom}), 127.3 (C_{arom}), 79.5 (C-7), 64.5 (C-9), 55.7 (C-OMe), 39.8 (C-8), 39.3 (C-3), 36.9 (C-4), 30.5 (C_q-TBS), 26.1 ($C(CH_3)_3$-Si), 20.9 (C-11), 20.6 (C-2), 14.3 (C-1), 12.7 (C-10), 1.2 (C-), -5.4 (2 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{27}H_{44}F_3O_4Si$ $[M + H]^+$: 517.2955, found: 517.2951.

Synthesis of Compound 301

(2*S*,3*R*,6*S*,*E*)-1-((*Tert*-butyldimethylsilyl)oxy)-2,6-dimethylnon-4-en-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

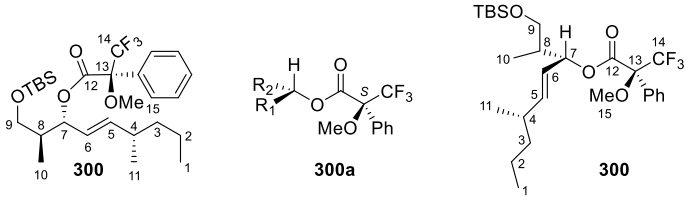


Alcohol **238** (5.60 mg, 18.63 µmol, 1.00 equiv) was preloaded into the reaction vial as well as dry pyridine (4.80 µL, 59.62 µmol, 3.20 equiv) before both compounds were dissolved in DCM (0.29 mL) and (*S*)-MTPA-Cl (6.62 µL, 35.40 µmol, 1.90 equiv) was added. After that, the mixture was stirred at room temperature overnight. Subsequently, the latter was partitioned between water (0.5 mL) and Et_2O (0.5 mL), the layers were separated and the aqueous layer extracted with Et_2O (3 x 0.5 mL). Then, the combined organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure. The crude product was purified by column chromatography yielding 2.90 mg (5.61 µmol, 30%) of a slightly yellow oil.

$\mathbf{R_f}$ = 0.46 (10:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +5.6 ° (c = 0.36 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.44 (ddd, *J* = 4.9, 3.4, 2.1 Hz, 5H, H_{arom}), 5.68 (dd, *J* = 15.5, 8.0 Hz, 1H, H-5), 5.50 – 5.44 (m, 1H, H-6), 3.53 (d, *J* = 1.2 Hz, 3H, OMe), 3.51 – 3.48 (m, 3H; H-7, H-9), 1.30 – 1.22 (m, 4H, H-2, H-3), 0.96 (d, *J* = 6.7 Hz, 3H, , H-11), 0.90 (s, 9H, $C(CH_3)_3$-Si), 0.91 – 0.85 (m, 3H, H-1), 0.88 (d, *J* = 3.1 Hz, 3H, H-10), 0.03 (d, *J* = 1.6 Hz, 6H, CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 161.1 (C-12), 144.1 (C-5), 131.0 (C_{arom}), 130.7 (C-6), 129.2 (C_{arom}), 127.3 (C_{arom}), 79.4 (C-7), 64.6 (C-9), 56.3 (C-OMe), 39.8 (C-8), 39.3 (C-3), 36.9 (C-4), 30.5 (C_q-TBS), 26.1 ($C(CH_3)_3$-Si), 20.9 (C-11), 20.6 (C-2), 14.3 (C-1), 12.8 (C-10), -5.4 (CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{27}H_{44}F_3O_4Si$ $[M + H]^+$: 517.2955, found: 517.2953.

*Table 15: Evaluation of ^{1}H-NMR of the achieved diastereomers. The difference in chemical shifts for each of the analogous pairs of protons for the S- and R-MTPA esters **300** and **301** were determined.*

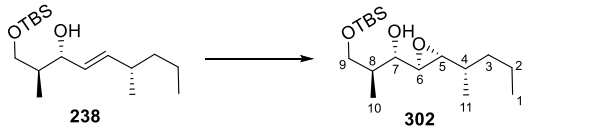
# H	δ S-ester [ppm]	δ R-ester [ppm]	$\Delta\delta^{S-R}$ [ppm]	$\Delta\delta^{S-R}$ [Hz]
5	5.75	5.68	0.07	49
4	2.17	2.15	0.02	14
3	1.27	1.25	0.02	14
2	1.27	1.25	0.02	14
1	0.89	0.88	0.01	7
11	0.97	0.96	0.01	7
8	1.95	1.99	- 0.04	- 28
9	3.45	3.50	- 0.05	- 35
10	0.83	0.88	- 0.05	- 35
TBS	0.01	0.03	- 0.02	- 14



As the $\Delta\delta^{S-R}$ values for H-5, H-4, H-3, H-2, H-1, H-11 are positive those protons belong to R_1 while H-8, H-9, H-10 and the protons of the TBS-group go with R_2. Thus, the configuration of the newly formed stereocenter in compound **238** is confirmed to be (*R*).

Synthesis of Compound 302

(1*S*,2*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-2-methyl-1-((2*R*,3*R*)-3-((*S*)-pentan-2-yl)oxiran-2-yl)propan-1-ol



Chemical Formula: $C_{17}H_{36}O_3Si$
Exact Mass: 316,2434
Molecular Weight: 316,5570

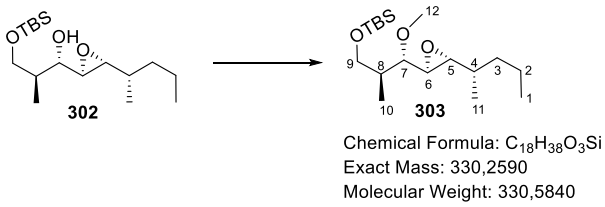
(+)-DIPT (2.53 µL, 12.08 µmol, 0.30 equiv) was dissolved in DCM (0.13 mL) and stirred over flame dried crushed 3 Å MS for 30 minutes at room temperature. Then, the mixture was cooled to -30 °C and Ti(*i*-OPr)$_4$ (4.77 µL, 16.10 µmol, 0.40 equiv) as well as *tert*-butyl hydroperoxide (29.19 µL, 261.68 µmol, 6.50 equiv) were added dropwise followed by stirring of the mixture at -30 °C for 30 minutes. Hereafter, mono-protected allylic alcohol **238** (12.10 mg, 40.26 µmol, 1.00 equiv) was dissolved in DCM (0.1 mL) and slowly added to the reaction which continued stirring at -30 °C for 44 hours. The molecular sieves were removed

from the mixture by filtration over Celite and washing with DCM. Afterwards, 2 M NaOH (3 mL) was added and the biphasic mixture stirred vigorously for 1 hour at room temperature. The layers were separated and the aqueous layer extracted with DCM (3 x 3 mL). Adjecently, the combined organic layers were dried over $MgSO_4$, concentrated in vacuo and the crude product purified by column chromatography (SiO_2, 10:1 CH/EE) to observe the desired product as a colourless oil (13.40 mg, 42.33 µmol, quant).

R_f = 0.23 (10:1 CH/EE). **α_D^{20}** = +41.3 ° (c = 0.46 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 3.81 (dd, *J* = 10.0, 4.6 Hz, 1H, H-9), 3.67 – 3.62 (m, 1H, H-9'), 3.44 (ddd, *J* = 7.4, 4.9, 2.9 Hz, 1H, H-7), 3.15 (d, *J* = 3.1 Hz, 1H, OH), 2.76 (dt, *J* = 4.2, 2.9 Hz, 1H, H-6), 2.71 (dd, *J* = 7.3, 2.4 Hz, 1H, H-5), 1.84 (pd, *J* = 6.8, 4.5 Hz, 1H, H-8), 1.53 – 1.21 (m, 5H, H-2, H-3, H-4), 0.99 (d, *J* = 6.9 Hz, 3H, H-10), 0.94 (d, *J* = 6.8 Hz, 3H, H-11), 0.90 (d, *J* = 0.8 Hz, 12H, H-1, 3 x CH_3-TBS), 0.08 (s, 6H, 2 x CH_3-TBS). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 74.5 (C-7), 67.4 (C-9), 60.6 (C-5), 58.8 (C-6), 39.5 (C-8), 37.2 (C-3), 35.6 (C-4), 26.0 (3 x CH_3-TBS), 20.5 (C-2), 16.0 (C-11), 14.5 (C-1), 13.2 (C-10), -5.5 (2 x CH_3-TBS). **HRMS (ESI)** *m/z*: calcd for $C_{17}H_{37}O_3Si$ $[M + H]^+$: 317.2506, found: 317.2496.

Synthesis of Compound 303

***Tert*-butyl((2*S*,3*S*)-3-methoxy-2-methyl-3-((2*S*,3*R*)-3-((*S*)-pentan-2-yl)oxiran-2-yl)propoxy)dimethylsilane**



Chemical Formula: $C_{18}H_{38}O_3Si$
Exact Mass: 330,2590
Molecular Weight: 330,5840

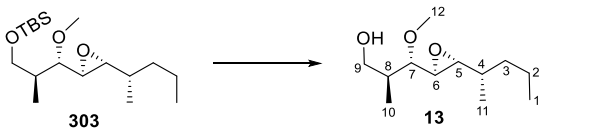
Sodium hydride (60% dispersion in mineral oil, 4.09 mg, 102.35 µmol, 6.00 equiv) was suspended in THF (0.17 mL) prior to adding epoxide **302** (5.40 mg, 17.06 µmol, 1.00 equiv) dissolved in THF (0.17 mL) at 0 °C. Then, a catalytic amount of DMAP (1.04 mg, 8.53 µmol, 0.50 equiv) as well as MeI (7.43 µL, 119.41 µmol, 7.00 equiv) were added to the reaction which was allowed to warm to room temperature and stirred for 16 hours. Afterwards, the reaction was quenched with NH_4Cl (0.50 mL), the layers were separated and the aqueous layer extracted with Et_2O (3 x 0.50 mL). The combined organic layers were washed with brine (1 x 2 mL), dried over $MgSO_4$ and the solvent evaporated under reduced pressure. As a last step,

the crude product was purified by column chromatography (SiO_2, 40:1 CH/EE) to observe 2.70 mg (8.17 µmol, 48%) of the desired product as a colourless oil.

R_f = 0.14 (40:1 CH/EE). **α_D^{20}** = +67.2 ° (c = 0.23 in CH_2Cl_2). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 3.65 (dd, *J* = 9.8, 5.1 Hz, 1H, H-9), 3.57 (dd, *J* = 9.8, 6.2 Hz, 1H, H-9'), 3.35 (s, 3H, H-12), 2.94 (t, *J* = 5.9 Hz, 1H, H-7), 2.74 – 2.68 (m, 2H, H-5, H-6), 1.93 – 1.84 (m, 1H, H-8), 1.51 – 1.23 (m, 5H, H-2, H-3, H-4), 0.98 (d, *J* = 7.0 Hz, 3H, H-10), 0.95 (d, *J* = 6.8 Hz, 3H, H-11), 0.93 – 0.90 (m, 3H, H-1), 0.90 (s, 9H, 3 x CH3-TBS), 0.05 (d, *J* = 0.9 Hz, 6H, 2 x CH3-TBS). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 82.1 (C-7), 64.9 (C-9), 61.7 (C-5), 58.9 (C-12), 56.9 (C-6), 40.2 (C-8), 37.3 (C-3), 35.9 (C-4), 26.1 (3 x CH3-TBS), 20.5 (C-2), 16.0 (C-11), 14.5 (C-1), 13.3 (C-10), -5.3 (2 x CH3-TBS). **HRMS (ESI)** *m/z*: calcd for $C_{18}H_{39}O_3Si$ $[M + H]^+$: 331.2663, found: 331.2659.

Synthesis of Compound 13

(2*S*,3*S*)-3-Methoxy-2-methyl-3-((2*S*,3*R*)-3-((*S*)-pentan-2-yl)oxiran-2-yl)propan-1-ol



Chemical Formula: $C_{12}H_{24}O_3$
Exact Mass: 216,1725
Molecular Weight: 216,3210

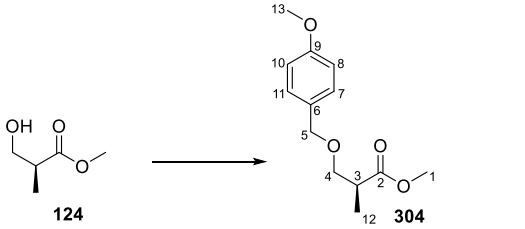
TBS-ether **303** (2.70 mg, 8.17 µmol, 1.00 equiv) was dissolved in THF (0.44 mL) and the stirred solution cooled to 0 °C. Then, TBAF (1.0 M in THF, 24.50 µL, 24.50 µmol, 3.00 equiv) was added dropwise to the solution at 0 °C and the resulting mixture was stirred at room temperature for 20 hours. Afterwards, water (1 mL) was added to the reaction, the layers were separated and the aqueous layer extracted with DCM (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, the solvent removed in vacuo and the crude product purified by column chromatography (SiO_2, packed with 10:1 CH/EE, eluted with 4:1 CH/EE) to observe the desired product as a colourless oil (600.00 µg, 2.77 µmol, 34%).

R_f = 0.11 (5:1 CH/EE). **α_D^{20}** = +65 ° (c = 0.43 in CH_2Cl_2). **^{1}H** NMR ($CDCl_3$, 700 MHz) δ = 3.73 (dt, *J* = 11.5, 4.6 Hz, 1H, H-9), 3.62 (ddd, *J* = 11.2, 6.6, 4.6 Hz, 1H, H-9'), 3.43 (s, 3H, H-12), 2.95 (dd, *J* = 6.3, 5.6 Hz, 1H, H-7), 2.76 (d, *J* = 1.1 Hz, 1H, H-6), 2.76 – 2.74 (m, 1H, H-5), 2.61 (t, *J* = 6.0 Hz, 1H, OH), 2.04 – 1.96 (m, 1H, H-8), 1.52 (ddt, *J* = 12.7, 10.3, 5.5 Hz, 1H, H-3), 1.47 – 1.33 (m, 3H, H-2, H-4), 1.29 (dddd, *J* = 12.7, 10.5, 7.7, 5.0 Hz, 1H, H-3'), 1.04 (d, *J* = 7.0 Hz, 3H, H-10), 0.98 (d, *J* = 6.8 Hz, 3H, H-11), 0.91 (t, *J* = 7.3 Hz, 3H, H-1). **^{13}C** NMR ($CDCl_3$, 175 MHz) δ = 85.5 (C-7),

66.2 (C-9), 62.5 (C-5), 58.9 (C-12), 56.5 (C-6), 38.8 (C-8), 36.9 (C-3), 35.7 (C-4), 20.2 (C-2), 16.0 (C-11), 14.4 (C-1), 13.3 (C-10). **HRMS (ESI)** *m/z*: calcd for $C_{12}H_{25}O_3$ $[M + H]^+$: 217.1798, found: 217.1798.

Synthesis of Compound 304

Methyl (*S*)-3-((4-methoxybenzyl)oxy)-2-methylpropanoate



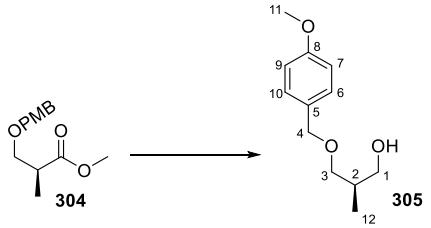
Chemical Formula: $C_{13}H_{18}O_4$
Exact Mass: 238,1205
Molecular Weight: 238,2830

(*S*)-*Roche* ester (**124**) (500.00 mg, 4.23 mmol, 1.00 equiv) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (1.20 g, 4.23 mmol, 1.00 equiv) were dissolved in DCM (8.46 mL). Camphorsulfonic acid (39.5 mg, 0.17 mmol, 0.04 equiv) was added and the reaction mixture stirred at room temperature for 19 hours. Afterwards 0.1 M NaOH (1.7 mL) was added. The aqueous layer was diluted with water, the layers were separated and the aqueous layer extracted with DCM (3 x 2 mL). The combined organic layers were washed with brine (1 x 8 mL) and dried over $MgSO_4$. Afterwards, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, 1:1 CH/EE) to obtain 806.34 mg (3.38 mmol, 80%) of a colourless oil.

$\mathbf{R_f}$ = 0.54 (1:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +7.0° (c = 1.00, in $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.24 – 7.20 (m, 2H, H-7, H-11), 6.89 – 6.84 (m, 2H, H-8, H-10), 4.41 (s, 2H, H-5), 3.79 (s, 3H, H-13), 3.65 (s, 3H, H-1), 3.60 (dd, *J* = 9.1, 7.2 Hz, 1H, H-4), 3.46 (dd, *J* = 9.1, 5.8 Hz, 1H, H-4'), 2.73 (pd, *J* = 7.1, 5.8 Hz, 1H, H-3), 1.14 (d, *J* = 7.1 Hz, 3H, H-12). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 175.5 (C-2), 159.7 (C-9), 130.9 (C-6), 129.6 (C-7, C-11), 114.0 (C-8, C-10), 73.1 (C-5), 72.2 (C-4), 55.6 (C-13), 51.9 (C-1), 40.6 (C-3), 14.1 (C-12). **HRMS (ESI)** *m/z*: calcd for $C_{13}H_{18}O_4Na$ $[M + Na]^+$: 261.1097, found: 261.1095.

Synthesis of Compound 305

(*R*)-3-((4-Methoxybenzyl)oxy)-2-methylpropan-1-ol



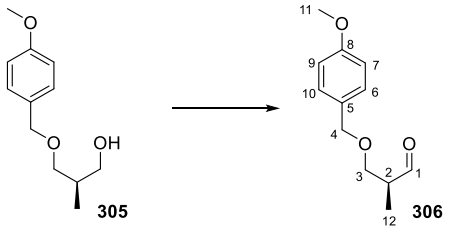
Chemical Formula: $C_{12}H_{18}O_3$
Exact Mass: 210,1256
Molecular Weight: 210,2730

PMB-protected (*S*)-*Roche* ester **304** (805.00 mg, 3.38 mmol, 1.00 equiv) was dissolved in THF (22.41 mL) and cooled to -78 °C. DIBAl-H (1.0 M in THF, 7.39 mL, 7.39, mmol, 2.20 equiv) was added dropwise to the cooled solution. After the addition the reaction mixture was allowed to warm to room temperature and stirred for an additional hour. Saturated aqueous potassium, sodium tartrate solution (22 mL) was added and the biphasic mixture stirred at room temperature for two hours until both layers appaered to be clear. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure before the crude product was purified by column chromatography (SiO_2, 1:1 CH/EE) to yield a slightly yellow liquid (639.65 mg, 3.04 mmol, 90%).

$\mathbf{R_f}$ = 0.31 (1:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +15.0° (c = 1.00 , in $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 7.27 – 7.22 (m, 2H, H-6, H-10), 6.89 – 6.85 (m, 2H, H-7, H-9), 4.42 (d, *J* = 1.4 Hz, 2H, H-4), 3.79 (s, 3H, H-11), 3.56 – 3.52 (m, 2H, H-1), 3.50 (ddd, *J* = 9.1, 4.8, 0.5 Hz, 1H, H-3), 3.39 (dd, *J* = 9.1, 7.8 Hz, 1H, H-3‘), 2.03 – 1.96 (m, 1H, H-2), 0.86 (d, *J* = 7.0 Hz, 3H, H-12). **^{13}C** NMR (CD_2Cl_2, 125 MHz) δ = 159.7 (C-8), 130.9 (C-5), 129.6 (C-6, C-10), 114.1 (C-7, C-9), 75.4 (C-3), 73.3 (C-4), 67.9 (C-1), 55.6 (C-11), 36.2 (C-2), 13.7 (C-12). **HRMS (ESI)** *m/z*: calcd for $C_{12}H_{18}O_3Na$ $[M + Na]^+$: 233.1148, found: 233.1148.

Synthesis of Compound 306

(*S*)-3-((4-Methoxybenzyl)oxy)-2-methylpropanal



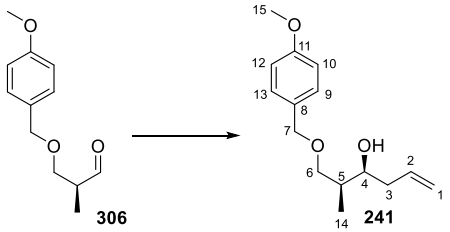
Chemical Formula: $C_{12}H_{16}O_3$
Exact Mass: 208,1099
Molecular Weight: 208,2570

Alcohol **305** was transformed to the respective aldehyde under *Parikh-Doering* conditions. Thus, SO_3*pyridine complex (1.48 g, 6.18 mmol, 3.25 equiv) was preloaded into the reaction flask and dissolved in DMSO (9.50 mL). The solution was stirred for five minutes at room temperature prior to cooling it to 0 °C and adding DIPEA (0.99 ml, 5.71 mmol, 3.00 equiv) dropwise. Then, the alcohol **305** (400.00 mg, 1.90 mmol, 1.00 equiv) was dissolved in DCM (9.50 mL) and added dropwise to the stirred solution which continued stirring at 0 °C for 45 minutes. After that, $NaHCO_3$ (20 mL) was added to quench the reaction, the layers were separated and the aqueous layer extracted with DCM (3 x 20 mL). Hereafter, the combined organic layers were washed with $CuSO_4$ (2 x 60 mL), NH_4Cl (2 x 60 mL) and brine (1 x 60 mL) before they were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was used in the next reaction without further purification (356.12 mg, 1.71 mmol, 90%).

$\mathbf{R_f}$ = 0.30 (4:1 CH/EE).$\boldsymbol{\alpha_D^{20}}$ = +29.0° (c = 1.00 , in $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 9.67 (d, *J* = 1.6 Hz, 1H, H-1), 7.25 – 7.21 (m, 2H, H-6, H-10), 6.89 – 6.85 (m, 2H, H-7, H-9), 4.43 (d, *J* = 0.6 Hz, 2H, H-4), 3.79 (s, 3H, H-11), 3.68 – 3.59 (m, 2H, H-3), 2.66 – 2.56 (m, 1H, H-2), 1.09 (d, *J* = 7.1 Hz, 3H, H-12). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 204.1 (C-1), 159.8 (C-8), 130.7 (C-5), 129.6 (C-6, C-10), 114.1 (C-7, C-9), 73.3 (C-4), 70.4 (C-3), 55.6 (C-11) 47.3 (C-2), 10.9 (C-12). **HRMS (ESI)** *m/z*: calcd for $C_{12}H_{16}O_3Na$ $[M + Na]^+$: 231.0992, found: 231.0997.

Synthesis of Compound 241

(2*S*,3*S*)-1-((4-Methoxybenzyl)oxy)-2-methylhex-5-en-3-ol



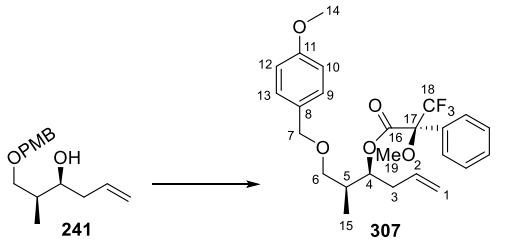
Chemical Formula: $C_{15}H_{22}O_3$
Exact Mass: 250,1569
Molecular Weight: 250,3380

In a pressure tube (-)-$(Ipc)_2$BOMe (667.78 mg, 2.11 mmol, 1.25 equiv) was dissolved in Et_2O (2.11 mL) and the solution cooled to 0 °C. Then, allyl MgBr (1.0 M in Et_2O, 2.03 ml, 2.03 mmol, 1.20 equiv) was added to the solution over five minutes. The reaction mixture was stirred at 0 °C for 75 minutes before it was cooled to -78 °C and aldehyde **306** (351.70 mg, 1.69 mmol, 1.00 equiv) dissolved in Et_2O (1.25 mL) was added over 15 minutes. Afterwards, the mixture was kept at -78 °C and stirred for three hours. After that, it was diluted with THF (6.3 mL), 3 M NaOH (3.2 mL) and 35% H_2O_2 (3.13 mL) at -78 °C, allowed to warm to room temperature and then refluxed at 70 °C for an hour. Thereafter, the reaction mixture was cooled to room temperature, the layers were separated and the aqueous layer extracted with Et_2O (3 x 6 mL) followed by washing the combined organic layers with $Na_2S_2O_3$ (2 x 20 mL). The organic phase was dried over $MgSO_4$, the solvent removed under reduced pressure and the crude product purified by column chromatography (SiO_2, packed in 20:1 CH/EE, eluted first with 15:1 CH/EE, then 10:1 CH/EE) yielding 300.00 mg (1.20 mmol, 71%) of a colourless oil.

R_f = 0.17 (4:1 CH/EE). **α_D^{20}** = - 4.0° (c = 1.00 , in $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.26 – 7.23 (m, 2H, H-9, H-13), 6.89 – 6.85 (m, 2H, H-10, H-12), 5.84 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H, H-2), 5.11 – 5.04 (m, 2H, H-1), 4.44 – 4.39 (m, 2H, H-7), 3.79 (s, 3H, H-15), 3.76 (ddt, *J* = 9.7, 6.7, 2.9 Hz, 1H, H-4), 3.50 – 3.44 (m, 2H, H-6), 2.19 (tt, *J* = 7.2, 1.3 Hz, 2H, H-3), 1.88 – 1.83 (m, 1H, H-5), 0.93 – 0.90 (m, 3H, H-14). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 159.7 (C-11), 136.4 (C-2), 130,9 (C-8), 129.6 (C-9, C-13), 117.0 (C-1), 114.1 (C-10, C-12), 74.6 (C-6), 73.3 (C-4), 73.3 (C-7), 55.6 (C-15), 39.3 (C-3), 38.0 (C-5), 10.9 (C-14). **HRMS (ESI)** *m/z*: calcd for $C_{15}H_{23}O_3$ $[M + H]^+$: 251.1642, found: 251.1637.

Synthesis of Compound 307

(2*S*,3*S*)-1-((4-Methoxybenzyl)oxy)-2-methylhex-5-en-3-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

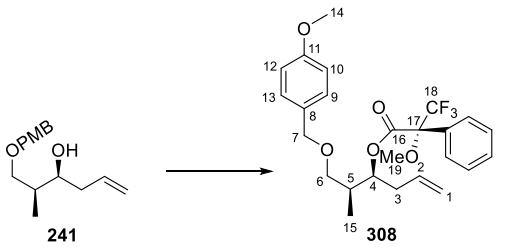


Olefin **241** (5.00 mg, 19.97 µmol, 1.00 equiv) as well as dry pyridine (4.99 µL, 61.92 µmol, 3.10 equiv) were dissolved in DCM (0.18 mL) and (*R*)-MTPA-Cl (7.10 µL, 37.95 µmol, 1.90 equiv) was added. The reaction was stirred at room temperature over night before the mixture was partitioned between water (0.5 mL) and Et_2O (0.5 mL), the layers were sepearted and the aqueous layer extracted with Et_2O (3 x 0.5 mL). Afterwards, the combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo. A slightly yelloe oil was obtained (9.05 mg, 19.40 µmol, 97%).

R_f = 0.24 (8:1 CH/EE). **α_D^{20}** = - 3.2 ° (c = 0.93, in $CHCl_3$). **^{1}H** NMR ($CDCl_3$, 500 MHz) δ = 7.54 – 7.49 (m, 2H, H_{arom}), 7.43 – 7.33 (m, 3H, H_{arom}), 7.24 (d, *J* = 8.7 Hz, 2H, H-9, H-13), 6.87 (d, *J* = 8.7 Hz, 2H, H-10, H-12), 5.67 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H, H-2), 5.40 – 5.34 (m, 1H, H-4), 5.08 – 4.98 (m, 2H, H-1), 4.38 (d, *J* = 5.4 Hz, 2H, H-7), 3.80 (s, 3H, H-14), 3.47 (s, 3H, H-19), 3.26 (d, *J* = 6.5 Hz, 2H, H-6), 2.48 – 2.39 (m, 1H, H-3), 2.37 – 2.28 (m, 1H, H-3'), 2.12 – 2.03 (m, 1H, H-5), 0.92 (d, *J* = 7.0 Hz, 3H, H-15). **^{13}C** NMR ($CDCl_3$, 126 MHz) δ = 166.0 (C-16), 159.1 (C-11), 133.1 (C-8),132.1 (C-2), 130.3 (C_{arom}), 129.4 (C-9, C-13), 129.1 (C_{arom}), 128.2 (C_{arom}), 127.6 (C_{arom}), 118.1 (C-1, C-18), 113.7 (C-10, C-12), 76.3 (C-4, C-17), 72.7 (C-7), 71.6 (C-6), 55.2 (C-14, C-19), 36.3 (C-5), 36.1 (C-3), 11.0 (C-15). **HRMS (ESI)** *m/z*: calcd for $C_{25}H_{29}F_3O_5Na$ $[M + Na]^+$: 489.1853, found: 489.1853.

Synthesis of Compound 308

(2*S*,3*S*)-1-((4-Methoxybenzyl)oxy)-2-methylhex-5-en-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate



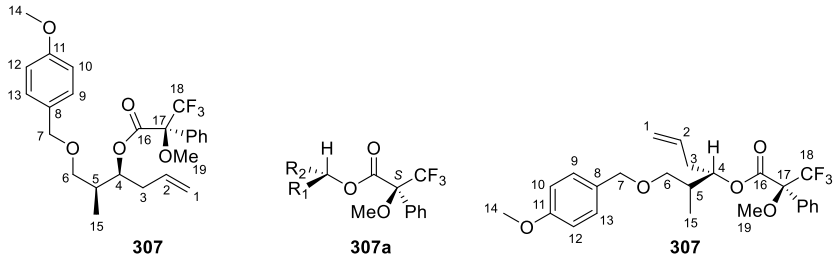
Chemical Formula: $C_{25}H_{29}F_3O_5$
Exact Mass: 466,1967
Molecular Weight: 466,4972

Alcohol **241** (5.00 mg, 19.97 µmol, 1.00 equiv) was mixed with dry pyridine (4.99 µL, 61.92 µmol, 3.10 equiv) and both compounds were dissolved in DCM (0.18 mL) prior to the addition of (*S*)-MTPA-Cl (7.10 µL, 37.95 µmol, 1.90 equiv). The reaction was stirred at room temperature overnight before the mixture was partitioned between water (0.5 mL) and Et_2O (0.5 mL), the layers were sepearted and the aqueous layer extracted with Et_2O (3 x 0.5 mL). Afterwards, the combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo. After that, a slightly yellow oil was obtained (9.01 mg, 19.32 µmol, 97%).

$\mathbf{R_f}$ = 0.22 (8:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = +29.0° (c = 1.00 , in $CHCl_3$). **^{1}H** NMR ($CDCl_3$, 500 MHz) δ = 7.59 – 7.52 (m, 2H, H_{arom}), 7.44 – 7.32 (m, 3H, H_{arom}), 7.23 (d, *J* = 8.6 Hz, 2H, H-9, H-13), 6.87 (d, *J* = 8.6 Hz, 2H, H-10, H-12), 5.75 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H, H-2), 5.43 – 5.37 (m, 1H, H-4), 5.13 – 5.04 (m, 2H, H-1), 4.33 (d, *J* = 11.5 Hz, 2H, H-7), 3.80 (s, 3H, H-14), 3.53 (s, 3H, H-19), 3.21-3.10 (m, 2H, H-6), 2.54 – 2.46 (m, 1H, H-3), 2.44 – 2.35 (m, 1H, H-3‘), 2.09 – 2.02 (m, 1H, H-5), 0.86 (d, *J* = 7.0 Hz, 3H, H-15). **^{13}C** NMR ($CDCl_3$, 126 MHz) δ = 166.2 (C-16), 159.4 (C-11), 133.5 (C-8),132.6 (C-2), 130.6 (C_{arom}), 129.6 (C-9, C-13), 129.4 (C_{arom}), 128.4 (C_{arom}), 127.6 (C_{arom}), 118.4 (C-1, C-18), 114.0 (C-10, C-12), 76.5 (C-4, C-17), 73.0 (C-7), 71.7 (C-6), 55.6 (C-14), 55.4 (C-19), 36.4 (C-3), 36.0 (C-5), 11.0 (C-15). **HRMS (ESI)** *m/z*: calcd for $C_{25}H_{29}F_3O_5Na$ $[M + Na]^+$: 489.1853, found: 489.1859.

*Table 16: Evaluation of ^{1}H-NMR of the achieved diastereomers. The difference in chemical shifts for each of the analogous pairs of protons for the S- and R-MTPA esters **307** and **308** were determined.*

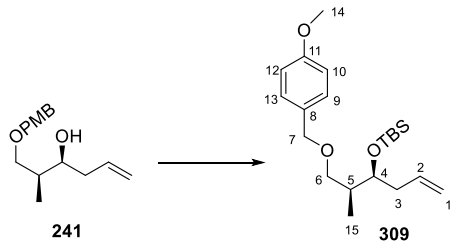
# H	δ *S*-ester [ppm]	δ *R*-ester [ppm]	$\Delta\delta^{S-R}$ [ppm]	$\Delta\delta^{S-R}$ [Hz]
5	2.08	2.06	0.02	10
6	3.26	3.16	0.10	50
7	4.38	4.33	0.05	25
9, 13	7.24	7.23	0.01	5
15	0.92	0.86	0.06	30
3	2.44	2.50	- 0.06	- 30
3'	2.33	2.40	- 0.07	- 35
2	5.67	5.75	- 0.08	- 40
1	5.03	5.09	- 0.06	- 30



Due to the assignement of H-5, H-6, H-7, H-9, H-13 and H-15 to R_1 and H-3, H-3', H-2 and H-1 to R_2 it can be deduced that the configuration of the secondary alcohol in compound **241** has to be (*S*).

Synthesis of compound 309

***Tert*-butyl(((2*S*,3*S*)-1-((4-methoxybenzyl)oxy)-2-methylhex-5-en-3-yl)oxy)dimethylsilane**



Chemical Formula: $C_{21}H_{36}O_3Si$
Exact Mass: 364,2434
Molecular Weight: 364,6010

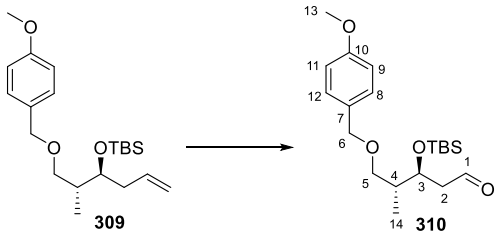
Compound **241** (269.30 mg, 1.08 mmol, 1.00 equiv) was dissolved in DCM (2.63 mL) and the solution was treated with 2,6-lutidine (187.94 µL, 1.61 mmol, 1.50 equiv) before the reaction mixture was cooled to 0 °C. Then, TBSOTf (370.58 µL, 1.61 mmol, 1.50 equiv) was added dropwise and the mixture continued stirring at 0 °C for two hours. Afterwards, water (4 mL) was added, the layers separated and the aqueous layer extracted with DCM (3 x 4 mL). Subsequently, the combined organic layers were dried over $MgSO_4$, the solvent was

evaporated under reduced pressure and the crude product purified by column chromatography (SiO_2, 50:1 CH/EE) yielding 264.70 mg (726.00 µmol, 68%) of a slightly yellow oil.

R_f = 0.10 (30:1 CH/EE). **α_D^{20}** = -6.0° (c = 1.00, $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.25 – 7.22 (m, 2H, H-9, H-13), 6.88 – 6.84 (m, 2H, H-10, H-12), 5.77 (dddd, *J* = 17.1, 10.1, 7.5, 6.9 Hz, 1H, H-2), 5.06 – 4.97 (m, 2H, H-1), 4.42 – 4.32 (m, 2H, H-7), 3.85 (ddd, *J* = 7.4, 5.9, 3.0 Hz, 1H, H-4), 3.79 (s, 3H, H-14), 3.42 (dd, *J* = 9.0, 7.1 Hz, 1H, H-6), 3.24 (dd, *J* = 9.0, 6.5 Hz, 1H, H-6'), 2.28 – 2.15 (m, 2H, H-3), 1.86 (hd, *J* = 6.9, 2.9 Hz, 1H, H-5), 0.88 (d, *J* = 0.8 Hz, 9H, $C(CH_3)_3$), 0.86 (d, *J* = 6.9 Hz, 3H, H-15), 0.06 – 0.03 (m, 6H, 2 x CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 159.5 (C-11), 136.0 (C-2), 131.4 (C-8), 129,6 (C-9, C-13), 129.4 (C-10, C-12), 116.7 (C-1), 73.2 (C-6), 72.9 (C-7), 72.2 (C-4), 55.6 (C-14), 40.0 (C-3), 37.9 (C-5), 26.1 ($C(CH_3)_3$), 18.4 (C_q-TBS), 10.8 (C-15), -4.0 (CH_3-Si), -4.7 (CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{21}H_{37}O_3Si$ $[M + H]^+$: 365.2506, found: 365.2506.

Synthesis of Compound 310

(3*S*,4*S*)-3-((*Tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-4-methylpentanal



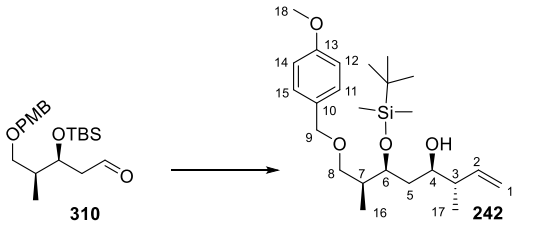
Chemical Formula: $C_{20}H_{34}O_4Si$
Exact Mass: 366,2226
Molecular Weight: 366,5730

Olefin **309** (443.40 mg, 1.22 mmol, 1.00 equiv) was dissolved in DCM/MeOH (14:1, 27.73 mL) and ten drops of a 0.1% Sudan III solution (in DCM) were added staining the solution slightly red. Afterwards, the reaction mixture was cooled to -78 °C and a stream of ozone was bubbled through the solution until it turned colourless. Remaining ozone was purged with Argon before PPh_3 (478.47 mg, 1.82 mmol, 1.50 equiv) was added and the solution warmed to room temperature. It was continued stirring at room temperature for 90 minutes before the solvent was evaporated under reduced pressure and the crude product purified by column chromatography (SiO_2, packed with 30:1 CH/EE, eluted with 20:1 CH/EE) yielding 333.00 mg of a colourless oil (908.41 µmol, 75%).

$\mathbf{R_f}$ = 0.28 (7:1 CH:EE). $\boldsymbol{\alpha_D^{20}}$ = -6.0° (c = 1.00, $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 500 MHz) δ = 9.75 (t, *J* = 2.4 Hz, 1H, H-1), 7.26 – 7.23 (m, 2H, H-8, H-12), 6.89 – 6.85 (m, 2H, H-9, H-11), 4.39 (d, *J* = 6.1 Hz, 2H, H-6), 4.37 – 4.32 (m, 1H, H-3), 3.79 (s, 3H, H-13), 3.45 (dd, *J* = 9.2, 6.7 Hz, 1H, H-5), 3.30 (dd, *J* = 9.1, 6.0 Hz, 1H, H-5'), 2.56 – 2.52 (m, 2H, H-2), 1.89 (pdd, *J* = 6.9, 6.0, 3.7 Hz, 1H, H-4), 0.91 (d, *J* = 6.9 Hz, 3H, H-14), 0.87 (s, 9H, $C(CH_3)_3$), 0.07 (s, 3H, CH_3-Si), 0.04 (s, 3H, CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 126 MHz) δ = 202.2 (C-1), 159.7 (C-10), 131.3 (C-7), 129.6 (C-8, C-12), 114.1 (C-9, C-11), 73.1 (C-5), 72.3 (C-6), 68.8 (C-3), 55.7 (C-13), 49.5 (C-4), 40.0 (C-2), 26.0 ($C(CH_3)_3$), 12.1 (C-14), -4.3 (2 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd. for $C_{20}H_{34}O_4SiNa^+$ $[M + Na]^+$: 389.2119, found: 389.213.

Synthesis of Compound 242

(3*S*,4*R*,6*S*,7*S*)-6-((*Tert*-butyldimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-3,7-dimethyloct-1-en-4-ol



Chemical Formula: $C_{24}H_{42}O_4Si$
Exact Mass: 422,2852
Molecular Weight: 422,6810

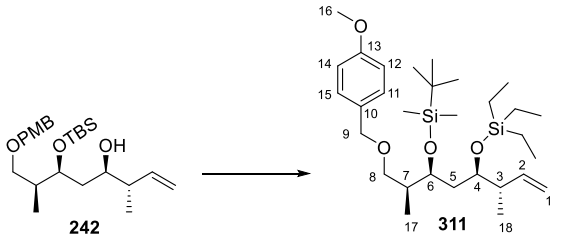
Potassium *tert*-butoxide (155.96 mg, 1.39 mmol, 1.53 equiv) was preloaded into a *Schlenk* tube, dispersed in THF (1.62 mL) and cooled to -78 °C. Then, *trans*-2-butene (50.97 mg, 908.41 µmol, 1.00 equiv) was condensed in a seperate tube and transferred to the reaction using a transfer cannula. *n*-BuLi (2.5 M in hexanes, 523.25 µL, 1.31 mmol, 1.44 equiv) was added over 30 minutes and the resulting yellow solution was allowed to warm to -45 °C, stirred at this temperature for 10 minutes before it was re-cooled to -78 °C. Thereafter, a solution of (-)-$(Ipc)_2$BOMe (445.41 mg, 1.41 mmol, 1.55 equiv) in THF (1.92 mL) was slowly added over 1 hour leading to a colourless reaction mixture which was stirred at -78 °C for one hour. To the latter BF_3*OEt_2 (218.62 µL, 1.77 mmol, 1.95 equiv) was added dropwise followed by the addition of a stock solution (dried over 3 Å MS at -20 °C o.n.) of aldehyde **310** (333.00 mg, 908.41 µmol, 1.00 equiv) in THF (1.94 mL) over 60 minutes. Afterwards, the solution was stirred for additional four hours at -78 °C prior to the addition of 2 M NaOH (8.72 mL) and 35% H_2O_2 (1.65 mL). The biphasic mixture was warmed to room temperature

and vigorously stirred overnight. Thereafter, the layers were separated and the aqueous layer extracted with Et_2O (3 x 10 mL) before the combined organic layers were washed with brine (1 x 30 mL) and dried over Na_2SO_4. Adjecently, the solvent was evaporated in vacuo and the crude product purified by column chromatography (SiO_2, packed with 15:1 CH/EE, eluted with 10:1 CH/EE) yielding 287.80 mg (680.89 µmol, 75%) of the desired product as a colourless oil.

R_f = 0.10 (10:1 CH/EE). **α_D^{20}** = -6.0° (c = 1.00, $CHCl_3$). **^{1}H** (CD_2Cl_2, 700MHz) δ = 7.24 - 7.22 (m, 2H, H-11, H-15), 6.88 - 6.85 (m, 2H, H-12, H-14), 5.80 (ddd, J = 17.1, 10.5, 7.7 Hz, 1H, H-2), 5.05 - 4.99 (m, 2H, H-1), 4.41 (d, J = 11.6 Hz, 1H, H-9), 4.34 (d, J = 11.6 Hz, 1H, H-9'), 4.07 (ddd, J = 8.5, 4.5, 3.7 Hz, 1H, H-6), 3.79 (s, 3H, H-18), 3.60 (ddt, J = 9.2, 4.7, 2.4 Hz, 1H, H-4), 3.30 (dd, J = 9.4, 7.8 Hz, 1H, H-8), 3.24 (dd, J = 9.4, 6.1 Hz, 1H, H-8'), 2.19 - 2.14 (m, 1H, H-3), 2.11 - 2.05 (m, 1H, H-7), 1.46 (dd, J = 4.5, 2.7 Hz, 1H, H-5), 1.42 - 1.39 (m, 1H, H-5'), 1.00 (d, J = 6.9 Hz, 3H, H-16), 0.90 (s, 9H, 3 x CH3), 0.88 (d, J = 7.0 Hz, 3H, H-17), 0.11 (s, 3H, CH3-Si), 0.10 (s, 3H, CH3-Si). **^{13}C** (CD_2Cl_2, 176 MHz) δ = 159.6 (C-13), 141.1 (C-2), 132.3 (C-10), 129.5 (C-11, C-15), 115.1 (C-1), 114.0 (C-12, C-14), 74.2 (C-4, C-6), 73.0 (C-9), 72.6 (C-8), 55.6 (C-18), 44.3 (C-3), 39.4 (C-7), 35.4 (C-5), 26.0 (3 x CH3), 18.3 (Cq-Si), 16.0 (C-16), 11.7 (C-17), -4.1 (CH3-Si), -4.5 (CH3-Si). **HRMS (ESI)** m/z: calcd for $C_{24}H_{42}O_4SiNa$ $[M + Na]^+$: 445.2745, found: 445.2739.

Synthesis of Compound 311

(5*S*,7*R*)-7-((*S*)-But-3-en-2-yl)-9,9-diethyl-5-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,3,3-tetramethyl-4,8-dioxa-3,9-disilaundecane



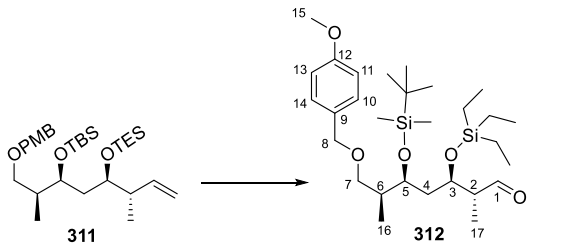
Imidazole (141.87 mg, 2.08 mmol, 8.00 equiv) was preloaded into the reaction flask and dried under HV for five minutes. Afterwards, secondary alcohol **242** (110.10 mg, 260.48 µmol, 1.00 equiv) was dissolved in DCM (2.61 mL) and added to the imidazole. The mixture was stirred at room temperature until the imidazole has mostly dissolved (five minutes). Then, triethylsilyl chloride (65.58 µL, 390.72 µmol, 1.50 equiv) was added and the resulting mixture

stirred at room temperature for 1.5 hours. Hereafter, another portion of TESCl (65.58 µL, 390.72 µmol, 1.50 equiv) was added and the reaction stirred at room temperature overnight. After that, NH_4Cl (5 mL) was added, the layers were separated and the aqueous layer extracted with DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ before the solvent was removed in vacuo. Lastly, the crude product was purified by column chromatography (SiO_2, 30:1 CH/EE) to obtain a colourless viscous oil (69.40 mg, 129.25 µmol, 50%).

R_f = 0.09 (30:1 CH/EE). **α_D^{20}** = -2.0° (c = 1.00, $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.24 (dq, *J* = 9.4, 2.5 Hz, 2H, H-11, H-15), 6.85 (dd, *J* = 8.9, 2.5 Hz, 2H, H-12, H-14), 5.76 (ddd, *J* = 17.0, 10.7, 7.6 Hz, 1H, H-2), 5.06 – 4.95 (m, 2H, H-1), 4.43 – 4.33 (m, 2H, H-9), 3.88 (td, *J* = 7.1, 2.5 Hz, 1H, H-4), 3.78 (s, 3H, H-16), 3.68 (ddd, *J* = 7.9, 5.2, 3.2 Hz, 1H, H-6), 3.46 (dd, *J* = 8.8, 6.1 Hz, 1H, H-8), 3.23 (dd, *J* = 8.8, 7.4 Hz, 1H, H-8'), 2.32 (td, *J* = 7.2, 3.0 Hz, 1H, H-3), 1.86 (ddt, *J* = 13.7, 6.7, 3.3 Hz, 1H, H-7), 1.58 (ddd, *J* = 13.8, 7.3, 5.2 Hz, 1H, H-5), 1.46 - 1.42 (m, 1H, H-5'), 1.01 (d, *J* = 6.8 Hz, 3H, H-18), 0.96 – 0.91 (m, 9H, $C(CH_3)_3$-TES), 0.87 (s, 9H, $C(CH_3)_3$-TBS), 0.82 (d, *J* = 6.9 Hz, 3H, H-17), 0.60 (dd, *J* = 8.4, 7.6 Hz, 6H, CH_2-Si), 0.04 (s, 3H, CH_3-Si), 0.03 (s, 3H, CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 159.6 (C-13), 140.5 (C-2), 131.7 (C-10), 129.1 (C-11, C-15), 114.5 (C-1), 113.5 (C-12, C-14), 73.2 (C-8), 73.0 (C-9), 73.0 (C-6), 72.5 (C-4), 55.2 (C-16), 43.0 (C-3), 37.8 (C-7), 37.5 (C-5), 25.7 ($C(CH_3)_3$-TBS), 14.5 (C-18), 10.7 (C-17), 6.7 ($C(CH_3)_3$-TES), 5.3 (CH_2-Si), -4.5 (CH_3-Si), -5.0 (CH_3-Si). **HRMS (ESI)** m/z: calcd for $C_{30}H_{57}O_4Si_2$ $[M + H]^+$: 537.3790, found: 537.3797.

Synthesis of Compound 312

(2*R*,3*R*,5*S*,6*S*)-5-((*Tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,6-dimethyl-3-((triethylsilyl)oxy)heptanal



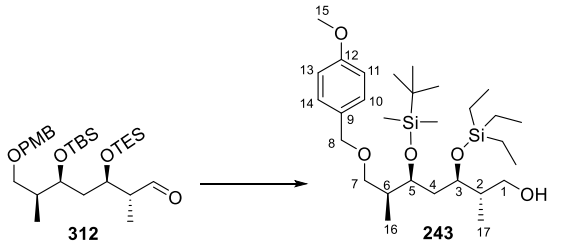
Chemical Formula: $C_{29}H_{54}O_5Si_2$
Exact Mass: 538,3510
Molecular Weight: 538,9160

To a stirred solution of terminal olefin **311** (98.00 mg, 182.51 µmol, 1.00 equiv) in acetone/water (10:1, 2.03 mL) was added NMO*H_2O (49.34 mg, 365.03 µmol, 2.00 equiv) as well as OsO_4 (4% in H_2O, 58.00 µL, 9.13 µmol, 0.05 equiv). The reaction mixture was stirred for 42 hours at room temperature before it was quenched with $Na_2S_2O_3$ solution (3 mL). The organic phase was separated and the aqueous layer extracted with DCM (3 x 3 mL). Afterwards, the combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was redissolved in toluene (2.34 mL) and $Pb(OAc)_4$ (96.94 mg, 209.89 µmol, 1.15 equiv) was added prior to stirring the mixture at room temperature for 30 minutes. The mixture was filtered through Celite® and the solvent removed in vacuo. Thereafter, the crude product was purified by column chromatography (SiO_2, packed with 30:1 CH/EE, eluted with 15:1 CH/EE) to observe 81.00 mg (150.30 µmol, 82%) of a slightly yellow oil.

R_f = 0.29 (15:1 CH/EE). **α_D^{20}** = -3.8° (c = 0.80, $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 400 MHz) δ = 9.69 (d, *J* = 1.9 Hz, 1H, H-1), 7.26 – 7.21 (m, 2H, H-10, H-14), 6.89 – 6.83 (m, 2H, H-11, H-13), 4.43 – 4.32 (m, 2H, H-8), 4.09 – 4.00 (m, 1H, H-3), 3.97 – 3.90 (m, 1H, H-5), 3.78 (s, 3H, H-15), 3.46 (dd, *J* = 8.8, 6.4 Hz, 1H, H-7), 3.26 (dd, *J* = 8.8, 7.0 Hz, 1H, H-7'), 2.47 (d, *J* = 6.7 Hz, 3H, H-2, H-4), 1.93 (m, 1H, H-6), 1.13 (d, *J* = 7.0 Hz, 3H, H-17), 0.93 – 0.89 (m, 9H, 3 x CH_3-TES), 0.87 (s, 9H, $C(CH_3)_3$), 0.84 (d, *J* = 6.9 Hz, 3H, H-16), 0.64 – 0.54 (m, 6H, CH_2-Si), 0.03 (d, *J* = 2.9 Hz, 6H, CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 126 MHz): δ = 204.8 (C-1), 159.5 (C-12), 131.4 (C-9), 129.6 (C-10, C-14), 113.9 (C-11, C-13), 73.0 (C-5), 72.7 (C-3), 70.9 (C-8), 69.8 (C-7), 55.6 (C-15), 51.6 (C-2), 39.5 (C-6), 38.3 (C-4), 26.0 (3 x CH_3-C), 18.3 (C_q-Si), 11.2 (C17), 10.3 (C-16), 7.1 (3 x CH_3 TES), 5.4 (3 x CH_2 TES), -4.1 (CH_3 TBS), -4.5 (CH_3 TBS). **HRMS (ESI)** m/z: calcd for $C_{29}H_{54}O_5Si_2H$ $[M+H]^+$: 539.3583, found: 539.3587.

Synthesis of Compound 243

(2*S*,3*R*,5*S*,6*S*)-5-((*Tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,6-dimethyl-3-((triethylsilyl)oxy)heptan-1-ol



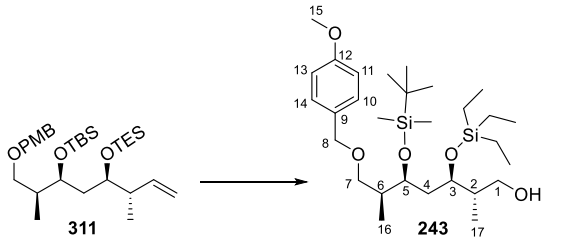
Chemical Formula: $C_{29}H_{56}O_5Si_2$
Exact Mass: 540,3666
Molecular Weight: 540,9320

Freshly prepared aldehyde **312** (42.70 mg, 79.23 µmol, 1.00 equiv) was dissolved in THF (0.59 mL) and the solution cooled to -78 °C. Then, DIBAl-H (1.0 M in CH, 174.31 µL, 174.31 µmol, 2.20 equiv) was added dropwise to the solution which was stirred at -78 °C for 1.5 hours. Hereafter, potassium, sodium tartrate (1 mL) was added, the biphasic mixture warmed to room temperature and stirred for one hour until both layers appeared clear. The aqueous layer was separated and extracted with DCM (3 x 1 mL) before the combined organic layers were washed with brine (1 x 5 mL) and dried over $MgSO_4$. After the solvent was evaporated under reduced pressure the crude product was purified by column chromatography (SiO_2, 10:1 CH/EE) yielding 29.60 mg (54.72 µmol, 69%) of a colourless oil.

R_f = 0.16 (5:1 CH/EE). **α_D^{20}** = -3.8° (c = 1.00, $CHCl_3$). **^{1}H** NMR (CD_2Cl_2, 700 MHz) δ = 7.26 – 7.22 (m, 2H, H-10, H-14), 6.87 – 6.84 (m, 2H, H-11, H-13), 4.43 – 4.35 (m, 2H, H-8), 3.87 (td, *J* = 6.6, 2.9 Hz, 1H, H-3), 3.81 (ddd, *J* = 7.5, 5.7, 2.7 Hz, 1H, H-5), 3.78 (s, 3H, H-15), 3.75 (ddd, *J* = 10.8, 4.1, 2.8 Hz, 1H, H-1), 3.50 (dd, *J* = 8.8, 5.8 Hz, 1H, H-7), 3.45 (ddd, *J* = 10.9, 7.4, 4.9 Hz, 1H, H-1'), 3.26 (dd, *J* = 8.8, 7.4 Hz, 1H, H-7'), 2.35 (dd, *J* = 7.7, 3.1 Hz, 1H, OH), 1.94 – 1.87 (m, 1H, H-6), 1.78 – 1.70 (m, 1H, H-2), 1.60 - 1.56 (m, 2H, H-4), 1.03 (d, *J* = 7.1 Hz, 3H, H-17), 0.94 (t, *J* = 8.0 Hz, 9H, $C(CH_3)_3$-TES), 0.88 (s, 9H, $C(CH_3)_3$-TBS), 0.88 (d, *J* = 6.9 Hz, 3H, H-16), 0.61 (q, *J* = 8.0 Hz, 6H, 2 x CH_2-Si), 0.04 (s, 6H, 2 x CH_3-Si). **^{13}C** NMR (CD_2Cl_2, 176 MHz) δ = 159.5 (C-12), 131.4 (C-9), 129.6 (C-10, C-14), 113.9 (C-11, C-13), 73.9 (C-3), 73.0 (C-8), 72.5 (C-7), 70.6 (C-5), 64.8 (C-1), 55.6 (C-15), 39.0 (C-6), 38.7 (C-4), 38.5 (C-2), 26.1 ($C(CH_3)_3$-TBS), 18.4 (C_q-TBS), 14.2 (C-17), 11.9 (C-16), 7.1 ($C(CH_3)_3$-TES), 5.4 (CH_2-Si), -4.1 (CH_3-Si), -4.4 (CH_3-Si). **HRMS (ESI)** m/z: calcd for $C_{29}H_{57}O_5Si_2$ $[M + H]^+$: 541.3739, found: 541.3735.

Synthesis of Compound 243

(2*S*,3*R*,5*S*,6*S*)-5-((*Tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,6-dimethyl-3-((triethylsilyl)oxy)heptan-1-ol



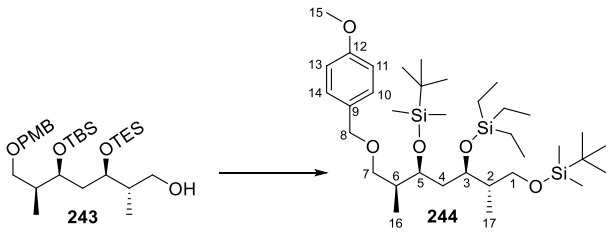
Chemical Formula: $C_{29}H_{56}O_5Si_2$
Exact Mass: 540,3666
Molecular Weight: 540,9320

Olefin **311** (22.00 mg, 40.97 µmol, 1.00 equiv) was dissolved in DCM/MeOH (14:1, 0.93 mL) and a 0.1% solution of Sudan III in DCM (10 drops) was added until the solution appeared slightly red. Afterwards, the prepared solution was cooled to -78 °C and a stream of ozone was bubbled through the solution until the latter turned colourless. Residual ozone was purged with Argon before $NaBH_4$ (7.83 mg, 204.86 µmol, 5.00 equiv) was added, the solution warmed to room temperature and stirred for three hours. After that, water (2 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. Lastly, the crude product was purified by column chromatography (SiO_2, 10:1 CH/EE) providing the primary alcohol as a colourless oil (11.20 mg, 20.71 µmol, 51%).

$\mathbf{R_f}$ = 0.16 (5:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = -3.8° (c = 1.00, $CHCl_3$). **^{1}H** NMR (700 MHz, CD_2Cl_2) δ = 7.26 – 7.22 (m, 2H, H-10, H-14), 6.87 – 6.84 (m, 2H, H-11, H-13), 4.43 – 4.35 (m, 2H, H-8), 3.87 (td, *J* = 6.6, 2.9 Hz, 1H, H-3), 3.81 (ddd, *J* = 7.5, 5.7, 2.7 Hz, 1H, H-5), 3.78 (s, 3H, H-15), 3.75 (ddd, *J* = 10.8, 4.1, 2.8 Hz, 1H, H-1), 3.50 (dd, *J* = 8.8, 5.8 Hz, 1H, H-7), 3.45 (ddd, *J* = 10.9, 7.4, 4.9 Hz, 1H, H-1'), 3.26 (dd, *J* = 8.8, 7.4 Hz, 1H, H-7'), 2.35 (dd, *J* = 7.7, 3.1 Hz, 1H, OH), 1.94 – 1.87 (m, 1H, H-6), 1.78 – 1.70 (m, 1H, H-2), 1.60 - 1.56 (m, 2H, H-4), 1.03 (d, *J* = 7.1 Hz, 3H, H-17), 0.94 (t, *J* = 8.0 Hz, 9H, $C(CH_3)_3$-TES), 0.88 (s, 9H, $C(CH_3)_3$-TBS), 0.88 (d, *J* = 6.9 Hz, 3H, H-16), 0.61 (q, *J* = 8.0 Hz, 6H, 2 x CH_2-Si), 0.04 (s, 6H, 2 x CH_3-Si). **^{13}C** NMR (176 MHz, CD_2Cl_2) δ = 159.5 (C-12), 131.4 (C-9), 129.6 (C-10, C-14), 113.9 (C-11, C-13), 73.9 (C-3), 73.0 (C-8), 72.5 (C-7), 70.6 (C-5), 64.8 (C-1), 55.6 (C-15), 39.0 (C-6), 38.7 (C-4), 38.5 (C-2), 26.1 ($C(CH_3)_3$-TBS), 18.4 (C_q-TBS), 14.2 (C-17), 11.9 (C-16), 7.1 ($C(CH_3)_3$-TES), 5.4 (CH_2-Si), -4.1 (CH_3-Si), -4.4 (CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{29}H_{57}O_5Si_2$ $[M + H]^+$: 541.3739, found: 541.3733.

Synthesis of Compound 244

(5*S*,7*R*,8*S*)-5-((*S*)-1-((4-Methoxybenzyl)oxy)propan-2-yl)-2,2,3,3,8,11,11,12,12-nonamethyl-7-((triethylsilyl)oxy)-4,10-dioxa-3,11-disilatridecane



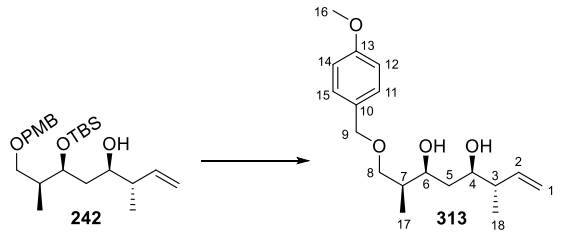
Chemical Formula: $C_{35}H_{70}O_5Si_3$
Exact Mass: 654,4531
Molecular Weight: 655,1950

A solution of alcohol **243** (33.00 mg, 61.01 µmol, 1.00 equiv) in DCM (0.31 mL) was treated with 2,6-lutidine (10.60 µL, 91.51 µmol, 1.50 equiv). After that, the mixture was cooled to 0 °C and TBSOTf (19.70 µL, 91.51 µmol, 1.50 equiv) was added dropwise. The resulting mixture was stirred at 0 °C for four hours before water (0.5 mL) was added. Subsequently, the layers were separated and the aqueous layer extracted with DCM (3 x 1 mL). The combined organic layers were dried over $MgSO_4$and the solvent evaporated in vacuo. Hereafter, the crude product was purified by column chromatography (SiO_2, 40:1 CH/EE) yielding 30.40 mg (46.40 µmol, 76%) of a colourless oil.

R_f = 0.13 (40:1 CH/EE). **α_D^{20}** = -5.4 ° (c = 0.87 in CH_2Cl_2). **^{1}H** NMR (700 MHz, CD_2Cl_2) δ = 7.26 – 7.23 (m, 2H, H-10, H-14), 6.86 – 6.83 (m, 2H, H-11, H-13), 4.41 (d, *J* = 11.4 Hz, 1H, H-8), 4.35 (d, *J* = 11.4 Hz, 1H, H-8'), 4.01 (ddd, *J* = 9.5, 4.4, 1.9 Hz, 1H, H-5), 3.87 (dt, *J* = 9.5, 3.3 Hz, 1H, H-3), 3.78 (s, 3H, H-15), 3.44 (dd, *J* = 7.1, 5.4 Hz, 2H, H-1), 3.42 – 3.39 (m, 1H, H-7), 3.25 (dd, *J* = 8.8, 7.1 Hz, 1H, H-7'), 1.92 (hd, *J* = 6.9, 1.9 Hz, 1H, H-6), 1.85 (dtt, *J* = 10.5, 7.7, 5.3 Hz, 1H, H-2), 1.62 (ddd, *J* = 13.8, 9.6, 2.9 Hz, 1H, H-4), 1.43 – 1.39 (m, 1H, H-4'), 0.92 (t, *J* = 8.0 Hz, 9H, CH_3-TES), 0.89 (s, 9H, $C(CH_3)_3$), 0.87 (s, 9H, $C(CH_3)_3$), 0.83 (dd, *J* = 6.9, 0.8 Hz, 6H, H-16, H-17), 0.58 (q, *J* = 7.9 Hz, 6H, 3 x CH_2-Si), 0.05 (s, 3H, CH_3-Si), 0.04 (s, 3H, CH_3-Si), 0.03 (s, 3H, CH_3-Si), 0.02 (s, 3H, CH_3-Si). **^{13}C** NMR (175 MHz, CD_2Cl_2) δ = 159.4 (C-12), 131.6 (C-9), 129.5 (C-10, C-14), 113.9 (C-11, C-13), 73.8 (C-7), 72.9 (C-8), 70.2 (C-3), 69.6 (C-5), 65.5 (C-1), 55.6 (C-15), 42.3 (C-2), 37.0 (C-6), 36.8 (C-4), 26.1 ($C(CH_3)_3$), 26.1 ($C(CH_3)_3$), 18.5 (C_q-TBS), 18.4 (C_q-TBS), 11.1 (C-16/17), 10.1 (C-16/17), 7.2 (3 x CH_3-TES), 5.6 (3 x CH_2-Si), -3.9 (CH_3-Si), -4.7 (CH_3-Si), -5.4 (CH_3-Si), -5.4 (CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{35}H_{71}O_5Si_3$ $[M + H]^+$: 655.4604, found: 655.4604.

Synthesis of Compound 313

(2*S*,3*S*,5*R*,6*S*)-1-((4-Methoxybenzyl)oxy)-2,6-dimethyloct-7-ene-3,5-diol



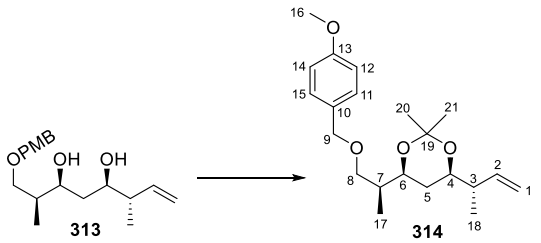
Chemical Formula: $C_{18}H_{28}O_4$
Exact Mass: 308,1988
Molecular Weight: 308,4180

TBS-ether **242** (92.10 mg, 217.89 µmol, 1.00 equiv) was dissolved in THF (11.70 mL) and the resulting solution cooled to 0 °C. Afterwards, TBAF (1.0 M in THF, 653.68 µL, 653.68 µmol, 3.00 equiv) was added dropwise at 0 °C and then the solution was allowed to warm to room temperature and stirred for 3.5 hours. Next, water (15 mL) was added, the layers were separated and the aqueous layer extracted with DCM (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, the solvent was removed under reduced pressure and the crude product purified by column chromatography (SiO_2, 3:1 CH/EE) to obtain 59.90 mg (194.22 µmol, 89%) of the desired diol.

R_f = 0.16 (3:1 CH/EE). **α_D^{20}** = -17.8 ° (c = 1.02 in CH_2Cl_2). **^{1}H** NMR (500 MHz, CD_2Cl_2) δ = 7.27 – 7.23 (m, 2H, H-11, H-15), 6.90 – 6.86 (m, 2H, H-12, H-14), 5.85 – 5.77 (m, 1H, H-2), 5.07 (q, *J* = 1.0 Hz, 1H, H-1), 5.05 – 5.03 (m, 1H, H-1'), 4.47 – 4.38 (m, 2H, H-9), 3.95 (dq, *J* = 9.4, 3.0 Hz, 1H, H-6), 3.79 (s, 3H, H-16), 3.69 (q, *J* = 5.5 Hz, 1H, H-4), 3.50 – 3.47 (m, 2H, H-8), 2.21 (dddt, *J* = 8.1, 7.2, 5.2, 1.1 Hz, 1H, H-3), 1.91 – 1.82 (m, 1H, H-7), 1.50 – 1.46 (m, 2H, H-5), 1.02 (d, *J* = 6.9 Hz, 3H, H-18), 0.90 (d, *J* = 7.1 Hz, 3H, H-17). **^{13}C** NMR (125 MHz, CD_2Cl_2) δ = 159.8 (C-13), 141.2 (C-2), 130.8 (C-11, C-15), 129.7 (C-12, C-14), 115.4 (C-1), 114.2 (C-10), 76.4 (C-4), 75.7 (C-6), 74.4 (C-8), 73.5 (C-9), 55.7 (C-16), 44.8 (C-3), 39.2 (C-7), 37.0 (C-5), 15.9 (C-18), 11.5 (C-17). **HRMS (ESI)** m/z: calcd for $C_{18}H_{28}O_4Na$ $[M + Na]^+$: 331.1880, found: 331.1877.

Synthesis of Compound 314

(4*R*,6*S*)-4-((*S*)-But-3-en-2-yl)-6-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxane

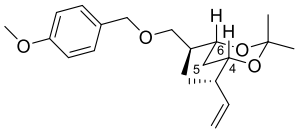


Chemical Formula: $C_{21}H_{32}O_4$
Exact Mass: 348,2301
Molecular Weight: 348,4830

A solution of diol **313** (123.90 mg, 401.73 µmol, 1.00 equiv) in DCM (5.02 mL) was treated with 2,2-DMP (2.46 mL; 20.09 mmol, 50.00 equiv) followed by the addition of *p*-TsOH (6.92 mg, 40.17 µmol, 0.10 equiv). The reaction was stirred at room temperature for two hours. Afterwards, $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers dried over $MgSO_4$. Then, the solvent was removed under reduced pressure and the crude product purified by column chromatography (SiO_2, 20:1 CH/EE) to obtain the desired product as a colourless oil (143.40 mg, 411.50 µmol, quant).

R_f = 0.09 (20:1 CH/EE). **α_D^{20}** = -19 ° (c = 1.0 in CH_2Cl_2). **^{1}H** NMR (700 MHz, CD_2Cl_2) δ = 7.26 – 7.22 (m, 2H, H-11, H-15), 6.88 – 6.84 (m, 2H, H-12, H-14), 5.83 (ddd, *J* = 17.7, 10.5, 7.3 Hz, 1H, H-2), 5.01 (ddd, *J* = 11.6, 2.0, 1.2 Hz, 1H, H-1), 5.00 – 4.98 (m, 1H, H-1'), 4.41 – 4.34 (m, 2H, H-9), 3.84 (ddd, *J* = 11.6, 5.1, 2.5 Hz, 1H, H-6), 3.78 (s, 3H, H-16), 3.68 (ddd, *J* = 11.4, 5.7, 2.5 Hz, 1H, H-4), 3.41 (dd, *J* = 9.1, 6.2 Hz, 1H, H-8), 3.29 (dd, *J* = 9.1, 5.9 Hz, 1H, H-8'), 2.21 – 2.14 (m, 1H, H-3), 1.74 – 1.67 (m, 1H, H-7), 1.37 (s, 3H, H-20/21), 1.33 – 1.30 (m, 1H, H-5), 1.30 – 1.29 (m, 3H, H-20/21), 1.23 (dt, *J* = 12.7, 11.6 Hz, 1H, H-5'), 0.97 (d, *J* = 6.9 Hz, 3H, H-18), 0.92 (d, *J* = 6.9 Hz, 3H, H-17). **^{13}C** NMR (175 MHz, CD_2Cl_2) δ = 159.5 (C-13), 141.4 (C-2), 131.3 (C-10), 129.6 (C-11, C-15), 114.3 (C-1), 113.9 (C-12, C-14), 98.6 (C-19), 73.0 (C-9), 73.0 (C-4), 72.3 (C-8), 70.1 (C-6), 55.6 (C-16), 43.0 (C-3), 39.1 (C-7), 31.4 (C-5), 30.3 (C-20/21), 19.9 (C-20/21), 15.4 (C-18), 12.5 (C-17). **HRMS (ESI)** *m/z*: calcd for $C_{31}H_{33}O_4$ $[M + H]^+$: 349.2373, found: 349.2372.

Table 17: Confirmation of the given structure by the ^{1}H-^{1}H coupling constants.

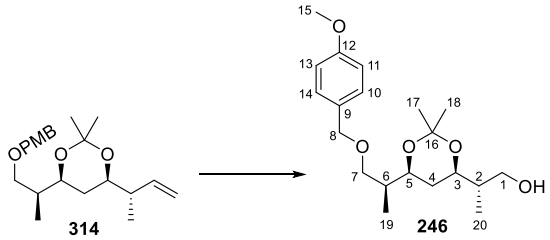


$^{3}J_{4,6}$ = 11.6 Hz

$^{3}J_{6,4}$ = 11.6 Hz

Synthesis of Compound 246

(*S*)-2-((4*R*,6*S*)-6-((*S*)-1-((4-Methoxybenzyl)oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-1-ol



Chemical Formula: $C_{20}H_{32}O_5$
Exact Mass: 352,2250
Molecular Weight: 352,4710

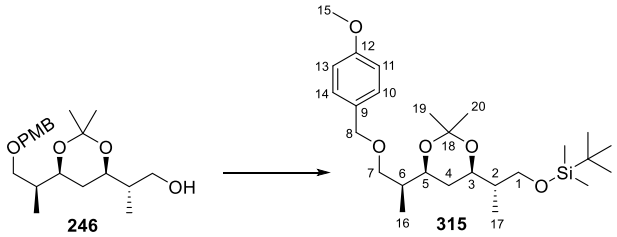
Terminal olefin **314** (140.00 mg, 401.74 µmol, 1.00 equiv) was dissolved in DCM/MeOH (14:1, 9.13 mL) and 10 drops of a 0.1% Sudan III solution in DCM were added until the solution appearde slightly red. The prepared solution was cooled to -78 °C and a stream of ozone was bubbled through the solution until it turned colourless. Excess ozone was purged with Argon before $NaBH_4$ (76.76 mg, 2.01 mmol, 5.00 equiv) was added and the mixture allowed to warm to room temperature. Then, it was stirred for two hours before it was quenched by the addition of water (10 mL). The organic layer was separated and subsequently the aqueous layer was extracted with DCM (3 x 10 mL). Thereafter, the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. Lastly, the crude product was purified by column chromatography (SiO_2, 3:1 CH/EE) yielding 115.60 mg (327.97 µmol, 82%) of the desired primary alcohol as a colourless oil.

R_f = 0.08 (5:1 CH/EE). **α_D^{20}** = -18.3 ° (c = 0.88 in CH_2Cl_2). **^{1}H** NMR (500 MHz, CD_2Cl_2) δ = 7.26 – 7.22 (m, 2H, H-10, H-14), 6.89 – 6.85 (m, 2H, H-11, H-13), 4.43 – 4.35 (m, 2H, H-8), 3.90 (ddd, *J* = 11.7, 5.0, 2.5 Hz, 1H, H-5), 3.79 (s, 3H, H-15), 3.75 (ddd, *J* = 11.4, 7.8, 2.5 Hz, 1H, H-3), 3.57 – 3.51 (m, 2H, H-1), 3.42 (dd, *J* = 9.1, 6.4 Hz, 1H, H-7), 3.31 (dd, *J* = 9.1, 5.7 Hz, 1H, H-7'), 2.75 (dd, *J* = 6.6, 5.1 Hz, 1H, OH), 1.78 – 1.71 (m, 1H, H-6), 1.71 – 1.62 (m, 1H, H-2), 1.47 (dt, *J* = 12.7, 2.5 Hz, 1H, H-4), 1.42 (d, *J* = 0.7 Hz, 3H, H-17/18), 1.33 (q, *J* = 0.7 Hz, 3H, H-17/18), 1.32 – 1.25 (m, 1H, H-4'), 0.94 (d, *J* = 6.9 Hz, 3H, H-19), 0.83 (d, *J* = 7.0 Hz, 3H, H-20). **^{13}C** NMR (125

MHz, CD_2Cl_2) δ = 159.7 (C-12), 131.4 (C-9), 129.6 (C-10, C-14), 114.1 (C-11, C-13), 98.9 (C-16), 75.6 (C-3), 73.1 (C-8), 72.3 (C-7), 70.2 (C-5), 67.8 (C-1), 55.7 (C-15), 41.1 (C-2), 39.1 (C-6), 33.0 (C-4), 30.4 (C-17/18), 20.0 (C-17/18), 13.1 (C-20), 12.4 (C-19). **HRMS (ESI)** m/z: calcd for $C_{20}H_{33}O_5$ $[M + H]^+$: 353.2323, found: 353.2318.

Synthesis of Compound 315

***Tert*-butyl((*S*)-2-((4*R*,6*S*)-6-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propoxy)dimethylsilane**



Chemical Formula: $C_{26}H_{46}O_5Si$
Exact Mass: 466,3115
Molecular Weight: 466,7340

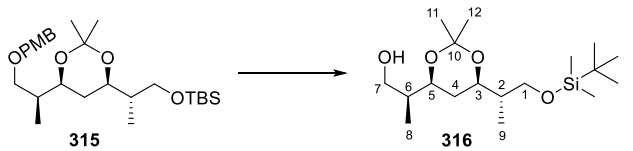
A solution of alcohol **246** (14.70 mg, 41.71 µmol, 1.00 equiv) in DCM (0.21 mL) was treated with imidazole (4.26 mg, 62.56 µmol, 1.50 equiv). After the imidazole was mostly dissolved the solution was cooled to 0 °C and TBSCl (9.43 mg, 62.56 µmol, 1.50 equiv) was added. The reaction mixture was warmed to room temperature and stirred for six hours prior to the addition of water (0.5 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 1 mL). Afterwards, the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. In the end, the crude product was purified by column chromatography (SiO_2, 20:1 CH/EE) to obtain a colourless oil (19.00 mg, 40.71 µmol, 98%).

$\mathbf{R_f}$ = 0.31 (10:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = -17 ° (c = 0.75 in CH_2Cl_2). **^{1}H** NMR (400 MHz, CD_2Cl_2) δ = 7.27 – 7.21 (m, 2H, H-10, H-14), 6.89 – 6.83 (m, 2H, H-11, H-13), 4.38 (d, *J* = 2.6 Hz, 2H, H-8), 3.84 (ddd, *J* = 11.7, 5.1, 2.5 Hz, 1H, H-5), 3.78 (s, 3H, H-15), 3.74 (ddd, *J* = 11.5, 7.6, 2.4 Hz, 1H, H-3), 3.57 (d, *J* = 5.0 Hz, 2H, H-1), 3.43 (dd, *J* = 9.1, 6.1 Hz, 1H, H-7), 3.30 (dd, *J* = 9.1, 6.0 Hz, 1H, H-7'), 1.72 (dt, *J* = 12.5, 6.3 Hz, 1H, H-6), 1.63 – 1.55 (m, 1H, H-2), 1.44 – 1.37 (m, 1H, H-4), 1.37 (d, *J* = 0.7 Hz, 3H, H-19/20), 1.29 (d, *J* = 0.7 Hz, 3H, H-19/20), 1.19 (q, *J* = 11.9 Hz, 1H, H-4'), 0.93 (d, *J* = 6.9 Hz, 3H, H-16), 0.89 (s, 9H, $C(CH_3)_3$), 0.85 (d, *J* = 6.9 Hz, 3H, H-17), 0.03 (s, 6H, 2 x CH_3-Si). **^{13}C** NMR (175 MHz, CD_2Cl_2) δ = 159.6 (C-12), 131.4 (C-9), 129.5 (C-10, C-14), 114.0 (C-11,

C-13), 98.5 (C-18), 73.1 (C-8), 72.4 (C-7), 70.3 (C-5), 70.1 (C-3), 64.5 (C-1), 55.6 (C-15), 41.4 (C-2), 39.2 (C-6), 31.7 (C-4), 30.3 (C-19/20), 26.1 (3 x CH3-TBS), 20.0 (C-19/20), 12.6 (C-16), 12.5 (C-17), -5.4 (2 x CH3-TBS). **HRMS (ESI)** m/z: calcd for $C_{26}H_{46}O_5SiNa$ $[M + Na]^+$: 489.3007, found: 489.3010.

Synthesis of Compound 316

(*S*)-2-((4*S*,6*R*)-6-((*S*)-1-((*Tert*-butyldimethylsilyl)oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-1-ol



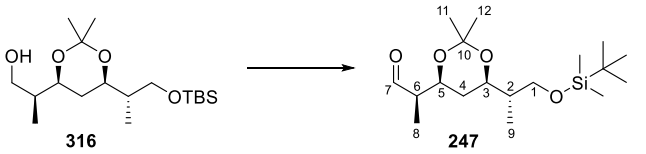
Chemical Formula: $C_{18}H_{38}O_4Si$
Exact Mass: 346,2539
Molecular Weight: 346,5830

To a solution of PMB-ether **315** (27.50 mg, 58.92 µmol, 1.00 equiv) in DCM (1.47 mL) was added pH 7 buffer (0.15 mL) as well as DDQ (13.37 mg, 58.92 µmol, 1.00 equiv). The mixture was stirred at room temperature for 90 minutes before water was added (3 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 x 3 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo. Finally, the crude product was purified by column chromatography (SiO_2, 10:1 CH/EE) yielding a colourless oil (15.40 mg, 44.43 µmol, 75%).

$\mathbf{R_f}$ = 0.09 (10:1 CH/EE). $\boldsymbol{\alpha_D^{20}}$ = -25 ° (c = 0.56 in CH_2Cl_2). **^{1}H** NMR (700 MHz, CD_2Cl_2) δ = 4.01 (ddd, *J* = 11.8, 4.1, 2.6 Hz, 1H, H-5), 3.80 (ddd, *J* = 11.4, 7.4, 2.5 Hz, 1H, H-3), 3.64 (ddd, *J* = 11.4, 7.4, 4.5 Hz, 1H, H-7), 3.61 – 3.55 (m, 2H, H-1), 3.51 (ddd, *J* = 10.8, 6.3, 4.3 Hz, 1H, H-7'), 2.47 (dd, *J* = 6.3, 4.6 Hz, 1H, OH?), 1.87 – 1.80 (m, 1H, H-6), 1.62 (dqd, *J* = 11.8, 7.0, 4.8 Hz, 1H, H-2), 1.40 (s, 3H, H-11/12), 1.39 (t, *J* = 2.6 Hz, 1H, H-4), 1.33 (s, 3H, H-11/12), 1.34 – 1.28 (m, 1H, H-4'), 0.89 (s, 9H, $C(CH_3)_3$), 0.89 (d, *J* = 2.9 Hz, 3H, H-9), 0.88 (d, *J* = 2.3 Hz, 3H, H-8), 0.04 (d, *J* = 0.7 Hz, 6H, 2 x CH_3-Si). **^{13}C** NMR (175 MHz, CD_2Cl_2) δ = 98.8 (C-10), 73.2 (C-5), 70.1 (C-3), 66.0 (C-7), 64.4 (C-1), 41.3 (C-2), 39.6 (C-6), 30.4 (C-11/12), 29.7 (C-4), 26.1 ($C(CH_3)_3$), 19.8 (C-11/12), 12.6 (C-9), 11.8 (C-8), -5.4 (2 x CH_3-Si). **HRMS (ESI)** m/z: calcd for $C_{18}H_{39}O_4Si$ $[M + H]^+$: 347.2612, found: 347.2607.

Synthesis of Compound 247

(*R*)-2-((4*S*,6*R*)-6-((*S*)-1-((*Tert*-butyldimethylsilyl)oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propanal



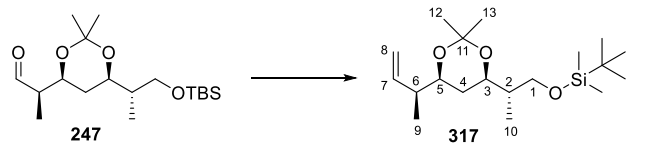
Chemical Formula: $C_{18}H_{36}O_4Si$
Exact Mass: 344,2383
Molecular Weight: 344,5670

The observed alcohol **316** (14.60 mg, 42.13 µmol, 1.00 equiv) was dissolevd in DMSO (1.00 mL) and IBX (35.39 mg, 126.38 µmol, 3.00 equiv) was added. The mixture was stirred at room temperature for 90 minutes prior to the addition of water (2 mL). The layers were separated and the aqueous layer extracted with DCM (3 x 2 mL). Then, the combined organic layers were dried over $MgSO_4$ and the solvent evaporated. As a last step, the crude product was purified by column chromatography to obtain the desired aldehyde as a colourless oil (14.80 mg, 42.95 µmol, quant).

R_f = 0.29 (10:1 CH/EE). **α_D^{20}** = -23 ° (c = 0.44 in CH_2Cl_2). **^{1}H** NMR (500 MHz, CD_2Cl_2) δ = 9.72 (d, *J* = 1.1 Hz, 1H, H-7), 4.25 (ddd, *J* = 11.8, 4.7, 2.6 Hz, 1H, H-5), 3.83 (ddd, *J* = 11.5, 7.5, 2.4 Hz, 1H, H-3), 3.63 – 3.53 (m, 2H, H-1), 2.42 (qdd, *J* = 7.1, 4.6, 1.1 Hz, 1H, H-6), 1.66 – 1.57 (m, 1H, H-2), 1.49 (dt, *J* = 12.6, 2.5 Hz, 1H, H-4), 1.41 (d, *J* = 0.7 Hz, 3H, H-11/12), 1.31 (q, *J* = 0.6 Hz, 3H, H-11/12), 1.30 – 1.22 (m, 1H, H-4'), 1.07 (d, *J* = 7.1 Hz, 3H, H-8), 0.89 (s, 9H, $C(CH_3)_3$), 0.87 (d, *J* = 7.0 Hz, 3H, H-9), 0.04 (s, 6H, 2 x CH_3-Si). **^{13}C** NMR (125 MHz, CD_2Cl_2) δ = 204.6 (C-7), 98.9 (C-10), 66.9 (C-5), 69.5 (C-3), 64.3 (C-1), 51.3 (C-6), 41.3 (C-2), 31.2 (C-4), 30.1 (C-11/12), 26.1 ($C(CH_3)_3$), 19.8 (C-11/12), 12.5 (C-9), 8.3 (C-8), -5.4 (CH_3-Si).

Synthesis of Compound 317

((*S*)-2-((4*R*,6*S*)-6-((*S*)-But-3-en-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)propoxy)(tert-butyl)dimethylsilane



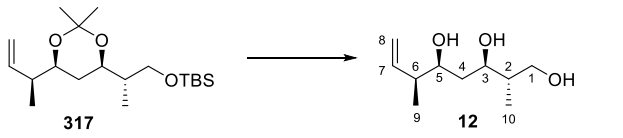
Chemical Formula: $C_{19}H_{38}O_3Si$
Exact Mass: 342,2590
Molecular Weight: 342,5950

In a seperate flask KO*t*Bu (11.82 mg, 105.35 µmol, 2.50 equiv) was dissolved in THF (105.35 µL) and added over 20 minutes to a dispersion of methyltriphenylphosphonium bromide (19.20 mg, 52.67 µmol, 1.25 equiv) in THF (53 µL) at 0 °C. The ice bath was removed and the solution stirred for 30 minutes at room temperature before freshly prepared aldehyde **247** (14.52 mg, 42.14 µmol, 1.00 equiv) was dissolved in THF (0.42 mL) and added to the mixture which was stirred for another hour at room temperaure. After that, 1 M HCl (1.0 mL) was added, the layers separated and the aqueous layer extracted with DCM (3 x 1 mL). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Lastly, the crude product was purified by column chromatography (SiO_2, 40:1 CH/EE) yielding 7.30 mg (21.31 µmol, 51%) of the desired olefin as a colourless oil.

R_f = 0.21 (40:1 CH/EE). **α_D^{20}** = -27.2 ° (c = 0.53 in CH_2Cl_2). **^{1}H** NMR (400 MHz, CD_2Cl_2) δ = 5.75 (ddd, *J* = 17.3, 10.4, 7.7 Hz, 1H, H-7), 5.07 – 4.98 (m, 2H, H-8), 3.74 (ddd, *J* = 11.7, 7.4, 2.4 Hz, 1H, H-3/5), 3.61 – 3.54 (m, 3H, H-1, H-3/5), 2.15 (q, *J* = 7.1 Hz, 1H, H-6), 1.65 – 1.56 (m, 1H, H-2), 1.48 (dt, J = 12.8, 2.5 Hz, 1H, H-4), 1.38 (d, *J* = 0.7 Hz, 3H, H-12/13), 1.31 (d, *J* = 0.7 Hz, 3H, H-12/13), 1.13 – 1.04 (m, 1H, H-4'), 1.01 (d, *J* = 6.8 Hz, 3H, H-9), 0.88 (s, 9H, 3 x CH3-TBS), 0.85 (d, *J* = 7.0 Hz, 3H, H-10), 0.03 (s, 6H, 2 x CH3-TBS). **^{13}C** NMR (175 MHz, CD_2Cl_2) δ = 140.9 (C-7), 114.9 (C-8), 98.6 (C-11), 72.9 (C-3/5), 70.1 (C-3/5), 64.5 (C-1), 43.9 (C-6), 41.4 (C-2), 31.9 (C-4), 30.4 (C-12/13), 26.1 (3 x CH3-TBS), 20.0 (C-12/13), 18.6 (C-), 15.9 (C-9), 12.5 (C-10), -5.4 (2 x CH_3-Si). **HRMS (ESI)** *m/z*: calcd for $C_{19}H_{39}O_3Si$ $[M + H]^+$: 343.2663, found: 343.2660.

Synthesis of Compound 12

(2*S*,3*R*,5*S*,6*S*)-2,6-Dimethyloct-7-ene-1,3,5-triol



In a last step both protecting groups were cleaved under acidic conditions. Therefore, compound **317** (9.10 mg, 26.56 µmol, 1.00 equiv) was dissolved in wet THF/dry MeOH (1:1, 0.2 mL) and the solution cooled to 0 °C. After that, CSA (3.09 mg, 13.28 µmol, 0.50 equiv) was added. The ice bath was removed and the reaction stirred for three hours while slowly warming to room temperature. Then, Et_2O (1 mL) and $NaHCO_3$ (1 mL) were added, the layers

separated and the aqueous layer extracted with Et_2O (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, the solvent removed under reduced pressure and the crude product purified by column chromatography (SiO_2, 1:1 CH/EE). The desired triol was obtained as a colourless oil (1.50 mg, 7.97 µmol, 30%).

R_f = 0.12 (40:1 CH/EE). **α_D^{20}** = -26.8 ° (c = 0.36 in CH_2Cl_2). **^{1}H** NMR (500 MHz, $CDCl_3$) δ = 5.79 (ddd, *J* = 16.9, 10.8, 7.4 Hz, 1H, H-7), 5.14 – 5.08 (m, 2H, H-8), 3.82 – 3.74 (m, 3H, H-1, H-3, H-5), 3.64 (dd, *J* = 10.9, 7.3 Hz, 1H, H-1), 2.36 – 2.25 (m, 1H, H-6), 1.78 – 1.68 (m, 2H, H-2, H-4), 1.51 (dd, *J* = 14.4, 10.4 Hz, 1H, H-4'), 1.05 (d, *J* = 6.9 Hz, 3H, H-9), 0.89 (d, *J* = 7.0 Hz, 3H, H-10). **^{13}C** NMR (125 MHz, $CDCl_3$) δ = 140.4 (C-7), 116.1 (C-8), 79.0 (C-3), 76.5 (C-5), 67.7 (C-1), 44.3 (C-6), 40.7 (C-2), 38.0 (C-4), 14.4 (C-9), 14.1 (C-10). **HRMS (ESI)** m/z: calcd for $C_{10}H_{21}O_3$ $[M + H]^+$: 189.1485, found: 189.1483.

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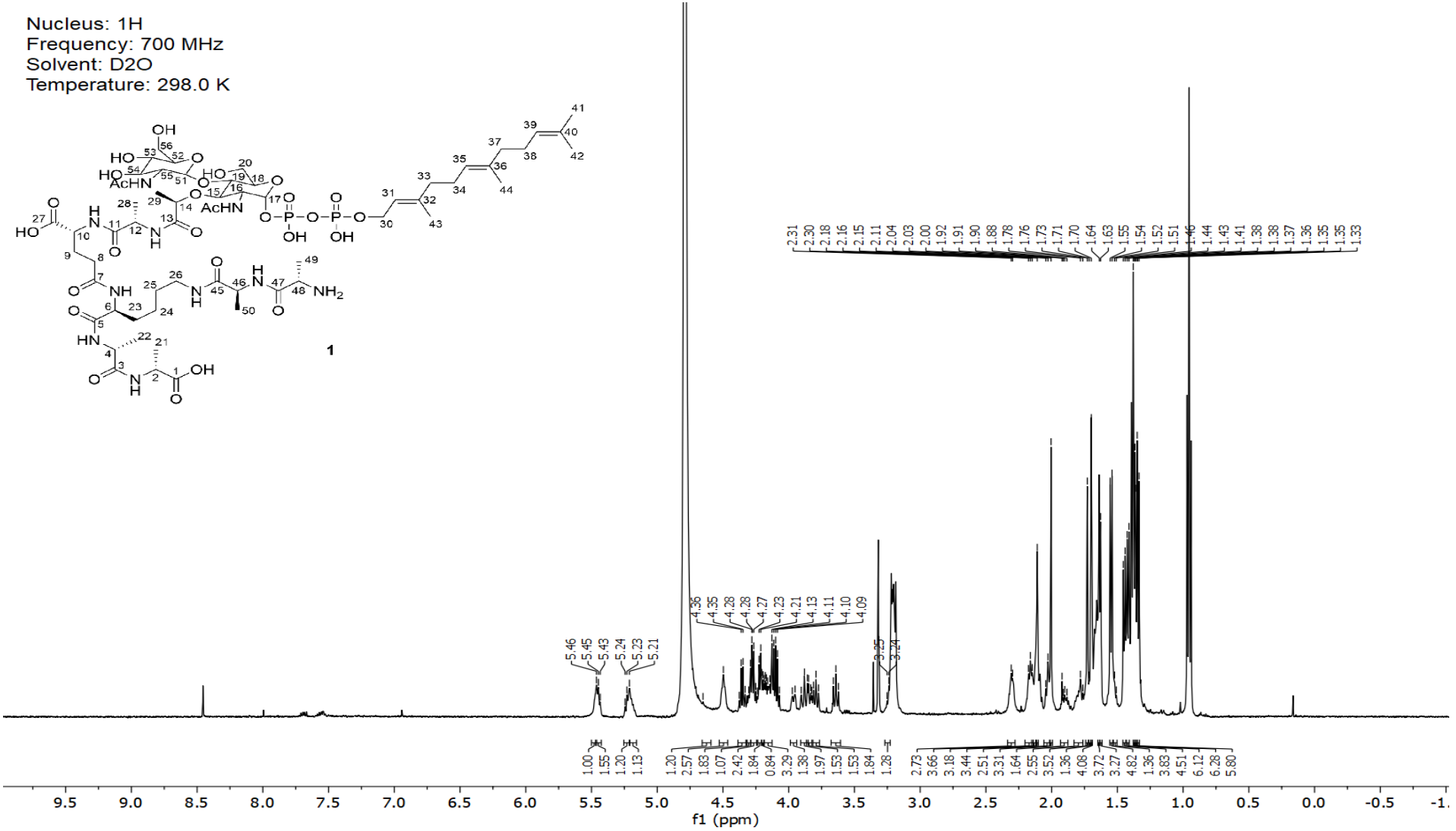
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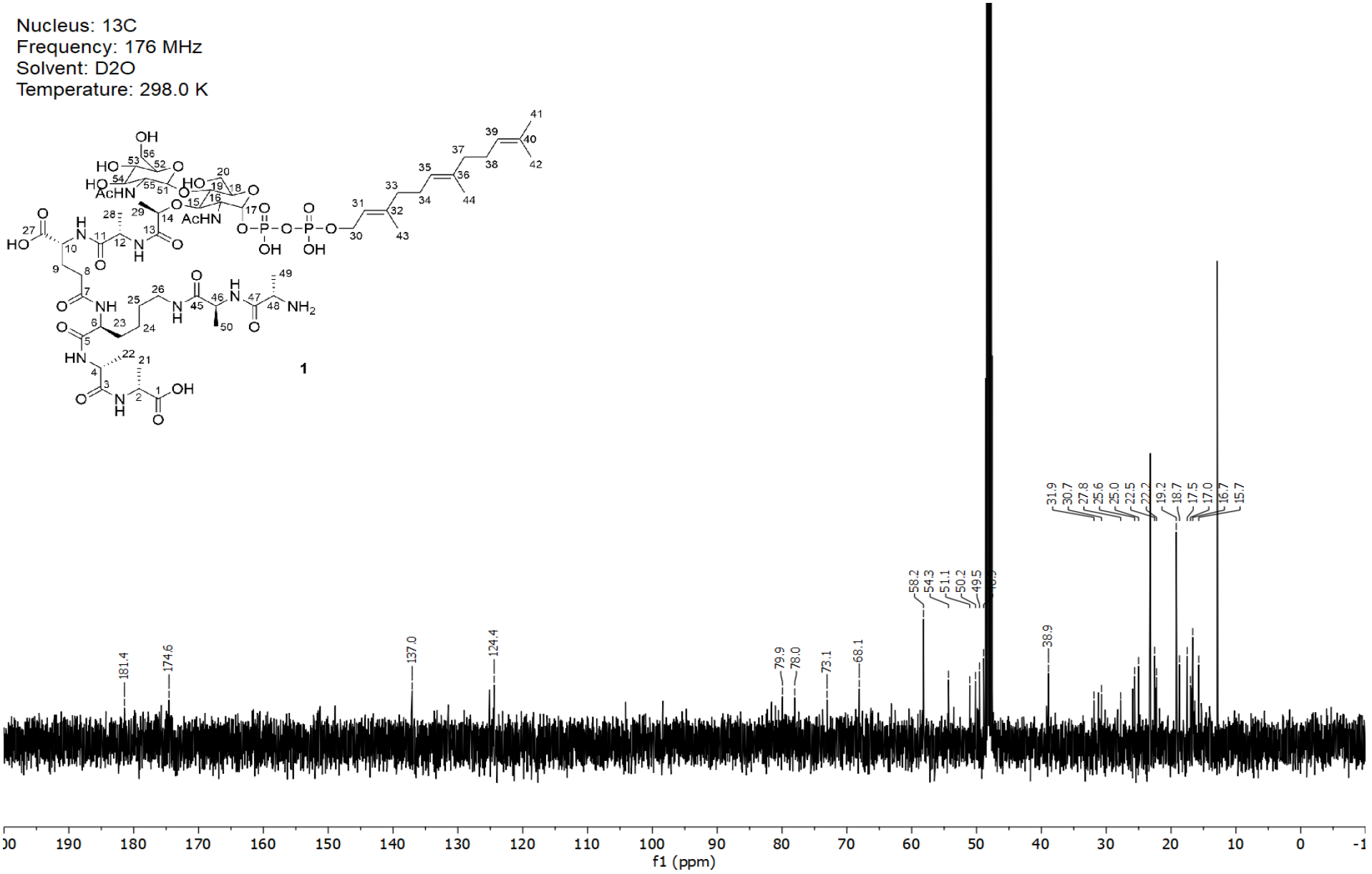
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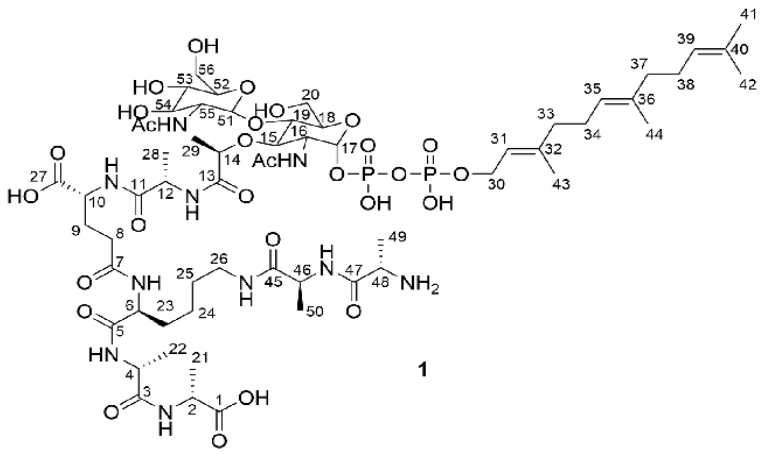
5 Appendix

5.1 Spectra Part I

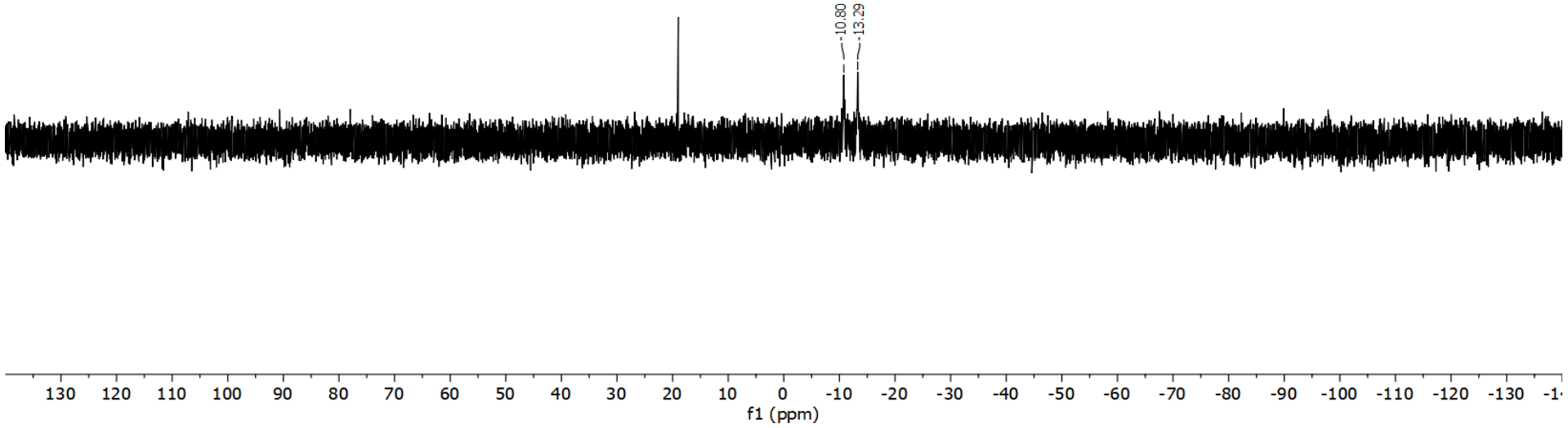



Nucleus: 13C
Frequency: 176 MHz
Solvent: D2O
Temperature: 298.0 K
1
181.4
174.6
137.0
124.4
79.9
78.0
73.1
68.1
58.2
54.3
51.1
50.2
49.5
38.9
31.9
30.7
27.8
25.6
25.0
22.5
22.2
19.2
18.7
17.5
17.0
16.7
15.7
f1 (ppm)

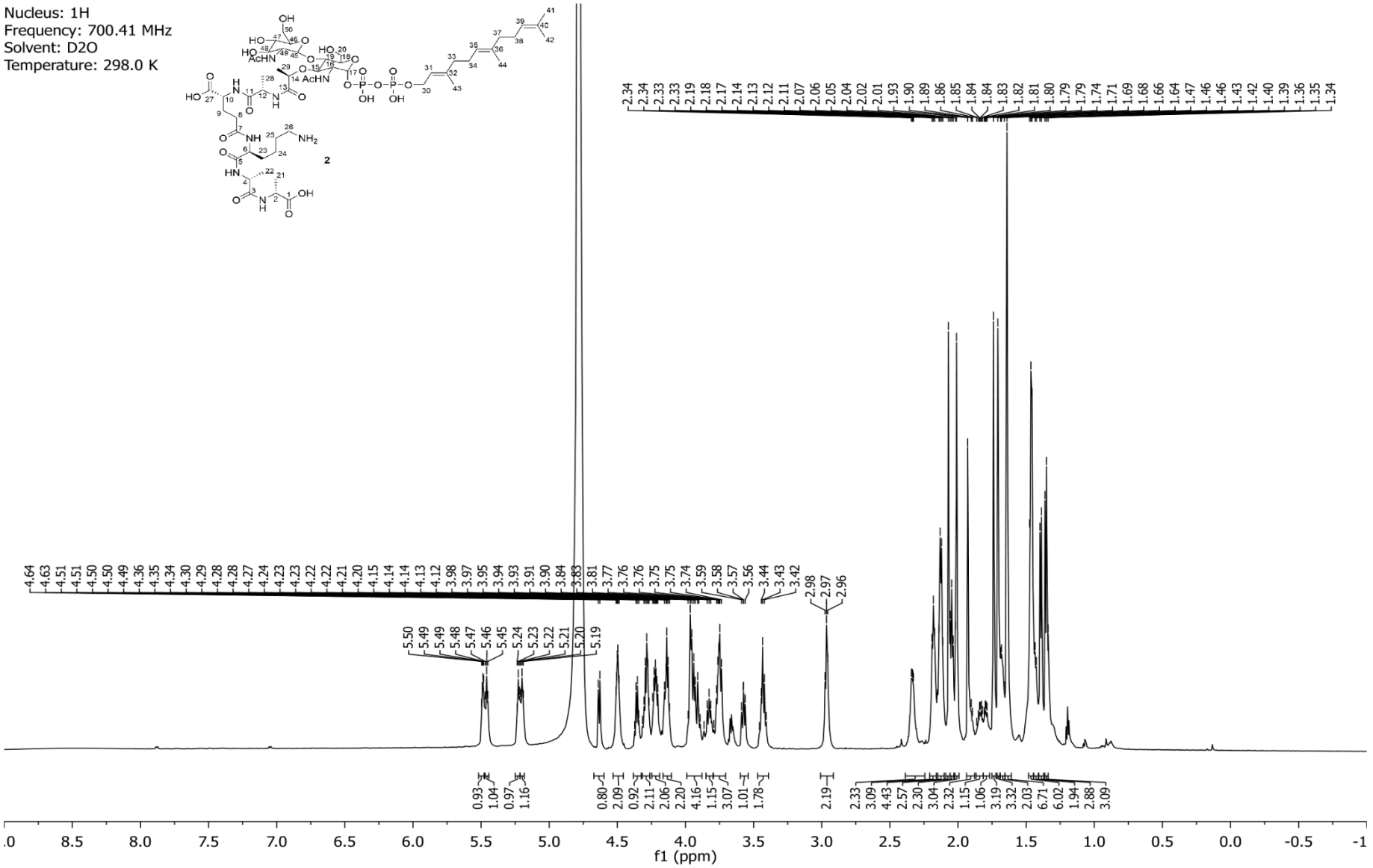
Nucleus: 31P
Frequency: 284 MHz
Solvent: D2O
Temperature: 298.0 K



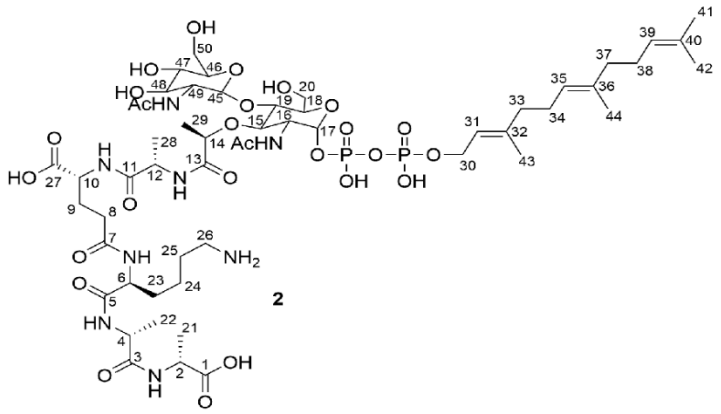
1



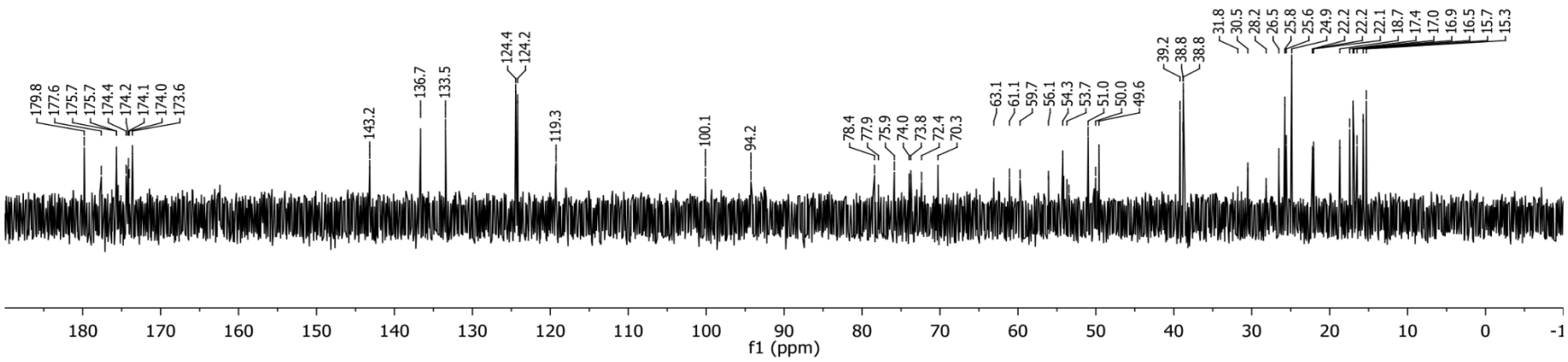
6. Appendix


Nucleus: 1H
Frequency: 700.41 MHz
Solvent: D2O
Temperature: 298.0 K
2
f1 (ppm)

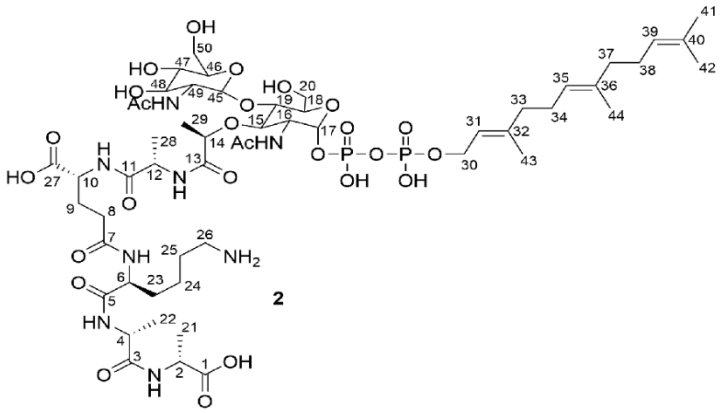
Nucleus: 13C
Frequency: 176.12 MHz
Solvent: D2O
Temperature: 298.0 K



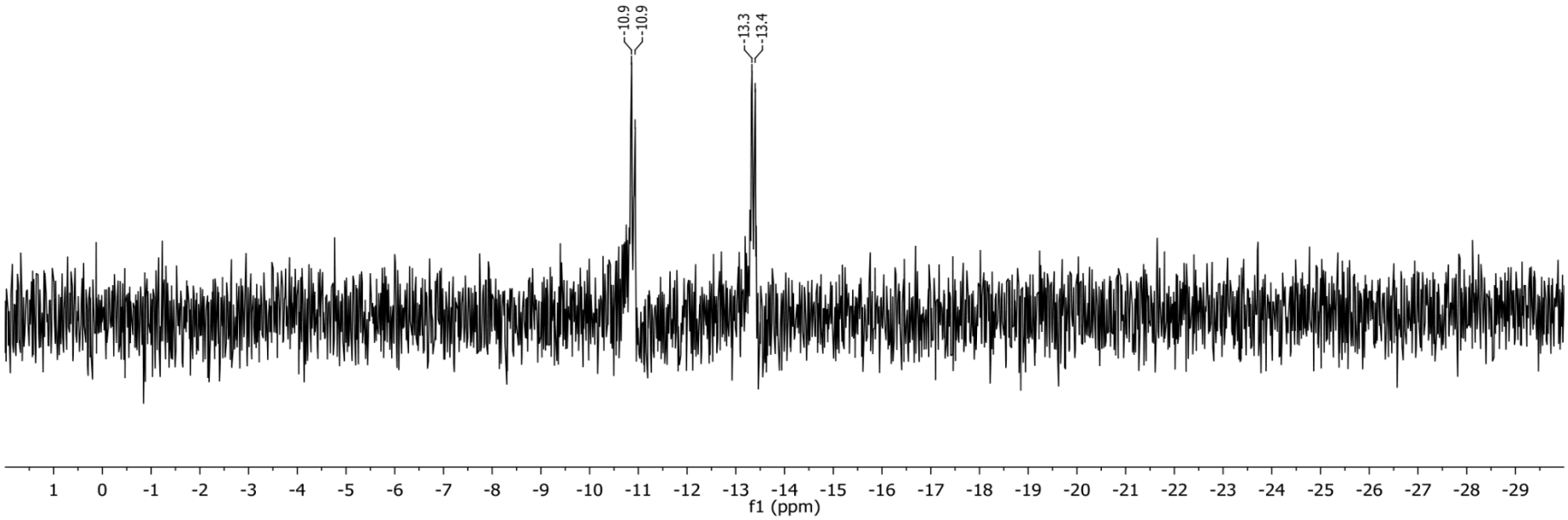
2



Nucleus: 31P
Frequency: 283.53 MHz
Solvent: D2O
Temperature: 298.0 K

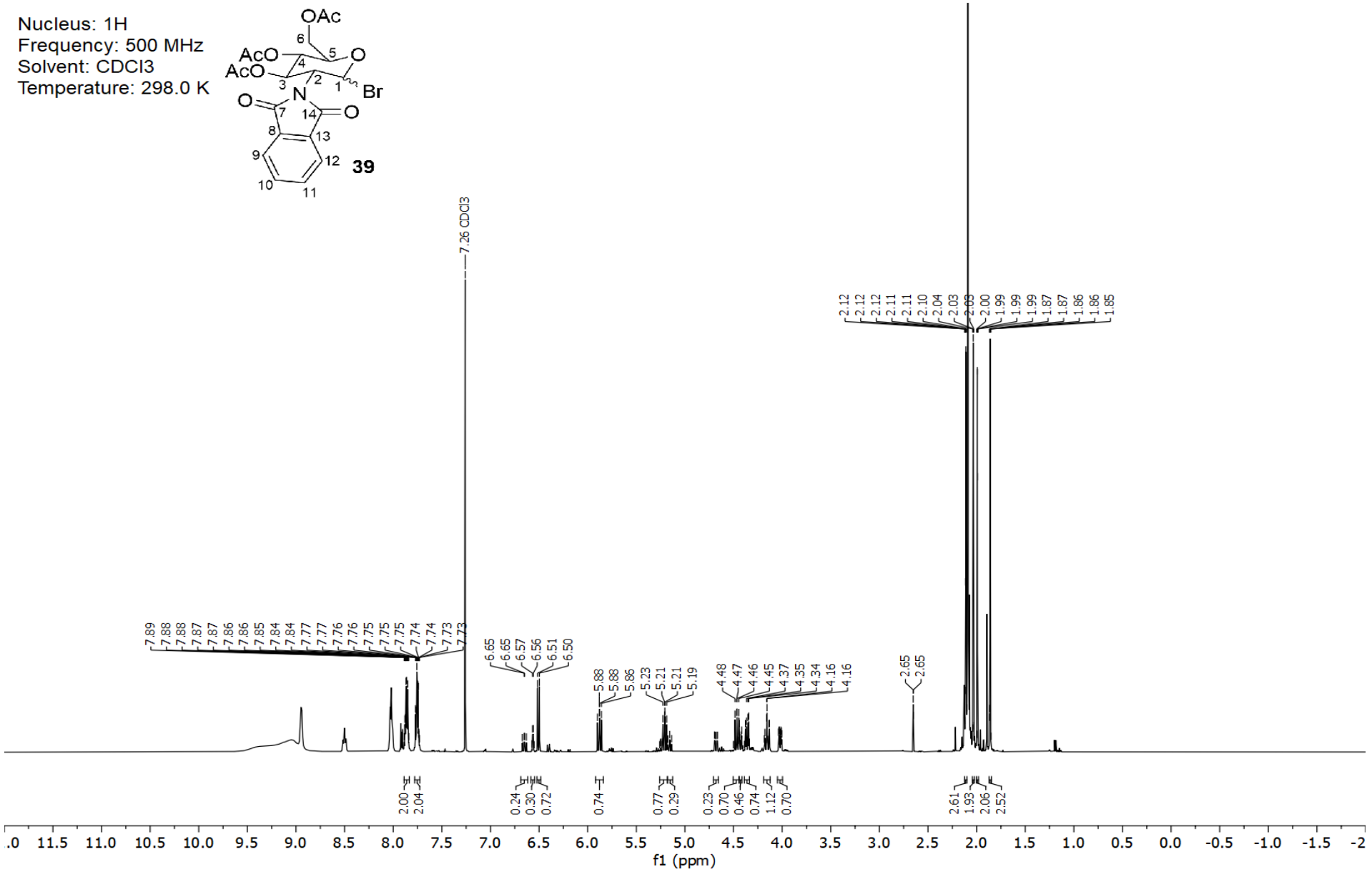


2

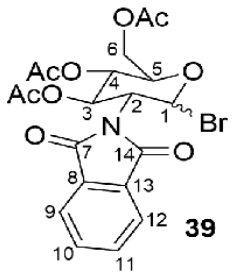


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Solvent: CDCl3
Temperature: 298.0 K

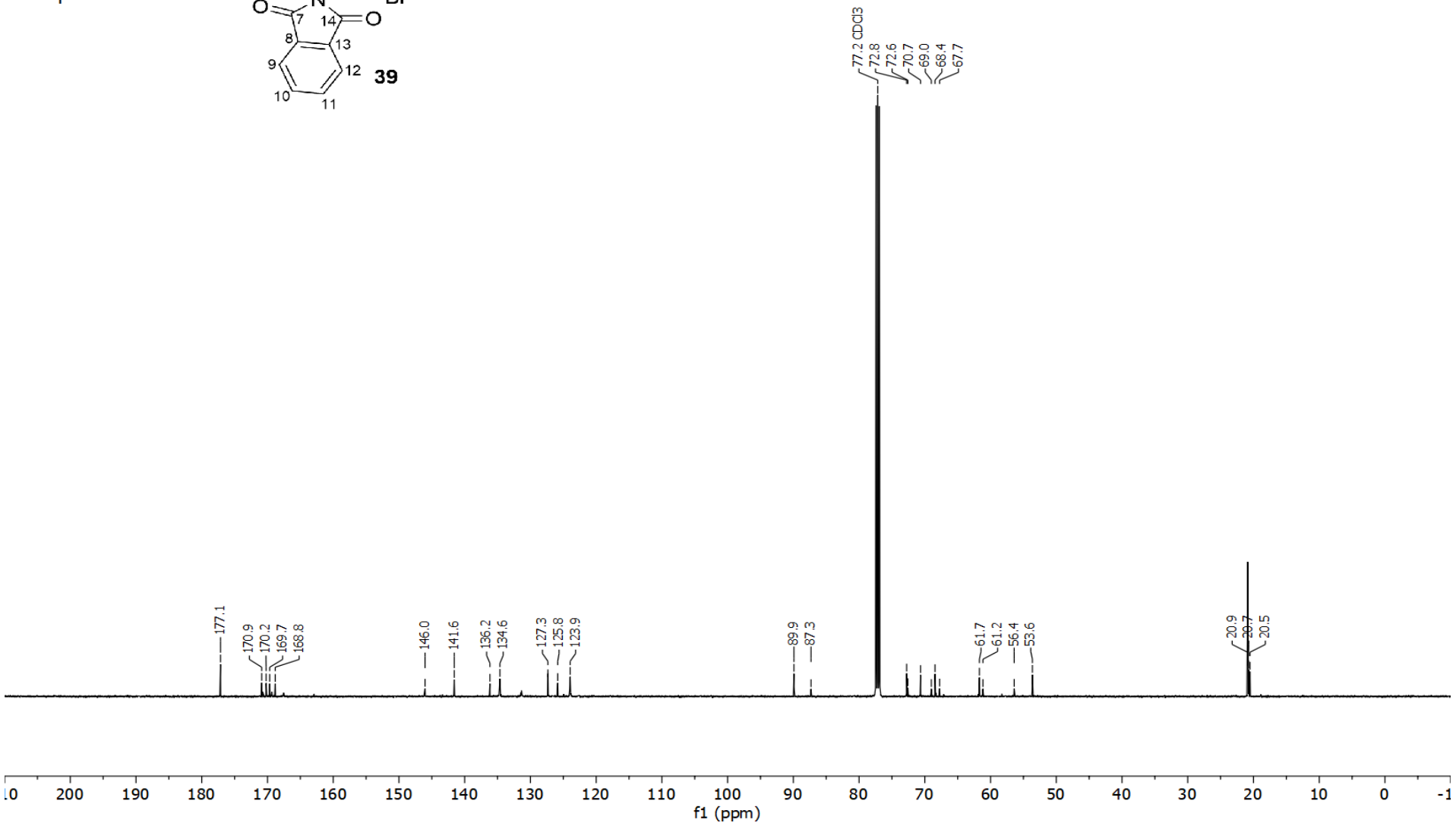
39

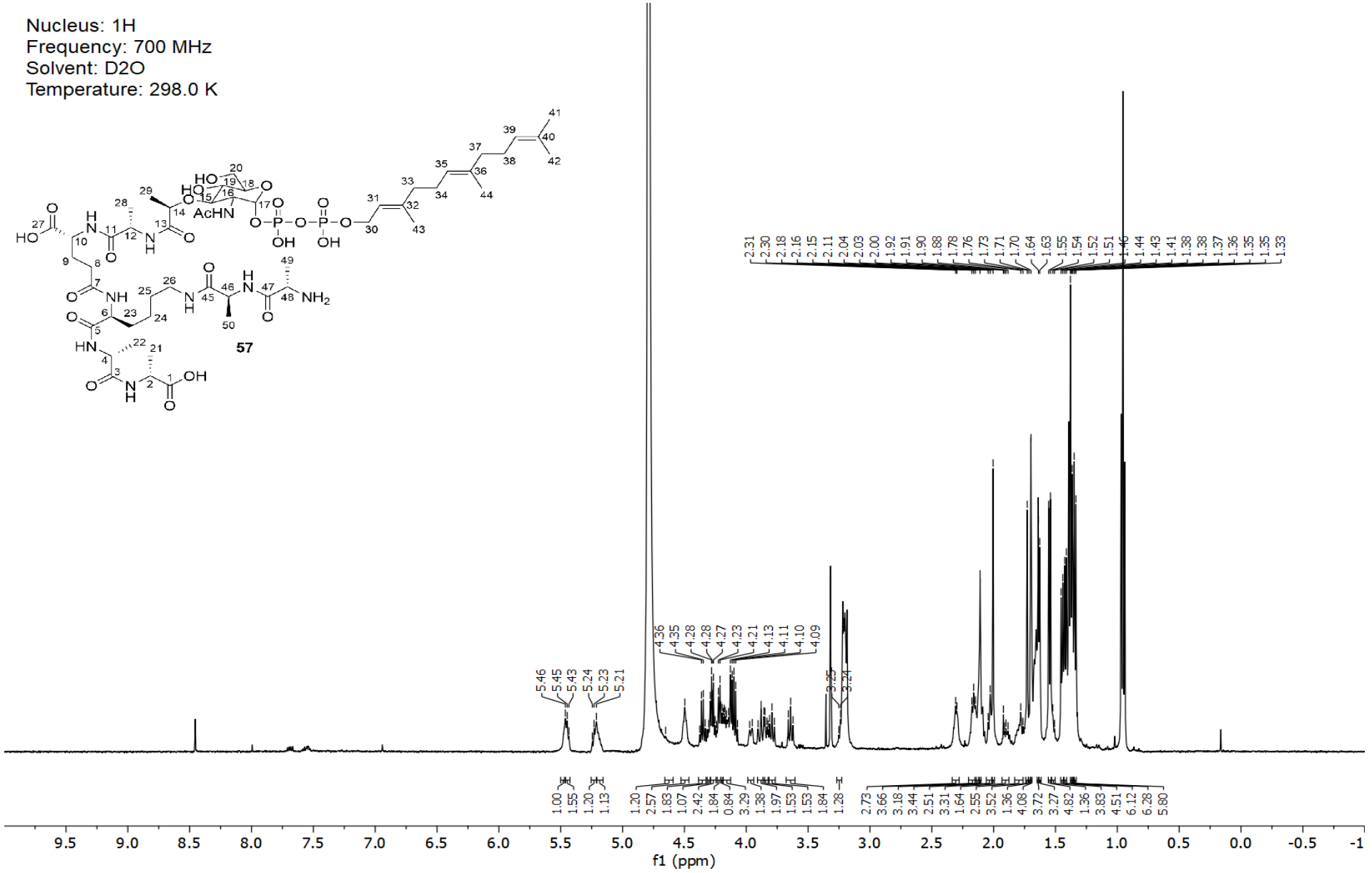


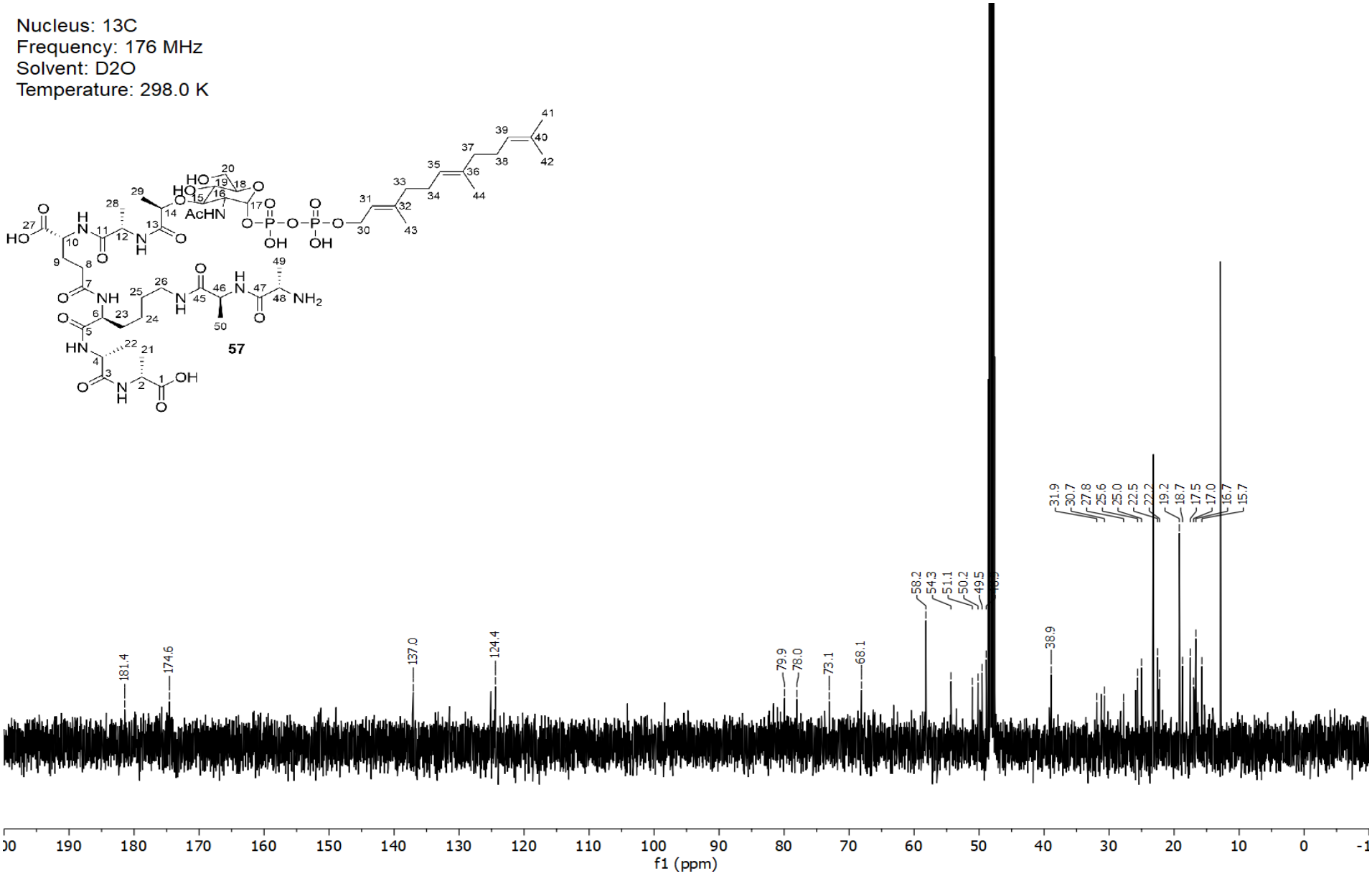
Nucleus: 13C
Frequency: 125 MHz
Solvent: D2O
Temperature: 298.0 K



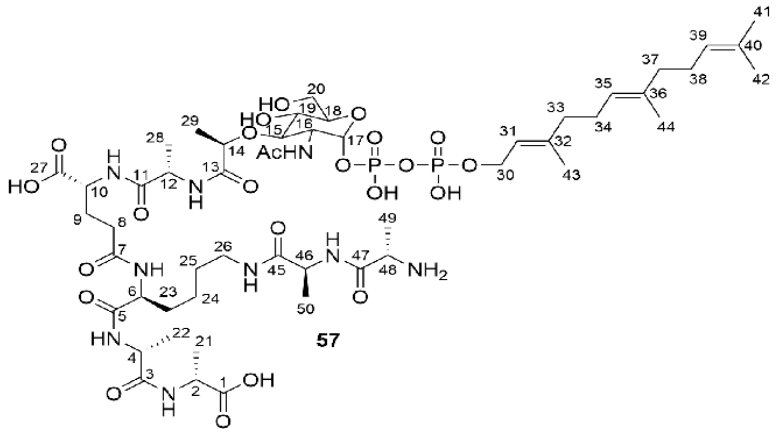
39



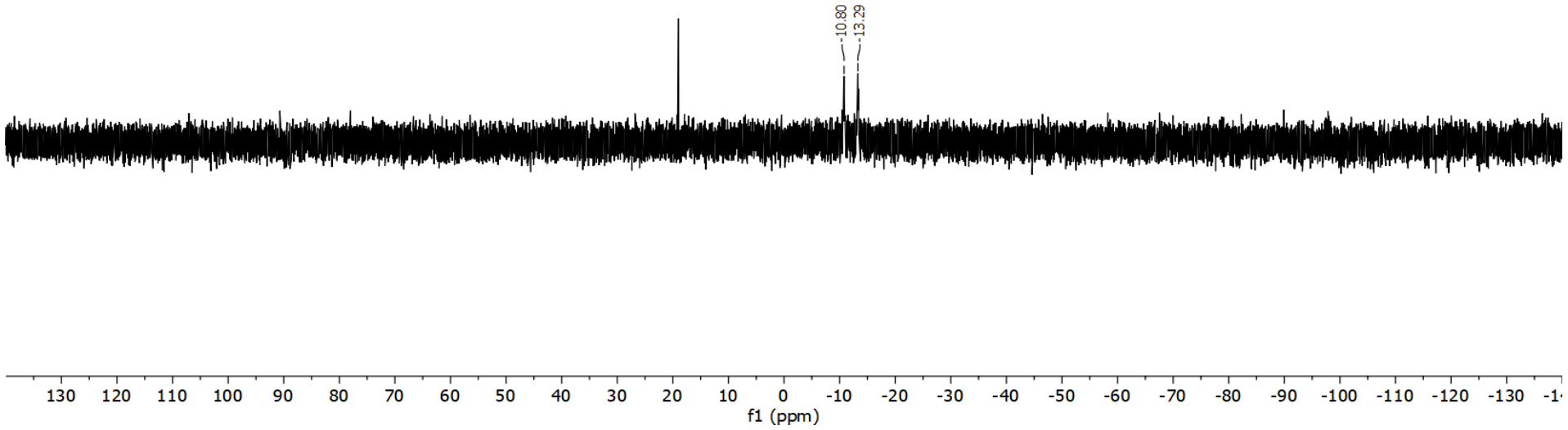

Nucleus: 1H
Frequency: 700 MHz
Solvent: D2O
Temperature: 298.0 K
57
f1 (ppm)


Nucleus: 13C
Frequency: 176 MHz
Solvent: D2O
Temperature: 298.0 K
57
181.4
174.6
137.0
124.4
79.9
78.0
73.1
68.1
58.2
54.3
51.1
50.2
49.5
38.9
31.9
30.7
27.8
25.6
25.0
22.5
22.2
19.2
18.7
17.5
17.0
16.7
15.7
f1 (ppm)

Nucleus: 31P
Frequency: 284 MHz
Solvent: D2O
Temperature: 298.0 K

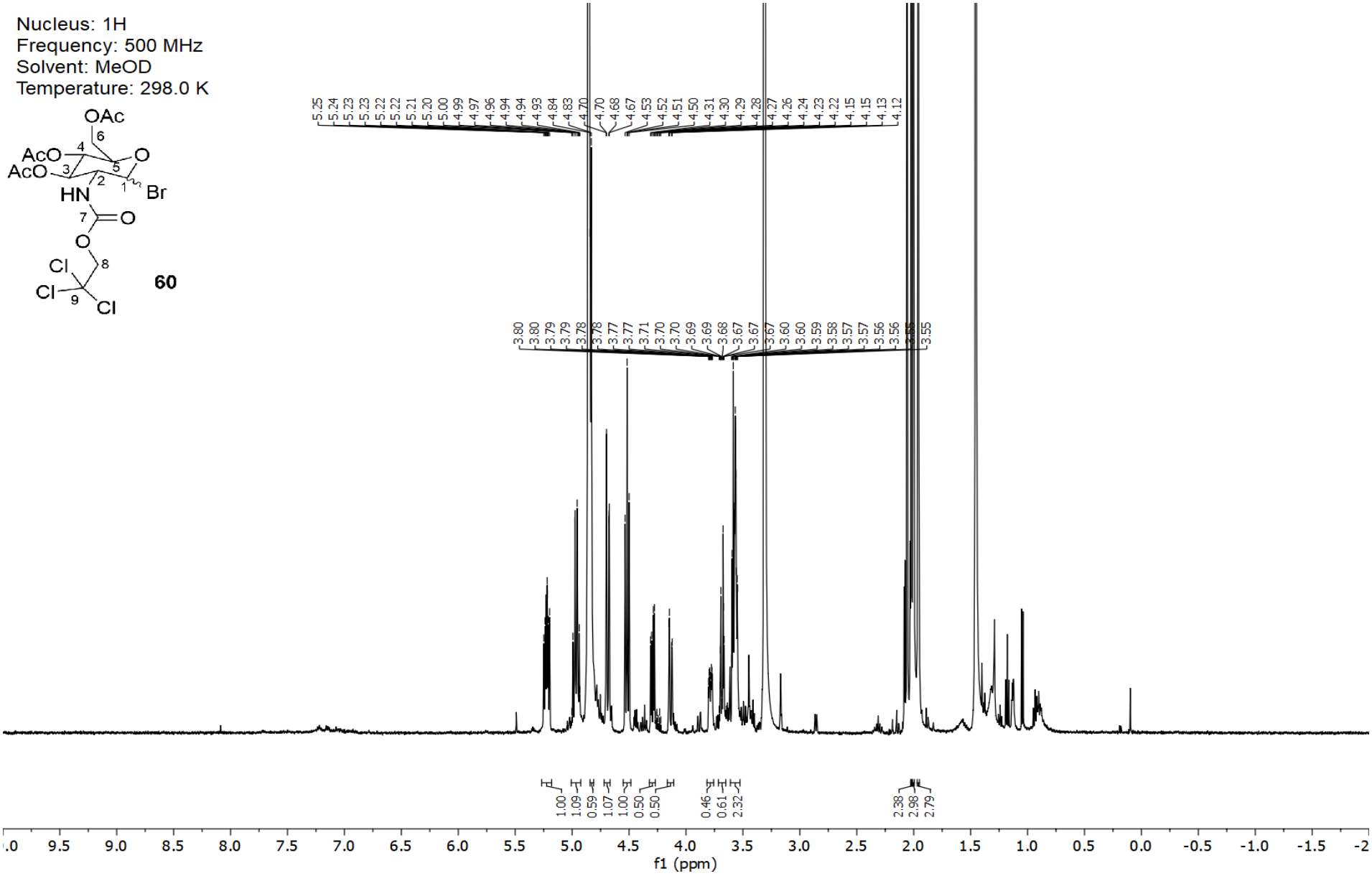


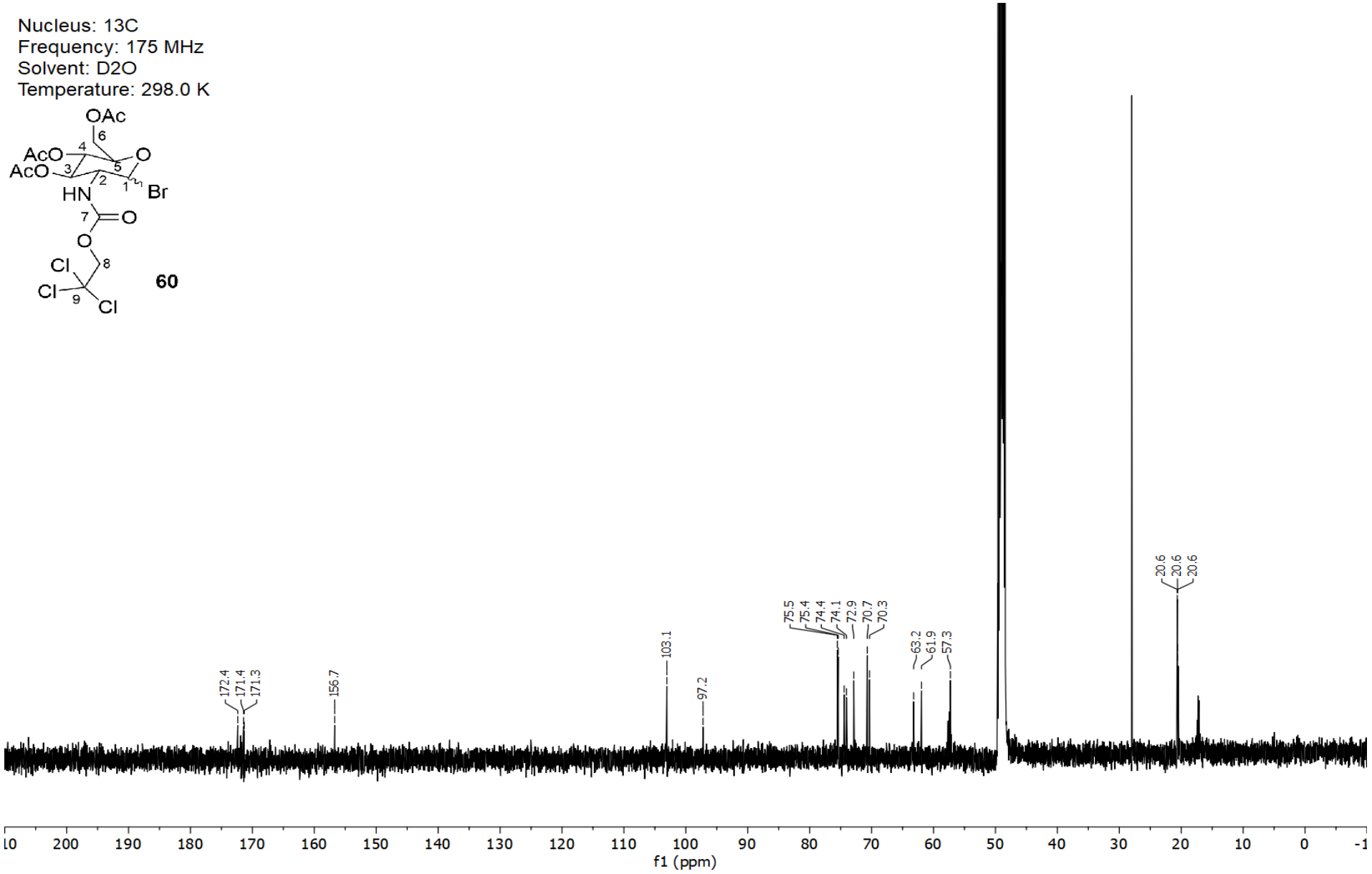
57



Nucleus: 1H
Frequency: 500 MHz
Solvent: MeOD
Temperature: 298.0 K

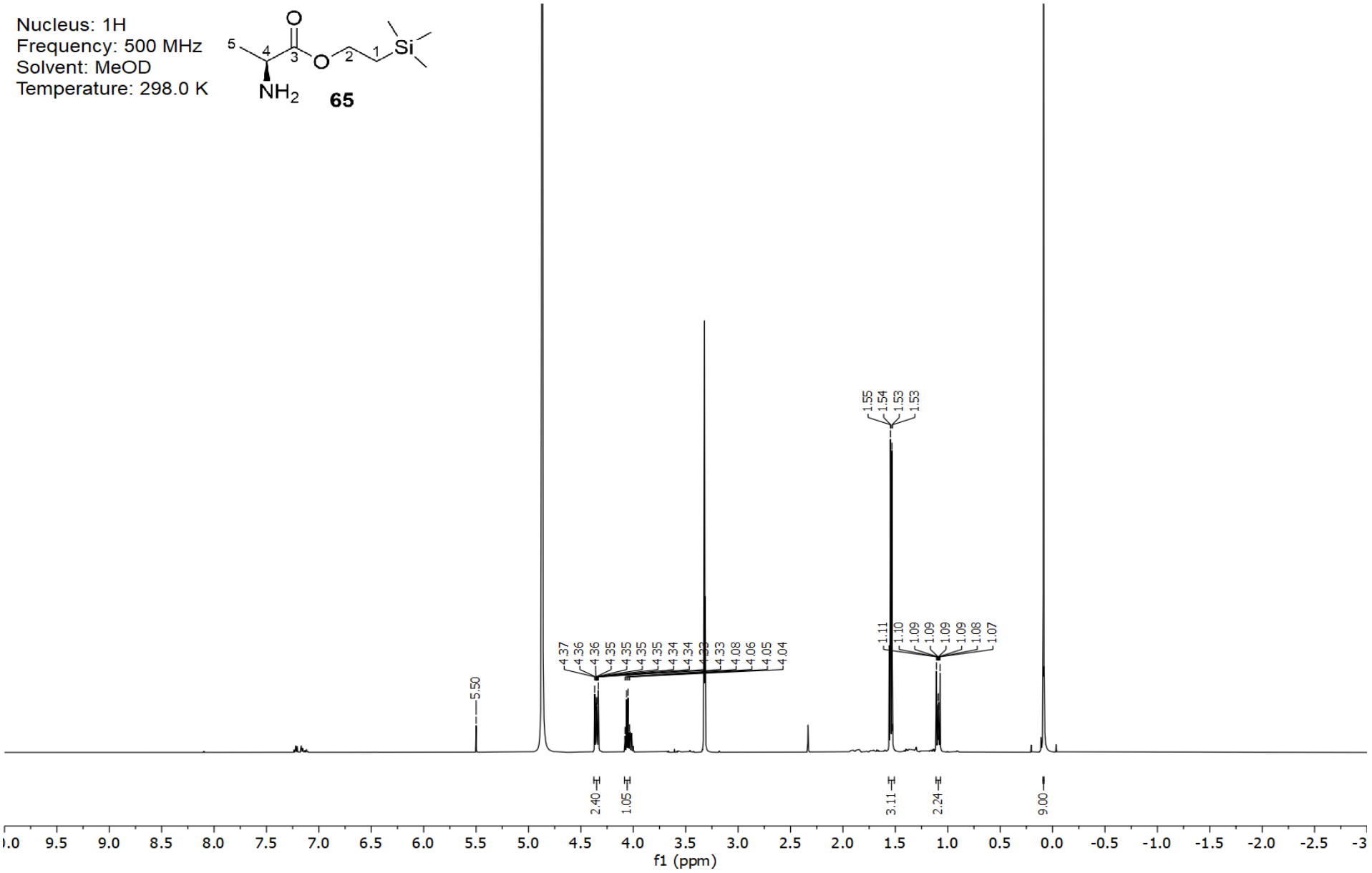
60




Nucleus: 13C
Frequency: 175 MHz
Solvent: D2O
Temperature: 298.0 K
OAc
AcO
AcO
HN
Br
O
Cl
Cl
Cl
60
172.4
171.4
171.3
156.7
103.1
97.2
75.5
75.4
74.4
74.1
72.9
70.7
70.3
63.2
61.9
57.3
20.6
20.6
20.6
f1 (ppm)

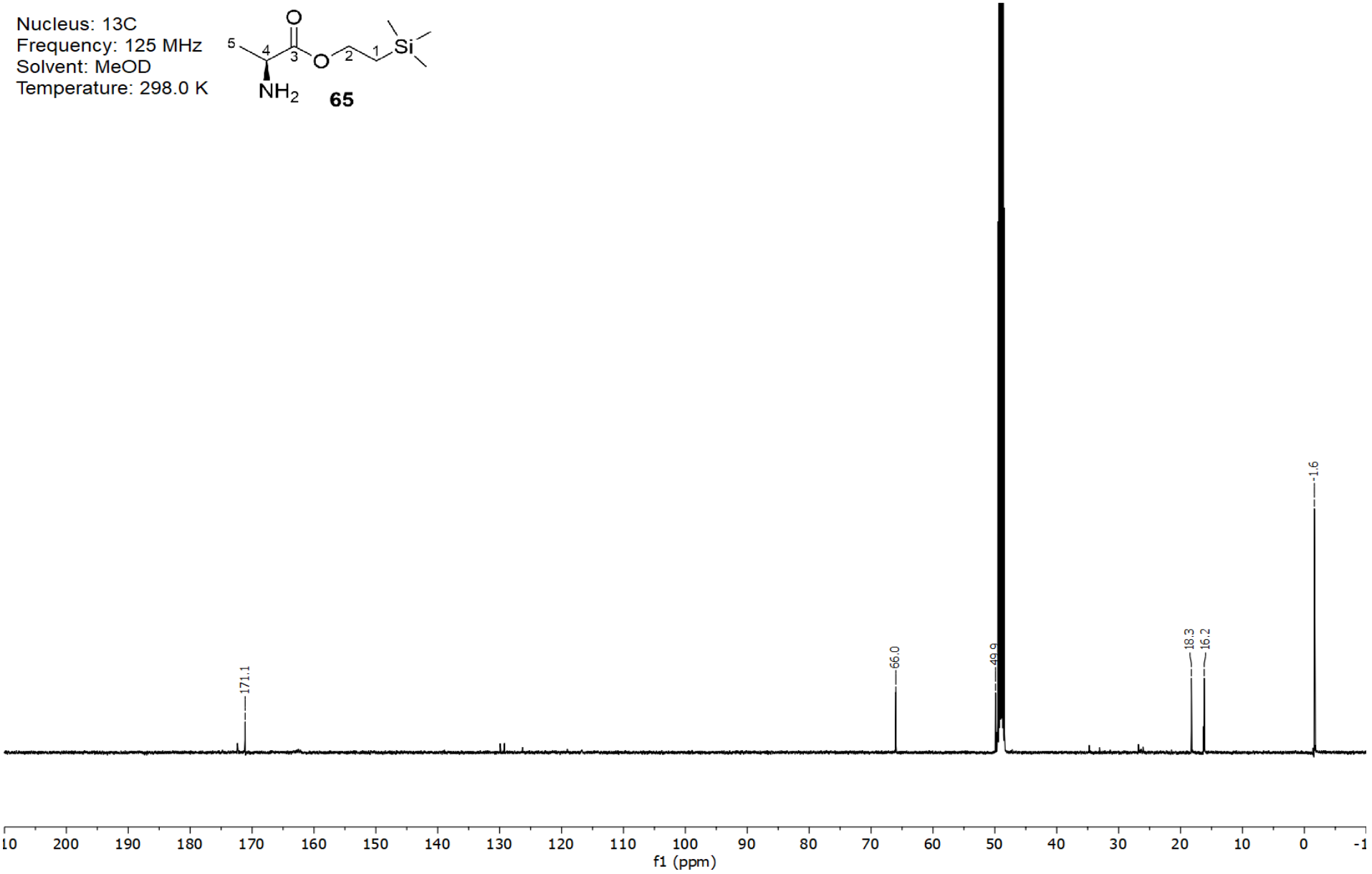
Nucleus: 1H
Frequency: 500 MHz
Solvent: MeOD
Temperature: 298.0 K

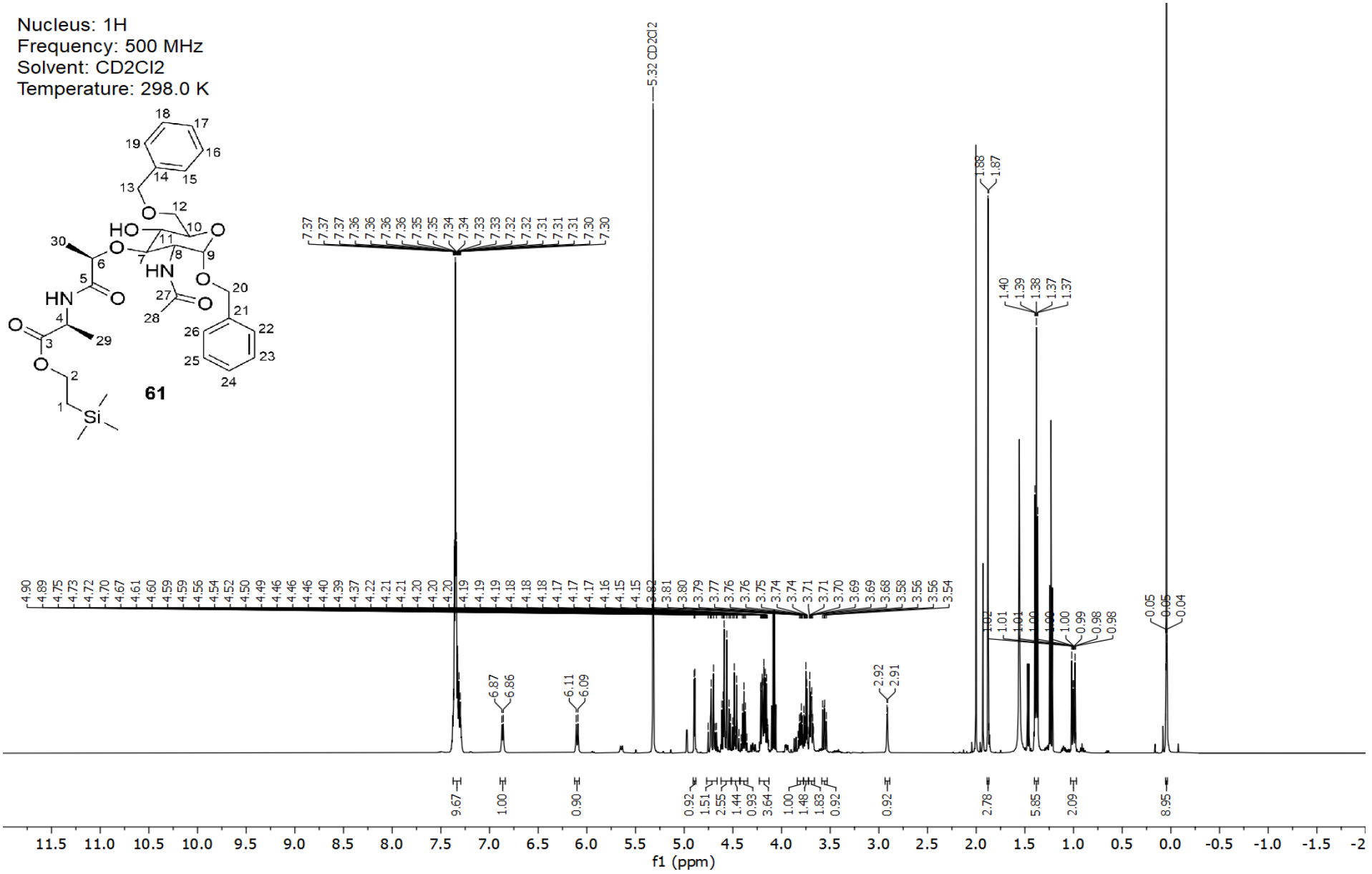
65

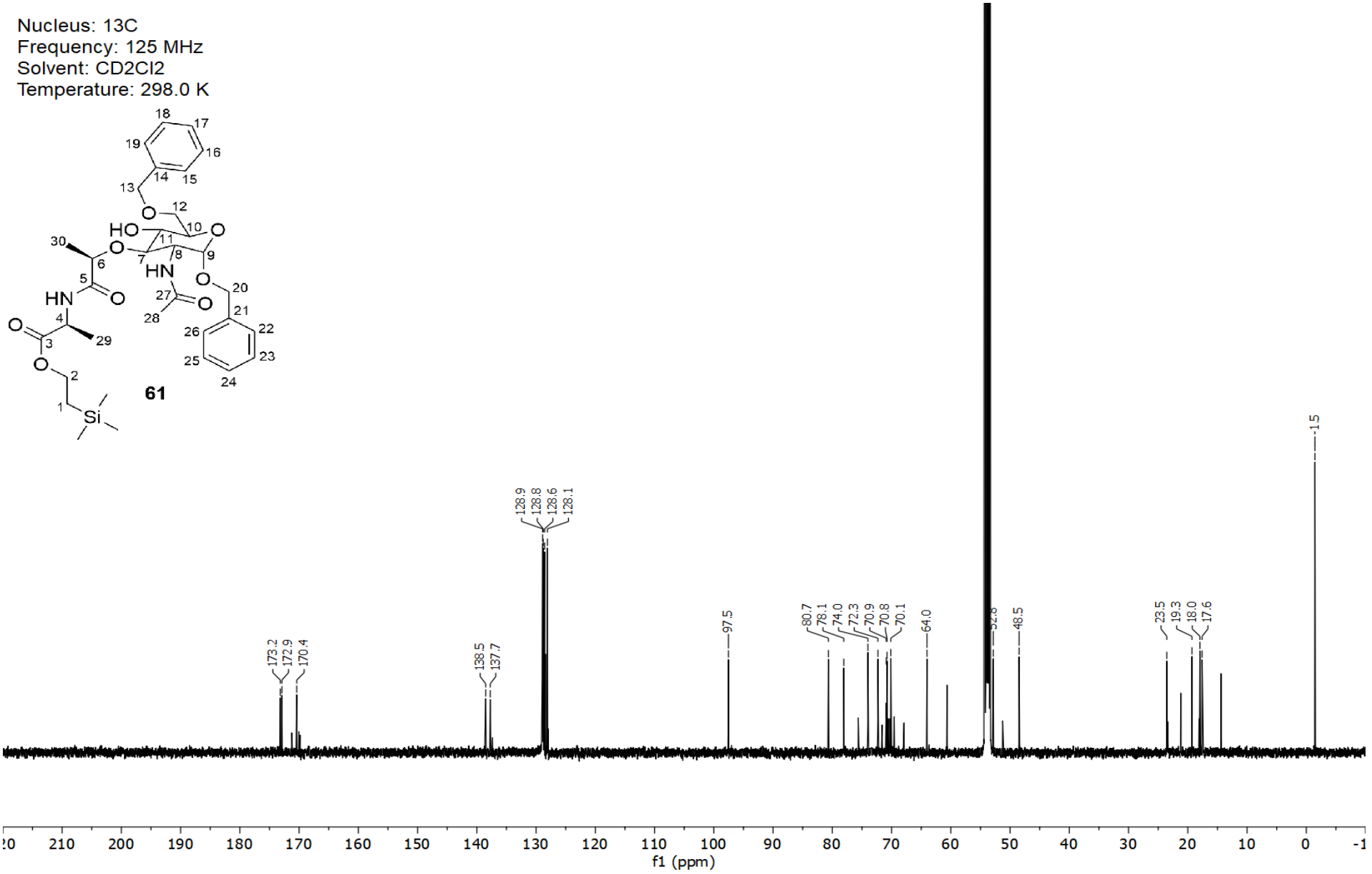


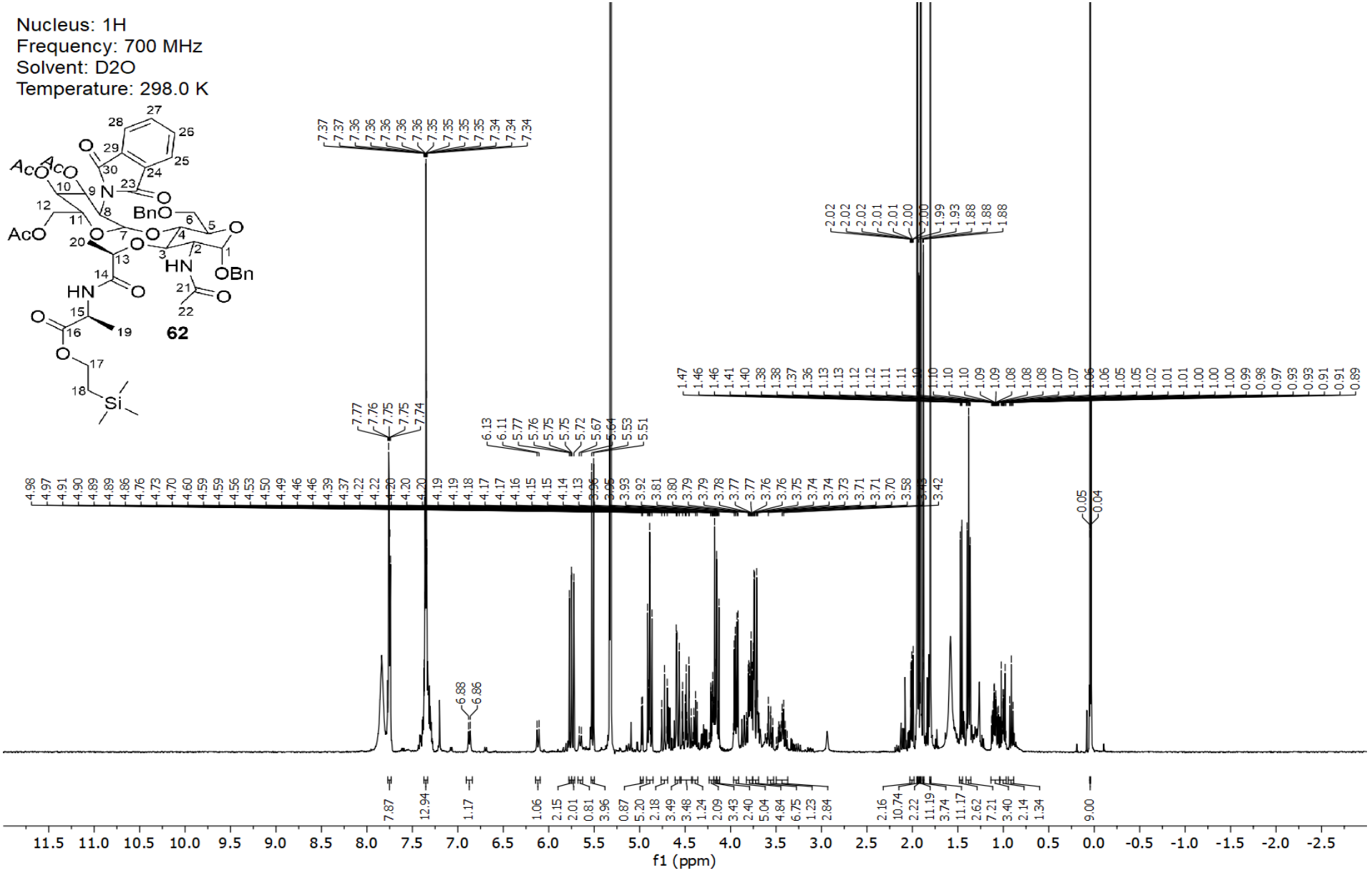
Nucleus: 13C
Frequency: 125 MHz
Solvent: MeOD
Temperature: 298.0 K

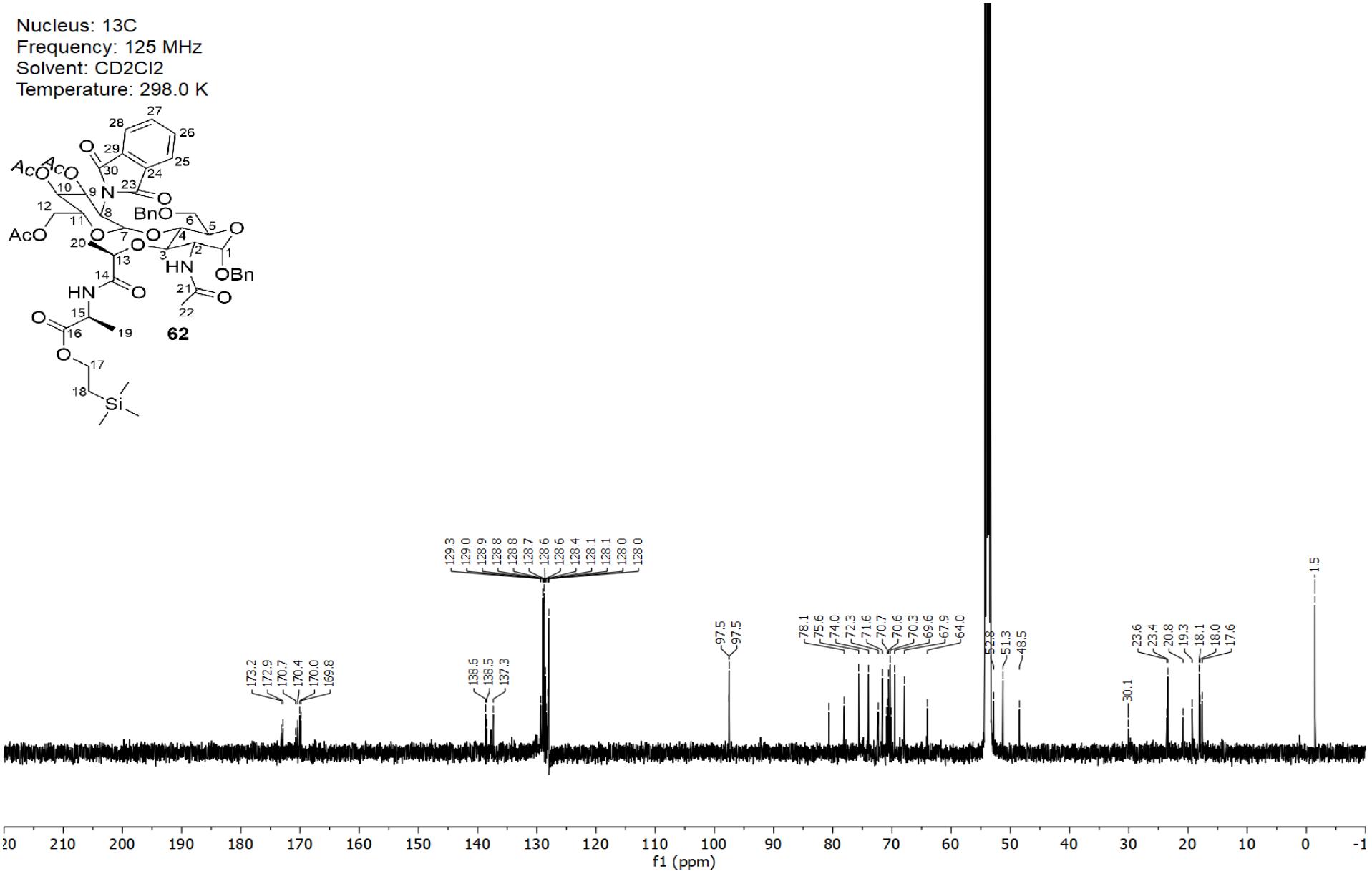
65

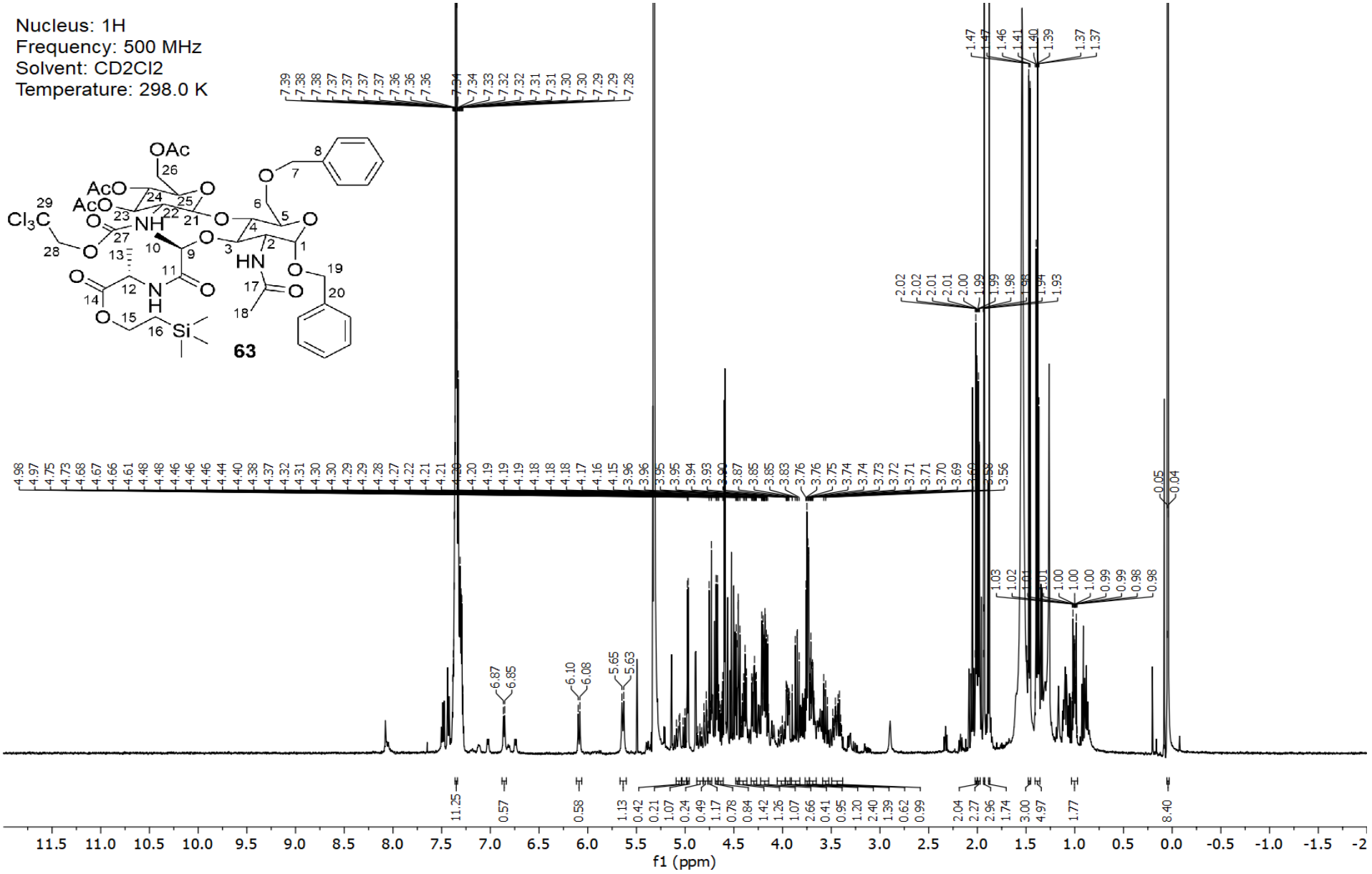



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
61
5.32 CD2Cl2
f1 (ppm)

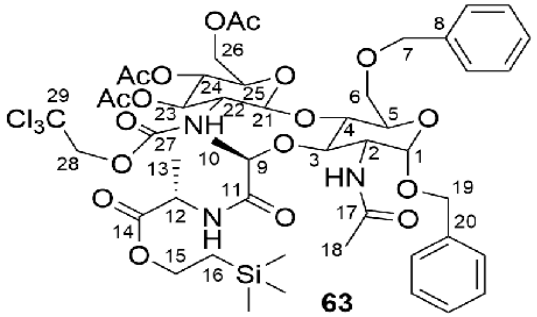

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
61
173.2
172.9
170.4
138.5
137.7
128.9
128.8
128.6
128.1
97.5
80.7
78.1
74.0
72.3
70.9
70.8
70.1
64.0
52.8
48.5
23.5
19.3
18.0
17.6
-1.5
f1 (ppm)


Nucleus: 1H
Frequency: 700 MHz
Solvent: D2O
Temperature: 298.0 K
62
f1 (ppm)

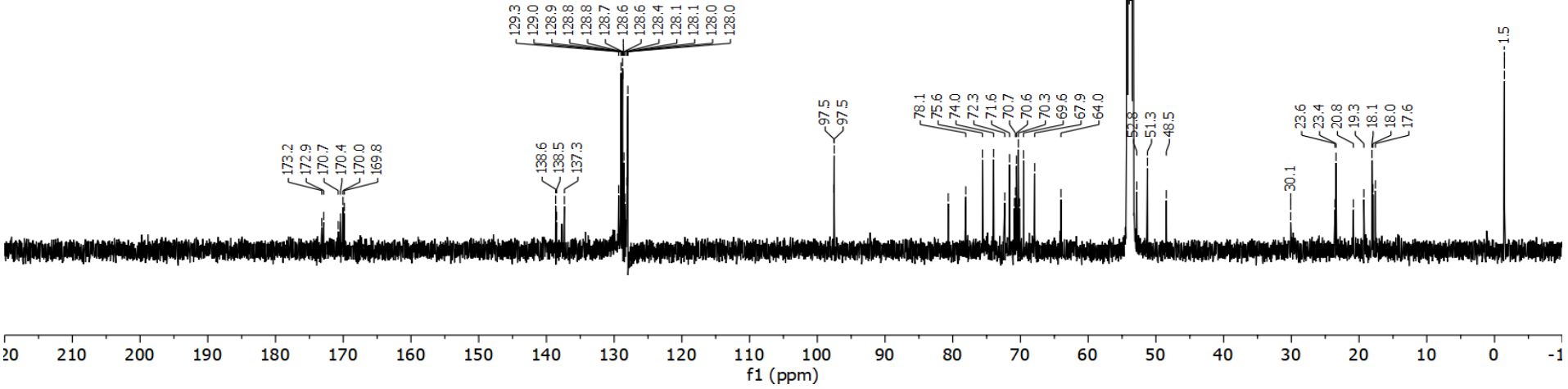

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
62
173.2
172.9
170.7
170.4
170.0
169.8
138.6
138.5
137.3
129.3
129.0
128.9
128.8
128.8
128.7
128.6
128.6
128.4
128.1
128.1
128.0
128.0
97.5
97.5
78.1
75.6
74.0
72.3
71.6
70.7
70.6
70.3
69.6
67.9
64.0
52.8
51.3
48.5
30.1
23.6
23.4
20.8
19.3
18.1
18.0
17.6
-1.5
f1 (ppm)


Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
63
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

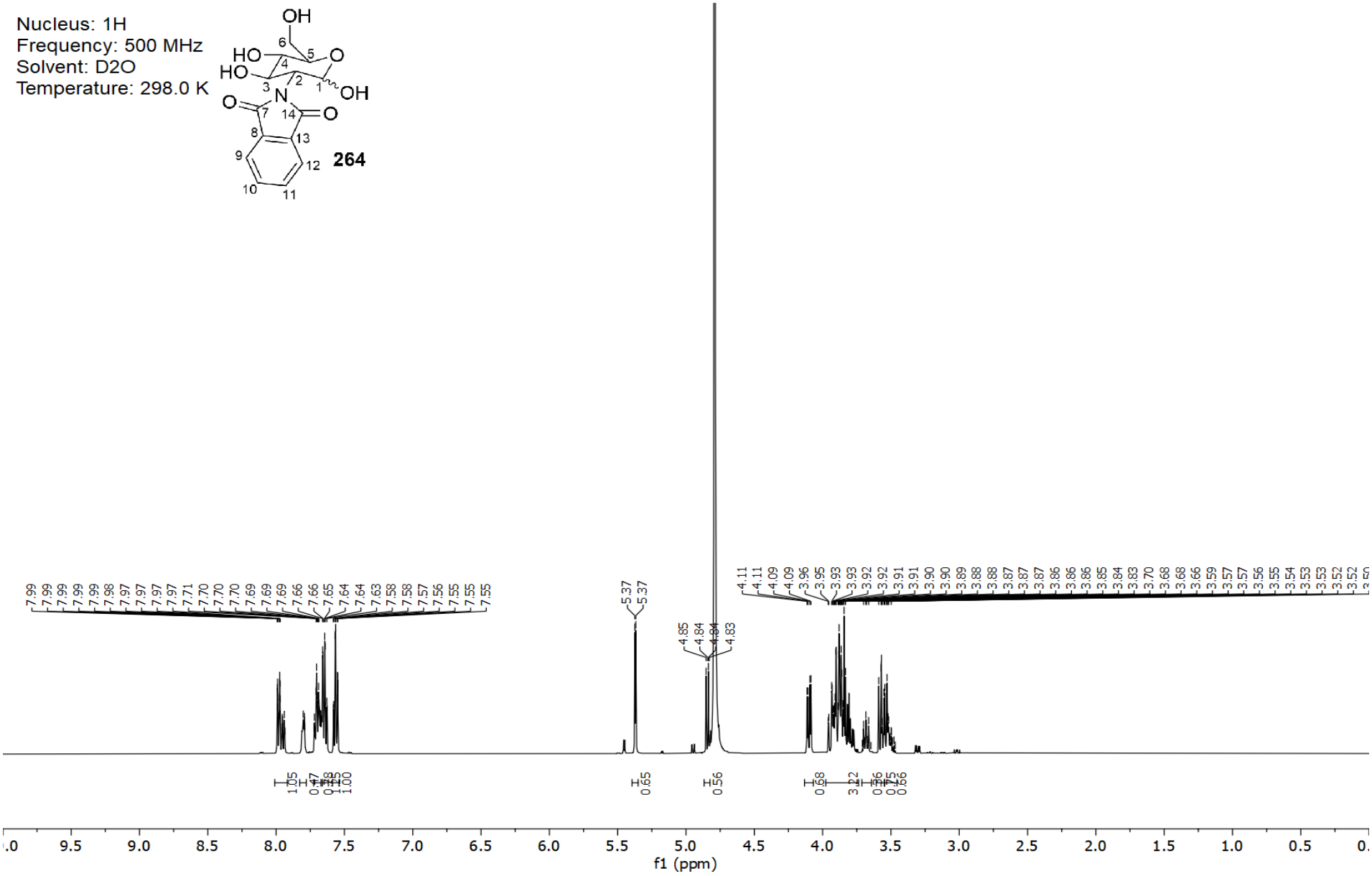


63

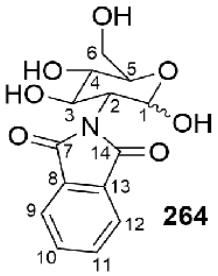


Nucleus: 1H
Frequency: 500 MHz
Solvent: D2O
Temperature: 298.0 K

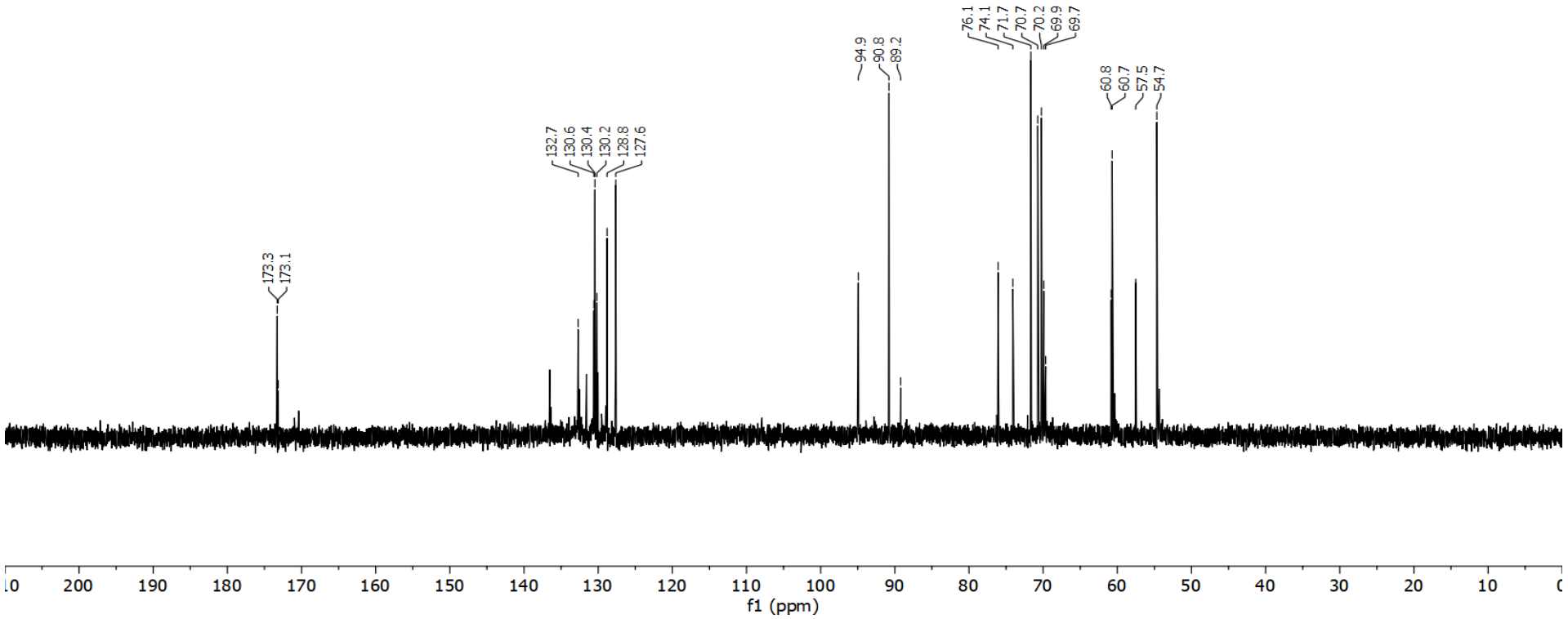
264



Nucleus: 13C
Frequency: 125 MHz
Solvent: D2O
Temperature: 298.0 K

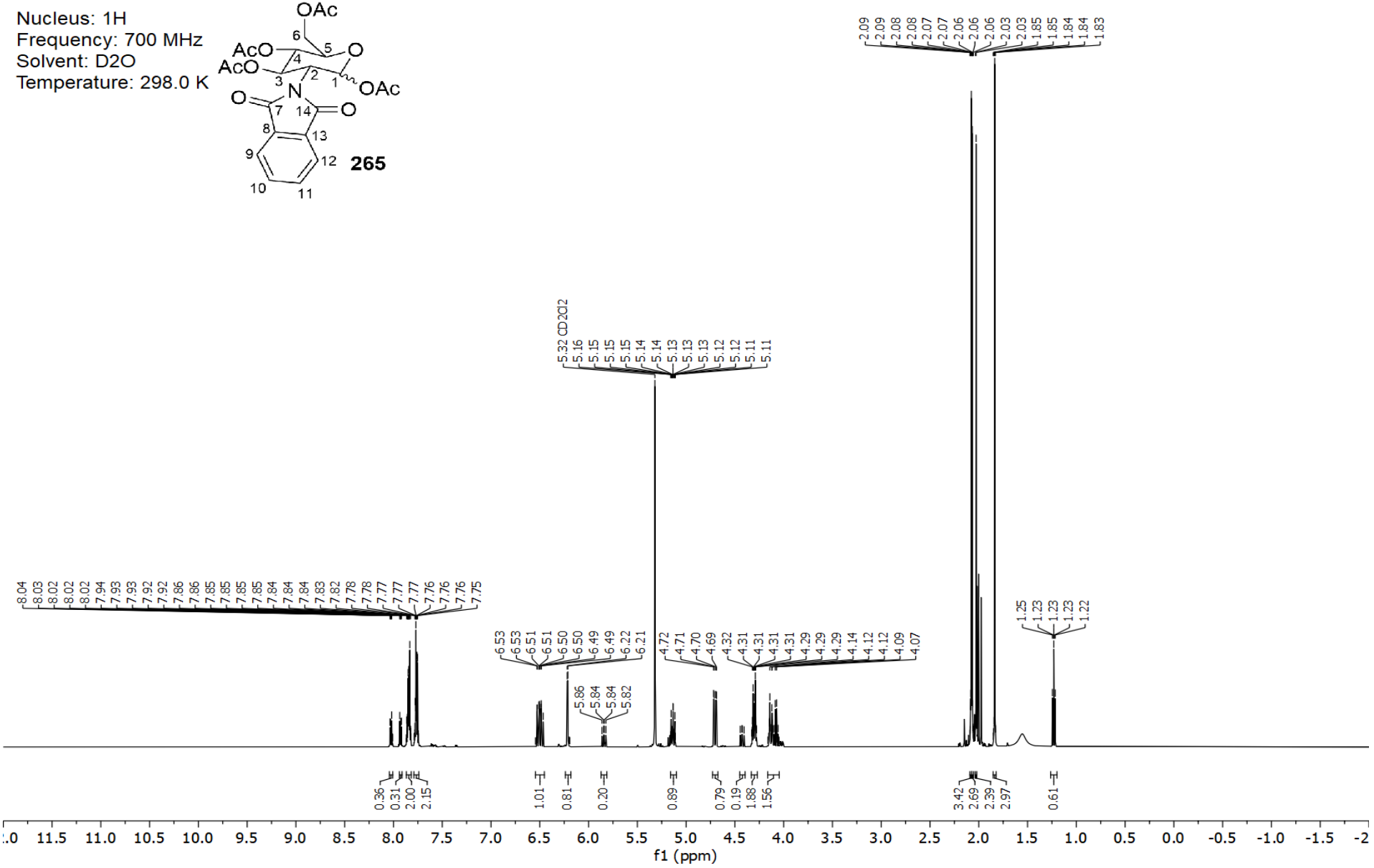


264



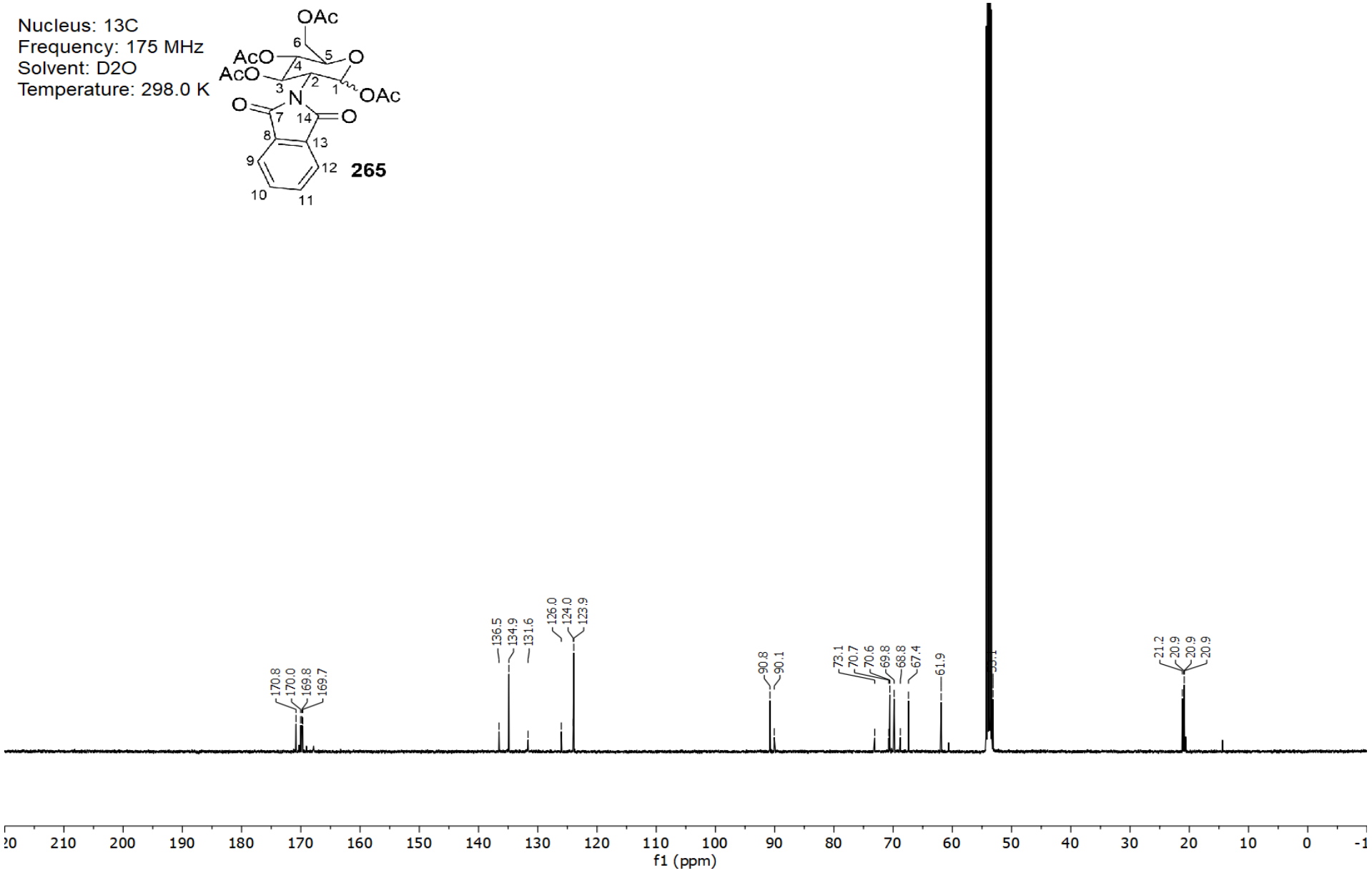
Nucleus: 1H
Frequency: 700 MHz
Solvent: D2O
Temperature: 298.0 K

265



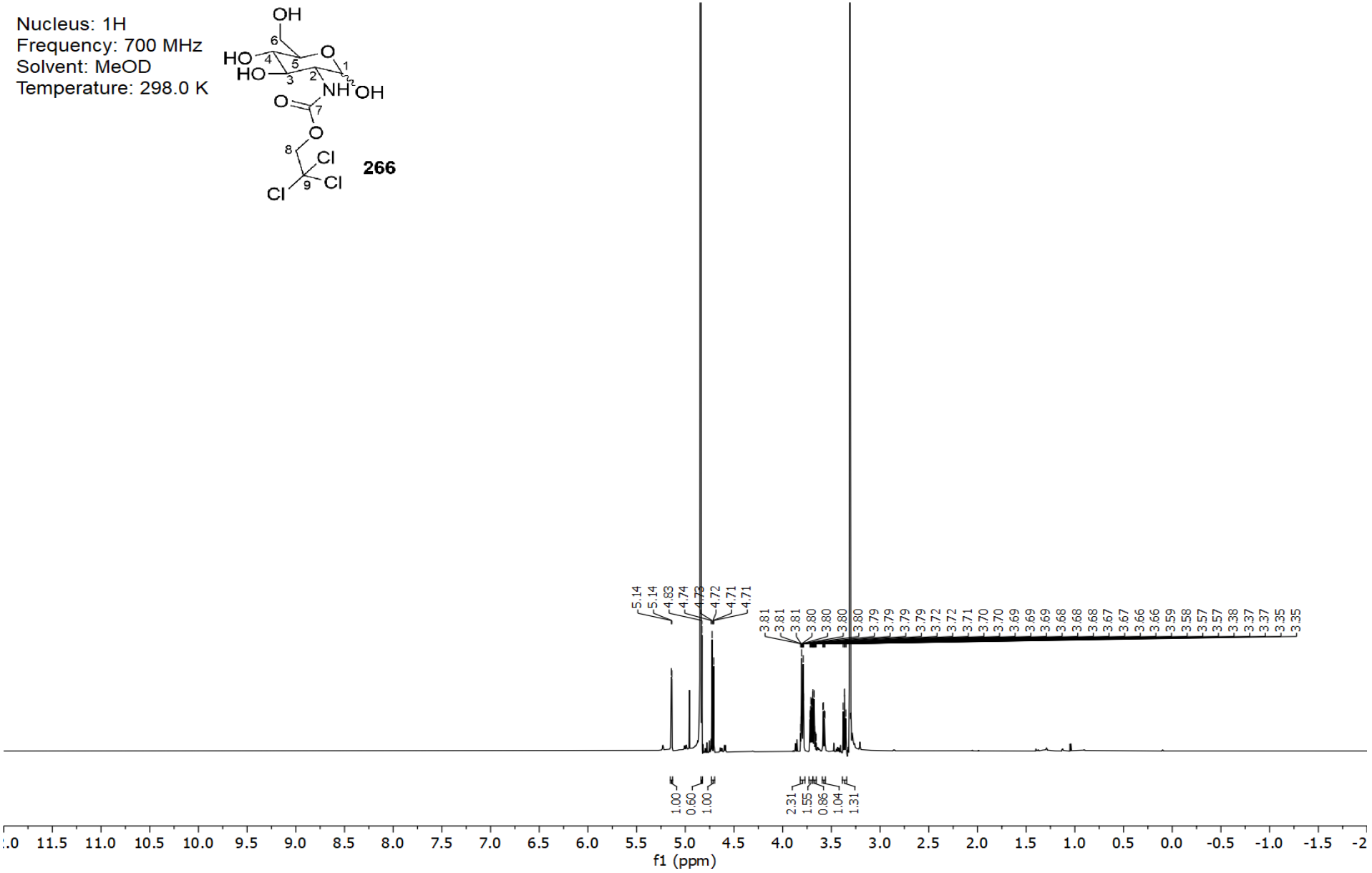
Nucleus: 13C
Frequency: 175 MHz
Solvent: D2O
Temperature: 298.0 K

265



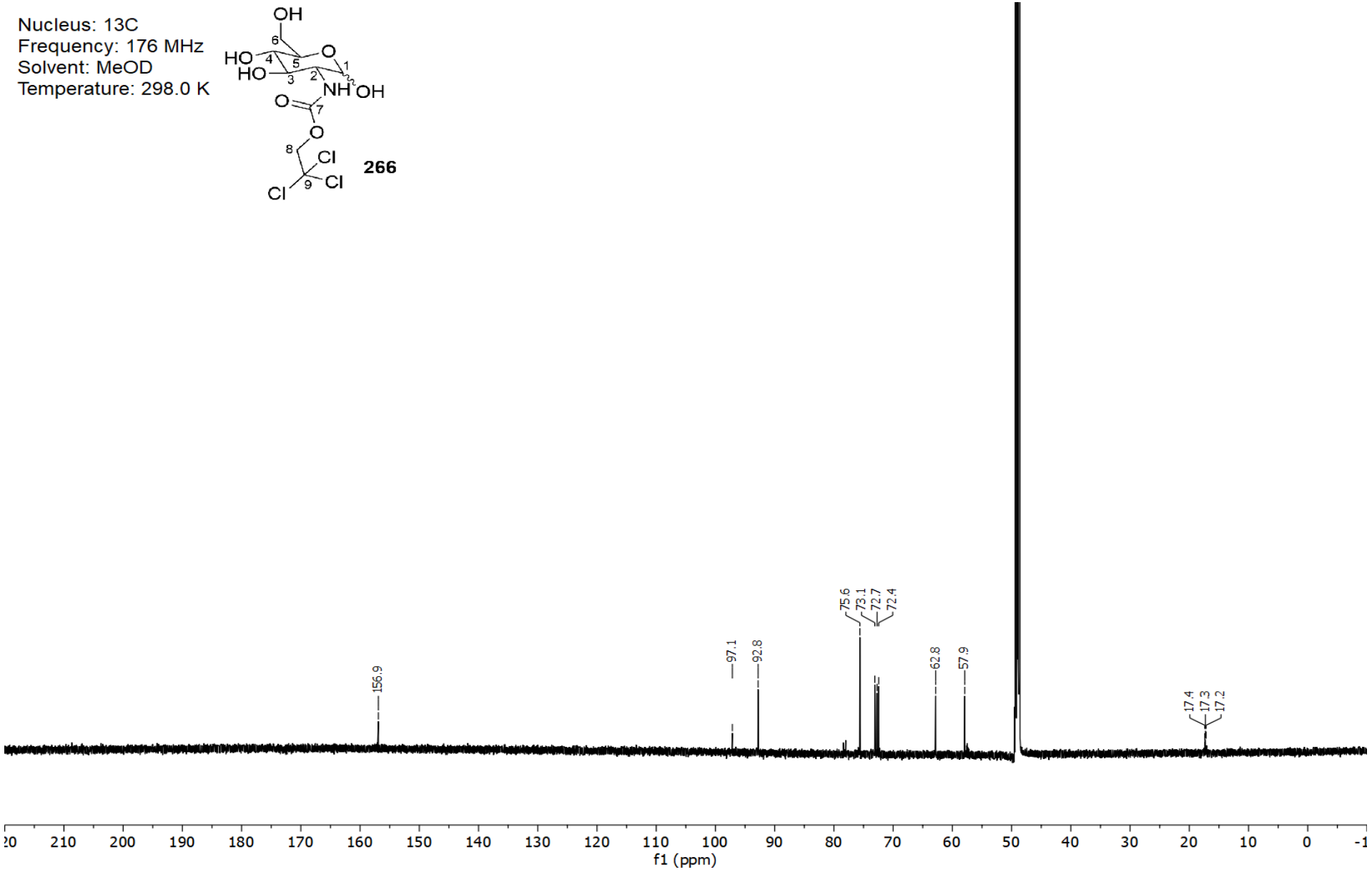
Nucleus: 1H
Frequency: 700 MHz
Solvent: MeOD
Temperature: 298.0 K

266



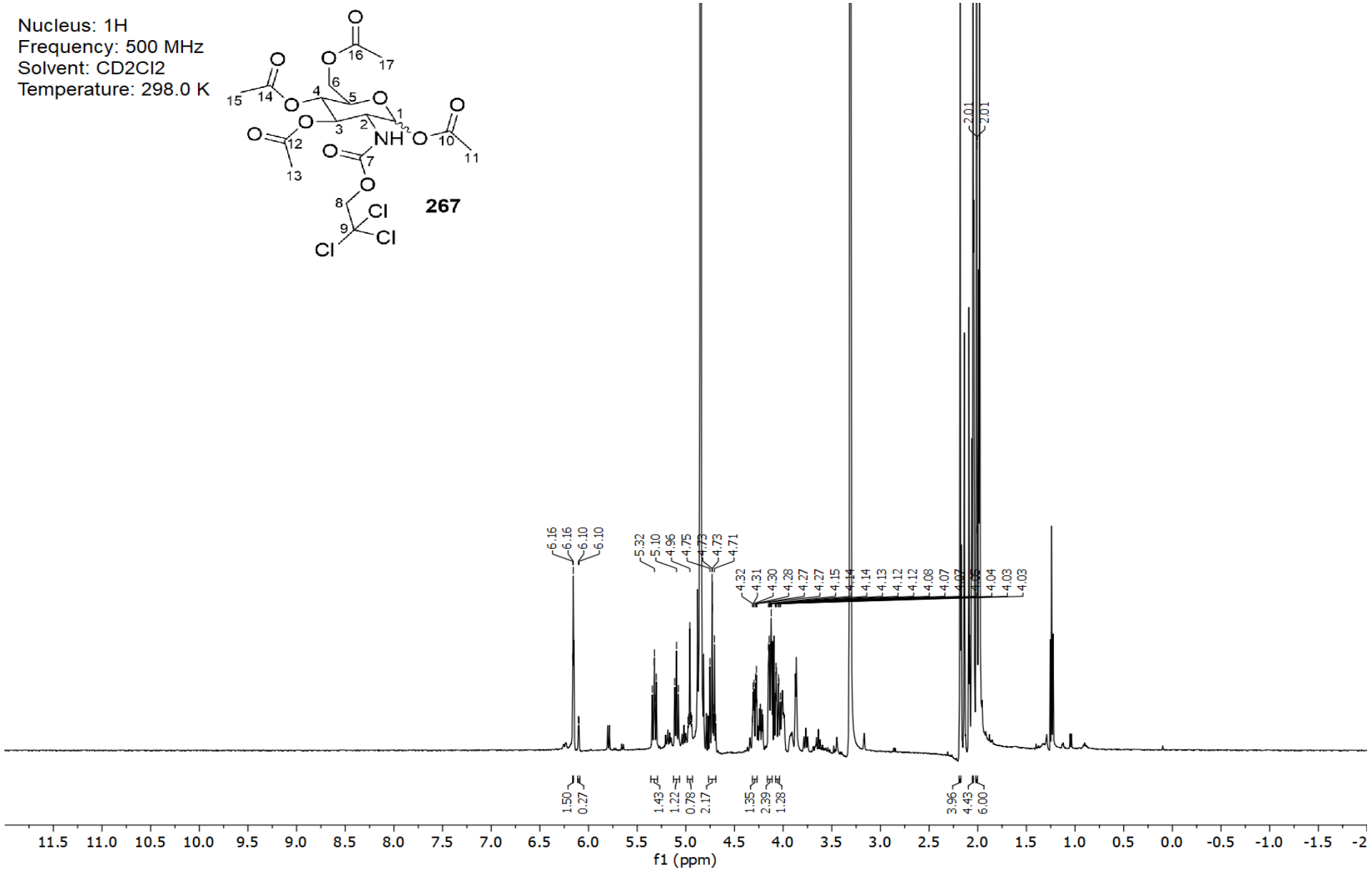
Nucleus: 13C
Frequency: 176 MHz
Solvent: MeOD
Temperature: 298.0 K

266



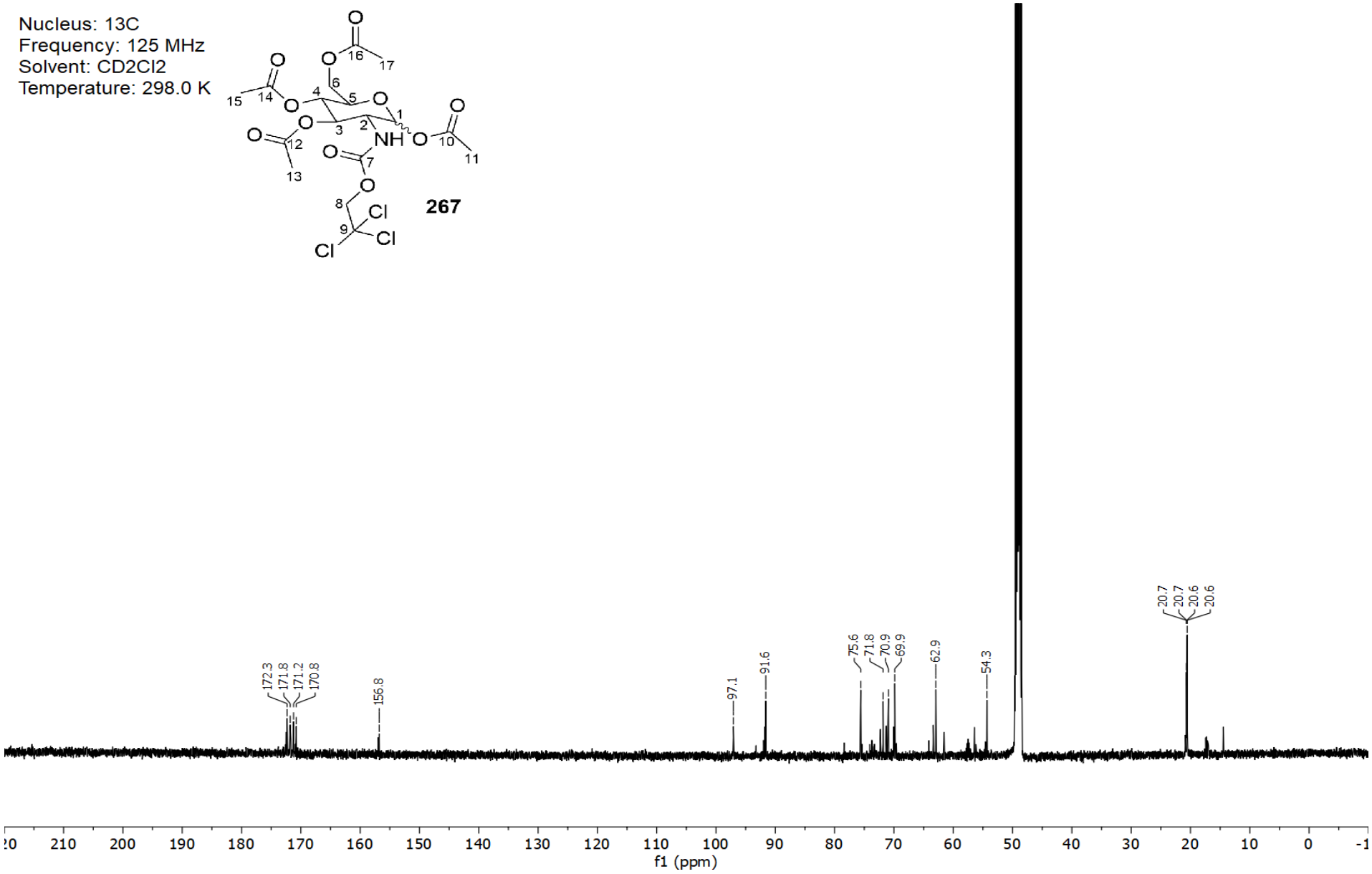
Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

267

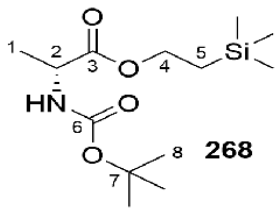


Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

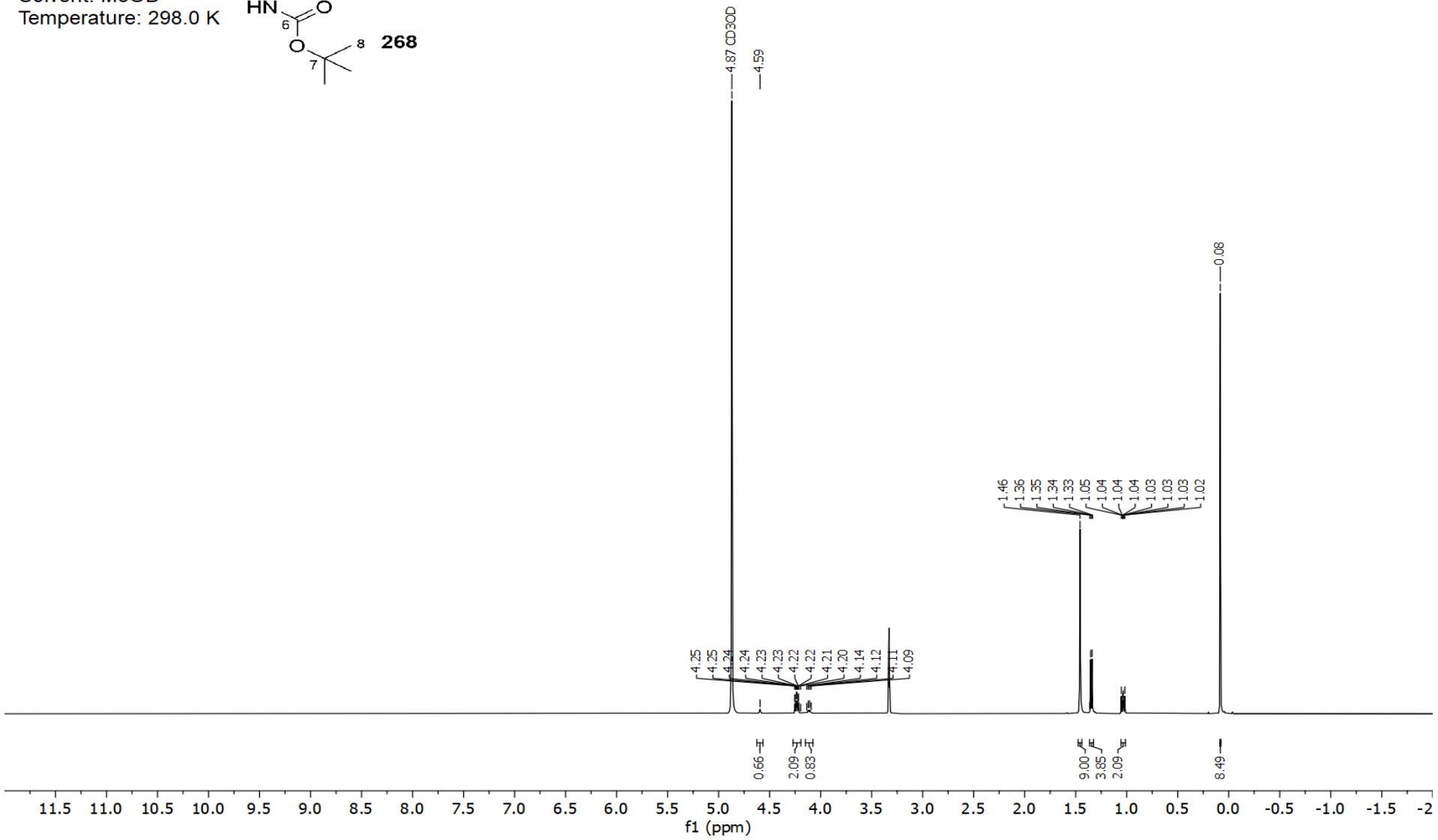
267



Nucleus: 1H
Frequency: 500 MHz
Solvent: MeOD
Temperature: 298.0 K

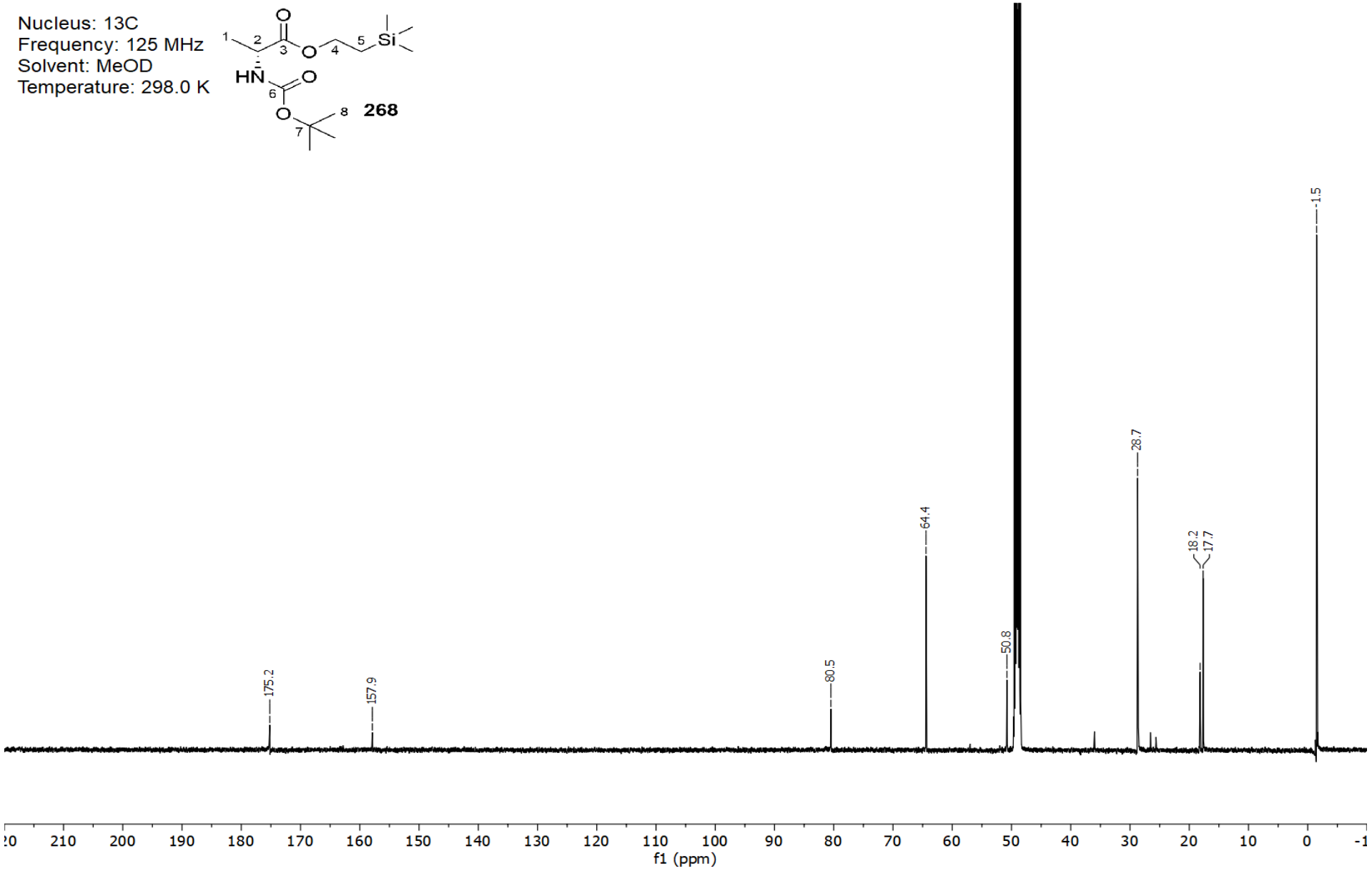


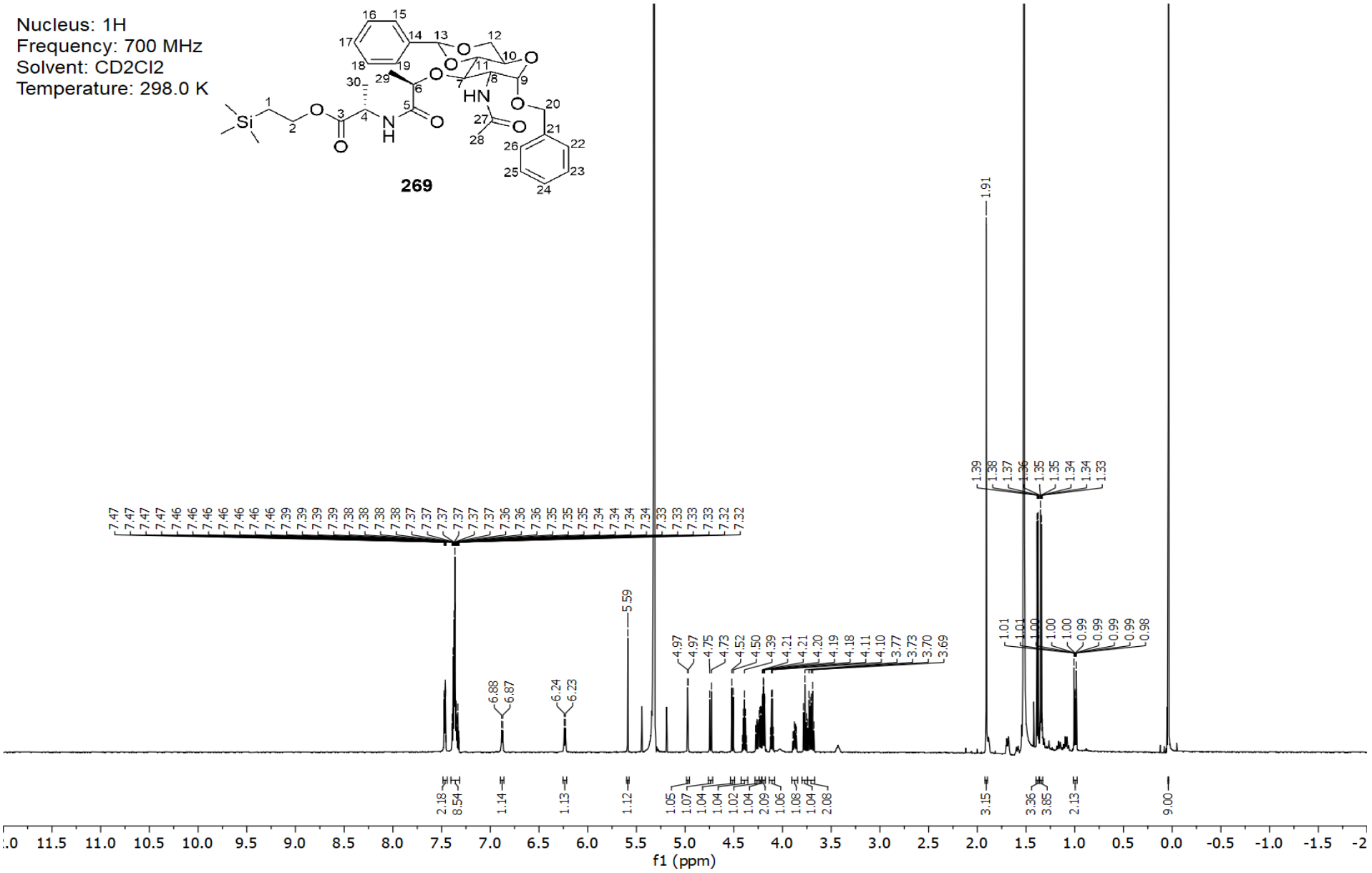
268



Nucleus: 13C
Frequency: 125 MHz
Solvent: MeOD
Temperature: 298.0 K

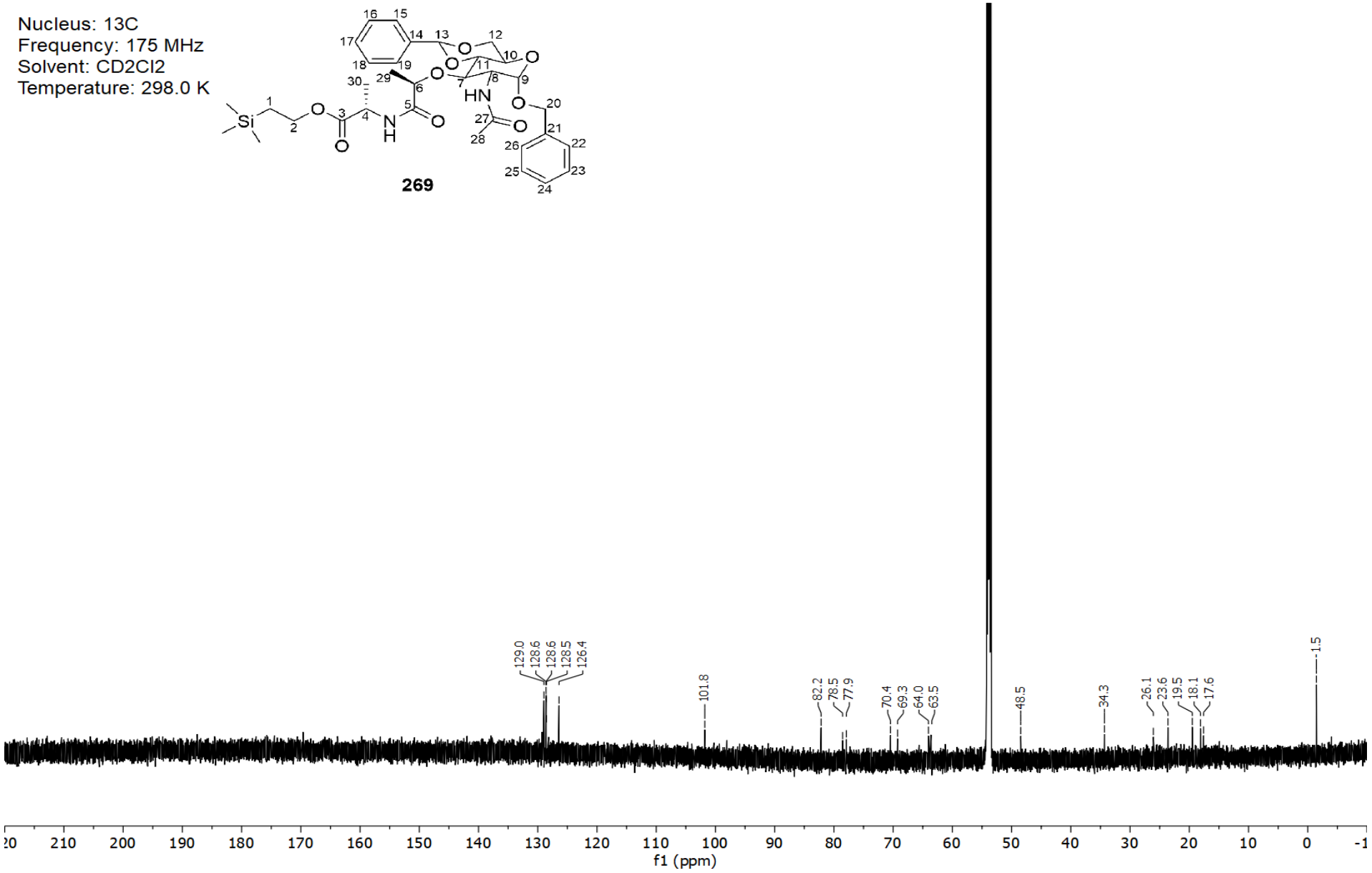
268

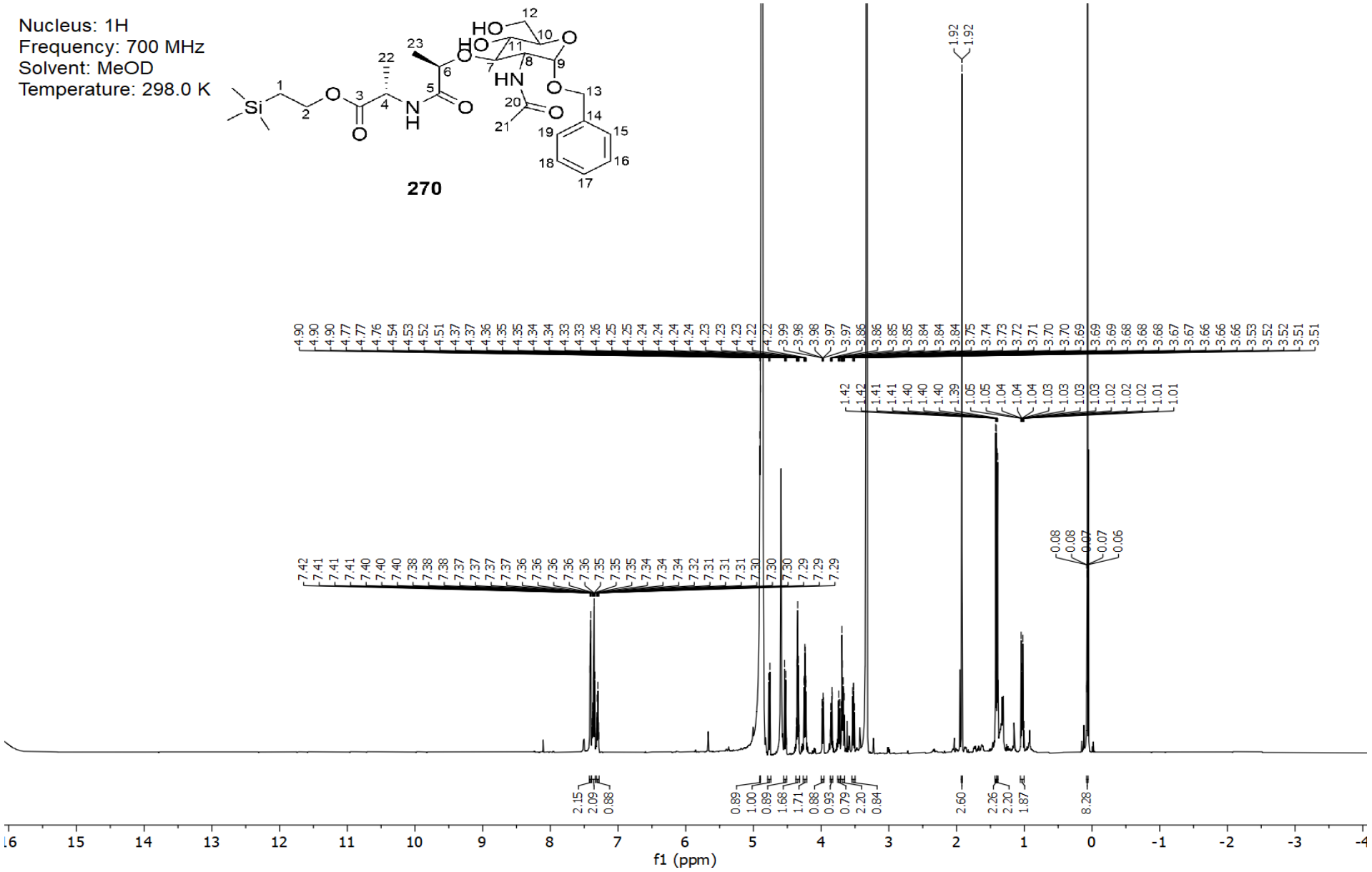



Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
269
f1 (ppm)

Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

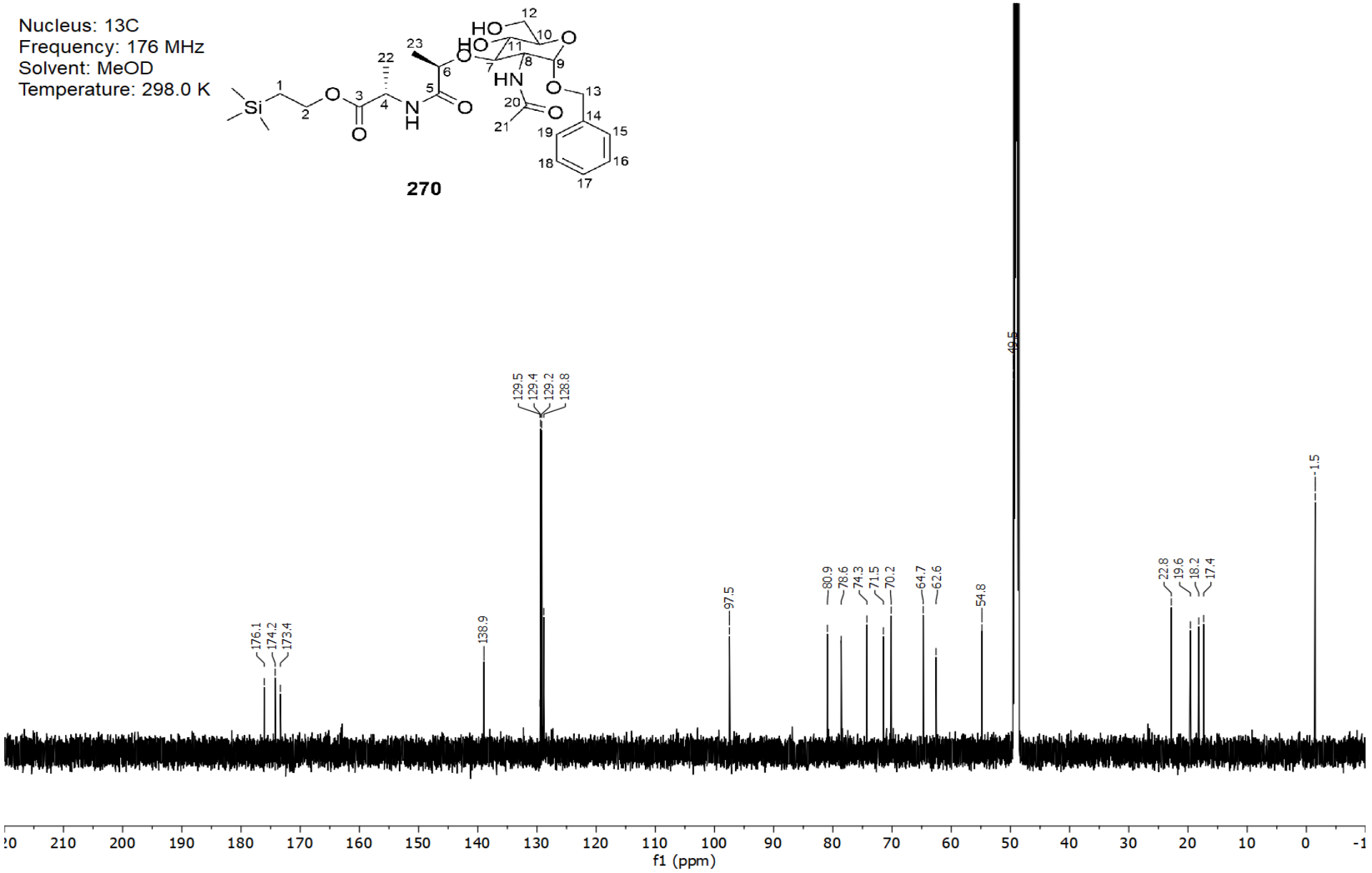
269

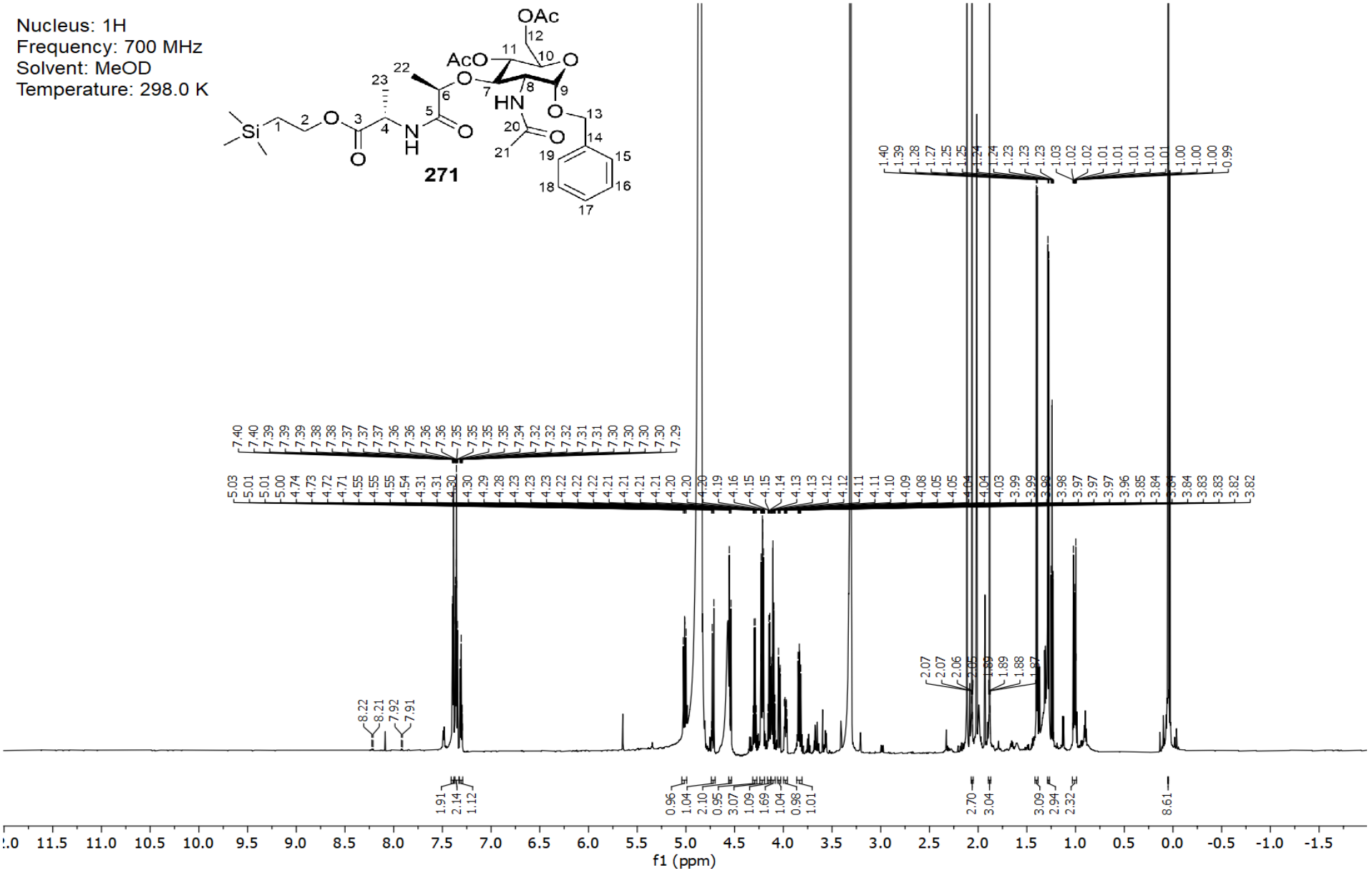



Nucleus: 1H
Frequency: 700 MHz
Solvent: MeOD
Temperature: 298.0 K
270
f1 (ppm)

Nucleus: 13C
Frequency: 176 MHz
Solvent: MeOD
Temperature: 298.0 K

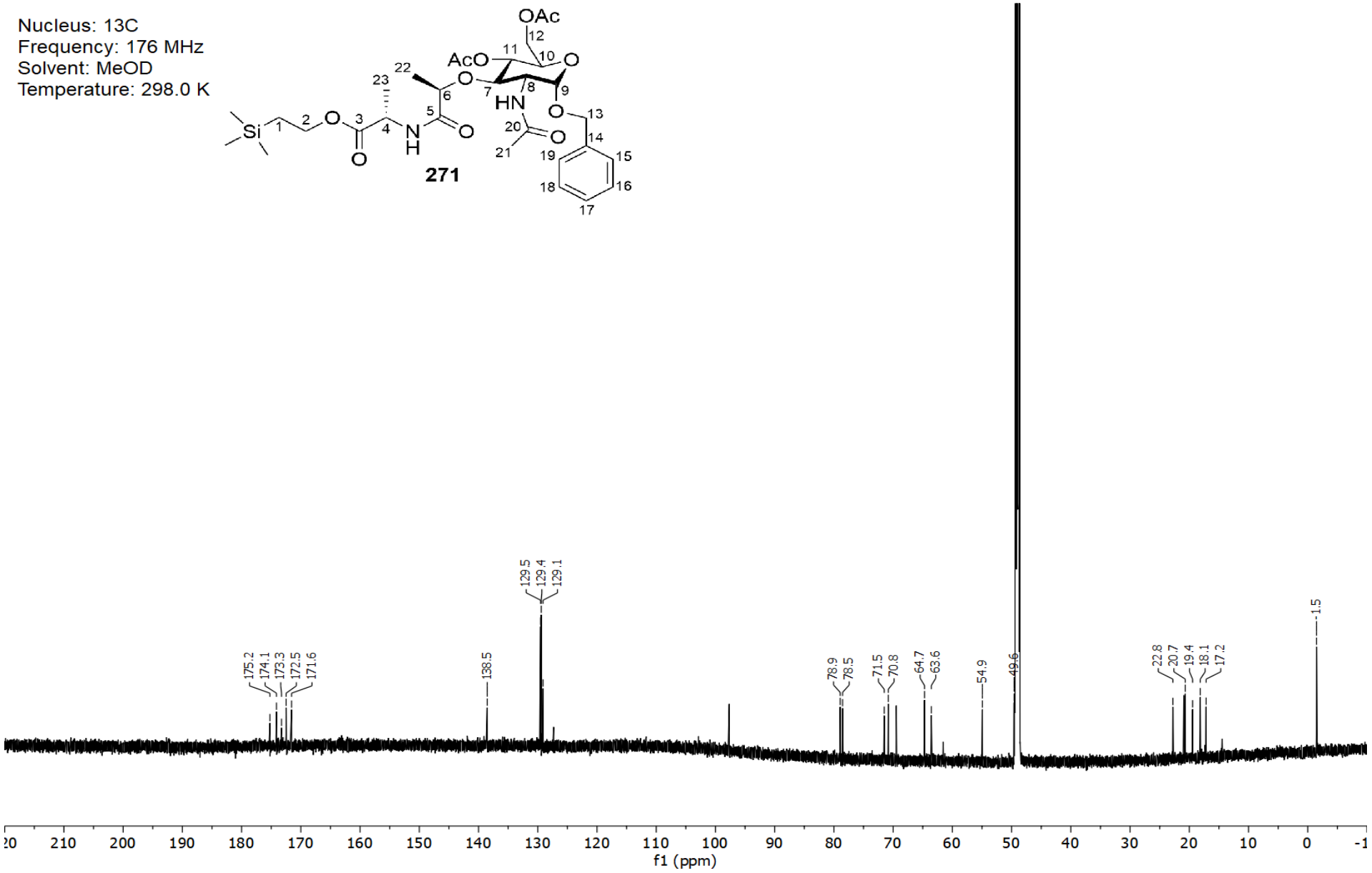
270




Nucleus: 1H
Frequency: 700 MHz
Solvent: MeOD
Temperature: 298.0 K
271
f1 (ppm)

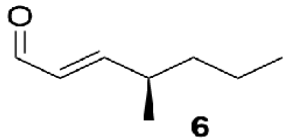
Nucleus: 13C
Frequency: 176 MHz
Solvent: MeOD
Temperature: 298.0 K

271

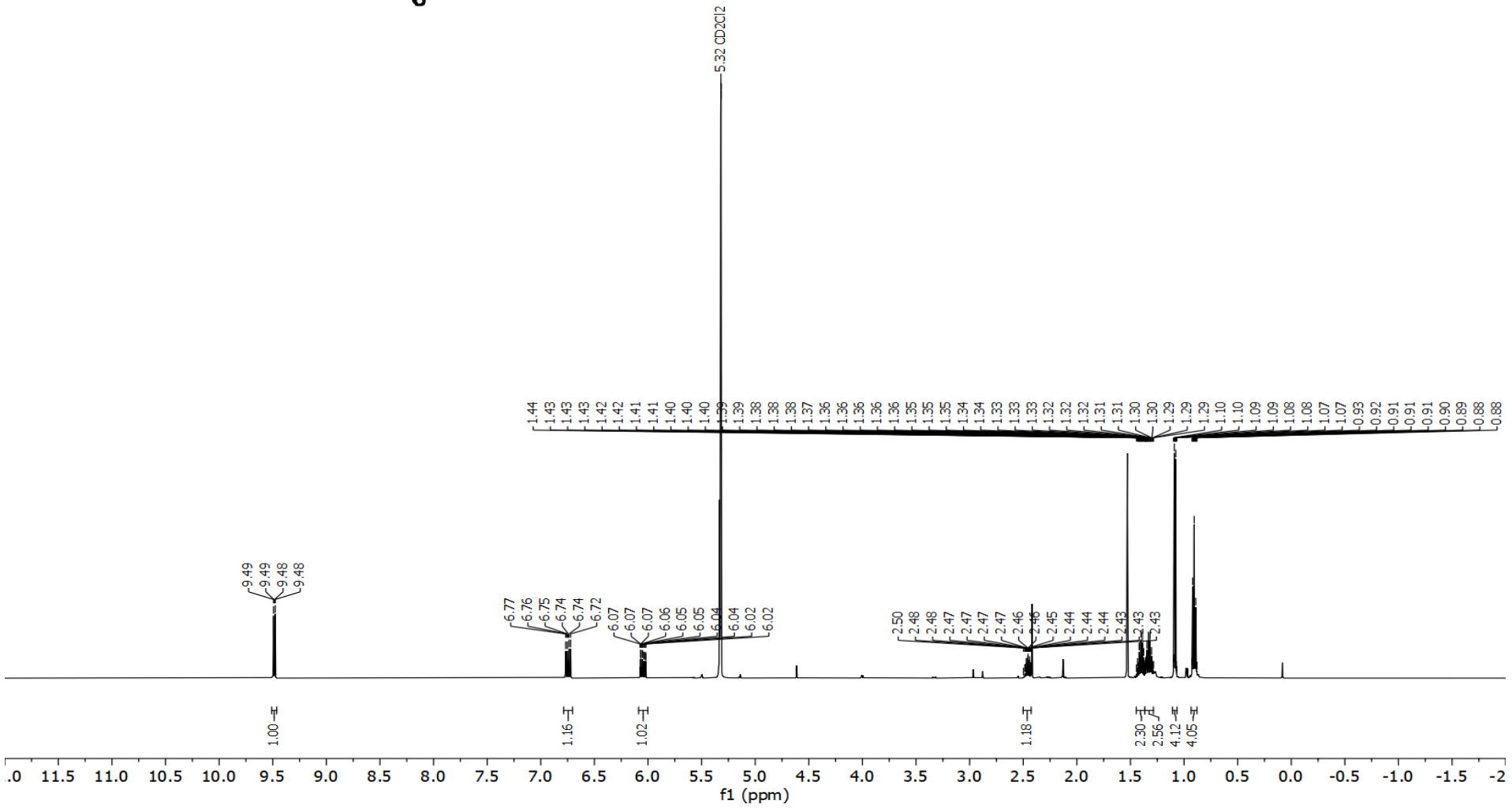


5.2 Spectra Part II

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

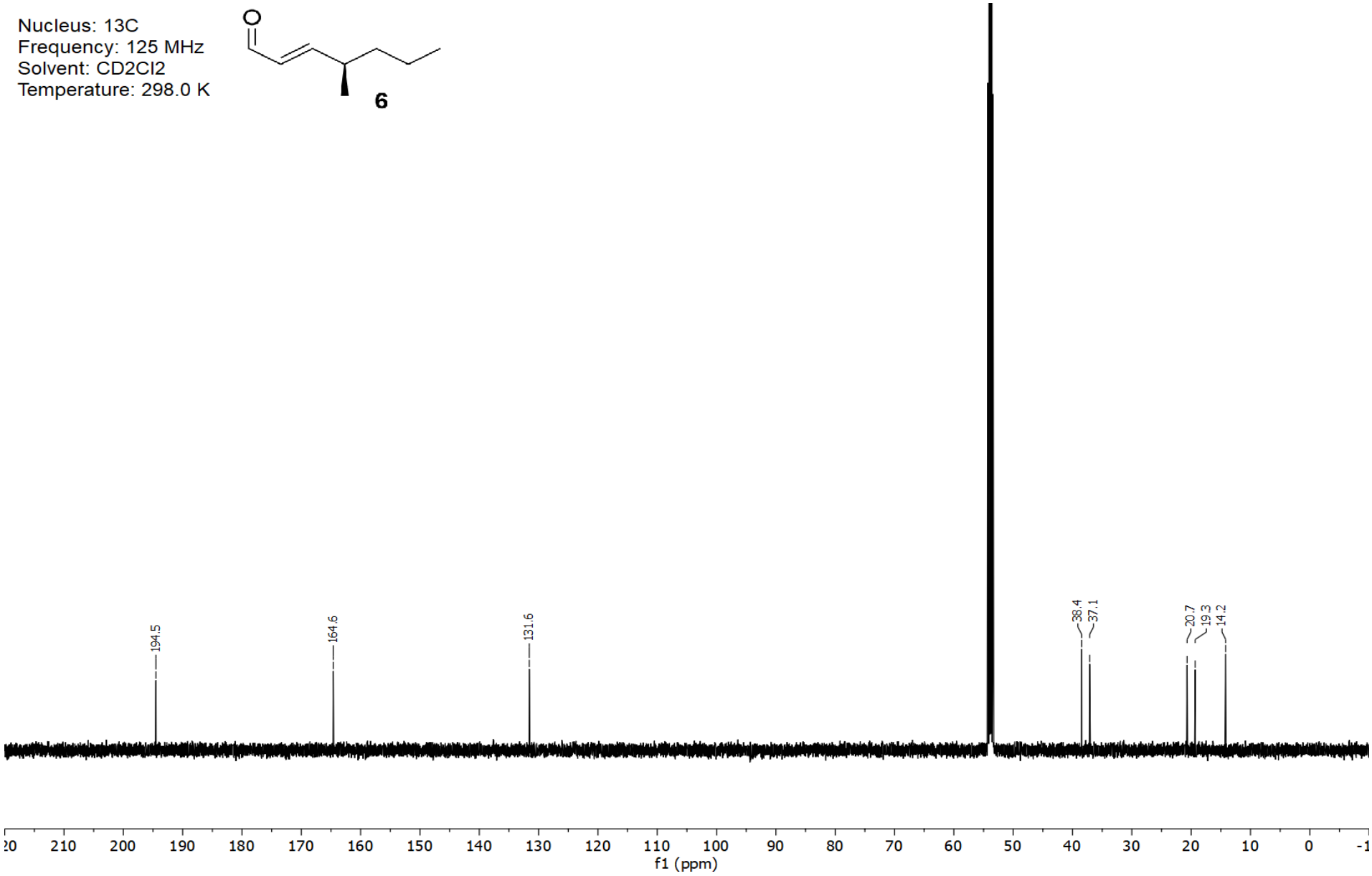


6

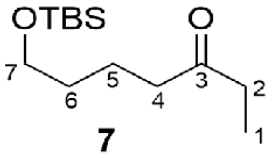


Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

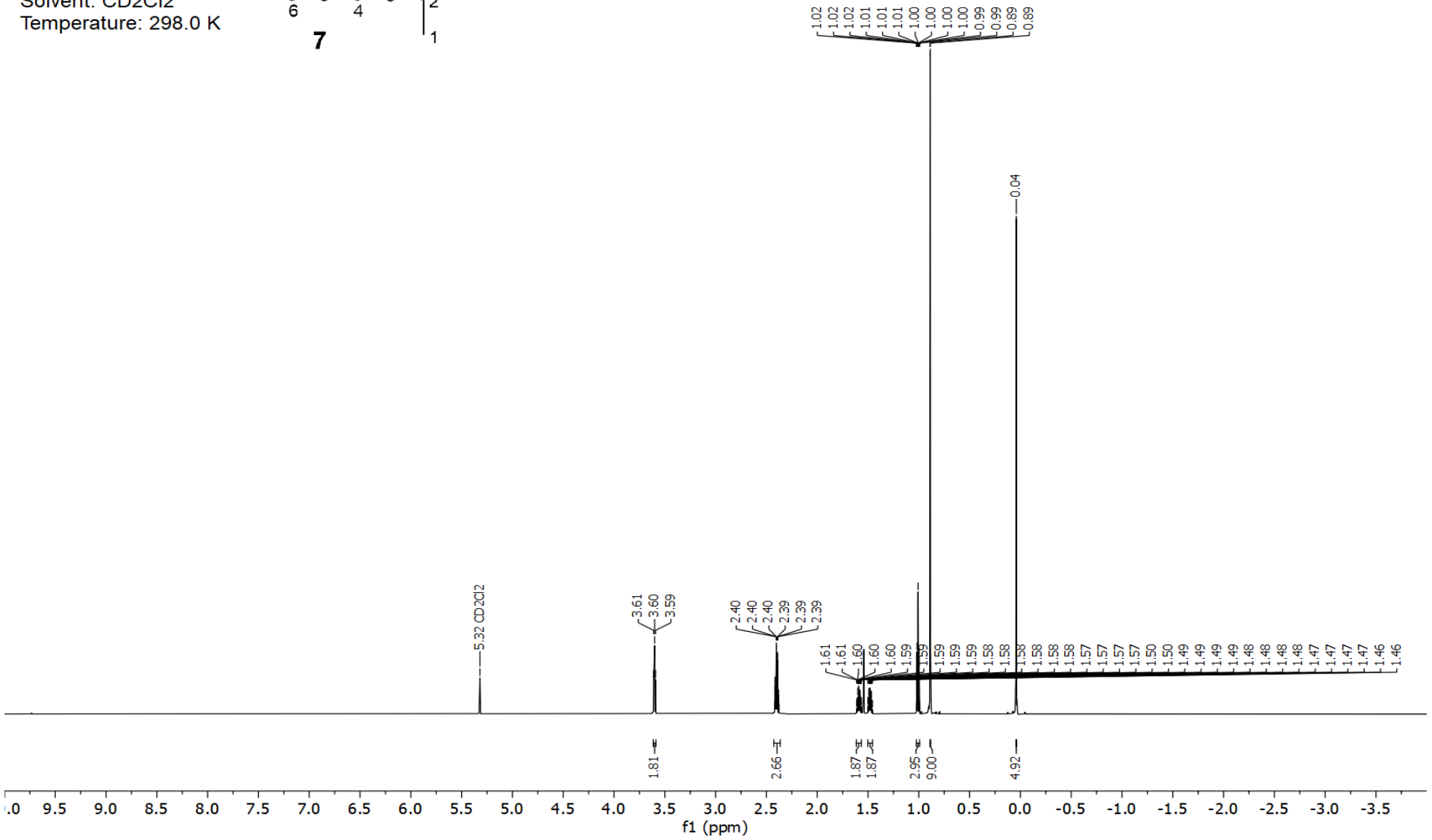
6



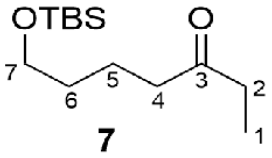
Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K



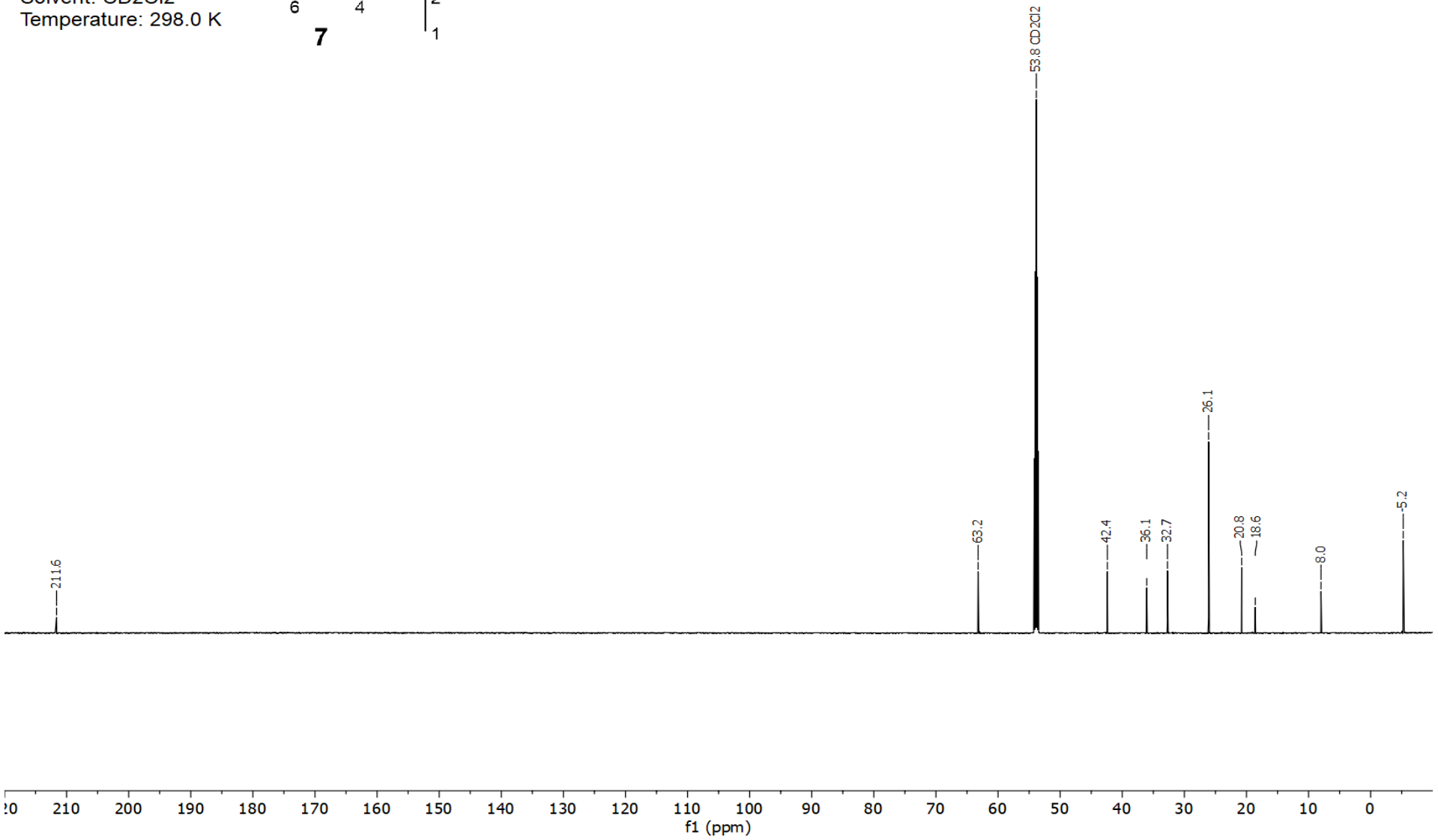
7

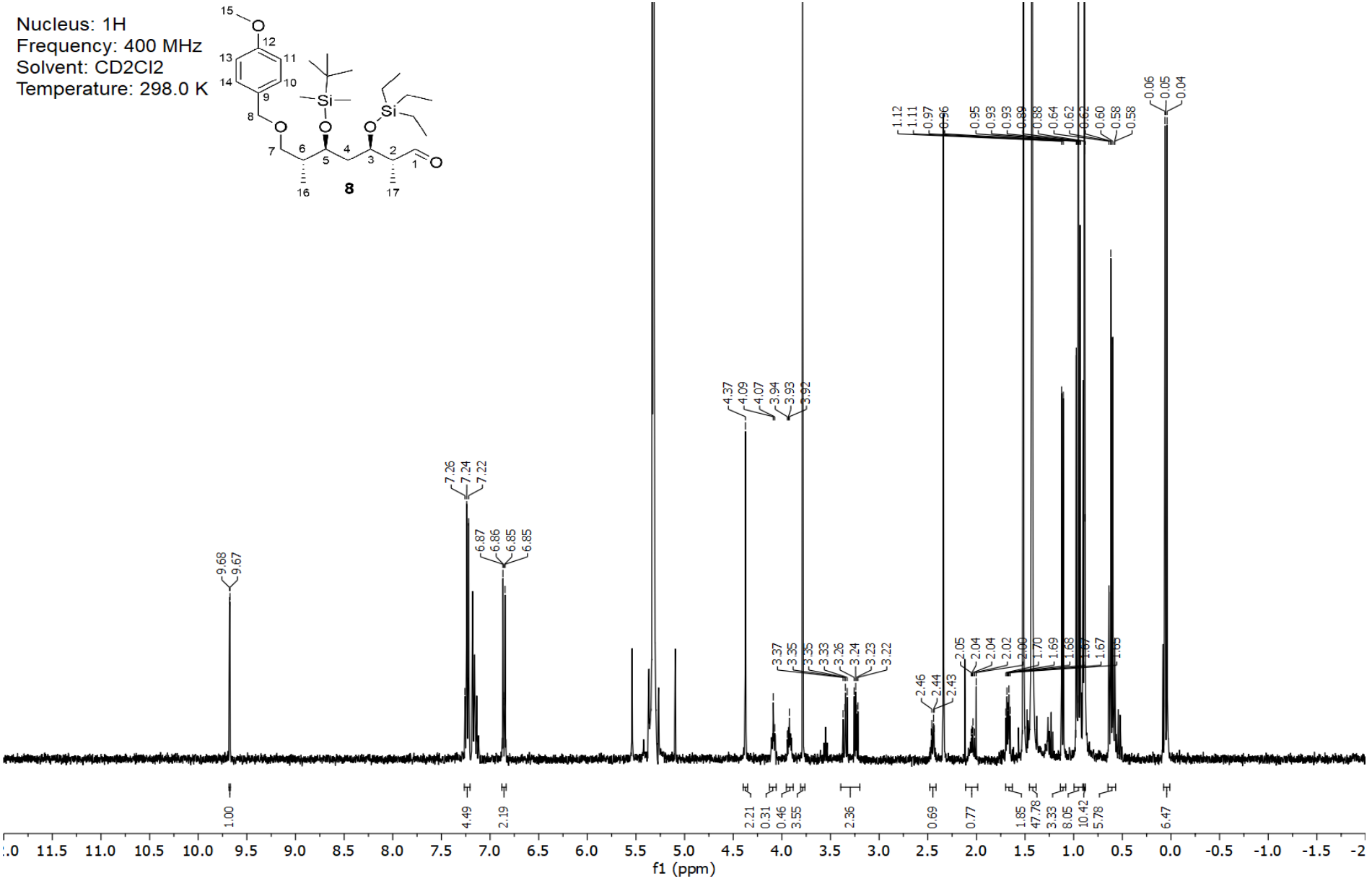


Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

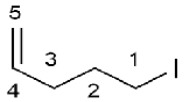


7

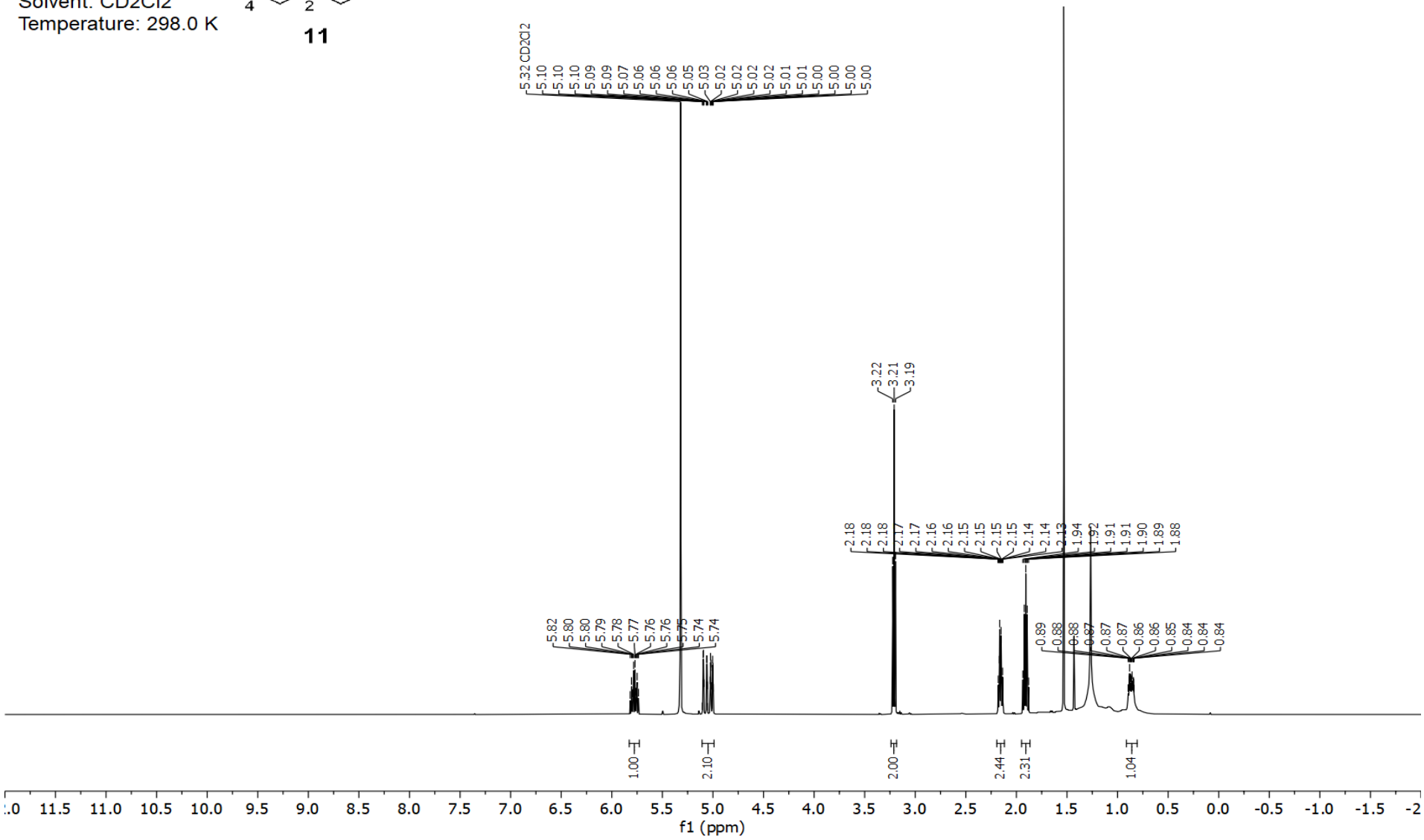



Nucleus: 1H
Frequency: 400 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
8
f1 (ppm)

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

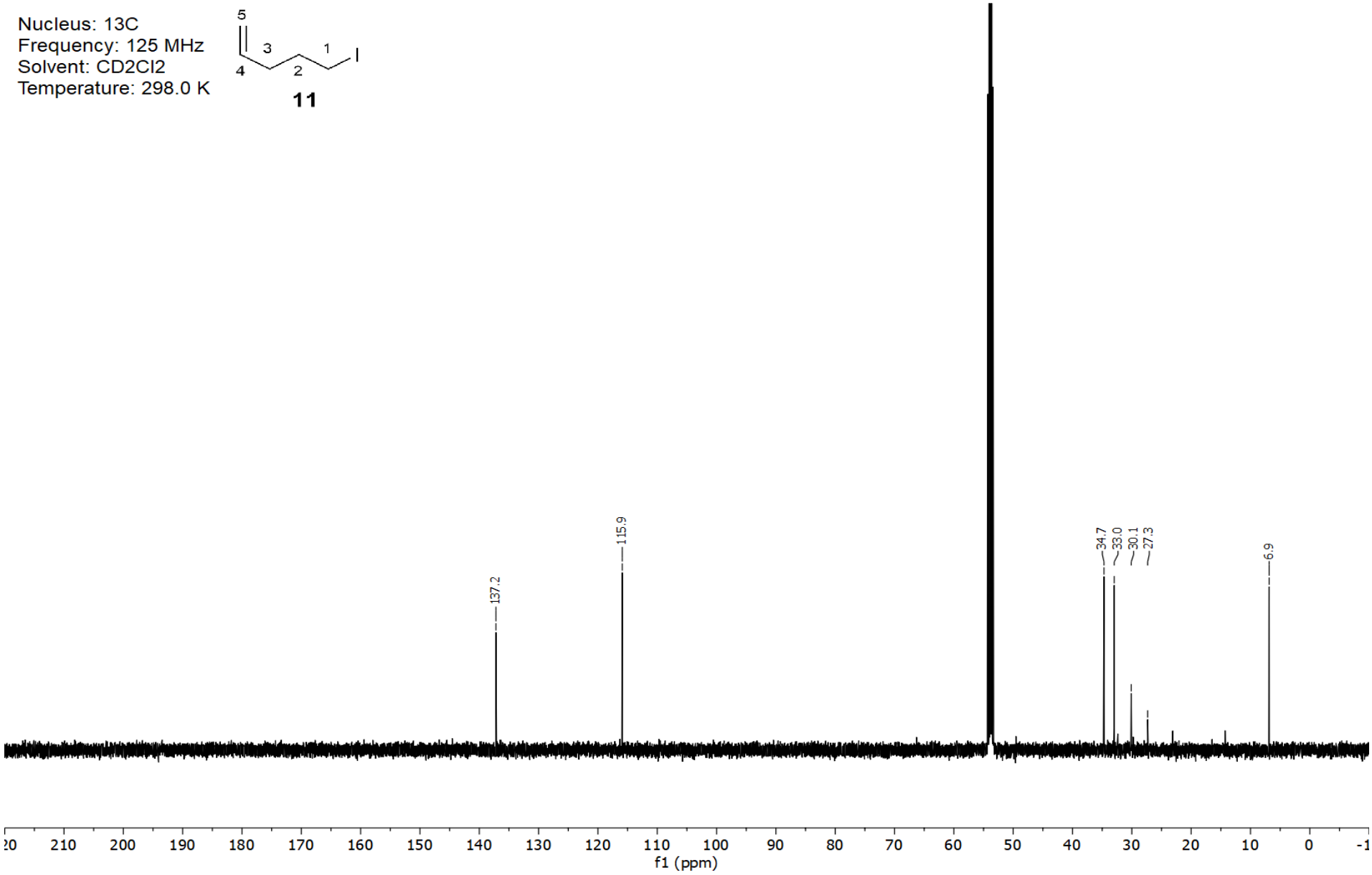


11

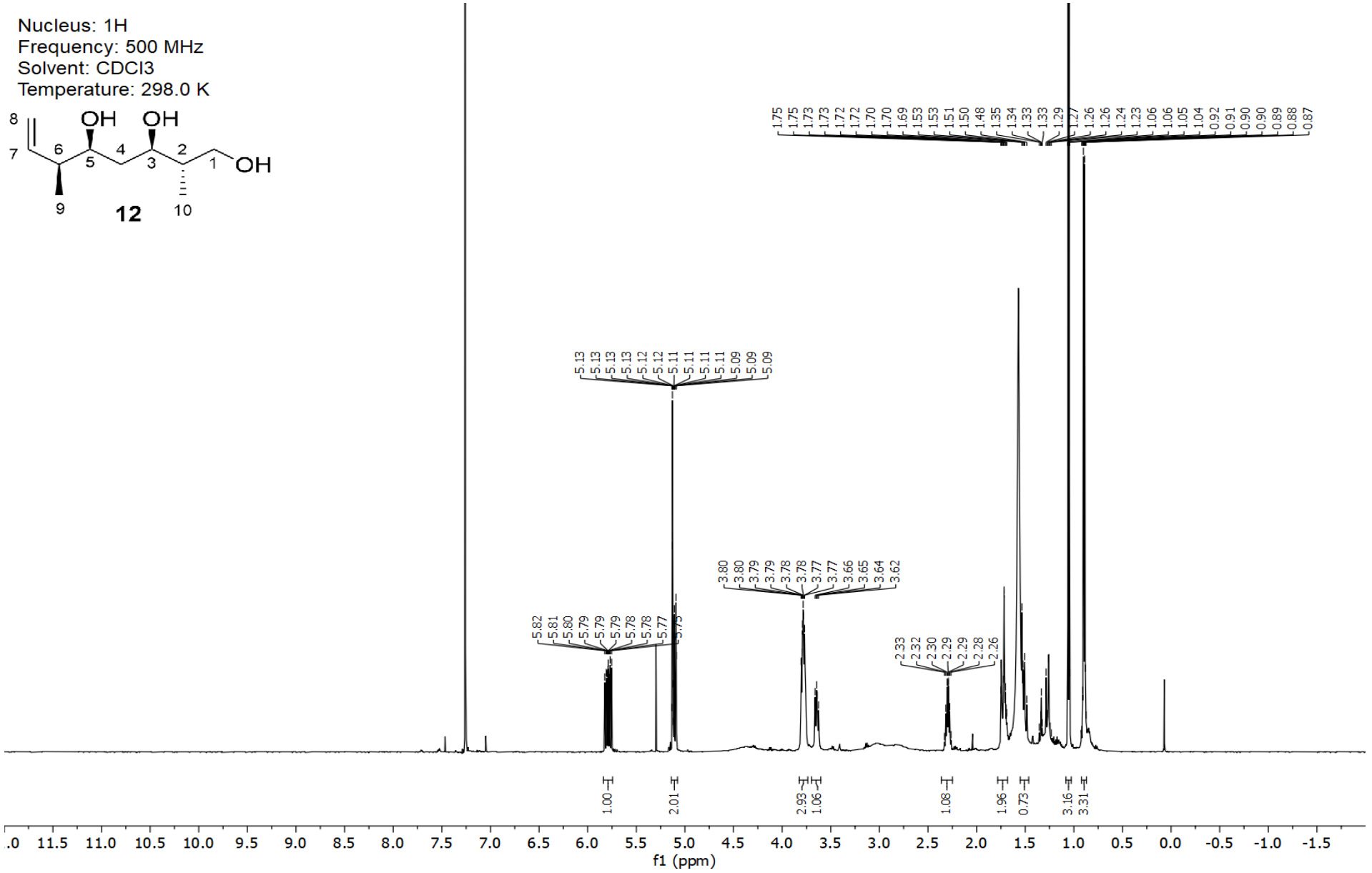


Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

11

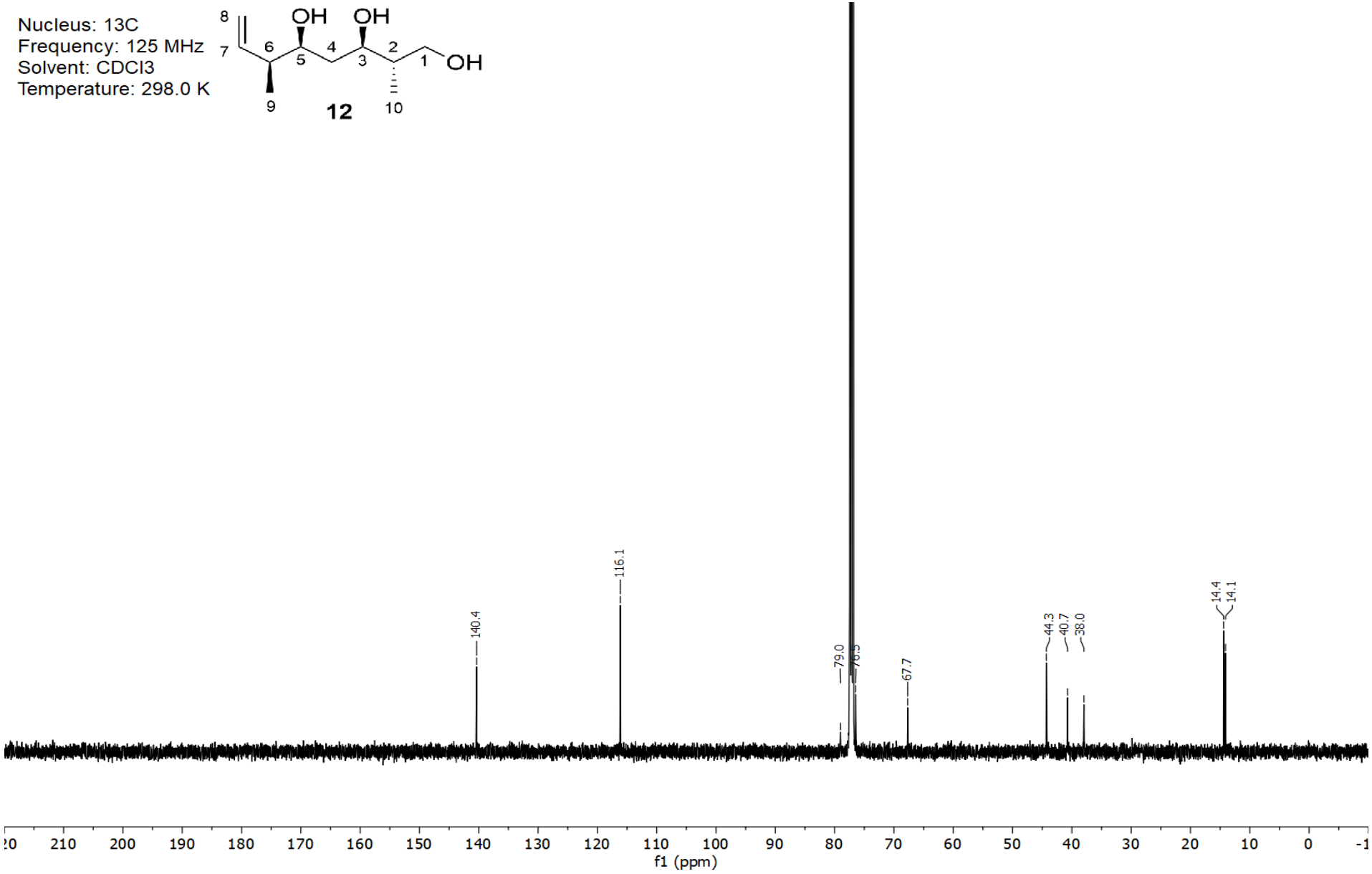


6. Appendix

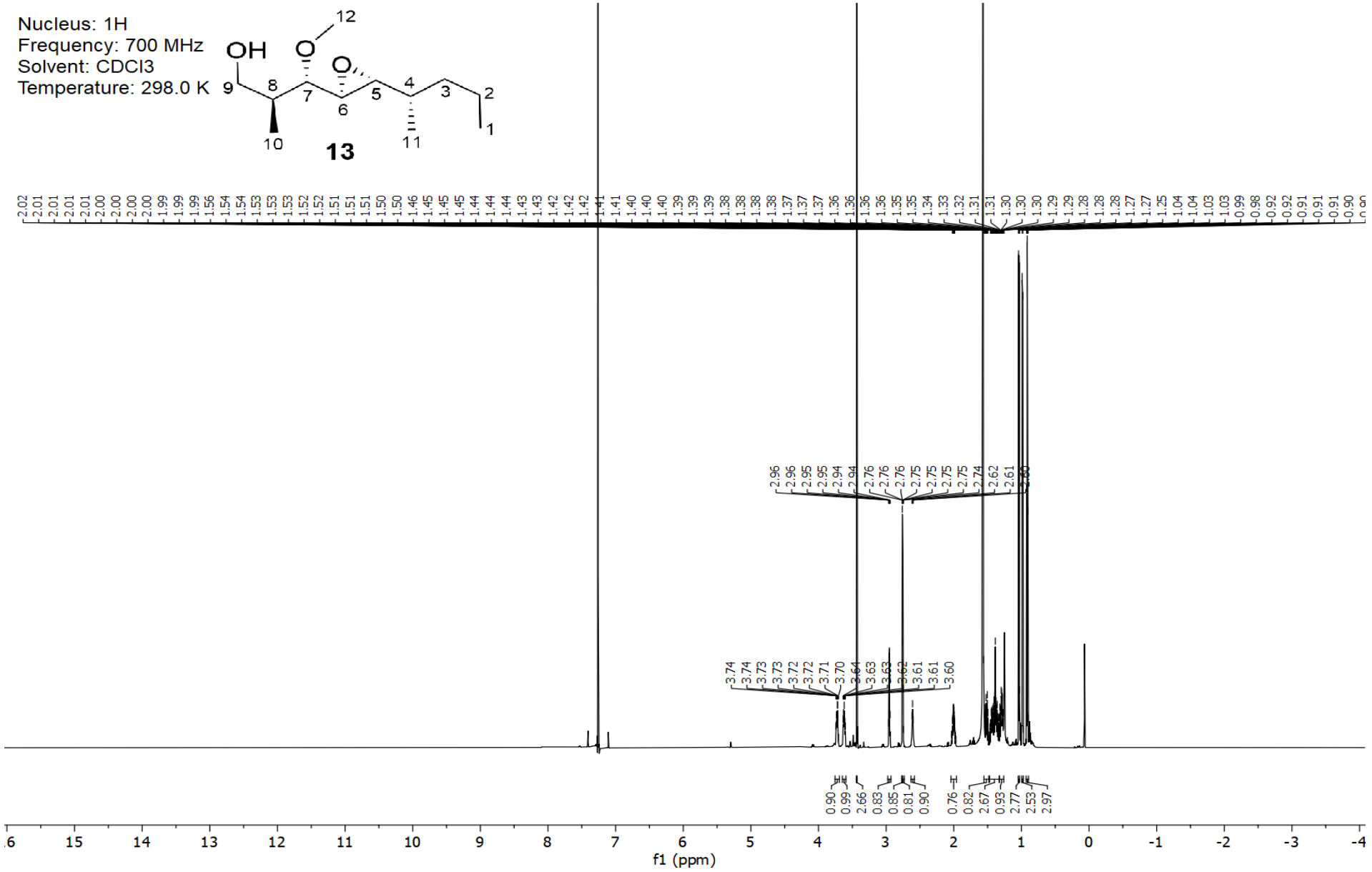

Nucleus: 1H
Frequency: 500 MHz
Solvent: CDCl3
Temperature: 298.0 K
OH
OH
OH
12
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CDCl3
Temperature: 298.0 K

12

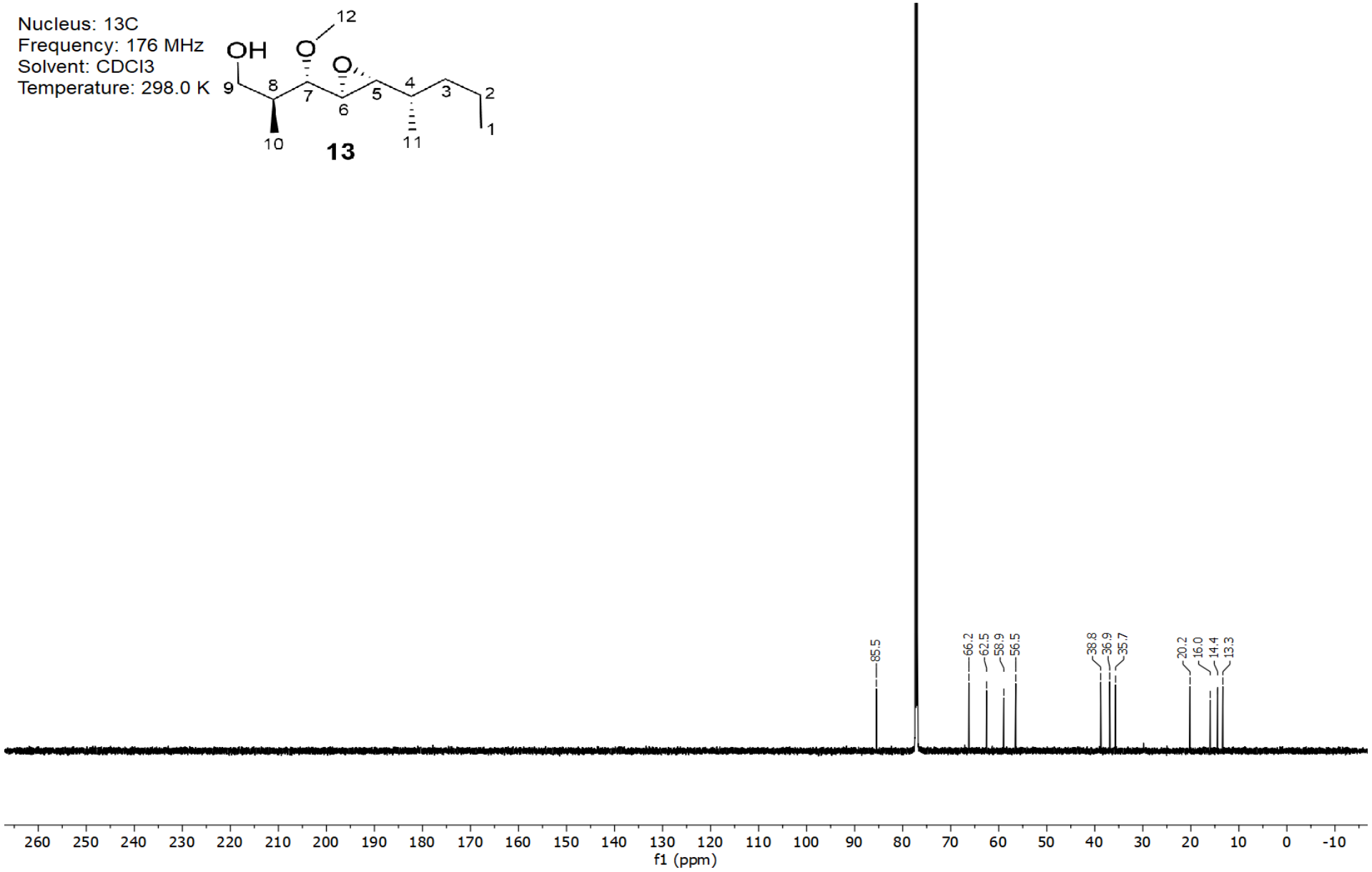


6. Appendix

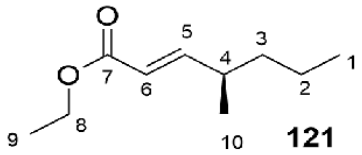

Nucleus: 1H
Frequency: 700 MHz
Solvent: CDCl3
Temperature: 298.0 K
OH
O
O
12
9
8
7
6
5
4
3
2
1
10
11
13
f1 (ppm)

Nucleus: 13C
Frequency: 176 MHz
Solvent: CDCl3
Temperature: 298.0 K

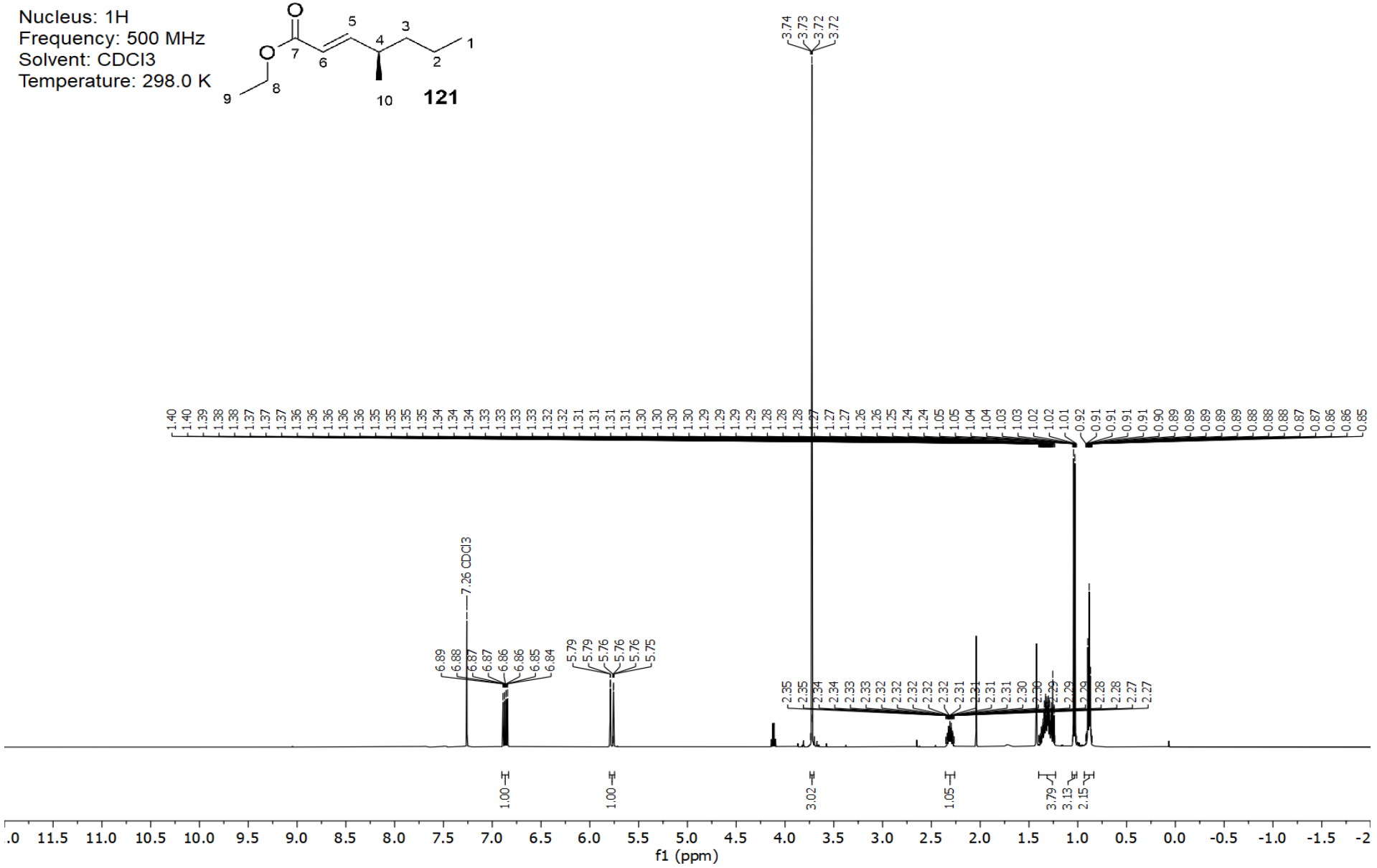
13



Nucleus: 1H
Frequency: 500 MHz
Solvent: CDCl3
Temperature: 298.0 K

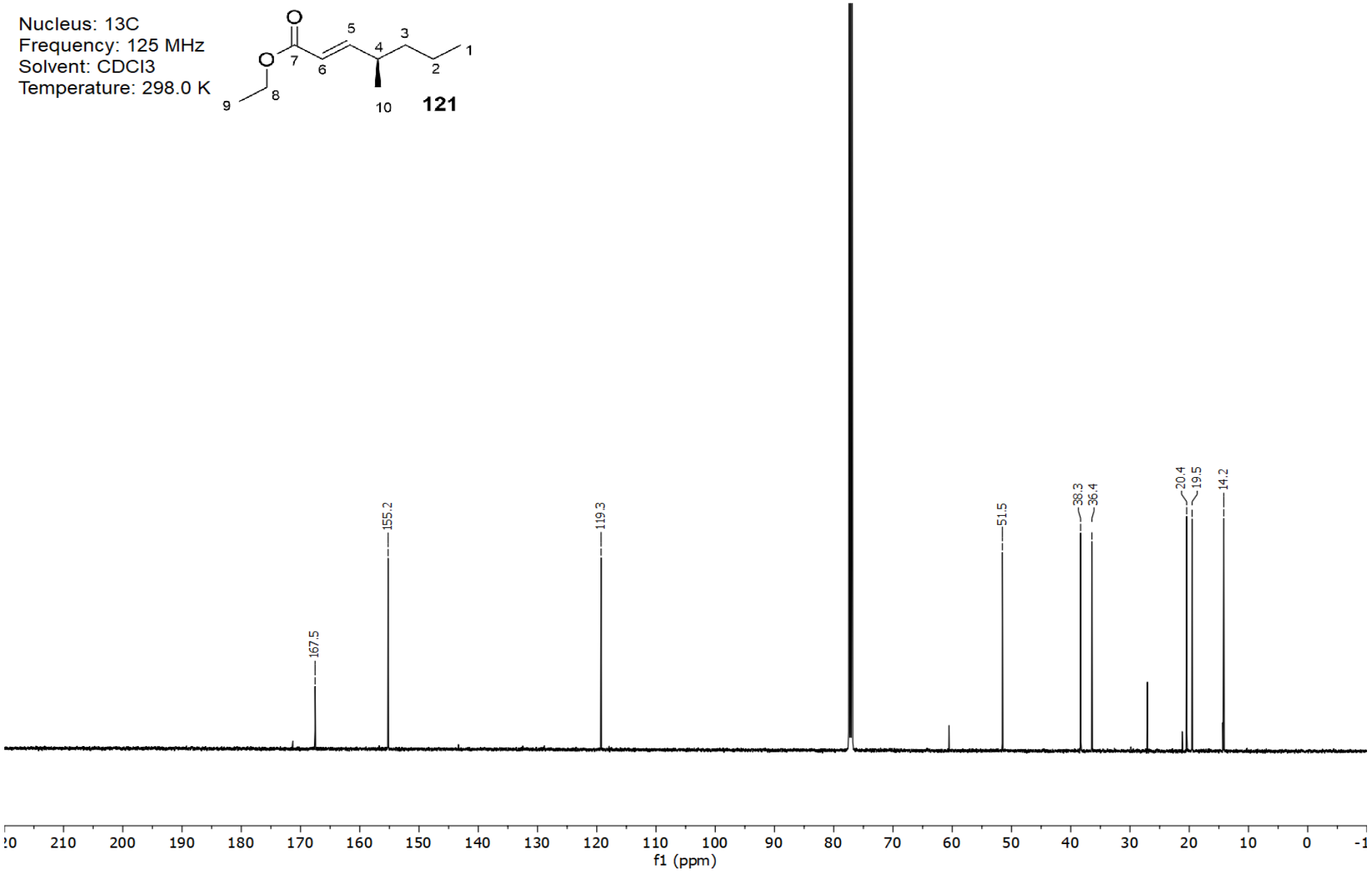


121



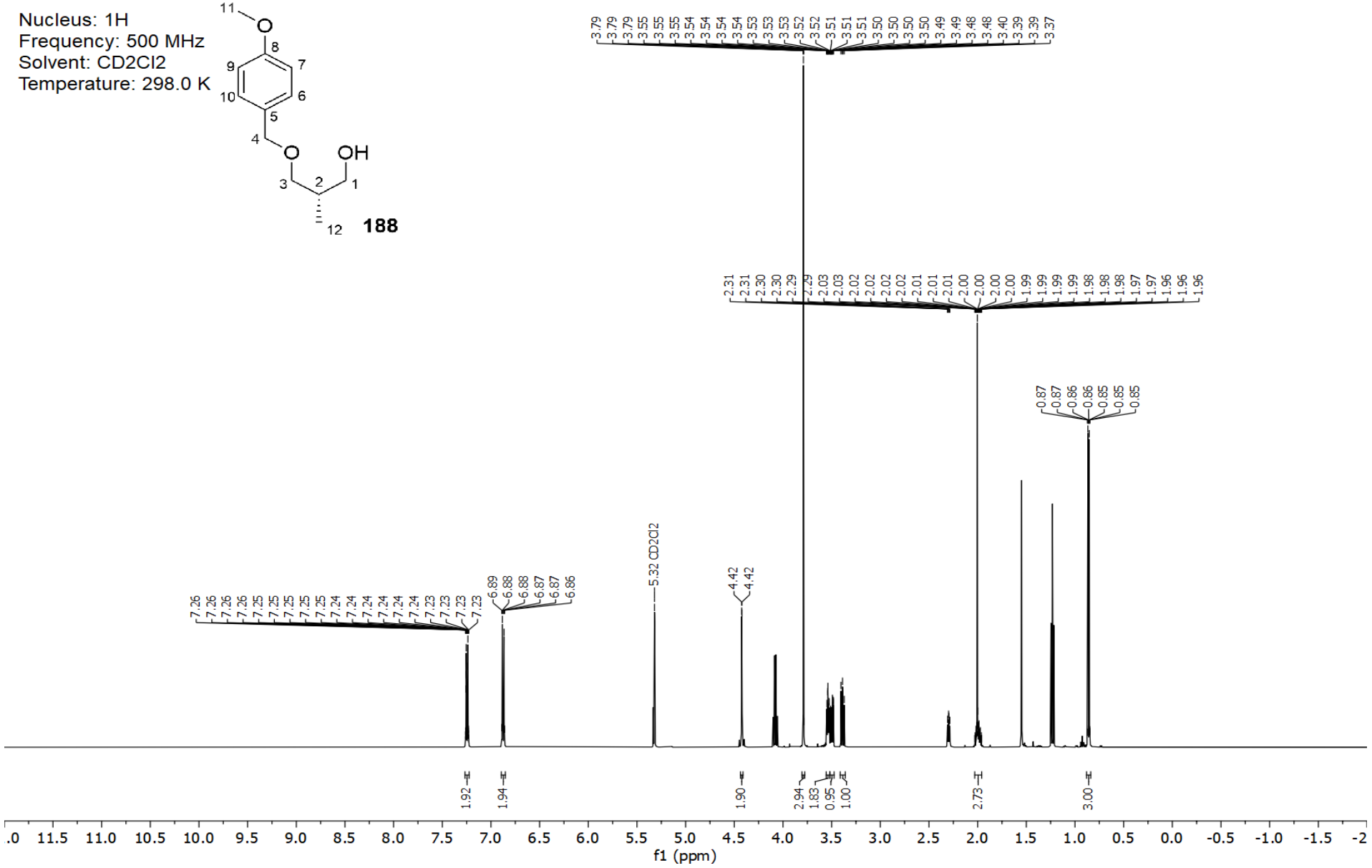
Nucleus: 13C
Frequency: 125 MHz
Solvent: CDCl3
Temperature: 298.0 K

121



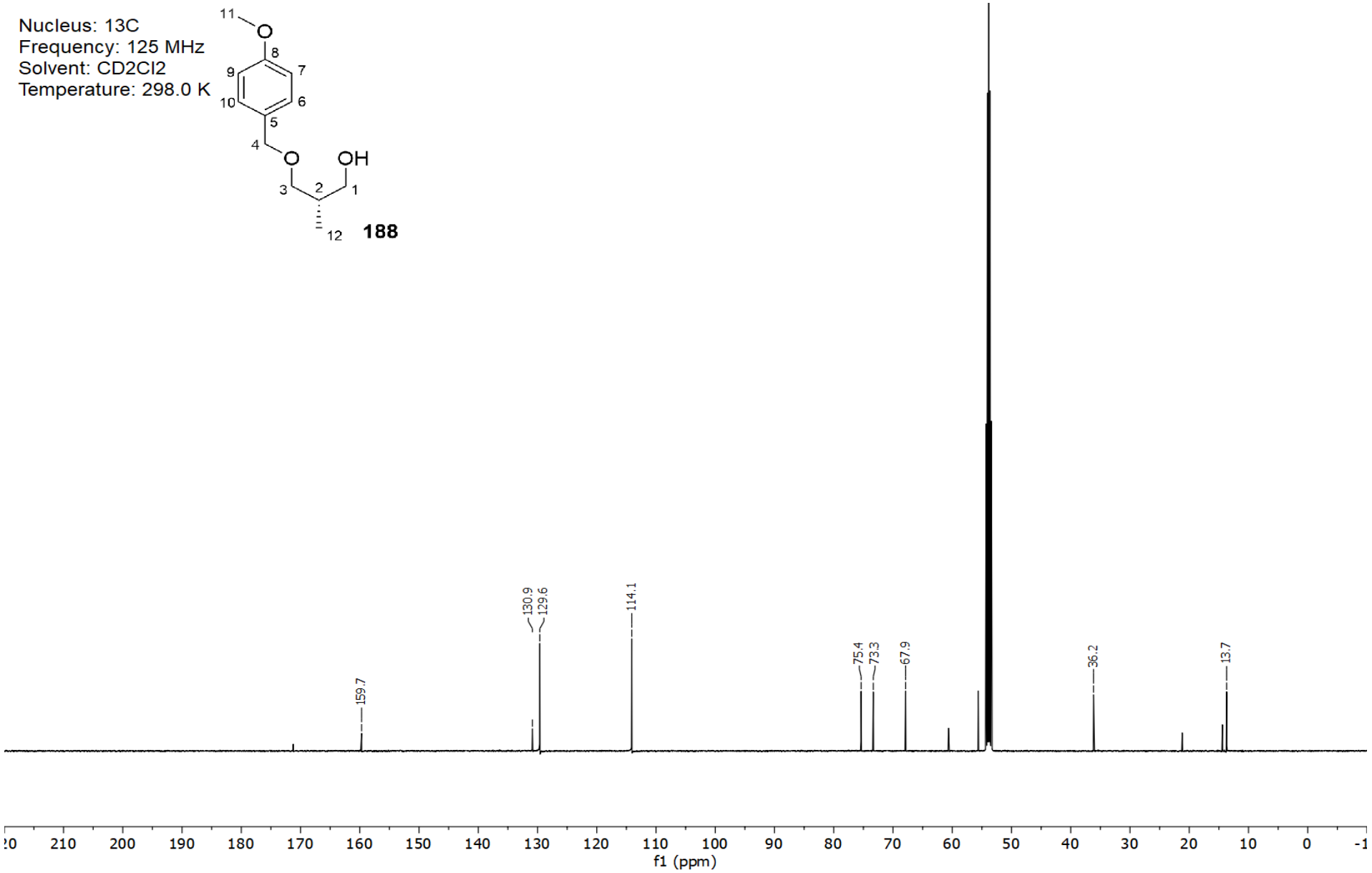
Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

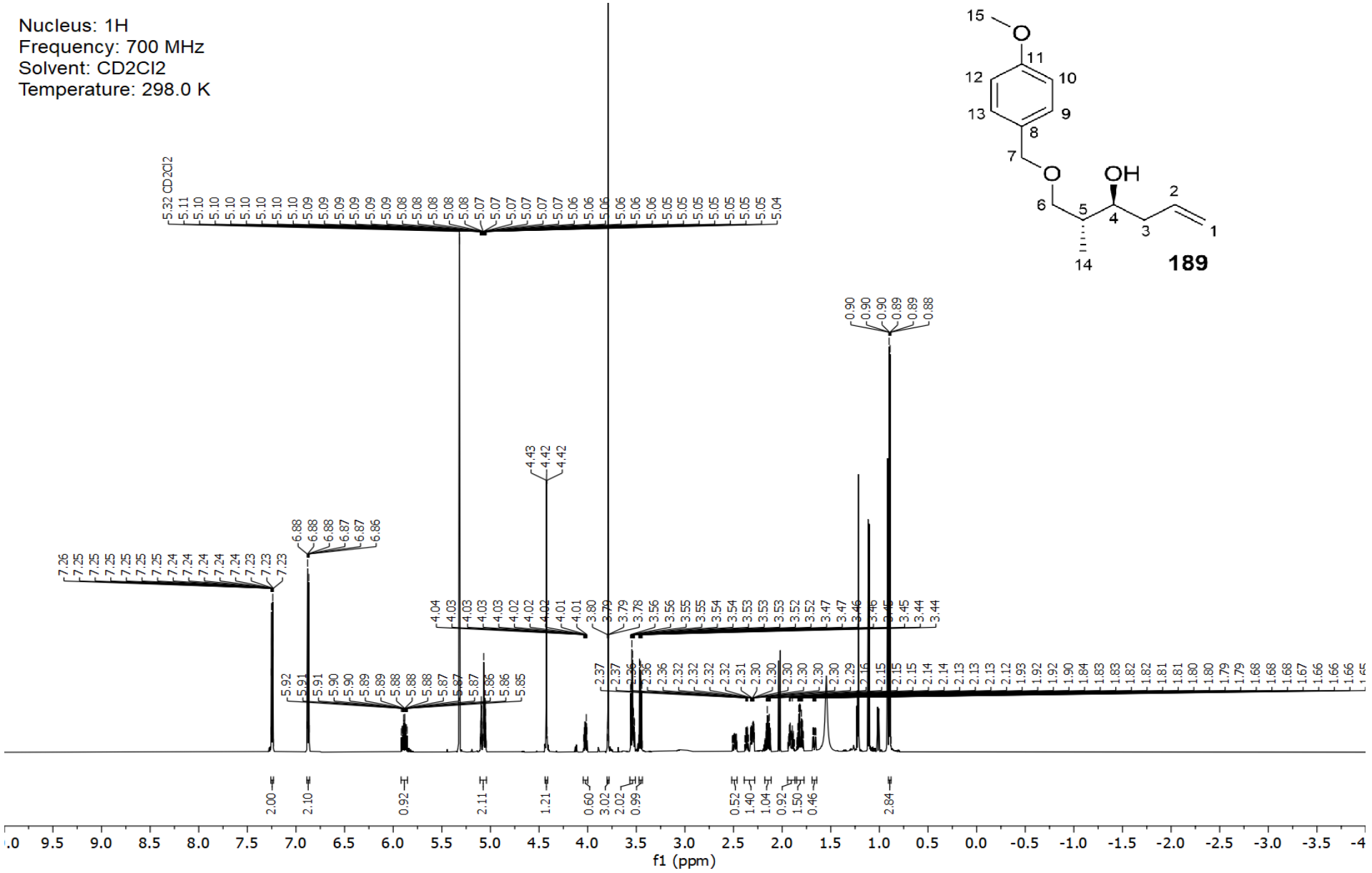
188

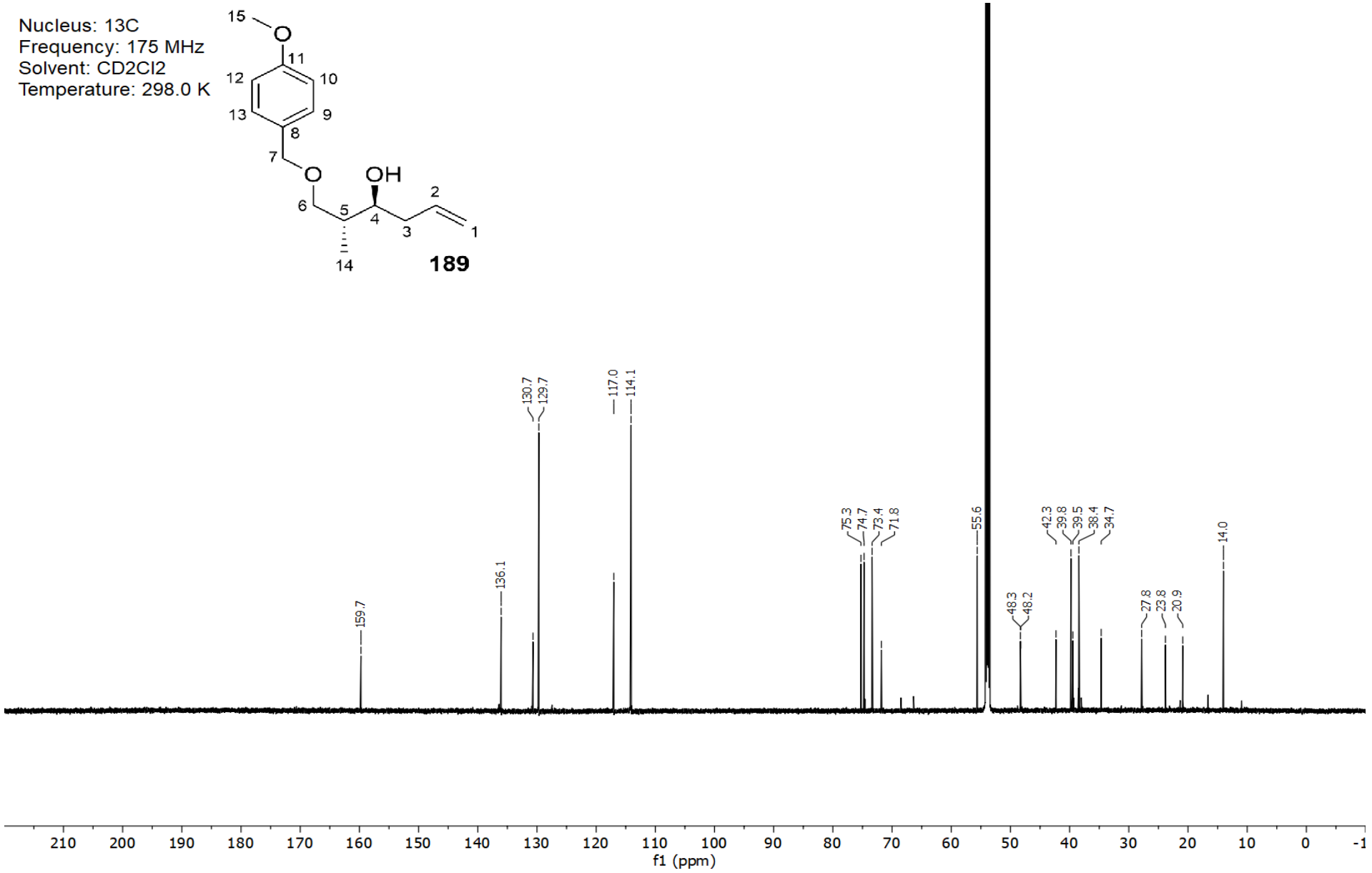


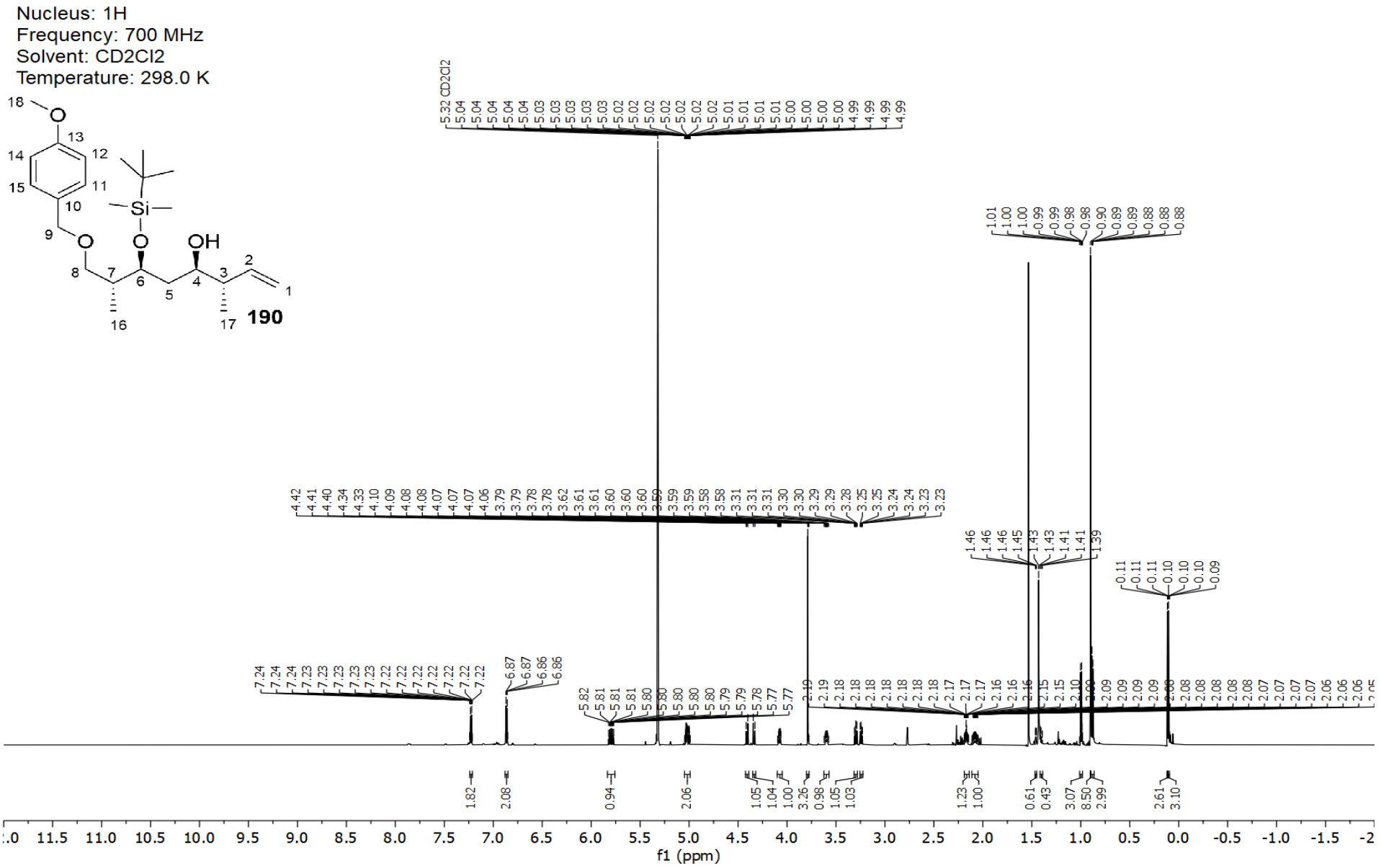
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

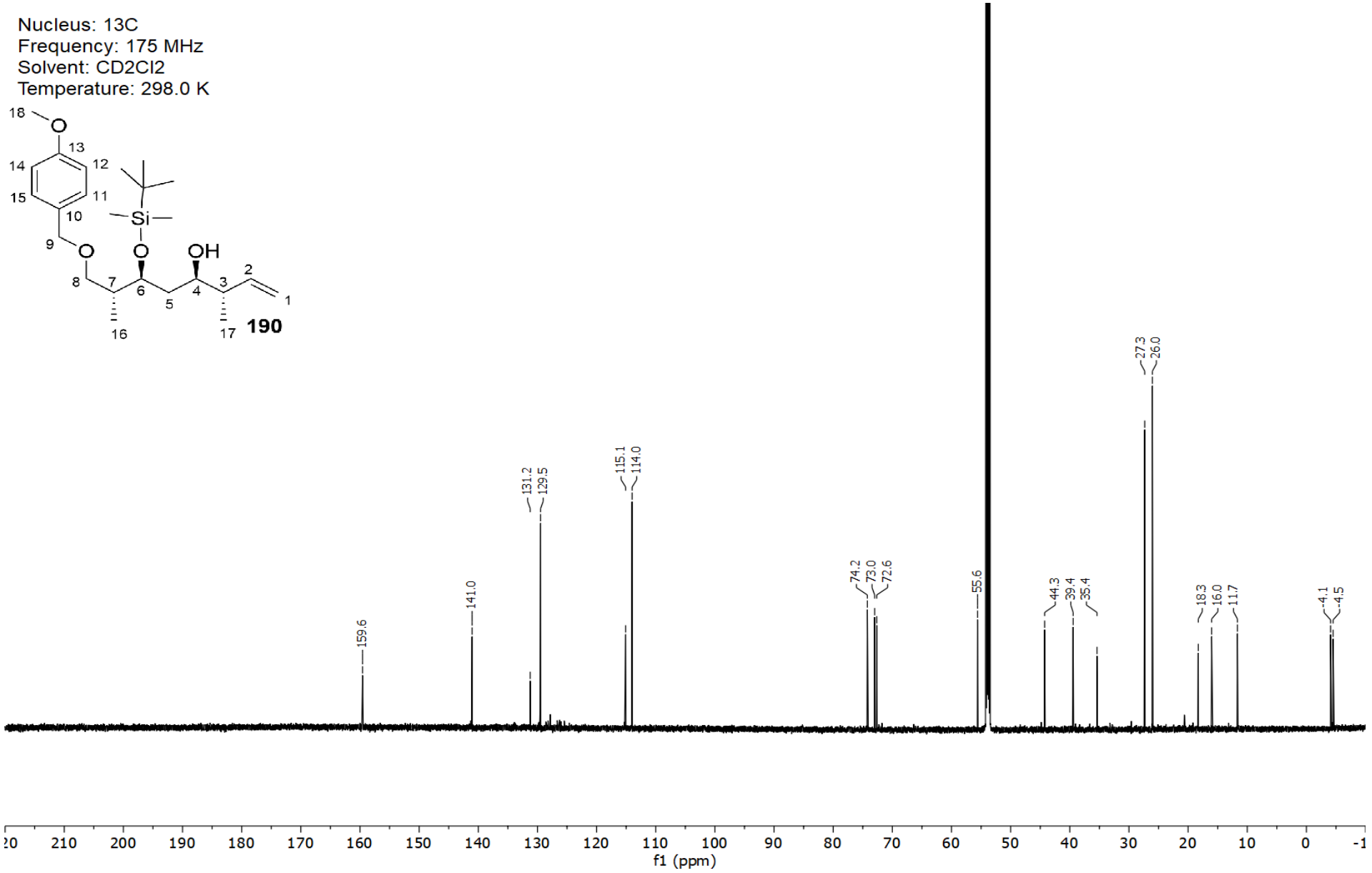
188



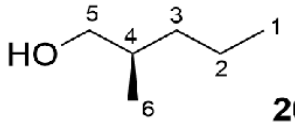

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
189
f1 (ppm)


Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
15
O
11
12
10
13
9
8
7
O
OH
6
5
4
2
3
1
14
189
159.7
136.1
130.7
129.7
117.0
114.1
75.3
74.7
73.4
71.8
55.6
48.3
48.2
42.3
39.8
39.5
38.4
34.7
27.8
23.8
20.9
14.0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

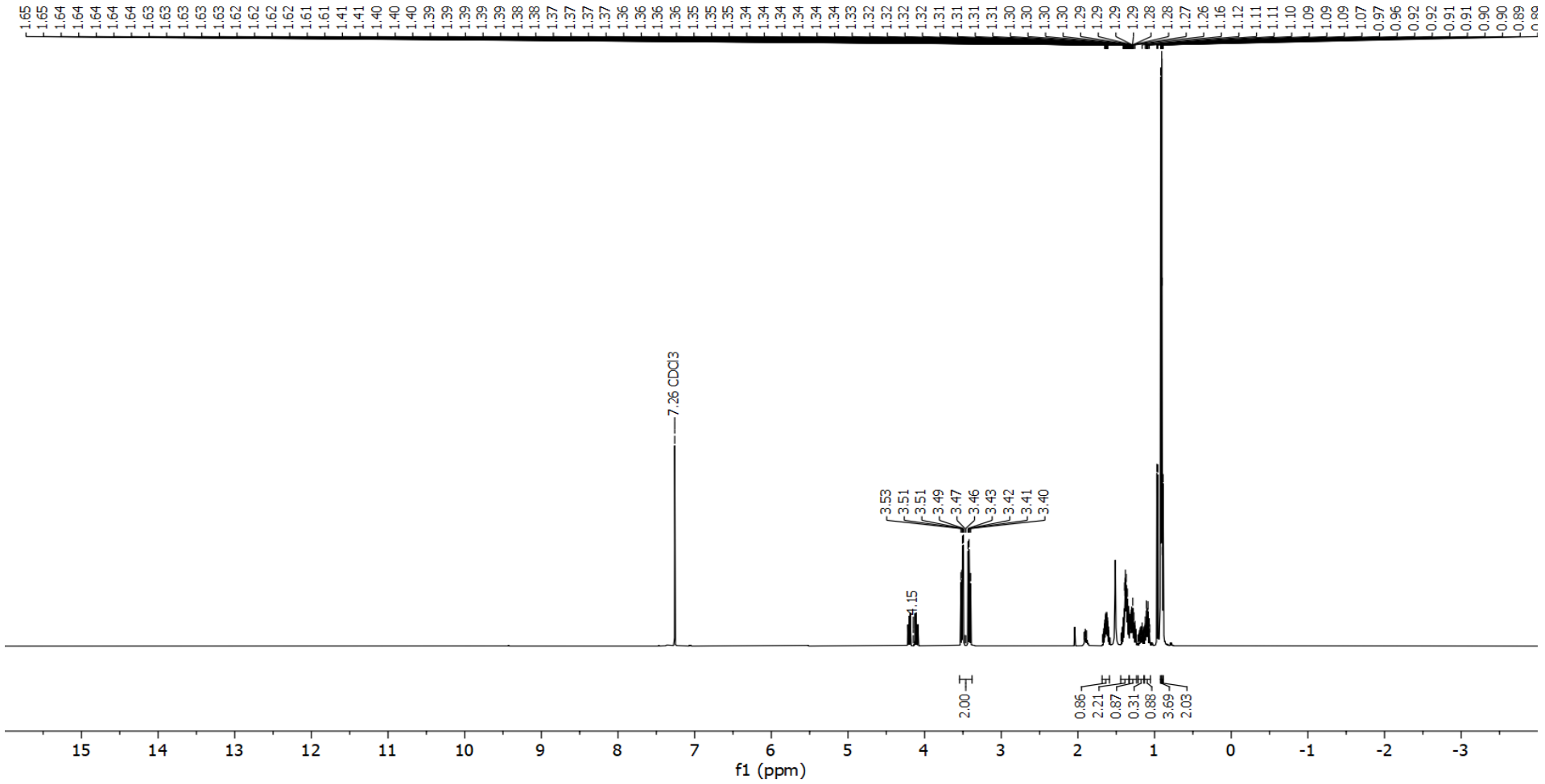

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
190
f1 (ppm)


Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
190
159.6
141.0
131.2
129.5
115.1
114.0
74.2
73.0
72.6
55.6
44.3
39.4
35.4
27.3
26.0
18.3
16.0
11.7
-4.1
-4.5
f1 (ppm)

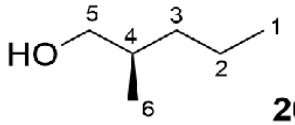
Nucleus: 1H
Frequency: 500 MHz
Solvent: CDCl3
Temperature: 298.0 K



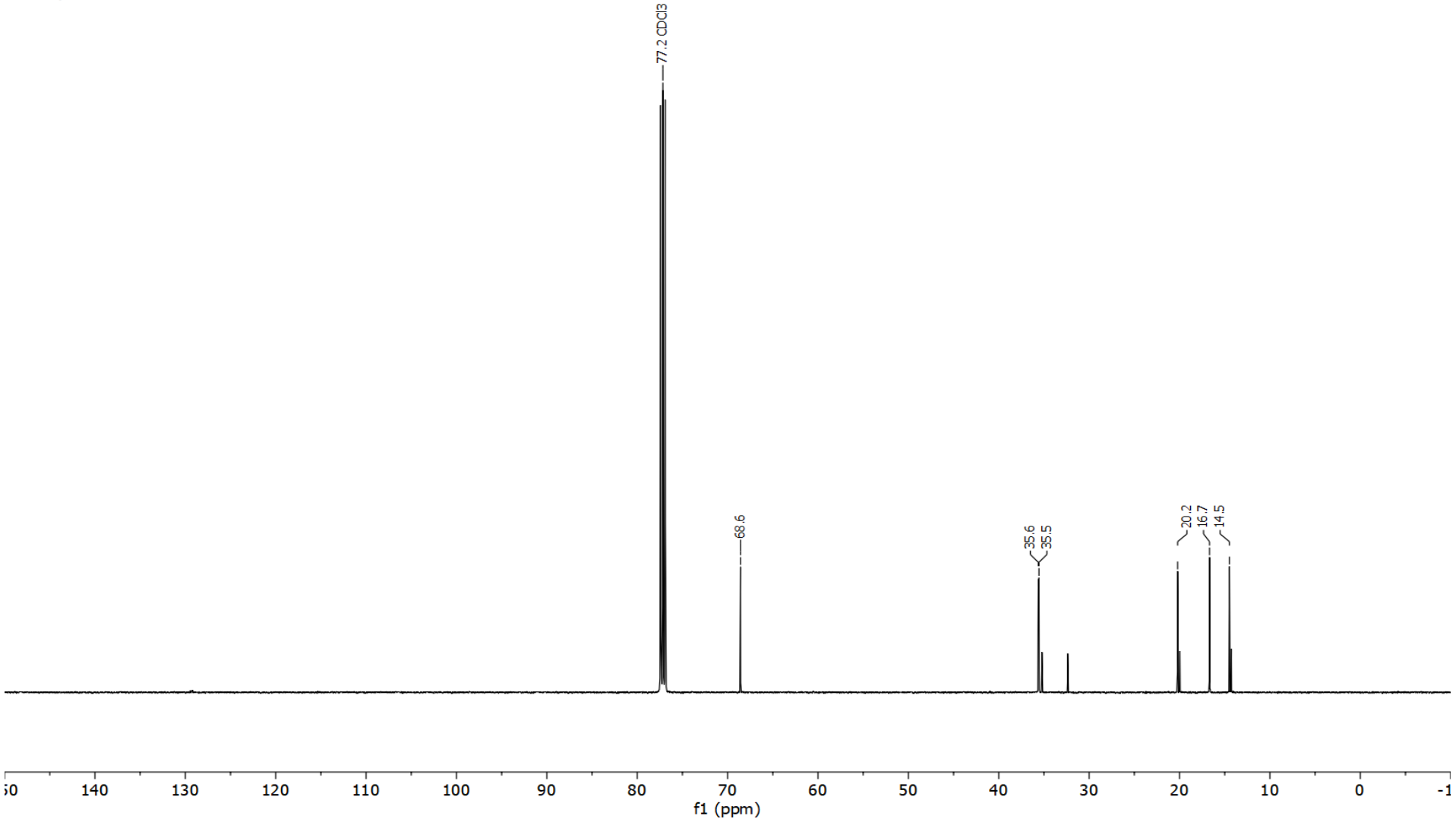
201

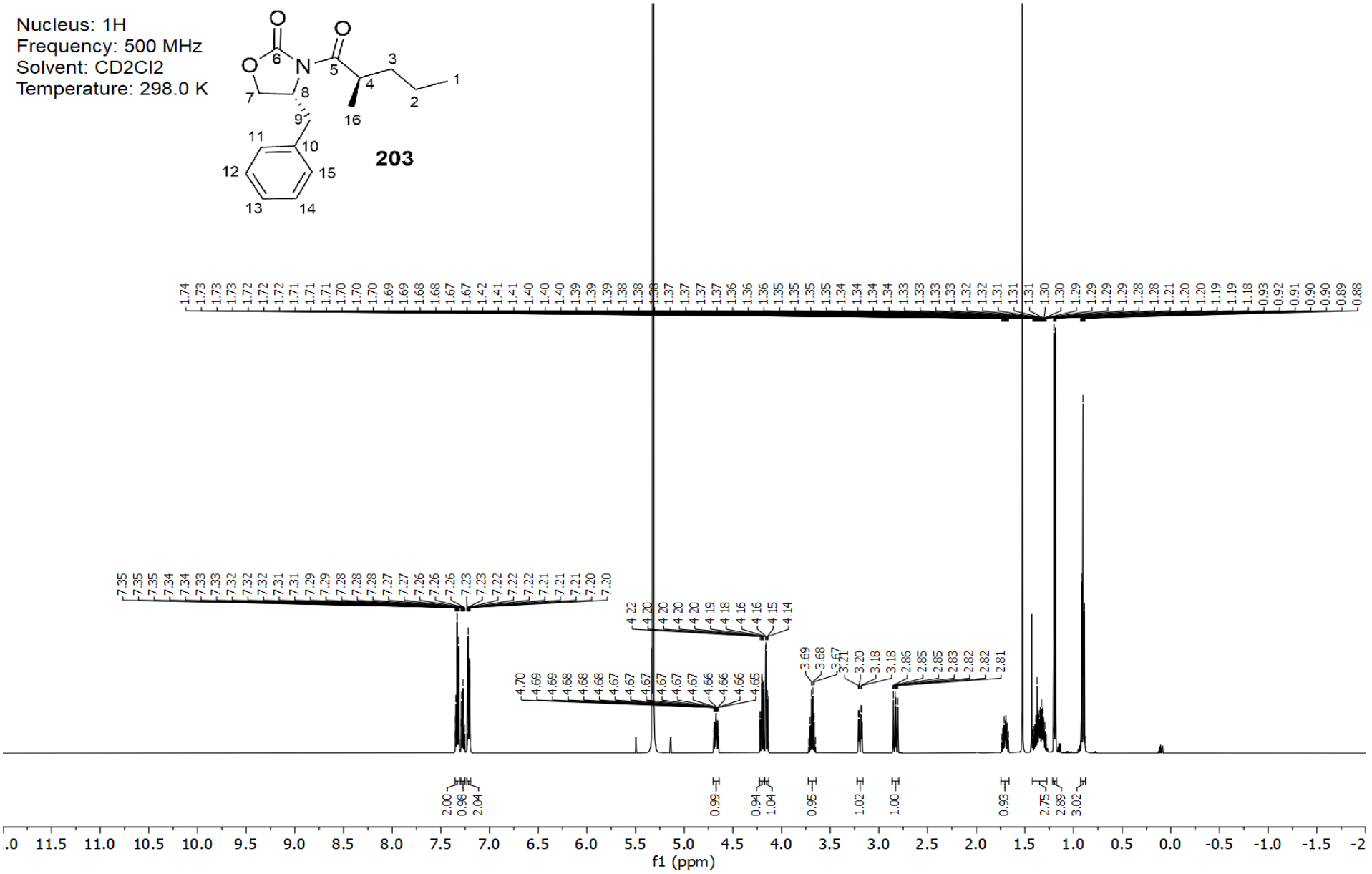


Nucleus: 13C
Frequency: 125 MHz
Solvent: CDCl3
Temperature: 298.0 K



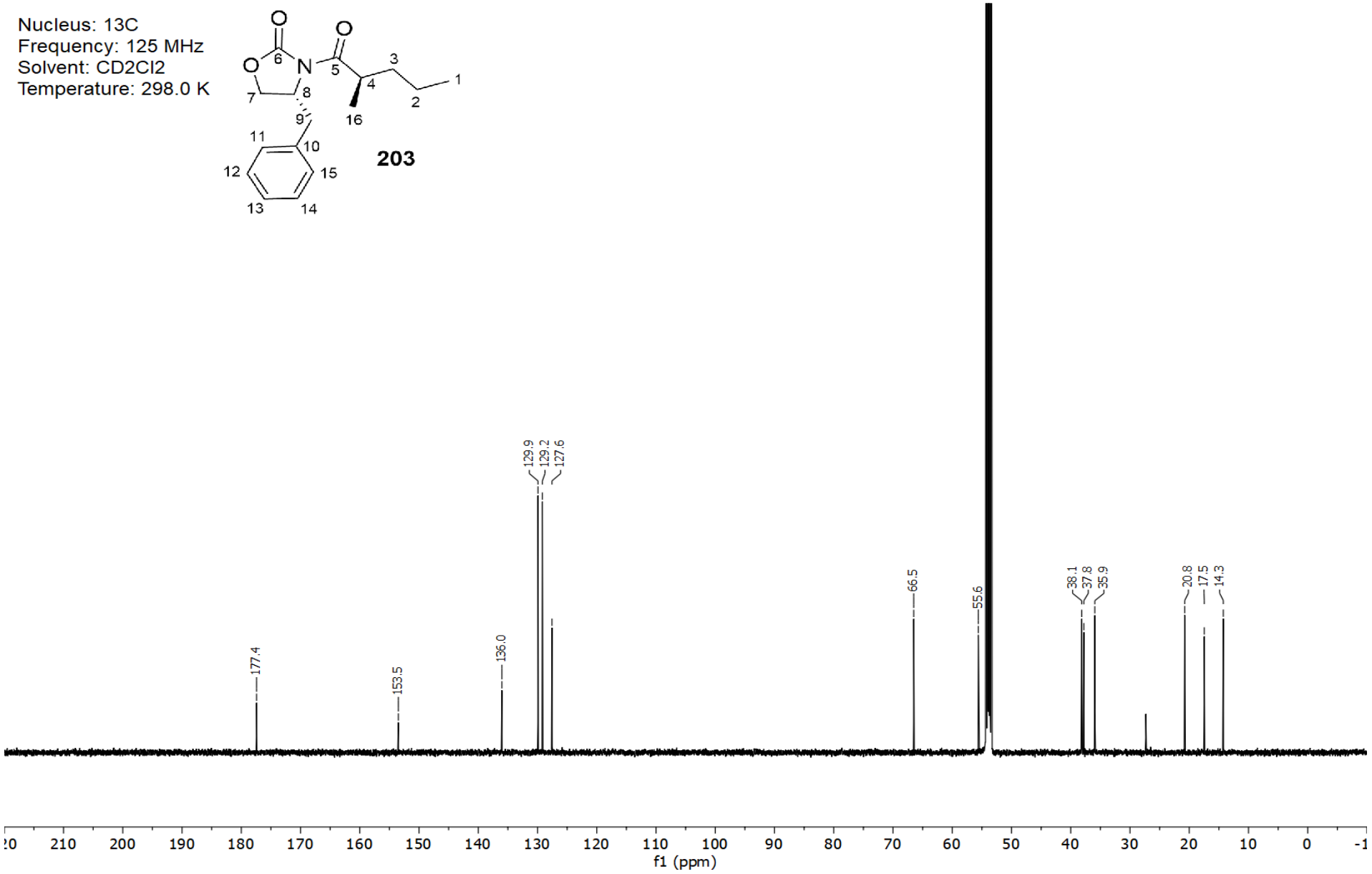
201




Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
203
f1 (ppm)

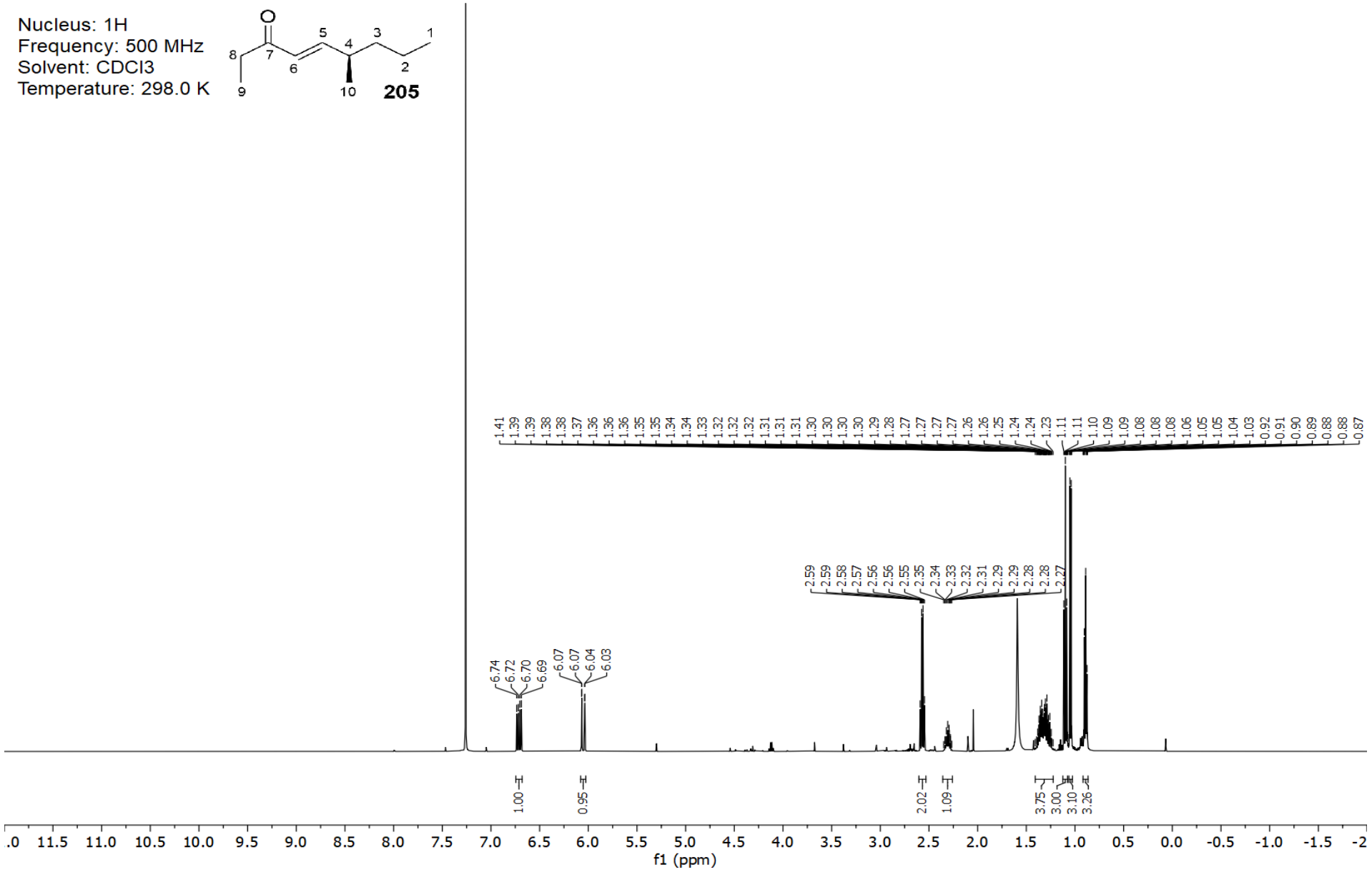
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

203



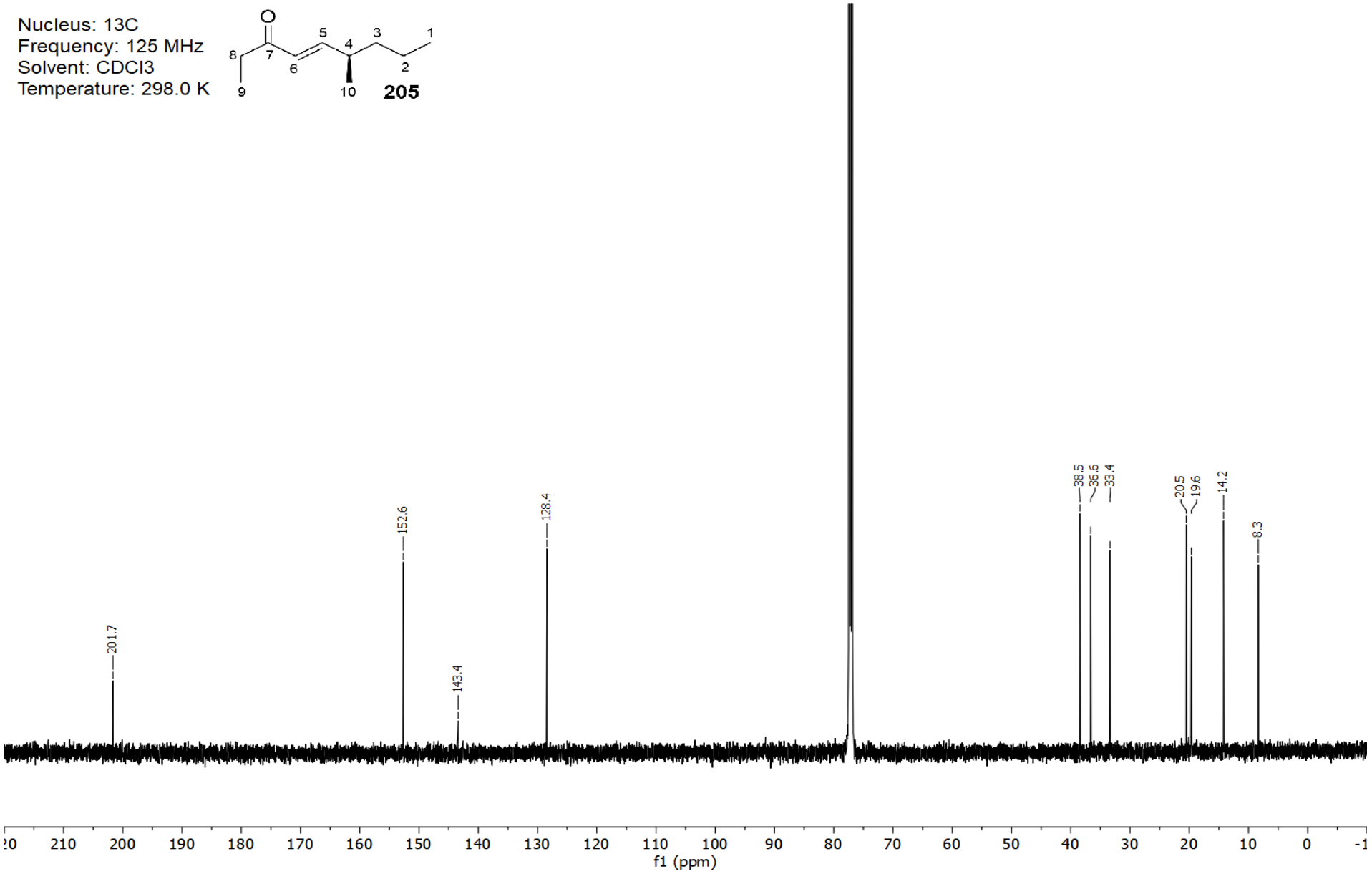
Nucleus: 1H
Frequency: 500 MHz
Solvent: CDCl3
Temperature: 298.0 K

205



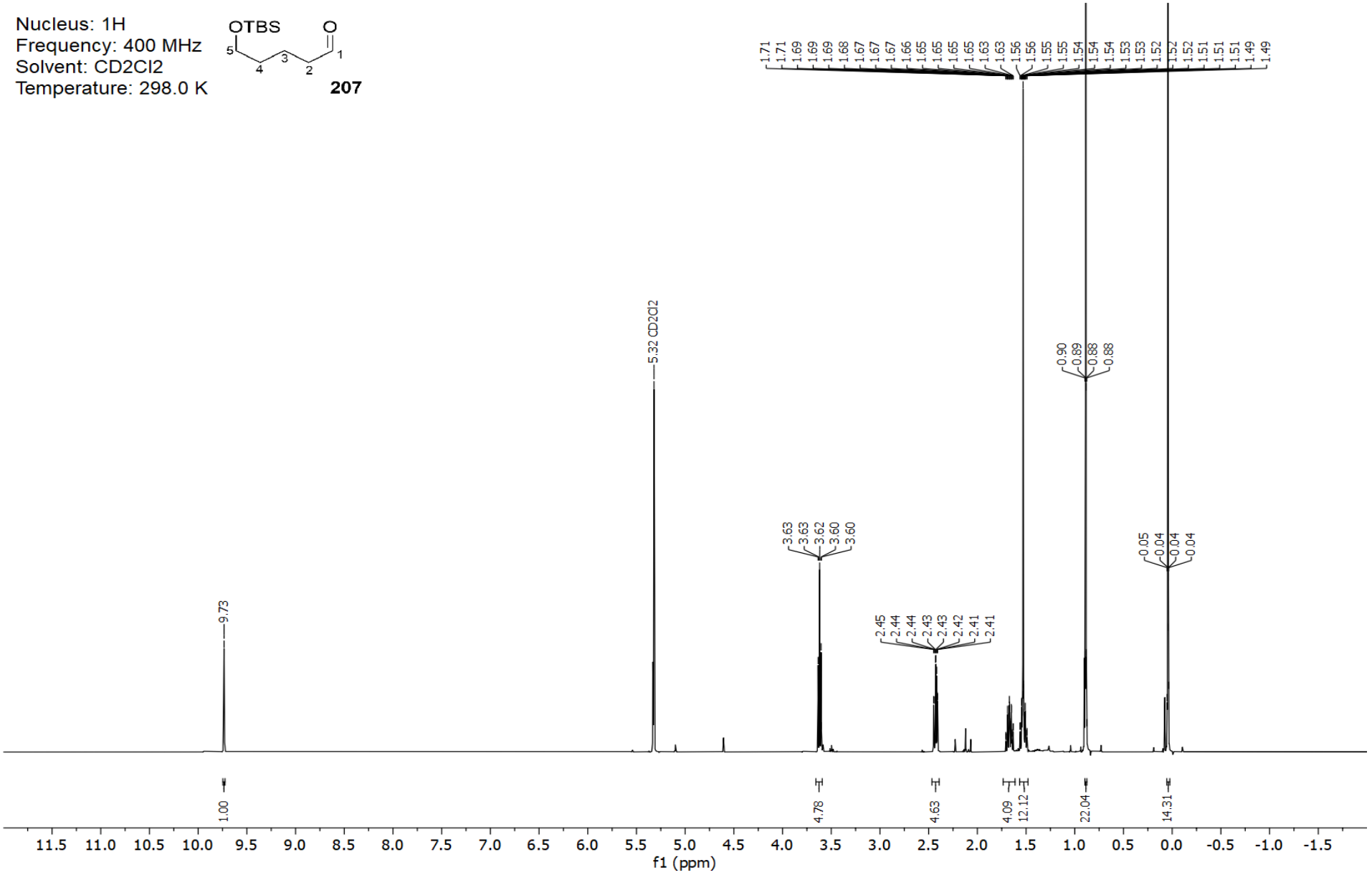
Nucleus: 13C
Frequency: 125 MHz
Solvent: CDCl3
Temperature: 298.0 K

205

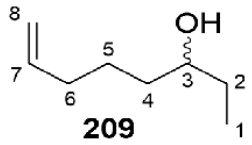


Nucleus: 1H
Frequency: 400 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

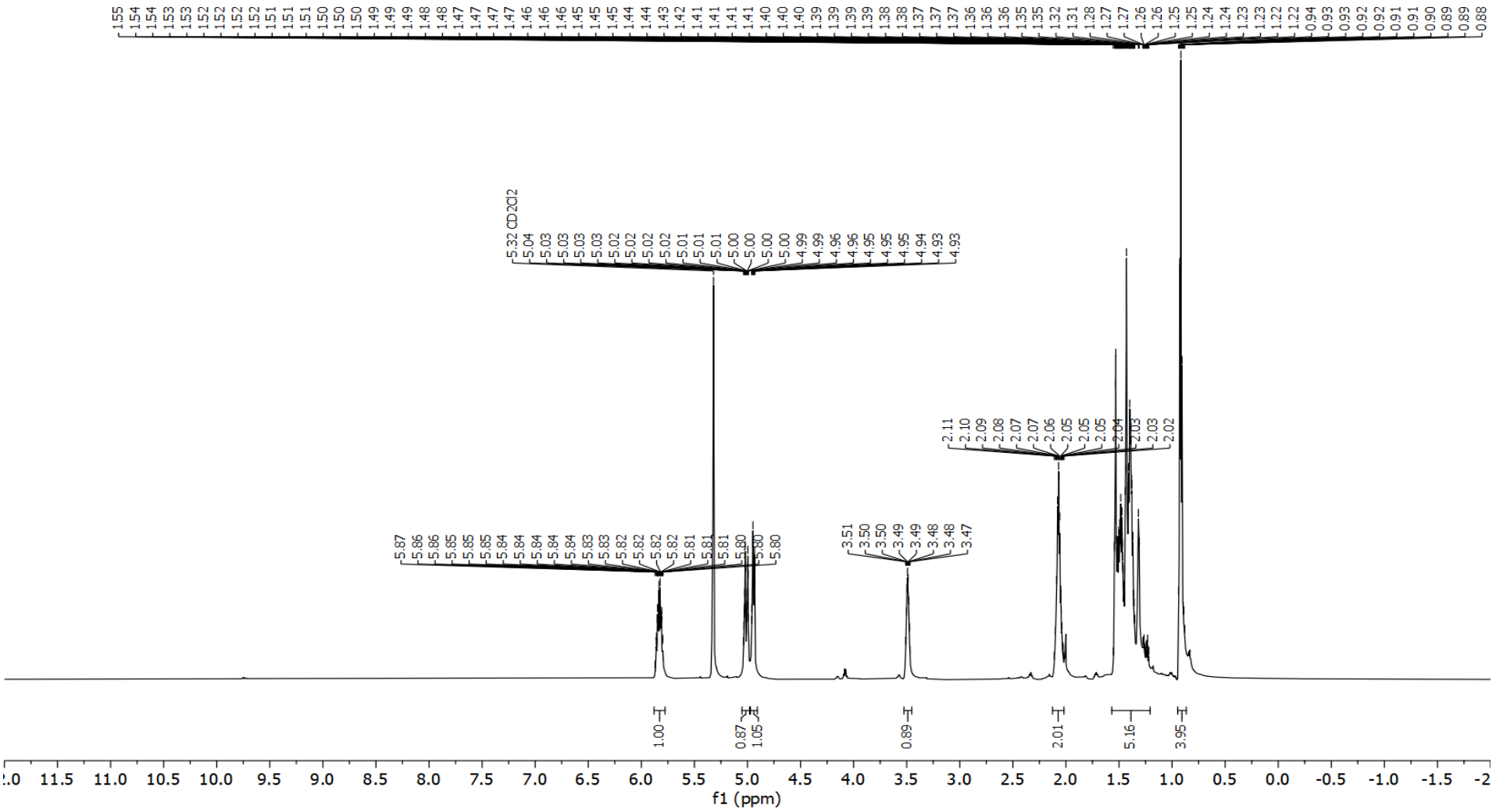
207



Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

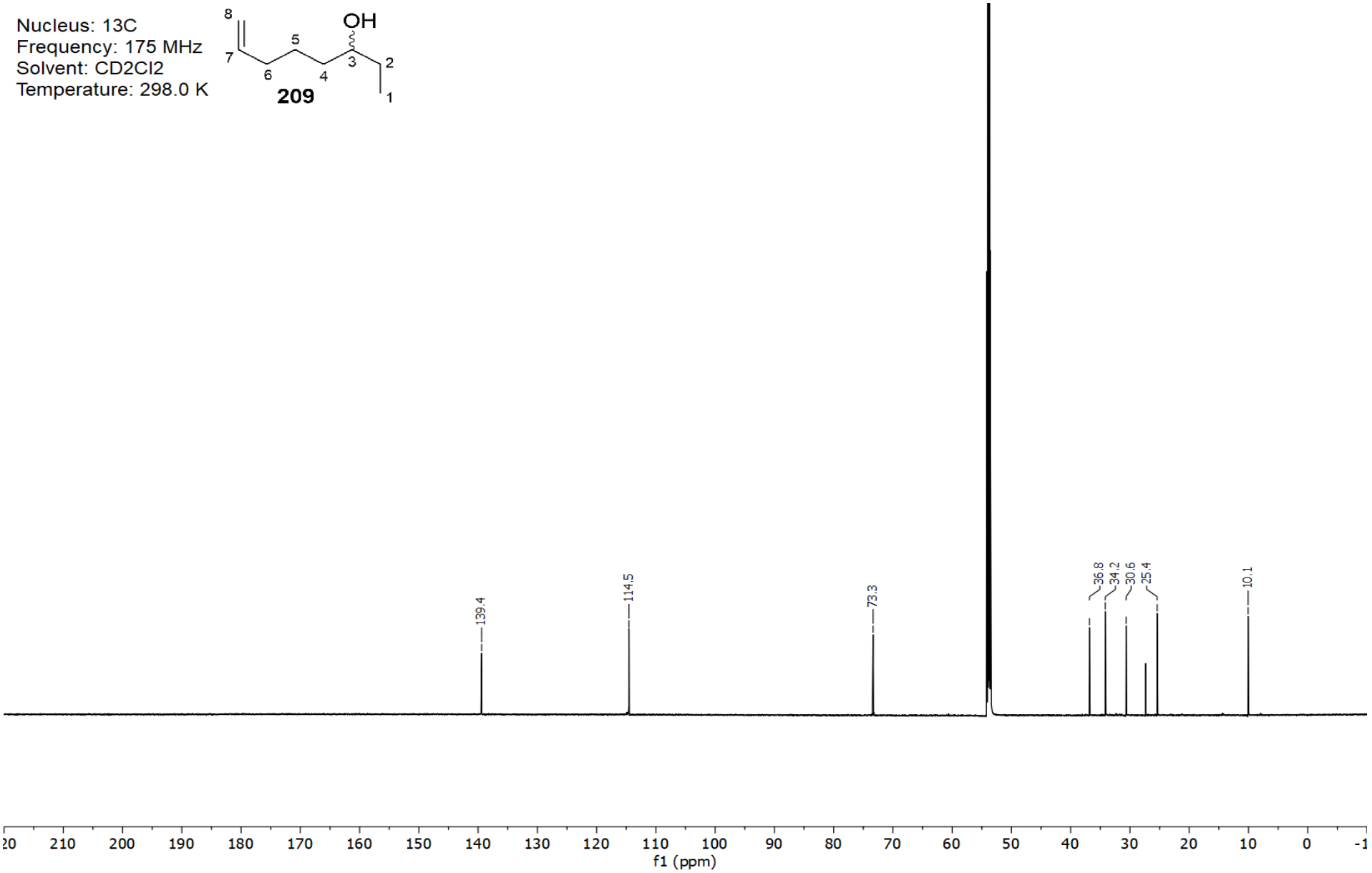


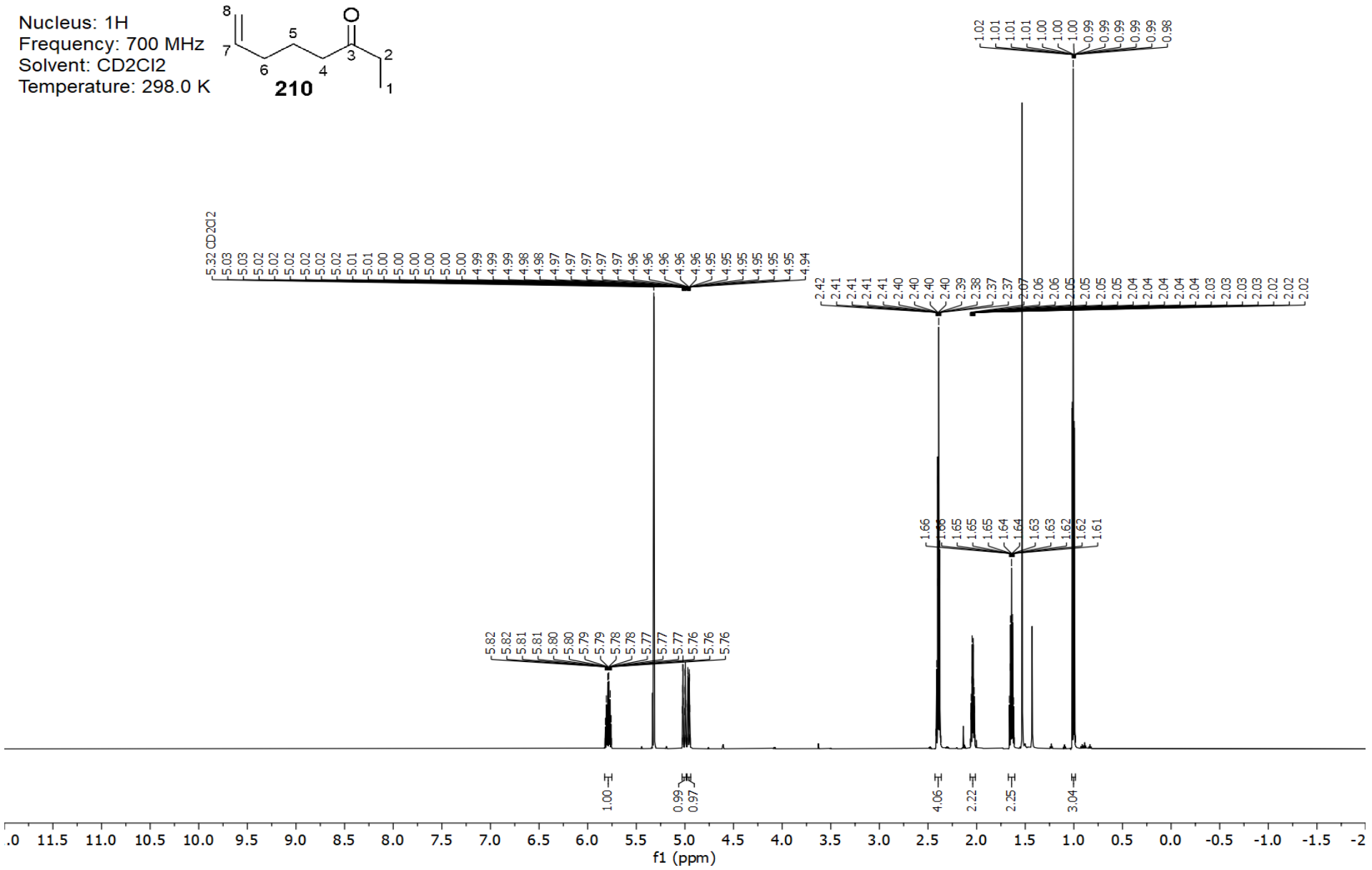
209



Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

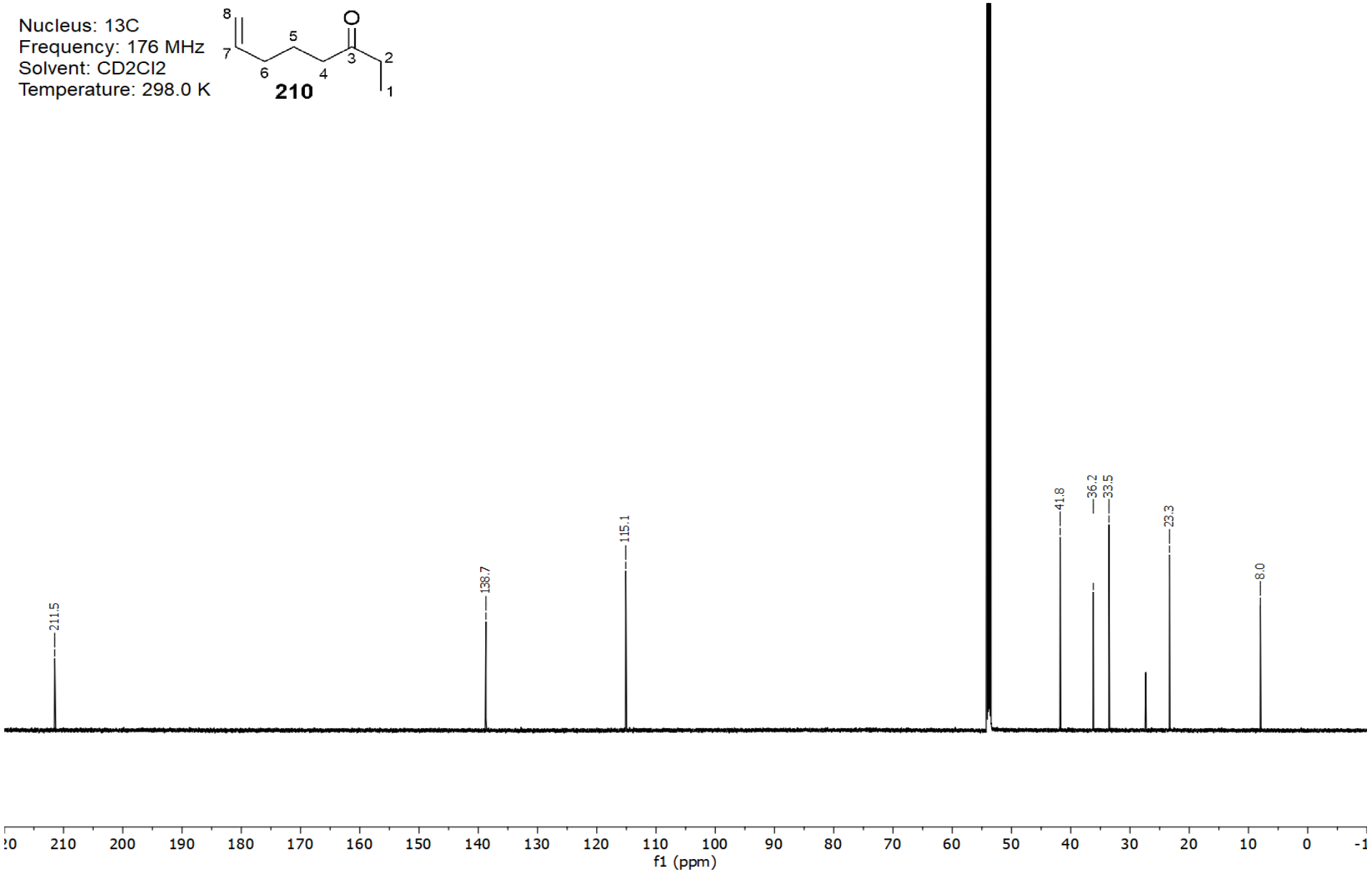
209

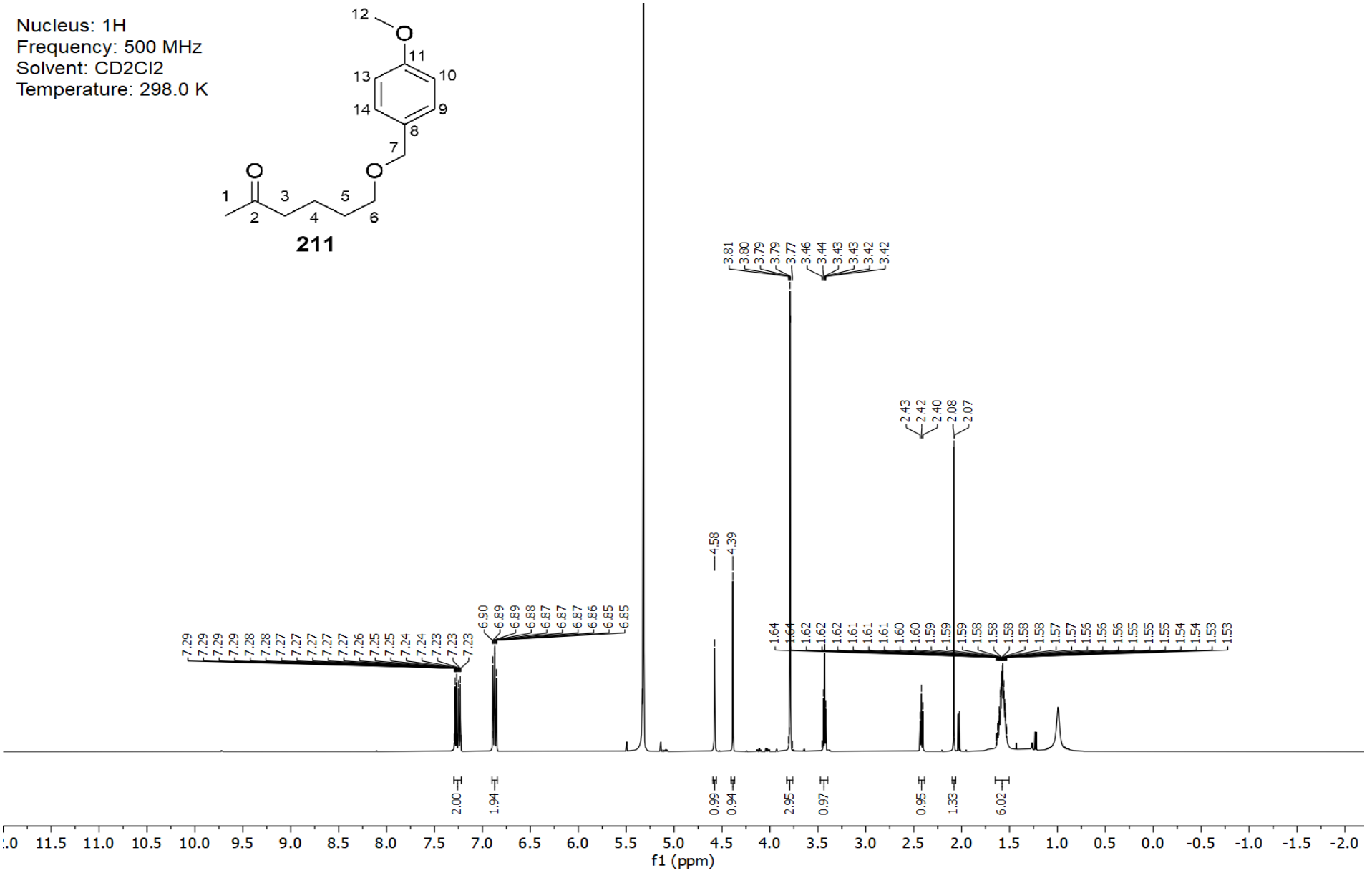



Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
210
f1 (ppm)

Nucleus: 13C
Frequency: 176 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

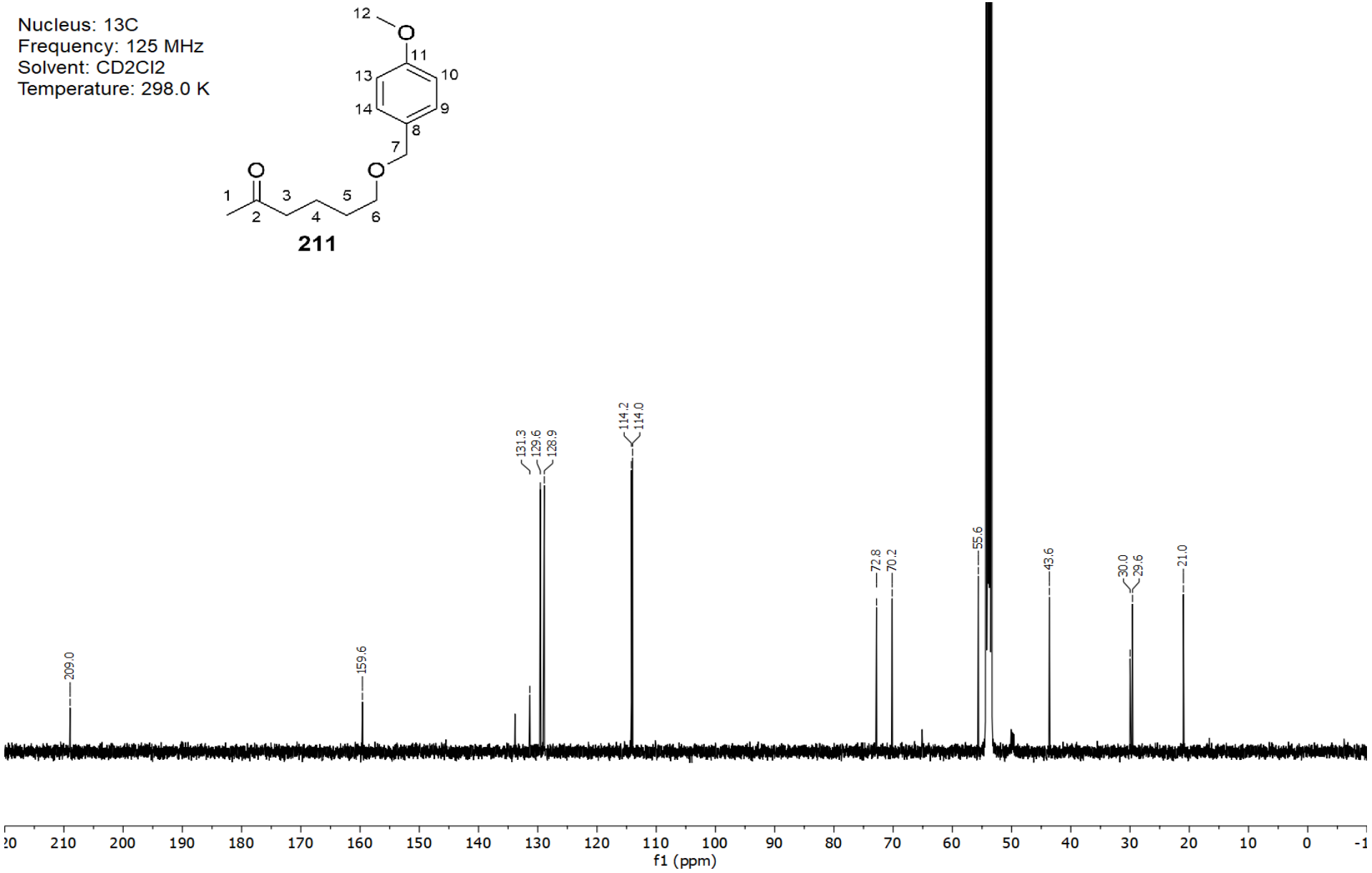
210

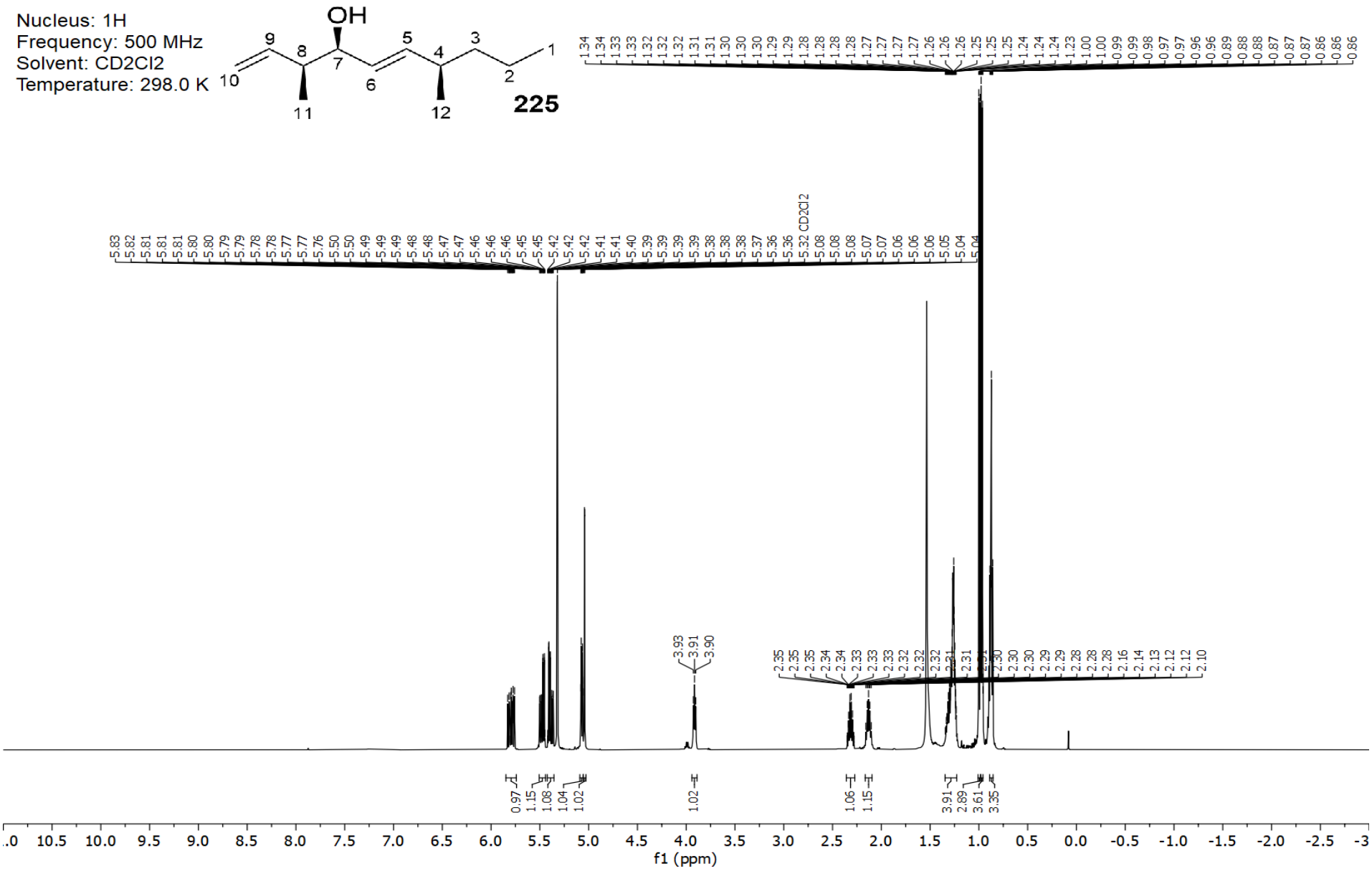



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
211
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

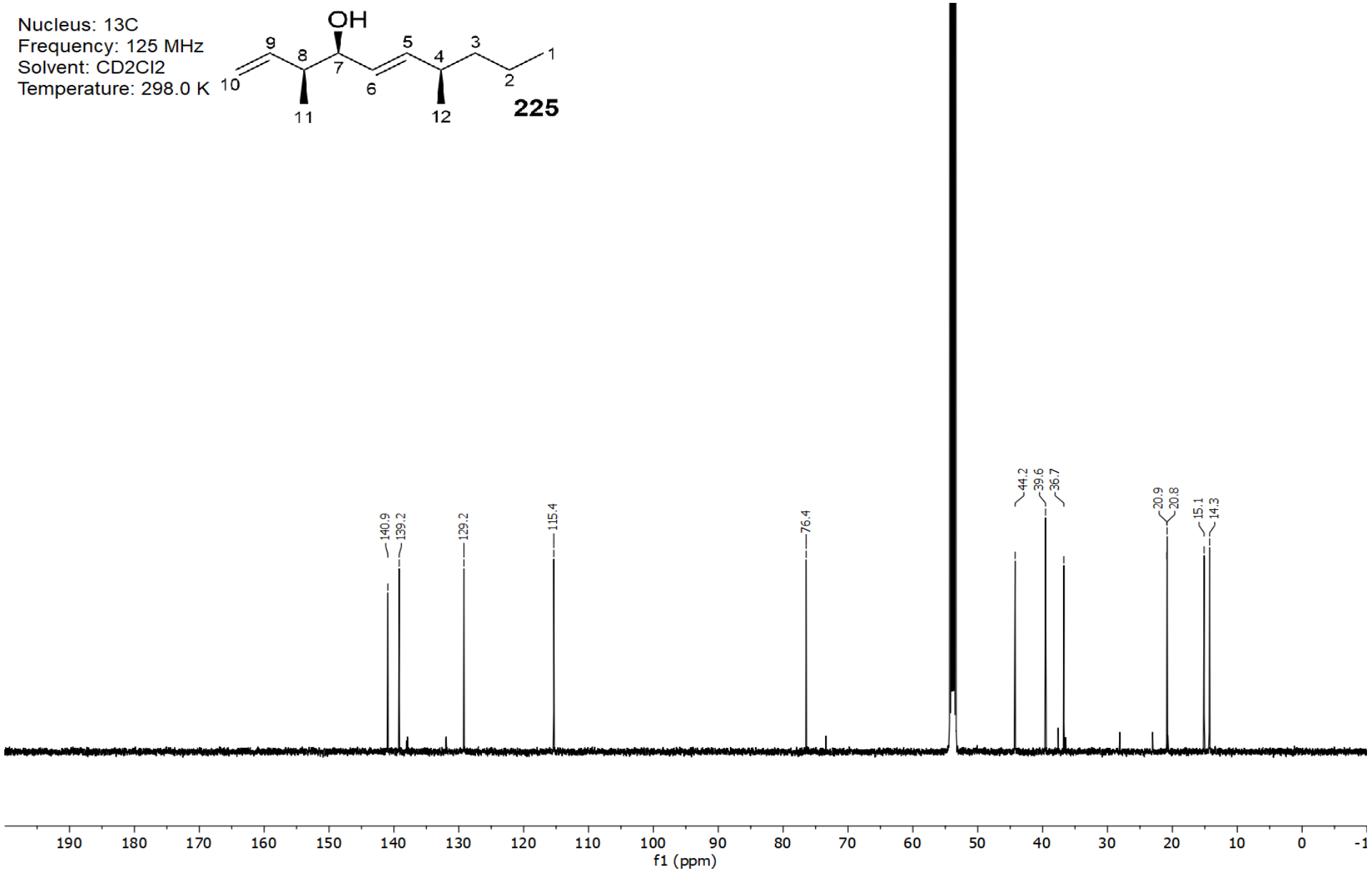
211

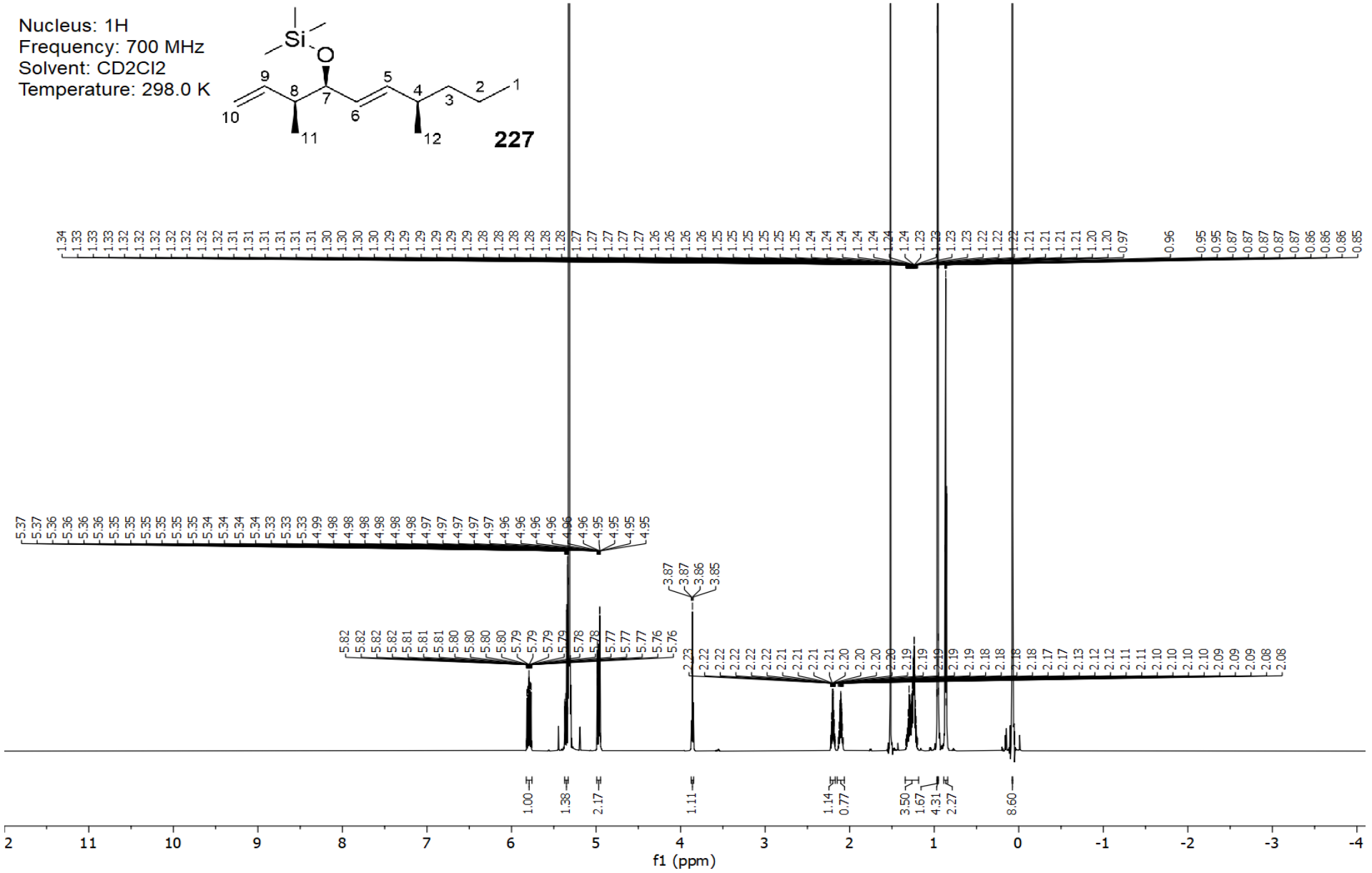



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
OH
225
CD2Cl2
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

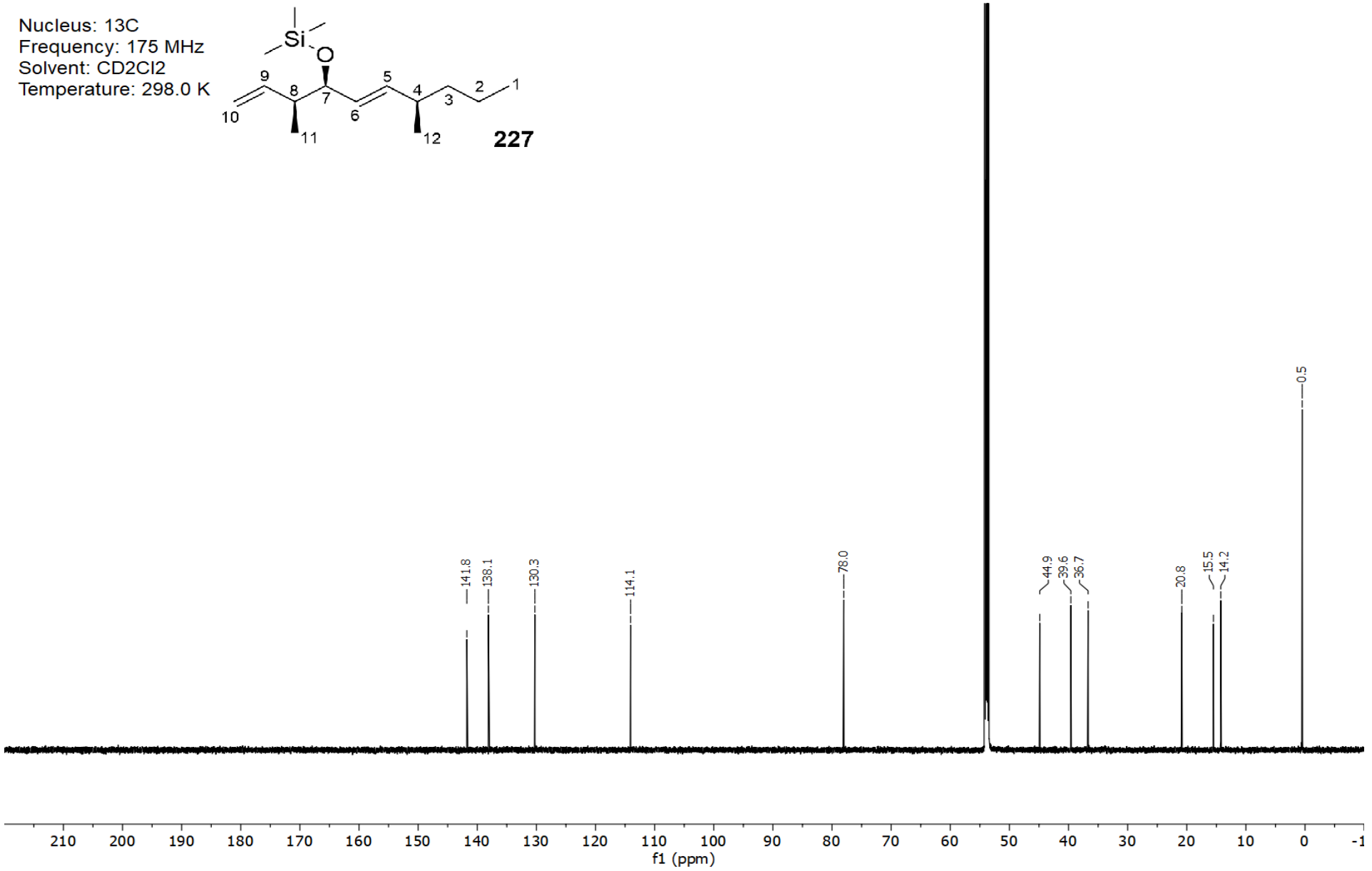
225

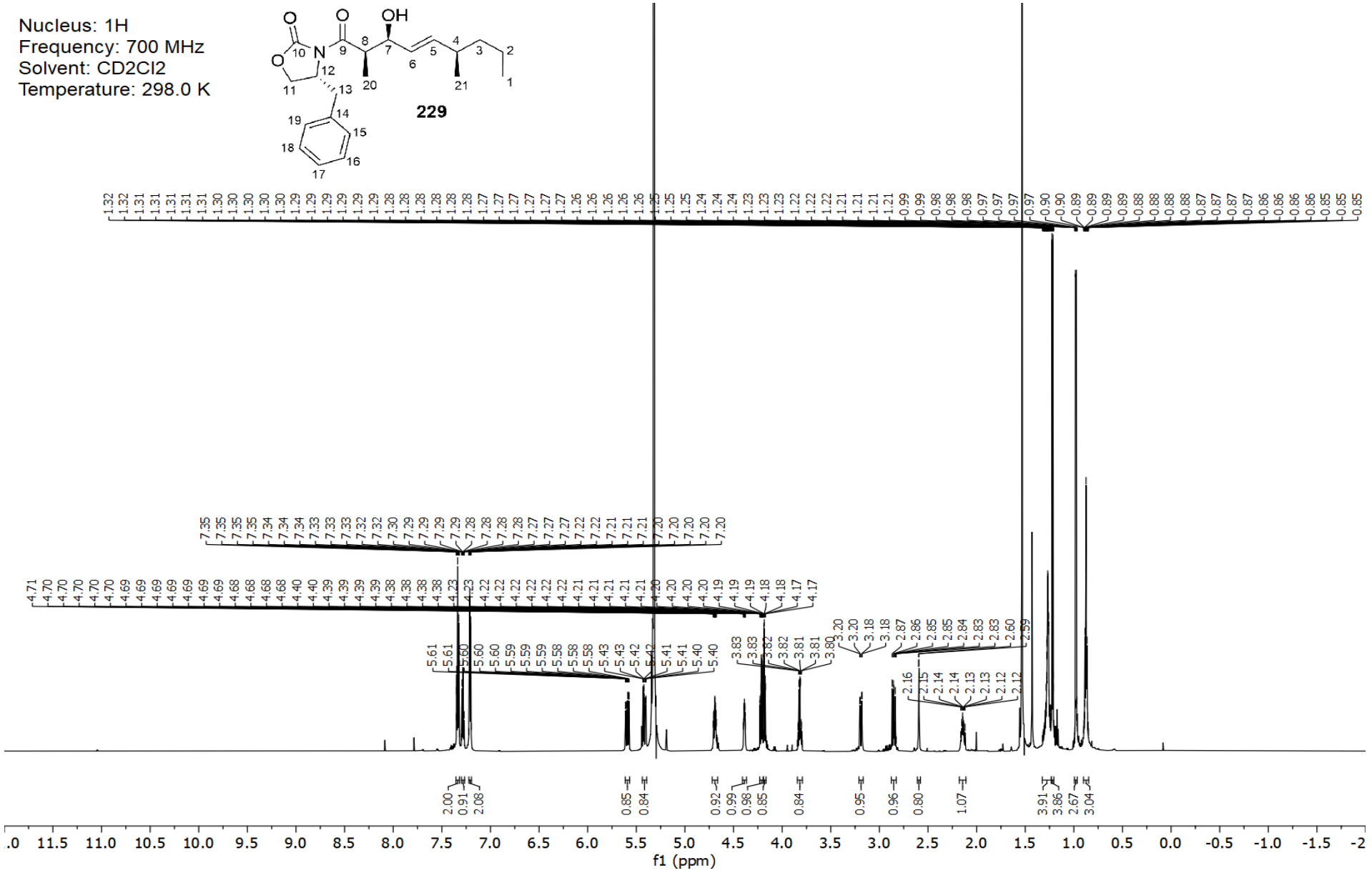


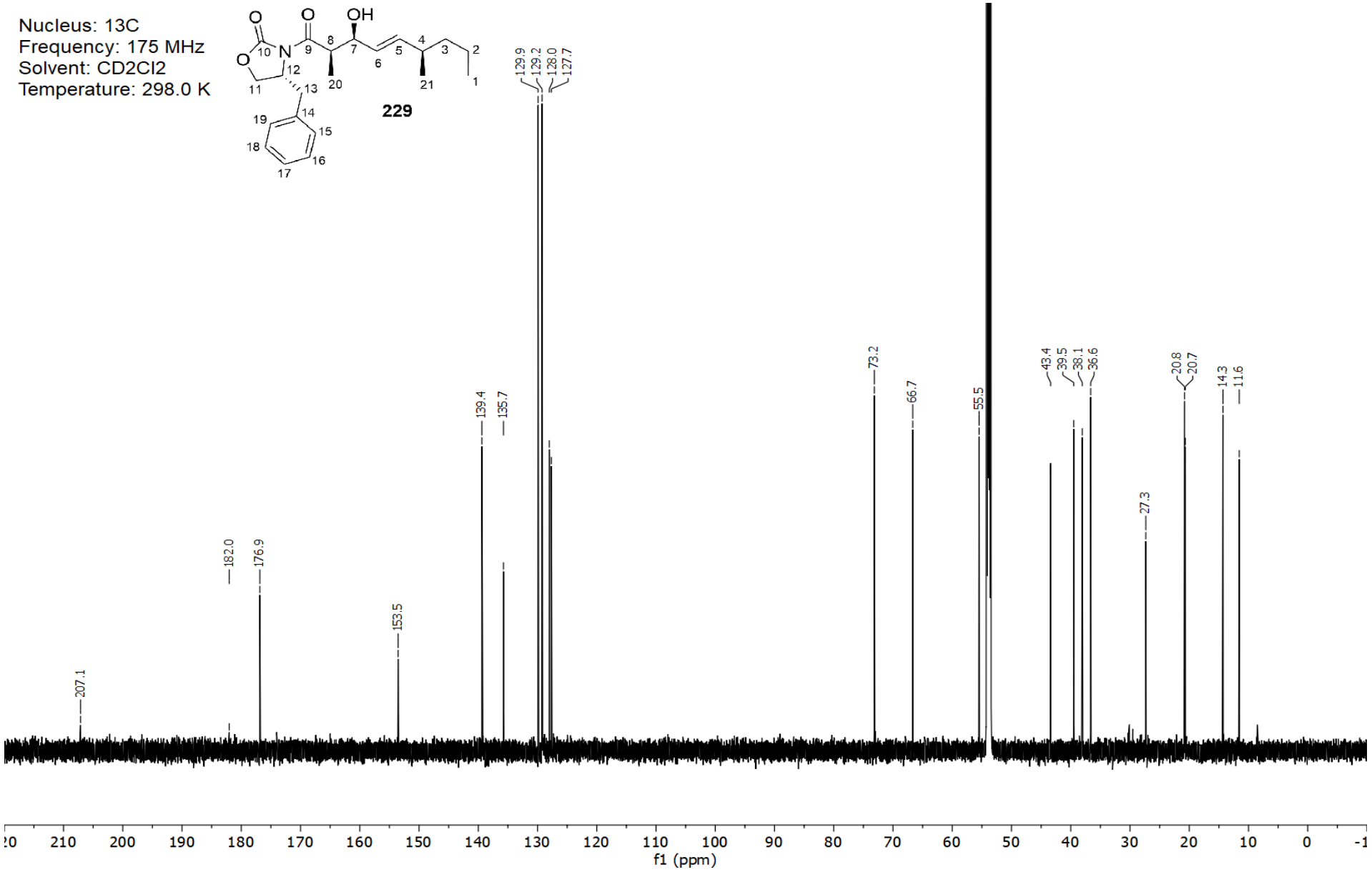

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
227
f1 (ppm)

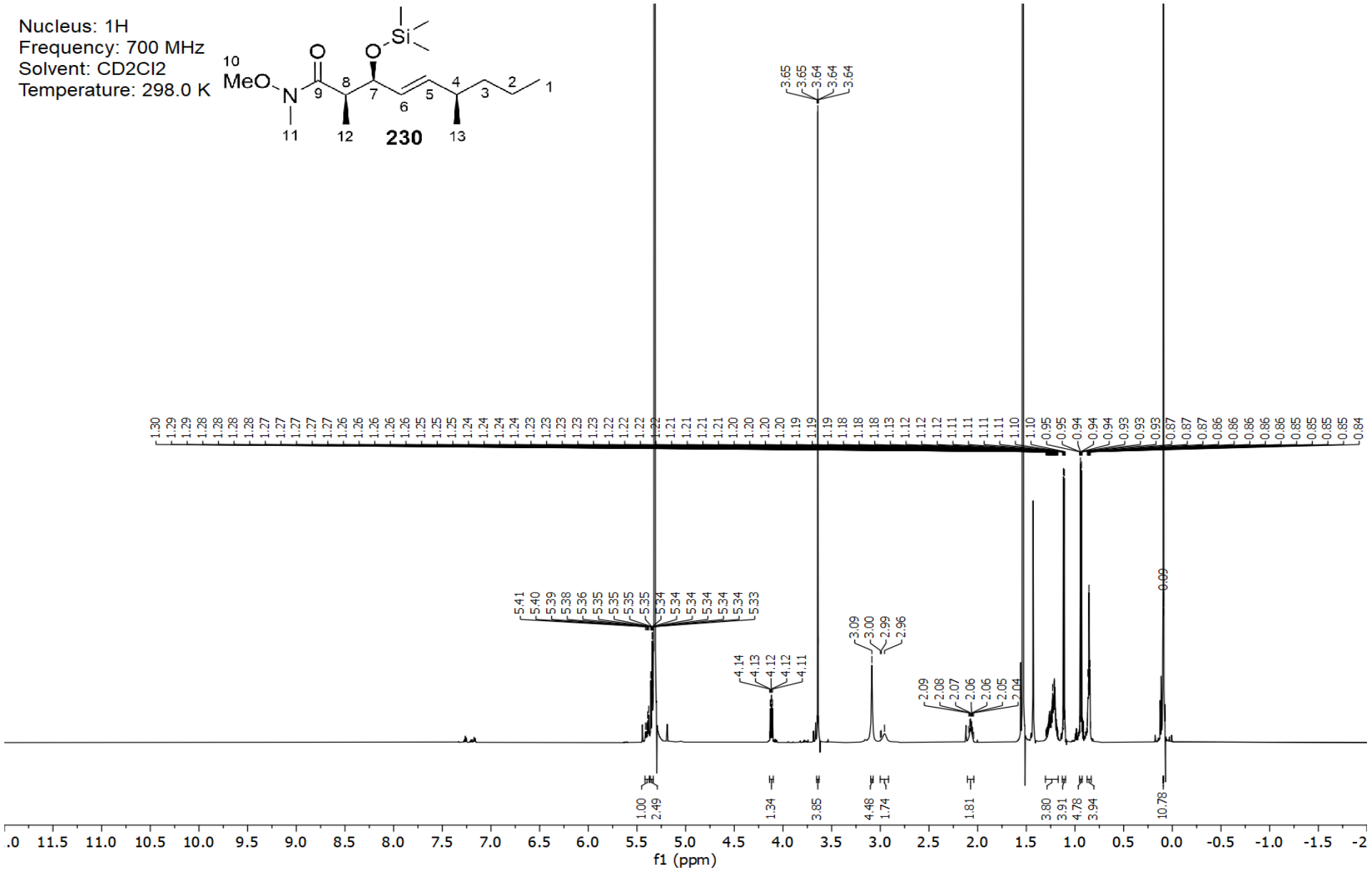
Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

227



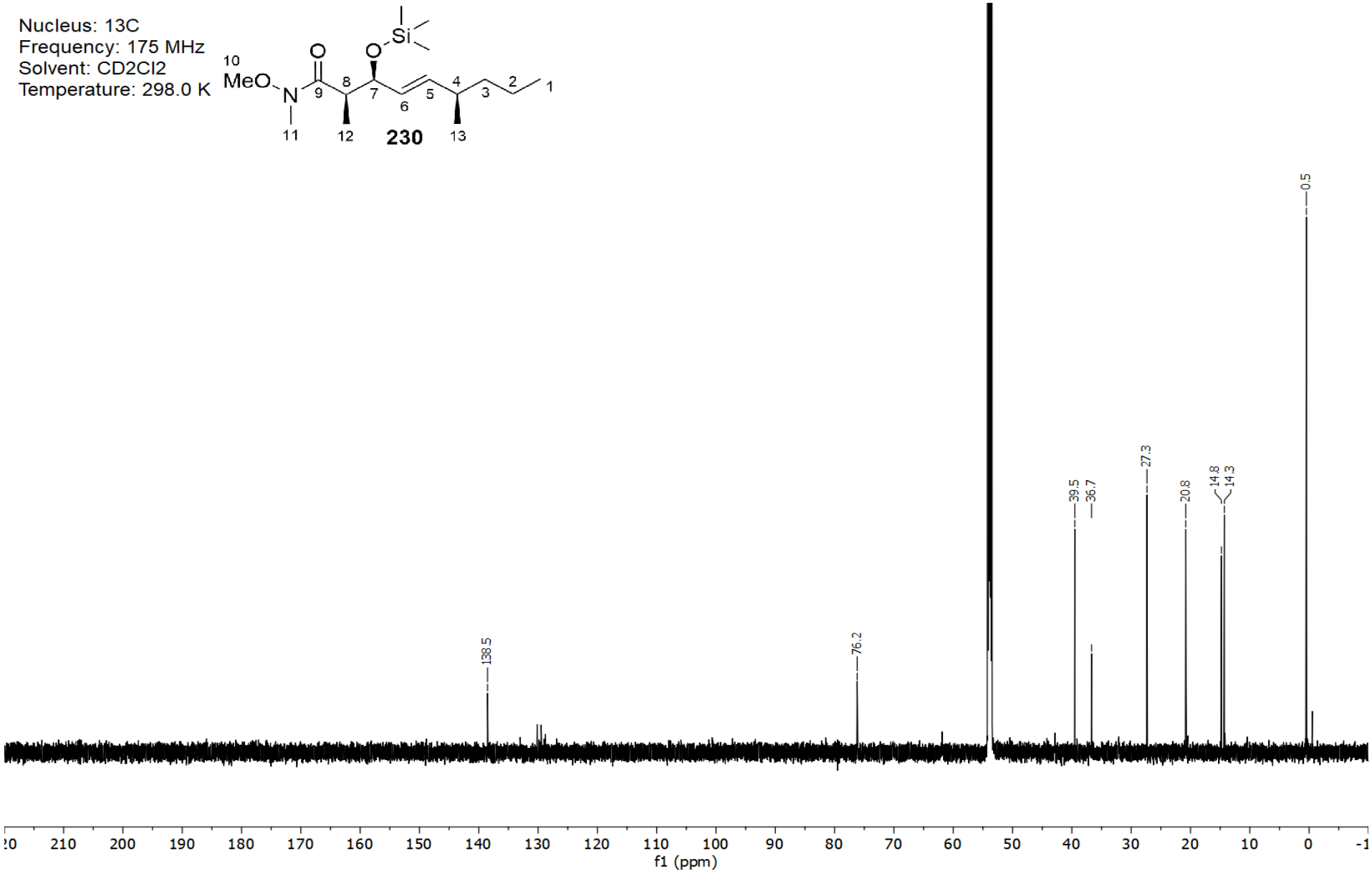

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
229
f1 (ppm)

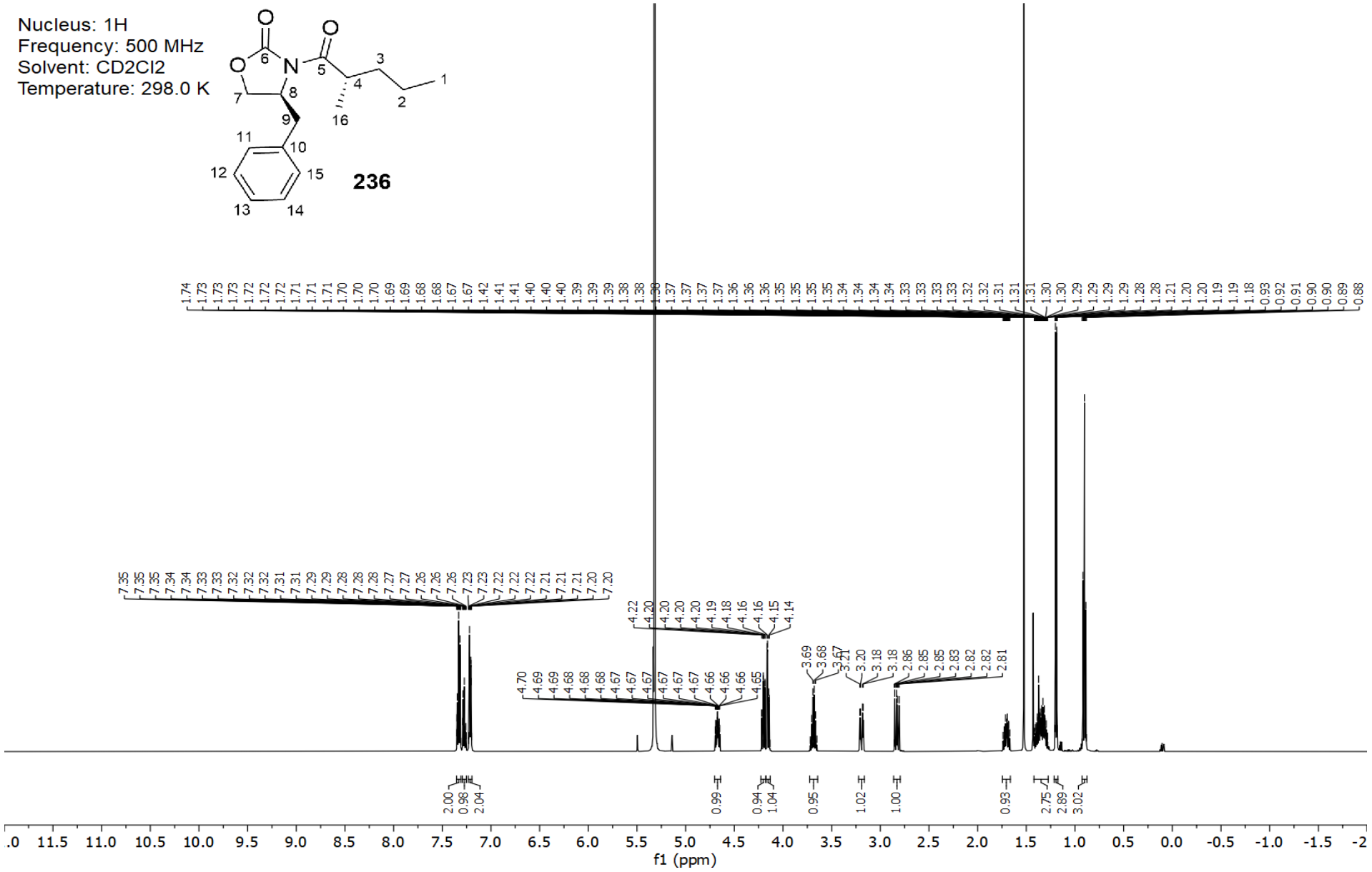

Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
229
207.1
182.0
176.9
153.5
139.4
135.7
129.9
129.2
128.0
127.7
73.2
66.7
55.5
43.4
39.5
38.1
36.6
27.3
20.8
20.7
14.3
11.6
f1 (ppm)


Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
230
f1 (ppm)

Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

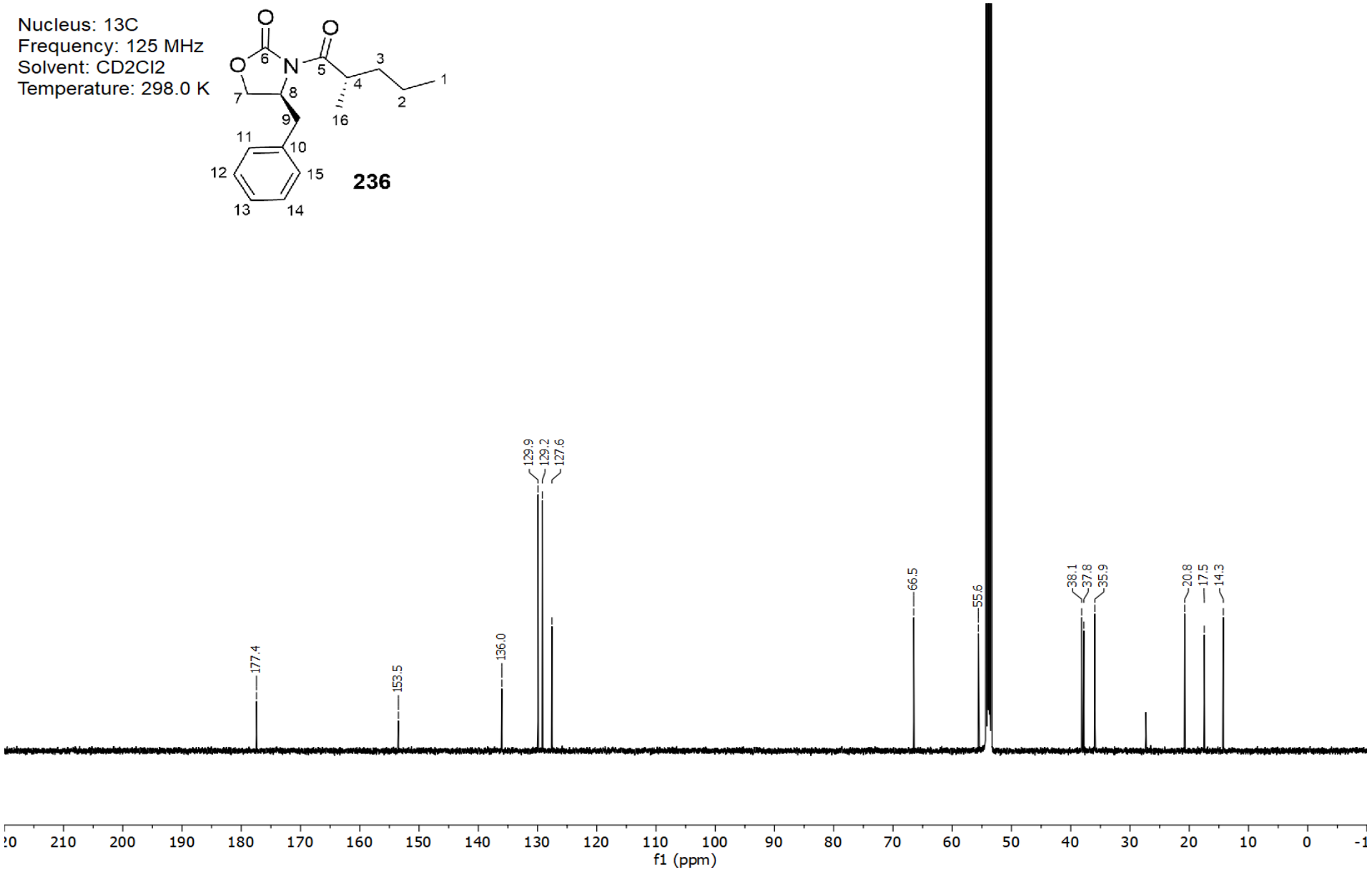
230



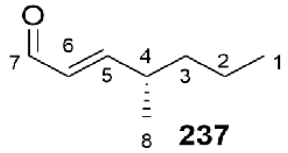

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
236
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD_2Cl_2
Temperature: 298.0 K

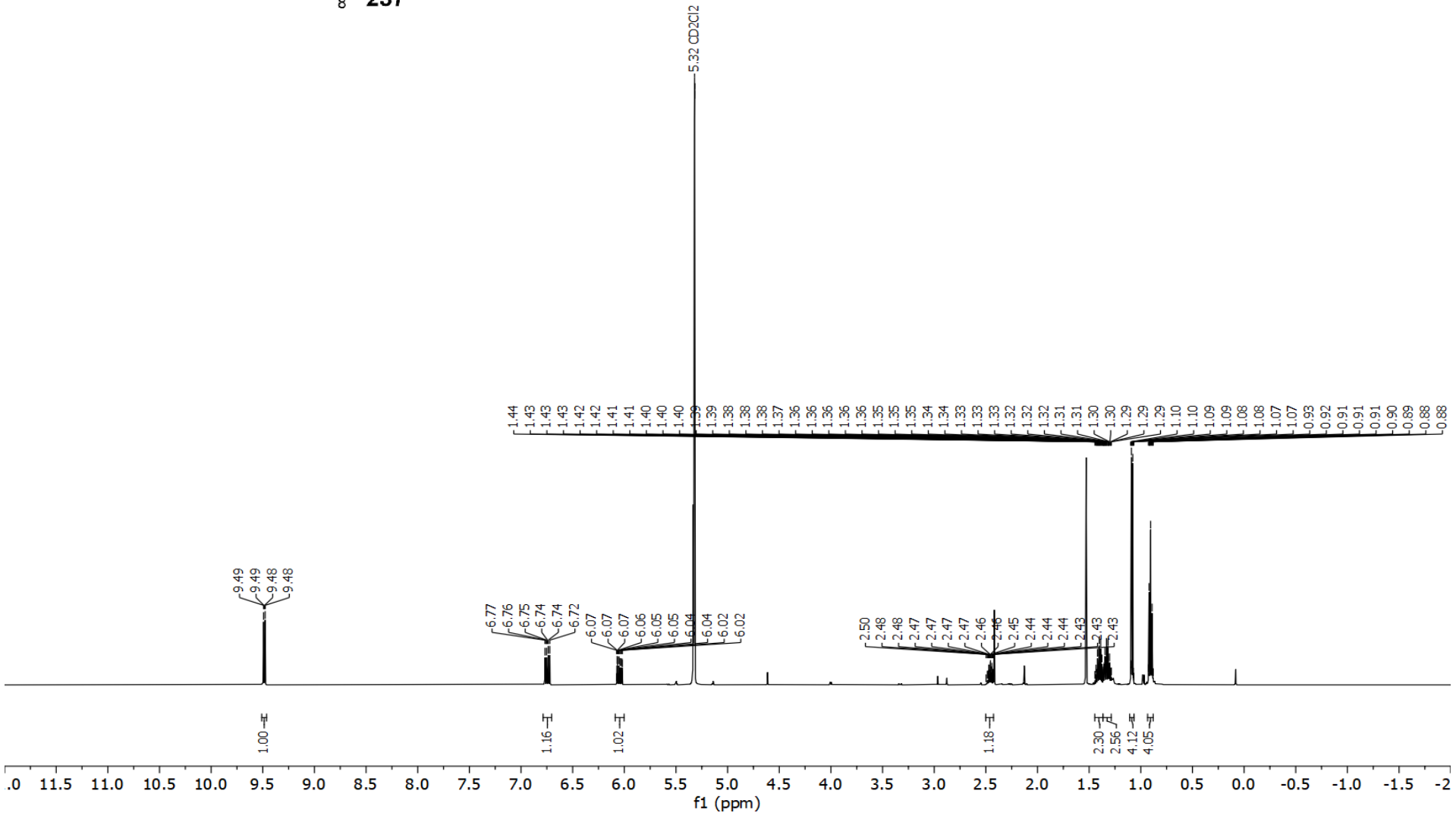
236



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

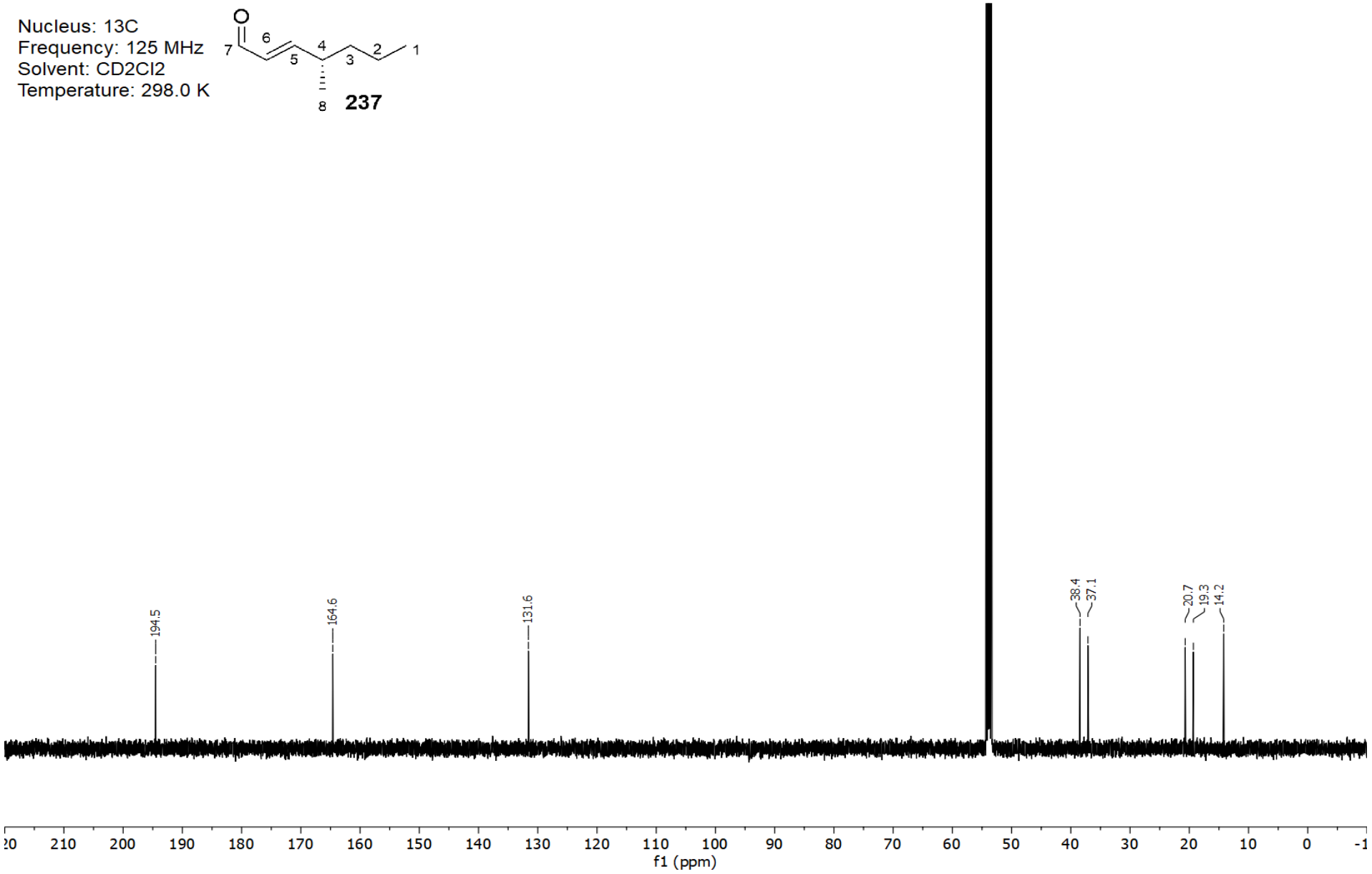


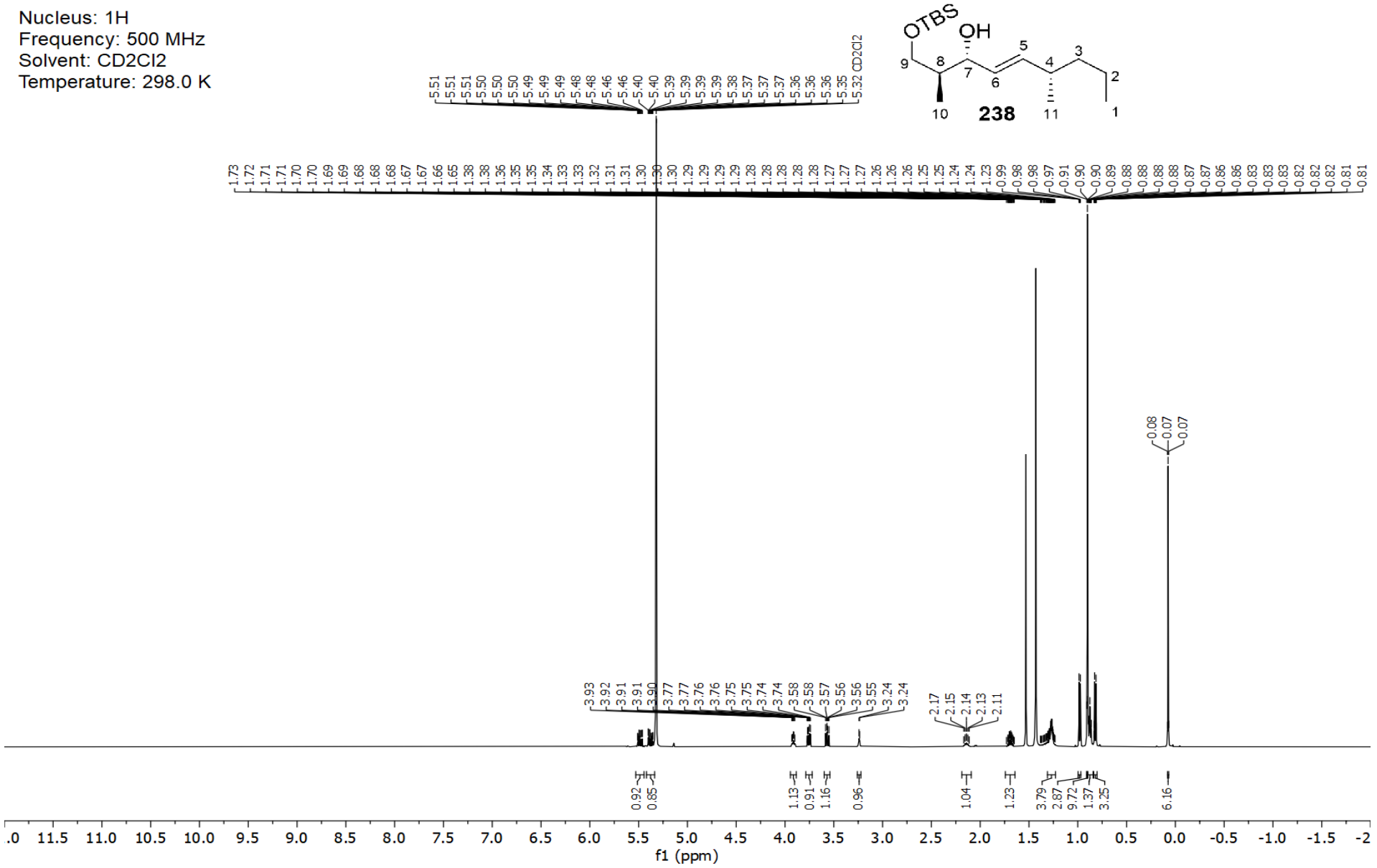
237



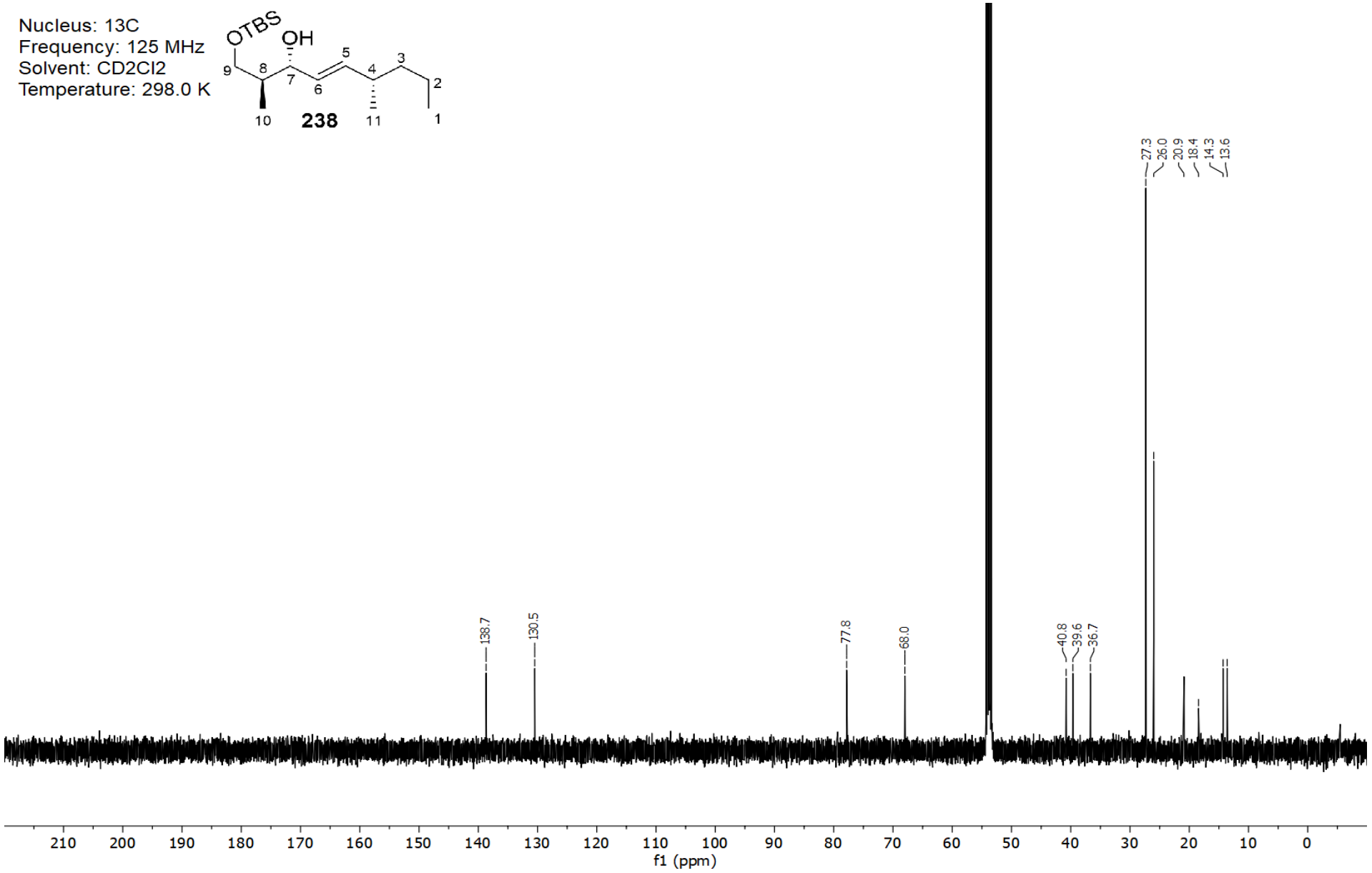
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

237

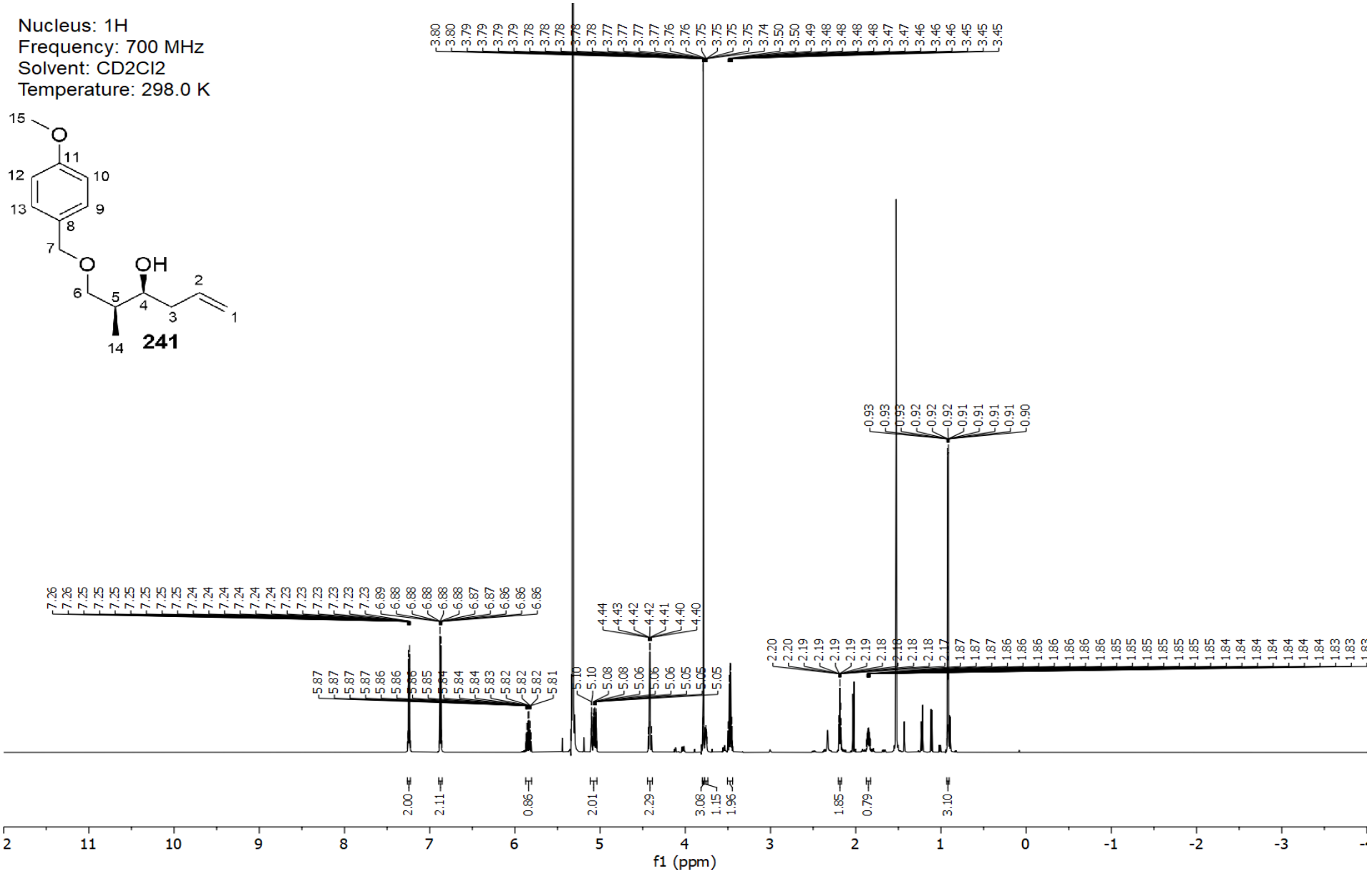



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
OTBS
OH
238
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

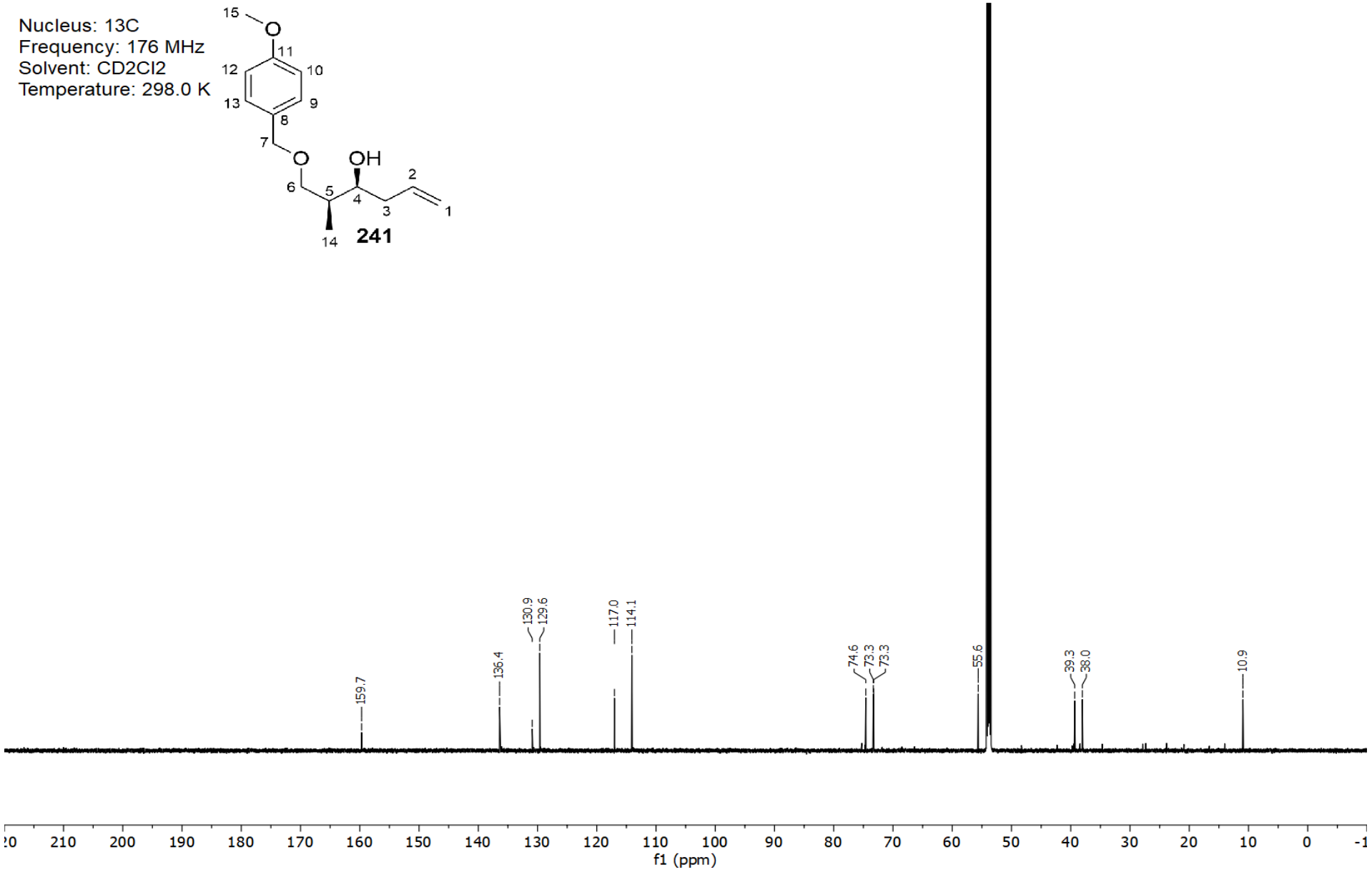


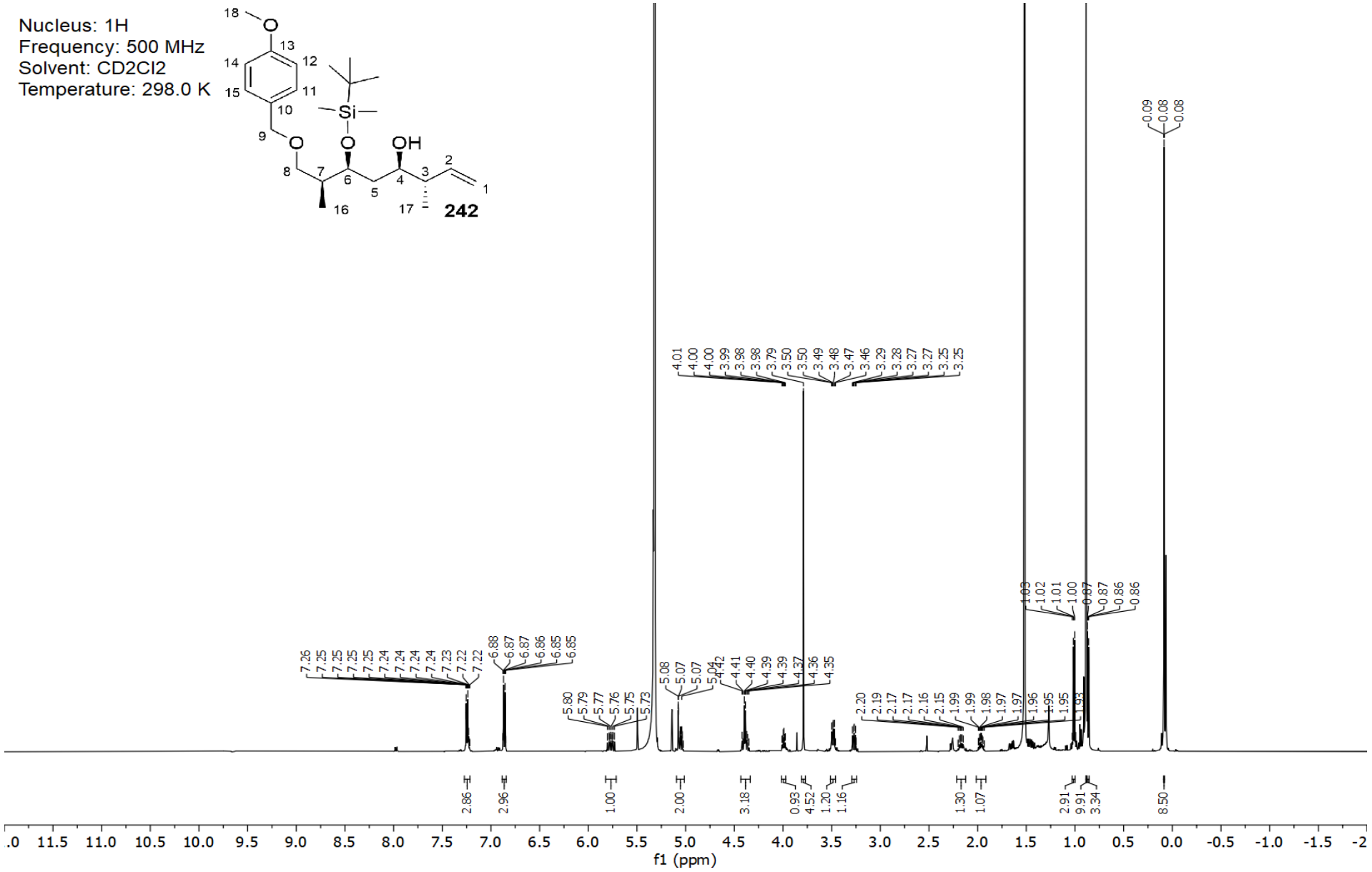
6. Appendix


Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
241
f1 (ppm)

Nucleus: 13C
Frequency: 176 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

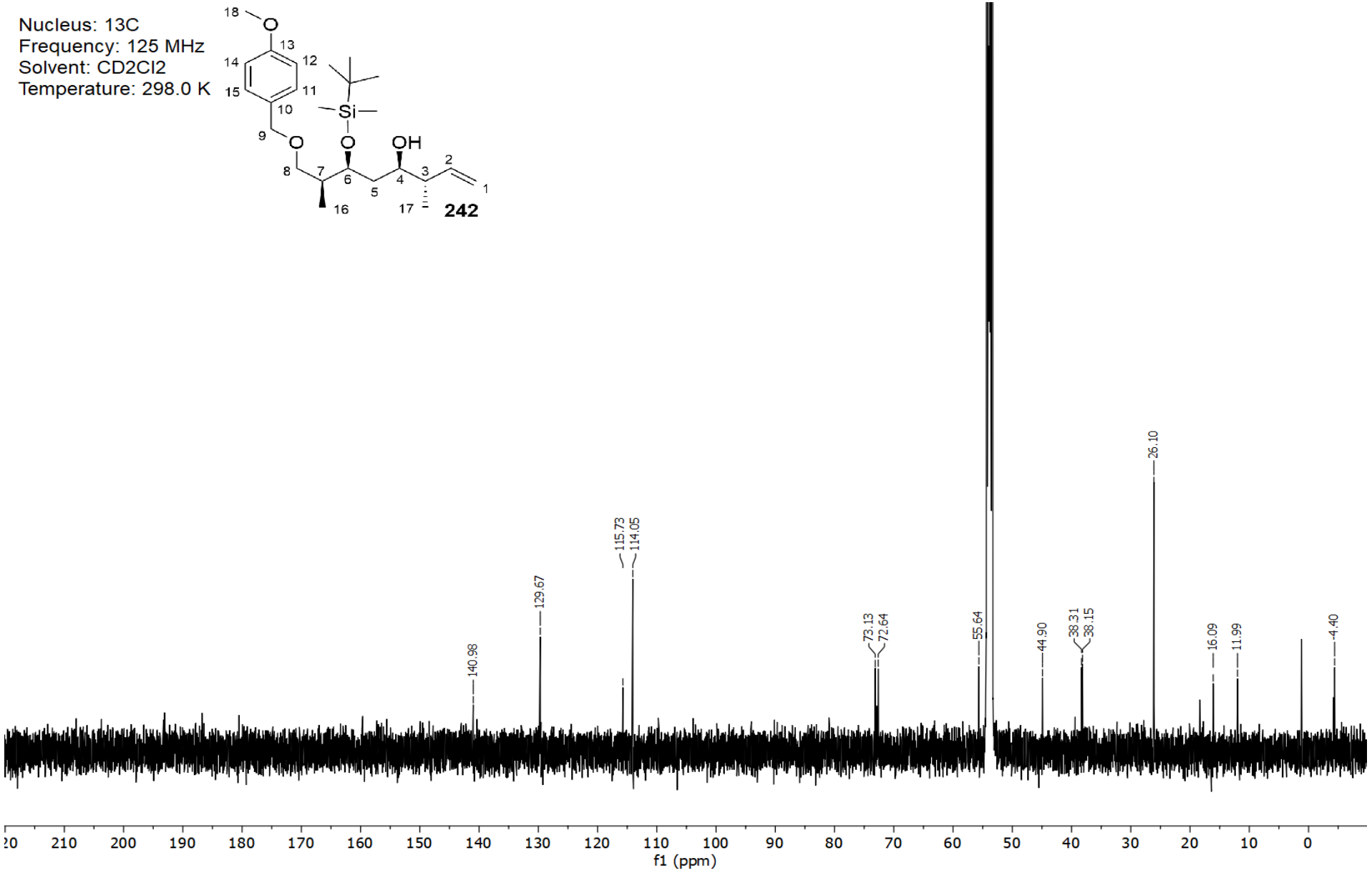
241



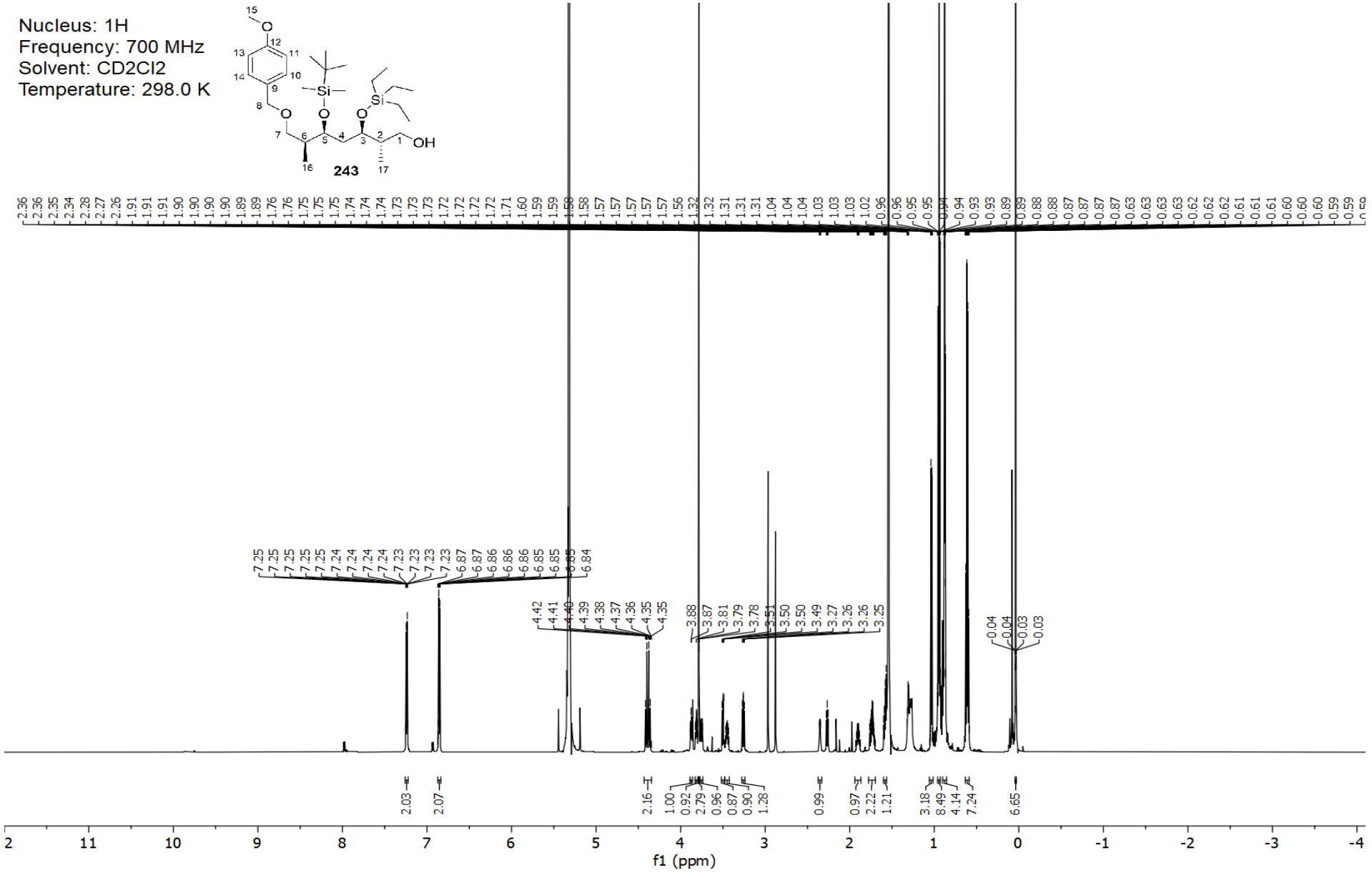

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
242
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

242

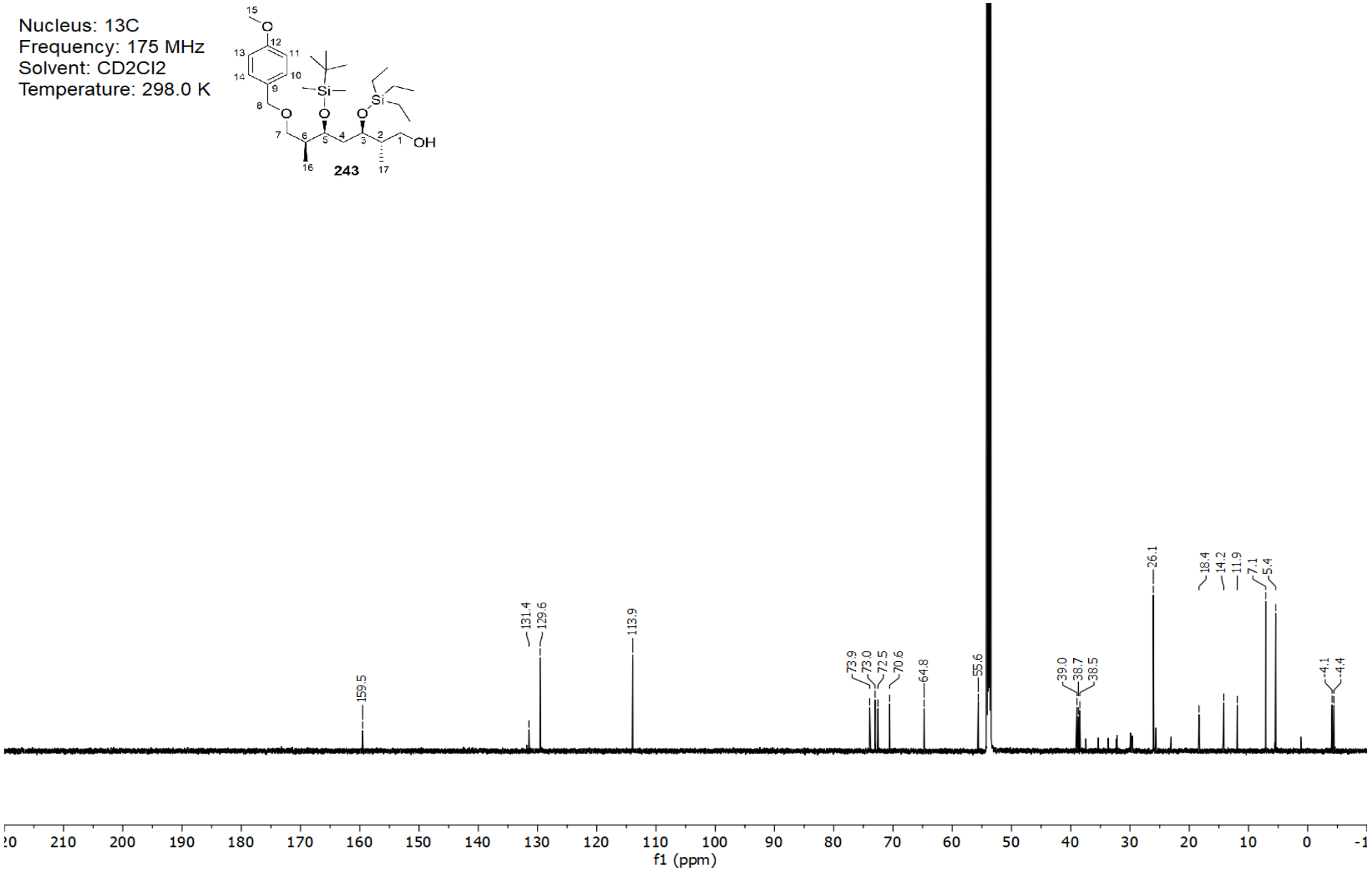


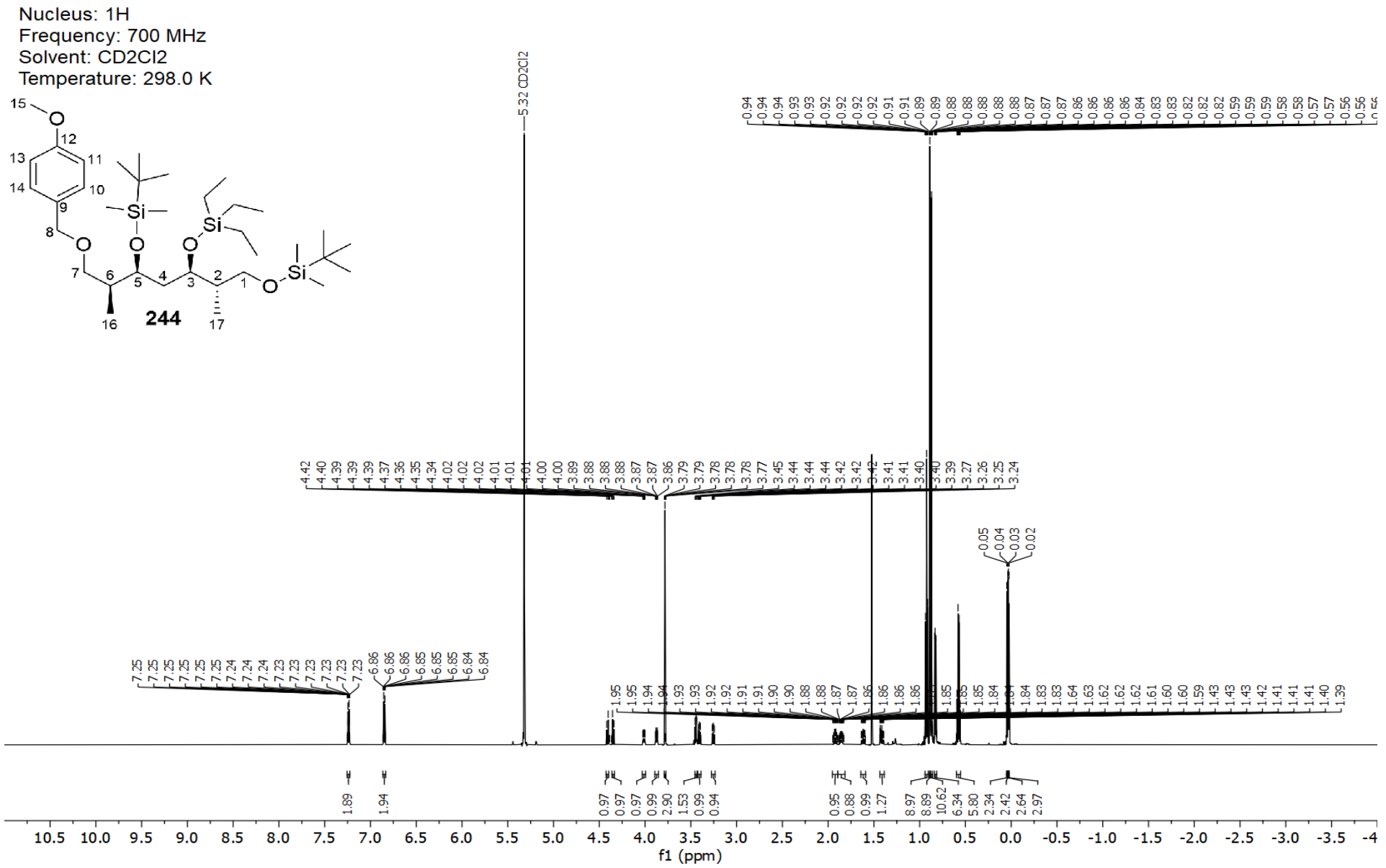
6. Appendix

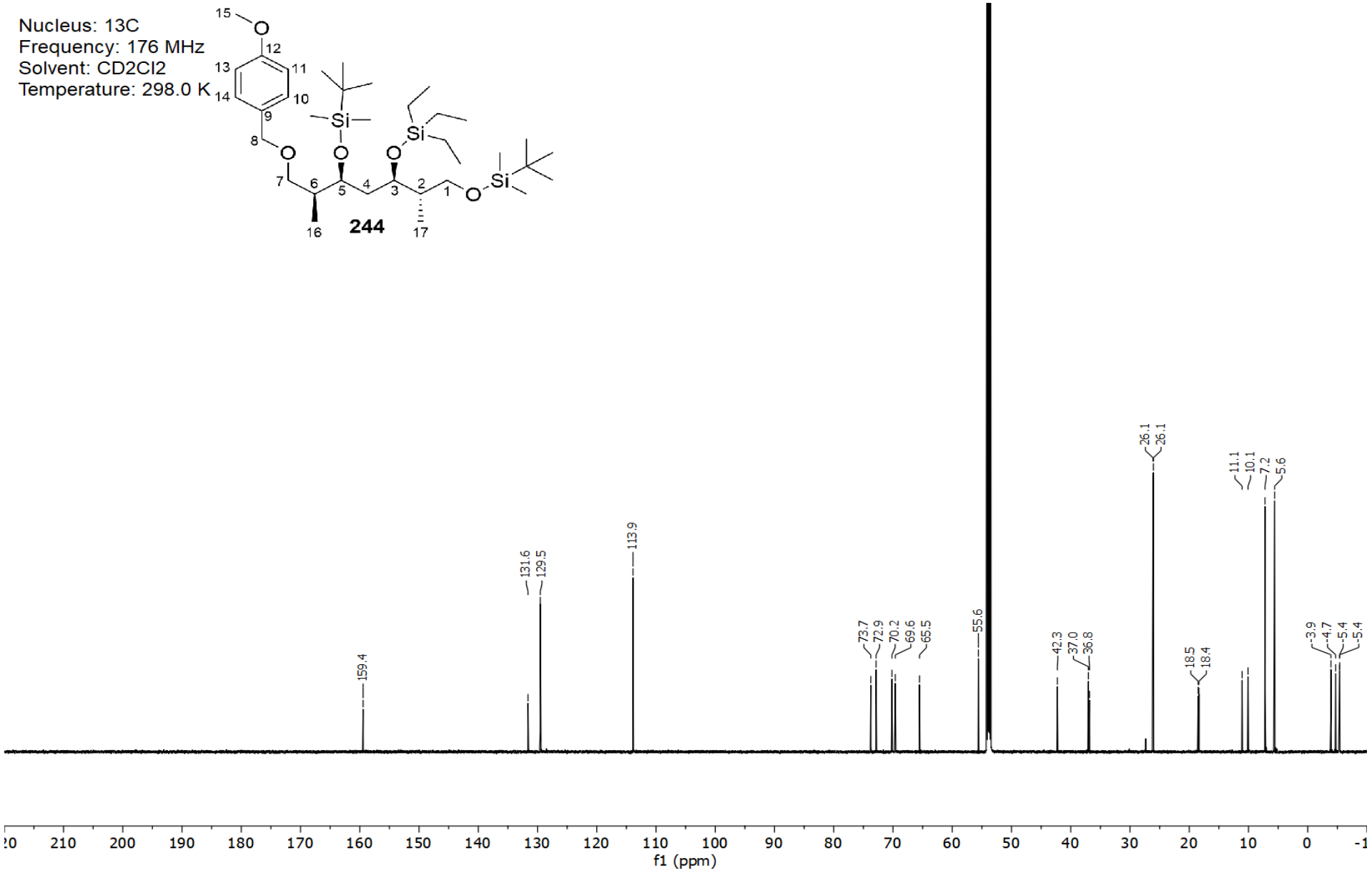

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
243
f1 (ppm)

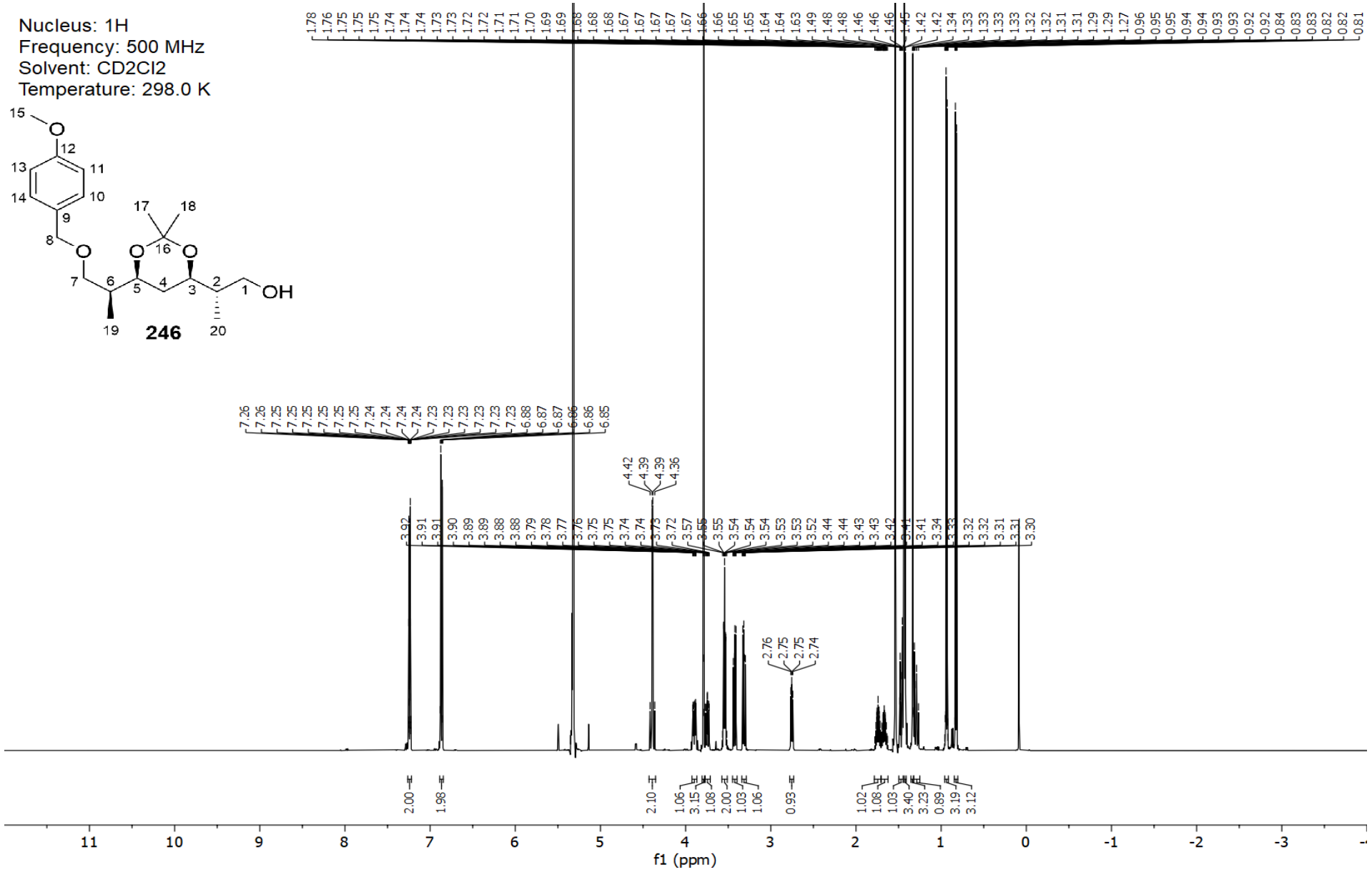
Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

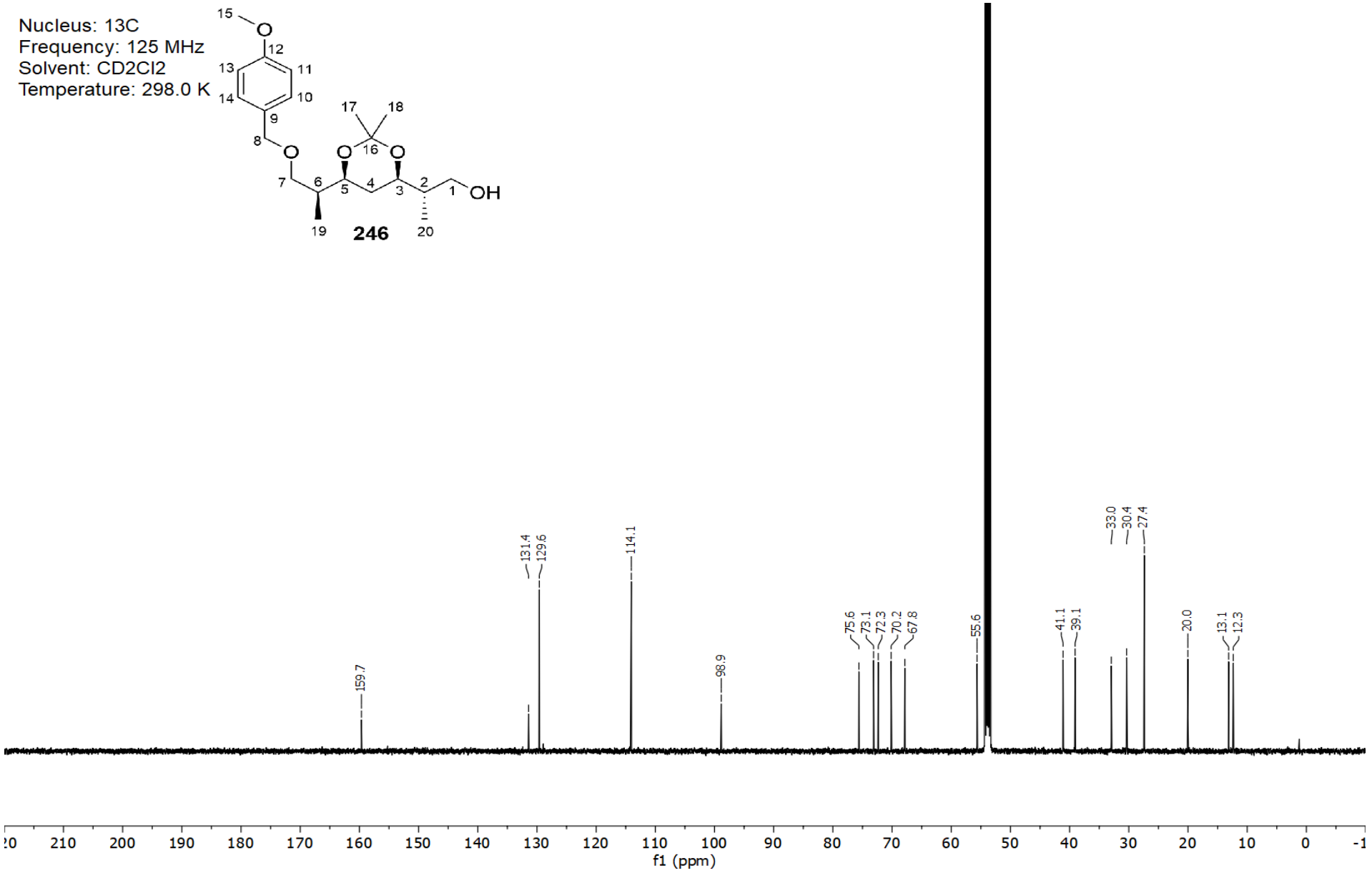
243

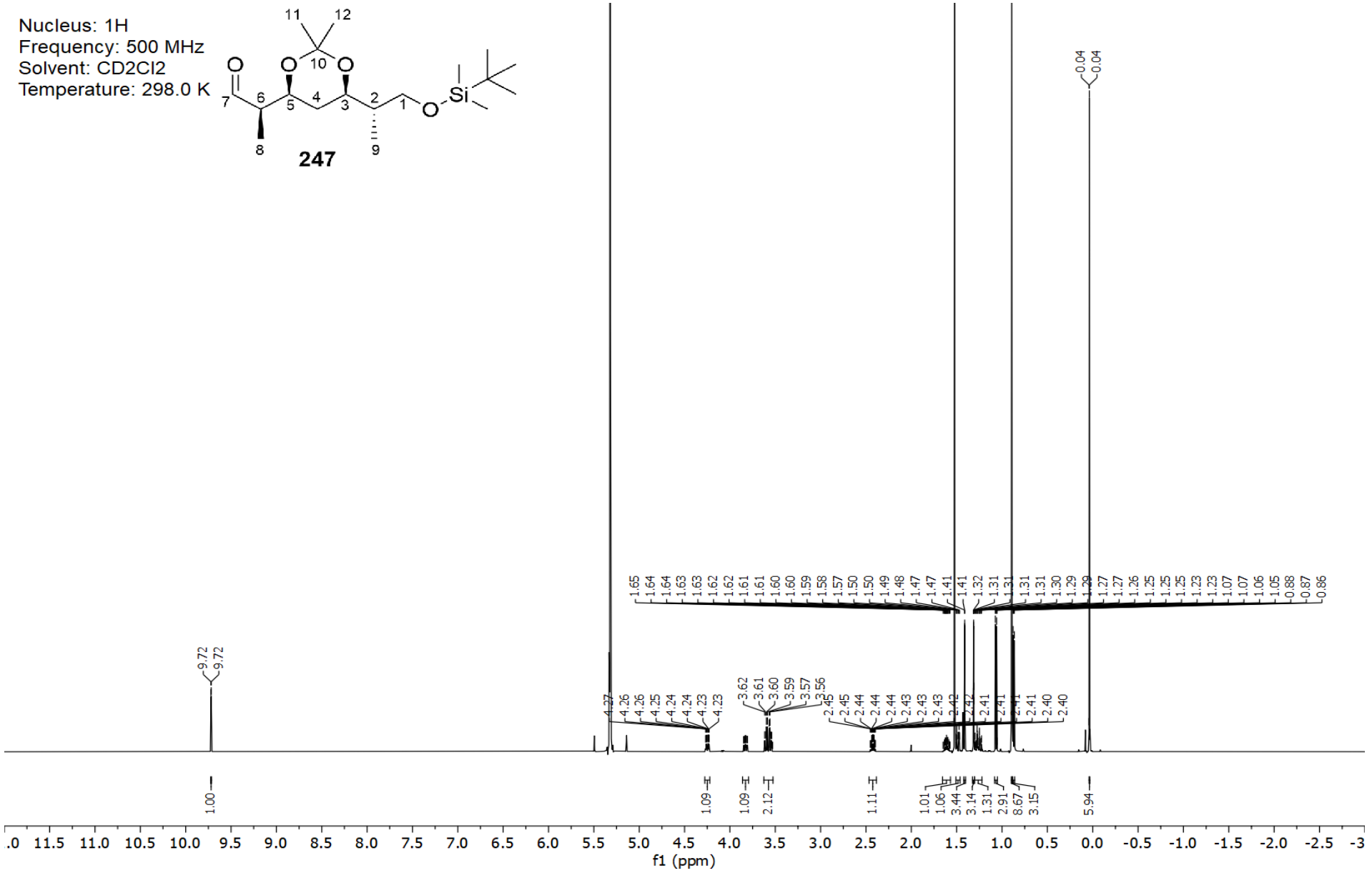



Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
244
5.32 CD2Cl2
f1 (ppm)


Nucleus: 13C
Frequency: 176 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
244
159.4
131.6
129.5
113.9
73.7
72.9
70.2
69.6
65.5
55.6
42.3
37.0
36.8
26.1
26.1
18.5
18.4
11.1
10.1
7.2
5.6
-3.9
-4.7
-5.4
-5.4
f1 (ppm)

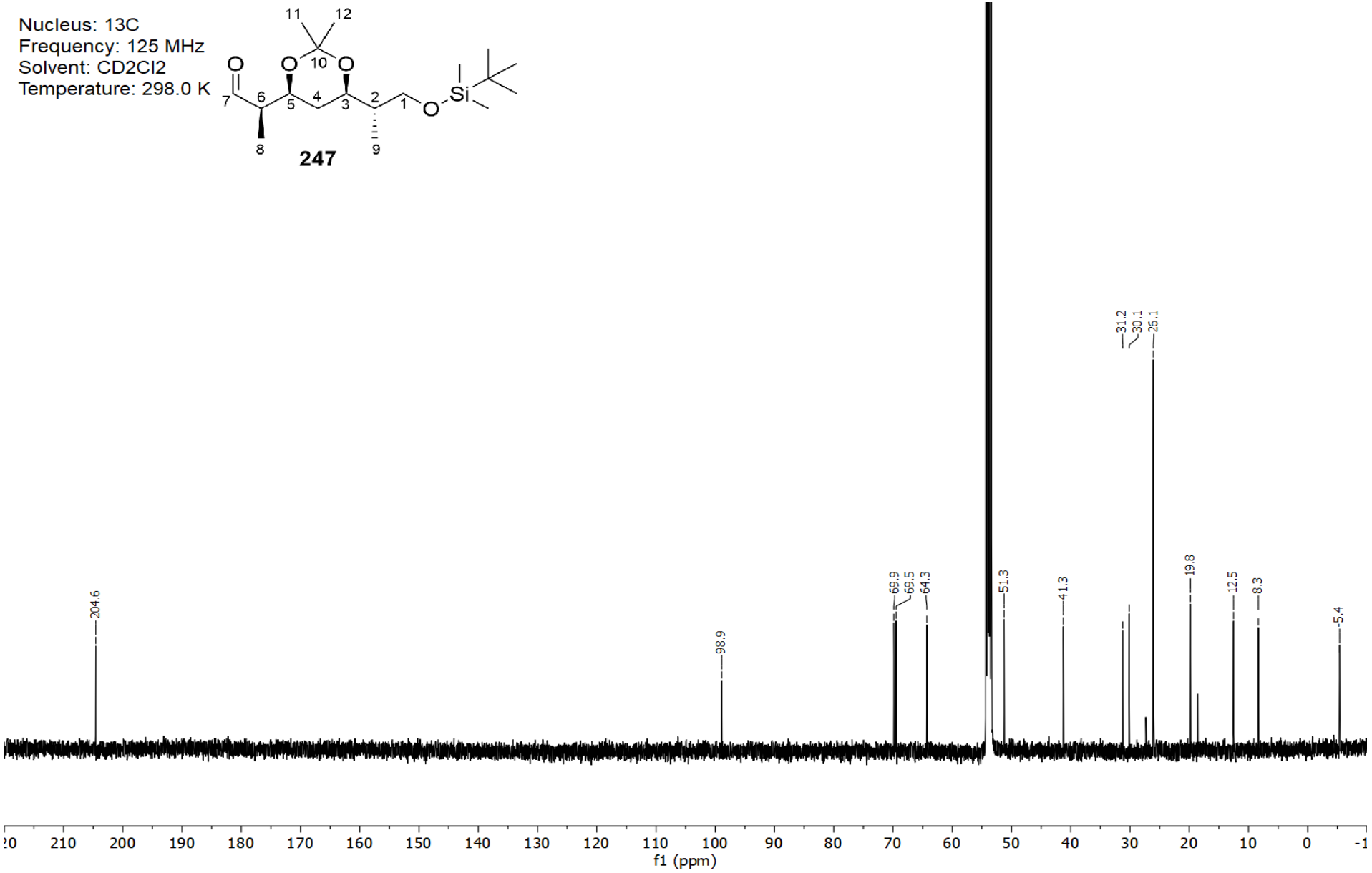

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
246
f1 (ppm)

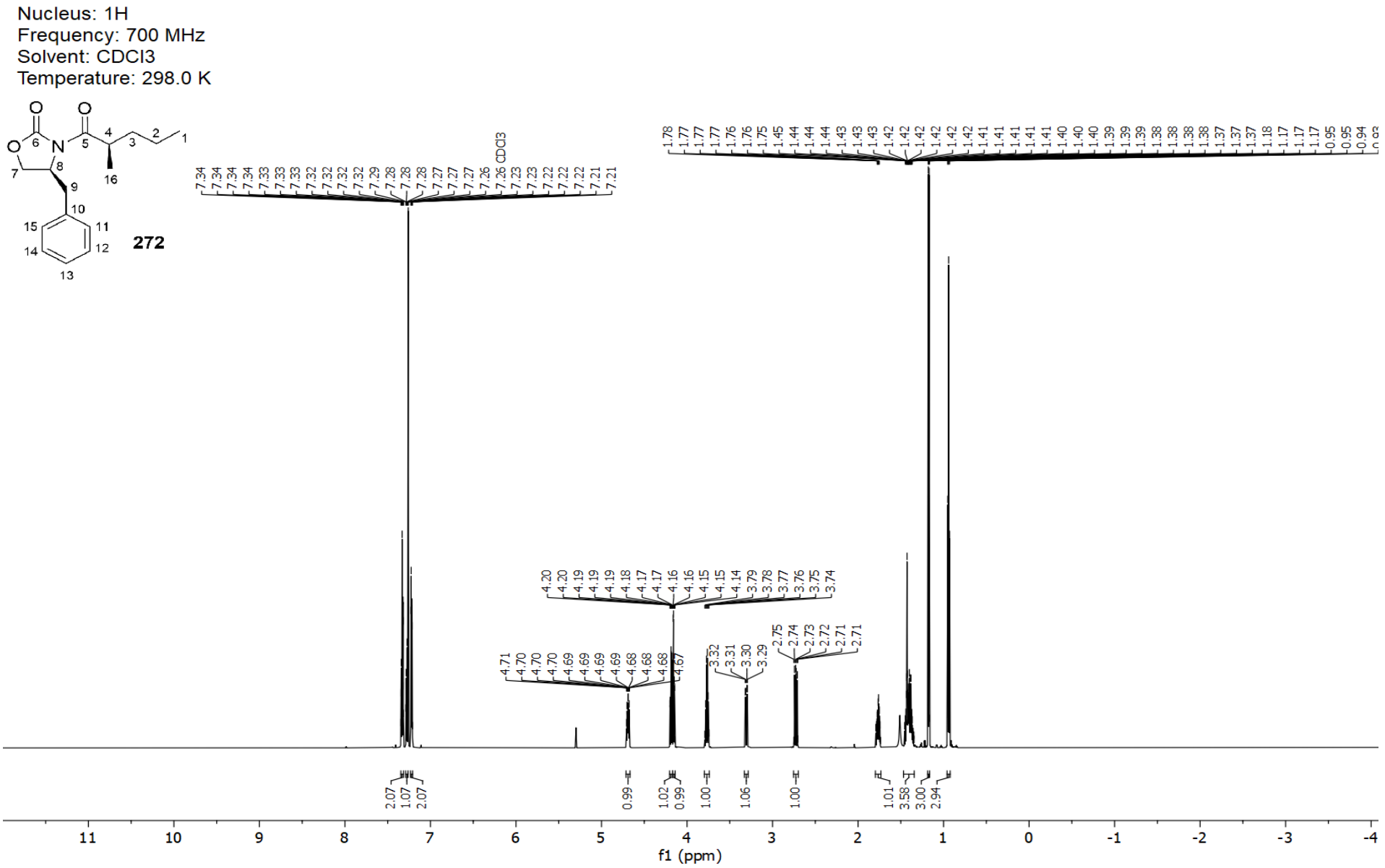

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
246
159.7
131.4
129.6
114.1
98.9
75.6
73.1
72.3
70.2
67.8
55.6
41.1
39.1
33.0
30.4
27.4
20.0
13.1
12.3
f1 (ppm)

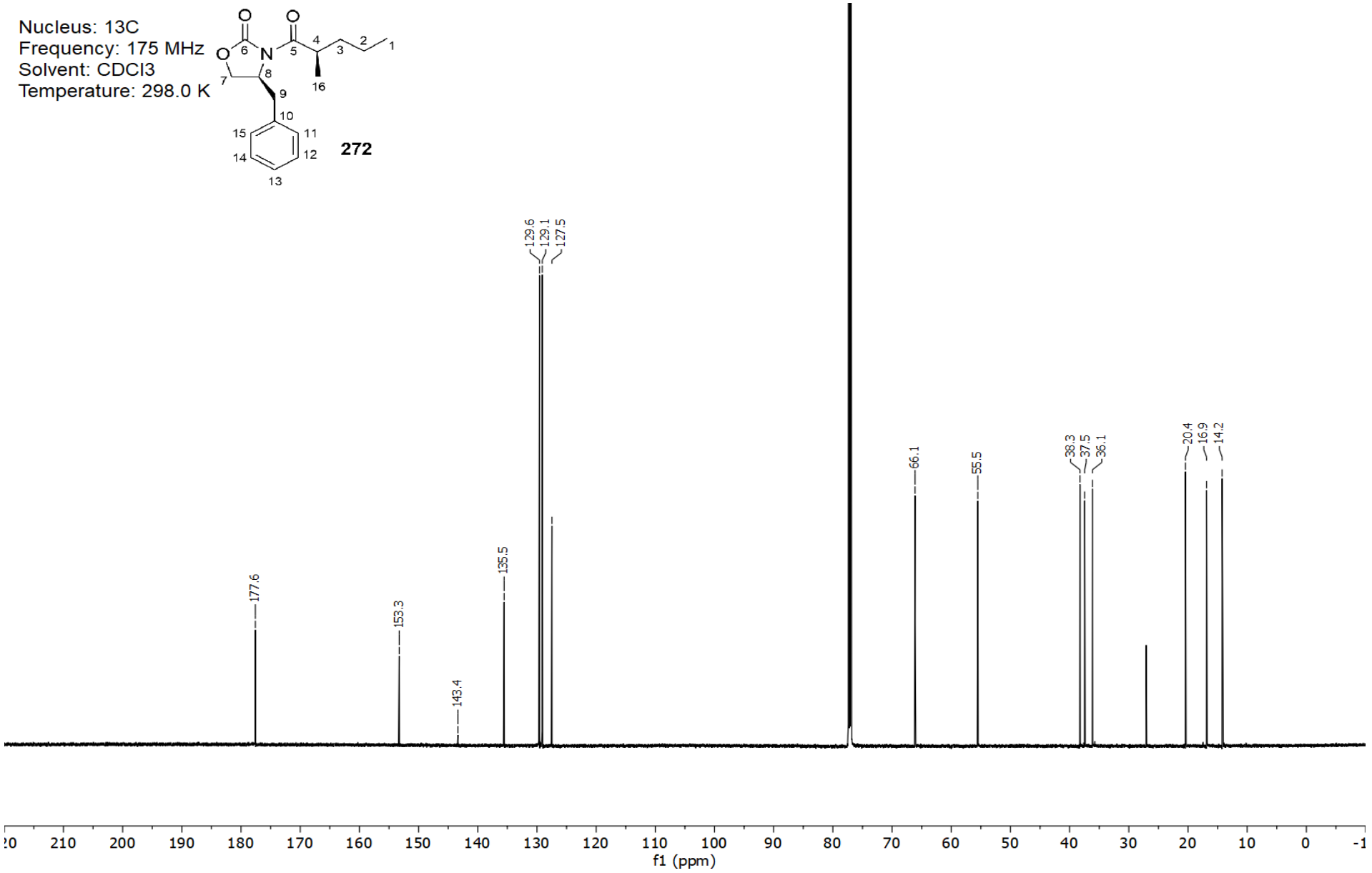

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
247
f1 (ppm)

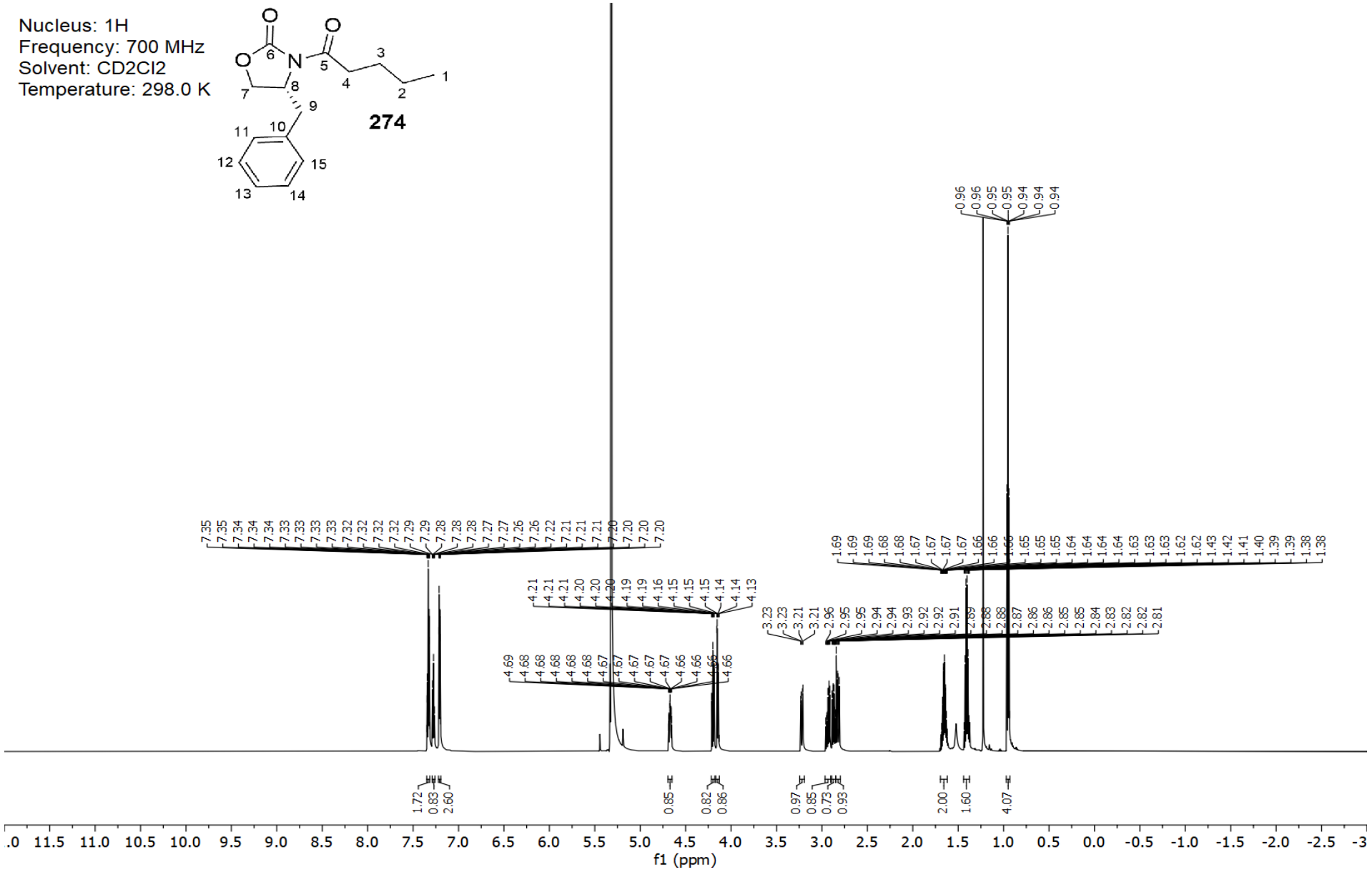
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

247



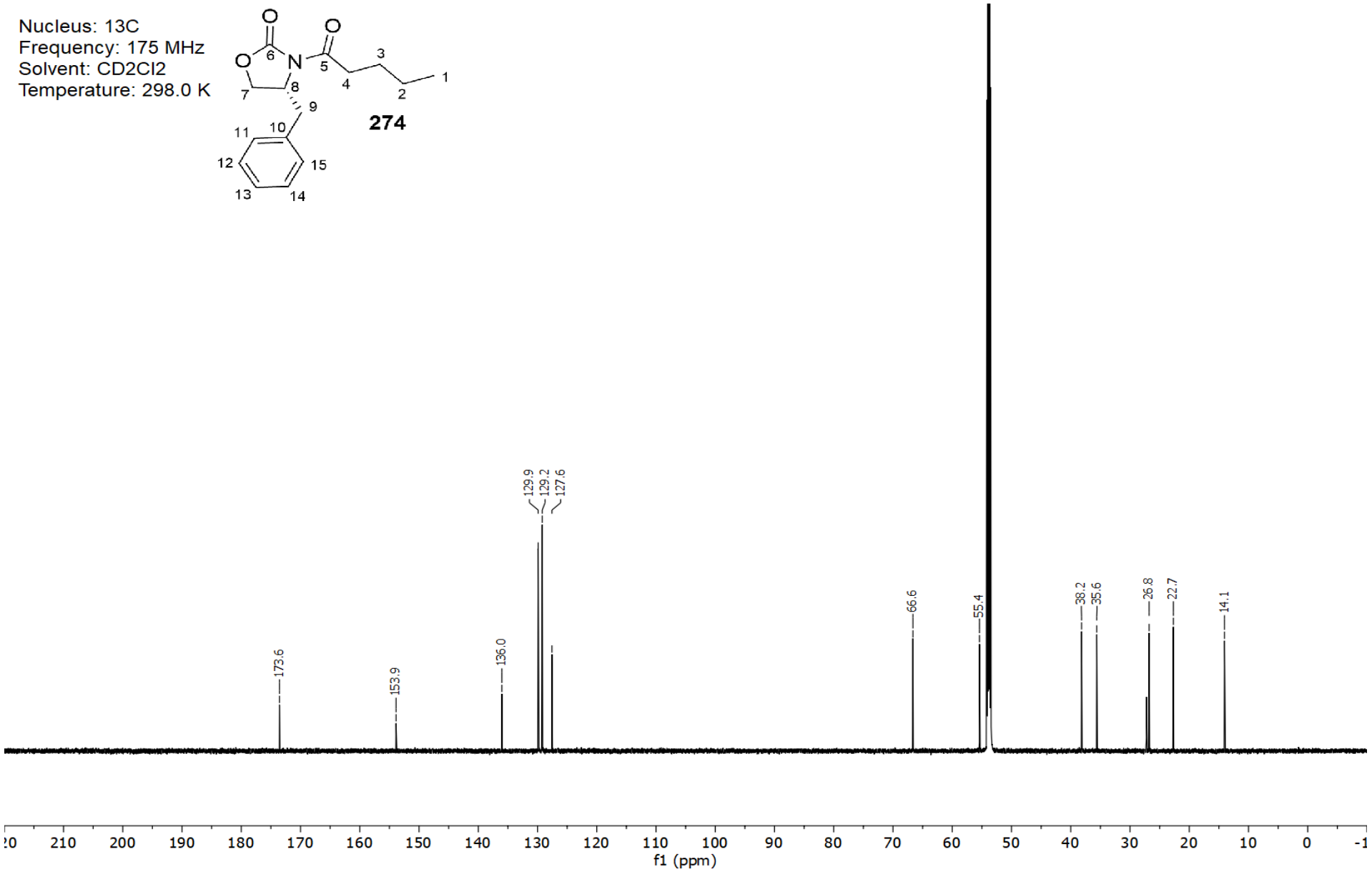

Nucleus: 1H
Frequency: 700 MHz
Solvent: CDCl3
Temperature: 298.0 K
272
CDCl3
f1 (ppm)

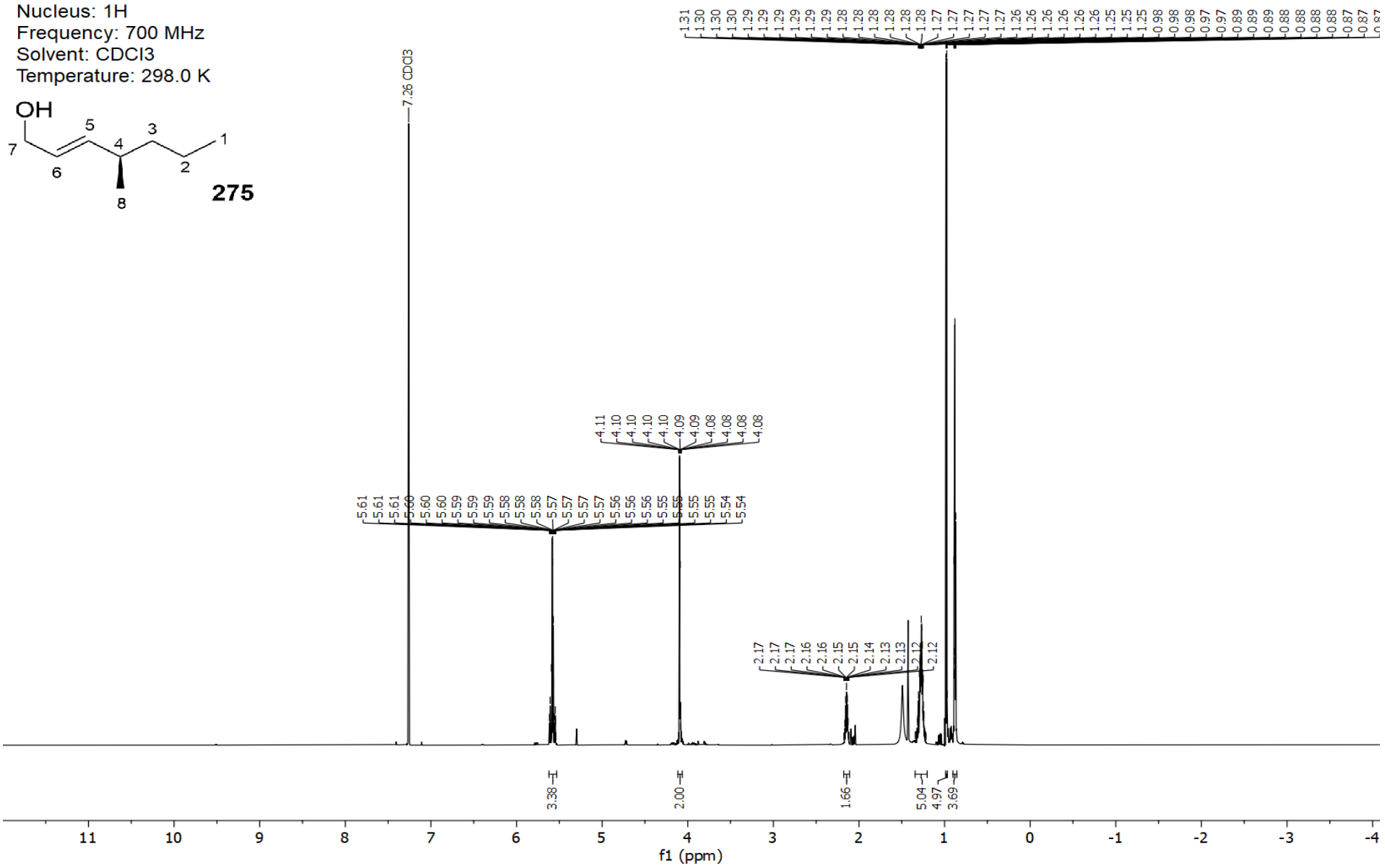

Nucleus: 13C
Frequency: 175 MHz
Solvent: CDCl3
Temperature: 298.0 K
272
177.6
153.3
143.4
135.5
129.6
129.1
127.5
66.1
55.5
38.3
37.5
36.1
20.4
16.9
14.2
f1 (ppm)


Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
274
f1 (ppm)

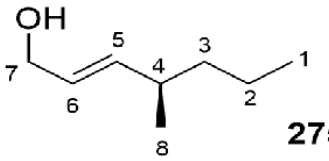
Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

274

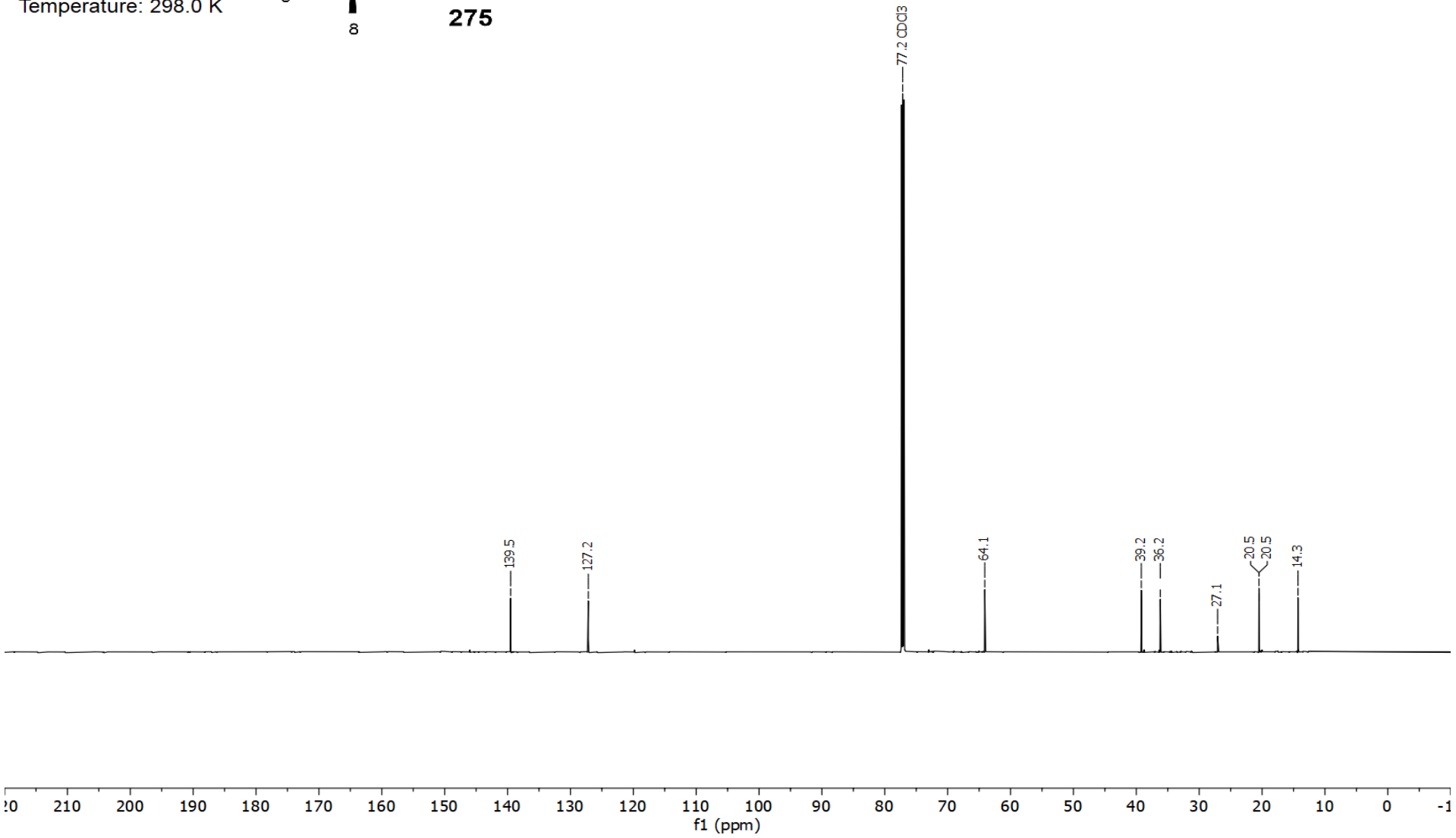


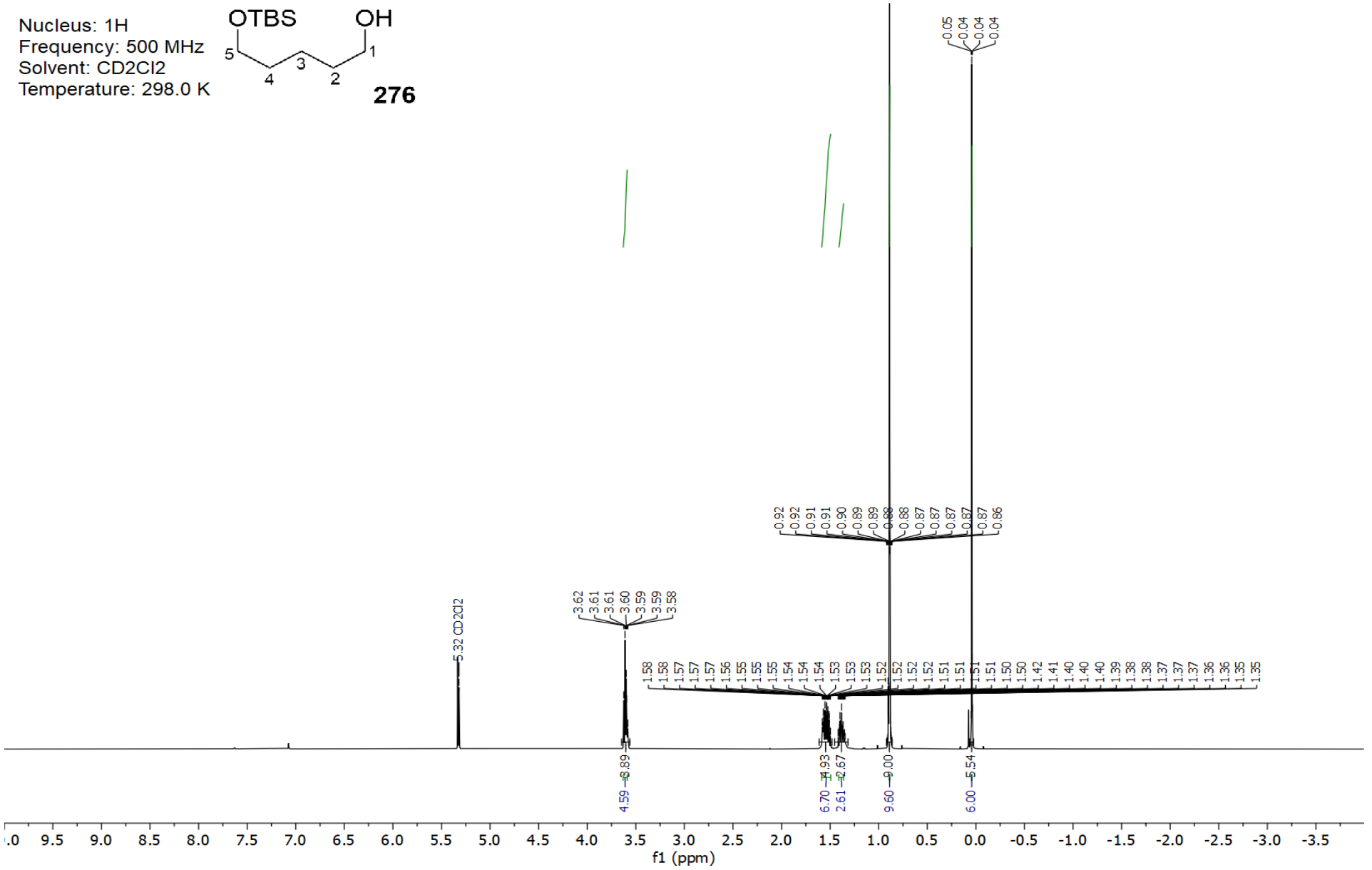

Nucleus: 1H
Frequency: 700 MHz
Solvent: CDCl3
Temperature: 298.0 K
OH
275
7.26 CDCl3
f1 (ppm)

Nucleus: 13C
Frequency: 176 MHz
Solvent: CDCl3
Temperature: 298.0 K

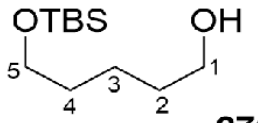


275

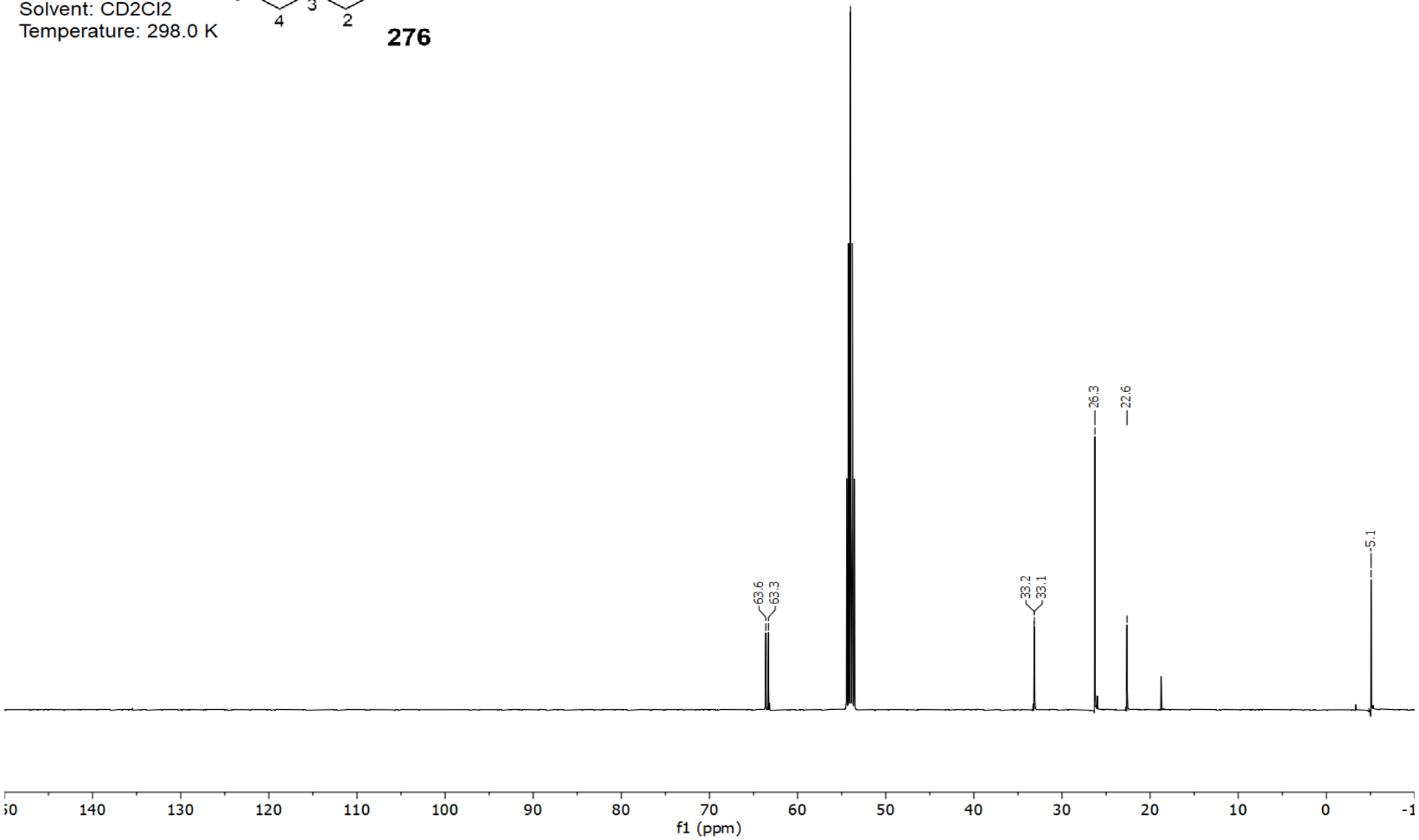



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
OTBS
OH
5
4
3
2
1
276
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

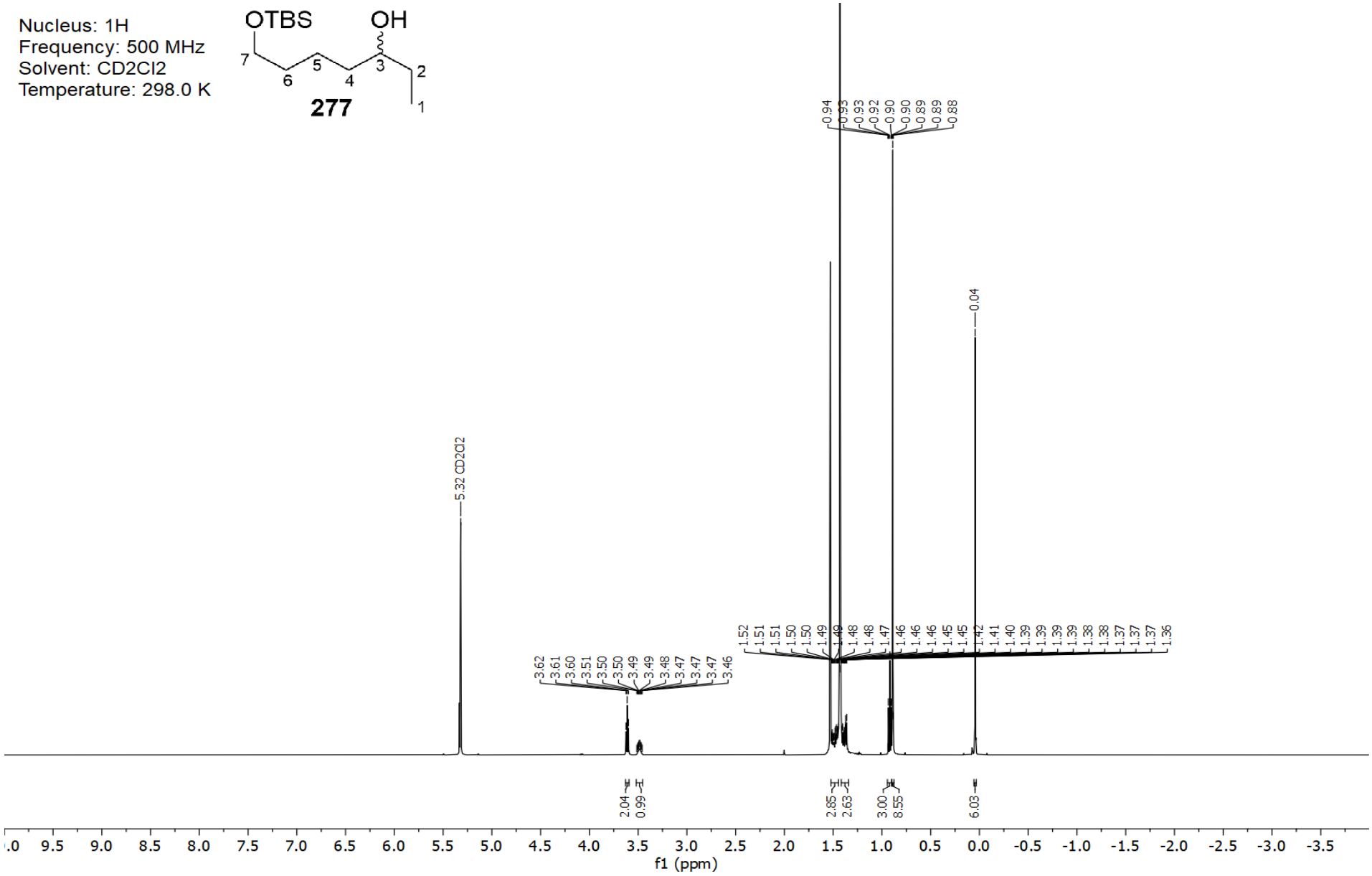


276



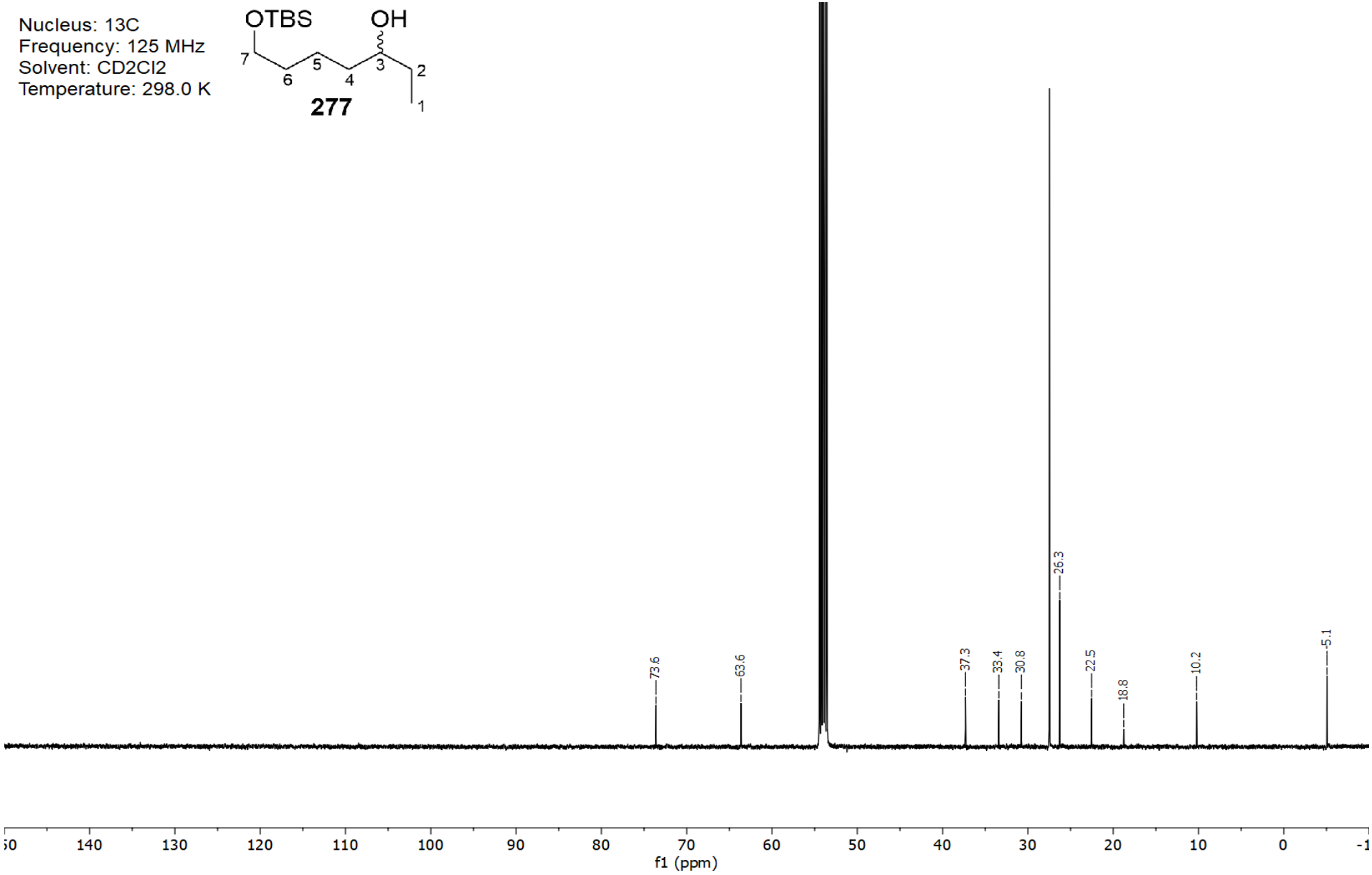
Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

277

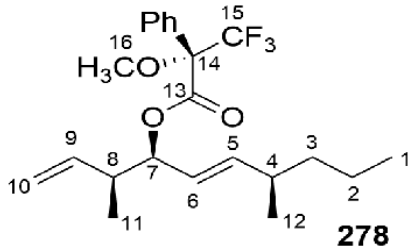


Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

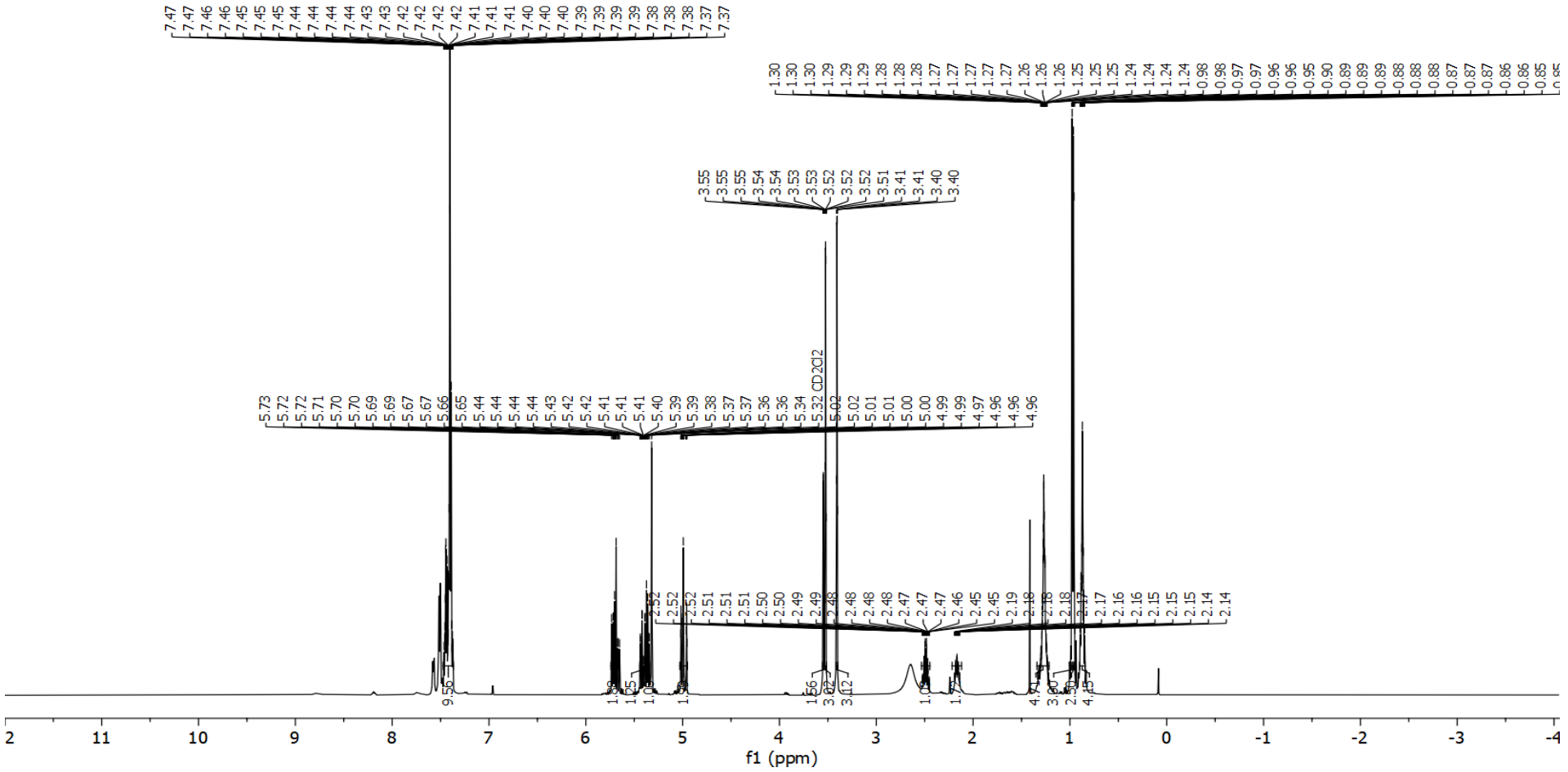
277



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

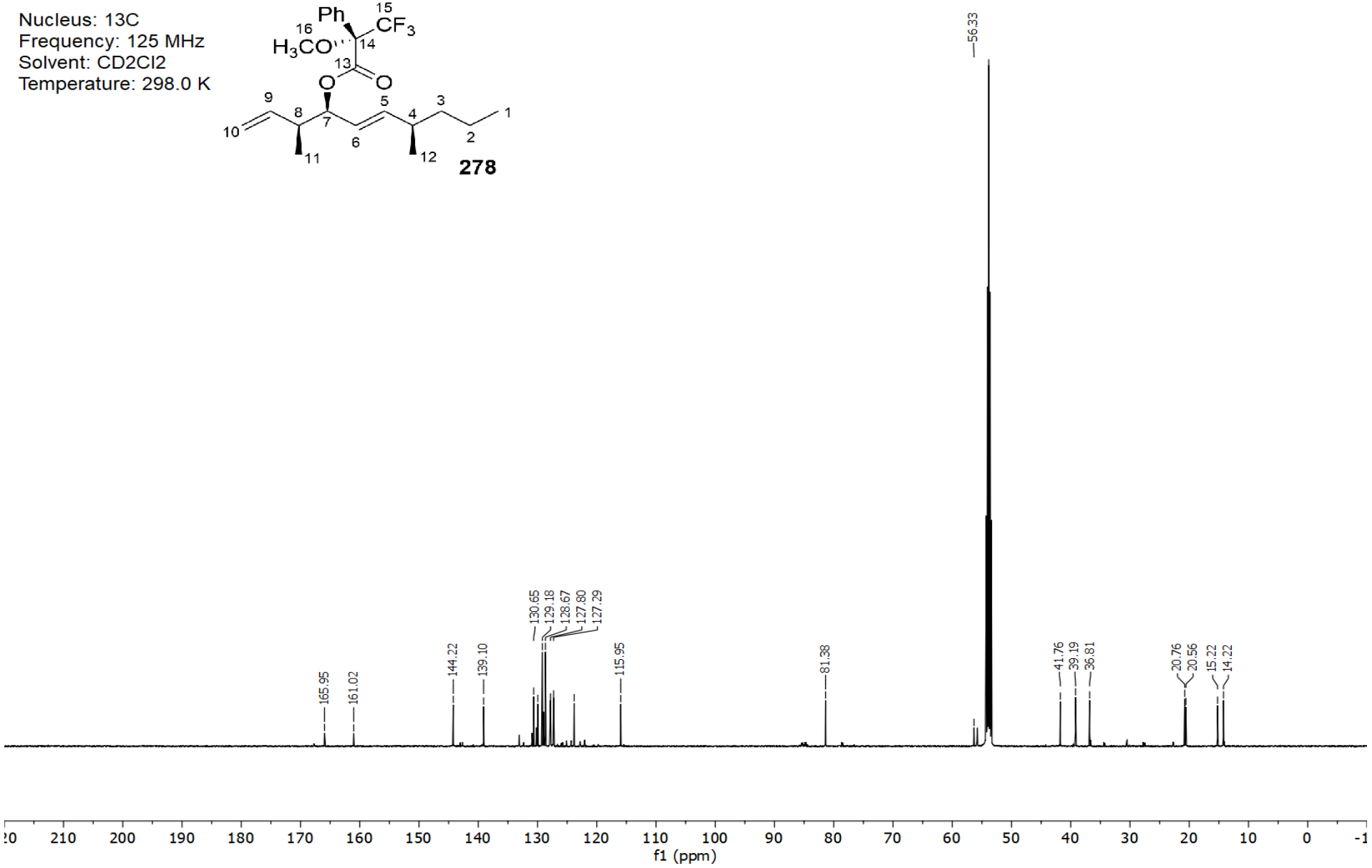


278

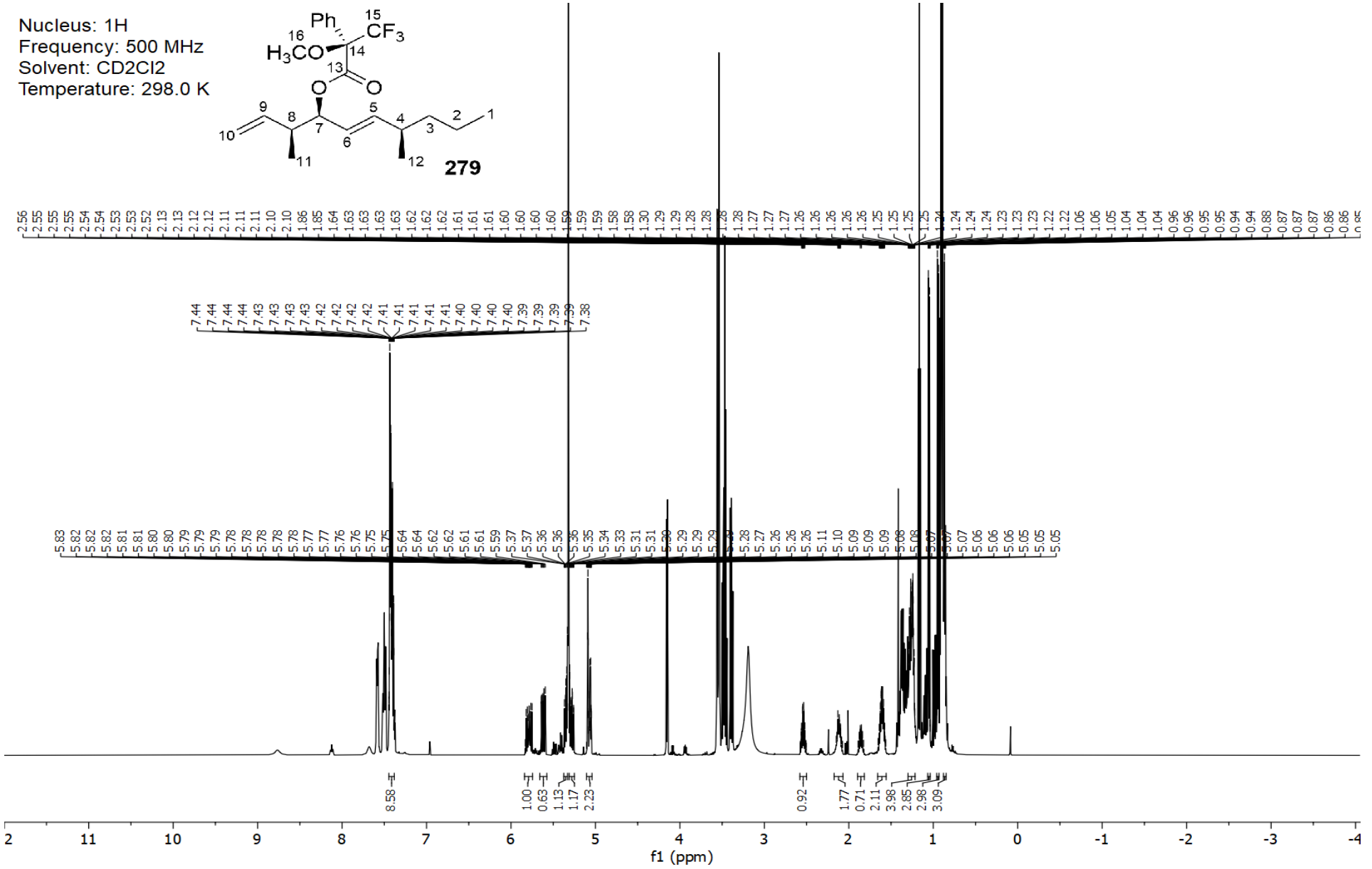


Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

278

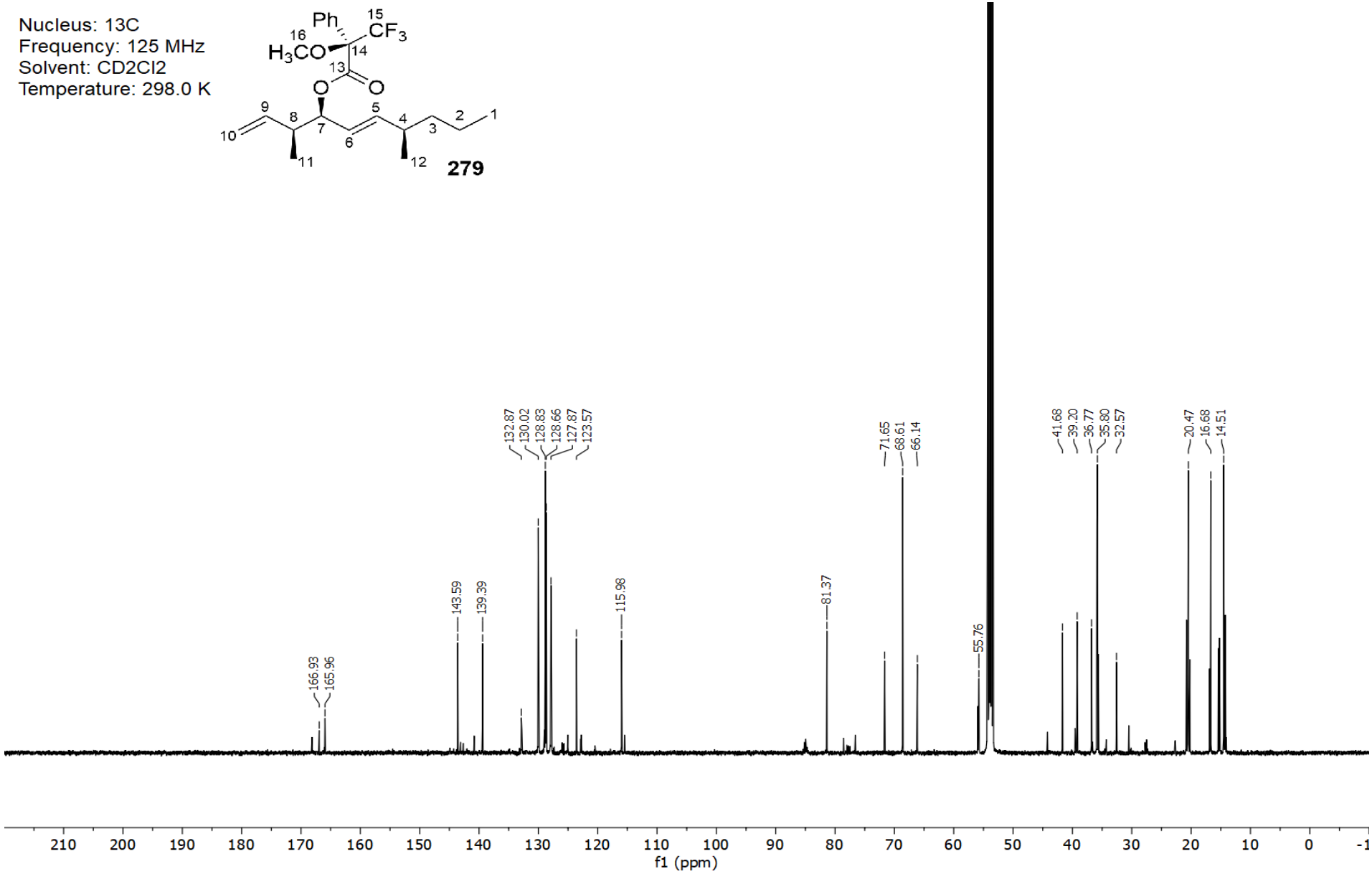


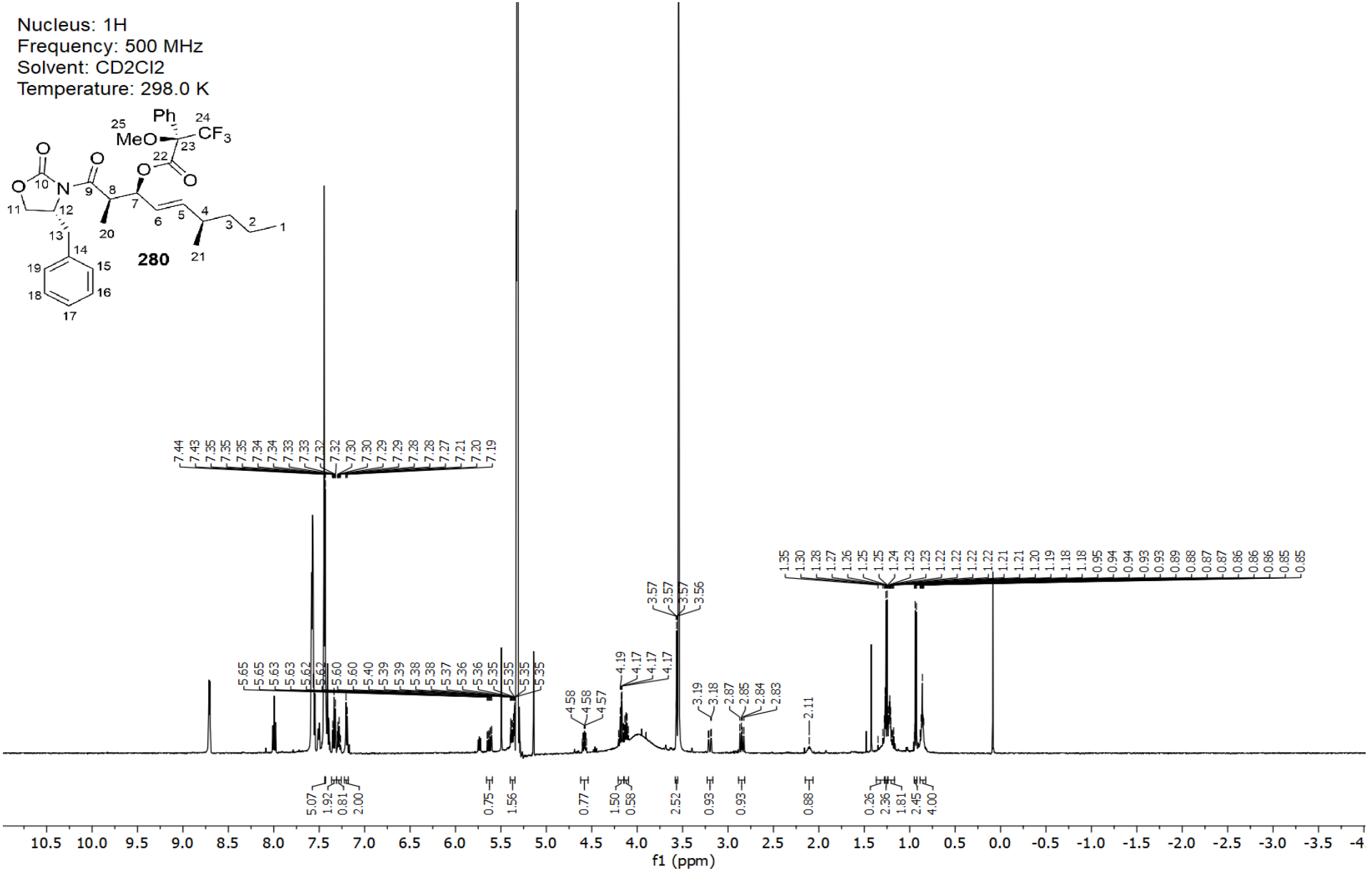
6. Appendix

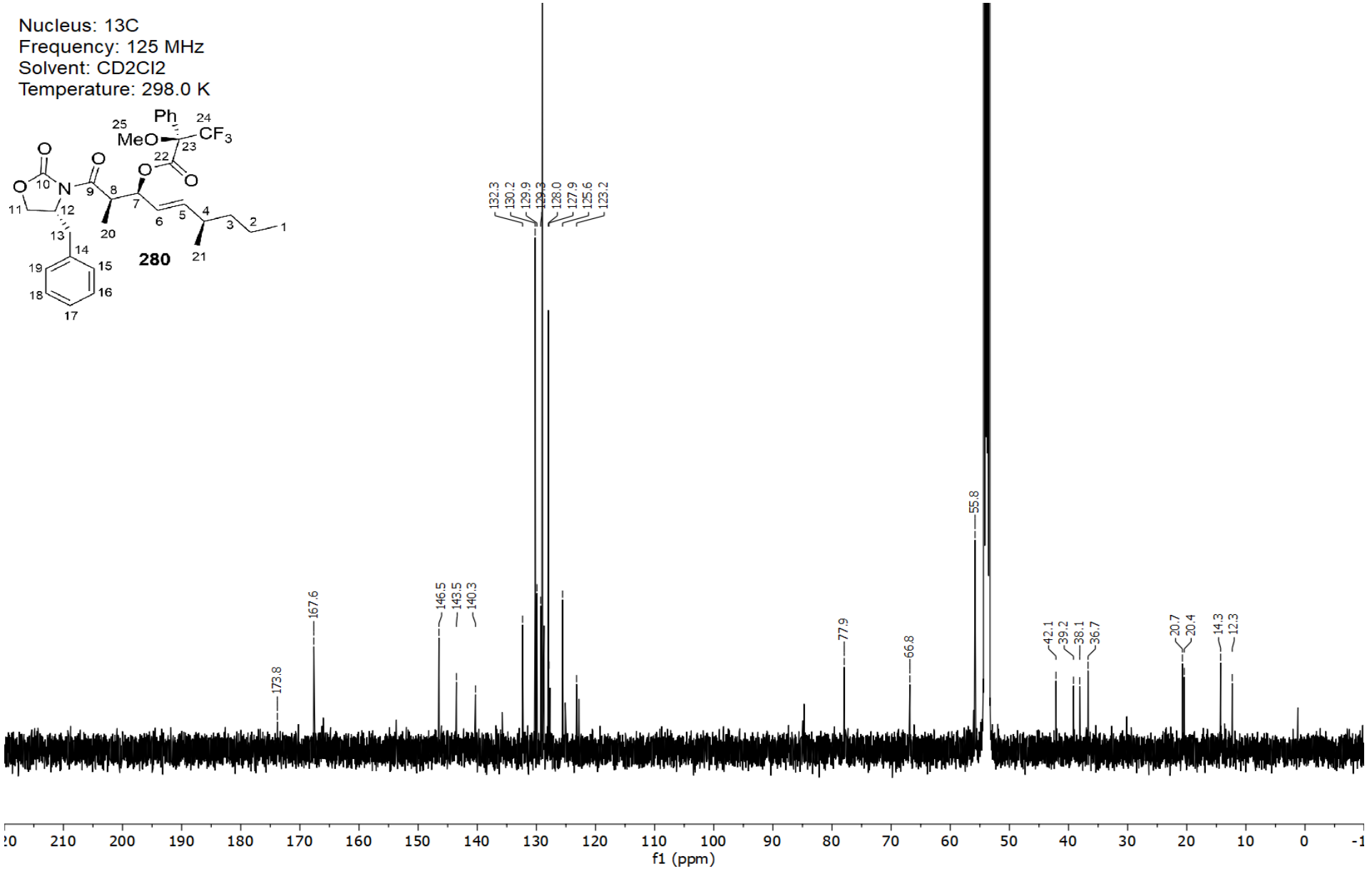

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
279
f1 (ppm)

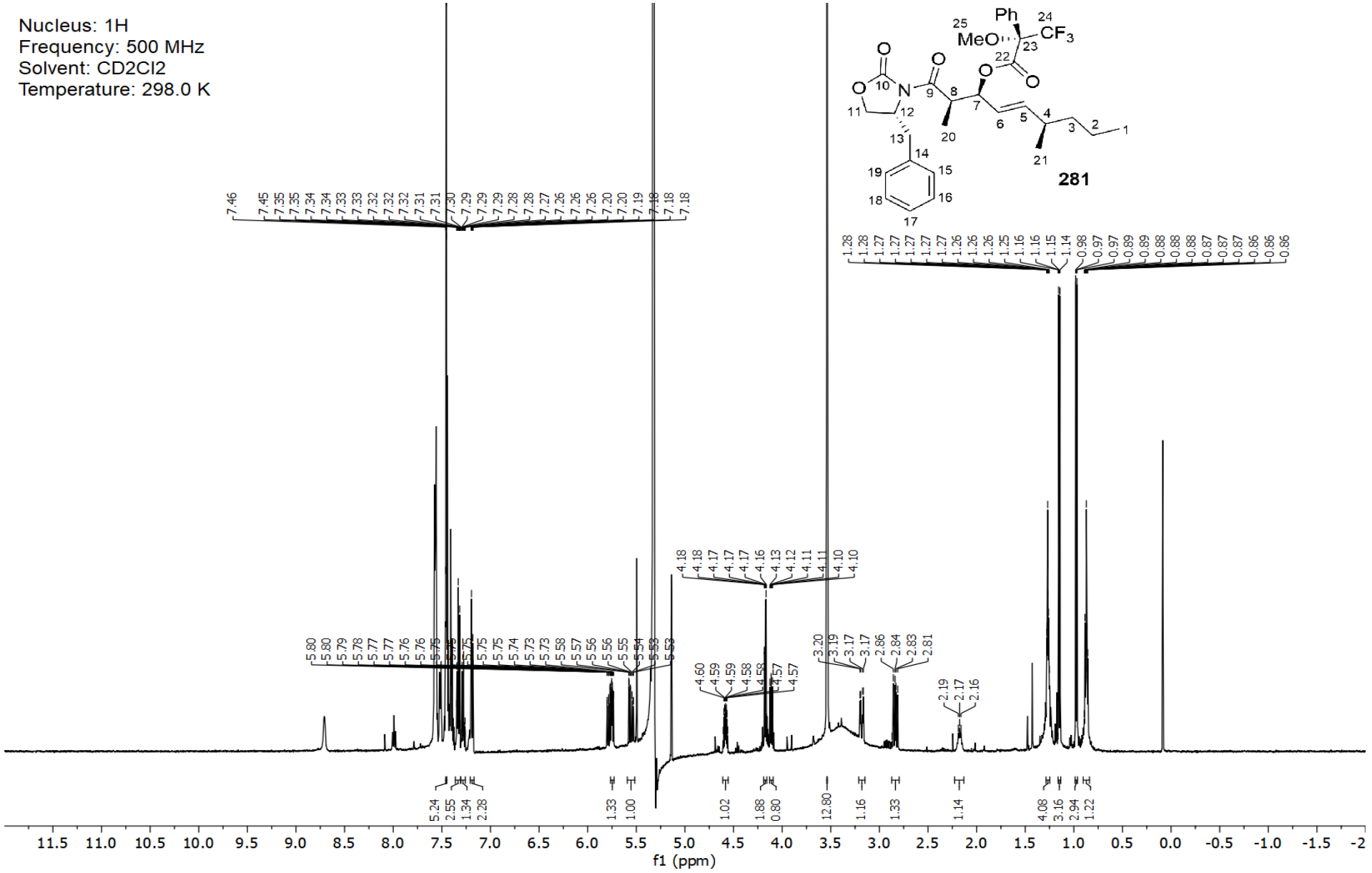
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

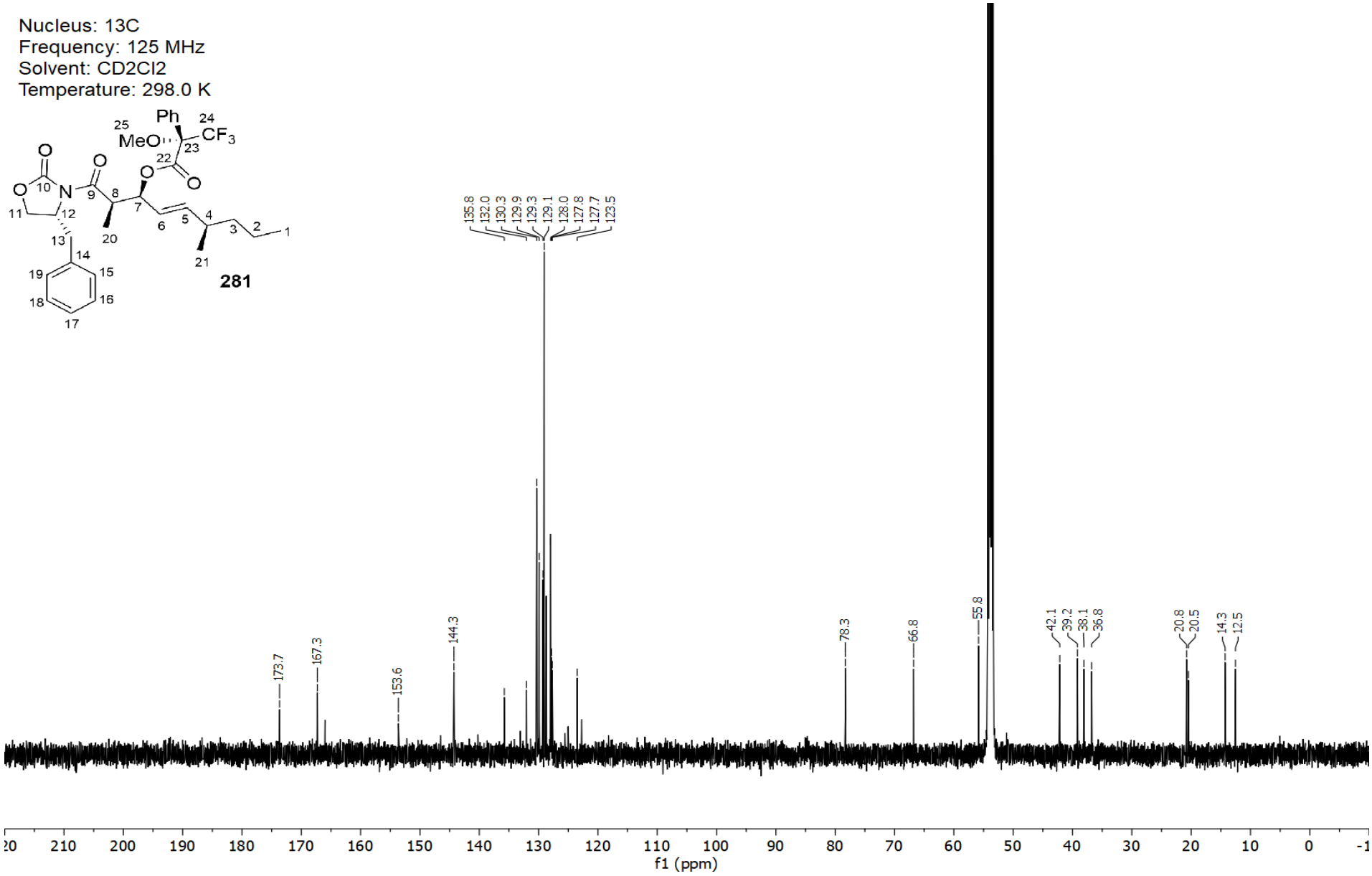
279



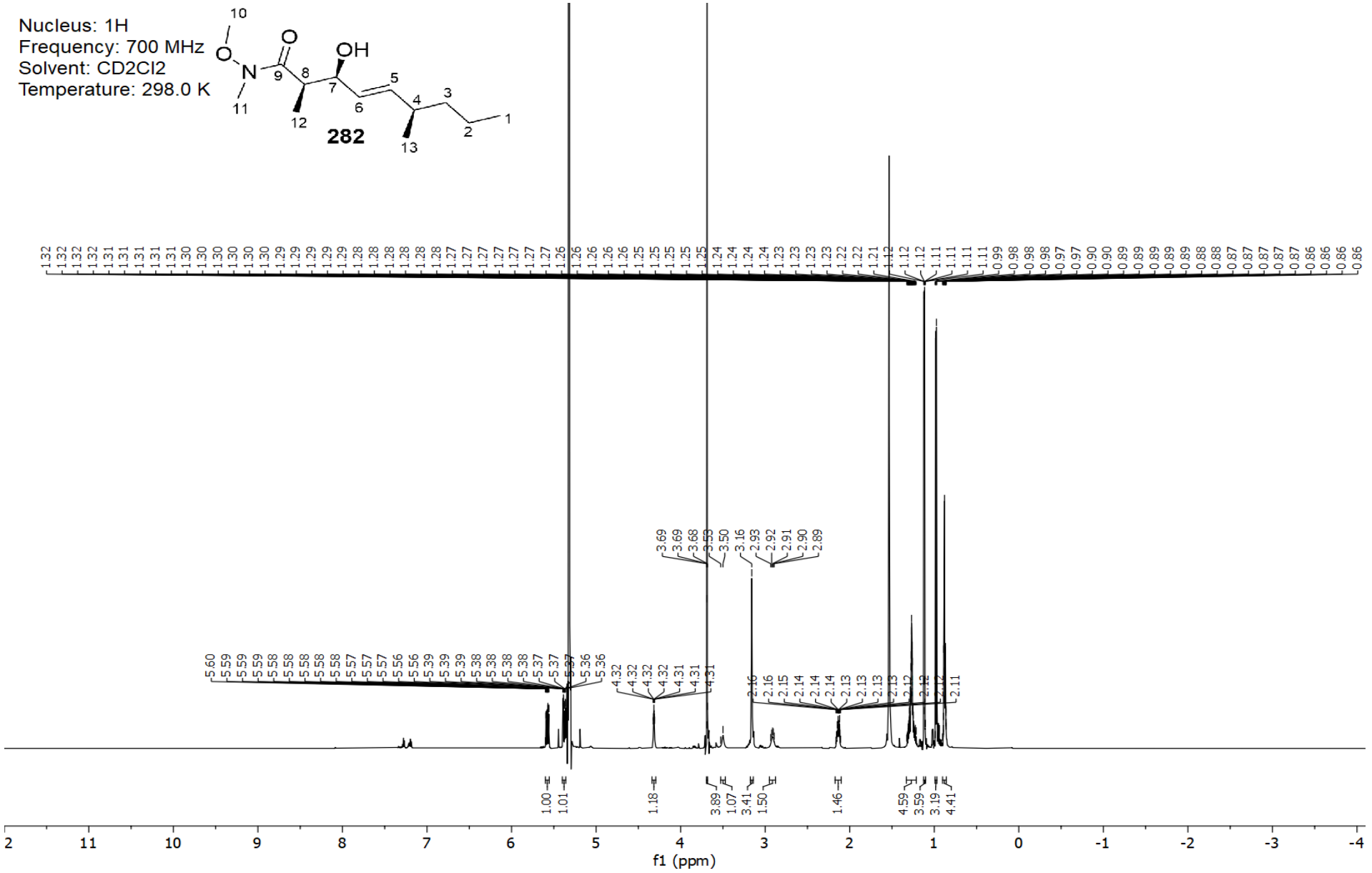

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
280
f1 (ppm)

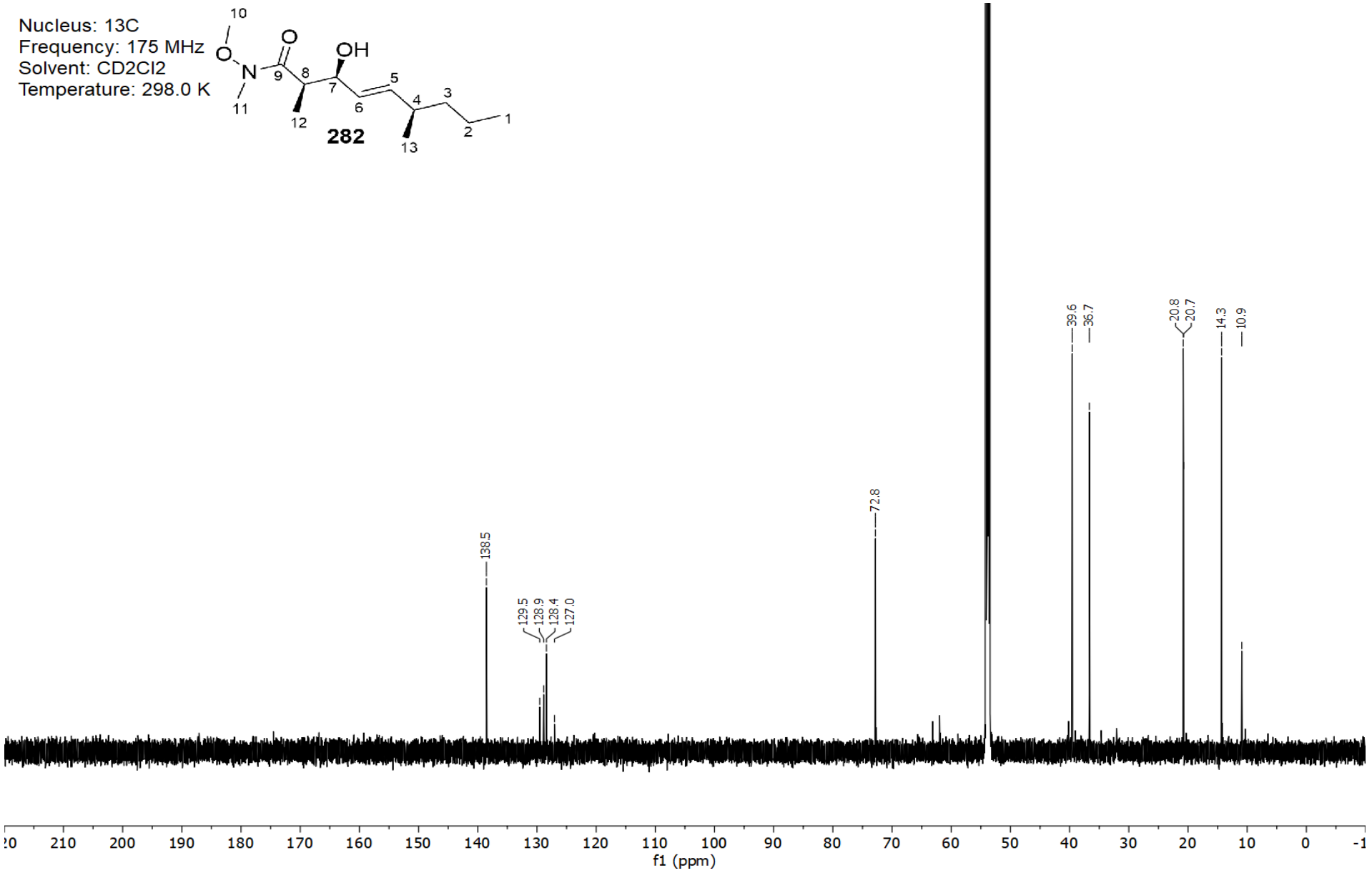

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
280
132.3
130.2
129.9
129.3
128.0
127.9
125.6
123.2
173.8
167.6
146.5
143.5
140.3
77.9
66.8
55.8
42.1
39.2
38.1
36.7
20.7
20.4
14.3
12.3
f1 (ppm)

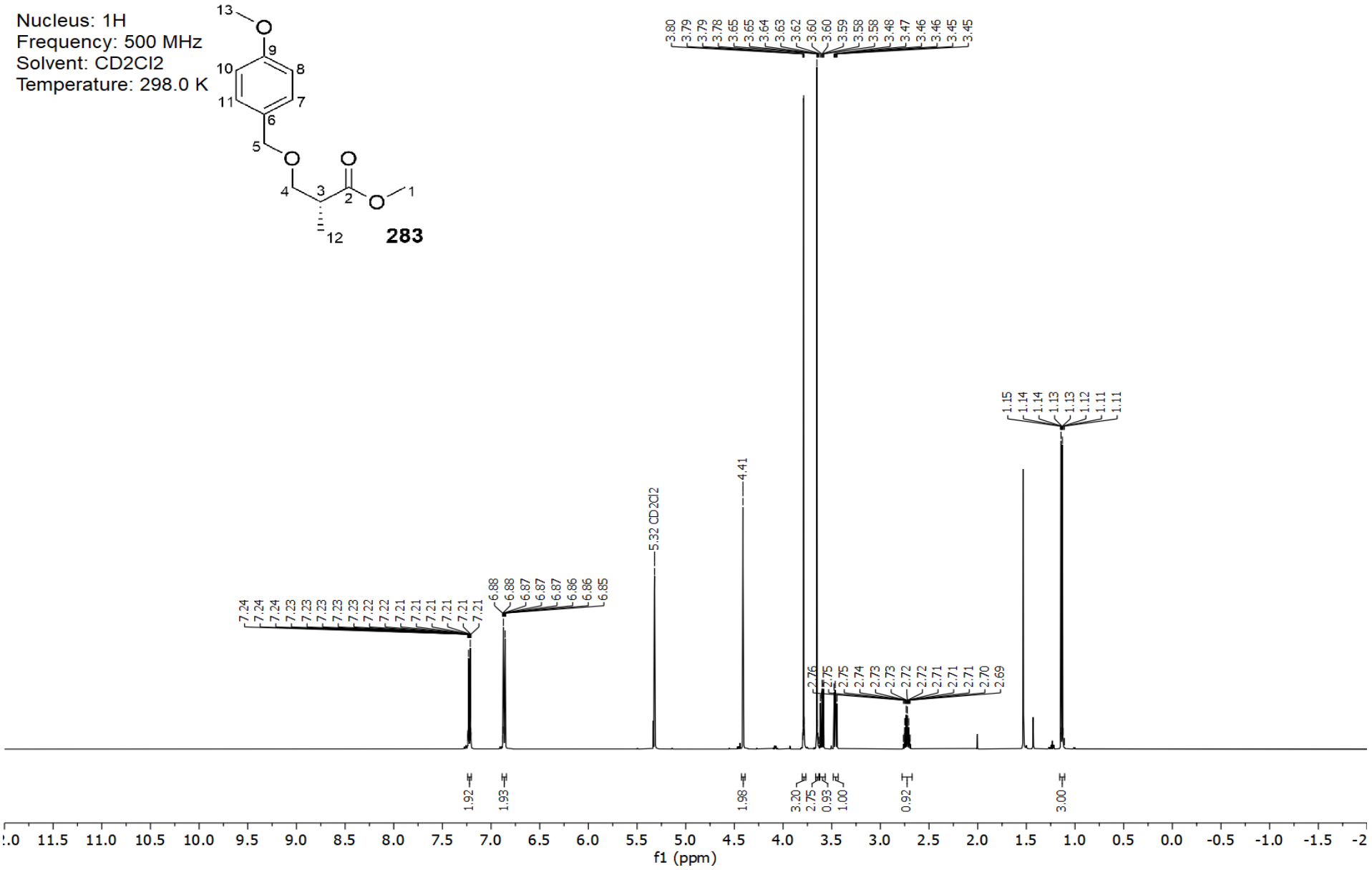

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
281
f1 (ppm)

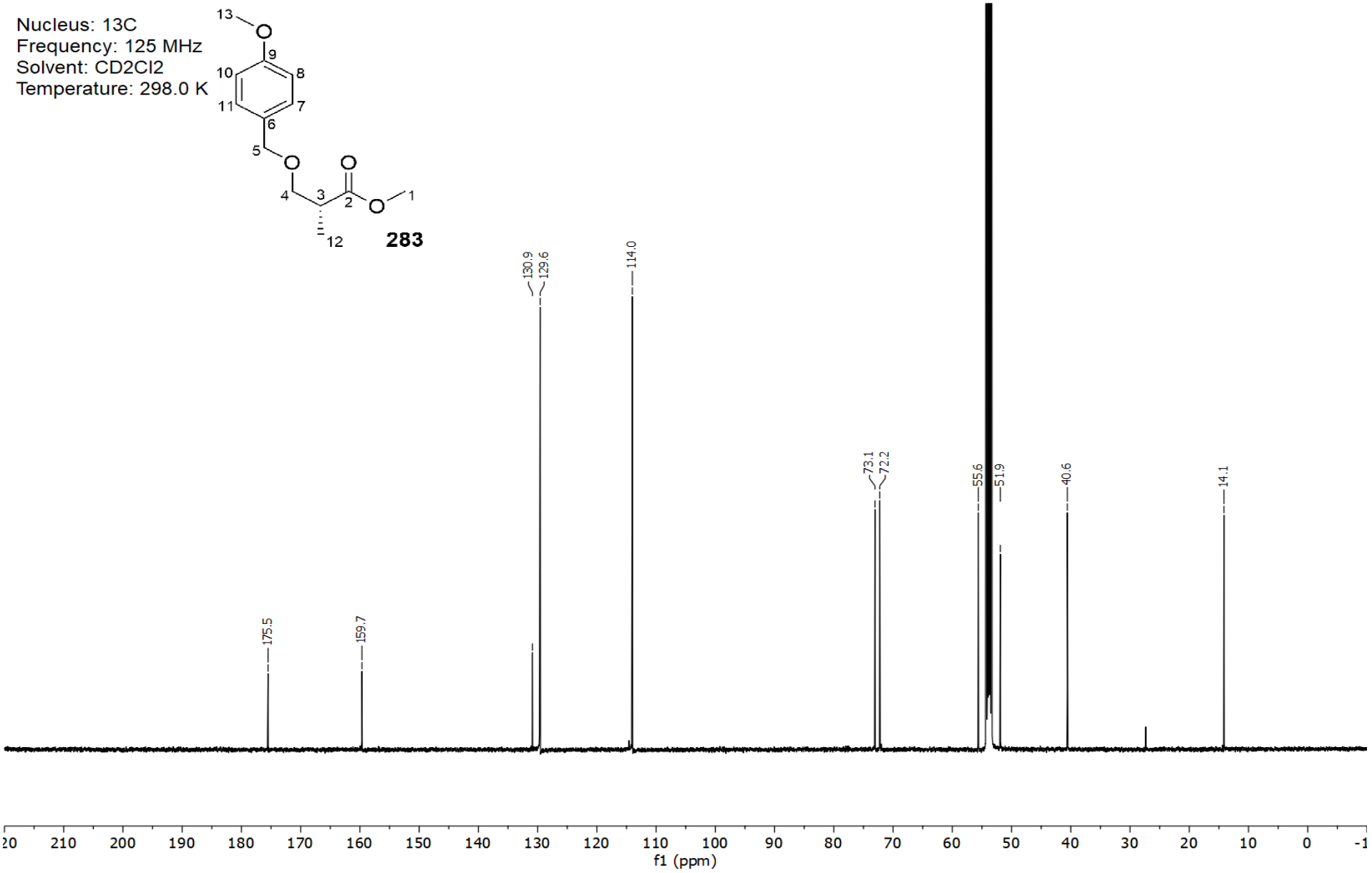

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
281
135.8
132.0
130.3
129.9
129.3
129.1
128.0
127.8
127.7
123.5
173.7
167.3
153.6
144.3
78.3
66.8
55.8
42.1
39.2
38.1
36.8
20.8
20.5
14.3
12.5
f1 (ppm)

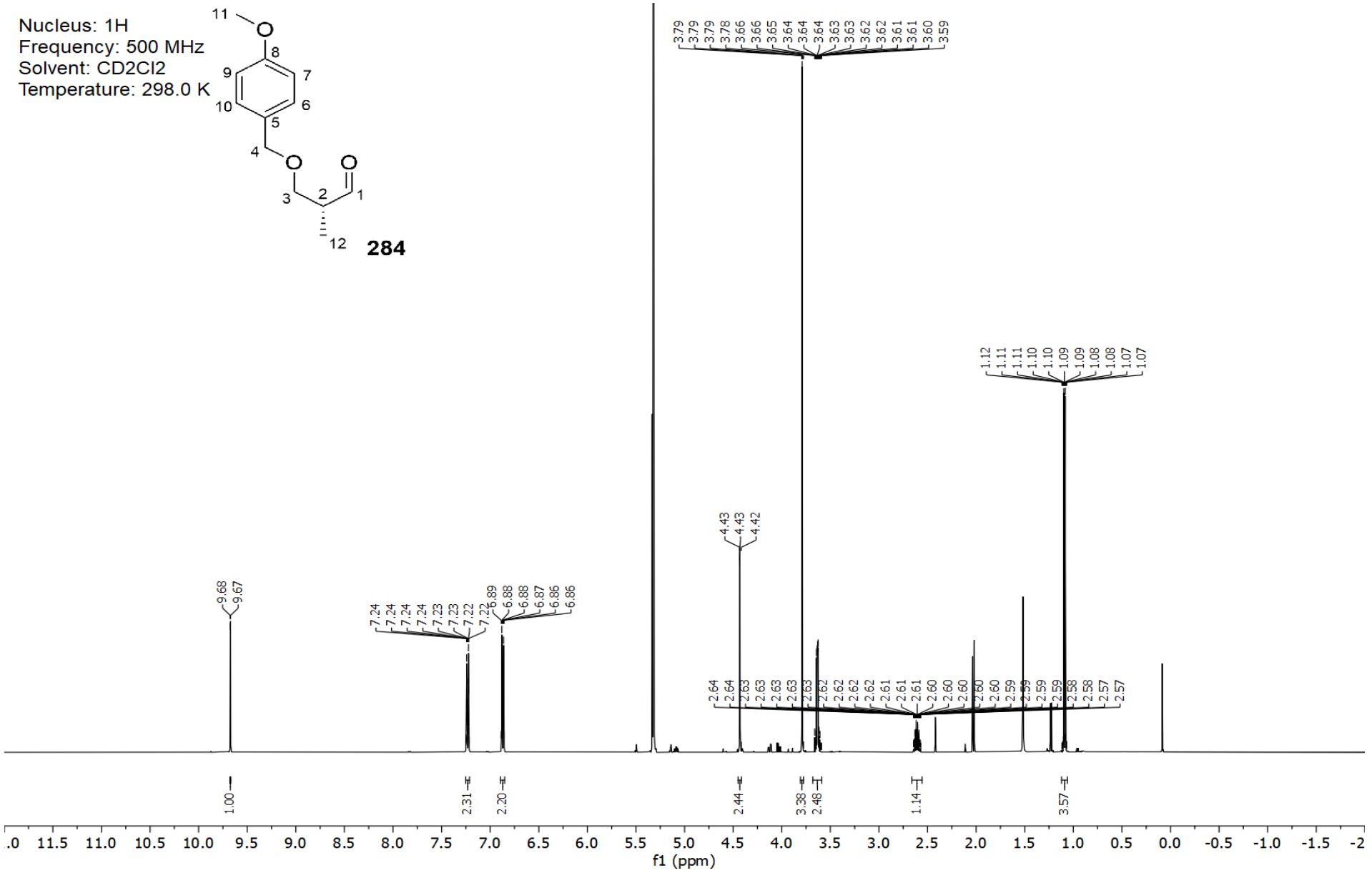
6. Appendix


Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
282
f1 (ppm)


Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
282
138.5
129.5
128.9
128.4
127.0
72.8
39.6
36.7
20.8
20.7
14.3
10.9
f1 (ppm)

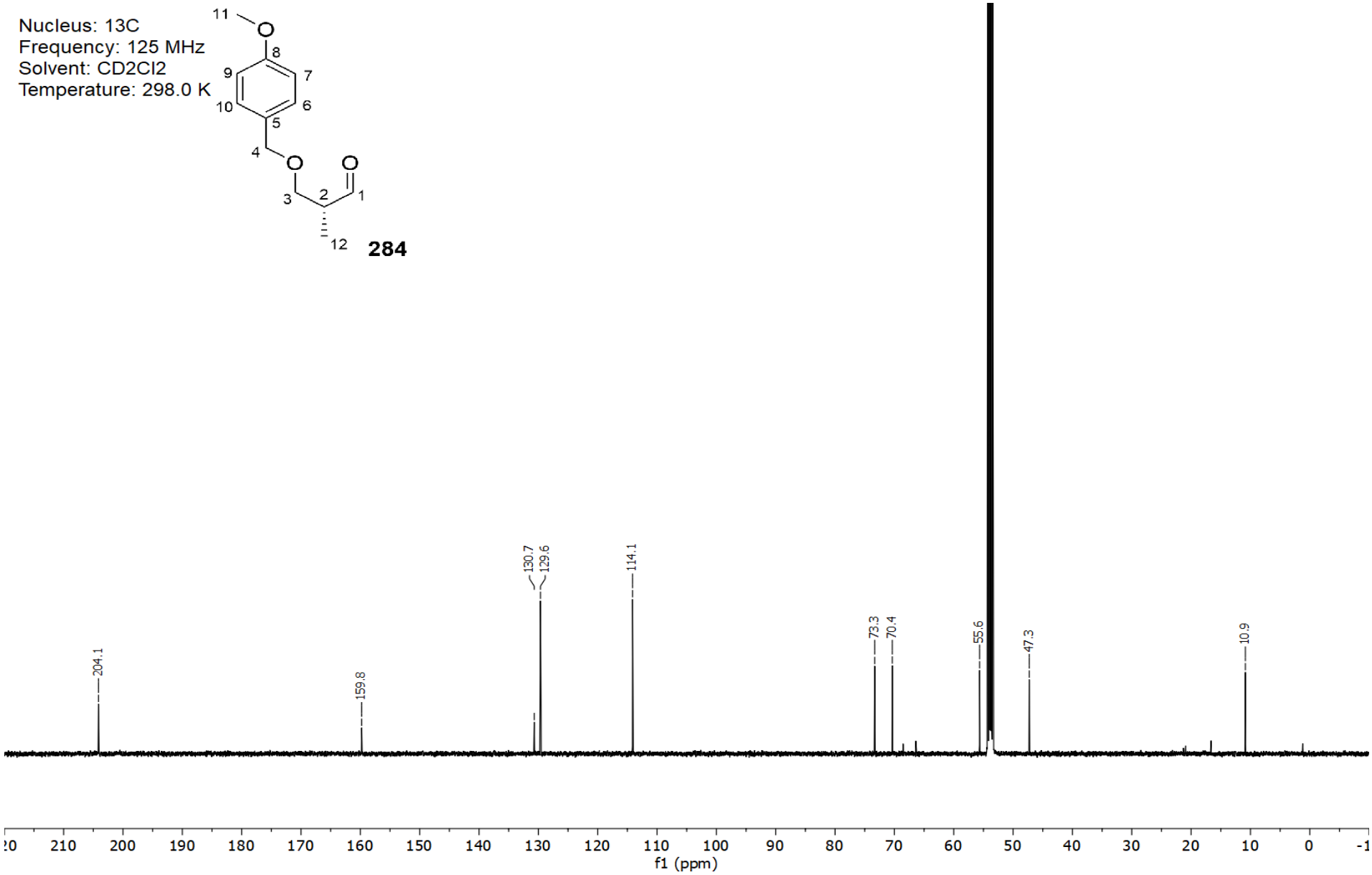

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
283
5.32 CD2Cl2
4.41
f1 (ppm)


Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
283
175.5
159.7
130.9
129.6
114.0
73.1
72.2
55.6
51.9
40.6
14.1
f1 (ppm)

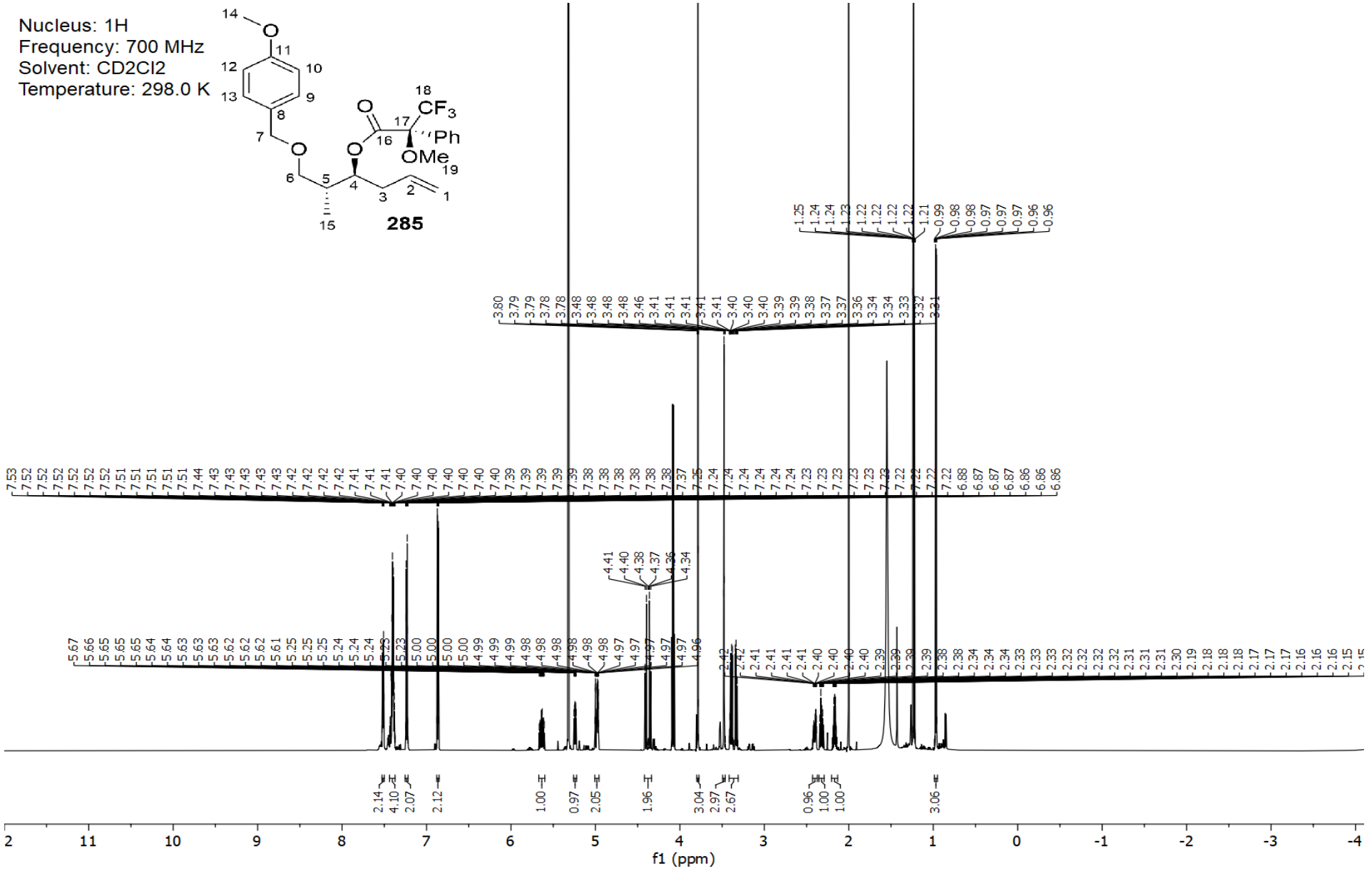

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
284
f1 (ppm)

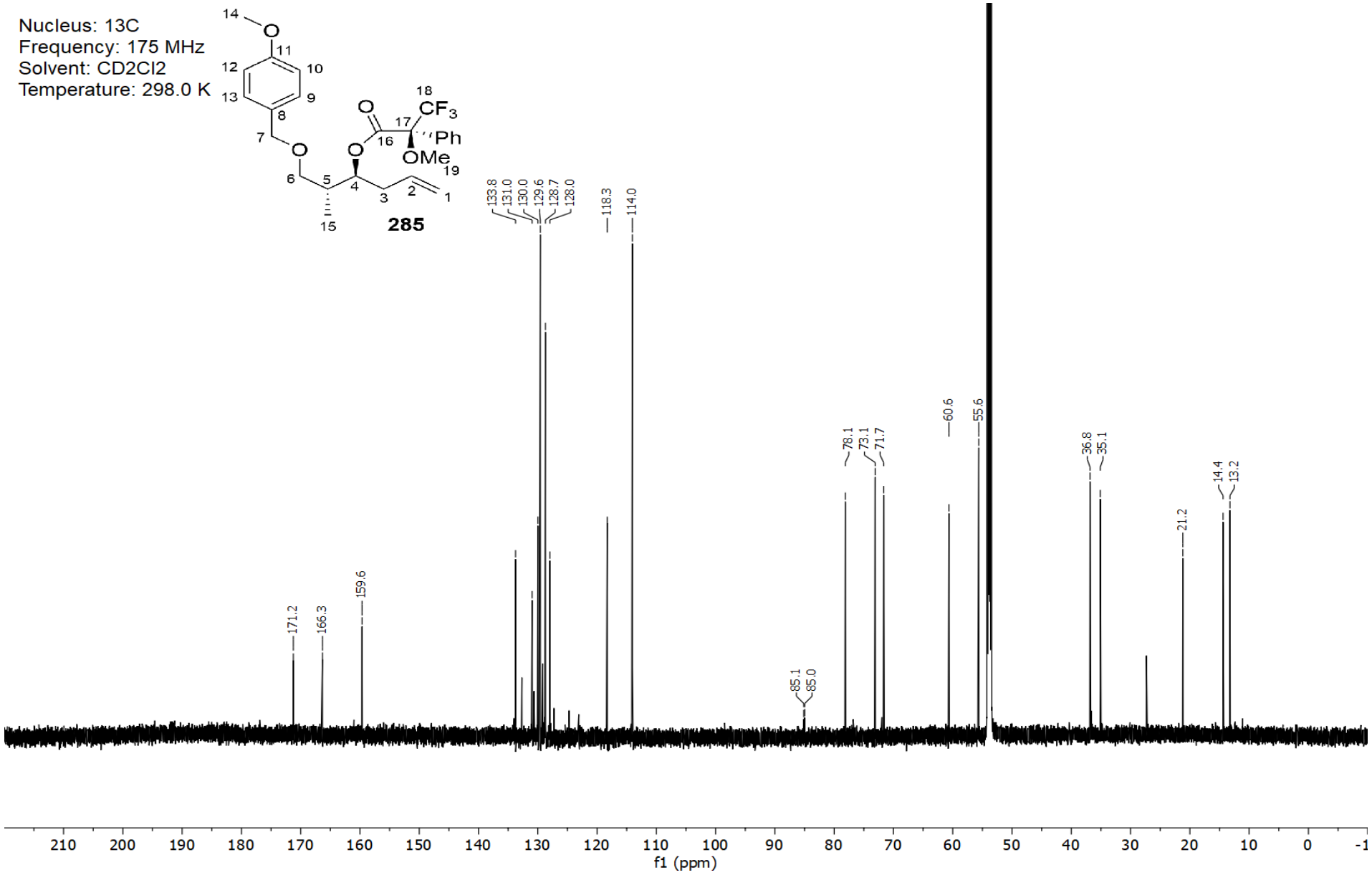
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

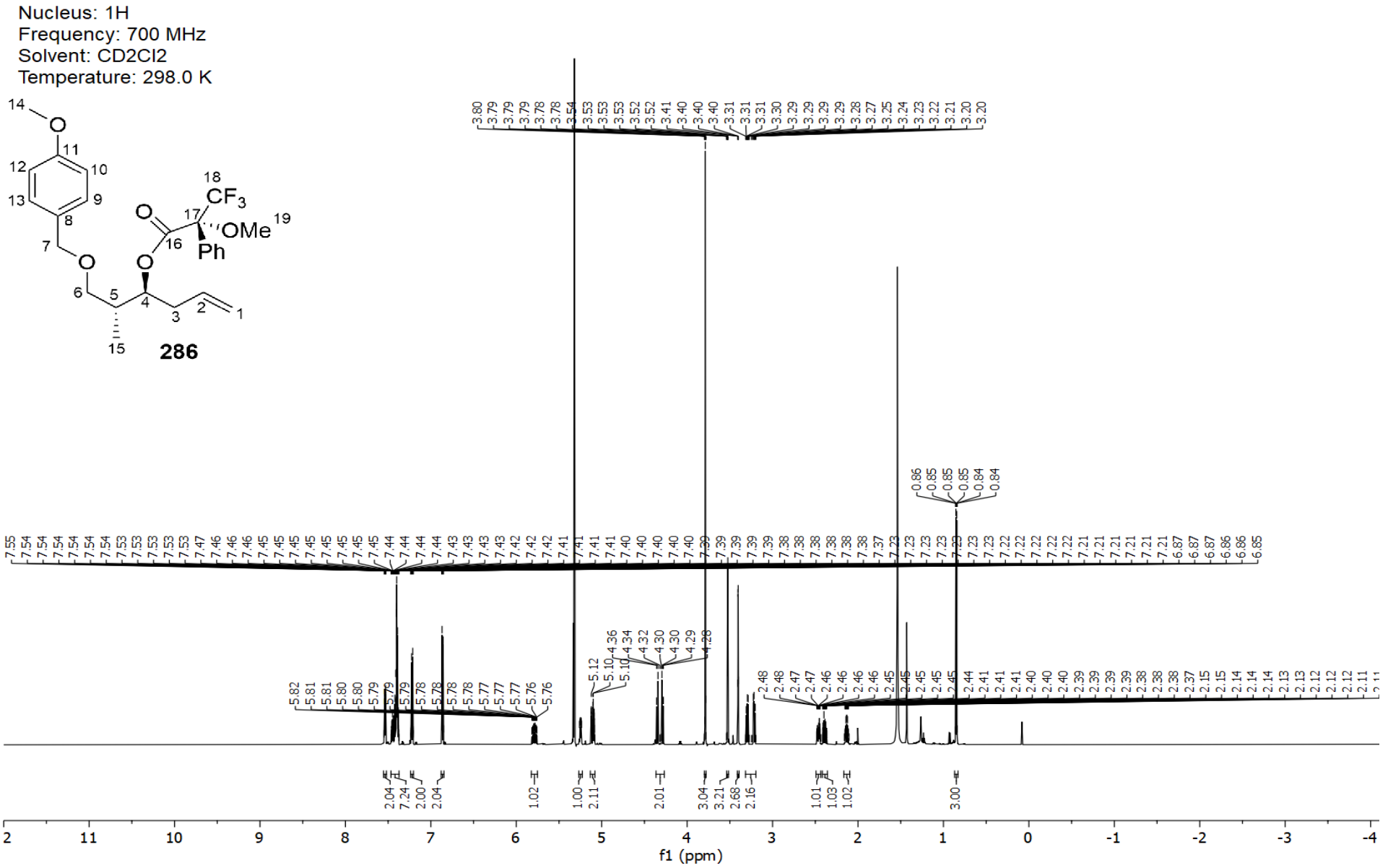
284



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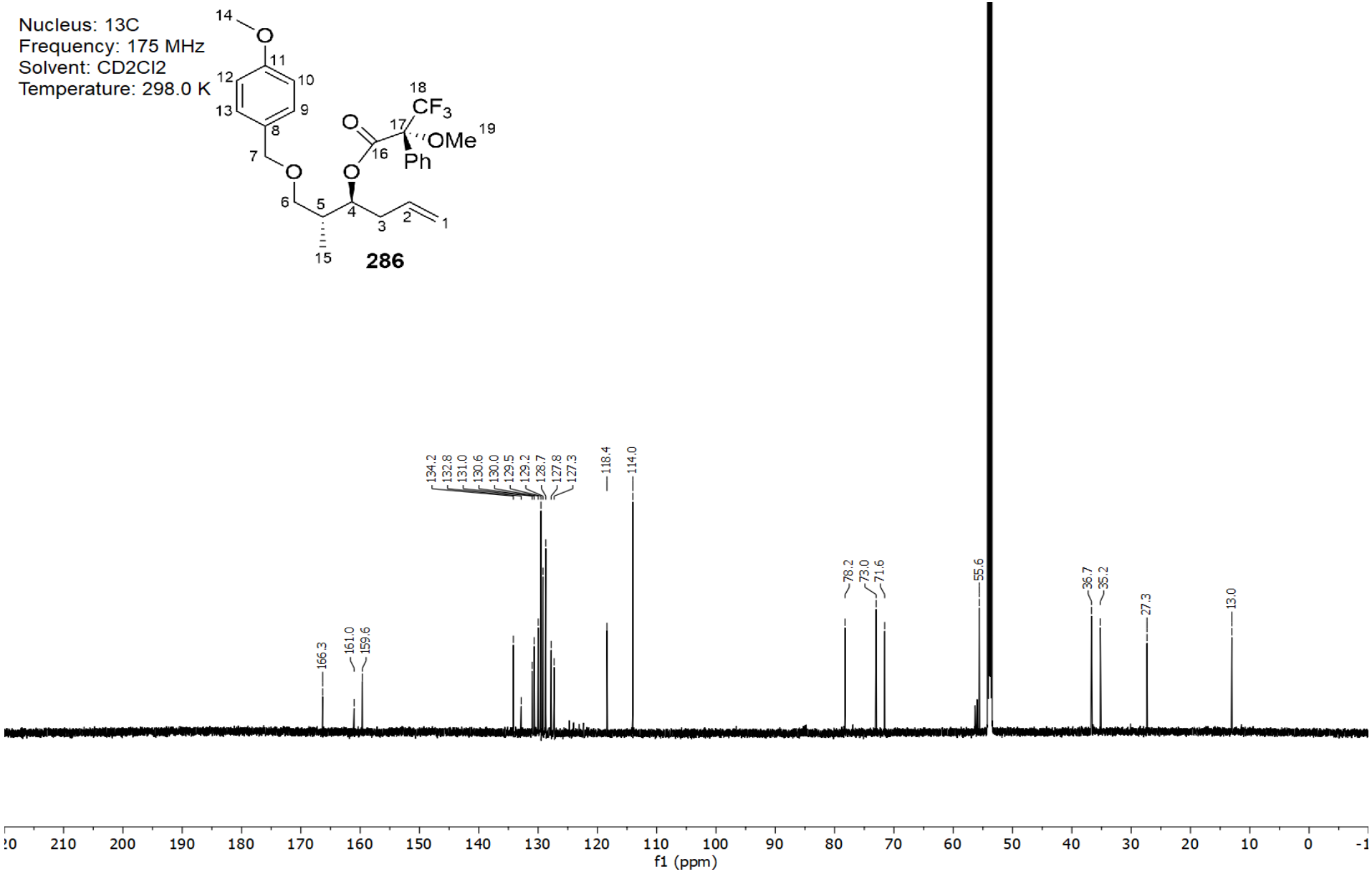

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
285
f1 (ppm)

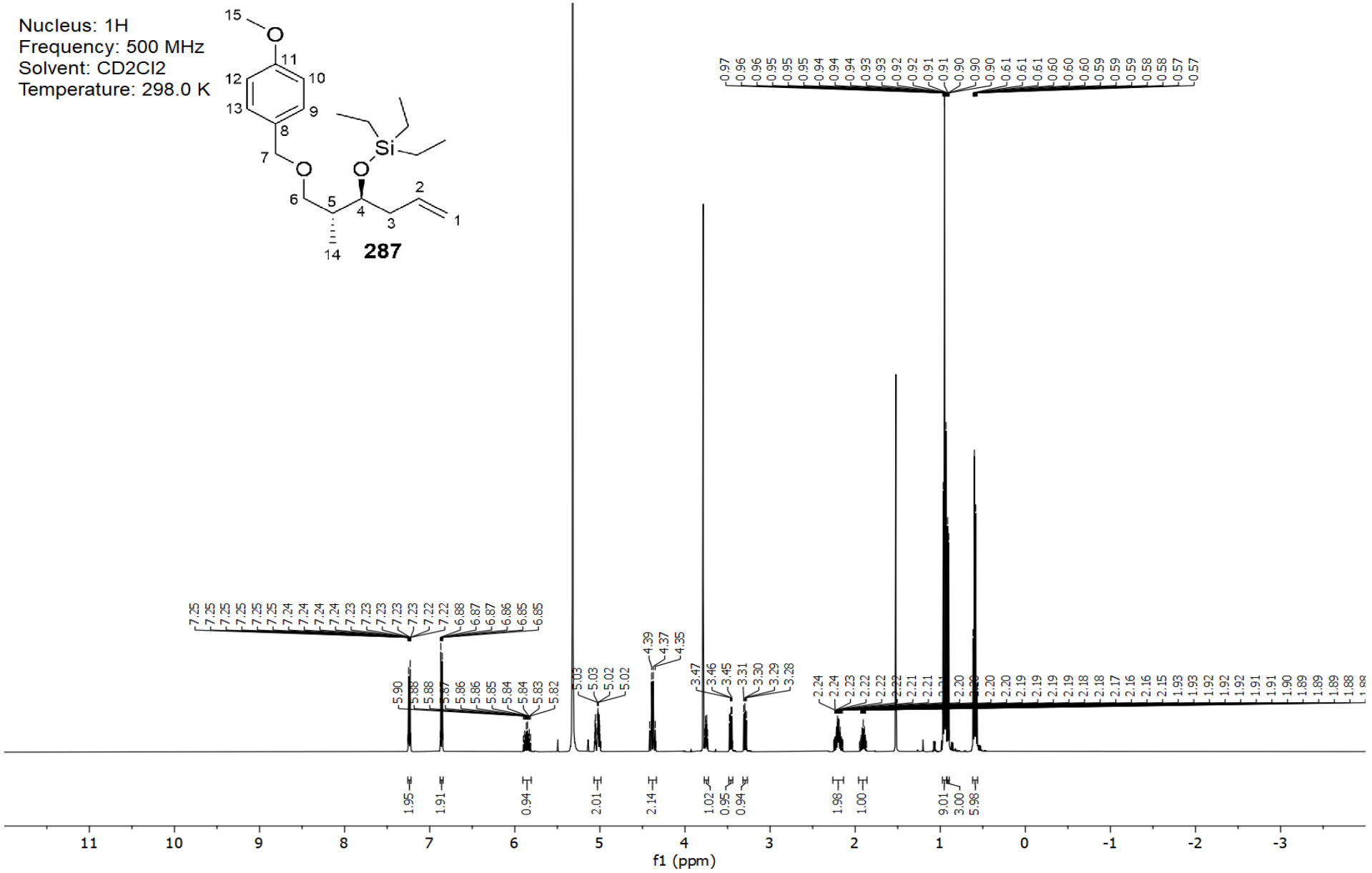

Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
285
133.8
131.0
130.0
129.6
128.7
128.0
118.3
114.0
78.1
73.1
71.7
60.6
55.6
36.8
35.1
21.2
14.4
13.2
171.2
166.3
159.6
85.1
85.0
f1 (ppm)


Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
286
f1 (ppm)

Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

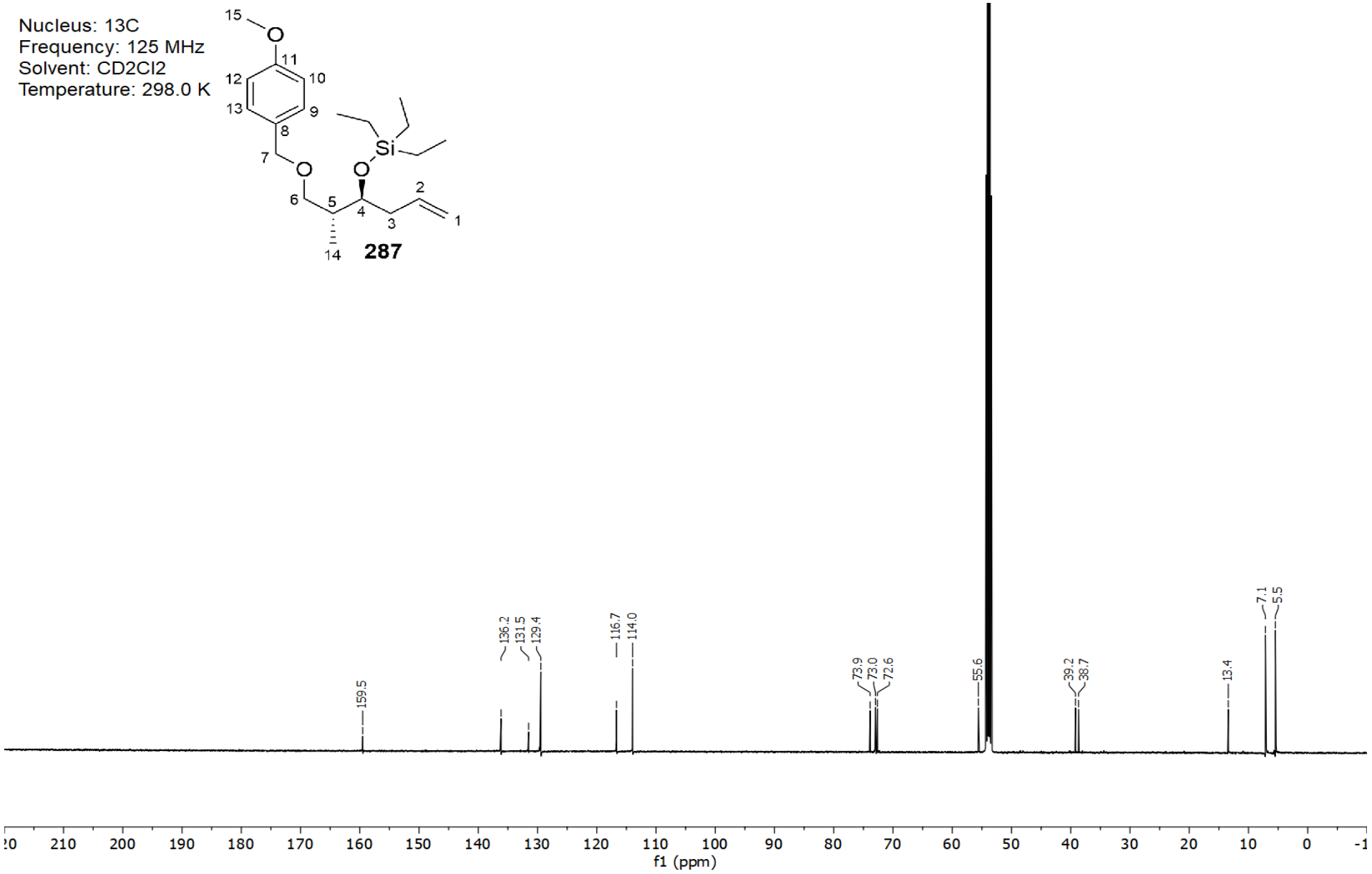
286



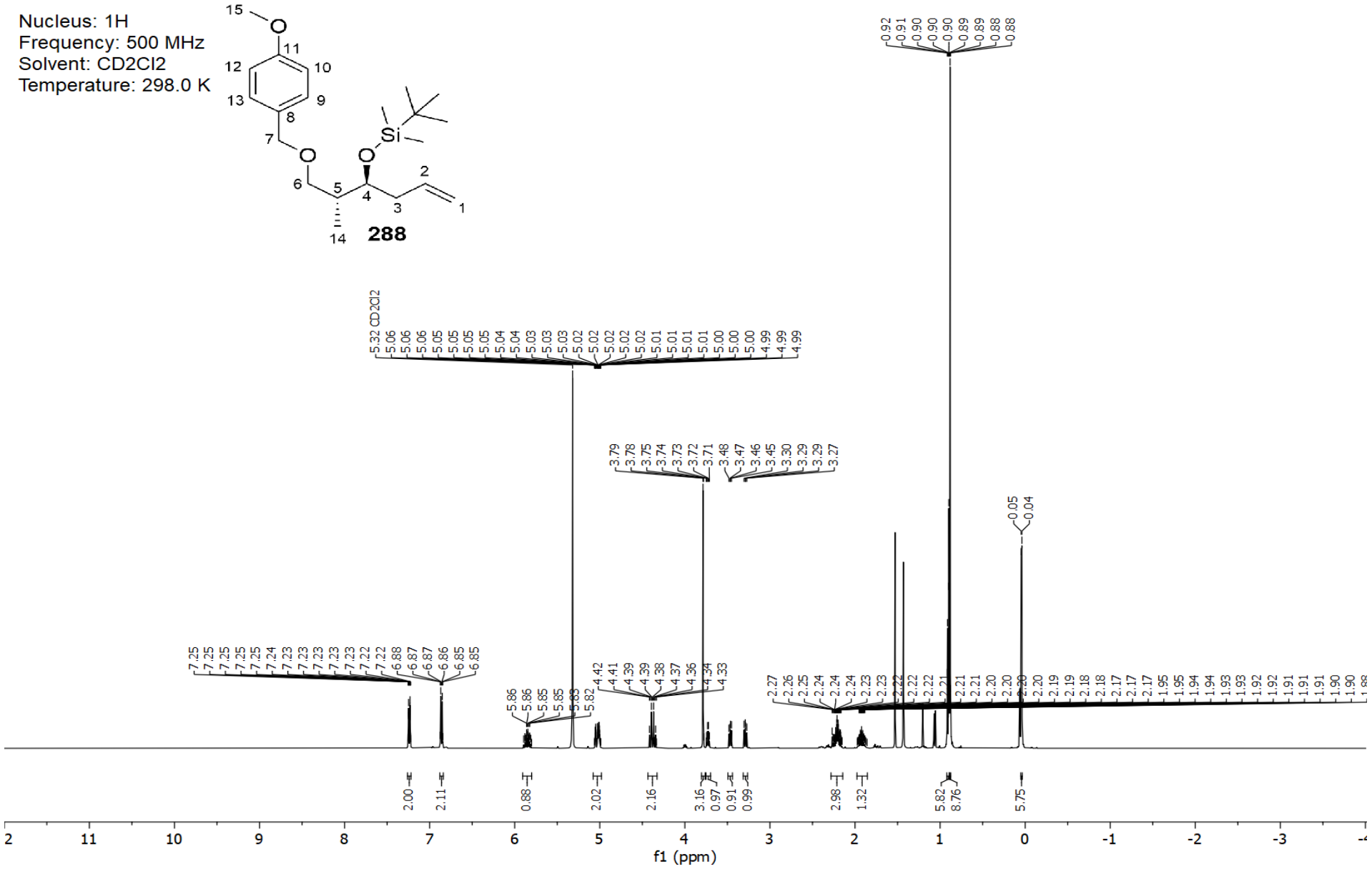

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
287
f1 (ppm)

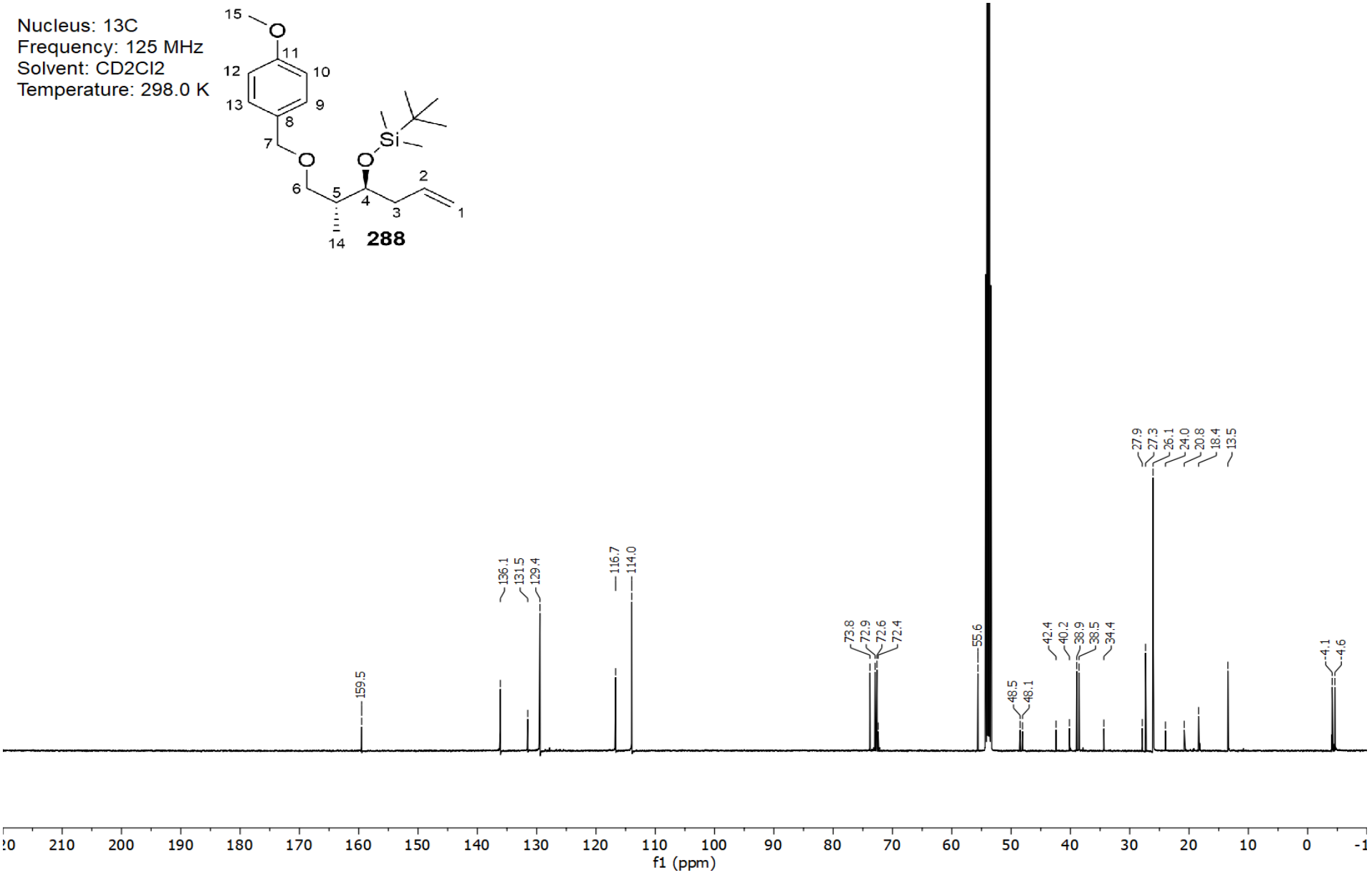
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

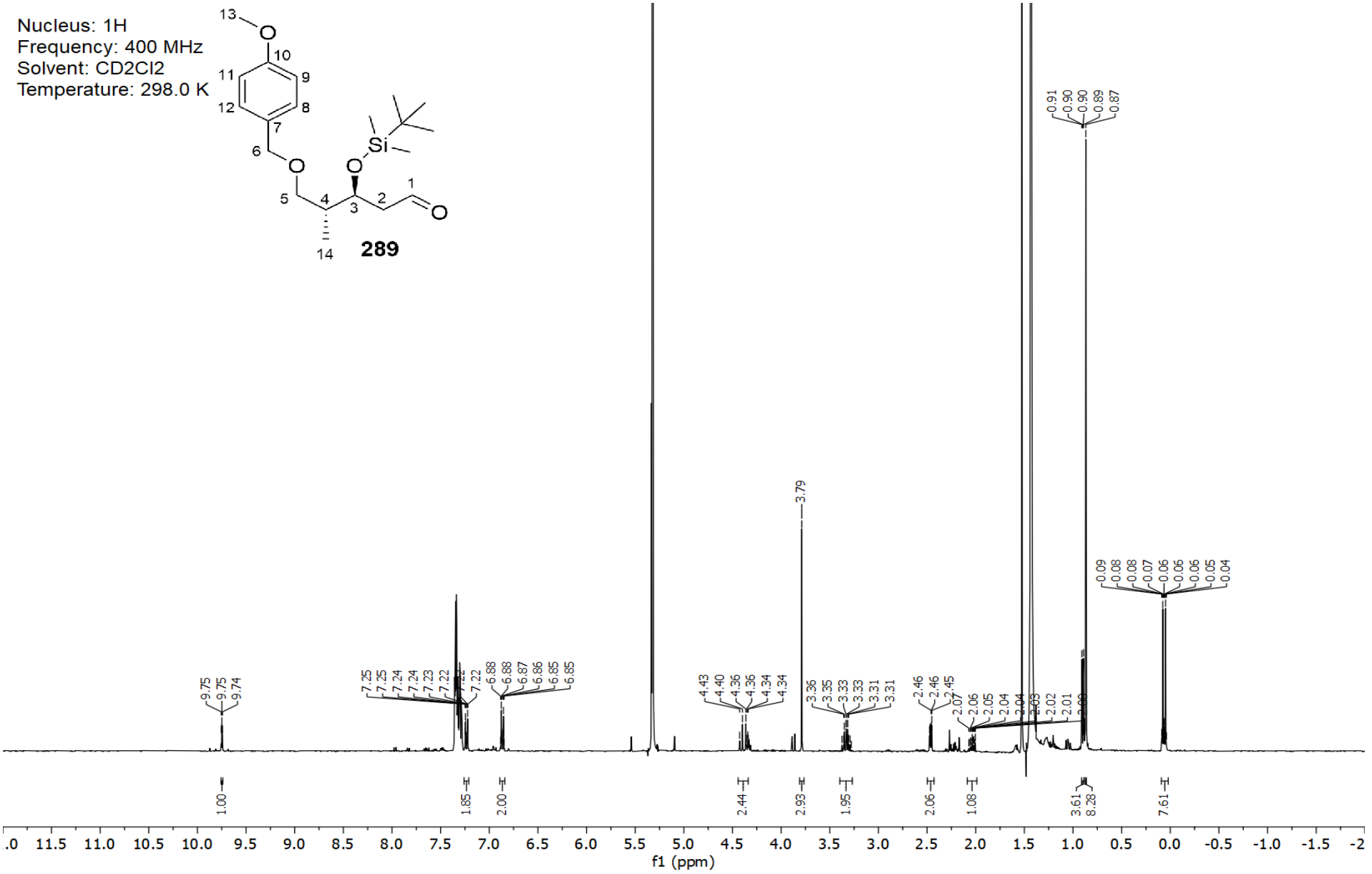
287

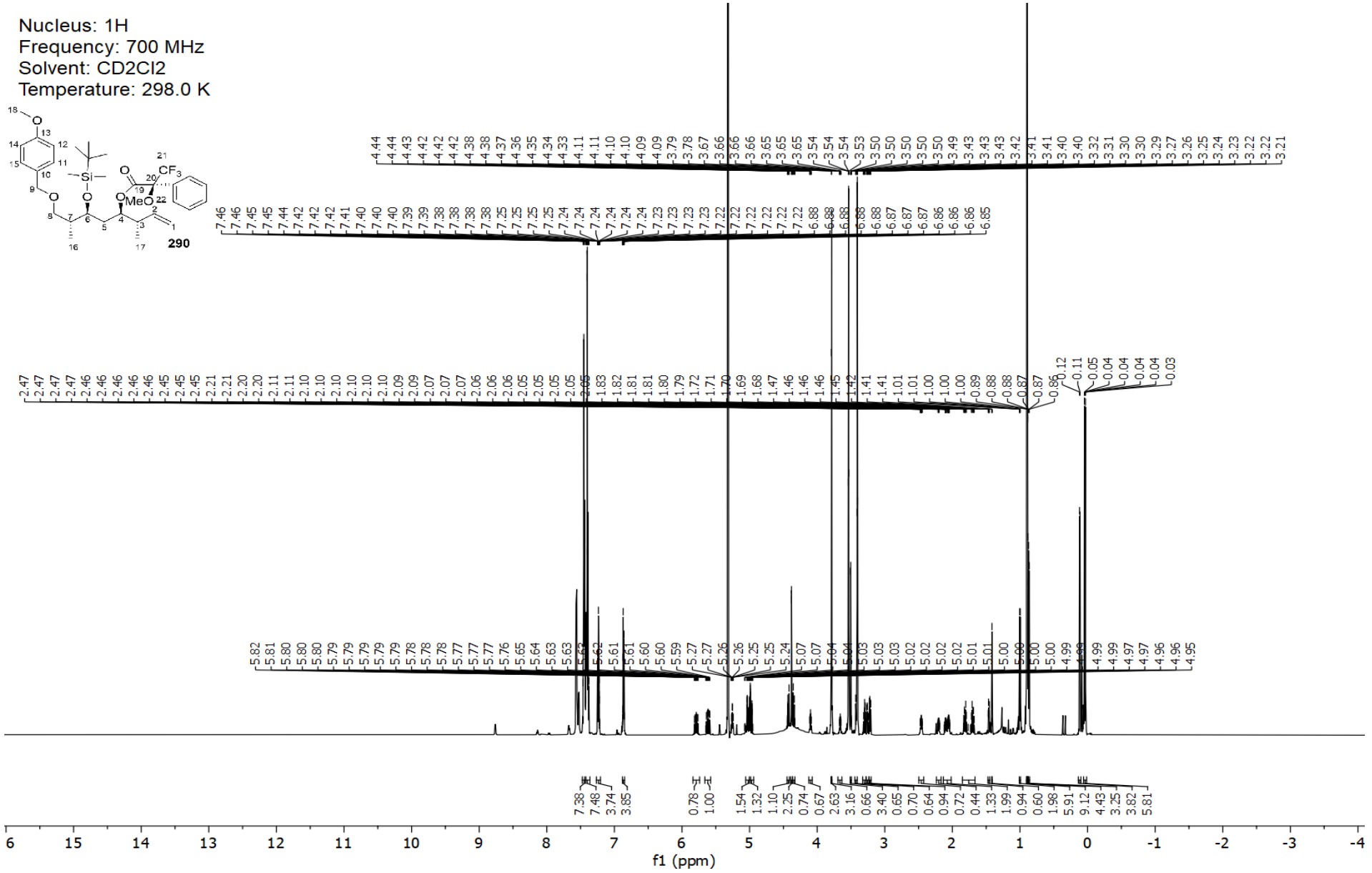


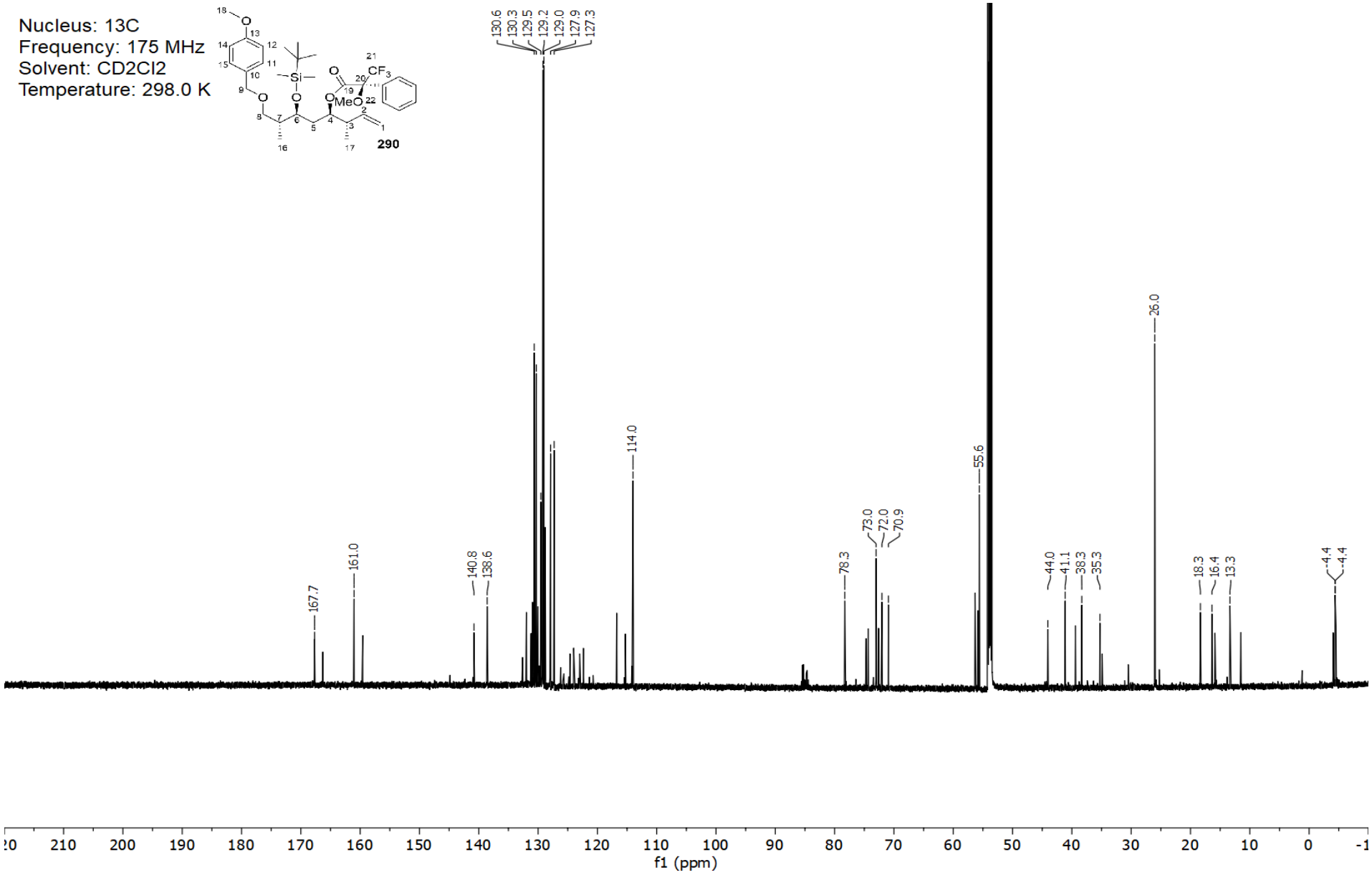
6. Appendix


Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
288
CD2Cl2
f1 (ppm)

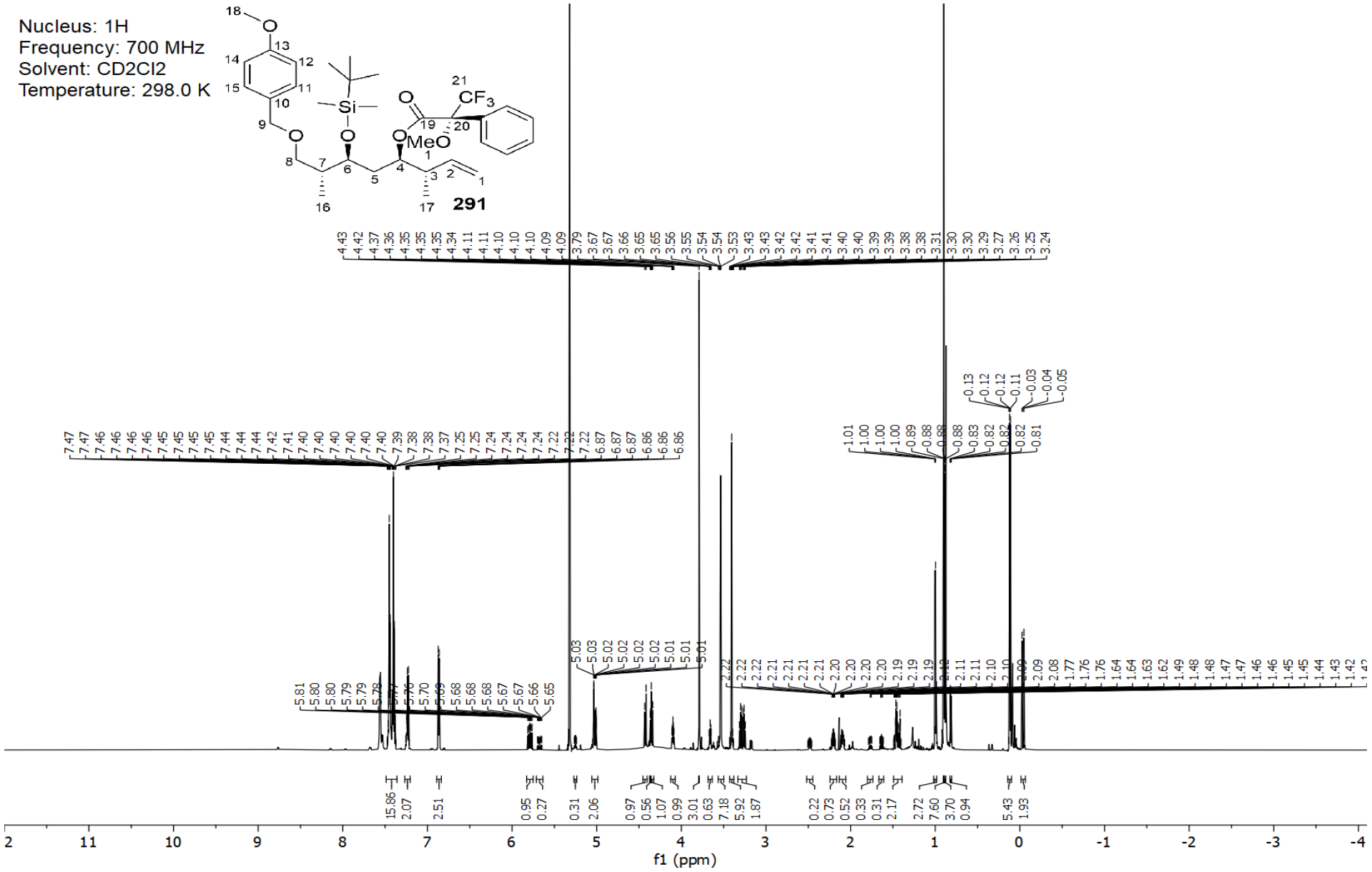

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
288
159.5
136.1
131.5
129.4
116.7
114.0
73.8
72.9
72.6
72.4
55.6
48.5
48.1
42.4
40.2
38.9
38.5
34.4
27.9
27.3
26.1
24.0
20.8
18.4
13.5
-4.1
-4.6
f1 (ppm)


Nucleus: 1H
Frequency: 400 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
289
f1 (ppm)


Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
290
f1 (ppm)

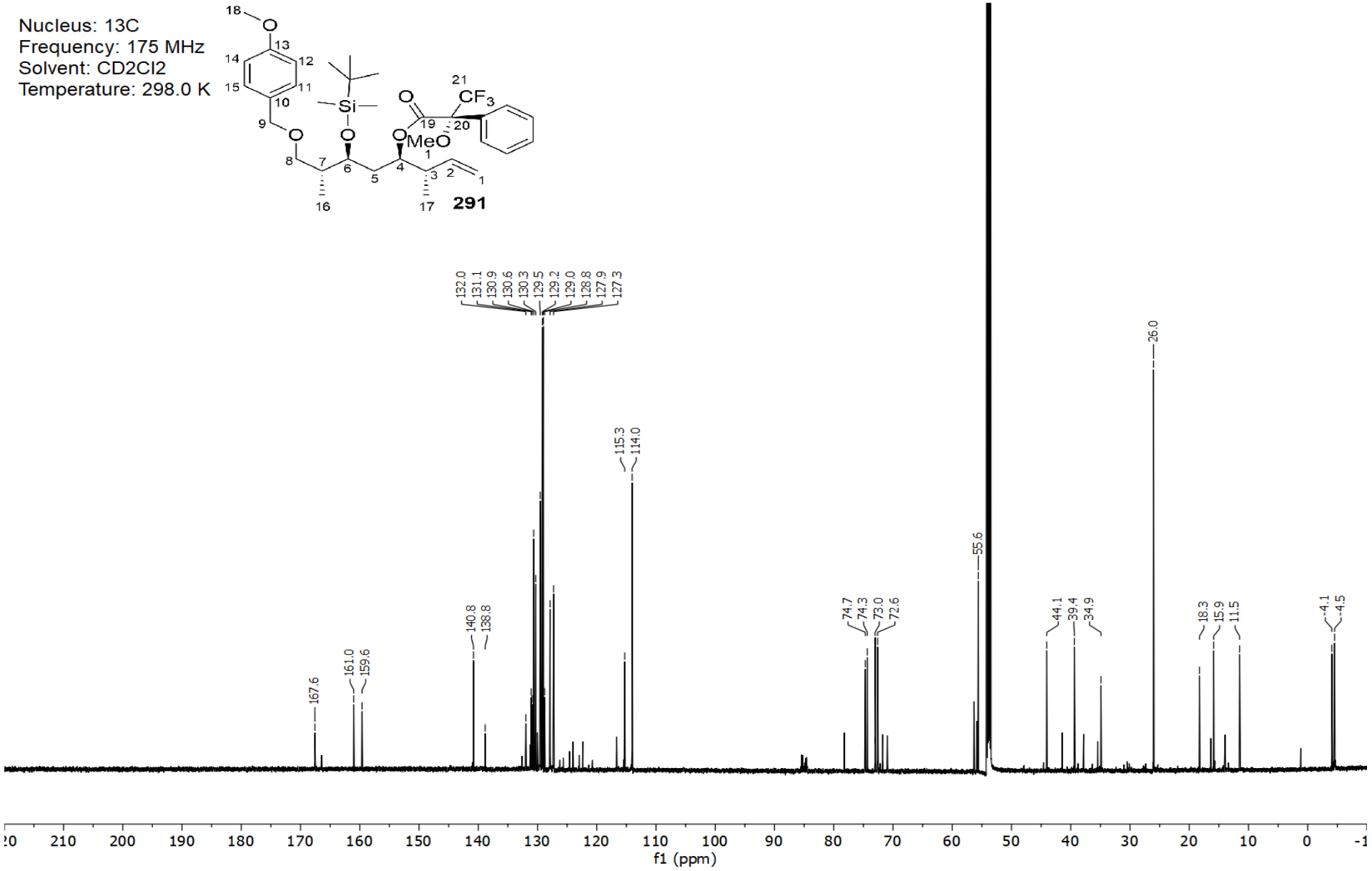

Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
290
130.6
130.3
129.5
129.2
129.0
127.9
127.3
167.7
161.0
140.8
138.6
114.0
78.3
73.0
72.0
70.9
55.6
44.0
41.1
38.3
35.3
26.0
18.3
16.4
13.3
-4.4
-4.4
f1 (ppm)

6. Appendix

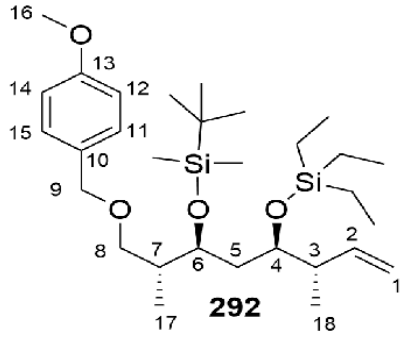

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
291
f1 (ppm)

Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

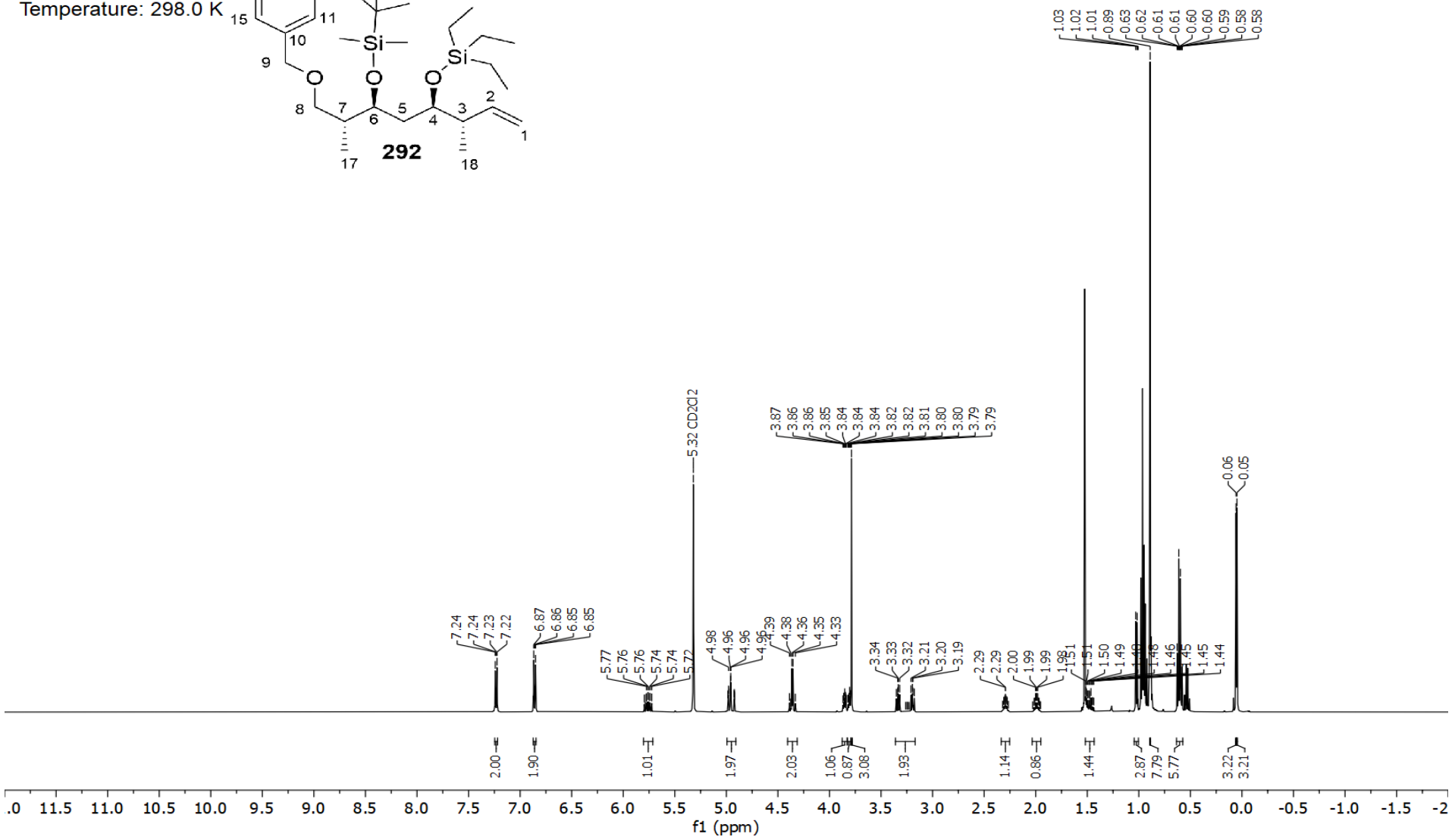
291

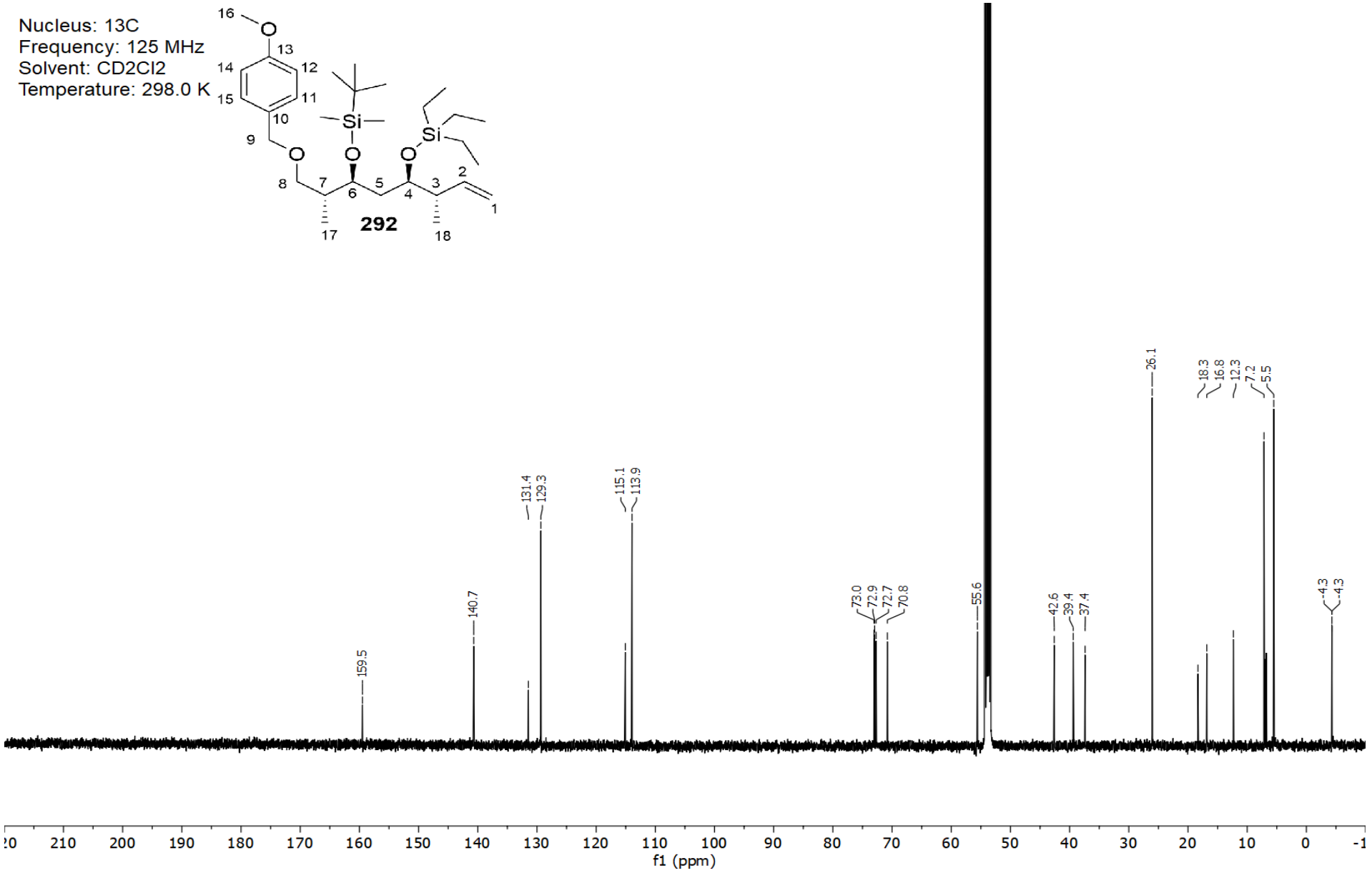


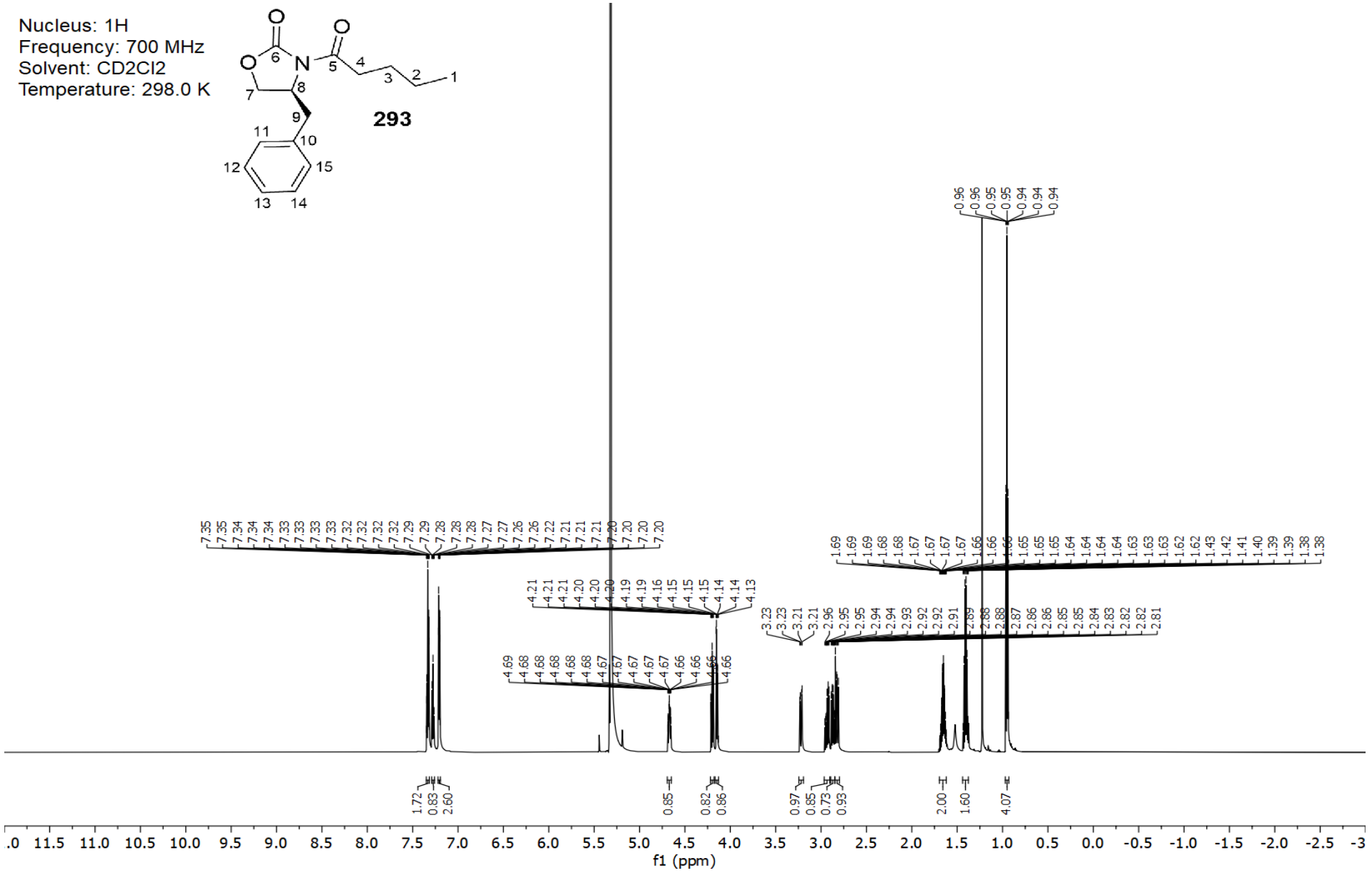
Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K



292

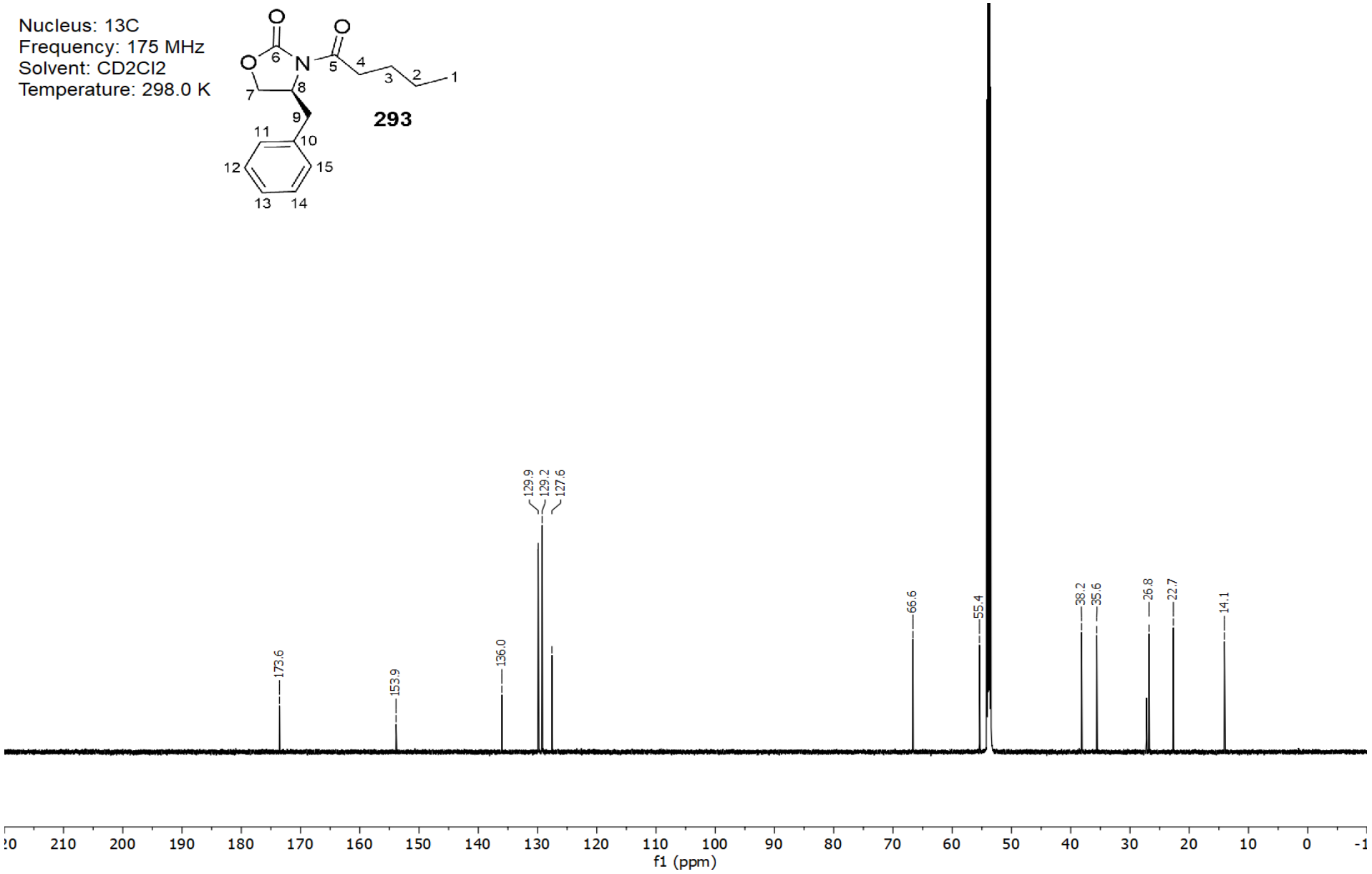



Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
292
159.5
140.7
131.4
129.3
115.1
113.9
73.0
72.9
72.7
70.8
55.6
42.6
39.4
37.4
26.1
18.3
16.8
12.3
7.2
5.5
-4.3
-4.3
f1 (ppm)


Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
293
f1 (ppm)

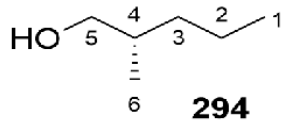
Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

293

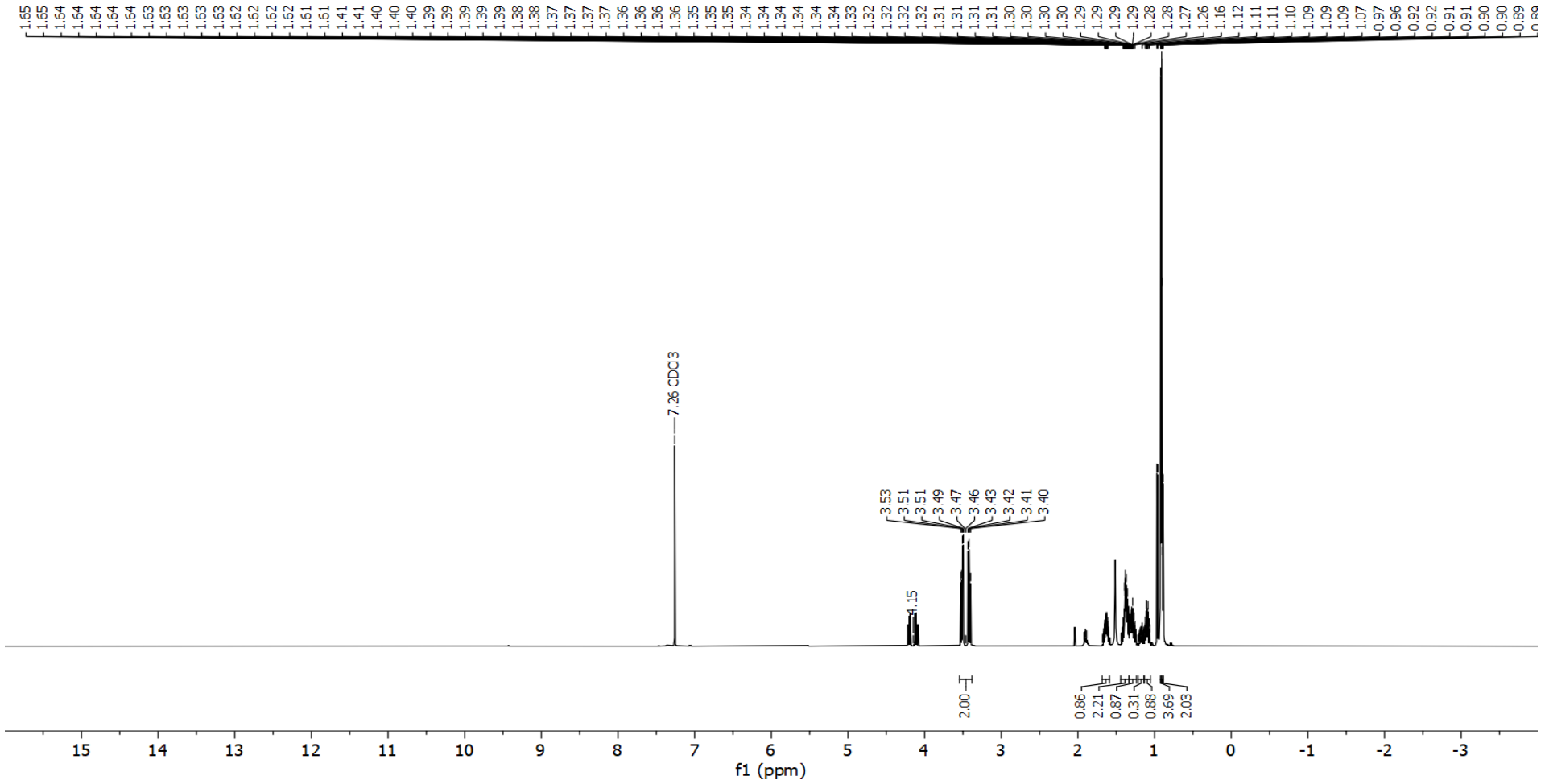


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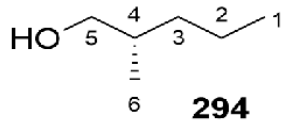
Nucleus: 1H
Frequency: 500 MHz
Solvent: CDCl3
Temperature: 298.0 K



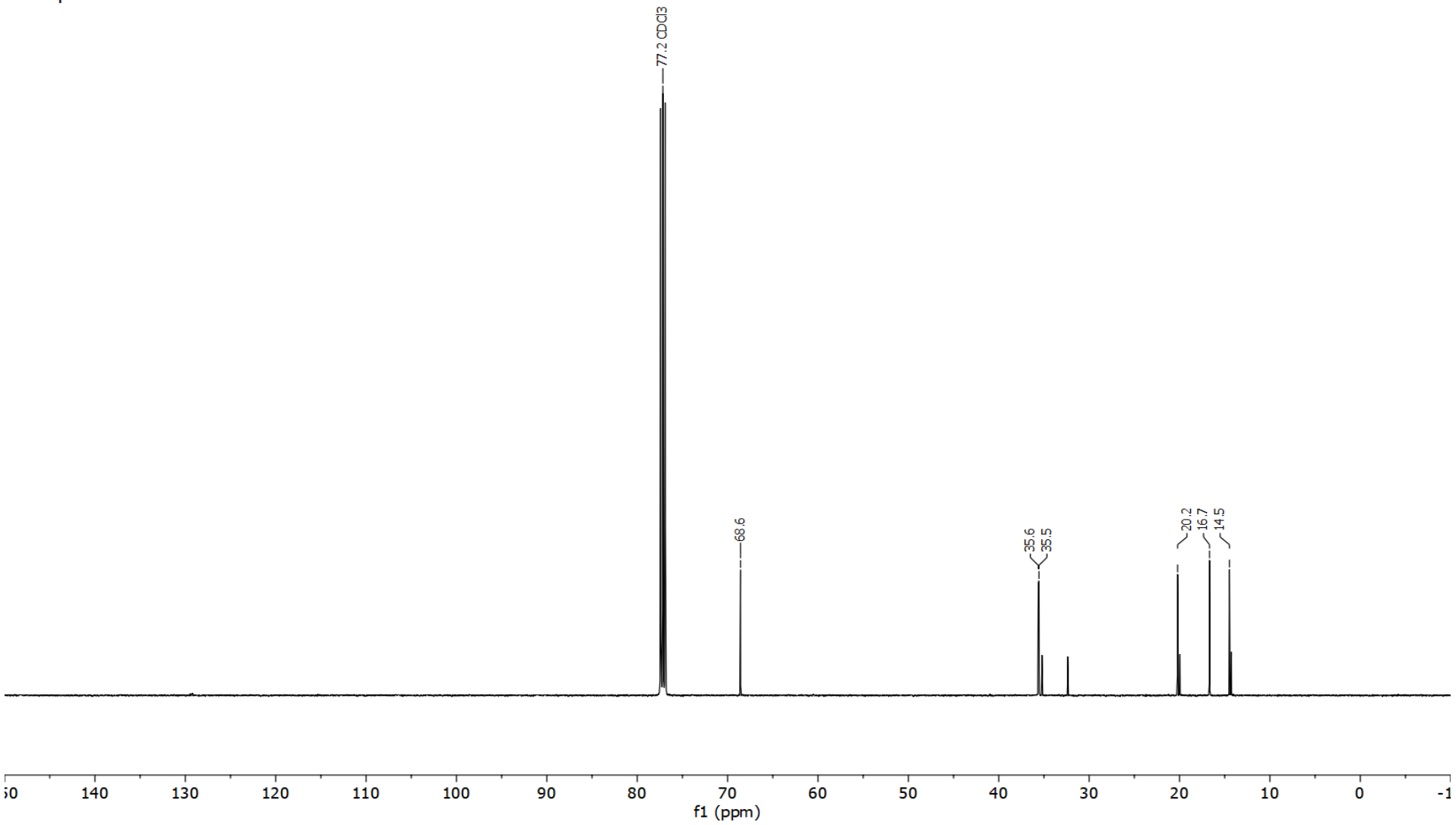
294



Nucleus: 13C
Frequency: 125 MHz
Solvent: CDCl3
Temperature: 298.0 K



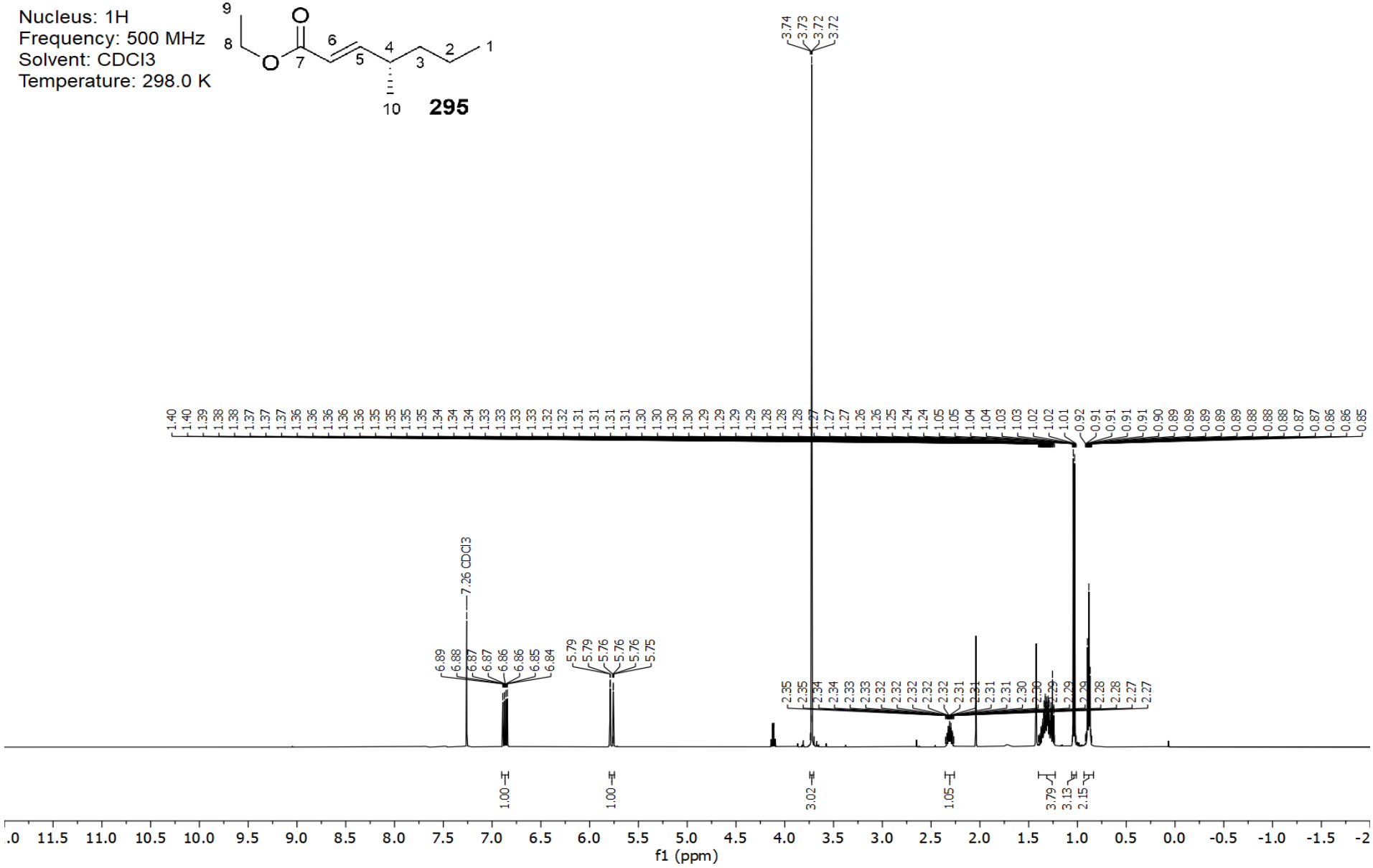
294



6. Appendix

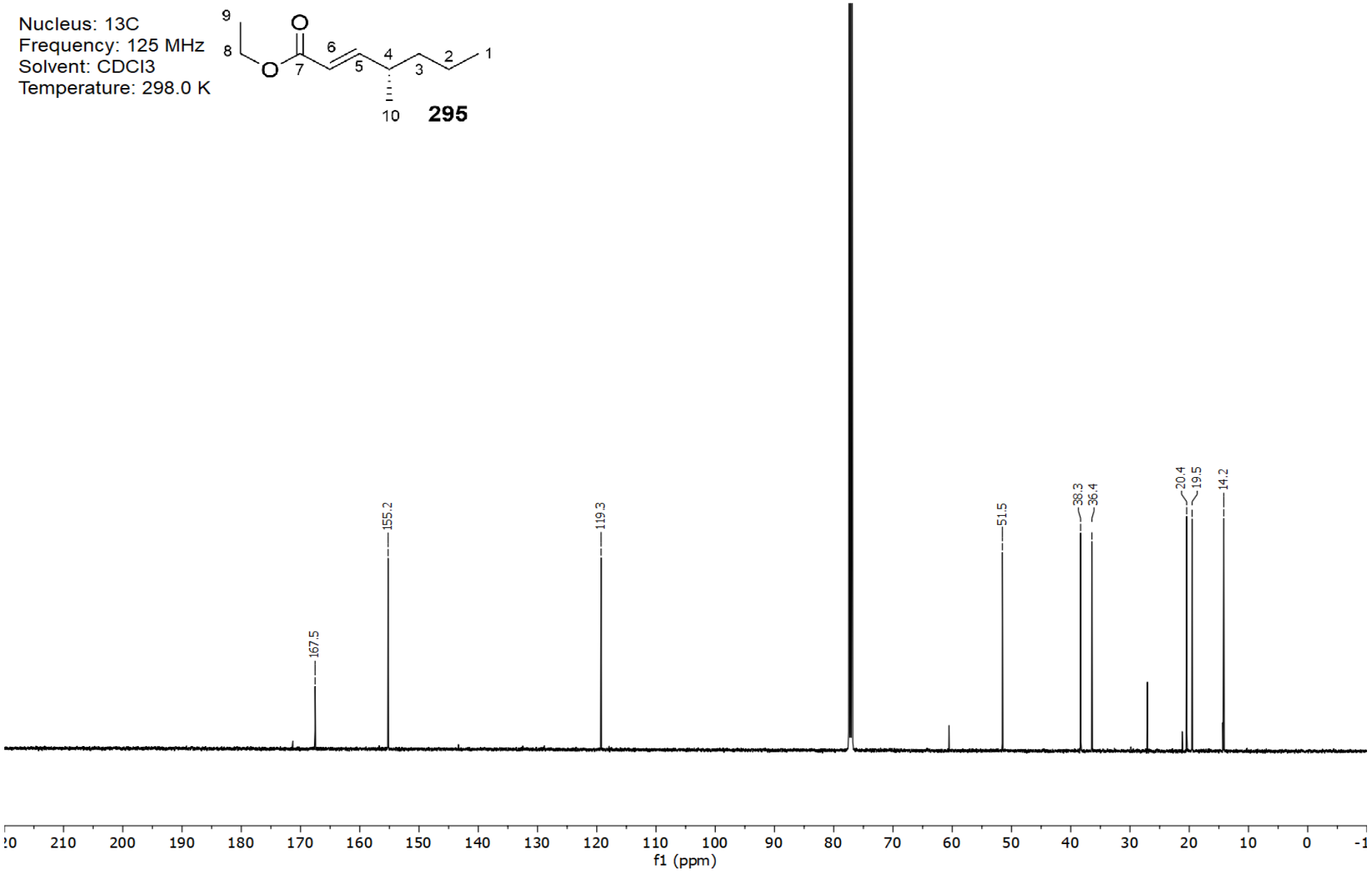
Nucleus: 1H
Frequency: 500 MHz
Solvent: CDCl3
Temperature: 298.0 K

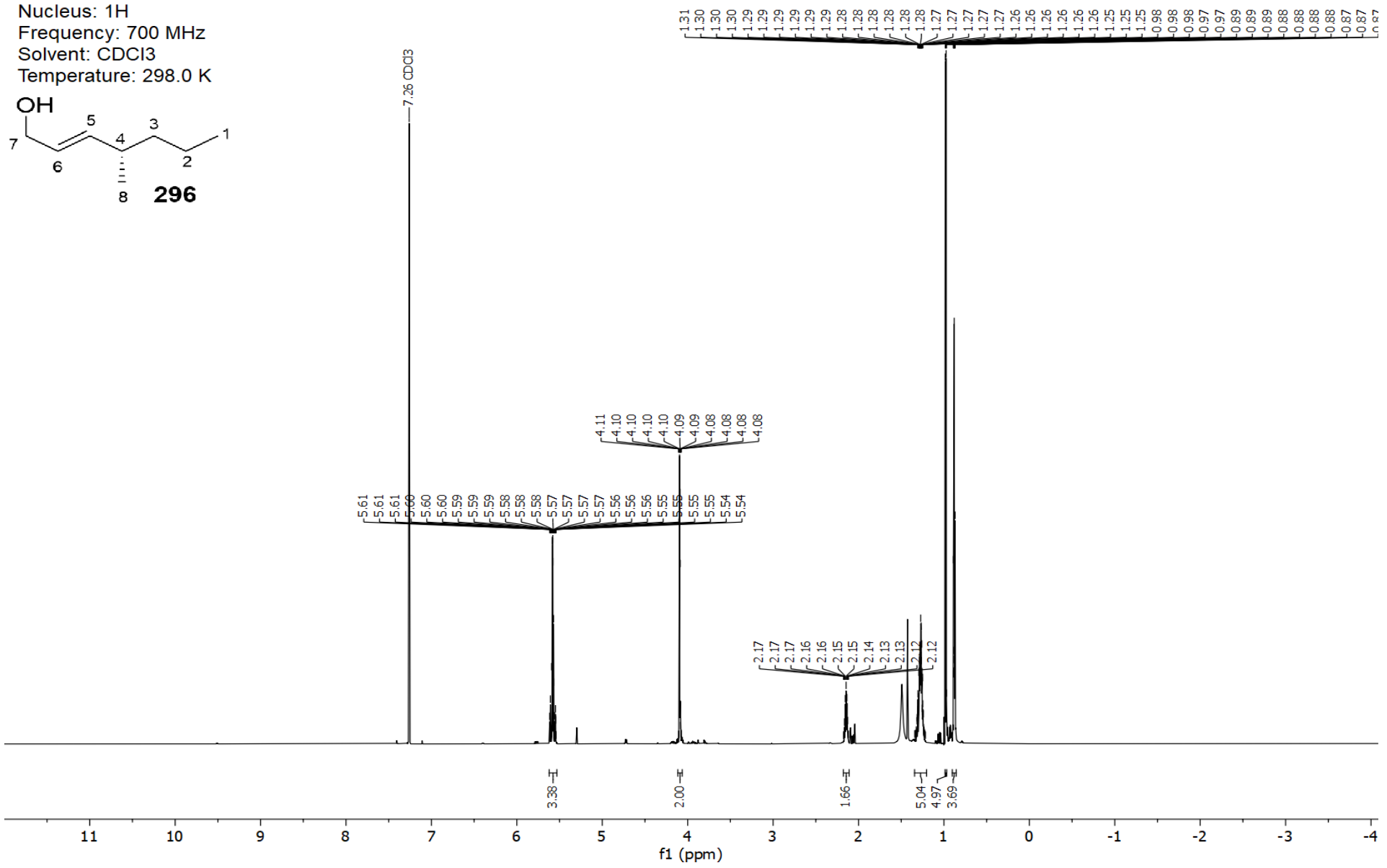
295



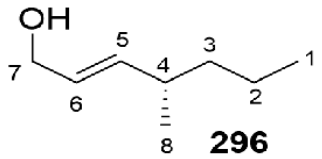
Nucleus: 13C
Frequency: 125 MHz
Solvent: CDCl3
Temperature: 298.0 K

295

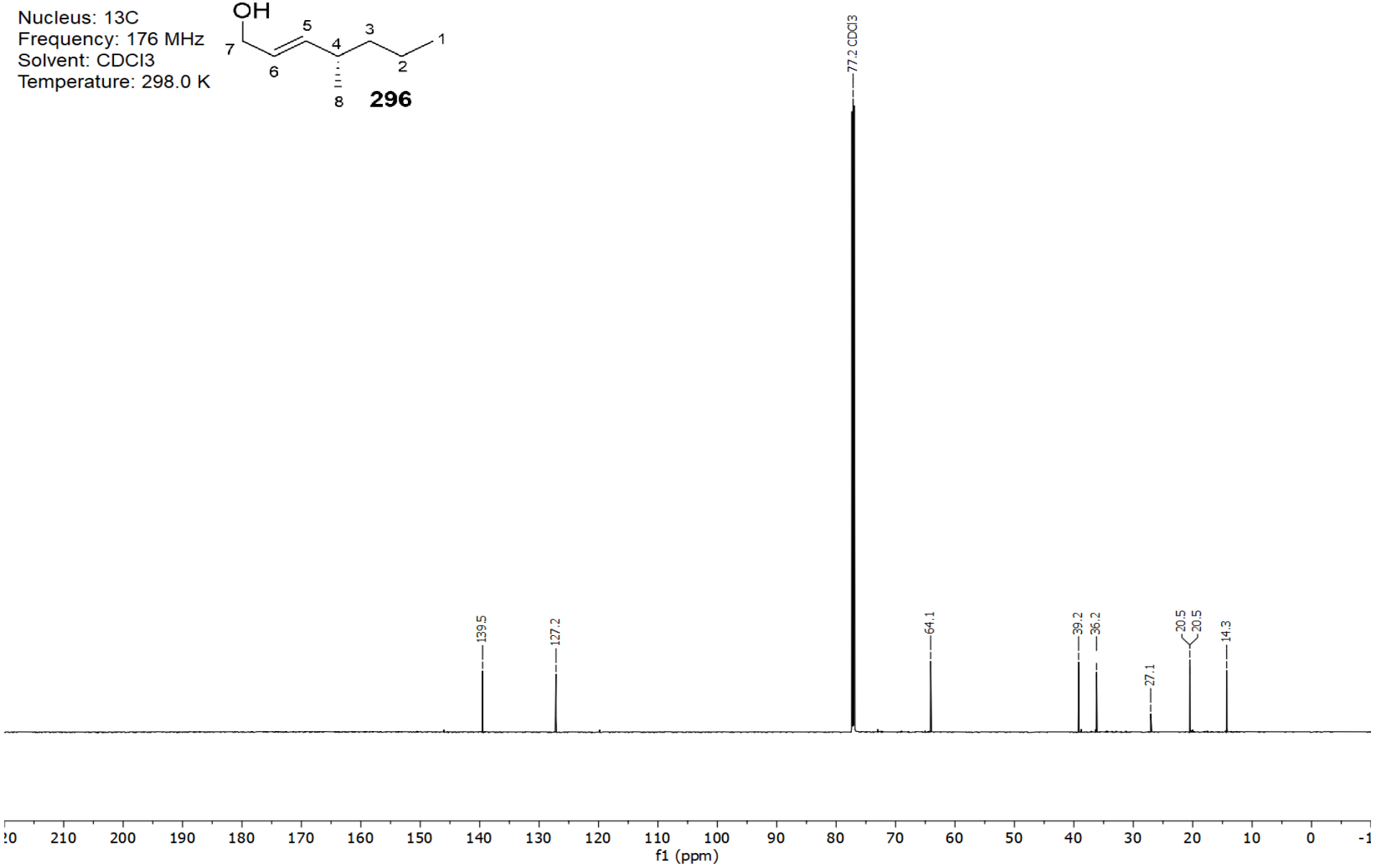


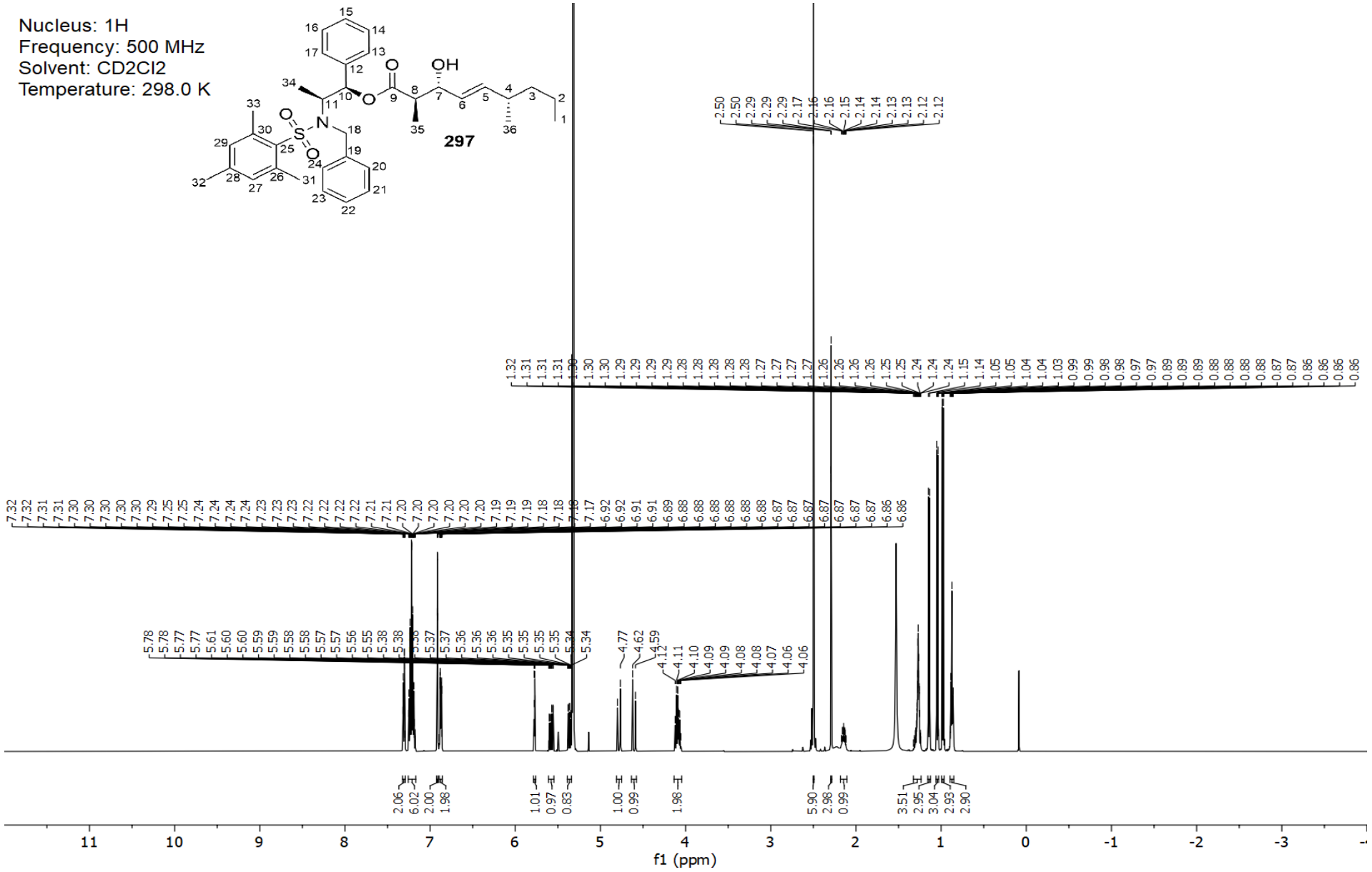

Nucleus: 1H
Frequency: 700 MHz
Solvent: CDCl3
Temperature: 298.0 K
OH
296
7.26 CDCl3
f1 (ppm)

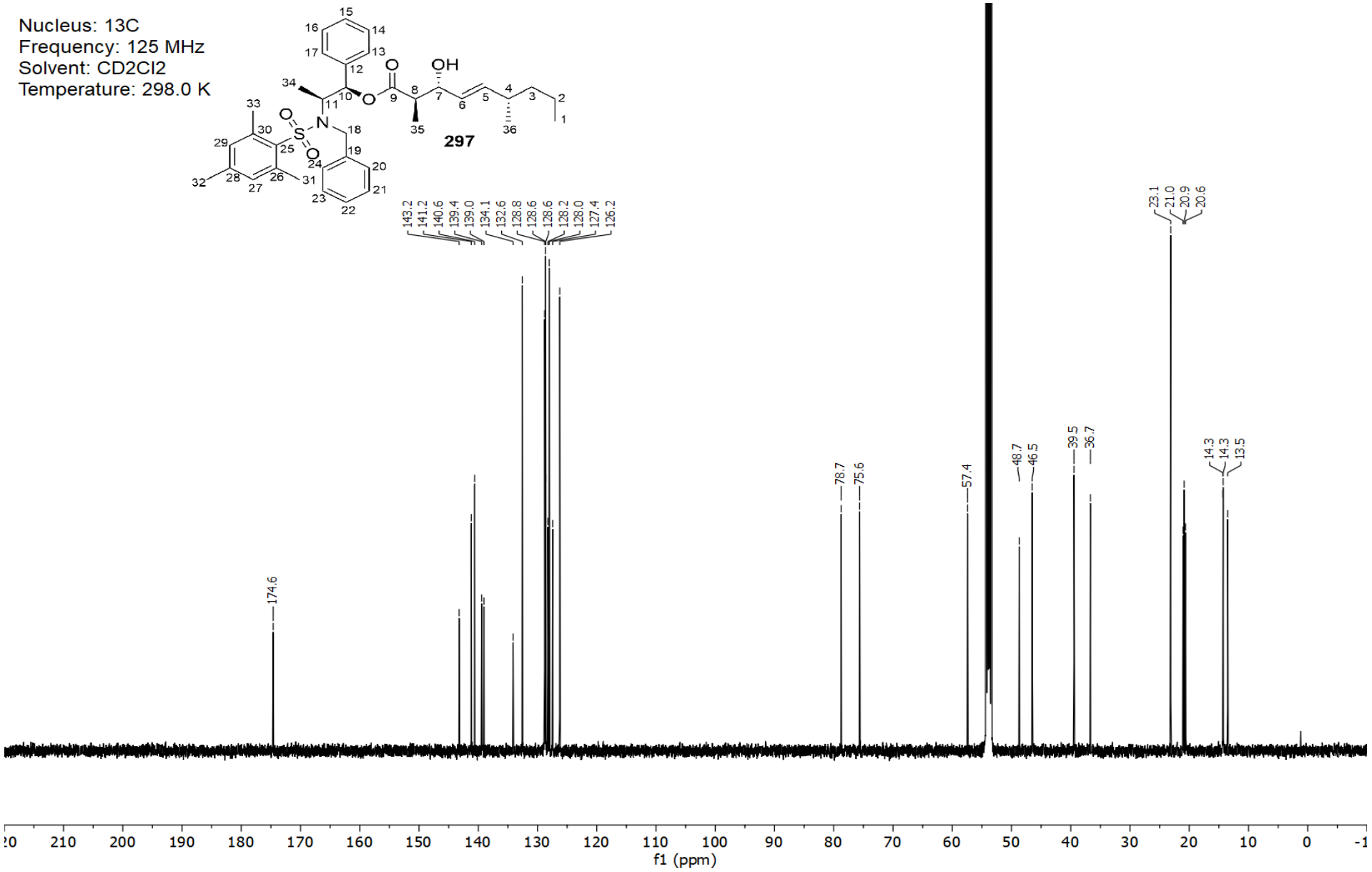
Nucleus: 13C
Frequency: 176 MHz
Solvent: CDCl3
Temperature: 298.0 K

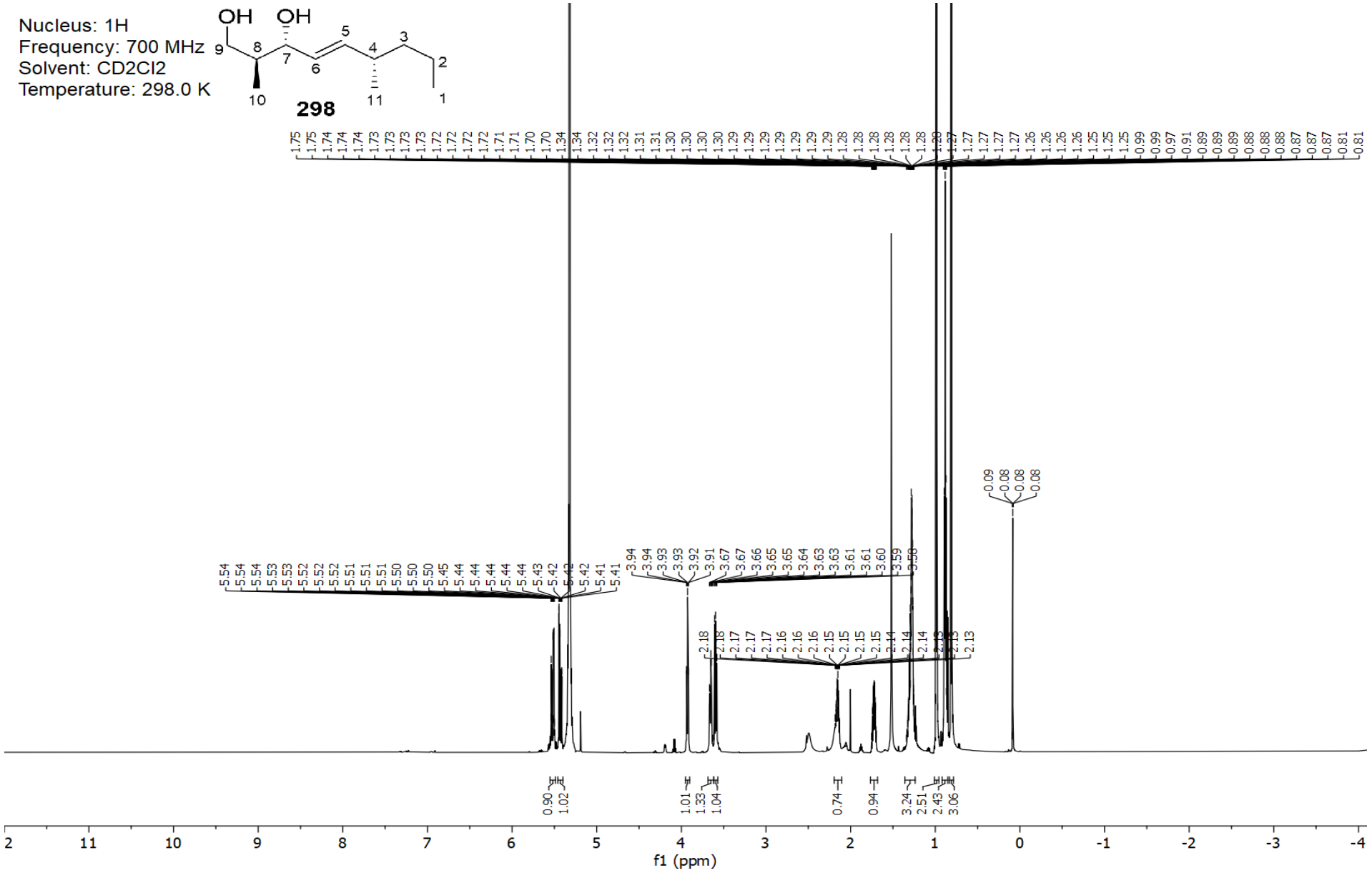


296



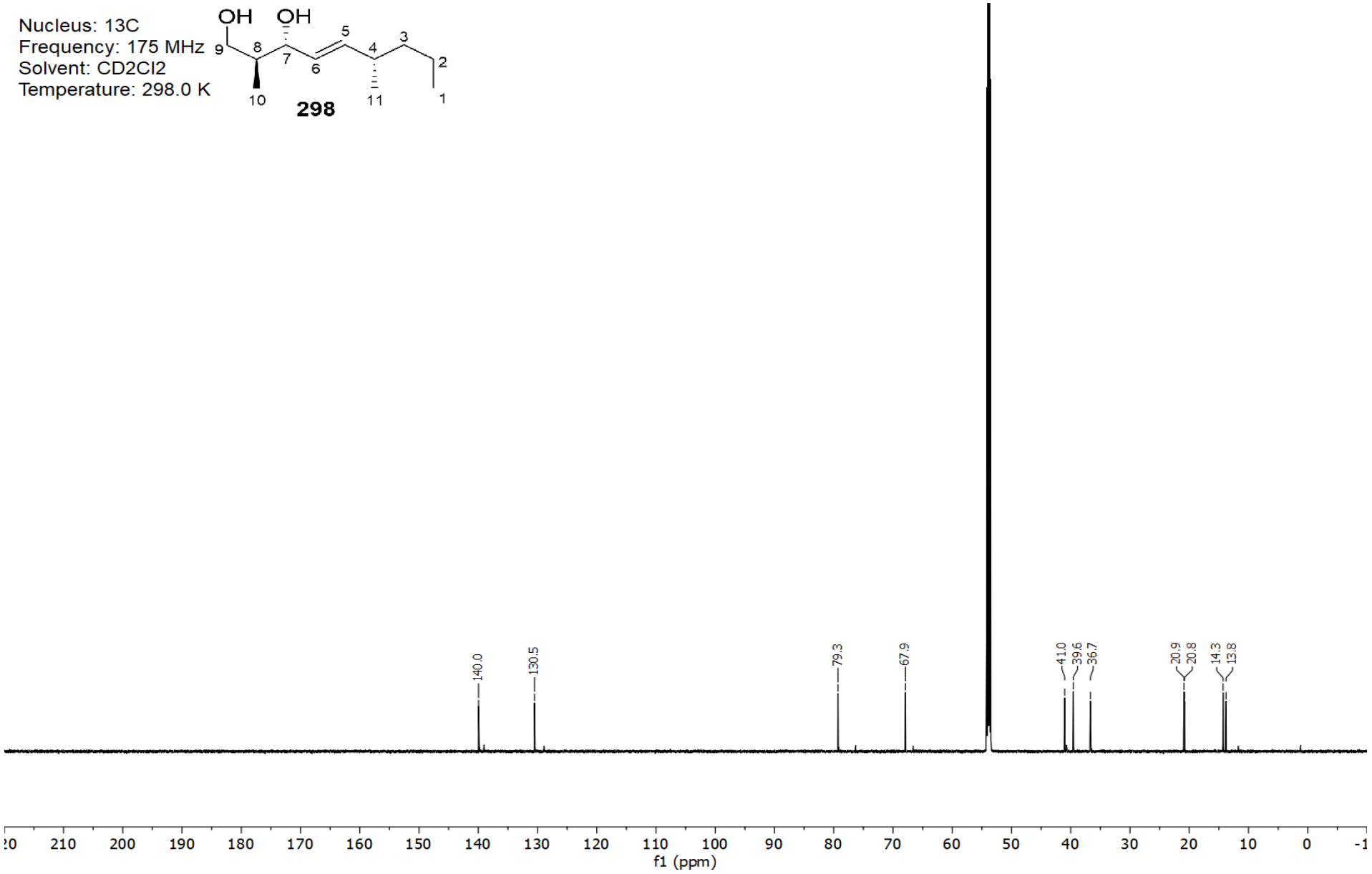

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
297
f1 (ppm)


Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
297
143.2
141.2
140.6
139.4
139.0
134.1
132.6
128.8
128.6
128.6
128.2
128.0
127.4
126.2
174.6
78.7
75.6
57.4
48.7
46.5
39.5
36.7
23.1
21.0
20.9
20.6
14.3
14.3
13.5
f1 (ppm)

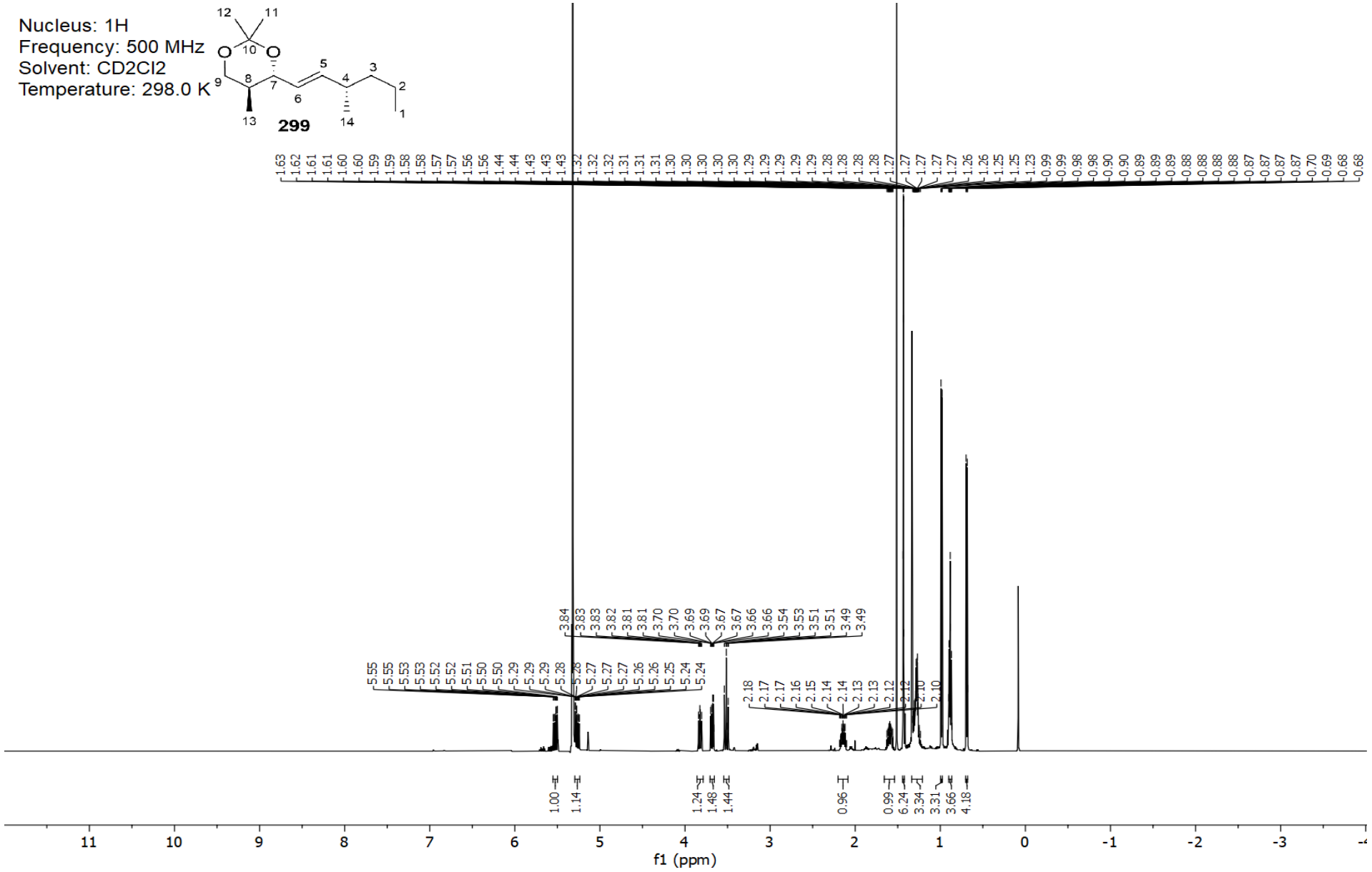

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
OH
OH
298
f1 (ppm)

Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

298

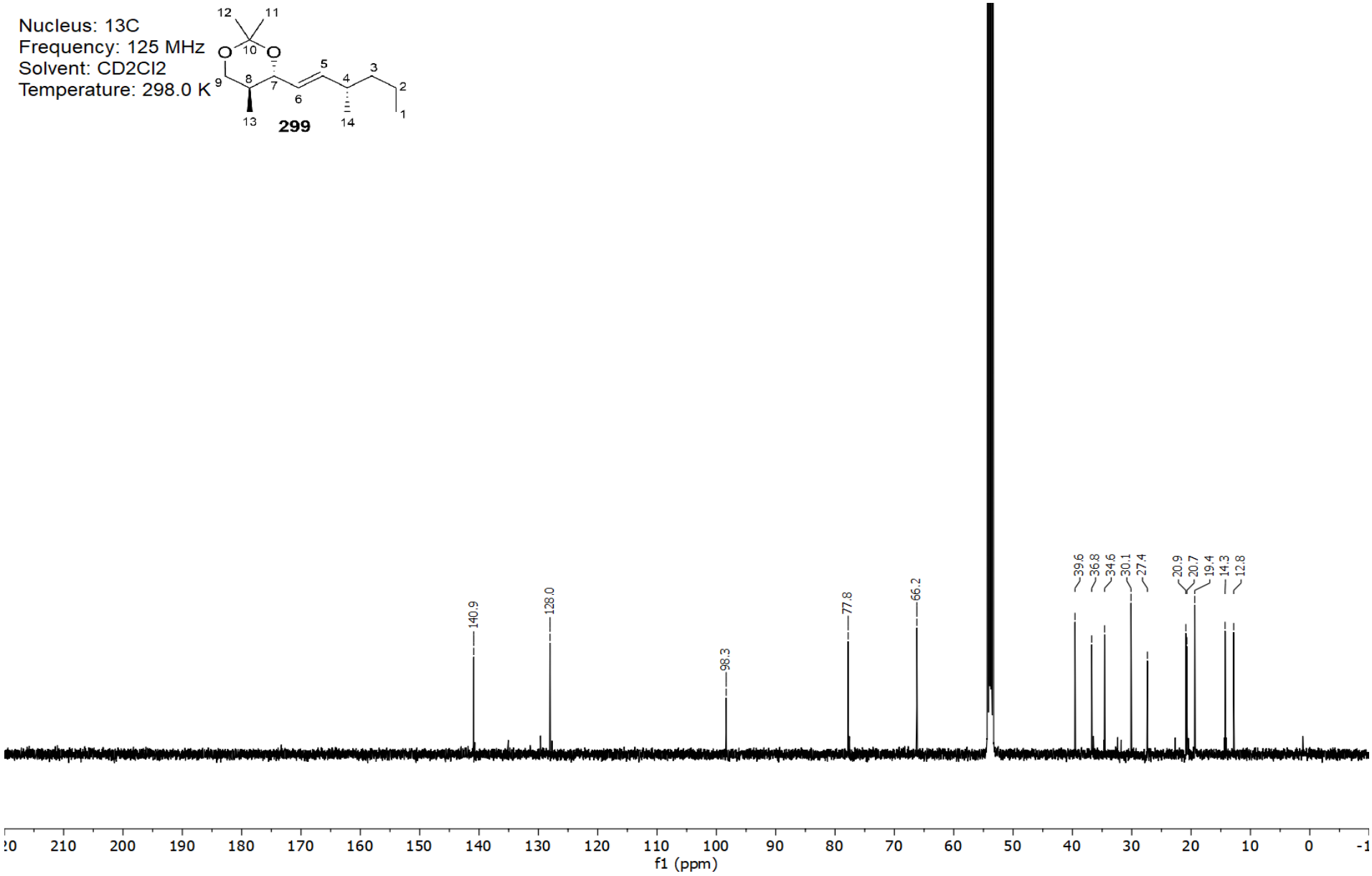


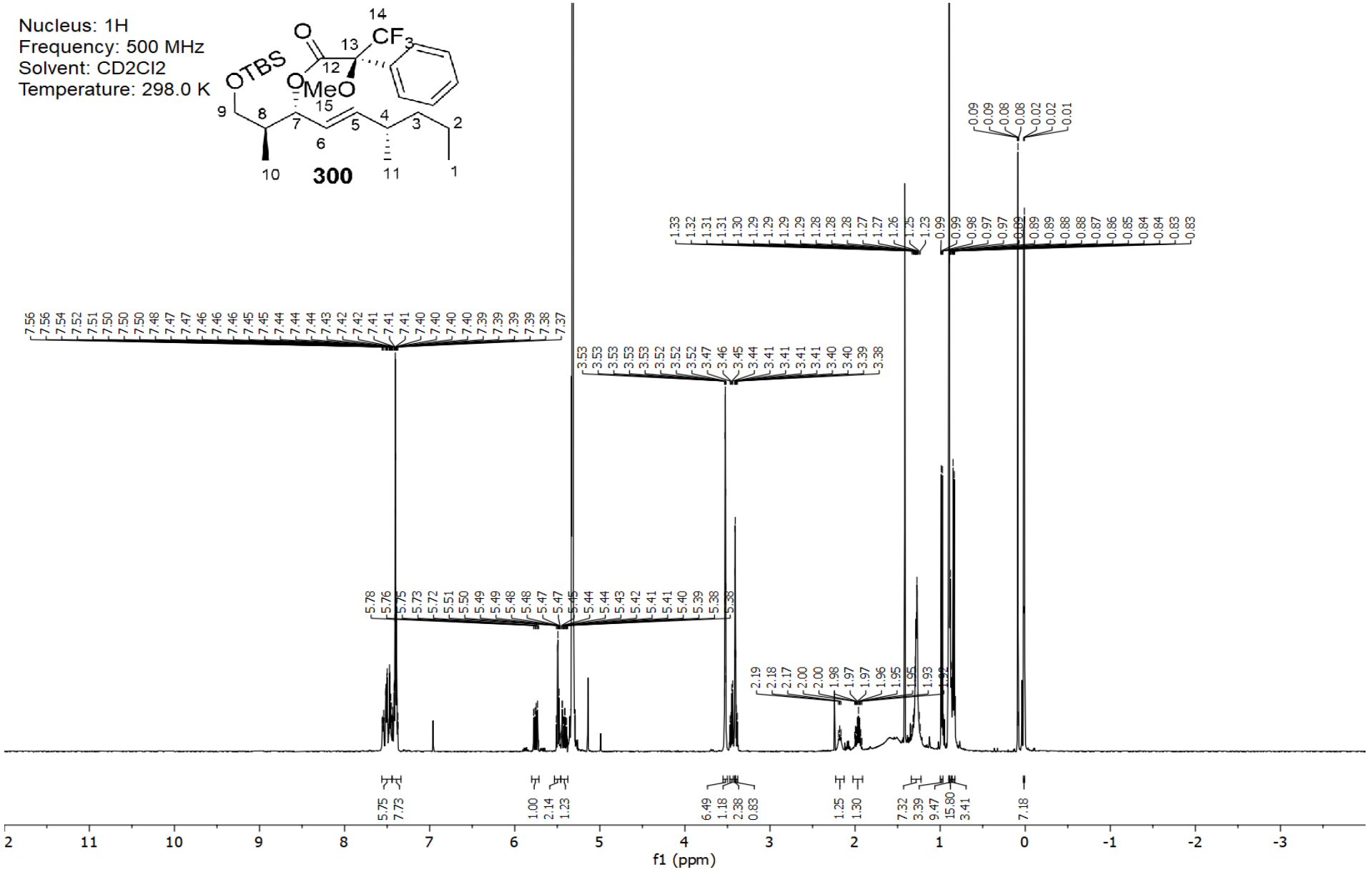
6. Appendix


Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
299
f1 (ppm)

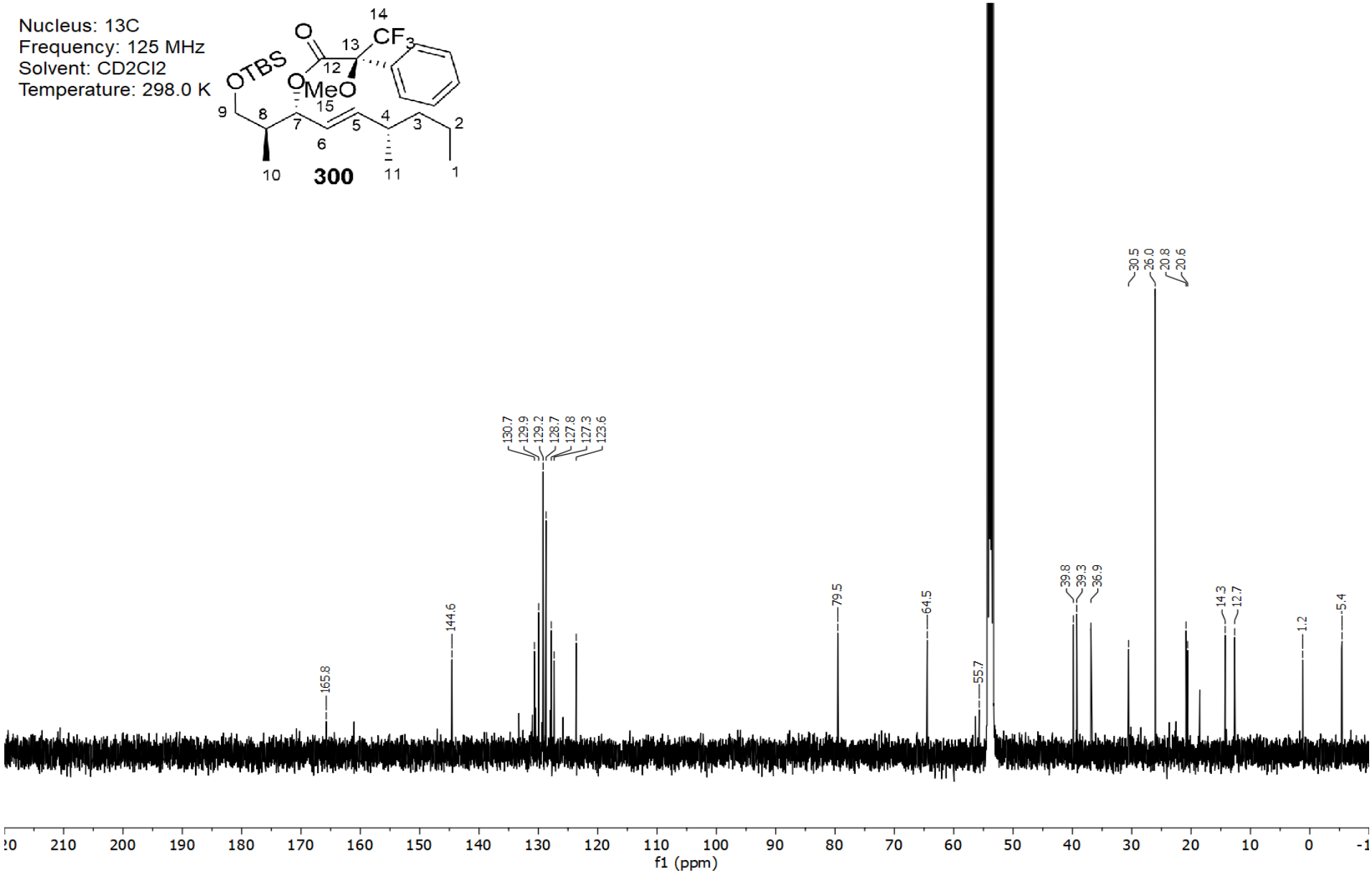
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

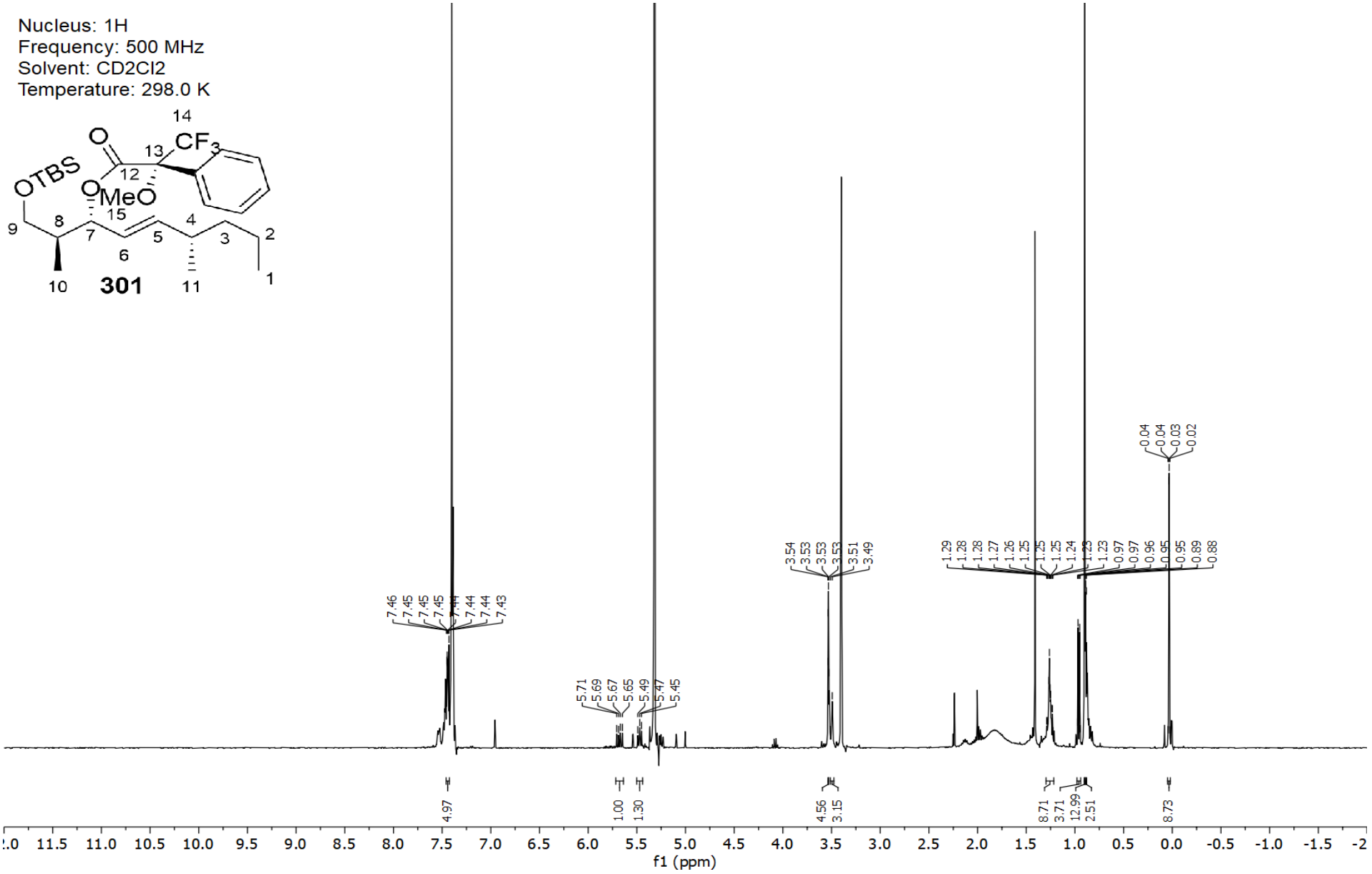
299

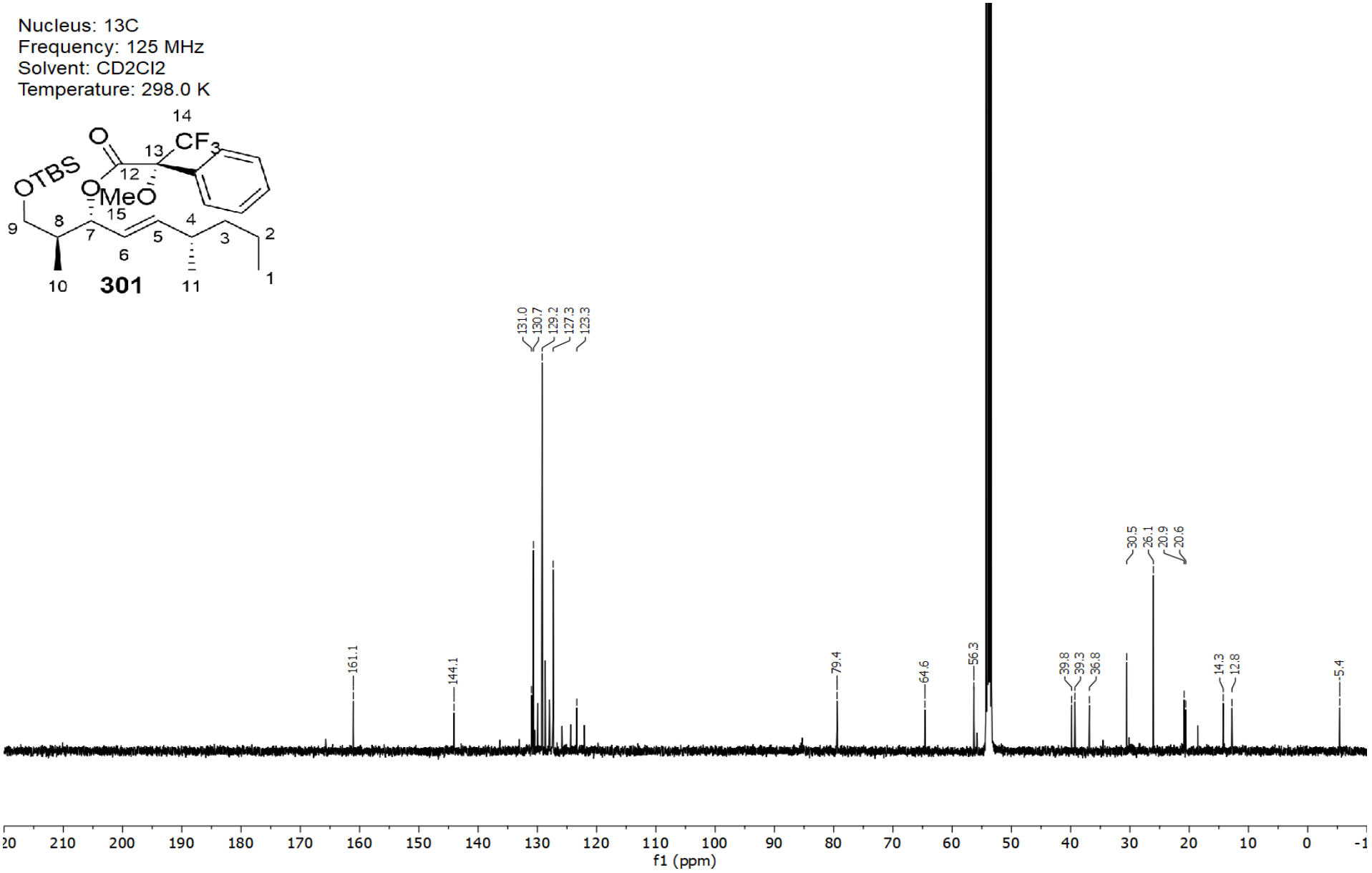



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
OTBS
MeO
CF3
300
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

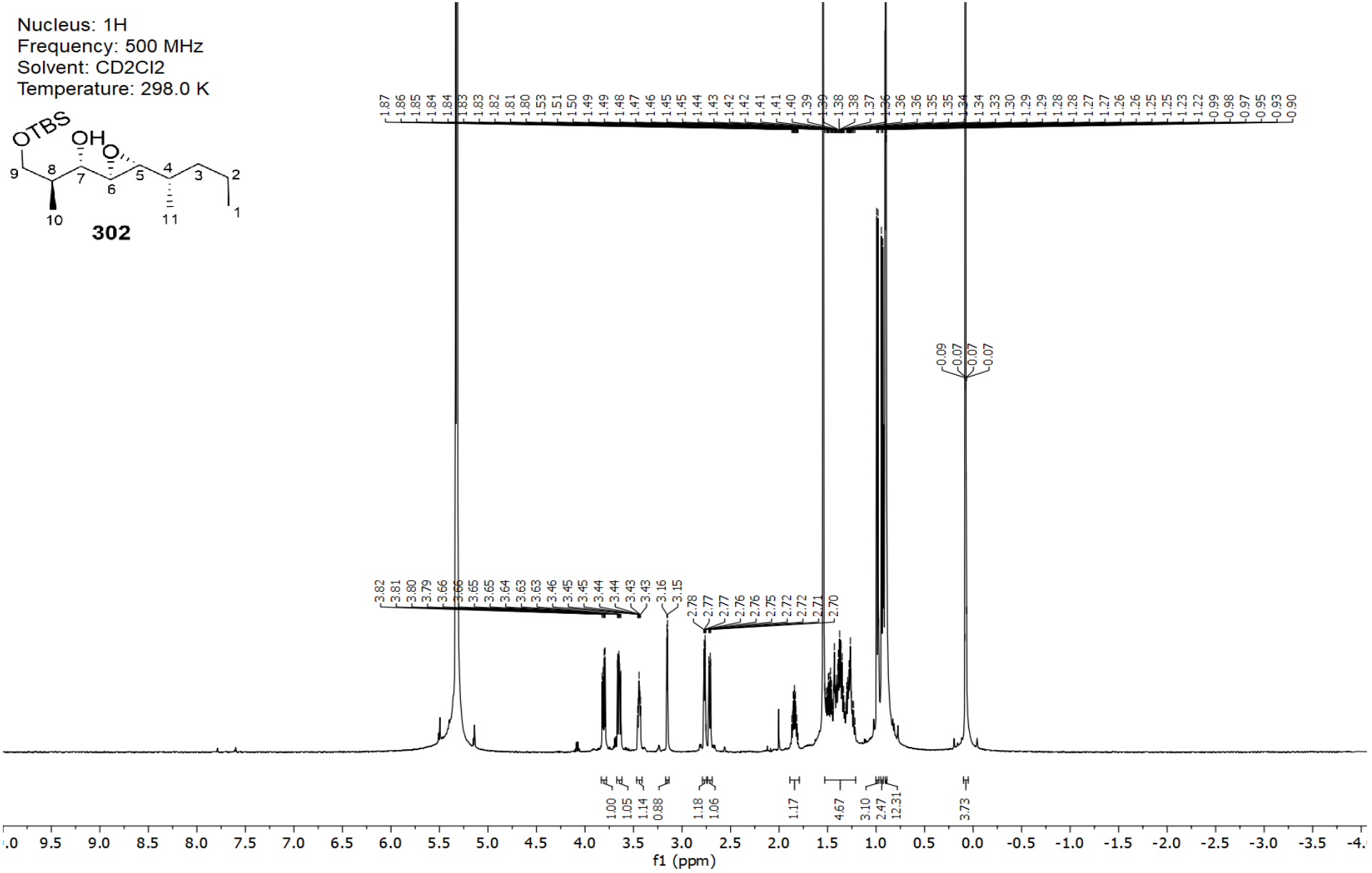



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
OTBS
MeO
CF3
301
f1 (ppm)


Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
OTBS
MeO
CF3
301
131.0
130.7
129.2
127.3
123.3
161.1
144.1
79.4
64.6
56.3
39.8
39.3
36.8
30.5
26.1
20.9
20.6
14.3
12.8
-5.4
f1 (ppm)

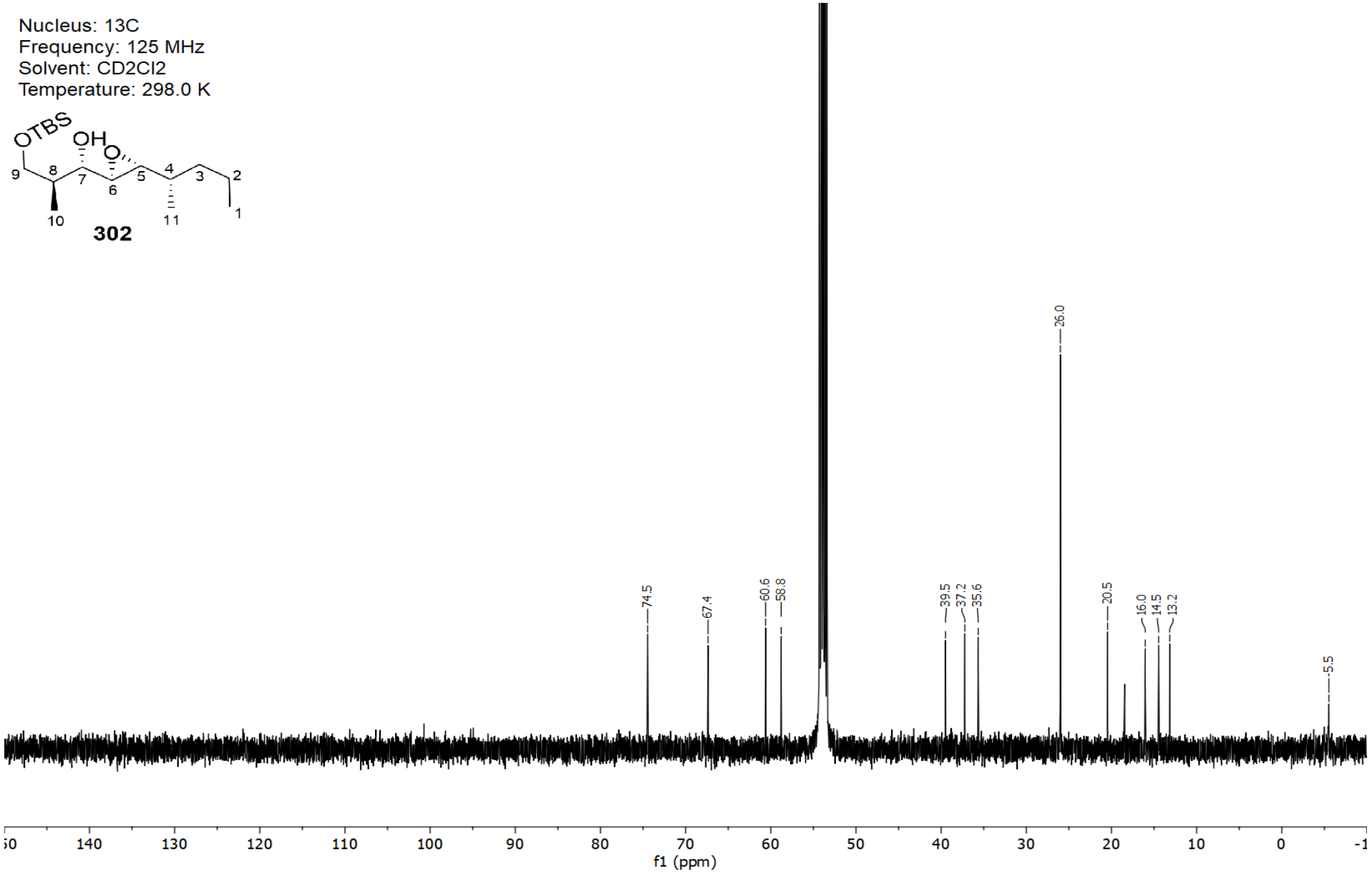
Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

302



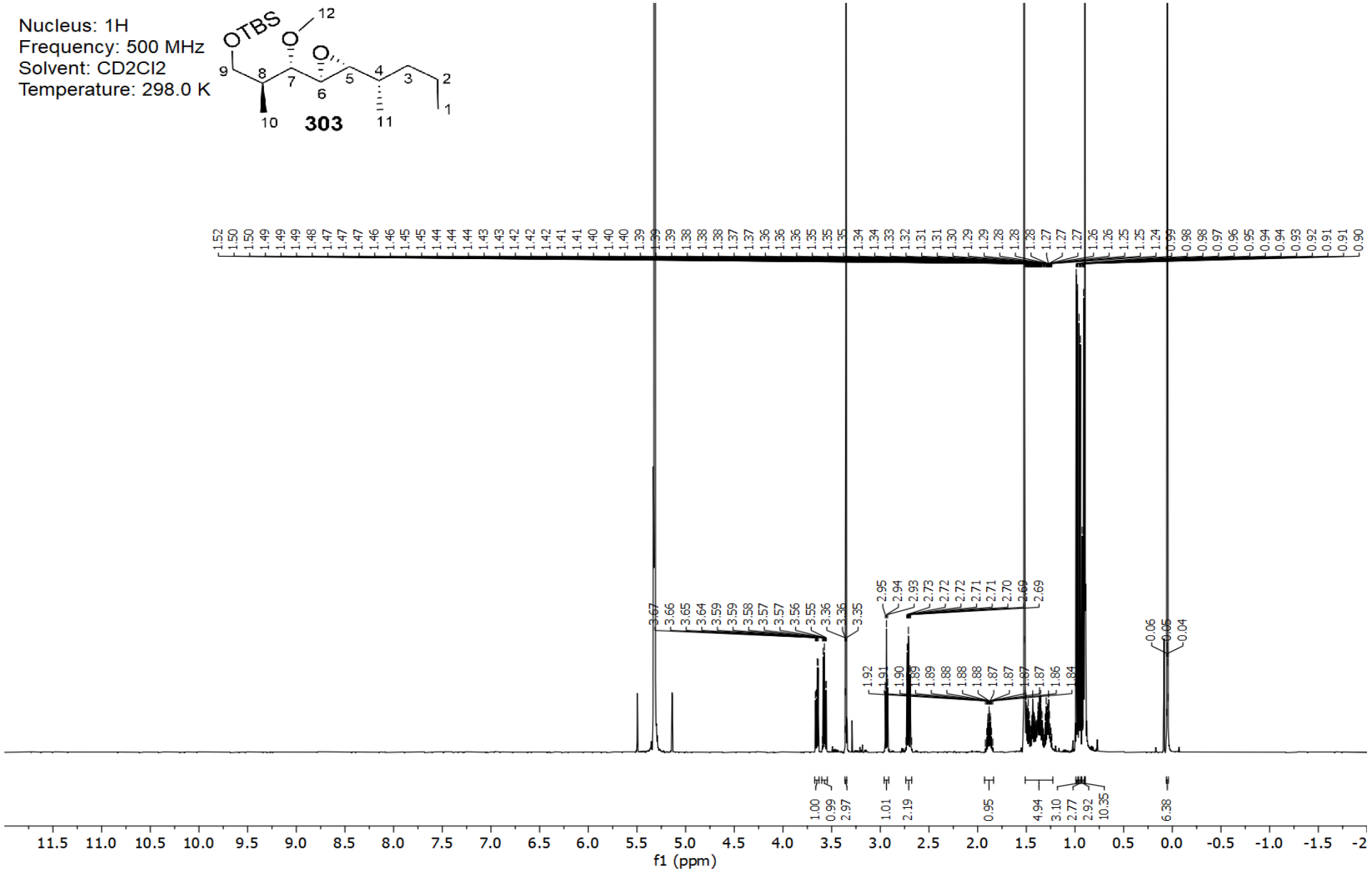
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

302



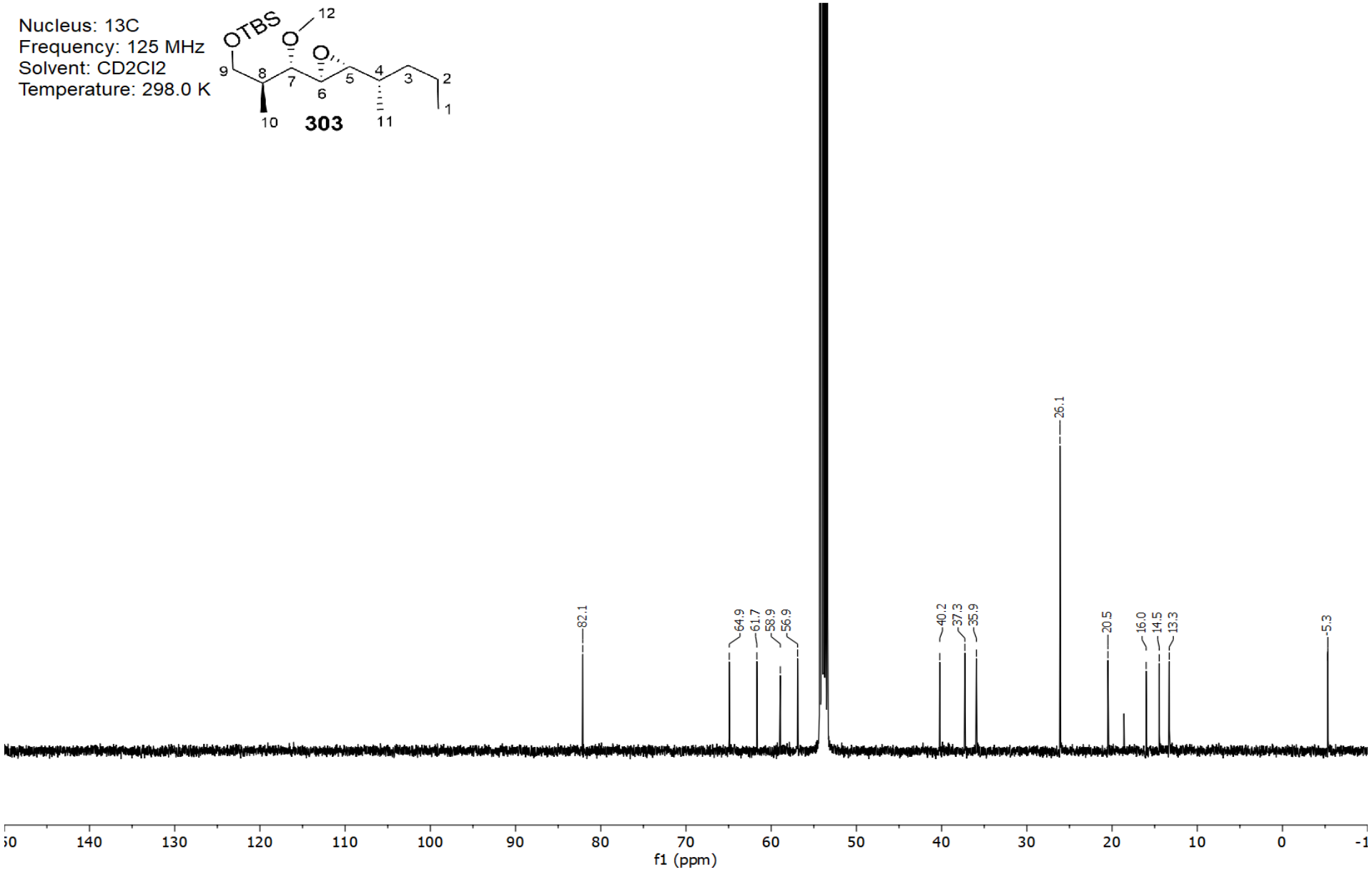
Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

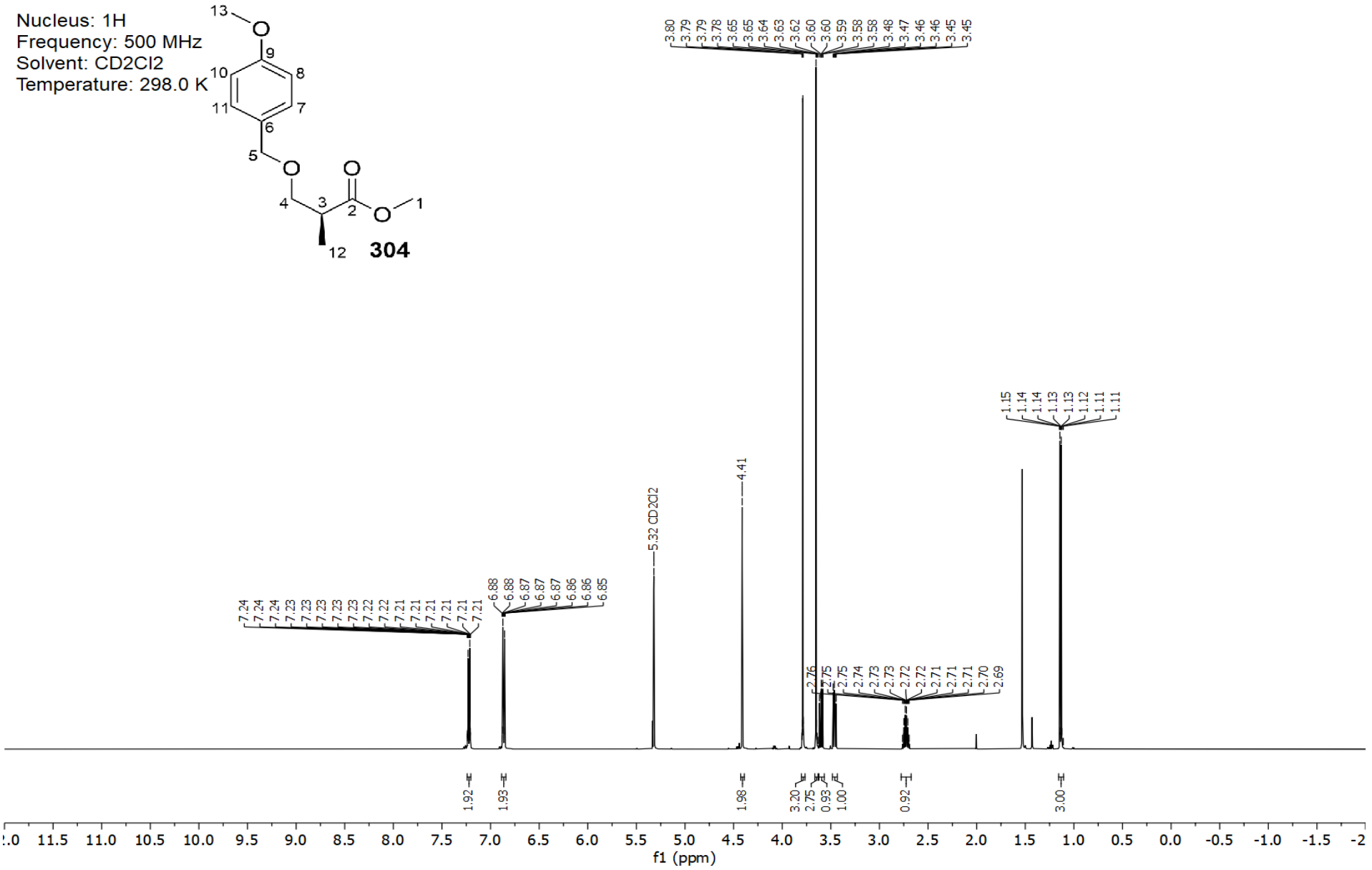
303

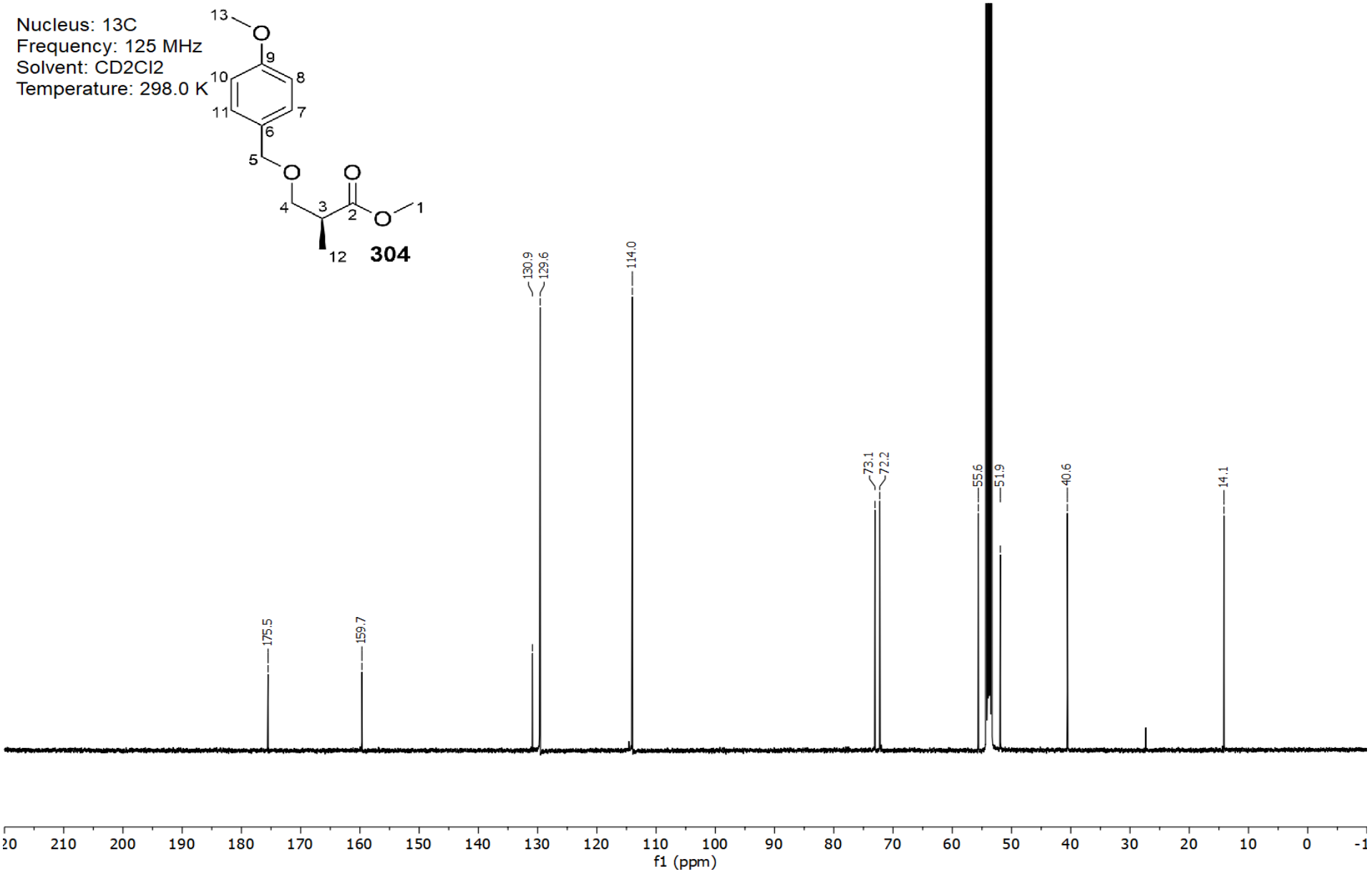


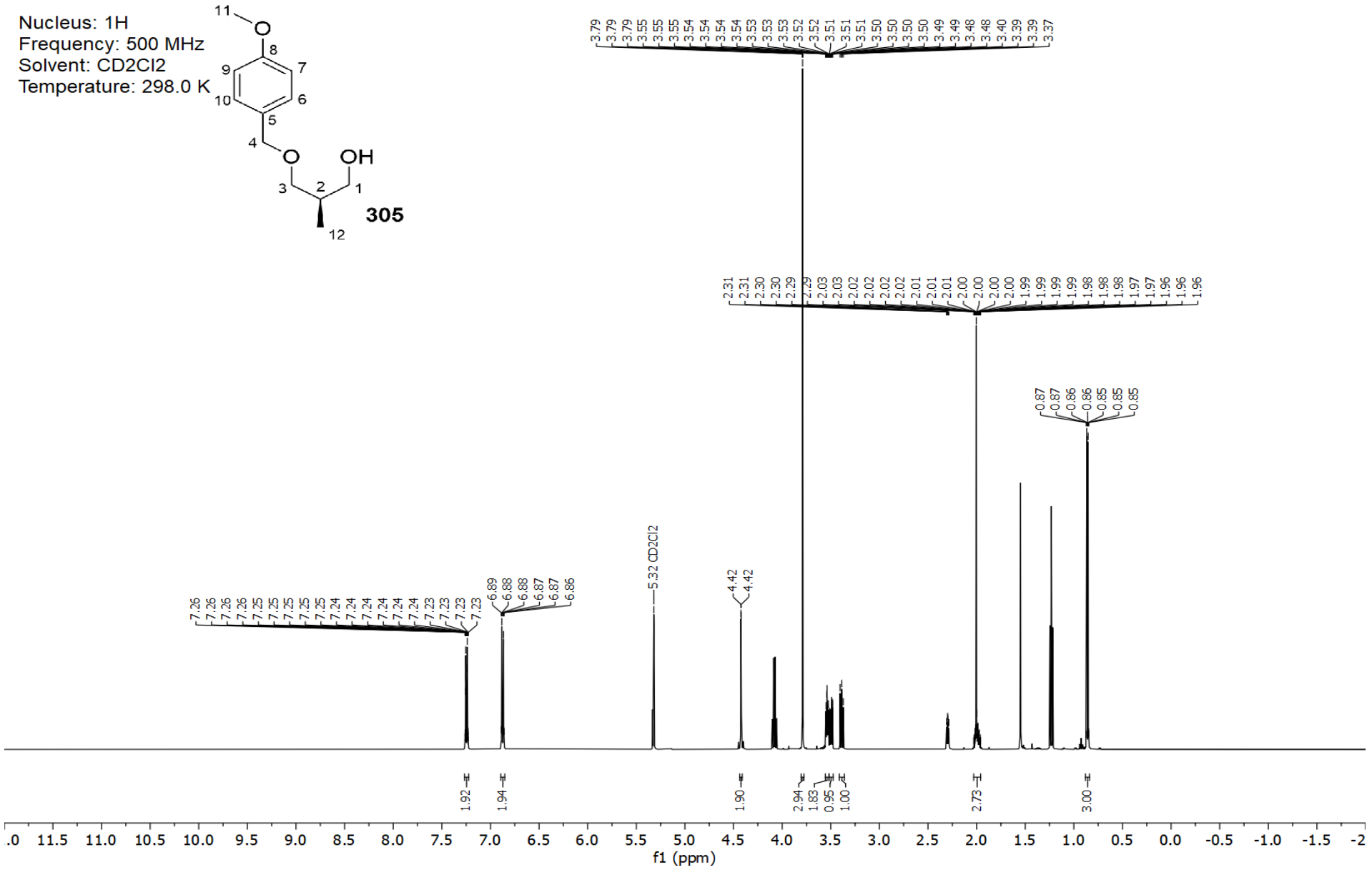
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

303



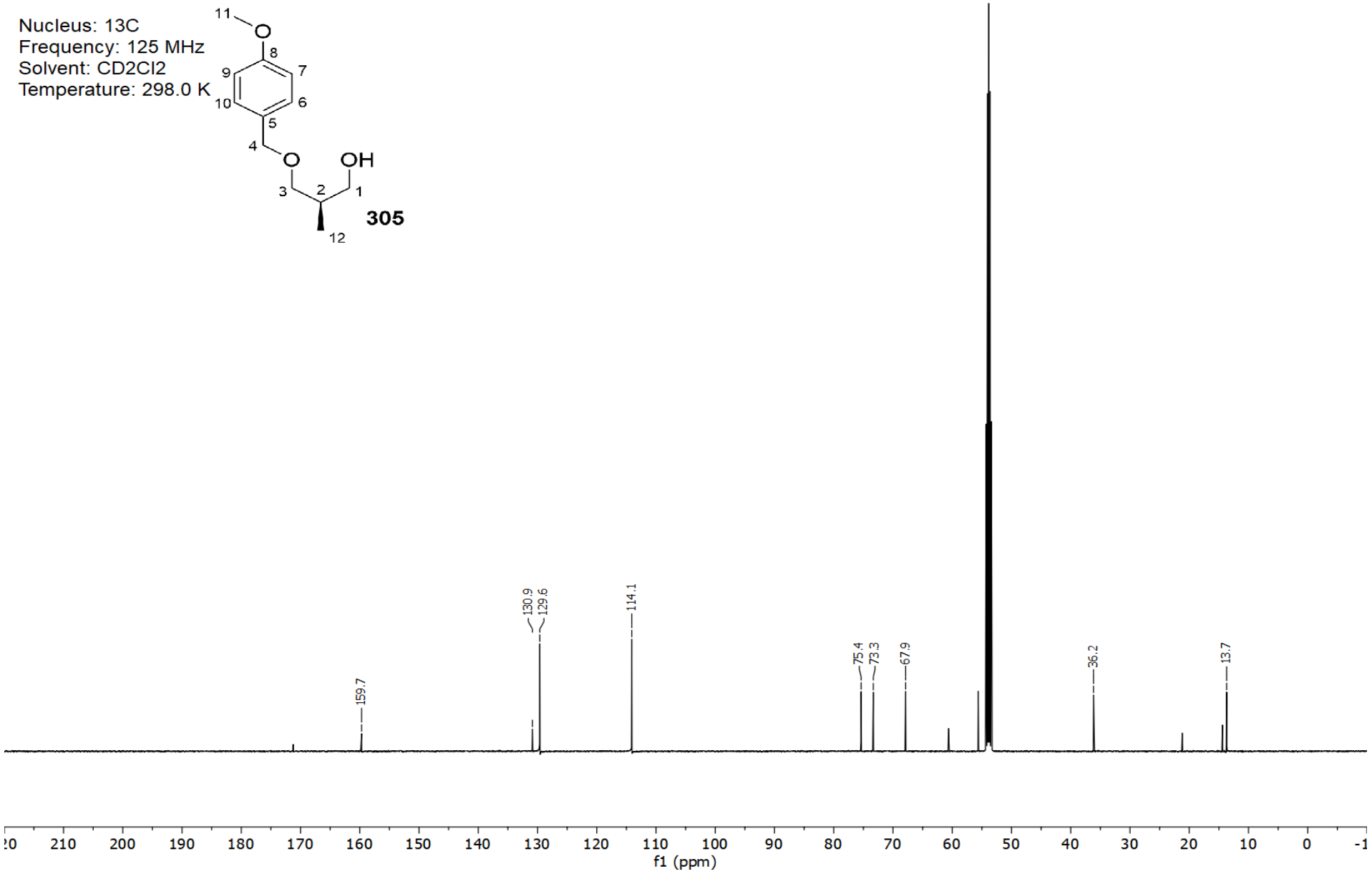

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
304
5.32 CD2Cl2
4.41
f1 (ppm)

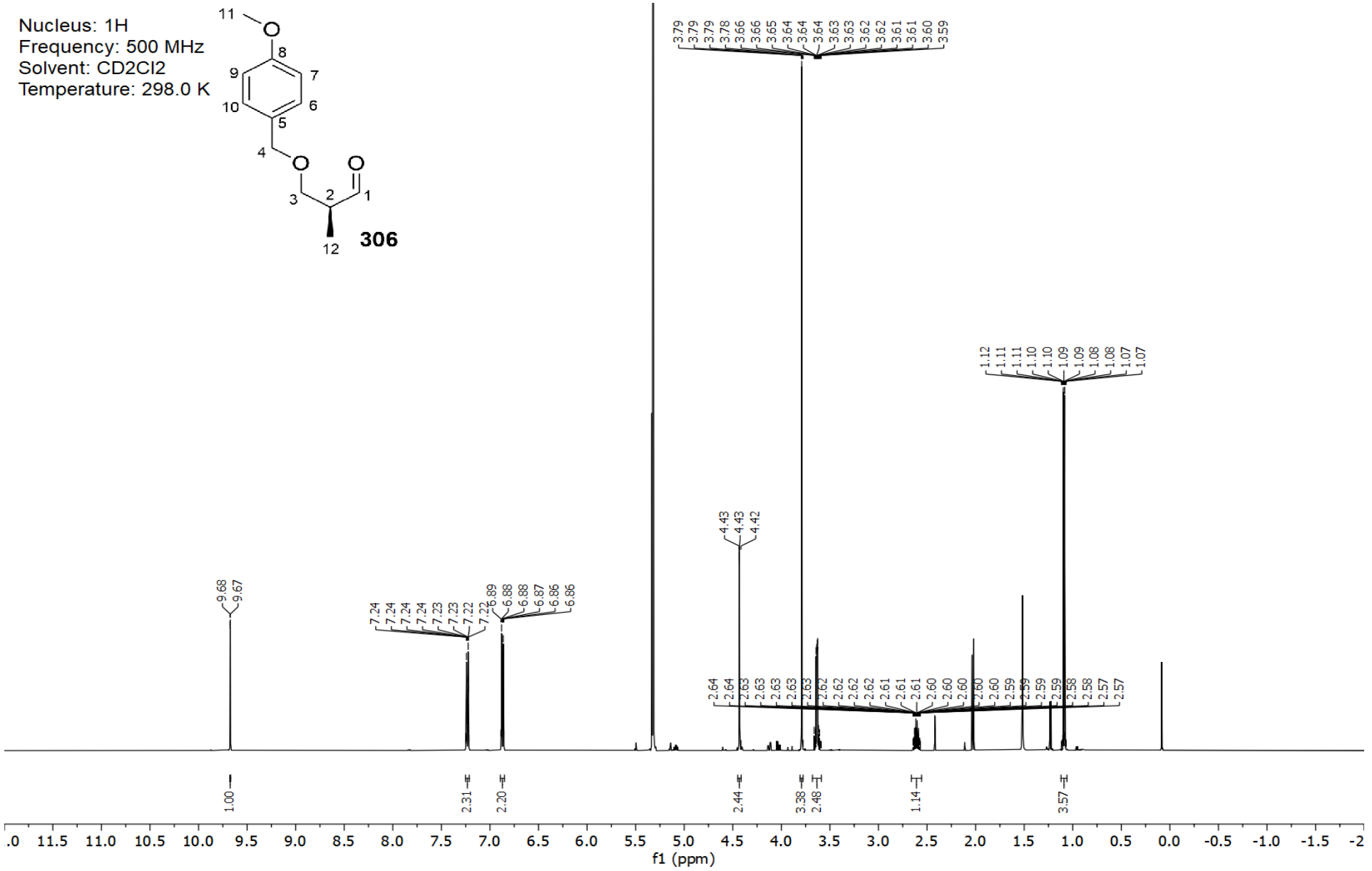

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
304
175.5
159.7
130.9
129.6
114.0
73.1
72.2
55.6
51.9
40.6
14.1
f1 (ppm)


Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
305
5.32 CD2Cl2
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

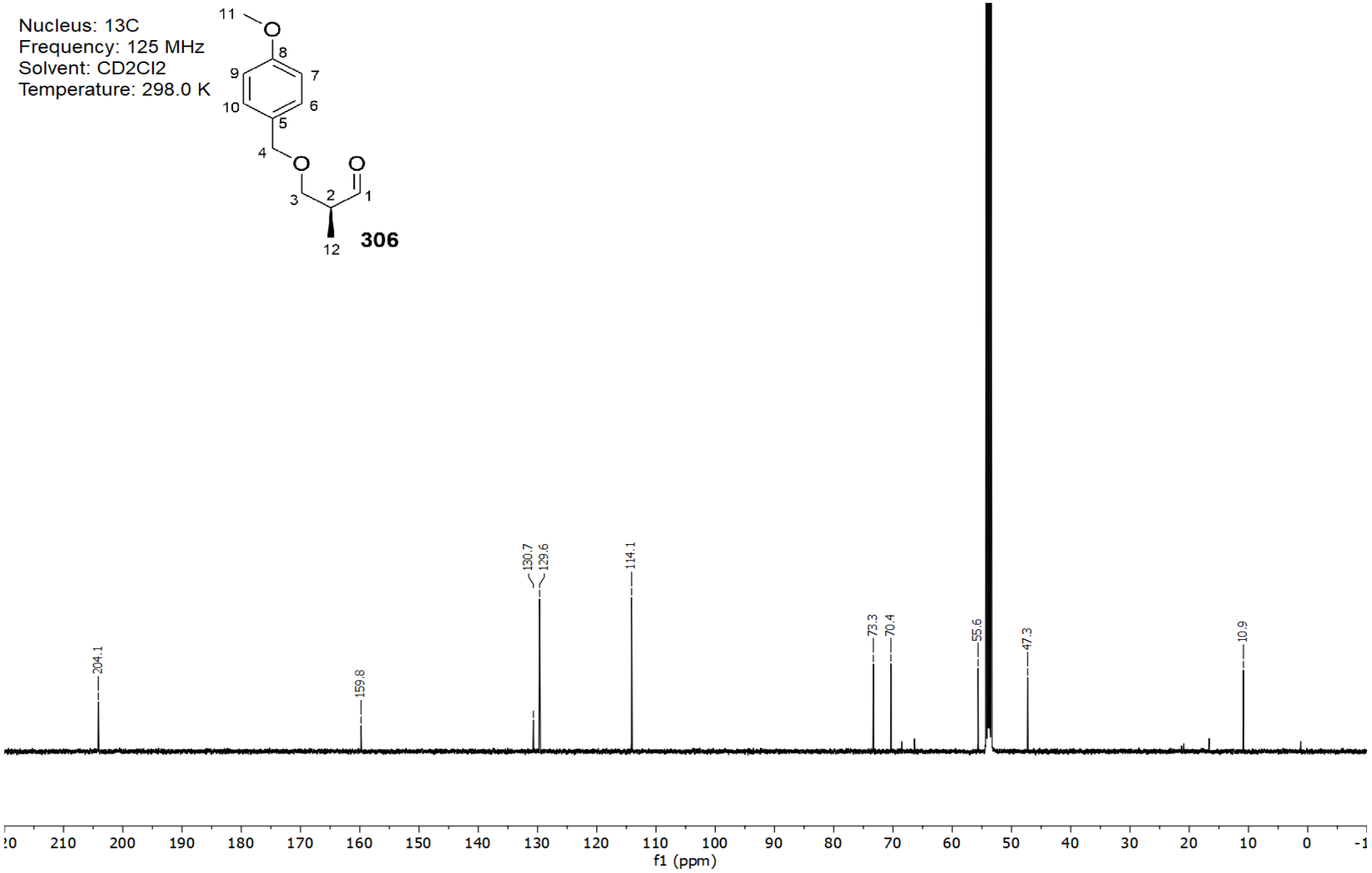
305

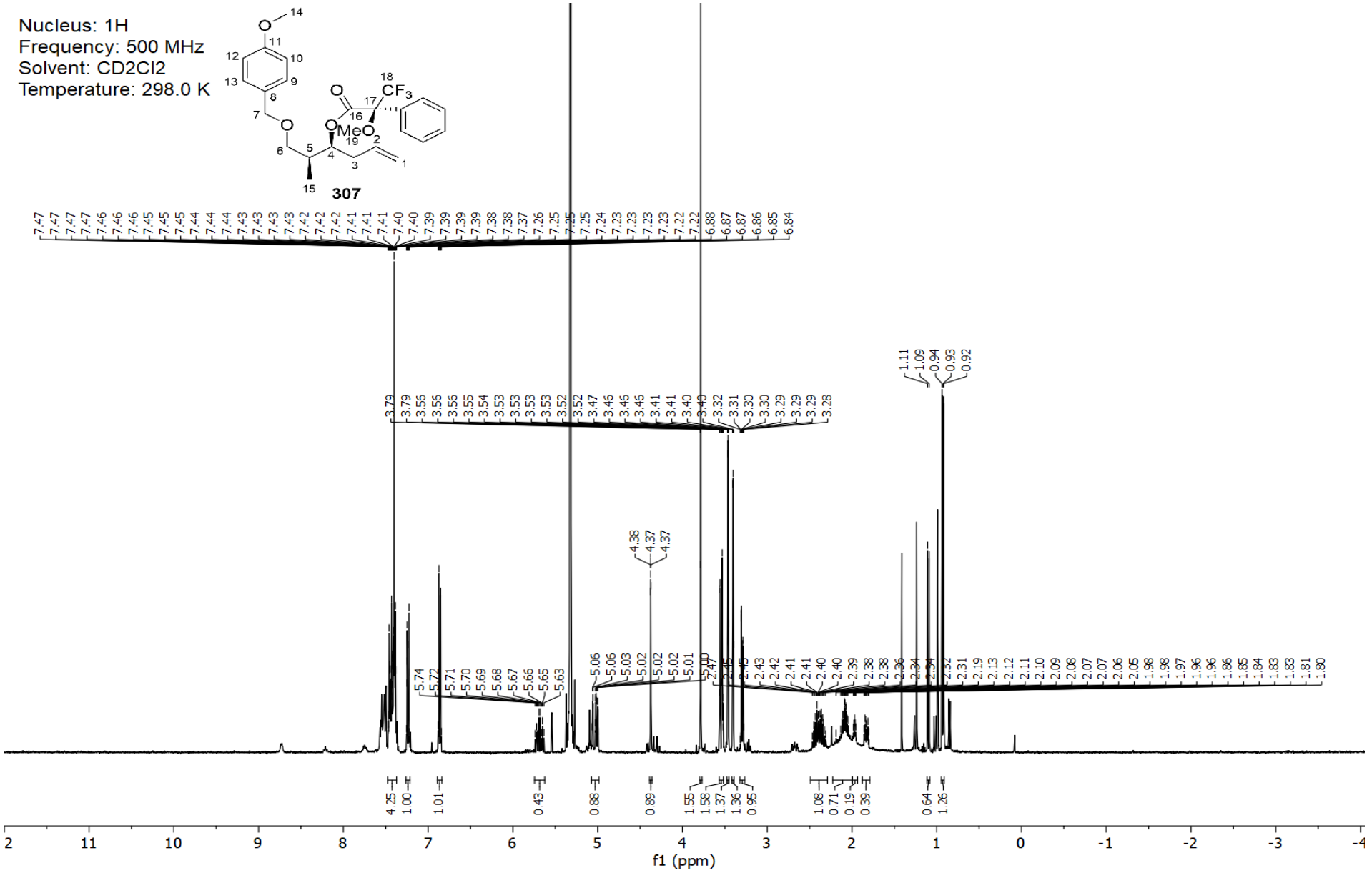



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
306
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

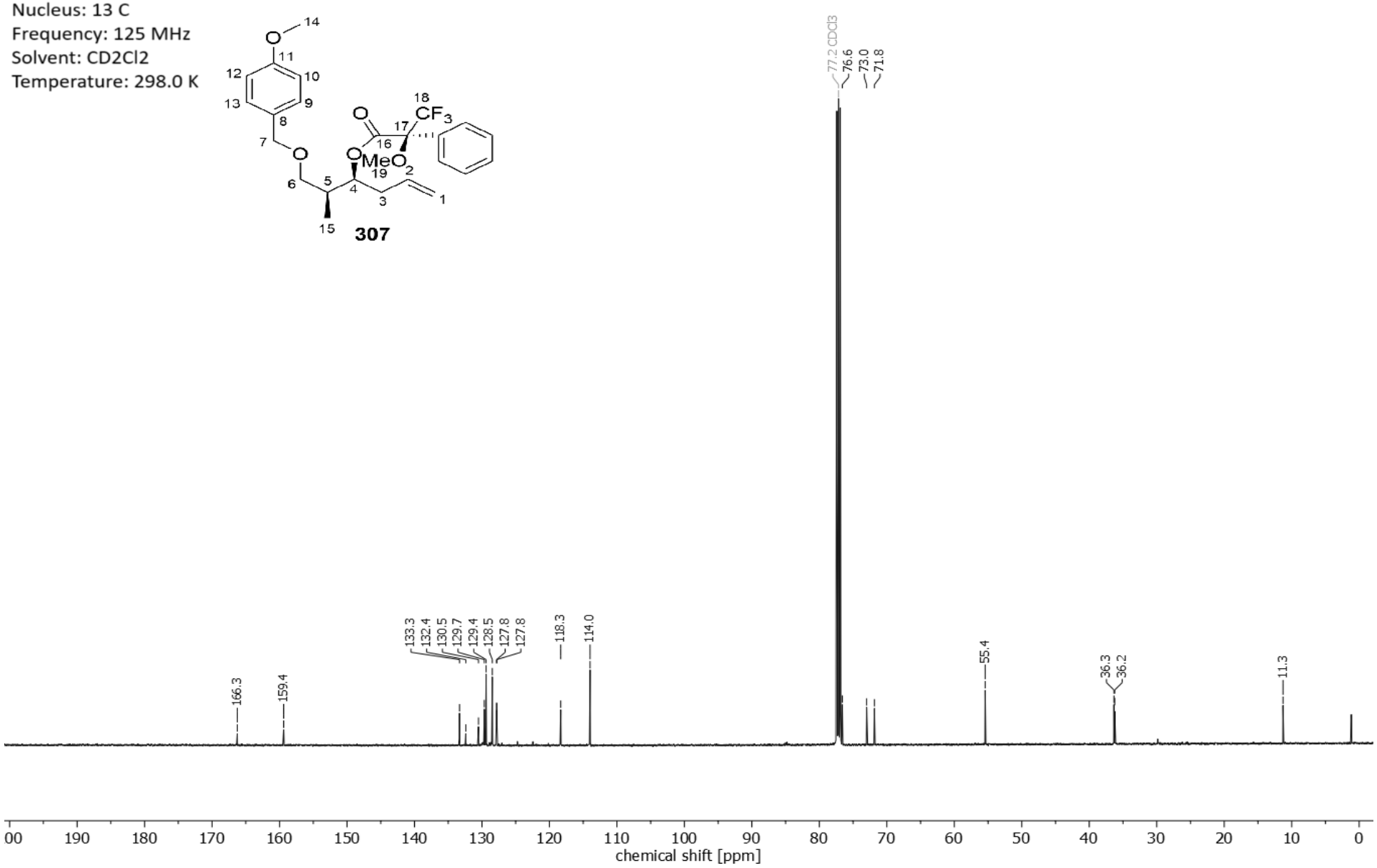
306



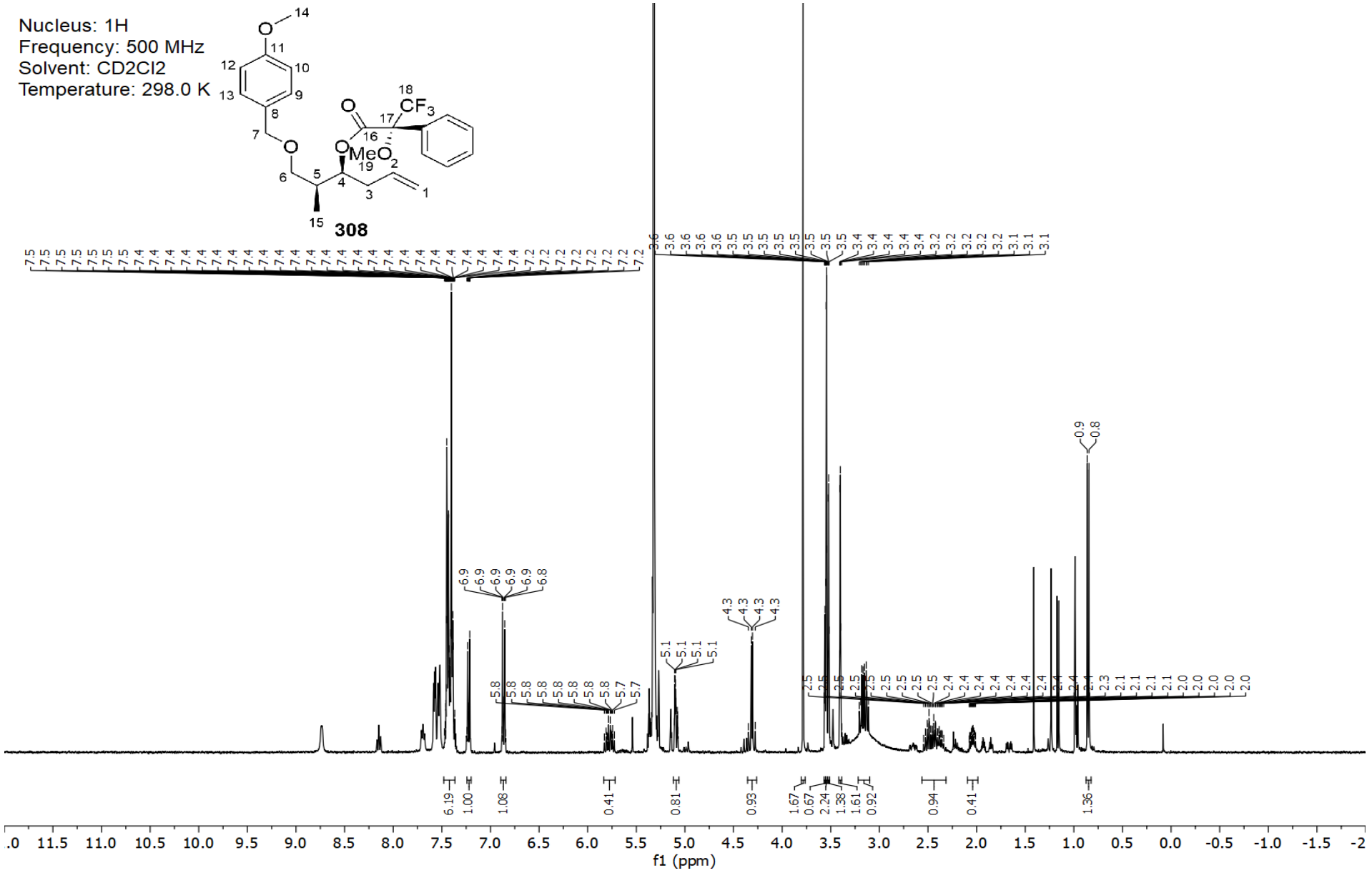

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
307
f1 (ppm)

Nucleus: 13 C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

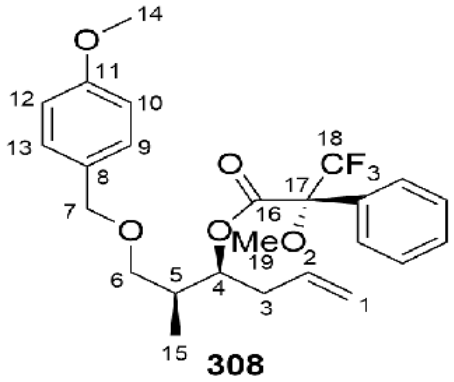
307



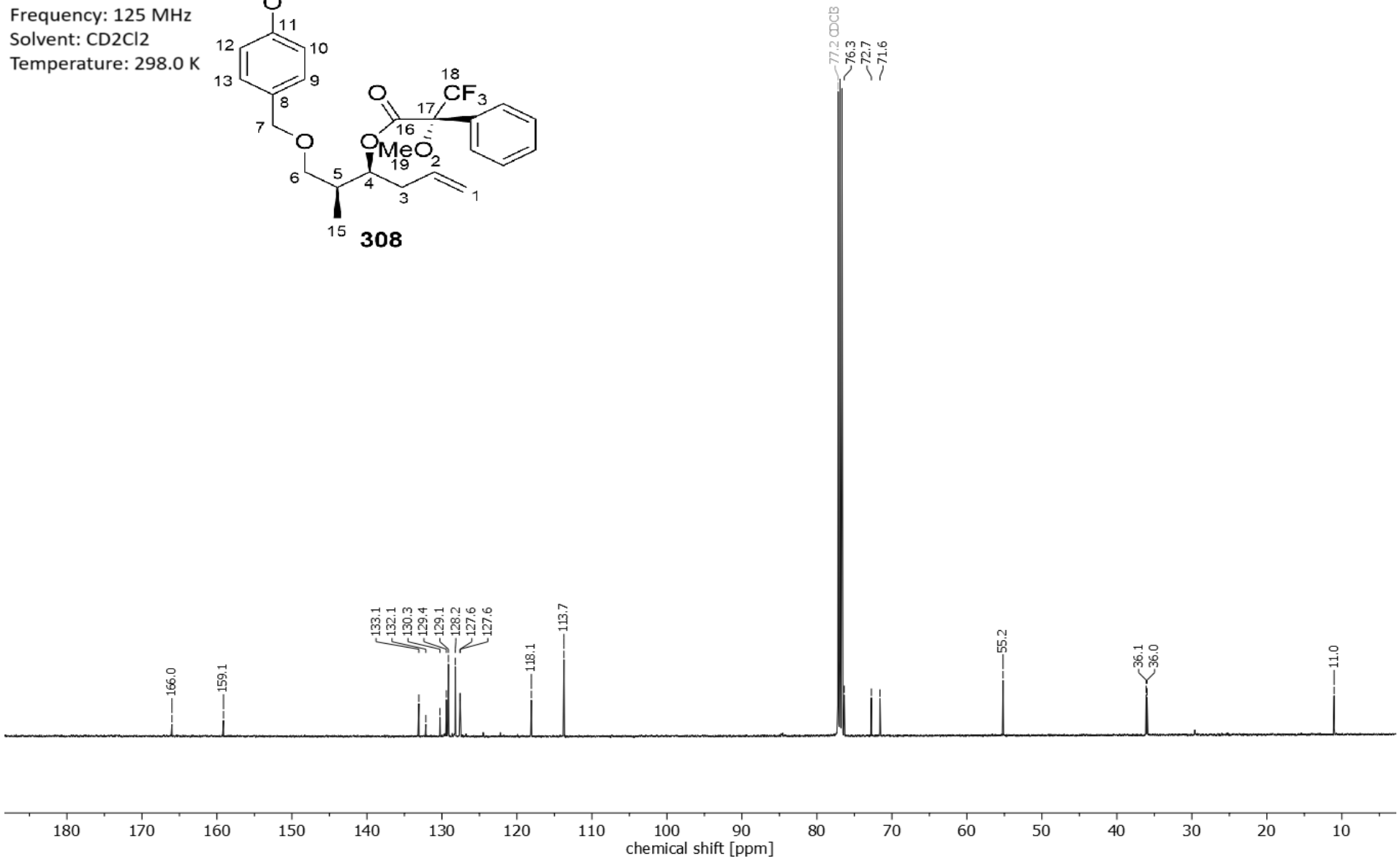
6. Appendix

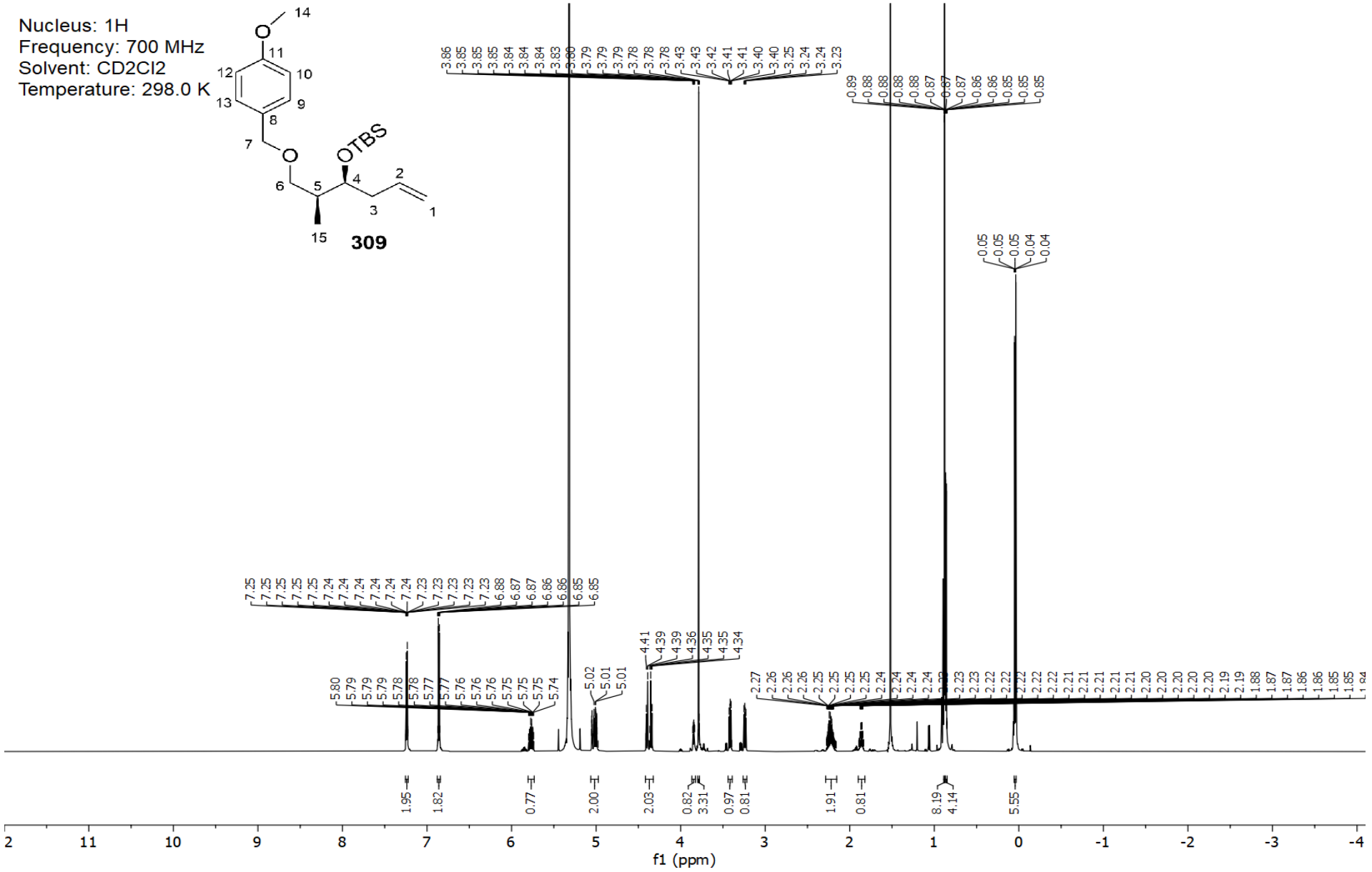

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
308
f1 (ppm)

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K



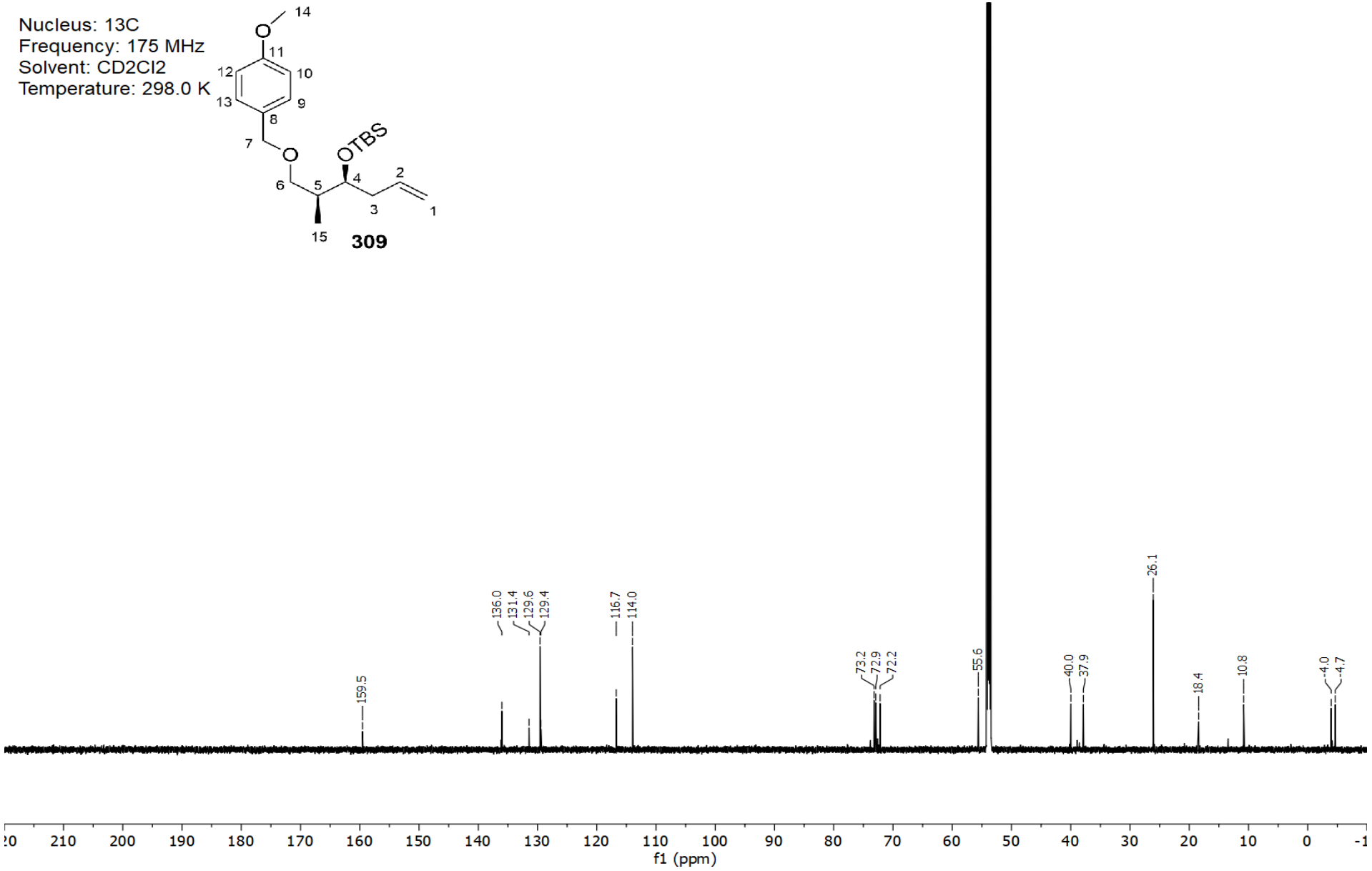
308

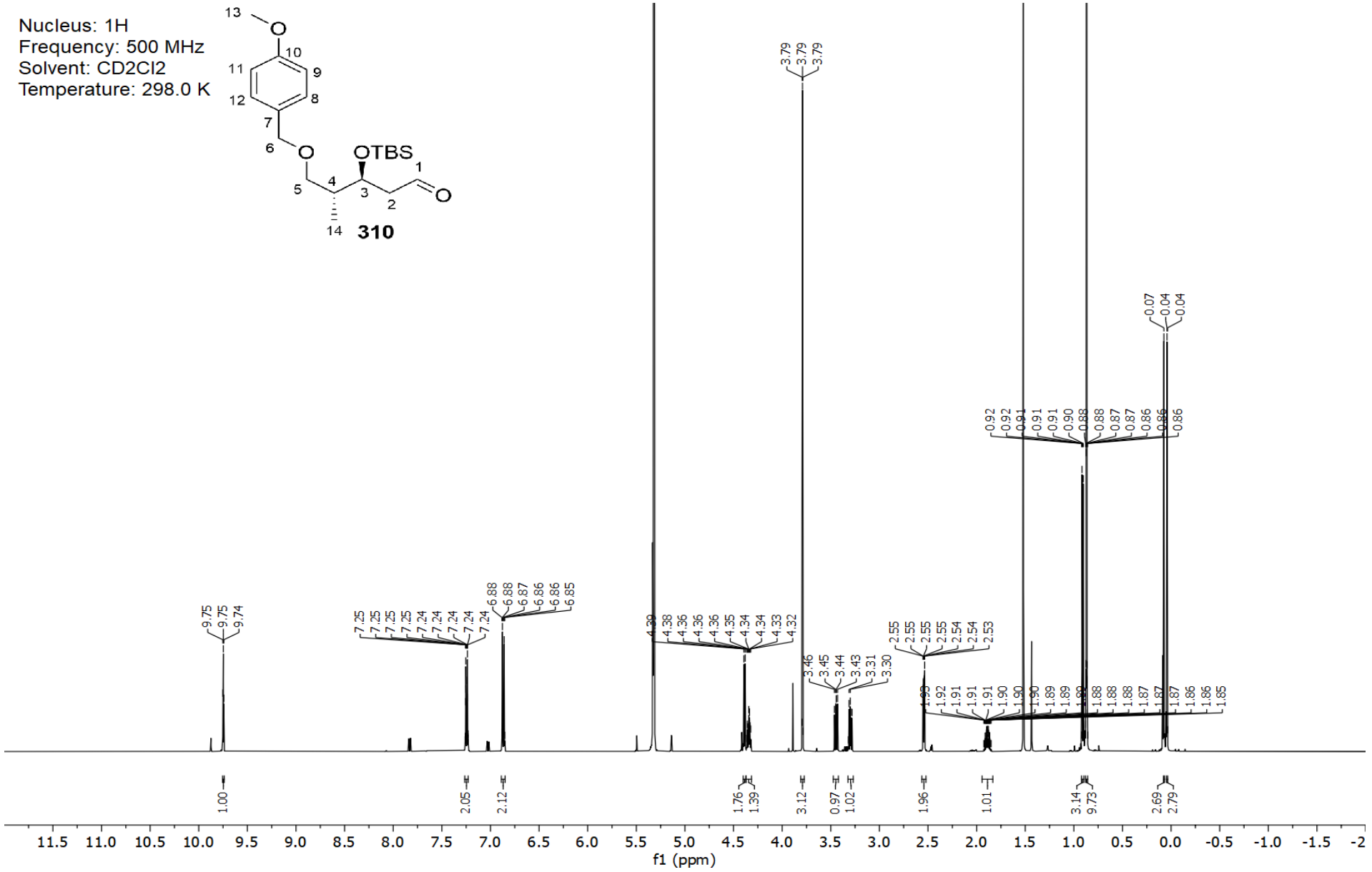


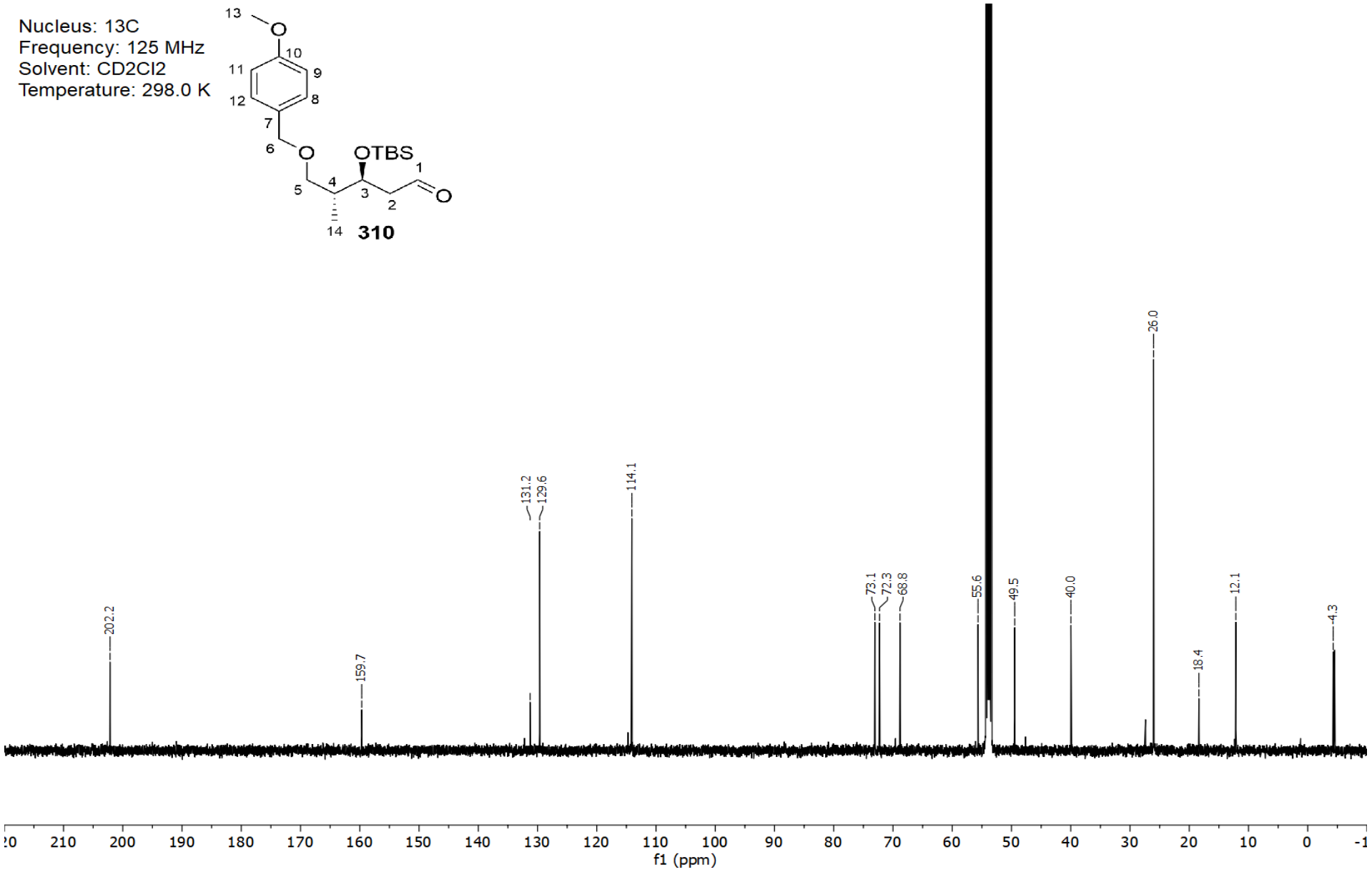

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
OTBS
309
f1 (ppm)

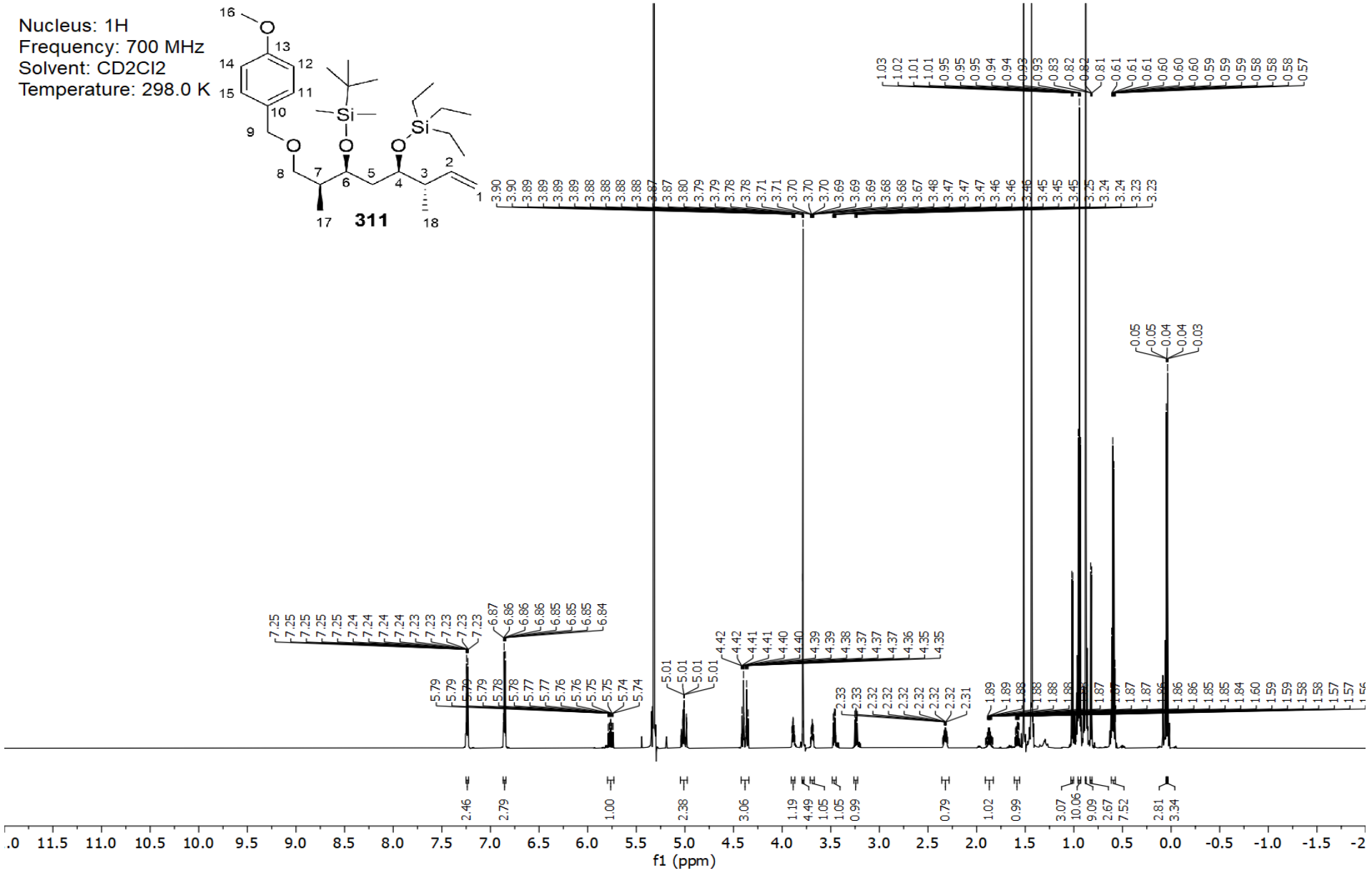
Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

309

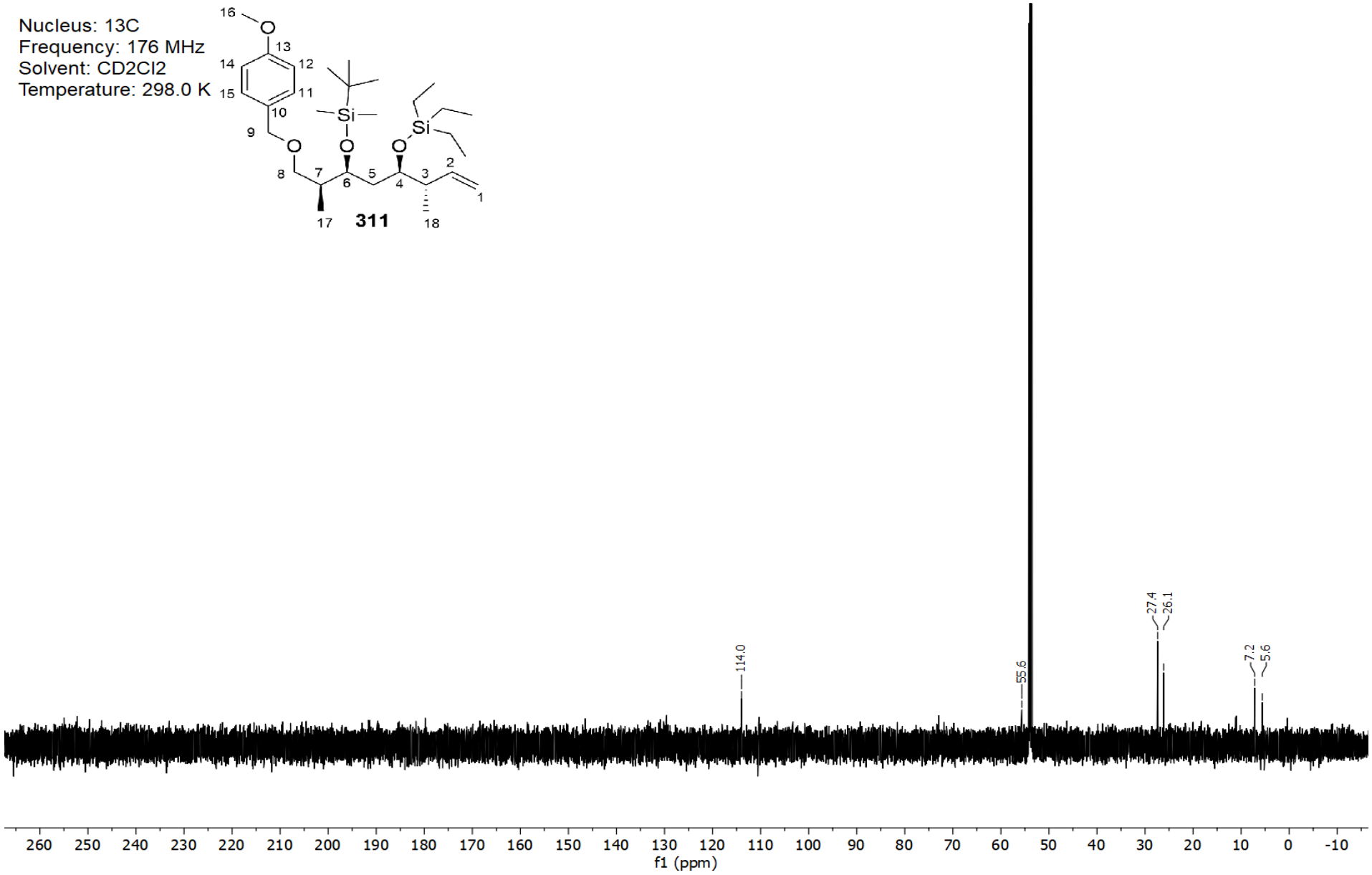



Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
OTBS
310
f1 (ppm)

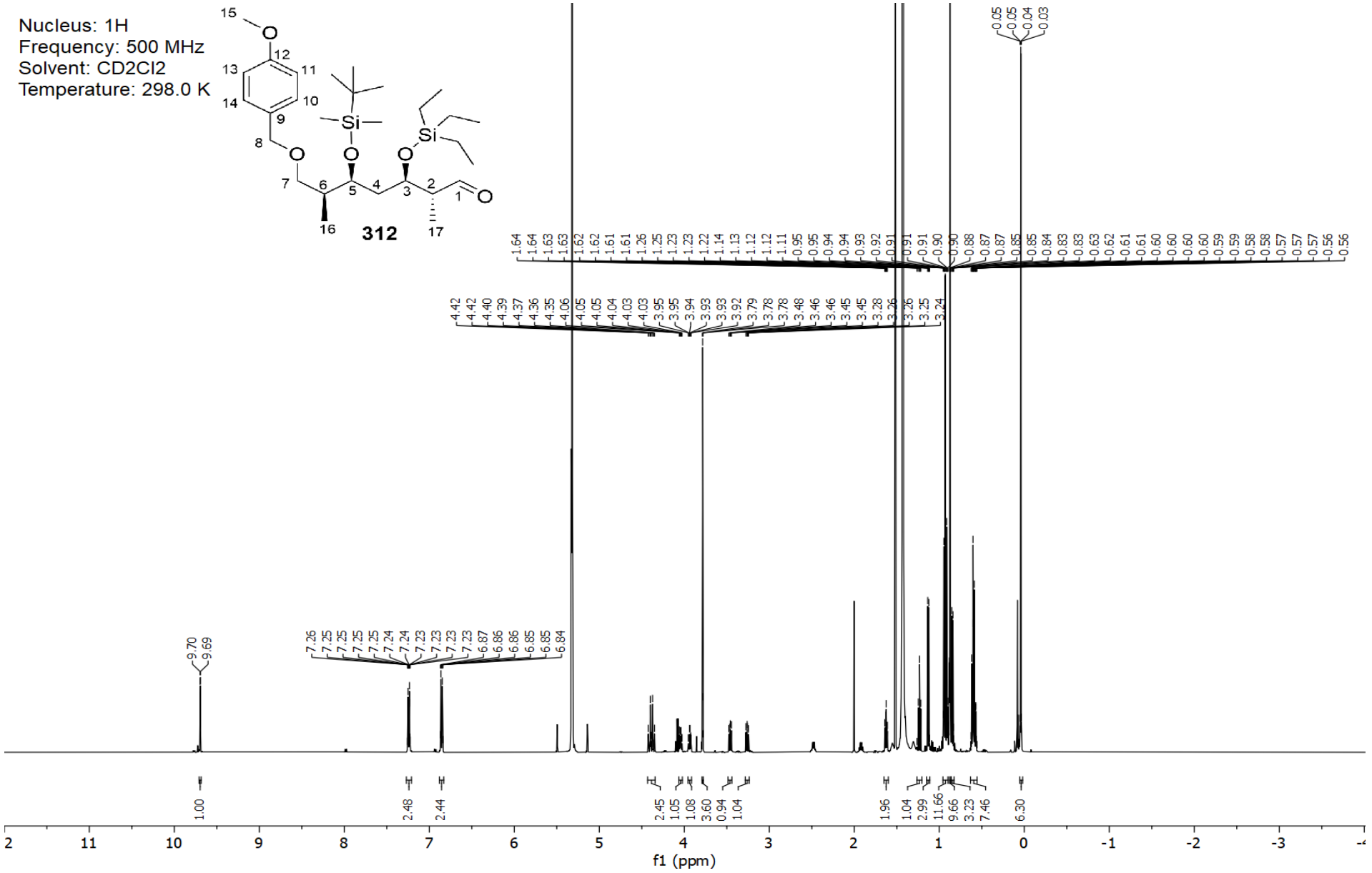

Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
OTBS
310
202.2
159.7
131.2
129.6
114.1
73.1
72.3
68.8
55.6
49.5
40.0
26.0
18.4
12.1
4.3
f1 (ppm)


Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
311
f1 (ppm)

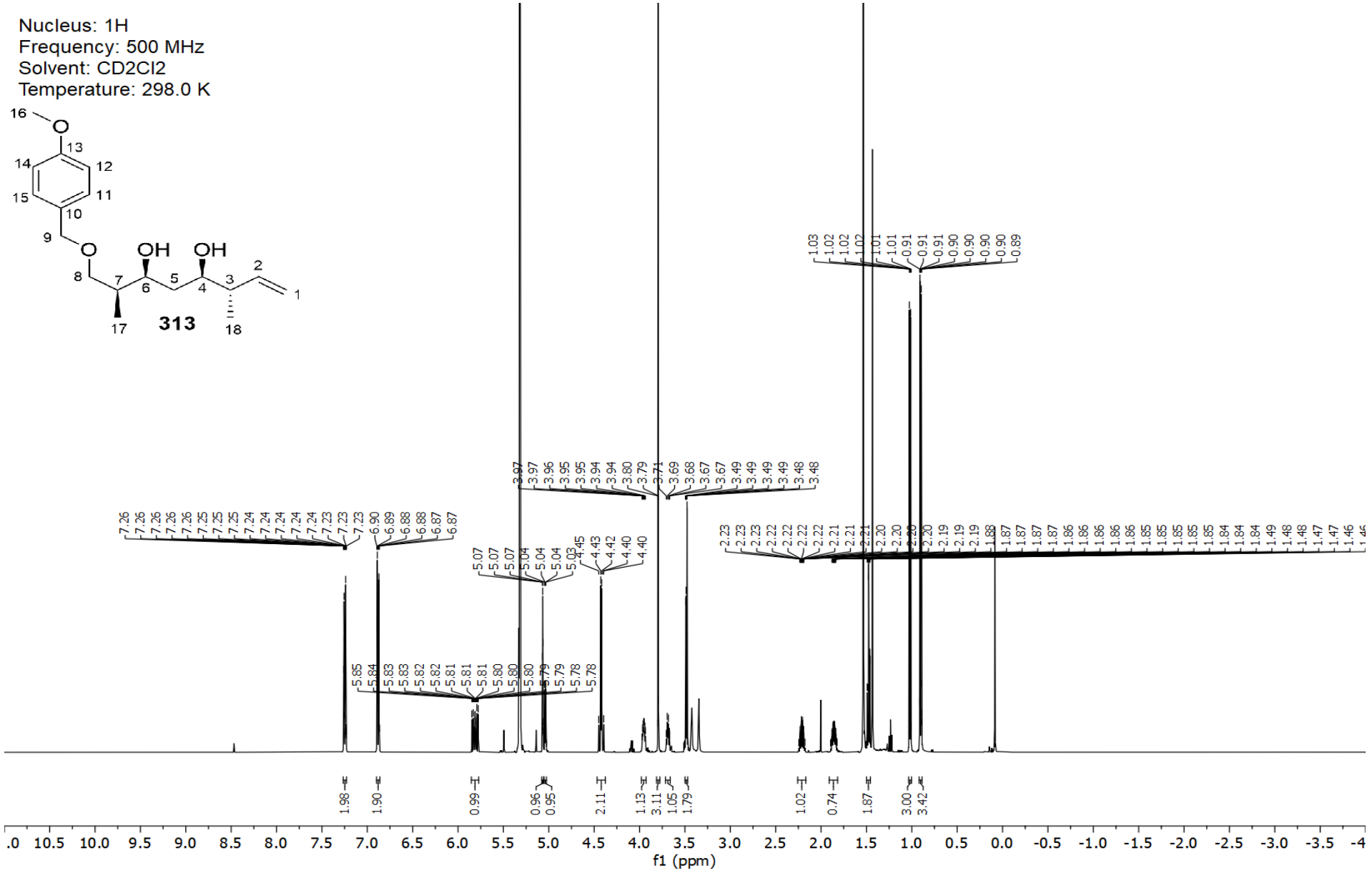
Nucleus: 13C
Frequency: 176 MHz
Solvent: CD2Cl2
Temperature: 298.0 K



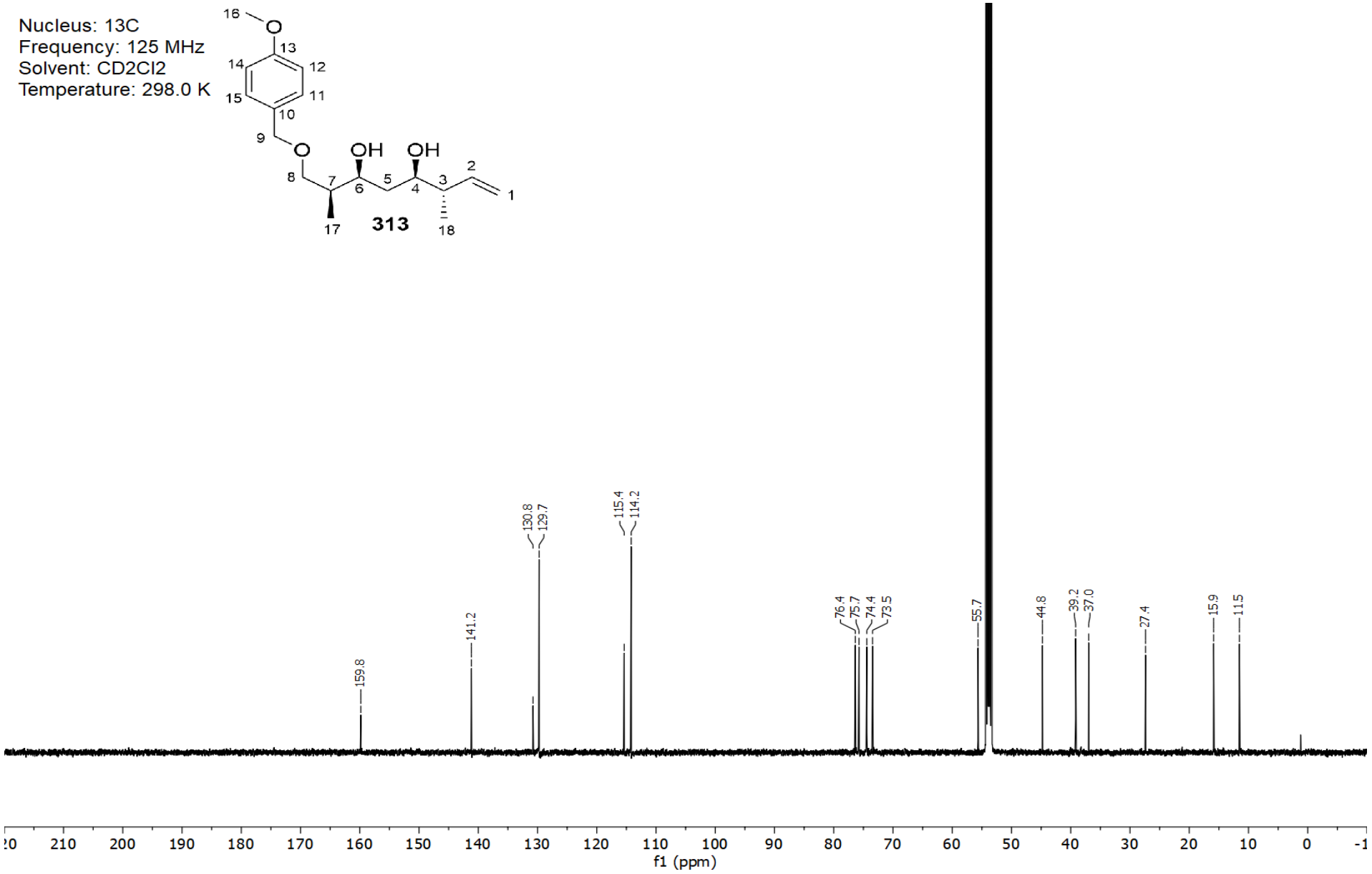
6. Appendix

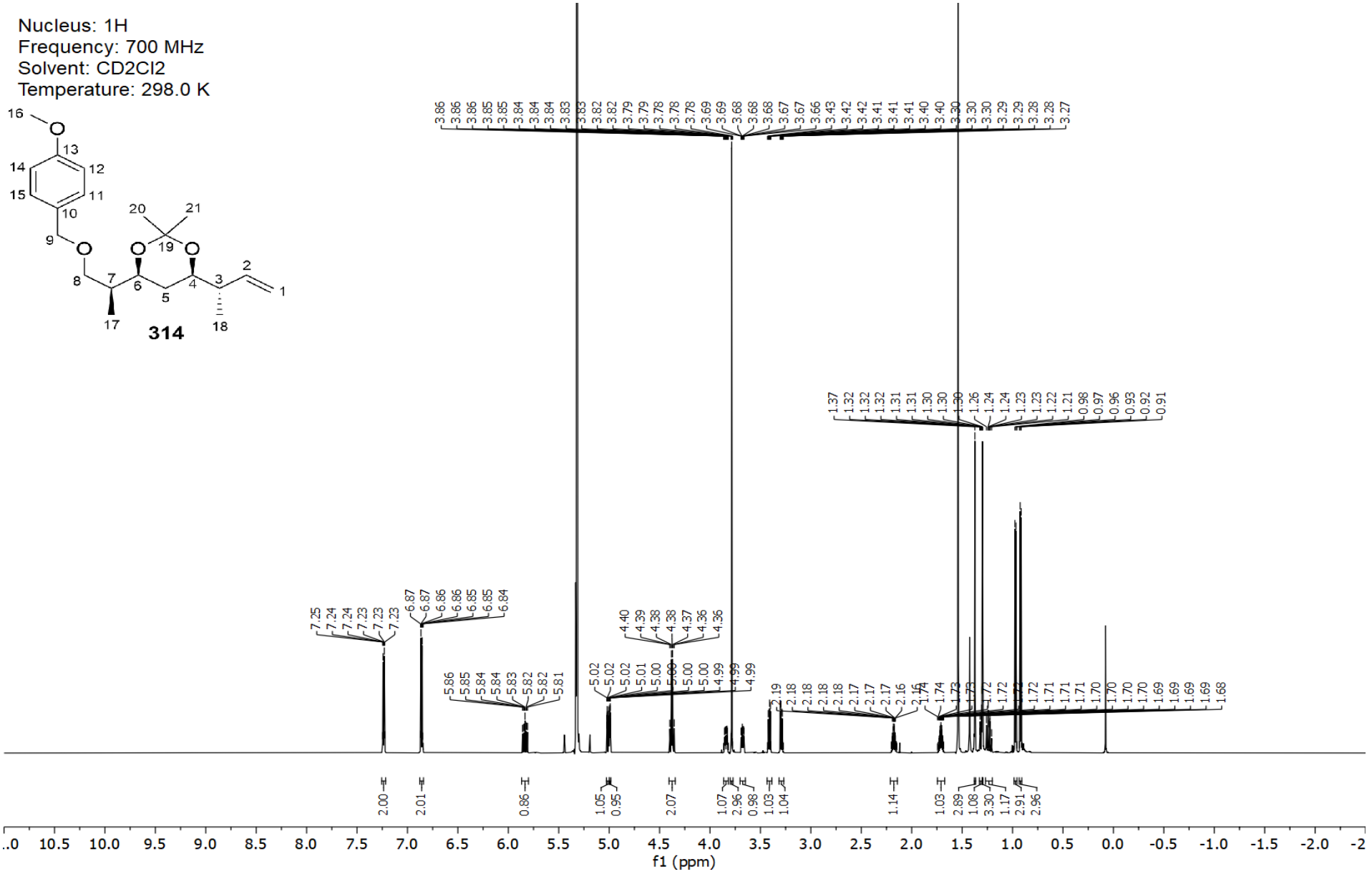

Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
312
f1 (ppm)

6. Appendix


Nucleus: 1H
Frequency: 500 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
313
f1 (ppm)

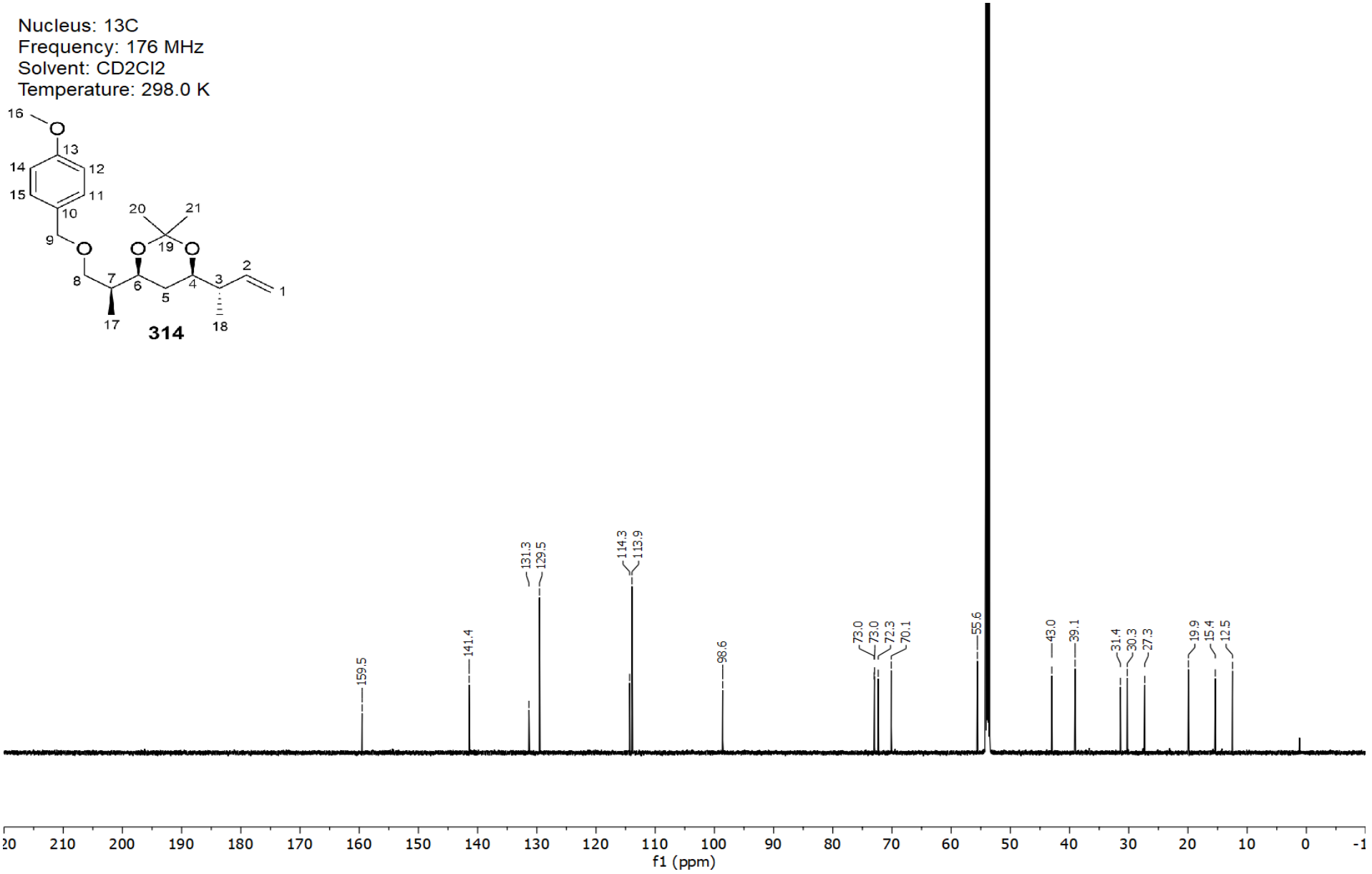
Nucleus: 13C
Frequency: 125 MHz
Solvent: CD2Cl2
Temperature: 298.0 K



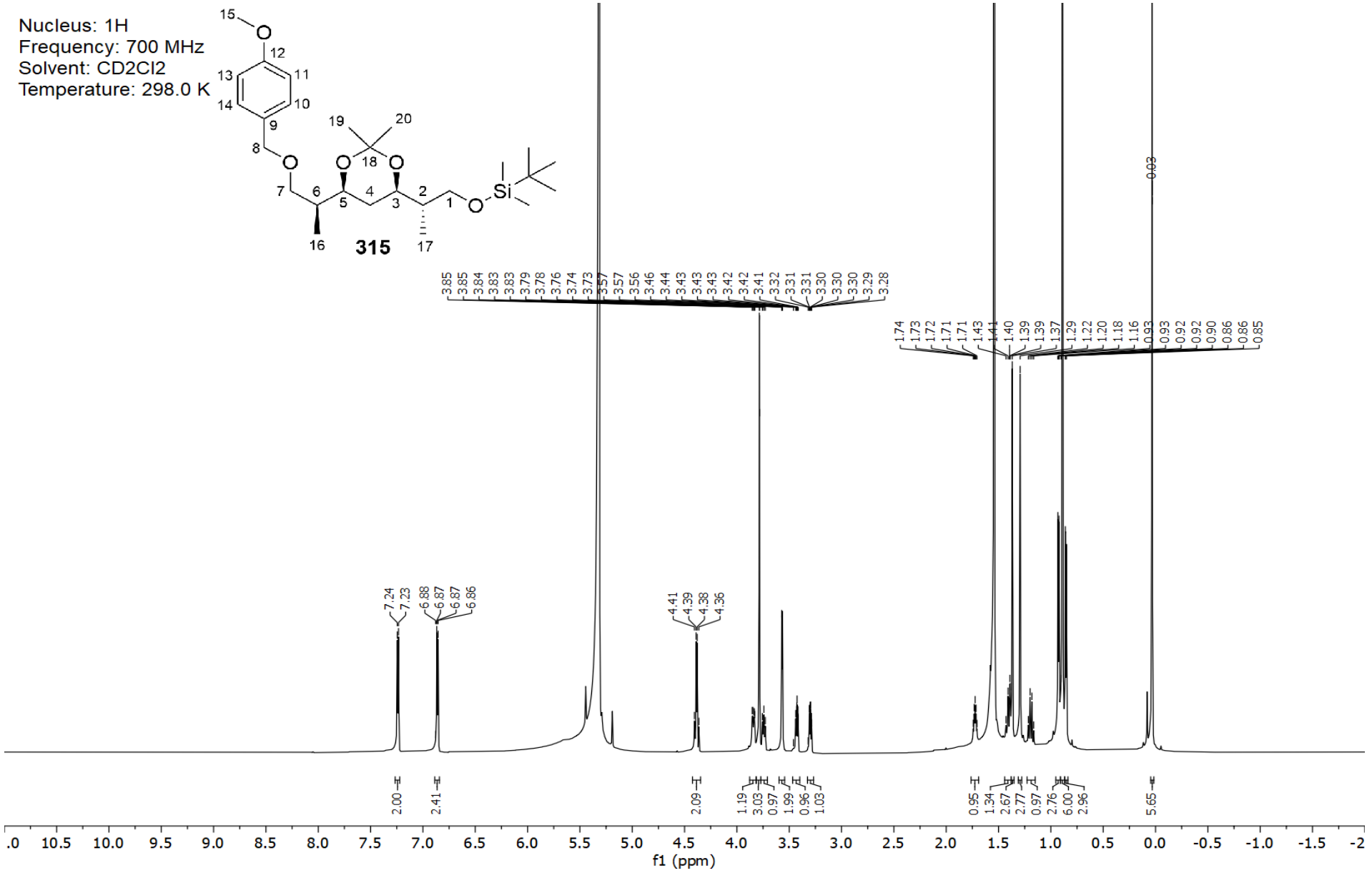

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
314
f1 (ppm)

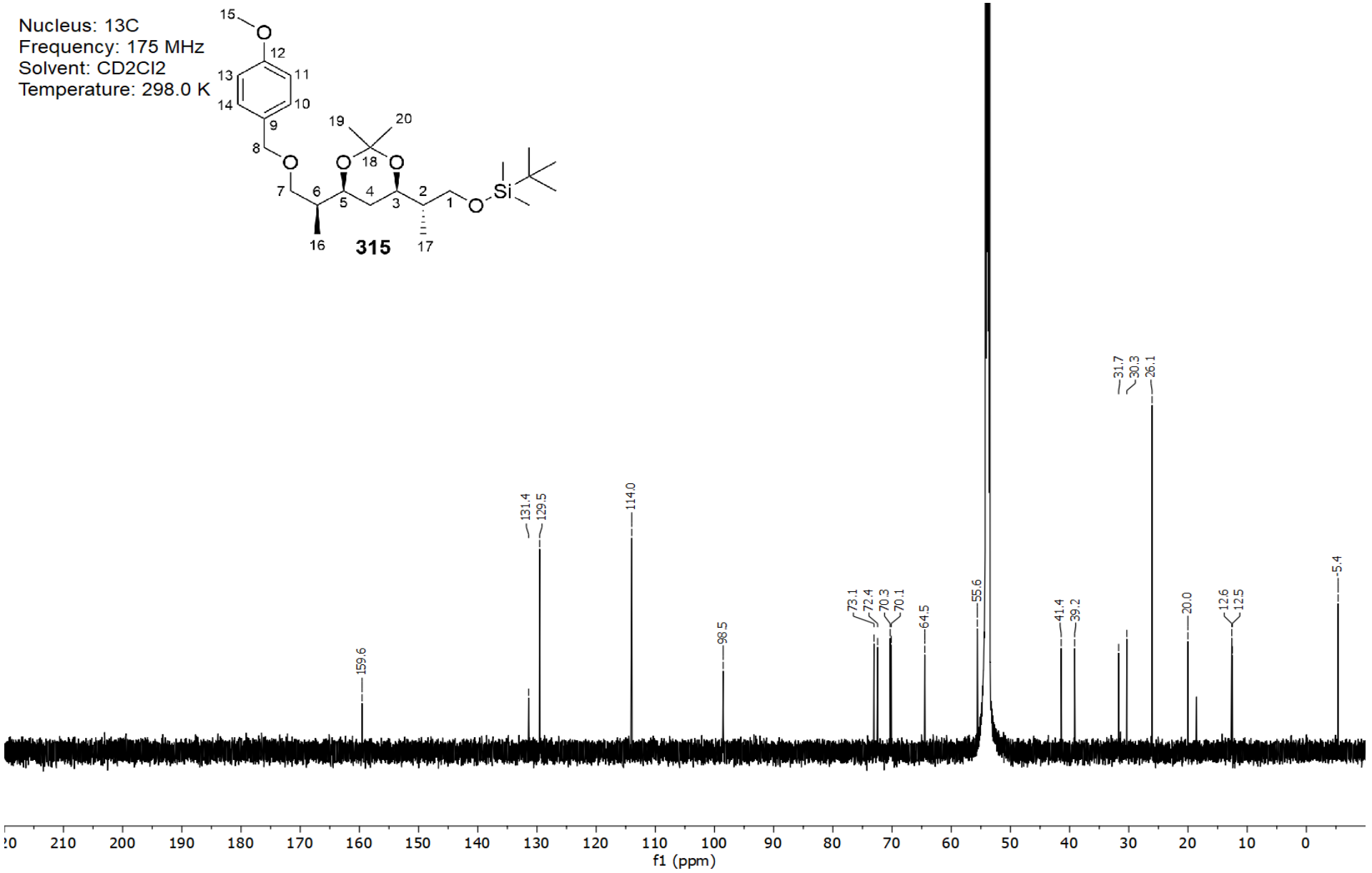
Nucleus: 13C
Frequency: 176 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

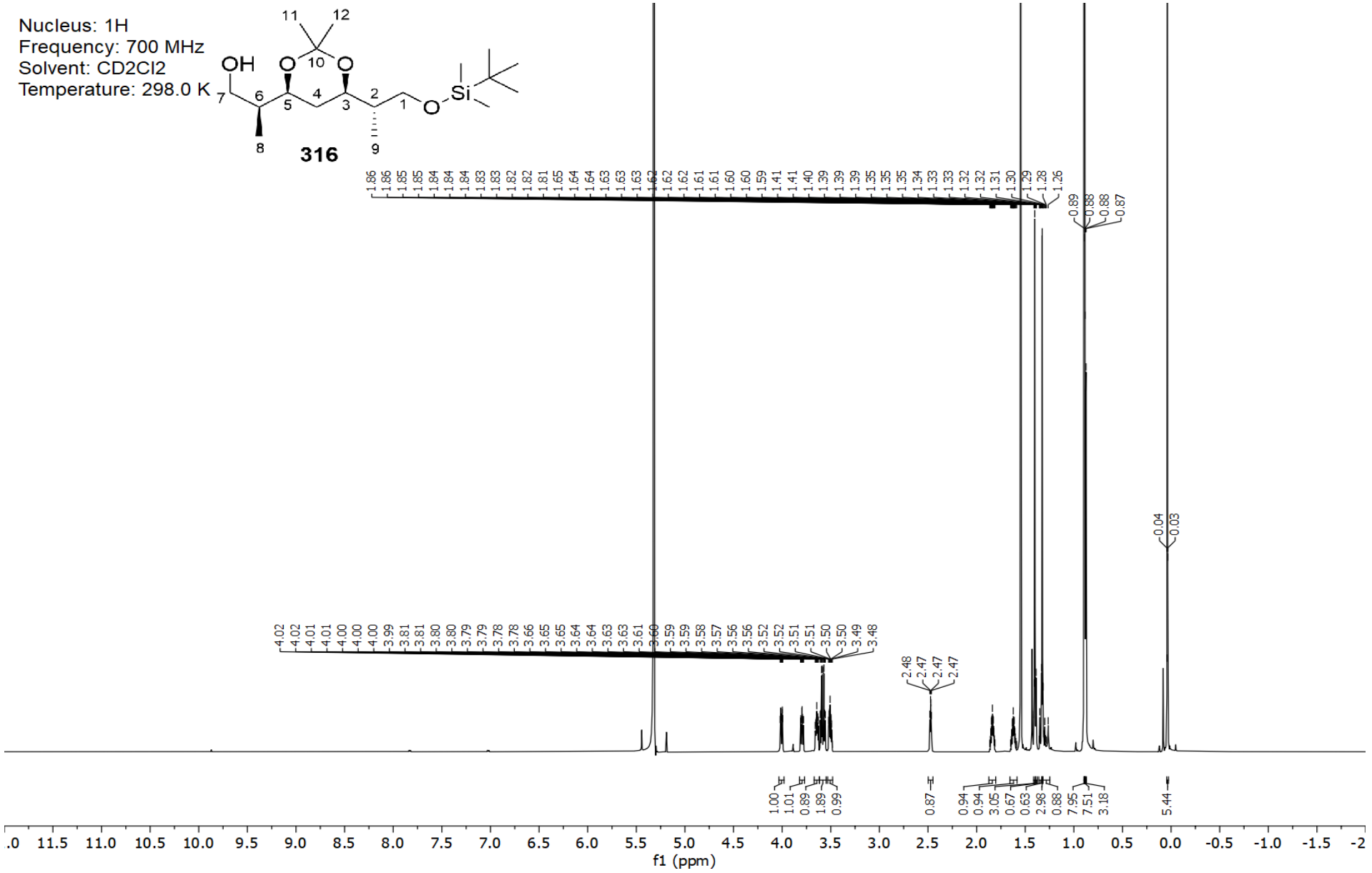
314



6. Appendix

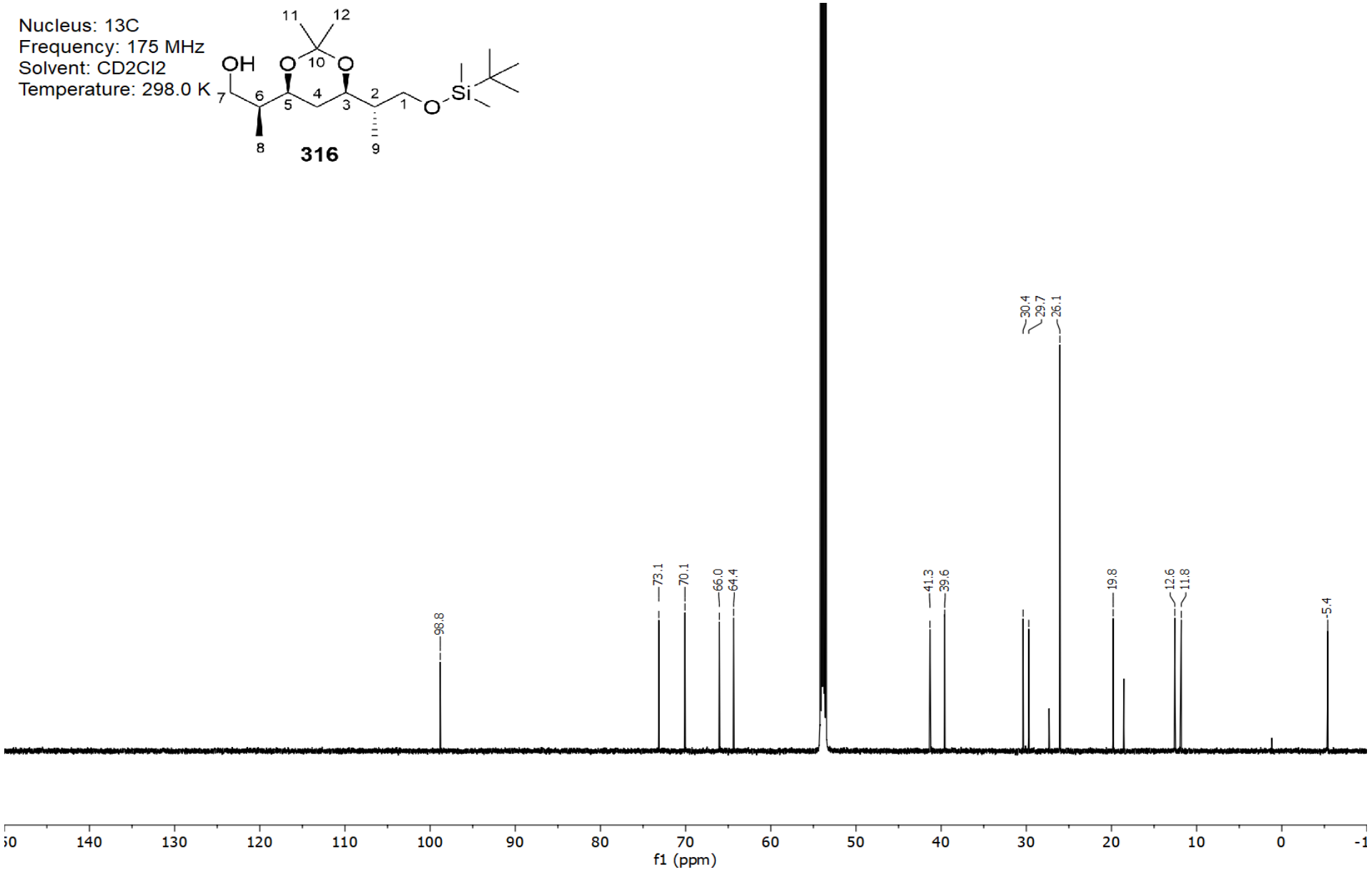

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
315
f1 (ppm)

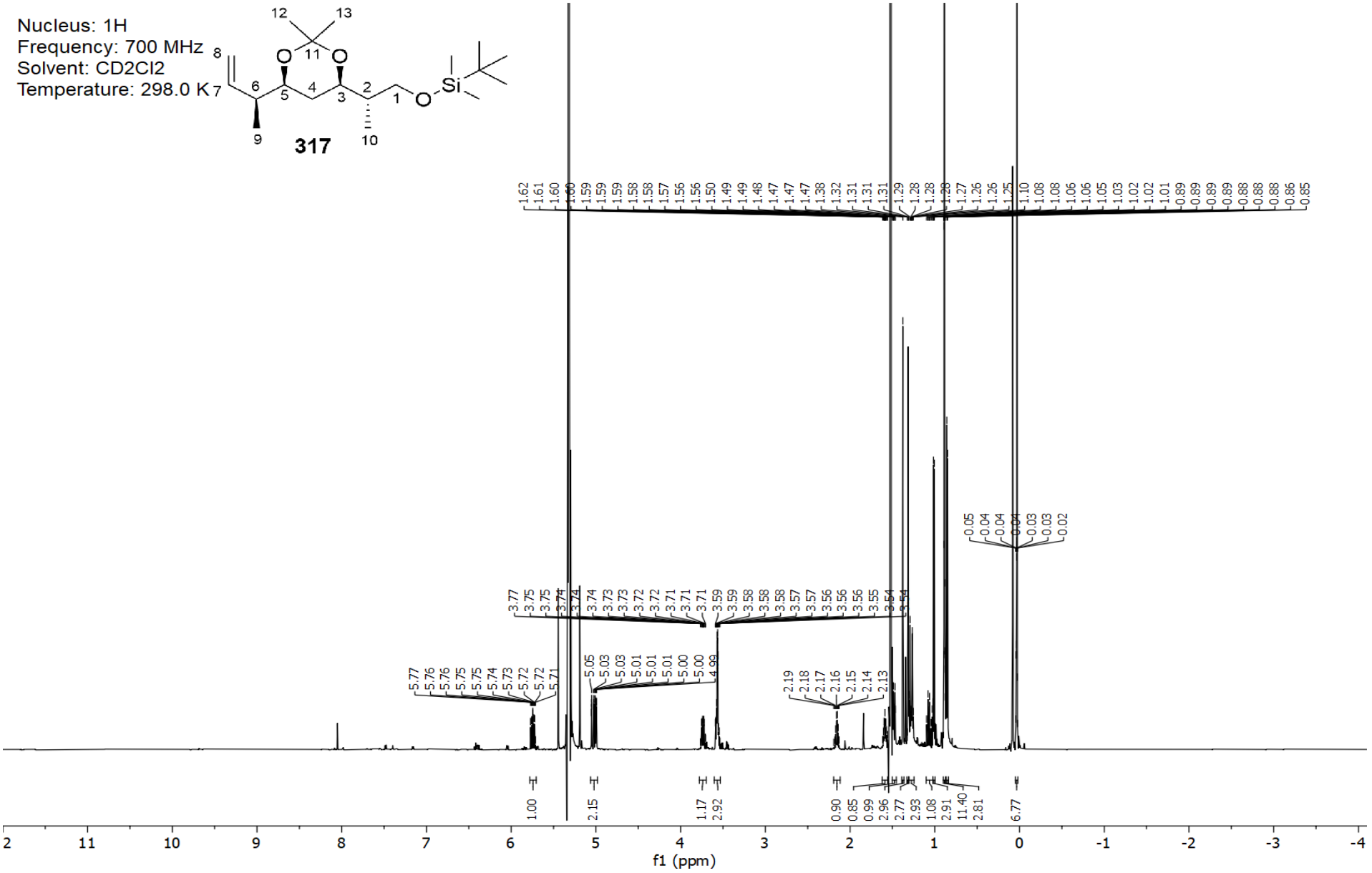

Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
315
159.6
131.4
129.5
114.0
98.5
73.1
72.4
70.3
70.1
64.5
55.6
41.4
39.2
31.7
30.3
26.1
20.0
12.6
12.5
5.4
f1 (ppm)

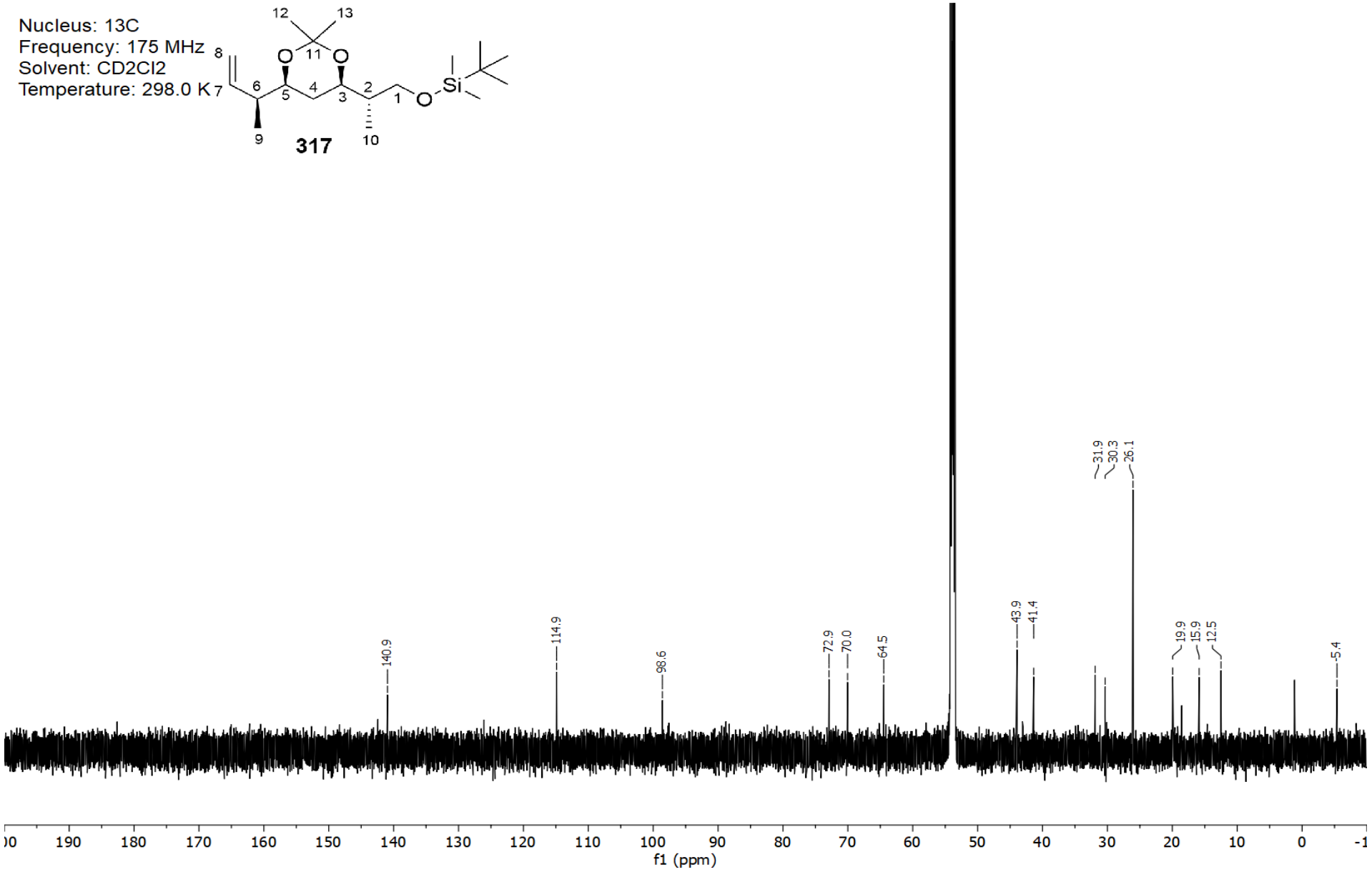

Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
316
f1 (ppm)

Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K

316




Nucleus: 1H
Frequency: 700 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
317
f1 (ppm)


Nucleus: 13C
Frequency: 175 MHz
Solvent: CD2Cl2
Temperature: 298.0 K
317
140.9
114.9
98.6
72.9
70.0
64.5
43.9
41.4
31.9
30.3
26.1
19.9
15.9
12.5
-5.4
f1 (ppm)