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New Synthetic Transformations Utilizing Silyloxyallyl Cations and Epoxonium Ions as Reactive Intermediates

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NEW SYNTHETIC TRANSFORMATIONS UTILIZING
SILYLOXYALLYL CATIONS AND EPOXONIUM IONS AS
REACTIVE INTERMEDIATES

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Chemistry

by
Alexander Houston Cleveland
B.S., Tennessee Technological University, 2015
August 2020

This work is dedicated to my Grandparents;

Jack and Della Houston

Fred and Geneva Cleveland

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List of Abbreviations

$[\alpha]^{20}_D$	absolute optical rotation
$^{\circ}\text{C}$	degrees Celsius
α	alpha
β	beta
Δ	chemical shift
γ	gamma
μg	microgram
μL	microliter
^1H	proton NMR
^{13}C	carbon NMR
\AA	angstrom
Ac	acetate
b	broad
BDE	bond dissociation energy
$\text{BF}_3 \cdot \text{OEt}_2$	boron trifluoride diethyl etherate
Bn	benzyl
Boc	tert-butoxycarbonyl
BTC	<i>bis</i> (trichloromethyl) carbonate
Bu	butyl
Bs	besylate
CDCl_3	deuterated chloroform

cm ⁻¹	per centimeter
CO	carbon monoxide
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DCE	dichloroethane
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
equiv	equivalent
er	enantiomeric ratio

ESI	electrospray ionization
Et	ethyl
f	wavenumber
FT-IR	Fourier-transform infrared
g	gram
GC-MS	gas chromatography mass spectrometry
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
$h\nu$	light
Hz	Hertz
IC ₅₀	half maximal inhibitory concentration
<i>i</i> Pr	isopropyl
<i>i</i> PrOH	isopropanol
J	coupling constant
JBCA	J -based Configurational Approach
kg	kilogram
LA	Lewis acid
LDA	lithium diisopropylamide
LiAlH ₄	lithium aluminum hydride
LUMO	lowest occupied molecular orbital
m	multiplet
M ⁺	molecular ion

MBSA	methoxybenzene sulfonate
<i>m</i> CPBA	meta-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
mL	milliliter
mM	millimolar
mmol	millimol
Ms	mesyl
MS	molecular sieves
<i>m/z</i>	mass-to-charge ratio
NaOMe	sodium methoxide
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMQPF ₆	<i>N</i> -methylquinolinium hexafluorophosphate
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nuc	nucleophile
<i>p</i> Tol	para-tolyl
<i>p</i> TsOH	para-toluenesulfonic acid

Ph	phenyl
Ph ₃ PO	triphenylphosphine oxide
PMB	para-methoxybenzyl
ppm	parts per million
PPTS	pyridinium para-toluenesulfonate
Py	pyridine
Py ₂ •H ₂ SO ₄	dipyridinium sulfate
Py•MBSA	pyridinium para-methoxybenzene sulfonate
Py•TfOH	pyridinium triflate
Py•TsOH	pyridinium para-toluenesulfonate
R _f	retention factor
r.r.	regiometric ratio
s	singlet
S _N 2	bimolecular nucleophilic substitution
S _N 1	unimolecular nucleophilic substitution
t	triplet
TBAF	tetra-N-butylammonium fluoride
TBDPS	tert-butyldiphenyl silyl
TBS	tert-butyldimethylsilyl
TES	triethylsilyl
TMS	trimethylsilyl
<i>t</i> Bu	tert-butyl
TEA	triethylamine

TEMPO2,2,6,6-tetramethylpiperidine-1-oxyl
Tftriflate
TFAtrifluoroacetic acid
THFtetrahydrofuran
TLCthin layer chromatography
Tstosyl
UVultraviolet

Abstract

The development of new chemical transformations is of paramount importance in organic chemistry. In fact the study and creation of new reactions often uncovers new chemical reactivities and creates a new area of chemistry. The purpose of this dissertation is to present the development of new synthetic reactions that were uncovered through previous discoveries. Additionally the underlying theme of this work relies on the intermediacy of cationic reactive intermediates such as silyloxyallyl cations and epoxonium ions. Chapters 1 and 2 present the reactivity of novel silyloxyallyl cations. These cationic species are generated via the mild ionization of α -hydroxy silylenol ethers with $\text{Py}\cdot\text{TfOH}$ and are intercepted by various nucleophiles with exquisite regiochemical control. The role of solvent effects and in situ generated water were examined as these factors aided in the generation and stabilization of these unique intermediates.

Chapter 3 examines the role of triphosgene-amine base mixtures for the chlorination of simple alcohols, diols, and ketones. Methods for the synthesis of vicinal dichlorides is presented in Chapter 4, as well as our recent contribution utilizing triphosgene-pyridine for the chlorination of unactivated epoxides. This study showcased the utility of triphosgene-pyridine mixtures via the chlorination of numerous aliphatic epoxides with commonly utilized oxygen atom protecting groups. Additionally mechanistic analyses revealed the presence of several transitional intermediates that aided in the understanding of how triphosgene is able to chlorinate epoxides, and alcohols. Also the stereochemical outcome of this process was examined revealing a stereospecific process, similar to our previous investigations.

Lastly Chapter 5 provides a brief review of bicyclic epoxonium ions and methods for their generation, as well as their utility in the synthesis of interesting heterocycles. Also Chapter 5 illustrates our attempts at applying the information we gained from our previous projects utilizing

triphosgene and pyridinium acids for the chemoselective cyclization of epoxides to novel chlorinated pyran and pyranoside heterocycles. Ultimately through this study we were able to uncover the unprecedented chemoselective activation of an epoxyketone with triphosgene, as well as discover a novel counterion based selectivity during the ionization of epoxyketones.

Chapter 1: Direct Nucleophilic Capture of Oxyallyl and Silyloxyallyl Cations

1.1 Purpose

The purpose of this chapter is to summarize the history of direct nucleophilic capture of unsubstituted and substituted oxyallyl cations. This minireview will focus on previous strategies for the generation of these electrophilic intermediates and their direct capture by nucleophiles, such as substituted indoles. A novel strategy for the generation and regioselective interception of silyloxyallyl cations will be presented. Lastly, the utility of the silyloxyallyl cation intermediate for the synthesis of biologically relevant *N*-heterocycles will also be discussed.

1.2 History of Oxyallyl Cations and Classical Methods for their Generation

Oxyallyl cations are three-carbon centered, zwitterionic intermediates containing a delocalized positive charge across an allylic system with a negatively charged oxygen substituent located at the 2-position. These electrophilic intermediates offer a broad fluidity of reactivity in the realm of organic synthesis as they can participate in numerous electrocyclization processes, *i.e.* [3+2], [3+3] and [4+3],¹⁻⁶ as well as take part in nucleophilic interception by carbon and heteroatom centered nucleophiles (Figure 1.1).

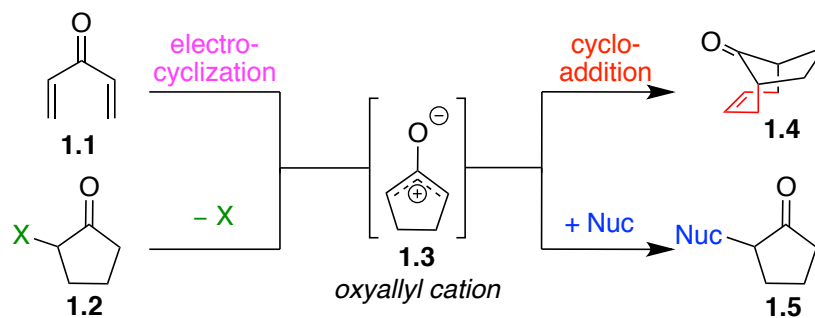
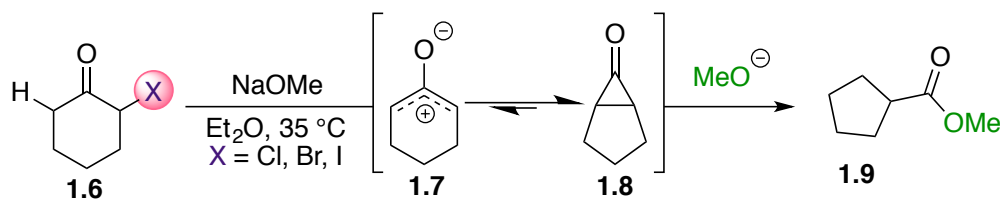


Figure 1.1 Strategies for Oxyallyl Cation Generation

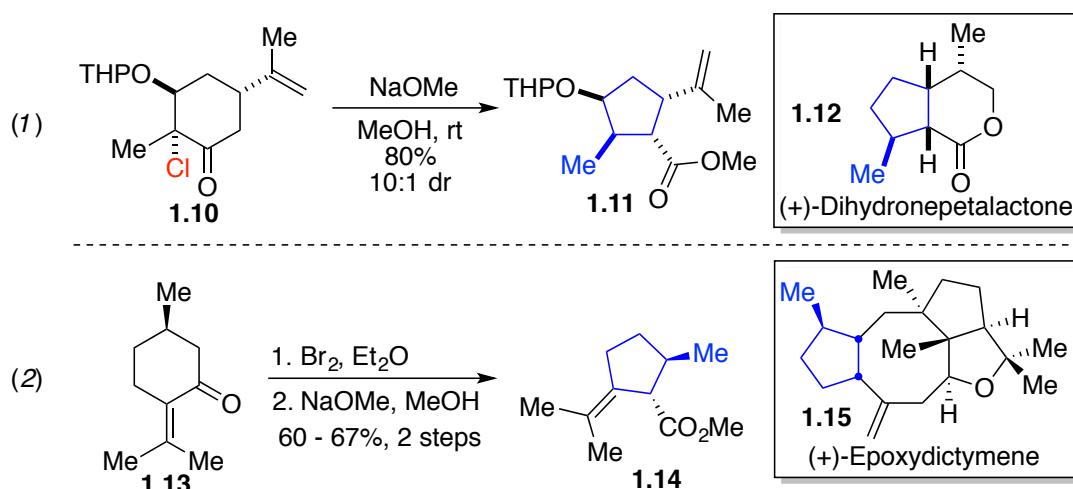
While electrocyclization processes have been extensively studied and numerous synthetic strategies have been created utilizing these intermediates, a relatively underexplored avenue of reactivity is the direct nucleophilic capture of the oxyallyl cation by nucleophiles leading to α - or α' -branched products. Specifically the interception of these intermediates with biologically relevant indole nucleophiles leads to novel structural motifs that creates a new chemical space for the development of new medicines. Herein this chapter will serve as a guide to illustrate the methods developed by Chi and MacMillan for the direct capture of symmetrical oxyallyl cations. Additionally a new strategy developed by my colleagues focusing on the capture of unsymmetrical silyloxyallyl cations with various nucleophiles.

While various methods for the generation of symmetric oxyallyl cations exist, there are two essential approaches for the formation of **1.3**. The first and oldest strategy involves an El_{cb} -like ionization of an α -halo ketone in appropriate solvent and base leading to a ring contracted product (Scheme 1.1). Known as the Favorskii rearrangement,⁷ this transformation was discovered in 1864 wherein Favorskii discovered the ring contraction of α -halo cyclohexanone derivatives under basic conditions. For example using NaOMe in MeOH, α -halo ketone **1.6** can be contracted to cyclopentane **1.9** containing an exocyclic methyl ester substituent (Scheme 1.1). This process has been widely studied over the years and is generally understood to proceed via putative oxyallyl cation **1.7** generated upon the ionization and deprotonation of ketone **1.6**. Intermediate **1.7** is then proposed to be in equilibrium with the strained, fused cyclopropanone **1.8**. This strained ketone is then intercepted by methoxide anion at the carbonyl carbon leading to ring-contracted cyclopentane product **1.9**.⁸ The hardness of nucleophile is pertinent to form the desired ring-contracted product. If a soft nucleophile is used then the reaction fails to produce the product.⁹⁻¹⁰



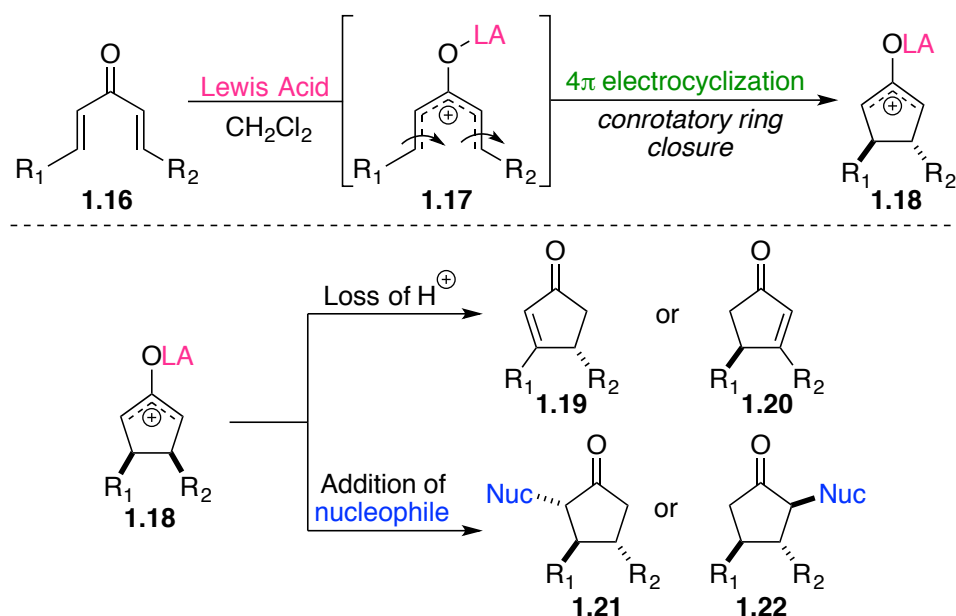
Scheme 1.1 The Favorskii Rearrangement

The Favorskii rearrangement has found significant utility in the synthesis of complex molecules. For example, Lee utilized the Favorskii rearrangement to synthesize the densely functionalized cyclopentane core of (+)-Dihydronepetalactone (Scheme 1.2).¹¹ Beginning with α -chloro ketone **1.10** in the presence of NaOMe, contraction of the (–)-carvone skeleton led to cyclopentane **1.11** in 80% yield. Interestingly this transformation proceeded under good diastereocontrol, yielding **1.11** in a 10:1 diastereomeric ratio. Schreiber et al also utilized the Favorskii rearrangement in his synthesis of (+)-Epoxydictymene.¹² From (R)-pulgelone **1.13**, bromination of the exocyclic alkene furnished brominated product that subsequently underwent a Favorskii Rearrangement under basic conditions furnishing cyclopentane **1.14**, stereospecifically.



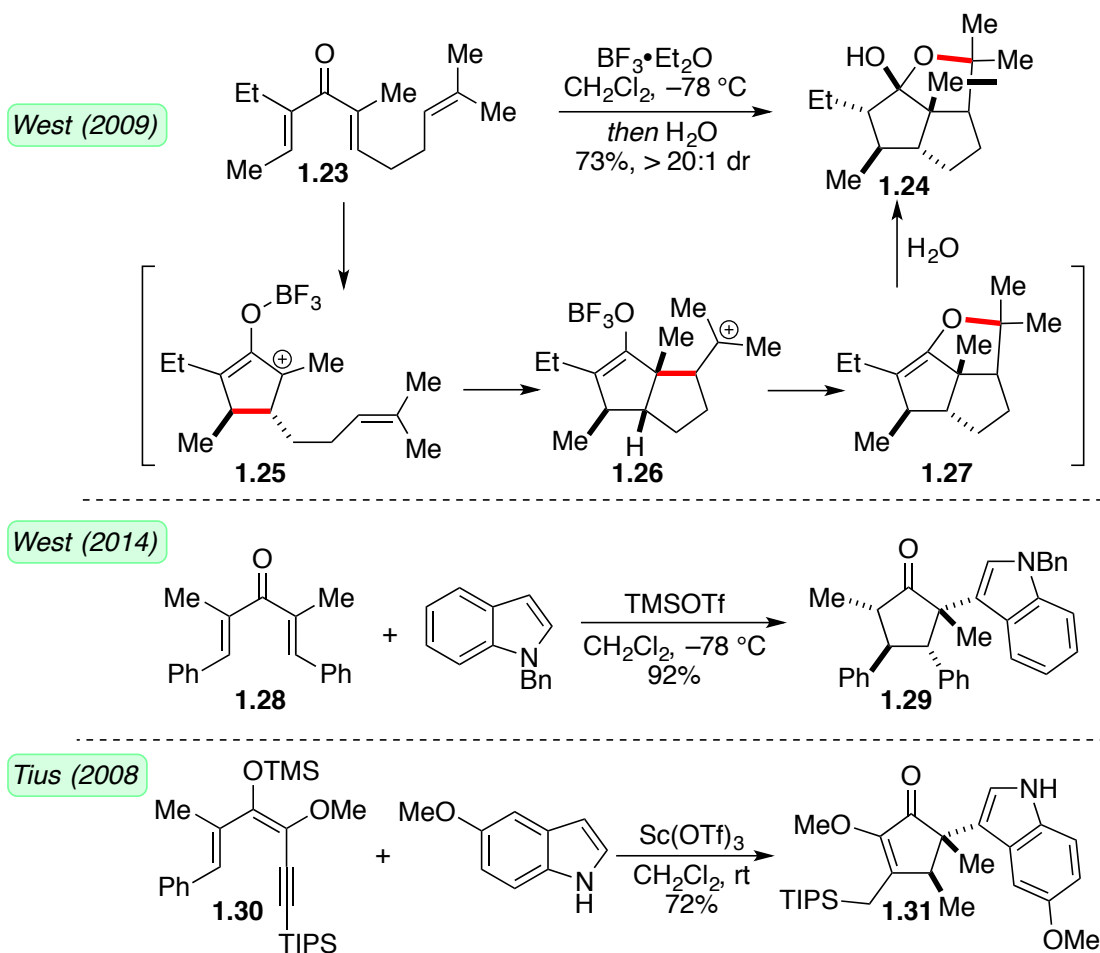
Scheme 1.2 Favorskii Rearrangement in Complex Molecule Synthesis

The second strategy for generating these cationic intermediates involves activating a divinyl ketone with either a Lewis or Brønsted acidic conditions, known as the Nazarov Cyclization.¹³⁻¹⁵ While several groups are owed credit for the discovery of this transformation, it was Nazarov in the late 1940s and mid-50s who extensively studied the products and reactive intermediates of the cyclization and proposed that the activation of divinyl ketones proceeds through a pentadienylic cation before the ensuing pericyclic cyclization.¹⁶⁻¹⁸ The mechanism for the Nazarov Cyclization is illustrated in Scheme 1.3. Activation of divinyl ketone **1.16** with an aforementioned acid source permits the formation of acyclic pentadienyl cation **1.17**. The activation of the carbonyl theoretically shrinks the HOMO-LUMO gap allowing for the necessary orbital overlap of the vinyl groups. This event then allows for a conrotatory, 4π -electrocyclic ring-closure generating intermediate oxyallyl cation **1.18**.¹⁹ Ensuing elimination of a proton leads to isomeric cyclopentenones **1.19** or **1.20**.²⁰⁻²⁴ It's important to note that the concerted cyclization places any substituent on the terminal ends of the vinyl groups, *anti* to each other within the ring.



Scheme 1.3 Mechanism for the Nazarov Cyclization

While the loss of a proton leads to the formation of cyclopentenone products, an alternative relies on the ability of a nucleophile to capture the putative cation **1.18**. Using either carbon or heteroatom nucleophile, this strategy permits the formation of new value-added products not allowed via typical enolate chemistry. This reactivity pattern has since become known as an “Interrupted Nazarov Cyclization”, a phrase coined by the West Group in 2009.²⁵⁻²⁶ The interrupted Nazarov proceeds via an identical reaction pathway as the classic Nazarov Cyclization; however, a nucleophile interrupts indiscriminate loss of proton from **1.18** leading to α -substituted ketone **1.21** or its regioisomer **1.22**. As a proof of concept, West and his team synthesized trienone **1.23** with a pendant alkene distal to the divinyl ketone functionality and subjected it to Lewis acidic activation. In fact upon treatment of **1.23** with $\text{BF}_3 \cdot \text{OEt}_2$ at -78°C , tricycle **1.24** was formed in 73% as a single diastereomer (Scheme 1.4).^{21, 27} This transformation suggestively involves oxyallyl cation generation **1.25** that is subsequently quenched by the distal alkene liberating a more stable tertiary carbocation **1.26**. Lateral cyclization by the masked enolate forms the final five-membered furan ring system **1.27**, where upon aqueous workup liberates hemiketal **1.24** as the final product. Given the success of this proof of concept experiment, West and his team have since used the Interrupted Nazarov Cyclization strategy to synthesize a variety of α -substituted ketones by employing various nucleophiles. Specifically, West utilized biologically relevant N-benzylated indole²⁶ as a coupling partner with the symmetric divinyl ketone **1.28** generating medicinally relevant α -indolyl ketone **1.29** in 92% yield and excellent diastereoselectivity. Additionally, a report by Tius also developed an interrupted Nazarov process to synthesize α -indoyl ketone **1.31** from vinyl-propargyl trimethylsilylenoether **1.30** in 72% yield and $>20:1$ d.r. (Scheme 1.4).²⁸ These seminal reports by West and Tius have since laid the ground work for future discoveries.

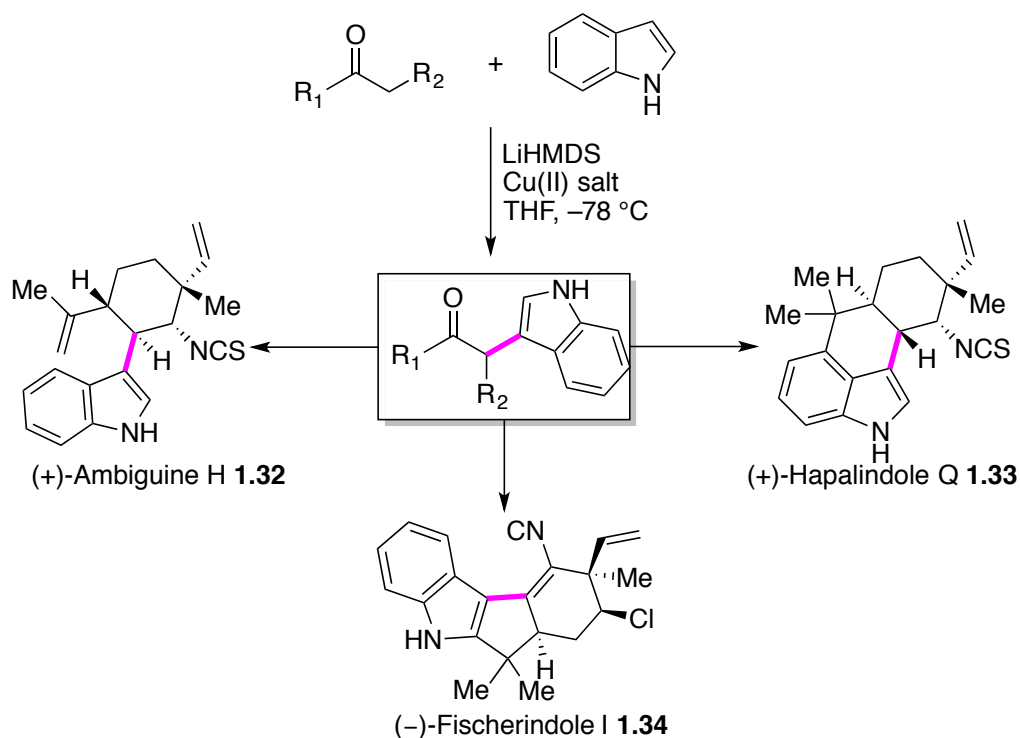


Scheme 1.4 Examples of the Interrupted Nazarov Reaction

1.3 Synthesis of α -Indoyl Ketones via Nucleophilic Capture of Oxyallyl Cations

Functionalization of the α -carbon of carbonyl compounds is of paramount importance in organic chemistry. From simple enolate alkylations to stereoselective aldol reactions, this reactive site is routinely manipulated in the efforts of generating value-added molecules. Recently, the synthesis α -indoyl ketones has received a considerable amount of attention from the synthetic community.²⁹⁻³¹ These readily diversifiable motifs are primed for further functional group interconversions, and the heterocyclic indole substituent maps onto a series of complex natural products. While structurally appealing, the synthesis of these small molecules is a non-trivial

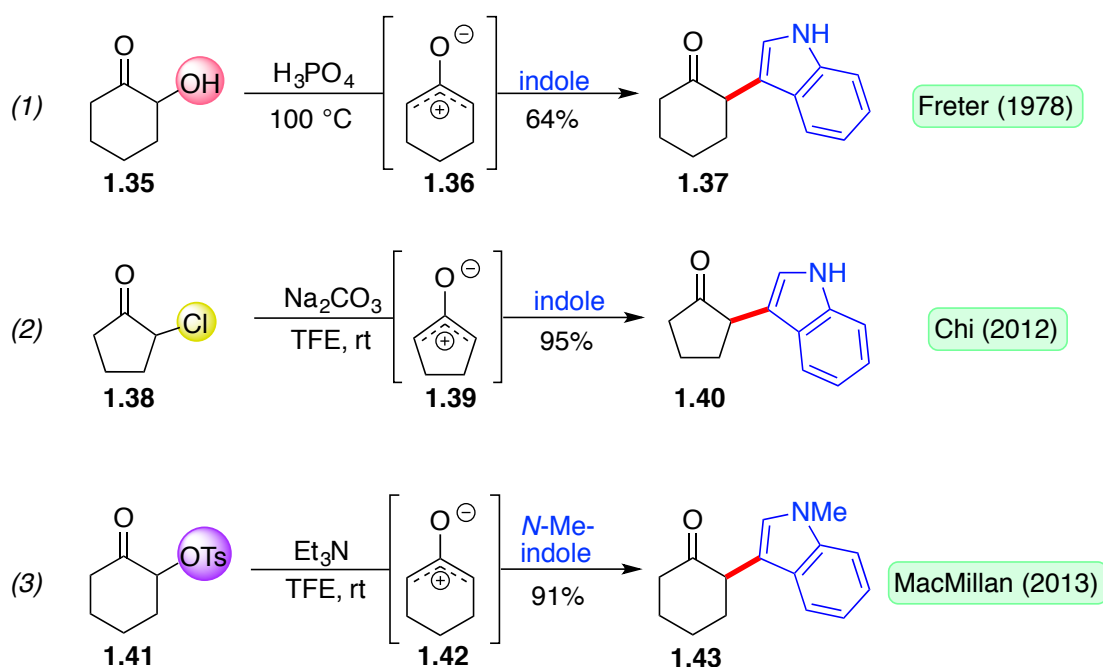
exercise considering the mismatched nucleophilic reactivity of the α -carbon of carbonyls compared to nucleophilic indoles. However while challenging, several groups have been able to umpole the nucleophilic reactivity of the carbonyl compound employing it as an electrophile, which can be intercepted by nucleophilic indole forming the desired α -indoyl ketone. Specifically, the Baran lab has developed a Cu(II)-promoted oxidative coupling of simple ketones with indoles (Scheme 1.5).³²⁻³³ This unique strategy has allowed Baran to realize the syntheses of several indole containing alkaloid natural products from the Haplaindole family.



Scheme 1.5 Baran's Oxidative Coupling Strategy and Application to Total Synthesis

However while Baran's work is elegant and robust, a simpler strategy for α -indoyl ketone formation involves trapping of the in situ generated oxyallyl cation generated from a Favorskii-like process.³⁴ By biasing the reaction conditions from strong bases to weak bases and soft

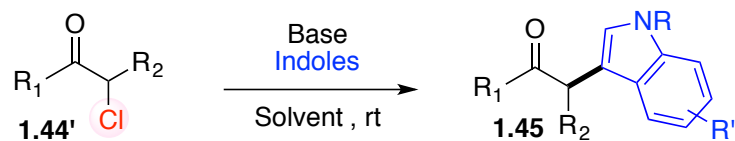
nucleophiles the reaction can be stalled at the oxyallyl cation, leading to the interception by indole affording α -indoyl ketone products over typical Favorskii products. While the idea is simple enough, only a few reports exist exploiting this “Interrupted Favorskii Rearrangement”.



Scheme 1.6 The First Examples of Direct Nucleophilic Capture of Oxyallyl Cations

One of the earliest pioneers in developing this chemistry, Freter and coworkers disclosed the first example of direct nucleophilic capture of an oxyallyl cation by ionizing α -hydroxy cyclohexanone **1.35** in aqueous H_3PO_4 at $100\text{ }^{\circ}\text{C}$.³⁵ The intermediate electrophile **1.36** was presumably generated and intercepted with indole leading to α -indoyl cyclohexanone **1.37** in 64% yield (Scheme 1.6, *eqn 1*). While innovative and unique Freter’s discovery unfortunately remained buried in the chemical literature for ~30 years. However in the early 2000s Freter’s discovery garnished a renewed interest and inspired the development of a milder strategy.

Table 1.1 Summary of Chi's Indole and Nucleophile Scope



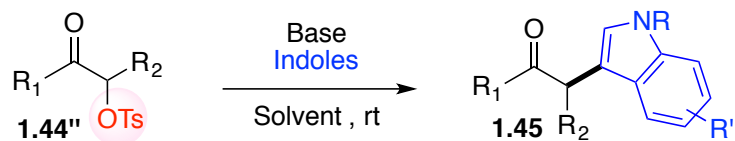
Chi's Conditions: Na₂CO₃ (1.2 equiv.), TFE (0.5 M), rt

entry	ketone	nucleophile	product	yield ^[a]
1	 1.44a		 1.45a	92%
2	 1.44b		 1.45b	84%
3	 1.44c		 1.45c	94%
4	 1.44d		 1.45d	90%
5	 1.44e		 1.45e	95%
6	 1.44f		 1.45f	95%

^[a] Isolated yield after column chromatography

In 2012, Chi and coworkers showcased a milder ionization strategy by subjecting α -chloro cyclopentanone **1.44** to basic TFE (Scheme 1.6, *eqn 2*).³⁶ In the presence of various indoles, Chi's protocol produced α -indoyl cyclopentanone products **1.45** in high yields in relatively short reaction times, tolerating electron rich and poor indole nucleophiles such as 5-methoxyindole and 5-nitroindole, respectively (Table 1.1). Additionally Chi's chemistry permitted the use of six-membered and acyclic α -chloro ketones, **1.44e** and **1.44f** providing the respective coupled products **1.45e** and **1.45f** in 95% yields. It is important to note that the key to reaction success relies on two controlling elements: the ability of TFE to activate the α -chloro ketone through hydrogen bonding interactions and the polarity of the solvent to stabilize charged intermediates. Following Chi's work, MacMillan and coworkers produced an analogous strategy by subjecting α -tosylated ketone **1.41** to Et₃N in TFE forming α -indoylated **1.43** (Scheme 1.6, *eqn 3*).³⁷⁻³⁸ Similar to Chi's strategy, a broad array of ketone substrates were freely accepted yielding α -indoyl products in high yields under relatively quick reaction times, although only *N*-methylated indole was tolerated. However, MacMillan's conditions permitted the use of nucleophilic partners other than indole. In fact various substituted phenols, amines and simple alcohols readily coupled revealing α -substituted products (Table 1.1 cont'd, entries 9-6).

Table 1.2 Summary of MacMillan's Indole and Nucleophile Scope

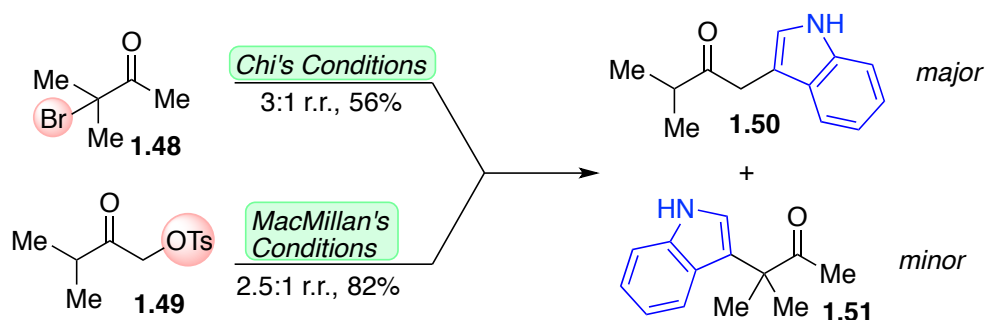


MacMillan's Conditions: Et₃N (1.2 equiv.), TFE (2.0 M), rt

entry	ketone	nucleophile	product	yield ^[a]
1	 1.44g		 1.45g	75%
2	 1.44h		 1.45h	72%
3	 1.44i		 1.45i	87%
8	 1.44j		 1.45j	91%
9	 1.44k		 1.45k	76%
6	 1.44l		 1.45l	67%

^[a] Isolated yield after column chromatography

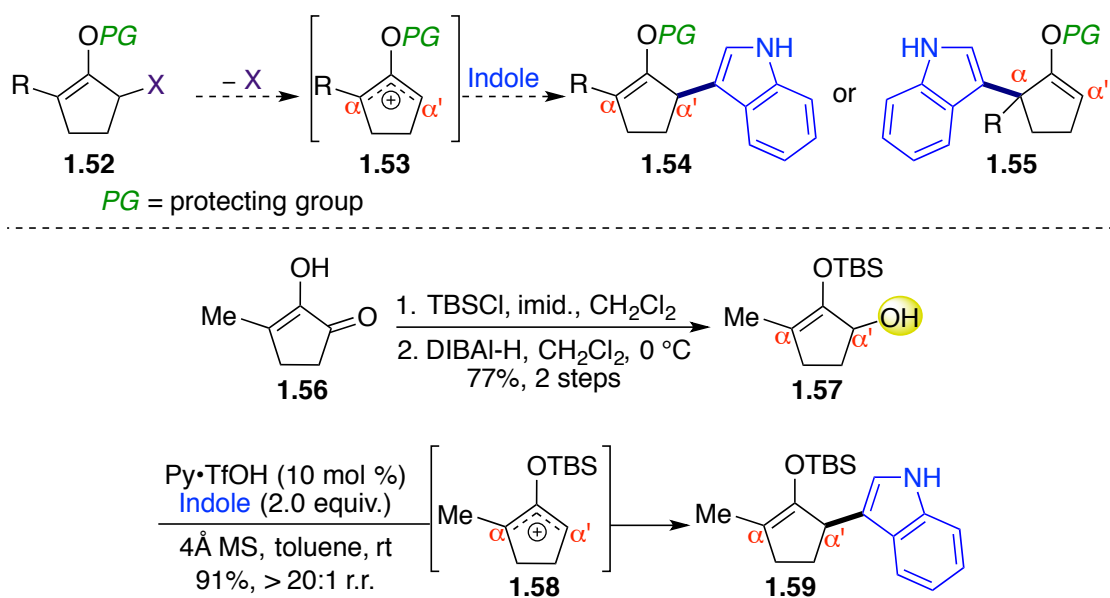
In an attempt to address the regioselectivity issues of in situ generated unsymmetrical oxyallyl cations, Kartika and coworkers proposed masking the oxygen of the oxyallyl cation as a silyl ether.³⁹⁻⁴⁰ Presumably the “protected” oxyallyl cation would modulate the electronics and sterics of the presumed cation and allow for the regioselective capture at either the α - or α' -position. In fact support for this hypothesis was somewhat founded as the work developed by Tius involved the cyclization of vinyl-propargyl trimethylsilyl enoether motifs that presumably proceeded via silyloxyallyl cation intermediates (Scheme 1.4).²⁸



Scheme 1.7 Regioselectivity Challenges

In an attempt to realize this hypothesis, my colleagues synthesized α -hydroxy silylenol ether **1.57** in two-steps from commercially available 3-methyl-1,2-cyclopentanedione **1.56**. α -hydroxy silylenol ether **1.57** was chosen as the model substrate due to its lability to weak Brønsted acids, as the ionization needs to be facile under ambient conditions to circumvent hydrolysis of the sensitive silylenol ether moiety. Gratifyingly, upon treatment of **1.57** to catalytic amounts of Py•TfOH in the presence of indole afforded α' -indoyl silylenol ether **1.59** in 91% after 66 hours, as a single regioisomer. A brief optimization revealed that only 10 mol % of Py•TfOH was needed, along with 2.0 equiv of indole in toluene. Toluene was chosen as the reaction solvent as it is

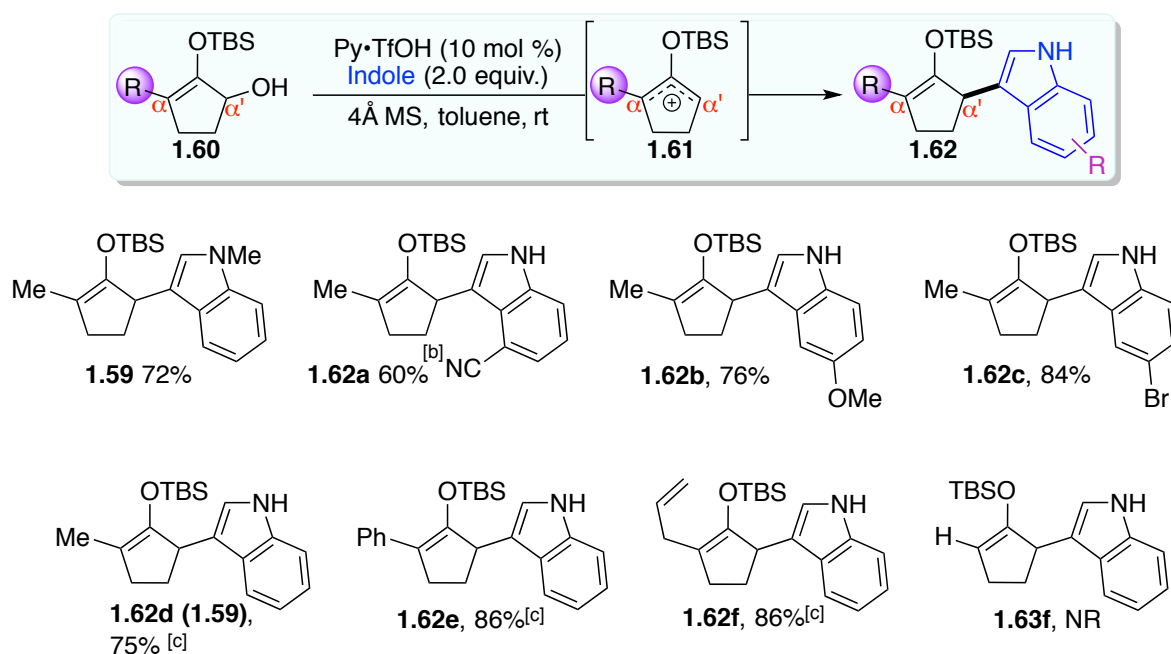
known that ionization of an alcohol leaving group is kinetically favored over decomposition of silylenol ether functional groups in a nonpolar solvent. However the addition of 4Å MS were necessary as protodesilylation products were discovered upon prolonged reaction times.



Scheme 1.8 Hypothesis and Proof of Concept

A brief scope α' -indoylated silylenol ether substrates is shown in Table 1.3. A wide variety of indoles ranging from electron poor 4-cyanoindole to electron rich 5-methoxyindole were tolerated under the optimized reaction conditions, forming the corresponding products **1.62a** and **1.62b** in 60% and 76%, respectively with >20:1 r.r. My colleagues showcased the utility of 5-bromoindole generating the corresponding α' -indoyl silylenol ether **1.62c** in 84% yield. This product is appealing as it could be further functionalized via cross-coupling or lithiation strategies producing more structurally complex architectures. Also, the reaction proved indiscriminate to diverse α -substituents as the desired α' -indoyl products were formed with exquisite regiochemical control and good yields (Table 1.3). The regioisomeric tertiary alcohols starting materials were

necessary for the synthesis of products **1.62d-1.63f** had to be used due the lack of a better synthetic plan to generate the secondary alcohols but all tertiary examples led to the formation of their corresponding α' -indoyl silylenol ether. It is presumed that upon ionization the same unsymmetrical silyloxyallyl cation intermediate forms and is then intercepted by indole. In fact, my colleagues tested this hypothesis with the synthesis of **1.62d (1.59)** from the regioisomeric tertiary alcohol of **1.57**. Gratifyingly the product was produced as a single regioisomer and with a slight increase in yield from 72% to 75%. Several α -substituents were tolerated including phenyl and allyl groups. Interestingly without a stabilizing α -group no reaction proceeds **1.63f**.



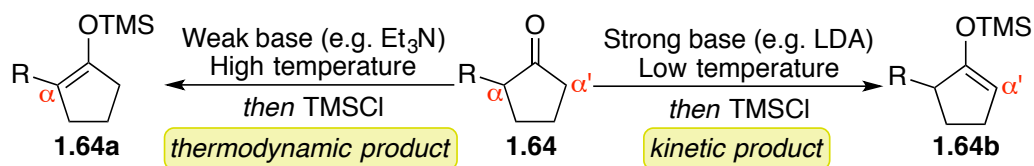
^[a] Isolated yield after flash column chromatography. ^[b] Starting material not fully consumed. ^[c] From tertiary alcohol starting materials. ^[d] No reaction under the optimized conditions

Scheme 1.9 Scope of Indoles and α -substituents

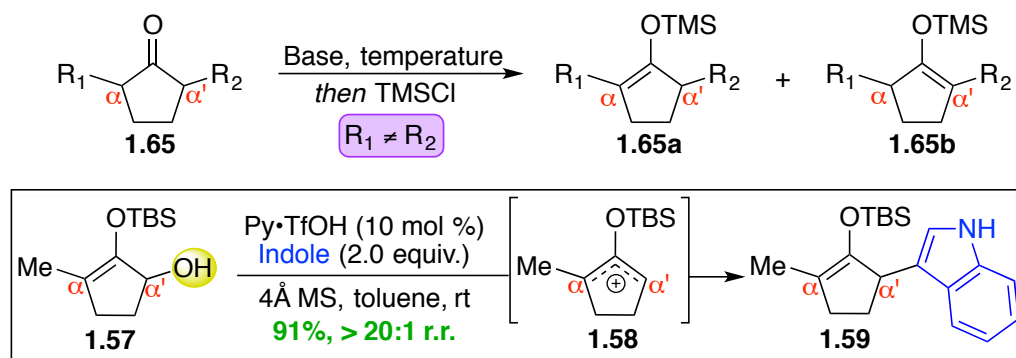
An added advantage of this method is that it solves a longstanding problem of regioselective silylenol ether generation from differentiated α, α' -substituted ketones. Classically,

treatment of α -substituted ketone **1.64** with silyl chloride and weak base at room or elevated temperatures provides the thermodynamically favored silylenol ether **1.64a**. While conversely, treatment of ketone **1.64** with silyl chloride and a strong base at cryogenic temperatures produces the kinetically favored product **1.64b**. These two strategies are textbook enolization strategies, but both strategies fail to give regioselective enolization when sterically and electronically α,α' -disubstituted ketone **1.65** is employed. The method developed by my colleagues allows for complete regiochemical control of both the nucleophilic addition as well as controlling the regiochemistry of the silylenol ether functionality.

Classic Silylenol Ether formation



Problem

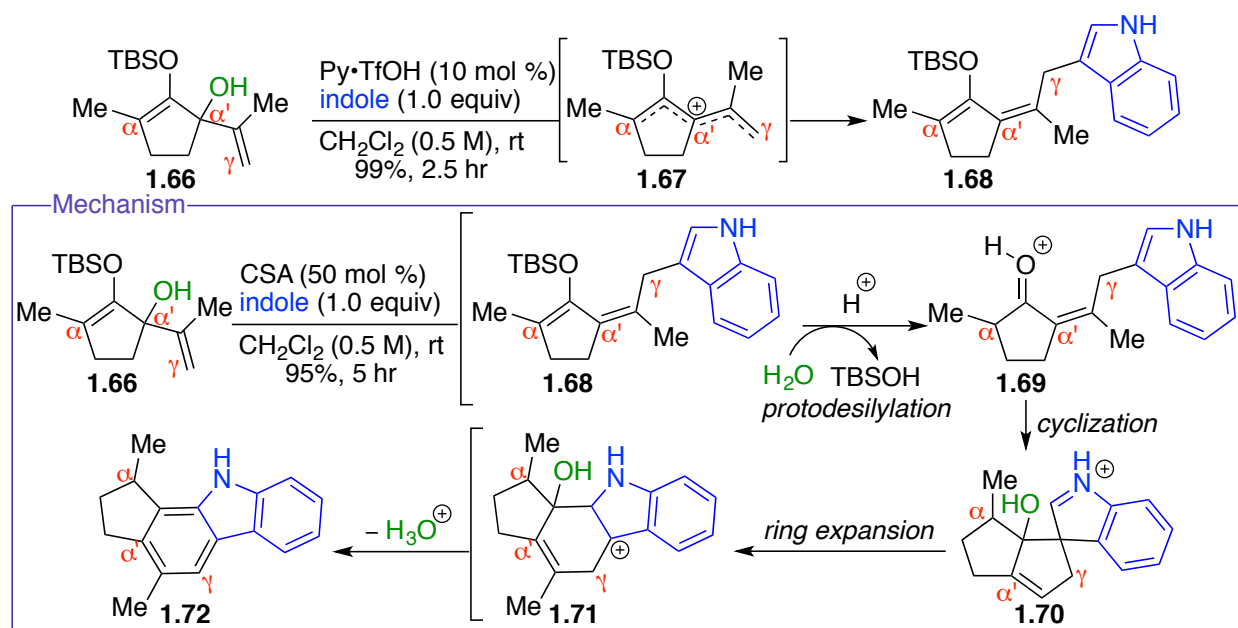


Scheme 1.10 Problem with Classical Enolization Methods and Silyloxyallyl Cation Solution

1.5 Synthesis of Novel Heterocycles via Nucleophilic Capture of the Silyloxyallyl Cation

Since its initial inception the utility of the silyloxyallyl cation has been expanded to encompass the synthesis of novel, biologically relevant heterocycles (Scheme 1.11). Extending

from their seminal works, my colleagues showed that treatment of vinyl substituted α -hydroxy silylenol ether **1.66** with Py•TfOH permitted the migration of the cationic center, generating 2-silyloxy(pentadienyl) cation **1.67**. This conjugated system allows for delocalization of the positive charge which is then open to interception by indole at the γ -carbon yielding γ -functionalized product **1.68**. While functionalization at the γ -position is interesting a more appetizing transformation occurs by simply changing the acid source to the more acidic CSA. The stronger acid leads to a cascade process that ultimately yields heterocyclic carbazole **1.72** in 95% after 5 hours of reaction time. This process proved to be robust and indiscriminate of double bond geometry yielding several carbazole products in high yields.⁴¹⁻⁴²



Scheme 1.11 γ -Functionalization and Carbazole Synthesis

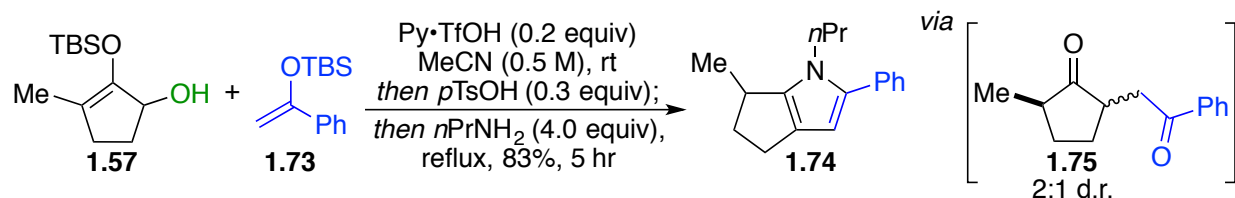
The mechanism of this transformation is believed to proceed first by regioselective γ -functionalization with indole, followed by protodesilylation affording α,β -unsaturated ketone

1.69. Given the acidic media, ketone **1.69** most likely exists as the protonated oxonium and is thus poised for intramolecular attack by tethered indole leading to the formation of congested tricycle

1.70. Ring expansion and loss of H₂O rearomatizes the indole liberating the desired carbazole

1.72. Carbazoles have a wide utility but are commonly used as medicines like NSAIDs.⁴³⁻⁴⁵

Lastly my coworkers have described an extension of the Paal-Knorr pyrrole synthesis through silyloxyallyl cation chemistry. Facile ionization of α -hydroxy silylenol ether **1.57** with catalytic Py•TfOH in the presence of acetophenone-derived silylenol ether **1.73** led to an in situ generated monosilylated 1,4-diketone.⁴⁶⁻⁴⁷ Further addition of *p*TsOH and *n*PrNH₂, followed by reflux liberated the aliphatic pyrrole **1.74** in 83% overall yield. This one-pot, multicomponent process furnished several pyrrole products rapidly in good to excellent yields.⁴⁸



Scheme 1.12 Synthesis of Pyrroles

1.6 Conclusion

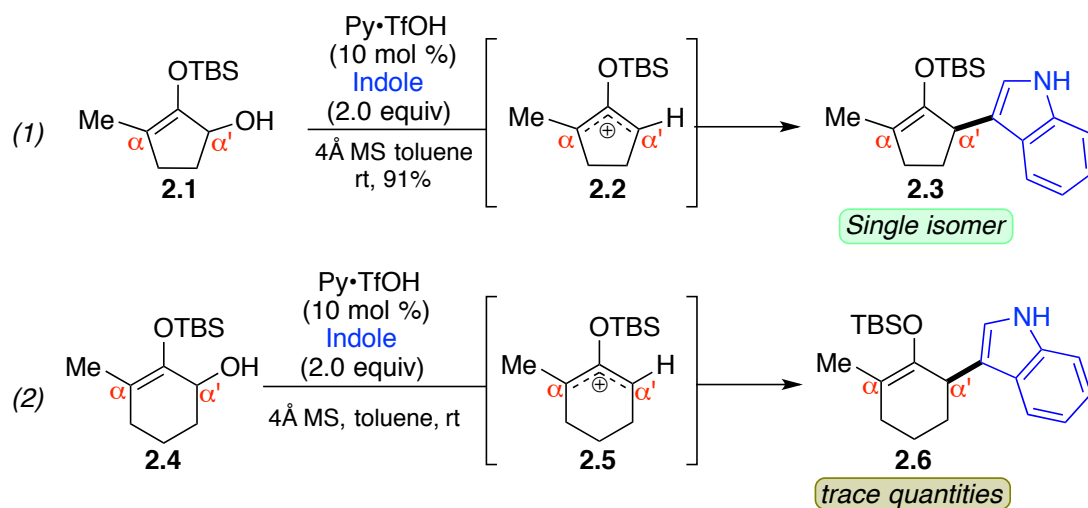
In conclusion, the utility of the oxyallyl cation and silyloxyallyl cation have been discussed. These classical intermediates have found a renewed utility through direct nucleophilic capture with various nucleophiles, including indoles. A recent advancement developed by my colleagues solves an outstanding problem concerning the regiochemical control of nucleophile addition, utilizing a silyloxyallyl cation intermediate. This chemistry reveal α' -indoyl silylenol ethers with excellent regiochemical control and moderate to good yields.

Chapter 2: A Study of Solvent and Water Stabilization Effects: Generation of the Six-Membered Silyloxyallyl Cation and its Regioselective Capture

2.1 Purpose

The purpose of this chapter is to present the stabilizing effects of acetonitrile and water towards the generation of the six-membered silyloxyallyl cation under mild Brønsted acid catalysis. The utility of this intermediate has broad applications as its regioselective capture by indole, silyl enolates and heteroatom nucleophiles lead to novel structural motifs. ¹H-NMR and HPLC studies were conducted to probe an observed rate enhancement promoted by in situ generated of water and will be presented. Lastly the findings from this study led to new and improved conditions for activation of the five-membered α' -hydroxy silylenol ether.

2.2 Expansion of the Previous Silyloxyallyl Cation Methodology



Scheme 2.1 Limitation with the Six-Membered Substrate

As mentioned in Chapter 1, our lab has discovered that subsection of α' -hydroxy silylenol ether **2.1** to catalytic Py \cdot TfOH in the presence of indole liberated α' -indoyl silylenol ether **2.3** in

good yields with excellent regiochemical control (>20:1 r.r.) (Scheme 2.1, *eqn. 1*).³⁹ Given these encouraging results my colleagues attempted to expand this chemistry and investigate the reactivity of the six-membered α' -hydroxy silylenol ether homologue. My colleagues subsequently synthesized α' -hydroxy silylenol ether **2.4** from commercially available 2-methyl-1,2-cyclohexanedione and exposed it to mild ionizing conditions (Scheme 2.1 *eqn. 2*). However after prolonged reaction times indole coupled silylenol ether **2.6** was formed in only trace quantities. To explain this lack of reactivity they hypothesized that emerging allylic strain prevents the ionization of **2.4** to cation **2.5** due to steric interference from the TBS ether.⁴⁹⁻⁵⁰ In attempt to support this hypothesis modeling studies of the ground state conformations of cations **2.2** and **2.5** (Figure 2.1) were conducted in our lab using a 6-311g(d,p) DFT, B3LYP basis set. These studies showed that as the cationic site of **2.5** begins to form a deviation of bond angles from ideality occurs leading to increased angle strain. Additional destabilizing steric repulsions also occur.⁴⁰

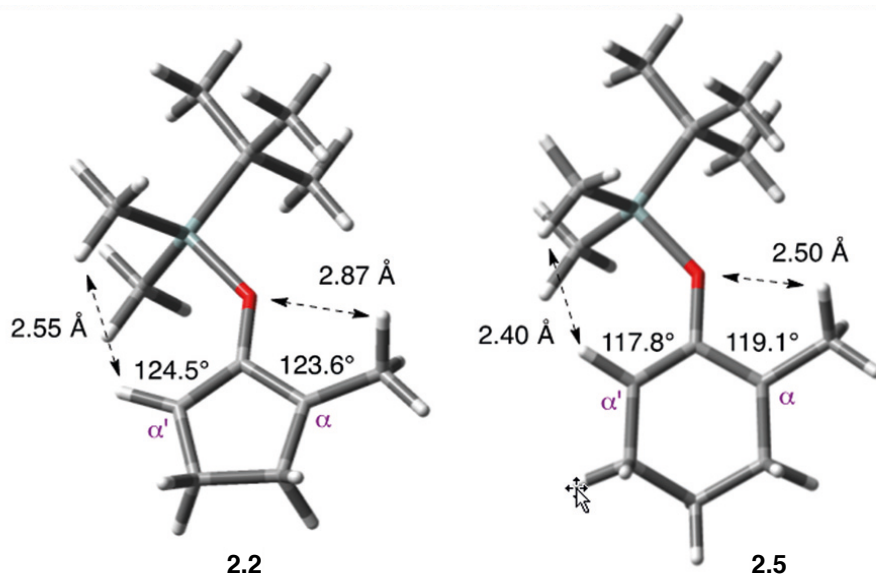
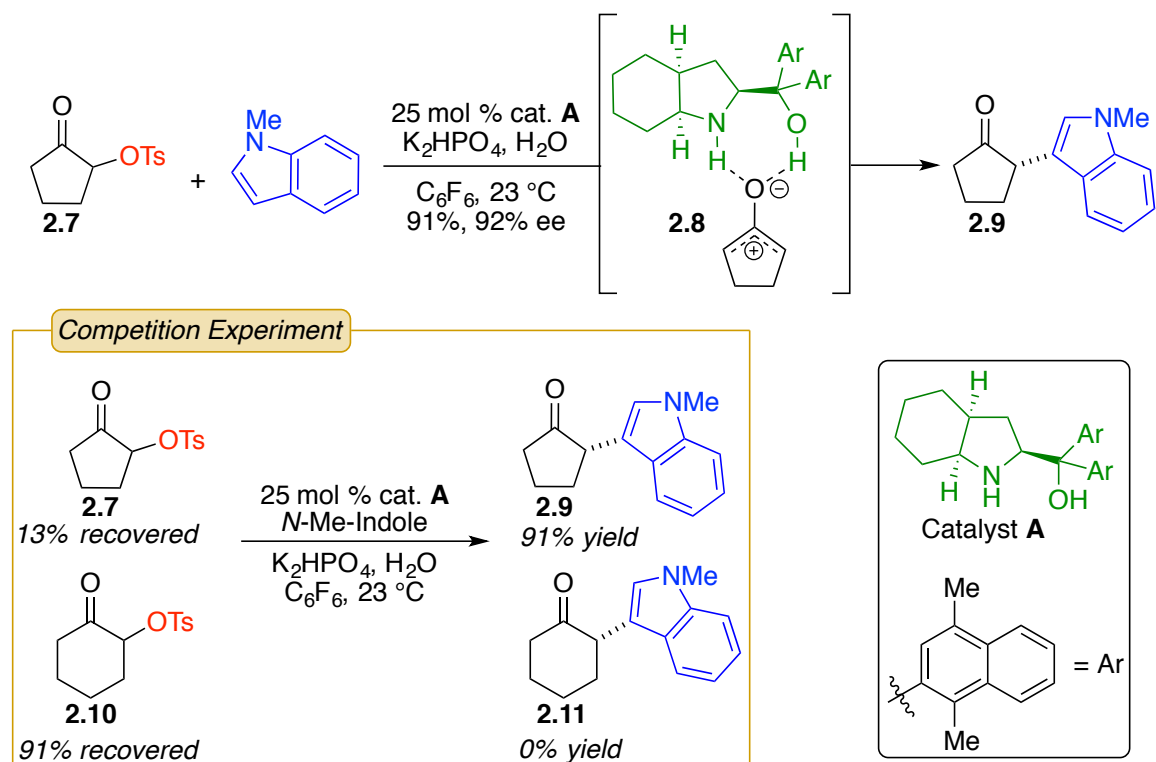


Figure 2.1 DFT Modeling Study of Ground State Conformations of **2.2** and **2.5**

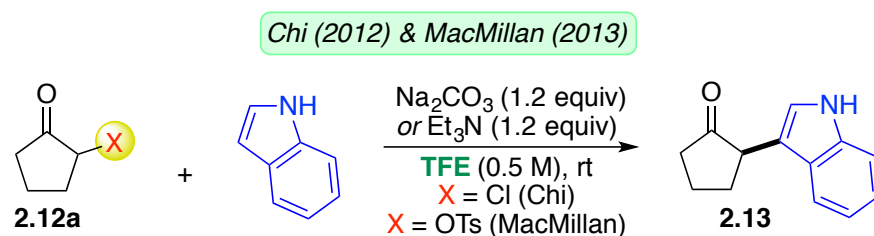
While surprising, this lack of reactivity is not unique to the chemistry developed in our lab as MacMillan and coworkers reported a similar observation in late 2016 (Scheme 2.2).³⁷⁻³⁸ In an attempt to advance their α -indoylation chemistry, MacMillan reported a catalytic, enantioselective variation. Combining α -tosyl cyclopentanone **2.7** with indole, K_2HPO_4 , and chiral prolinol catalyst **A**, enantioenriched **2.9** was formed in 91% yield and 92% *ee*. While trying to assemble insights about the reaction mechanism, they conducted a competition experiment with ketones **2.7** and **2.10** using their optimized asymmetric protocol. It was discovered that five-membered ketone **2.7** readily reacted forming coupled product **2.9** while ketone **2.10** was untouched and recovered in 91%. This lack in reactivity was attributed to unfavored ring strain that arises due to an increase in unsaturation in the six-membered ring.



Scheme 2.2 MacMillan's Enantioselective α -Functionalization

2.3 Overcoming the Limited Reactivity of the Six-Membered Silyloxyallyl Cation⁵¹

Given this thermodynamic constraint we began to search for alternative strategies that would aid in the stabilization of the transition state, allowing facile ionization to occur. While we initially thought stronger acids (CSA, TfOH) and elevated reaction temperatures could force the substrate to ionize, these experiments only led to intractable mixtures of products and protodesilylation of the silylenol ether functionality. Ultimately, we rationalized that the combination of α' -hydroxy silylenol ether **2.4** with a polarizing solvent would aid in the polarize the carbon-oxygen bond of the substrate and stabilize transient charged intermediates. In fact some precedent for this hypothesis exists from the works of Chi and MacMillan as both groups identified significant reaction enhancement when using polar TFE as solvent (Scheme 2.3).^{36, 38} In fact MacMillan commented how profound an effect TFE had on the success of ionizing α -tosyl ketones for nucleophilic capture. Solvent-aided activation of neutral substrate for substitution reactions is not a new concept as it was discovered by Hughes and Ingold in 1935 (Hughes-Ingold Rules).⁵²⁻⁵⁴



Scheme 2.3 Use of Polar Solvent by Chi and MacMillan

The idea of using polar solvents as the reaction media had previously been deemed nonsensical as seminal works in our lab deliberately used a nonpolar solvent in order to prevent unwanted protodesilylation of starting materials and α' -indoylated products.³⁹ Therefore as we began to explore the scope of polar solvents, we remained aware that we had to monitor the rate

of kinetically driven protodesilylation over proton transfer. Table 2.1 shows our attempts to explore this strategy. Our study began with the exposure of α' -hydroxy silylenol ether **2.4** to Py•TfOH in the slightly more polar CH₂Cl₂ in the presence of 4Å MS (entry 1). However, after extended reaction time (>300 h) only trace α' -indoyl product was observed.

Table 2.1 Reaction Optimization Study

entry	solvent	equiv of acid	additive	equiv of indole	time (h)	yield (%)
1	CH ₂ Cl ₂	0.1	4 Å MS	1.1	>300	trace ^[b]
2	CH ₂ Cl ₂	0.1	--	1.1	48	52
3	toluene	0.1	--	1.1	>300	40 ^[b]
4	MeCN	0.1	--	1.1	26	71
5	MeCN	0.2	--	1.1	26	82
6	MeCN	0.5	--	1.1	7	80
7	MeCN	1.0	--	1.1	3	85
8	MeCN	0.2	--	1.0	24	76
9	MeCN	0.2	--	2.0	25	81
10	MeCN	0.2	4Å MS	1.1	>300	18 ^[b]
11	MeCN	0.2	H ₂ O ^[c]	1.1	13	60

^[a] Isolated yields after column chromatography. ^[b] **2.4** was not fully consumed.

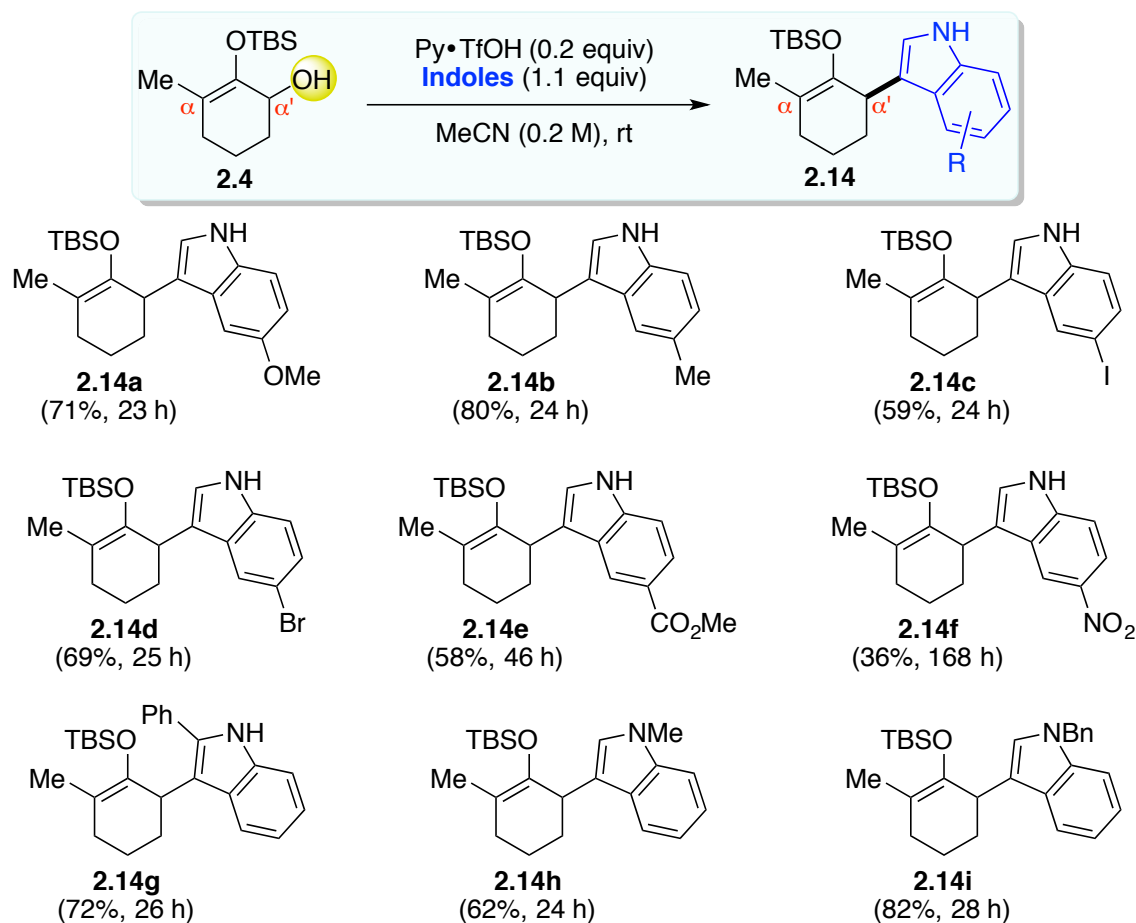
^[c] 0.1 equiv of water was added. ^[d] Compound **2.6** is racemic.

Concurrent with our previous rationale, 4Å MS were added to limit kinetic protodesilylation of the silylenol ether functionality, yet in this instance the emerging H₂O appeared to facilitate and expedite the reaction. Indeed with the removal of molecular sieves, target α' -indoyl silylenol ether **2.6** was formed in 52% yield after 48 hours (entry 2). Conversely, attempting the same additive free reaction in toluene led to incomplete consumption of **2.4**; suggesting that stabilizing solvent effects were indeed necessary for reaction success (entry 3).

Continuing to increase the polarity of the reaction media and the equivalents of Py•TfOH, **2.6** was afforded in 82% after 26 hours (entries 4 and 5). Entries 10 and 11 show our attempts initial to probe the role of *in situ* generated H₂O. First, 4Å MS were returned to the system and a significant retardation of reaction rate was observed, as well as incomplete consumption of starting material. Additionally 0.1 equiv of H₂O was added leading to a drastic decrease in reaction time, however the yield of the reaction diminished somewhat producing **2.6** in only 60%.

2.4 Scope of Indole Additions to α' -Hydroxy Silylenol Ether

With the optimal reaction conditions in hand, we subsequently explored the scope of various substituted indole nucleophiles (Scheme 2.4). Unsurprisingly electron-rich indoles reacted without issue, delivering 5-methoxyindole silylenol ether **2.14a** and 5-methylindole silylenol ether **2.14b** in 71% and 80% yields, respectively. The use of halogenated indoles provided iodinated and brominated products **2.14c** and **2.14d** in acceptable yields, showcasing the utility of these products for further downstream synthetic manipulations. Gratifyingly, our reaction also accepted electron deficient indoles. Reaction with methyl indole-5-carboxylate and 5-nitroindole, furnishing the corresponding indoyl coupling products **2.14f** and **2.14e**, however in diminished yields and longer reaction times. Sterically congested 2-phenylindole liberated α' -indolyl silylenol ether **2.14g** in 72% and in only 26 hours of reaction time. Additionally *N*-substituted indoles *N*-methyl indole and *N*-benzyl indole also generated their consequent coupled silylenol ether products **2.14h** and **2.14i** in 62% and 82% yields, respectively. It's important to mention that all products were formed with quantitative conversion of **2.4** and as sole α' -indoyl regioisomers (>20:1 r.r.). With the completion of the indole compatibility study we then turned our attention to probing the role of differentially substituted alkyl and aromatic α -substituents (Table 2.2).



[a] Isolated yields after column chromatography. [b] All products isolated >20:1 r.r.

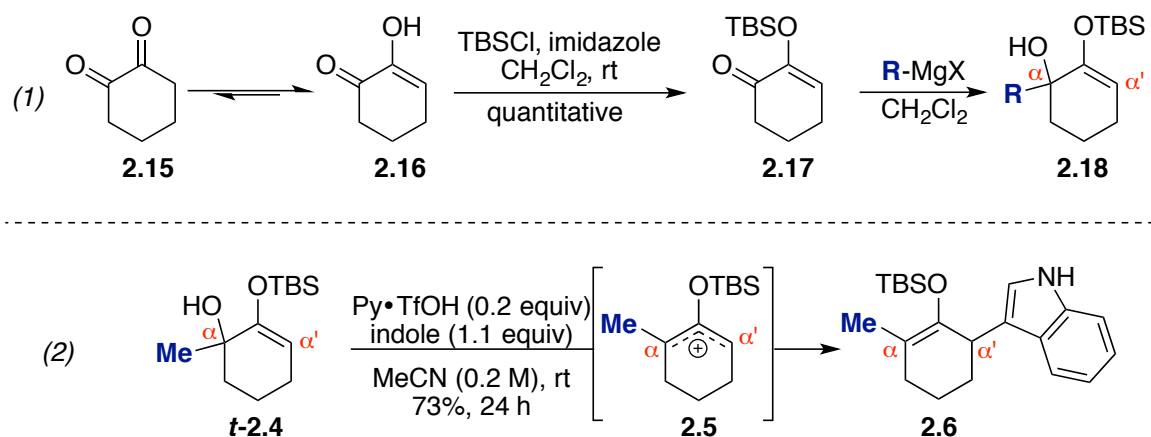
[c] Compounds **2.14** are racemic.

Scheme 2.4 Scope of Indole Additions to α' -Hydroxy Silylenol Ether **2.4**

2.5 Synthesis and Analysis of Tertiary α -Hydroxy Silylenol Ethers

Tertiary α -hydroxy silylenol ethers were synthesized in an analogous fashion concurrent with previous reports from our lab (Scheme 2.5, *eqn 1*).⁴⁷ Beginning with known diketone **2.15**, silyl protection as the TBS ether afforded the desired monosilylated-1,2-diketone **2.17** in quantitative yield. Subsequent substrate diversification was then be accomplished with various Grignard reagents yielding tertiary alcohols **2.18**. We hypothesized that ionization of these regioisomeric silylenol ethers under our optimized reaction conditions would produce

unsymmetrical silyloxyallyl cations **2.19** (Table 2.2). Similarly, the ensuing nucleophilic addition by indole should hypothetically occur at the α' -position with excellent regiochemical control. For a proof of concept study, we began with regioisomeric α,α' -hydroxyl methyl silylenol ether **t-2.4**. Activation of this substrate with catalytic Py•TfOH and in the presence of indole cleanly afforded α -methyl- α' -indole adduct **2.6** with a comparable yield and reaction time (Scheme 2.5, eqn 2).



Scheme 2.5 General Synthesis of Tertiary Alcohols and their Proof of Concept

Table 2.2 shows a complete substrate compatibility study. Various aliphatic chains revealed the tolerability of these groups at the α -carbon, as the respective α' -indolyl silylenol ether products **2.20a** – **2.20d** were formed in high yields (entries 1–4). Interestingly, sterically congested **2.18c** and **2.18d** underwent facile ionization and produced the corresponding products in only 5 and 6 hours; while the ionization allylic substituted **2.18b** (entry 2) proved to be rather sluggish taking 24 hours for reaction completion. As illustrated in entries 5–7, the effect of aromatic substituents was examined, beginning with α -tolyl substrate **2.18e**. Interestingly, exposure of this tertiary alcohol to optimized ionization conditions revealed an extremely slow reaction. Analogous treatment of *p*-chlorophenyl silylenol ether **2.18g** to ionization conditions

also lead to an exceptionally long reaction time. In fact reaction of **2.18g** failed to go to completion, even after greater than 20 days (>500 h).

Table 2.2 Scope of α -Substituted Silylenol Ether Products

entry	starting material	product	time	yield
1	 2.18a	 2.20a	16 h	79%
2	 2.18b	 2.20b	24 h	72% ^[b]
3	 2.18c	 2.20c	5 h	83%
4	 2.18d	 2.20d	6 h	76%
5	 2.18e	 2.20e	168 h	82%

^[a] Isolated yields after column chromatography. All products isolated in > 20:1 regioselectivity.

^[b] Prolonged reaction time caused decomposition of starting material. ^[c] Starting material was not fully consumed. ^[d] Compounds **2.20** are racemic.

Table 2.2a Scope of α -Substituted Silylenol Ether Products

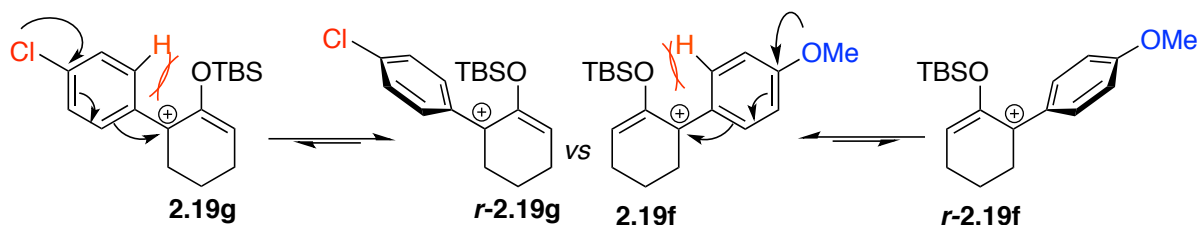
entry	starting material	product	time	yield
6	 2.18f	 2.20f	22 h	75%
7	 2.18g	 2.20g	>500 h	50% ^[c]
8	 2.18h	 2.20h	no reaction	

[a] Isolated yields after column chromatography. All products isolated in > 20:1 regioselectivity.

[b] Prolonged reaction time caused decomposition of starting material. [c] Starting material was not fully consumed. [d] Compounds **2.20** are racemic.

This sluggish reactivity is believed to be due to competing 1,3-allylic strain versus planarization of the aromatic group which would allow for stabilization of the positive charge of the oxyallyl cationic species (Scheme 2.6). This stereoelectronic phenomena naturally seemed reasonable as electron-rich *p*-methoxyphenyl silylenol ether **2.18f** rapidly formed coupled products **2.20f** in only 22 hours. Entries 7 and 8 also gave us insight about the stability of the proposed silyloxyallyl cationic intermediate as the *p*-chlorophenyl **2.18g** example possessed sluggish reactivity and unsubstituted α -hydroxyl silylenol ether **2.18** produced no coupled product

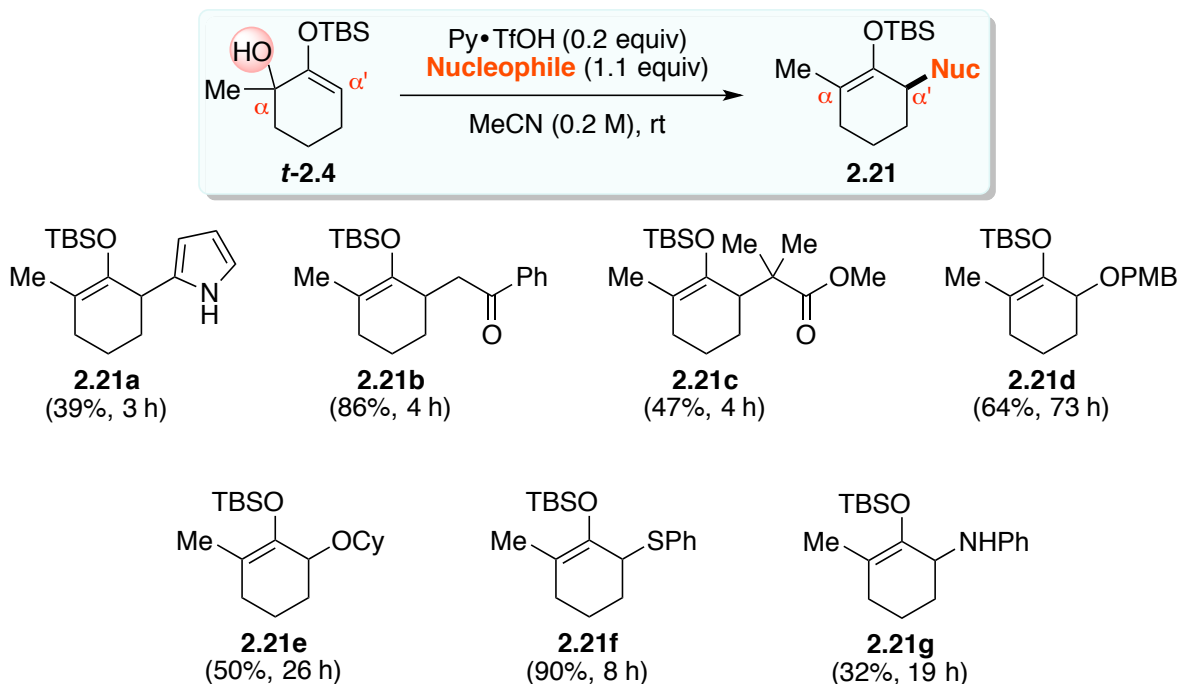
at all. Collective observations from Table 2.2 show that substitutions at the α -carbon are essential for stabilizing the silyloxyallyl cation, and that an S_N2' mechanism is unlikely.



Scheme 2.6 Hypothesis of Sluggish Reactivity of Aromatic Substituents

2.6 Study on the Effects of Heteroatom and Additional Carbon Nucleophiles

We continued our investigation by examining the utility of additional carbon-based nucleophiles, as well as heteroatom nucleophiles. We elected to utilize tertiary silylenol ether **2.4** for this study due to the cost to make **2.4**. Interestingly while indole readily coupled forming the desired products, benzothiophene and benzofuran nucleophiles failed to react leaving the starting material untouched. However the use of pyrrole readily captured the putative cationic intermediate forming silylenol ether **2.21a** in 39%. The use of acetophenone derived trimethylsilyl enolate and methyl trimethylsilyl dimethyl ketene acetal also rapidly furnished monosilylated 1,4-diketone adducts **2.21b** and **2.21c** in 86% and 47%, respectively. These results underscore the mildness of these reaction conditions as trimethylsilyl enolates are prone to rapid protodesilylation in acidic media. We then looked at employing heteroatom nucleophiles and uncovered the utility of primary and secondary alcohol nucleophiles. *Para*-methoxy benzyl alcohol and cyclohexanol readily afforded the anticipated coupled products **2.21d** and **2.21e** in 64% and 50%, respectively. Thiophenol and aniline nucleophiles also performed well, producing α' -functionalized products **2.21f** and **2.21g** in 90% and 30% yields.



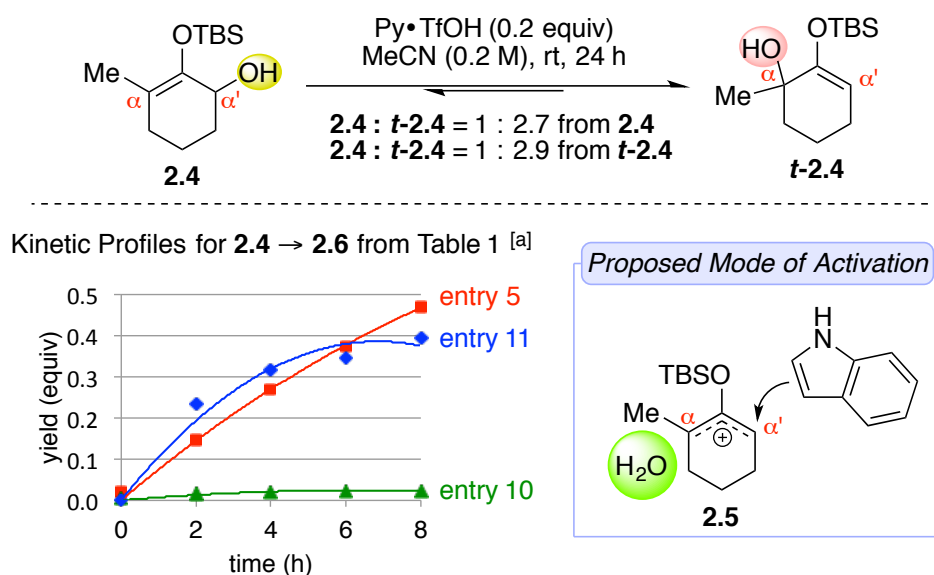
[a] Isolated yields after column chromatography. [b] All products isolated in > 20:1 r.r. [c] Compounds **2.21** are racemic

Scheme 2.7 Scope of Carbon and Heteroatom Nucleophiles

2.7 Probing the Role of in situ Generated Water

During the course of our optimization studies we uncovered an unexpected rate enhancement catalyzed by water presumably generated during the ionization of silylenol ether **2.4** (Table 2.1). To probe this interesting phenomena we subjected both secondary and tertiary α' -hydroxy silylenol ethers **2.4** and **t-2.4** to 0.2 equiv of $\text{Py}\cdot\text{TfOH}$ for 24 hours to monitor the migration of the hydroxyl group (Scheme 2.8). To our surprise ^1H -NMR analysis showed that tertiary silylenol ether **t-2.4** was favored from both experiments in about a 3:1 ratio. In an attempt to further study this H_2O promoted rate enhancement, we executed three distinct experiments and monitored their progress by HPLC analysis (Scheme 2.8). To establish a standard baseline, silylenol ether **2.4** was subjected to our optimized conditions and monitored by HPLC (Table 2.1,

entry 5). In a subsequent experiment we added 4Å MS to sequester any trace water generated during the reaction (Table 2.1, entry 10) and immediately observed a sluggish reaction with little production of **2.6** after 8 hours. Our last trial involved the addition of 0.1 equivalents of H₂O to the reaction media which cause a rapid production of product **2.6** after only 4 hours. These experiments combined with the polar activation of silylenol ether **2.4** by acetonitrile led us to proposed that silyloxyallyl cation **2.5** is stabilized by H₂O through a noncovalent interaction *en route* to nucleophilic capture by indole at the α'-position. While the exact role of H₂O is still unknown we believe that it blocks the congested tertiary α-position leaving the less congested α'-position open for nucleophilic attack by indole.

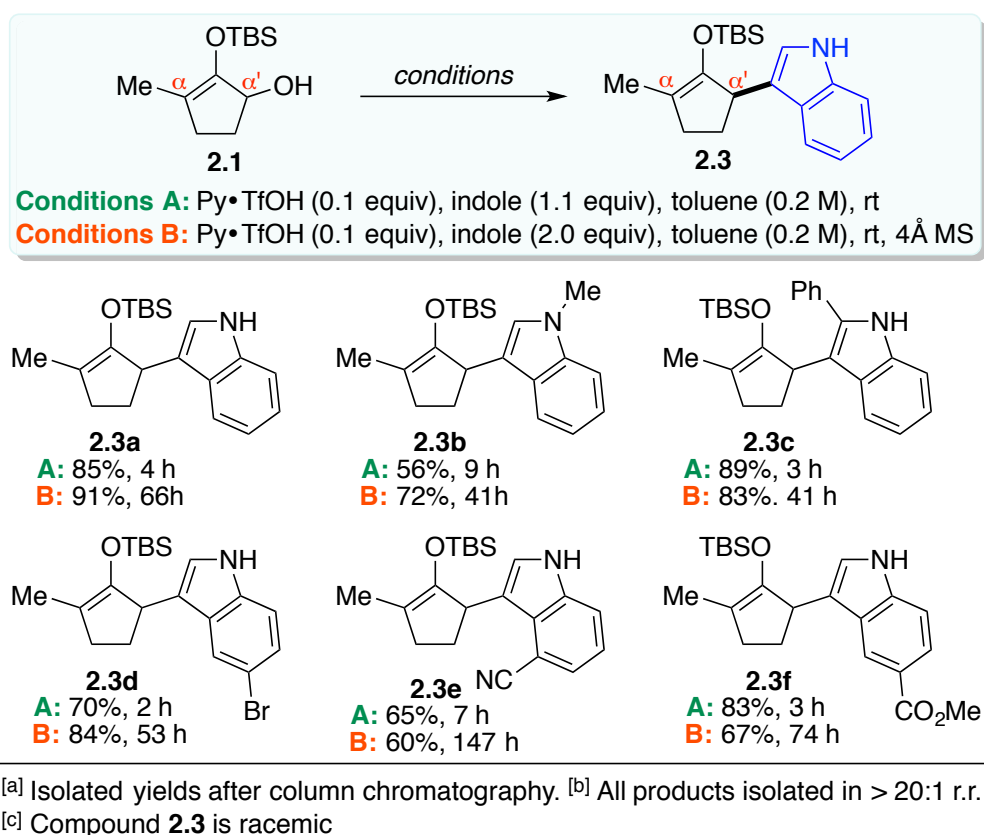


[a] Reactions monitored by HPLC analyses using 0.1 equiv of naphthalene as an internal standard

Scheme 2.8 Probing the Stabilization Effects of Water

The interesting H₂O promoted rate enhancement results thus led us to reinvestigate our initial silyloxyallyl cation discovery and study the effects of H₂O as it pertains to five-membered

system (Scheme 2.9). Since the initial reaction conditions (Conditions B) utilized 4Å MS, we devised a new set of reaction conditions, free of molecular sieves (Conditions A). Upon treatment of silylenol ethers **2.1** with Conditions A, we discovered that the desired indole coupled products **2.3** were formed in only a matter of hours rather than several days, as was the case with Conditions B. As evidenced by products **2.3a** – **2.3f**, the absence of MS did not affect the regioselectivity of the transformation, nor significantly reduce the yield and in some cases the improved the yield.



Scheme 2.9 Investigating the Effects of Trace Water in the Five-Membered System

2.8 Conclusion

In conclusion we have addressed the lack of reactivity of the six-membered silyloxyallyl cation utilizing stabilizing, polarizing solvent effects. Given the mildness of this reaction we were

able to showcase a broad scope of indole and heteroatom nucleophiles, as well as sensitive carbon based silylenol ether nucleophiles. Through an α -substituent compatibility study we discovered that aliphatic groups readily ionized liberating α' -indoyl products, while aromatic examples were sluggish. In addition, we uncovered a unique stabilization event controlled by water that is presumably generated during the ionization of substrate. This serendipitous discovery allowed us to reinvestigate the previously described five-membered silyloxyallyl cation chemistry and develop improved conditions that led to an increase in reaction rate and yields.

With the completion of this study we began to investigate the direct functionalization of hydroxyl groups through direct displacement (*i.e.* S_N2 pathways), rather than via ionization (*i.e.* S_N1 pathways). Direct displacement of an hydroxyl group allows for greater stereochemical control generated nonracemic mixtures of products if the alcohol is stereochemically defined. Significant works in this area have already been accomplished and are summarized in the proceeding chapter.

Chapter 3: Chlorination Strategies Facilitated by Triphosgene-Amine Base Activation of Unactivated Alcohols and Ketones

3.1 Purpose

The purpose of this chapter is to provide insights about the importance of organochlorides in society pertaining to their role in materials, pharmaceutical agents, and natural products chemistry. Significant attention will be paid toward the Chlorosulfolipid (CSL) family of natural products as their stereochemically complex array of chloride and hydroxyl substituents inspired a new chlorination strategy promoted by triphosgene-amine base activation. These novel chlorination strategies for the stereoselective chlorination of primary and secondary alcohols, 1,3-*syn* and 1,3-*anti* diols, as well as ketones will be summarized.

3.2 Brief Overview of Organochlorides and their Importance in Society

Organochlorides are a ubiquitous group of molecules with varying molecular architectures that are of paramount importance to the human race. The utility of chlorinated organic molecules varies vastly and are responsible for a many essential products we take for granted. To mention a few examples organochlorides are found in materials like PVC pipes⁵⁵ which are used for plumbing; as well as sucralose (Splenda®)⁵⁶ an artificial sweetener. Additionally organochlorides possess medicinal applications like Ceterizine (Zyrtec®)⁵⁷ an allergy medication and are in protective clothing like Dechlorane⁵⁸ a flame retardant material. While the afore mentioned examples are derived from synthetic labs, Mother Nature has created even more chlorinated molecules and in greater complexities. In fact there are over 2000 chlorine containing natural products on the planet located mostly in plants, aquatic life, insects, bacteria, fungi, and mammals.⁵⁹⁻⁶⁰ This vast selection of synthetic and naturally occurring compounds yields an abundance of possibilities as many organochlorides possess some biological activity.⁶¹⁻⁶²

Specifically Clindamycin an antibiotic is listed by the World Health Organization as one of their essential medicines, as it is commonly used in developing countries to treat mild to severe infections, including staph infections.⁶²⁻⁶⁴ Also when combined with quinine or chloroquine, Clindamycin has been utilized to combat malaria.⁶⁵ Additionally Zyrtec has been prescribed to treat seasonal allergies for over 30 years and is the 74th most prescribed medication in the US. A naturally occurring example, (+)-halomon is listed by the National Cancer Institute for preclinical drug development as it exhibits an extreme case of differential cytotoxicity.

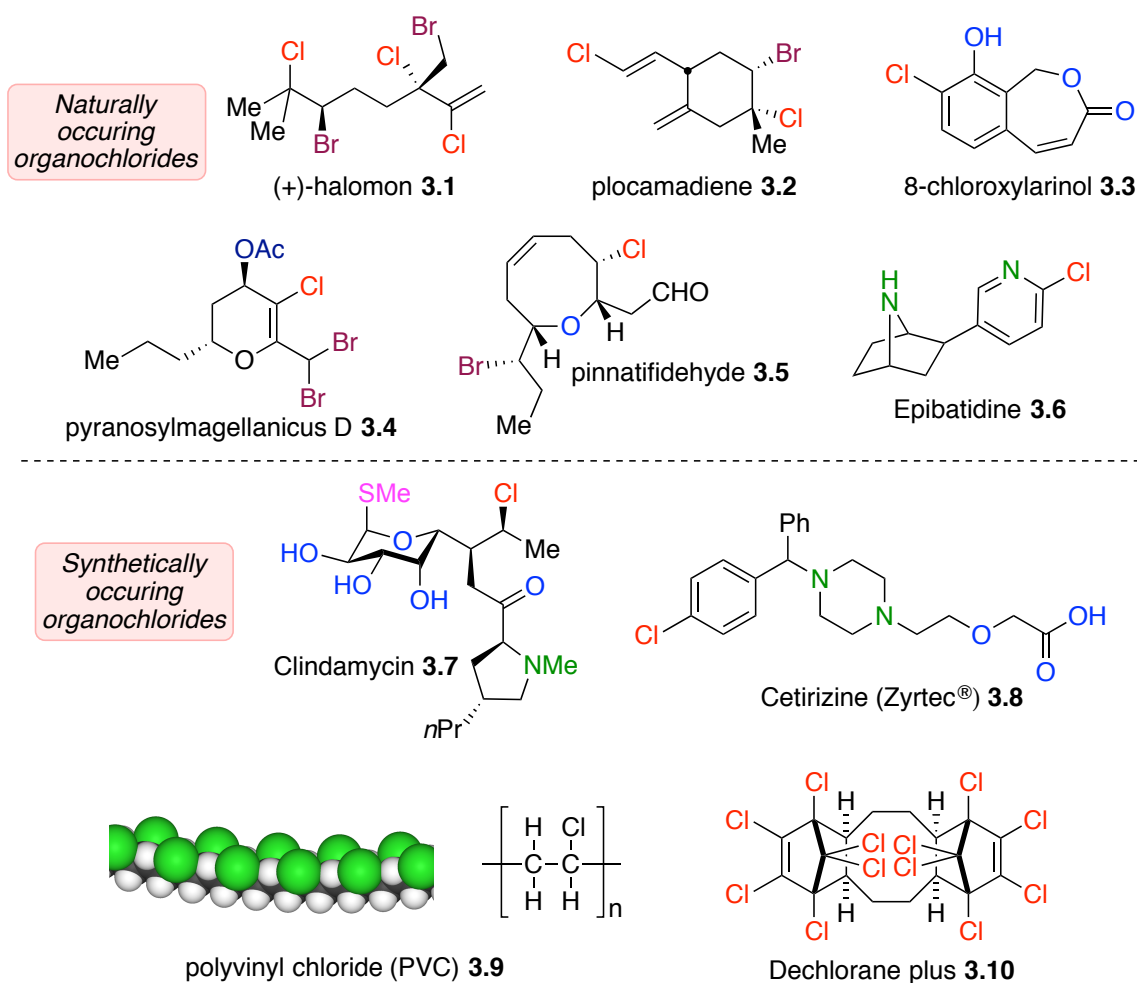


Figure 3.1 Examples of Naturally and Synthetically Occurring Organochlorides

While chlorinated pharmaceuticals and natural products are one potential application of organochlorides, another application of these privileged functional groups is their role as synthons for functional group interconversions. Specifically, carbon-chlorine bonds are routinely broken through nucleophilic substitution reactions, elimination reactions and even metal-catalyzed cross-coupling reactions. Even light-promoted heterolytic bond cleavages have been reported using organochlorides. Given the extreme utility of these functional groups a host of synthetic methods have been developed over the years to synthesize carbon-chlorine bonds.

3.3 Chlorosulfolipid Natural Products

This idea of generating C-Cl bonds with complete control of its stereochemical integrity, while doing so under mild, user-friendly conditions began with our interest in the Chlorosulfolipid Class of natural products (Figure 3.2).⁶⁶ First reported in 1969 by Haines and Vagelos, the chlorosulfolipids (CSL) have largely been ignored by synthetic organic chemists for roughly forty years.⁶⁷⁻⁶⁸ Since their first reported isolation, this family of natural products has grown to include lipid and protein kinase inhibitors, as well as causative agents of shellfish poisoning. Largely due to the advancement of modern analytical techniques, the absolute configuration of these natural products has since been established revealing very rich stereochemically diverse chloride substitutions along their aliphatic backbones. While studying the degradation of fatty acids of *Ochromonas danica*, Haines and Vagelos, independently, discovered a series of lipids containing a 22-carbon atom backbone with two sulfate esters and a up to six chlorine substituents. The most famous isolate from these reports has since become known as Danicalipin A **3.11**.⁶⁸⁻⁶⁹ Danicalipin A has become the flagship CSL as it possess vicinal dichlorides displaced by sulfate esters followed by a 1,3-*anti* dichloride motif. While some exceptions due exist this pattern of repeating dichloride units is essentially repeated across all CSL backbones.

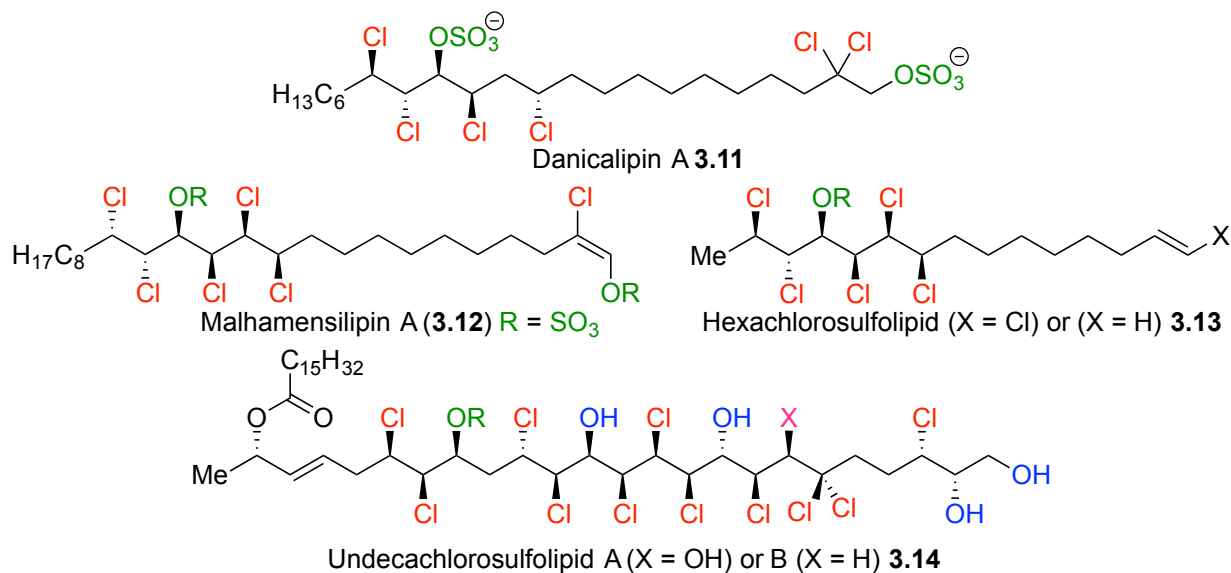


Figure 3.2 List of Chlorosulfolipid Natural Products

Roughly 25 years after Haines's and Vagelos's seminal works, Malhamensilipin A **3.12**, was discovered from the algae *Poterioochromonas malhamensis* pioneered by the efforts of Slate and Gerwick.⁷⁰ Unlike the germinal dichloride on the terminus of Danicalipin A, **3.12** contains a vinyl chloride functionality at its terminal end. Additionally Malhamensilipin was found to possess modest inhibitory activity of pp60^{v-src} protein tyrosine kinase (IC_{50} 35 μ M).⁷¹ This particular CSL also exhibited some antiviral and antimicrobial activity. From 2001 to 2004, Fattorusso reported the isolation of CLSs hexachlorosulfolipids **3.13** and undecachlorosulfolipids A and B **3.14** from the glands of toxic mussels in the Adriatic Sea.⁷²⁻⁷³ These lipids are believed to be responsible for Diarrhetic Shellfish Poisoning as they become bioaccumulated in the mussels during algal blooms, analogous to the Brevetoxins, during Red Tides. Some evidence for this bioaccumulation hypothesis exists stemmed from the works of Sheu. In 2010, Sheu and coworkers isolated CSLs **3.13** and **3.14** from octacoral *Dendronephthya griffini* in the Straits of Taiwan.⁷⁴ Sheu and his team isolated these two compounds from two independent organisms from entirely

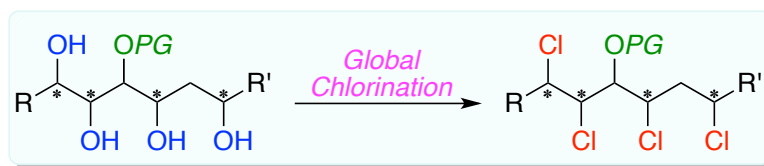
different habitats suggesting that the accumulation of CSLs is from dietary sources. Hexachlorosulfolipid **3.13** has since been discovered to have some cytotoxic activity against murine cells lines WEHI, J774, and P388 with double-digit micromolar activities. Analogous to **3.13**, undecachlorosulfolipids A and B **3.14** also contain some inherent cytotoxic properties against the same cancer cell lines as Hexachlorosulfolipid.

Since their first isolation in the late 1960s, the chlorosulfolipids remained largely untouched by synthetic chemists. Given that their aliphatic backbones contain a daunting tacticity of chlorine, sulfate, and hydroxyl substituents, plus the added unknown assignment of stereochemistries, the synthesis of these natural products remained dormant until the late 2000s.⁷⁵⁻
⁷⁷ However by realizing that chlorosulfolipid natural products are nothing more than electronic isoteres of acyclic polyketide natural products a *J*-based configuration analysis approach was developed to determine the relative stereochemistry of vicinal stereocenters. Fattorusso and Ciminiello were the first to realize that a *J*-based configuration analysis (JBCA) would be appropriate for the relative stereochemical determination of CSLs, given that this approach was originally developed for polyoxygenated polyketide natural products.⁷⁸⁻⁸⁰ Eventually, in 2009 Carreira and coworkers published the very first total synthesis of (±)-Hexachlorosulfolipid **3.13** with a landmark publication in *Nature* (Scheme 3.1).⁸¹ Using simplified hexanetriol derivatives, Carreira was able to model and develop a library of coupling constants ³*J* (H,H) between vicinal hydrogen methane carbons that had a heteroatom substituent, *i.e.* chloride or sulfate ester.⁸² Using this library along with Kishi's universal database approach⁸³⁻⁸⁴, Carreira and his team were able to determine the relative and absolute stereochemistries of chlorosulfolipid natural products.⁸⁵

Beginning with ethyl sorbate **3.15**, Carreira's team commenced their synthesis with a stereospecific dichlorination, followed by DIBAL-H reduction of the ester and diastereoselective

3.4 Global Chlorination of Polyhydroxylated Building Blocks

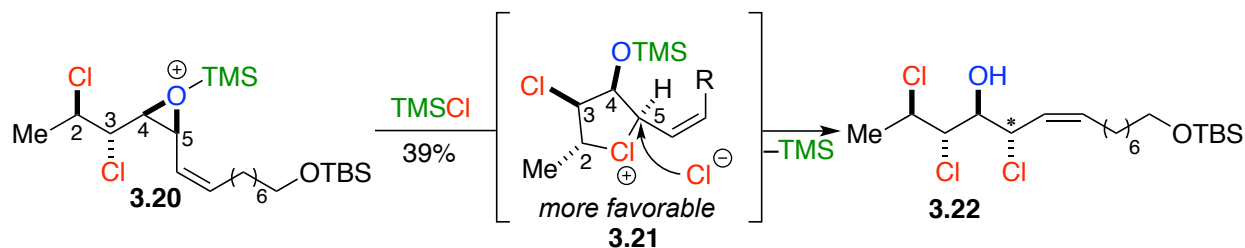
Given the trend in organic synthesis that focuses on multistep, one-pot protocols, we envisioned a new strategy for the synthesis of polychlorinated organics through global chlorination strategy of polyols. Global chlorination involves the stereoselective installation of all requisite carbon-chlorine bonds in their appropriate stereochemistries in one step. This strategy has not been attempted for the synthesis of Chlorosulfolipid fragments as all reported syntheses involve the linear construction of the carbon-chlorine appendages. Global chlorination should theoretically simplify the synthesis of the CSL family as the linear prefuctionalization of the aliphatic substrate with alkyl chlorides can lead to unanticipated reactions. Specifically epimerization and poor diastereocontrol may occur as chlorine can participate in neighboring group participation via chloronium ion species.



Scheme 3.2 Hypothesized Global Chlorination Event

For example, during Carreira's initial route towards the synthesis of **3.13** his team synthesized epoxide fragment **3.20** and subjected it to epoxide ring-opening promoted by TMSCl. However instead of forming the anticipated *syn*-chlorohydrin, the *anti*-diastereomer was realized upon the completion of their synthesis (Scheme 3.3).⁸¹ This unexpected selectivity was hypothesized to be due to neighboring group participation from the distal C-2 chloride which opens the activated epoxide at C-5 leading to five-membered chloronium ion **3.21**. This ion is then susceptible to nucleophilic attack by excess chloride ions leading to the formation of chlorohydrin

3.22. While global chlorination strategies have been used to synthesize polychlorinated aliphatics, these reports are scarce and limited in scope.⁹⁶ Given this void in the chemical space, we envisioned developing a toolbox of mono- and polychlorination reactions that could allow for the direct conversion of polyhydroxylated aliphatics to their complementary chlorinated isosteres.



Scheme 3.3 Carreira's Initial Route towards the Synthesis of **3.22**

3.5 Synthesis of Primary and Secondary Alkyl Chlorides via Triphosgene Activation

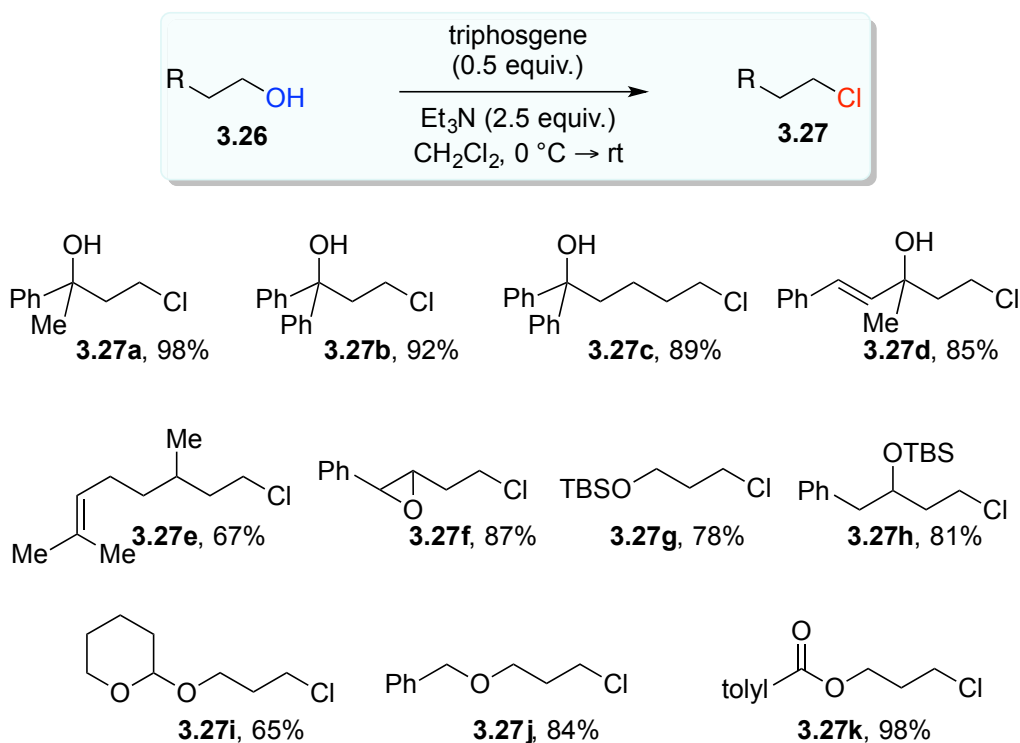
Attempts to realize the challenge of globally chlorinating polyols was initiated by my colleagues and resulted in establishing the foundation of our chlorination methodology. Beginning with 1,3-diol **3.23** they quickly established the utility of triphosgene as a chlorinating agent.⁹⁷ Triphosgene is a unique nonhygroscopic, crystalline phosgene equivalent that is benchtop stable, and does not require exceptionally dry reaction conditions.⁹⁸ However in the presence of an amine base like Et₃N or pyridine, triphosgene rapidly decomposes liberating an excess of chloride ions *in situ*.⁹⁹⁻¹⁰⁰ After a brief optimization study my colleagues realized that triphosgene proved to be a milder, robust chlorinating agent surpassing traditionally used SOCl₂ and PCl₅ (Table 3.1, entries 1 & 2). Triphosgene also proved to be advantageous as no waste byproducts were observed compared to Appel conditions (CCl₄, PPh₃) which generated wasteful triphenylphosphine oxide.¹⁰¹

Table 3.1 Optimization of Triphosgene–Et₃N Chlorination

entry	chlorinating agents	yield 3.24	yield 3.25
1	SOCl ₂	complex mixture	–
2	PCl ₅	complex mixture	–
3	CCl ₄ , PPh ₃	30%	–
4	triphosgene, PPh ₃	78%	–
5	triphosgene, Et₃N	98%	–
6	phosgene, Et ₃ N	89%	–
7	triphosgene, pyridine	–	86%
8	triphosgene, <i>i</i> Pr ₂ EtN	–	45%

^[a] Isolated yields after column chromatography

With the optimized conditions in hand, my coworkers explored the applicability of this transformation by chlorinating of series of unactivated primary alcohols (Scheme 3.4). Gratifyingly this transformation proved to be orthogonal by only chlorinating the primary alcohol. Additionally the tertiary alcohol functionalities were untouched during the course of the transformation generating the desired alkyl chloride products **3.27a** – **3.27d** in very high yields with no elimination products detected. In fact even allylic alcohol **3.27d** cooperated under the reaction conditions and no isomerized products were observed. To showcase the mildness of this transformation acid sensitive functionalities were incorporated into the starting materials. Acid-labile functional groups such as trisubstituted olefin **3.27e**, epoxide **3.27f** and TBS ethers **3.27g** and **3.27h** substrates readily reacted and formed the desired chlorinated products in good to excellent yields. No desilylated or epoxide ring-opened products were detected.

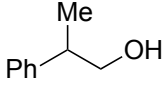
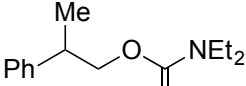
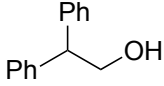
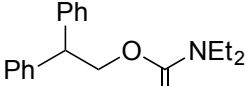
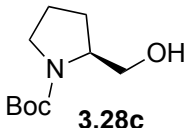
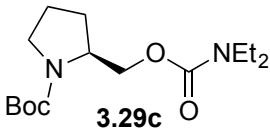
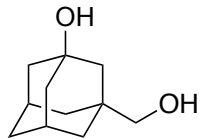
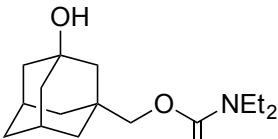


[a] Isolated yields after column chromatography.

Scheme 3.4 Scope of Primary Alcohol Substrates

While continuing their investigation, my colleagues began to study the effects of steric hindrance about the reactive site. The effects of α -branching towards the success of the reaction and these results are outline below (Table 3.2). While not all too surprising the incorporation of adjacent steric hindrance seemed to prevent the desired chlorination even from occurring and discovered upon subjection of **3.28a** to the optimized conditions liberated diethylcarbamate **3.29a** in 62% yield upon isolation. This unexpected reaction outcome proved to be general as analysis treatment of diphenyl substituted homobenzylic alcohol **3.28b** also produced its analogous carbamate product **3.29b**. Further study of this process revealed that treatment of deactivated prolinol **3.28c** and racemic adamantly diol **3.28d** to the optimized conditions again furnished the corresponding carbamate products in 73% and 62% yields, respectively.

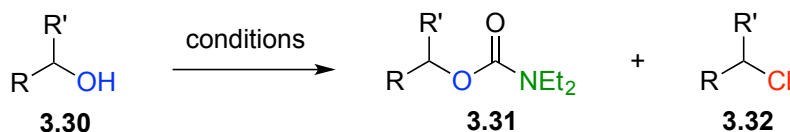
Table 3.2 Scope of α -branched Alcohols

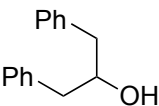
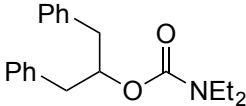
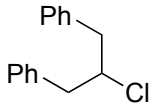
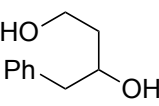
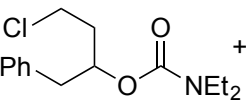
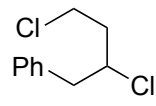
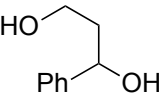
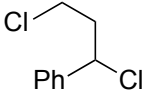
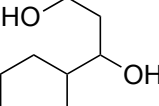
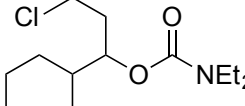
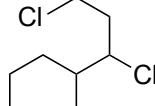
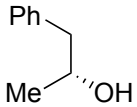
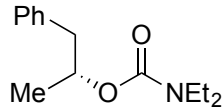
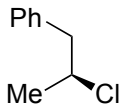
$ \begin{array}{ccc} \begin{array}{c} \text{R}_1 \\ \\ \text{CH} \\ \\ \text{R}_2 \\ \text{CH}_2\text{OH} \\ \mathbf{3.28} \end{array} & \xrightarrow[\text{CH}_2\text{Cl}_2, 0^\circ\text{C} \rightarrow \text{rt}]{\begin{array}{c} \text{triphosgene} \\ (0.5 \text{ equiv.}) \\ \text{Et}_3\text{N} (2.5 \text{ equiv.}) \end{array}} & \begin{array}{c} \text{R}_1 \\ \\ \text{CH} \\ \\ \text{R}_2 \\ \text{CH}_2\text{O} \\ \\ \text{C(=O)NEt}_2 \\ \mathbf{3.29} \end{array} \end{array} $			
entry	alcohol	product	yield
1	 $\mathbf{3.28a}$	 $\mathbf{3.29a}$	62%
2	 $\mathbf{3.28b}$	 $\mathbf{3.29b}$	85%
3	 $\mathbf{3.28c}$	 $\mathbf{3.29c}$	73%
4	 $\mathbf{3.28d}$	 $\mathbf{3.29d}$	62%

[a] Isolated yield after column chromatography.

Having established the reactivities of primary alcohols, attempts to probe the reactivities of secondary alcohols began and is summarized in Table 3.2. These studies began by exposure of 1,3-diphenylpropan-2-ol **3.30a** to the optimized chlorination conditions (Conditions A). Surprisingly almost equal mixtures of diethylcarbamate **3.31a** and secondary alkyl chloride **3.32a** were afforded in 40% and 50% yields, respectively. Continued subsection of homobenzylic diol **3.30b** with a two-fold increase in the molar equivalents of triphosgene and Et₃N (Conditions B) led to a roughly 1:4 mixture of diethylcarbamate to dichloride in favor of dichloride **3.32b**.

Table 3.3 Examination of Secondary Alcohols

Conditions A: triphosgene (0.5 equiv.), Et₃N (2.5 equiv.), CH₂Cl₂, 0 °C → rtConditions B: triphosgene (1.0 equiv.), Et₃N (5.0 equiv.), CH₂Cl₂, 0 °C → rt

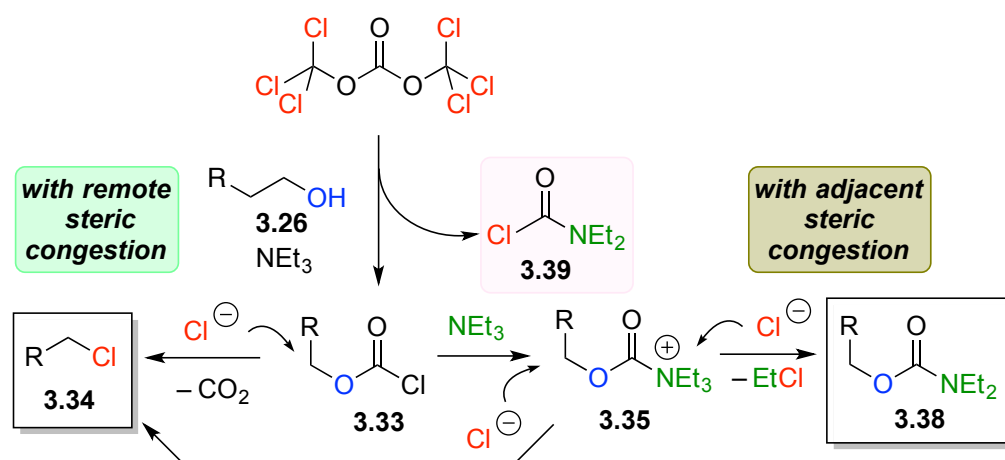
entry	conditions	alcohol	product (% yield)
1	A	 3.30a	 3.31a , 40% +  3.32a , 50%
2	B	 3.30b	 3.31b , 23% +  3.32b , 69%
3	B	 3.30c	 3.31c , 91%
4	B	 3.30d	 3.31d , 32% +  3.32d , 42%
5	A	 3.30e	 3.31e , 27% +  3.32e , 45%

[a] Isolated yields after column chromatography. [c] Lower yields attributed to the volatility of the alkyl chloride.

Analogous exposure of diol **3.30c** resulted in the formation of dichloride **3.31c** as the sole product, this result is not very surprising as the electrophilic benzylic site acts to activate the reactive benzylic alcohol for displacement by chloride. To further probe this observation saturated cyclohexyl diol **3.30d** was subjected to Conditions B and mixtures of diethylcarbamate **3.31d** and dichloride **3.32d** were generated in roughly 1:1 mixtures. To glean information about the reaction

mechanism treatment of enantioenriched alcohol **3.30e** with Conditions A yielded diethylcarbamate **3.31e** with a retention in stereochemistry, yet alkyl chloride **3.32e** was liberated with an inversion of stereochemistry, based on comparison of optical rotation data.

Ultimately, these chemical observations led to the proposal of the following reaction mechanism (Scheme 3.5). Activation of primary alcohol **3.26** with triphosgene and Et₃N most likely leads to the formation of chloroformate **3.33**. Chloroformylated **3.33** is then poised for direct nucleophilic displacement by chloride ions generating chlorinated product **3.34** or be further activated by Et₃N to triethylammonium carbamate **3.35**. In the presence of adjacent steric congestion, nucleophilic attack by chloride is impeded due to steric hindrance; therefore, dealkylation of one of the ethyl groups can occur accounting for the formation of diethyl carbamate **3.38**. However, in the presence of remote steric congestion, **3.35** can be displaced via chloride ions forming alkyl chloride **3.34**, via an S_N2 mechanism. Another observation is the formation of diethylcarbamoyl chloride **3.39** produced via the decompositions of triphosgene. This intermediate might presumably lead to the direct formation of diethylcarbamate **3.38**; however, addition of **3.23** to a premixed solution of triphosgene and Et₃N generated no reaction.



Scheme 3.5 Proposed Mechanism for the Chlorination of Primary Alcohols

3.6 Improved Conditions for the Chlorination of Secondary Alcohols

Triphosgene- Et_3N mixtures proved robust for the chlorination of primary and activated secondary alcohols but with adjacent steric congestion or unactivated secondary alcohols, a mixture of alkyl chloride and diethylcarbamate were formed. This paradigm in substrate limitation led to a follow up study by my colleagues to address these reactivity challenges (Table 3.4).¹⁰²

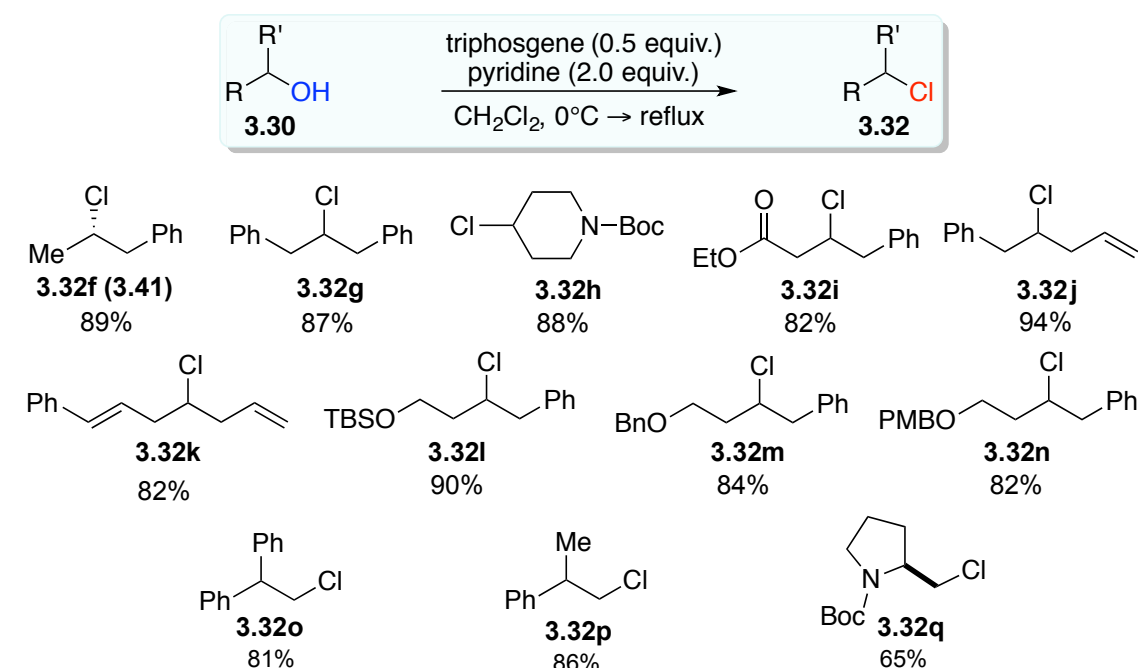
Table 3.4 Reaction Optimization for the Conversion of Secondary Alcohols to Chlorides

entry	Et_3N (equiv)	pyridine (equiv)	temperature	yield, %			
				3.39	3.40	3.41	3.42
1	1.00	1.20	0 °C → reflux	0	1	90	9
2	0	1.00	0 °C → rt	93	0	7	0
3	0	1.20	0 °C → rt	75	0	25	0
4	0	1.70	0 °C → rt	35	0	65	0
5	0	2.20	0 °C → rt	28	0	72	0
6	0	1.00	0 °C → reflux	69	0	31	0
7	0	1.20	0 °C → reflux	0	44	56	0
8	0	1.70	0 °C → reflux	2	0	98	0
9	0	2.20	0 °C → reflux	0	0	100	0

[a] Reaction components were added and warmed to the listed temperature. [b] Yields based on GC-MS analyses of the crude reaction mixtures, assuming each product elicited identical responses.

Their study began with enantioenriched alcohol **3.39**, subjecting it to a mixture of Et_3N and pyridine with triphosgene at 0 °C. Upon warming the reaction to reflux, a 1:90:9 mixture of chloroformate **3.40**, chloride **3.41**, and diethylcarbamate **3.42** was observed via GC-MS analysis (entry 1). This result suggested that Et_3N was unnecessary as it led to the formation of unwanted

3.42. A brief optimization realized that reactions with pyridine at room temperature never completely consumed alcohol **3.39** (entries 2 – 5). After warming the reaction to refluxing CH₂Cl₂ and increasing the molar equivalents of pyridine to 2.2 equiv, alkyl chloride **3.41** was produced in quantitative conversion, via GC-MS analysis of the crude reaction mixture (entry 9). As described in Section 3.5 this chlorination process most likely proceeds via an S_N2 displacement as **3.41** was produced with inversion of stereochemistry and it maintained its stereochemical integrity.

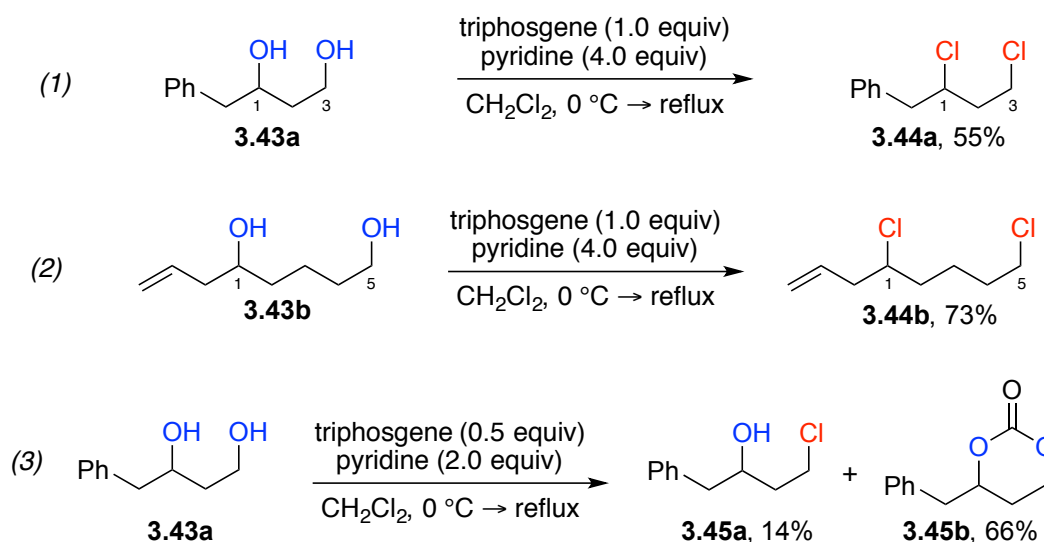


[a] Isolated yields after column chromatography. [b] < 10% elimination product detected via GC-MS

Scheme 3.6 Scope of Secondary Alcohols

With the optimized conditions in hand, the generality of the reaction was investigated via a scope of unactivated, aliphatic alcohols (Scheme 3.6). Esters, styrenyl and terminal olefins **3.32i** – **3.32k** as well as a series of oxygen atom protecting groups **3.32l** – **3.32n** afforded their respective chloride products in high yields. A limitation to the previous chlorination chemistry was steric

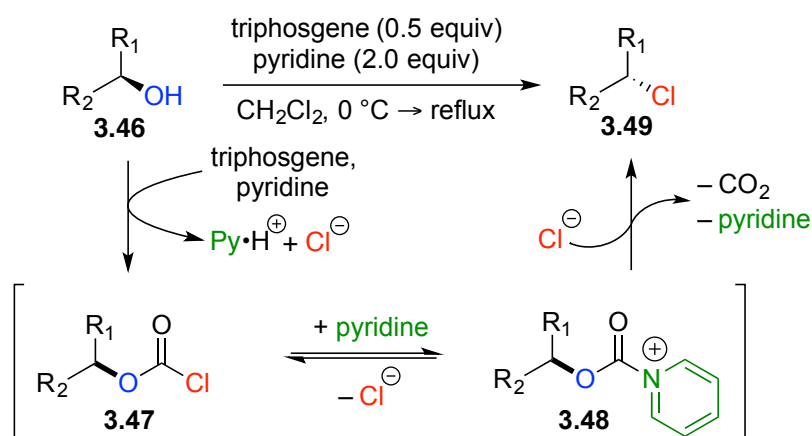
hindrance alpha to the reactive site, the newly optimized conditions superseded any steric bias forming chlorinated products **3.32o** – **3.32q** in excellent yields. These chlorination conditions provide an advantage over classic conditions ($\text{CCl}_4/\text{PPh}_3$, NCS, SOCl_2 etc) as no nuisance byproducts were formed. In fact quantitative conversion by GC-MS was observed leading to near quantitative product formation, except for roughly 10% elimination product.



Scheme 3.7 Chlorination of 1,3- and 1,5-Diols

In an attempt to explore the global chlorination of polyols, my colleagues examined the applicability of using triphosgene-pyridine mixtures to chlorinate 1,3- and 1,5-diols **3.43a** and **3.44a** (Scheme 3.7). Upon treatment of the two diol starting materials to 1.0 equiv of triphosgene and 2.0 equiv of pyridine, complementary dichloride products **3.44a** and **3.44b** were formed in 55% and 73% yields. Interestingly, chlorination of 1,3-diol **3.43a** provided 1,3-dichloride **3.44a** as the exclusive product. This suggests that chloroformylation of both alcohols precedes the competitive intramolecular six-membered carbonate formation. Indeed reduced loading of triphosgene-pyridine leads to mixtures of chlorohydrin **3.45a** and carbonate **3.45b** formation, in

favor of the six-membered carbonate (Scheme 3.7, *eqn 3*). The culmination of these data eludes to the following mechanism (Scheme 3.8). Combination of triphosgene-pyridine mixtures with alcohol **4.46** likely affords chloroformylated adduct **3.47**. Further activation by a second equivalent of pyridine presumably forms to pyridinium chloroformate **3.48**. The second activation steps further increases the electrophilicity of the secondary site, allowing for rapid decarboxylative nucleophilic displacement by chloride ions, affording alkyl chloride **3.49**. Given the quantitative conversion of alcohol to product, CO₂ and pyridine are assumed to be the only byproducts.



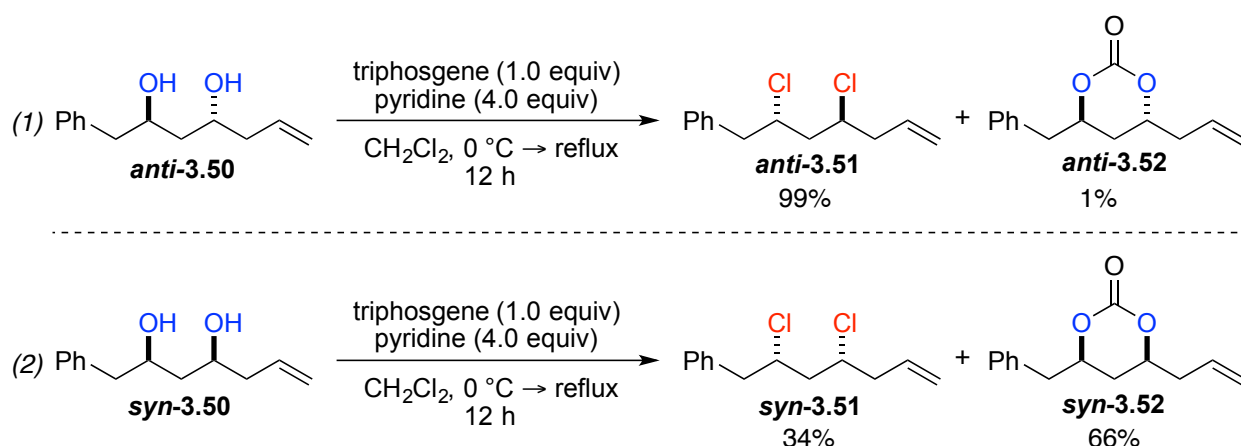
Scheme 3.8 Proposed Reaction Mechanism of the Chlorination of Secondary Alcohols

3.7 Stereoselective Synthesis of 1,3-Dichlorides via Triphosgene-Pyridine Activation

With the successful chlorination of 1,3-diols, my colleagues were then poised to tackle the synthesis of stereocomplementary 1,3-*syn* and 1,3-*anti* dichlorides.¹⁰³ This novel avenue complements known CSL syntheses as most reported syntheses focus on the construction of 1,2-dichlorides from an olefin or epoxide. The diastereoselective synthesis of 1,3-dichlorides from a 1,3-*syn* or 1,3-*anti* diols would add an additional synthetic strategy that could be used to construct these natural products. However it's important to remember that triphosgene is routinely used for

the conversion of 1,3-diols to cyclic carbonates. Therefore, competing 1,3-carbonate formation must be limited or impeded all together as carbonate formation is an irreversible process.

My colleagues began their investigation with the combination of homobenzylic diol **anti-3.50** with mixtures of triphosgene-pyridine in CH₂Cl₂ at 0 °C. After the successful addition of all reaction components, the mixture was subsequently warmed from 0 °C to reflux (Scheme 3.9, *eqn 1*). After 12 hours dichloride **anti-3.51** was generated in 90% yield as a single diastereomer (Scheme 3.9, *eqn 1*). GC-MS analysis of the crude reaction mixture revealed the presence of cyclic carbonate **anti-3.52** in a 99:1 ratio. Formation of the *anti*-cyclic carbonate is most likely disfavored due to steric, 1,3-diaxial interactions within the six-membered cyclic compound.

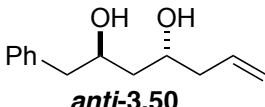
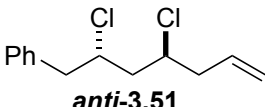
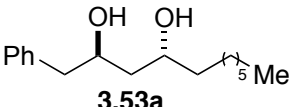
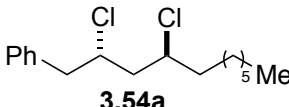
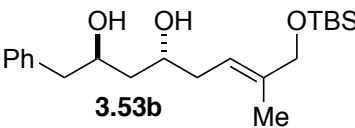
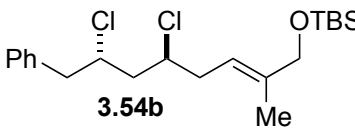
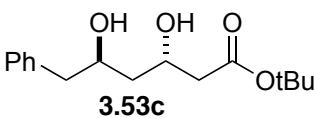
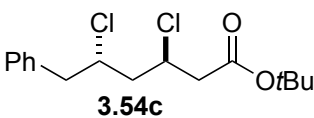


Scheme 3.9 Initial Studies of Triphosgene-Pyridine Chlorination of 1,3-diols

A scope of 1,3-*anti* diols was subsequently examined leading to clean, nearly quantitative conversion to their respective dichlorides (Table 3.5). All products were isolated as single diastereomers and presumed to be *anti*, based on analogy. Gratifyingly this dichlorination strategy allowed structurally complex alcohol **3.53b** affording the desired dichloride **3.54b** in 80%. This method also allowed for the conversion of δ,γ -dihydroxy ester **3.53c** to the dichloride product in

a modest yield of 73%. Also, this method proved to be tolerant of acid sensitive functional groups such as the TBS ethers, trisubstituted olefin, and *tert*-butyl ester.

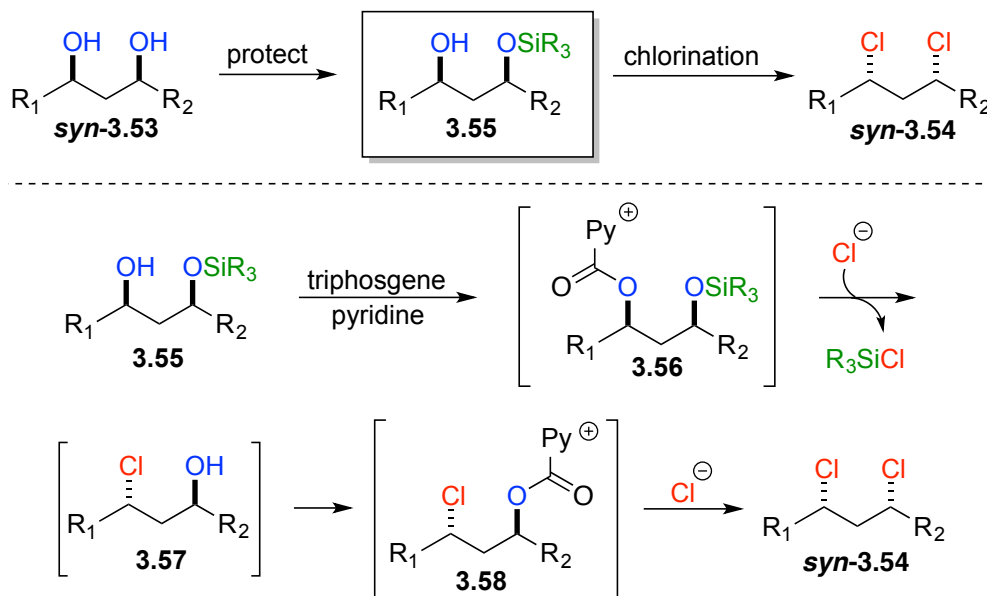
Table 3.5 Scope of 1,3-*anti* Diols

$ \begin{array}{ccc} \begin{array}{c} \text{OH} \quad \text{OH} \\ \quad \\ \text{R}_1 - \text{CH} - \text{CH} - \text{R}_2 \\ \text{anti-3.53} \end{array} & \xrightarrow[\text{CH}_2\text{Cl}_2 \text{ (60 - 100 mM)}]{\text{triphosgene (1.0 equiv)} \\ \text{pyridine (4.0 equiv)} \\ 0^\circ\text{C} \rightarrow \text{reflux}} & \begin{array}{c} \text{Cl} \quad \text{Cl} \\ \quad \\ \text{R}_1 - \text{CH} - \text{CH} - \text{R}_2 \\ \text{anti-3.54} \end{array} \end{array} $			
entry	starting material ^[b]	product ^[c]	yield ^[a]
1	 anti-3.50	 anti-3.51	90%
2	 3.53a	 3.54a	65%
3	 3.53b	 3.54b	80%
4	 3.53c	 3.54c	73%

^[a] Isolated yields after column chromatography. ^[b] Starting materials are racemic but in > 20:1 d.r. ^[c] Products formed as a single diastereomer.

While 1,3-*anti* dichlorination provided their respective dichloride products as single diastereomers, conversion of the *syn*-diastereomeric alcohols proved more challenging (Scheme 3.9, eqn 2). For example, subjection of *syn*-3.50 to identical chlorination conditions as revealed the formation of dichloride *syn*-3.51 as a ~1:2 mixture in favor of carbonate *syn*-3.52. 1,3-*syn*-

carbonate is most likely favored as its conformation possesses no unfavored 1,3-diaxial interactions in the chair conformation. This result suggests that upon chloroformylation of one of the *syn*-alcohols, rapid intramolecular carbonate formation occurs before the second alcohol can be chloroformylated or the preceding chlorination event can occur on the first alcohol.

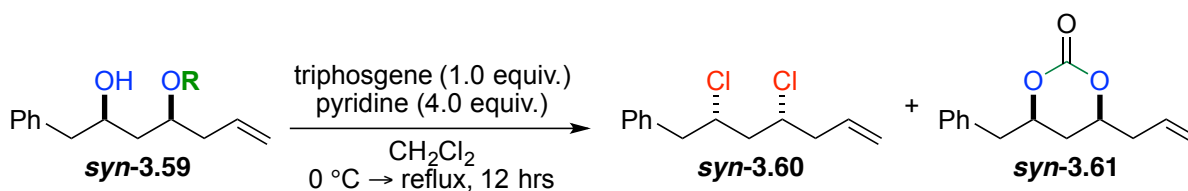


Scheme 3.10 Protection of Chlorination Strategy for 1,3-*syn* diols

Inspired by the work of Farrás, my colleagues chose to examine the mono-protection of 1,3-*syn* diol **syn-3.53** as a silyl ether. Farrás and coworkers showcased the cleavage of a TBS ether by chloride ions was possible in refluxing DMF.¹⁰⁴ Given this literature precedent my colleagues began to apply this strategy to their chemistry (Scheme 3.10). Monosilylated diol **3.55** can presumably be converted to putative pyridinium chloroformate **3.56** via triphosgene-pyridine activation. This electrophilic intermediate is then susceptible to nucleophilic attack by chloride ions liberating pyridine and producing monochlorinated product **3.57**. As mentioned previously the decomposition of triphosgene by pyridine leads to the liberation of a large excess of chloride

ions. This excess is then presumably suited to attack the silicon atom¹⁰⁵ of the silyl ether liberating β -chloroalcohol **3.57**. This reactive intermediate can then undergo analogous pyridinium chloroformylation followed by nucleophilic chlorination, liberating 1,3-*syn* dichloride **syn-3.54**. The key to this reaction's success is identifying an appropriate silyl group that can be easily removed by chloride ions. Table 3.6 outlines their study and reaction optimization.

Table 3.6 Screening and Reaction Optimization with 1,3-*syn* Monosilyl Ether



entry	R	Conc. (mM) ^[a]	syn-3.60 : syn-3.61 ^[b]
1	H	25	34 : 66
2	SiMe ₃	25	65 : 35
3	SiEt ₃	25	32 : 68
4	SiMe₂Ph	25	80 : 20
5	SiMePh ₂	25	65 : 35
6	SiMe ₂ Ph	5	69 : 31
7	SiMe ₂ Ph	100	80 : 20
8	SiMe₂Ph	500	99 : 1

[a] Concentration based on starting material **syn-3.59**. [b] Ratios of **syn-3.60** to **syn-3.61** determined by GC-MS analyses of the crude reaction mixtures.

As shown in entries 2–5, several silyl ethers such as trimethylsilyl, triethylsilyl and dimethylphenylsilyl and diphenylmethylsilyl were examined toward the optimized reaction conditions. Interestingly, dimethylphenylsilyl ether was found to be the most labile to the optimized conditions forming a 4:1 mixture of dichloride **syn-3.60** to carbonate **syn-3.61** (entry 4). Evidently this process was found to be dependent on solvent concentration (entries 6–8) and a brief

optimization revealed increasing the concentration from 25 mM to 500 mM afforded the desired dichloride **syn-3.60** in a ratio of 99:1 in favor of the dichloride product (entry 8).

Table 3.7 Scope of 1,3-*syn* Diols

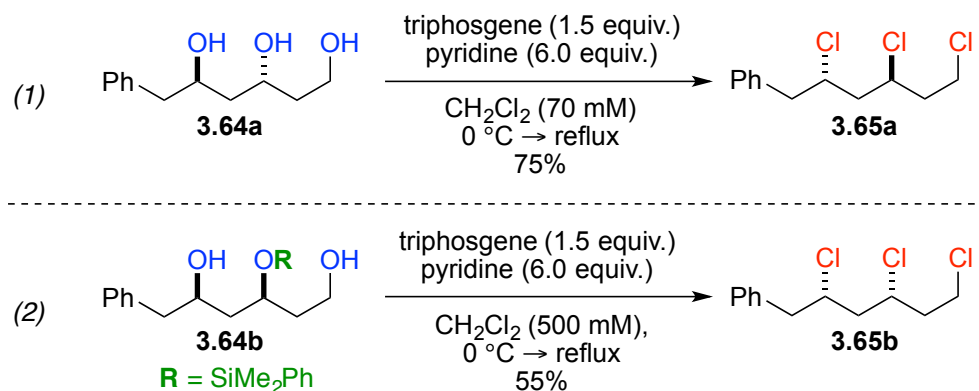
$ \begin{array}{c} \text{OH} \quad \text{OR} \\ \quad \\ \text{R}_1 - \text{CH} - \text{CH} - \text{R}_2 \\ \text{syn-3.62} \\ \text{R} = \text{SiMe}_2\text{Ph} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2 \text{ (500 mM), } 0^\circ\text{C} \rightarrow \text{reflux}]{\text{triphosgene (1.0 equiv), pyridine (4.0 equiv)}} \begin{array}{c} \text{Cl} \quad \text{Cl} \\ \quad \\ \text{R}_1 - \text{CH} - \text{CH} - \text{R}_2 \\ \text{syn-3.63} \end{array} $			
entry	starting material ^[b]	product ^[c]	yield ^[a]
1	 syn-3.59	 syn-3.60	76%
2	 3.62a	 3.63a	82%
3	 3.62b	 3.63b	94%
4	 3.62c	 3.63c	92%

^[a] Isolated yields after column chromatography. ^[b] Starting materials are racemic but in > 20:1 d.r. ^[c] Products formed as a single diastereomer.

An analogous substrate scope study was then conducted utilizing the diastereomeric 1,3-*syn* monosilylated diols to the newly optimized conditions. Model substrate **syn-3.59** was examined first and upon exposure to triphosgene-pyridine mixtures at reflux yielded 1,3-*syn* dichloride **syn-3.60** in 76%. Subsequent treatment of advanced monosilylated diol **3.62b** to the

same conditions produced its dichlorinated counterpart with no obvious decomposition in 94%. Lastly, *tert*butyl ester **3.62c** also reacted cleanly afforded 1,3-*syn* dichloride **3.63c** in 92%.

As a final aim to explore the strategy of global chlorination, my colleagues continued their substrate scope studies with the investigation of the reactivities of 1,3,5-*anti*/ *syn* triols (Scheme 3.11). Beginning with 1,3,5-*anti* triol **3.64a** they showed that by tripling the stoichiometric equivalents of triphosgene to 1.5 equiv. and pyridine to 6.0 equiv., trichloride **3.65a** could be formed with presumed inversion of stereochemistry. Analysis of the crude reaction mixture showed that the reaction produced trichloride **X** in clean, quantitative conversion and in 75% isolated yield. Analogous treatment of 1,3,5-*syn* triol **3.64b** with identical triphosgene-pyridine loading but at 500 mM concentration afforded trichloride **3.65b** in 55% yield.



Products isolated as single isomers with presumed inversion of stereochemistry

Scheme 3.11 Synthesis of 1,3,5-*anti* and 1,3,5-*syn* Trichlorides

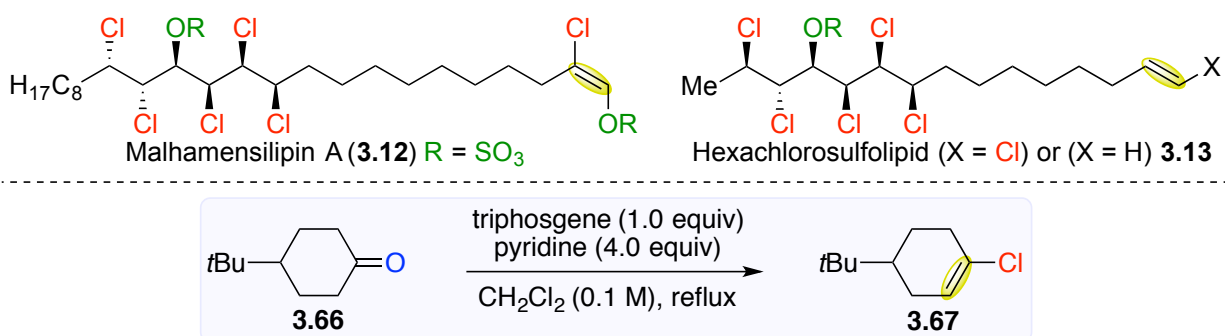
Lastly, it's necessary to mention that determination of the relative stereochemistries of the dichlorinated and trichlorinated products proved to be challenging. However using a technique developed by Carman and Nougier, the relative stereochemistry of the 1,3-*syn* vs 1,3-*anti*

diastereomers could be deduced by directly comparing the ^{13}C NMR chemical shifts of the chlorinated methine carbons, relative to the adjacent methylene carbons.¹⁰⁶⁻¹⁰⁷

3.8 Synthesis of Vinyl Chlorides via from Unactivated Ketones

Another important structural motif that the CSLs display is a vinyl chloride. As illustrated in Scheme 3.12, CSLs **3.12** and **3.13** have either a terminally substituted or internally substituted vinyl chloride functionality. Vinyl chlorides are also routinely used for various metal-mediated carbon-carbon and carbon-heteroatom bond formations.¹⁰⁸⁻¹⁰⁹ Given their extreme importance for synthetic chemists several reports exist detailing various methods to synthesize vinyl chlorides; however, most rely on very acidic and harsh chlorination conditions (PCl_3 , PCl_5 , POCl_3)¹¹⁰ that can readily hydrolyze the newly generated vinyl chloride as well as lead to substrate limitations.

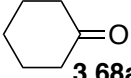
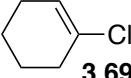
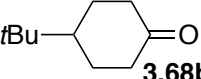
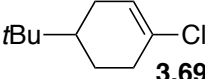
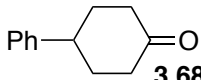
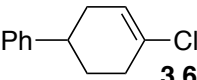
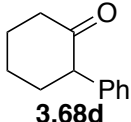
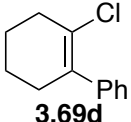
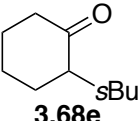
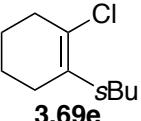
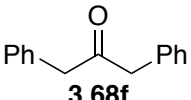
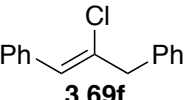
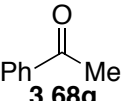
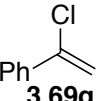
Naturally efforts to expand our established chlorination methodology utilizing triphosgene-pyridine continued by developing a new strategy to chlorinate unactivated, aliphatic ketones vinyl chlorides.¹¹¹ This strategy has been exploited previously; in fact, there are several reports that detail the synthesis of vinyl chlorides from alkynes, α,β -unsaturated carbonyls, vinyl trifluoroborates, vinyl triflates, and cyclopropenes.¹¹²⁻¹¹⁷ My colleagues realized that a ketone would provide an appropriate retron for vinyl chloride. Using 4-*tert*butyl-1-cyclohexanone and with detailed, meticulous analysis of crude reaction mixtures, my colleague produced the optimized reaction conditions shown in Scheme 3.12. It was discovered that at room temperature conversion of ketone **3.66** to vinyl chloride **3.67** plateaued at about 80% conversion with 4.0 equiv of pyridine. After increasing the reaction temperature to reflux conversion remained stalled at 80%; therefore the stoichiometric loading of triphosgene was increased to 1.0 equivalent and 100% conversion of **3.66** to vinyl chloride **3.67** was observed.



Scheme 3.12 Optimized Conditions for Vinyl Chlorination

With the optimized conditions in hand, a ketone substrate compatibility investigation commenced shown in Tables 3.8 and 3.9. GC yields and isolated yields were presented together as the isolation of vinyl chlorides is quite challenging. In fact my colleagues reported that buffering the SiO_2 with Et_3N prior to chromatographic purification failed to prevent hydrolysis of the crude vinyl chloride mixtures. Chlorination of substituted cyclohexanones **3.68a** – **3.68e** afforded quantitative conversion via GC analysis in moderate to excellent isolated yields. Cyclohexanone derived vinyl chloride **3.69a** most likely decomposed during chromatographic purification and is also quite volatile. However chlorination of heavier cyclohexanones **3.68b** and **3.68c** produced their respective vinyl chloride in 80% and 93% isolated yields. Surprisingly subsection of α -substituted ketones **3.68e** and **3.68f** to chlorination conditions failed to generate single regioisomeric products, instead producing inseparable mixtures of regioisomers in 3:1 and 6:1 r.r., respectively. This result is most likely governed by statistics, as there is an extra proton at the unsubstituted α -carbon, relative to the substituted carbon. Additionally, vinyl chlorination of acyclic ketones proceeded smoothly. Again the low yields are most likely attributed to decomposition on silica gel and volatility.

Table 3.8 Scope of Aliphatic Ketones

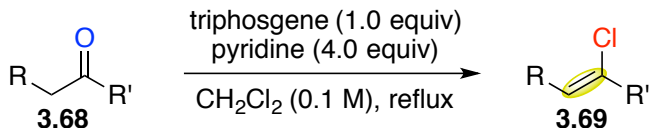
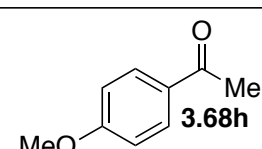
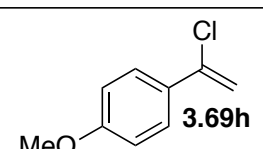
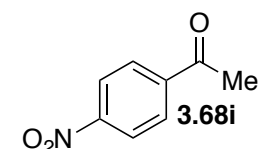
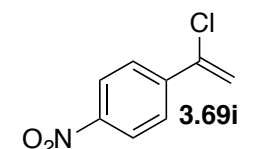
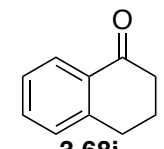
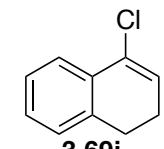
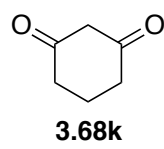
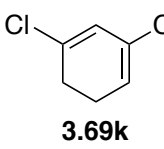
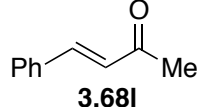
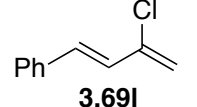
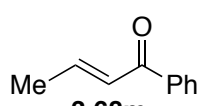
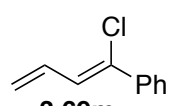
$ \begin{array}{c} \text{R}-\text{CH}_2-\text{C}(=\text{O})-\text{R}' \\ \text{3.68} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2 (0.1 \text{ M}), \text{ reflux}]{\text{triphosgene (1.0 equiv)} \\ \text{pyridine (4.0 equiv)}} \begin{array}{c} \text{R}-\text{CH}=\text{C}(\text{Cl})-\text{R}' \\ \text{3.69} \end{array} $					
entry	starting material	product	GC yield ^[a]	Isolated yield ^[b]	time (h)
1	 3.68a	 3.69a	100%	20% ^[c]	16
2	 3.68b	 3.69b	100%	80%	15
3	 3.68c	 3.69c	100%	93%	24
4	 3.68d	 3.69d	85% (3:1 r.r.)	42%	24
5	 3.68e	 3.69e	66% (6:1 r.r.)	34%	24
6	 3.68f	 3.69f	43% (5:1 Z:E)	23% ^[c] (5:1 Z:E)	72
7	 3.68g	 3.69g	71%	33% ^[c]	48

^[a] GC yields from analysis of crude reaction mixtures. ^[b] Isolated yields after column chromatography. ^[c] Low yields due to decomposition during purification.

Additional benzylic ketones **3.68g** – **3.68j** were examined, affording their corresponding vinyl chlorides in excellent and moderate GC yields, but lower isolated yields. Not surprisingly the *p*-NO₂ example **3.68i** reacted sluggishly at 72 hours for 51% conversion. Chlorination of α -tetralone **3.68j** proceeded smoothly, with 98% conversion. Additionally, vinyl chlorination of 1,3-

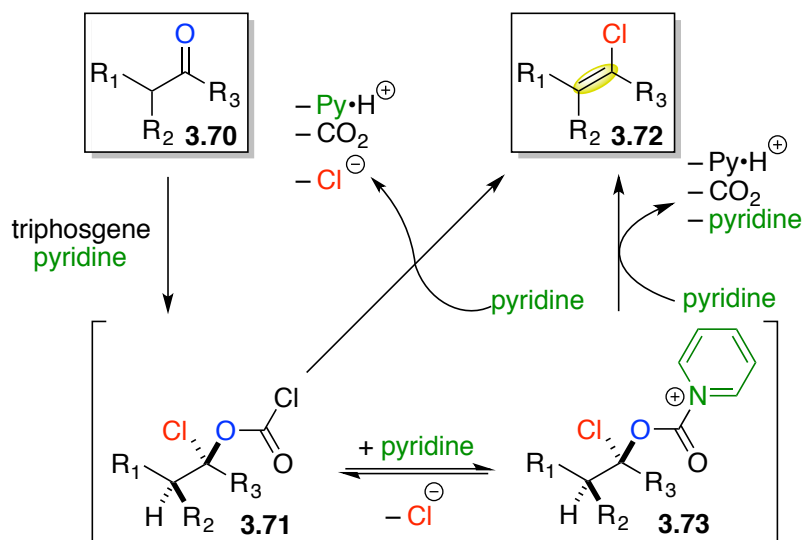
diketone **3.68k** was tolerated under the optimized reaction conditions. Lastly, chlorination of α,β -unsaturated examples **3.68l** and **3.68m** provided a mixed bag of product formation. Chlorination of **3.68l** proceeded smoothly with 100% conversion, albeit low isolated yield generating conjugated vinyl chloride; however, chlorination of regioisomeric **3.68m** failed and only trace amounts of product was observed after 24 hours.

Table 3.9 Ketone Substrate Study Continued

<div style="text-align: center;">  </div>					
entry	starting material	product	GC yield ^[a]	Isolated yield ^[b]	time (h)
8	 3.68h	 3.69h	89%	22% ^[c]	48
9	 3.68i	 3.69i	51%	54%	72
10	 3.68j	 3.69j	98%	54%	24
11	 3.68k	 3.69k	79%	41%	24
12	 3.68l	 3.69l	100%	25% ^[c]	24
13	 3.68m	 3.69m	trace	—	24

^[a] GC yields from analysis of crude reaction mixtures. ^[b] Isolated yields after column chromatography. ^[c] Low yields due to decomposition during purification.

Collectively, these substrate studies led to the proposal of the following mechanism (Scheme 3.13). Combination of ketone **3.70** with triphosgene-pyridine presumably generates a geminal substituted chloro-chloroformate **3.71**. Analogous to a tetrahedral intermediate this unstable intermediate can react through two separate mechanistic pathways. One pathway involves the decomposition of **3.71** upon deprotonation at the α -carbon by pyridine, liberating CO_2 plus an additional equivalent of chloride ion, forming vinyl chloride **3.72**. The second proposed pathway involves further activating the geminal chloro-chloroformate by pyridine generating pyridinium carbamate **3.73**. Further decomposition of intermediate **X** via deprotonation at the α -carbon by ultimately leads to vinyl chloride **3.72**. It's entirely possible that both reactive pathways could be operative at the same time leading to the formation of **3.71**.



Scheme 3.13 Proposed Mechanism for Vinyl Chloride Formation

3.9 Conclusion

In conclusion an overview of triphosgene-amine base promoted chlorination has been presented. This extremely versatile dual component mixture allows for the mild, selective chlorination of both primary and secondary alcohols, 1,3-*syn/anti* diols, and ketones. While additionally developed for the global chlorination of polyols, this methodology has become an essential chlorination reaction that has found utility outside of our lab, amongst the synthetic community. In fact, Prof. Dirk Trauner (Univ. Columbia) stated in his synthesis of Carinatine A chlorination of a primary alcohol with triphosgene-Et₃N mixtures outperformed classical chlorination strategies.¹¹⁸ Additionally, Prof. Christopher Vanderwal has utilized triphosgene-pyridine mixture to stereoselectively install a secondary alkyl chloride and reported no loss in stereochemical purity.¹¹⁹ With the generation of these general and mild chlorination strategies, we then began to explore other oxygen containing functionalities that would readily convert to their corresponding alkyl chlorides. Additionally the synthesis of vicinal dichloride using triphosgene-pyridine chemistry remained elusive as the conversion of 1,2-diols to dichlorides remained elusive.

Chapter 4: Synthesis of Vicinal Dichlorides from Unactivated Terminal Epoxides via Triphosgene-Pyridine Activation

4.1 Purpose

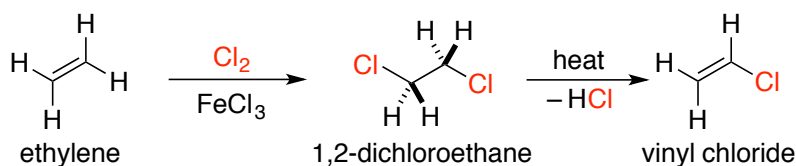
The purpose of this chapter is to review strategies for the synthesis of vicinal dichlorides. There are two different types of reactivities that are employed to accomplish the task of installing the 1,2-dichloride motif. The most well studied pathway utilizes an electrophilic chlorine source such as elemental chlorine or *N*-chlorosuccinimide and an olefin generally. The second strategy utilizes a nucleophilic source of chlorine like simple chloride ions and an epoxide generating the dichloride motif via a chlorohydrin intermediate. A brief review of these approaches will be discussed. Also a recent advancement from our lab will be presented on the chlorination of epoxides via triphosgene-pyridine activation. An appropriate scope of substrates will be examined as well as a model to predict the stereochemical outcome.

4.2 Dichlorination Strategies for Vicinal Dichloride Synthesis

As mentioned previously the installation of carbon-chlorine bonds remains a very active area of research amongst synthetic chemists. While we have seen how monochlorination, 1,3-dichlorination strategies and even vinyl chlorination^{97, 102-103, 111} can be very advantageous strategies for the synthesis of polychlorinated small molecules (Chapter 3), another chlorination strategy revolves around the synthesis of 1,2-dichlorides, otherwise known as vicinal dichlorides. Vicinal dichlorides are a unique structural motif found in various natural products but have recently been given significant attention due to their presence in the Chlorosulfolipid family.^{74, 87, 89, 120} Given this widespread interest several reports for dichloride syntheses have been reported.

4.3 Recent Strategies for Vicinal Dichloride Synthesis from Olefins

Classically the synthesis of vicinal dichlorides is accomplished via the passing of chlorine gas (Cl_2) over an alkene at elevated temperatures and pressures, or in the presence of a metal catalyst. This method is robust and has been used by the chemical industry for well over 100 years. In fact, the dichlorination of ethylene is a key step in DuPont's production of polyvinyl chloride (PVC).¹²¹⁻¹²² The combination of ethylene and Cl_2 gases over an FeCl_3 catalyst produces 1,2-dichloroethane. This simple feedstock chemical is then cracked under high temperatures to vinyl chloride monomer. This monomer is then polymerized under various processes liberating PVC. However, while the utility of gaseous Cl_2 in the chemical industry is extremely common, its danger and requirement for special gas handling apparatus render its use in an academic lab challenging. Therefore several synthetic methods have been developed to circumvent this issue.

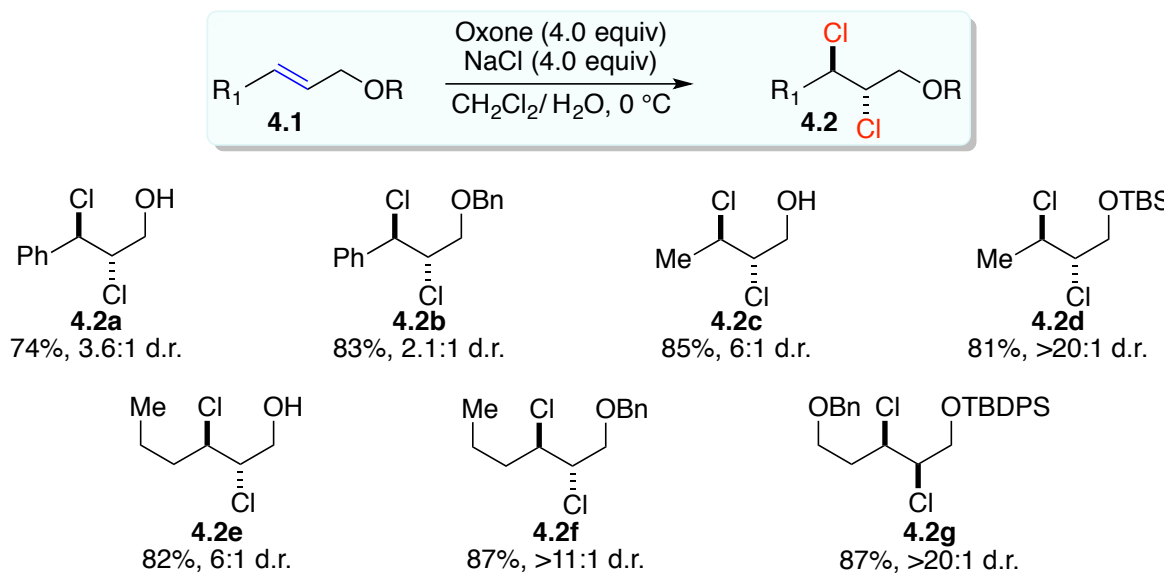


Scheme 4.1 Synthesis of Vinyl Chloride Monomer

4.3.1 Dichlorination *in situ* Generated Molecular Chlorine

In 2013 Tong and coworkers reported the dichlorination of olefins using mixture of Oxone[®] and table salt, NaCl .¹²³⁻¹²⁴ Tong's report detailed the combination of these two reagents in biphasic CH_2Cl_2 in the presence of cinnamyl alcohol **4.1**, afforded the desired 1,2-dichloride **4.2** (Scheme 4.2). This method provided *syn* and *anti*-dichloride products when the respective *cis* or *trans* olefin were used, in good to excellent diastereomeric ratios. The mechanism for this transformation is believed to involve the oxidation of chloride ions to elemental chlorine, or its equivalents, as this

observation was supported through UV-Vis analysis after the combination of Oxone[®] and NaCl. The resulting chlorination reaction presumably proceeds via the established mechanism by which Cl₂ chlorinates an olefin, by presumably generating a facially nonselective chloronium ion intermediate¹²⁵⁻¹²⁶ that is intercepted by chloride leading to the dichloride product.



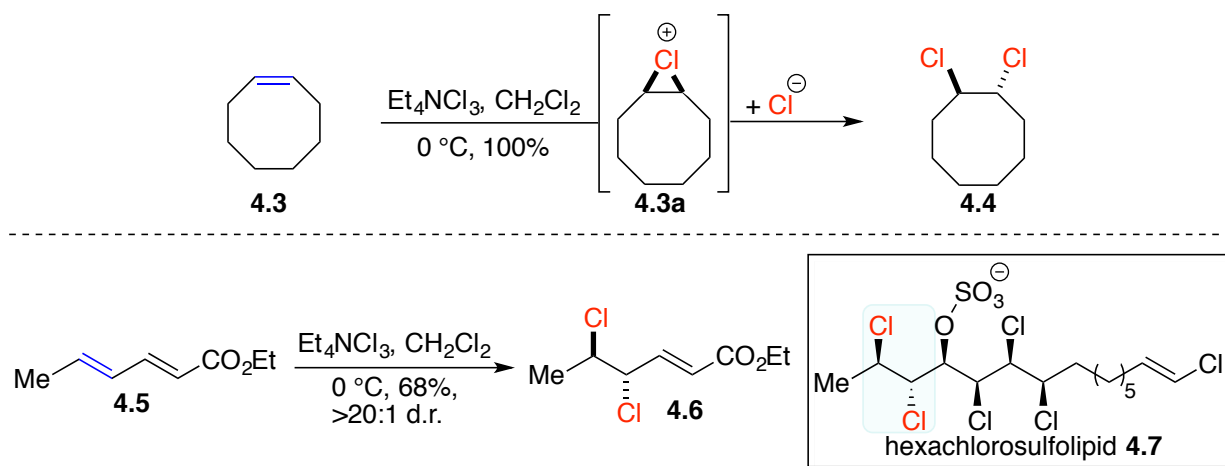
[a] Isolated yields after column chromatography.

Scheme 4.2 Dichlorination of *trans*-alkenes

4.3.2 Dichlorination with Mioskowski's Reagent: Et₄NCl₃

In 1923 Chattaway and Hoyle were the first to discover that tetraethylammonium chloride (Et₄NCl) could be oxidized to tetraethylammonium trichloride (Et₄NCl₃) by passing chlorine gas over the white solid liberating a yellow, hygroscopic salt.¹²⁷ While several studies concerning the bonding of this salt had been reported since its initial discovery, it wasn't until 1997 when Mioskowski discovered its utility as an oxidant and chlorination agent by chlorinating cyclic alkenes (Scheme 4.3).¹²⁸ For example the dichlorination of cyclooctene **4.3** can be accomplished in quantitative yield by combining the olefin and Et₄NCl₃ and stirring in CH₂Cl₂ at 0 °C. While

still hazardous Et_4NCl_3 has found extensive use as a preparative scale chlorine source as it is a solid that can be measured out in a fume hood and is easier to control the stoichiometric amounts relative to Cl_2 gas. In fact Carreira applied Et_4NCl_3 in the first step of his synthesis of Hexachlorosulfolipid **4.7**. Beginning with ethyl sorbate **4.5**, Carreira was able to generate 1,2-*anti* dichloride **4.6** stereospecifically in 68% yield and in >20:1 d.r.⁸¹

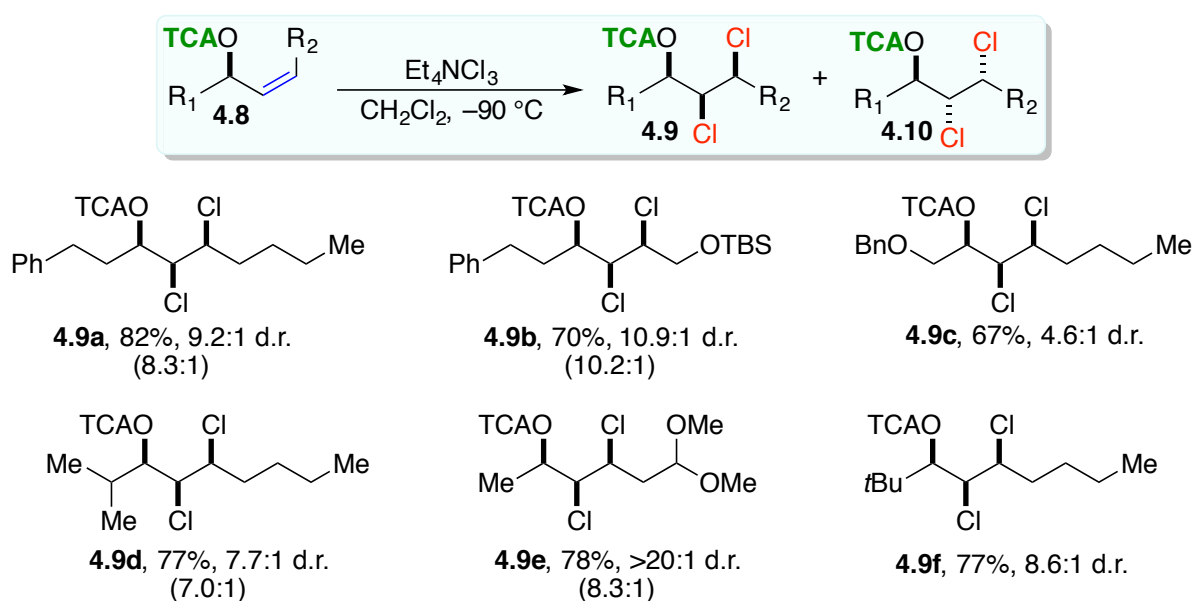


Scheme 4.3 Examples Utilizing Mioskowski's Reagent

While the exact mechanism of vicinal dichloride formation with Mioskowski's reagent is not known, it is believed to be distinct from the mechanism provided by direct chlorination with molecular chlorine. However, given the high degree of stereospecificity of this transformation it is plausible that a chloronium ion forms via some redox process and is then intercepted by chloride ions via an *anti*-addition leading to the observed 1,2-*anti* dichloride products.¹²⁹⁻¹³⁰ In fact the high stereospecificity observed when this reagent is used is one clear advantage over the use of elemental chlorine, which frequently leads to poor diastereoselectivities.

Significant attention has been paid to render chlorination with the Mioskowski reagent stereoselective by using a directing group such as an allylic alcohol or allylic acetate. The current

leader in this area of research is from the Vanderwal Lab located at the University of California-Irvine. Vanderwal's lab has demonstrated that reactions of (*Z*)-allylic trichloroacetates with Et₄NCl₃ enables stereoselective formation of a *syn,syn*-hydroxydichloride stereotriad found in the Chlorosulfolipids (Scheme 4.4).⁸⁸ Combination of **4.8** with Et₄NCl₃ in CH₂Cl₂ at -90 °C afforded *syn,syn*-hydroxydichloride products **4.9** in good yields and moderate to excellent diastereoselectivities. This reaction proved tolerant to various aliphatic substituents **4.9a–4.9f** and even some heteroatom groups, although with diminished diastereoselectivities. Presumably the observed diastereoselectivity is governed by the directing group abilities of the trichloroacetate. This process seemingly avoids eclipsing allylic strain leading to enhanced diastereoselectivities.

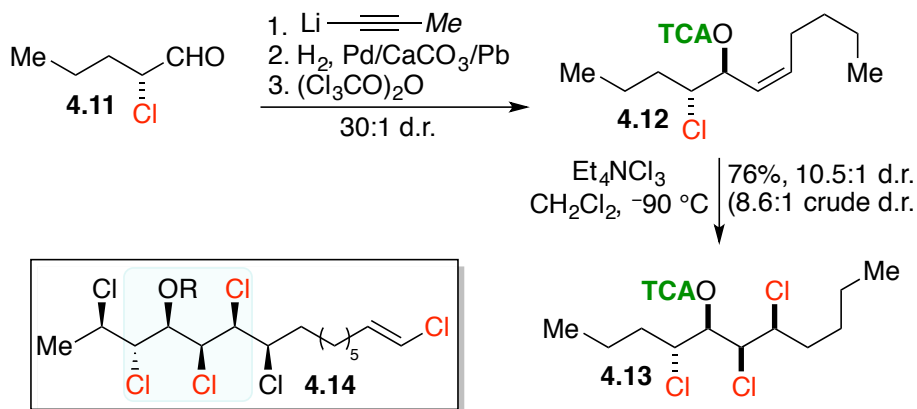


[a] Isolated yields after column chromatography. [b] Crude d.r.'s shown in parantheses

Scheme 4.4 Vanderwal's Stereoselective Dichlorination of (*Z*)-Allylic Trichloroacetates

As a proof of concept study, Vanderwal and his team decided to assemble a model Chlorosulfolipid using this diastereoselective dichlorination (Scheme 4.5). Starting with racemic

α -chloroaldehyde **4.11**, asymmetric alkynylide addition followed by partial hydrogenation and acetylation revealed (*Z*)-allylic trichloroacetate **4.12** in excellent diastereocontrol of 30:1 d.r. Subsequent treatment of **4.12** with Et₄NCl₃ generated trichloride **4.13** in 76% isolated yield and in 10.5:1 diastereomeric ratio. This stereotetrad clearly maps onto chlorosulfolipid **4.14**.



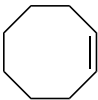
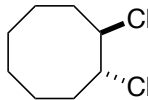
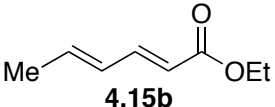
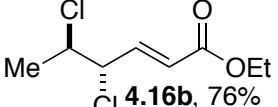
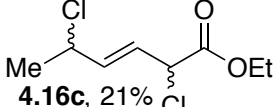
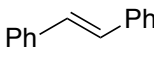
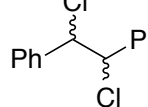
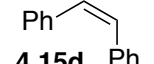
Scheme 4.5 Vanderwal's Dichlorination Strategy in Natural Product Synthesis

4.3.3 Dichlorination with NCS and Ph₃P: An Organic Source of Chlorine

Another useful dichlorination strategy involves the use of organic *N*-chlorosuccinimide (NCS) and triphenylphosphine (PPh₃). While previous methods utilize an inorganic source of chlorine (Cl₂, Et₄NCl₃ etc) Yoshimitsu et al utilizes a benchtop stable, nonhazardous electrophilic chlorine source, NCS. This dual-component mixture offers a mild, simple protocol for the dichlorination of olefins, with moderate stereospecificity.¹³¹ Analogous to the aforementioned protocols the 1,2-*anti* dichlorinated products are typically favored when *trans* alkenes are used. For example subjection of cyclooctene **4.15a** to NCS/PPh₃ mixtures forms *anti*-dichloride **4.16a** as a single diastereomer in 93% yield (Table 4.1, entry 1). Ethyl sorbate **4.15b** is similarly dichlorinated to vicinal dichloride **4.16b** in 76% yield, however 1,4-dichlorinated **4.16c** was also

isolated. The formation of **4.16c** is presumably due to an S_N2' -type process which accounts for the migration of the double bond. Lastly (*E*)- and (*Z*)-stilbene also react under the optimized conditions forming a mixture of diastereomers. These mixtures do not suggest an alternative reaction mechanism, rather the attack of the putative chloronium ion is not regioselective.

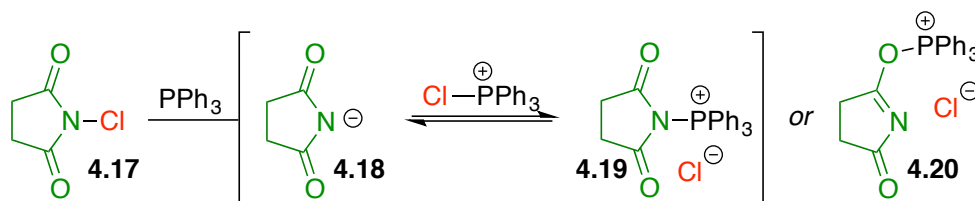
Table 4.1 Scope of Yoshimitsu's Dichlorination Strategy

$ \begin{array}{c} \text{R}_1\text{---CH=CH---R}_2 \\ \textbf{4.15} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{ rt}]{\text{NCS (3.0 equiv)} \\ \text{Ph}_3\text{P (1.5 equiv)}} \begin{array}{c} \text{R}_1\text{---CH(Cl)---CH(Cl)---R}_2 \\ \textbf{4.16} \end{array} $		
entry	olefin	product
1	 4.15a	 4.16a , 93%
2	 4.15b	 4.16b , 76%  4.16c , 21%
3	 4.15c	 4.16d , 77%, 1:1 syn :anti
4	 4.15d	4.16d , 81%, 1:1 syn :anti

[a] Isolated yields after column chromatography.

When NCS and PPh_3 are combined it's believed that the nucleophilic PPh_3 attacks the chlorine of the N-Cl bond generating chlorophosphonium salt **4.18** (Scheme 4.6). It's then feasible that this contact ion pair exists in equilibria with succinidylphosphonium salt **4.19** or as independent salt **4.20**. Regardless, the mechanism for this reaction is believed to involve

chloronium ion generation from either NCS or chlorophosphonium ion and the olefin, followed by nucleophilic attack by chloride ion. While simple and user friendly, this reaction suffers from a lack of regioselectivity of nucleophilic attack by chloride leading to poor stereospecificities.

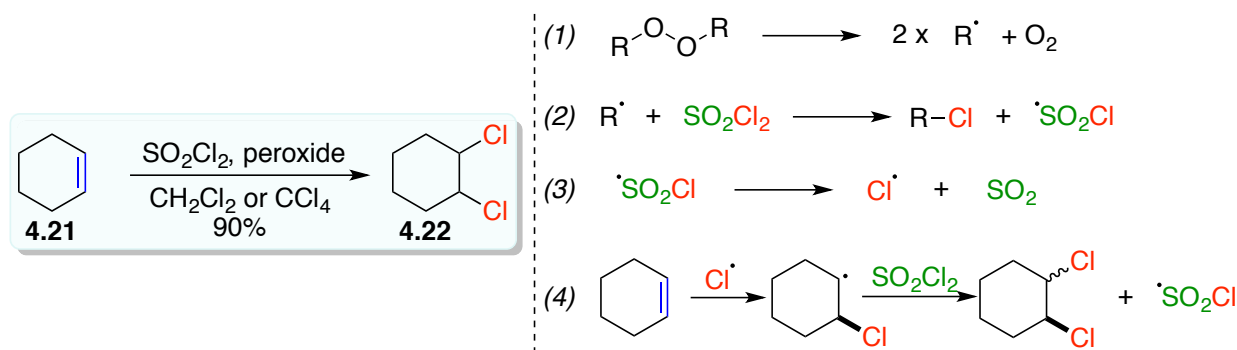


Scheme 4.6 Active Chlorinating Agent from NCS/ PPh₃ Mixtures

4.3.4 Dichlorination via Free Radical Processes

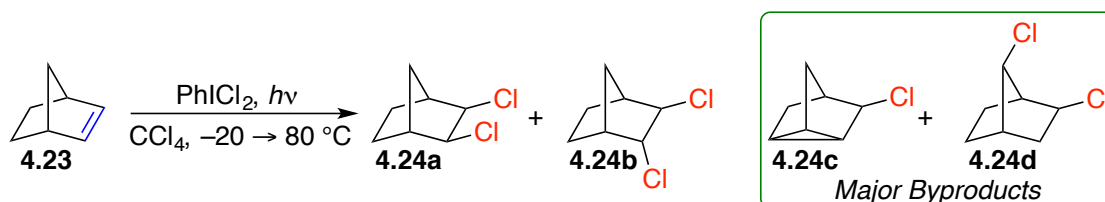
Free radical chlorination is a powerful process for the synthesis of alkyl chlorides, as well as the synthesis of heterocycles. While challenging to control the selectivities of products, there are a few reports on the radical dichlorination of alkenes providing useful vicinal dichloride building blocks.¹³² One of the earliest reports of radical dichlorination originates from the lab of the late H.C. Brown (Scheme 4.7).¹³³ Brown studied the formation of 1,2-cyclohexane dichloride **4.22** from the combination of sulfuryl chloride (SO₂Cl₂) with cyclohexene **4.21** in a chlorinated solvent. Remarkably, Brown discovered if freshly distilled cyclohexene was employed, the reaction would stall or fail to react. This observation eluded to the role of a peroxide acting as an initiator generating an alkyl radical that could abstract chlorine from SO₂Cl₂, liberating an alkyl chloride. In fact the addition of stale benzophenone or *t*BuOOH drove the reaction to completion. The proposed mechanism for this transformation presumably generates a sulfuryl radical from the decomposition of peroxide and SO₂Cl₂. Naturally a sulfuryl radical is quite unstable and rapidly

decomposes liberating a chlorine atom and sulfur dioxide. The chlorine atom is then poised to promote further decomposition of SO_2Cl_2 or react with the substrate forming the product.



Scheme 4.7 Radical Dichlorination of Alkenes

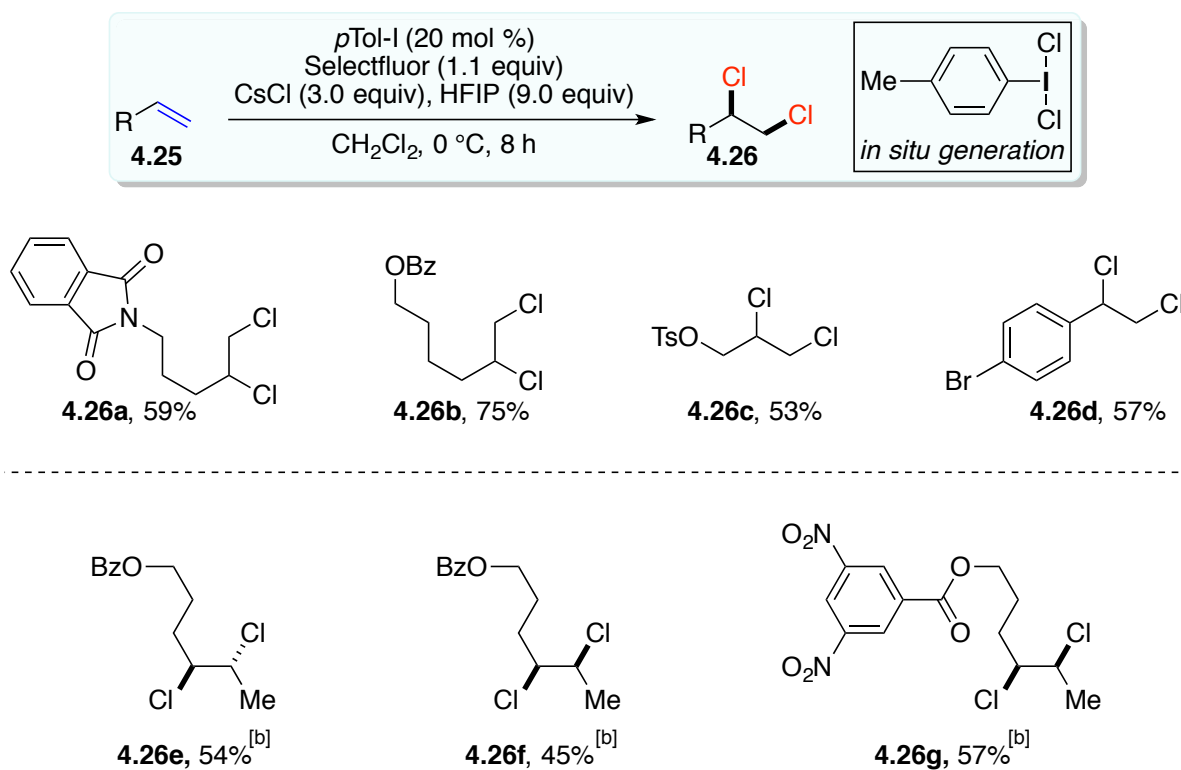
This discovery ultimately led to further developments of free radical mediated dichlorination reactions.¹³⁴⁻¹³⁶ Specifically reactions using hypervalent iodine sources such as PhICl_2 as the initiator and chloride source were found to chlorinate alkenes.¹³⁷ This hypervalent iodine reagent possess rather unusual reactivities as it can react via an ionic process or in the presence of light or some initiator, through a free radical process. With the latter in mind, it was discovered that the combination of norbornene **4.23** with PhICl_2 under irradiation by visible light generates diastereomeric mixtures of dichlorides **4.24a** and **4.24b**.¹³⁸⁻¹³⁹



Scheme 4.8 Radical Chlorination with PhICl_2

4.3.5 Ionic Dichlorination with PhICl_2 and Attempts at Enantioselectivity

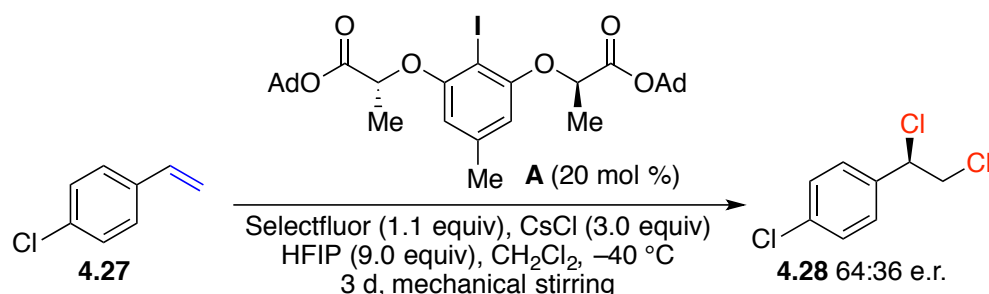
As mentioned previously, dichlorination reactions with PhICl_2 typically proceed through a free radical mechanism; however, without an initiator present it's possible for this reagent to react through an ionic mechanism. In doing so this reaction yields the corresponding dichloride products with the anticipated stereospecificities afforded by the alkene geometry. This reagent was first discovered in 1886 by German chemist Conrad Willgerodt and while it has seen significant use as a chlorinating reagent, most reports use this reagent in stoichiometric amounts and some in super stoichiometric amounts.¹⁴⁰⁻¹⁴² However in late 2019 over 100 years since its initial discovery Gilmour and coworkers developed a catalytic dichlorination strategy that generates an toluyl derivative of PhICl_2 *in situ*, eliminating the hazardous preparation of this reagent (Scheme 4.9).¹⁴³



[a] Isolated yields after column chromatography. [b] Single diastereomers formed.

Scheme 4.9 Dichlorination via Catalytic Generation of ArICl_2

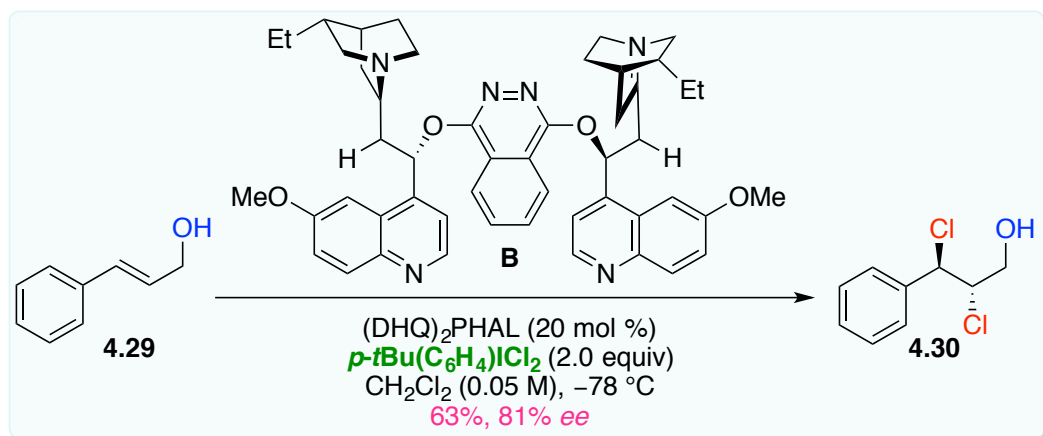
By combining tolyliodide (pTol-I) with organic oxidant Selectfluor[®] and inorganic salt CsCl, vicinal dichlorides can be generated from terminal and internal olefins in only 8 hours and in modest yields. This reaction provided the desired dichloride products from both terminal and substituted alkenes with high stereospecificity. The mechanism follows a similar trend for ionic chlorination reactions and presumably involves electrophilic chloronium ion formation that is attacked by chloride. Interestingly, the reaction necessitated the addition of HFIP as an additive, although the exact role of HFIP is unknown. Comparing the reaction mixtures of *in situ* generated 4-MePhICl₂ with that of independently prepared 4-MePhICl₂ matched eluded to the *in situ* generation of Willgerodt's reagent. Furthermore, Gilmour tried to examine the applicability of a C-2 symmetric aryl iodide **A** in an attempt to render the reaction enantioselective. With *p*-chlorostyrene **4.27** as a model substrate, dichlorinated **4.28** was afforded in modest 64:36 *e.r.*



Scheme 4.10 Attempt Towards a Stereoselective Reaction

Gilmour and his team aren't the only synthetic chemists who have attempted to synthesize stereochemically defined vicinal dichlorides from an aryl hypervalent iodide. Nicolaou et al developed a strategy using a cinchona alkaloid derived catalyst **B** in the presence of a bulky hypervalent aryl iodide, *p*-*t*BuPhICl₂.¹⁴⁴ Using this reagent combination in CH₂Cl₂ at -78 °C, Nicolaou was able to dichlorinate cinnamyl alcohols **4.29** in modest *ee*'s and yields (Table 4.2).

Table 4.2 Nicolaou's Stereoselective Dichlorination Strategy



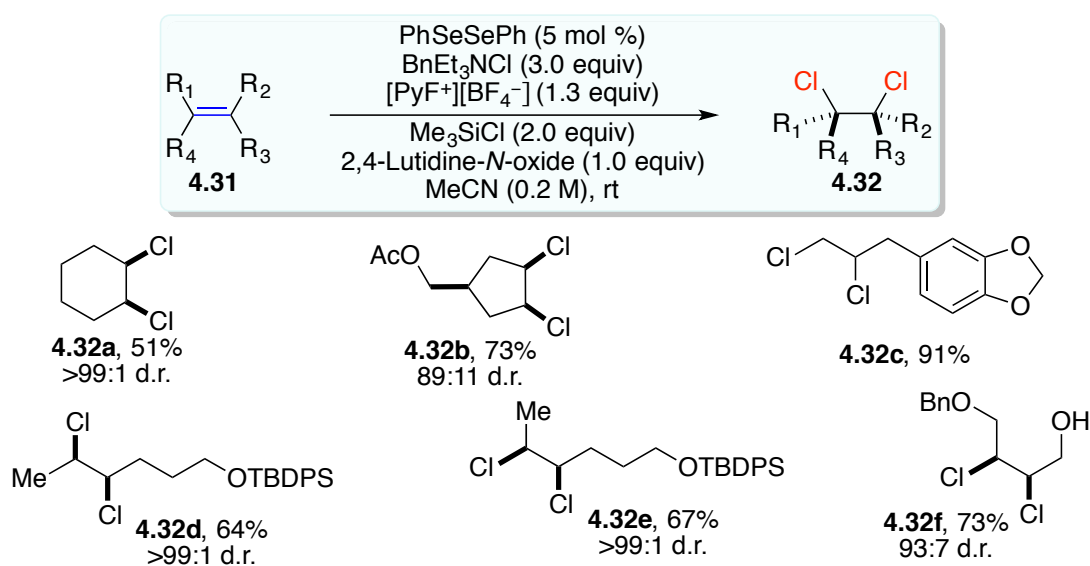
substrate	product	yield (%)	ee (%)
 4.29a	 4.30a	65	44
 4.29b	 4.30b	75	48
 4.29c	 4.30c	73	72
 4.29d	 4.30d	35	25
 4.29e	 4.30e	32	<5

[a] Isolated yields after column chromatography.

During the course of his study, he and his team realized that competing regioselective ring opening of the presumed chloronium intermediate proved problematic and yielded 1,2-dichloride products with low enantiomeric excess. Also, the dichlorination of *cis*-allylic alcohol **4.29d** yielded very little product and with little to no enantiocontrol. An additional mechanistic control did reveal the importance of the alcohol moiety, as protecting it as a TES ether **4.29e** afforded no enantiomeric excess. Presumably this result suggests that hydroxyl group is necessary to ensure proper binding of substrate to the catalyst to ensure high enantiomeric excess

4.3.6 Stereoselective *syn*-Dichlorination of Alkenes

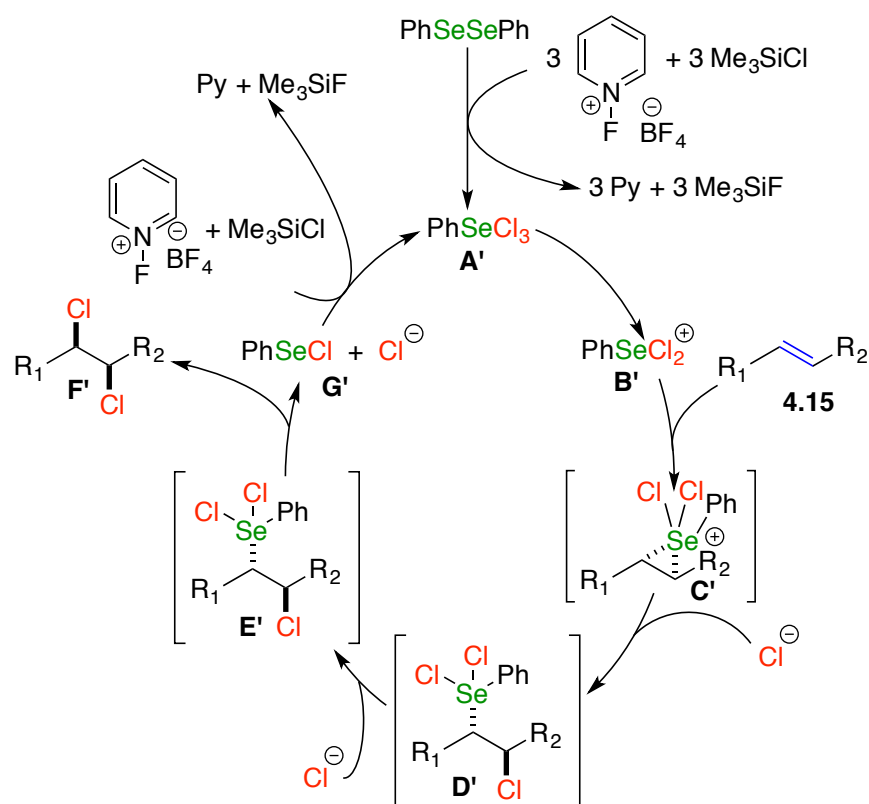
All of the dichlorination strategies summarized to this point have similarly involved the formation of a cyclic chloronium ion, followed by nucleophilic attack by chloride in a stereoinvertive process (*i.e.* *anti*-addition) forming the dichloride. This archaic reactivity is a stereospecific process and determined by the olefin geometry of the substrate. Denmark coworkers have developed a catalytic *syn*-dichlorination strategy of simple alkenes (Scheme 4.11).¹⁴⁵



[a] Isolated yields after column chromatography. [b] d.r.s determined on crude reaction mixtures.

Scheme 4.11 Denmark's *syn*-Dichlorination Strategy

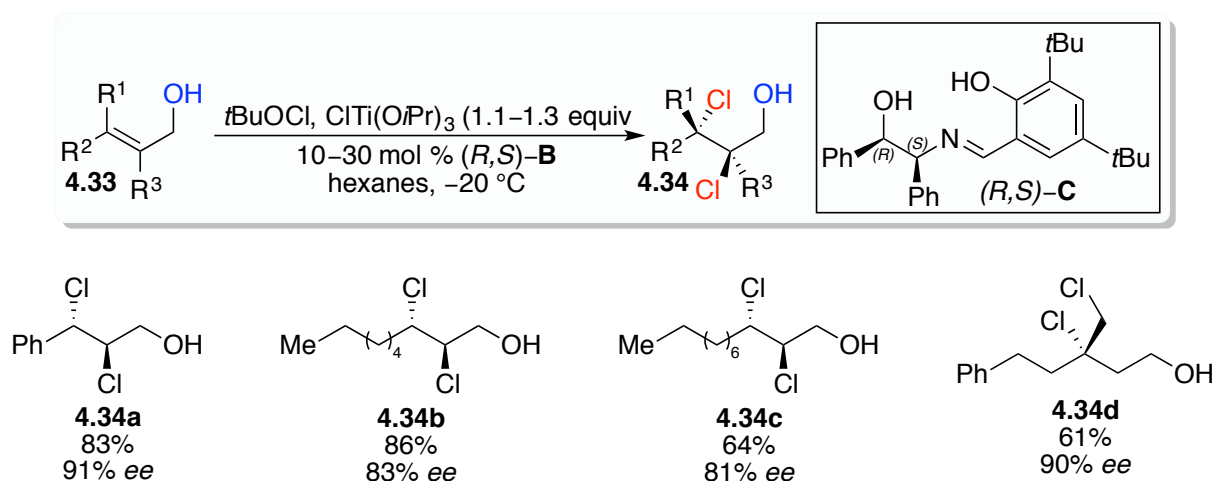
All products are afforded in excellent diastereoselectivities, albeit modest yields. The proposed mechanism for this catalytic process is outlined below. The catalytic cycle likely initiates with the oxidative formation of PhSeCl_3 **A'** from PhSeSePh , promoted by *N*-fluoropyridinium and Me_3SiCl releasing pyridine and Me_3SiF . Dissociation of chloride from **A'** leads to the formation of the active dichloroselenium ion **B'** which is reasonably electrophilic. At this step the introduction of olefin **4.15** presumably captures **B'** en route to selenarium ion **C'** which is isoelectronic to a chloronium ion. Subsequent nucleophilic attack by chloride forms β -chlorophenylselenium dichloride **D'**. Given the extreme excess of chloride ions, stereospecific attack of **D'** by chloride ions allows for desired 1,2-*syn*-dichloride **F'** formation while releasing PhSeCl **G'**. PhSeCl is then available to be oxidized back to the catalytically active PhSeCl_3 **A'**.



Scheme 4.12 Catalytic Cycle for Stereoselective *syn*-Dichlorination

4.3.7 Catalytic Enantioselective Dichlorination of Allylic Alcohols

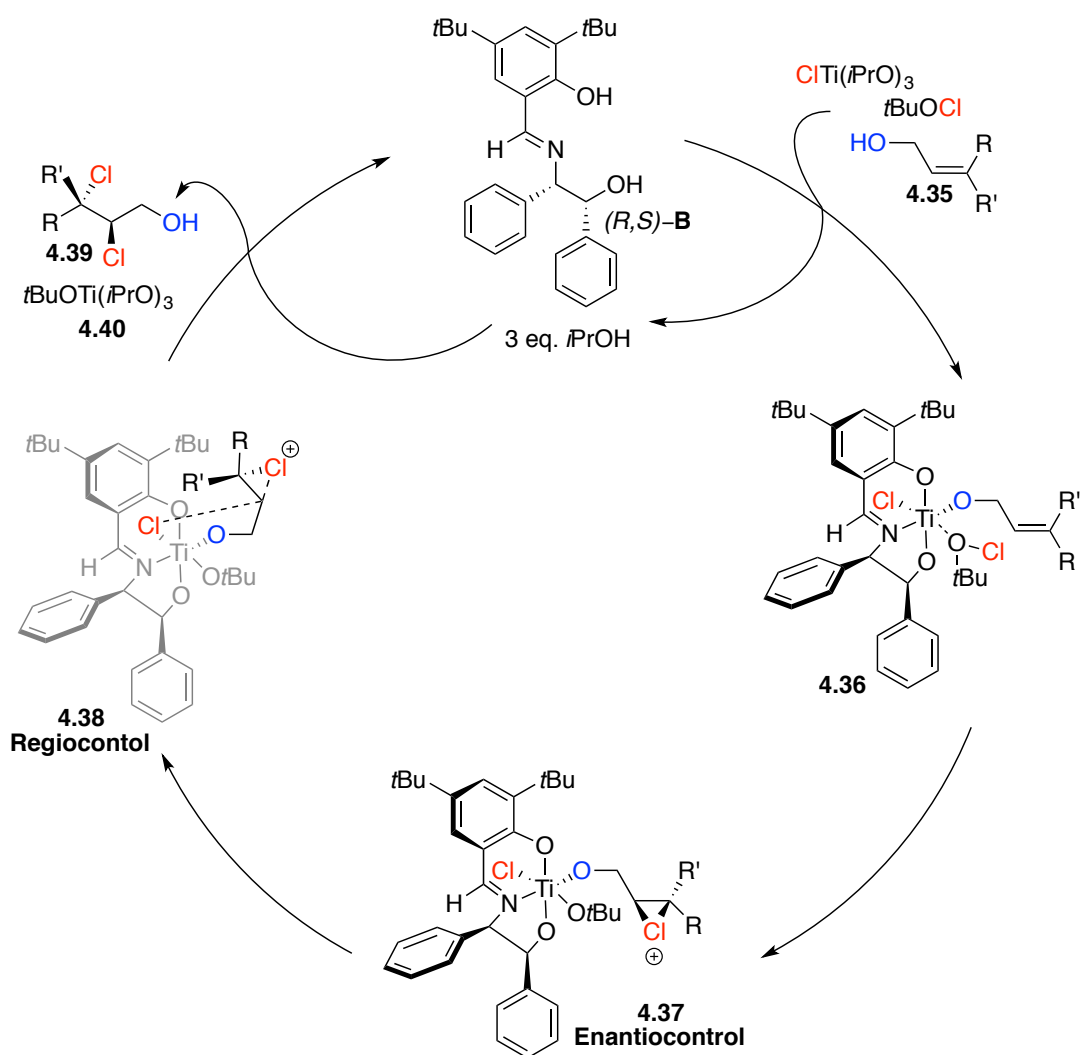
To conclude this mini review of dichlorination strategies of olefins, this last report originates from the Burns Lab. In the Burns Lab stereoselective halogenation is the main driving force for discovery. Similar to Nicolaou's conditions, Burns and his team were cognizant of regioselective addition of nucleophile to a presumed chloronium or bromonium ion. Therefore to combat this issue of regioselectivity he and his team devised that the chelation of a ligand and halogen source to a metal center would allow for regiocontrol, and the addition of a chiral ligand might lead to some stereoinduction as well.^{93, 146-147} In an attempt to synthesize a chlorosulfolipid natural product, Burns and his team developed a dichlorination strategy shown in Scheme 4.13. Using an allylic alcohol in the presence of a Ti-precatalyst and *t*BuOCl electrophile, Burns et al were able to synthesize 1,2-dichlorides in high yields and enantiomeric excess, governed by the chiral Ephedrine-Salen ligand. This robust process tolerates a broad scope of substitutions amongst the allylic alcohol and the alcohol functionality allows for rapid diversification.



[a] Isolated yields after column chromatography.

Scheme 4.13 Burns Stereoselective Dichlorination of Allylic Alcohols

The catalytic cycle for this process most likely proceeds through the following pathway (Scheme 4.14). Complexation of $\text{ClTi}(\text{iPrO})_3$ with alcohol **4.35**, $t\text{BuOCl}$ and ephedrine ligand $(R,S)\text{-B}$ generates active octahedral complex **4.36** with the liberation of three equivalents of $i\text{PrOH}$. The rigidity of this complex naturally allows for stereoselective chloride delivery to allylic alcohol from electrophilic $t\text{BuOCl}$. The bulkiness of the ligand subsequently affects some regiocontrol to the reaction and directs the trajectory of the chloride to chloronium species **4.37**. This terminal step then affords the desired dichlorinated product **4.39** and regenerates the catalyst.



Scheme 4.14 Burn's Enantioselective Dichlorination Catalytic Cycle

4.4 Vicinal Dichlorination of Epoxides: A Variation on a Theme

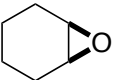
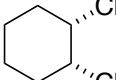
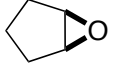
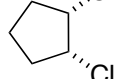
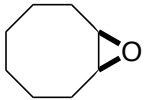
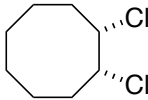
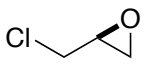
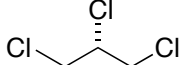
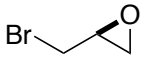
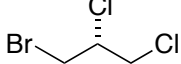
While we have seen that chlorination of olefins allows for the direct formation of vicinal dichlorides, another avenue for dichlorination utilizes terminal or substituted epoxides as synthetic equivalents. As the chlorination of alkenes is widely studied and implemented in synthesis, it generally does not allow the selective dichlorination of one olefin over the other when multiple π -bonds are present in the molecule. Additionally the use of epoxides as synthons typically provides enantioenriched dichloride products when enantioenriched epoxides are used. Similar to the dichlorination of olefins, the chlorination of epoxides also proceeds stereospecifically and tolerates a broad scope of substituted epoxides and functional groups. These methods also offer an advantage over dichlorination of olefins as polyepoxides can be chlorinated revealing tetrachloride products and it also supplements the synthetic chemist's toolbox in the event that the dichlorination of an olefin fails or is not an orthogonal strategy. This section will serve as a minireview focusing on these dichlorination strategies. Also examples where these transformations are employed towards the synthesis of complex chlorosulfolipid fragments will also be presented. Lastly, an addition to this area of chemistry from our lab will be discussed.

4.4.1 Kirkpatrick's CCl_4 - PPh_3 Dichlorination of Epoxides

The first reported examples of converting epoxides to vicinal dichlorides was reported by Kirkpatrick in the early 1970s.¹⁴⁸⁻¹⁴⁹ Kirkpatrick and his team realized that refluxing cyclic and acyclic epoxides **4.41** with PPh_3 in CCl_4 resulted in the formation of vicinal dichloride products **4.42** (Table 4.3). While limited in substrate scope, this report disclosed the relative 1,2-*syn* stereochemistry from cyclic epoxides **4.41a-4.41c** which is in contrast to the dichlorination of olefins that produces the 1,2-*anti* diastereomer. Kirkpatrick's method also proved to be quite operationally simple to conduct as all dichloride products were isolated by filtration and

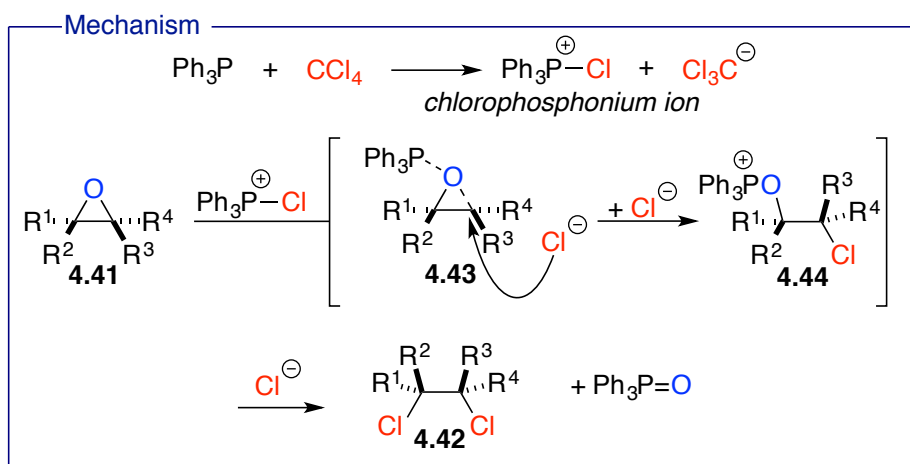
rotaryevaporation. While limited mechanistic investigations were reported the combination of reagents is analogous to that of the Appel reaction.¹⁰¹ Therefore the first step of this reaction almost certainly involves the attack of CCl₄ by Ph₃P generating chlorophosphonium salt which also liberates an equivalent of chloride ion (Scheme 4.15). This salt is relatively electrophilic and can subsequently react with epoxide **4.41** through a concerted stereoinvertive, ring-opening of the epoxide by chloride ions forming oxophosphonium ion **4.44**. It's also possible that the epoxide is opened by chloride ions prior to combination with chlorophosphonium ion generating a chlorohydrin which then reacts. Regardless, it's assumed that phosphonium **4.44** is generated and subsequently displaced by chloride ions leading to the formation of dichloride product **4.42** and triphenylphosphine oxide (Ph₃P=O), with completion inversion of stereochemistry of the epoxide.

Table 4.3 Kirkpatrick's Dichlorination of Epoxides

$ \begin{array}{c} \text{R}^1 \quad \text{R}^4 \\ \diagdown \quad \diagup \\ \text{O} \\ \diagup \quad \diagdown \\ \text{R}^2 \quad \text{R}^3 \\ \textbf{4.41} \end{array} \xrightarrow[\text{reflux, 1-2 h}]{\text{Ph}_3\text{P, CCl}_4} \begin{array}{c} \text{R}^2 \quad \text{R}^3 \\ \text{R}^1 \text{---} \text{C} \text{---} \text{C} \text{---} \text{R}^4 \\ \quad \\ \text{Cl} \quad \text{Cl} \\ \textbf{4.42} \end{array} + \text{Ph}_3\text{P=O} $			
entry	epoxide	product	yield (%)
1	 4.41a	 4.42a	80
2	 4.41b	 4.42b	80
3	 4.41c	 4.42c	75
4	 4.41d	 4.42d	60
5	 4.41e	 4.42e	50

[a] Isolated yields upon filtration and rotaryevaporation.

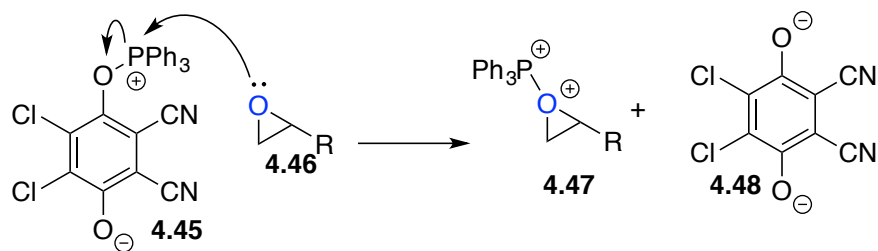
Going forward, the general transformation of epoxides to 1,2-dichlorides will involve a similar mechanistic pathway to the one just discussed. Most transformations involving epoxides use Ph_3P as way to decompose the chloride source, the formation of a chlorophosphonium salt typically precedes any further steps in the mechanism. Attack of this salt by an epoxide followed by simultaneous ring-opening or vice versa forms an activated α -chlorophosphonium chlorohydrin species that can then be displaced by chloride ions. Concurrent to the formation of the dichloride product, triphenylphosphine oxide ($\text{Ph}_3\text{P}=\text{O}$) is also generated.



Scheme 4.15 Mechanism Kirkpatrick's Chlorination Reaction

4.4.2 Iranpoor's DDQ- Ph_3P Dichlorination of Epoxides

Over 30 years after Kirkpatrick's seminal report, Iranpoor developed an analogous dichlorination strategy employing mixtures of Ph_3P and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) along with a quaternary ammonium salt, such as $n\text{Bu}_4\text{NCl}$ or $n\text{Bu}_4\text{NBr}$ in MeCN at reflux.¹⁵⁰⁻¹⁵¹ Unlike Kirkpatrick's strategy instead of using carcinogenic CCl_4 , Iranpoor utilized organic oxidant DDQ to activate Ph_3P and $n\text{Bu}_4\text{NCl}$ as an inexpensive chloride source.



Scheme 4.16 Iranpoor's Proposed Activation Mode

Comparable to Kirkpatrick's strategy, Iranpoor proposed the combination of Ph_3P and DDQ would generate an electrophilic phosphonium salt that could readily be attacked by an epoxide leading to a cascade process (Scheme 4.16). A deviation to the mechanism previously discussed, the use of DDQ ultimately circumvents chlorophosphonium ion generation prior to product formation, although $\text{Ph}_3\text{P}=\text{O}$ is also formed. Additionally an interesting advantage of Iranpoor's strategy involves modulation of the amount of $n\text{Bu}_4\text{NCl}$. If only 1.2 equiv of $n\text{Bu}_4\text{NCl}$ is used chlorohydrin **4.49** is the major product but if 2.2 equiv of $n\text{Bu}_4\text{NCl}$ is added then the reaction proceeds to dichloride **4.50** (Table 4.4). As shown below the use of styrene oxide led to the formation of chlorohydrin regioisomers **4.49a** and **4.49a'** in a 5:1 ratio in favor of **4.49a**. Additionally subjection of glycidol **4.46b** to 1.2 equiv of $n\text{Bu}_4\text{NCl}$ led to exclusive formation of internal chlorohydrin **4.49b**. Iranpoor's report also allows for modulation of halogenated product through simply changing the quaternary ammonium salt. Simply employing $n\text{Bu}_4\text{NI}$ or $n\text{Bu}_4\text{NBr}$ as the halogen source allows for vicinal diiodide or dibromide formation, a unique advantage over the dehalogenation of olefins. Unfortunately Iranpoor's dichlorination strategy is even less atom economical compared to Kirkpatrick's as both $\text{Ph}_3\text{P}=\text{O}$ and 2,3-dichloro-5,6-dicyano-1,4-biphenol are formed as waste byproducts that must be removed by chromatographic purification.

Table 4.4 Iranpoor's Synthesis of Chlorohydrins and Vicinal Dichlorides

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> <p> PPh_3 (1.2 equiv) DDQ (1.2 equiv) $n\text{Bu}_4\text{NCl}$ (n equiv) MeCN, reflux, 30 min </p> </div> <div style="text-align: center;"> <p>DDQ</p> </div> </div>				
entry	epoxide	$n = 1.2$ equiv		$n = 2.2$ equiv
1		 4.49a, 75%	 4.49a', 15%	 4.50a, 70%
2		 4.49b, 75%		 4.50b, 78%
3		 4.49c, 96%		
4		 4.49d, 88%		
5				 4.50e, 80%

[a] Isolated yields after column chromatography

4.4.3 Trichloroisocyanuric Acid- Ph_3P Promoted Dichlorination

Trichloroisocyanuric acid (TCCA) has long been used as a bactericide, algicide and general disinfectant.¹⁵² In fact TCCA is usually responsible for the chlorine-like odor found after public recreational areas like swimming pools and bath houses have been cleaned. TCCA is a white solid prepared from the chlorination of cyanuric acid, a triazine derivative, with Cl_2 and NaOH . TCCA is relatively inexpensive and easy to handle and therefore has found extensive utility amongst

synthetic chemists as a versatile reagent. In fact, combination of TCCA with Ph_3P and epoxide **4.41** results in the formation of vicinal dichloride **4.42** (Table 4.5) in moderate to good yields.¹⁵³

Table 4.5 Dichlorination with TCCA- Ph_3P Mixtures

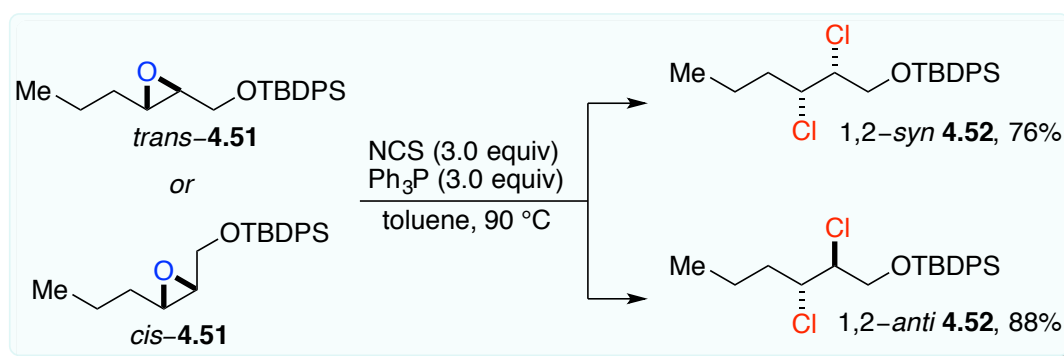
<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> <p>Reaction scheme showing the conversion of epoxide 4.41 to vicinal dichloride 4.42 using TCCA and PPh_3 in MeCN at reflux.</p> </div> <div style="text-align: center;"> <p>Chemical structure of TCCA (2,2,6,6-tetrachloro-1,3,5-triazine-4(1H)-one).</p> </div> </div>			
entry	epoxide	product	yield (%)
1	<p>4.41f</p>	<p>4.41f</p>	78
2	<p>4.41g</p>	<p>4.41g</p>	85
3	<p>4.41h</p>	<p>4.41h</p>	87
4	<p>4.41i</p>	<p>4.41i</p>	74

[a] Isolated yields after column chromatography. [b] Reaction monitored by GC-MS.

Analogous to the previous dichlorination strategies discussed, $\text{Ph}_3\text{P}=\text{O}$ is formed during the course of the reaction, as well as cyanuric acid. The mechanism for this transformation presumably involves the attack of one of the nitrogen-chlorine bonds by Ph_3P forming $\text{Ph}_3\text{P}-\text{Cl}$ salt. This electrophile is then susceptible to attack by the epoxide oxygen leading to a downhill energetic process forming the desired vicinal dichloride and $\text{Ph}_3\text{P}=\text{O}$ byproduct.

4.4.4 Yoshimitsu's NCS-Ph₃P and NCS-Ph₂PCI Dichlorination Strategy

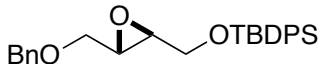
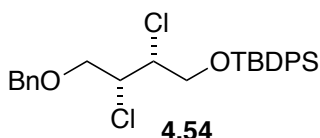
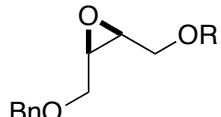
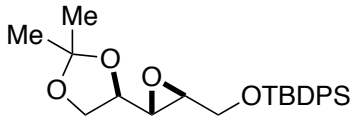
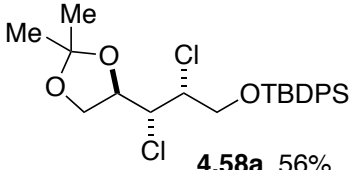
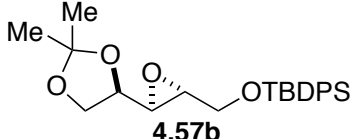
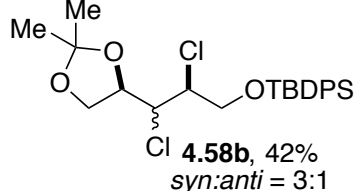
While several dichlorination strategies have been published since Kirkpatrick's initial discovery, few really examine the functional group tolerance of their respective reactions. Nor do they apply them to complex molecules or attempt to chlorinate more than one epoxy group at a time. Inspired by the Chlorosulfolipid family of natural products, Yoshimitsu and his team revealed a strategy that allows for the polychlorination of unactivated, enantiomerically enriched polyepoxide substrates stereospecifically with a 1:1 mixture of NCS and Ph₃P.¹⁵⁴



Scheme 4.17 Yoshimitsu's Dichlorination Strategy

To begin his study, Yoshimitsu showed that diastereomeric pairs of epoxides **4.51** could readily be dichlorinated revealing their respective 1,2-*syn* and 1,2-*anti* dichlorides **4.52**, in 76% and 88% yields, respectively. The generality of this method was showcased through a scope of *trans* and *cis*-epoxide substrates shown below in Table 4.6. Yoshimitsu's discovery was exhibited with a series of *cis*/*trans* isomeric epoxides as well as through a series of oxygen atom protecting groups. Additionally Yoshimitsu and his team revealed that this transformation could take place both at 90 °C and 45 °C, albeit longer reaction times were reported for the latter.

Table 4.6 Yoshimitsu's Substrate Scope

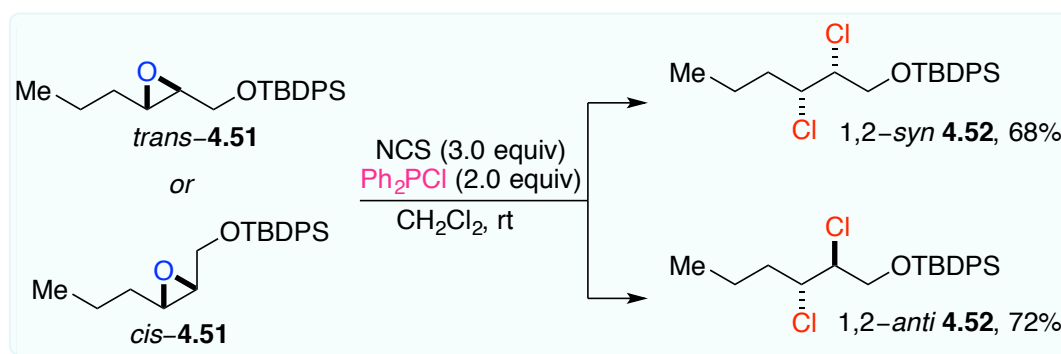
entry	epoxide	temp. (°C)	product	time (h)
1	 4.53		 4.54	
		90	82%	3.4
		45	80%	22
2	 4.55a , R = TBDPS	90	4.56a , 79%	2.7
3	4.55a , R = TBDPS	45	5.56a , 84%	48
4	4.55b , R = TBS	90	5.56b , 69%	1
5	4.55c , R = Piv	90	5.56c , 82%	1.5
6	 4.57a	90	 4.58a , 56%	1
7	 4.57b	90	 4.58b , 42% <i>syn:anti</i> = 3:1	2.7

[a] Isolated yields after column chromatography. [b] Epoxides prepared in >20:1 d.r. [c] Some minor elimination products formed 8%–30%.

The resulting dichlorinated products were formed in good to excellent yields and relatively short reaction times, only small amounts of elimination products were detected. An important result is that the desired diastereomeric dichloride could be selected by just changing the geometry of the starting epoxide. Interestingly *anti*-epoxyketal **4.57b** reportedly gave a mixture of epimeric

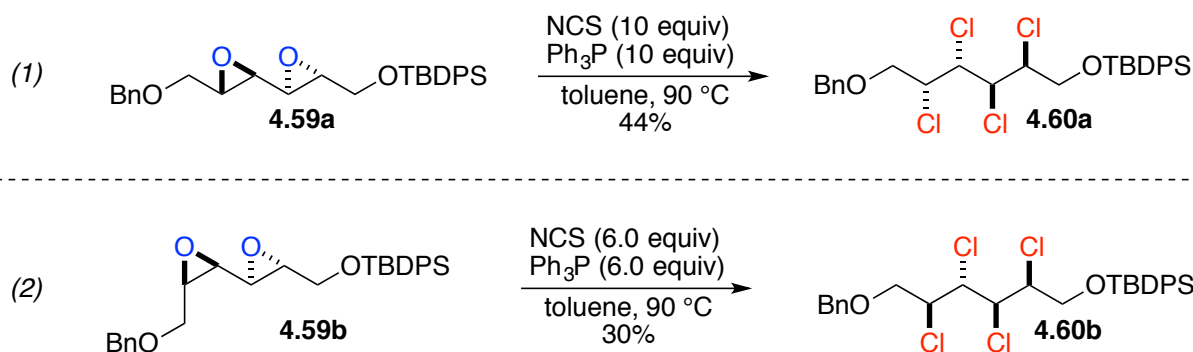
dichloride products. Finally Yoshimitsu's dichlorination strategy has become extremely useful synthetically as all epoxide starting materials could be synthesized in high enantiomeric excess using Sharpless's asymmetric epoxidation of allylic alcohols protocol.

An alternative set of conditions was also presented using mixtures of Ph_2PCl and NCS. This improved protocol allowed for the dichlorination of epoxides in CH_2Cl_2 at room temperature, relative to the previous strategy that used toluene at 90°C (Scheme 4.18). This reagent combination tolerated alkenyl substituted epoxides with no rearrangement products observed. However attempts at dichlorination aryl substituted epoxides resulted in modest yields of products.



Scheme 4.18 Improved Strategy for the Dichlorination of Epoxides

Lastly, Yoshimitsu and his team was able to apply the initial conditions (NCS/ Ph_3P) for the tetrachlorination of diastereomeric pairs *trans,trans*-**4.59a** and *cis,trans*-**4.59b** diepoxides (Scheme 4.19). Although limited in scope at the time of Yoshimitsu's initial publication, 2,3,4,5-tetrachlorides **4.60a** and **4.61b** were formed in 44% and 30% yields, respectively, as single diastereomers. No epimerized products were reported; however, the only caveat is the extreme excess of NCS and Ph_3P (> 5 equiv) was needed for complete conversion of starting materials. This dichlorination strategy has since been employed in complex molecules synthesis.⁹⁴



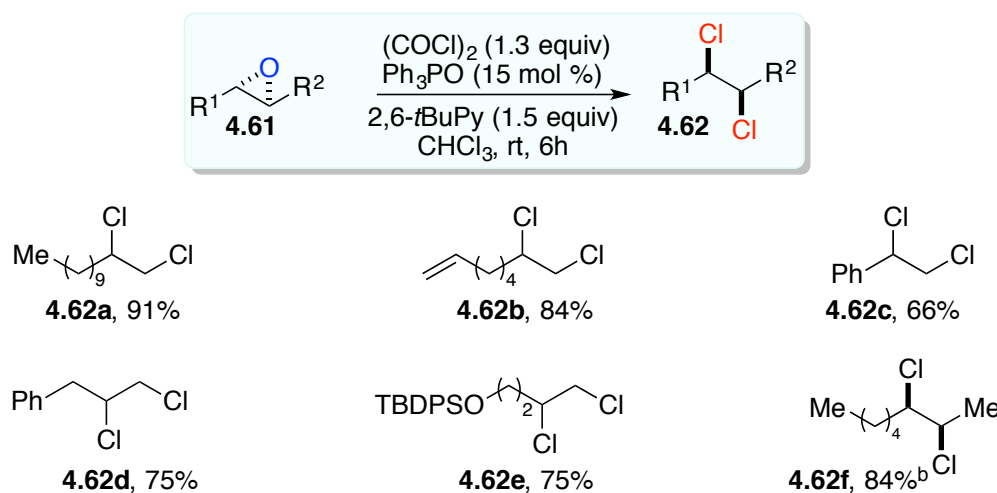
Scheme 4.19 Tetrachlorination of *bis*-Epoxides

4.4.5 Denton's Oxalyl Chloride and Catalytic $\text{Ph}_3\text{P}=\text{O}$ Dichlorination of Epoxides

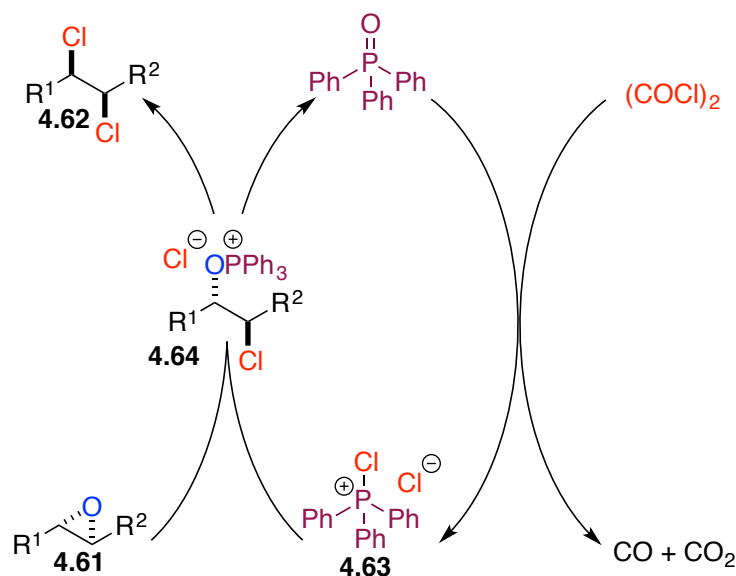
As reported throughout this minireview of dichlorination strategies, the biggest limitation of the aforementioned reactions is the production of stoichiometric amounts of $\text{Ph}_3\text{P}=\text{O}$. While the formation of this byproduct is often a thermodynamic driving force for the conversion of epoxide to dichloride, it usually must be removed via chromatographic separation. This operation ultimately leads to diminished yields of the corresponding dichloride products. To circumvent this problem Denton et al reported a strategy employing $\text{Ph}_3\text{P}=\text{O}$ as a catalyst with oxalyl chloride $(\text{COCl})_2$ as the terminal oxidant and chloride source. This reaction proved to broadly tolerate both terminal and internal epoxide substrates producing the resulting dichloride products in moderate to high yields (Scheme 4.20).¹⁵⁵⁻¹⁵⁶ This procedure offered a significant advancement over the previously reported dichlorination strategies as only 15 mol % $\text{Ph}_3\text{P}=\text{O}$ was needed and cheap $(\text{COCl})_2$ served as both oxidant and as the chloride source. Bulky 2,6-*t*BuPy was also added to act as an acid scavenger and prevent unwanted chlorohydrin formation.

The proposed catalytic cycle is shown in Scheme 4.20. $\text{Ph}_3\text{P}=\text{O}$ is converted from a P(V) oxidation state to chlorophosphonium chloride **4.63**, a P(IV) oxidation state after combination with $(\text{COCl})_2$. Gaseous CO_2 and CO are presumably exuded from the reaction mixture. Interception

of **4.63** with epoxide **4.61** results in the formation of α -chloro phosphonium adduct **4.64** which further reacts with chloride ions via an S_N2 process liberating dichloride **4.63** and regenerating catalyst $\text{Ph}_3\text{P}=\text{O}$. If trace HCl is present in the $(\text{COCl})_2$ the it's possible that epoxide **4.61** could be ring-opened leading to a chlorohydrin. Chlorohydrin formation is believed to be a terminal product preventing further reaction; therefore, 2,6-*t*BuPy was added.



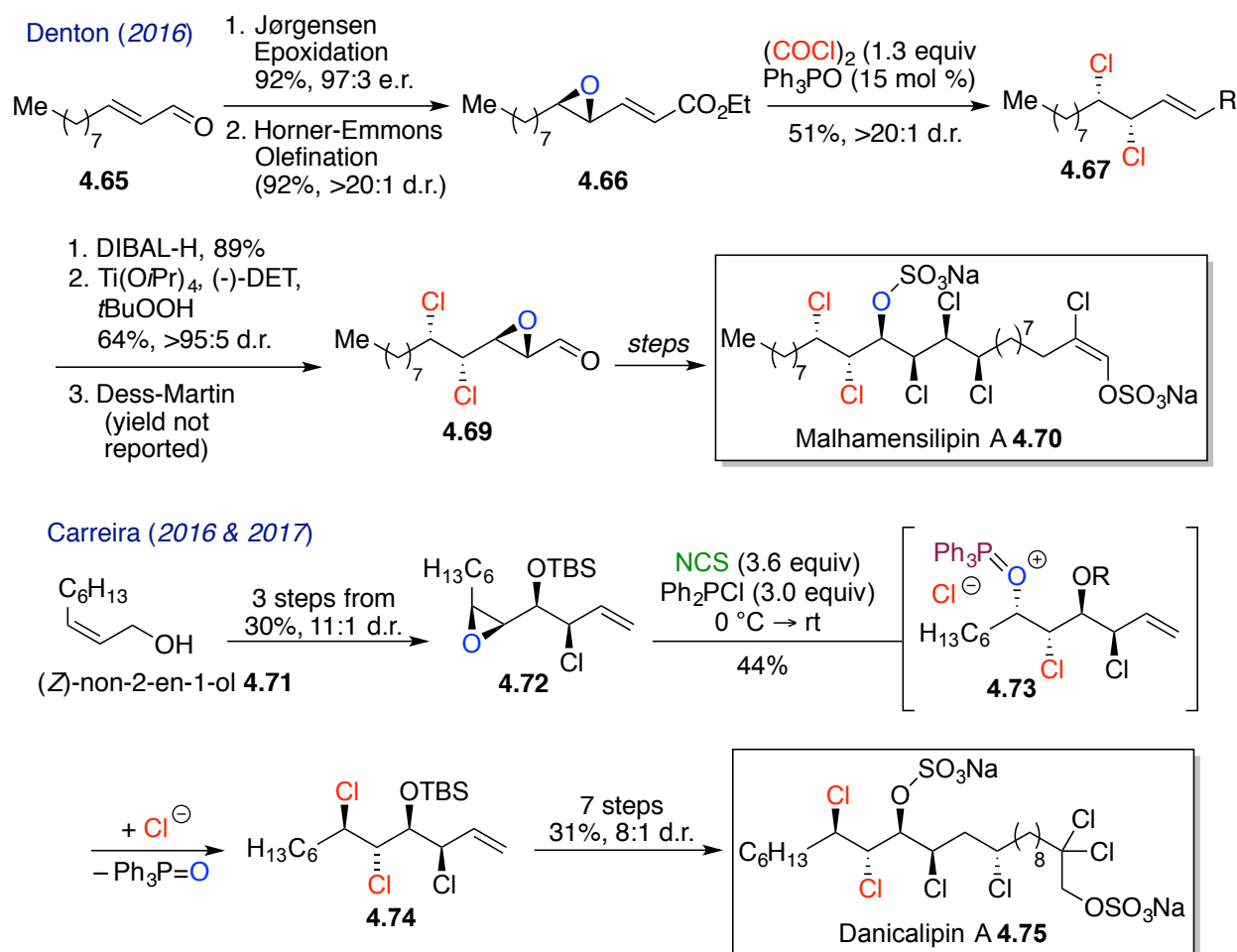
[a] Isolated yields after column chromatography. [b] Yield based of ^1H NMR analysis with $\text{C}_2\text{H}_2\text{Cl}_4$ as internal standard



Scheme 4.20 Denton's Catalytic Dichlorination Strategy

4.5 Dichlorination of Epoxides in Total Synthesis Applications

Similar to the dichlorination of olefins, dichlorination of epoxides has found its way into the realm of total synthesis, specifically the total synthesis of Chlorosulfolipids. Given their broad array of chlorine substituents with various *syn* and *anti*-relative stereochemistries, polychlorination of polyepoxides would provide a direct one-pot strategy to add advanced molecular complexity to simple starting materials. While there are multiple syntheses of Chlorosulfolipids that involve dichlorination of epoxides as a key step, only two syntheses will be discussed within this document however all other examples are cited in the references chapter (Scheme 4.21).^{94, 157}



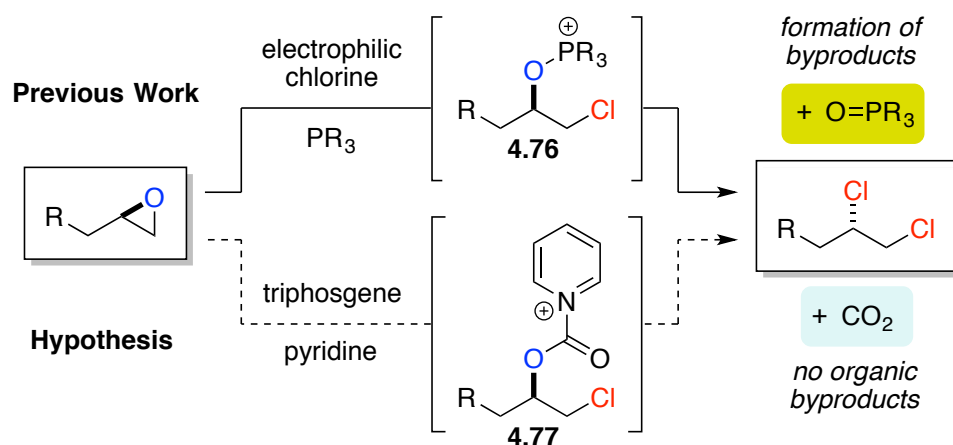
Scheme 4.21 Dichlorination of Epoxides in Applied in Total Synthesis

In pursuit of Malhamensilipin A **4.70**, Denton^{95, 158} and coworkers utilized his catalytic dichlorination strategy to install the first 1,2-*syn* dichloride motif. Commencing their synthesis from commercially available (*E*)-enal **4.65**, asymmetric epoxidation and Horner-Emmons olefination generated epoxide **4.66** with the desired *trans*-orientation in >20:1 d.r. Upon treatment with (COCl)₂ and catalytic Ph₃P=O, *syn*-dichloride **4.67** was formed in 51% yield as a single diastereomer. To finish the synthesis of the western fragment, reduction of the ester with DIBAL-H followed by directed Sharpless asymmetric epoxidation then Dess-Martin oxidation of the primary alcohol provided aldehyde **4.69** in 3 steps from dichloride. A second example naturally comes from the Carreira Lab. Being the pioneer of Chlorosulfolipid syntheses, Carreira also disclosed a report transforming an epoxide, stereospecifically, to the resulting dichloride in his synthesis of Danicalipin A.^{90, 159} Epoxide **4.73** was synthesized in 3 steps, 30% yield, 11:1 d.r. from commercially available (*Z*)-non-2-en-1-ol **4.71**. Using Yoshimitsu's improved dichlorination protocol, Carreira and his team successfully produced dichloride **4.74** in 44% with complete control of stereochemistry. Only 7 additional steps were needed to complete the synthesis, affording Danicalipin A **4.75** in 31% yield and 8:1 d.r.

4.6 Triphosgene-Pyridine Promoted Chlorination of Epoxides¹⁶⁰

As shown above the chlorination of epoxides is a powerful tool for the construction of 1,2-dichlorides yet the largest limitation all of the previously mentioned strategies is the formation of wasteful byproducts, mainly Ph₃P=O. With that limitation in mind we assumed that our established triphosgene-pyridine chlorination methodology would provide a significant advancement as the only byproducts generated from our chemistry is CO₂. Chlorination attempts with triphosgene-pyridine has already been established by our group as a mild, operationally simple strategy that produces the desired chlorinated products in high yields and purities. We

hypothesized that we could use this strategy to chlorinate epoxides via similar intermediates as we previously disclosed. Activation of an epoxide with mixtures of triphosgene-pyridine could potentially lead to the intermediacy of pyridinium carbamate **4.77** upon ring opening of the epoxide and chloroformylation of the resulting chlorohydrin intermediate. Subsequent nucleophilic substitution by chloride ions would then form a vicinal dichloride with only CO₂ as a byproduct.



Scheme 4.22 Chlorination of Epoxides via Triphosgene-Pyridine Activation

The results of our proof of concept study and optimization studies are summarized in Table 4.7. Using 2-benzyloxirane **4.78** as a model substrate, we utilized 1.0 equiv of triphosgene and 4.0 equiv of pyridine in dichloromethane for the initial experiments. While the reaction at room temperature produced intractable mixtures, dichloride **4.79** was successfully produced in 62% yield by warming the reaction to reflux (entries 1-2). The ensuing optimization study revealed that the use of 2.0 equiv of pyridine at 0.5 M concentration produced the highest yield of 1,2-dichloride **4.79** (entries 3-5). As indicated in entry 6, pyridine was found to play a crucial role as removing it from the reaction medium, only a trace amount of product was observed by GC-MS analysis. A final attempt to optimize the reaction proved that only 0.5 equiv of triphosgene and 2.0 equiv of

pyridine was necessary to generating the corresponding product in satisfactory 88% yield (entry 7). Attempts to probe the reaction mechanism by reducing the loading of pyridine to 0.1 equiv (entry 9) revealed incomplete consumption of starting materials after 6 days of reaction time.

Table 4.7 Optimization of Vicinal Dichlorination with Triphosgene-Pyridine

Reaction scheme: Epoxide **4.78** (1-phenyl-2-oxirane) reacts with triphosgene and pyridine in CH_2Cl_2 at temperature for 3 hours to yield vicinal dichloride **4.79** (1,2-dichloro-1-phenylethane).

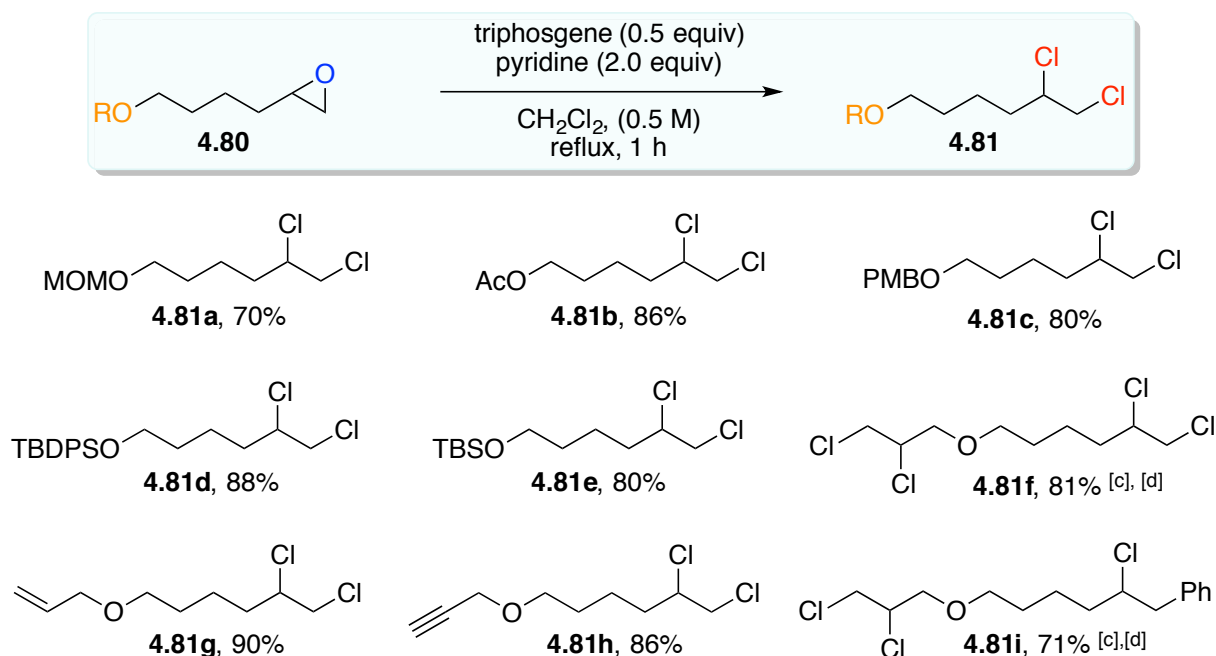
entry	triphosgene (equiv)	pyridine (equiv)	temperature	concentration (M)	yield (%) [a,b]
1	1.0	4.0	rt	0.2	mixture [c]
2	1.0	4.0	reflux	0.2	62
3	1.0	4.0	reflux	0.5	81
4	1.0	2.0	reflux	0.5	89
5	1.0	2.0	reflux	1.0	80
6	1.0	0.0	reflux	0.5	NR
7	0.5	2.0	reflux	0.5	88
8	0.5	1.0	reflux	0.5	83
9	0.5	0.1	reflux	0.5	45 [d]

[a] Reaction progress monitored by GC analysis. [b] Isolated yields after column chromatography.

[c] Complex mixtures observed. [d] Reaction never reached completion after 6 days.

With the optimized reaction conditions in hand, we then examined the scope of epoxides (Scheme 4.23). All epoxide substrates were synthesized from the epoxidation of commercially available 6-hexen-1-ol, then protection (Chapter 7). Our dichlorination strategy proved to be compatible with essential oxygen atom protecting groups, such as MOM **4.81a**, acetyl **4.81b**, PMB **4.81c**, TBDPS **4.81d**, and TBS **4.81e**, furnishing the desired alkyl dichlorides in excellent yields. Our ability to chlorinate epoxides using triphosgene and pyridine is highly advantageous, considering that this methodology enables the production of vicinal dichlorides orthogonally in the presence of π -systems, which are typically employed as precursors for the formation of 1,2-

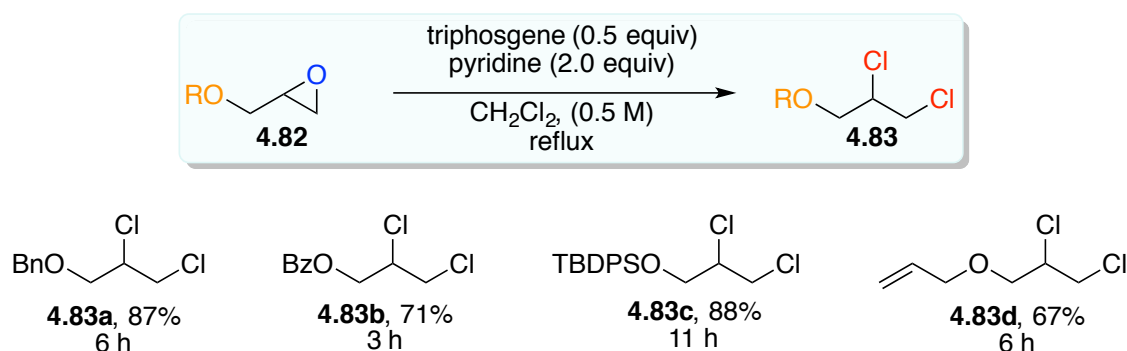
dichlorides. For instance, the use of substrates containing allyl and propargyl groups afforded products **4.81g** and **4.81h** in high yields, and both the allyl and propargyl groups remained untouched during the course of the reaction. The ability to chlorinate epoxides in the presence of π -bonds with triphosgene-pyridine is highly advantageous, as this allows an orthogonal production of vicinal dichlorides in the presence of allylic and propargylic functionalities. This is a non-trivial retrosynthetic plan, as the traditional production of vicinal dichlorides involves the addition of Cl_2 equivalents across π -bonds. Additionally tetrachlorinated and trichlorinated adducts **4.81f** and **4.81i** could be formed by simply doubling the molar equivalents of triphosgene and pyridine to 1.0 equiv and 4.0 equiv, respectively. It's important to note that no deprotected products were observed during the course of the reaction.



[a] Progress of reaction monitored by GC. [b] Isolated yield after column chromatography. [c] Inseparable mixture of diastereomers. [d] 1.0 equiv of triphosgene and 4.0 equiv of pyridine was used.

Scheme 4.23 Examination of Protecting Group Compatibility

Lastly the utility of industrially relevant glycidols were also examined (Scheme 4.24). Various dichlorinated glycerols could be produced cleanly and in relatively high yields however the decrease in yield is attributed to volatility. Also no deallylated products or tetrachlorinated products were detected when **4.83d** was produced. It is also important to mention that every dichlorinated product was formed through impeccably clean and quantitative conversions based on GC-MS analyses of the crude reaction mixtures. This is an austere advantage over traditional dichlorination reactions as terminal chlorohydrin formation and elimination products are common products formed. Also no wasteful byproducts were observed.

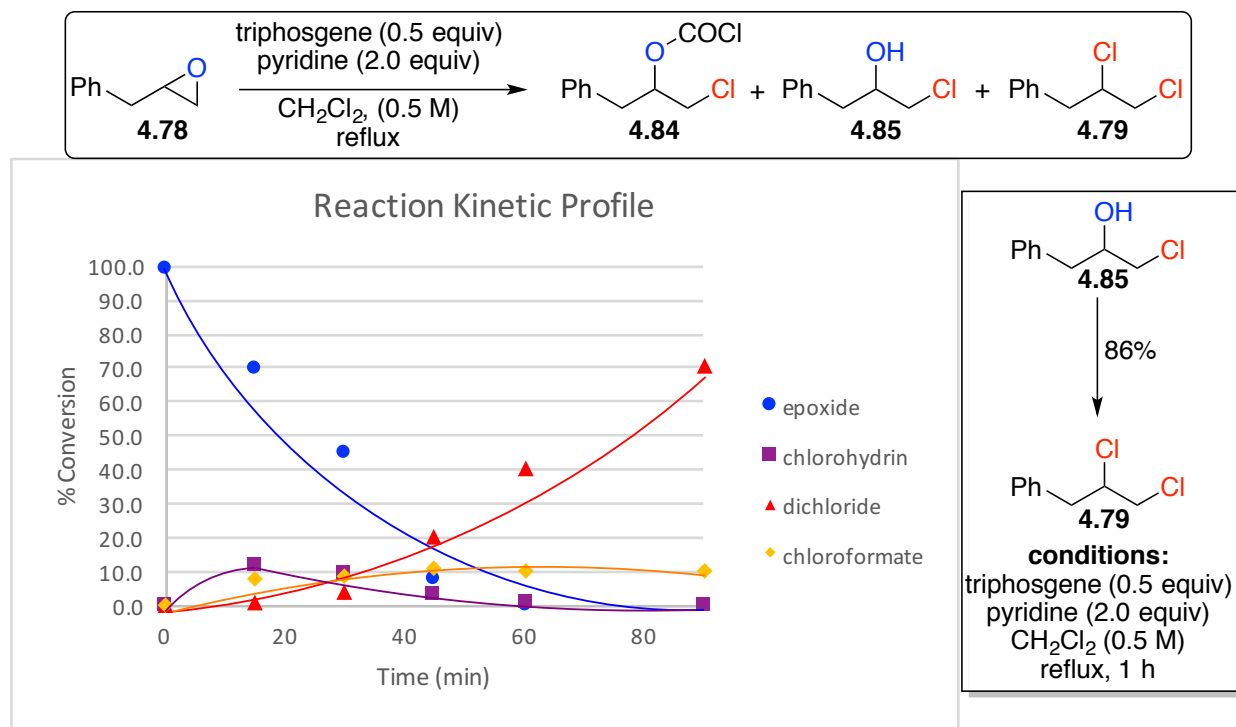


[a] Progress of reaction monitored by GC. [b] Isolated yield after column chromatography.

Scheme 4.24 Dichloroglycerol Synthesis

To glean some insights about the reaction mechanism, we designed and executed several key experiments as depicted in Scheme 4.25. First, we monitored the progress of the reaction by periodically subjecting aliquots of the crude reaction mixture to GC-MS analyses using our model substrate 2-benzyloxirane **4.78**. This study revealed the presence of two transient intermediates, β -chloro-chloroformate **4.84** and chlorohydrin **4.85**. Attempts to isolate these compounds only led to the isolation of chlorohydrin **4.85**. In fact the chloroformylated species **4.84** was not detected

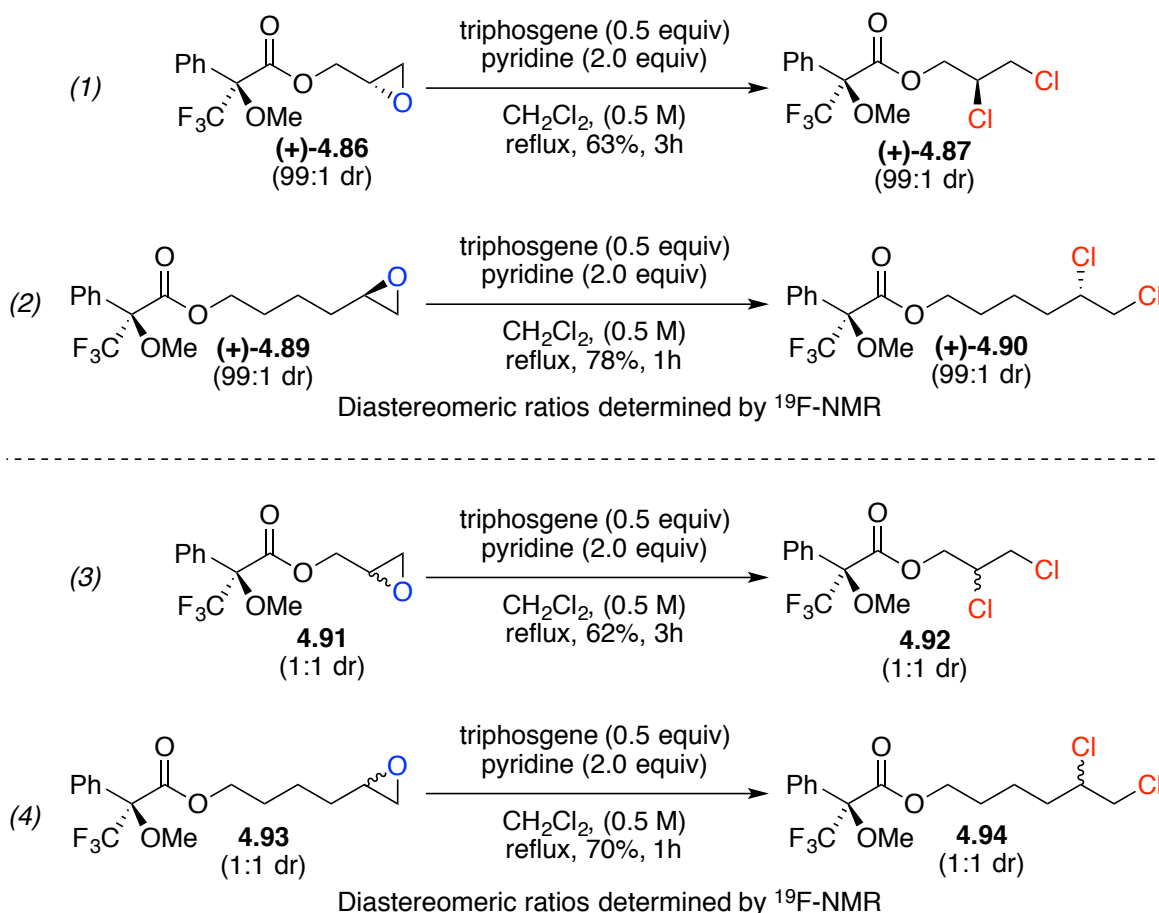
upon aqueous workup, suggesting that **4.85** might be generated as a byproduct from the hydrolysis of **4.84**. Nonetheless, the role of chlorohydrin **4.85** as intermediate could not be ruled out, considering that treatment of this compound with the optimized conditions furnished vicinal dichloride **4.79** in 86% yield. Monitoring the progress of this reaction by GC-MS again revealed the presence of β -chloro-chloroformate **4.84**.



Scheme 4.25 Kinetic Profile of Triphosgene-Pyridine Dichlorination Reaction

Our attention then turned to interrogating the stereochemical outcome of this reaction. With the use of diastereomerically pure Mosher ester-derived (*R*)-glycidol (+)-**4.86**, stereocomplementary vicinal dichloride (+)-**4.87** was formed as a single diastereomer in 63% yield (>99:1 d.r. determined via ^{19}F -NMR) (Scheme 4.46, *eqn 1*). Additionally, (2*R*)-oxiranebutanol (+)-**4.89** was subjected to identical conditions generating its corresponding vicinal dichloride (+)-

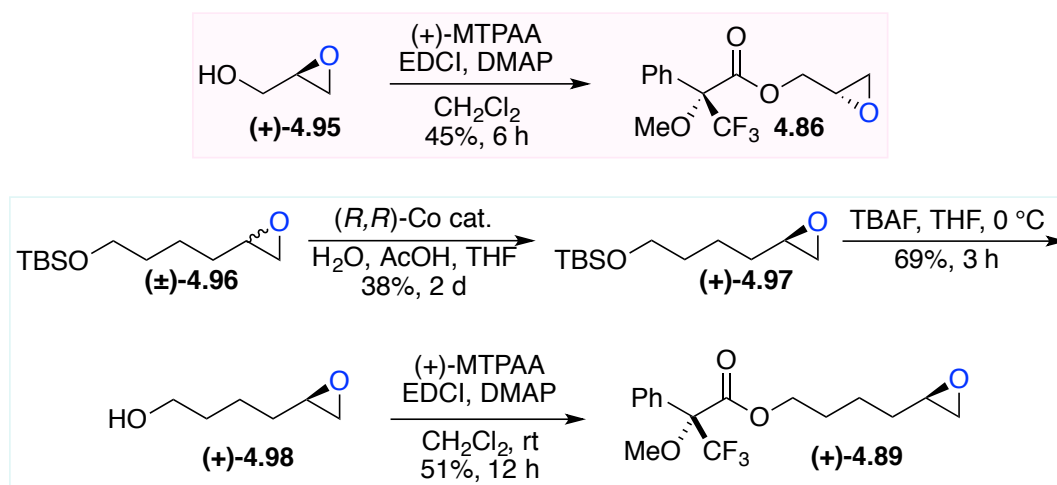
4.90 with a presumed inversion of stereochemistry. Control experiments were conducted using racemic forms of **(+)-4.86** and **(+)-4.89**. By monitoring the reaction via ^{19}F -NMR analysis, 1:1 mixture of diastereomers of starting materials and chlorinated products from both experiments were observed (Scheme 4.26 eqns 3 and 4).



Scheme 4.26 Stereochemical Interrogation via Diastereomeric Epoxide Pairs

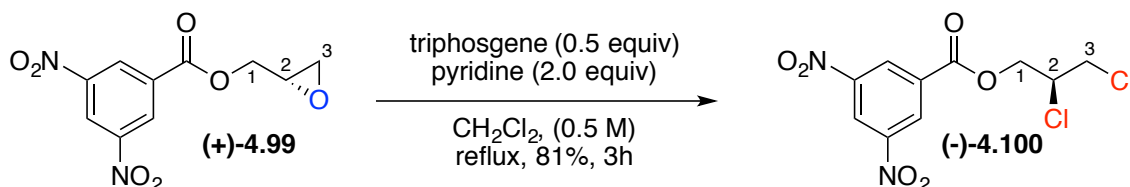
Chiral epoxides **(+)-4.86** and **(+)-4.89** were synthesized directly from commercially available (*R*)-glycidol **(+)-4.95** and TBS-protected epoxide **(±)-4.96**. The enantiomers of epoxide **(±)-4.96** were resolved using Jacobsen's hydrolytic kinetic resolution revealing enantioenriched **(+)-4.97**. Subsequent deprotection and benzylation with Mosher's Acid afforded epoxide **(+)-**

4.89 in >99:1 d.r. determined by ^{19}F -NMR. Diastereomeric pairs **4.91** and **4.93** were synthesized in an analogous fashion using racemic starting materials.



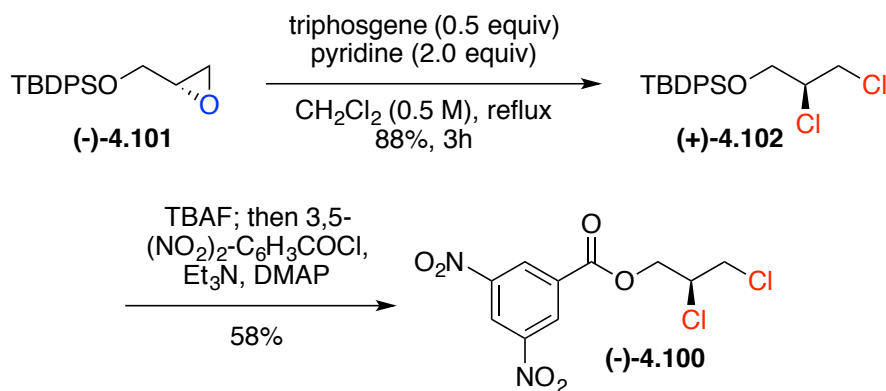
Scheme 4.27 Synthesis of Chiral Epoxides

Lastly in an attempt to determine the absolute stereochemical outcome of this dichlorination reaction we synthesized crystalline 3,5-dinitrobenzoate ester-protected (*R*)-glycidol **(+)-4.99**. Upon subjection of **(+)-4.99** to our optimized reaction conditions, we realized the resulting dichloride **(-)-4.100** in 81% yield after 3 hours. X-Ray crystallographic analysis of epoxide **(+)-4.99** and dichloride **(-)-4.100** revealed an inversion of stereochemistry at C-2.



Scheme 4.28 Determination of the Absolute Stereochemistry of **(-)-4.100**

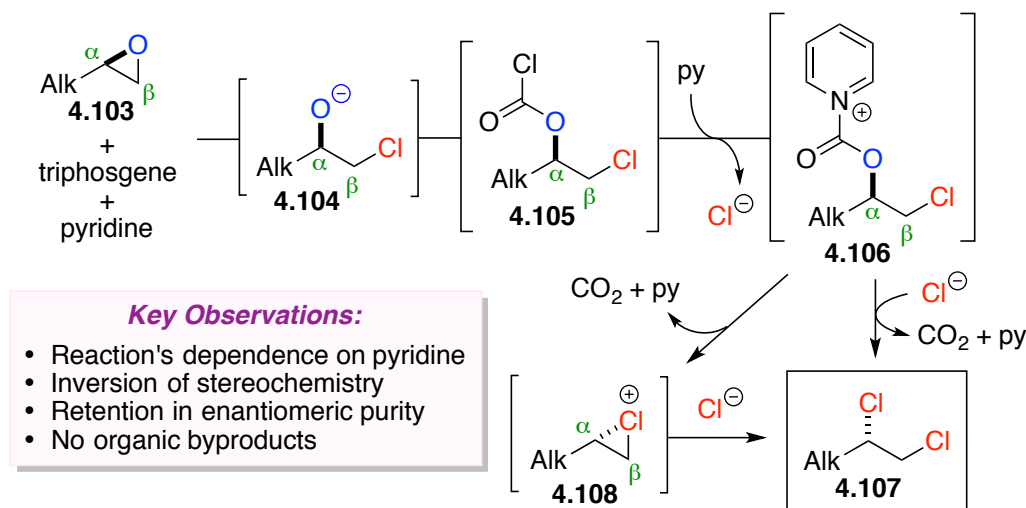
As the benzoate carbonyl from the dinitrobenzoyl group is proximal to the reactive site it was necessary to examine the possibility of anchimeric assistance. TBDPS-protecting (*R*)-glycidol (**(-)-4.101**) was generated and dichlorinated yielding vicinal dichloride **(+)-4.102** in 88%. The resulting dichloride product was then in a one-pot process, deprotected with TBAF and benzoylated with 3,5-(NO₂)₂-BzCl producing crystalline **(-)-4.100** in 58%. All spectroscopic and optical rotation data was identical from the previously reported synthesis of **(-)-4.100**.



Scheme 4.29 Ruling Out Anchimeric Assistance from the Benzoate Group

Finally, the culmination of these experimental observations resulted in the following mechanistic proposal (Scheme 4.30). These findings ultimately led us to propose the following mechanism. Reaction of epoxide **4.103** with triphosgene and pyridine produces transient β -chloro-chloroformate **4.105** via nucleophilic ring opening at the β -carbon by chloride ions, followed by *in situ* chloroformylation of the emerging chlorohydrin anion **4.104**. Analogous to our previous studies, β -chloro-chloroformate **4.105** can then be activated by pyridine to pyridinium carbamate **4.106**, allowing for the penultimate decarboxylative nucleophilic substitution by chloride ions to produce the observed dichloride **4.107**. However, given the close proximity of the electrophilic

α -carbon to an adjacent chlorine substituent, a second decomposition pathway could be operative leading to the formation chloronium ion **4.108** from **4.10** liberating pyridine and CO₂. The ensuing nucleophilic attack of this intermediate by chloride ions, again at the sterically accessible β -carbon, would result in the production of vicinal dichloride **4.107**. Both mechanistic pathways account for the observed stereoinversion at the α -carbon.



Scheme 4.30 Proposed Reaction Mechanism

4.7 Conclusion

In conclusion this chapter provides a review of dichlorination strategies using substituted olefins or substituted epoxides. Both strategies generate 1,2-dichlorides, vicinal dichlorides, stereospecifically resulting in advanced polychlorinated architectures. This chapter also illustrates a new dichlorination strategy of unactivated terminal epoxides using mixtures of triphosgene-pyridine. This strategy generated the corresponding vicinal dichlorides stereospecifically in high yields and clean, quantitative conversion. This methods offers a solution to the classically utilized Ph₃P-promoted dichlorination strategy as no nuisance waste byproducts are formed. With the

completion of this project, the strategy of converting simple functional groups to alkyl chlorides comes to a close. In that regard we turned our attention away from simple functional group interconversions to more advanced synthetic challenges. Specifically we initiated a new plan to synthesize heterocyclic building blocks that are of medicinal importance. Since we also have a strong interest in developing new reactions and studying their mechanisms, we also wanted to explore the reactivity of bicyclic epoxonium ions and their role in heterocycles synthesis.

Chapter 5: A Review of Epoxonium Ions and their Application for the Synthesis of Chlorine Substituted Pyranosides

5.1 Purpose

The purpose of this chapter is to review strategies for the generation of bicyclic epoxonium ions from medium ring ether heterocycles and acyclic epoxides and showcase their utility in synthesis. Baldwin's Rules for Ring Closure will be reviewed to demonstrate how the reactivities of epoxonium ions differ from common acid or base promoted epoxide cyclizations. Strategies for the cyclization of acyclic, terminal epoxides developed by Murai, MacDonald and Floreancig will be discussed. Finally the successful cyclization of unactivated epoxyketones to pyranoside heterocycles promoted by pyridinium acid in combination with triphosgene will be presented. Mechanistic analyses supporting the formation of a transient epoxonium ion will be discussed, as well as a model illustrating a novel counterion biased chemoselectivity.

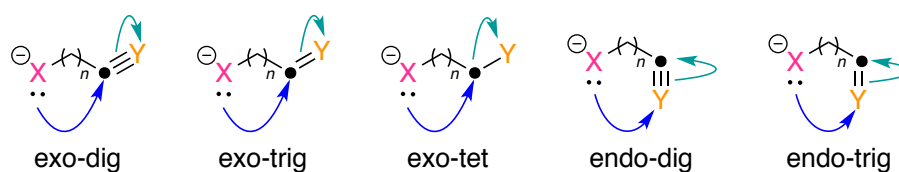
5.2 Baldwin's Rules for Ring Closure

The synthesis of a target molecule whether that be a complex natural product or macromolecule typically begins with the development of a retrosynthetic plan. Retrosynthetic analysis¹⁶¹ is a powerful tool wherein the synthetic chemist envisions working backwards starting with the target molecule and dissecting it into smaller fragments. These fragments known as synthons can further be broken down into smaller and smaller components of the target molecule until the chemist arrives at either commercially available materials or ones that can be synthesized in few steps from commercial sources. However while an extremely powerful tool, retrosynthetic analyses wouldn't be possible without the inherent knowledges of chemical reactivity, specifically whether a reaction is going to produce the correct regioisomer, stereoisomer, or react with multiple functional groups. Obviously this is a complex process that requires careful thought and planning;

however the art of dismembering a molecule has become less daunting due to the development of chemical models or rules to explain reactivity patterns and predict reaction outcomes.

A specific set of rules that have been developed to aid in the retrosynthesis of target molecules and has found broad utility are the Baldwin's Rules for Ring Closure.¹⁶²⁻¹⁶⁴ These empirical rules were developed by Sir Jack Baldwin in the late 1970s to predict the outcome of a cyclization reaction of a carbocyclic system. The success of the cyclization reaction is denoted as either *avored* (F) meaning likely to produce the desired product; or *isavored* (D) which is not likely to produce the desired cyclized product. However deviations do occur and these rules are not law, more like guidelines. Baldwin's Rules provide a model for the attack of a carbon-leaving group bond ($\bullet\text{-Y}$) by heteroatom, carbon or radical nucleophile (X) (Table 5.1). However, Baldwin's rules do not predict the reactivities of electrocyclization reactions.

Table 5.1 Baldwin's Rules for Ring Closure



Ring size	Exo-dig	Exo-trig	Exo-tet	Endo-dig	Endo-trig	Endo-tet
3	D	F	F	F	D	—
4	D	F	F	F	D	—
5	F	F	F	F	D	D
6	F	F	F	F	F	D
7	F	F	F	F	F	—

F = Favored cyclization; D = Disfavored cyclization

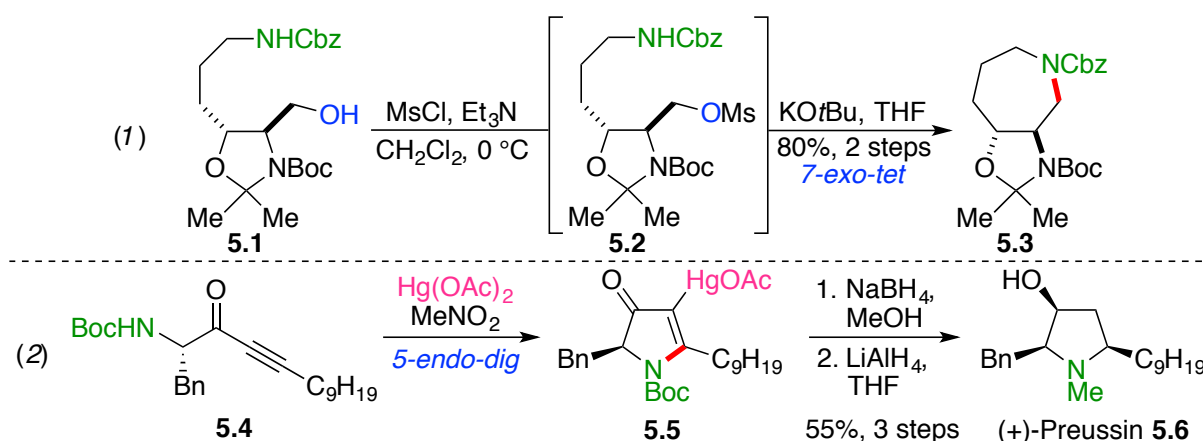
Baldwin's Rules use the following descriptors to predict a successful ring closure reaction:

- 1) The size of the ring formed *i.e.* 3-7 atoms within the cyclic framework.
- 2) Whether the bond

broken is *exocyclic* or *endocyclic* to the newly formed ring. 3) The hybridization of the carbon atom that is attacked, *i.e.* sp , sp^2 , or sp^3 . The last descriptor also provides information about the angle of trajectory of the incoming nucleophile determined by Bürgi and Dunitz.¹⁶⁵⁻¹⁶⁶ These descriptors are represented using the following nomenclature *n-endo/exo-hybridization* to represent the corresponding cyclization reaction. As already mention, this nomenclature governs:

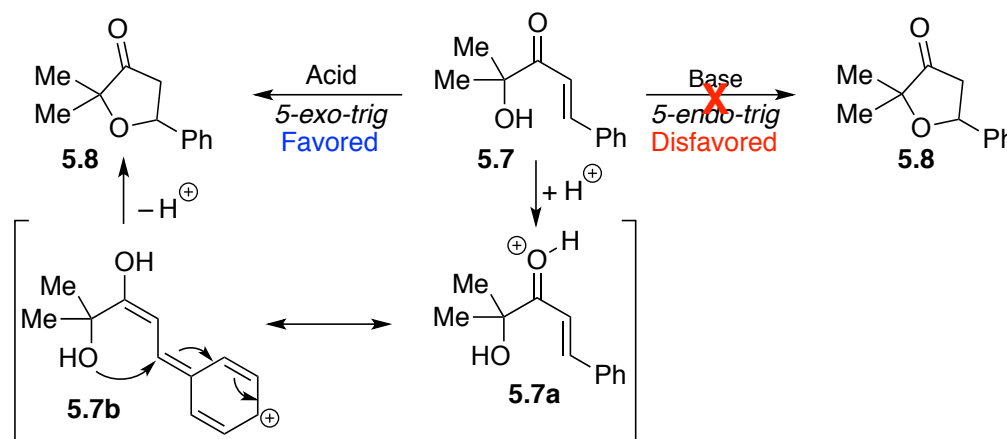
- 1) The size of the newly formed ring (*n*).
- 2) Whether the broken bond is exocyclic (*exo*) or endocyclic (*endo*) to the newly formed ring.
- 3) The hybridization of the carbon atom attacked during ring closure. The hybridizations are represented as: tetragonal, *tet*, for sp^3 -hybridized atoms, trigonal, *trig*, for sp^2 -hybridized atoms, and digonal, *dig*, for sp -hybridized atoms.

Scheme 5.1 *eqn. 1* illustrates a favored exocyclic ring-formation used toward the synthesis of fungal metabolite balanol.¹⁶⁷ To synthesize the desired azepane fragment Nicolaou and his team mesylated primary alcohol **5.1** in the presence of a Cbz-protected amine and upon treatment with KOtBu in THF, a *7-exo-tet* ring closure occurred liberating heterocycle **5.3** in 80%, over two steps. A favored cyclization, the descriptor is 7 for the size of the newly formed ring, *exo* because the broken bond is exocyclic to the ring, and *tet* due to the sp^3 -hybridization of mesylated **5.1**.



Scheme 5.1 Examples of Baldwin's Rules for Ring Closure

A second example illustrates an endocyclic cyclization (Scheme 5.1, eqn 2). Complexation of $\text{Hg}(\text{OAc})_2$ to α -amino ynone **5.4** initiated a favored *5-endo-dig* cyclization affording pyrrolidinone **5.5**. This organomercury species was then reduced with NaBH_4 to reduce the C–Hg bond, then LiAlH_4 to reduce the pyrrolidinone ring to pyrrolidine, (+)-preussin **5.6** in 55% yield over three steps.¹⁶⁸ Again 5 is the size of the newly formed ring, *endo* because the breakage of the alkyne results in the endocyclic transfer of electrons, *dig* due to the *sp*-hybridization. Lastly Baldwin's Rules can help explain reaction mechanisms when supported by experimental observations.¹⁶⁹ For example, the attempted cyclization of α -hydroxyenone **5.7** under basic conditions fails to produce any product. If the base-promoted mechanism involves deprotonation of the hydroxyl group, followed by cyclization then this process would be considered *5-endo-trig* which is disfavored under Baldwin's Rules. However, treatment of **5.7** with acid results in the formation of the desired furanone product **5.8** presumably through a *5-exo-trig* cyclization.



Scheme 5.2 5-endo-trig vs 5-exo-trig

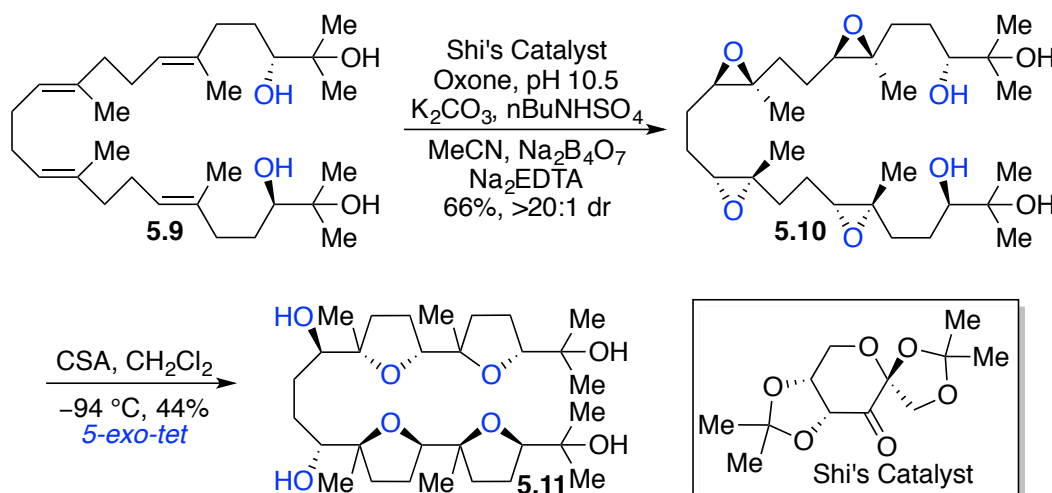
It's imperative to note that Baldwin's Rules are just a model to help predict the outcome of a cyclization. They do not govern chemical reactivity but they qualitatively illustrate the

necessary trajectories a nucleophile must have in order for favorable orbital overlap to occur, forming a chemical bond. The *5-endo-trig* cyclization is not disfavored because Baldwin said so, it is a disfavored mechanistic pathway because attack of the enone by alkoxide does not possess enough overlap of the frontier molecular orbitals to necessitate bond formation. Simply delocalizing the π -conjugation by one carbon atom leads to less strain and favored orbital overlap (**5.7a** \rightarrow **5.7b**). Baldwin's Rules are general and will usually predict the appropriate reactivity of the ring closing reaction, but they are not laws and several exceptions and limitations exist.¹⁷⁰⁻¹⁷³ These rules were originally developed for 1st-Row elements only (C, N, O) and application to 2nd-Row elements usually deviates from the rules as they are larger and more polarizable than the 1st-Row elements. However 1st-Row elements are not infallible to deviation either.¹⁷⁴⁻¹⁷⁵

5.3 Epoxonium Ions and Strategies for Their Generation

Epoxides are cyclic, three-membered oxygen containing heterocycles that possess two electrophilic carbon atoms about the cyclic structure. Given the small size of the ring, these heterocycles possess roughly 20 to 24 kcal/mol of ring strain.¹⁷⁶⁻¹⁷⁷ This inherent ring strain permits the α -carbons of an epoxide to be quite electrophilic leading to their use as synthons for alcohols and small heterocycles. In fact a well-known reactivity of epoxides involves the cyclization of an alcohol onto an epoxide producing a cyclic ether product. For instance, E.J. Corey exploited an epoxide-opening cascade *en route* to the synthesis of the natural product glabrescol.¹⁷⁸ In his synthesis, Corey generated tetraepoxy intermediate **5.10** from **5.9** exploiting Shi's organocatalytic, asymmetric epoxidation strategy¹⁷⁹, forming all epoxides in 66% yield and >20:1 d.r. Subsequent activation of **5.10** with stoichiometric CSA at reduced temperature, initiated a favored *5-exo-tet* cyclization producing **5.11**. This nucleophilic attack of the epoxide by the hydroxyl group resulted in the formation of four tetrahydrofuran rings in 44% yield and excellent

diastereoselectivity. This innate reactivity of an epoxide is routinely exploited for heterocycles synthesis as the oxygen atom is weakly basic and activated by various acid sources.¹⁸⁰⁻¹⁸²



Scheme 5.3 Corey's Epoxide-Opening Cascade

More specifically, acidic activation of an epoxide forms oxonium species **5.12a** or **5.12b**, uniquely known as monocyclic epoxonium ions. Like in Corey's synthesis of glabrescol activation of one of the epoxides with CSA presumably generates a monocyclic epoxonium ion that is then intercepted by the pendant alcohol via S_N2 process forming the observed ring system. However an additional activation strategy of epoxide activation is possible that reverses the innate electrophilicity of the epoxide and umpoles it for use as a nucleophile. This umpolung strategy relies on the oxygen atom of the epoxide to attack an electrophilic species forming what is known as a bicyclic epoxonium ion, or simply an epoxonium ion **5.13** (Figure 5.1). Bicyclic epoxonium ions are unstable, extremely strained electrophiles and are formed via an analogous nucleophilic cyclization process previously mentioned or through ring expansion of a medium ring oxygen containing heterocycle, such as a tetrahydrofuran or tetrahydropyran ring.¹⁸³⁻¹⁸⁴ These bicyclic

intermediates showcase a deviation to Baldwin's Rules as attack of epoxonium ions can lead to the formation of *endocyclic* or *exocyclic* product mixtures depending on reaction conditions.

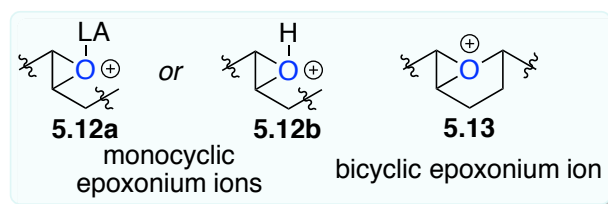
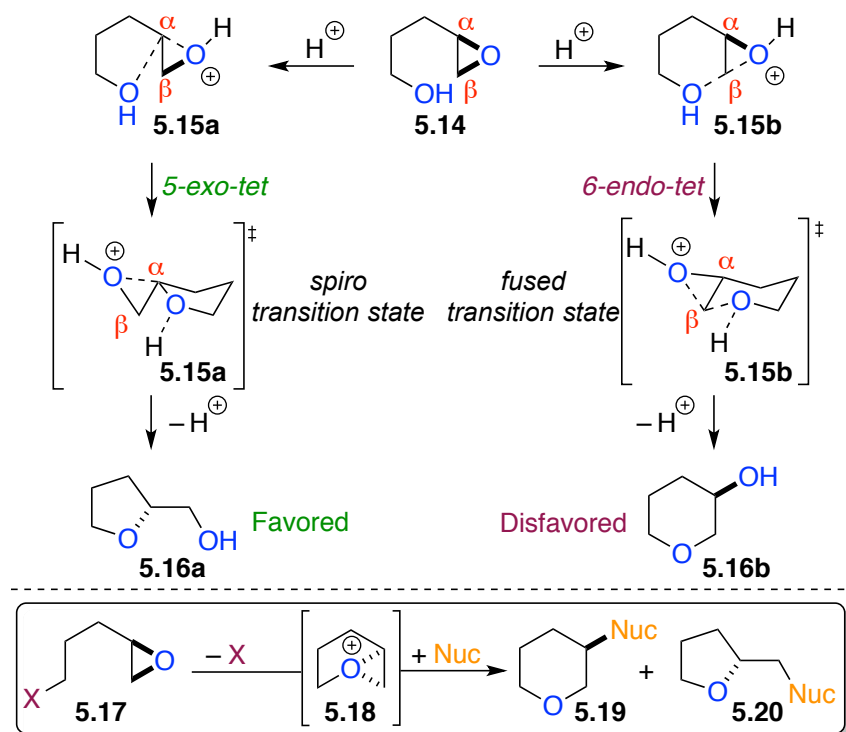


Figure 5.1 Epoxonium Ions

Recall that epoxide ring openings exclusively proceeds via *n-exo-tet* cyclizations forming the smaller ring system over the larger (Scheme 5.4). Activation of epoxyalcohol **5.14** with either an acid or base promotes the cyclization of the alcohol onto either the α -position or β -position of the epoxide. Attack of the epoxide at the α -position generally proceeds via *spirocyclic* transition state **5.15a**. This mechanistic pathway proceeds with the least amount of angle strain in the transition state and is *avored* forming five-membered tetrahydrofuranol **5.16a** (*5-exo-tet*), in this example. An additional trajectory of attack involves attacking the β -position of **5.14**. This mode of attack proceeds through a *fused* transition state forming *endocyclic* tetrahydropyranol product **5.16b** and is disfavored (*5-endo-tet*) due to an increase in angle strain in the transition state. *Exo-tet* processes are generally applicable to larger ring systems such as *6-exo-tet* and *7-exo-tet* processes are also favored via *spirocyclic-like* transition states.¹⁸⁵ However, if the desired product is the *endocyclic* product then simple acid or base catalyzed process will typically fail to form the desired product. Therefore it is necessary to design a system that allows for bicyclic epoxonium ion formation. The generation and utility of a bicyclic epoxonium ion circumvents the constrained,

fused transition states of the cyclization of an epoxyalcohol and provides a pathway for the formation of the endocyclic products, which are disfavored under Baldwin's Rules.



Scheme 5.4 Epoxide Ring Openings

Interestingly both cyclization processes that proceed via monocyclic and bicyclic epoxonium ions are believed to be key intermediates in the biosynthesis of marine polyether natural products, an example from this family is show below.^{182, 186-187} These polymeric-like, *trans*-fused macromolecules possess a repeating array of tetrahydropyranyl and oxepanyl ethers that are substituted with several methyl and hydroxyl groups with assorted stereochemistries. These incredibly complex natural products are most likely produced by dinoflagellate organisms found in the Oceans and Gulfs across the world. These aquatic products are quite toxic to marine life as well as humans and are typically encountered during large algal blooms. These blooms

known as Red Tides occur when marine microorganisms encounter a large amount of nutrients that have been disturbed from the sea floor and rise to the surface leading to the overexpression of photosynthetic components of the algae forming red to brown colors.¹⁸⁸ Red tides are a natural phenomenon and are not necessarily a cause for alarm; however, they do trigger mass fish kills that can last up to two weeks affecting commercial fishing operations.¹⁸⁹⁻¹⁹¹ These algal blooms also deposit toxins which can be up taken by bivalve organisms and shellfish which when consumed by humans can lead to severe health complications and even death.

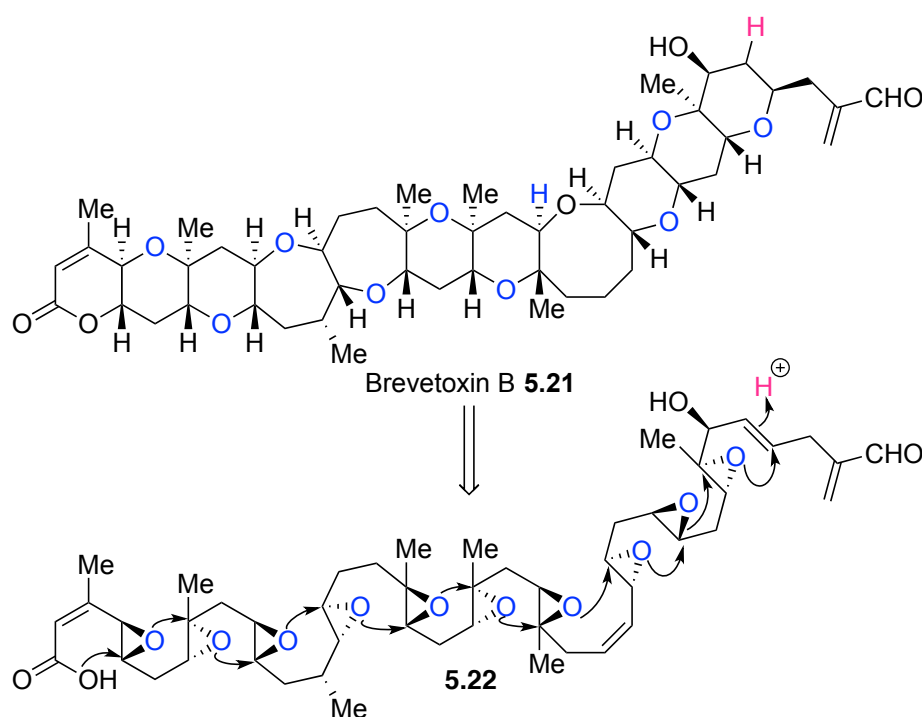
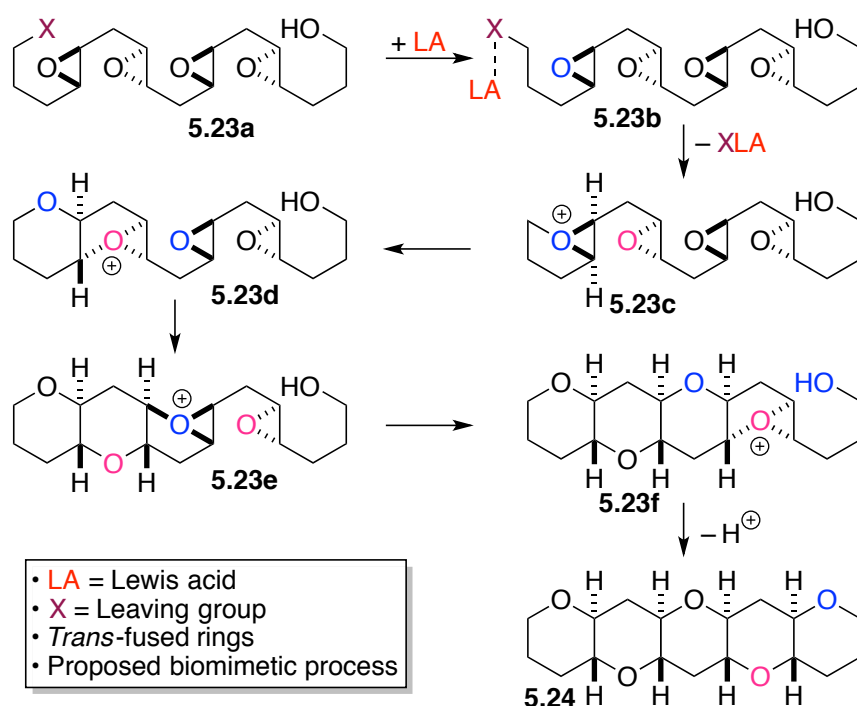


Figure 5.2 Nakanishi's Domino Polyepoxide Cyclization

One of the most heavily researched polyether natural product class is the Brevetoxins, more specifically Brevetoxin B (Figure 5.2).¹⁹²⁻¹⁹³ The Brevetoxins are believed to be biosynthesized through cascade processes from polyepoxide precursors. In fact Nakanishi reported that

Brevetoxin B is most likely generated from polyepoxide precursor **5.22** and through acid-activation, a cascade process erupts generating the aforementioned biotoxin.¹⁹⁴⁻¹⁹⁶ While several debates exist whether the biosynthetic mechanism proceeds through bicyclic epoxonium ion formation and capture, or through *normal* ring-opening of monocyclic epoxonium ions, some scientists believe it may be a combination of both.¹⁹⁷ However, the drastic control of *trans*-fused arrangement of rings provides some support for a discreet bicyclic epoxonium ion mechanism.



Scheme 5.5 Epoxonium Ion Cascade

Described in detail, these cascades presumably happen through a tandem ring-opening/cyclization events of the epoxide which allows for cascade processes until the target compound is formed. However, the regioselectivity of epoxide opening proves problematic and the most plausible pathway involves tandem bicyclic epoxonium ion formation followed by attack from an

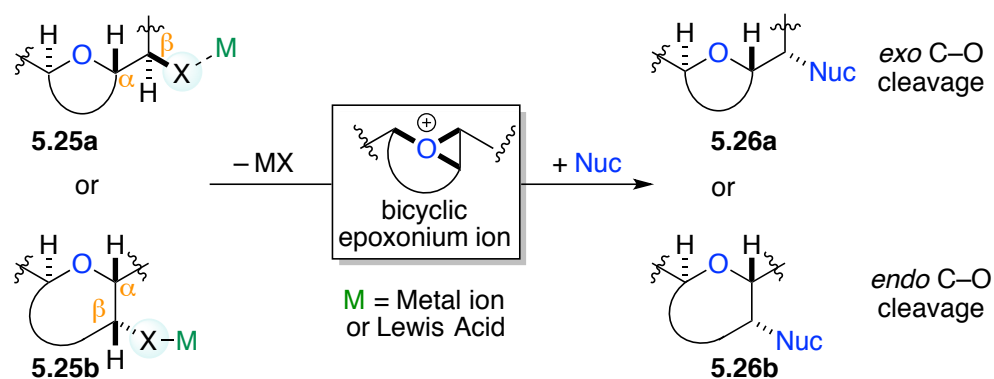
adjacent epoxide. This proposed cascade process is outline in Scheme 5.5.¹⁸³ Beginning with tetraepoxide **5.23a**, activation of a leaving group an acid source allows for nucleophilic substitution generating bicyclic epoxonium ion **5.23b**. The ensuing interception presumably happens via an analogous substitutive process liberating ring-strain forming **5.23c**. The liberation of ring strain drives this process forward until the terminal epoxide reacts forming *trans*-fused polyether product **5.24**. This obviously is an oversimplified examples as these natural products contain a mixture of five-, six-, and seven-membered rings within their polyether architectures. Nonetheless it is suggested that the epoxonium ion mechanism provides a selective pathway for the *endo*-substituted regiochemistry, as well as the observed *trans*-fusion.

As mentioned previously there are two known pathways available for generating bicyclic epoxonium ions. One pathway involves attack of a leaving group by the oxygen atom from a medium ring ether (*i.e.* tetrahydrofuran or tetrahydropyran) generating a bicyclic epoxonium ion. Subsequent trapping with a nucleophile at the endocyclic position forms a ring expanded product. The other strategy involves the direct cyclization of an acyclic epoxide onto an activated leaving group forming the aforesaid oxonium ion. This latter process is the most common example found in the literature and several methods have been developed exploiting this reactivity. This type of reactivity is applicable to cascade polyepoxide cyclizations and serious attention has been paid to exploiting this process for polyether natural products synthesis.

5.3.1 Ring Expansion via Nucleophilic Capture of an Epoxonium Ion

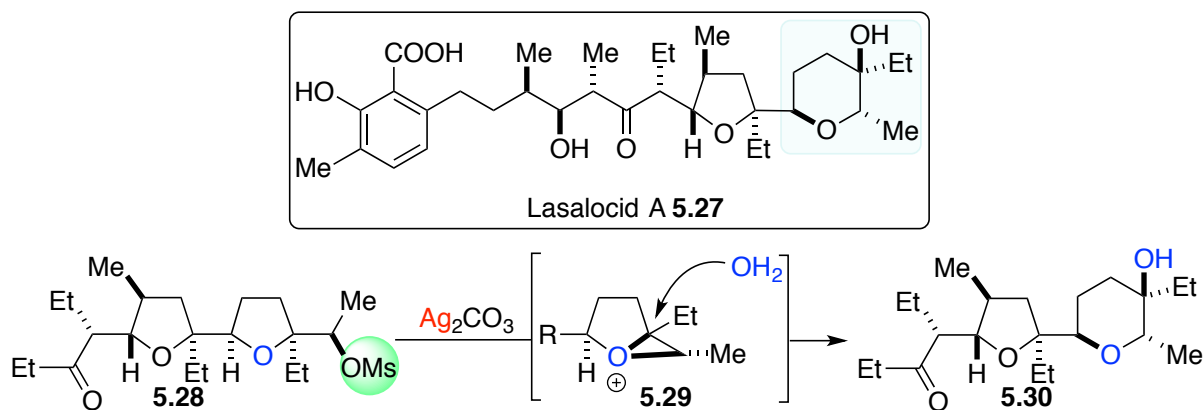
Activation of a leaving group that is located at the β -position relative to the oxygen atom of a cyclic ether is one unique way to generate a bicyclic epoxonium ion (Scheme 5.6). This intermediate is then available for biased regioselective capture by a nucleophile at either the *exo*-position or the *endo*-position. If exocyclic capture occurs then no ring expansion product is formed

and only a formal substitution reaction occurs; although, if endocyclic capture predominates then the desired ring expansion occurs generating the Baldwin *disfavored endo*-product. The ratio of these two products is typically controlled via substitutions at either the endocyclic position or exocyclic position of the substrate. Additionally stereoelectronic effects also aid in modulating product selectivity via electron-donating or withdrawing groups.¹⁸²⁻¹⁸³



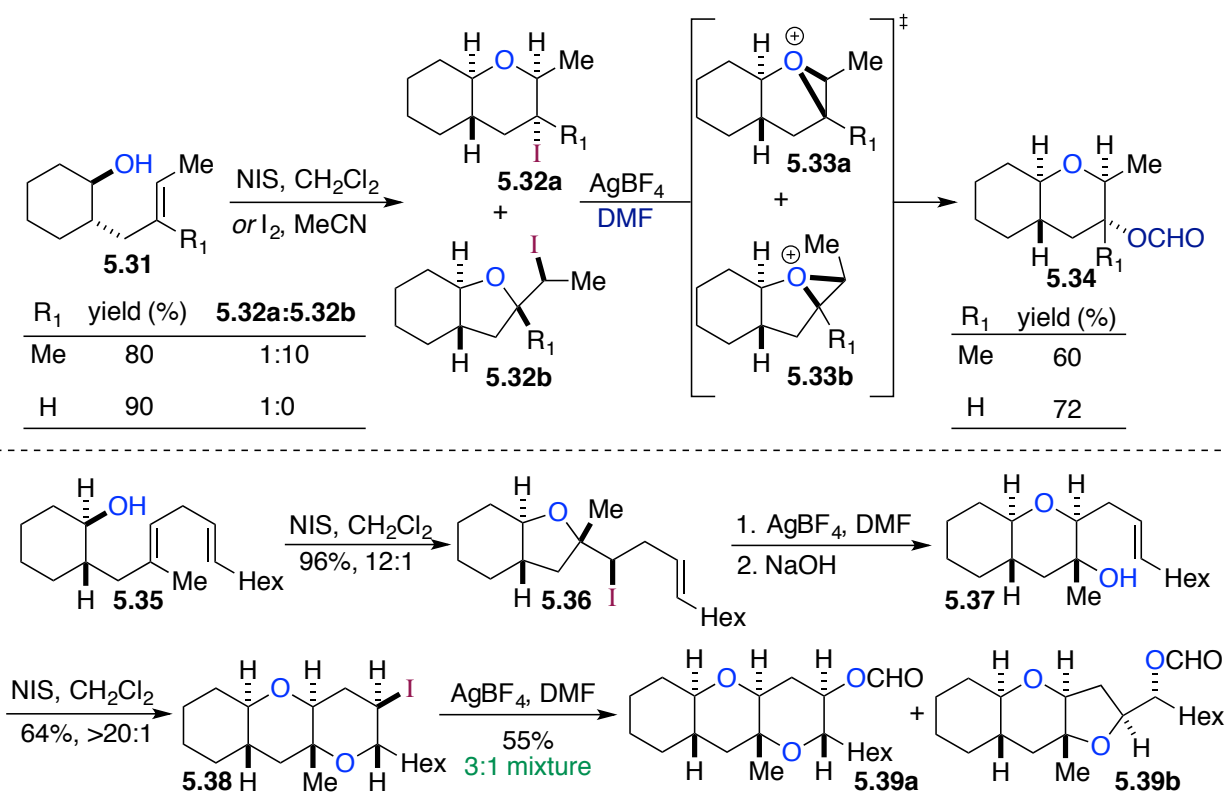
Scheme 5.6 Ring Expansion via Nucleophilic Capture of an Epoxonium Ion

One of the first examples of this type of reactivity was reported by Kishi in the late 70s. Kishi and his team were attempting the total synthesis of Lasalocid A and devised that the six-membered ring at the eastern terminus of the natural product could be generated through a bicyclic epoxonium ion mediated ring expansion (Scheme 5.7).¹⁹⁸ In fact they reported that activation of β -mesyl tetrahydrofuran **5.28** with Ag_2CO_3 afforded ring expanded tetrahydropyran **5.30** in 65% yield, with 12% recovered starting material. Kishi and his team hypothesized that the observed product was likely formed via an intermediary cation **5.29**. Regioselective nucleophilic capture of the resulting cation at the endocyclic position afforded **5.30** with an inversion of stereochemistry.



Scheme 5.7 Kishi's Ring Expansion Strategy

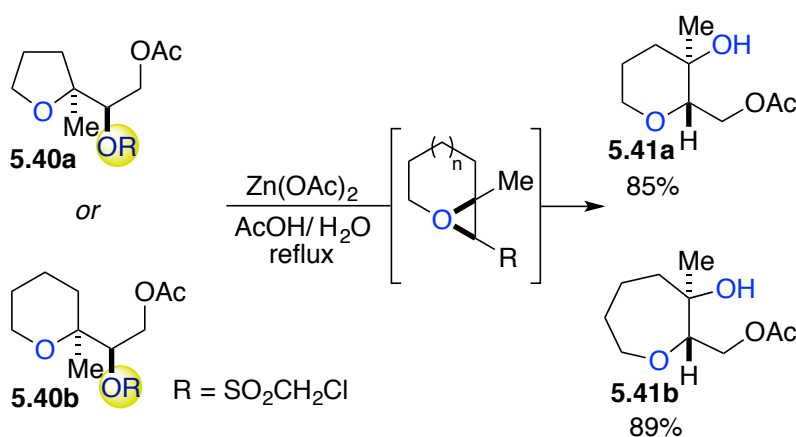
An analogous strategy developed by Bartlett involves an iodoetherification/ AgBF_4 -promoted ring expansion (Scheme 5.8).¹⁹⁹⁻²⁰⁰ Simple treatment of substituted cyclohexanol with *N*-iodosuccinimide (NIS) or molecular iodine affords iodoetherificated products **5.32a** and **5.32b**. When $\text{R}_1 = \text{Me}$, a 1:10 mixture of six- vs five-membered products are formed, while if $\text{R}_1 = \text{H}$, the six-membered heterocycle **5.32a** is formed almost exclusively. However, this mixture of regioisomeric products proves inconsequential as exposure of both products to AgBF_4 in DMF yields endocyclic cis-fused tetrahydrochromane **5.34** as the sole regioisomer in 60% and 72% when $\text{R}_1 = \text{Me}$ or H , respectively. Bartlett's protocol is also applicable towards iterative iodoetherification/ring expansion strategies for the formation of *trans*-fused polyether scaffolds (Scheme 5.8). Similarly, subjection of *trans*-fused cyclohexanol **5.35** with NIS yields *trans*-fused tetrahydrofuran in 96% yield, but in a 12:1 mixture with tetrahydropyran. Subsequent AgBF_4 promoted ionization and hydrolysis affords tetrahydrochromane **5.37** in two steps. An iterative sequence of reactions subsequently affords a mixture of *trans*-fused polyether products in 55% yield with excellent diastereoselectivity of $>20:1$. However a mixture of both endocyclic **5.39a** and exocyclic **5.39b** were formed in a 3:1 ratio.



Scheme 5.8 Iodoetherification/ AgBF₄ Mediated Ring Expansion

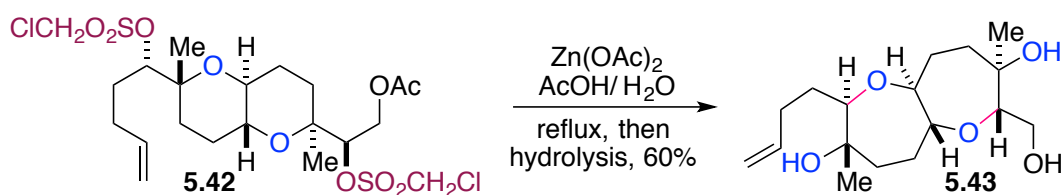
An additional ring expansion strategy was developed by Nakata and coworkers.²⁰¹⁻²⁰² Nakata was a student of Kishi's during the synthesis of Lasalocid A and gained inspiration toward ring expanding sulfonate substituted heterocycles. Nakata's conditions afford an improved generalized strategy for the ring expansion of small oxygen containing heterocycles utilizing a similar strategy as discovered by Kishi. Using a similar protecting group strategy, Nakata protected β -hydroxy medium ring ether substrates **5.40a** or **5.40b** as a monochloromethanesulfonate group (monochlate) and discovered that this leaving group was superior against simple methanesulfonate (mesylate) group. Activating tetrahydrofuran **5.40a** and its homologue tetrahydropyran **5.40b** with Zn(OAc)₂ provided the respective ring expanded products **5.41a** and **5.41b** in 85% and 89% yields, respectively. This reaction most likely involves

chelation of Zn(II) to the chloride of the monochlate group forcing the formation of a strained bicyclic epoxonium ion. This intermediate is subsequently available for regioselective, nucleophilic capture at the *endo*-position leading to the desired products, in excellent yields.



Scheme 5.9 Nakata's Ring Expansion Methodology

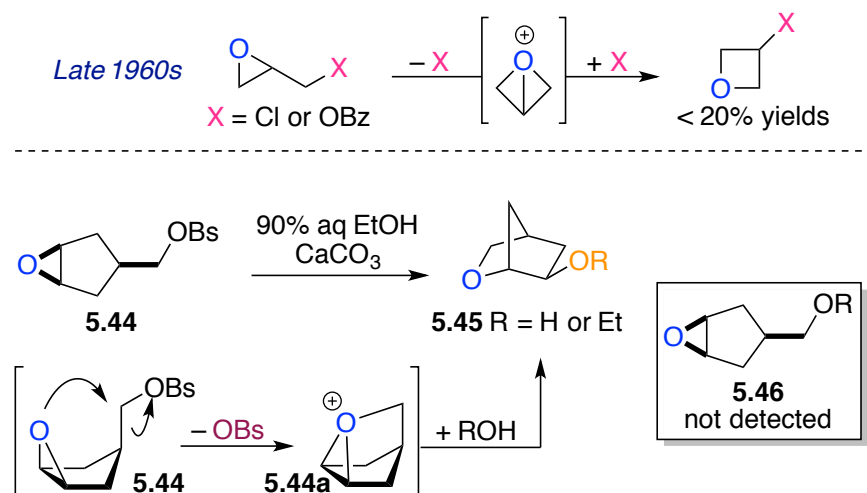
To further test the generality of his method, Nakata applied this reaction to the synthesis of the CD-ring system of Hemibrevetoxin B (Scheme 5.10).²⁰³ Beginning with *trans*-fused ether **5.42** successful activation with Zn(OAc)₂ in AcOH/ H₂O mixtures effected the desired ring expansion to fused oxepane. Hydrolysis of the acetylated alcohols yielded triol **5.43** in 60%, over two steps. An additional 26 steps were needed to finish the molecule.²⁰⁴



Scheme 5.10 Nakata's Synthesis of the CD-ring Fragment of Hemibrevetoxin B

5.3.2 Epoxonium Ion Generation from Acyclic Epoxides

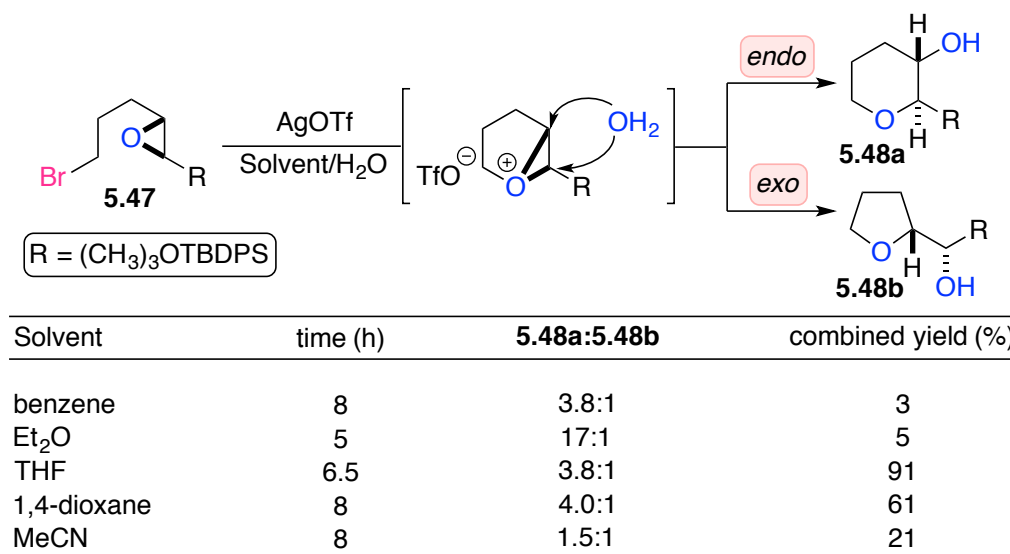
The generation of epoxonium ions from epoxides has been known for over 50 years. By examining the rates of solvolysis of epichlorohydrin and glycidol derivatives, researchers discovered the formation of substituted oxetane rings in the reaction mixtures, albeit in low yields (Scheme 5.11).²⁰⁵⁻²⁰⁷ This perplexing result was attributed to neighboring group participation from the epoxide oxygen atom acting to stabilize the forming positive charge from the loss of the leaving group. A more recent solvolysis study by David further supported these early observations.²⁰⁸



Besylate (OBs) substituted epoxide **5.44** was stirred in a CaCO₃ buffered alcoholic solution at room temperature. Instead of the expected substituted ether or hydrolysis products **5.46**, David

discovered that the reaction media afforded bicyclic heterocycle **5.45** as a mixture of ethyl ether and alcohol. The most probable mechanistic pathway involves a displacement of the sulfonated hydroxyl group by the epoxide oxygen, leading to bridged, bicyclic epoxonium ion **5.44a**. This cationic intermediate is presumably intercepted by EtOH or trace H₂O leading to the observed product mixture. Excitingly, these solvolysis studies have since sparked a new area of discovery utilizing epoxonium ions as electrophiles for nucleophilic capture.

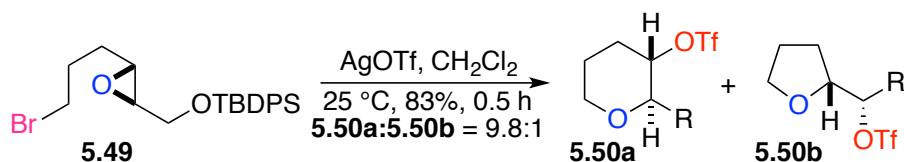
Table 5.2 Murai's Hypothesis and Reaction Optimization



[a] Ratio of **5.48a**:**5.48b** determined after acetylation

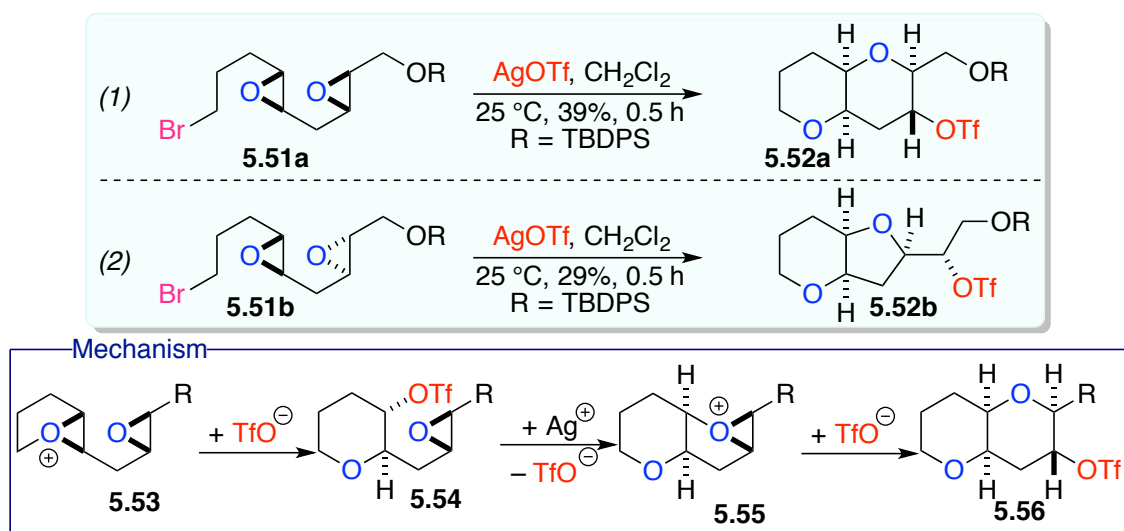
Following the works of David, Murai and his team initiated a study to develop a general strategy for epoxonium ion generation from acyclic epoxides. Additionally Murai and team were inspired by Nakanishi's hypothesis on the synthesis of polyether natural products and became interested in the cyclization of acyclic epoxides to epoxonium ions and study the regioselectivity of nucleophilic addition to either the exocyclic or endocyclic positions.¹⁸⁶ The development of a method that yields predominantly *endo*-adduct would allow for experimental study of Nakanishi's

hypothesis and shed some light on the biosynthesis of *trans*-fused polyether natural products. Murai commenced his studies with bromoepoxide **5.47**. This model substrate was chosen due to ease of synthesis and the literature reports that Ag(I) salts preferentially activate halogen atoms over other Lewis basic motifs within a molecule. Indeed activation of epoxide **5.47** with AgOTf in a 5:1 mixture of organic solvent and water led to the formation of complex mixtures of endocyclic and exocyclic products **5.48a** and **5.48b**, respectively. Product selectivity was found to be extremely dependent on solvent, as only polar solvents afforded appreciable amounts of products. As shown in Table 5.2 benzene and Et₂O only liberated trace amounts of products but in impressive ratios, but switching to more polar THF afforded a 3.8:1 mixture of heterocyclic products in a 91% combined yield. The resulting reaction optimization revealed that 1,4-dioxane afforded the best ratio of *endo* over *exo* products at 4:1, but only in 61% yield. A follow up study by Murai showed that subjection of analogous epoxide **5.49** with AgOTf in CH₂Cl₂ afforded roughly a 10:1 mixture of *endo:exo* products in a combined yield of 83% (Scheme 5.12). Surprisingly the triflate anion acted as a nucleophile capturing the putative bicyclic epoxonium ion. This was a rather surprising result as triflate anions are known as strong leaving groups and rarely behave as nucleophiles except under extremely unique circumstances. A continued study of this system revealed that **5.50a** and **5.50b** lie in equilibria during the reaction, with endocyclic **5.50a** being the thermodynamically favored product. In fact when the reaction of **5.49** and AgOTf in CH₂Cl₂ is allowed to run at –15 °C for 30 minutes, **5.50b** is favored in 1:16 suggesting that *exocyclic* capture is kinetically favored. Indeed Murai discovered that continued stirring for greater than five hours at –15 °C, **5.50a** is formed almost exclusively at 16:1 ratio.



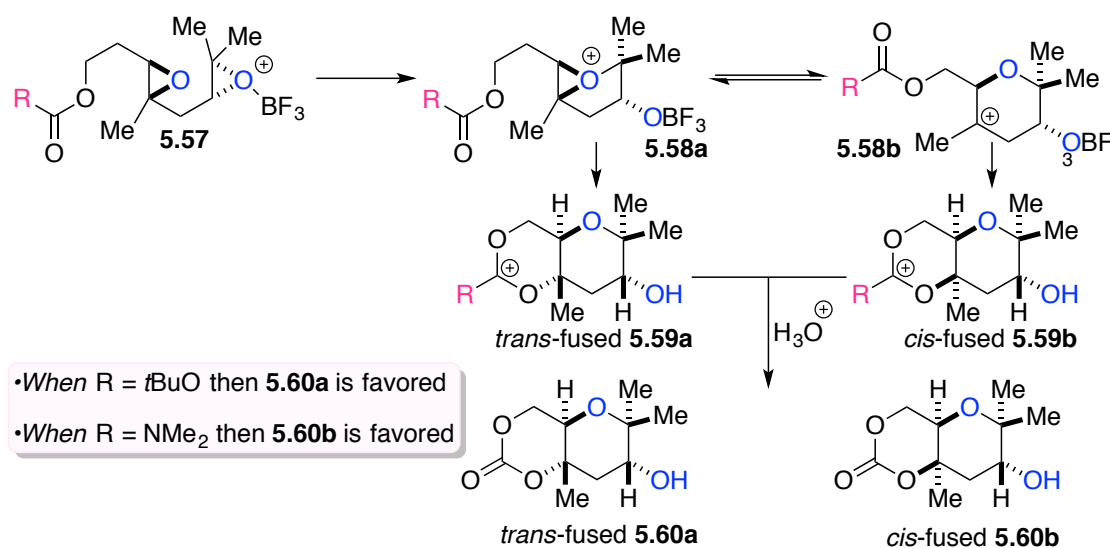
Scheme 5.12 Murai's Study Continued

Murai subsequently studied the applicability of this strategy for iterative cascade processes. Beginning with *cis*-diepoxide **5.51a** activation with AgOTf in CH_2Cl_2 afforded *cis*-fused ether **5.52a** in 39% (Scheme 5.13, *eqn 1*). Analogous treatment of diastereomeric *trans*-diepoxide **5.51b** revealed an identical *cis*-fusion of the ring system (Scheme 5.13 *eqn 2*). While expecting to form the *trans*-fused ring system, Murai proposed that once the first epoxonium ion cyclization occurs, intermolecular addition of triflate ion outcompetes a second epoxide cyclization, generating *endo*-tetrahydropyran **5.54**, as this species could be isolated by prematurely quenching the reaction. Subsequent activation of **5.54** with AgOTf allows for a second cyclization *en route* to the observed *cis*-fused product upon attack by epoxide. **5.51b** presumably undergoes an similar process.



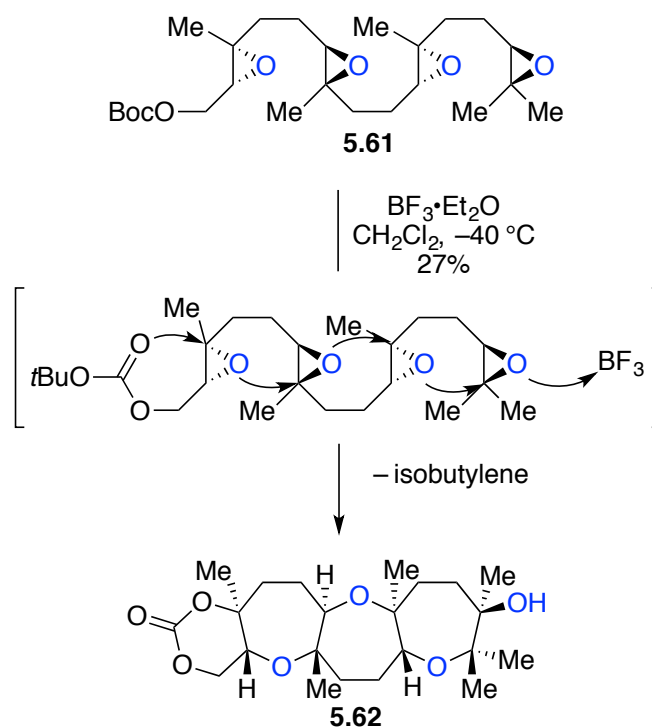
Scheme 5.13 Murai's Cascade Approach

However, shortly after Murai's work was published McDonald developed a polyepoxide cyclization cascade generating *trans*-fused polyether products.²⁰⁹⁻²¹¹ Using strategically placed methyl-substituted epoxides, McDonald was able to achieve exquisite regioselectivity of the nucleophilic capture of the recognized epoxonium ions. While McDonald's conditions require cryogenic temperatures, it is reported that the reaction occurs via a tandem cyclization of the epoxide followed by *endo*-selective capture of the corresponding bicyclic epoxonium ion by the tethered epoxides and capping group (*i.e.* carbonate or amide). The added Me-groups help to stabilize neighboring positive charges of the ensuing cationic intermediates; additionally, the observed *trans*-fused diastereoselectivity was found to be dependent on the capping group that captures the final epoxonium ion. MacDonald and his team proposed that once epoxonium ion formation occurs, tertiary carbocation formation is possible upon scission of the C–O bond of the bicyclic epoxonium ion. However the carbocation can exist as a dynamic mixture of carbocation vs oxonium ion and when R = *t*BuO, **5.58a** predominates leading to *trans*-fused **5.60a**, while tertiary carbocation **5.58b** persists when R = NMe₂ forming the *cis*-fused product **5.60b**.



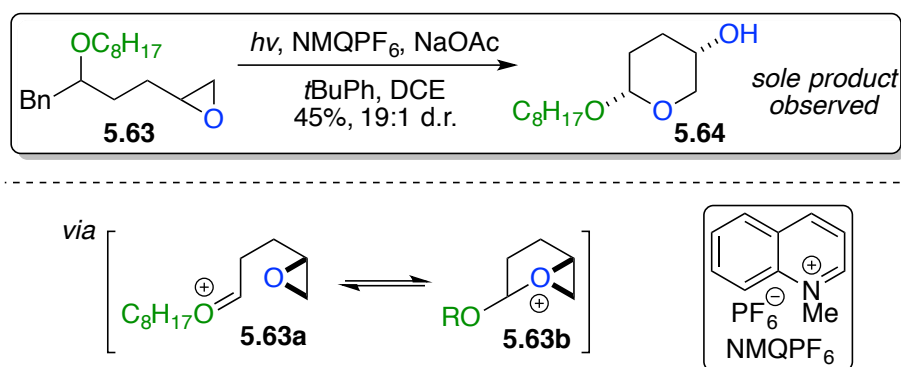
Scheme 5.14 Model for the Observed Diastereoselectivity

McDonald's landmark achievement was then reached when he and his team cyclized optically pure tetraepoxide **5.61** affording fused tetracycle **5.62** in 27% yield with all *trans*-fused ring systems. The mechanism for this transformation presumably initiates with the activation of the terminal epoxide distal to the carbonate with $\text{BF}_3 \cdot \text{OEt}_2$. The monocyclic epoxonium ion is then primed for regioselective attack by the neighboring epoxide leading to bicyclic epoxonium ion formation. This process most likely produces a cascade process. The pendant *tert*-butoxy carbonate caps the last cationic intermediate and terminates the reaction liberating isobutylene. Interestingly the use of *tert*-butoxy ester led to the formation of only *trans*-fused centers, suggesting that only intramolecular trapping of epoxonium ions occurs.



Scheme 5.15 McDonald's Polyether Cyclization Cascade

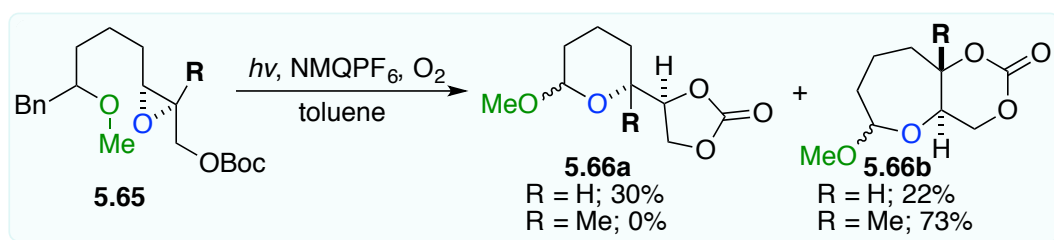
The last example of bicyclic epoxonium ion formation from acyclic epoxides stems from the lab of Paul Floreancig. Floreancig has become a pioneer in photochemical benzylic oxidations and has reported capture of oxonium or iminium species with various nucleophiles.²¹²⁻²¹³ A natural extension of this strategy ultimately involves the oxidation of a benzylic carbon followed by capture from a pendant epoxide.²¹⁴ This type of reactivity was disclosed in 2007, where Floreancig and his team discovered that oxidation of homobenzylic ether **5.63** with $h\nu$ and NMQPF₆ as sensitizer, afforded tetrahydropyranol **5.64** in 45% yield and 19:1 d.r. Presumably upon oxidation, oxonium ion **5.63a** is immediately captured by the epoxide leading to bicyclic epoxonium ion. The resulting ring opening event results in the formation of *endocyclic* product **5.64**.



Scheme 5.16 Floreancig's Epoxonium Ion Cyclization

This discovery thus set the stage for further development and expansion to substituted epoxides and polyepoxide substrates (Scheme 5.17). Exposure of methyl ether **5.65** to analogous oxidation conditions generated an almost 1:1 mixture of exocyclic carbonate **5.66a** in 30% and endocyclic carbonate **5.66b** in 22% upon nucleophilic quench by the terminal Boc group, when R = H.²¹² Oxygen from the air was needed as a terminal oxidant and toluene was used as a cosensitizer along with NMQPF₆. The observed diastereoselectivities of the products were found

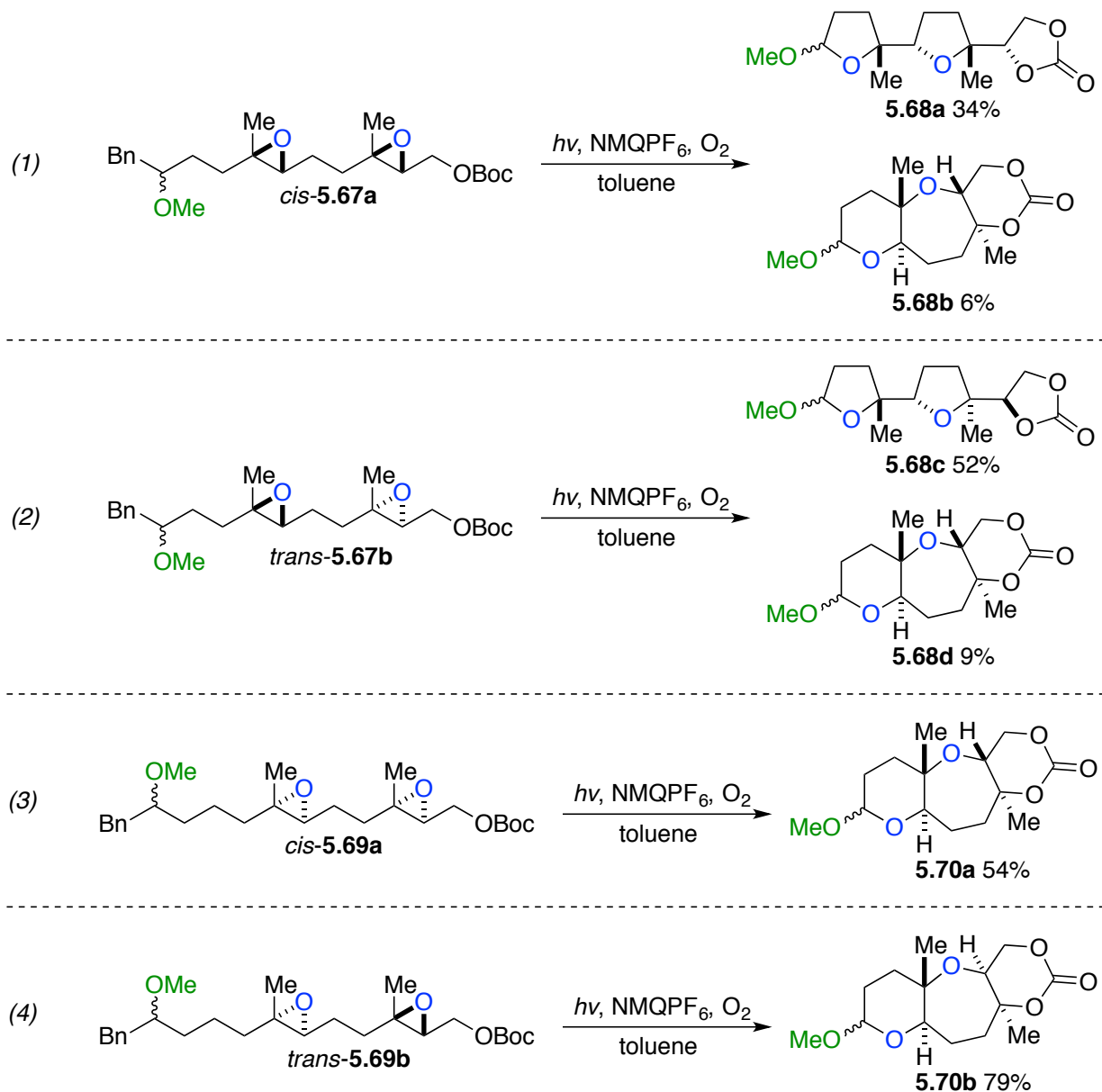
to be >20:1, but as a 1:1 mixture of anomers. It appears that the transition state for this transformation is approximately equal in energy as both heterocycles are formed in roughly equal amounts. A second possibility is that the dissociation of the carbonate of oxepane **5.66b** occurs via a ring expansive epoxonium ion leading to the formation of pyran product **5.66a**. Not surprisingly, simple addition of a Me-group to the epoxide led to exclusive formation of endocyclic carbonate **5.66b** in a good yield of 73%. This result is consistent with McDonald's observations as the selective installation of a Me-substituted epoxide led to a polyoxepane tetracycle.



Scheme 5.17 Application of Floreancig's Conditions to Substituted Epoxides

To probe the reaction mechanism and develop a model to predict product selectivities, Floreancig designed a series of *cis* and *trans* diepoxide substrates (Scheme 5.18).^{213, 215} Treatment of *cis*-**5.67a** and *trans*-**5.67b** to the optimized conditions afforded the all *exo*-products **5.68a** and **5.68c**, as the major product, and the all *endo*-products as minor (*eqn 1-2*). These cyclization reactions presumably proceed via [3.1.0] bicyclic epoxonium ions that are opened by the second epoxide, regioselectively. No cross products produced via an initial *exo*-cyclization followed by *endo*-cyclization, or vice versa were observed in the reaction mixtures. These results suggest that addition of an epoxide to a [3.1.0] epoxonium ion is faster when addition occurs at the *exo*-positions relative to *endo*-addition. Only *syn*-addition products were observed for *endo*-products **5.68b** and **5.68d**, this suggests that addition of epoxide outcompetes the addition of carbonate,

suggesting that epoxides are more nucleophilic than carbonates. Analogous treatment of diepoxides **5.69a** and **5.69b** generated predominantly *endo*-products. The cyclization of these epoxides proceeds exclusively through a larger [4.1.0] bicyclic epoxonium ion that is intercepted by sequential *endo*-cyclizations. These dense tricycles were formed in moderate to good yields.



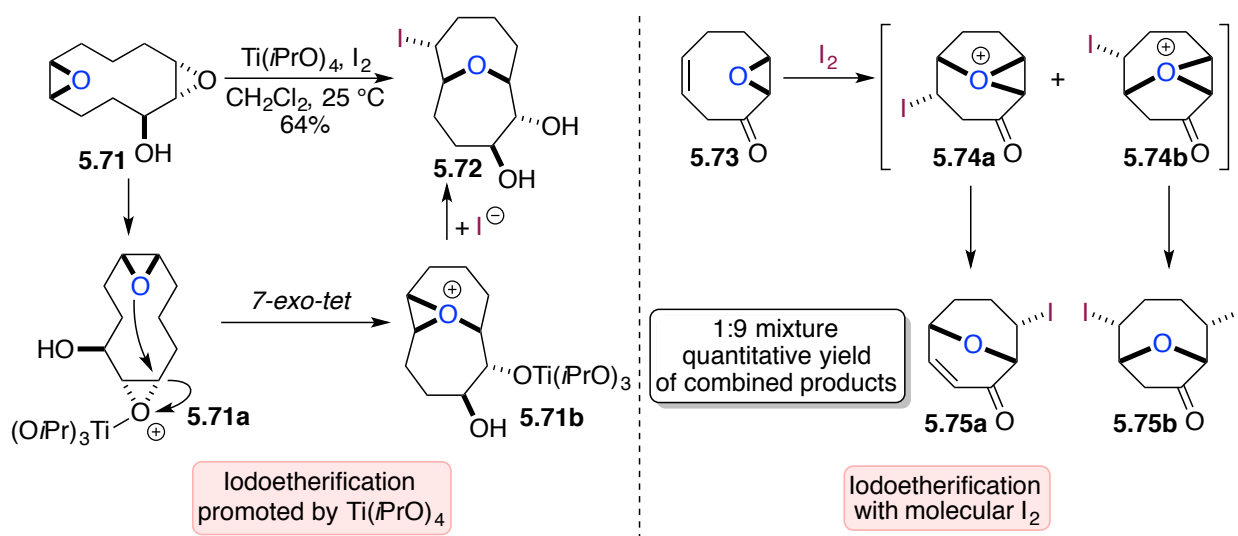
Scheme 5.18 Cyclization via [3.1.0] and [4.1.0] Bicyclic Epoxonium Ion

These experimental results show that the outcome of an epoxide cyclizing onto an epoxonium ion are extremely structure dependent. However a general trend can be extracted by examining the ring size of the epoxonium ion. Specifically, it appears that [3.1.0] bicyclic epoxonium ions prefer to undergo *exocyclic* nucleophilic capture, while homologous [4.1.0] bicyclic epoxonium ions prefer the *endo*-pathway. While difficult to rationalize experimentally, computational studies from the Houk group provided evidence that *endo*-pathways are generally favored when a looser transition state possessing more S_N1 -like character is formed and can be stabilized via adjacent substitution, a common theme throughout this review. On the contrary, smaller [3.1.0] ions seem to distort the necessary conformation needed to accommodate an S_N1 -like transition, leading to the *exocyclic* product. The results from Floreancig's work as well as all of the examples illustrated throughout this section show that product selectivity is inherently governed by the structure of the starting epoxide. Solvent effects can modulate product regioselectivities to some extent but the reactivity of the resulting bicyclic epoxonium ion is governed by stereoelectronic effects.

5.4 Examples of Nucleophilic Capture of Epoxonium Ions by Halogen Nucleophiles

Bicyclic epoxonium ions are versatile transient intermediates for the synthesis of substituted monocyclic medium ring ether heterocycles, as well as polycyclic *cis*- and *trans*-fused polyether oligomers. While these strategies are powerful for polyether synthesis, they require extensive engineering of the cyclization precursors, and do not investigate in detail the capture by other nucleophiles through *intermolecular* processes. One interesting avenue for nucleophilic capture of epoxonium ions involves the use of halogen nucleophiles. Halogen atoms are uniquely nucleophilic and are poised for further diversification leading to value-added products. One of the first reported examples of this type of reactivity was described by Martín. Treatment of diepoxide

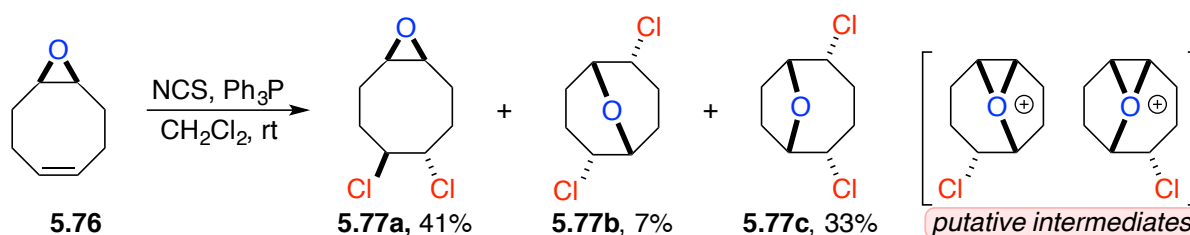
carbocycle **5.71** with mixtures of $\text{Ti}(\text{iPrO})_4$ and molecular iodine in CH_2Cl_2 afforded bicycle **5.72** in 64% yield.²¹⁶⁻²¹⁷ This transformation presumably proceeds via hydroxyl-group directed activation of the proximal epoxide allowing for regioselective attack of the monocyclic epoxonium ion by the distal epoxide forming bicyclic epoxonium ion **5.71a**. **5.71a** possesses two electrophilic sites of attack and iodide ions attacks the exocyclic position forming the observed bicycle. **5.72** is most likely the thermodynamic product as attack at the endocyclic position would theoretically be reversible in the presence of excess $\text{Ti}(\text{iPrO})_4$ allowing for the regeneration of **5.71b**.



Scheme 5.19 Martín's Ring Expansion Strategy Promoted by $\text{Ti}(\text{iPrO})_4$ and I_2

An analogous strategy again reported by Martín involves the ionic addition of molecular iodine across an olefin forming iodoetherificated octanones.²¹⁷ Subjection of epoxyketone **5.73** with I_2 liberates bicyclic ketones **5.75b** and **5.75a** in a 1:9 ratio, respectively. It's understood that the reaction of I_2 with the olefin forms a cationic iodonium species that is rapidly trapped by the epoxide forming epoxonium ions **5.74a** and **5.74b**. Subsequent attack by iodide ions generates the observed products. There are a few other examples from Martín that revolve around a similar

theme of activating an olefin or epoxide with Lewis acid-I₂ mixtures forming complex carbocyclic structures. However, a similar report by Yoshimitsu examines the dichlorination of olefins using NCS/Ph₃P mixtures in the presence of an epoxide. This is the only example to my knowledge that involves the attack of a bicyclic epoxonium species with chloride ions liberating alkyl chloride products. As mentioned in the previous chapter (Chapter 4.3.3) dichlorination of olefins can be accomplished through the combination of substrate with NCS/Ph₃P in CH₂Cl₂.¹³¹ Interestingly, Yoshimitsu discovered that in the presence of epoxide **5.76**, the desired vicinal dichloride **5.77a** was formed, but two unexpected bicycles **5.77b** and **5.77c** were also formed, albeit in low yield. While the mechanism was not investigated, comparison of the product mixtures to those of Martín reveal a trend. Bicyclo[3.1.3]octane **5.77b** is formed in only 7% yield, while bicyclo[2.1.3]octane is formed in 33% yield. **5.77b** is the major product, as bicyclic ketone **5.75b** was the major product for Martín. This result suggests that the formation of epoxonium ion intermediate most likely accounts for the observed products, and that the [2.1.3] bicyclic product is the thermodynamically more stable product, given the reduced ring strain and torsional strain in the product.



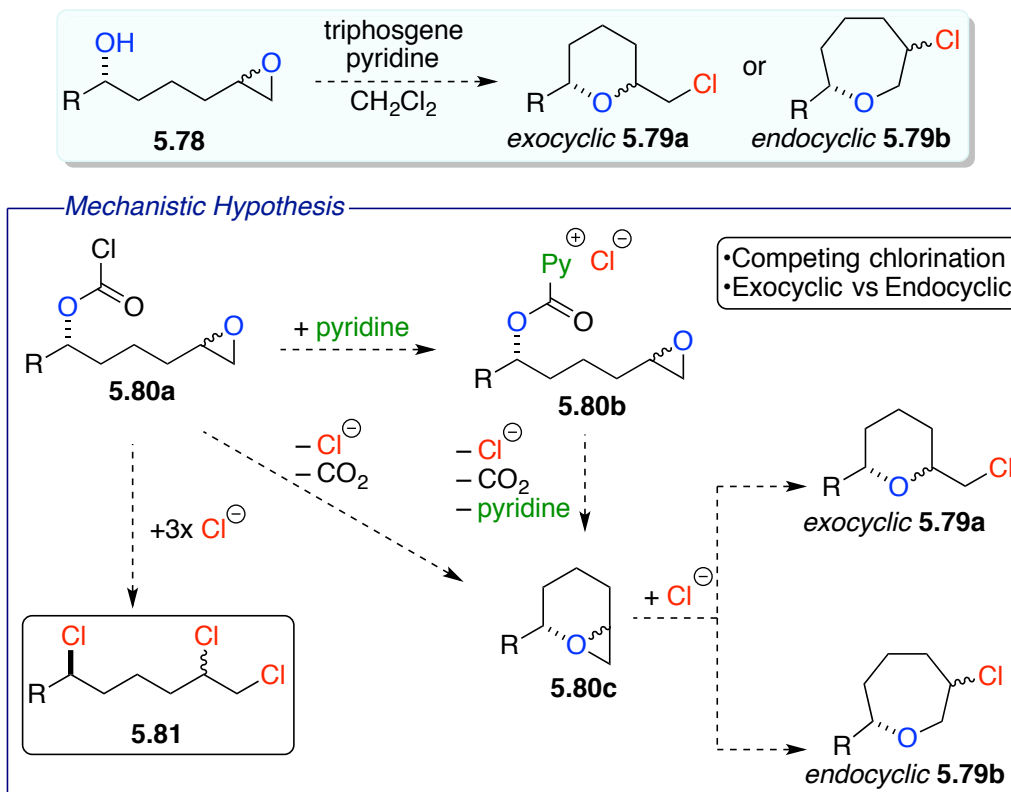
Scheme 5.20 Yoshimitsu's Epoxonium Ion Discovery

These inciteful discoveries by Martín and Yoshimitsu illustrate the utility of regioselective capture of epoxonium ions by halogen nucleophiles. The halogenated products are then positioned for further synthetic derivatization generating more complex heterocycles, specifically

demonstrated by Martin's works. The next avenue for discovery must come from the direct cyclization of an epoxide en route to bicyclic epoxonium ion formation. This is where our investigation began. To date no examples of acyclic epoxide cyclization and subsequent capture by halogen nucleophiles has been reported, at least to our knowledge. Given our broad interest in chlorinated organics and our established triphosgene-pyridine chlorination methodology, we felt motivated to investigate these modes of reactivity.

5.5 Attempts at the Generation and Capture of Epoxonium Ions by Chloride Ions

As summarized above bicyclic epoxonium ions are unique reactive intermediates that allow for the synthesis of small oxygen-containing heterocycles in only one step that are not typically favored by Baldwin's Rules. Due to the limited examples showcasing chloride ions as nucleophiles, we surmised that our established triphosgene-pyridine technology would supplement this area of chemistry and provide a new platform for discovery. Our study began by envisioning the cyclization of epoxyalcohols to bicyclic epoxonium ions by activating the hydroxyl group in combination with triphosgene-pyridine mixtures. Based on our previously established chlorination conditions, the combination of mixtures of triphosgene and pyridine with an appropriate alcohol would activate the substrate releasing chloride ions upon decomposition of triphosgene by pyridine. Therefore based on analogy, we believed we could similarly activate unactivated epoxyalcohols. However this proposal is not without significant challenges as stated previously epoxyalcohols are known to cyclize forming the *n-exo-tet* products (Chapter 5.2); however, if the nucleophilic hydroxyl group is masked or protected then the *favoured* Baldwin cyclization cannot occur. We proposed that masking the hydroxyl group of **5.78** would allow for the epoxide to cyclize generating a transient epoxonium ion which could afford regioisomeric products **5.79a** or **5.79b** after interception by chloride. Our proposal is outlined in detail below.

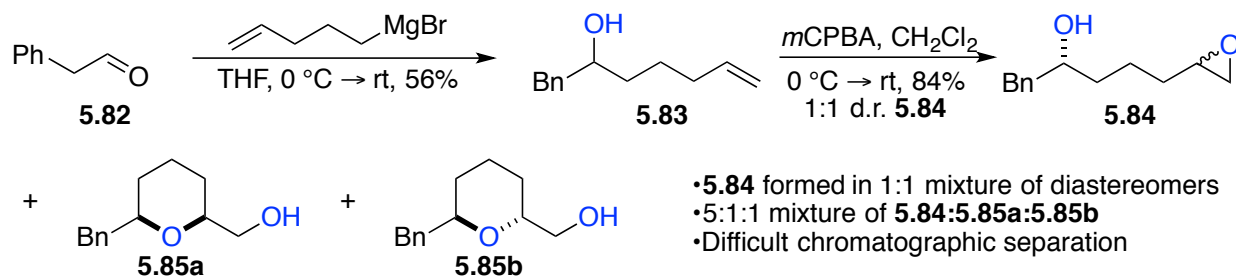


Scheme 5.21 Proposed Cyclization Strategy Mediated by Triphosgene-Pyridine

Our developed chlorination chemistry^{97, 102-103, 111, 160} is generally understood to proceed via acylation of an alcohol to chloroformylated species **5.80a**. We then surmise that this intermediate can be further activated to pyridinium carbamate **5.80b** by the excess amounts of pyridine in the system. We then propose that **5.80b** should be a labile leaving group that can be displaced intramolecularly by the pendant epoxide generating putative bicyclic epoxonium ion **5.80c**. Ultimately it may not be necessary for chloroformylated **5.80a** to be activated by pyridine to effect the epoxide cyclization, as both intermediates can undergo self-decomposition liberating the same cationic intermediate, releasing CO₂. Theoretically the loss of CO₂ would act as a driving force to epoxonium ion formation. Regardless, with the formation of ion **5.80c** we predict its capture to occur by chloride ions leading to either exocyclic **5.79a** or endocyclic **5.79b** products.

Additionally we remained cognizant that chloroformate **5.80a** could be converted to trichloride **5.81** as both hydroxyl and epoxide functional groups are labile to chlorination (Scheme 5.21).

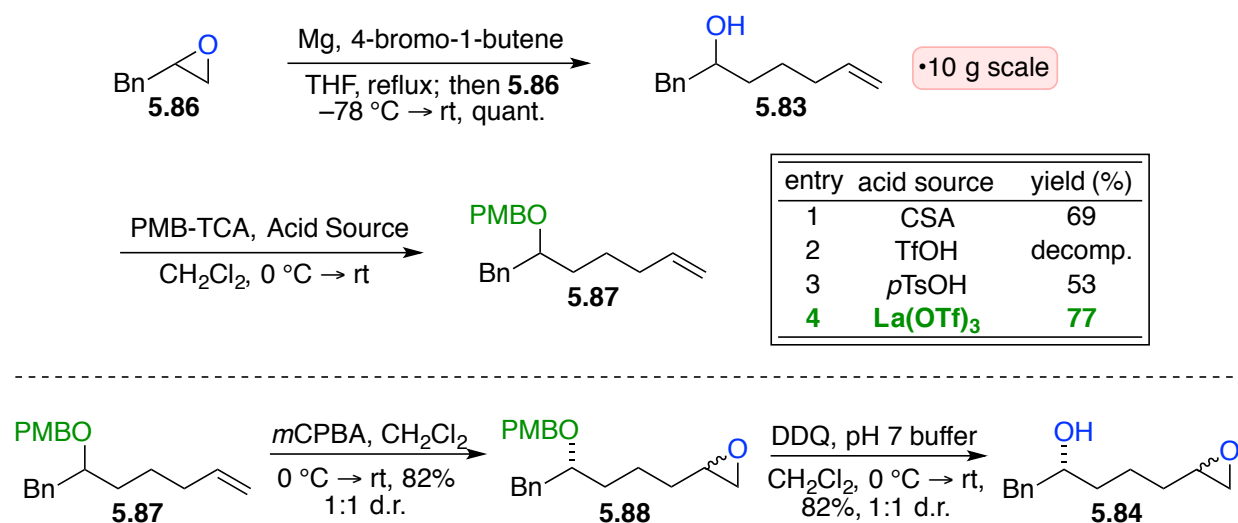
To initiate our study we chose benzyl-substituted epoxyalcohol **5.84** as our model substrate (Schemes 5.22). Freshly distilled phenylacetaldehyde was treated with in situ generated 5-pentenyl grignard in THF at 0 °C affording homobenzylic alcohol **5.83** in 56% yield.²¹⁸ Prilezhaev epoxidation with *m*CPBA revealed the desired epoxyalcohol, but in a 5:1 mixture of **5.84** with cyclized tetrahydropyransols **5.85a** and **5.85b** in a combined yield of 84%. The slight acidity of the reaction media most likely catalyzes the unwanted heterocycle formation once **5.84** is formed. Attempts to eliminate the formation of **5.85a** and **5.85b** by buffering the reaction mixture with NaHCO₃ or pH 7 buffer resulted in little change in the composition of the product mixture.



Scheme 5.22 Initial Route to Model Epoxyalcohol **5.84**

To overcome the formation of unwanted pyranols, a second strategy was initiated to synthesize model substrate **5.84** (Scheme 5.23). Homobenzylic alcohol **5.83** was formed via regioselective ring-opening of benzyloxirane **5.86** via in situ generated organocuprate affording **5.83** in quantitative yield. To prevent heterocycles formation during the epoxidation step, **5.83** was protected as the *p*-methoxybenzyl (PMB) ether. It was necessary to screen a series of acid sources as typical catalytic activation with CSA or PPTS (Py•TsOH) led to incomplete

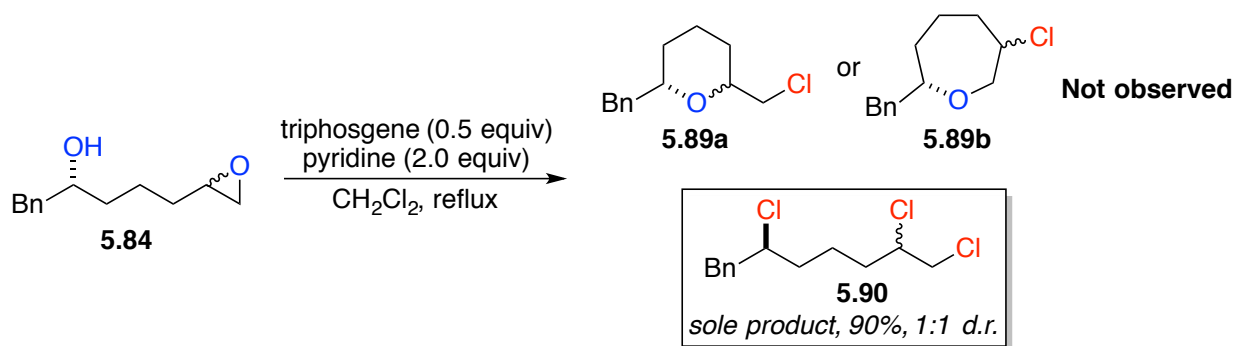
consumption of **5.83**. Also activation with catalytic TfOH produced decomposition products. Fortunately, catalytic $\text{La}(\text{OTf})_3$ ²¹⁹ afforded PMB-protected alcohol **5.87** in 77% yield with 100% conversion as judged by TLC analysis. Subsequent epoxidation generated the requisite epoxide **5.88** in 82%, as a 1:1 mixture of inseparable diastereomers. Buffered DDQ deprotection²²⁰ afforded epoxyalcohol **5.84** in 82% yield and 52% yield in four steps from **5.83**. No unwanted tetrahydropyran byproducts were formed during deprotection step, but trace amounts were generated during the purification of crude epoxyalcohol, even with buffered stationary phase.



Scheme 5.23 Second Route to Model Epoxyalcohol **5.84**

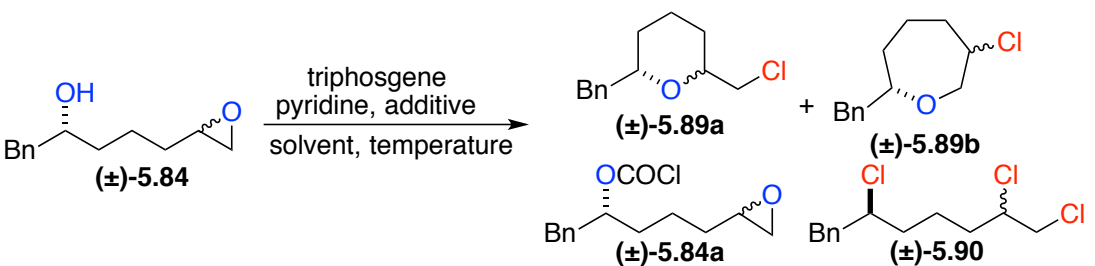
With model epoxyalcohol in hand we began our ambitious study by exposing **5.84** to mixtures of triphosgene-pyridine in CH_2Cl_2 . In an attempt to prevent unwanted di- or trichlorinated products from forming, a substoichiometric amount of triphosgene (0.5 equiv) was utilized, previous reports from our lab utilized at least 1.0 equiv of triphosgene for the chlorination of more than one functional group. Unfortunately even with a reduced loading of triphosgene, combination of epoxyalcohol with triphosgene and pyridine in CH_2Cl_2 at reflux formed trichloride

5.90 as the sole product, in near perfect yield of 90%. The reaction proved to be exquisitely clean, affording trichloride in quantitative conversion and heterocyclic products **5.98a** and **5.89b** were not detected by crude GC-MS analysis of the reaction mixture.



Scheme 5.24 Initial Attempted Cyclization of Epoxyalcohol **5.84**

While the formation of trichloride was at least predicted we were surprised that no heterocyclic products were formed in even trace amounts. Although while trichloride **5.90** was the sole product, this result created a series of questions about the mechanism of chlorination of alcohols in the presence of epoxides. Specifically questions about the relative rates of chlorination between the two corresponding functional groups. Based on our previous chlorination reports, we believed that the chlorination of hydroxyl group is faster than that of epoxides. Chlorination of **5.84** would of course liberate an epoxychloride functionality first, leaving the epoxide to then undergo dichlorination producing the observed trichloride. In fact GC-MS analysis of the crude reaction mixture from Scheme 5.24 revealed an m/z value that corresponded to the chloroformylation of the alcohol with the epoxide intact. We also suspected that the reaction temperature was effecting the trichlorination of **5.84**, over cyclization as we only observe dichlorination of the epoxides in refluxing CH_2Cl_2 ¹⁶⁰.

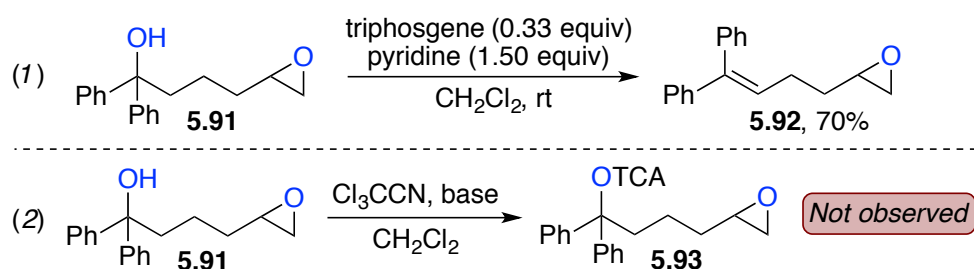
Table 5.3 Effect of Additives, Solvent, and Temperature for the Cyclization of **5.84**


entry	equiv of triphosgene	equiv of pyridine	additive (equiv)	solvent	temperature	product ^[a]
1	1.50	1.50	–	THF	0 °C → reflux	5.90
2	0.33	1.50	BF ₃ •OEt ₂ (0.10)	CH ₂ Cl ₂	0 °C → reflux	5.89a , 1:1 d.r. ^[b]
3	0.33	1.50	TBSOTf (1.00)	CH ₂ Cl ₂	0 °C → rt	complex mix
4	0.33	1.50	AlCl ₃ (1.00)	CH ₂ Cl ₂	–78 °C → rt	5.84a ^[c]
5	0.33	1.50	AlCl ₃ (1.00)	CH ₂ Cl ₂	0 °C → rt	5.84a ^[c]
6	0.33	1.50	AlCl ₃ (1.00)	THF	0 °C → rt	complex mix.

[a] Reactions monitored by GC-MS analysis. [b] Product most likely formed via 6-exo-tet cyclization. [c] Believed to be chloroformate based on isotope pattern and m/z

To probe these hypotheses, we examined the effect of additives, as well as reaction solvent and temperature (Table 5.3). We initiated this study by subjecting **5.84** to an excess of triphosgene and pyridine in THF as all previous chlorination reports from our lab necessitated the use of CH₂Cl₂ as solvent to effect the desired chlorination. Ultimately trichloride **5.90** was still observed via GC-MS analyses. We then reduced the loading of triphosgene to 0.33 equivalences and began exploring Lewis acid additives. We initially proposed that these additives might activate any chloroformylated species to effect the desired epoxide cyclization. Unfortunately the addition of Lewis Acids either led to the favored 6-exo-tet Baldwin cyclization (entry 2) followed by chlorination or led to chloroformylation of the alcohol but no cyclization (entries 4-5). Performing the reaction in THF, the addition of Lewis acids only formed complex mixtures of products (entries 6, 7). The only promising result was that the hydroxyl group could in fact be chloroformylated,

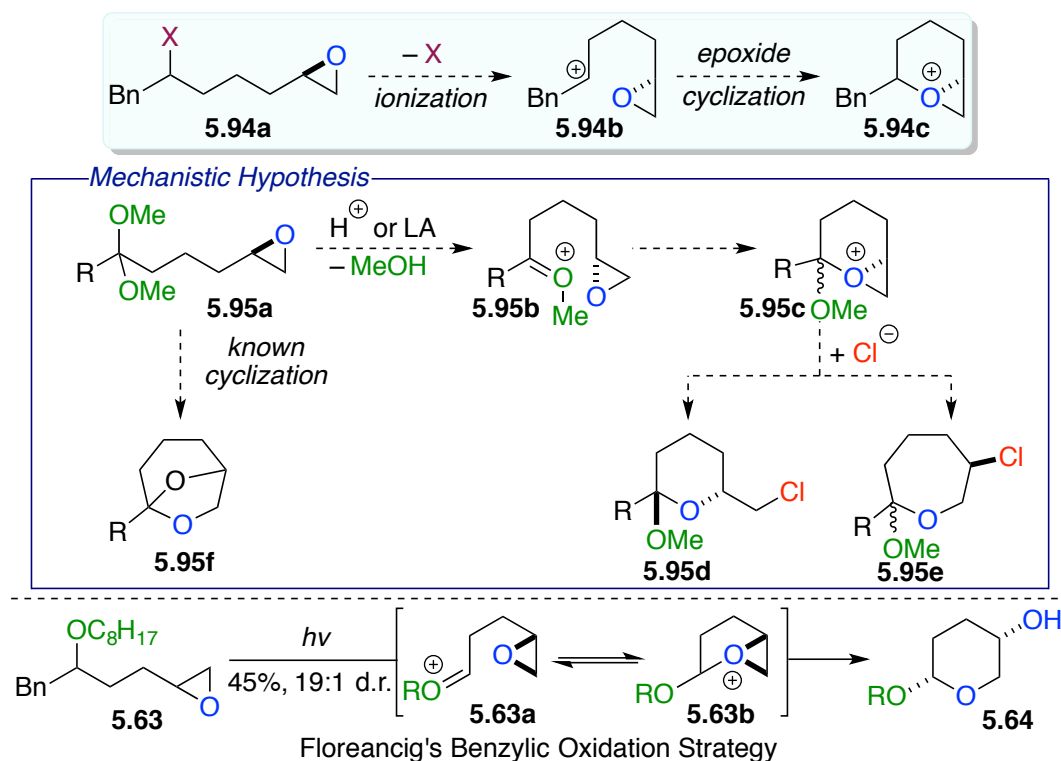
as observed by GC-MS analysis of the crude reaction mixture. The results summarized in Table 5.3 suggested that epoxyalcohols are too reactive towards Baldwin favored cyclization and a better leaving group is necessary. Therefore we subjected tertiary epoxyalcohol **5.91** to 0.33 equiv of triphosgene and 1.50 equiv of pyridine (Scheme 5.25, *eqn 1*). Regrettably no cyclization was observed and only elimination product **5.92** was isolated; however while frustrating this result did in fact lead to a new direction involving the triphosgene-pyridine promoted elimination of tertiary alcohols.²²¹ Attempts at enhancing the ionization potential of **5.91** by masking it as the trichloroacetimidate were unsuccessful as no reaction occurred.



Scheme 5.25 Attempts Toward the Cyclization Tertiary Epoxyalcohol

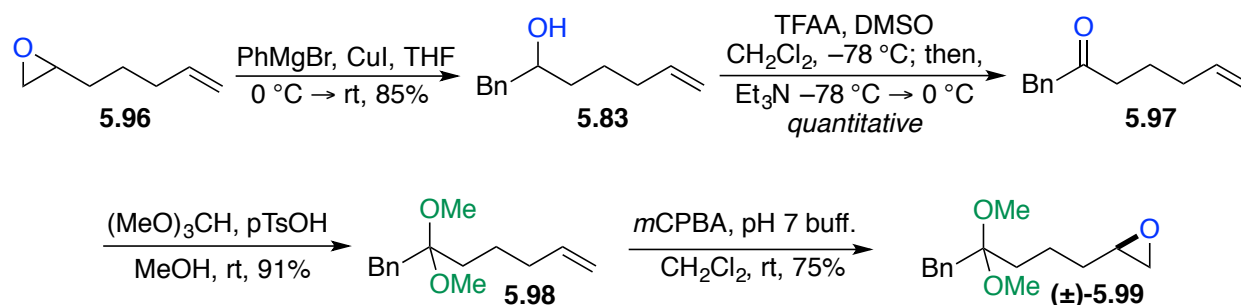
While the cyclization of epoxyalcohols to six- or seven-membered heterocycles failed, we remained undiscouraged. Believing that chlorination superseded cyclization, we realized simple epoxyalcohols were too reactive and a different functional group was needed. Additionally we realized to effect the desired cyclization, a formal oxidation of the site of attack was necessary. Given our lack of success with ionizing tertiary alcohols, we turned our attention to dimethyl ketals. Dimethyl ketals are isoelectronic with carbonyls and are formed for use as carbonyl protecting groups, masking carbonyls from reacting. An added benefit of dimethyl ketals is that they are weakly basic and can be activated with weak organic acids. We hypothesized that

chemoselective activation of ketal could formally oxidize the ketal carbon leading to the formation of oxonium ion **5.95b** (Scheme 5.26). Assuming that reversible ketal formation is slow, then we predicted that **5.95b** could be intercepted by the distal epoxide leading to bicyclic epoxonium ion formation **5.95c**. This bicyclic intermediate is then poised to accept chloride ions leading to the formation of chlorine-substituted **5.95d** or **5.95e**. We were cognizant that the formation of bicyclic ketal **5.95f** could be problematic as these motifs are typically generated via the acid catalyzed rearrangement of epoxyketals and epoxyketones. Fortunately we believed we could circumvent this problem as bicyclic ketals are generated by activating the epoxide prior to cyclization by the ketal functionality. Ultimately we believed by carefully modulating the acidity of the reaction media, chemoselective activation of the ketal over the epoxide would be possible. Additionally the formation of bicyclic epoxonium ions from ketals possess some rapport in the literature.^{212, 214}



Scheme 5.26 Proposed Activation and Cyclization of Dimethyl Ketals

The synthesis of dimethyl ketal (\pm)-**5.99** began similarly to that of epoxyalcohol **5.84**. Regioselective ring opening of epoxide **5.96** with PhMgBr and CuI yielded homobenzylic alcohol **5.83** in 85% yield with excellent regiocontrol.²²² Modified Swern oxidation with mixtures of TFAA and DMSO afforded ketone **5.97** in quantitative yield. Penultimate ketal formation using trimethoxymethane ((MeO)₃CH), catalytic TsOH in MeOH, formed **5.98** in 91% after aqueous workup. Chromatographic purification was unnecessary. Lastly epoxidation of **5.98** required the use of a buffered, biphasic reaction media using pH 7 buffer and CH₂Cl₂ along with *m*CPBA. This solvent combination was used to prevent any unwanted hydrolysis of the ketal functionality and to prevent unwanted bicycle formation. Gratifyingly, epoxyketal (\pm)-**5.99** was formed in 75% yield and no bicyclic ketal was observed after stirring overnight.



Scheme 5.27 Synthesis of Dimethyl Ketal (\pm)-**5.99**

With dimethyl ketal (\pm)-**5.99** in hand, we commenced our investigation by examining the applicability of triphosgene and Py•TfOH mixtures with various solvents and reaction temperatures (Table 5.4). Py•TfOH was chosen as we envisioned we could decompose the starting material with the use of strong acids. Also pyridinium acid sources were chosen because they are weak acids, but they also contain an equivalent of pyridine. Concurrent with our previous reports, pyridine is required to decompose triphosgene to phosgene and liberate the desired chloride ion

nucleophiles. Our investigation began with the subjection of (\pm)-**5.99** to a mixture of 0.33 equiv of triphosgene and 1.00 equiv of Py•TfOH in CH₂Cl₂ at 0 °C then warming to reflux (entry 1). This ultimately led to decomposition and a complex mixture of products. Sequential experiments raised the equivalents of triphosgene and Py•TfOH to 1.00 and 1.50 equiv and reduced the reaction temperature to –78 °C. However after stirring overnight, only bicycle (\pm)-**5.101** was formed (entries 2-4). Interestingly, high resolution mass spectrometry of the crude reaction mixture revealed the presence of a chlorinated compound with the molecular ion fragment that is consistent with the formation of (\pm)-**5.100**. Several attempts were made to isolate the mystery chlorinated compound but these trials failed to produce any isolable materials. Solvent screen of other nonpolar solvents such as toluene and DCE again failed to produce any desired materials as only (\pm)-**5.101** or intractable mixtures were formed (entries 4-5).

Table 5.4 Reaction Optimization of Dimethyl Ketal Cyclization

entry	equiv of triphosgene	equiv of Py•TfOH	solvent	temperature	product, yield (%) ^[a]
1	0.33	1.00	CH ₂ Cl ₂	0 °C, then reflux	complex mix
2	1.00	1.00	CH ₂ Cl ₂	–78 °C	5.101 , 45%
3	1.50	1.50	CH ₂ Cl ₂	–78 °C	5.101 , 56%
4	1.50	1.50	toluene	–78 °C	5.101 , 50% ^[b]
5	1.50	1.50	DCE	–78 °C	complex mix

^[a] Isolated yields after column chromatography. ^[b] 20% hydrolyzed ketone formed.

The combination of results from Table 5.4 imply that the epoxide functionality is presumably activated over the ketal. Attack of a monocyclic epoxonium ion by ketal or ketone is

known in the literature and is generally understood to be the accepted mechanistic pathway for the formation of bicyclic ketals.²²³⁻²²⁷ The formation of monocyclic epoxonium ion is theoretically reversible; however, the cyclization of carbonyl onto the oxonium ion should be thermodynamically favorable due to the alleviation of ring strain. Additionally the activation of the ketal with acid should produce an equilibria between MeOH and oxonium ion from the ketal. Given the results from Table 5.4 it's possible that (±)-**5.99** is being hydrolyzed to the ketone and subsequently undergoing cyclization producing the observed bicycle. In fact upon stirring (±)-**5.99** in toluene, ~20% of hydrolyzed ketone was recovered from the reaction mixture (entry 4). With these results in mind, we redeveloped our conditions utilizing 4Å MS to remove any trace H₂O from the reaction mixture and envisioned utilizing a more polar solvent to stabilize any transient charged intermediates. As seen in Chapter 2, the use of polarizing solvents drastically effects the relative rates of reaction, presumably by stabilizing charged intermediates.

We then reevaluated our approach to this transformation and discovered that the use of 1,4-dioxane yielded β-chlorinated pyranoside (±)-**5.100** in 50% yield as a 10:1 mixture with bicycle (±)-**5.101** (Table 5.5, entry 1). Ensuing optimization revealed that 0.5 equiv of triphosgene and 1.10 equiv of Py•TfOH were able to afford the same mixture of products in 10:1 ratio, and 70% combined yield after methanolic quench (entry 2). Bulky 2,6-lutidinium triflate was also utilized as acid source but only 56% combined yield of products was formed but in a drastically reduced ratio of 3:1 in favor of pyranoside (±)-**5.100**. We had an interest in developing a one-pot process to generate fully saturated pyran (±)-**5.102** in one step and realized this goal by quenching the reaction with equimolar equivalents of BF₃•OEt₂ and Et₃SiH. Continued reaction development revealed the use of Py•TsOH (PPTS) as this pyridinium acid afforded racemic (±)-**5.201** in 73% as a single diastereomer (entry 5). The loading of triphosgene was reduced to 0.33 equiv and only

1.10 equiv of Py•TsOH was needed producing the optimized reaction conditions and (±)-**5.102** in 80% yield. Py₂•H₂SO₄ was also found to be compatible (entry 4), except this acid proved to be extremely hygroscopic and readily absorbed moisture from the air becoming an amorphous solid.

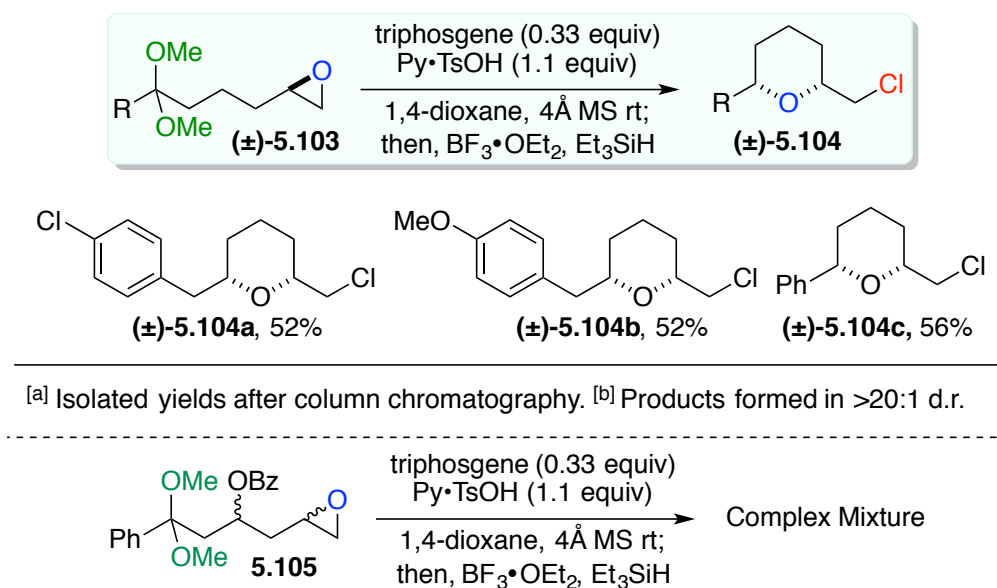
Table 5.5 Effects of Solvent and Pyridinium Acids on Reaction Success

entry	equiv of triphosgene	pyridinium salt (equiv)	quenching agent	5.100:5.101	yield (%) ^[a]
1	2.00	Py•TfOH (2.00)	MeOH	10:1	50 ^[b]
2	0.50	Py•TfOH (1.10)	MeOH	10:1	70 ^[b]
3	0.50	Lut•TfOH (1.10)	MeOH	3:1	56 ^[b]
4	0.50	Py ₂ •H ₂ SO ₄ (1.10)	BF ₃ •OEt ₂ & Et ₃ SiH	(±)- 5.102	68 ^{[c], [d]}
5	0.50	Py•TsOH (1.10)	BF ₃ •OEt ₂ & Et ₃ SiH	(±)- 5.102	73 ^{[c], [d]}
6	0.33	Py•TsOH (1.10)	BF₃•OEt₂ & Et₃SiH	(±)-5.102	80 ^{[c], [d]}

[a] Isolated yields after column chromatography. [b] Combined yields of **5.100** & **5.101**. [c] Sole product observed. [d] 1.5 equiv of BF₃•OEt₂ & Et₃SiH added.

A small scope of substrates was then generated using an analogous pathway beginning with epoxide **5.96** (Scheme 5.28). Substituted homobenzylic aromatics directly afforded the fully saturated heterocycles (±)-**5.104a** and (±)-**5.104b** in moderate yields of 52%, upon reductive quench. Benzoyl ketal also readily yielded the desired product (±)-**5.104c** in 56% after 1 hour of reaction time. Gratifyingly, all three products were formed in relatively clean and quantitative conversion as single diastereomers with presumed 2,6-*syn* relative stereochemistries. No bicyclic products were observed upon workup. Treatment of diastereomerically impure 3-benzoylated epoxyketal **5.105** with the optimized conditions formed a complex mixture of products. This is most likely due to the fact that **5.105** is a 1:1 diastereomeric mixture, and the benzoate functionality

could be activated with the acid and react with any oxonium ion intermediates leading to separate nonproductive reactive pathways.



Scheme 5.28 Scope of Tetrahydropyran Products

While aromatic epoxyketals could be generated rather easily, attempts at synthesizing aliphatic epoxyketals proved problematic (Table 5.6). For example, subsection of aliphatic ketone **5.107** to the optimized ketalization conditions of 10 equiv of $\text{CH}(\text{OMe})_3$ and 0.2 equiv of *p*TsOH in MeOH afforded no reaction with complete recovery of starting ketone (entry 1). Changing the reaction solvent to toluene and warming to reflux again afforded no dimethyl ketal (entry 2). Increasing the molar equivalents of $\text{CH}(\text{OMe})_3$ to 20 equiv and warming to reflux in both MeOH and toluene again failed to produce the desired ketal **5.108** (entries 3-4). Even refluxing the reaction mixture of ketone $\text{CH}(\text{OMe})_3$, catalytic *p*TsOH and 10 equiv of MeOH while attached to a Dean-Stark apparatus still failed to liberate the desired dimethyl ketal. While **5.107** is shown as the model substrate, this transformation was repeated with both *i*Bu- and *n*Pr-substituted ketones;

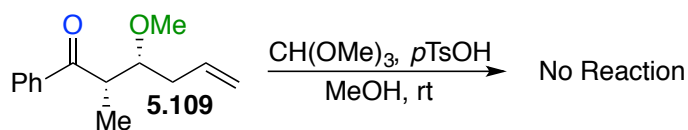
however, repeating the same conditions shown in Table 5.6 failed to produce the desired product. While perplexing we believe that the generation of aliphatic dimethyl ketals is not favored as the carbonyl carbon isn't electrophilic enough to be attacked by MeOH even under rigorous conditions. It could also be possible that the aliphatic tail of the molecule lies in a conformation that hinders the carbonyl carbon to some extent preventing the desired reaction from occurring.

Given this unexpected difficulty we turned our attention to converting substituted phenyl ketone **5.109** to its ketal believing that ketalization should be a facile process, providing our earlier synthesis of benzoyl ketal. However to our surprise subjection of **5.109** to a series of ketalization conditions similar to those reported in Table 5.6, again, failed to yield any dimethyl ketal product. It's possible that this lack of reactivity is due to steric repulsions about the carbonyl group from the α -methyl and β -methoxy substituents leading to reversible ketone formation. This lack in reactivity ultimately led us to once again reevaluate our transformation.

Table 5.6 Progress Towards the Synthesis of Aliphatic Dimethyl Ketals

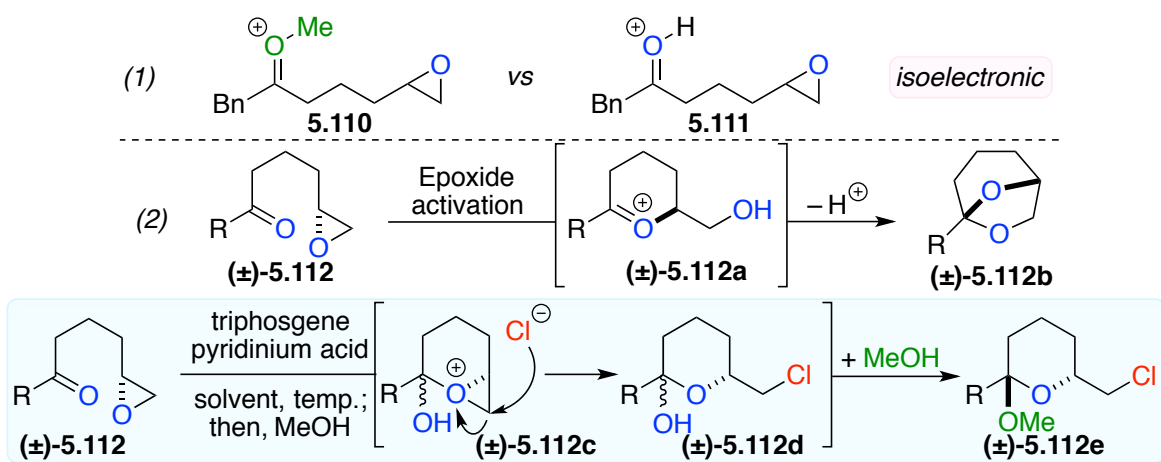
entry	CH(OMe) ₃ (equiv)	pTsOH (equiv)	solvent	temp.	yield (%)
1	10	0.2	MeOH	rt	No reaction
2	10	0.2	toluene	reflux	No reaction
3	20	0.2	MeOH	reflux	No reaction
4	20	0.2	toluene	reflux	No reaction
5	20	0.1	MeOH	reflux	No reaction
6	10	0.2	toluene	reflux	No reaction ^[a]

[a] 10 equiv MeOH added and attached to Dean-Stark apparatus



5.6 Chemoselective Cyclization of Epoxyketones to Epoxonium Ions via Brønsted Acid

While the synthesis of epoxyketals proved problematic, we decided reduce the complexity of our model substrate and investigate simple epoxyketones as precursors to epoxonium ion formation and subsequent capture. This strategy would remove the need for troublesome dimethyl ketal formation and we believed that the protonation of a ketone should be analogous to the activated oxonium species of a ketal *i.e.* formally oxidizing the electrophilic site for attack (Scheme 5.29 eqn 1). Similar to our ketal strategy, biasing the source of Brønsted acid and modulating the stability of charged intermediates via solvent effects should effect the chemoselective activation of the ketone over the epoxide. As mentioned previously, epoxyketones and epoxyketals are prone to rearrangement to bicyclic ketals.²²³ This process is generally understood to proceed via the activation of the epoxide functionality of (\pm)-**5.112** with Brønsted or Lewis acids, followed by 6-*exo-tet* cyclization from the ketone. Oxocarbenium ion (\pm)-**5.112a** is the rapidly intercepted by the pendant hydroxyl group liberating ketal (\pm)-**5.112b** after proton transfer. This process was already observed and described during our epoxyketal studies and we remained confident that modulating the pyridinium acid would allow for a chemoselective activation of the ketone.



Scheme 5.29 New Cyclization Strategy with Epoxyketones

Our general strategy remained the same as described previously. In detail we proposed that the chemoselective activation of the ketone would provide an efficient electrophile for bicyclic epoxonium ion formation. Cyclic oxonium (\pm)-**5.112c** is then susceptible to regioselective capture at the *exocyclic* position forming intermediate pyranoside (\pm)-**5.112d**. Methanolic quench and subsequent work up would then ideally produce chlorine-substituted pyranoside (\pm)-**5.112e**. Parallel with our previous observations, we predict exocyclic (\pm)-**5.112e** to be the major product.

Table 5.7 Synthesis of Homobenzylic Epoxyketone

entry	equiv of <i>m</i> CPBA	solvent	additive	5.97	5.113	5.101	5.114
1	1.50	CH ₂ Cl ₂	—	0%	50%	50%	0%
2	1.50	CH ₂ Cl ₂	pH 7 buffer ^[b]	—	—	—	—
3	1.50	CH ₂ Cl ₂	NaHCO ₃ ^[b]	—	—	—	—
4	1.50	Et ₂ O	—	39%	47%	0%	0%
5	2.00	Et ₂ O	—	0%	0%	0%	75%
6	0.75	Et₂O	—	44%	64%	0%	0%

^[a] Isolated yields after column chromatography. ^[b] Intractable mixtures formed.

Our study began with the synthesis of model epoxyketone (\pm)-**5.113**. (\pm)-**5.113** is synthesized via the same route as epoxyketal (\pm)-**5.99**, however the epoxidation step became problematic due to the slightly acidic conditions (Table 5.7). The use of 1.5 equiv of *m*CPBA in CH₂Cl₂ led to the formation of the desired product, but bicyclic ketal (\pm)-**5.101** was formed in nearly equimolar amounts. (entry 1) Attempts at buffering the reaction media with pH 7 buffer and NaHCO₃ surprisingly formed emulsions and intractable mixtures (entries 2-3). Serendipitously a dramatic change in reactivity was observed by simply exchanging the reaction

solvent from CH₂Cl₂ to Et₂O, as epoxyketone (±)-**5.113** was formed in 47% with 39% of unreacted starting material even after prolonged reaction time (entry 4). In an attempt to force the reaction to complete conversion 2.0 equiv of *m*CPBA was employed but surprisingly led to the exclusive formation of Baeyer-Villiger product (±)-**5.114** in 75% (entry 5) after stirring overnight. Reducing the loading of oxidant back to 1.5 equiv led to variable results that were often unreproducible; therefore it was necessary to use a substoichiometric amount of *m*CPBA to provide reproducible results. In fact with the addition of half of the optimized amount of *m*CPBA (0.75 equiv), (±)-**5.113** was formed in 64% yield based on 44% recovery of the starting **5.97**. Epoxyketone was found to be exceptionally acid sensitive and great care had to be taken during its isolation as trace acid would cause unwanted bicyclic ketal formation. In fact during sample preparation for ¹H-NMR analysis, (±)-**5.113** rearranged from the trace acid present in CDCl₃ (Figure 5.3).

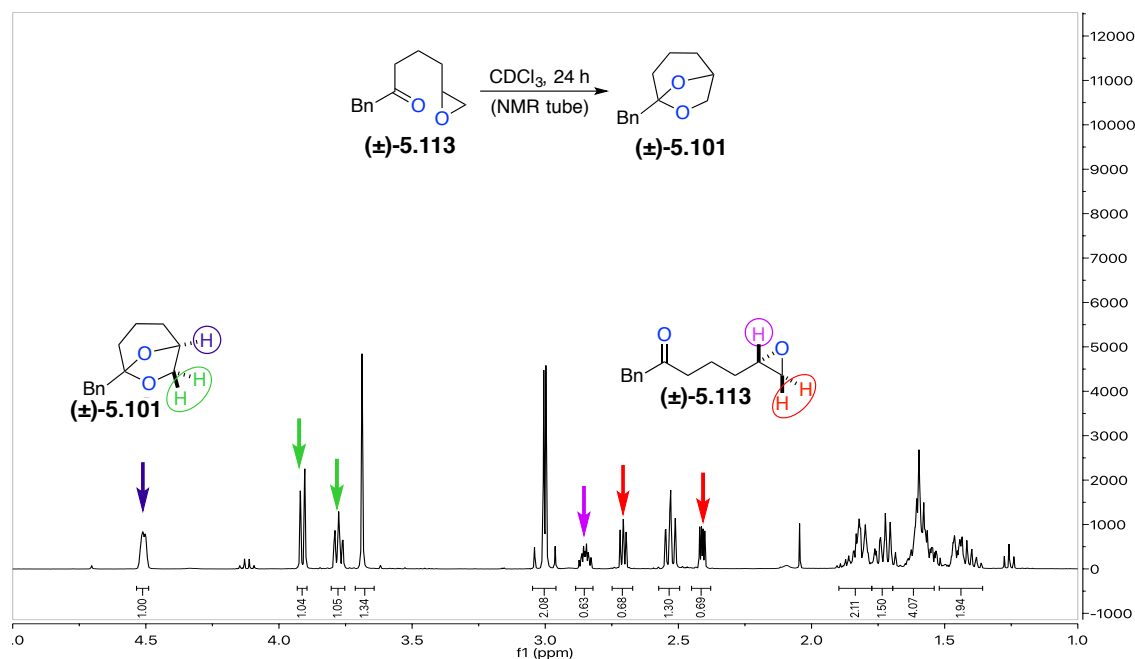


Figure 5.3 Trace Acid Promoted Rearrangement of Epoxyketone (±)-**5.113**

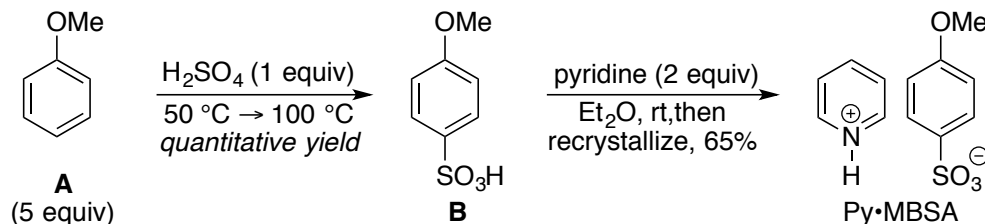
With model epoxyketone in hand, our investigation began by exposing (\pm)-**5.113** to mixtures of triphosgene and pyridinium sulfonates in 1,4-dioxane. Given the aforementioned acid-sensitivity of (\pm)-**5.113**, we knew this would be a challenging transformation to conduct, but hypothesized that by biasing the relative electronics of the sulfonate counterion a selective protonation of the ketone over the epoxide might occur. Given the relative basicity of the corresponding ketone and epoxide functionalities, biasing the acidity of the pyridinium sulfonate acid by modulating the sulfonate counterion might bias which group is activated over the other. Our pilot study was initiated by treating (\pm)-**5.113** with Py•TsOH in 1,4-dioxane with 4 Å MS at room temperature. Immediately, a 2:1 mixtures of pyranoside (\pm)-**5.100** and ketal (\pm)-**5.101** was formed in 37% yield after methanolic quench (Table 4, entry 1). Indeed, by exchanging the acid to Py•TfOH the selectivity of products reversed in favor of (\pm)-**5.101** (entry 2). As a result, we utilized Py•TsOH and examined a series of polar aprotic solvents (entries 3-5). Ultimately, 1,2-dimethoxyethane (1,2-DME) was chosen, as a 6:1 mixture of products was formed in 60% yield after 1 hour at room temperature (entry 5). Given our initial results (entries 1-5), we designed and synthesized a novel electron rich pyridinium sulfonic acid, pyridinium *para*-methoxybenzenesulfonate (Py•MBSA) via sulfonation of anisole **A** to sulfonic acid **B** followed by neutralization with pyridine. Entry 7 shows our initial attempt utilizing Py•MBSA at room temperature. Gratifyingly, (\pm)-**5.100** was formed in a 6:1 mixture, but in only 38% yield. Ultimately, it was necessary to reduce the reaction temperature to $-20\text{ }^{\circ}\text{C}$, affording the target pyranoside in a 20:1 mixture, in 73% yield (entry 9). Systematically, pyridinium sulfonates were chosen due to their weak acidity and ease of synthesis from commercially available materials. Also the complexed equivalent of pyridine should theoretically aid in the decomposition of triphosgene, liberating excess chloride ions. Additionally, the loading of triphosgene was kept at

0.33 equiv. This reduced loading in principle delivers only 1.0 equiv of chloride ion. Increased loadings of triphosgene led to intractable mixtures and extremely low yields of pyranoside (\pm)-**5.100**. During the course of this reaction optimization study we were able to grow a crystal of target pyranoside **X** and subject it to X-Ray Crystallographic analysis. Upon examining the X-Ray structure we determined the relative configuration of (\pm)-**5.100** to be 2,6-*syn* across the ring.

Table 5.8 Reaction Optimization and Discovery

entry	pyridinium acid	solvent	temp.	5.100:5.101 ^[b]	yield (%) ^[a]
1	Py•TsOH	1,4-dioxane	rt	2:1	37
2	Py•TfOH	1,4-dioxane	rt	1:2	61
3	Py•TsOH	THF	rt	3:1	37
4	Py•TsOH	Et ₂ O	rt	-	- [c]
5	Py•TsOH	1,2-DME	rt	5:1	60
6	Py•TfOH	1,2-DME	rt	2:5	76
7	Py•MBSA	1,2-DME	rt	6:1	38
8	Py•MBSA	1,2-DME	0 °C	12:1	51
9	Py•MBSA	1,2-DME	-20 °C	20:1	73
10	Py•HCl	1,2-DME	-20 °C	8:1	46

[a] Isolated yield after column chromatography. [b] Ratios determined via ¹H-NMR on crude mixtures. [c] Intractable slurry formed. Py•MBSA – pyridinium 4-methoxybenzenesulfonate



We continued our optimization study by modifying the optimized reaction conditions in an attempt to discern the role of triphosgene and probe the observed counterion dependency (Table

5.9). Subjection of (\pm)-**5.1113** to the optimized conditions exchanging Py•MBSA for Py•TfOH revealed a similar trend as reported in Table 5.8 (entry 2). A 2:3 ratio of pyranoside to bicyclic ketal was formed suggesting that a very electron poor triflate counterion favors bicycle formation. An analogous experiment was conducted substituting Py•TsOH in place of Py•MBSA and an exciting ratio of 20:1 in favor of (\pm)-**5.100** was observed; however, this reaction produced an heterogeneous emulsion making the isolation challenging. In fact only 20% of pyranoside product could be extracted from the reaction mixture. Entries 4-5 examined the role of triphosgene. Removal of the chloride source from the reaction mixture of course yielded no pyranoside; yet, no cyclization to ketal (\pm)-**5.101** was detected at $-20\text{ }^{\circ}\text{C}$ nor at room temperature. This result was unexpected as we originally observed bicyclic ketal formation with only a trace amount of acid. Our study continued with the removal of Py•MBSA from the reaction mixture. Surprisingly upon combination of (\pm)-**5.113** with triphosgene and molecular sieves at $-20\text{ }^{\circ}\text{C}$, a 1:1 mixture of pyranoside and ketal was produced after 26 hours. This result was also proved to be a surprise and we believe that molecular sieves were active in the decomposition of triphosgene as it is known that triphosgene is sensitive to decomposition in the presence of various metal frameworks and nucleophiles.^{99, 228-230} We also were curious if the Lewis acidic molecular sieves could be activating the substrate for an unselective cyclization accounting for the observed 1:1 mixture of products. A successive control experiment without 4Å MS again revealed the formation of a 1:1 mixture of heterocyclic products, albeit after an extended 72 hours of reaction time (entries 6-7). While MS were initially added to remove water from our earlier attempts at cyclization we began to think they acted as some sort of Lewis acidic additive. To further probe the role of 4Å MS, epoxyketone (\pm)-**5.113** was stirred in a heterogeneous mixture of 4Å MS in 1,2-DME overnight at $-20\text{ }^{\circ}\text{C}$ but this study resulted in no reaction (entry 8). Finally we examined the role of triphosgene

(entries 9-10). Organic chloride source Et₄NCl was added instead of triphosgene and no reaction occurred after 24 hours. Additionally, phosgene was substituted for triphosgene and after 2 hours, (±)-**5.100** was formed in 36% yield, as an 18:1 mixture in favor of pyranoside, suggesting that triphosgene does in fact decompose releasing chloride ions and phosgene gas.

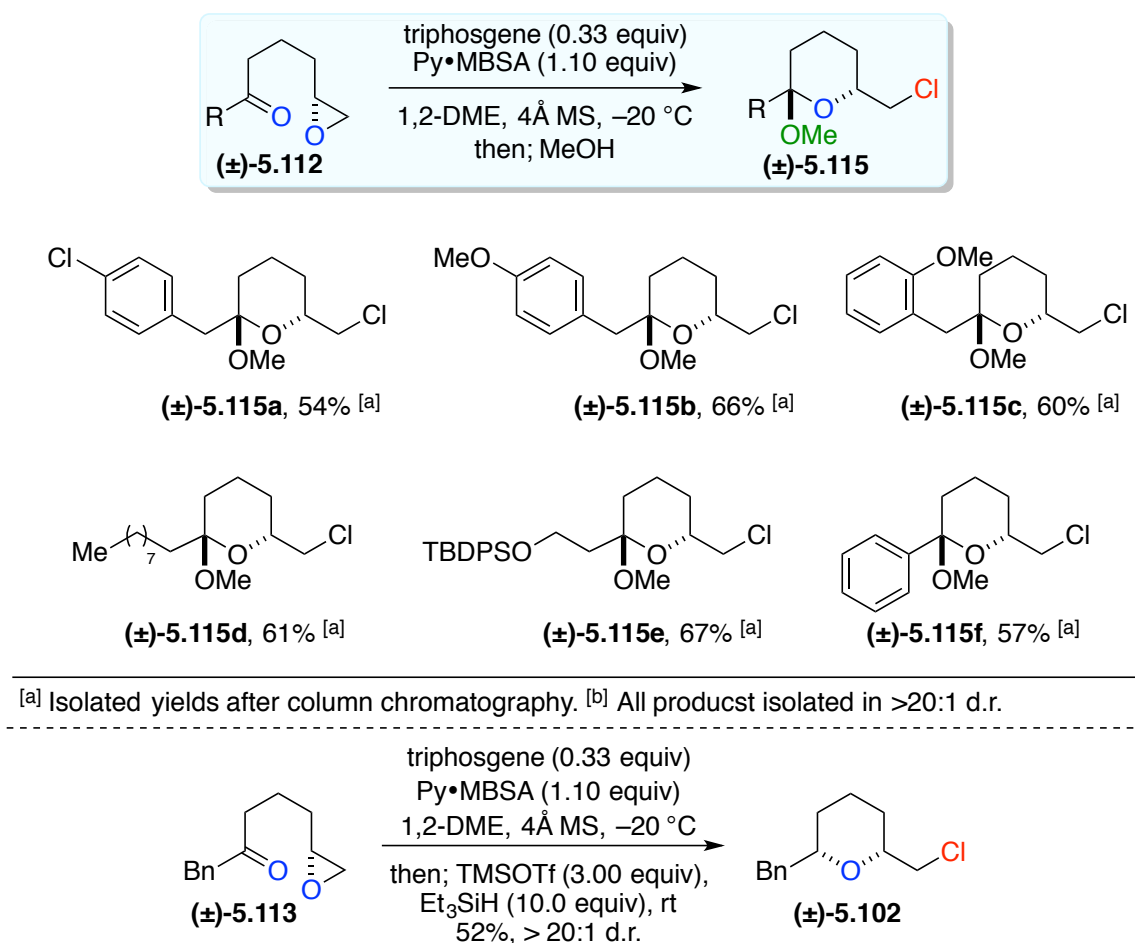
Table 5.9 Deviation from Optimized Conditions Experiments

entry	Deviation from optimized conditions	5.100 : 5.101	yield (%) ^[a]	time (hr)
1	<i>no change</i>	20:1	73	1
2	Py•TfOH instead of Py•MBSA	2:3	45	1
3	Py•TsOH instead of Py•MBSA	20:1	20	1
4	No triphosgene	—	NR	—
5	No triphosgene, room temp.	—	NR	—
6	No Py•MBSA	1:1	99	26
7	No Py•MBSA or 4 Å MS	1:1	50	72
8	4 Å MS only	—	NR	—
9	Et ₄ NCl instead of triphosgene	—	NR	—
10	phosgene instead of triphosgene	18:1	36	2

^[a] Isolated yields after column chromatography. ^[b] (±)**5.100** and (±)**5.101** are inseparable.

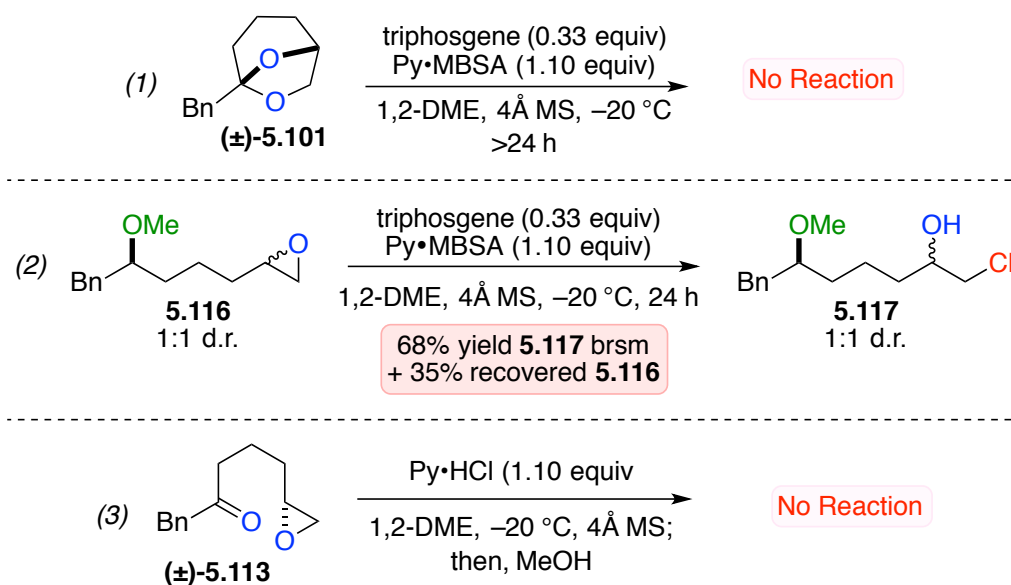
With the completion of the reaction optimization we continued our investigation by examining the generality of the transformation through a scope of substrate study shown in Scheme 5.30. Substituted aromatic homobenzylic ketones produced the requisite methyl pyranosides (±)-**5.115a**-(±)-**5.115c** in moderate to good yields ranging from 54% to 66%. However, aliphatic substituted ketones afforded the corresponding pyranoside products (±)-**5.115d** and (±)-**5.115e** in slightly increased yields of 61% and 67% yields, respectively. Phenyl substituted pyranoside was

revealed in 57%, as the sole product in the reaction mixture, no bicycle was observed via crude NMR analysis. Lastly, fully saturated (\pm)-**5.102** could be formed upon reductive quench promoted by $\text{BF}_3 \cdot \text{OEt}_2$ and Et_3SiH in 52%, upon warming to room temperature overnight. Gratifyingly, all products presented in Scheme 5.3 were afforded as single diastereomers and all relative stereochemistries of products were assigned based on analogy with (\pm)-**5.100**.²³¹ Lastly, it's extremely important to note that the reaction temperature is crucial in preventing unwanted bicycle formation. If the temperature rises above $-20\text{ }^\circ\text{C}$ the selectivity falls drastically yielding mixtures of pyranoside and bicycle products in $\sim 10:1$ ratios.



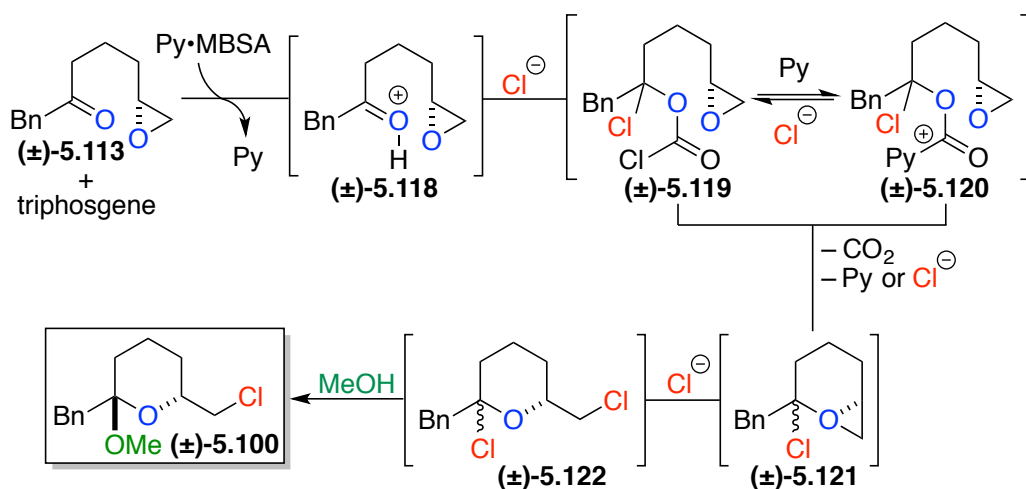
Scheme 5.30 Scope of Substrate Study

With the scope of substrate studies complete we returned our attention to probing the reaction mechanism. Bicyclic ketal (\pm)-**5.101** was treated with the optimized reaction conditions and no reaction was observed after 24 hours (Scheme 5.31 *eqn 1*). This result suggests that (\pm)-**5.101** is not a reactive intermediate and is a byproduct produced through a separate process. The intermediacy of chlorohydrin was also examined. Ether **5.116** was combined with Py•MBSA and triphosgene at $-20\text{ }^{\circ}\text{C}$ and after 24 hours, chlorohydrin **5.117** was formed in 68% yield with 35% unreacted starting materials (Scheme 5.31, *eqn 2*). The incomplete conversion of starting material to product proposes that the formation of chlorohydrin is a disfavored. Also rather surprisingly the reaction of (\pm)-**5.113** with Py•HCl yielded no reaction. Additionally the results from Table 5.9 entries 9 and 10 elude to the role of triphosgene as more than just a source of chloride ions. In fact reaction of epoxyketone (\pm)-**5.113** with Py•MBSA and Et₄NCl afforded no product, even after stirring overnight. Where an analogous reaction with phosgene produced the expected pyranoside (\pm)-**5.100** in 2 hours, however in reduced yield.



Scheme 5.31 Mechanistic Controls

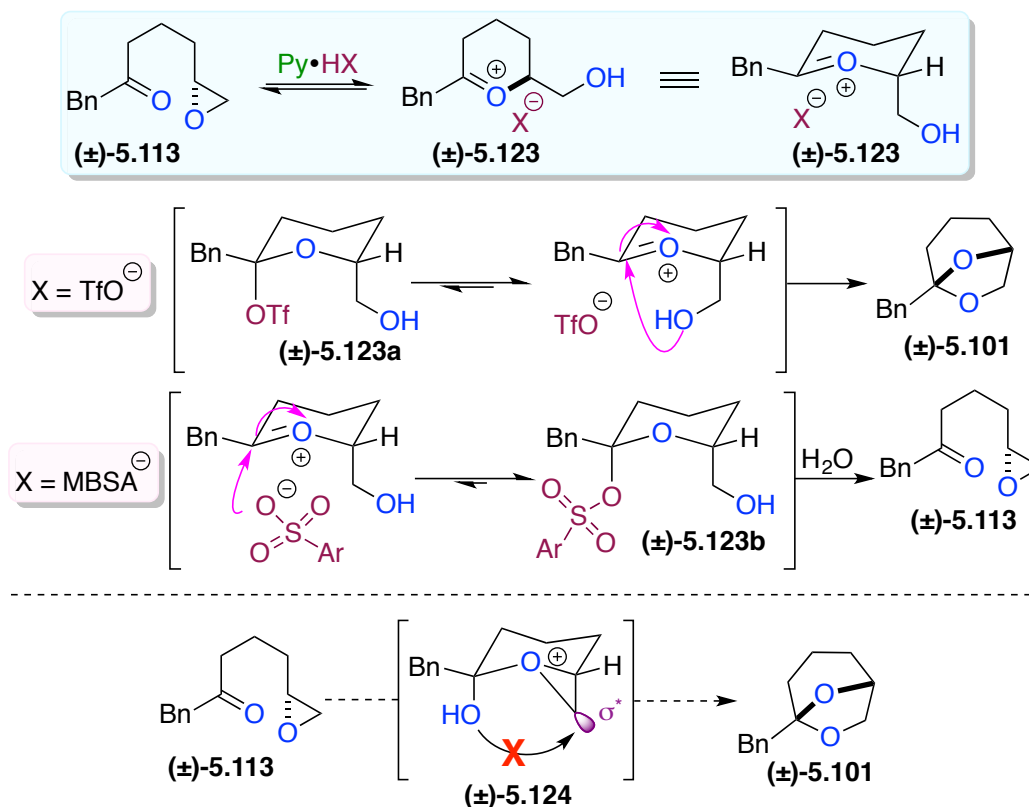
Ultimately these findings elude to the following mechanism. We predict protonation of the ketone of (\pm)-**5.113** initiates the reaction leading to oxonium ion (\pm)-**5.118**. This first step additionally releases an equivalent of pyridine which is the able to assist in the decomposition of triphosgene releasing chloride ions. Subsequent attack of (\pm)-**5.118** by chloride ions ultimately reveals geminal α -chloro chloroformate analogous to our chlorovinylolation chemistry. This intermediate can also exists in equilibria with pyridinium carbamate (\pm)-**5.120**. However both species presumably undergo self-decomposition liberating CO₂ and chloride ion or pyridine en route to bicyclic epoxonium ion formation. It is unclear if the loss of chloroformylated species reveals an α -chloro stabilized carbocation or if a nucleophilic displacement occurs. Regardless with the formation of (\pm)-**5.121** regioselective attack at the exocyclic positions most likely forms chlorine-substituted α -chloropyranoside (\pm)-**5.122**. Methanolic quench then reveals (\pm)-**5.100**. Based upon our findings from Table 5.9, we believe that epoxyketone (\pm)-**5.113** may also aide in the decomposition of triphosgene but at a slower rate than that of pyridine. Also triphosgene is slightly acidic and at temperatures above $-20\text{ }^{\circ}\text{C}$, bicyclic ketal formation begins to occur.



Scheme 5.32 Proposed Mechanism

Lastly to account for the observed counterion effects prompting the formation of bicyclic ketal over pyranoside we propose the following model. As mentioned previously epoxyketone (\pm)-**5.113** can rearrange to bicyclic ketal (\pm)-**5.101** promoted by an acid source.²²⁶ It is likely that this process proceeds via the formation of oxocarbenium ion (\pm)-**5.123** which is associated with the conjugate base of the acid through ionic interaction. As shown in Tables 5.8 and 5.9, the use of Py•TfOH favors the formation of ketal (\pm)-**5.101**. It is our hypothesis that upon formation of oxocarbenium ion **X** the weakly nucleophilic triflate ion attacks the anomeric carbon of (\pm)-**5.123**, leading to α -sulfonated pyranoside (\pm)-**5.123a**. While not typically employed as nucleophiles, triflate ions have been reported to add to anomeric carbons of glycosyl donors generated glycosyl triflate intermediates. In fact these glycosyl triflate intermediates have been observed and characterized by low temperature ($-78\text{ }^{\circ}\text{C}$) NMR studies by Crich and co-workers.²³²⁻²³⁴ However given the weak nucleophilicity of triflate anions and the warmer reaction temperature ($-20\text{ }^{\circ}\text{C}$), we believe that intermediate (\pm)-**5.123a** decomposes back to its respective contact ion pairs leaving (\pm)-**5.123** unmasked and open for intramolecular capture by the pendant alcohol generating bicyclic ketal (\pm)-**5.101**. In contrast we propose that if Py•MBSA activates the epoxide of (\pm)-**5.113** then the more nucleophilic *p*-methoxybenzenesulfonate counterion can add to oxocarbenium ion (\pm)-**5.123b** forming a more stable α -sulfonated pyranoside. Inspired by the works of Schuerch²³⁵ we believe pyranoside (\pm)-**5.123b** is more stable than is triflate-substituted counterpart leaving the anomeric position blocked and unavailable for bicyclic ketal formation. Unfortunately attempts to isolate α -sulfonated pyranoside (\pm)-**5.123b** have been unsuccessful as these intermediates are extremely sensitive to moisture and decompose rapidly upon aqueous workup. Additionally we believe that the formation of ketal (\pm)-**5.101** is only possible through the activation of the epoxide followed by 6-*exo* cyclization by the ketone. If a mechanism involving bicyclic

epoxonium ion formation were operative, capture of oxonium (\pm)-5.124 by the hemiketal hydroxyl would require significant torsional strain and is therefore unlikely.



Scheme 5.33 Model to Account for Counterion Bias

5.7 Conclusion

This chapter has served to summarize the history and utility of monocyclic and bicyclic epoxonium ions. These transient intermediates have found extensive use in the ring expansion of medium ring ether motifs to larger more structurally appealing heterocycles, as well as found a broader use as intermediates in polyepoxide cascade processes. In terms of the latter, significant attention has been paid to constructing *trans*-fused polyether motifs in an attempt to study the biosynthesis of dinoflagellate produced toxins, like Brevetoxin B. Pioneered by Murai,

McDonald, and Floreancig they laid the foundation for future discoveries. Our contribution to this area has focused on the cyclization of acyclic terminal epoxides onto unactivated dimethyl ketals and ketones. While the former suffered from substrate limitations, the cyclization of epoxyketones to pyranosides has been an exciting discovery that converts simple aliphatic epoxyketones to pyranoside motifs which are relevant to natural products and drug development chemists. During our studies we uncovered a novel Brønsted acid promoted chemoselective activation of the ketone over the epoxide and developed a novel pyridinium acid source to afford complete chemoselective activation of the ketone over the epoxide. While significant work still needs to be done, we have preliminarily studied and proposed two mechanistic pathways to account for pyranoside formation, as well as account for the observed chemoselective activation of the ketone over the epoxide. This study is near complete and will be published in a peer reviewed journal in due course.

Appendix A: Copyright Release



Effects of Solvent and Residual Water on Enhancing the Reactivity of Six-Membered Silyloxyallyl Cations toward Nucleophilic Addition

Author: Joshua A. Malone, Alexander H. Cleveland, Frank R. Fronczek, et al

Publication: Organic Letters

Publisher: American Chemical Society

Date: Sep 1, 2016

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Mechanistic Perspectives in the Regioselective Indole Addition to Unsymmetrical Silyloxyallyl Cations

Author: Caitlin G. Bresnahan, Kiara A. Taylor-Edinbyrd, Alexander H. Cleveland, et al

Publication: The Journal of Organic Chemistry

Publisher: American Chemical Society

Date: Jun 1, 2019

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Synthesis of Vicinal Dichlorides via Activation of Aliphatic Terminal Epoxides with Triphosgene and Pyridine

Author: Alexander H. Cleveland, Frank R. Fronczek, Rendy Kartika

Publication: The Journal of Organic Chemistry

Publisher: American Chemical Society

Date: Mar 1, 2018

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Appendix B: Experimental Procedures

General Information

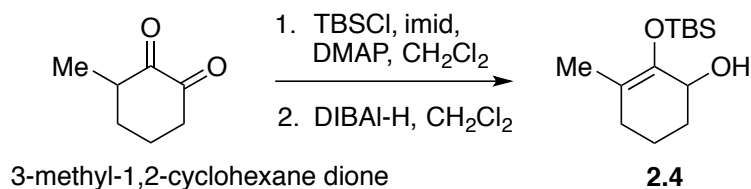
Unless otherwise noted, all materials were used as received from commercial suppliers without further purification. All anhydrous reactions were performed using oven-dried or flame-dried glassware, which was then cooled under vacuum and purged with nitrogen gas. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), acetonitrile, toluene, and diethyl ether (Et_2O) were filtered through activated 3 Å molecular sieves under nitrogen contained in an M-Braun Solvent Purification System. All reactions were monitored by EMD analytical thin layer chromatography (TLC Silica Gel 60 F₂₅₄, Glass Plates) and analyzed with 254 nm UV light and / or anisaldehyde – sulfuric acid or potassium permanganate treatment. Silica gel for column chromatography was purchased from Dynamic Adsorbents, Inc. or Sigma Aldrich (Flash Silica Gel 32-63u).

Unless otherwise noted, all ^1H and ^{13}C NMR spectra were recorded in CDCl_3 using a Bruker Ascend 400 spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C or Bruker Ascend 500 spectrometer operating at 500 MHz for ^1H and 125 MHz for ^{13}C . Chemical shifts (δ) are reported in ppm relative to residual CHCl_3 as an internal reference (^1H : 7.26 ppm, ^{13}C : 77.23 ppm). Coupling constants (J) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), (septet), h (heptet), b (broad), and m (multiplet). FT-IR spectra were recorded on Bruker Tensor 27 spectrometer and OPUS 6.5 Data Collection Program, and absorption frequencies were reported in reciprocal centimeters (cm^{-1}). High Resolution Mass Spectrometry – Electron Spray Ionization (HRMS-ESI) analyses were performed by the Louisiana State University Mass Spectrometry Facility using an Agilent 6210 Instrument. X-ray structure analyses were performed by the Louisiana State University X-ray

Structure Facility using a Bruker APEX-II CCD diffractometer. Thermo Scientific TG-SQC GC Column (15m x 0.25mm x 0.25 μ m) using a modified gradient of 40 °C to 300 °C over 29 minutes using helium as the carrier gas. The detector utilized was a Thermo Scientific ISQD QD mass spectrometer with the mass range limit set from 60 – 400 amu and with the ion source temperature set at 200 °C. Solvent delay was set to 5.00 minutes for each trial.

Experimental Procedures for Chapter 2

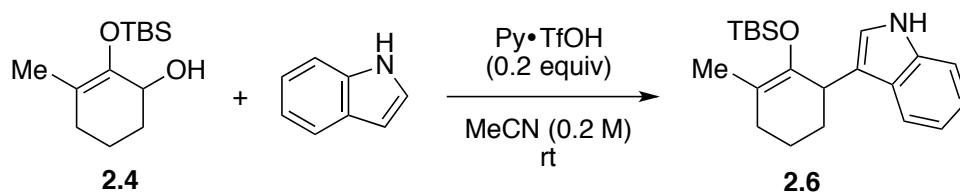
2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-ol (**2.4**)



Prepared according to the procedure reported by Stepherson J. R.; Fronczek. F. R.; Kartika R.

Chem. Commun. **2016**, 52, 2300.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-indole (**2.6**)



Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). Indole (119 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 26 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 3% EtOAc in hexanes to give compound **2.6** in 82% yield (231 mg, 0.676 mmol) as a colorless oil.

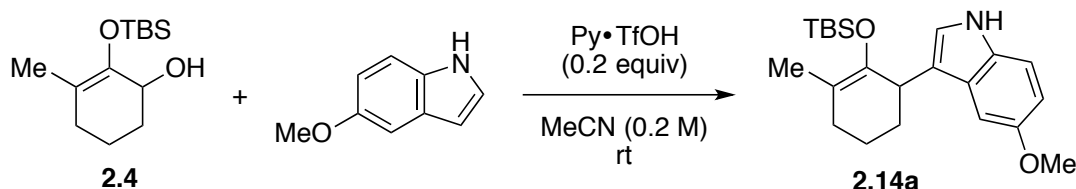
¹H NMR (500 MHz): δ = 7.91 (bs, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H), 3.71 (s, 1H), 2.15 - 2.07 (m, 1H), 2.06 - 1.93 (m, 3H), 1.91 - 1.85 (m, 1H), 1.72 (s, 3H), 1.60 - 1.44 (m, 2H), 0.78 (s, 9H), -0.01 (s, 3H), -0.11 (s, 3H).

¹³C NMR (125 MHz): δ = 143.84, 136.49, 127.07, 123.06, 121.44, 118.93, 118.88, 118.75, 112.65, 110.95, 37.02, 31.14, 30.55, 25.77, 19.13, 18.25, 16.88, -3.86, -4.04.

IR: f (cm⁻¹) = 3418, 3321, 2927, 1680, 1455, 1253, 1166, 1090, 1008, 939, 095, 828, 775, 735, 669, 582, 485.

HRMS: (M+H)⁺ = 342.2248 calculated for C₂₁H₃₂NOSi; 342.2257 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-5-methoxy-1*H*-indole (2.14a)



Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). 5-Methoxyindole (134 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 23 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 2% EtOAc in hexanes to give compound **2.14a** in 71% yield (217 mg, 0.584 mmol) as a colorless oil.

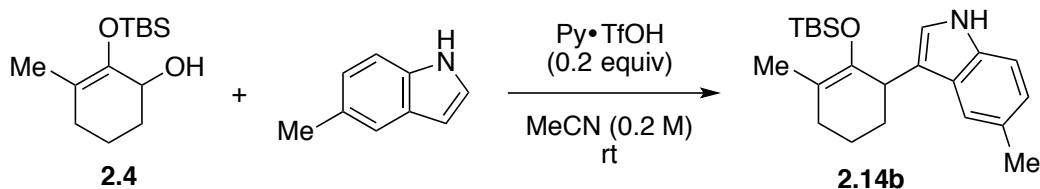
¹H NMR (400 MHz): δ = 7.80 (bs, 1H), 7.22 (d, J = 8.7 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 6.92 (d, J = 2.1 Hz, 1H), 6.83 (dd, J = 8.7, 6.4 Hz, 1H), 3.86 (s, 3H), 3.63 (s, 1H), 2.15 - 1.81 (m, 4H), 1.71 (s, 3H), 1.61 - 1.43 (m, 2H), 0.77 (s, 9H), -0.03 (s, 3H), -0.12 (s, 3H).

¹³C NMR (100 MHz): δ = 153.65, 143.84, 131.72, 127.52, 123.93, 118.52, 112.58, 111.53, 111.36, 101.15, 55.96, 37.07, 31.11, 30.57, 25.77, 19.22, 18.25, 16.85, -3.86, -4.04.

IR: $f(\text{cm}^{-1})$ = 2928, 1680, 1483, 1251, 1196, 1041, 917, 830, 776.

HRMS: $(\text{M}+\text{H})^+ = 372.2353$ calculated for $\text{C}_{22}\text{H}_{34}\text{NO}_2\text{Si}$; 372.2363 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-5-methyl-1*H*-indole (2.14b)



Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). 5-Methylindole (119 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 1% EtOAc in hexanes to give compound **2.14a** in 80% yield (234 mg, 0.697 mmol) as a colorless oil.

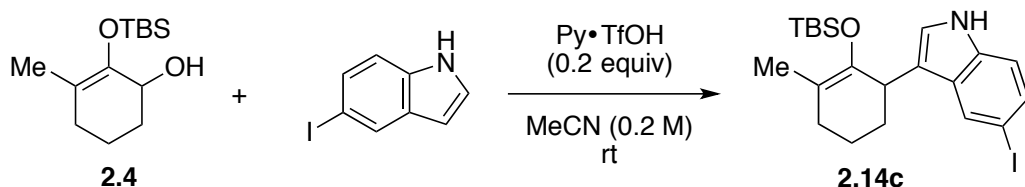
¹H NMR (500 MHz): δ = 7.81 (bs, 1H), 7.36 (s, 1H), 7.23 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 3.67 (s, 1H), 2.47 (s, 3H), 2.14 - 2.05 (m, 1H), 2.04 - 1.86 (m, 3H), 1.71 (s, 3H), 1.56 - 1.44 (m, 2H), 0.80 (s, 9H), -0.02 (s, 3H), -0.11 (s, 3H).

¹³C NMR (125 MHz): δ = 143.91, 134.84, 128.02, 127.29, 123.29, 123.02, 118.52, 118.17, 112.53, 110.59, 36.93, 30.95, 30.54, 25.80, 21.59, 19.00, 18.27, 16.86, -3.86, -4.00.

IR: $f(\text{cm}^{-1})$ = 3414, 2927, 2855, 1679, 1461, 1252, 1166, 942, 830, 776, 589.

HRMS: $(\text{M}+\text{H})^+ = 356.2404$ calculated for $\text{C}_{22}\text{H}_{34}\text{NOSi}$; 356.2405 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-5-iodo-1*H*-indole (2.14c)



Alcohol **2.4** (224 mg, 0.924 mmol) was dissolved in acetonitrile (4.6 mL). 5-Iodoindole (248 mg, 1.02 mmol) was then added, followed by pyridinium triflate (42 mg, 0.185 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 5% EtOAc in hexanes to give compound **2.14c** in 59% yield (254 mg, 0.543 mmol) as a light pink solid.

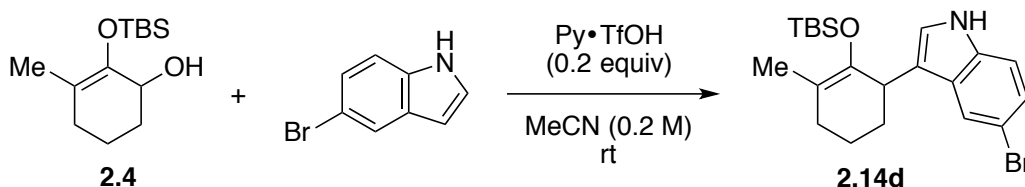
¹H NMR (400 MHz): δ = 7.98 (s, 1H), 7.92 (d, J = 1.8 Hz, 1H), 7.41 (dd, J = 8.4, 1.6 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.89 (dd, J = 2.4, 0.8 Hz, 1H), 2.16 - 1.89 (m, 2H), 11.88 - 1.78 (m, 1H), 1.73 (s, 3H), 1.56 - 1.42 (m, 1H), 0.79 (s, 9H), 0.01 (s, 3H), -0.09 (s, 3H).

¹³C NMR (100 MHz): δ = 143.60, 135.72, 129.97, 129.89, 127.99, 124.15, 118.45, 113.38, 113.24, 82.76, 37.14, 31.80, 31.40, 30.69, 25.98, 22.87, 19.31, 18.45, 17.12, 14.34, -3.77.

IR: $f(\text{cm}^{-1})$ = 3426, 2927, 2854, 1680, 1454, 1349, 1319, 1253, 1165, 1090, 1005, 939, 906, 863, 828, 775, 731, 672, 653, 579, 492, 417.

HRMS: $(\text{M}+\text{H})^+ = 468.1214$ calculated for $\text{C}_{21}\text{H}_{31}\text{INOSi}$; 468.1222 experimental.

5-bromo-3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-indole (2.14d)



Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). 5-Bromoindole (178 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 25 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 1% EtOAc in hexanes to give compound **2.14d** in 69% yield (239 mg, 0.568 mmol) as a light blue solid.

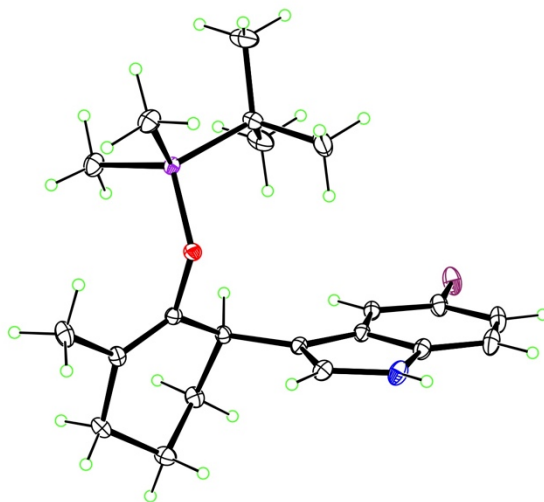
^1H NMR (500 MHz): δ = 7.95 (bs, 1H), 7.71 - 7.67 (m, 1H), 7.25 - 7.19 (m, 2H), 6.95 (s, 1H), 3.62 (s, 1H), 2.15 - 2.05 (m, 1H), 2.05 - 1.91 (m, 2H), 1.86 - 1.78 (m, 1H), 1.71 (s, 3H), 1.57 - 1.44 (m, 2H), 0.91 - 0.64 (m, 9H), -0.00 - -0.03 (m, 3H), -0.10 - -0.13 (m, 3H).

^{13}C NMR (125 MHz): δ = 143.36, 135.06, 128.83, 124.31, 121.48, 118.59, 113.12, 112.43, 112.34, 77.25, 77.00, 76.75, 36.98, 31.19, 30.49, 25.75, 19.15, 18.23, 16.89, -3.85, -4.00.

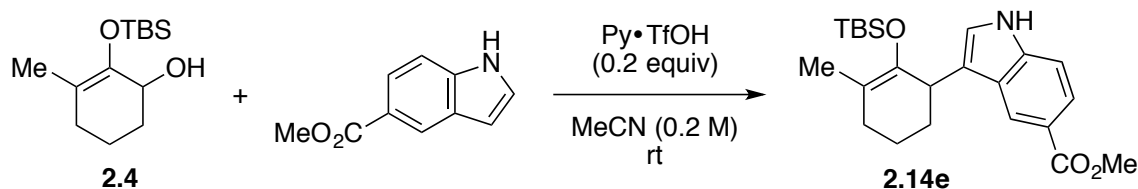
IR: $f(\text{cm}^{-1})$ = 3429, 2927, 2855, 1680, 1458, 1345, 1322, 1253, 1166, 1091, 1005, 939, 908, 884, 863, 227, 674, 582, 293.

HRMS: $(\text{M}+\text{H})^+ = 420.1353$ calculated for $\text{C}_{21}\text{H}_{31}\text{BrNOSi}$; 420.1360 experimental.

X-ray structure:



Methyl 3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-indole-5-carboxylate (2.14e)



Alcohol **2.4** (180 mg, 0.742 mmol) was dissolved in acetonitrile (3.7 mL). Methyl indole-5-carboxylate (143 mg, 0.817 mmol) was then added, followed by pyridinium triflate (34 mg, 0.148 mmol). After stirring for 46 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 20% EtOAc in hexanes to give compound **2.14e** in 58% yield (173 mg, 0.584 mmol) as a white solid.

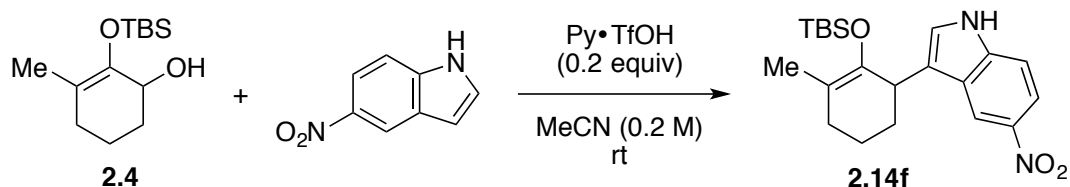
^1H NMR (500 MHz): δ = 8.36 – 8.34 (m, 1H), 8.11 (s, 1H), 7.88 (dd, J = 8.6, 1.6 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 3.93 (s, 3H), 3.72 (bs, 1H), 2.15 - 2.06 (m, 1H), 2.05 - 1.96 (m, 2H), 1.89 - 1.82 (m, 1H), 1.70 (s, 3H), 1.54 - 1.46 (m, 2H), 0.76 (s, 9H), -0.03 (s, 3H), -0.13 (s, 3H).

^{13}C NMR (125 MHz): δ = 168.36, 143.37, 139.07, 126.69, 124.31, 122.99, 121.90, 121.12, 120.32, 113.17, 110.64, 77.25, 77.00, 76.75, 51.81, 36.92, 31.34, 30.48, 25.73, 25.31, 19.07, 18.21, 16.87, -3.88, -4.03.

IR: $f(\text{cm}^{-1})$ = 2949, 2856, 1691, 1616, 1580, 1547, 1435, 1389, 1360, 1344, 1309, 1284, 1244, 1190, 1178, 1167, 1122, 1031, 1006, 985, 909, 864, 774, 731, 676, 627, 589, 526, 475.

HRMS: $(\text{M}+\text{H})^+ = 400.2302$ calculated for $\text{C}_{23}\text{H}_{34}\text{NO}_3\text{Si}$; 400.2308 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-5-nitro-1*H*-indole (2.14f)



Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). 5-Nitroindole (147 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 168 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 4% EtOAc in hexanes to give compound **2.14f** in 36% yield (144 mg, 0.373 mmol) as a yellow solid.

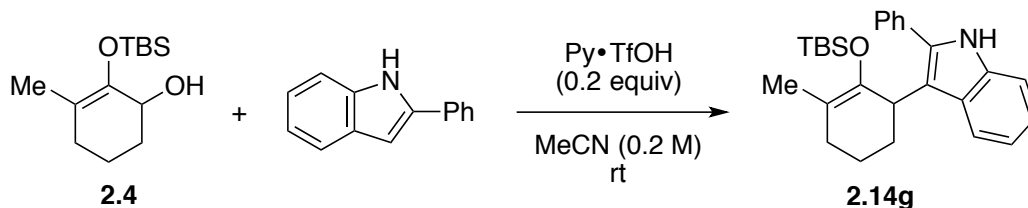
¹H NMR (500 MHz): δ = 8.57 (s, 1H), 8.29 (bs, 1H), 8.09 (dd, J = 6.8, 2.2 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 3.71 (s, 1H), 2.16 - 2.08 (m, 1H), 2.08 - 1.99 (m, 2H), 1.86 - 1.80 (m, 1H), 1.72 (s, 3H), 1.55 - 1.48 (m, 2H), 0.74 (s, 9H), 0.00 (s, 3H), -0.11 (s, 3H).

¹³C NMR (125 MHz): δ = 142.79, 141.46, 139.37, 126.46, 125.92, 121.70, 117.43, 116.39, 113.83, 110.89, 37.09, 31.66, 30.44, 19.31, 18.16, 16.91, -3.88, -4.01.

IR: f (cm⁻¹) = 3368, 2928, 2856, 1681, 1622, 1515, 1470, 1376, 1325, 1256, 1167, 1091, 941, 912, 777, 739, 588.

HRMS: (M+H)⁺ = 387.2098 calculated for C₂₁H₃₁N₂O₃Si; 387.2104 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-2-phenyl-1*H*-indole (2.14g)



Alcohol **2.4** (200 mg, 0.824 mmol) was dissolved in acetonitrile (4.0 mL). 2-Phenylindole (144 mg, 0.907 mmol) was then added, followed by pyridinium triflate (38 mg, 0.165 mmol). After stirring for 26 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 1% EtOAc in hexanes to give compound **2.14g** in 72% yield (242 mg, 0.580 mmol) as a white solid.

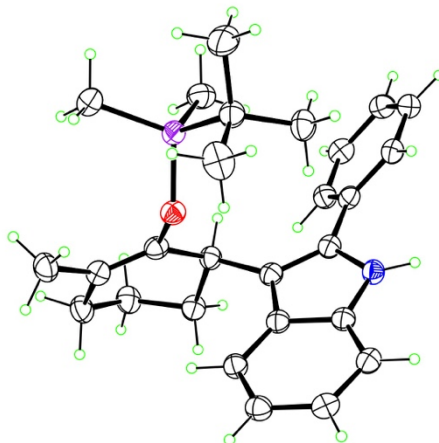
^1H NMR (500 MHz): δ = 7.90 (bs, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.34 (dd, J = 17.3, 8.8 Hz, 2H), 7.15 (t, J = 8.1 Hz, 1H), 7.05 (t, J = 7.9 Hz, 1H), 3.78 (s, 1H), 2.29 - 1.97 (m, 5H), 1.88 - 1.80 (m, 1H), 1.62 (s, 3H), 0.53 (s, 9H), -0.24 (s, 3H), -0.45 (s, 3H).

^{13}C NMR (125 MHz): δ = 143.80, 135.92, 134.51, 133.73, 128.73, 128.48, 128.26, 127.40, 121.72, 120.86, 119.15, 116.01, 112.66, 110.32, 77.25, 77.00, 76.75, 37.47, 33.69, 31.11, 25.46, 22.21, 17.95, 17.11, -4.05, -4.51.

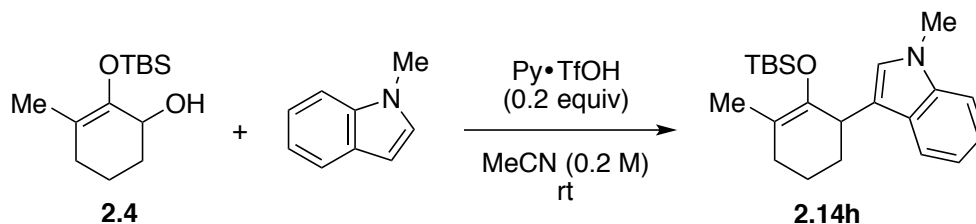
IR: $f(\text{cm}^{-1})$ = 2926, 2854, 1671, 1603, 1486, 1456, 1342, 1311, 1256, 1176, 1071, 1011, 938, 907, 829, 775, 697, 670, 583, 563, 482.

HRMS: $(\text{M}+\text{H})^+ = 418.2561$ calculated for $\text{C}_{27}\text{H}_{36}\text{NOSi}$; 418.2576 experimental.

X-ray structure:



3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1-methyl-1*H*-indole (2.14h)



Alcohol **2.4** (103 mg, 0.425 mmol) was dissolved in acetonitrile (2.1 mL). *N*-methyl indole (58 μ l, 0.468 mmol) was then added, followed by pyridinium triflate (19 mg, 0.0850 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 12% DCM in hexanes to give compound **2.14h** in 65% yield (99 mg, 0.277 mmol) as a colorless oil.

^1H NMR (400 MHz): δ = 7.56 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.0 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.80 (s, 1H), 3.74 (s, 3H), 3.68 (s, 1H), 2.14 - 1.89 (m, 3H), 1.87 - 1.80

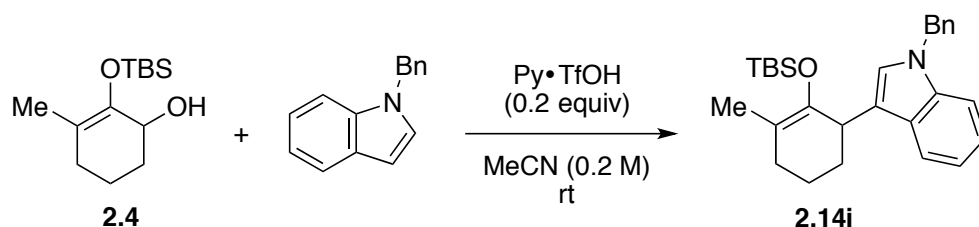
(m, 1H), 1.71 (s, 3H), 1.61 - 1.52 (m, 1H), 1.51 - 1.41 (m, 1H), 0.77 (s, 9H), -0.03 (s, 3H), -0.12 (s, 3H).

^{13}C NMR (100 MHz): δ = 144.00, 137.18, 127.89, 127.45, 120.94, 118.91, 118.30, 117.15, 77.31, 76.99, 76.67, 36.91, 32.55, 31.30, 30.54, 25.78, 19.06, 18.27, 16.87, -3.81, -4.04.

IR: $f(\text{cm}^{-1})$ = 2924, 2854, 1680, 1462, 1250, 1178, 1163, 939, 914, 830, 776, 740.

HRMS: $(\text{M}+\text{H})^+$ 356.2404 calculated for $\text{C}_{22}\text{H}_{34}\text{NOSi}$; 356.2408 experimental.

1-benzyl-3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-indole (2.14i)



Alcohol **2.4** (100 mg, 0.412 mmol) was dissolved in acetonitrile (2.0 mL). *N*-benzylindole (94 mg, 0.454 mmol) was then added, followed by pyridinium triflate (20 mg, 0.0824 mmol). After stirring for 28 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 20% DCM in hexanes to give compound **2.14i** in 82% yield (146 mg, 0.338 mmol) as a colorless oil.

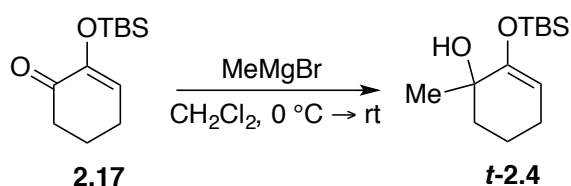
^1H NMR (400 MHz): δ = 7.76 (d, J = 7.9 Hz, 1H), 7.30 - 7.21 (m, 2H), 7.20 (d, J = 8.2 Hz, 2H), 7.13 - 7.08 (m, 3H), 7.04 - 6.99 (m, 1H), 6.90 (s, 1H), 5.25 (s, 2H), 4.83 (t, J = 4.1 Hz, 1H), 2.35 (ddd, J = 12.9, 9.4, 3.3 Hz, 1H), 2.25 - 2.07 (m, 2H), 1.73 - 1.65 (m, 1H), 1.62 - 1.49 (m, 5H), 0.62 (s, 9H), 0.09 (s, 3H), -0.09 (s, 3H).

¹³C NMR (125 MHz): δ = 155.19, 137.94, 137.19, 128.61, 127.32, 126.71, 126.51, 126.48, 122.51, 121.15, 120.95, 118.18, 109.46, 101.14, 77.25, 77.00, 76.75, 49.79, 39.85, 38.51, 25.48, 25.41, 24.71, 19.80, 17.90, -4.68.

IR: $f(\text{cm}^{-1})$ = 2927, 2855, 1655, 1465, 1329, 1247, 954, 912, 836, 776, 736.

HRMS: (M+H)⁺ 432.2717 calculated for C₂₈H₃₈NOSi; 432.2719 experimental.

2-((*tert*-butyldimethylsilyl)oxy)-1-methylcyclohex-2-en-1-ol (*t*-2.4)



Ketone **2.17** (3.64 g, 16.1 mmol) was dissolved in dichloromethane (80 mL), and the solution was cooled to 0 °C. Methylmagnesium bromide (10.7 mL, 3.0 M in Et₂O) was then added dropwise. After stirring for 2 hours at room temperature, the reaction was quenched with 1:1 DI water and saturated NH₄Cl solution (5 mL). The crude mixture was filtered through a celite plug and sequentially washed with DCM (500 mL) and DI H₂O (300 mL). The aqueous layer was then extracted with DCM (3 x 50 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes → 10% EtOAc in hexanes to give product ***t*-2.4** in 81% yield (3.15 g, 13.0 mmol) as a clear oil.

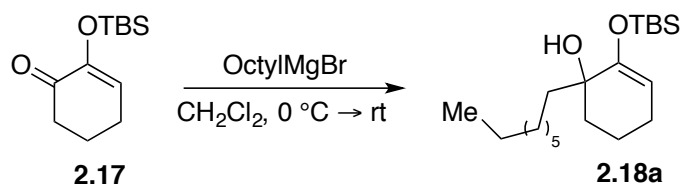
¹H NMR (500 MHz): δ = 4.76 (t, J = 4.0 Hz, 1H), 2.23 (s, 1H), 2.11 - 1.95 (m, 2H), 1.84 - 1.71 (m, 2H), 1.67 (dddt, J = 13.3, 10.1, 5.7, 2.8 Hz, 1H), 1.58 - 1.49 (m, 1H), 1.32 (s, 3H), 0.94 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H).

¹³C NMR (125 MHz): δ = 152.70, 102.89, 77.25, 77.20, 77.00, 76.75, 70.36, 37.65, 27.13, 26.06, 25.79, 24.41, 19.94, 18.16, -4.39, -4.71.

IR: f (cm⁻¹) = 2959, 2931, 2858, 1661, 1462, 1363, 1258, 1192, 1173, 1090, 1014, 959, 900, 796, 685, 669, 604, 484.

HRMS: (M+H)⁺ = 243.1775 calculated for C₁₃H₂₇O₂Si; 243.1782 experimental.

2-((*tert*-butyldimethylsilyl)oxy)-1-octylcyclohex-2-en-1-ol (2.18a)



Ketone **2.17** (300 mg, 1.32 mmol) was dissolved in dichloromethane (6.6 mL), and the solution was cooled to 0 °C. Octylmagnesium bromide (1.0 mL, 2.0 M in Et₂O) was then added dropwise. After stirring for 16 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes → 3% EtOAc in hexanes to give product **2.18a** in 86% yield (372 mg, 1.09 mmol) as a clear yellow oil.

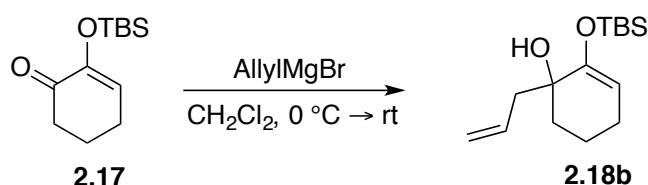
¹H NMR (500 MHz): δ = 4.80 (dd, J = 4.7, 3.3 Hz, 1H), 2.08 - 2.01 (m, 1H), 1.99 - 1.93 (m, 2H), 1.76 (ddd, J = 13.4, 10.0, 3.5 Hz, 1H), 1.71 - 1.51 (m, 5H), 1.30 - 1.23 (m, 12H), 0.94 (s, 9H), 0.88 (t, J = 7.1 Hz, 3H), 0.19 (s, 3H), 0.17 (s, 3H).

¹³C NMR (125 MHz): δ = 152.50, 103.71, 77.25, 77.00, 76.75, 72.52, 39.56, 34.25, 31.88, 30.25, 29.62, 29.28, 25.78, 24.40, 23.98, 22.66, 19.39, 18.15, 14.10, -4.54, -4.57.

IR: $f(\text{cm}^{-1}) = 3600, 2926, 2855, 1657, 1462, 1251, 1176, 917, 836, 778, 673$.

HRMS: $(\text{M}+\text{H})^+$ 341.2870 calculated for $\text{C}_{20}\text{H}_{41}\text{O}_2\text{Si}$; 341.2868 experimental.

1-allyl-2-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-ol (2.18b)



Ketone **2.17** (308 mg, 1.36 mmol) was dissolved in dichloromethane (7.0 mL), and the solution was cooled to 0 °C. Allylmagnesium bromide (2.0 mL, 1.0 M in Et_2O) was then added dropwise. After stirring for 18 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes \rightarrow 5% EtOAc in hexanes to give product **2.18c** in 77% yield (283 mg, 1.05 mmol) as a clear oil.

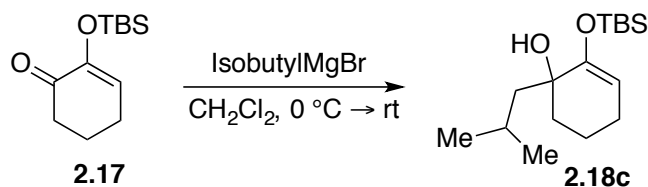
^1H NMR (500 MHz): $\delta = 5.81$ (ddt, $J = 16.2, 11.2, 7.4$ Hz, 1H), 5.09 - 5.05 (m, 2H), 4.83 (t, $J = 4.5, 3.4$ Hz, 1H), 2.45 - 2.35 (m, 2H), 2.12 (s, 1H), 2.10 - 2.02 (m, 1H), 2.01 - 1.93 (m, 1H), 1.78 (ddd, $J = 13.2, 9.5, 3.5$ Hz, 1H), 1.71 - 1.65 (m, 1H), 1.64 - 1.60 (m, 1H), 1.57 - 1.51 (m, 1H), 0.94 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H).

^{13}C NMR (125 MHz): $\delta = 151.95, 134.41, 117.70, 104.06, 77.25, 77.20, 77.00, 76.75, 71.90, 44.14, 34.42, 25.79, 25.73, 24.31, 19.21, 18.16, -4.52, -4.57$.

IR: $f(\text{cm}^{-1}) = 3475, 3075, 2857, 2375, 2189, 2171, 2158, 2068, 2006, 1939, 1703, 1640, 1554, 1471, 1435, 1389, 1337, 1283, 1240, 1168, 1086, 939, 912, 836, 778, 674, 573, 489, 424.$

HRMS: $(\text{M}^\bullet)^+ = 251.1826$ calculated for $\text{C}_{15}\text{H}_{27}\text{OSi}$; 251.1833 experimental.

2-((*tert*-butyldimethylsilyl)oxy)-1-isobutylcyclohex-2-en-1-ol (2.18c)



Ketone **2.17** (300 mg, 1.32 mmol) was dissolved in dichloromethane (6.6 mL), and the solution was cooled to 0 °C. Isobutylmagnesium bromide (1.0 mL, 2.0 M in Et_2O) was then added dropwise. After stirring for 16 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes \rightarrow 2% EtOAc in hexanes to give product **2.18c** in 50% yield (200 mg, 0.703 mmol) as a clear oil.

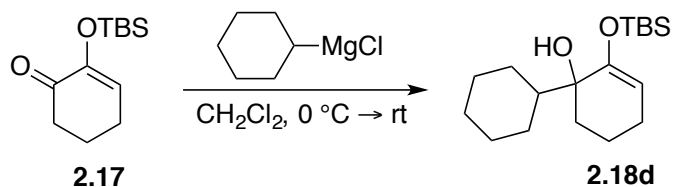
^1H NMR (500 MHz): $\delta = 4.77$ (dd, $J = 4.5, 3.5$ Hz, 1H), 2.10 - 2.03 (m, 1H), 2.01 - 1.94 (m, 1H), 1.87 - 1.68 (m, 3H), 1.67 - 1.59 (m, 1H), 1.59 - 1.49 (m, 3H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.95 (s, 9H), 0.92 (d, $J = 6.7$ Hz, 3H), 0.18 (s, 3H), 0.17 (s, 3H).

^{13}C NMR (125 MHz): $\delta = 153.05, 103.27, 77.34, 77.29, 77.09, 76.84, 72.83, 47.60, 34.39, 25.91, 24.97, 24.48, 24.46, 24.08, 19.62, 18.27, -4.41, -4.54.$

IR: $f(\text{cm}^{-1}) = 3591, 2929, 1657, 1463, 1362, 1250, 1169, 919, 836, 778, 673.$

HRMS: $(\text{M}+\text{H})^+ = 285.2244$ calculated for $\text{C}_{16}\text{H}_{33}\text{O}_2\text{Si}$; 285.2239 experimental.

2-((*tert*-butyldimethylsilyl)oxy)-[1,1'-bi(cyclohexan)]-2-en-1-ol (2.18d)



Ketone **2.17** (200 mg, 0.883 mmol) was dissolved in dichloromethane (4.4 mL), and the solution was cooled to 0 °C. Cyclohexylmagnesium chloride (0.66 mL, 2.0 M in Et₂O) was then added dropwise. After stirring for 22 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes → 2% EtOAc in hexanes to give product **2.18d** in 43% yield (119 mg, 0.384 mmol) as a clear oil.

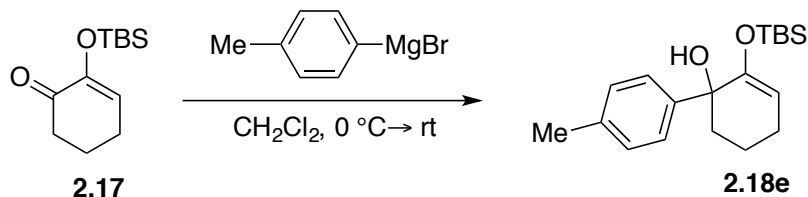
¹H NMR (500 MHz): δ = 4.86 (dd, *J* = 6.0, 2.7 Hz, 1H), 2.04 - 1.96 (m, 1H), 1.95 - 1.87 (m, 2H), 1.83 - 1.77 (m, 1H), 1.75 - 1.64 (m, 4H), 1.61 - 1.48 (m, 4H), 1.27 - 0.95 (m, 5H), 0.94 (s, 9H), 0.92 - 0.87 (m, 1H), 0.18 (d, *J* = 7.2 Hz, 6H).

¹³C NMR (125 MHz): δ = 152.21, 104.91, 77.00, 74.97, 45.82, 30.84, 28.96, 27.21, 27.08, 27.04, 26.12, 25.99, 24.53, 19.36, 18.39, -4.28, -4.47.

IR: *f* (cm⁻¹) = 3605, 2927, 1657, 1360, 1238, 1176, 963, 928, 912, 892, 827, 777, 732.

HRMS: (M+H)⁺ = 333.2220 calculated for C₁₈H₃₄O₂Si; 333.2221 experimental.

6-((*tert*-butyldimethylsilyl)oxy)-4'-methyl-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-ol (2.18e)



Ketone **2.17** (200 mg, 0.883 mmol) was dissolved in dichloromethane (4.4 mL), and the solution was cooled to 0 °C. *p*-Tolyl magnesium bromide (1.33 mL, 1.0 M in THF) was then added dropwise. After stirring for 18 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes → 3% EtOAc in hexanes to give product **2.18e** in 62% yield (174.5 mg, 0.5478 mmol) as a clear yellow oil.

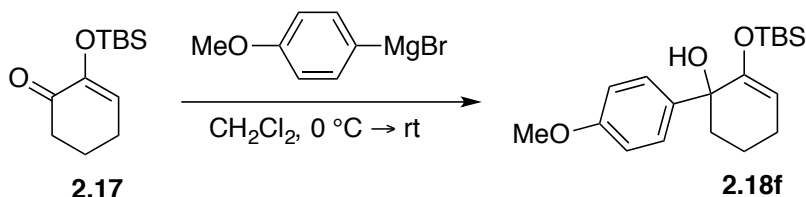
¹H NMR (500 MHz): δ = 7.36 (d, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 2H), 5.05 (t, *J* = 4.0 Hz, 1H), 2.73 (s, 1H), 2.33 (s, 3H), 2.23 - 2.09 (m, 2H), 2.06 - 1.99 (m, 1H), 1.94 - 1.88 (m, 1H), 1.66 - 1.58 (m, 1H), 1.49 - 1.40 (m, 1H), 0.72 (s, 9H), 0.18 (s, 3H), 0.06 (s, 3H).

¹³C NMR (125 MHz): δ = 150.66, 143.65, 136.21, 128.34, 126.04, 104.83, 78.62, 77.25, 77.00, 76.75, 75.25, 39.48, 25.47, 24.35, 21.00, 19.14, 17.90, -4.35, -5.00.

IR: *f* (cm⁻¹) = 3581, 2929, 1662, 1461, 1361, 1241, 1175, 1050, 1006, 937, 916, 813, 776, 671, 536, 480.

HRMS: (M+Na)⁺ = 341.1907 calculated for C₁₉H₃₀O₂SiNa; 341.1905 experimental.

6-((*tert*-butyldimethylsilyl)oxy)-4'-methoxy-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-ol (2.18f)



Ketone **2.17** (196 mg, 0.864 mmol) was dissolved in dichloromethane (4.3 mL), and the solution was cooled to 0 °C. *p*-Methoxyphenyl magnesium bromide (2.6 mL, 0.5 M in THF) was then added dropwise. After stirring for 18 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes → 4% EtOAc in hexanes to give product **2.18f** in 64 % yield (185 mg, 0.552 mmol) as a clear oil.

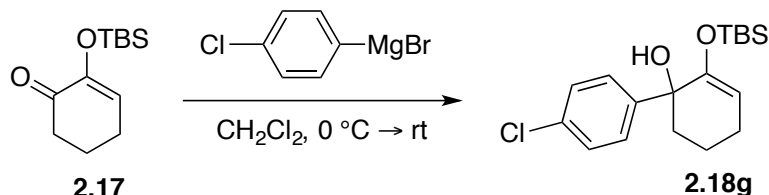
¹H NMR (400 MHz): δ = 7.39 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 5.04 (t, *J* = 4.0 Hz, 1H), 3.80 (s, 3H), 2.73 (s, 1H), 2.24 - 2.07 (m, 2H), 2.06 - 1.97 (m, 1H), 1.94 - 1.86 (m, 1H), 1.67 - 1.57 (m, 1H), 1.49 - 1.37 (m, 1H), 0.72 (s, 9H), 0.18 (s, 3H), 0.07 (s, 3H).

¹³C NMR (100 MHz): δ = 158.44, 150.61, 138.82, 127.31, 113.00, 104.80, 77.32, 77.00, 76.68, 75.06, 55.23, 39.51, 25.49, 24.35, 19.14, 17.90, -4.36, -4.96.

IR: *f*(cm⁻¹) = 3576, 2949, 2931, 2856, 1661, 1609, 1583, 1508, 1463, 1296, 1242, 1174, 1071, 916, 829, 778.

HRMS: (M+Na)⁺ = 357.1856 calculated for C₁₉H₃₀NaO₃Si; 357.1858 experimental.

6-((*tert*-butyldimethylsilyl)oxy)-4'-chloro-3,4-dihydro-[1,1'-biphenyl]-1(2*H*)-ol (2.18g)



Ketone **2.17** (300 mg, 1.33 mmol) was dissolved in dichloromethane (6.6 mL), and the solution was cooled to 0 °C. 4-Chlorophenylmagnesium bromide (1.98 mL, 1.0 M in THF) was then added dropwise. After stirring for 17 hours at room temperature, the reaction was quenched with DI water (5 mL) and then saturated NH₄Cl solution (5 mL). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes → 2% EtOAc in hexanes to give product **2.18g** in 55% yield (248 mg, 0.731 mmol) as a colorless oil.

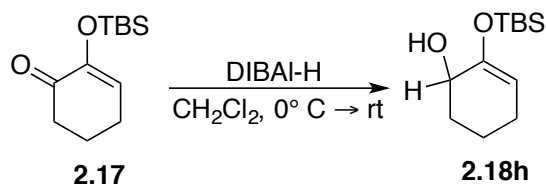
¹H NMR (500 MHz): δ = 7.43 - 7.40 (m, 2H), 7.29 - 7.26 (m, 2H), 5.07 (t, J = 3.7 Hz, 1H), 2.74 (s, 1H), 2.23 - 2.10 (m, 2H), 2.03 (ddd, J = 10.6, 10.4, 2.8 Hz, 1H), 1.86 (ddd, J = 13.1, 7.6, 3.0 Hz, 1H), 1.67 - 1.60 (m, 1H), 1.47 - 1.39 (m, 1H), 0.71 (s, 9H), 0.18 (s, 3H), 0.07 (s, 3H).

¹³C NMR (125 MHz): δ = 150.13, 145.34, 132.47, 127.78, 127.61, 105.21, 75.08, 39.46, 25.42, 24.28, 18.99, 17.87, -4.42, -4.97.

IR: f (cm⁻¹) = 3575, 2930, 2857, 1660, 1486 1471, 1400, 1361, 1337, 1241, 1208, 1175, 1140, 1090, 959, 915, 825, 809, 778, 672, 509.

HRMS: (M+Na)⁺ = 361.1361 calculated for C₁₈H₂₇ClO₂SiNa; 361.1372 experimental.

2-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-ol (2.18h)



Ketone **2.17** (300 mg, 1.33 mmol) was dissolved in dichloromethane (6.6 mL), and the solution was cooled to 0 °C. Diisobutylaluminium hydride (2.0 mL, 1.0 M in heptane) was then added dropwise. After stirring for 2 hours at room temperature, the reaction was quenched with DI water (5 mL) and then aqueous HCl solution (5 mL, 1.0 M). The aqueous layer was extracted with dichloromethane (4 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residual crude materials were then purified with column chromatography (buffered with 2% TEA) using 100% hexanes → 4% EtOAc in hexanes to give product **2.18h** in 54% yield (163 mg, 0.715 mmol) as a clear oil.

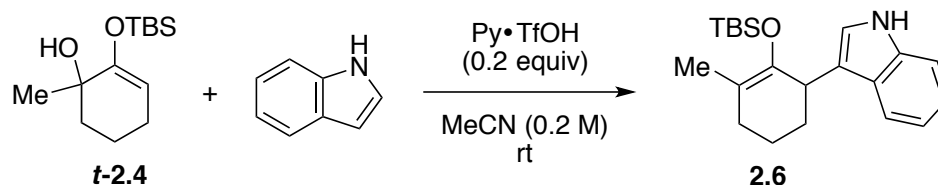
¹H NMR (500 MHz): δ = 4.90 (t, J = 4.0, 1H), 4.04 (t, J = 3.3 Hz, 1H), 2.25 (s, 1H), 2.11 - 2.03 (m, 1H), 2.01 - 1.86 (m, 2H), 1.74 - 1.60 (m, 2H), 1.55 - 1.47 (m, 1H), 0.94 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H).

¹³C NMR (125 MHz): δ = 150.67, 105.51, 77.25, 77.00, 76.75, 67.70, 31.12, 25.72, 24.16, 19.05, 18.06, -4.44, -4.53.

IR: f (cm⁻¹) = 3259, 2929, 1664, 1462, 1252, 1198, 1056, 993, 920, 894, 833, 777, 672.

HRMS: (M+H)⁺ 229.1618 calculated for C₁₂H₂₅O₂Si; 229.1625 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-indole (2.6)



Alcohol **t-2.4** (100 mg, 0.413 mmol) was dissolved in acetonitrile (2.0 mL). Indole (53 mg, 0.454 mmol) was then added, followed by pyridinium triflate (19 mg, 0.0825 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes → 2% EtOAc in hexanes to give compound **2.6** in 73% yield (104 mg, 0.304 mmol) as a colorless oil.

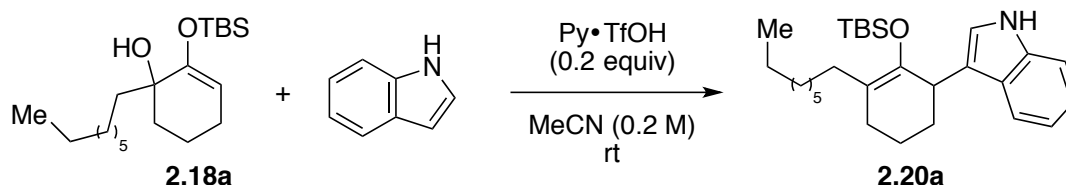
¹H NMR (500 MHz): δ = 7.91 (bs, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H), 3.71 (s, 1H), 2.15 - 2.07 (m, 1H), 2.06 - 1.93 (m, 3H), 1.91 - 1.85 (m, 1H), 1.72 (s, 3H), 1.60 - 1.44 (m, 2H), 0.78 (s, 9H), -0.01 (s, 3H), -0.11 (s, 3H).

¹³C NMR (125 MHz): δ = 143.84, 136.49, 127.07, 123.06, 121.44, 118.93, 118.88, 118.75, 112.65, 110.95, 37.02, 31.14, 30.55, 25.77, 19.13, 18.25, 16.88, -3.86, -4.04.

IR: f (cm⁻¹) = 3418, 3321, 2927, 1680, 1455, 1253, 1166, 1090, 1008, 939, 095, 828, 775, 735, 669, 582, 485.

HRMS: (M+H)⁺ = 342.2248 calculated for C₂₁H₃₂NOSi; 342.2257 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-octylcyclohex-2-en-1-yl)-1*H*-indole (2.20a)



Alcohol **2.18a** (100 mg, 0.294 mmol) was dissolved in acetonitrile (1.5 mL). Indole (40 mg, 0.339 mmol) was then added, followed by pyridinium triflate (14.11 mg, 0.0616 mmol). After stirring for 16 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 2% EtOAc in hexanes to give compound **2.20a** in 79% yield (79 mg, 0.179 mmol) as a colorless oil.

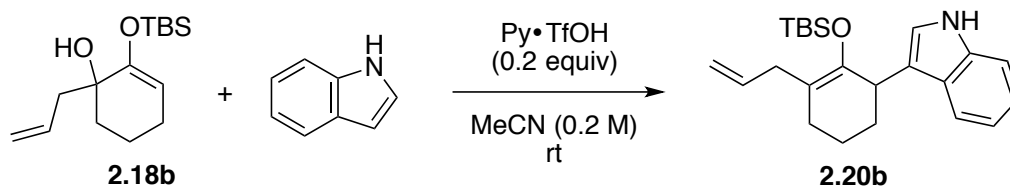
^1H NMR (500 MHz): δ = 7.89 (bs, 1H), 7.58 (d, J = 1.2 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.16 (t, J = 7.0 Hz, 1H), 7.09 (t, J = 7.1 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 3.69 (t, J = 4.5 Hz, 1H), 2.321 - 2.264 (m, 1H), 2.08 - 2.03 (m, 2H), 1.96 - 1.88 (m, 3H), 1.51 - 1.41 (m, 3H), 1.36 - 1.26 (m, 12H), 0.90 (t, J = 6.8 Hz, 3H), 0.77 (s, 9H), -0.01 (s, 3H), -0.19 (s, 3H).

^{13}C NMR (125 MHz): δ = 151.95, 104.65, 77.25, 77.00, 74.71, 45.56, 30.59, 28.70, 26.95, 26.83, 26.79, 25.87, 25.74, 24.28, 19.11, 18.14, -4.53, -4.73.

IR: $f(\text{cm}^{-1})$ = 2925, 2854, 1456, 1251, 1166, 907, 831, 776, 732, 670.

HRMS: $(\text{M}+\text{H})^+ = 440.3343$ calculated for $\text{C}_{28}\text{H}_{46}\text{NOSi}$; 440.3331 experimental.

3-(3-allyl-2-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)-1*H*-indole (2.20b)



Alcohol **2.18b** (146 mg, 0.544 mmol) was dissolved in acetonitrile (2.70 mL). Indole (70 mg, 0.598 mmol) was then added, followed by pyridinium triflate (25 mg, 0.109 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 5% EtOAc in hexanes to give compound **2.20b** in 72% yield (115 mg, 0.313 mmol) as a colorless oil.

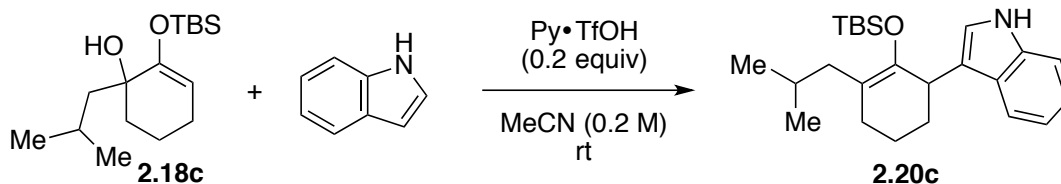
¹H NMR (500 MHz): δ = 7.91 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.1 Hz, 1H), 7.09 (t, J = 7.1 Hz, 1H), 6.94 (d, J = 1.7 Hz, 1H), 5.85 (ddt, J = 16.8, 10.0, 6.7 Hz, 1H), 5.04 (dd, J = 17.1, 10.1 Hz, 1H), 3.72 (s, 1H), 3.04 (dd, J = 14.2, 6.4 Hz, 1H), 2.79 (dd, J = 14.4, 7.0 Hz, 1H), 2.12 - 1.86 (m, 4H), 1.54 - 1.41 (m, 2H), 0.77 (s, 9H), -0.01 (s, 3H), -0.18 (s, 3H).

¹³C NMR (125 MHz): δ = 144.46, 137.20, 136.51, 126.97, 123.19, 121.51, 119.00, 118.83, 118.62, 114.55, 114.40, 110.99, 77.25, 77.20, 77.00, 76.75, 36.91, 35.10, 30.72, 27.78, 25.73, 18.79, 18.23, -3.91, -3.97.

IR: $f(\text{cm}^{-1})$ = 2928, 2855, 1673, 1456, 1360, 1310, 1251, 1224, 1199, 1164, 942, 910, 888, 829, 776, 738, 671, 581.

HRMS: $(\text{M}+\text{H})^+ = 368.2404$ calculated for $\text{C}_{23}\text{H}_{34}\text{NOSi}$; 368.2407 experimental.

3-(2-(((*tert*-butyldimethylsilyl)oxy)-3-isobutylcyclohex-2-en-1-yl)-1*H*-indole (2.20c)



Alcohol **2.18c** (50 mg, 0.176 mmol) was dissolved in acetonitrile (0.87 mL). Indole (23 mg, 0.193 mmol) was then added, followed by pyridinium triflate (8.1 mg, 0.0354 mmol). After

stirring for 5 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 2% EtOAc in hexanes to give compound **2.20c** in 83% yield (56 mg, 0.146 mmol) as a colorless oil.

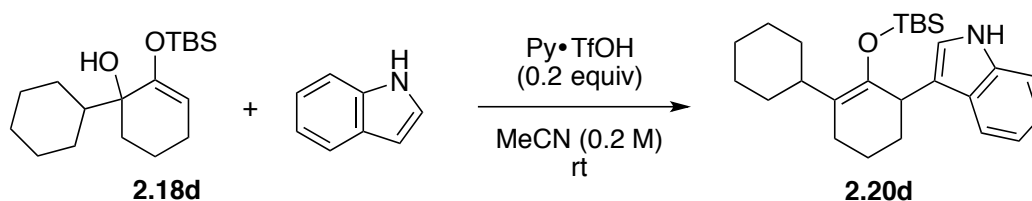
^1H NMR (500 MHz): δ = 7.89 (bs, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 8.1, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.96 (s, 1H), 3.73 (t, J = 4.4 Hz, 1H), 2.33 (dd, J = 13.0, 8.2 Hz, 1H), 2.08 - 2.02 (m, 2H), 1.99 - 1.80 (m, 3H), 1.76 (dd, J = 13.1, 6.9 Hz, 1H), 1.55 - 1.41 (m, 2H), 0.97 (d, J = 4.5 Hz, 6H), 0.79 (s, 9H), 0.01 (s, 3H), -0.20 (s, 3H).

^{13}C NMR (125 MHz): δ = 144.40, 136.49, 127.01, 123.24, 121.46, 118.79, 116.11, 110.99, 77.25, 77.00, 76.75, 39.44, 36.99, 30.71, 28.53, 26.66, 25.81, 22.97, 18.92, 18.22, -3.92.

IR: $f(\text{cm}^{-1})$ = 2952, 2928, 1710, 1671, 1456, 1361, 1252, 1225, 1161, 931, 907, 830, 775.

HRMS: $(\text{M}+\text{H})^+ = 384.2717$ calculated for $\text{C}_{24}\text{H}_{38}\text{NOSi}$; 384.2715 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-[1,1'-bi(cyclohexan)]-1-en-3-yl)-1*H*-indole (**2.20d**)



Alcohol **2.18d** (50 mg, 0.161 mmol) was dissolved in acetonitrile (0.8 mL). Indole (20.74 mg, 0.1771 mmol) was then added, followed by pyridinium triflate (7.37 mg, 0.0322 mmol). After stirring for 6 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 2% EtOAc in hexanes to give compound **2.20d** in 76% yield (50 mg, 0.122 mmol) as a colorless oil.

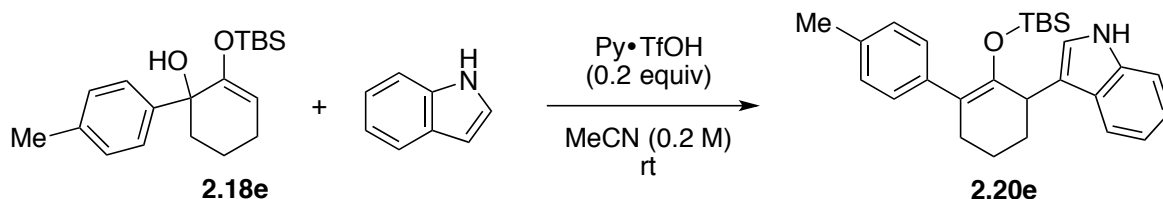
¹H NMR (500 MHz): δ = 7.88 (bs, 1H), 7.58 (d, J = 7.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.16 (t, J = 8.1 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.91 (d, J = 1.7 Hz, 1H), 3.68 (t, J = 4.4 Hz, 1H), 2.87 (t, J = 11.9 Hz, 1H), 2.06 - 1.95 (m, 2H), 1.91 - 1.84 (m, 2H), 1.80 - 1.73 (m, 2H), 1.71 - 1.59 (m, 2H), 1.54 - 1.49 (m, 1H), 1.47 - 1.41 (m, 2H), 1.37 - 1.25 (m, 4H), 1.21 - 1.12 (m, 1H), 0.78 (s, 9H), -0.00 (s, 3H), -0.17 (s, 3H).

¹³C NMR (125 MHz): δ = 142.31, 136.51, 127.01, 123.21, 121.59, 121.41, 119.06, 118.91, 118.87, 110.95, 37.08, 36.92, 31.31, 30.40, 30.19, 26.95, 26.87, 26.45, 25.78, 23.31, 18.83, 18.26, -3.91, -4.15.

IR: f (cm⁻¹) = 3416, 3304, 2925, 2850, 1660, 1445, 1308, 1250, 1138, 1092, 938, 829, 776, 740.

HRMS: (M+H)⁺ = 410.2874 calculated for C₂₆H₄₀NOSi; 410.2862 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-4'-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1H-indole (2.20e)



Alcohol **2.18e** (50 mg, 0.157 mmol) was dissolved in acetonitrile (0.8 mL). Indole (20 mg, 0.173 mmol) was then added, followed by pyridinium triflate (7.2 mg, 0.0313 mmol). After stirring for 168 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes → 2% EtOAc in hexanes to give compound **2.20e** in 75% yield (49 mg, 0.118 mmol) as a colorless oil.

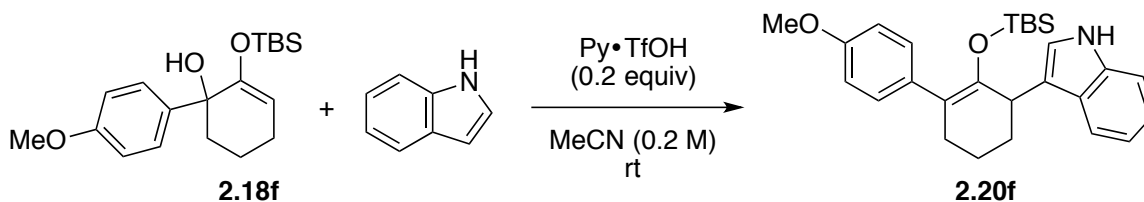
¹H NMR (400 MHz): δ = 7.94 (bs, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 7.15 - 7.10 (m, 4H), 3.78 (t, J = 4.9 Hz, 1H), 2.67 - 2.57 (m, 1H), 2.35 (s, 3H), 2.31 - 2.22 (m, 1H), 2.14 - 1.95 (m, 2H), 1.76 - 1.58 (m, 2H), 0.55 (s, 9H), -0.17 (s, 3H), -0.42 (s, 3H).

¹³C NMR (100 MHz): δ = 145.98, 138.97, 136.51, 135.09, 128.75, 128.35, 126.99, 122.91, 121.54, 119.05, 119.02, 118.97, 117.85, 111.02, 77.32, 77.00, 76.68, 37.94, 31.18, 30.34, 25.47, 21.15, 19.81, 17.94, -4.33, -4.45.

IR: f (cm⁻¹) = 3418, 2927, 2855, 1511, 1455, 1251, 1157, 909, 828, 777, 734, 579, 494.

HRMS: (M+H)⁺ = 418.2561 calculated for C₂₇H₃₆NOSi; 418.2562 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-4'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1H-indole (2.20f)



Alcohol **2.28f** (67 mg, 0.201 mmol) was dissolved in acetonitrile (1.0 mL). Indole (26 mg, 0.222 mmol) was then added, followed by pyridinium triflate (9.2 mg, 0.0402 mmol). After stirring for 22 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 20% DCM in hexanes to give compound **2.20f** in 75% yield (66 mg, 0.151 mmol) as a colorless oil.

¹H NMR (400 MHz): δ = 7.94 (bs, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 8.3 Hz, 3H), 7.19 (t, J = 7.1 Hz, 1H), 7.14 - 7.07 (m, 2H), 6.86 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 3.77 (t, J = 5.0 Hz,

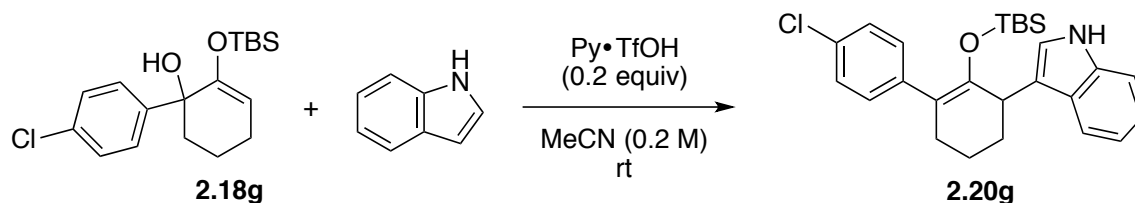
1H), 2.66 - 2.55 (m, 1H), 2.30 - 2.21 (m, 1H), 2.13 - 1.95 (m, 2H), 1.76 - 1.57 (m, 1H), 0.54 (s, 9H), -0.17 (s, 3H), -0.41 (s, 3H).

¹³C NMR (100 MHz): δ = 157.59, 145.87, 136.52, 134.46, 129.89, 126.99, 122.87, 121.55, 119.07, 119.02, 117.41, 113.13, 111.02, 77.32, 77.00, 76.68, 55.28, 37.98, 31.23, 30.39, 25.49, 19.89, 17.96, -4.31, -4.41.

IR: f (cm⁻¹) = 3056, 2947, 2931, 2854, 1648, 1607, 1573, 1455, 1337, 1288, 1242, 1177, 1131, 1157, 1089, 988, 909, 860, 777, 732, 668.

HRMS: (M+H)⁺ = 434.2510 calculated for C₂₇H₃₆NO₂Si; 434.2503 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-4'-chloro-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1H-indole (2.20g)



Alcohol **2.28g** (75 mg, 0.221 mmol) was dissolved in acetonitrile (1.1 mL). Indole (29 mg, 0.243 mmol) was then added, followed by pyridinium triflate (10.1 mg, 0.0442 mmol). After stirring for >500 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes → 20% DCM in hexanes to give compound **2.20g** in 50% yield (46 mg, 0.105 mmol) as a colorless oil.

¹H NMR (500 MHz): δ = 7.95 (bs, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.37 (t, J = 7.9 Hz, 3H), 7.27 (d, J = 9.8 Hz, 2H), 7.20 (t, J = 7.1 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 7.08 (s, 1H), 3.78 (t, J = 4.8 Hz,

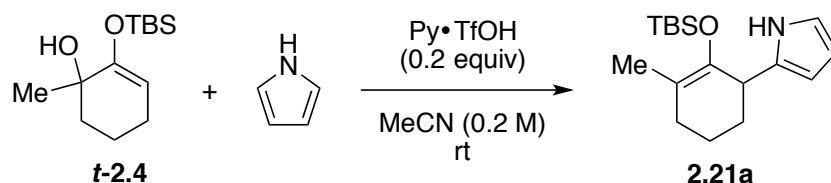
1H), 2.66 - 2.54 (m, 1H), 2.29 - 2.21 (m, 1H), 2.12 - 1.96 (m, 2H), 1.75 - 1.58 (m, 2H), 0.54 (s, 9H), -0.17 (s, 3H), -0.39 (s, 3H).

¹³C NMR (125 MHz): δ = 146.98, 140.36, 136.50, 131.11, 130.23, 127.78, 126.87, 122.82, 121.65, 119.11, 118.94, 118.67, 116.76, 111.07, 77.25, 77.00, 76.75, 37.85, 31.03, 30.06, 25.41, 19.65, 17.92, -4.23, -4.32.

IR: $f(\text{cm}^{-1})$ = 2927, 2855, 1644, 1489.

HRMS: $(\text{M}+\text{H})^+ = 438.2014$ calculated for $\text{C}_{26}\text{H}_{33}\text{ClNOSi}$; 438.2016 experimental.

2-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1*H*-pyrrole (2.21a)



Alcohol **t-2.4** (75 mg, 0.309 mmol) was dissolved in acetonitrile (1.5 mL). Pyrrole (24 μL , 0.340 mmol) was then added, followed by pyridinium triflate (14 mg, 0.0618 mmol). After stirring for 3 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 25% DCM in hexanes to give compound **2.21a** in 39% yield (35 mg, 0.119 mmol) as a brown oil.

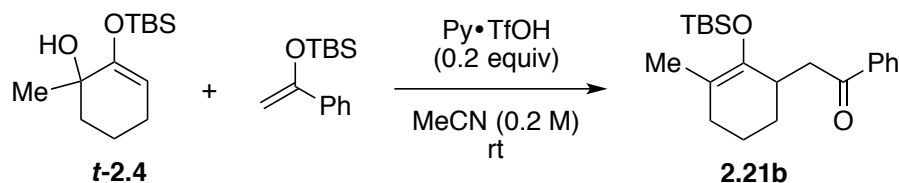
¹H NMR (500 MHz): δ = 8.42 (bs, 1H), 6.65 (dd, J = 3.0, 1.4 Hz, 1H), 6.24 - 6.11 (m, 1H), 5.94 (s, 1H), 3.44 (s, 1H), 2.18 - 2.01 (m, 1H), 2.05 - 1.89 (m, 2H), 1.67 (s, 3H), 1.59 - 1.50 (m, 2H), 0.93 (s, 6H), 0.10 (s, 3H), 0.04 (s, 3H).

¹³C NMR (125 MHz): δ = 143.11, 134.38, 115.45, 114.14, 107.92, 104.18, 38.51, 31.12, 30.54, 25.82, 19.45, 18.22, 16.94, -4.06, -4.09.

IR: f (cm^{-1}) = 3460, 2928, 2856, 1679, 1470, 1341, 1314, 1252, 1164, 1119, 1090, 1026, 1005, 936, 911, 883, 776, 702, 667.

HRMS: $(\text{M}+\text{H})^+ = 292.2091$ calculated for $\text{C}_{17}\text{H}_{30}\text{NOSi}$; 292.2085 experimental.

2-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-1-phenylethan-1-one (2.21b)



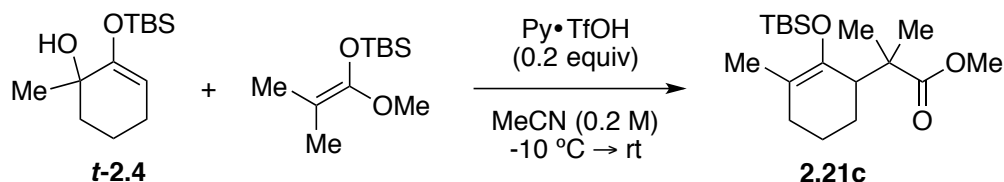
Alcohol **t-2.4** (118 mg, 0.487 mmol) was dissolved in acetonitrile (2.4 mL). Trimethyl((1-phenylvinyl)oxy)silane (200 μl , 0.973 mmol) was then added, followed by pyridinium triflate (22 mg, 0.097 mmol). After stirring for 4 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 15% EtOAc in hexanes to give compound **2.21b** in 86% yield (144 mg, 0.417 mmol) as a colorless oil.

^1H NMR (500 MHz): δ = 7.98 (d, J = 7.65 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 3.32 (dd, J = 17.4, 2.3 Hz, 1H), 3.05 (dd, J = 17.5, 10.85 Hz, 1H), 2.87 (bs, 1H), 2.06 - 1.90 (m, 2H), 1.89 - 1.79 (m, 1H), 1.62 (s, 3H), 1.54 - 1.39 (m, 3H), 0.93 (s, 9H), 0.11 (d, J = 11.7 Hz, 6H).

^{13}C NMR (125 MHz): δ = 199.84, 144.61, 137.51, 132.89, 128.53, 127.97, 113.77, 99.97, 77.25, 77.00, 76.75, 41.15, 34.88, 30.67, 28.99, 25.93, 19.67, 18.28, 17.12, -3.73, -4.32.

2.21b is known see: Stepherson J. R.; Fronczek. F. R.; Kartika R. *Chem. Commun.* **2016**, 52, 2300.

Methyl 2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)-2-methylpropanoate
(2.21c)



Alcohol **t-2.4** (66 mg, 0.272 mmol) was dissolved in acetonitrile (1.4 mL). After cooling the solution to -10 °C, dimethylketene methyl trimethylsilyl acetal (166 μ L, 0.817 mmol) was then added, followed by pyridinium triflate (12 mg, 0.054 mmol). After stirring for 4 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 10% EtOAc in hexanes to give compound **2.21c** in 47% yield (42 mg, 0.128 mmol) as a colorless oil.

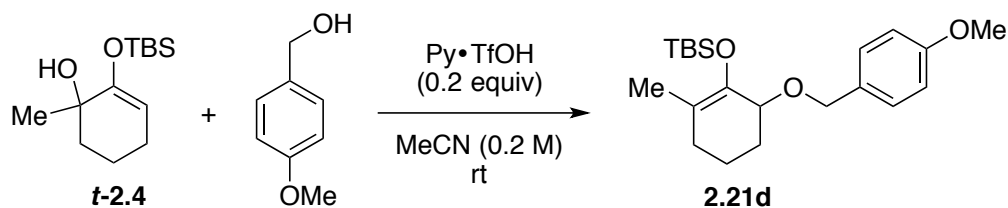
^1H NMR (400 MHz): δ = 3.65 (s, 3H), 2.56 (bs, 1H), 1.91 (bs, 2H), 1.69 - 1.60 (m, 2H), 1.46 (s, 3H), 1.35 - 1.33 (m, 2H), 1.30 (s, 3H), 1.09 (s, 3H), 0.95 (s, 9H), 0.14 (s, 3H), 0.01 (3H).

^{13}C NMR (100 MHz): δ = 178.57, 144.00, 116.55, 77.32, 77.00, 76.68, 51.55, 46.84, 44.92, 30.59, 27.38, 26.24, 26.01, 21.66, 21.07, 18.35, 17.85, -2.23, -4.35.

IR: $f(\text{cm}^{-1})$ = 2929, 2858, 1732, 1672, 1471, 1388, 1361, 1250, 1157, 1128, 1085, 1007, 911, 830, 776, 676.

HRMS: $(\text{M}+\text{H})^+ = 327.2355$ calculated for $\text{C}_{18}\text{H}_{35}\text{O}_3\text{Si}$; 327.2359 experimental.

***tert*-butyl((6-((4-methoxybenzyl)oxy)-2-methylcyclohex-1-en-1-yl)oxy)dimethylsilane
(2.21d)**



Alcohol **t-2.4** (75 mg, 0.309 mmol) was dissolved in acetonitrile (1.5 mL). 5-methoxybenzyl alcohol (76 μ L, 0.619 mmol) was then added, followed by pyridinium triflate (14 mg, 0.0618 mmol). After stirring for 73 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 60% DCM in hexanes to give compound **2.21d** in 64% yield (72 mg, 0.199 mmol) as a colorless oil.

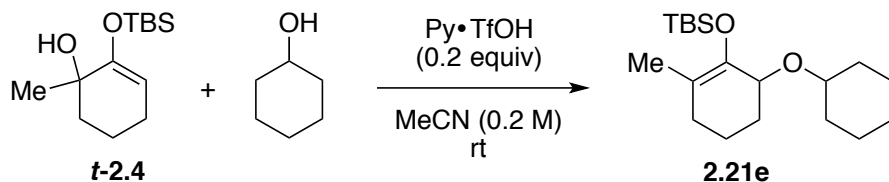
^1H NMR (400 MHz): δ = 7.28 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.52 (d, J = 11.1 Hz, 1H), 4.40 (d, J = 11.1 Hz, 1H), 3.79 (s, 3H), 2.08 - 1.91 (m, 3H), 1.84 - 1.69 (m, 1H), 1.61 (s, 3H), 1.58 - 1.44 (m, 2H), 0.95 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (125 MHz): δ = 158.87, 142.88, 131.36, 129.17, 116.93, 113.57, 77.25, 77.00, 76.75, 75.14, 70.04, 55.26, 30.68, 27.87, 25.99, 18.41, 17.75, 16.97, -3.83, -3.85.

IR: f (cm^{-1}) = 2929, 1613, 1513, 1462, 1245, 1172, 1076, 1076, 914, 828, 776, 672.

HRMS: $(\text{M}+\text{H})^+ = 362.2350$ calculated for $\text{C}_{21}\text{H}_{34}\text{O}_3\text{Si}$; 363.2359 experimental.

***tert*-butyl((6-(cyclohexyloxy)-2-methylcyclohex-1-en-1-yl)oxy)dimethylsilane (2.21e)**



Alcohol **t-2.4** (93 mg, 0.384 mmol) was dissolved in acetonitrile (2.0 mL). Cyclohexanol (80 μ L, 0.767 mmol) was then added, followed by pyridinium triflate (17 mg, 0.0767 mmol). After stirring for 26 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 5% EtOAc in hexanes to give compound **2.21e** in 50% yield (62 mg, 0.191 mmol).

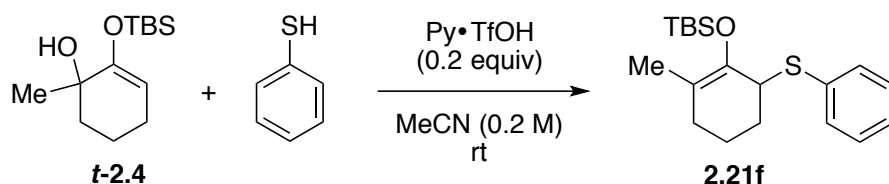
^1H NMR (500 MHz) δ = 3.77 (s, 1H), 3.35 - 3.29 (m, 1H), 2.01 - 1.84 (m, 6H), 1.79 - 1.70 (m, 3H), 1.61 - 1.42 (m, 7H), 1.35 - 1.09 (m, 6H), 0.96 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (125 MHz): δ =143.38, 116.62, 77.25, 77.00, 76.75, 75.89, 72.71, 34.23, 32.88, 30.76, 29.30, 25.95, 25.79, 24.92, 24.81, 18.31, 17.51, 17.33, -3.19, -3.73.

IR: $f(\text{cm}^{-1})$ = 2929, 2855, 1678, 1450, 1380, 1351, 1251, 1224, 1173, 1078, 1023, 986, 952, 920, 830, 776, 675.

HRMS: $(\text{M} + \text{H})^+$ 325.2557 calculated for $\text{C}_{19}\text{H}_{37}\text{O}_2\text{Si}$; 325.2569 experimental.

***tert*-butyldimethyl((2-methyl-6-(phenylthio)cyclohex-1-en-1-yl)oxy)silane (2.21f)**



Alcohol **t-2.4** (75 mg, 0.309 mmol) was dissolved in acetonitrile (1.5 mL). Thiophenol (35 μ L, 0.340 mmol) was then added, followed by pyridinium triflate (14 mg, 0.0618 mmol). After stirring for 8 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with

column chromatography using 100% hexanes \rightarrow 20% DCM in hexanes to give compound **2.21f** in 90% yield (94 mg, 0.280 mmol) as a colorless oil.

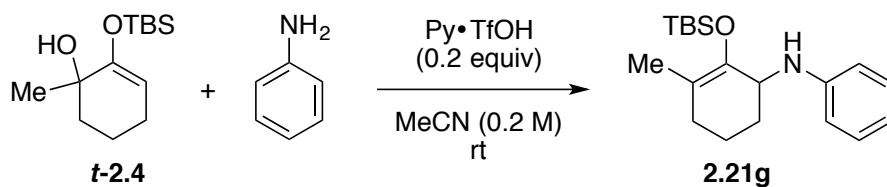
^1H NMR (400 MHz) δ = 7.43 - 7.36 (m, 2H), 7.32 - 7.25 (m, 2H), 7.22 - 7.17 (m, 1H), 3.71 (s, 1H), 2.15 - 1.76 (m, 5H), 1.64 (s, 3H), 1.58 - 1.51 (m, 1H), 0.99 (s, 9H), 0.17 (d, J = 7.5 Hz, 6H).

^{13}C NMR (125 MHz): δ = 140.95, 136.65, 131.09, 128.73, 126.32, 116.74, 49.18, 30.30, 29.86, 25.95, 18.43, 18.17, 17.23, -3.68, -3.82.

IR: $f(\text{cm}^{-1})$ = 3073, 2856, 1672, 1462, 1438, 1313, 1251, 1207, 1121, 1088, 942, 856, 828, 755, 690 588.

HRMS: $(\text{M}+\text{H})^+$ 335.1859 calculated for $\text{C}_{19}\text{H}_{31}\text{OSSi}$; 335.1866 experimental.

***N*-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclohex-2-en-1-yl)aniline (**2.21g**)**



Alcohol ***t*-2.4** (113 mg, 0.466 mmol) was dissolved in acetonitrile (2.3 mL). Aniline (50 μL , 0.513 mmol) was then added, followed by pyridinium triflate (21 mg, 0.0932 mmol). After stirring for 24 hours at room temperature, the reaction was quenched with triethylamine (0.4 mL) and then concentrated under reduced pressure. The crude mixture was then directly purified with column chromatography using 100% hexanes \rightarrow 5% EtOAc in hexanes to give compound **2.21g** in 32% yield (48 mg, 0.151 mmol).

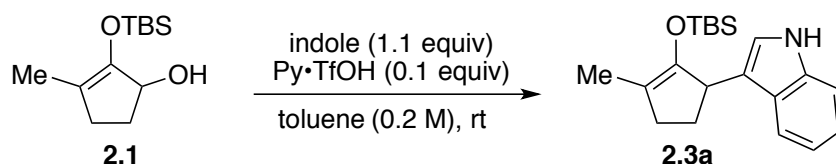
^1H NMR (500 MHz): δ = 7.16 (t, J = 8.5 Hz, 2H), 6.67 (t, J = 8.3 Hz, 1H), 6.57 (d, J = 8.5 Hz, 2H), 3.95 (s, 1H), 3.84 (s, 2H), 2.09 - 1.89 (m, 4H), 1.69 (s, 3H), 1.66 (s, 6H), 1.64 - 1.51 (m, 2H), 0.91 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H).

¹³C NMR (125 MHz): δ = 147.47, 142.56, 129.21, 116.79, 115.85, 112.78, 99.96, 77.25, 77.00, 76.75, 51.58, 30.44, 29.69, 28.75, 25.87, 18.35, 18.16, 16.83, -3.92, -4.00.

IR: f (cm⁻¹) = 2927, 2856, 1680, 1601, 1501, 1471, 1428, 1346, 1309, 1250, 1169, 1110, 1074, 1006, 934, 917, 828, 776, 745, 690, 672, 603, 506.

HRMS: (M+H)⁺ = 318.2275 calculated for C₁₉H₃₁NOSi, 318.2269 experimental.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1*H*-indole (2.3a)

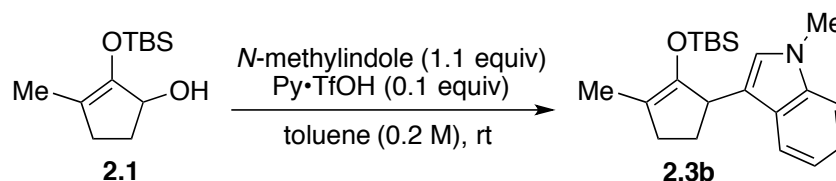


Alcohol **2.1** (145 mg, 0.635 mmol) was dissolved in toluene (3.2 mL). Indole (82 mg, 0.698 mmol) was then added, followed by pyridinium triflate (15 mg, 0.064 mmol). The reaction was stirred for 4 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 95: 5 hexanes: EtOAc to give product **2.3a** in 85% yield (177 mg, 0.540 mmol) as a clear oil.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.86 (s, 1H), 7.65 (d, J = 9.7 Hz, 1H), 7.35 (d, J = 8.2 Hz, 1H), 7.21 (t, J = 7.2 Hz, 1H), 7.14 (t, J = 7.1 Hz, 1H), 7.00 (s, 1H), 4.03 (m, 1H), 2.49 – 2.35 (m, 2H), 2.34 – 2.23 (m, 1H), 1.92 (m, 1H), 1.75 (s, 3H), 0.88 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ (ppm) = 147.87, 136.51, 127.13, 121.54, 119.35, 119.27, 118.90, 113.54, 110.93, 76.75, 42.52, 32.27, 29.80, 25.64, 18.11, 12.46, -4.19, -4.26.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1-methyl-1*H*-indole (2.3b)

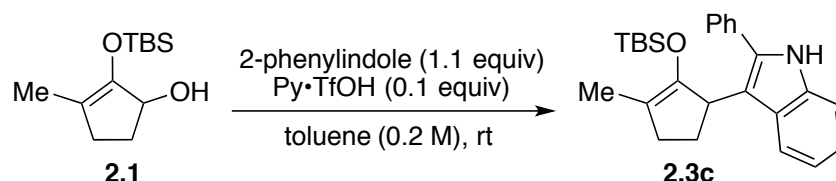


Alcohol **2.1** (175 mg, 0.327 mmol) was dissolved in toluene (1.6 mL). *N*-methylindole (45 μ L, 0.360 mmol) was then added, followed by pyridinium triflate (7 mg, 0.032 mmol). The reaction was stirred for 9 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 88: 12 hexanes: CH₂Cl₂ to give product **2.3b** in 56% yield (63 mg, 0.184 mmol) as a clear oil.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.58 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.20 (t, *J* = 7.1 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.85 (s, 1H), 3.99 – 3.94 (m, 1H), 3.73 (s, 3H), 2.42 – 2.30 (m, 2H), 2.28 – 2.21 (m, 1H), 1.88 – 1.80 (m, 1H), 1.69 (s, 3H), 0.82 (s, 9H), -0.05 (s, 3H), -0.11 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 148.01, 137.23, 127.57, 126.38, 121.08, 119.42, 118.30, 117.81, 113.43, 108.95, 42.39, 32.51, 32.23, 30.08, 25.65, 18.14, 12.45, -4.16, -4.23.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-2-phenyl-1*H*-indole (2.3c)



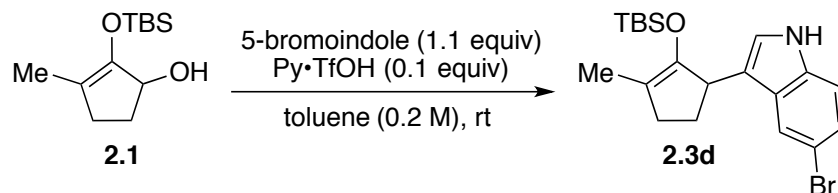
Alcohol **2.1** (111 mg, 0.489 mmol) was dissolved in toluene (2.4 mL). 2-Phenylindole (104 mg, 0.538 mmol) was then added, followed by pyridinium triflate (11 mg, 0.048 mmol). The

reaction was stirred for 3 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 99:1 hexanes: EtOAc to give product **2.3c** in 89% yield (176 mg, 0.432 mmol) as a brown oil.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.92 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 7.0 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.37 (d, J = 7.4 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8.1 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 4.18 4.21 – 4.15 (m, 1H), 2.53 – 2.44 (m, 1H), 2.43 – 2.33 (m, 2H), 2.21 – 2.11 (m, 1H), 1.68 (s, 3H), 0.64 (s, 9H), -0.35 (s, 3H), -0.45 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 147.98, 136.22, 135.15, 133.32, 128.60, 128.58, 128.09, 127.55, 121.91, 120.80, 119.24, 115.53, 112.44, 42.32, 32.84, 29.02, 25.46, 18.01, 12.71, -4.50, -4.68.

5-bromo-3-(2-(((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1*H*-indole (2.3d)

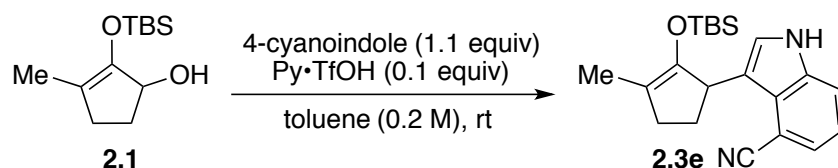


Alcohol **2.1** (112 mg, 0.490 mmol) was dissolved in toluene (2.5 mL). 5-Bromoindole (106 mg, 0.539 mmol) was then added, followed by pyridinium triflate (11 mg, 0.049 mmol). The reaction was stirred for 2 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 95:5 hexanes: EtOAc to give product **2.3d** in 70% yield (138 mg, 0.339 mmol) as a clear oil.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.92 (s, 1H), 7.71 (s, 1H), 7.26 – 7.23 (m, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.99 (d, *J* = 3.1 Hz, 1H), 3.95 – 3.88 (m, 1H), 2.42 – 2.23 (m, 3H), 1.87 – 1.77 (m, 1H), 1.69 (s, 3H), 0.82 (s, 9H), -0.03 (s, 3H), -0.09 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ (ppm) = 147.39, 135.08, 128.91, 124.40, 122.73, 121.94, 119.16, 113.89, 112.34, 112.27, 42.35, 32.20, 29.73, 25.60, 25.34, 18.07, 12.43, -4.20, -4.25.

3-(2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1*H*-indole-4-carbonitrile
(2.3e)

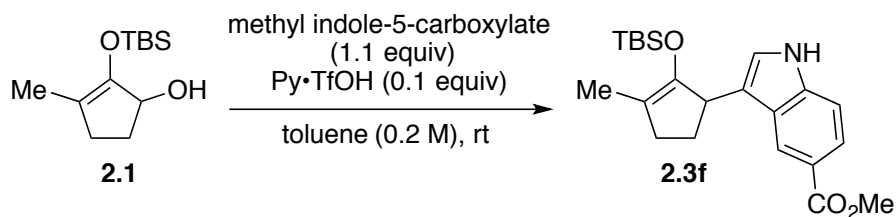


Alcohol **2.1** (125 mg, 0.547 mmol) was dissolved in toluene (2.7 mL). 4-Cyanoindole (85 mg, 0.601 mmol) was then added, followed by pyridinium triflate (12 mg, 0.054 mmol). The reaction was stirred for 7 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 95:5 hexanes : EtOAc to give product **2.3e** in 65% yield (63 mg, 0.184 mmol) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 8.30 (s, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 4.46 – 4.34 (m, 1H), 2.68 – 2.50 (m, 1H), 2.24 (t, *J* = 7.0 Hz, 2H), 1.77 – 1.70 (m, 1H), 1.69 (s, 3H), 0.84 (s, 9H), 0.06 (s, 3H), -0.10 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 146.73, 136.58, 126.87, 126.14, 124.87, 121.10, 119.63, 119.33, 115.83, 114.91, 101.86, 41.61, 31.69, 31.41, 25.61, 18.08, 12.27, -4.26, -4.33.

Methyl 3-(2-(((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1*H*-indole-5-carboxylate (2.3f)



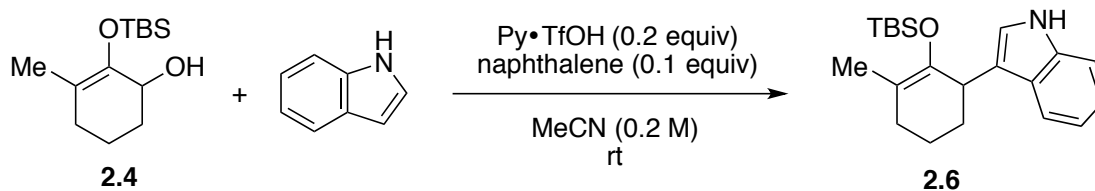
Alcohol **2.1** (112 mg, 0.490 mmol) was dissolved in toluene (2.4 mL). methyl indole-5-carboxylate (91 mg, 0.520 mmol) was then added, followed by pyridinium triflate (11 mg, 0.047 mmol). The reaction was stirred for 3 hours when it reached completion as monitored by TLC. The mixture was then concentrated in *vacuo* to obtain crude material, which was purified by flash column chromatography with 95:5 hexanes : EtOAc to give product **2.3f** in 83% yield (151 mg, 0.392 mmol) as a clear oil.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 8.36 (s, 1H), 8.12 (s, 1H), 7.88 (d, *J* = 6.2, 1.6 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.05 (s, 1H), 4.04 – 3.97 (m, 1H), 3.93 (s, 3H), 2.48 – 2.21 (m, 3H), 1.81 (m, 1H), 1.69 (s, 3H), 0.81 (s, 9H), -0.03 (s, 3H), -0.11 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ (ppm) = 147.38, 139.08, 126.87, 123.12, 122.63, 122.37, 121.11, 121.01, 114.06, 110.56, 51.79, 42.26, 32.20, 29.99, 25.60, 18.09, 12.40, -4.20, -4.26.

HPLC Analyses

Table 2.1 (Entry 5)

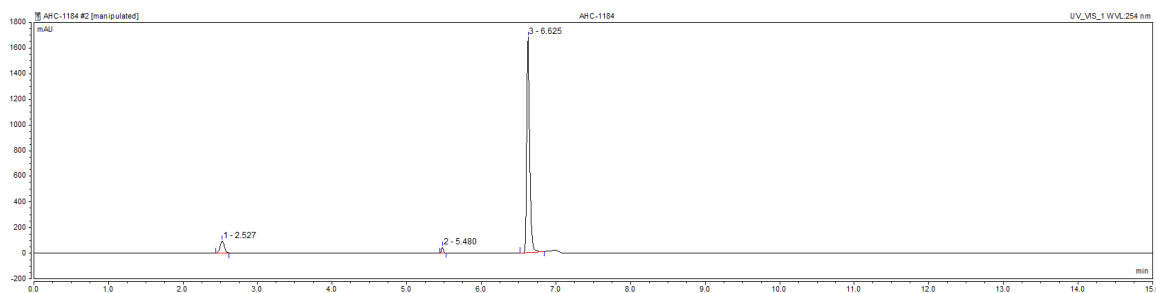


Alcohol **2.4** (528 mg, 2.18 mmol) was dissolved in acetonitrile (10.9 mL). Indole (280 mg, 2.39 mmol) and naphthalene (28 mg, 0.218 mmol) were then added, followed by pyridinium triflate (100 mg, 0.435 mmol). The reaction progress was monitored by HPLC every two hours by diluting a 50 μ L aliquot of the reaction mixture to 1 mL solution of 1% triethylamine in hexanes. This dilute sample was injected through a Hypersil GOLD Silica column (150 x 4.6 mm) using a linear gradient of 0-3% isopropanol in hexanes over 15 minutes at a flow rate of 1mL/min. The UV detector was set at 254 nm.

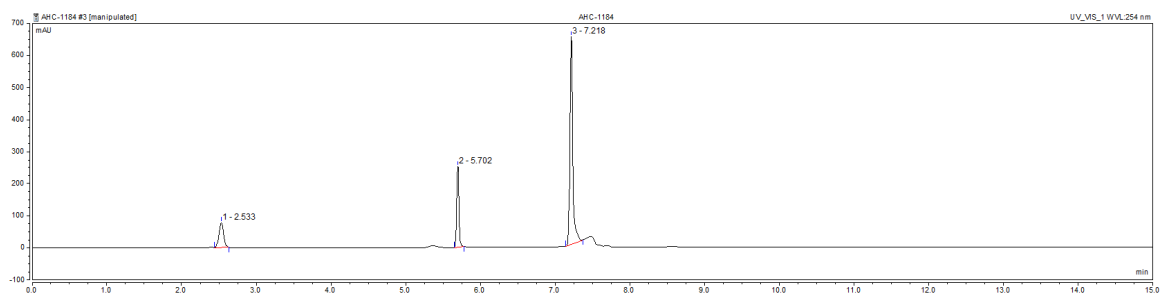
Table C.1 (Entry 5) Kinetic Profile of Table 2.1 Entry 5

Time (h)	Naphthalene		Silylenol Ether 2.6		2.6/ Naphthlene
	Retention Time (min)	Area	Retention time (min)	Area	
0	2.53	6.58	5.48	1.37	0.02
2	2.53	5.67	5.70	8.33	0.15
4	2.43	6.40	5.28	17.33	0.27
6	2.40	5.84	5.28	21.83	0.37
8	2.43	4.97	6.14	23.32	0.47

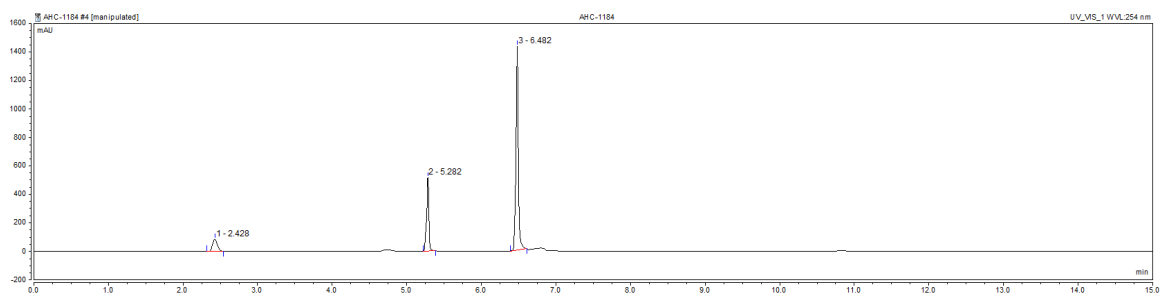
Time 0 h



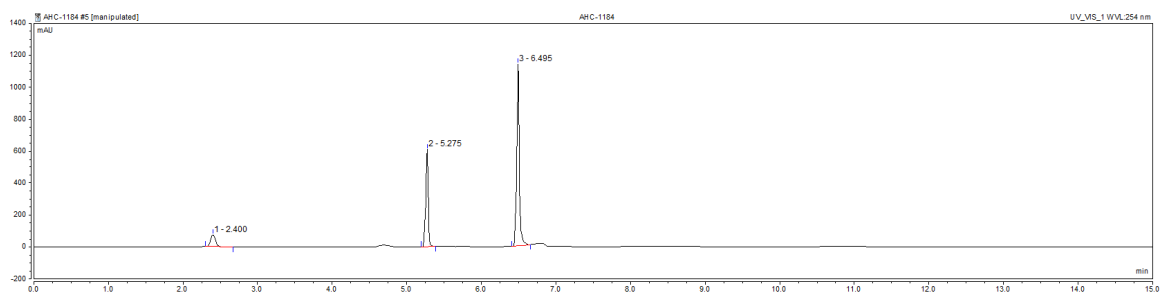
Time 2 h



Time 4 h



Time 6 h



Time 8 h

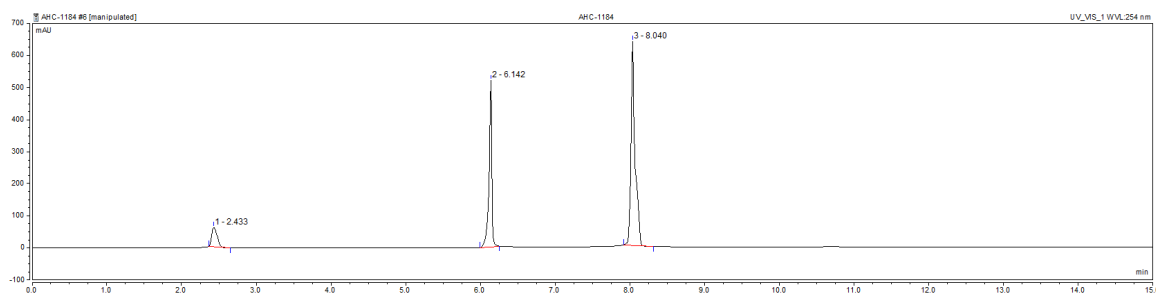
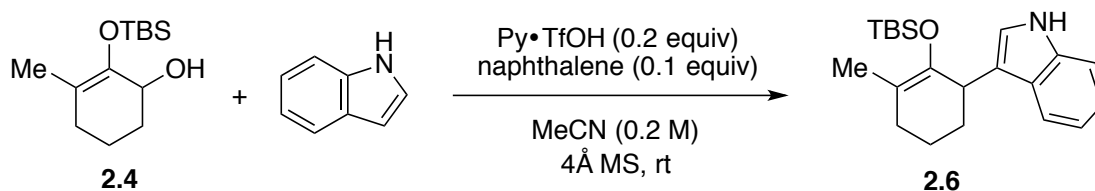


Table 2.1 (Entry 10)

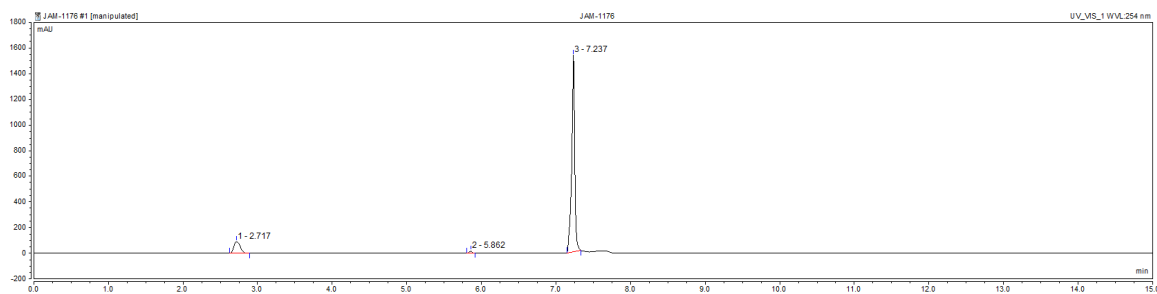


Alcohol **2.4** (526 mg, 2.17 mmol) was dissolved in acetonitrile (10.8 mL). Indole (279 mg, 2.38 mmol), naphthalene (28 mg, 0.217 mmol), and 4Å molecular sieves (577 mg) were then added, followed by pyridinium triflate (99 mg, 0.434 mmol). The reaction progress was monitored by HPLC every two hours by diluting a 50 µL aliquot of the reaction mixture to 1 mL solution of 1% triethylamine in hexanes. This dilute sample was injected through a Hypersil GOLD Silica column (150 x 4.6 mm) using a linear gradient of 0-3% isopropanol in hexanes over 15 minutes at a flow rate of 1mL/min. The UV detector was set at 254 nm.

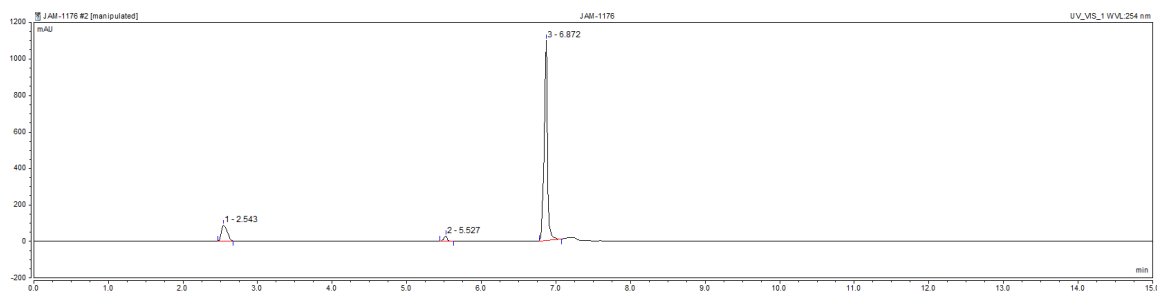
Table C.2. Kinetic Profile of Table 2.1 (Entry 10)

Time (h)	Naphthalene		Silylenol Ether 2.6		2.6/ Naphthlene
	Retention Time (min)	Area	Retention time (min)	Area	
0	2.72	8.66	5.86	0.60	0.01
2	2.54	7.97	5.53	1.31	0.02
4	2.56	6.55	5.57	1.27	0.02
6	2.65	7.95	5.64	1.87	0.02
8	2.23	7.82	5.05	1.83	0.02

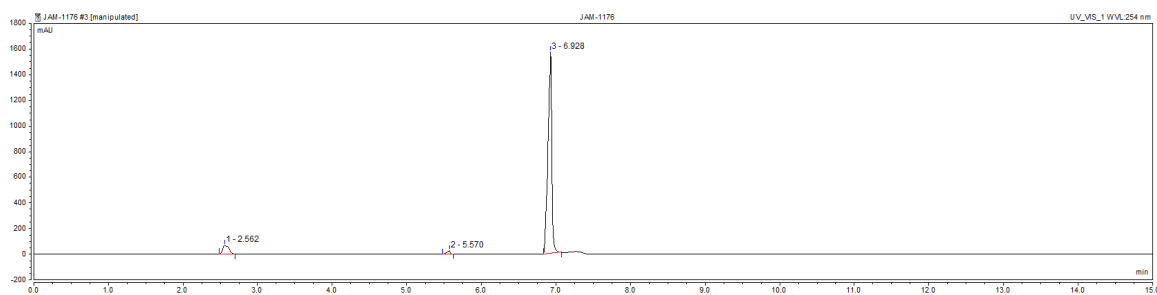
Time 0 h



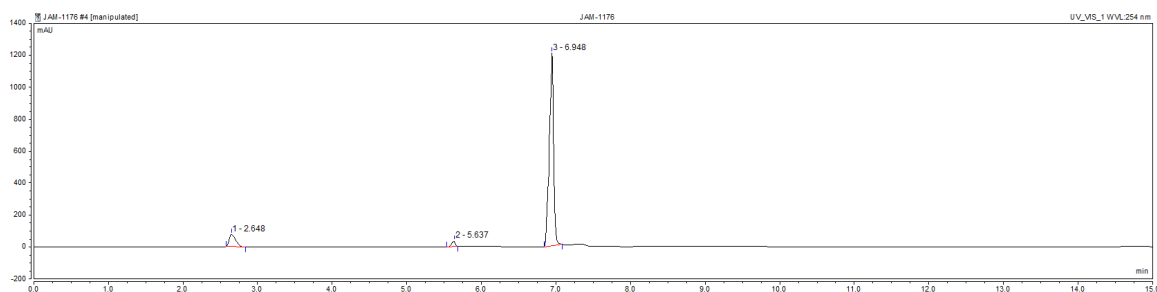
Time 2 h



Time 4 h



Time 6 h



Time 8 h

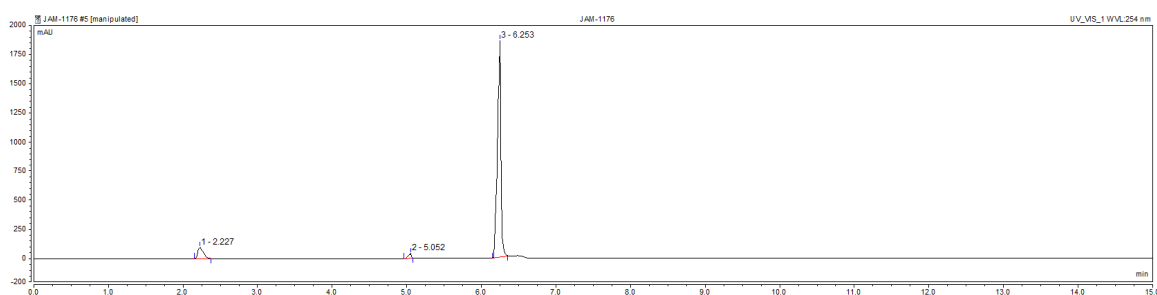
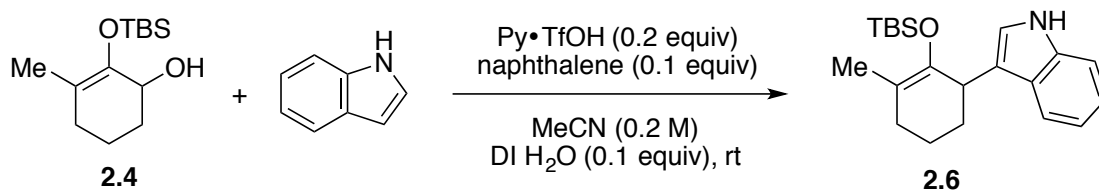


Table 2.1 (Entry 11)

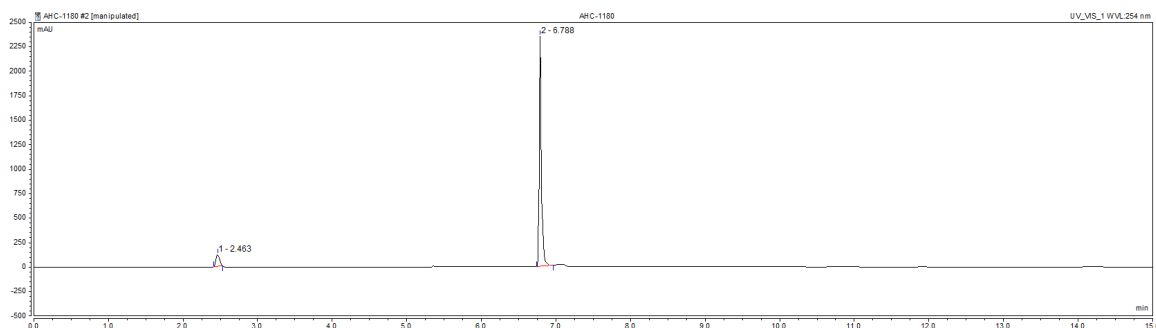


Alcohol **2.4** (502 mg, 2.07 mmol) was dissolved in acetonitrile (10.4 mL). Indole (266 mg, 2.27 mmol), naphthalene (26 mg, 0.207 mmol), and DI water (4.0 μ L, 0.207 mmol) were then added, followed by pyridinium triflate (95 mg, 0.414 mmol). The reaction progress was monitored by HPLC every two hours by diluting a 50 μ L aliquot of the reaction mixture to 1 mL solution of 1% triethylamine in hexanes. This dilute sample was injected through a Hypersil GOLD Silica column (150 x 4.6 mm) using a linear gradient of 0-3% isopropanol in hexanes over 15 minutes at a flow rate of 1mL/min. The UV detector was set at 254 nm.

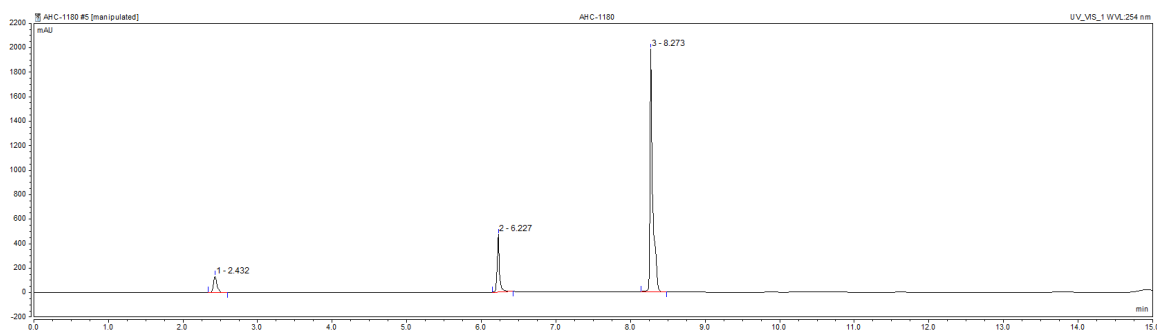
Table C.3 Kinetic Profile of Table 2.1 (Entry 11)

Time (h)	Naphthalene		Silylenol Ether 2.6		2.6/ Naphthlene
	Retention Time (min)	Area	Retention time (min)	Area	
0	2.46	6.67	0.00	0.00	0.00
2	2.43	7.37	6.23	17.18	0.23
4	2.31	7.68	4.99	24.19	0.32
6	2.27	7.59	4.96	26.17	0.34
8	2.26	7.24	4.88	28.44	0.39

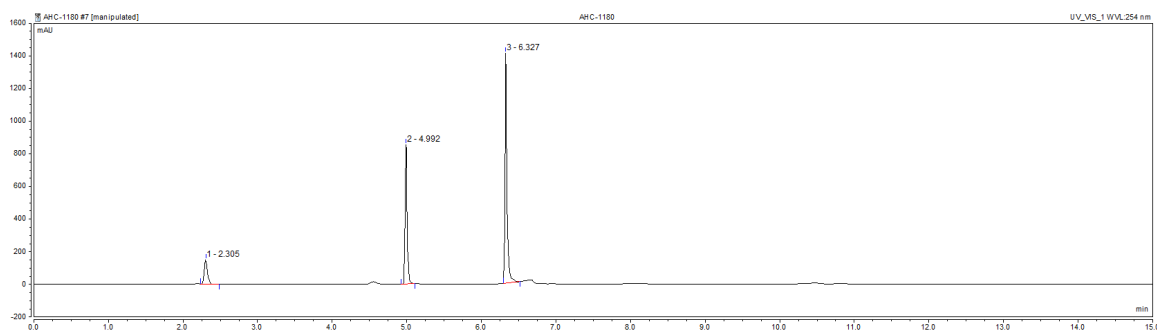
Time 0 h



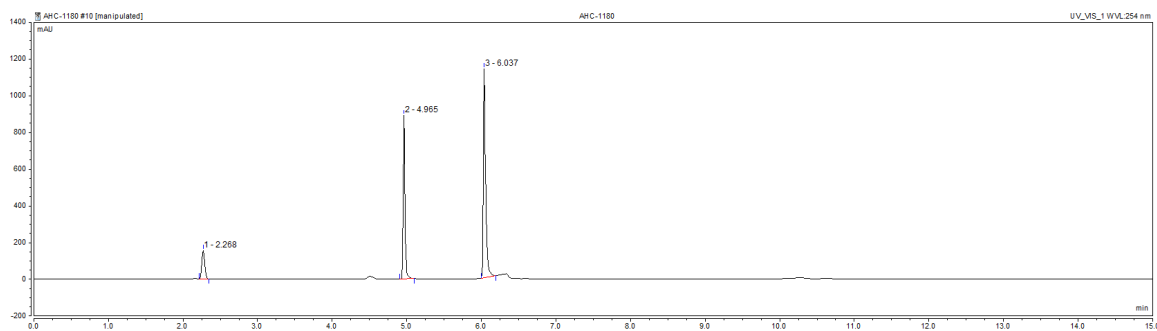
Time 2 h



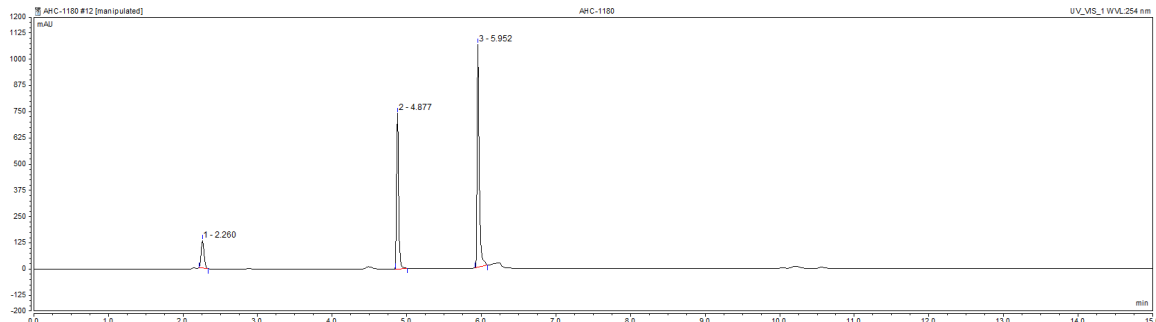
Time 4 h



Time 6 h

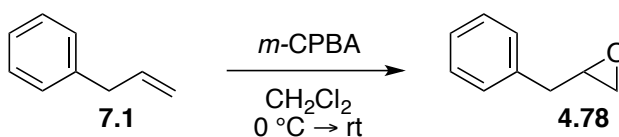


Time 8 h



Experimental Procedures for Chapter 4

2-benzyloxirane (**4.78**)

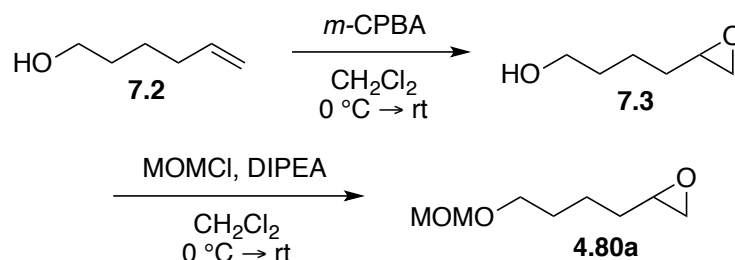


Allyl benzene **7.1** (1.17 mL, 8.46 mmol) was added to a 100-mL round-bottom flask and dissolved in CH_2Cl_2 (17 mL). The solution was then cooled to $0\text{ }^\circ\text{C}$ and *m*CPBA (2.80 g, 12.7 mmol, 77 wt %) was added in one portion. The solution was allowed to warm to room temperature overnight. After completion of reaction as determined by TLC, the reaction was cooled to $0\text{ }^\circ\text{C}$ and quenched with 1 M NaOH (10 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were then dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% - 20% EtOAc in hexanes gradient affording epoxide **4.78** as a clear oil in 91% yield (340 mg, 1.45 mmol).

^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.32 (m, 2H), 7.31 – 7.24 (m, 3H), 4.31 – 4.24 (m, 1H), 3.74 (dd, $J = 11.3, 4.5$ Hz, 1H), 3.67 (dd, $J = 14.1, 5.6$ Hz, 1H), 3.32 (dd, $J = 14.6, 7.3$ Hz, 1H), 3.08 (dd, $J = 14.2, 7.3$ Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 136.3, 129.5, 128.6, 127.2, 61.0, 47.5, 41.0.

2-(4-(methoxymethoxy)butyl)oxirane (**4.80a**)



5-hexen-1-ol **7.2** (1.5 mL, 12.5 mmol) was added to a 50-mL round-bottom flask and dissolved in CH_2Cl_2 (12 mL). The solution was subsequently cooled to 0 °C, *m*-CPBA (4.20 g, 18.7 mmol, 77 wt %) was added in one portion. The reaction mixture was allowed to warm to room temperature. Upon complete consumption of starting material as determined by TLC, the solution was cooled to 0 °C and quenched with 1 M NaOH (5 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% - 35% EtOAc in hexanes gradient affording epoxide **7.3** as a clear oil in 86% yield, (1.25 g, 10.8 mmol).

^1H NMR (400 MHz, CDCl_3) δ 3.66 – 3.60 (m, 2H), 2.93 – 2.88 (m, 1H), 2.76 – 2.71 (m, 1H), 2.48 – 2.44 (m, 1H), 1.65 – 1.49 (m, 6H).

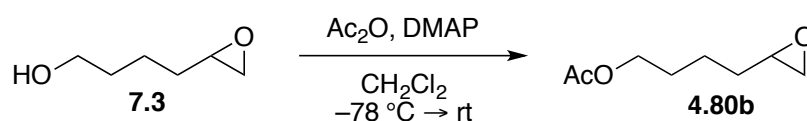
^{13}C NMR (101 MHz, CDCl_3) δ 62.5, 52.2, 47.0, 32.3, 32.1, 22.2.

Epoxide **7.3** (207 mg, 1.78 mmol) was added to a 50-mL round bottom flask. The epoxide was subsequently dissolved in CH_2Cl_2 (7 mL) and DIPEA (477 μL , 2.67 mmol) was added. MOMCl (203 μL , 2.67 mmol) was then added dropwise and off gassing was observed. After 4 hours, the reaction was determined to be complete by TLC analysis and 2 M HCl (2 mL) was

added to quench. Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient affording **4.80a** as a clear oil in 73% yield (209 mg, 1.30 mmol). ¹H NMR (400 MHz, CDCl₃) δ 4.61 (s, 2H), 3.53 (t, *J* = 6.5 Hz, 2H), 3.35 (s, 3H), 2.93 – 2.88 (m, 1H), 2.74 (dd, *J* = 5.0, 3.9 Hz, 1H), 2.46 (dd, *J* = 5.1, 2.9 Hz, 1H), 1.70 – 1.61 (m, 2H), 1.59 – 1.50 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 96.4, 67.5, 55.1, 52.2, 47.00, 32.2, 29.5, 22.7.

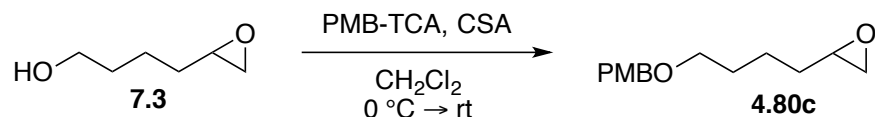
4-(oxiran-2-yl)butyl acetate (**4.80b**)



Epoxide **7.3** (200 mg, 1.72 mmol) was added to a 50-mL round bottom flask followed by DMAP (212 mg, 1.89 mmol). CH₂Cl₂ (4.7 mL) was added and the solution was cooled to – 78 °C. Acetic anhydride (179 μL, 1.89 mmol) was added dropwise and the temperature was maintained at – 78 °C. After 1 hour the reaction was determined to be complete by TLC analysis. The crude solution was allowed to warm to room temperature and quenched with 15% NaOH (2 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 15% EtOAc in hexanes gradient affording **4.80b** as a clear oil in 80% yield (200 mg, 1.26 mmol). ¹H NMR (400 MHz, CDCl₃) δ 4.05 (t, *J* = 5.7 Hz, 2H), 2.92 – 2.86 (m, 1H), 2.75 – 2.71 (m, 1H), 2.48 – 2.43 (m, 1H), 2.03 (s, 3H), 1.72 – 1.63 (m, 2H), 1.63 – 1.46 (m, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 171.2, 64.21, 52.04, 46.95, 32.01, 28.35, 22.47, 20.93.

2-(4-((4-methoxybenzyl)oxy)butyl)oxirane (4.80c)

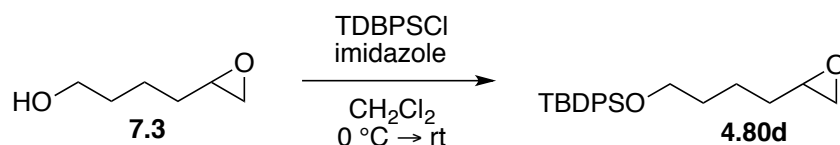


Epoxide **7.3** (193 mg, 1.66 mmol) was added to a vacuum purged 50-mL round bottom flask followed by PMB-TCA (690 μL , 3.32 mmol). CH_2Cl_2 (8.3 mL) was subsequently added to dissolve the reaction components and the solution was cooled to $0\text{ }^\circ\text{C}$. CSA (38 mg, 0.166) was added in one portion and the reaction was allowed to gradually warm to room temperature. After 43 hours, the reaction was determined to be complete by TLC analysis and NaHCO_3 (2 mL) was added to quench the reaction. Upon the separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient affording **4.80c** as a clear oil in 71% (277 mg, 1.17 mmol).

^1H NMR (400 MHz, CDCl_3) δ 7.27 (d, $J = 7.9$ Hz, 2H), 6.89 (d, $J = 10.0$ 2H), 4.44 (s, 2H), 3.81 (s, 3H), 3.46 (t, $J = 8.6$ Hz, 2H), 2.93 – 2.88 (m, 1H), 2.74 (t, $J = 4.2$, Hz, 1H), 2.46 (dd, $J = 5.1$, 2.5 Hz, 1H), 1.71 – 1.62 (m, 2H), 1.58 – 1.50 (m, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 159.1, 130.7, 129.2, 113.7, 72.5, 69.8, 55.24, 52.2, 47.0, 32.3, 29.51, 22.7.

***tert*-butyl(4-(oxiran-2-yl)butoxy)diphenylsilane (4.80d)**

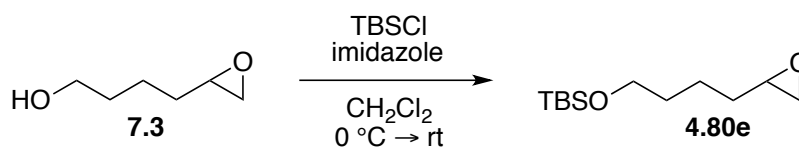


Epoxide **7.3** (177 mg, 1.52 mmol) was combined with imidazole (114 mg, 1.67 mmol) in a 50-mL round-bottom flask. CH₂Cl₂ (3.0 mL) added and the solution was cooled to 0 °C. TBDPSCl (430 μL, 1.67 mmol) was added dropwise. After stirring overnight, the reaction was quenched with 2 M HCl (2 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography using a 1% EtOAc in hexanes gradient affording **4.80d** as a clear oil in 71% (380 mg, 1.07 mmol).

¹H NMR (400 MHz, CDCl₃) δ 7.69 – 7.64 (m, 4H), 7.45 – 7.35 (m, 5H), 3.68 (t, *J* = 5.6 Hz, 2H), 2.93 – 2.86 (m, 1H), 2.74 (t, *J* = 4.7 Hz, 1H), 2.45 (dd, *J* = 5.1, 2.8 Hz, 1H), 1.66 – 1.49 (m, 2H), 1.05 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 135.5, 134.8, 134.0, 129.5, 127.707 127.6, 63.6, 52.3, 47.1, 32.3, 32.2, 26.9, 22.3, 19.2.

***tert*-butyldimethyl(4-(oxiran-2-yl)butoxy)silane (**4.80e**)**



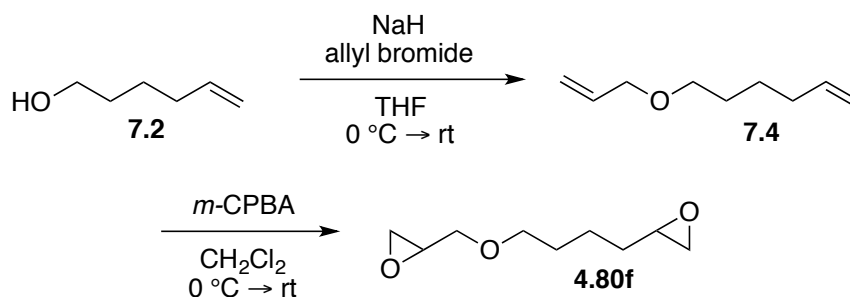
Epoxide **7.3** (284 mg, 2.44 mmol) was added to a 50-mL round-bottom flask and dissolved in CH₂Cl₂ (12 mL). TBSCl (387 mg, 2.57 mmol) was subsequently added and the solution was cooled to 0 °C. Imidazole (250 mg, 3.67 mmol) followed by DMAP (10 mg) were then added and the reaction as allowed to warm to room temperature. After stirring for 3 hours, the reaction was cooled and quenched with 2 M HCl (3 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄,

filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography using a 5% EtOAc in hexanes gradient affording **4.80e** as a clear oil in 89% yield (501 mg, 2.17 mmol).

¹H NMR (400 MHz, CDCl₃) δ 3.64 – 3.59 (m, 2H), 2.94 – 2.88 (m, 1H), 2.74 (dd, *J* = 5.0, 3.9 Hz, 1H), 2.46 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.62 – 1.48 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 62.9, 52.3, 47.1, 32.6, 32.3, 26.0, 22.3, 18.3, -5.30.

2-((4-(oxiran-2-yl)butoxy)methyl)oxirane (**4.80f**)



5-hexen-1-ol **7.2** (480 μL, 3.99 mmol) was added to a 50-mL round-bottom flask and dissolved in THF (8.0 mL). The resulting solution was cooled to 0 °C. Neat NaH (240 mg, 9.98 mmol) was added in one portion and after the cessation of gas evolution, allyl bromide (520 μL, 5.99 mmol) was added slowly, dropwise. After stirring overnight, the reaction was determined to be complete by TLC analysis and cooled to 0 °C. The reaction was then quenched with saturated NH₄Cl (5 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 5% - 10% EtOAc in hexanes gradient affording **7.4** as a clear oil in 85% yield (475 mg, 3.38 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.91-5.86 (m, 1H), 5.80 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.23 (d, *J* = 16.3 Hz, 1H), 5.16 (d, *J* = 10.5, 1H), 5.00 (d, *J* = 17.1 Hz, 1H), 4.96 (d, *J* = 9.9 Hz, 1H), 3.96 (d, *J* = 5.6 Hz, 2H), 3.43 (t, *J* = 6.7 Hz, 2H), 2.07 (q, *J* = 7.2 Hz, 2H), 1.66 – 1.55 (m, 2H), 1.52 – 1.39 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 138.7, 135.1, 116.6, 114.5, 71.7, 70.2, 33.5, 29.2, 25.5.

Bis-alkene **7.4** (458 mg, 3.27 mmol) was added to a 50-mL round-bottom flask, followed by CH₂Cl₂ (7.0 mL). The solution was subsequently cooled to 0 °C. *m*CPBA (2.20 g, 9.80 mmol, 77 wt %) was added in one portion and the solution was allowed to warm to room temperature overnight. Upon complete consumption of starting material as determined by TLC, the solution was cooled to 0 °C and quenched with 1 M NaOH (3 mL). Upon separation of the two layers the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography using a 10% - 20% EtOAc in hexanes gradient eluting **4.80f** as an inseparable mixture of diastereomers as a clear oil in 65% yield, (364 mg, 2.11 mmol).

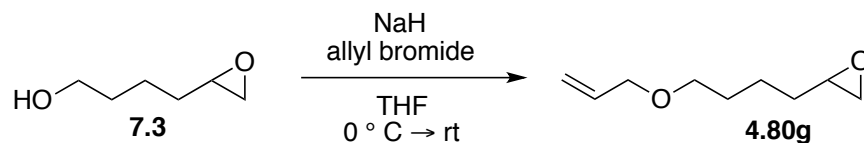
¹H NMR (400 MHz, CDCl₃) δ 3.70 (dd, *J* = 11.8, 2.8 Hz, 1H), 3.49 (qt, *J* = 8.9, 6.1 Hz, 2H), 3.35 (dd, *J* = 11.2, 6.2 Hz, 1H), 3.15 – 3.10 (m, 1H), 2.92 – 2.87 (m, 1H), 2.75 (dt, *J* = 19.8, 4.3 Hz, 2H), 2.59 (dd, *J* = 5.0, 2.5 Hz, 1H), 2.45 (dd, *J* = 5.1, 3.1 Hz, 1H), 1.63 (p, *J* = 7.2, 6.4 Hz, 2H), 1.58 – 1.48 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 71.4, 71.2, 52.1, 50.8, 47.0, 44.2, 32.2, 29.4, 22.6.

IR (cm⁻¹): ν = 3050, 2992, 2932, 2862, 1481, 1457, 1434, 1411, 1337, 1256, 1159, 1104, 910, 835, 758, 480, 434.

HRMS-ESI: (*M*⁺ + *H*⁺) = 173.1172 calculated for C₉H₁₆O₃, experimental = 173.1175.

2-(4-(allyloxy)butyl)oxirane (4.80g)

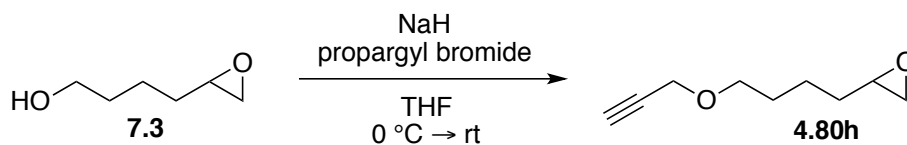


Epoxide **7.3** (183 mg, 1.57 mmol) was added to a 50-mL round-bottom flask and dissolved in THF (2.0 mL). The resulting solution was cooled to 0 °C. Neat NaH (77 mg, 3.15 mmol) was added in one portion and after the cessation of gas evolution, allyl bromide (136 μ L, 1.57 mmol) was added slowly, dropwise. After stirring overnight, the reaction was determined to be complete by TLC analysis and cooled to 0 °C. The reaction was then quenched with saturated NH_4Cl (1.0 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography using a 5% - 10% EtOAc in hexanes gradient affording **4.80g** as a clear oil in 87% yield (214 mg, 1.37 mmol).

^1H NMR (400 MHz, CDCl_3) δ 5.89 (ddt, J = 16.0, 10.7, 5.7 Hz 1H), 5.21 (dd, J = 13.8, 6.6 Hz, 2H), 3.94 (dd, J = 5.6, 1.7 Hz, 2H), 3.42 (t, J = 6.2 Hz, 2H), 3.03 – 2.82 (m, 1H), 2.72 (dd, J = 10.9, 1.8 Hz, 1H), 2.45 (dd, J = 9.4, 1.9 Hz, 1H), 1.63 (t, J = 7.7 Hz, 2H), 1.56 – 1.45 (m, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 134.9, 116.7, 71.7, 70.0, 52.2, 47.0, 32.2, 29.5, 22.7.

2-(4-(prop-2-yn-1-yloxy)butyl)oxirane (4.80h)

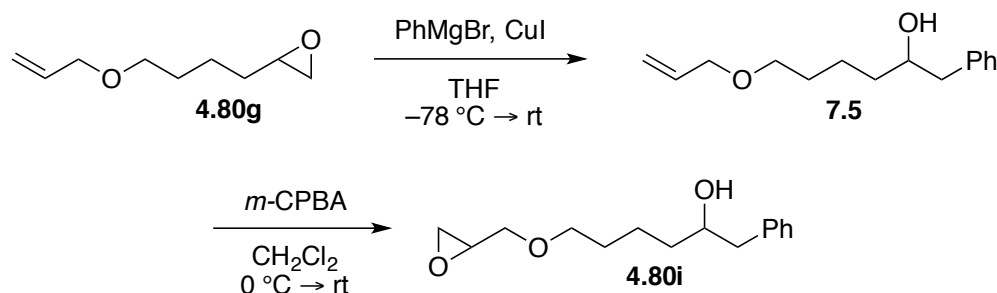


Epoxide **7.3** (324 mg, 2.79 mmol) was added to a 50-mL round-bottom flask and dissolved in THF (2.8 mL). The resulting solution was cooled to 0 °C. Neat NaH (134 mg, 5.58 mmol) was quickly added in one portion and after the cessation gas evolution, propargyl bromide (311 μ L, 2.79 mmol) was added slowly, dropwise. After 6 hours, the reaction was determined to be complete by TLC analysis and cooled to 0 °C. The reaction was then quenched with saturated NH₄Cl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography using a 5% - 15% EtOAc in hexanes gradient affording **4.80h** as a yellow oil in 55% yield (237 mg, 1.54 mmol). **¹H NMR** (400 MHz, Chloroform-*d*) δ 4.12 (t, *J* = 2.1 Hz, 2H), 3.52 (dd, *J* = 7.7, 5.6 Hz, 2H), 2.92 – 2.87 (m, 1H), 2.76 – 2.71 (m, 1H), 2.48 – 2.43 (m, 1H), 2.41 (t, *J* = 2.6 Hz, 1H), 1.68 – 1.60 (m, 2H), 1.58 – 1.49 (m, 4H). **¹³C NMR** (101 MHz, CDCl₃) δ 79.9, 77.3, 77.00, 76.7, 74.1, 69.8, 58.0, 52.1, 47.0, 32.2, 29.2, 22.6.

IR (cm⁻¹): ν = 3262, 3047, 2861, 1480, 1442, 1094, 944, 916, 783, 753.

HRMS-ESI: ($M^+ + H$) = 155.1067 calculated for C₉H₁₅O₂, experimental = 155.1070.

6-(oxiran-2-ylmethoxy)-1-phenylhexan-2-ol (**4.80i**)



CuI (30 mg, 0.160 mmol) was added 50-mL round-bottom flask while the flask was still hot. The flask was then vacuum purged with N₂ and gradually cooled to room temperature. Phenylmagnesium bromide (1.1 mL, 3.20 mmol, 3 M in THF) was added to the flask and the solution was cooled to -78 °C. After cooling for 5 minutes, epoxide **X** (250 mg, 1.60 mmol) was added via cannula in a solution of THF (5.3 mL), dropwise. After 5 minutes, the reaction was then warmed to 0 °C. After 1 hour, the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (1 mL), while still at 0 °C. Upon separation of the two layers, the aqueous layer was back extracted with Et₂O (3 x 10 mL). The combined organic layers were, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% - 20% EtOAc in hexanes gradient affording **7.5** as a clear oil in 91% yield (340 mg, 1.45 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.31 (t, *J* = 7.2 Hz, 2H), 7.26 – 7.20 (m, 3H), 5.91 (ddt, *J* = 17.2, 10.8, 5.6 Hz, 1H), 5.27 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.17 (dd, *J* = 10.3, 1.5 Hz, 1H), 3.96 (d, *J* = 5.7, 1.5 Hz, 2H), 3.88 – 3.79 (m, 1H), 3.44 (t, *J* = 6.3, 1.3 Hz, 2H), 2.83 (dd, *J* = 13.9, 4.4 Hz, 1H), 2.66 (dd, *J* = 13.6, 8.1 Hz, 1H), 1.68 – 1.42 (m, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 138.5, 135.0, 129.4, 128.5, 126.4, 116.7, 72.5, 71.8, 70.2, 44.0, 36.5, 29.6, 22.4.

IR (cm⁻¹): *f*= 3415, 3062, 3026, 2935, 2860, 1602, 1495, 1454, 1347, 1269, 1100, 1030, 997, 923, 853, 746, 700, 670, 664, 604, 540, 510.

HRMS-ESI: (*M* + H⁺) = 235.1693 calculated for C₁₅H₂₃O₂, experimental = 235.1695.

Alcohol **7.5** (340 mg, 1.45 mmol) was added to 50-mL round-bottom flask, and dissolved in CH₂Cl₂ (3 mL). The solution was then cooled to 0 °C and *m*CPBA (535 mg, 2.17 mmol, 70 wt %) was added in one portion. The solution was allowed to warm to room temperature gradually.

After 28 hours, the reaction was determined to be complete by TLC analysis. The reaction was then cooled to 0 °C and quenched with 1 M NaOH (3 mL). After separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography using a 10% - 50% EtOAc in hexanes gradient affording **4.80i** as a 1:1 mixture of inseparable diastereomers as a clear oil in 83% yield, (303 mg, 1.21 mmol).

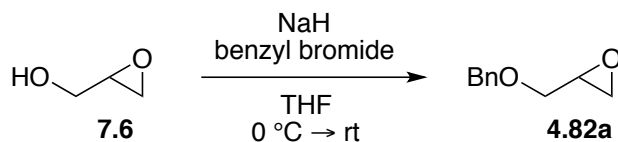
¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.28 (m, 4H), 7.26 – 7.19 (m, 6H), 3.87 – 3.79 (m, 2H), 3.71 (dd, *J* = 11.7, 3.3 Hz, 2H), 3.59 – 3.45 (m, 4H), 3.37 (dd, *J* = 11.7, 5.8 Hz, 2H), 3.17 – 3.11 (m, 2H), 2.87 – 2.77 (m, 4H), 2.66 (dd, *J* = 13.5, 8.4 Hz, 2H), 2.60 (dd, *J* = 5.2, 2.9 Hz, 2H), 1.67 – 1.42 (m, 12H).

¹³C NMR (126 MHz, CDCl₃) δ 138.6, 129.4, 128.6, 126.5, 72.5, 71.5, 71.5, 50.9, 44.3, 44.1, 36.5, 29.6, 22.3.

IR (cm⁻¹): *f*= 3446, 3059, 3026, 3000, 2935, 2862, 1601, 1495, 1394, 1253, 1159, 1030, 852, 701, 604, 508.

HRMS-ESI: (*M* + *H*⁺) = 251.1642 calculated for C₁₅H₂₃O₃, experimental = 251.1649.

2-((benzyloxy)methyl)oxirane (**4.82a**)



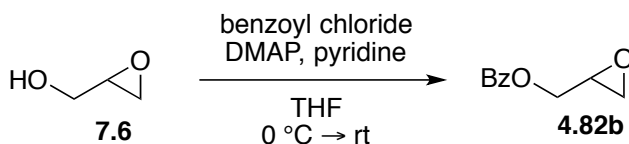
Glycidol **7.6** (447 μL, 6.75 mmol) was added to a 100-mL round-bottom flask and dissolved in THF (23 mL). The resulting solution was then cooled to 0 °C. Neat NaH (200 mg, 8.20 mmol) was then added in one portion. After the cessation of the evolution of gas, benzyl bromide (1.20 mL, 10.1 mmol) was added slowly, dropwise. After 7 hours, the reaction was

determined to be complete by TLC analysis and the reaction mixture was cooled to 0 °C. The cooled solution was then quenched with saturated NH₄Cl (5 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography 5% – 10% EtOAc in hexanes gradient affording **4.82a** as a clear oil in quantitative yield.

¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.27 (m, 5H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 3.77 (dd, *J* = 11.6, 3.1 Hz, 1H), 3.45 (dd, *J* = 11.3, 5.9 Hz, 1H), 3.22 – 3.16 (m, 1H), 2.83 – 2.78 (m, 1H), 2.62 (dd, *J* = 5.4, 2.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 137.9, 128.4, 127.7, 73.3, 70.8, 50.8, 44.3.

oxiran-2-ylmethyl benzoate (**4.82b**)



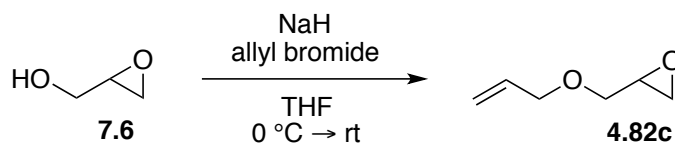
DMAP (82 mg, 0.675 mmol) was added to a 100-mL round-bottom flask. Glycidol **7.6** (895 μL, 13.5 mmol) and pyridine (1.15 mL, 14.2 mmol) were added stepwise and the contents were subsequently dissolved in CH₂Cl₂ (13 mL). The solution was then cooled to 0 °C before the dropwise addition of benzoyl chloride (1.65 mL, 14.2 mmol). After stirring for 6 hours, the reaction was determined to be complete by TLC analysis and subsequently cooled to 0 °C. The cooled reaction mixture was then quenched with 2 M HCl (3 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was

then purified by column chromatography using a 5% - 10% EtOAc in hexanes gradient affording **4.82b** as clear oil in 21% yield (498 mg, 2.79 mmol).

¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, *J* = 8.2 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 2H), 4.65 (dd, *J* = 12.2, 3.1 Hz, 1H), 4.17 (dd, *J* = 12.9, 6.1 Hz, 1H), 3.34 (m, 1H), 2.89 (t, *J* = 4.4 Hz, 1H), 2.73 (dd, *J* = 4.9, 2.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 166.2, 133.2, 129.7, 129.6, 128.4, 49.5, 44.7.

2-((allyloxy)methyl)oxirane (**4.82c**)

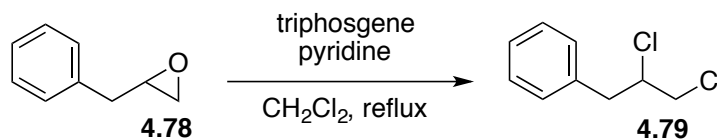


Glycidol **7.6** (448 μL, 6.75 mmol) was added to a 50-mL round-bottom flask and dissolved in THF (13 mL). The resulting solution was then cooled to 0 °C. Neat NaH (324 mg, 8.20 mmol) was added in one portion and after the cessation of the evolution of gas, allyl bromide (1.20 mL, 10.1 mmol) was added slowly, dropwise. After 7 hours, the reaction was determined to be complete by TLC analysis and the reaction was cooled to 0 °C. The cooled solution was then quenched with saturated NH₄C (5 mL). Upon separation of the two layers, the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography using a 10% – 20% EtOAc in hexanes gradient affording **4.82c** as a clear oil in 43% yield (334 mg, 2.93 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.89 (ddt, *J* = 16.2, 11.0, 5.9 Hz, 1H), 5.28 (d, *J* = 17.8 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 4.03 (dq, *J* = 13.0, 5.9 Hz, 2H), 3.71 (dd, *J* = 11.6, 3.1 Hz, 1H), 3.39 (dd, *J* = 11.2, 5.2 Hz, 1H), 3.18 – 3.12 (m, 1H), 2.79 (t, *J* = 4.4 Hz, 1H), 2.60 (dd, *J* = 5.2, 2.6 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 134.4, 117.3, 72.2, 70.7, 50.7, 44.3.

(2,3-dichloropropyl)benzene (4.79)

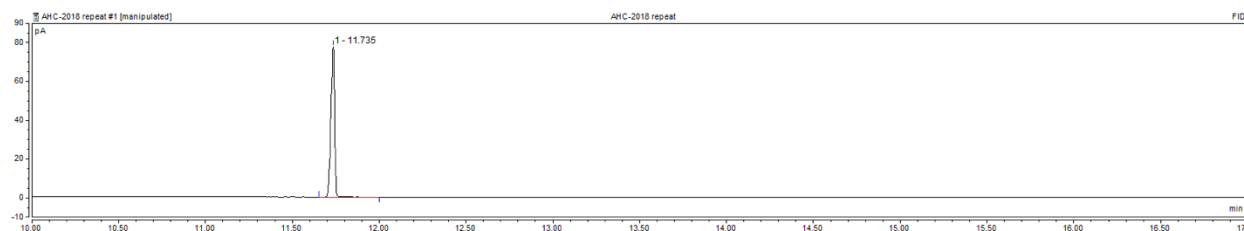


Epoxide **4.78** (111 mg, 0.827 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (1.6 mL), followed by the addition of triphosgene (123 mg, 0.414 mmol). After complete dissolution of triphosgene, pyridine (134 μL , 1.65 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 3 hours, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.79** as a clear oil in 88% yield (137 mg, 0.724 mmol).

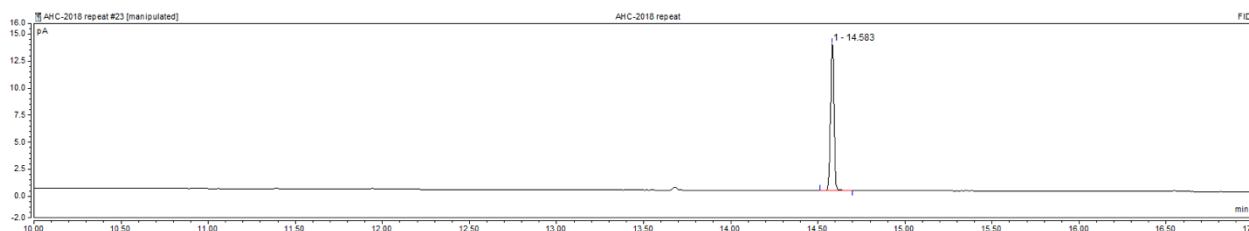
^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.32 (m, 2H), 7.31 – 7.26 (m, 3H), 4.30 – 4.24 (m, 1H), 3.74 (dd, J = 11.2, 4.4 Hz, 1H), 3.67 (dd, J = 11.3, 6.8 Hz, 1H), 3.32 (dd, J = 14.2, 5.2 Hz, 1H), 3.08 (dd, J = 14.2, 7.6 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 136.3, 129.5, 128.6, 127.2, 61.0, 47.4, 41.0.

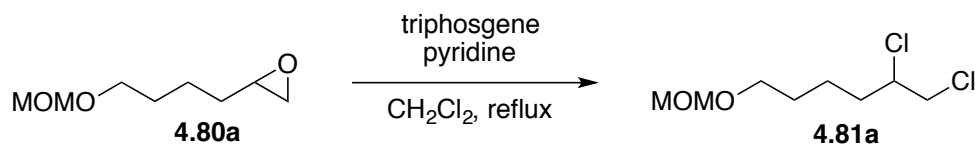
GC Trace of Epoxide **4.78**



GC Trace of Dichloride **4.79**



1,2-dichloro-6-(methoxymethoxy)hexane (**4.81a**)



Epoxide **4.80a** (113 mg, 0.705 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (1.4 mL), followed by the addition of triphosgene (105 mg, 0.353 mmol). After complete dissolution of triphosgene, pyridine (114 μL , 1.41 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.81a** as a clear oil in 70% yield (107 mg, 0.497 mmol).

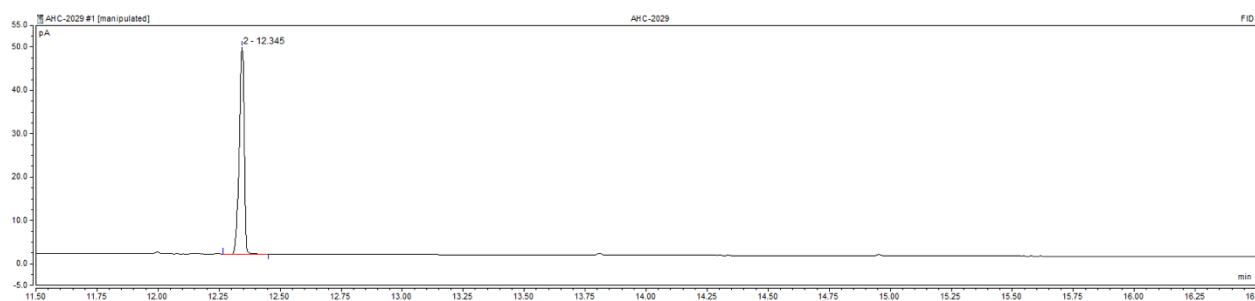
^1H NMR (400 MHz, CDCl_3) δ 4.61 (s, 2H), 4.04 (dddd, $J = 8.7, 7.5, 5.0, 3.6$ Hz, 1H), 3.77 (dd, $J = 11.3, 5.1$ Hz, 1H), 3.65 (dd, $J = 11.3, 7.6$ Hz, 1H), 3.57 – 3.51 (m, 2H), 3.36 (s, 3H), 2.04 (m, 1H), 1.84 – 1.47 (m, 4H).

^{13}C NMR (100 MHz, CDCl_3) δ 96.5, 67.4, 61.0, 55.2, 48.1, 34.8, 29.1, 22.7.

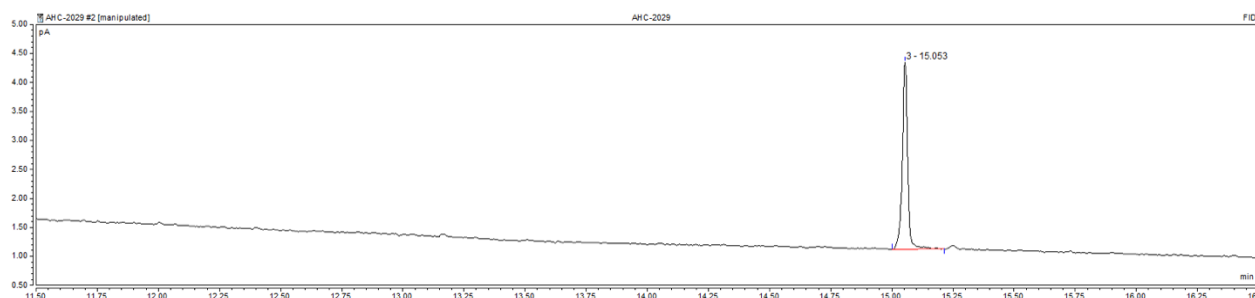
IR (cm^{-1}): $\nu = 2941, 2871, 2823, 2772, 1457, 1440, 1146, 1109, 1041, 918, 729, 669$.

HRMS-ESI: ($\text{M}^+ + \text{Na}^+$) = 237.0420 calculated for $\text{C}_8\text{H}_{16}\text{Cl}_2\text{NaO}_2$, experimental = 237.0416.

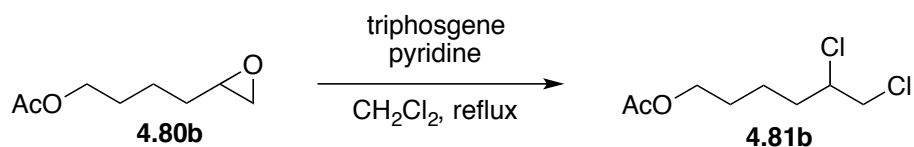
GC Trace of Epoxide **4.80a**



GC Trace of Dichloride **4.81a**



5,6-dichlorohexyl acetate (4.81b)



Epoxide **4.80b** (131 mg, 0.828 mmol) was added to a vacuum cooled, nitrogen purged 15-mL pressure vessel. Freshly distilled CH_2Cl_2 (1.6 mL) was added to the vessel, followed by

triphosgene (123 mg, 0.414 mmol). After total dissolution of triphosgene, pyridine (134 μ L, 1.66 mmol) was added and the vessel was sealed and refluxed. After 1 hour, complete consumption of starting material was determined by GC; the reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography using a 10% EtOAc/Hex gradient affording **4.81b** as a clear oil in 86% yield (151 mg, 0.708 mmol).

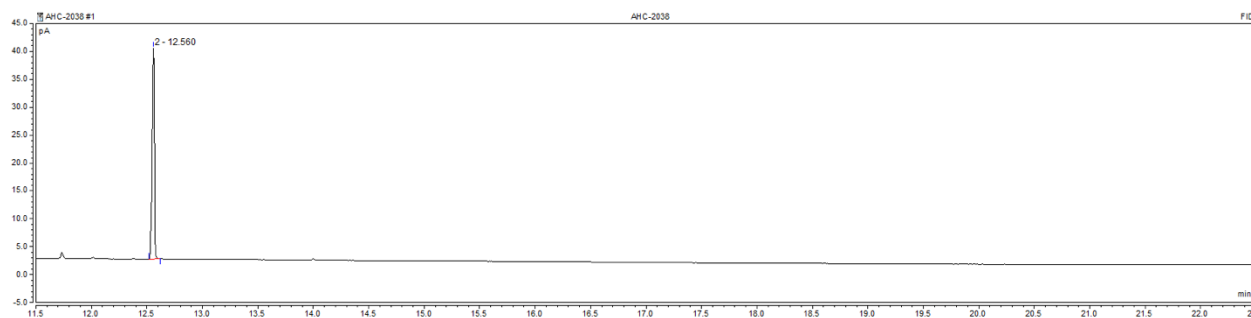
^1H NMR (400 MHz, CDCl_3) δ 4.08 (t, J = 6.3 Hz, 2H), 4.05 – 3.98 (m, 1H), 3.77 (dd, J = 10.8, 5.0 Hz, 1H), 3.64 (dd, J = 10.7, 6.9 Hz, 1H), 2.08 – 1.98 (m, 4H), 1.79 – 1.59 (m, 4H), 1.56 – 1.45 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 171.1, 64.0, 60.8, 48.0, 34.6, 28.0, 22.4, 20.9.

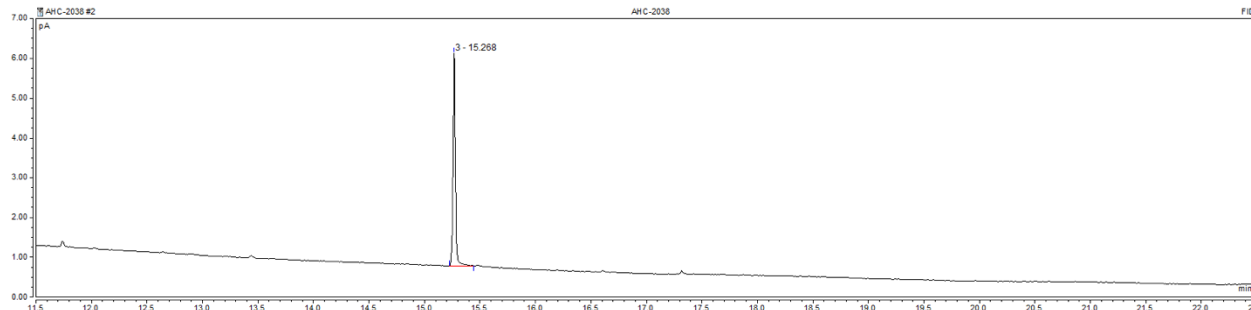
IR (cm^{-1}): f = 2953, 1733, 1434, 1365, 1233, 1039, 807, 729, 662, 607.

HRMS-ESI: ($\text{M}^+ + \text{H}^+$) = 213.0444 calculated for $\text{C}_8\text{H}_{15}\text{Cl}_2\text{O}_2$, experimental = 213.0452

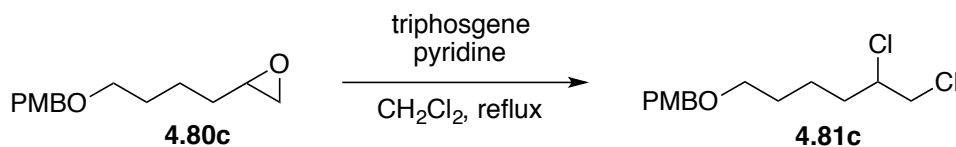
GC Trace of Epoxide **4.80b**



GC Trace of Dichloride **4.81b**



1-(((5,6-dichlorohexyl)oxy)methyl)-4-methoxybenzene (**4.81c**)



Epoxide **4.80c** (122 mg, 0.516 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (1.0 mL), followed by the addition of triphosgene (76 mg, 0.258 mmol). After complete dissolution of triphosgene, pyridine (83 μL , 1.03 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.81c** as a clear oil in 80% yield (135 mg, 0.463 mmol).

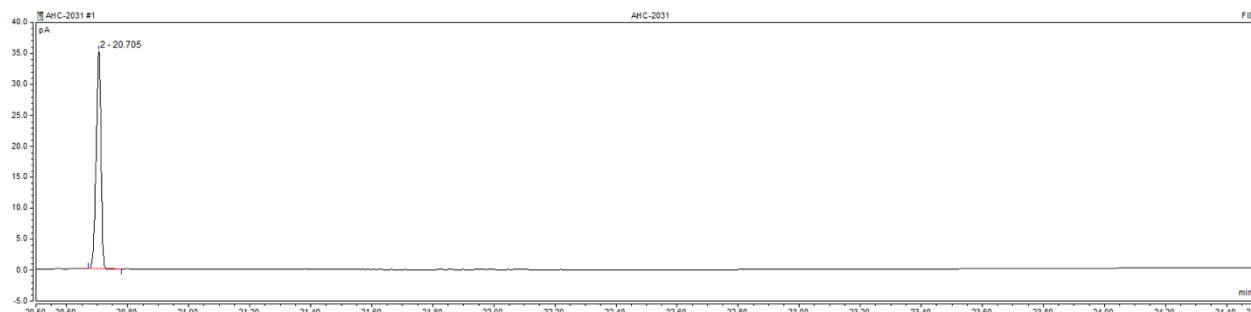
^1H NMR (400 MHz, CDCl_3) δ 7.26 (d, J = 8.4 Hz 2H), 6.89 (d, J = 8.6 Hz 2H), 4.44 (s, 2H), 4.07 – 3.98 (m, 1H), 3.81 (s, 3H), 3.75 (dd, J = 11.2, 5.3 Hz, 1H), 3.64 (dd, J = 11.2, 7.2 Hz, 1H), 3.46 (t, J = 6.2 Hz, 2H), 2.04 – 1.95 (m, 1H), 1.78 – 1.45 (m, 5H).

^{13}C NMR (101 MHz, CDCl_3) δ 159.2, 130.6, 129.2, 113.8, 72.6, 69.6, 61.1, 55.3, 48.2, 34.9, 29.1, 22.7.

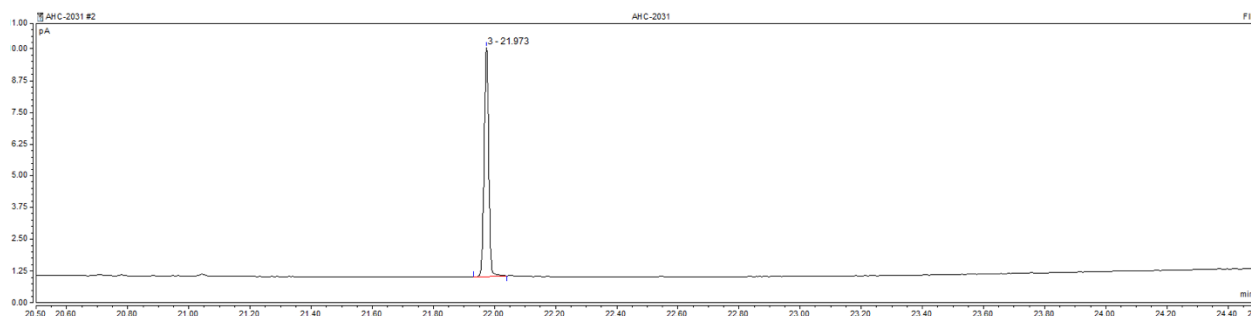
IR (cm^{-1}): ν = 3001, 2936, 1612, 1585, 1458, 1361, 1301, 1244, 1209, 1172, 1097, 1034, 820, 730, 661, 570, 446.

HRMS-ESI: ($\text{M}^+ + \text{Na}^+$) = 313.0733 calculated for $\text{C}_{14}\text{H}_{20}\text{Cl}_2\text{NaO}_2$, experimental = 313.0722.

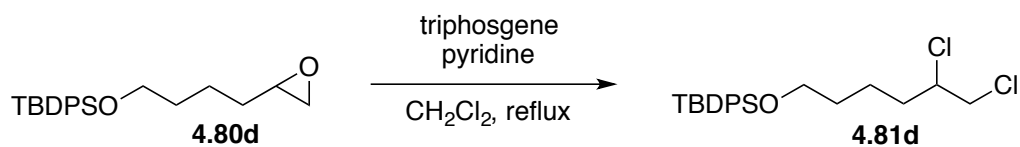
GC Trace of Epoxide **4.80c**



GC Trace of Dichloride **4.81c**



***tert*-butyl((5,6-dichlorohexyl)oxy)diphenylsilane (4.81d)**



Epoxide **4.80d** (122 mg, 0.516 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH₂Cl₂ (1.0 mL), followed by the addition of triphosgene (76 mg, 0.258 mmol). After complete dissolution of triphosgene, pyridine (83 μ L, 1.03 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.81d** as a clear oil in 88% yield (135 mg, 0.463 mmol).

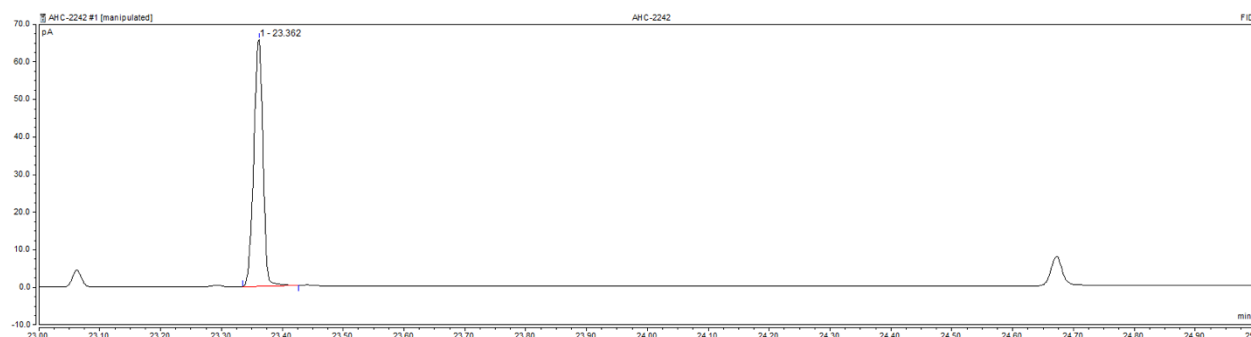
¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, J = 8.4 Hz 2H), 6.89 (d, J = 8.6 Hz 2H), 4.44 (s, 2H), 4.07 – 3.98 (m, 1H), 3.81 (s, 3H), 3.75 (dd, J = 11.2, 5.3 Hz, 1H), 3.64 (dd, J = 11.2, 7.2 Hz, 1H), 3.46 (t, J = 6.2 Hz, 2H), 2.04 – 1.95 (m, 1H), 1.78 – 1.45 (m, 5H).

¹³C NMR (101 MHz, CDCl₃) δ 159.2, 130.6, 129.2, 113.8, 72.6, 69.6, 61.1, 55.3, 48.2, 34.8, 29.1, 22.7.

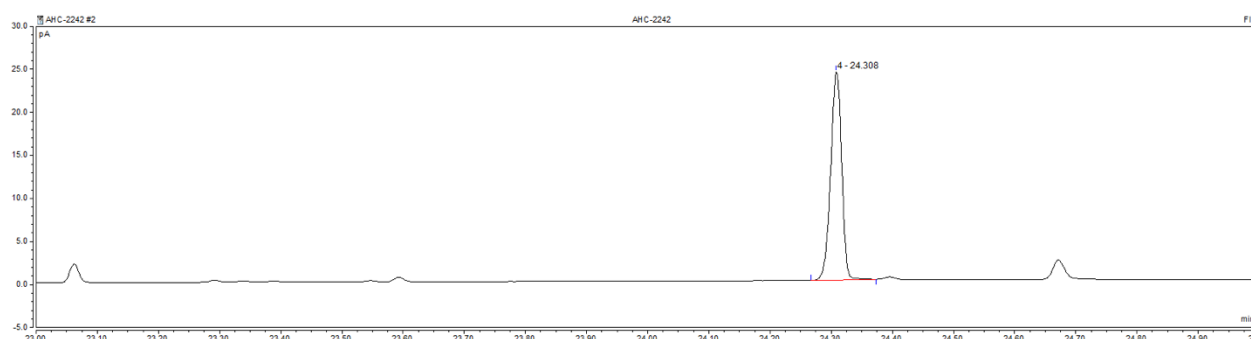
IR (cm⁻¹): ν = 3001, 2936, 1612, 1585, 1458, 1361, 1301, 1244, 1209, 1172, 1097, 1034, 820, 730, 661, 570, 446.

HRMS-ESI: ($M^+ + Na^+$) = 313.0733 calculated for C₁₄H₂₀Cl₂NaO₂, experimental = 313.0722.

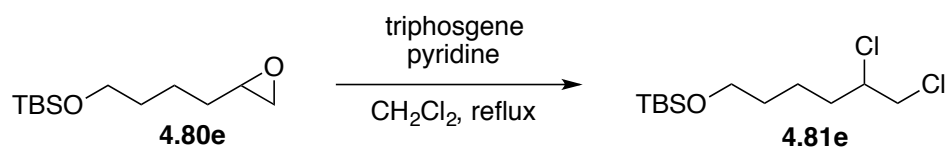
GC Trace of Epoxide **4.80d**



GC Trace of Dichloride **4.81d**



tert-butyl((5,6-dichlorohexyl)oxy)dimethylsilane (**4.80e**)



Epoxide **4.80e** (154 mg, 0.668 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (1.3 mL), followed by the addition of triphosgene (99 mg, 0.334 mmol). After complete dissolution of triphosgene, pyridine (108 μL , 1.34 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over

Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.81e** as a clear oil in 80% yield (135 mg, 0.463 mmol).

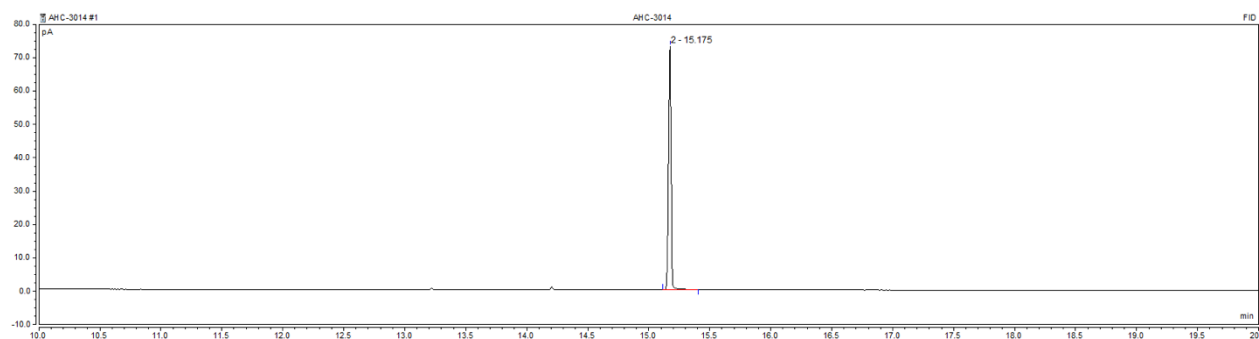
¹H NMR (400 MHz, CDCl₃) δ 4.09 – 3.99 (m, 1H), 3.76 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.68 – 3.61 (m, 3H), 2.07 – 1.96 (m, 1H), 1.79 – 1.67 (m, 1H), 1.67 – 1.44 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 62.7, 61.2, 48.2, 34.9, 32.1, 26.0, 22.3, 18.3, -5.3.

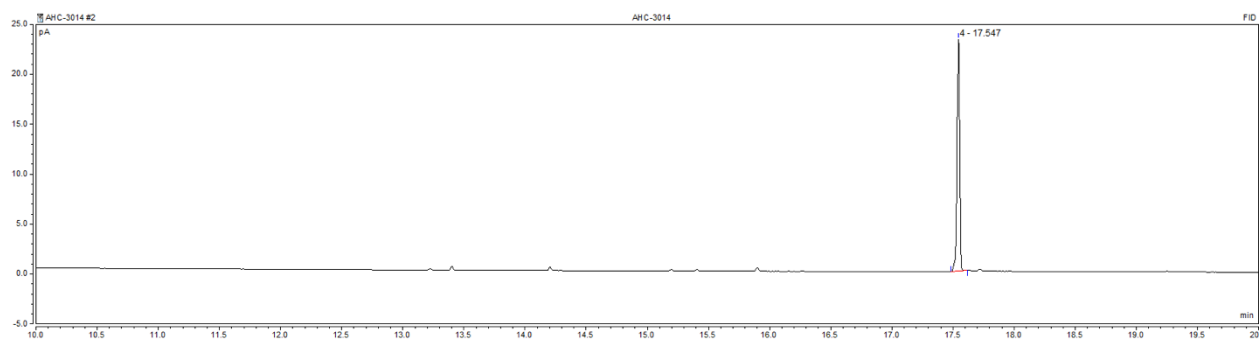
IR (cm⁻¹): *f* = 2929, 2857, 1472, 1387, 1253, 1095, 1006, 833, 774, 661.

HRMS-ESI: (M+H⁺) = 285.1203 calculated for C₁₂H₂₇Cl₂Osi, experimental = 285.1204.

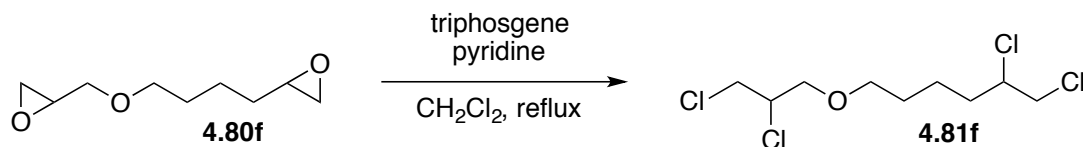
GC Trace of Epoxide **4.80e**



GC Trace of Dichloride **4.81e**



1,2-dichloro-6-(2,3-dichloropropoxy)hexane (**4.81f**)



Epoxide **4.80f** (152 mg, 0.883 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH₂Cl₂ (1.8 mL), followed by the addition of triphosgene (262 mg, 0.883 mmol). After complete dissolution of triphosgene, pyridine (285 μ L, 3.53 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 2 hours, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.81f** as a clear oil in 81% yield (201 mg, 0.713 mmol).

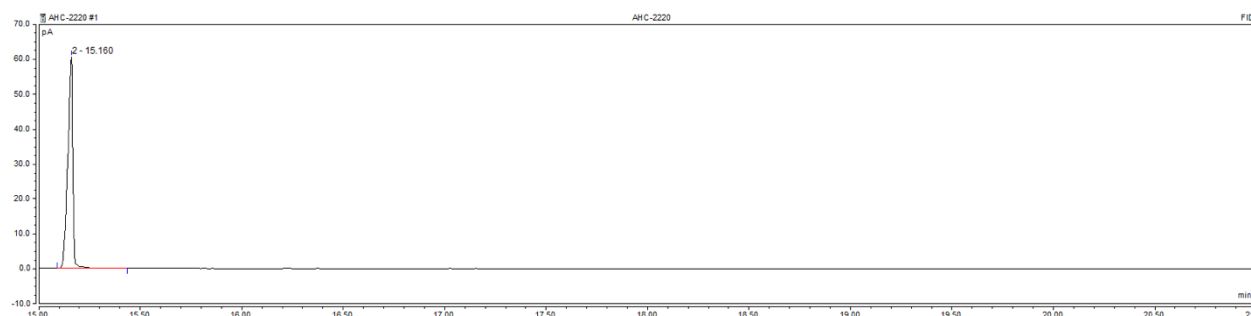
¹H NMR (400 MHz, CDCl₃) δ 4.16 (p, J = 11.2, 5.2 Hz, 1H), 4.08 – 4.00 (m, 1H), 3.85 (dd, J = 11.2, 6.2 Hz, 1H), 3.75 (dq, J = 11.2, 5.4 Hz, 4H), 3.65 (dd, J = 11.2, 7.6 Hz, 1H), 3.53 (t, J = 6.3 Hz, 2H), 2.08 – 1.99 (m, 1H), 1.80 – 1.44 (m, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 71.3, 71.0, 60.9, 58.2, 48.1, 45.3, 34.7, 28.8, 22.5.

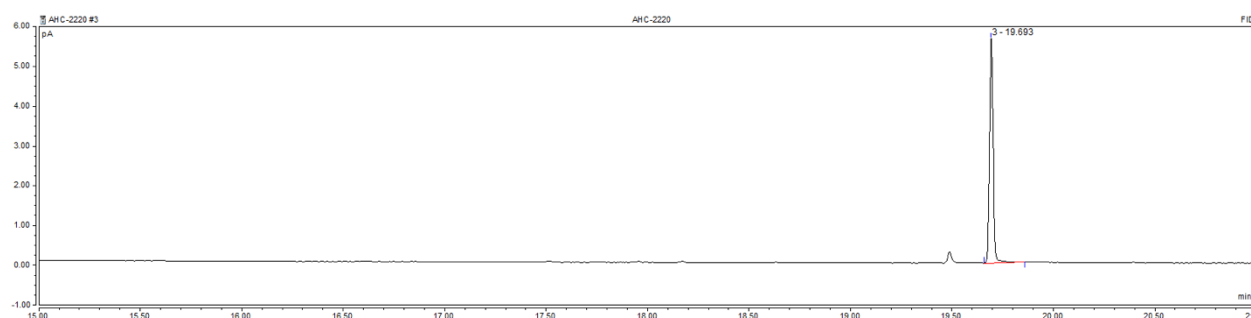
IR (cm⁻¹): ν = 2944, 2866, 1667, 1457, 1432, 1256, 1117, 924, 818, 731, 662, 445.

HRMS-ESI: ($M^+ + H^+$) = 281.0028 calculated for C₉H₁₇Cl₄O, experimental = 281.0028.

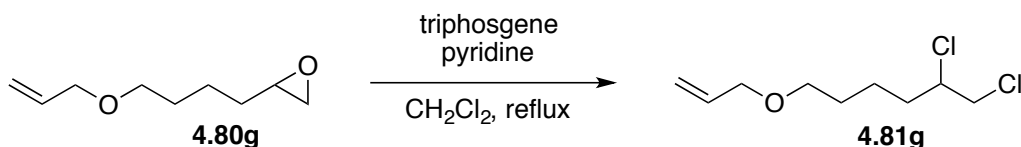
GC Trace of Epoxide **4.80f**



GC Trace of Dichloride **4.81f**



6-(allyloxy)-1,2-dichlorohexane (**4.81g**)



Epoxide **4.80g** (119 mg, 0.762 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (1.5 mL), followed by the addition of triphosgene (113 mg, 0.381 mmol). After complete dissolution of triphosgene, pyridine (123 μL , 1.52 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then

purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.81g** as a clear oil in 90% yield (145 mg, 0.687 mmol).

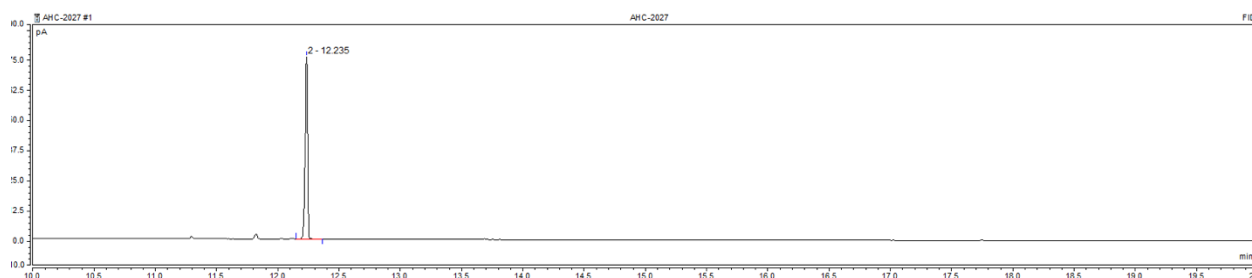
^1H NMR (400 MHz, CDCl_3) δ 5.91 (ddt, $J = 15.9, 10.3, 5.6$ Hz, 1H), 5.42 – 4.93 (m, 2H), 4.04 (dddd, $J = 8.9, 7.4, 5.1, 3.7$ Hz, 1H), 3.97 (dt, $J = 5.6, 1.5$ Hz, 2H), 3.84 – 3.58 (m, 2H), 3.45 (t, $J = 6.0$ Hz, 2H), 2.38 – 1.90 (m, 1H), 1.83 – 1.37 (m, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 134.9, 116.8, 71.9, 69.9, 61.1, 48.2, 34.9, 29.1, 22.7.

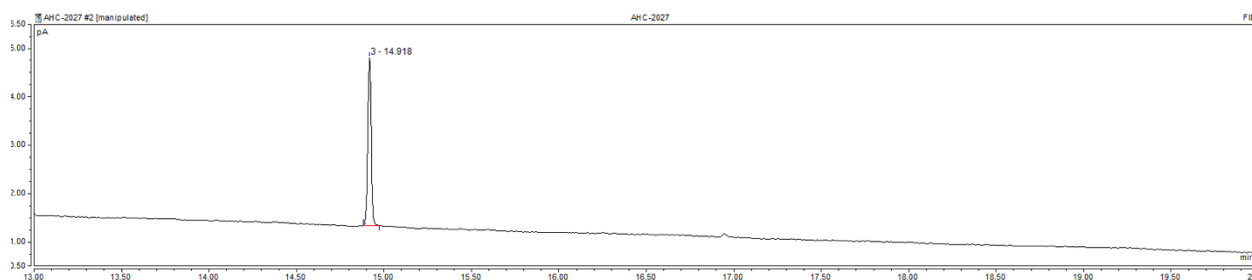
IR (cm^{-1}): $\nu = 3014, 2940, 2861, 1646, 1478, 1456, 1102, 995, 923, 730, 669, 664, 475$.

HRMS-ESI: ($\text{M}^+ + \text{H}^+$) = 211.0651 calculated for $\text{C}_9\text{H}_{17}\text{Cl}_2\text{O}$, experimental = 211.0648.

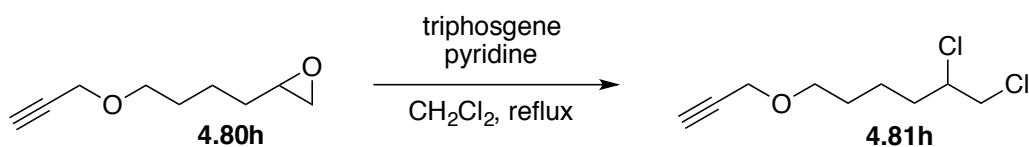
GC Trace of Epoxide **4.80g**



GC Trace of Dichloride **4.81g**



1,2-dichloro-6-(prop-2-yn-1-yloxy)hexane (4.81h)



Epoxide **4.80h** (123 mg, 0.797 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH₂Cl₂ (1.6 mL), followed by the addition of triphosgene (118 mg, 0.399 mmol). After complete dissolution of triphosgene, pyridine (130 μ L, 1.60 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (2 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.81h** as a clear oil in 86% yield (144 mg, 0.689 mmol).

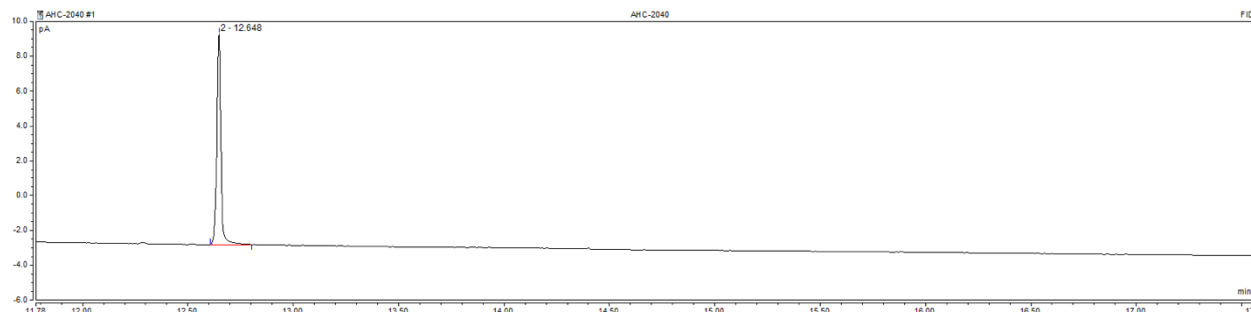
¹H NMR (400 MHz, CDCl₃) δ 4.13 (d, J = 2.6 Hz, 2H), 4.08 – 3.99 (m, 1H), 3.76 (dd, J = 11.2, 5.1 Hz, 1H), 3.65 (dd, J = 11.6, 7.3 Hz, 1H), 3.54 (t, J = 6.0 Hz, 2H), 2.42 (t, J = 2.3 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.80 – 1.71 (m, 1H), 1.71 – 1.57 (m, 3H), 1.55 – 1.46 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 79.9, 74.2, 69.7, 61.0, 58.1, 48.2, 34.8, 28.9, 22.6.

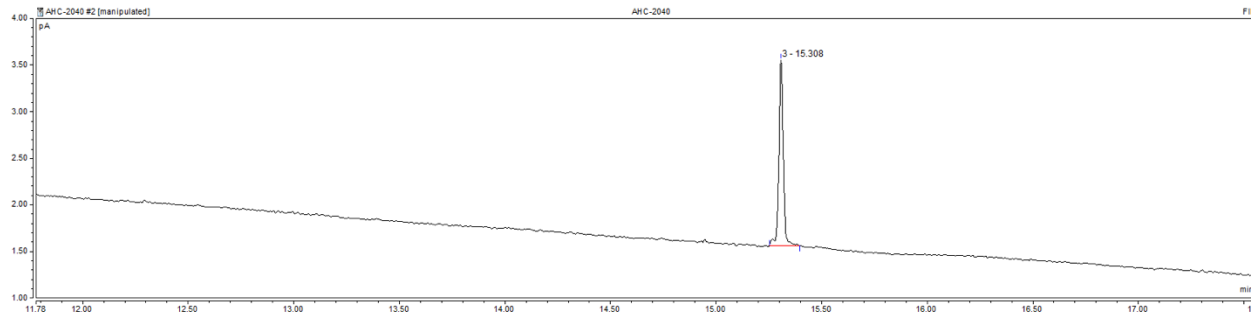
IR (cm⁻¹): ν = 3296, 2944, 2864, 1438, 1355, 1270, 1181, 1097, 1017, 919, 814, 728, 659.

HRMS-ESI: ($M^+ + H^+$) = 209.0494 calculated for C₉H₁₅Cl₂O, experimental = 209.0494.

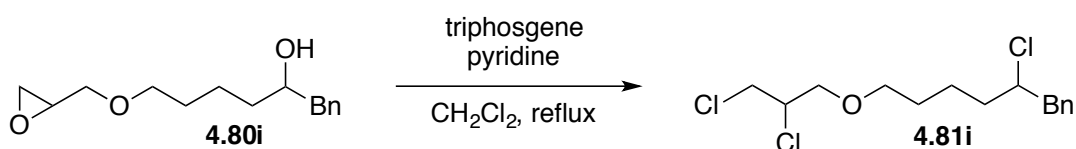
GC Trace of Epoxide **4.80h**



GC Trace of Dichloride **4.81h**



(2-chloro-6-(2,3-dichloropropoxy)hexyl)benzene (**4.81i**)



Epoxide **4.80i** (122 mg, 0.487 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (1.0 mL), followed by the addition of triphosgene (144 mg, 0.487 mmol). After complete dissolution of triphosgene, pyridine (158 μL , 1.95 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (2 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.81i** as a clear oil in 71% yield (111 mg, 0.343 mmol).

^1H NMR (400 MHz, CDCl_3) δ 7.32 (t, $J = 7.9$ Hz, 4H), 7.28 – 7.24 (m, 2H), 7.21 (d, $J = 7.5$ Hz, 4H), 4.18 – 4.06 (m, 4H), 3.84 (dd, $J = 11.3, 6.3$ Hz, 2H), 3.77 (dd, $J = 11.4, 5.3$ Hz, 2H), 3.74 –

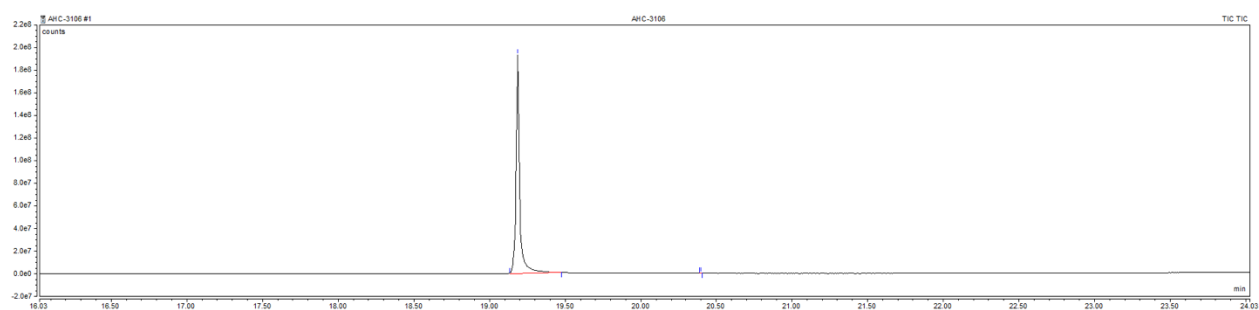
3.66 (m, 4H), 3.49 (t, $J = 6.0$ Hz, 4H), 3.11 – 2.99 (m, 4H), 1.86 – 1.76 (m, 2H), 1.75 – 1.47 (m, 10H).

^{13}C NMR (126 MHz, CDCl_3) δ 138.0, 129.3, 128.4, 126.8, 76.7, 71.4, 71.1, 63.7, 58.3, 45.3, 45.1, 37.3, 28.9, 23.1.

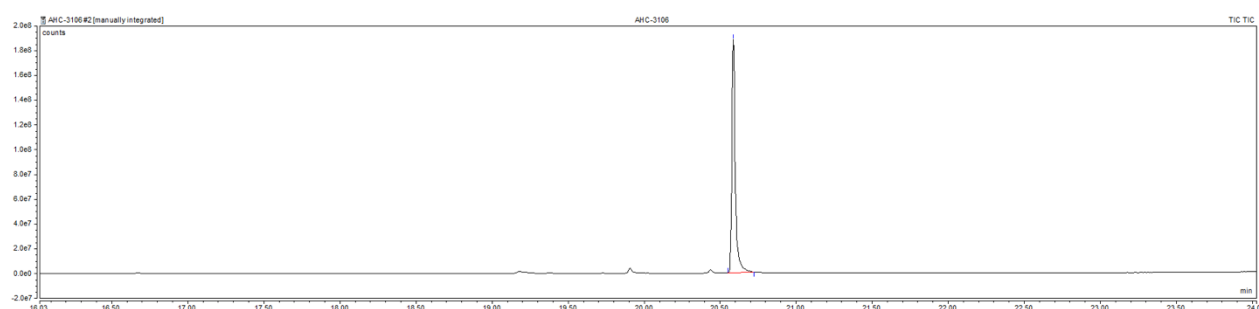
IR (cm^{-1}): $\nu = 3028, 2942, 2865, 1495, 1454, 1366, 1254, 1119, 1030, 925, 748, 700, 677, 613, 565$.

HRMS-ESI: ($\text{M} + \text{Na}^+$) = 345.0550 calculated for $\text{C}_{15}\text{H}_{21}\text{Cl}_3\text{NaO}$, experimental = 345.0562.

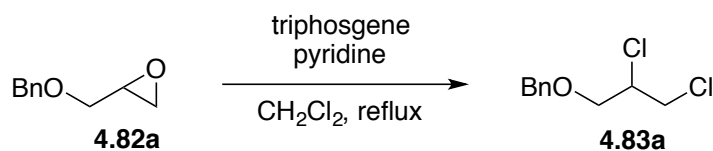
GC Trace of Epoxide **4.80i**



GC Trace of Dichloride **4.81i**



((2,3-dichloropropoxy)methyl)benzene (**4.83a**)

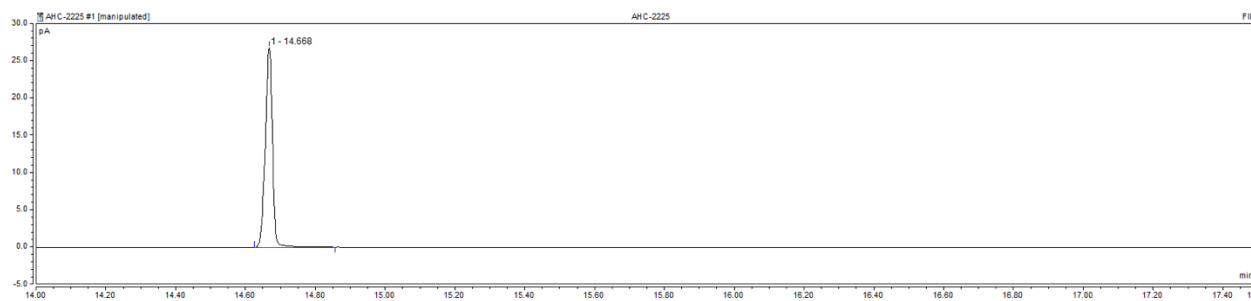


Epoxide **4.82a** (188 mg, 1.16 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH₂Cl₂ (2.3 mL), followed by the addition of triphosgene (172 mg, 0.579 mmol). After complete dissolution of triphosgene, pyridine (187 μ L, 2.32 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 6 hours, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.83a** as a clear oil in 87% yield (222 mg, 1.01 mmol).

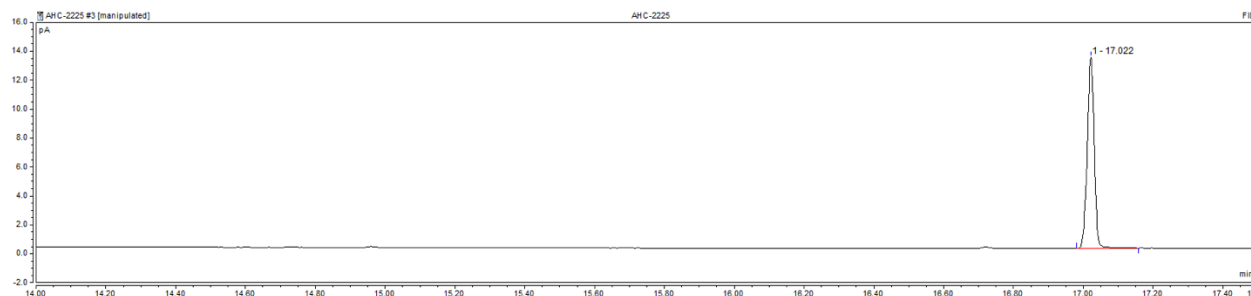
¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.31 (m, 5H), 4.65 – 4.57 (m, 2H), 4.19 (p, J = 5.3 Hz, 1H), 3.89 (dd, J = 11.6, 6.6 Hz, 1H), 3.83 – 3.75 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 137.5, 128.5, 127.9, 127.7, 73.5, 70.4, 58.3, 45.3.

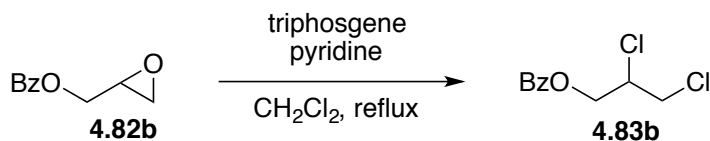
GC Trace of Epoxide **4.82a**



GC Trace of Dichloride **4.83a**



2,3-dichloropropyl benzoate (4.83b)

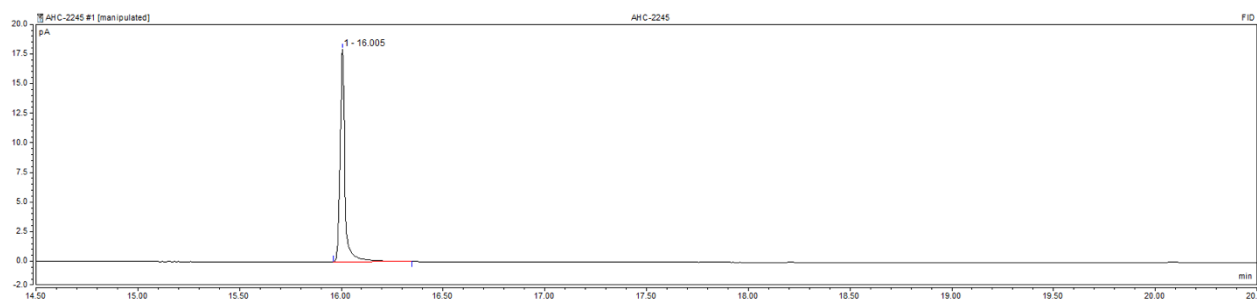


Epoxide **4.82b** (218 mg, 1.22 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (2.5 mL), followed by the addition of triphosgene (181 mg, 0.612 mmol). After complete dissolution of triphosgene, pyridine (198 μL , 2.45 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 3 hours, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (2 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.83b** as a clear oil in 71% yield (202 mg, 0.867 mmol).

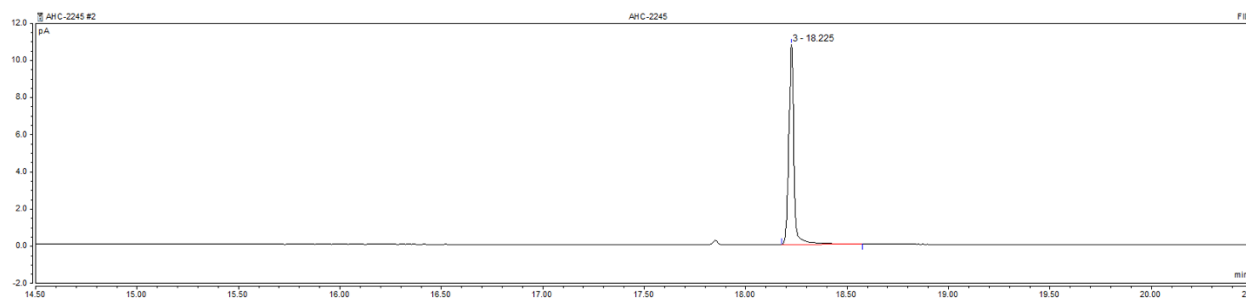
^1H NMR (400 MHz, CDCl_3) δ 8.06 (d, J = 8.2 Hz, 2H), 7.60 (t, J = 7.6 Hz 1H), 7.47 (t, J = 7.6 Hz, 2H), 4.71 – 4.61 (m, 2H), 4.42 – 4.36 (m, 1H), 3.87 (d, J = 6.4 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 165.8, 133.4, 129.7, 129.3, 128.5, 64.7, 56.9, 44.7.

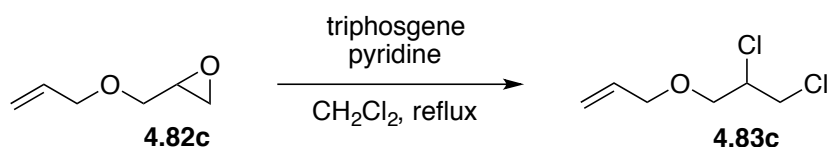
GC Trace of Epoxide **4.82b**



GC Trace of Dichloride **4.83b**



3-(2,3-dichloropropoxy)prop-1-ene (**4.83c**)

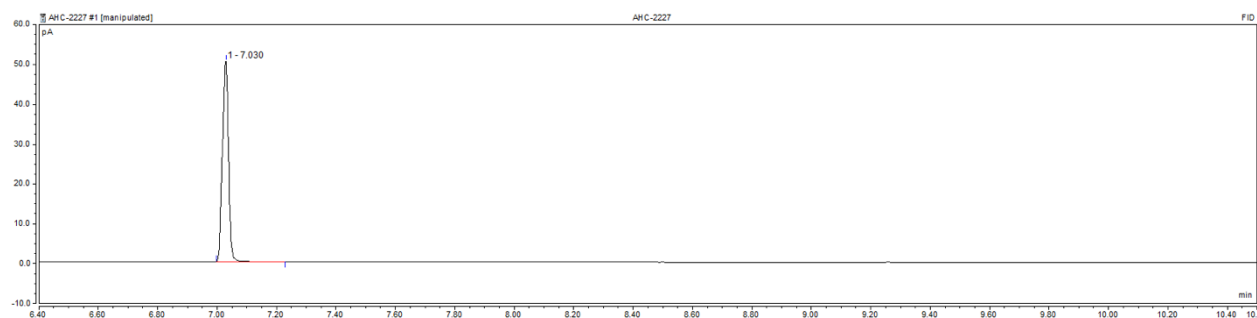


Epoxide **4.82c** (165 mg, 1.45 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (2.9 mL), followed by the addition of triphosgene (215 mg, 0.723 mmol). After complete dissolution of triphosgene, pyridine (234 μL , 2.89 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 6 hours, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (2 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.83c** as a clear oil in 67% yield (165 mg, 0.976 mmol).

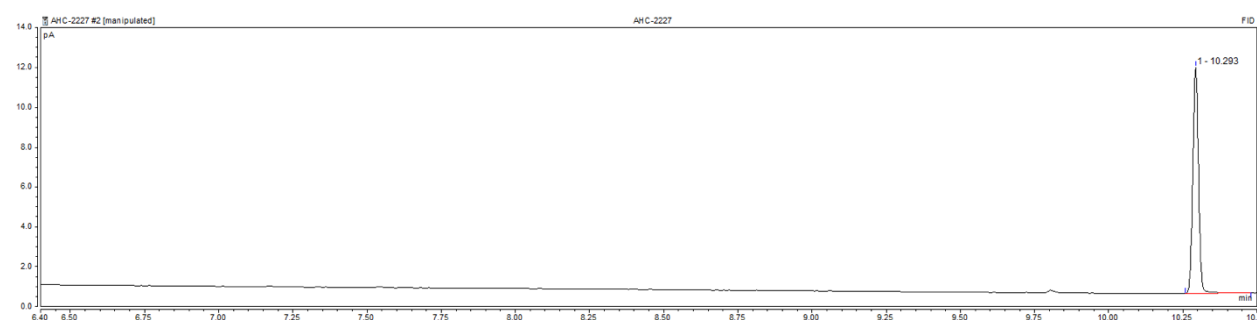
^1H NMR (400 MHz, CDCl_3) δ 5.90 (ddt, J = 16.0, 10.7, 5.3 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.22 (dt, J = 10.7 Hz, 1H), 4.17 (p, J = 10.8, 5.1 Hz, 1H), 4.06 (d, J = 5.2 Hz, 2H), 3.86 (dd, J = 11.3, 6.6 Hz, 1H), 3.79 (dd, J = 11.4, 5.2 Hz, 1H), 3.74 (dd, J = 4.6, 1.5 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 134.0, 117.7, 72.4, 70.2, 58.3, 45.2.

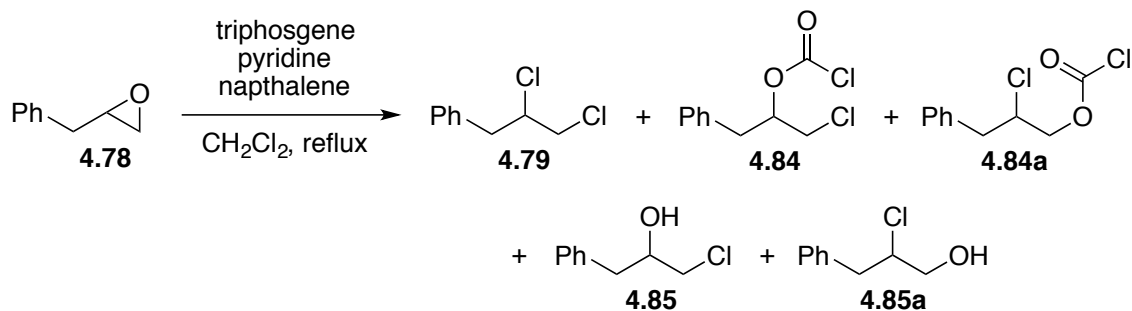
GC Trace of Epoxide **4.78**



GC Trace of Dichloride **4.79**



Monitoring the Reaction Profile of **4.78** → **4.79** by GC/MS



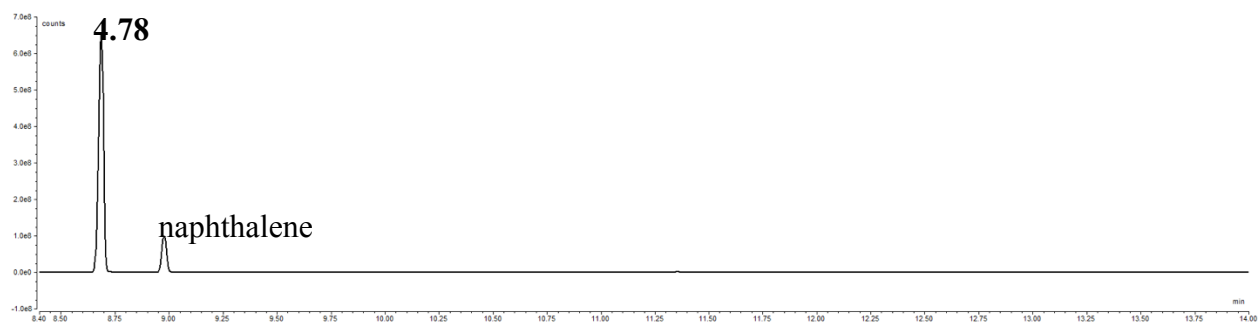
Epoxide **4.78** (532 mg, 3.96 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (8.0 mL), followed by the addition of triphosgene (587 mg, 1.98 mmol) and naphthalene (47 mg, 0.396 mmol). After complete dissolution of the starting materials, pyridine (640 μL , 7.93 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. During the course of the reaction small 100 μL aliquots were removed and diluted

in with 300 μL CH_2Cl_2 every 15 minutes. This diluted sample was then injected through a Thermo Scientific TG-SQC GC Column (15m x 0.25mm x 0.25 μm) using a modified gradient of 40 $^\circ\text{C}$ to 300 $^\circ\text{C}$ over 29 minutes using helium as the carrier gas. The detector utilized was a Thermo Scientific ISQD QD mass spectrometer with the mass range limit set from 60 – 400 amu and with the ion source temperature set at 200 $^\circ\text{C}$.

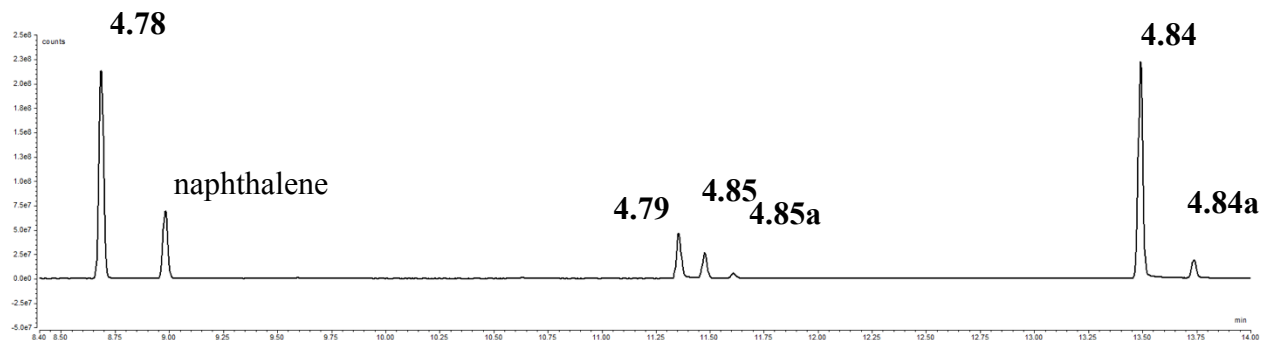
reaction time (min)	% area epoxide	% area chloroformate	% area halohydrin	% area dichloride	% area naphthalene
0	87	0	0	0	13
30	36	37	8	4	12
60	0	50	0	37	9
120	0	10	0	80	10
210	0	0	0	91	9

Retention Time: t_R **4.78** = 8.69 min; t_R naphthalene = 8.98 min; t_R **4.85** = 11.36 min; t_R **4.79** = 11.48 min; t_R **4.85a** = 11.61 min; t_R **4.84** = 13.49 min; t_R **4.84a** = 13.74 min.

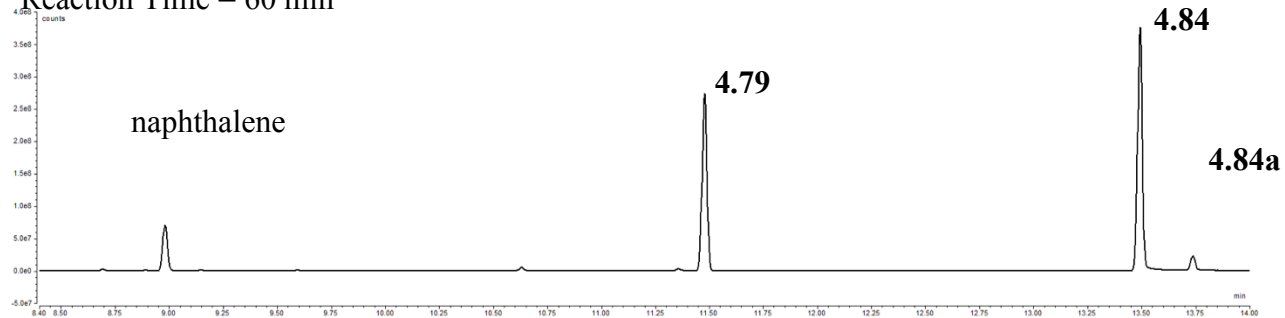
Reaction Time = 0 min



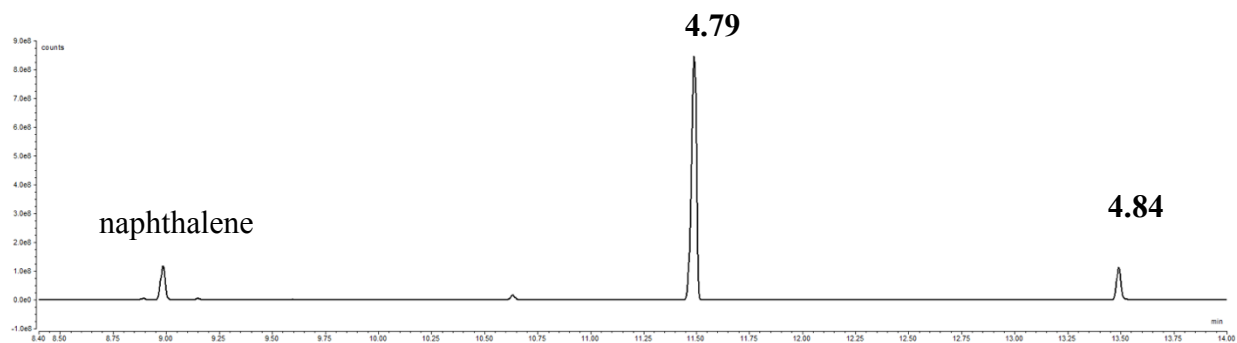
Reaction Time = 30 min



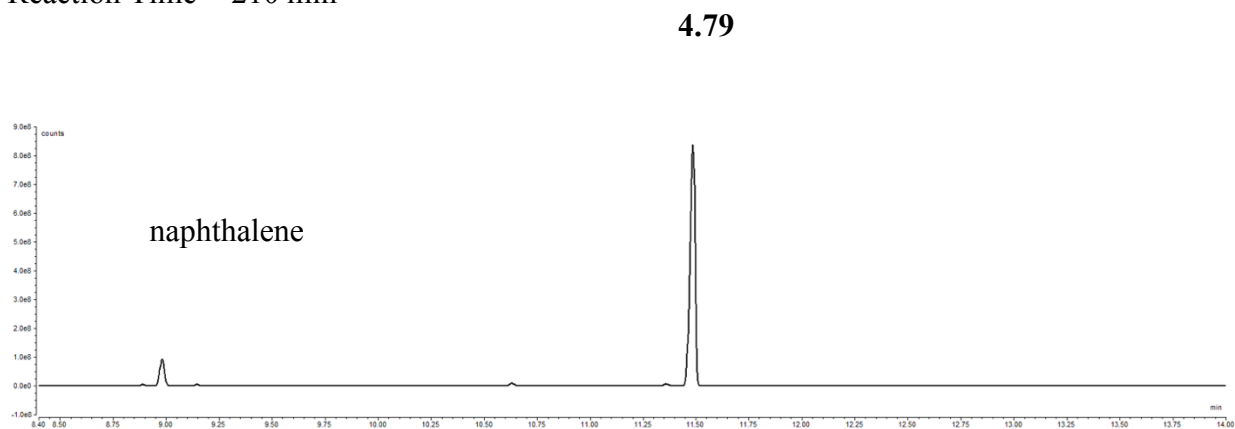
Reaction Time = 60 min

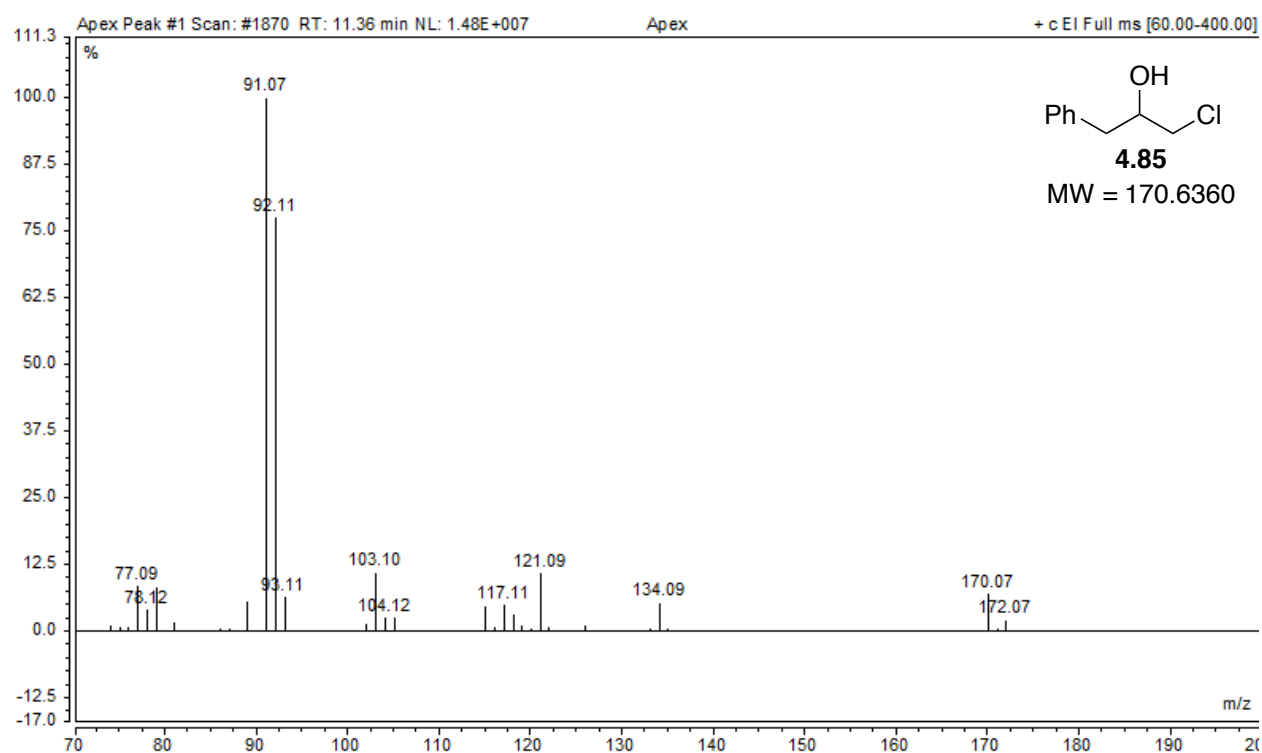
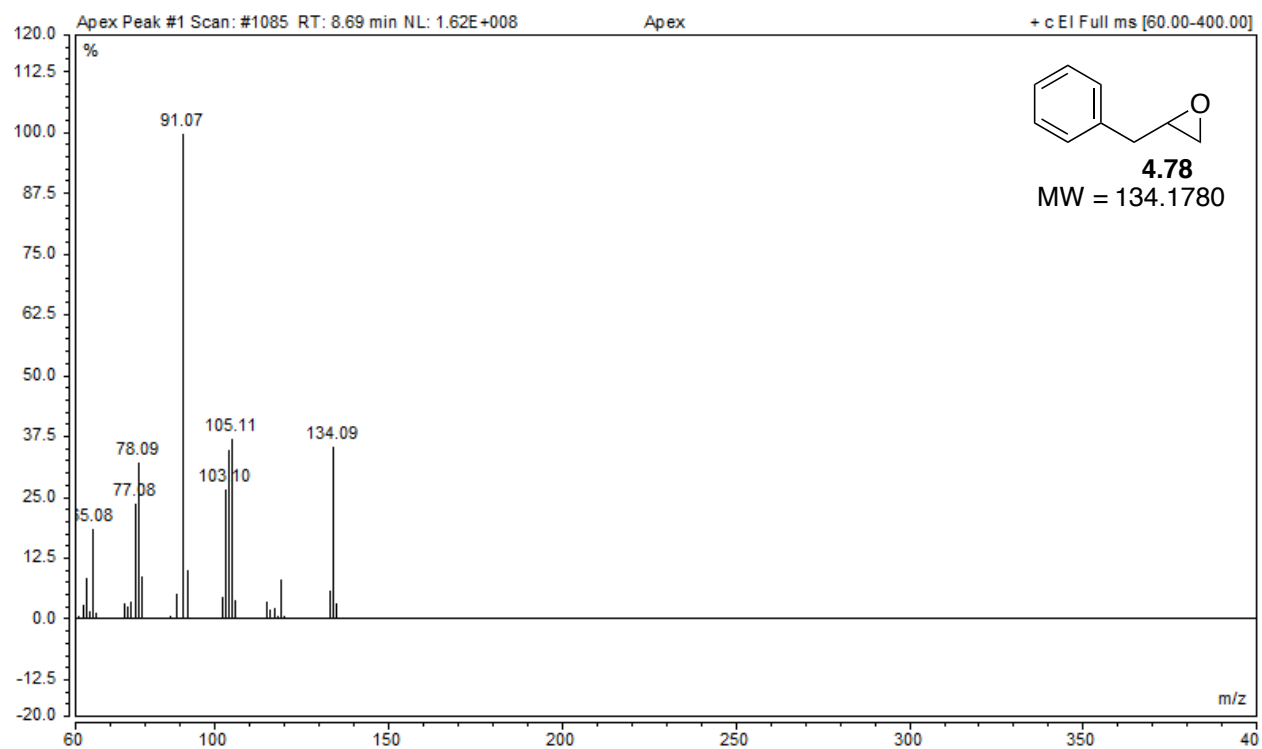


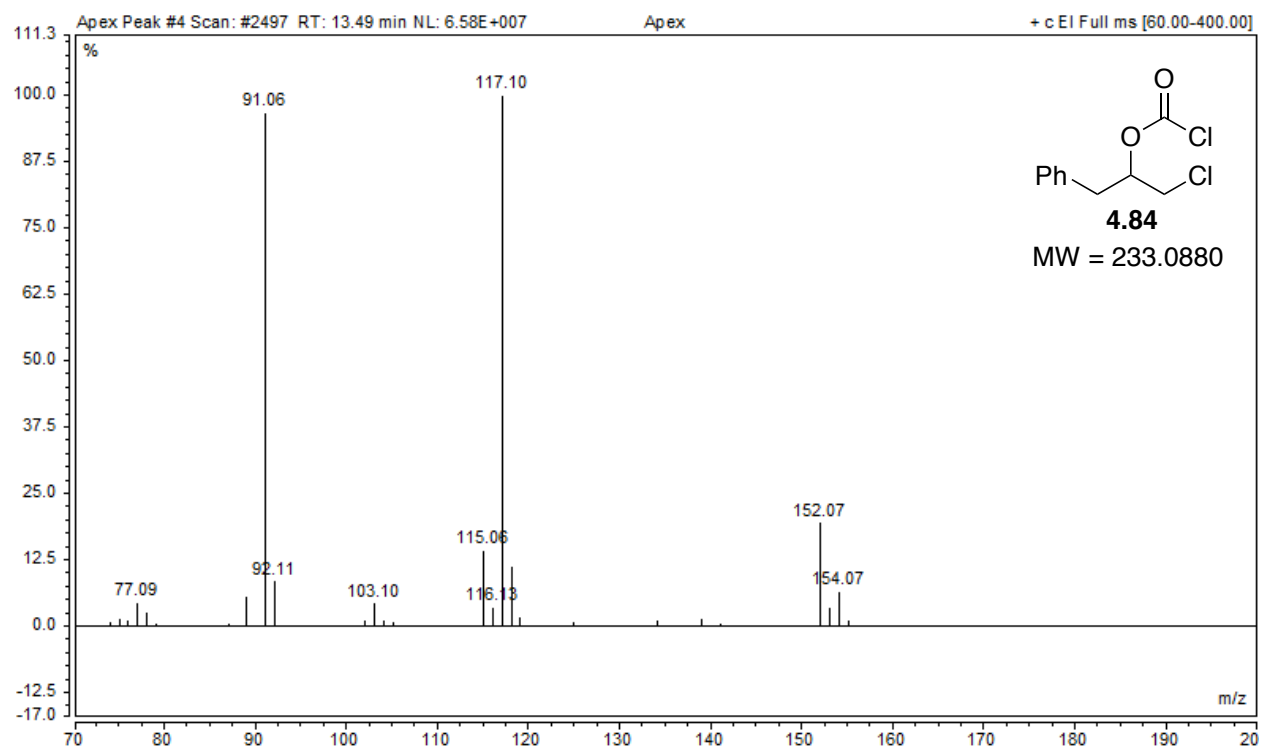
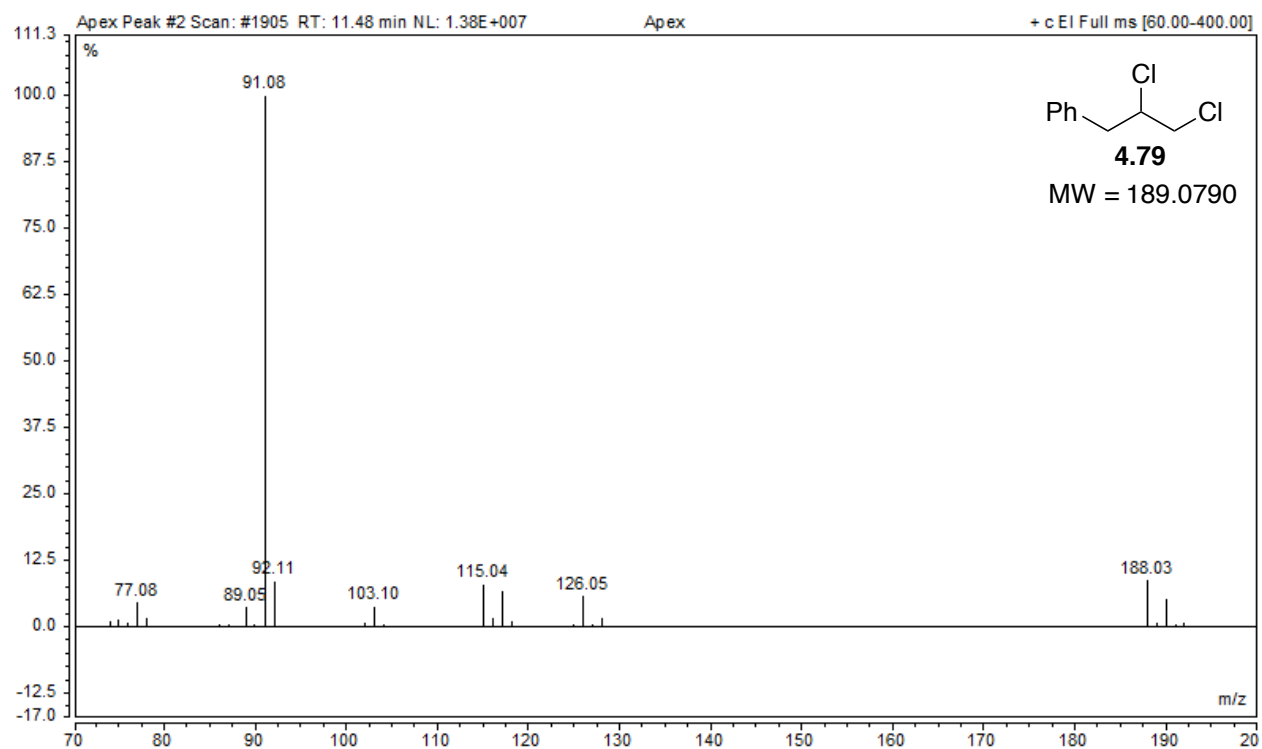
Reaction Time = 120 min



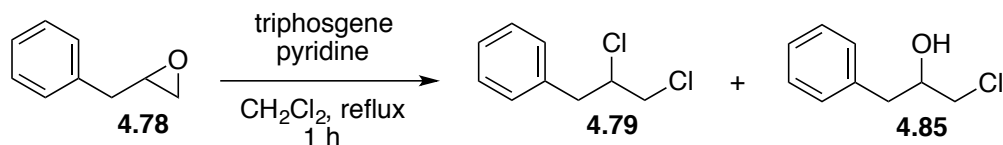
Reaction Time = 210 min







Isolation of 1-chloro-3-phenylpropan-2-ol (**4.85**)



Epoxide **4.78** (288 mg, 2.15 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (4.3 mL), followed by the addition of triphosgene (317 mg, 1.07 mmol). After complete dissolution of triphosgene, pyridine (347 μL , 4.29 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour the reaction was quenched prematurely with 2 M HCl (3 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 5% - 15% EtOAc in hexanes gradient to afford halohydrin **4.85** (210 mg, 1.23 mmol) and dichloride **4.79** (66 mg, 0.349 mmol).

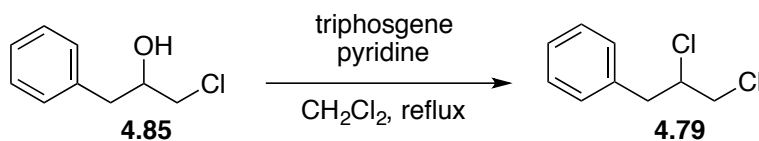
^1H NMR (400 MHz, CDCl_3) δ 7.38 – 7.31 (m, 2H), 7.30 – 7.21 (m, 3H), 4.11 – 4.02 (m, 1H), 3.62 (dd, J = 11.3, 3.9 Hz, 1H), 3.51 (dd, J = 11.2, 6.2 Hz, 1H), 2.90 (d, J = 6.6 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 136.99, 129.31, 128.65, 126.79, 77.32, 77.00, 76.68, 72.20, 49.14, 40.57.

IR (cm^{-1}): f = 3389, 3028, 2952, 2922, 1602, 1495, 1454, 1298, 1196, 1083, 1044, 960, 914, 885, 830, 744, 625, 556, 499.

HRMS-ESI: ($\text{M}+\text{H}^+-\text{H}_2\text{O}$) = 153.0466 calculated for $\text{C}_9\text{H}_{10}\text{Cl}$, experimental = 153.0464.

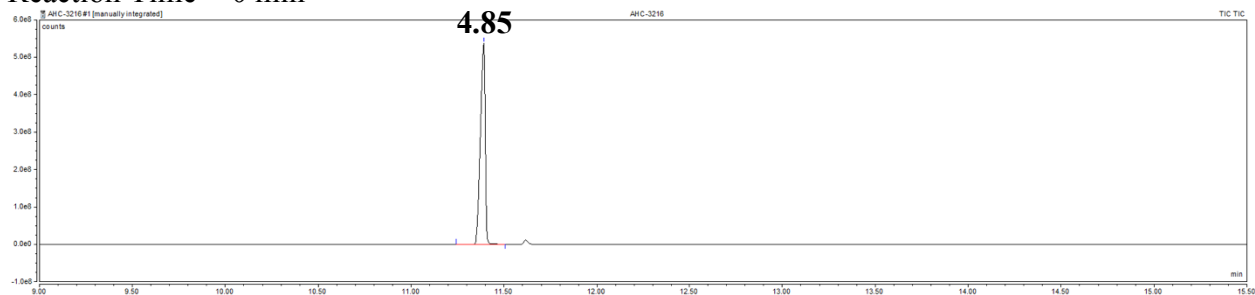
Synthesis of (2,3-dichloropropyl)benzene (**4.79**) from 1-chloro-3-phenylpropan-2-ol (**4.85**)



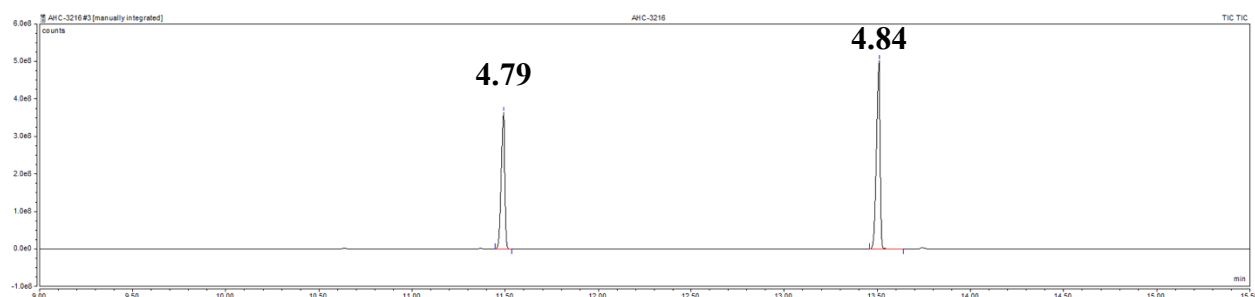
Chlorohydrin **4.85** (53 mg, 0.311 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (0.6 mL), followed by the addition of triphosgene (46 mg, 0.155 mmol). After complete dissolution of triphosgene, pyridine (50 μL , 0.621 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.79** as a clear oil in 86% yield (50 mg, 0.265 mmol). NMR spectra are identical to those of dichloride **4.79** prepared from epoxide **4.78**.

Retention Time: t_R **4.85** = 11.39 min; t_R **4.79** = 11.49 min; t_R **4.84** = 13.50 min.

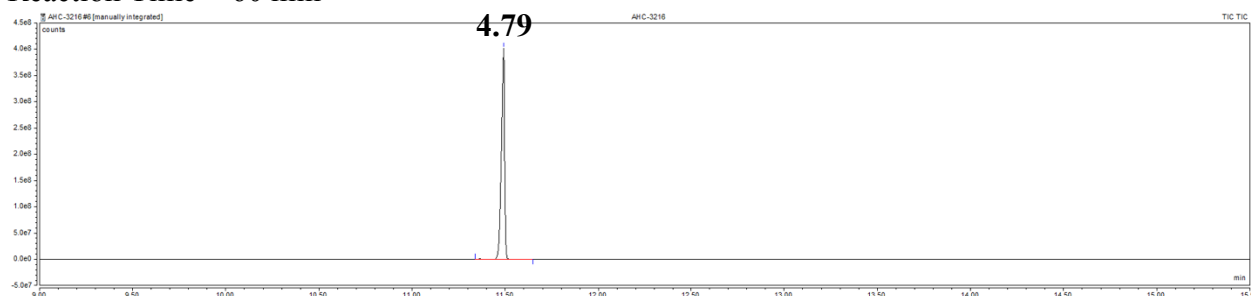
Reaction Time = 0 min



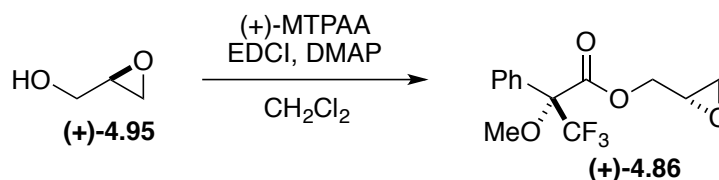
Reaction Time = 20 min



Reaction Time = 60 min



((*S*)-oxiran-2-yl)methyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((+)-4.86)



(*R*)-(+)- α -Methoxy- α -trifluoromethylphenylacetic acid (72 mg, 0.306 mmol) was added to a 50-mL round-bottom flask followed by (*R*)-glycidol **(+)-4.95** (19 μ L, 0.291 mmol). The two components were then dissolved in CH_2Cl_2 (2.9 mL) and stirred vigorously. EDCI (84 mg, 0.436 mmol) and DMAP (39 mg, 0.320 mmol) were subsequently added and dissolved. After 6 hours, the reaction was determined to be complete by TLC analysis and quenched with H_2O (2 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a gradient of 20% EtOAc/Hex affording **(+)-4.86** as a clear oil in 45% yield (38 mg, 0.131 mmol).

^1H NMR (400 MHz, CDCl_3) δ 7.57 – 7.50 (m, 2H), 7.44 – 7.36 (m, 3H), 4.66 (dd, J = 12.4, 3.2 Hz, 1H), 4.21 (dd, J = 12.3, 5.6 Hz, 1H), 3.57 (s, 3H), 3.29 – 3.23 (m, 1H), 2.86 – 2.80 (m, 1H), 2.66 (dd, J = 4.8, 2.6 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 166.4, 132.0, 129.7, 128.5, 127.3, 127.3, 124.6, 121.7, 65.9, 55.5, 48.7, 44.1.

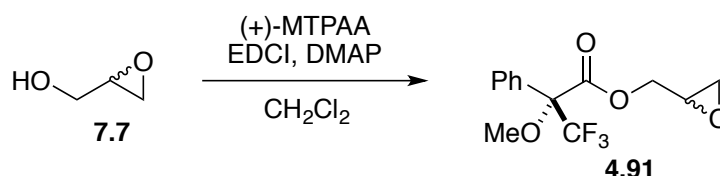
¹⁹F NMR (376 MHz, CDCl₃) δ -71.77.

IR (cm⁻¹): ν = 3004, 2953, 2925, 2850, 1749, 1451, 1346, 1165, 1081, 999, 901, 817, 764, 717, 645, 580, 508, 426.

HRMS-ESI: (M+H⁺) = 291.0839 calculated for C₁₃H₁₄F₃O₄, experimental = 291.0841.

[α]_D²⁵ = +80.4° (*c* = 1 CDCl₃).

oxiran-2-ylmethyl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (7.7)



(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (72 mg, 0.307 mmol) was added to a 50-mL round-bottom flask followed by glycidol **7.7** (19 μL, 0.293 mmol). The two components were then dissolved in CH₂Cl₂ (2.9 mL) and stirred vigorously. EDCI (84 mg, 0.439 mmol) and DMAP (39 mg, 0.322 mmol) were subsequently added and dissolved. After 6 hours, the reaction was determined to be complete by TLC analysis and quenched with H₂O (2 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography using a gradient of 20% EtOAc/Hex eluting **4.91** as an inseparable mixture of diastereomers, as a clear oil in 45% yield (38 mg, 0.131 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.58 – 7.50 (m, 7H), 7.47 – 7.37 (m, 10H), 4.69 – 4.58 (m, 2H), 4.23 – 4.17 (m, 2H), 3.57 (s, 6H), 3.28 – 3.21 (m, 2H), 2.86 – 2.80 (m, 2H), 2.68 – 2.61 (m, 2H).

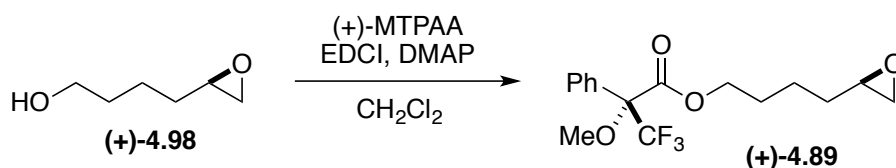
¹³C NMR (126 MHz, CDCl₃) δ 166.3, 132.0, 131.9, 129.7, 128.5, 127.3, 124.3, 122.0, 77.3, 66.3, 65.9, 55.5, 48.7, 48.7, 44.5, 44.5.

¹⁹F NMR (376 MHz, CDCl₃) δ -71.77.

IR (cm⁻¹): $\tilde{\nu}$ = 2956, 2924, 2850, 1749, 1451, 1345, 1242, 1165, 1119, 1081, 1020, 999, 901, 848, 801, 764, 717, 697, 645, 551, 509, 424.

HRMS-ESI: (M+H⁺) = 291.0839 calculated for C₁₃H₁₄F₃O₄, experimental = 291.084.

4-((R)-oxiran-2-yl)butyl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((+)-4.89)



(R)-(+)- α -Methoxy- α -trifluoromethylphenylacetic acid (196 mg, 0.839 mmol) was added to a 50-mL round-bottom flask containing epoxide (+)-4.98 (80 mg, 0.799 mmol).²³⁶ The two components were then dissolved in CH₂Cl₂ (8 mL) and stirred vigorously. EDCI (230 mg, 1.20 mmol) and DMAP (195 mg, 1.60 mmol) were subsequently added and dissolved. After spinning overnight, the reaction was determined to be complete by TLC analysis and quenched with H₂O (5 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography using a 20% EtOAc/Hex gradient affording (+)-4.89 as a clear oil in 51% yield (135 mg, 0.406 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.55 – 7.47 (m, 2H), 7.43 – 7.37 (m, 3H), 4.33 (ddt, J = 24.1, 17.5, 6.6 Hz, 2H), 3.55 (s, 3H), 2.89 – 2.84 (m, 1H), 2.73 (t, J = 4.5 Hz, 1H), 2.43 (dd, J = 5.1, 2.6 Hz, 1H), 1.77 (p, J = 6.9 Hz, 2H), 1.63 – 1.46 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 166.6, 132.3, 129.6, 128.4, 128.3, 127.3, 124.4, 122.2, 84.9, 84.7, 84.5, 84.3, 66.1, 55.4, 51.9, 46.9, 31.8, 28.1, 22.3.

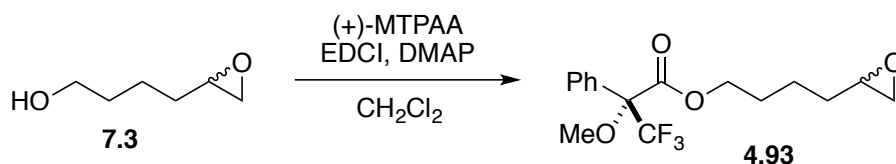
¹⁹F NMR (471 MHz, Chloroform-*d*) δ -71.59.

IR (cm⁻¹): ν = 3045, 2948, 2850, 1745, 1587, 1541, 1452, 1387, 1164, 1080, 997, 916, 882, 821, 732, 697, 599, 550, 463, 409.

HRMS-ESI: (M+ H⁺) = 333.1308 for C₁₆H₂₀F₃O₄, experimental = 333.1302.

[α]_D²⁵ = +47.0° (*c* = 1 CDCl₃).

4-(oxiran-2-yl)butyl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**4.93**)



(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (372 mg, 0.159 mmol) was added to a 50-mL round-bottom flask containing epoxide **7.3** (176 mg, 1.52 mmol). The two components were then dissolved in CH₂Cl₂ (15 mL) and stirred vigorously. EDCI (435 mg, 2.27 mmol) and DMAP (370 mg, 3.03 mmol) were subsequently added and dissolved. After spinning overnight, the reaction was determined to be complete by TLC analysis and quenched with H₂O (5 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography using a 20% EtOAc/Hex gradient affording **4.93** as a clear oil in 40% yield (196 mg, 0.606 mmol).

¹H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.48 (m, 2H), 7.42 – 7.37 (m, 3H), 4.40 – 4.26 (m, 2H), 3.56 (s, 3H), 2.89 – 2.81 (m, 1H), 2.73 (t, *J* = 4.6 Hz, 1H), 2.43 (dd, *J* = 4.7, 2.7 Hz, 1H), 1.81 – 1.70 (m, 2H), 1.63 – 1.43 (m, 5H).

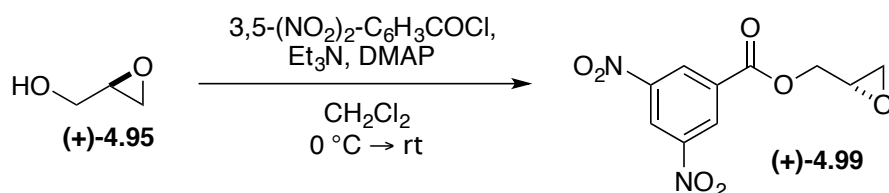
¹³C NMR (126 MHz, CDCl₃) δ 166.55, 132.28, 129.59, 128.40, 127.26, 124.43, 122.14, 84.68, 84.46, 77.25, 77.00, 76.75, 66.13, 66.11, 55.41, 51.90, 51.88, 46.84, 31.80, 28.06, 22.31, 22.30.

¹⁹F NMR (471 MHz, CDCl₃) δ -71.59.

IR (cm⁻¹): ν = 2947, 2849, 1746, 1452, 1411, 1257, 1167, 1122, 1081, 1021, 998, 917, 839, 766, 717, 698, 509.

HRMS-ESI: (M+ H⁺) = 333.1304 for C₁₆H₂₀F₃O₄, experimental = 333.1308.

(S)-oxiran-2-ylmethyl 3,5-dinitrobenzoate ((+)-4.99)



(R)-glycidol **(+)-4.95** (448 μ L, 6.75 mmol) was added to an oven-dried 100-mL round-bottom flask. Triethylamine (2.82 mL, 20.3 mmol) and DMAP (~10 mg) were combined with the epoxide and subsequently dissolved in CH₂Cl₂ (27 mL). The resulting solution was cooled to 0 °C and 3,5-dinitrobenzoyl chloride was added via cannula as a 1 M solution in CH₂Cl₂ (1.80 g, 7.80 mmol, 7.8 mL). The dark orange solution was allowed to warm to room temperature gradually. After 3 hours the reaction was determined to be complete by TLC analysis and 5 mL of 2 M HCl was added to quench. Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography using a 10% - 30% EtOAc/Hex gradient eluting epoxide **(+)-4.99** in 85% (1.78 g, 6.64 mmol) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 9.25 (t, *J* = 2.2 Hz, 1H), 9.19 (d, *J* = 2.2 Hz, 2H), 4.81 (dd, *J* = 13.2, 2.9 Hz, 1H), 4.27 (dd, *J* = 12.3, 6.6 Hz, 1H), 3.40 (tdd, *J* = 6.8, 4.1, 2.7 Hz, 1H), 2.97 (dd, *J* = 4.8, 4.1 Hz, 1H), 2.76 (dd, *J* = 4.8, 2.6 Hz, 1H).

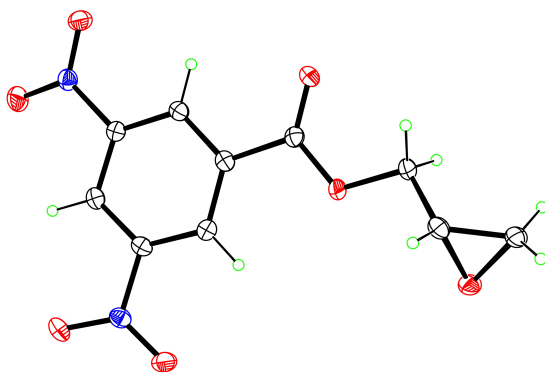
¹³C NMR (101 MHz, CDCl₃) δ 162.3, 148.7, 133.3, 129.6, 122.6, 67.5, 48.9, 44.7.

IR (cm⁻¹): *f* = 3099, 1730, 1629, 1540, 1461, 1342, 1274, 1165, 1077, 982, 921, 864, 773, 719.

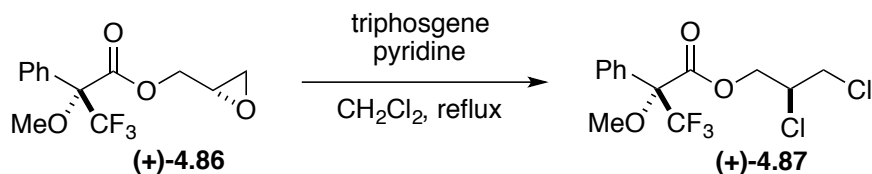
HRMS-ESI: (*M*+*H*⁺) = 269.0404 calculated for C₁₀H₉N₂O₇, experimental = 269.0411.

[α]_D²⁵ = +32.8° (*c* = 1 CDCl₃).

X-Ray Structure:



(*S*)-2,3-dichloropropyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((+)-4.87)



Epoxide **(+)-4.86** (25 mg, 0.0861 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH₂Cl₂ (170 μL), followed by the addition of triphosgene (13 mg, 0.0431 mmol). After complete dissolution of triphosgene, pyridine (14 μL, 0.172 mmol) was

added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 3 hours, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product (+)-**4.87** as a clear oil in 63% yield (19 mg, 0.0550 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.55 – 7.51 (m, 2H), 7.44 – 7.40 (m, 3H), 4.69 (dd, *J* = 12.1, 4.5 Hz, 1H), 4.61 (dd, *J* = 11.7, 5.6 Hz, 1H), 4.32 – 4.26 (m, 1H), 3.74 (dd, *J* = 11.5, 6.1 Hz, 1H), 3.70 (dd, *J* = 11.6, 7.6 Hz, 1H), 3.57 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 166.0, 131.8, 129.8, 128.5, 127.4, 124.3, 122.0, 65.7, 55.8, 55.5, 44.0.

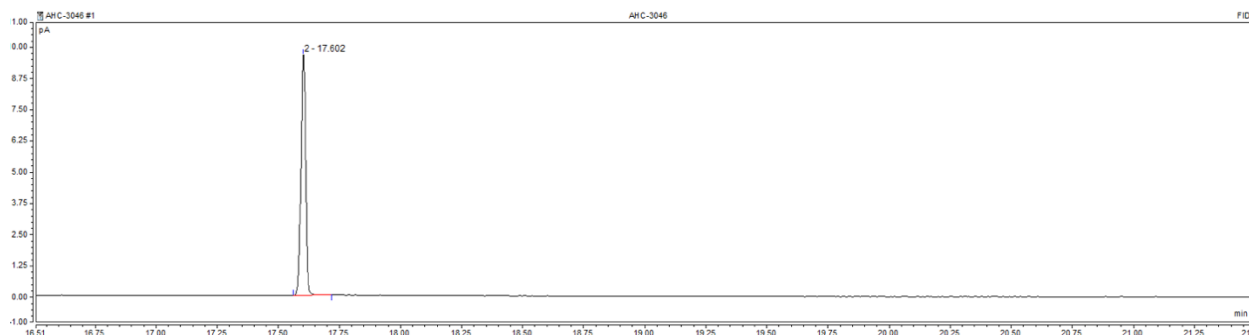
¹⁹F NMR (471 MHz, CDCl₃) δ -71.66.

IR (cm⁻¹): *f* = 2965, 2850, 1754, 1493, 1380, 1238, 1120, 1107, 1017, 873, 764, 696, 642, 568, 508.

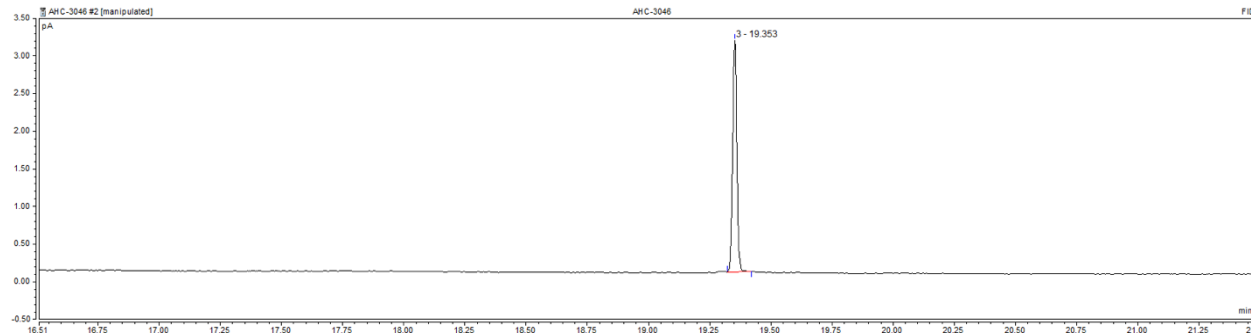
HRMS-ESI: (M+H⁺) = 345.0267 calculated for C₁₃H₁₄Cl₂F₃O₃, experimental = 345.0262.

[α]_D²⁵ = +15.6° (*c* = 1 CDCl₃).

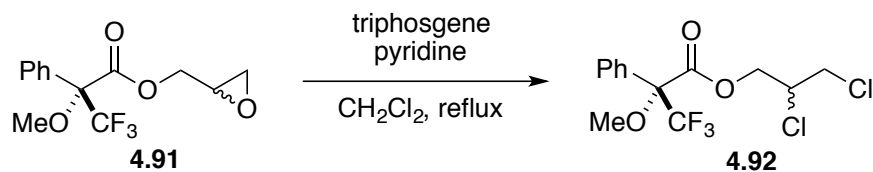
GC Trace of Epoxide (+)-**4.86**



GC Trace of Dichloride (+)-**4.87**



oxiran-2-ylmethyl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**4.92**)



Epoxide **4.91** (54 mg, 0.186 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (370 μL), followed by the addition of triphosgene (27 mg, 0.0930 mmol). After complete dissolution of triphosgene, pyridine (30 μL , 0.372 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 3 hours, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.92** as a clear oil in 62% yield (40 mg, 0.116 mmol).

^1H NMR (500 MHz, CDCl_3) δ 7.57 – 7.51 (m, 4H), 7.48 – 7.38 (m, 6H), 4.72 – 4.59 (m, 4H), 4.32 – 4.26 (m, 2H), 3.76 – 3.63 (m, 4H), 3.60 – 3.56 (m, 6H).

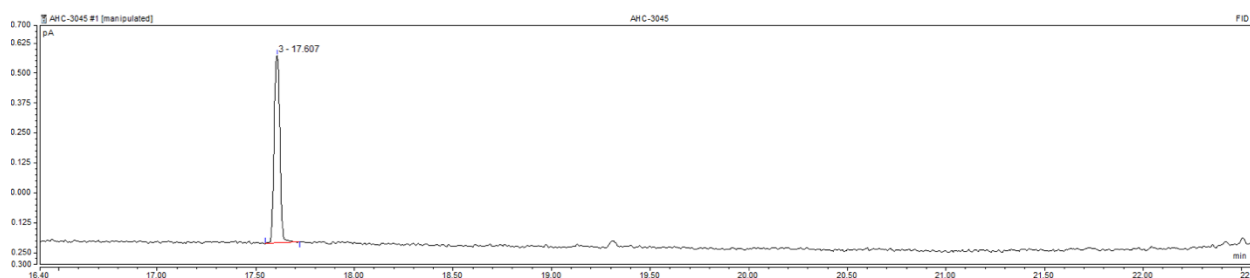
^{13}C NMR (126 MHz, CDCl_3) δ 166.0, 131.8, 129.8, 128.5, 127.3, 127.3, 124.3, 122.0, 65.6, 65.5, 55.8, 55.7, 55.6, 55.6, 44.0, 43.9.

^{19}F NMR (471 MHz, CDCl_3) δ -71.66, -71.73.

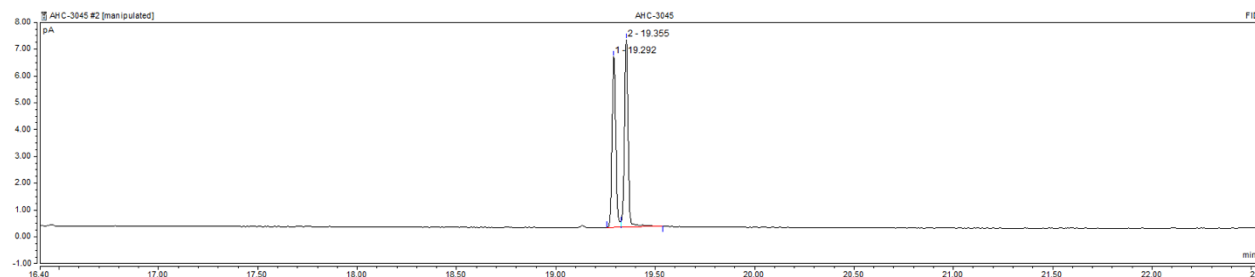
IR (cm^{-1}): ν = 2953, 2850, 1753, 1494, 1451, 1379, 1236, 1165, 1120, 1081, 1017, 914, 814, 764, 717, 696, 641, 568, 549, 507.

HRMS-ESI: ($\text{M}+\text{H}^+$) = 345.0267 calculated for $\text{C}_{13}\text{H}_{14}\text{Cl}_2\text{F}_3\text{O}_3$, experimental = 345.0271.

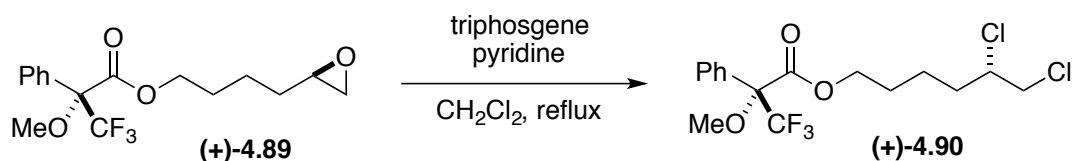
GC Trace of Epoxide **4.91**



GC Trace of Dichloride **4.92**



(S)-5,6-dichlorohexyl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((+)-4.90)



Epoxide **(+)-4.89** (74 mg, 0.223 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (0.5 mL), followed by the addition of triphosgene (33 mg,

0.111 mmol). After complete dissolution of triphosgene, pyridine (36 μ L, 0.445 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product (+)-**4.90** as a clear oil in 78% yield (67 mg, 0.173 mmol).

^1H NMR (500 MHz, CDCl_3) δ 7.54 – 7.50 (m, 2H), 7.43 – 7.39 (m, 3H), 4.38 (dt, J = 11.0, 6.4 Hz, 1H), 4.31 (dt, J = 11.0, 6.4 Hz, 1H), 3.97 (tdd, J = 8.6, 5.0, 3.5 Hz, 1H), 3.74 (dd, J = 11.3, 5.0 Hz, 1H), 3.59 (dd, J = 11.4, 7.8 Hz, 1H), 3.56 (d, J = 1.5 Hz, 3H), 2.04 – 1.95 (m, 1H), 1.81 – 1.68 (m, 3H), 1.68 – 1.58 (m, 1H), 1.51 – 1.42 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 166.6, 132.4, 129.6, 128.4, 128.3, 127.3, 124.5, 122.2, 84.8, 84.5, 65.9, 60.6, 55.4, 47.9, 34.4, 27.8, 22.24.

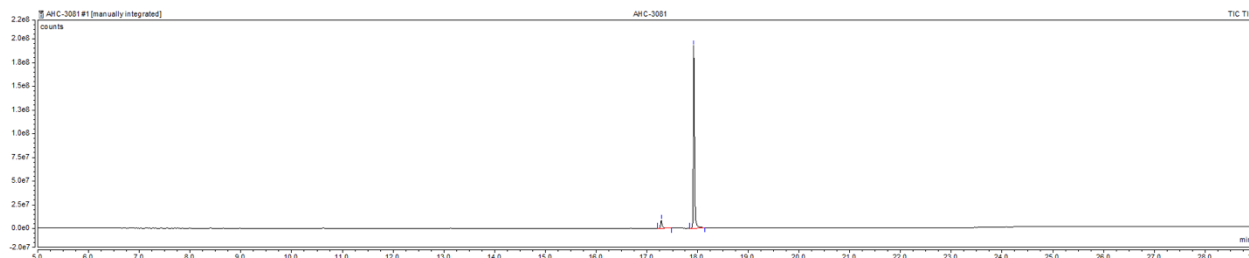
^{19}F NMR (471 MHz, CDCl_3) δ -71.56.

IR (cm^{-1}): ν = 2952, 2849, 1745, 1495, 1265, 1121, 1021, 998, 818, 731, 662, 549, 409.

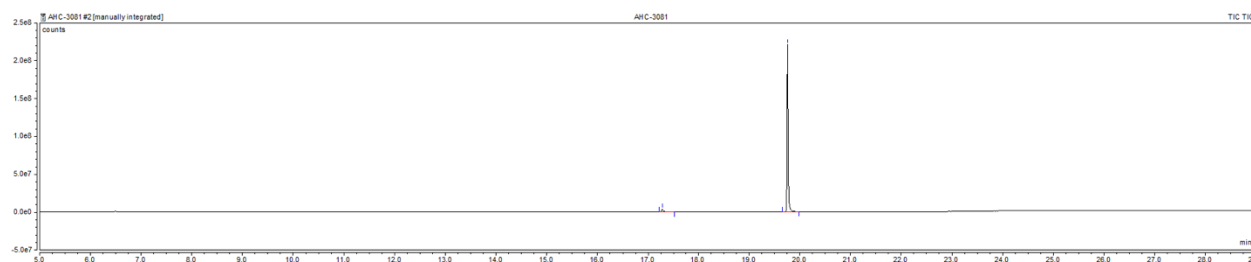
HRMS-ESI: ($\text{M} + \text{H}^+$) = 387.0736 calculated for $\text{C}_{16}\text{H}_{20}\text{Cl}_2\text{F}_3\text{O}_3$, experimental = 387.0733.

$[\alpha]^{20}_{\text{D}}$ = +21.6° (c = 1, CDCl_3).

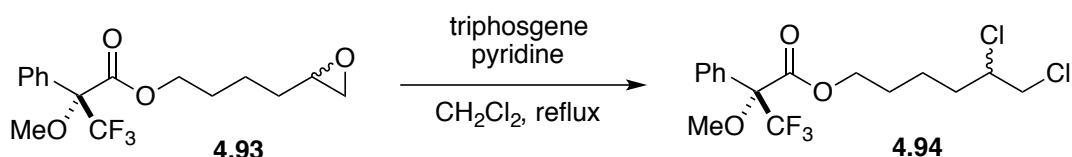
GC Trace for Epoxide (+)-**4.89**



GC Trace for Dichloride (+)-**4.90**



5,6-dichlorohexyl (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**4.94**)



Epoxide **4.93** (86 mg, 0.266 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (0.5 mL), followed by the addition of triphosgene (40 mg, 0.133 mmol). After complete dissolution of triphosgene, pyridine (43 μL , 0.532 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After 1 hour, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (1 mL). Upon separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **4.94** as a clear oil in 70% yield (72 mg, 0.186 mmol).

^1H NMR (400 MHz, Chloroform-*d*) δ 7.55 – 7.50 (m, 2H), 7.43 – 7.38 (m, 3H), 4.41 – 4.27 (m, 2H), 4.02 – 3.94 (m, 1H), 3.74 (dd, J = 11.2, 5.2 Hz, 1H), 3.59 (dd, J = 11.3, 8.0, 1.3 Hz, 1H), 3.56 (s, 3H), 2.05 – 1.95 (m, 1H), 1.83 – 1.55 (m, 4H), 1.52 – 1.39 (m, 1H).

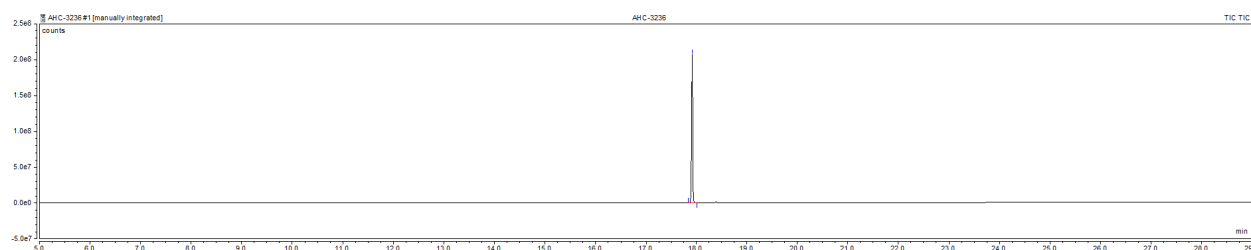
^{13}C NMR (126 MHz, CDCl_3) δ 166.55, 132.27, 129.62, 128.44, 127.25, 124.43, 122.14, 84.70, 84.47, 60.59, 60.57, 55.45, 47.90, 34.38, 27.76, 22.22.

^{19}F NMR (471 MHz, CDCl_3) δ -71.59.

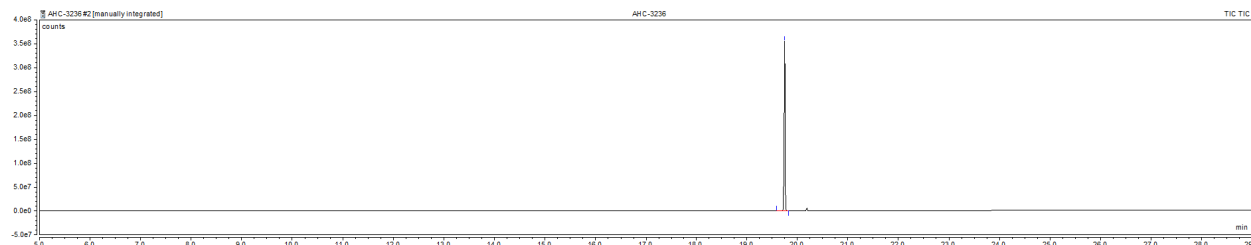
IR (cm^{-1}): ν = 2953, 2847, 1745, 1494, 1451, 1258, 1164, 1120, 1081, 918, 804, 765, 716, 697, 662, 549, 509.

HRMS-ESI: ($\text{M} + \text{H}^+$) = 387.0736 calculated for $\text{C}_{16}\text{H}_{20}\text{Cl}_2\text{F}_3\text{O}_3$, experimental = 387.0744.

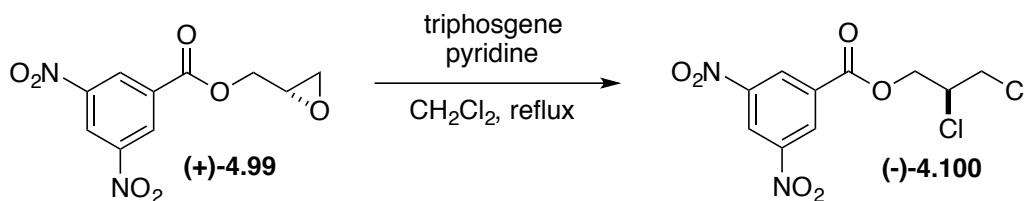
GC Trace for Epoxide **4.93**



GC Trace for Dichloride **4.94**



(S)-2,3-dichloropropyl 3,5-dinitrobenzoate ((-)-**4.100**)



Epoxide **(+)-4.99** (166 mg, 0.619 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH_2Cl_2 (1.2 mL), followed by the addition of triphosgene (92 mg, 0.309 mmol). After complete dissolution of triphosgene, pyridine (100 μL , 1.24 mmol) was added.

The vessel was sealed and heated to gentle reflux in a warm sand bath. After 3 hours, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (2 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **(-)-4.100** as a clear oil in 81% yield (161 mg, 0.498 mmol).

¹H NMR (400 MHz, CDCl₃) δ 9.26 (t, *J* = 2.0 Hz, 1H), 9.17 (d, *J* = 2.0 Hz, 2H), 4.85 (dd, *J* = 11.6, 4.1 Hz, 1H), 4.75 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.49 – 4.41 (m, 1H), 3.93 (dd, *J* = 11.6, 4.7 Hz, 1H), 3.85 (dd, *J* = 11.7, 8.2 Hz, 1H).

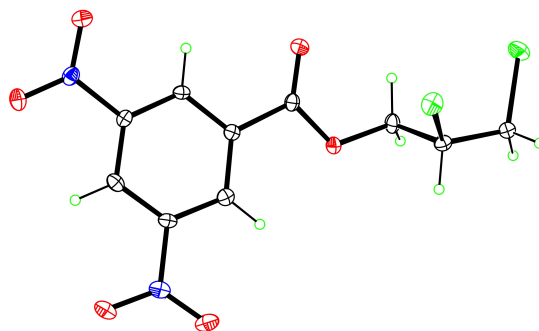
¹³C NMR (126 MHz, CDCl₃) δ 161.9, 148.8, 133.0, 129.5, 122.8, 66.475 56.2, 44.3.

IR (cm⁻¹): *f* = 3124, 3107, 3097, 1729, 1543, 1446, 1390, 1365, 1329, 1294, 1256, 1168, 1075, 987, 910, 818, 716, 631, 571, 472.

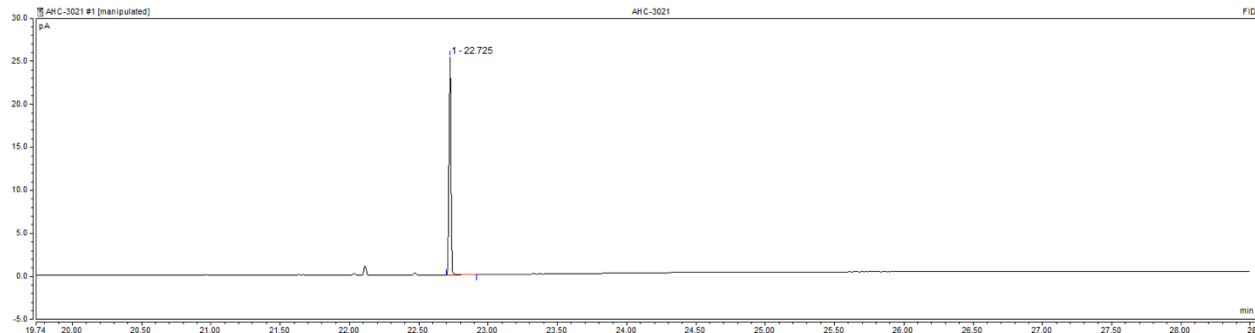
HRMS-ESI: (*M*+Cl⁻) = 356.9453 calculated for C₁₀H₈Cl₃N₂O₆, experimental = 356.9456.

[α]_D²⁵ = -21.0° (*c* = 1 CDCl₃).

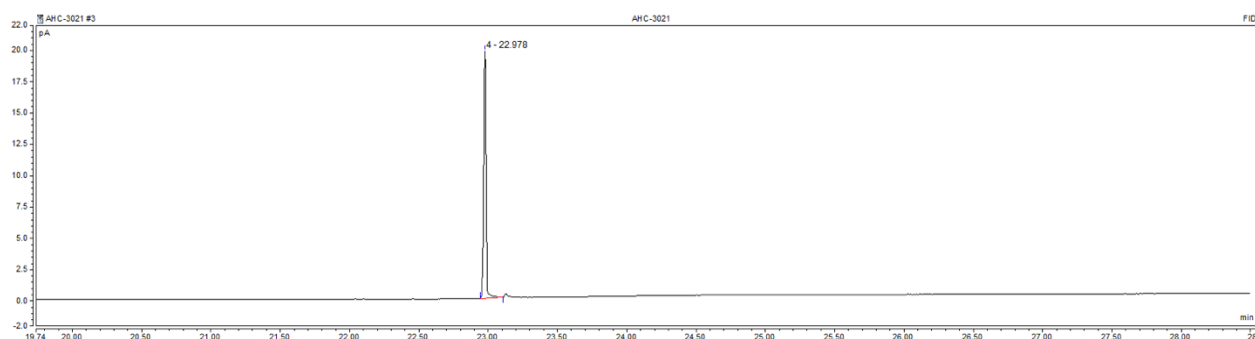
X-Ray Structure:



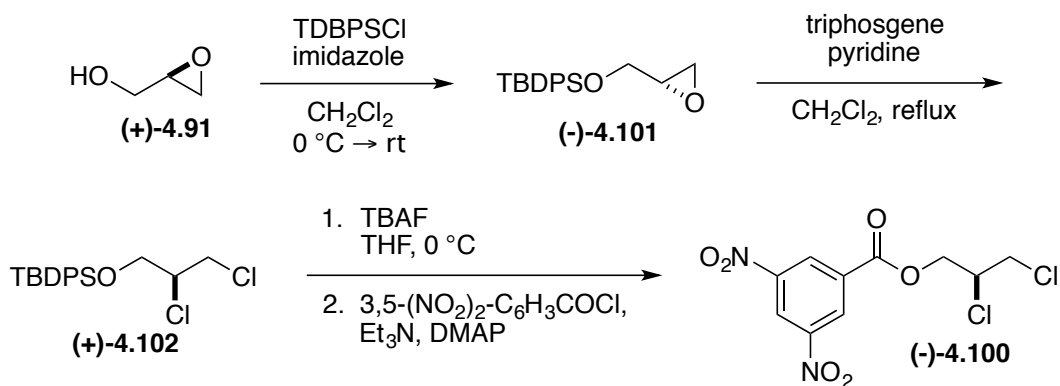
GC Trace for Epoxide (+)-4.99



GC Trace for Dichloride (-)-4.100



Exclusion of Anchimeric Assistance



(S)-tert-butyl(oxiran-2-ylmethoxy)diphenylsilane ((-)-4.101)

(R)-glycidol (+)-4.91 (250 μL , 3.77 mmol) was added to a 100-mL round-bottom flask and dissolved in THF (25 mL). After cooling the solution to 0 $^\circ\text{C}$, imidazole (513 mg, 7.53 mmol) was added in one portion followed by the dropwise addition of TBDPSCI (1.25 mL, 4.90 mmol).

After warming to room temperature overnight, the reaction was quenched with NaHCO₃ (5 mL). Upon separation of the two layers, the aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic layers were, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography using a 2% EtOAc/Hex gradient affording **(-)-4.101** as a clear oil in 72% yield (1.00 g, 3.20 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.71 – 7.67 (m, 4H), 7.46 – 7.37 (m, 6H), 3.85 (dd, *J* = 11.9, 3.4 Hz, 1H), 3.71 (dd, *J* = 11.7, 4.8 Hz, 1H), 3.16 – 3.09 (m, 1H), 2.75 (t, *J* = 4.6 Hz, 1H), 2.61 (dd, *J* = 5.2, 2.5 Hz, 1H), 1.06 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 135.6, 135.6, 133.3, 129.7, 127.707 64.3, 52.3, 44.5, 26.7, 19.24.
[α]_D²⁰ = -2.9° (*c* = 1, CDCl₃).

(S)-tert-butyl(2,3-dichloropropoxy)diphenylsilane ((+)-4.102)

Epoxide **(-)-4.101** (454 mg, 0.145 mmol) was added to a 15-mL pressure vessel. This compound was dissolved in CH₂Cl₂ (2.9 mL), followed by the addition of triphosgene (215 mg, 0.726 mmol). After complete dissolution of triphosgene, pyridine (235 μL, 2.90 mmol) was added. The vessel was sealed and heated to gentle reflux in a warm sand bath. After stirring overnight, the starting material was fully consumed as determined by GC analysis. The reaction was cooled to room temperature and quenched with 2 M HCl (3 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography using a 10% EtOAc in hexanes gradient to afford product **(+)-4.102** as a clear oil in 88% yield (473 mg, 1.29 mmol).

¹H NMR (400 MHz, CDCl₃) δ 7.73 – 7.67 (m, 4H), 7.49 – 7.39 (m, 6H), 4.15 – 4.07 (m, 1H), 4.04 – 3.96 (m, 2H), 3.88 (m, 2H), 1.10 (s, 9H).

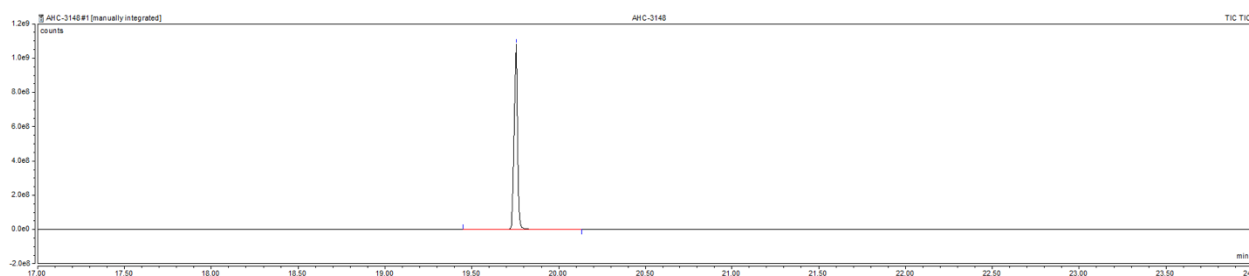
¹³C NMR (126 MHz, CDCl₃) δ 135.6, 135.5, 132.8, 132.7, 129.9, 127.8, 127.8, 64.1, 60.1, 44.8, 26.7, 19.3.

IR (cm⁻¹): $\tilde{\nu}$ = 3071, 3050, 2958, 2930, 2892, 2857, 1589, 1427, 1362, 1294, 1215, 1135, 1083, 1006, 936, 822, 731, 672, 613, 503, 425.

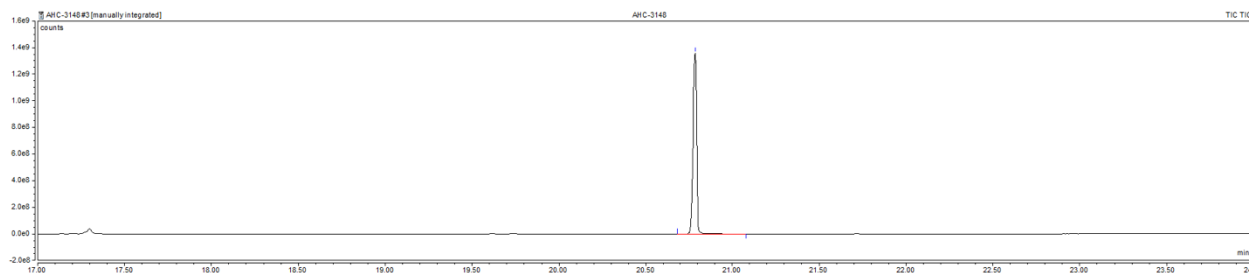
HRMS-ESI: (M+ H⁺) = 367.1046 calculated for C₁₉H₂₅Cl₂Osi, experimental = 367.1055.

[α]_D²⁰ = +21.6° (c = 1, CDCl₃)

GC Trace for Epoxide (-)-4.101



GC Trace for Dichloride (+)-4.102



(S)-2,3-dichloropropyl 3,5-dinitrobenzoate ((-)-4.100)

Dichloride (+)-4.201 (383 mg, 1.04 mmol) was added via cannula in THF (5.2 mL) to an oven-dried 50-mL round-bottom flask. The resulting solution was subsequently cooled to 0 °C and TBAF (1.56 mL, 1.56 mmol) was added slowly, dropwise. After 20 minutes, the reaction

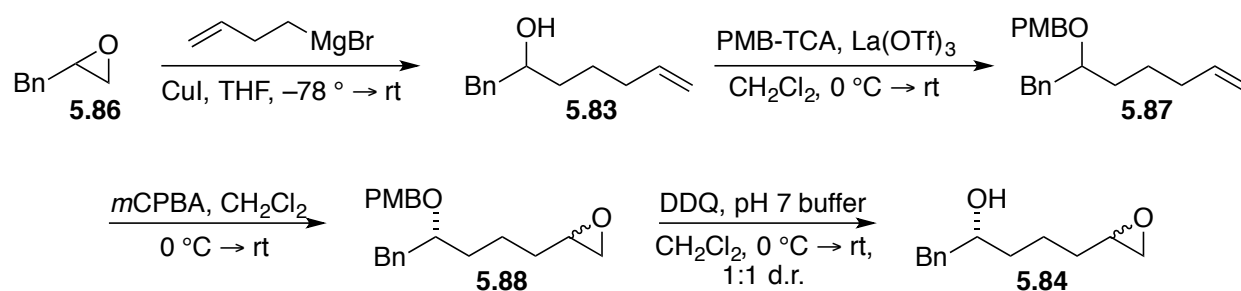
warmed to room temperature. After 1 hour, the dichloride had been completely consumed as determined by TLC analysis. The solution was then cooled back to 0 °C and Et₃N (435 μL, 3.12 mmol) was added. A solution of 3,5-dinitrobenzoyl chloride (252 mg, 1.09 mmol) and DMAP (13 mg, 0.104 mmol) was prepared in a conical flask dissolved THF (~3 mL). This pale yellow solution was subsequently added via cannula to the cooled flask containing the deprotected dichloride and Et₃N. After 3 hours, no deprotected dichloride was detected by TLC, and the reaction was quenched with NaHCO₃ (5 mL). Upon separation of the two layers, the aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic layers were, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by column chromatography using an isocratic gradient of 1% EtOAc/Hex gradient affording (-)-**4.100** as a white solid in 58% yield (194 mg, 0.600 mmol).

$[\alpha]^{20}_{\text{D}} = -20.0^{\circ}$ ($c = 0.8$, CDCl₃).

NMR spectra are identical to those of dichloride (-)-**4.100** prepared from epoxide (+)-**4.99**.

Experimental Procedures for Chapter 5

5-(oxiran-2-yl)-1-phenylpentan-2-ol (**5.84**)



1-phenylhept-6-en-2-ol (**5.83**)

Freshly ground Mg turnings (1.81 g, 74.5 mmol) were added to a 250-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic

I₂ (1–2 crystals) was added and the apparatus was heated gently to sublime the I₂ and coat the Mg turnings. Once coated, THF (20 mL) was added to cover the Mg. 4-bromo-1-butene (7.9 mL, 78.3 mmol) was subsequently added to the addition funnel and dissolved in THF (30 mL). The solution of alkyl bromide was then slowly added to the slurry of magnesium turnings, dropwise. After complete addition of 4-bromo-1-butene, the translucent solution was refluxed for 1 hour to consume the remaining Mg. After 1 hour, a 250-mL round-bottom flask was charged with CuI (1.42 g, 7.46 mmol) and combined with THF (30 mL). The resulting slurry was then cooled to –78 °C. Once cooled the solution of 3-butenylmagnesium bromide was transferred from the three-neck flask to the 250-mL round-bottom containing the cooled slurry of CuI via cannula. After approximately 30 minutes, benzyl oxirane **5.86** (5.00 g, 37.3 mmol) was added via cannula in a solution of THF (20 mL). After complete addition of **5.86** the reaction was allowed to warm to room temperature gradually. After 3 hours the reaction was determined to be complete by TLC analysis and then cooled to 0 °C and quenched with saturated NH₄Cl (20 mL). Upon separation of two layers the aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% EtOAc in hexanes gradient affording **5.83** as a clear oil in quantitative yield (7.10 g, 37.3 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.21 (m, 3H), 5.82 (ddt, *J* = 17.0, 10.4, 6.7 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.99 – 4.94 (m, 1H), 3.86 – 3.80 (m, 1H), 2.84 (dd, *J* = 13.5, 4.2 Hz, 1H), 2.65 (dd, *J* = 13.6, 8.5 Hz, 1H), 2.14 – 2.05 (m, 2H), 1.68 – 1.40 (m, 5H).

¹³C NMR (126 MHz, CDCl₃) δ 138.7, 138.5, 129.4, 128.6, 126.5, 114.6, 72.5, 44.1, 36.2, 33.7, 25.0.

1-methoxy-4-(((1-phenylhept-6-en-2-yl)oxy)methyl)benzene (**5.87**)

Alcohol **5.83** (1.05 g, 6.72 mmol) was combined with PMB-TCA (2.85 g, 10.1 mmol) in a 100-mL round bottom flask. CH₂Cl₂ (17 mL) was added and the resulting solution was cooled to 0 °C. La(OTf)₃ (785 mg, 1.34 mmol) was then added and the reaction was allowed to warm to room temperature overnight. After stirring overnight, the reaction was determined to be complete based on TLC analysis and diluted with DI H₂O (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **5.87** as a clear oil in 77% yield (1.61 g, 5.18 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.27 (m, 2H), 7.23 – 7.19 (m, 3H), 7.17 – 7.15 (m, 2H), 6.86 – 6.83 (m, 2H), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.97 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.95 – 4.91 (m, 1H), 4.38 (s, 2H), 3.80 (s, 3H), 3.57 (p, *J* = 6.0 Hz, 1H), 2.89 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.75 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.04 – 1.98 (m, 2H), 1.60 – 1.48 (m, 3H), 1.46 – 1.38 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 159.1, 139.2, 138.8, 130.9, 129.5, 129.4, 128.2, 126.0, 114.4, 113.7, 79.8, 77.3, 77.2, 77.0, 76.7, 71.1, 55.3, 40.9, 33.7, 33.5, 24.7.

IR: *f*(cm⁻¹) = 3027, 2999, 2859, 1639, 1611, 1511, 1453, 1441, 1172, 1082, 994, 910, 820, 740, 699, 517.

HRMS-ESI: (M+H⁺) = 311.20056 calculated for C₂₁H₂₇O₂, experimental 311.19757.

2-(4-((4-methoxybenzyl)oxy)-5-phenylpentyl)oxirane (**5.88**)

PMB ether **5.87** (2.85 g, 9.18 mmol) was added to a 100-mL round-bottom flask and dissolved in CH₂Cl₂ (18 mL). *m*CPBA (2.73 g, 11.0 mmol, 70 wt %) was added and the reaction

was stirred at room temperature. After stirring overnight the reaction was determined to be complete by TLC analysis and quenched with saturated NaHCO₃ (15 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 20% gradient of EtOAc in hexanes affording **5.88** and a clear oil in 78% yield (2.35 g, 7.20 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.27 (m, 2H), 7.23 – 7.19 (m, 3H), 7.17 (dd, *J* = 8.6, 3.7 Hz, 2H), 6.84 (dd, *J* = 8.6, 1.2 Hz, 2H), 4.42 – 4.36 (m, 2H), 3.80 (s, 3H), 3.58 (p, *J* = 6.0 Hz, 1H), 2.91 (ddd, *J* = 13.7, 6.3, 3.5 Hz, 1H), 2.88 – 2.84 (m, 1H), 2.77 – 2.70 (m, 2H), 2.41 (ddd, *J* = 7.7, 5.0, 2.7 Hz, 1H), 1.68 – 1.59 (m, 1H), 1.58 – 1.51 (m, 3H), 1.51 – 1.44 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 159.1, 139.0, 130.7, 130.7, 129.5, 129.4, 129.4, 128.3, 126.1, 113.7, 79.7, 79.7, 71.2, 71.1, 55.3, 52.2, 52.2, 47.1, 47.0, 40.8, 40.8, 33.8, 33.8, 32.5, 32.4, 22.0, 21.9.

IR: *f* (cm⁻¹) = 3027, 2998, 2860, 1611, 1512, 1495, 1441, 1348, 1301, 1245, 1172, 1083, 1033, 913, 821, 743, 700, 607, 548, 514.

HRMS-ESI: (M+Na⁺) = 349.17742 calculated for C₂₁H₂₆NaO₃, experimental 349.17727.

5-(oxiran-2-yl)-1-phenylpentan-2-ol (5.84**)**

Epoxide **5.88** (384 mg, 1.17 mmol) was combined with CH₂Cl₂ (5.8 mL) and pH 7 buffer (580 μL) in a 50-mL round-bottom flask. The resulting biphasic solution was cooled to 0 °C then DDQ (320 mg, 1.41 mmol) was added in one portion. After 1 hour, the reaction was determined to be complete by TLC analysis and diluted with DI H₂O (5 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and

concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% to 50% gradient of EtOAc in hexanes affording **5.84** as a clear oil in 77% yield (186 mg, 0.902 mmol).

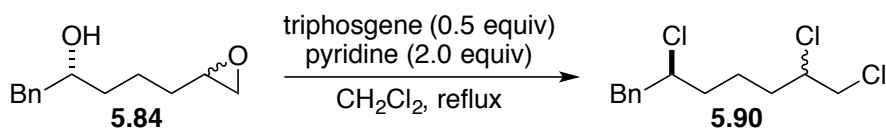
¹H NMR (500 MHz, CDCl₃) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.20 (m, 3H), 3.87 – 3.80 (m, 1H), 2.94 – 2.90 (m, 1H), 2.84 (ddd, *J* = 13.6, 4.4, 2.5 Hz, 1H), 2.75 (t, *J* = 4.8 Hz, 1H), 2.67 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.47 (td, *J* = 4.9, 2.7 Hz, 1H), 1.73 – 1.66 (m, 1H), 1.65 – 1.53 (m, 5H).

¹³C NMR (126 MHz, CDCl₃) δ 138.4, 129.4, 128.6, 126.5, 72.5, 72.4, 52.2, 52.2, 47.0, 47.0, 44.2, 44.1, 36.5, 36.5, 32.4, 32.3, 22.4, 22.2.

IR: *f* (cm⁻¹) = 3427, 3027, 2934, 2861, 1601, 1495, 1454, 1259, 1081, 1030, 914, 829, 746, 700, 503.

HRMS-ESI: (*M*+*H*⁺) = 207.13796 calculated for C₁₃H₁₉O₂, experimental 207.13786.

(2,6,7-trichloroheptyl)benzene (**5.90**)



Epoxyalcohol **5.84** (149 mg, 0.722 mmol) was combined with triphosgene (100 mg, 0.361 mmol) and CH₂Cl₂ (1.4 mL) in a 15-mL pressure vessel. Pyridine (114 μL, 1.44 mmol) was subsequently added and the solution was warmed to reflux. After 4 hours the reaction was determined to be complete by GC-MS analysis and cooled to room temperature. The reaction was then quenched with 2M HCl (2 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5%

gradient of EtOAc in hexanes affording **5.90** as a clear oil and as a 1:1 mixture of inseparable diastereomers in 90% yield (182 mg, 0.650 mmol).

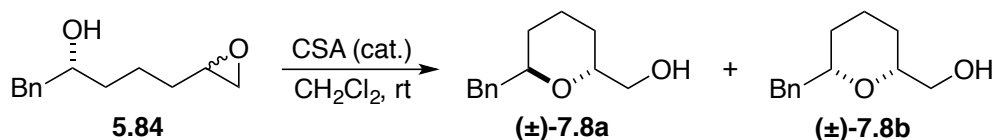
¹H NMR (500 MHz, CDCl₃) δ 7.35 – 7.31 (m, 4H), 7.28 – 7.26 (m, 2H), 7.22 (d, J = 7.3 Hz, 4H), 4.14 – 4.09 (m, 2H), 4.05 – 3.99 (m, 2H), 3.77 (dd, J = 11.2, 5.1 Hz, 2H), 3.67 – 3.63 (m, 2H), 3.12 – 3.01 (m, 4H), 2.06 – 1.96 (m, 2H), 1.94 – 1.67 (m, 8H), 1.60 – 1.52 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 129.3, 128.4, 126.8, 63.3, 60.8, 48.0, 45.0, 44.9, 36.8, 36.7, 34.5, 34.4, 22.9.

IR: $f(\text{cm}^{-1})$ = 2955, 2869, 1463, 1368, 1272, 1171, 733, 665, 613.

HRMS-ESI: (M+H⁺) = 225.1041 calculated for C₁₃H₁₈ClO, experimental 225.1049.

***Syn-/ Anti*-(6-benzyltetrahydro-2H-pyran-2-yl)methanol (**7.8a** and **7.8b**)**



Epoxyalcohol **5.84** (218 mg, 1.06 mmol) was added to a 15-mL pressure vessel and dissolved in CH₂Cl₂ (4.2 mL). Catalytic CSA (25 mg, 0.106 mmol) was added and the reaction was stirred at room temperature. After stirring overnight, the reaction was determined to be complete by TLC analysis and quenched with saturated NaHCO₃ (2 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 100% gradient of EtOAc in hexanes affording (**±**)-**7.8a** and (**±**)-**7.8b** as a clear oil as a 1:1 mixture of diastereomers in 86% combined yield (188 mg, 0.911 mmol).

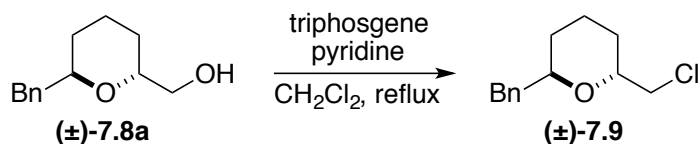
¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.27 (m, 4H), 7.21 (t, *J* = 7.2 Hz, 8H), 4.02 – 3.97 (m, 1H), 3.92 (dq, *J* = 8.2, 3.8 Hz, 1H), 3.69 – 3.64 (m, 1H), 3.58 – 3.41 (m, 7H), 3.02 – 2.97 (m, 1H), 2.92 – 2.88 (m, 1H), 2.81 – 2.76 (m, 1H), 2.68 (dd, *J* = 13.7, 6.2 Hz, 2H), 2.04 (dd, *J* = 8.6, 3.7 Hz, 1H), 1.88 – 1.82 (m, 2H), 1.76 (ddd, *J* = 8.7, 5.6, 3.3 Hz, 2H), 1.74 – 1.58 (m, 4H), 1.53 – 1.41 (m, 5H), 1.32 – 1.19 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 139.0, 138.7, 129.3, 129.1, 128.4, 128.2, 126.2, 126.1, 78.4, 72.8, 71.3, 66.3, 63.8, 42.9, 39.4, 31.1, 28.9, 27.0, 26.2, 23.0, 18.5.

IR: *f*(cm⁻¹) = 3425, 3061, 3026, 2859, 1603, 1453, 1369, 1234, 1153, 1040, 993, 947, 891, 865, 748, 607, 525, 484, 464, 416.

HRMS-ESI: (M+H⁺) = 207.13796 calculated for C₁₃H₁₉O₂, experimental 207.13776.

***Anti*-2-benzyl-6-(chloromethyl)tetrahydro-2*H*-pyran ((±)-7.9)**



Anti-pyranol (±)-**7.8a** (71 mg, 0.344 mmol) was added to a 15-mL pressure vessel and dissolved in CH₂Cl₂ (0.7 mL). Triphosgene (102 mg, 0.344 mmol) was added and followed by pyridine (28 μL, 0.344 mmol). The reaction was warmed to reflux. After 1 hour the reaction was determined to be complete based on GC-MS analysis. The solution was cooled to room temperature and quenched with the addition of 2M HCl (1 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording (±)-**7.9** as a clear oil as a single diastereomer in 66% yield (51 mg, 0.227 mmol).

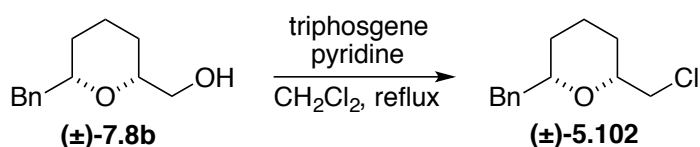
¹H NMR (500 MHz, CDCl₃) δ 7.30 – 7.27 (m, 2H), 7.22 – 7.19 (m, 3H), 4.03 – 3.97 (m, 2H), 3.59 (dd, *J* = 11.0, 6.4 Hz, 1H), 3.52 (dd, *J* = 11.1, 6.3 Hz, 1H), 2.99 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.77 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.81 – 1.71 (m, 2H), 1.67 – 1.61 (m, 2H), 1.57 – 1.51 (m, 1H), 1.45 – 1.39 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 138.7, 129.2, 128.3, 126.2, 73.4, 71.2, 45.7, 39.6, 28.4, 27.4, 18.1.

IR: *f*(cm⁻¹) = 3061, 3026, 2865, 1603, 1453, 1444, 1310, 1200, 1143, 1084, 997, 929, 896, 738, 698, 591, 512, 494, 471, 441, 421.

HRMS-ESI: (M+H⁺) = 225.10407 calculated for C₁₃H₁₈ClO, experimental 225.10433.

***Syn*-2-benzyl-6-(chloromethyl)tetrahydro-2*H*-pyran ((±)-5.102)**

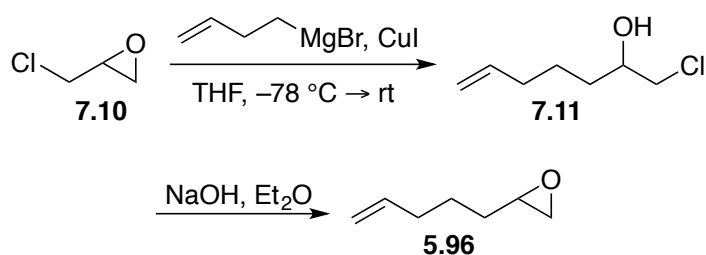


Syn-pyranol (±)-**7.8b** (77 mg, 0.373 mmol) was added to a 15-mL pressure vessel and dissolved in CH₂Cl₂ (0.7 mL). Triphosgene (111 mg, 0.373 mmol) was added and followed by pyridine (30 μL, 0.373 mmol). The reaction was warmed to reflux. After 1 hour the reaction was determined to be complete based on GC-MS analysis. The solution was cooled to room temperature and quenched with the addition of 2M HCl (1 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording (±)-**5.102** as a clear oil as a single diastereomer in 77% yield (64 mg, 0.285 mmol).

^1H NMR (500 MHz, CDCl_3) δ 7.30 – 7.26 (m, 2H), 7.25 – 7.19 (m, 3H), 3.58 – 3.51 (m, 3H), 3.48 – 3.43 (m, 1H), 2.97 (dd, J = 13.7, 6.4 Hz, 1H), 2.66 (dd, J = 13.7, 6.7 Hz, 1H), 1.89 – 1.84 (m, 1H), 1.75 – 1.71 (m, 1H), 1.59 – 1.54 (m, 1H), 1.47 (qt, J = 13.2, 3.9 Hz, 1H), 1.31 – 1.19 (m, 2H).
 ^{13}C NMR (126 MHz, CDCl_3) δ 138.6, 129.5, 128.1, 126.1, 79.0, 77.4, 47.5, 42.8, 30.6, 28.9, 23.0.
IR: $f(\text{cm}^{-1})$ = 3026, 2937, 2860, 1603, 1495, 1453, 1311, 1258, 1192, 1050, 1040, 1002, 935, 898, 738, 629, 595, 511, 454.

HRMS-ESI: ($\text{M}+\text{H}^+$) = 225.10407 calculated for $\text{C}_{13}\text{H}_{18}\text{ClO}$, experimental 225.10489.

Synthesis of 2-(pent-4-en-1-yl)oxirane (5.96)



1-chlorohept-6-en-2-ol (7.11)

Freshly ground Mg turnings (3.11 g, 130 mmol) were added to a 500-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I_2 (1–2 crystals) was added and the apparatus was heated gently to sublime the I_2 and coat the Mg turnings. Once coated THF (75 mL) was added to cover the Mg. 4-bromo-1-butene (13 mL, 130 mmol) was subsequently added to the addition funnel and dissolved in THF (25 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 30 minutes. After complete addition of 4-bromo-1-butene, the translucent solution was refluxed for an additional 30 minutes to consume the remaining Mg. Once all of the Mg had been consumed, the solution of 3-butenylmagnesium bromide (~ 1.3 M) was cooled to room temperature and diluted with an additional 100 mL of THF, before being cooled to -78°C . Once cooled, CuI (4.11 g, 21.6 mmol)

was added in one portion. After approximately 30 minutes, epichlorohydrin **7.10** (8.5 mL, 108 mmol) was added to the addition funnel, diluted with THF (30 mL) and added slowly to the solution containing the organometallic species. After complete addition of **7.10** the reaction was allowed to warm to room temperature overnight. After stirring overnight the reaction was quenched by the addition of saturated NH_4Cl (70 mL) dropwise. Upon complete separation of the two layers, the aqueous layer was extracted with Et_2O (3x50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 15% gradient of EtOAc in hexanes affording **7.11** as a clear oil in 84% yield (14.0 g, 0.945 mol).

^1H NMR (500 MHz, CDCl_3) δ 5.79 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.02 (dq, J = 17.1, 1.9 Hz, 1H), 4.98 – 4.95 (m, 1H), 3.84 – 3.77 (m, 1H), 3.63 (dd, J = 11.0, 3.2 Hz, 1H), 3.47 (dd, J = 10.6, 7.2 Hz, 1H), 2.19 – 2.12 (m, 1H), 2.12 – 2.05 (m, 2H), 1.62 – 1.52 (m, 2H), 1.51 – 1.39 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 138.2, 114.9, 71.3, 50.5, 33.5, 33.4, 24.7.

2-(pent-4-en-1-yl)oxirane (5.96**)**

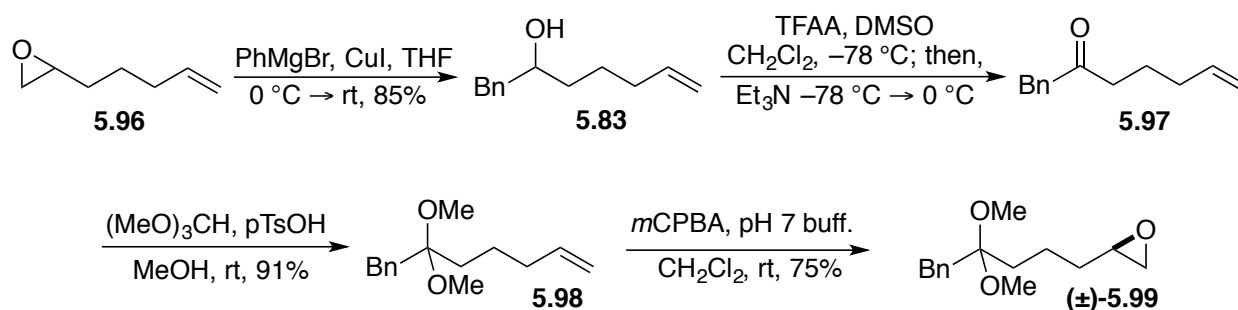
Chlorohydrin **7.11** (14.0 g, 94.9 mmol) was added to a xx-mL round-bottom flask and dissolved in Et_2O (95 mL). Freshly pulverized NaOH (11.4 g, 0.474 mol) was added in one portion and the reaction was stirred at room temperature. After 3 hours the reaction was determined to be complete by TLC analysis and subsequently cooled to 0 °C and diluted with DI H_2O (20 mL). Upon complete separation of layers, the aqueous layer was extracted with Et_2O (3x15 mL). The combined organic layers were then dried over Na_2SO_4 and carefully concentrated under reduced pressure revealing crude **5.96** as a colorless liquid. The resulting crude liquid was then distilled

under reduced pressure at 100 °C affording epoxide **5.96** in 82% yield as a clear liquid (8.73 g, 77.8 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.80 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.04 – 4.98 (m, 1H), 4.98 – 4.94 (m, 1H), 2.93 – 2.89 (m, 1H), 2.74 (t, *J* = 4.6 Hz, 1H), 2.46 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.15 – 2.08 (m, 2H), 1.59 – 1.50 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 138.3, 114.8, 52.2, 47.1, 33.4, 31.9, 25.2.

Synthesis of 2-(4,4-dimethoxy-5-phenylpentyl)oxirane ((±)-**5.99**)



1-phenylhept-6-en-2-ol (**5.83**)

CuI (453 mg, 2.38 mmol) was added to a 250-mL round-bottom flask while still hot and vacuum purged with N₂ while gradually cooling to room temperature. THF (40 mL) was added and the resulting slurry was cooled to 0 °C. After 5 minutes, PhMgBr (4.7 mL, 3 M in Et₂O) was added dropwise. After 10 minutes epoxide **5.96** (1.33 g, 11.9 mmol) was added via cannula in THF (20 mL). The resulting solution was stirred at 0 °C. After 2 hours, the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **5.83** and a clear oil in 83% yield (1.87 g, 9.83 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.21 (m, 3H), 5.82 (ddt, *J* = 17.0, 10.4, 6.7 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.99 – 4.94 (m, 1H), 3.86 – 3.80 (m, 1H), 2.84 (dd, *J* = 13.5, 4.2 Hz, 1H), 2.65 (dd, *J* = 13.6, 8.5 Hz, 1H), 2.14 – 2.05 (m, 2H), 1.68 – 1.40 (m, 5H).
¹³C NMR (126 MHz, CDCl₃) δ 138.7, 138.5, 129.4, 128.6, 126.5, 114.6, 72.5, 44.1, 36.2, 33.7, 25.0.

1-phenylhept-6-en-2-one (5.97)

TFAA (1.5 mL, 10.8 mmol) and CH₂Cl₂ (10 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to –78 °C for 10 minutes before DMSO (1.5 mL, 21.7 mmol) was added as a solution in CH₂Cl₂ (20 mL) slowly, dropwise. After 1 hour alcohol **5.83** (1.87 g, 9.85 mmol) was added via cannula in CH₂Cl₂ (20 mL). After 1 hour the reaction was determined to be complete by TLC analysis and Et₃N (6.9 mL, 49.3 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (15 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **5.97** and a clear oil in 79% yield (1.46 g, 7.76 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.72 (ddt, *J* = 17.2, 10.2, 6.7 Hz, 1H), 5.01 – 4.92 (m, 2H), 3.67 (s, 2H), 2.46 (t, *J* = 7.2 Hz, 2H), 2.01 (q, *J* = 6.9 Hz, 2H), 1.66 (p, *J* = 7.4 Hz, 2H).
¹³C NMR (101 MHz, CDCl₃) δ 208.1, 137.8, 134.2, 129.3, 128.6, 126.9, 115.1, 50.1, 41.0, 32.9, 22.6.

(2,2-dimethoxyhept-6-en-1-yl)benzene (5.98)

Ketone **5.97** (4.49 g, 23.9 mmol) was added to a 250-mL round-bottom flask and dissolved in MeOH (50 mL) and (MeO)₃CH (26 mL, 239 mmol). pTsOH (907 mg, 4.77 mmol) was subsequently added and the reaction was stirred at room temperature. After 1 hour the reaction was determined to be complete by TLC analysis and quenched by the addition of Et₃N (5 mL) then diluted with H₂O (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was used without further purification (5.24 g).

Ketal **5.98** (3.50 g, 14.9 mmol) was added to a 250-mL round-bottom flask and dissolved in CH₂Cl₂ (30 mL) and pH 7 buffer (30 mL). mCPBA (4.78 g, 19.4 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After stirring overnight, the reaction was quenched with 1M NaOH (20 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes buffered with 10% Et₃N affording epoxyketal (\pm)-**5.99** as a clear oil in 72% yield (2.68 g, 10.7 mmol).

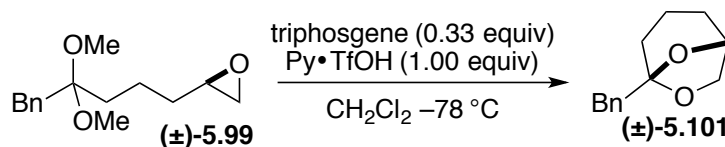
¹H NMR (400 MHz, CDCl₃) δ 7.26 (q, J = 3.1 Hz, 4H), 7.23 – 7.18 (m, 1H), 3.28 (d, J = 1.7 Hz, 6H), 2.92 (s, 2H), 2.83 – 2.77 (m, 1H), 2.67 (dd, J = 5.0, 3.9 Hz, 1H), 2.38 (dd, J = 5.1, 2.7 Hz, 1H), 1.54 – 1.38 (m, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 136.9, 129.7, 128.2, 126.4, 103.4, 51.9, 48.0, 47.0, 38.5, 32.4, 32.4, 20.2.

IR: $f(\text{cm}^{-1})$ = 3029, 2951, 2829, 1737, 1496, 1433, 1371, 1258, 1188, 1118, 1044, 914, 729, 628, 561, 494, 429.

HRMS-ESI: ($M+H^+$) = 251.16417 calculated for $C_{15}H_{23}O_3$, experimental 251.15627.

5-benzyl-6,8-dioxabicyclo[3.2.1]octane ((±)-5.101)



Epoxyketal (±)-5.99 (60 mg, 0.240 mmol) was combined with triphosgene (71 mg, 0.240 mmol) and CH_2Cl_2 (0.48 mL) in a 15-mL pressure vessel. The resulting solution was then cooled to $-78\text{ }^{\circ}C$ for five minutes then $Py\bullet TfOH$ (55 mg, 0.240 mmol) was added. After stirring for 6 hours the reaction was quenched with saturated $NaHCO_3$ (1 mL) and warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording bicyclic ketal (±)-5.101 as a clear oil in 45% yield (22 mg, 0.108 mmol).

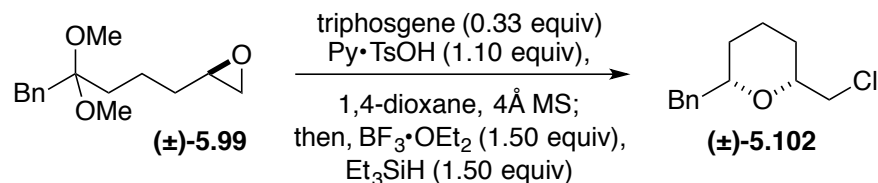
1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, $J = 4.4$ Hz, 4H), 7.25 – 7.21 (m, 1H), 4.53 – 4.49 (m, 1H), 3.91 (d, $J = 6.8$ Hz, 1H), 3.78 (t, $J = 6.6$ Hz, 1H), 3.00 (d, $J = 3.0$ Hz, 2H), 1.85 – 1.77 (m, 1H), 1.62 – 1.57 (m, 3H), 1.48 – 1.43 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 130.0, 127.6, 126.0, 108.1, 74.5, 68.7, 44.0, 33.2, 27.9, 16.5.

IR: $f(\text{cm}^{-1}) = 3062, 3029, 2949, 2849, 1604, 1453, 1238, 1107, 1075, 973, 902, 846, 760, 700, 663, 511, 466.$

HRMS: ($M+H^+$) = 205.1223 calculated for $C_{13}H_{17}O_2$, experimental 205.1216

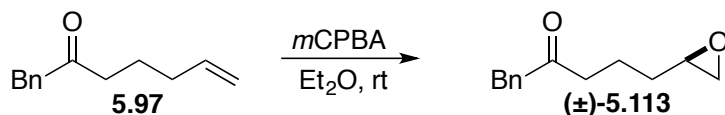
Syn-2-benzyl-6-(chloromethyl)tetrahydro-2H-pyran ((±)-5.102)



Epoxyketal **(±)-5.99** (43 mg, 0.172 mmol) was combined with triphosgene (17 mg, 0.0567 mmol), 4 Å MS (65 mg) and 1,4-dioxane (0.69 mL) in a 15-mL pressure vessel. Py•TsOH (47 mg, 0.189 mmol) was subsequently added and the reaction was stirred at room temperature. After stirring for 30 minutes, $\text{BF}_3 \cdot \text{OEt}_2$ (24 μL , 0.189 mmol) and Et_3SiH (30 μL , 0.189 mmol) were added. After stirring for 40 minutes the reaction was quenched with saturated NaHCO_3 (1 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording pyran **(±)-5.102** as a clear oil in 80% yield (30 mg, 0.133 mmol).

All spectra is in agreement with the formation of **(±)-5.102** from compound **(±)-7.8a**.

5-(oxiran-2-yl)-1-phenylpentan-2-one ((±)-5.113)



Ketone **5.97** (1.46 g, 7.76 mmol) was added to a 250-mL round-bottom flask and dissolved in Et_2O (40 mL). $m\text{CPBA}$ (2.86 g, 11.3 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 19 hours the reaction was quenched with saturated NaHCO_3 (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et_2O (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was

purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **5.97** as a clear oil (905 mg, 4.81 mmol). Further elution with a 10% gradient of EtOAc in hexanes afforded epoxyketone (\pm)-**5.113** as a clear oil in 43% yield based on recovered starting material (258 mg, 1.26 mmol).

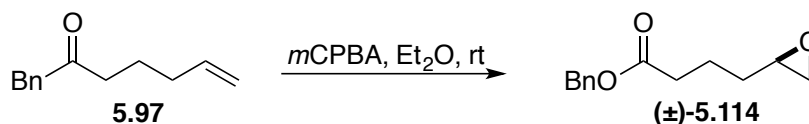
^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 7.24 – 7.21 (m, 2H), 3.71 (s, 2H), 2.90 – 2.84 (m, 1H), 2.73 (dd, J = 5.0, 2.8 Hz, 1H), 2.55 (td, J = 7.3, 1.4 Hz, 2H), 2.43 (dd, J = 5.0, 2.7 Hz, 1H), 1.79 – 1.72 (m, 2H), 1.64 – 1.54 (m, 1H), 1.47 – 1.39 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 207.9, 134.2, 129.4, 128.7, 127.0, 52.0, 50.2, 46.8, 41.2, 31.7, 20.1.

IR (cm^{-1}): ν = 3030, 2838, 1712, 1495, 1453, 1409, 1366, 1260, 1116, 1031, 922, 834, 733, 700, 475.

HRMS-ESI: ($\text{M}+\text{H}$) $^+$ = 205.12231 calculated for $\text{C}_{13}\text{H}_{17}\text{O}_2$, experimental 205.12284.

benzyl 4-(oxiran-2-yl)butanoate (\pm)-**5.114**



Ketone **5.97** (690 mg, 3.66 mmol) was added to a 50-mL round-bottom flask and dissolved in Et_2O (18 mL). *m*CPBA (2.71 g, 11.0 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 15 hours the reaction was determined to be complete by TLC analysis and quenched by the addition of 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et_2O (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a affording epoxy ester (\pm)-**5.114** as a clear oil in 50% yield (400 mg, 1.81 mmol).

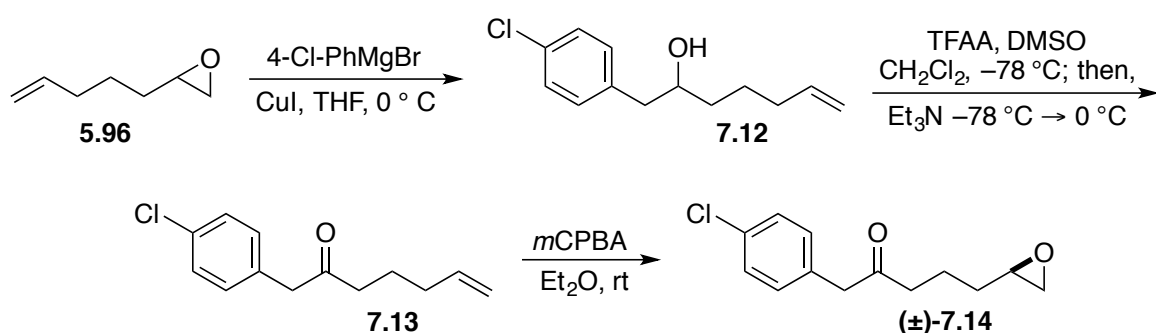
¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.31 (m, 5H), 5.12 (s, 2H), 2.90 (dddd, *J* = 6.6, 4.9, 4.0, 2.7 Hz, 1H), 2.74 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.48 – 2.40 (m, 3H), 1.90 – 1.76 (m, 2H), 1.62 (dddd, *J* = 13.8, 8.9, 6.3, 4.8 Hz, 1H), 1.58 – 1.50 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 173.0, 135.9, 128.5, 128.2, 128.2, 66.2, 51.8, 46.9, 33.8, 31.8, 21.4.

IR: *f* (cm⁻¹) = 2942, 1730, 1497, 1455, 1384, 1244, 1164, 1104, 1002, 916, 831, 738, 697, 577, 490.

HRMS-ESI: (M+H⁺) = 205.12231 calculated for C₁₃H₁₇O₂, experimental 205.11966.

1-(4-chlorophenyl)-5-(oxiran-2-yl)pentan-2-one ((±)-7.14)



1-(4-chlorophenyl)hept-6-en-2-ol (7.12)

CuI (187 mg, 0.982 mmol) was added to a 100-mL round-bottom flask while still hot and vacuum purged with N₂ while gradually cooling to room temperature. THF (8 mL) was added and the resulting slurry was cooled to 0 °C. After 5 minutes, 4-Cl-PhMgBr (5.9 mL, 1 M in Et₂O) was added dropwise. After 10 minutes epoxide **5.96** (550 mg, 4.91 mmol) was added via cannula in THF (8 mL). The resulting solution was stirred at 0 °C. After 1 hours, the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried

over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **7.12** as a white solid in 91% yield (1.00 g, 4.45 mmol).

¹H NMR (400 MHz, CDCl₃) δ 7.29 – 7.26 (m, 2H), 7.16 – 7.13 (m, 2H), 5.80 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 1H), 5.04 – 4.99 (m, 1H), 4.99 – 4.93 (m, 1H), 3.84 – 3.76 (m, 1H), 2.79 (dd, *J* = 13.5, 4.1 Hz, 1H), 2.63 (dd, *J* = 13.5, 8.4 Hz, 1H), 2.13 – 2.05 (m, 2H), 1.62 – 1.45 (m, 3H), 1.45 – 1.42 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 138.5, 137.0, 132.3, 130.7, 128.6, 114.7, 72.4, 43.3, 36.2, 33.6, 25.0.

1-(4-chlorophenyl)hept-6-en-2-one (7.13)

TFAA (1.0 mL, 7.19 mmol) and CH₂Cl₂ (5 mL) were combined in 100-mL round-bottom flask. The resulting solution was cooled to –78 °C for 10 minutes before DMSO (745 μL, 10.5 mmol) was added as a solution in CH₂Cl₂ (7 mL) slowly, dropwise. After 1 hour alcohol **7.12** (1.08 g, 4.79 mmol) was added via cannula in CH₂Cl₂ (12 mL). After 1 hour the starting material had been completely consumed as judged by TLC analysis and Et₃N (3.3 mL, 24.0 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (5 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **7.13** and a clear oil in 88% yield (945 mg, 4.24 mmol).

¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.27 (m, 2H), 7.15 – 7.10 (m, 2H), 5.72 (ddt, *J* = 16.7, 9.9, 6.7 Hz, 1H), 5.00 – 4.96 (m, 1H), 4.96 – 4.93 (m, 1H), 3.65 (s, 2H), 2.47 (d, *J* = 7.3 Hz, 2H), 2.05 – 1.99 (m, 2H), 1.67 (p, *J* = 7.4 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 137.8, 132.9, 132.6, 130.7, 128.8, 115.3, 49.2, 41.3, 32.9, 22.6.

1-(4-chlorophenyl)-5-(oxiran-2-yl)pentan-2-one ((±)-7.14)

Ketone **7.13** (1.69 g, 7.59 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (30 mL). *m*CPBA (2.81 g, 11.4 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 19 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **7.13** as a clear oil (529 mg, 2.37 mmol). Further elution with a 10% gradient of EtOAc in hexanes afforded epoxyketone ((±)-**7.14**) as a clear oil in 47% yield based on recovered starting material (584 mg, 2.45 mmol).

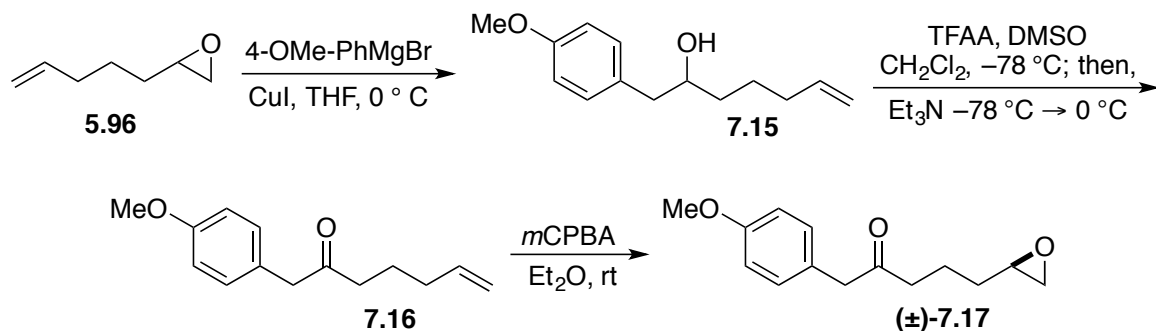
¹H NMR (500 MHz, CDCl₃) δ 3.66 (s, 2H), 2.86 (dtd, *J* = 6.8, 4.2, 2.7 Hz, 1H), 2.72 (dd, *J* = 5.0, 3.9 Hz, 1H), 2.53 (dd, *J* = 7.7, 6.9 Hz, 2H), 2.42 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.77 – 1.70 (m, 2H), 1.60 (dddd, *J* = 12.0, 8.6, 5.1, 3.5 Hz, 1H), 1.43 – 1.37 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 207.2, 133.0, 132.6, 130.7, 128.8, 51.9, 49.2, 46.7, 41.5, 31.6, 20.1.

IR (cm⁻¹): *f* = 3048, 2933, 1712, 1491, 1408, 1367, 1333, 1260, 1190, 1089, 1015, 924, 828, 671, 619, 493, 427.

HRMS-ESI: (M+H)⁺ = 239.08333 calculated for C₁₃H₁₆ClO₂, experimental 239.08314.

1-(4-methoxyphenyl)-5-(oxiran-2-yl)pentan-2-one ((±)-7.17)



1-(4-methoxyphenyl)hept-6-en-2-ol (7.15)

CuI (240 mg, 1.26 mmol) was added to a 100-mL round-bottom flask while still hot and vacuum purged with N₂ while gradually cooling to room temperature. THF (15 mL) was added and the resulting slurry was cooled to 0 °C. After 5 minutes, 4-MeO-PhMgBr (7.5 mL, 1 M in THF) was added dropwise. After 10 minutes epoxide **5.96** (698 mg, 6.23 mmol) was added via cannula in THF (15 mL). The resulting solution was stirred at 0 °C. After 1 hour, the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **7.15** and a clear oil in 81% yield (1.11 g, 5.04 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.13 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 5.82 (ddt, *J* = 16.5, 9.8, 6.7 Hz, 1H), 5.01 (d, *J* = 17.1 Hz, 1H), 4.96 (d, *J* = 9.8 Hz, 1H), 3.81 – 3.77 (m, 4H), 2.78 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.58 (dd, *J* = 13.6, 8.5 Hz, 1H), 2.13 – 2.05 (m, 2H), 1.63 – 1.46 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 158.3, 138.7, 130.4, 130.3, 114.6, 114.0, 72.6, 55.2, 43.1, 36.1, 33.7, 25.1.

1-(4-methoxyphenyl)hept-6-en-2-one (7.16)

TFAA (1.2 mL, 8.14 mmol) and CH₂Cl₂ (6 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to –78 °C for 10 minutes before DMSO (1.2 mL, 16.3 mmol) was added as a solution in CH₂Cl₂ (15 mL) slowly, dropwise. After 1 hour alcohol **7.15** (1.63 g, 7.40 mmol) was added via cannula in CH₂Cl₂ (20 mL). After 1 hour the starting material had been completely consumed as judged by TLC analysis and Et₃N (5.2 mL, 37.0 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **7.16** and a clear oil in 89% yield (1.44 g, 6.60 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.13 – 7.09 (m, 2H), 6.89 – 6.84 (m, 2H), 5.72 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 4.99 – 4.93 (m, 2H), 3.80 (s, 3H), 3.61 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 2.03 – 1.98 (m, 2H), 1.65 (p, *J* = 7.4 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 208.6, 158.6, 137.9, 130.4, 126.3, 115.1, 114.1, 55.2, 49.3, 40.9, 33.0, 22.7.

1-(4-methoxyphenyl)-5-(oxiran-2-yl)pentan-2-one ((±)-7.17)

Ketone **7.16** (1.33 g, 6.11 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (24 mL). *m*CPBA (2.26 g, 9.16 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 19 hours the reaction was quenched with 1M NaOH (10 mL). Upon

complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **7.16** as a clear oil (778 mg, 3.56 mmol). Further elution with a 10% gradient of EtOAc in hexanes afforded epoxyketone (\pm)-**7.17** as a clear oil in 52% yield based on recovered starting material (309 mg, 1.32 mmol).

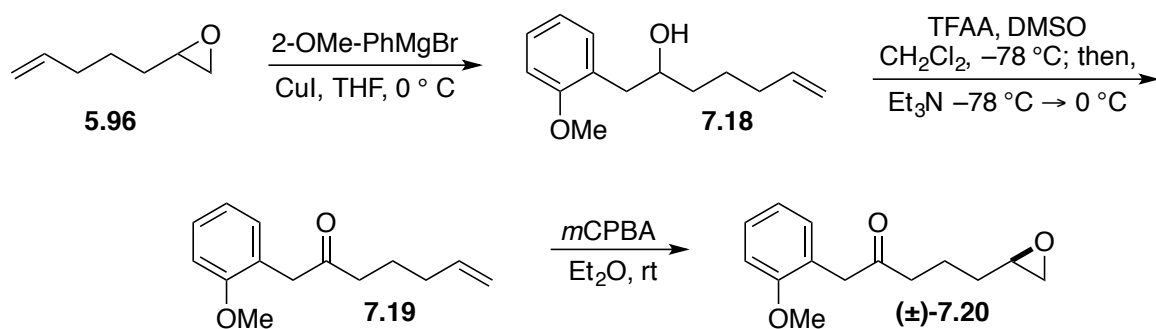
¹H NMR (400 MHz, CDCl₃) δ 7.13 – 7.09 (m, 2H), 6.88 – 6.84 (m, 2H), 3.79 (s, 3H), 3.62 (s, 2H), 2.87 – 2.82 (m, 1H), 2.70 (dd, J = 4.8, 4.3 Hz, 1H), 2.51 (t, J = 7.1 Hz, 2H), 2.41 (dd, J = 5.0, 2.7 Hz, 1H), 1.76 – 1.67 (m, 2H), 1.61 – 1.52 (m, 1H), 1.46 – 1.36 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 208.2, 158.6, 130.3, 126.2, 114.1, 55.2, 51.9, 49.3, 46.8, 41.1, 31.7, 20.1.

IR (cm⁻¹): ν = 2935, 2836, 1710, 1611, 1583, 1511, 1461, 1409, 1366, 1300, 1246, 1178, 1112, 1033, 924, 829, 519.

HRMS-ESI: (M+H)⁺ = 235.13287 calculated for C₁₄H₁₉O₃, experimental 235.13316.

1-(2-methoxyphenyl)-5-(oxiran-2-yl)pentan-2-one ((\pm)-**7.20**)



1-(2-methoxyphenyl)hept-6-en-2-ol (**7.18**)

CuI (400 mg, 2.10 mmol) was added to a 100-mL round-bottom flask while still hot and vacuum purged with N₂ while gradually cooling to room temperature. THF (20 mL) was added

and the resulting slurry was cooled to 0 °C. After 5 minutes, 2-OMe-PhMgBr (13 mL, 1 M in Et₂O) was added dropwise. After 10 minutes epoxide **5.96** (1.18 g, 10.5 mmol) was added via cannula in THF (15 mL). The resulting solution was stirred at 0 °C. After 3 hours, the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **7.18** as a white solid in 94% yield (2.18 g, 9.89 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.23 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.94 – 6.86 (m, 2H), 5.83 (ddt, *J* = 16.8, 10.2, 6.8 Hz, 1H), 5.01 (d, *J* = 17.4 Hz, 1H), 4.95 (d, *J* = 10.6 Hz, 1H), 3.88 – 3.81 (m, 4H), 2.90 (dd, *J* = 14.0, 3.7 Hz, 1H), 2.69 (dd, *J* = 13.1, 8.2 Hz, 1H), 2.12 – 2.02 (m, 2H), 1.65 – 1.57 (m, 1H), 1.54 – 1.47 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 138.9, 131.3, 127.8, 127.1, 120.7, 114.4, 110.4, 71.7, 55.3, 38.7, 36.6, 33.7, 25.1.

IR: *f* (cm⁻¹) = 3400, 3073, 2998, 2933, 2858, 2836, 1639, 1600, 1586, 1492, 1438, 1289, 1240, 1113, 1050, 996, 864, 729, 611, 478.

HRMS-ESI: (M+H⁺) = 221.15361 calculated for C₁₄H₂₁O₂, experimental 221.15427.

1-(2-methoxyphenyl)hept-6-en-2-one (7.19)

TFAA (1.5 mL, 10.8 mmol) and CH₂Cl₂ (10 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to -78 °C for 10 minutes before DMSO (1.5 mL, 21.7 mmol) was added as a solution in CH₂Cl₂ (20 mL) slowly, dropwise. After 1 hour alcohol **7.18** (2.18 g, 9.89 mmol) was added via cannula in CH₂Cl₂ (20 mL). After 1 hour the reaction was

determined to be complete by TLC analysis and Et₃N (6.9 mL, 49.5 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0 °C and quenched by the addition of 2M HCl (20 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording **7.19** and a clear oil in 85% yield (1.84 g, 8.41 mmol).

¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.23 (m, 1H), 7.12 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.92 (td, *J* = 7.4, 1.0 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 5.75 (ddt, *J* = 17.0, 10.0, 6.7 Hz, 1H), 5.01 – 4.93 (m, 2H), 3.80 (s, 3H), 3.66 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 2.03 (q, *J* = 7.0 Hz, 2H), 1.68 (p, *J* = 7.4 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 208.7, 157.3, 138.1, 131.2, 128.4, 123.7, 120.6, 115.0, 110.4, 55.3, 44.7, 41.0, 33.0, 22.8.

IR: *f* (cm⁻¹) = 3074, 2937, 2837, 1784, 1722, 1600, 1493, 1439, 1408, 1363, 1290, 1175, 1115, 1028, 911, 833, 751, 636, 453.

HRMS-ESI: (M+H⁺) = 219.13796 calculated for C₁₄H₁₉O₂, experimental 219.13820.

1-(2-methoxyphenyl)-5-(oxiran-2-yl)pentan-2-one ((±)-7.20)

Ketone **7.19** (945 mg, 4.33 mmol) was added to a 50-mL round-bottom flask and dissolved in Et₂O (17 mL). *m*CPBA (1.60 g, 6.49 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 12 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried

over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **7.19** as a clear oil (358 mg, 1.64 mmol). Further elution with a 20% gradient of EtOAc in hexanes afforded epoxyketone (\pm)-**7.20** as a clear oil in 63% yield based on recovered starting material (395 mg, 1.68 mmol)

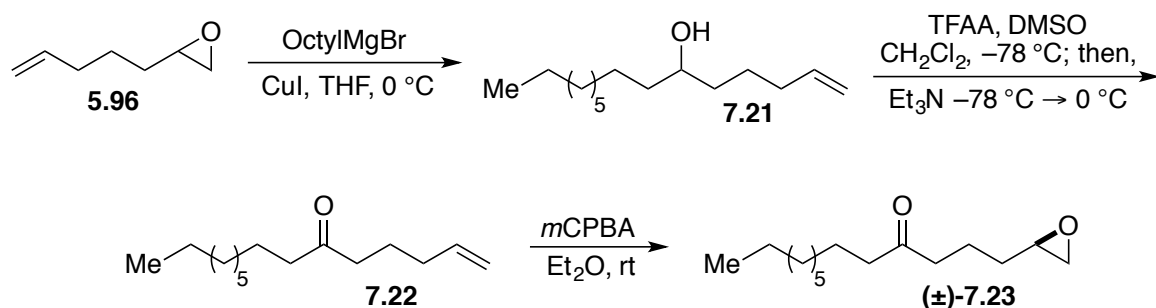
¹H NMR (500 MHz, CDCl₃) δ 7.27 – 7.23 (m, 1H), 7.12 (dd, J = 7.3, 1.1 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 2H), 2.89 – 2.84 (m, 1H), 2.72 (t, J = 5.0 Hz, 1H), 2.50 (td, J = 7.3, 1.4 Hz, 2H), 2.43 (dd, J = 4.9, 2.6 Hz, 1H), 1.77 – 1.70 (m, 2H), 1.59 – 1.53 (m, 1H), 1.50 – 1.43 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 208.3, 157.3, 131.2, 128.5, 123.5, 120.6, 110.4, 55.3, 52.0, 46.8, 44.8, 41.1, 31.7, 20.1.

IR: $f(\text{cm}^{-1})$ = 2937, 2838, 1712, 1600, 1494, 1461, 1440, 1408, 1365, 1290, 1245, 1177, 1114, 1049, 925, 834, 754, 557, 495, 454.

HRMS-ESI: ($M+H^+$) = 235.13287 calculated for C₁₄H₁₉O₃, experimental 235.13343

1-(oxiran-2-yl)tridecan-4-one (\pm)-**7.23**



pentadec-1-en-6-ol (**7.21**)

CuI (360 mg, 1.89 mmol) was added to a 100-mL round-bottom flask while still hot and vacuum purged with N₂ while gradually cooling to room temperature. THF (15 mL) was added

and the resulting slurry was cooled to 0 °C. After 5 minutes, OctylMgBr (5.6 mL, 2 M in THF) was added dropwise. After 10 minutes epoxide **5.96** (1.06 g, 9.46 mmol) was added via cannula in THF (15 mL). The resulting solution was stirred at 0 °C. After 30 minutes the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **7.21** as a clear oil in 94% yield (2.01 g, 8.88 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.81 (ddt, *J* = 17.3, 10.3, 6.6 Hz, 1H), 5.01 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.98 – 4.93 (m, 1H), 3.63 – 3.56 (m, 1H), 2.11 – 2.04 (m, 2H), 1.57 – 1.39 (m, 6H), 1.33 – 1.23 (m, 12H), 0.87 (t, *J* = 6.6 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 138.7, 114.5, 71.9, 37.5, 36.9, 33.7, 31.9, 29.7, 29.6, 29.6, 29.3, 25.6, 24.9, 22.7, 14.1.

pentadec-1-en-6-one (7.22)

Alcohol **7.21** (2.01 g, 8.88 mmol) was combined with CH₂Cl₂ (30 mL) in a 100-mL round-bottom flask. The solution was cooled to 0 °C followed by the addition of Dess-Martin Periodinane (5.64 g, 13.3 mmol) and NaHCO₃ (2.23 g, 26.6 mmol). The ice bath was removed after 10 minutes and the reaction was allowed to warm to room temperature. After stirring for 3 hours, the reaction was determined to be complete by TLC analysis and cooled to 0 °C prior to being quenched with saturated Na₂S₂O₃ (10 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then filtered through

a silica plug using a 10% EtOAc in hexanes gradient affording **7.22** as a clear oil in 89% (1.77 g, 7.89 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.77 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.04 – 4.95 (m, 2H), 2.39 (q, *J* = 7.7 Hz, 2H), 2.09 – 2.02 (m, 2H), 1.68 (p, 2H), 1.60 – 1.52 (m, 2H), 1.32 – 1.22 (m, 13H), 0.90 – 0.86 (m, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 211.3, 138.0, 115.1, 42.9, 41.8, 33.1, 31.9, 29.4, 29.4, 29.3, 23.9, 22.8, 22.6, 14.2, 14.1.

1-(oxiran-2-yl)tridecan-4-one ((±)-7.23)

Ketone **7.22** was added to a 100-mL round-bottom flask and dissolved in Et₂O (31 mL). *m*CPBA (2.91 g, 11.8 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 19 hours the reaction was determined to be complete by TLC analysis and quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording (±)-**7.23** and a white solid in 39% yield (733 mg, 3.05 mmol).

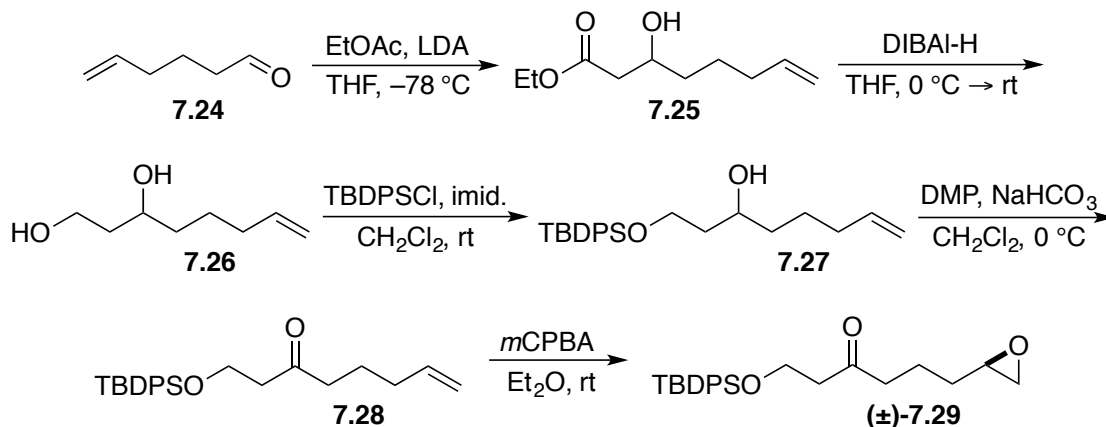
¹H NMR (500 MHz, CDCl₃) δ 2.92 – 2.88 (m, 1H), 2.74 (t, *J* = 4.5 Hz, 1H), 2.51 – 2.45 (m, 3H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.74 (p, *J* = 7.7 Hz, 2H), 1.65 – 1.53 (m, 4H), 1.50 – 1.43 (m, 1H), 1.32 – 1.22 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 210.8, 77.2, 52.0, 46.8, 42.9, 42.1, 31.9, 31.8, 29.4, 29.4, 29.3, 23.9, 22.7, 20.2, 14.1.

IR (cm⁻¹): *f* = 2923, 2854, 1712, 1460, 1410, 1374, 1259, 1130, 1070, 921, 834, 723, 426, 408.

HRMS-ESI: (M+H⁺) = 241.21621 calculated for C₁₅H₂₉O₂, experimental 241.21604.

Synthesis of 1-((*tert*-butyldiphenylsilyl)oxy)-6-(oxiran-2-yl)hexan-3-one ((±)-7.29)



ethyl 3-hydroxyoct-7-enoate (7.25)

To a 100-mL round-bottom flask was added *i*Pr₂NH (2.1 mL, 15.0 mmol) and THF (20 mL). The resulting solution was then cooled to 0 °C and *n*BuLi (6.0 mL, 2.5 M in hexanes) was added dropwise. After 30 minutes the solution of LDA was cooled to -78 °C and EtOAc (1.5 mL, 15.0 mmol) was added as a solution in THF (10 mL) dropwise. After 30 minutes aldehyde 7.24 was added via cannula in THF (10 mL). The reaction was stirred at -78 °C for 2 hours when the reaction was determined to be complete by TLC analysis and quenched with saturated NH₄Cl (10 mL) then warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording 7.25 as a clear oil in 60% yield, over two steps (1.12 g, 6.01 mmol).

¹H NMR (400 MHz, CDCl₃) δ 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.97 – 4.93 (m, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.04 – 3.97 (m, 1H), 2.96 (d, *J* = 4.0 Hz, 1H), 2.50 (dd, *J* = 16.5, 3.1 Hz, 1H), 2.40 (dd, *J* = 16.5, 9.1 Hz, 1H), 2.11 – 2.05 (m, 2H), 1.61 – 1.41 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 173.1, 138.5, 114.7, 67.8, 60.7, 41.3, 35.8, 33.5, 24.7, 14.2.

oct-7-ene-1,3-diol (7.26)

To a 100-mL round-bottom flask was added β-hydroxy ester **7.25** (700 mg, 3.76 mmol) and THF (12 mL). The resulting solution was cooled to 0 °C and DIBAL-H (12 mL, 1 M in heptane) was added dropwise. After 2 hours the reaction was determined to be complete by TLC analysis and quenched with saturated Rochelle's salt (5 mL) and 2M HCl (5 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of MeOH in CH₂Cl₂ affording **7.26** as a clear oil in 84% yield (458 mg, 3.17 mmol).

¹H NMR (500 MHz, CDCl₃) δ 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.97 – 4.94 (m, 1H), 3.91 – 3.80 (m, 3H), 2.57 – 2.49 (m, 2H), 2.11 – 2.05 (m, 2H), 1.79 – 1.62 (m, 2H), 1.57 – 1.40 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 114.7, 72.1, 61.8, 38.2, 37.2, 33.6, 24.8.

IR: *f*(cm⁻¹) = 3331, 3077, 2933, 2861, 2212, 2155, 1640, 1437, 1372, 1332, 1183, 1054, 995, 909, 828, 640.

HRMS-ESI: (M+H⁺) = 145.12231 calculated for C₈H₁₇O₂, experimental 145.12242.

1-((*tert*-butyldiphenylsilyl)oxy)oct-7-en-3-ol (7.27)

Diol **7.26** (458 mg, 3.17 mmol) was combined with imidazole (323 mg, 4.75 mmol) in a 50-mL round-bottom flask. CH₂Cl₂ (11 mL) added and the solution was cooled to 0 °C. TBDPSCI (866 μL, 3.33 mmol) was added dropwise. After stirring overnight, the reaction was determined

to be complete by TLC analysis and quenched by the addition of 2 M HCl (5 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography using a 1% EtOAc in hexanes gradient affording **7.27** as a clear oil in 41% (496 mg, 1.30 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.70 – 7.66 (m, 4H), 7.46 – 7.37 (m, 6H), 5.82 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.02 (dq, J = 17.0, 1.6 Hz, 1H), 4.97 – 4.93 (m, 1H), 3.93 – 3.82 (m, 2H), 3.25 – 3.20 (m, 1H), 2.12 – 2.06 (m, 2H), 1.75 – 1.62 (m, 2H), 1.59 – 1.50 (m, 2H), 1.50 – 1.41 (m, 2H), 1.06 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 138.8, 135.6, 135.5, 134.8, 133.0, 132.9, 129.8, 129.8, 127.8, 114.5, 71.7, 63.6, 38.3, 37.0, 33.8, 26.8, 26.6, 24.9.

IR: $f(\text{cm}^{-1})$ = 3406, 3071, 2930, 2857, 1640, 1470, 1427, 1389, 1188, 1109, 997, 909, 859, 822, 737, 701, 611, 431.

HRMS-ESI: (M+H⁺) = 383.24008 calculated for C₂₄H₃₅O₂Si, experimental 383.24032.

1-((*tert*-butyldiphenylsilyl)oxy)oct-7-en-3-one (7.28)

Alcohol **7.27** (496 mg, 1.30 mmol) was combined with CH₂Cl₂ (6.5 mL) in a 100-mL round-bottom flask. The solution was cooled to 0 °C followed by the addition of Dess-Martin Periodinane (823 mg, 1.94 mmol) and NaHCO₃ (324 mg, 3.89 mmol). The ice bath was removed after 10 minutes and the reaction was allowed to warm to room temperature. After stirring for 2 hours, the reaction was determined to be complete by TLC analysis and cooled to 0 °C prior to being quenched with saturated Na₂S₂O₃ (10 mL). Upon separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL). The combined organic layers were dried over

Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was then filtered through a silica plug using a 5% EtOAc in hexanes gradient affording **7.28** as a clear oil in 82% (408 mg, 1.07 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.67 – 7.64 (m, 4H), 7.45 – 7.37 (m, 6H), 5.76 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.04 – 4.99 (m, 1H), 4.99 – 4.96 (m, 1H), 3.94 (t, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 6.1 Hz, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 2.09 – 2.03 (m, 2H), 1.69 (p, *J* = 7.3 Hz, 2H), 1.03 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 209.7, 138.0, 135.5, 134.8, 133.4, 129.7, 127.7, 127.7, 115.2, 59.8, 45.5, 42.9, 33.1, 26.8, 22.5, 19.1.

1-((*tert*-butyldiphenylsilyl)oxy)-6-(oxiran-2-yl)hexan-3-one ((±)-7.29)

Ketone **7.28** (408 mg, 1.07 mmol) was added to a 50-mL round-bottom flask and dissolved in Et₂O (4.3 mL). *m*CPBA (397 mg, 1.61 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 12 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **7.28** as a clear oil (264 mg, 0.694 mmol). Further elution with a 10% gradient of EtOAc in hexanes afforded epoxyketone ((±)-**7.29**) as a clear oil in 92% yield based on recovered starting material (138 mg, 0.348 mmol).

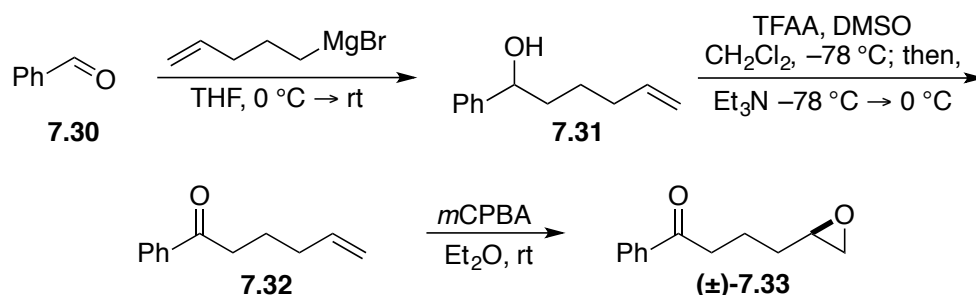
¹H NMR (400 MHz, CDCl₃) δ 7.68 – 7.63 (m, 4H), 7.46 – 7.35 (m, 6H), 3.94 (t, *J* = 6.2 Hz, 2H), 2.92 – 2.87 (m, 1H), 2.73 (dd, *J* = 5.0, 4.1 Hz, 1H), 2.63 (t, *J* = 6.2 Hz, 1H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.45 (dd, *J* = 5.0, 2.6 Hz, 1H), 1.80 – 1.71 (m, 2H), 1.65 – 1.57 (m, 1H), 1.53 – 1.44 (m, 1H), 1.03 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 209.1, 135.5, 133.4, 129.7, 127.6, 59.7, 51.9, 46.7, 45.4, 43.0, 31.7, 26.7, 19.9, 19.1.

IR: $f(\text{cm}^{-1})$ = 2931, 2857, 1714, 1472, 1428, 1109, 823, 740, 703, 613, 505.

HRMS-ESI: $(\text{M}+\text{H}^+) = 397.21935$ calculated for $\text{C}_{24}\text{H}_{33}\text{O}_3\text{Si}$, experimental 397.21857.

4-(oxiran-2-yl)-1-phenylbutan-1-one ((\pm)-7.33)



1-phenylhex-5-en-1-ol (7.31)

Freshly ground Mg turnings (1.37 g, 56.5 mmol) were added to a 500-mL three-neck round-bottom flask, with a pressure-equalizing addition funnel and condenser attached. Catalytic I_2 (1–2 crystals) was added and the apparatus was heated gently to sublime the I_2 and coat the Mg turnings. Once coated THF (25 mL) was added to cover the Mg. 5-bromo-1-pentene (6.7 mL, 56.5 mmol) was subsequently added to the addition funnel and dissolved in THF (25 mL). The solution of alkyl halide was slowly added to the slurry of magnesium turnings over 30 minutes. After complete addition of 5-bromo-1-pentene, the translucent solution was refluxed for an additional 1 hour to consume the remaining Mg. Once all of the Mg had been consumed, the solution of 4-pentenylmagnesium bromide (~ 1 M) was cooled to room temperature and diluted with an additional 50 mL of THF, before being cooled to 0 °C. After approximately 15 minutes, benzaldehyde **7.30** (4.8 mL, 47.1 mmol) was added to the addition funnel, diluted with THF (50 mL) and added slowly to the solution containing the Grignard reagent. After complete addition of

7.30 the reaction was allowed to warm to room temperature. After 30 minutes the reaction was determined to be complete by TLC analysis and quenched with the addition of saturated NH_4Cl (30 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et_2O (3x50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% to 10% gradient of EtOAc in hexanes affording **7.31** as a clear oil in 94% yield (7.82 g, 44.4 mmol).

^1H NMR (400 MHz, CDCl_3) δ 7.29 – 7.25 (m, 4H), 7.23 – 7.17 (m, 1H), 5.70 (ddt, J = 16.9, 10.1, 6.7 Hz, 1H), 4.91 (dq, J = 17.1, 1.5 Hz, 1H), 4.88 – 4.84 (m, 1H), 4.60 (dd, J = 7.5, 5.9 Hz, 1H), 1.99 (q, J = 7.2 Hz, 2H), 1.79 – 1.60 (m, 3H), 1.45 (dddd, J = 5.2, 7.6, 10.7, 17.0 Hz, 1H), 1.36 – 1.26 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 144.8, 138.5, 128.4, 127.5, 125.8, 114.7, 74.5, 38.5, 33.6, 25.1.

1-phenylhex-5-en-1-one (7.32)

TFAA (2.2 mL, 15.3 mmol) and CH_2Cl_2 (20 mL) were combined in 250-mL round-bottom flask. The resulting solution was cooled to -78°C for 10 minutes before DMSO (2.2 mL, 30.6 mmol) was added as a solution in CH_2Cl_2 (20 mL) slowly, dropwise. After 1 hour alcohol **7.31** (2.45 g, 13.9 mmol) was added via cannula in CH_2Cl_2 (20 mL). After 1 hour the reaction was determined to be complete by TLC analysis and Et_3N (9.7 mL, 69.5 mmol) was added slowly. The reaction was slowly warmed to room temperature over 30 minutes. Further reaction monitoring by TLC analysis determined that the reaction was complete. The reaction was then cooled to 0°C and quenched by the addition of 2M HCl (15 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography

using a 5% gradient of EtOAc in hexanes affording **7.32** and a clear oil in 79% yield (1.91 g, 11.0 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.97 – 7.95 (m, 2H), 7.55 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.48 – 7.44 (m, 2H), 5.82 (ddt, *J* = 17, 10.2, 6.7 Hz, 1H), 5.05 (dq, *J* = 17.1, 1.8 Hz, 1H), 5.01 – 4.98 (m, 1H), 2.98 (t, *J* = 7.3 Hz 2H), 2.16 (q, *J* = 6.9 Hz 2H), 1.86 (p, *J* = 7.5 Hz 2H).

¹³C NMR (126 MHz, CDCl₃) δ 200.2, 138.0, 137.0, 132.9, 128.5, 128.0, 115.3, 37.7, 33.2, 23.3.

4-(oxiran-2-yl)-1-phenylbutan-1-one ((±)-**7.33**)

Ketone **7.32** (1.91 g, 11.0 mmol) was added to a 100-mL round-bottom flask and dissolved in Et₂O (44 mL). *m*CPBA (4.04 g, 16.4 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After 20 hours the reaction was quenched with 1M NaOH (10 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et₂O (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording recovered ketone **7.32** as a clear oil (774 mg, 4.44 mmol). Further elution with a 10% gradient of EtOAc in hexanes afforded epoxyketone ((±)-**7.33**) as a clear oil in 64% yield based on recovered starting material (792 mg, 4.16 mmol).

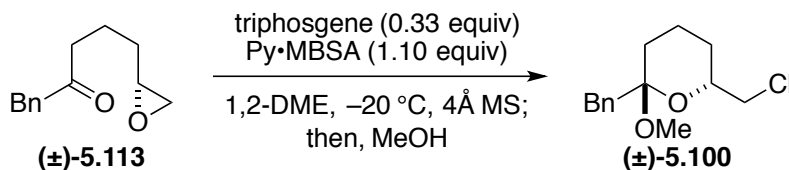
¹H NMR (500 MHz, CDCl₃) δ 7.96 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.1 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.08 – 3.04 (m, 2H), 2.98 – 2.94 (m, 1H), 2.78 – 2.75 (m, 1H), 2.50 – 2.48 (m, 1H), 1.96 – 1.89 (m, 2H), 1.76 – 1.69 (m, 1H), 1.62 – 1.53 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 199.7, 136.9, 133.0, 128.6, 128.0, 52.1, 46.8, 37.9, 31.9, 20.6.

IR (cm⁻¹): *f* = 3054, 2934, 1681, 1596, 1482, 1370, 1320, 1251, 1133, 1101, 1023, 973, 918, 869, 747, 691, 569, 492, 429.

HRMS-ESI: ($M+H^+$) = 191.10666 calculated for $C_{12}H_{15}O_2$, experimental 191.10682.

2-benzyl-6-(chloromethyl)-2-methoxytetrahydro-2H-pyran ((±)-5.100)



Epoxyketone **(±)-5.113** (67 mg, 0.328 mmol) and 4 Å MS (100 mg) were combined with 1,2-DME (1.3 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (32 mg, 0.108 mL) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (96 mg, 0.361 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.6 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (1 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **(±)-5.100** as a white solid in 73% yield as a single diastereomer (61 mg, 0.239 mmol).

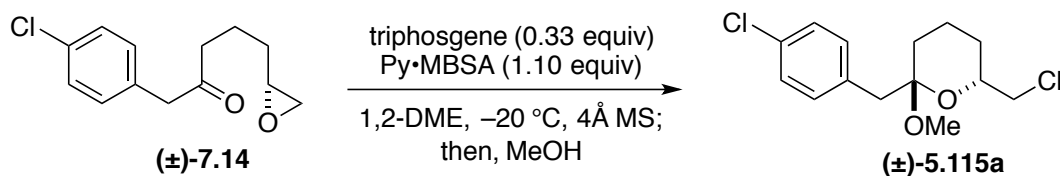
^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.27 (m, 1H), 7.27 – 7.20 (m, 4H), 3.81 (dddd, $J = 11.5, 7.0, 5.5, 2.3\text{ Hz}$, 1H), 3.56 – 3.47 (m, 2H), 3.41 (s, 3H), 3.01 (d, $J = 14.0\text{ Hz}$, 1H), 2.87 (d, $J = 14.1\text{ Hz}$, 1H), 1.84 – 1.71 (m, 1H), 1.65 – 1.59 (m, 1H), 1.58 – 1.51 (m, 1H), 1.49 – 1.42 (m, 1H), 1.31 (td, $J = 13.5, 4.7\text{ Hz}$, 1H), 1.17 (qd, $J = 12.6, 4.0\text{ Hz}$, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 136.8, 130.2, 128.0, 126.3, 99.9, 70.5, 47.7, 42.2, 31.9, 28.0, 18.3.

IR: $f(\text{cm}^{-1}) = 2943, 1712, 1495, 1453, 1217, 1092, 975, 903, 828, 734, 698, 657, 521, 477$.

HRMS-ESI: ($(M-\text{MeOH})+H^+$) = 223.08842 calculated for $C_{13}H_{16}\text{ClO}$, experimental 223.08839.

2-(4-chlorobenzyl)-6-(chloromethyl)-2-methoxytetrahydro-2H-pyran ((±)-5.115a)



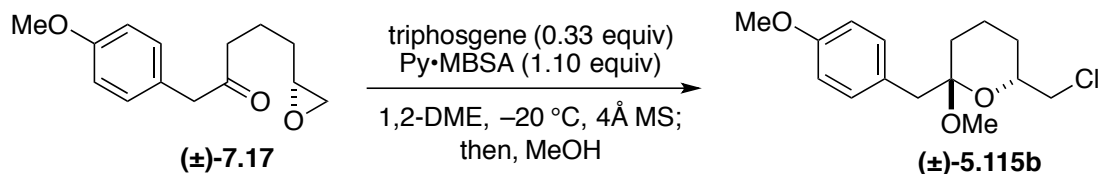
Epoxyketone (**±**)-**7.14** (41 mg, 0.173 mmol) and 4Å MS (100 mg) were combined with 1,2-DME (0.70 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (17 mg, 0.0572 mL) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (51 mg, 0.190 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.4 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (1 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording (**±**)-**5.115a** as a white solid in 54% yield as a single diastereomer (27 mg, 0.0940 mmol).

^1H NMR (500 MHz, CDCl_3) δ 7.25 – 7.22 (m, 2H), 7.18 – 7.16 (m, 2H), 3.80 (dtd, $J = 11.3, 5.4, 2.3$ Hz, 1H), 3.51 (d, $J = 5.5$ Hz, 2H), 3.38 (s, 3H), 2.91 (d, $J = 14.1$ Hz, 1H), 2.87 (d, $J = 14.1$ Hz, 1H), 1.77 (qt, $J = 13.3, 4.0$ Hz, 1H), 1.63 – 1.59 (m, 1H), 1.58 – 1.52 (m, 1H), 1.47 – 1.41 (m, 1H), 1.26 (td, $J = 13.5, 4.6$ Hz, 1H), 1.16 (qd, $J = 12.5, 4.0$ Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 135.3, 132.2, 131.6, 128.1, 99.7, 70.6, 47.8, 47.8, 41.6, 31.8, 27.9, 18.3.

IR: $f(\text{cm}^{-1}) = 2942, 2831, 1492, 1435, 1374, 1320, 1267, 1119, 1025, 969, 940, 871, 810, 737, 686, 623, 490, 456.$

6-(chloromethyl)-2-methoxy-2-(4-methoxybenzyl)tetrahydro-2H-pyran ((±)-5.115b)



Epoxyketone **(±)-7.17** (36 mg, 0.155 mmol) and 4 Å MS (54 mg) were combined with 1,2-DME (0.62 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (15 mg, 0.0512 mL) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (45 mg, 0.170 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.3 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (1 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **(±)-5.115b** as a white solid in 66% yield as a single diastereomer (29 mg, 0.103 mmol).

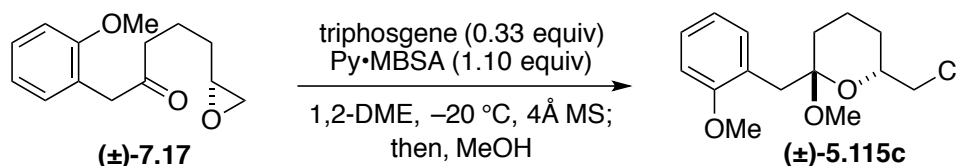
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.15 (d, $J = 8.2\text{ Hz}$, 2H), 6.82 (d, $J = 8.6\text{ Hz}$, 2H), 3.83 – 3.77 (m, 4H), 3.55 – 3.48 (m, 2H), 3.39 (s, 3H), 2.94 (d, $J = 14.0\text{ Hz}$, 1H), 2.80 (dd, $J = 14.0\text{ Hz}$, 1H), 1.77 (qt, $J = 13.4, 3.7\text{ Hz}$, 1H), 1.64 – 1.58 (m, 1H), 1.57 – 1.51 (m, 1H), 1.47 – 1.42 (m, 1H), 1.30 (td, $J = 13.5, 4.6\text{ Hz}$, 1H), 1.17 (dd, $J = 12.4, 4.0\text{ Hz}$, 1H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 158.1, 131.1, 128.8, 113.4, 100.0, 70.5, 55.2, 47.8, 47.7, 41.3, 31.9, 28.0, 18.3.

IR: $f(\text{cm}^{-1}) = 2939, 2833, 1612, 1459, 1350, 1243, 1119, 1064, 977, 905, 737, 626, 523, 473$.

HRMS-ESI: $((\text{M}-\text{MeOH})+\text{H}^+) = 253.09898$ calculated for $\text{C}_{14}\text{H}_{18}\text{ClO}_2$, experimental 253.09840.

6-(chloromethyl)-2-methoxy-2-(2-methoxybenzyl)tetrahydro-2H-pyran ((±)-5.115c)



Epoxyketone **(±)-7.17** (36 mg, 0.155 mmol) and 4 Å MS (54 mg) were combined with 1,2-DME (0.62 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^{\circ}\text{C}$ for at least 10 minutes. Triphosgene (15 mg, 0.0512 mL) was added and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ for another 5 minutes before Py•MBSA (45 mg, 0.170 mmol) was added. After stirring at $-20\text{ }^{\circ}\text{C}$ for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.3 mL) while still at $-20\text{ }^{\circ}\text{C}$. After 10 minutes saturated NaHCO_3 (1 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **(±)-5.115c** as a white solid in 66% yield as a single diastereomer (29 mg, 0.103 mmol).

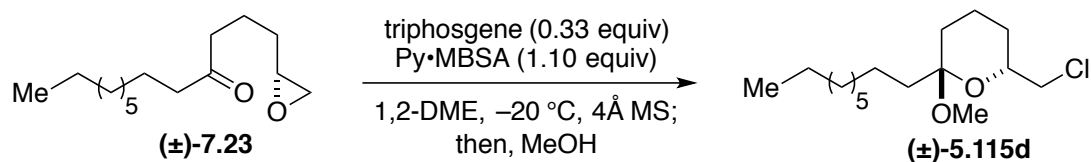
^1H NMR (400 MHz, CDCl_3) δ 7.27 (d, $J = 7.5\text{ Hz}$, 2H), 7.19 (t, $J = 7.8, 1.7\text{ Hz}$, 1H), 6.89 (t, $J = 7.5\text{ Hz}$, 1H), 6.85 (d, $J = 8.2\text{ Hz}$, 1H), 3.83 – 3.76 (m, 4H), 3.53 (dd, $J = 11.2, 6.5\text{ Hz}$, 1H), 3.48 (dd, $J = 11.1, 4.9\text{ Hz}$, 1H), 3.41 (s, 3H), 3.08 (d, $J = 14.0\text{ Hz}$, 1H), 2.94 (d, $J = 14.0\text{ Hz}$, 1H), 1.77 (qt, $J = 13.7, 4.0\text{ Hz}$, 1H), 1.66 – 1.59 (m, 1H), 1.57 – 1.48 (m, 1H), 1.37 (td, $J = 13.6, 4.7\text{ Hz}$, 1H), 1.17 (qd, $J = 12.7, 3.9\text{ Hz}$, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 157.9, 131.7, 127.4, 125.3, 120.2, 110.3, 100.4, 70.6, 55.3, 47.8, 47.8, 34.4, 31.3, 28.1, 18.4.

IR: $f(\text{cm}^{-1}) = 2940, 2834, 1600, 1493, 1438, 1348, 1323, 1289, 1201, 1174, 1123, 1094, 1024, 944, 848, 811, 657, 557, 518, 474$.

HRMS-ESI: ((M–MeOH)+H⁺) = 253.09898 calculated for C₁₄H₁₈ClO₂, experimental 253.09976.

6-(chloromethyl)-2-methoxy-2-nonyltetrahydro-2H-pyran ((±)-5.115d)



Epoxyketone **(±)-7.23** (76 mg, 0.316 mmol) and 4 Å MS (114 mg) were combined with 1,2-DME (1.3 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (31 mg, 0.104 mL) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (93 mg, 0.348 mmol) was added. After stirring at -20 °C for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.7 mL) while still at -20 °C. After 10 minutes saturated NaHCO₃ (1 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **(±)-5.115d** as a white solid in 79% yield as a single diastereomer (73 mg, 0.251 mmol).

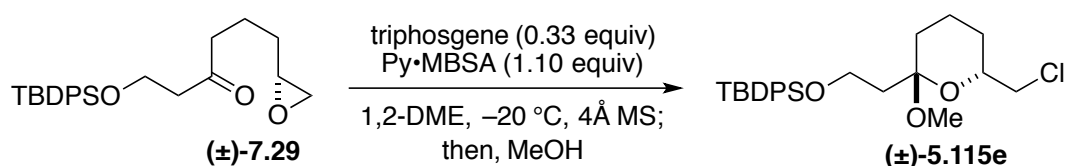
¹H NMR (500 MHz, CDCl₃) δ 3.77 (dddd, *J* = 11.5, 6.8, 4.8, 2.1 Hz, 1H), 3.49 (dd, *J* = 11.2, 6.5 Hz, 1H), 3.45 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.19 (s, 3H), 1.86 – 1.72 (m, 3H), 1.69 – 1.60 (m, 2H), 1.46 – 1.32 (m, 2H), 1.32 – 1.21 (m, 17H), 0.88 (t, *J* = 6.9 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 100.0, 100.0, 70.2, 47.8, 47.4, 36.3, 32.3, 31.9, 29.8, 29.5, 29.5, 29.3, 28.4, 23.2, 22.7, 18.5, 14.1.

IR: *f* (cm⁻¹) = 2923, 2853, 1722, 1460, 1377, 1201, 1123, 1096, 1028, 974, 934, 903, 857, 824, 740, 474.

HRMS-ESI: ((M – MeOH) + H⁺) = 259.18232 calculated for C₁₅H₂₈ClO, experimental 259.18261.

***tert*-butyl(2-(6-(chloromethyl)-2-methoxytetrahydro-2*H*-pyran-2-yl)ethoxy)diphenylsilane
(±)-5.115e**

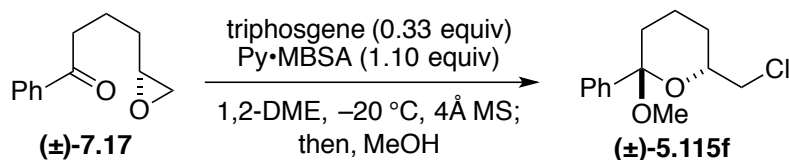


Epoxyketone (±)-7.29 (45 mg, 0.113 mmol) and 4 Å MS (67 mg) were combined with 1,2-DME (0.45 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (11 mg, 0.0370 mL) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (33 mg, 0.124 mmol) was added. After stirring at -20 °C for 1 hour, the reaction was determined to be complete by TLC analysis and quenched with MeOH (0.2 mL) and stirred for an additional 10 minutes. Saturated NaHCO₃ (0.5 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording (±)-5.115e as a clear oil in 67% yield as a single diastereomer (34 mg, 0.0761 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.70 – 7.66 (m, 4H), 7.44 – 7.35 (m, 7H), 3.79 – 3.67 (m, 3H), 3.46 (dd, *J* = 11.1, 6.5 Hz, 1H), 3.42 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.08 (s, 3H), 2.05 (ddd, *J* = 14.1, 8.3, 5.9 Hz, 1H), 1.90 – 1.84 (m, 1H), 1.77 (ddd, *J* = 17.3, 8.6, 4.0 Hz, 1H), 1.71 – 1.62 (m, 2H), 1.61 – 1.53 (m, 1H), 1.41 (td, *J* = 13.6, 4.6 Hz 1H), 1.21 (qd, *J* = 12.8, 4.1 Hz, 1H), 1.05 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 135.6, 135.6, 133.8, 129.6, 129.6, 127.6, 99.0, 70.2, 59.7, 47.7, 47.4, 39.0, 33.0, 28.2, 26.8, 19.1, 18.4.

6-(chloromethyl)-2-methoxy-2-phenyltetrahydro-2*H*-pyran ((±)-5.115f)



Epoxyketone **(±)-7.17** (101 mg, 0.531 mmol) and 4 Å MS (151 mg) were combined with 1,2-DME (2.1 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (52 mg, 0.175 mL) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (156 mg, 0.584 mmol) was added. After stirring at -20 °C for 1 hour the reaction was determined to be complete by TLC analysis and quenched with MeOH (1 mL) while still at -20 °C. After 10 minutes saturated NaHCO₃ (2 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording **(±)-5.115f** as a white solid in 57% yield as a single diastereomer (61 mg, 0.239 mmol).

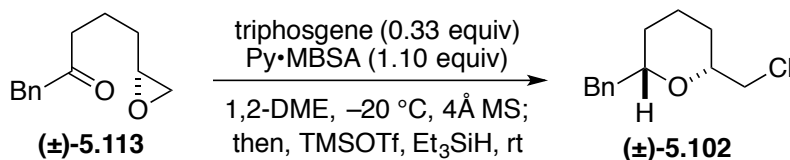
¹H NMR (500 MHz, CDCl₃) δ 7.50 (dd, *J* = 8.6, 1.5 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.30 (tt, *J* = 7.2, 1.4 Hz, 1H), 4.00 (dddd, *J* = 11.2, 5.5, 2.3 Hz, 1H), 3.66 (dd, *J* = 11.2, 6.1 Hz, 1H), 3.62 (dd, *J* = 11.2, 4.7 Hz, 1H), 3.03 (s, 3H), 2.08 – 1.98 (m, 2H), 1.79 – 1.69 (m, 2H), 1.52 – 1.45 (m, 1H), 1.45 – 1.36 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 142.5, 128.1, 127.6, 125.8, 99.9, 70.4, 49.0, 47.9, 37.1, 27.9, 19.2.

IR: *f*(cm⁻¹) = 2942, 2830, 1491, 1376, 1250, 1121, 1071, 1027, 946, 900, 853, 760, 700, 602, 519.

HRMS-ESI: ((M-MeOH)+H⁺) = 209.07277 calculated for C₁₂H₁₄ClO, experimental 209.07276.

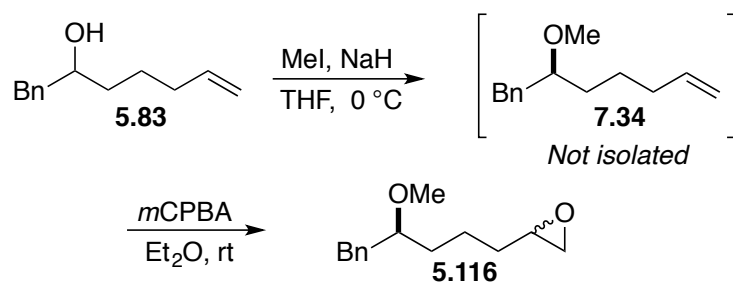
Syn-2-benzyl-6-(chloromethyl)tetrahydro-2*H*-pyran ((±)-5.102)



Epoxyketone (\pm)-**5.113** (92 mg, 0.450 mmol) and 4 Å MS (138 mg) were combined with 1,2-DME (1.8 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to $-20\text{ }^\circ\text{C}$ for at least 10 minutes. Triphosgene (44 mg, 0.148 mL) was added and the solution was stirred at $-20\text{ }^\circ\text{C}$ for another 5 minutes before Py•MBSA (132 mg, 0.495 mmol) was added. After stirring at $-20\text{ }^\circ\text{C}$ for 1 hour (\pm)-**5.113** was completely consumed as determined by TLC analysis. TMSOTf (244 μL , 1.35 mmol) and Et_3SiH (719 μL , 4.50 mmol) were then added and the reaction was allowed to warm to room temperature overnight. After stirring overnight, saturated NaHCO_3 (1 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 5% gradient of EtOAc in hexanes affording (\pm)-**5.102** as a clear oil in 52% yield as a single diastereomer (52 mg, 0.232 mmol).

All spectral data is in agreement with the reported synthesis of (\pm)-**5.102** from (\pm)-**5.99**.

2-(4-methoxy-5-phenylpentyl)oxirane (**5.116**)



Alcohol **5.83** (955 mg, 5.02 mmol) was added to a 100-mL round-bottom flask and dissolved in THF (10 mL). The resulting solution was cooled to 0 °C and NaH (240 mg, 10.0 mmol) was added in one portion. Once all bubbling had ceased, MeI (344 μ L, 5.52 mmol) was added dropwise. After 2 hours the reaction was determined to be complete by TLC analysis and quenched by the addition of saturated NH_4Cl (5 mL). Upon complete separation of the two layers, the aqueous layer was extracted with Et_2O (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was used without further purification (928 mg, 4.54 mmol).

Crude methyl ether **7.34** (928 mg, 4.54 mmol) was added to a 50-mL round-bottom flask and dissolved in CH_2Cl_2 (10 mL). *m*CPBA (1.46 g, 5.91 mmol, 70 wt %) was added and the reaction was stirred at room temperature. After stirring overnight the reaction was quenched with 1M NaOH (5 mL). Upon complete separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% to 20% gradient of EtOAc in hexanes affording **5.116** as a clear oil in 80% yield (800 mg, 3.63 mmol).

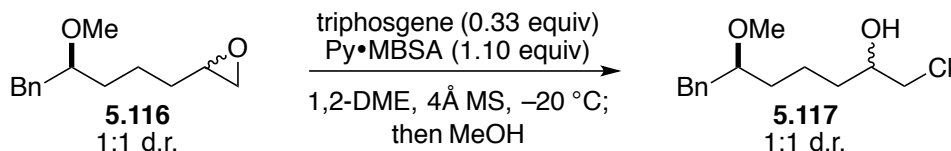
^1H NMR (500 MHz, CDCl_3) δ 7.31 – 7.26 (m, 4H), 7.22 – 7.18 (m, 6H), 3.40 – 3.35 (m, 2H), 3.33 (s, 3H), 3.33 (s, 3H), 2.87 (ddt, J = 8.8, 5.9, 2.7 Hz, 4H), 2.73 – 2.67 (m, 4H), 2.43 (ddd, J = 10.9, 5.1, 2.7 Hz, 2H), 1.66 – 1.57 (m, 1H), 1.56 – 1.44 (m, 11H).

^{13}C NMR (126 MHz, CDCl_3) δ 138.9, 138.9, 129.4, 128.2, 126.0, 82.2, 82.1, 57.0, 57.0, 52.2, 52.1, 47.0, 46.9, 40.1, 40.1, 33.4, 33.3, 32.5, 32.5, 21.9, 21.8.

IR: $f(\text{cm}^{-1})$ = 3026, 2933, 2862, 2822, 1495, 1410, 1259, 1089, 912, 744, 698, 597, 475, 431, 422.

HRMS-ESI: ($\text{M}+\text{H}^+$) = 221.15361 calculated for $\text{C}_{14}\text{H}_{21}\text{O}_2$, experimental 221.15355.

1-chloro-6-methoxy-7-phenylheptan-2-ol (**5.117**)



Methyl ether **5.116** (170 mg, 0.772 mmol) and 4 Å MS (255 mg) were combined with 1,2-DME (3.1 mL) in a 15-mL pressure vessel. The resulting mixture was cooled to -20 °C for at least 10 minutes. Triphosgene (76 mg, 0.255 mL) was added and the solution was stirred at -20 °C for another 5 minutes before Py•MBSA (226 mg, 0.849 mmol) was added. After stirring overnight at -20 °C the reaction was quenched with MeOH (1 mL) while still at -20 °C. After 10 minutes saturated NaHCO₃ (2 mL) was then added and the reaction was warmed to room temperature. Upon complete separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (3x10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography using a 10% gradient of EtOAc in hexanes affording chlorohydrin **5.117** (87 mg, 0.339 mmol) as a clear oil in 68% yield based on recovered starting material. Further elution with a 20% gradient of EtOAc in hexanes afforded recovered methyl ether **5.116** as a clear oil (60 mg, 0.272 mmol).

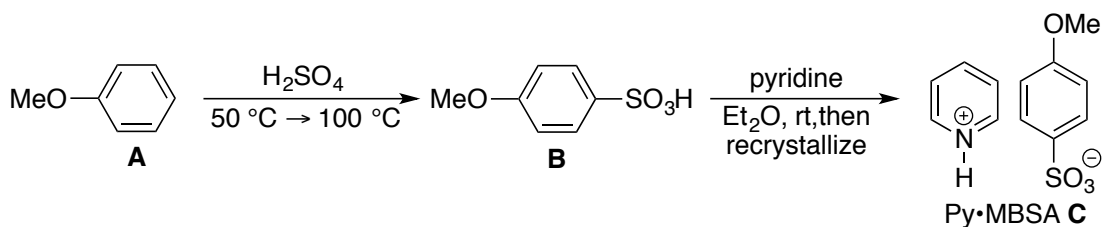
¹H NMR (500 MHz, CDCl₃) δ 7.29 (t, *J* = 7.4 Hz, 4H), 7.22 – 7.17 (m, 6H), 3.81 – 3.74 (m, 2H), 3.61 (ddd, *J* = 9.5, 6.0, 3.3 Hz, 2H), 3.48 – 3.43 (m, 2H), 3.40 – 3.35 (m, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 2.88 (ddd, *J* = 13.7, 5.9, 2.8 Hz, 2H), 2.69 (ddd, *J* = 13.6, 6.6, 3.2 Hz, 2H), 2.24 (d, *J* = 4.5 Hz, 1H), 2.25 – 2.22 (m, 1H), 2.20 – 2.17 (m, 1H), 1.56 – 1.33 (m, 10H).

¹³C NMR (126 MHz, CDCl₃) δ 138.8, 138.8, 129.4, 128.3, 126.1, 82.2, 82.1, 71.3, 71.3, 57.1, 57.0, 50.5, 50.4, 40.0, 40.0, 34.2, 34.1, 33.3, 21.5, 21.3.

IR: $\tilde{\nu}(\text{cm}^{-1})$ = 3415, 2933, 2864, 2825, 1495, 1453, 1359, 1258, 1181, 1155, 1094, 1030, 912, 699, 564, 505, 496, 457.

HRMS: $[(M-\text{MeOH})+\text{H}]^+ = 225.10407$ calculated for $\text{C}_{13}\text{H}_{18}\text{ClO}$, experimental 225.10468.

Synthesis of Py•MBSA (C)



Anisole **A** (100 mL, 0.925 mmol) was added to a 250-mL round-bottom flask and warmed to $50\text{ }^\circ\text{C}$. Concentrated H_2SO_4 (10 mL) was added dropwise and a reflux condenser was attached prior to warming the reaction to $100\text{ }^\circ\text{C}$. After 5 hours the reaction was cooled to room temperature and sulfonic acid **B** precipitated from the solution. The crude acid was washed with cold CHCl_3 (3x50 mL) to remove the excess anisole and filtered revealing an off white solid ($\sim 32\text{ g}$) that was used directly without further purification.

Sulfonic acid **B** (16.7 g, 89.0 mmol) was combined with Et_2O (180 mL) in a 500-mL round-bottom flask forming a pale red solution. Pyridine (14 mL, 178 mmol) was added dropwise and the solution turned colorless. After stirring overnight, a white solid precipitated from the solution. The reaction was concentrated under reduced pressure revealing **C** as an off white solid. The crude acid was then recrystallized from hot acetone affording pure Py•MBSA in 65% as a cubic, crystalline salt (15.4 g, 57.6 mmol). (Similar consistency to PPTS).

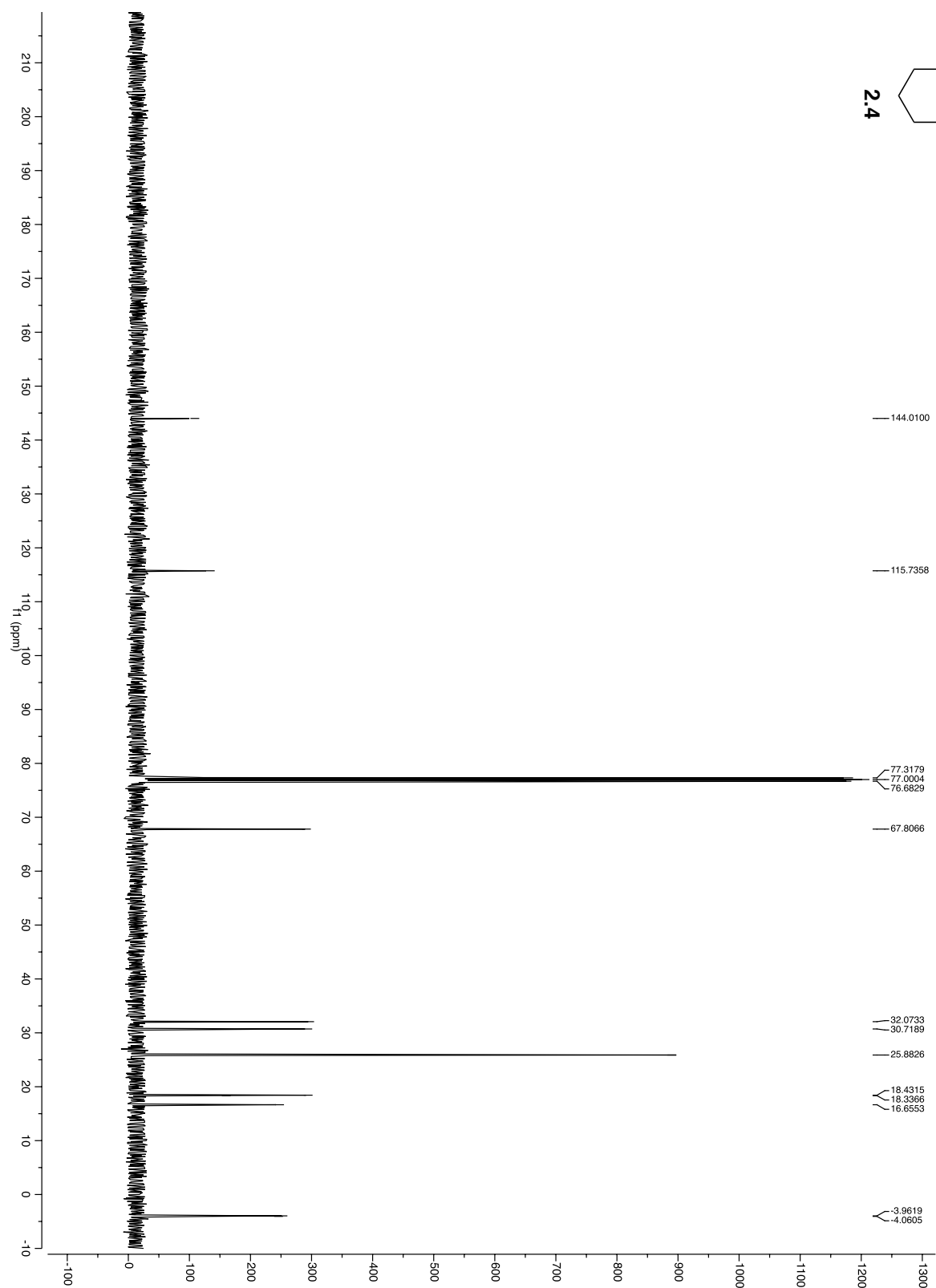
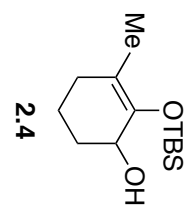
^1H NMR (500 MHz, CDCl_3) δ 9.00 (d, $J = 5.6\text{ Hz}$, 2H), 8.39 (tt, $J = 7.2, 1.6\text{ Hz}$, 1H), 7.93 (t, $J = 6.8\text{ Hz}$, 2H), 7.88 (d, $J = 8.6\text{ Hz}$, 2H), 6.88 (d, $J = 8.7\text{ Hz}$, 2H), 3.81 (s, 3H).

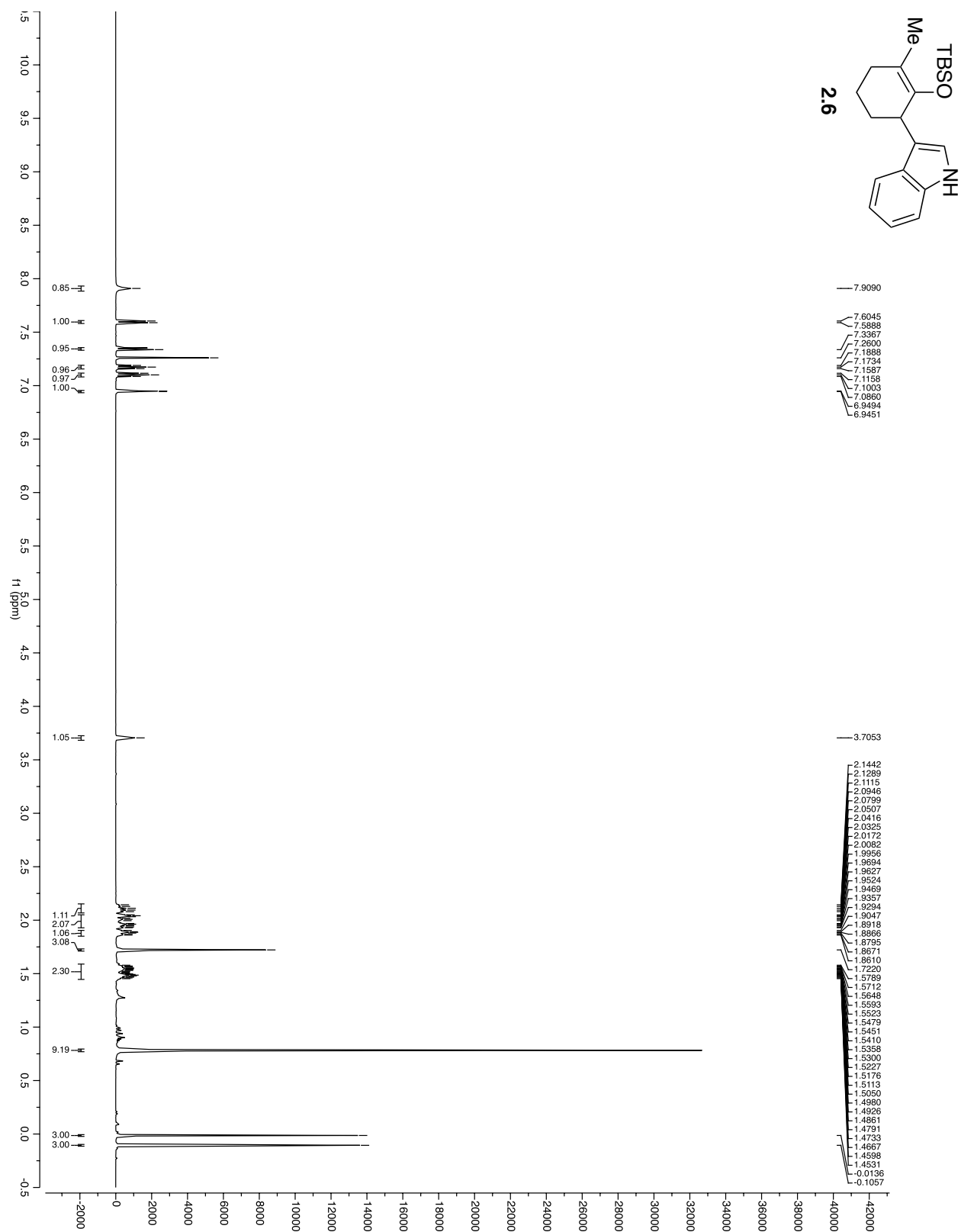
^{13}C NMR (126 MHz, CDCl_3) δ 161.0, 145.2, 142.5, 137.3, 127.8, 127.0, 113.5, 55.4.

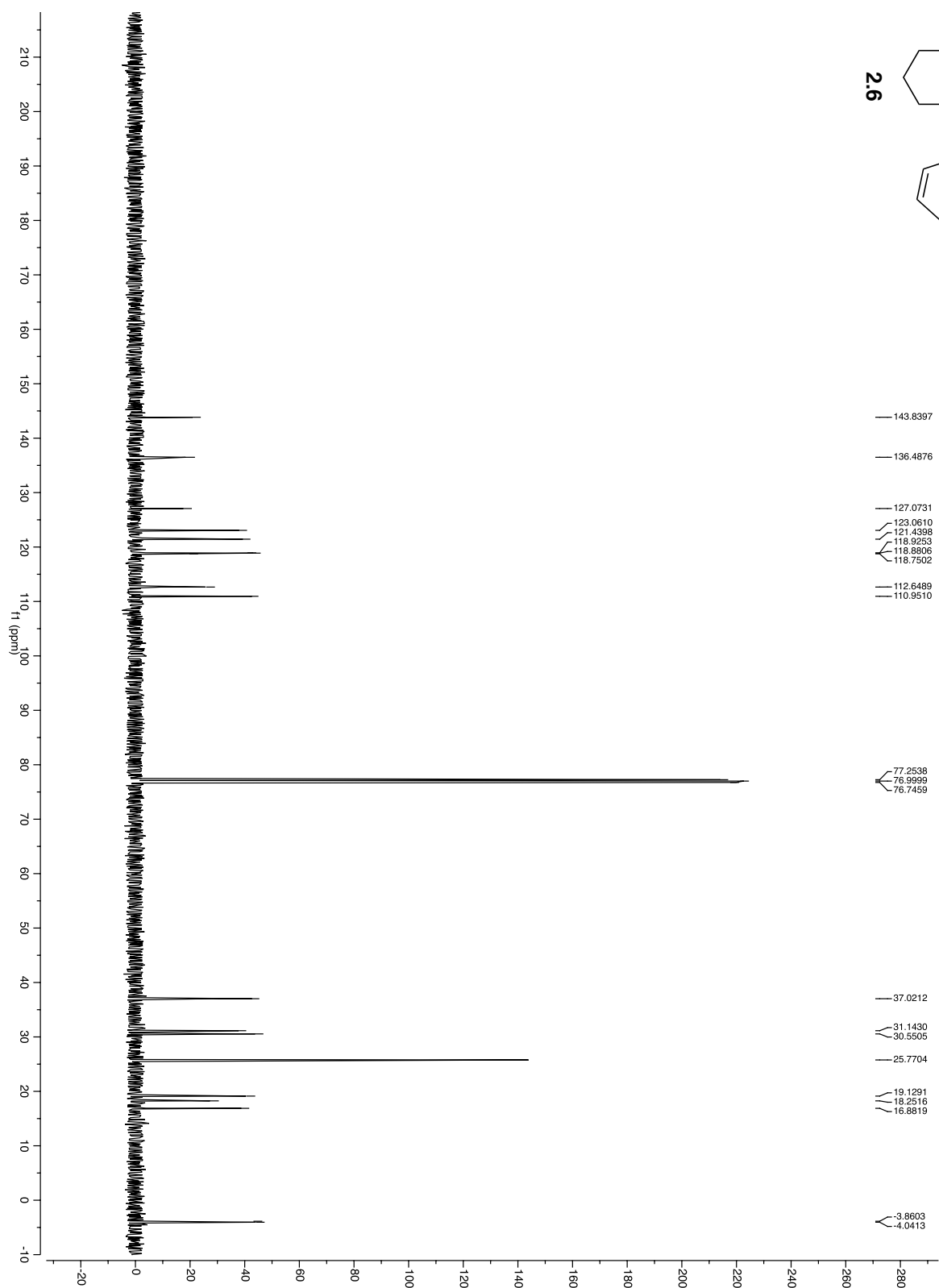
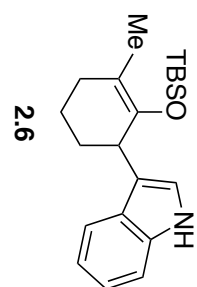
IR: $f(\text{cm}^{-1}) = 3450, 3069, 1596, 1546, 1488, 1159, 1119, 1023, 1001, 834, 801, 753, 682, 609, 577$.

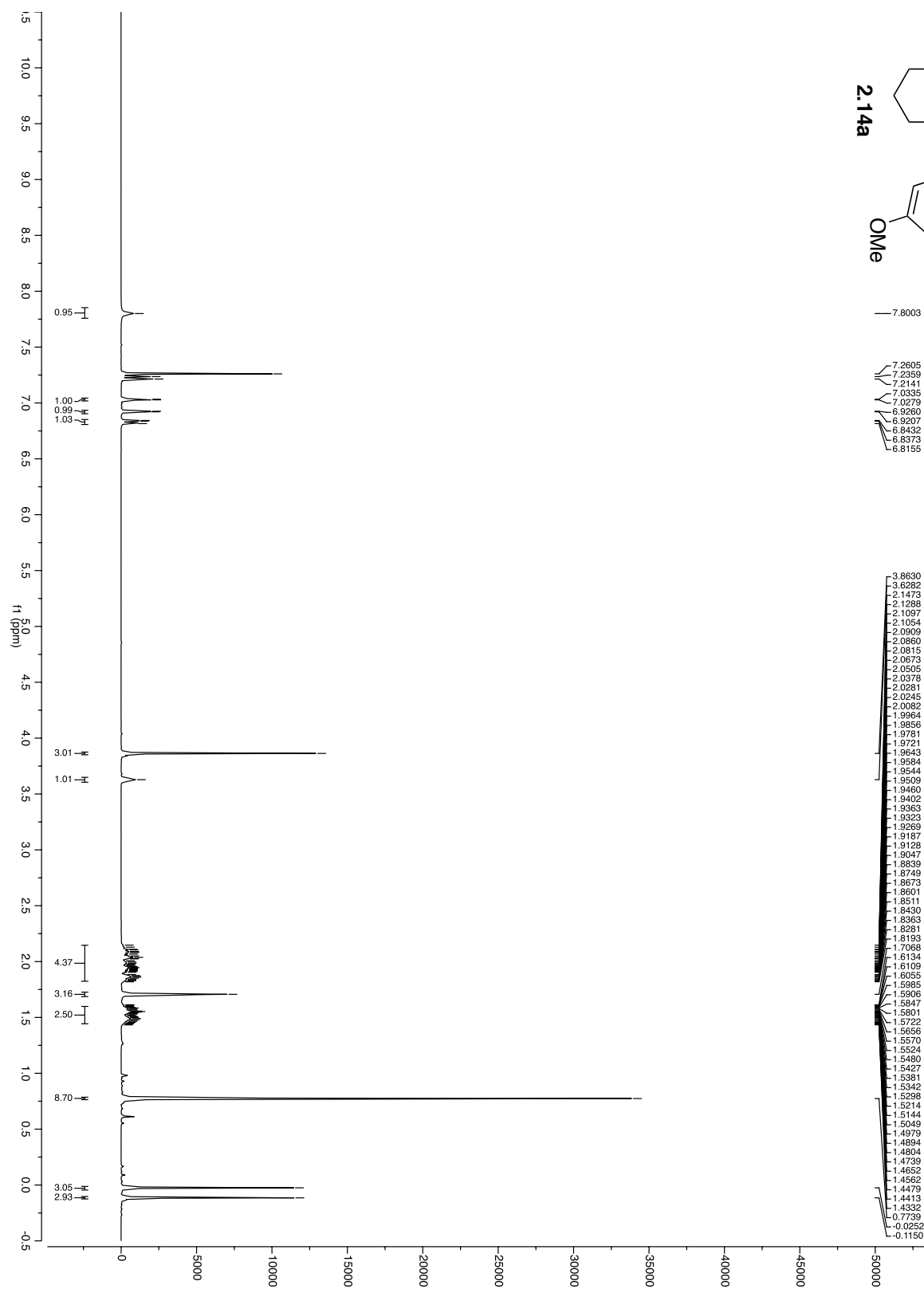
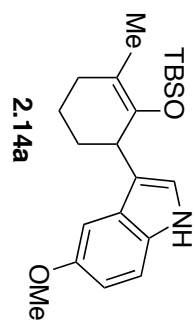
HRMS-ESI: $(M+Na^+) = 290.04575$ calculated for $C_{12}H_{13}NNaO_4$, experimental 290.04422.

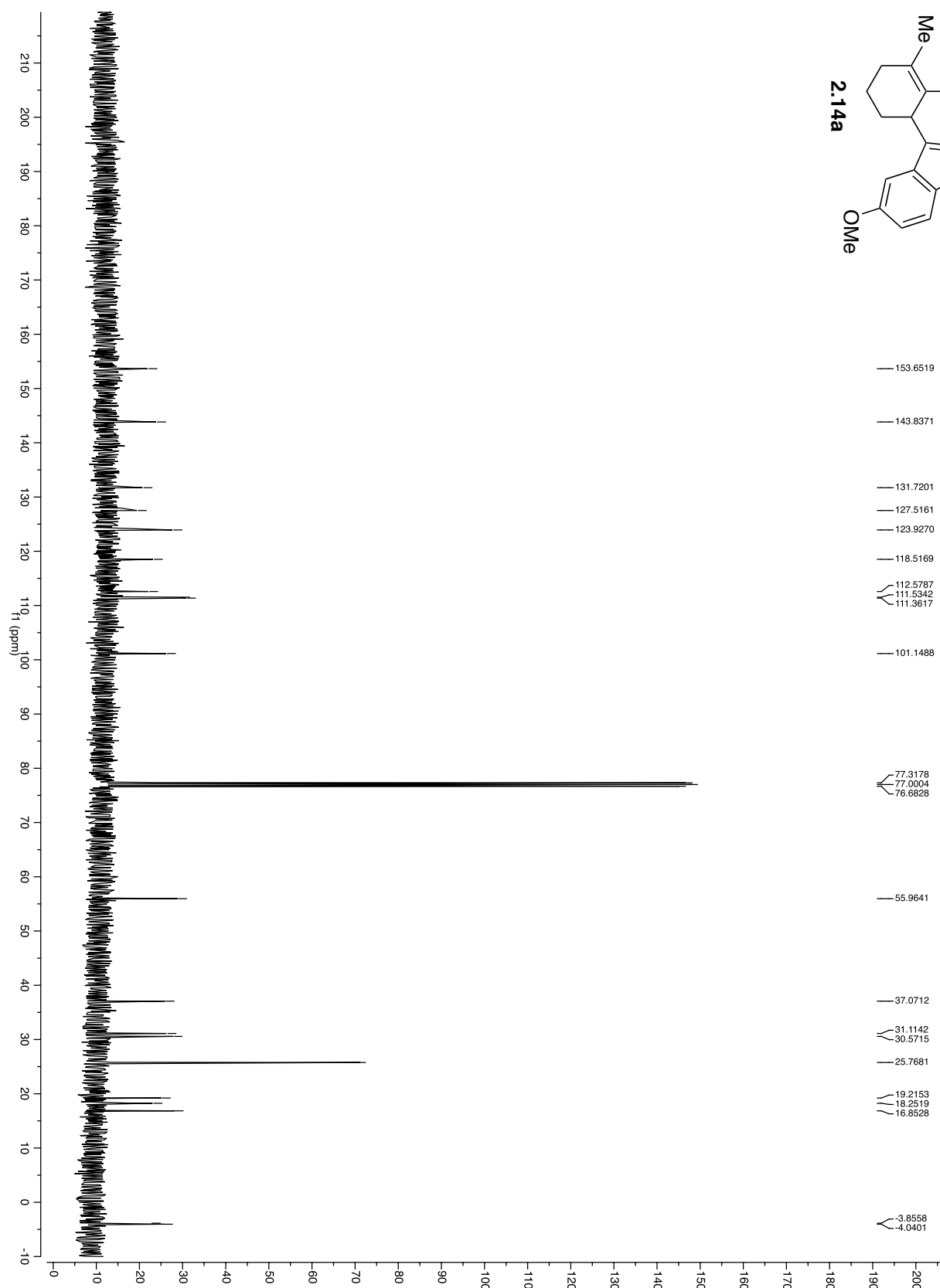
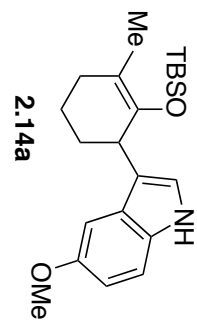


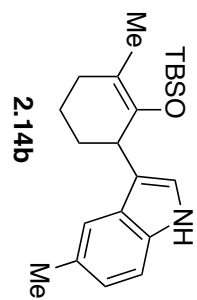






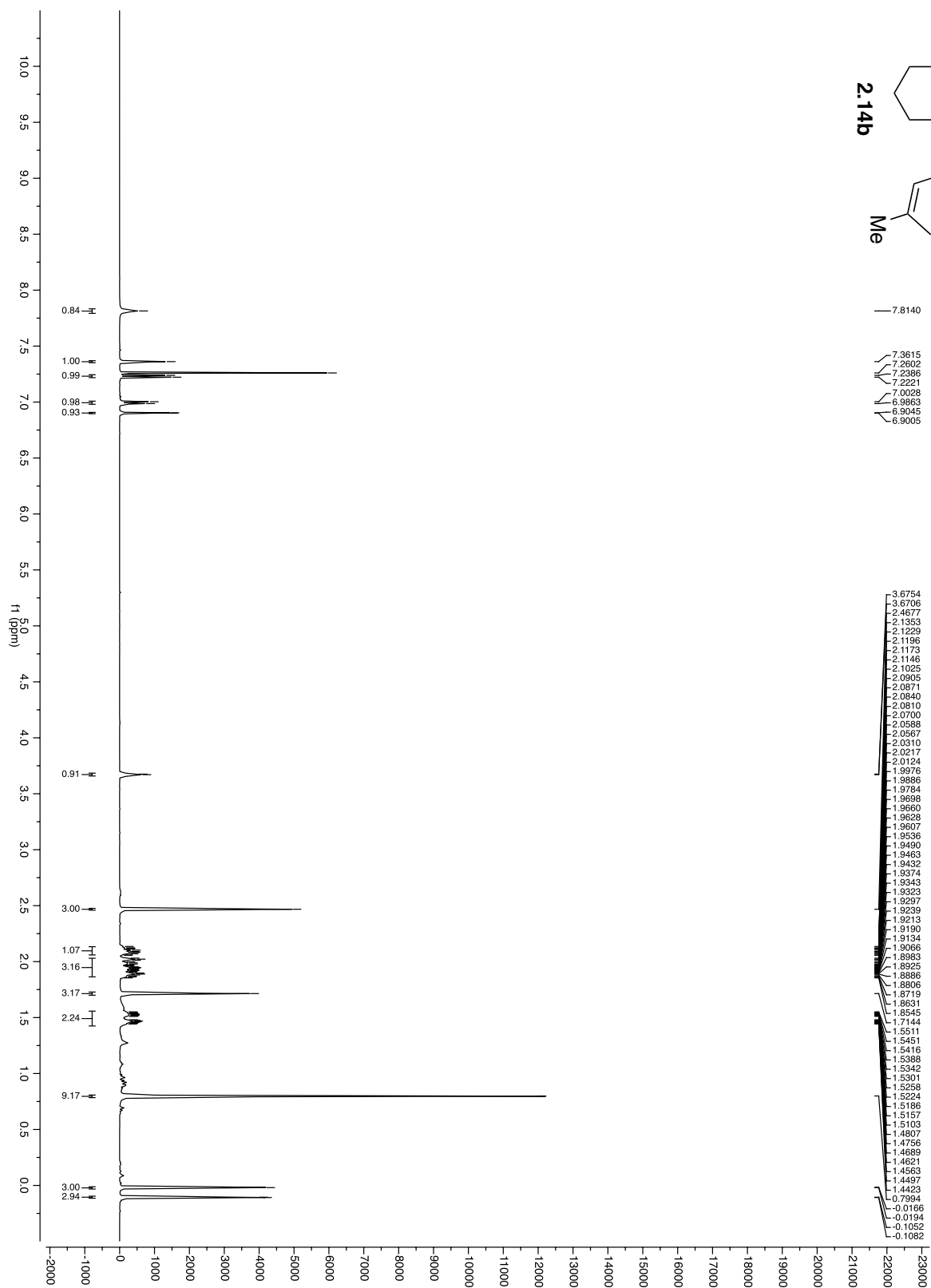


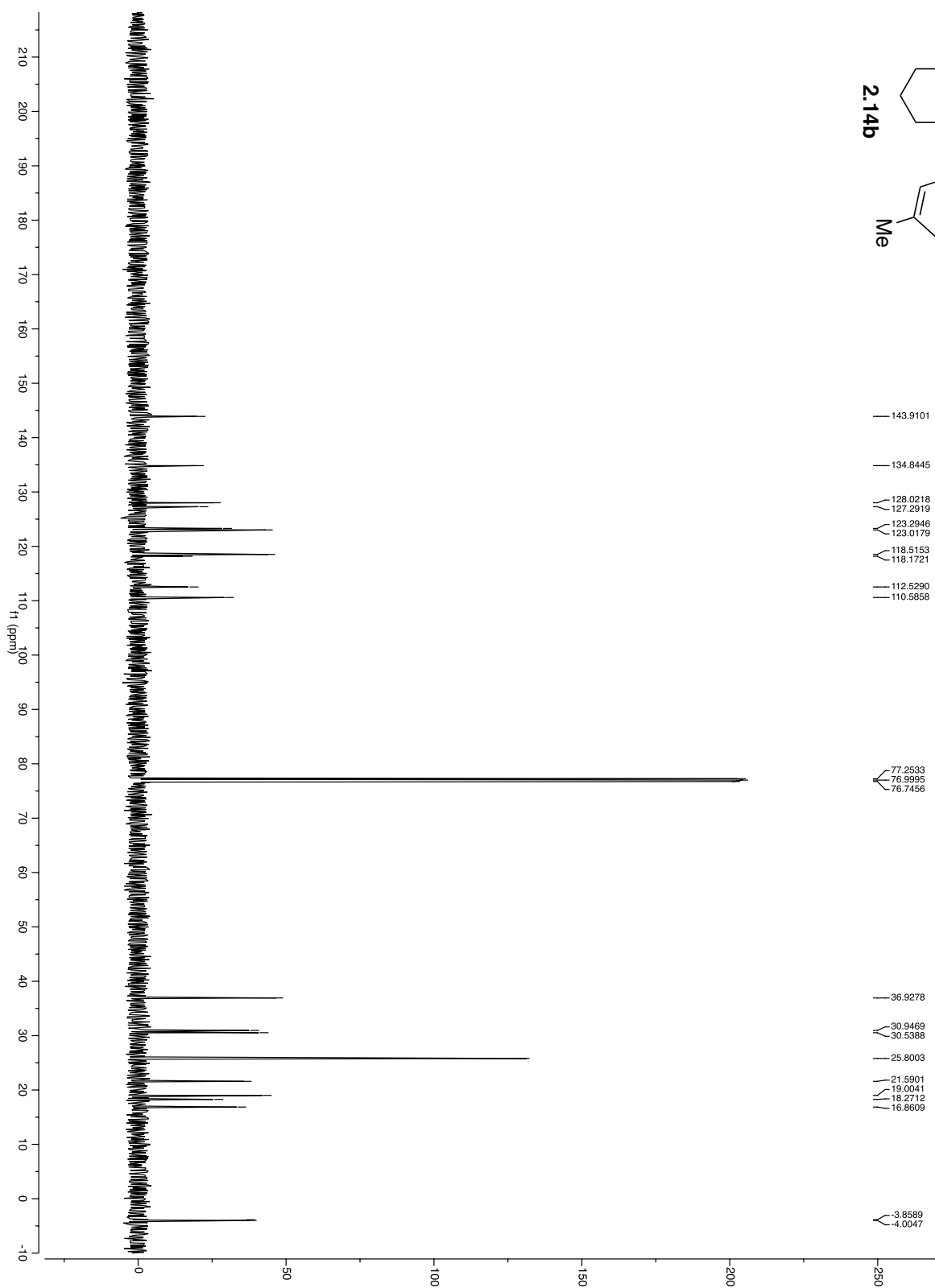
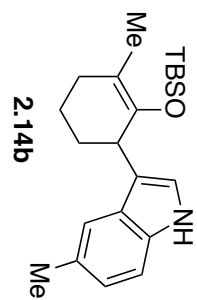


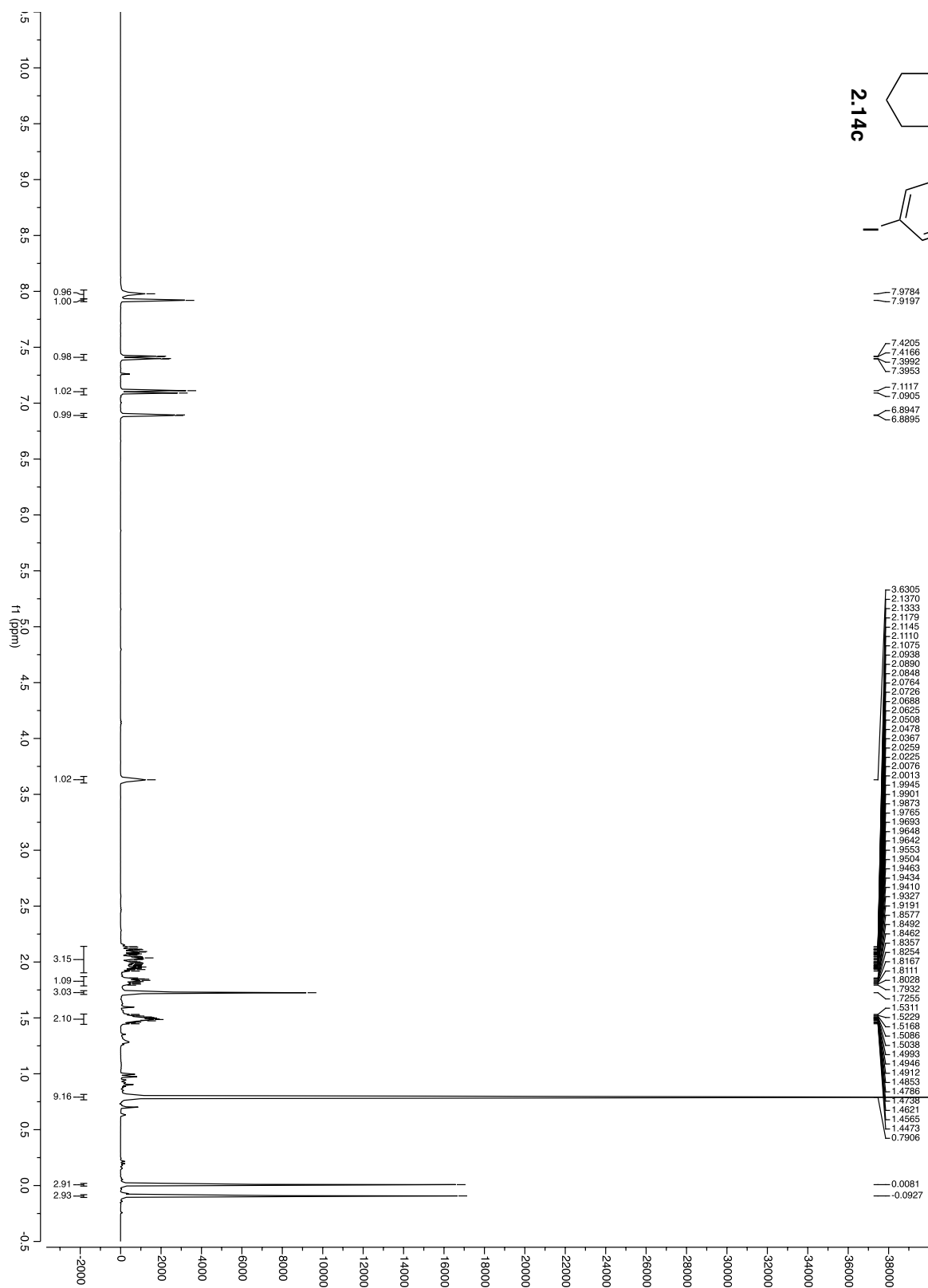
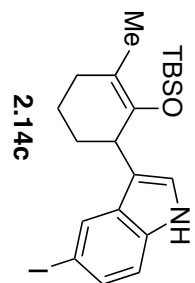


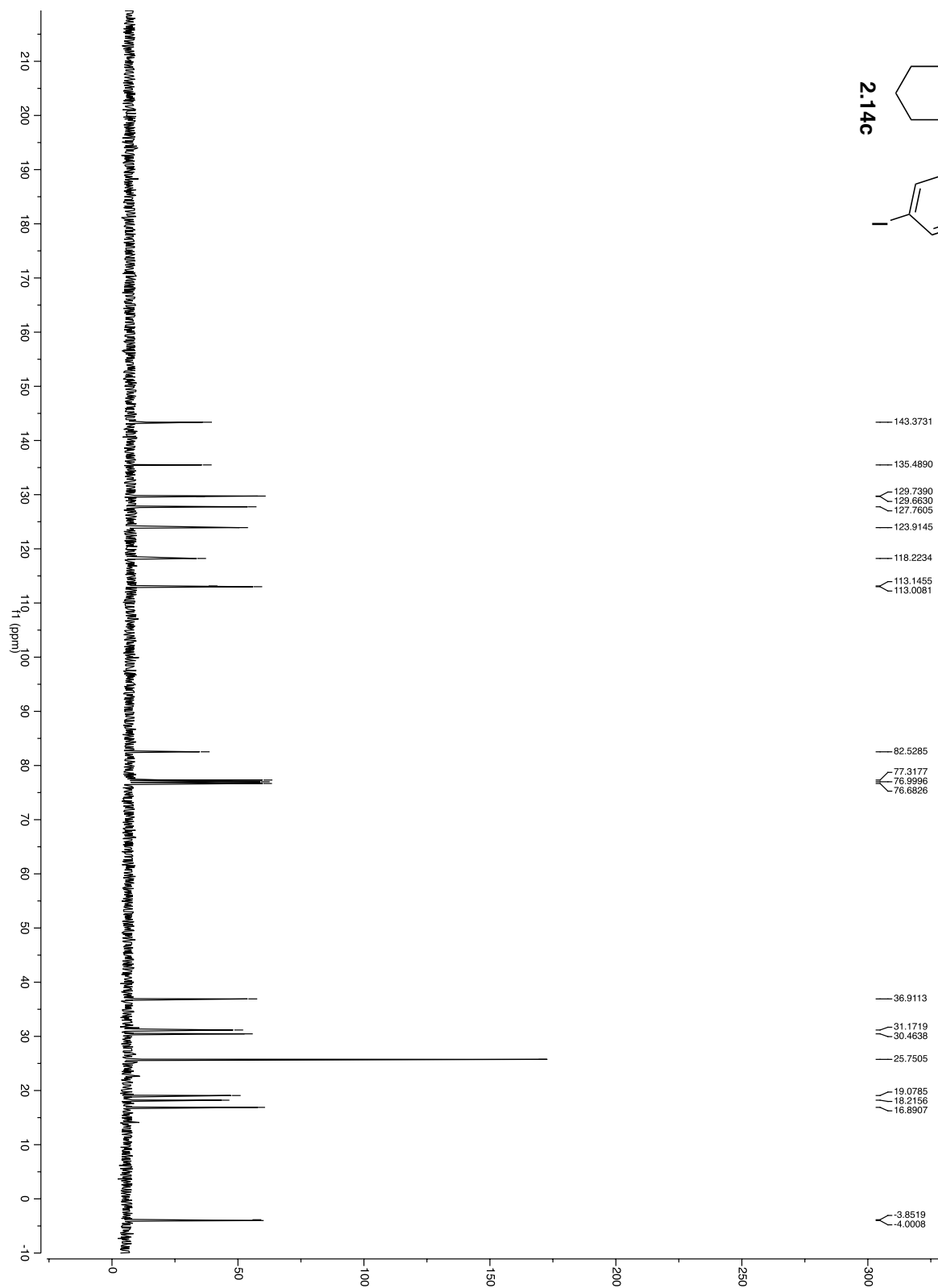
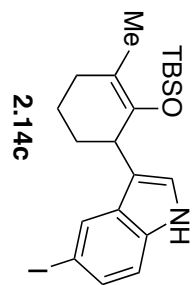
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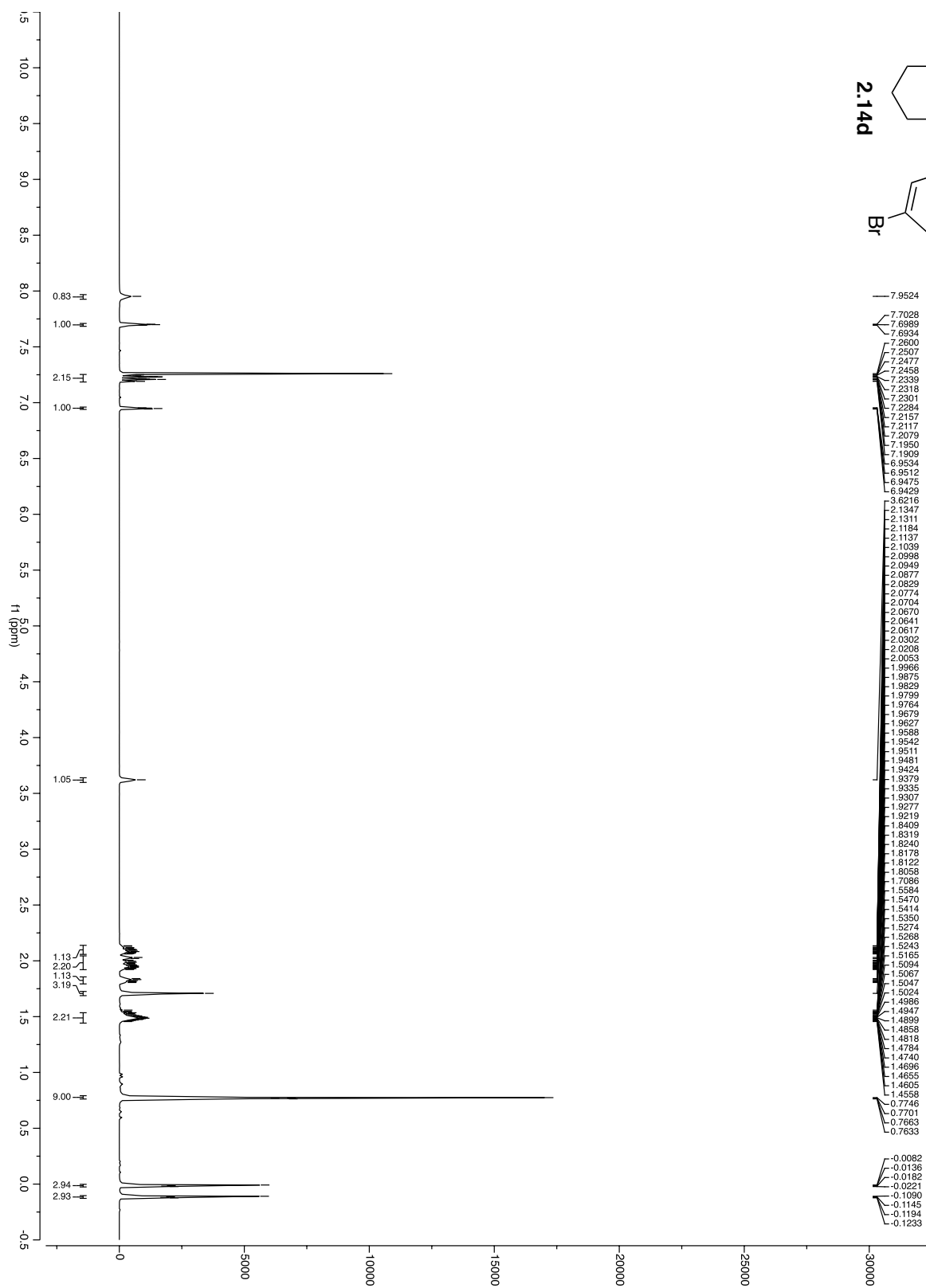
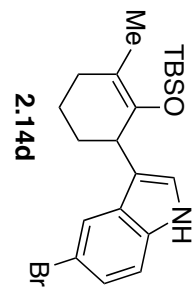
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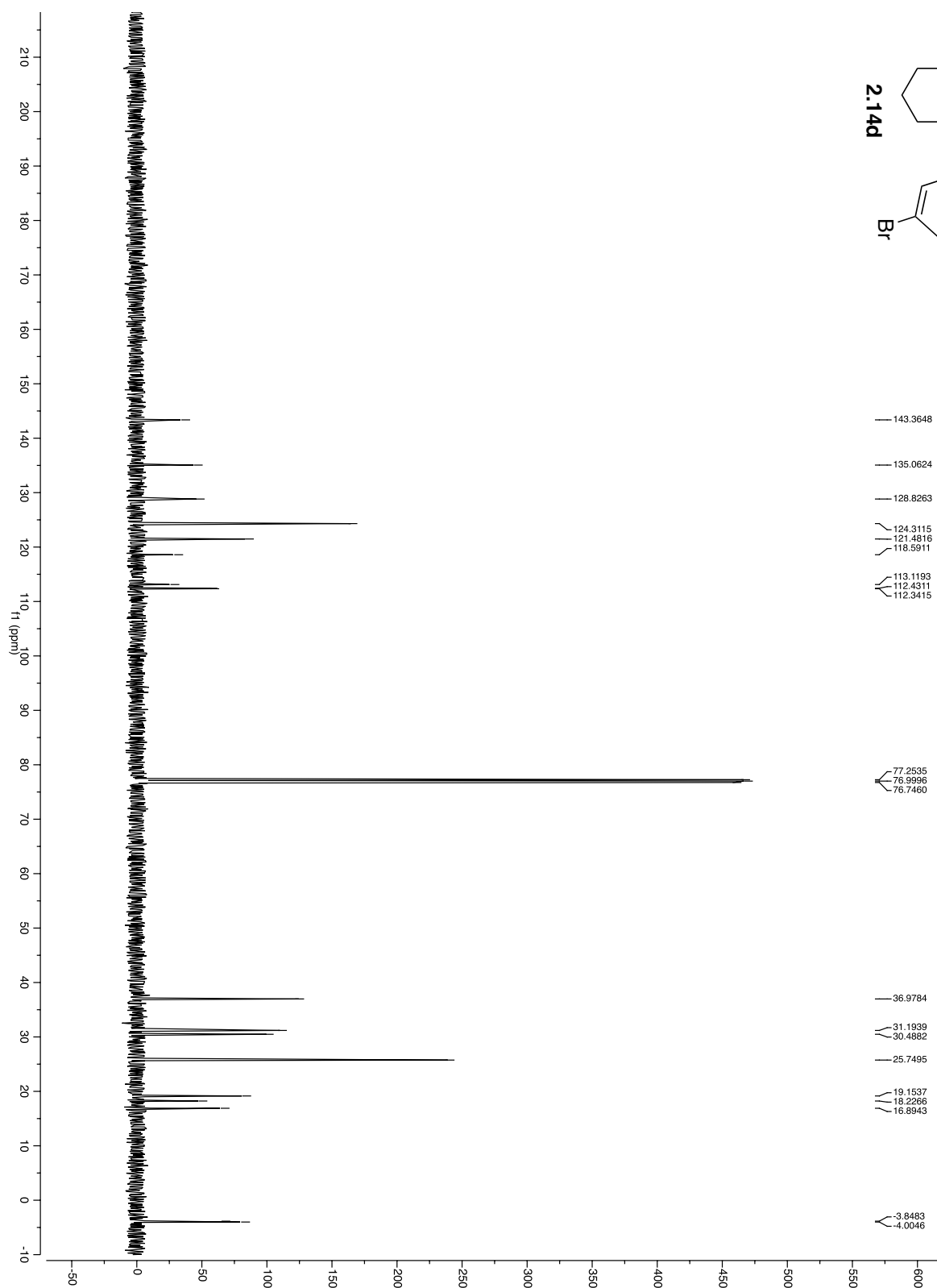
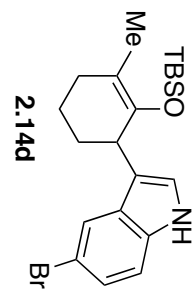


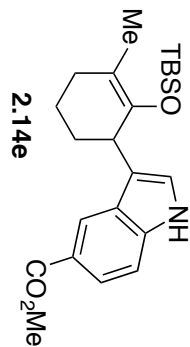


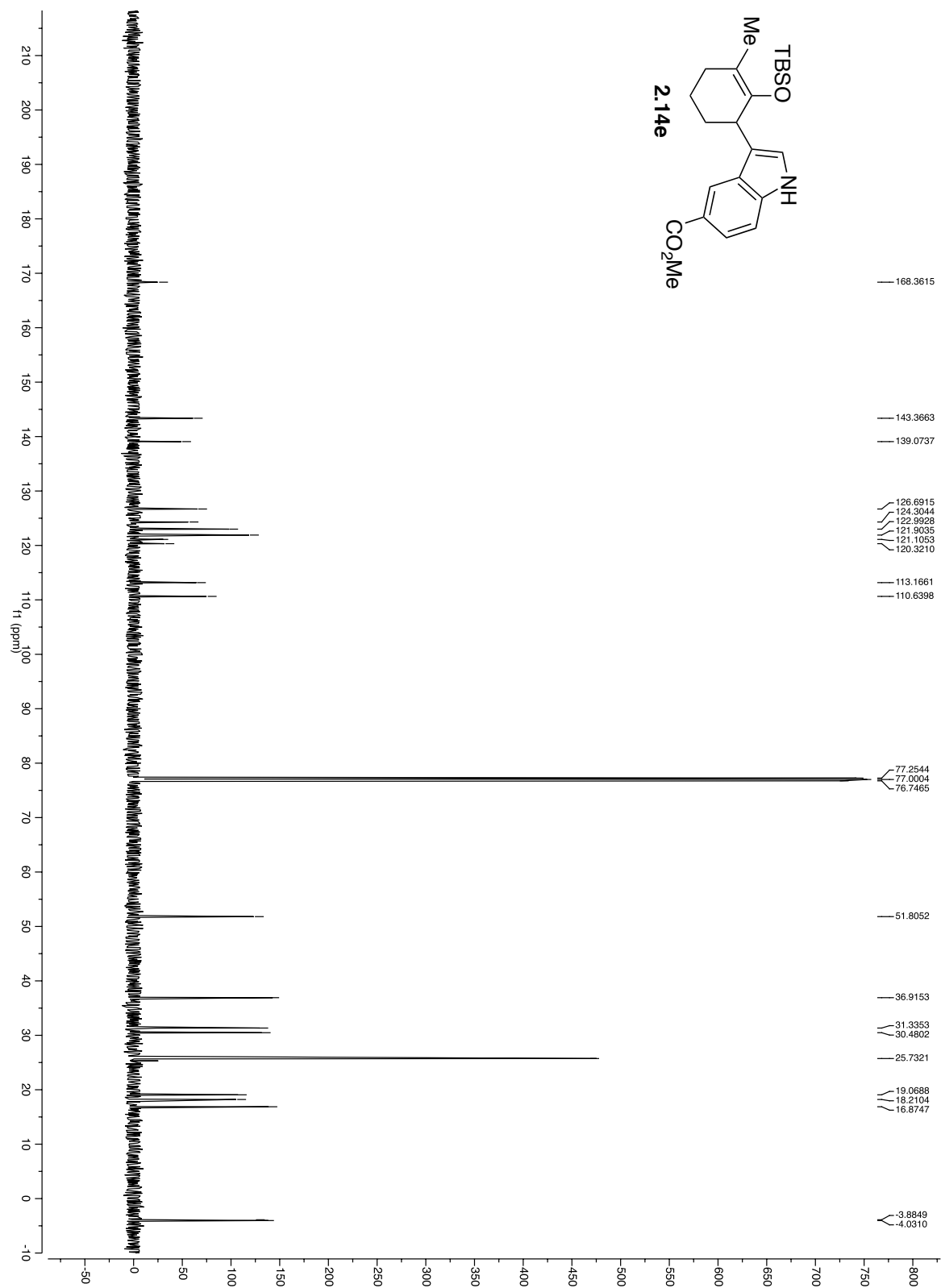


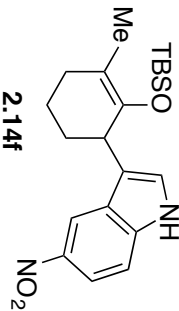


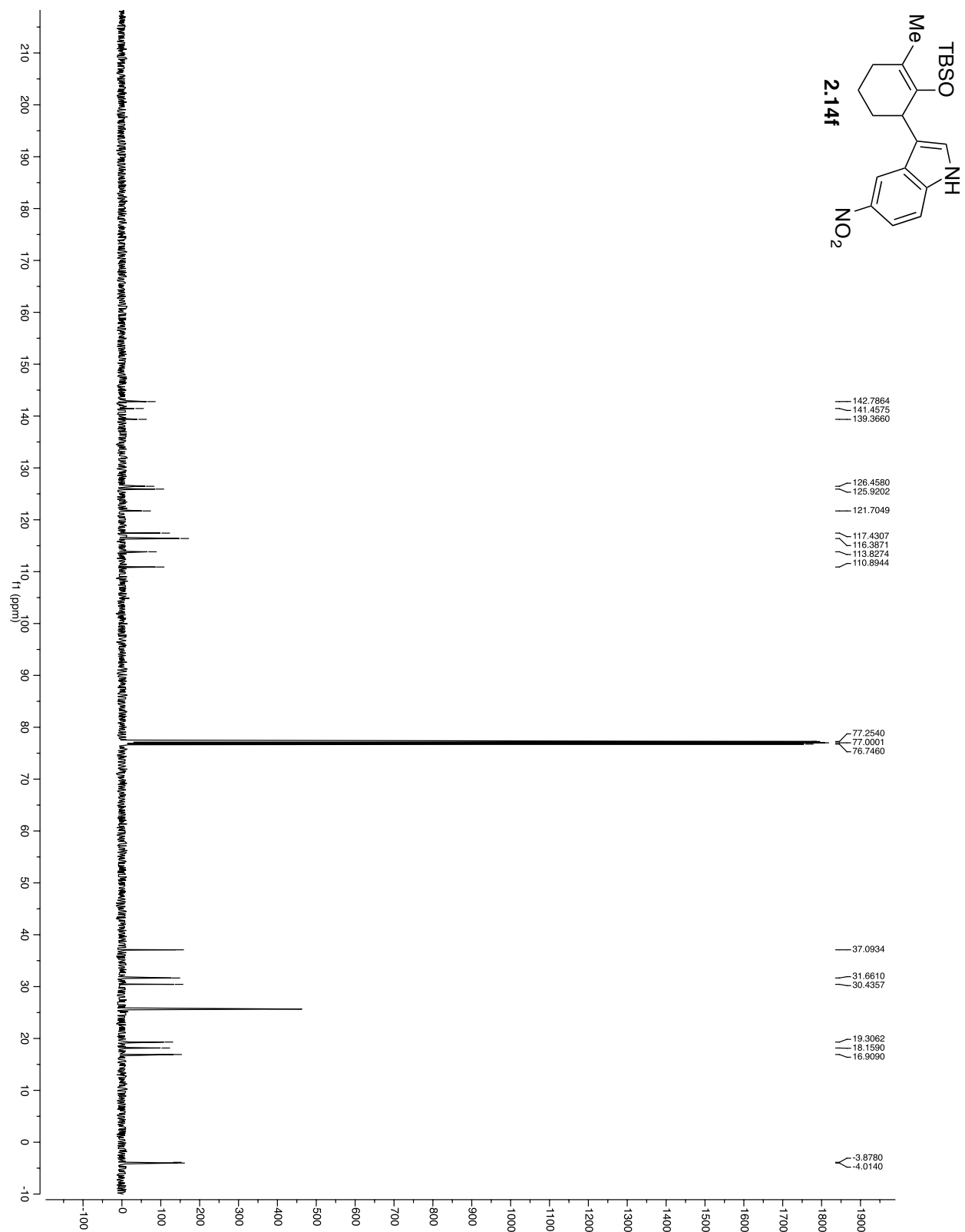


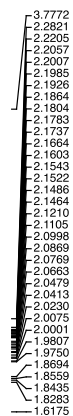


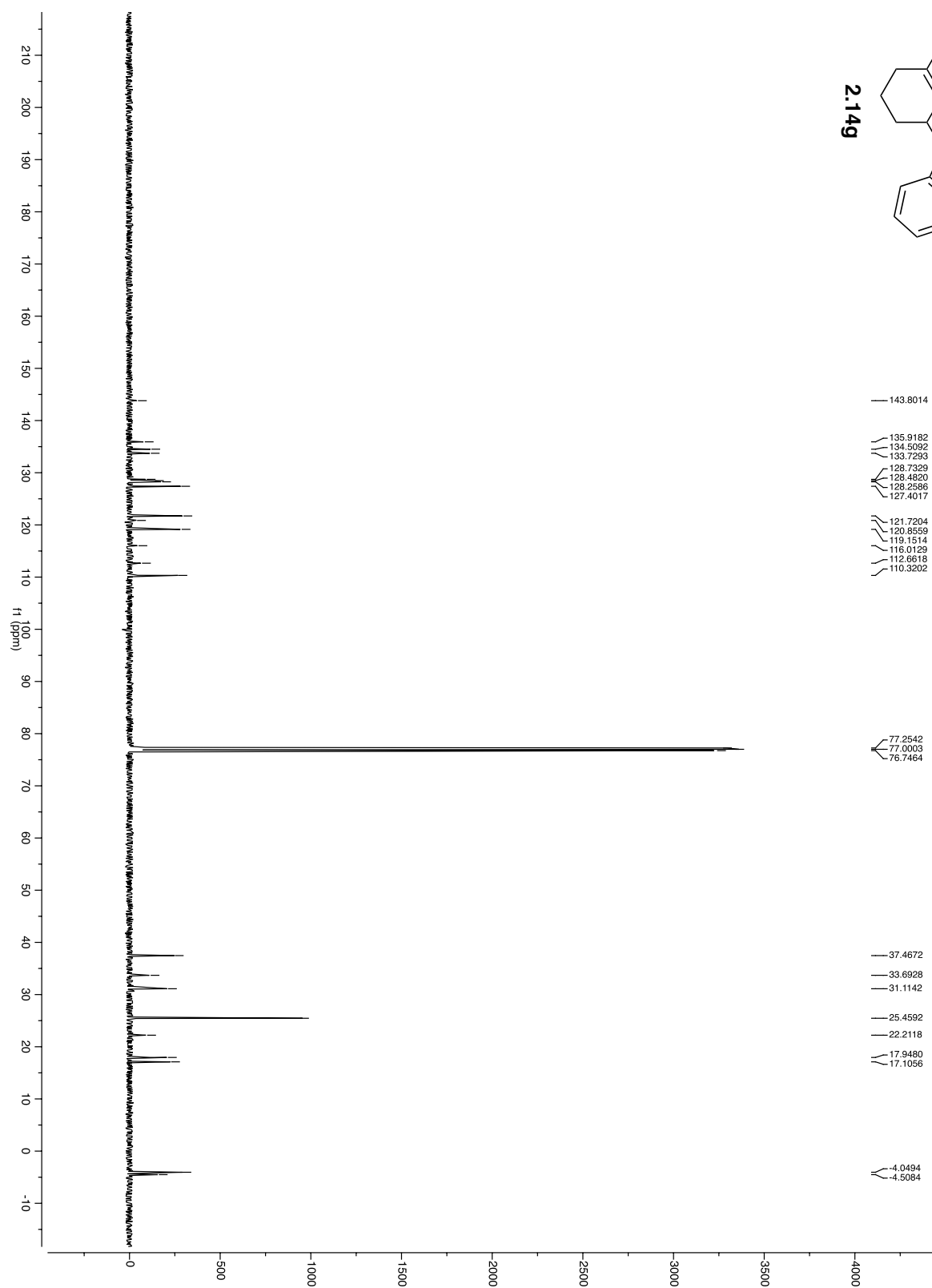
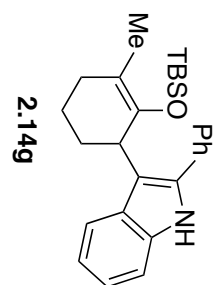


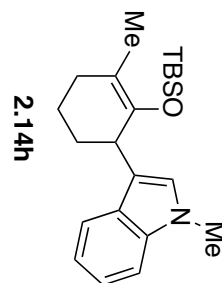




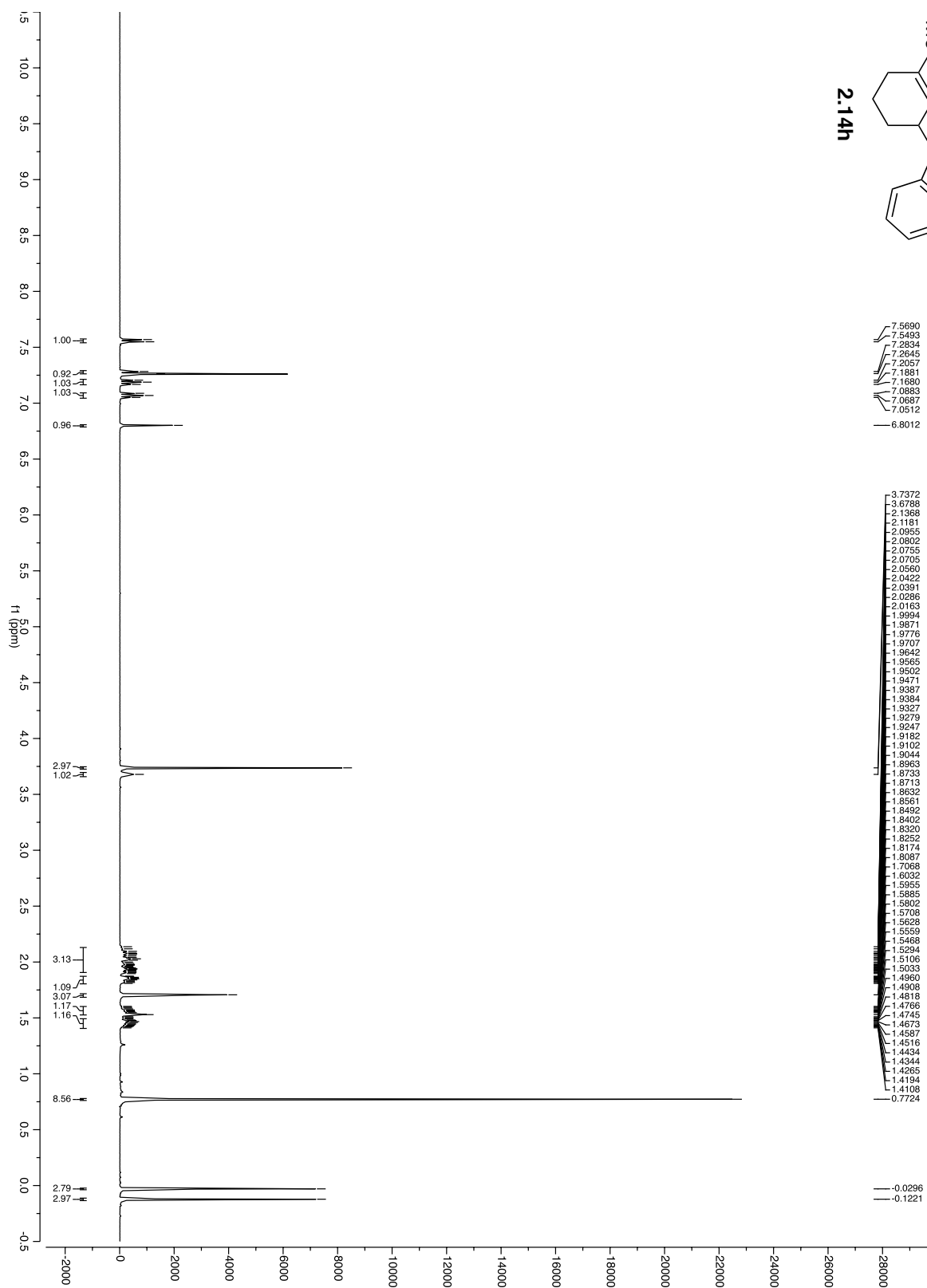




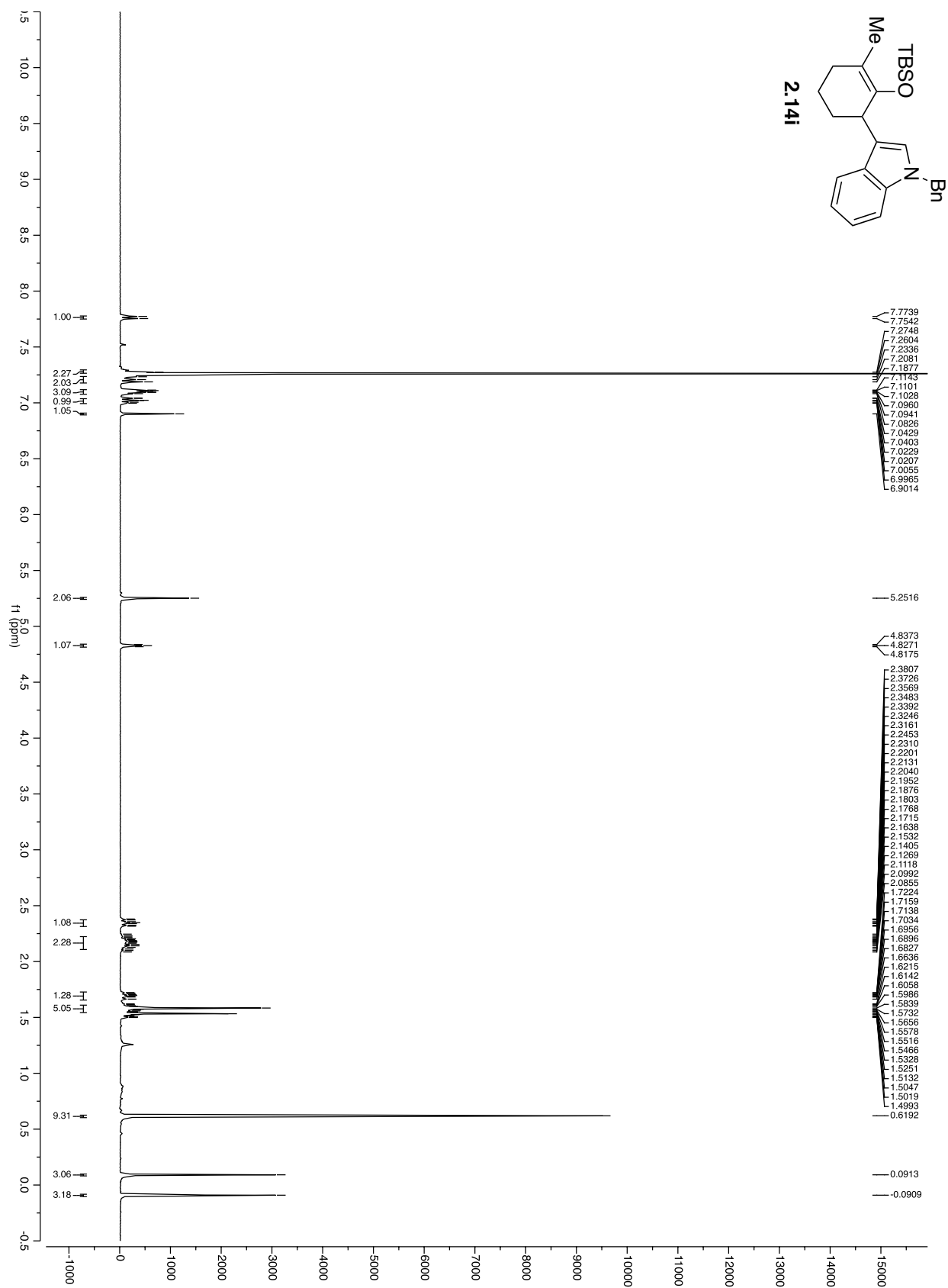


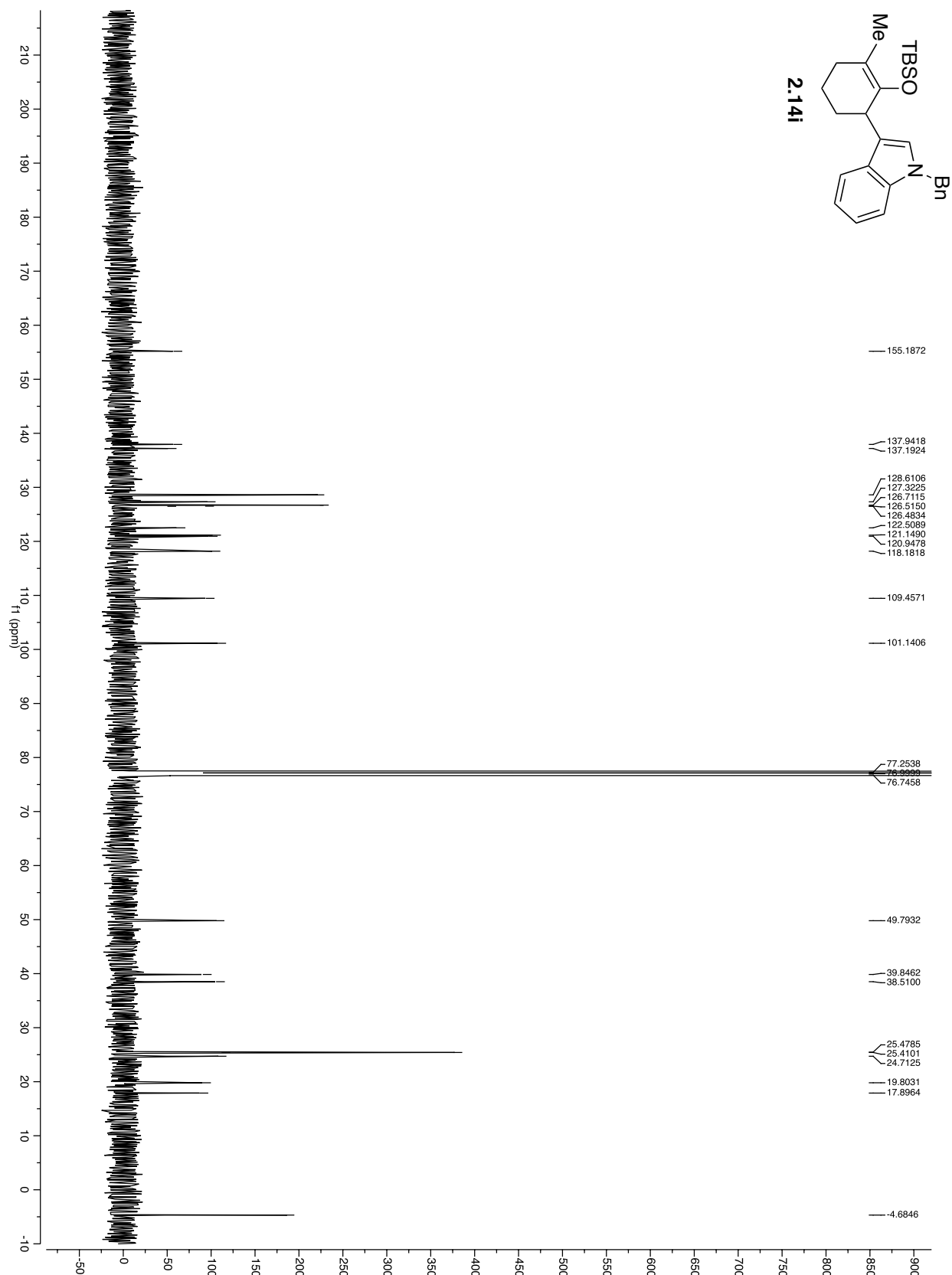


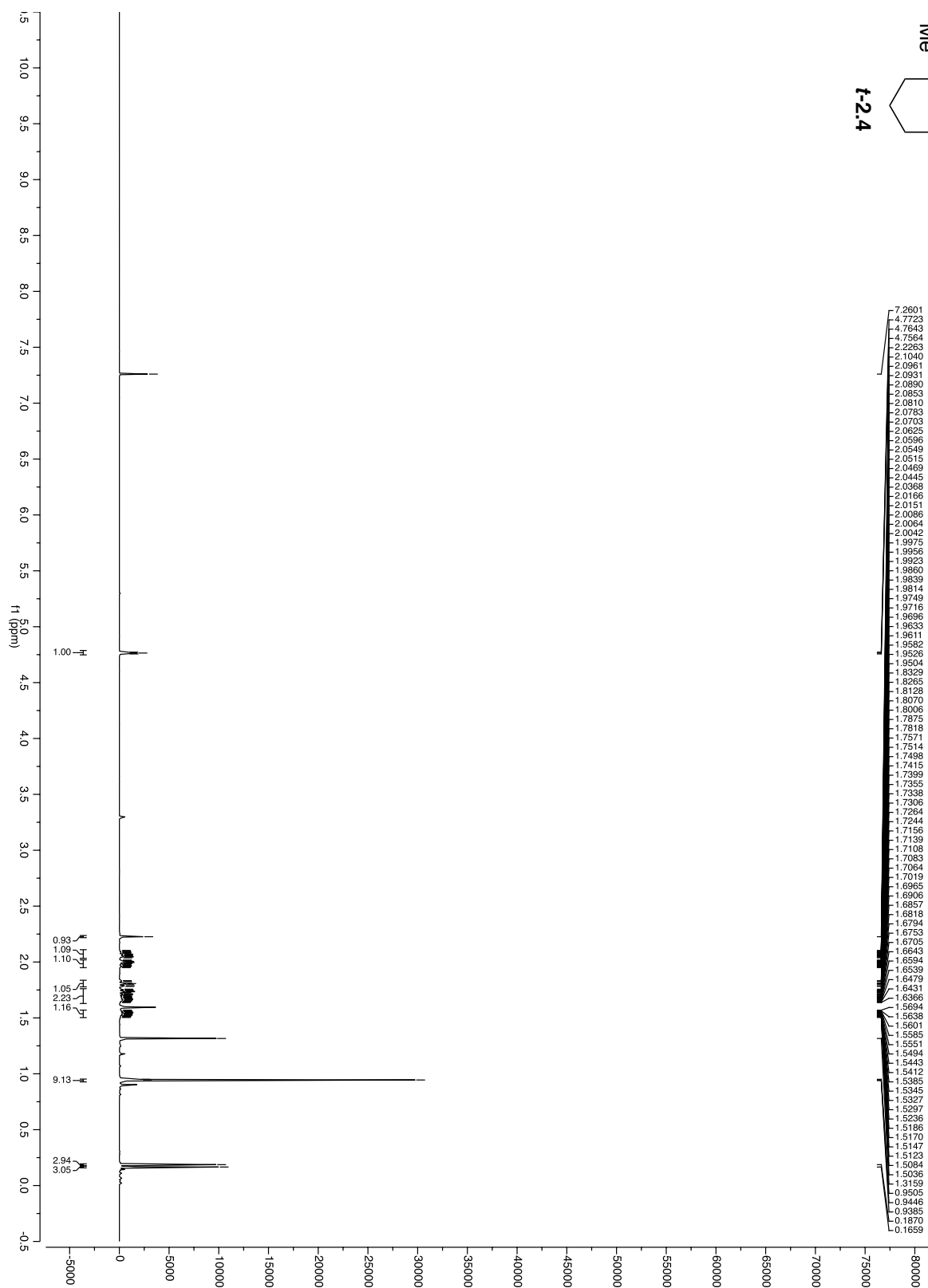
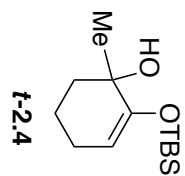
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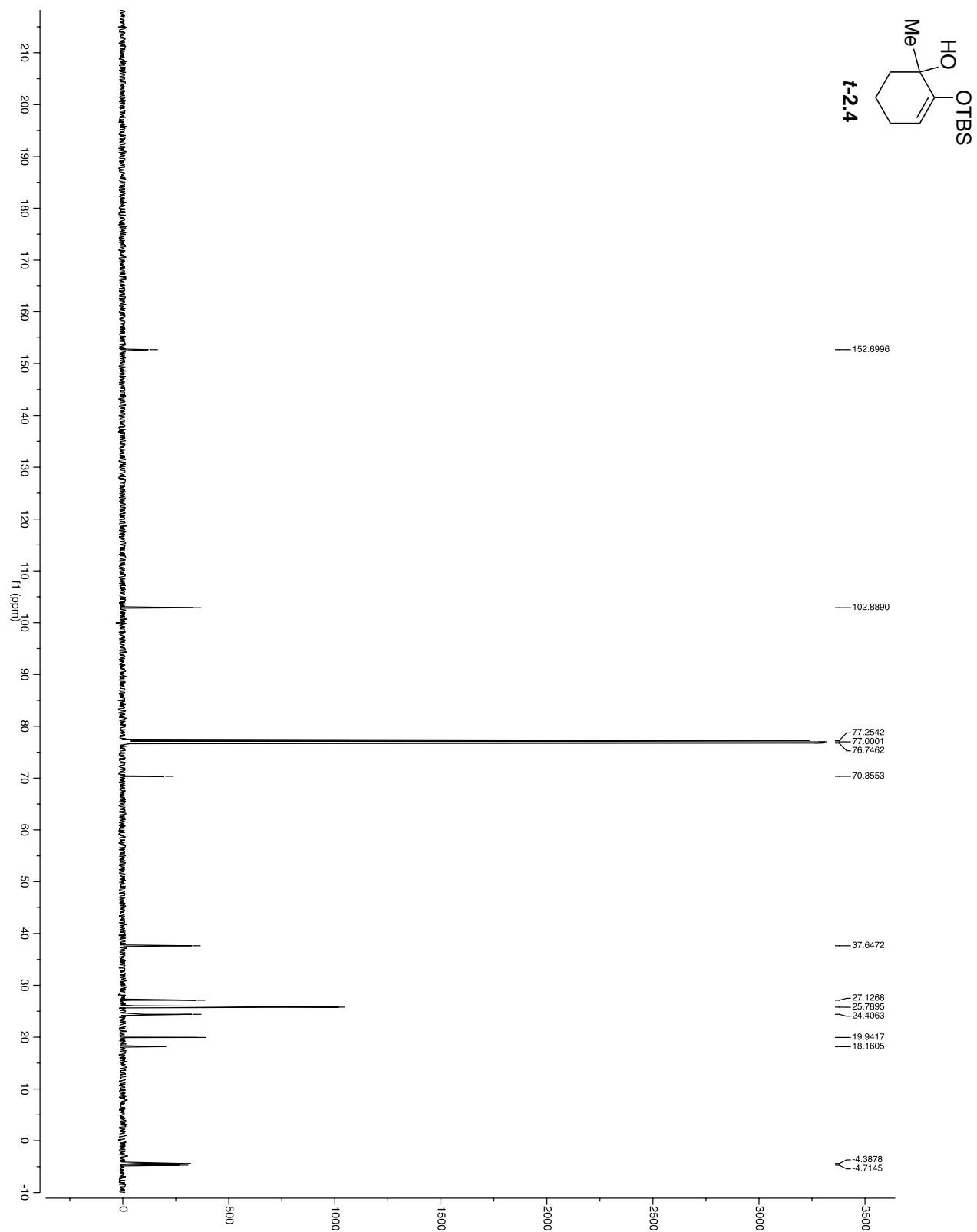


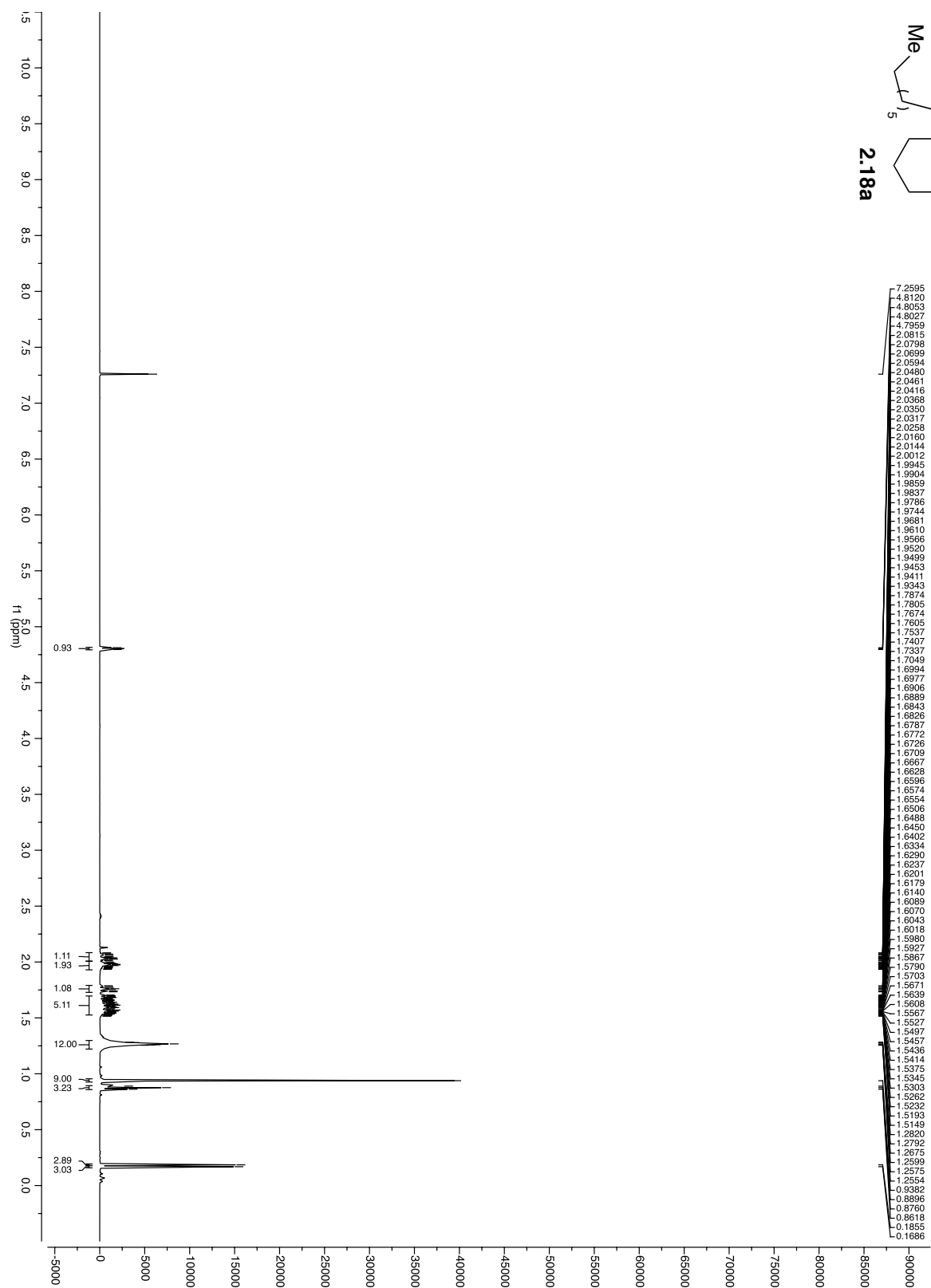
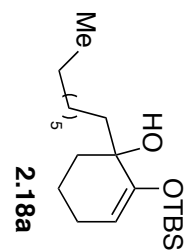




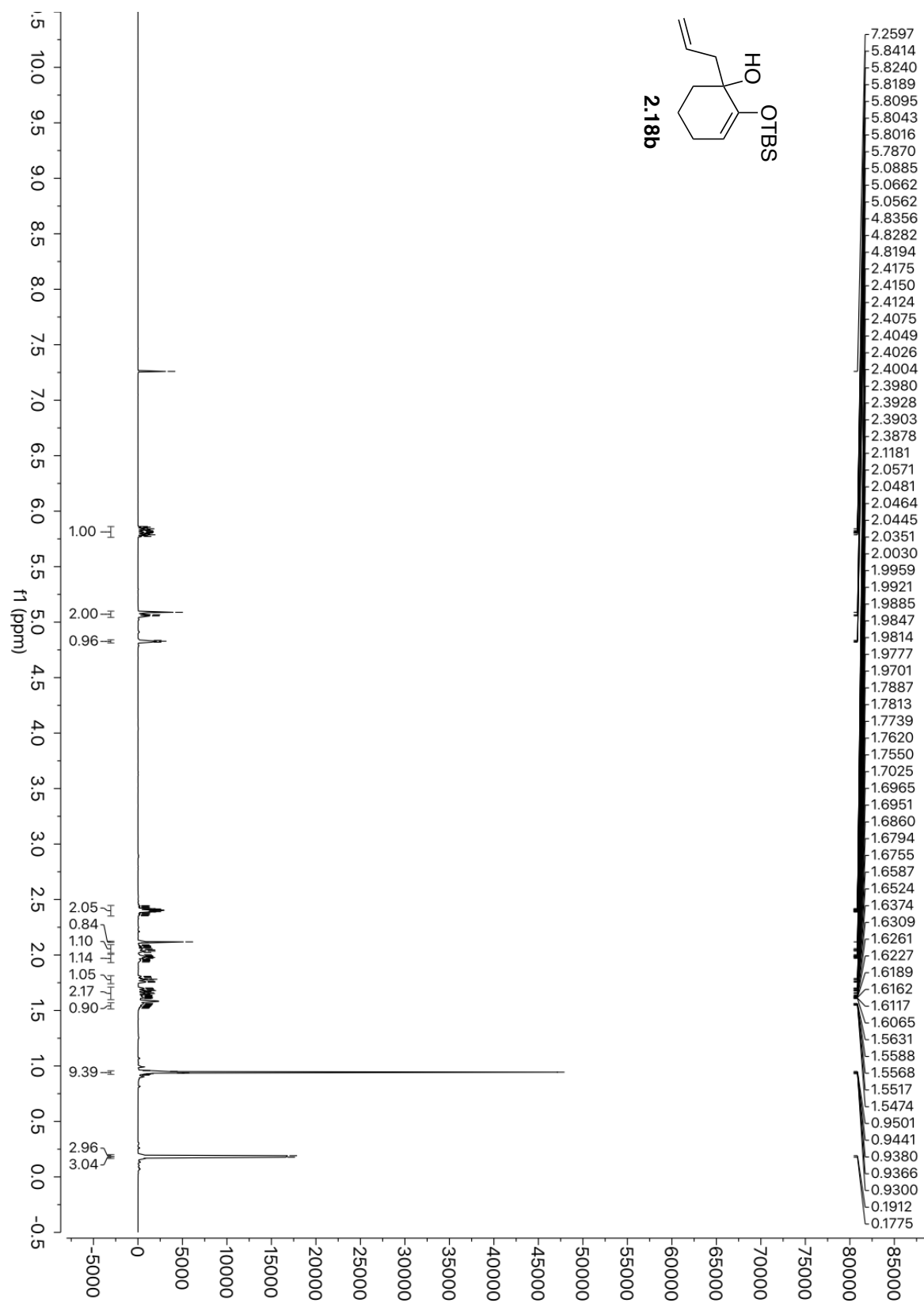


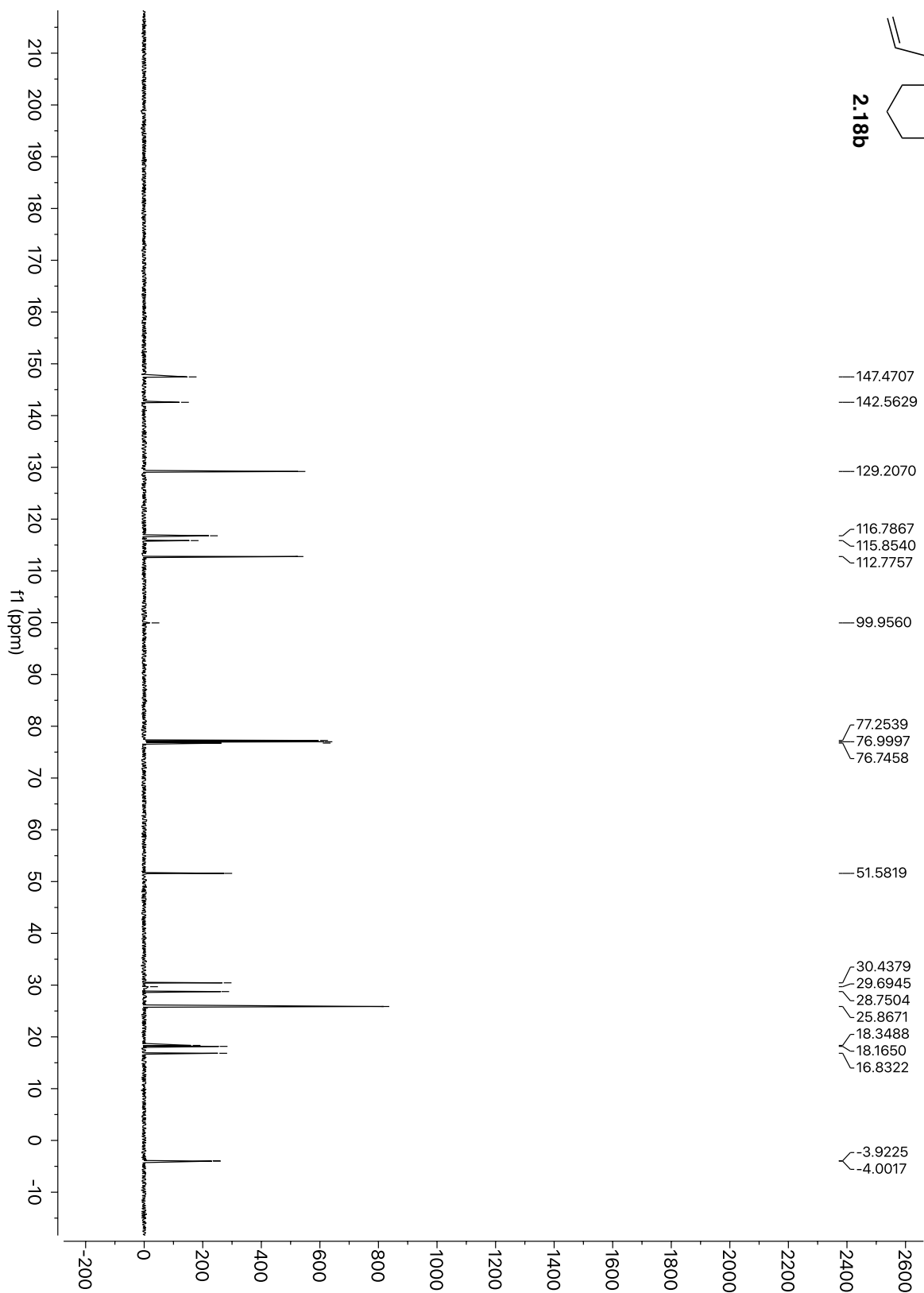
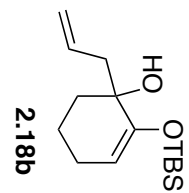


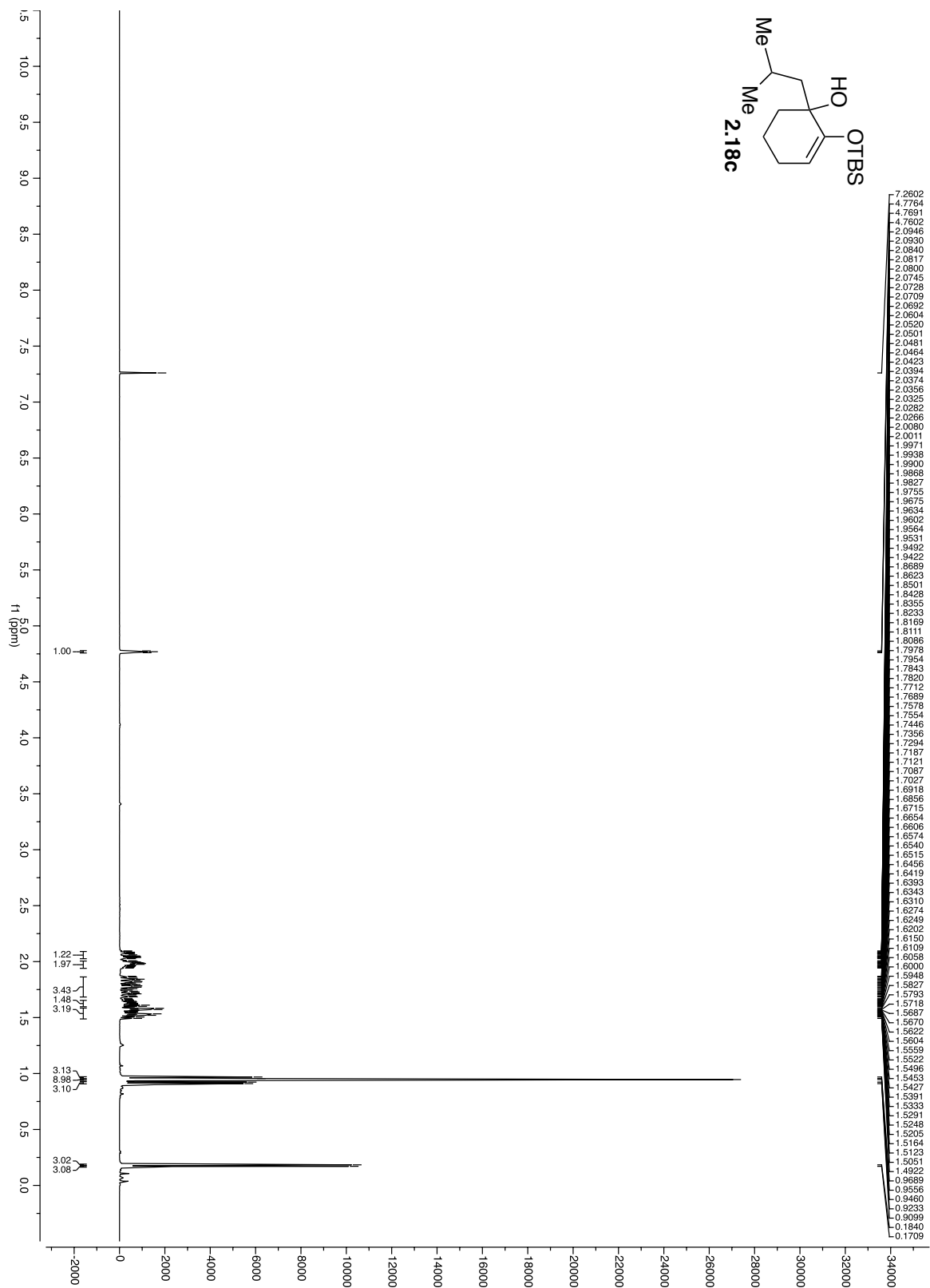
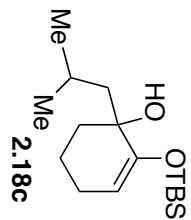


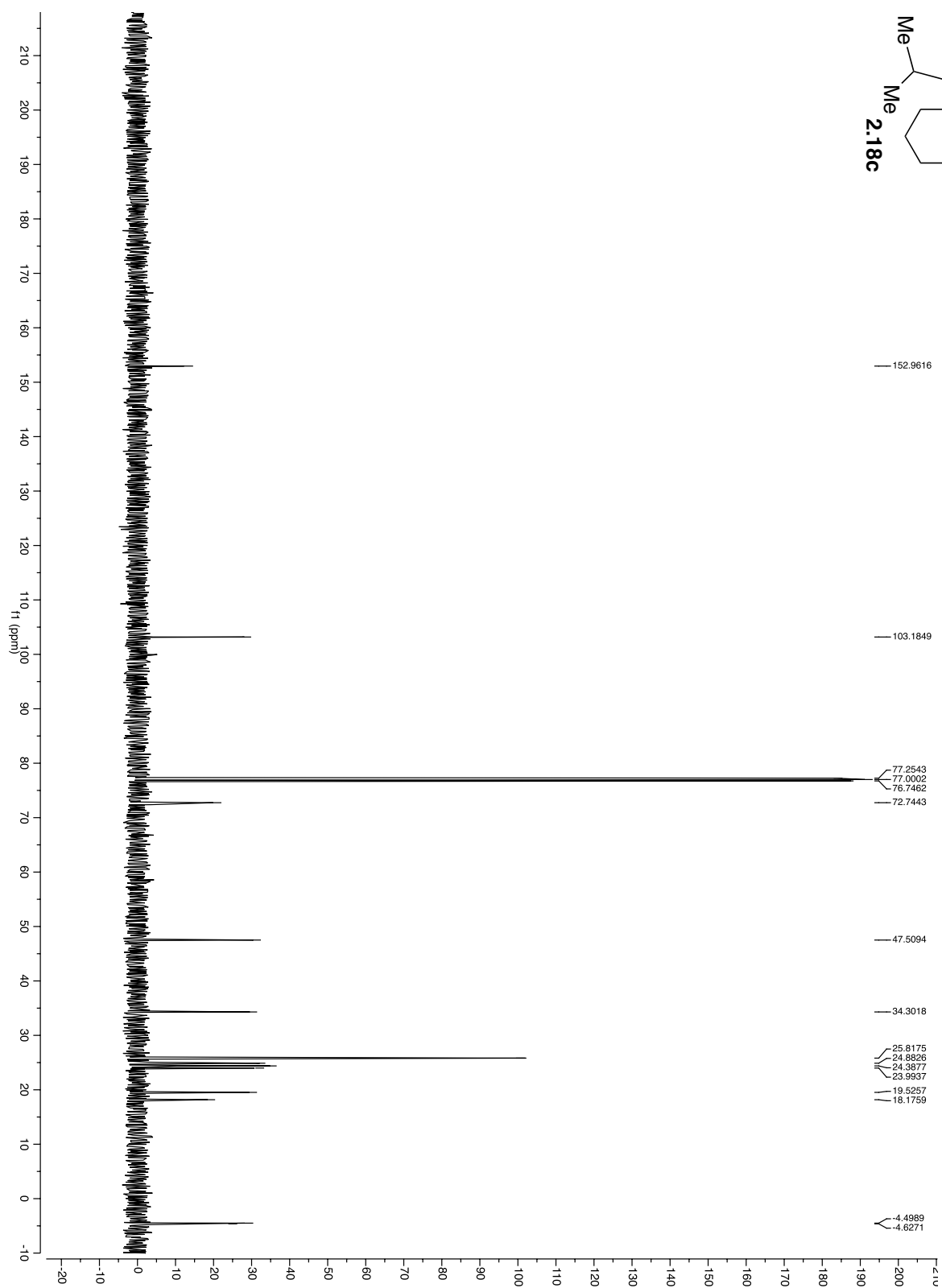
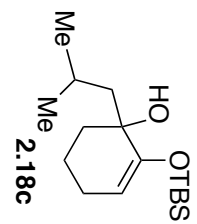


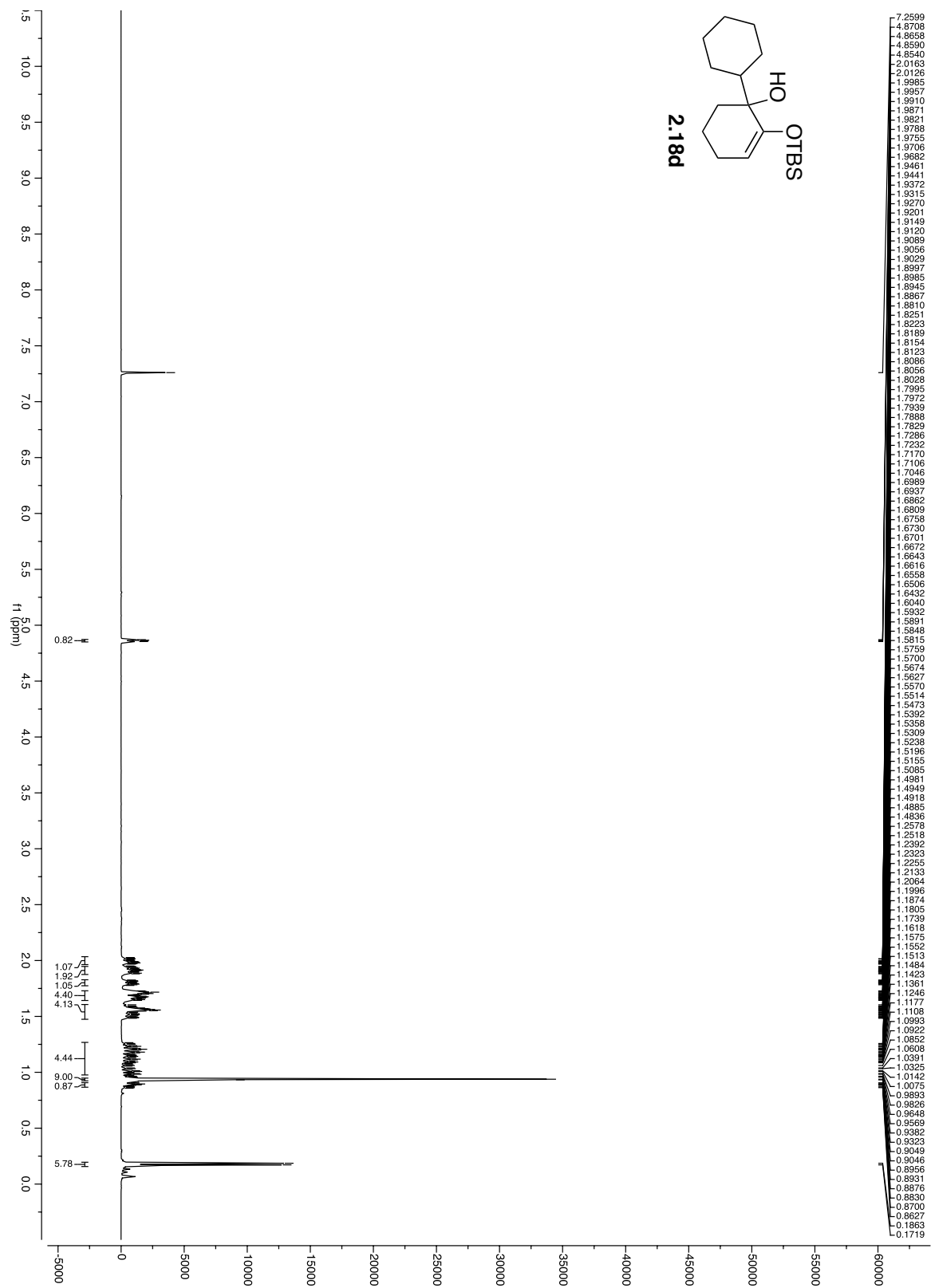




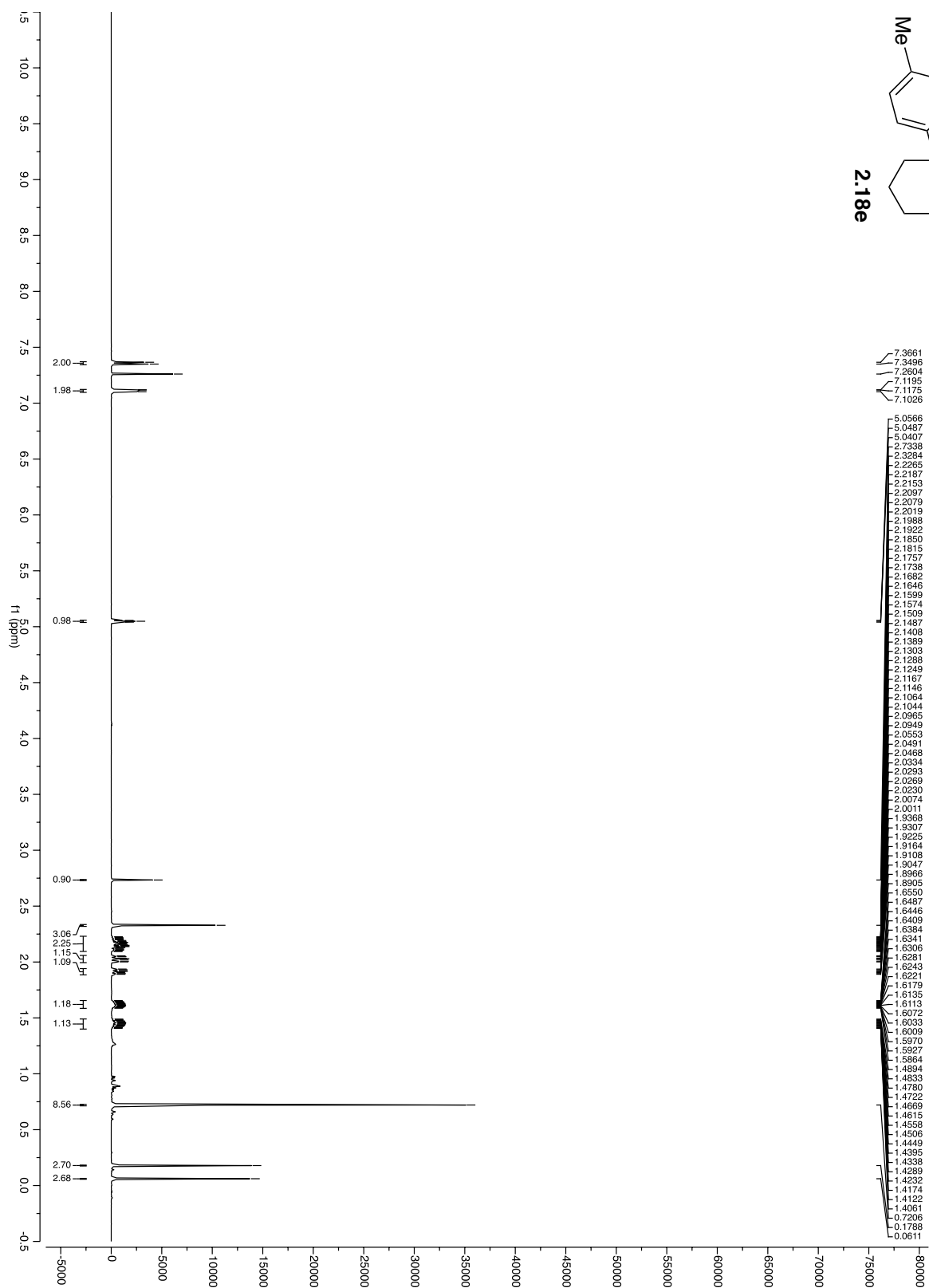
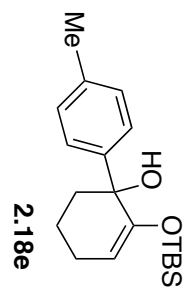




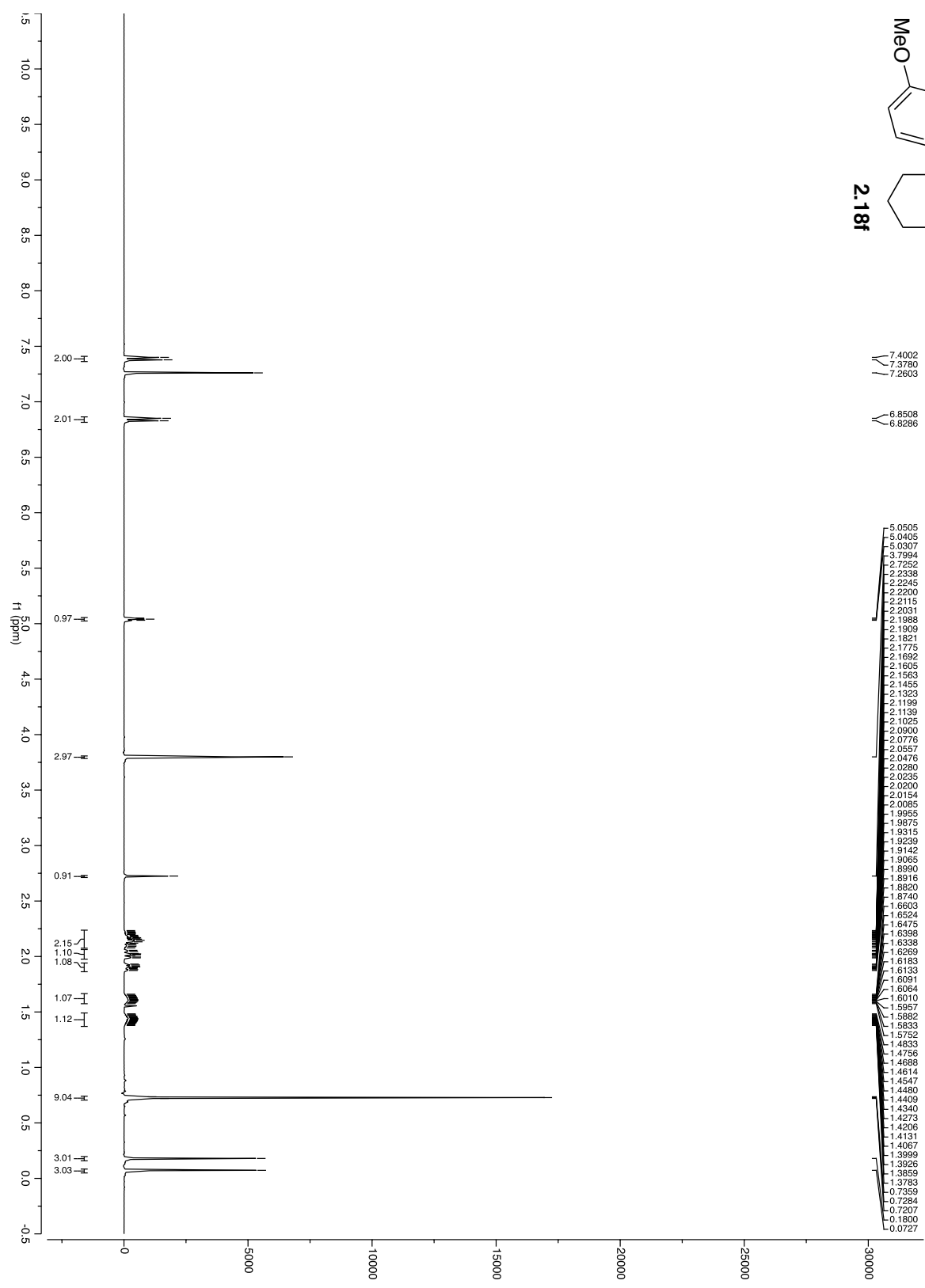
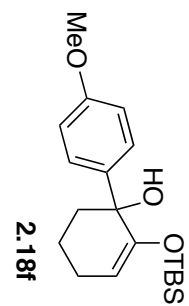


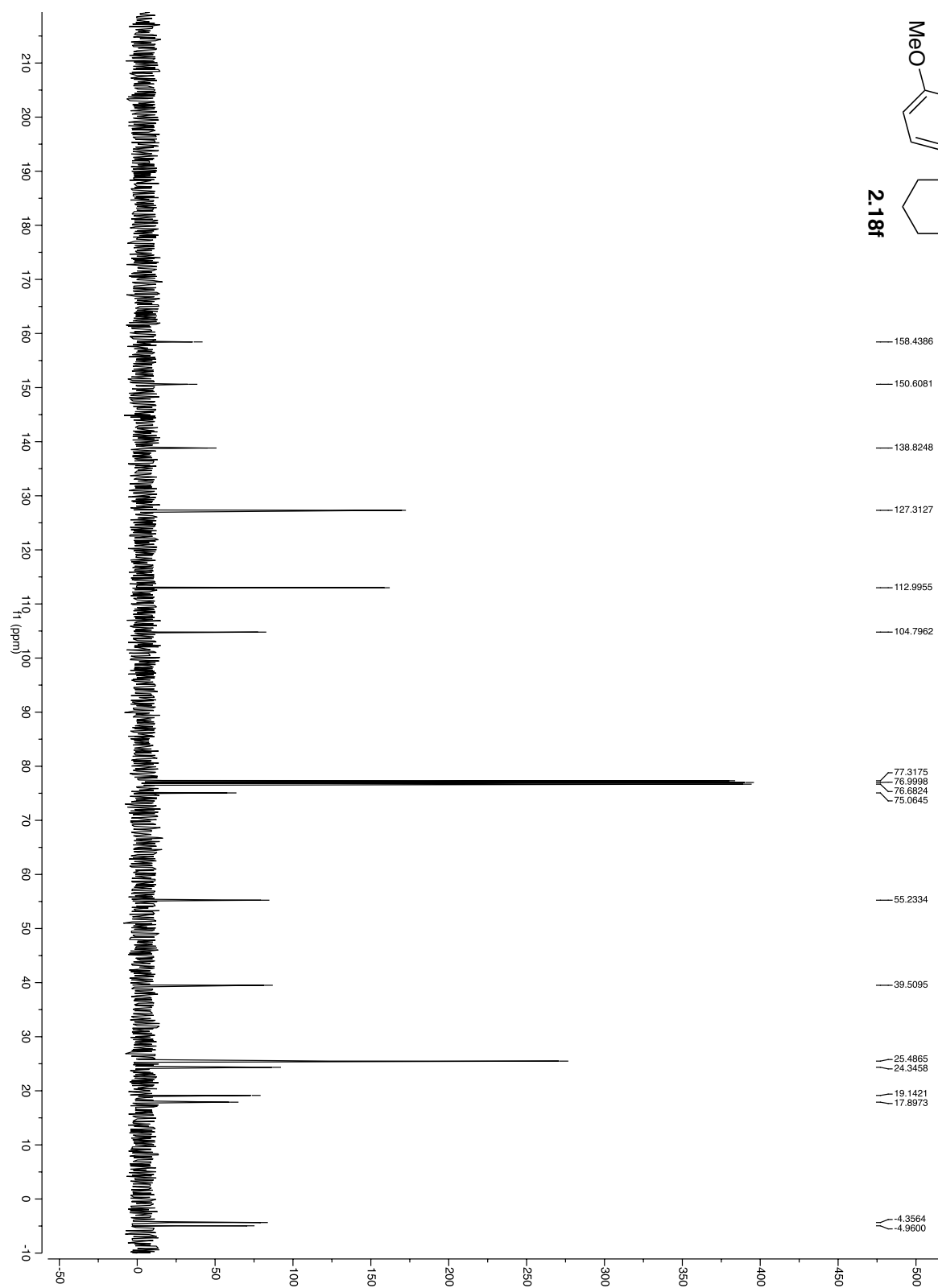
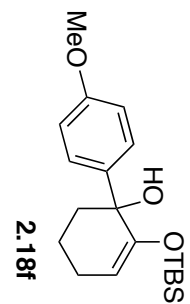


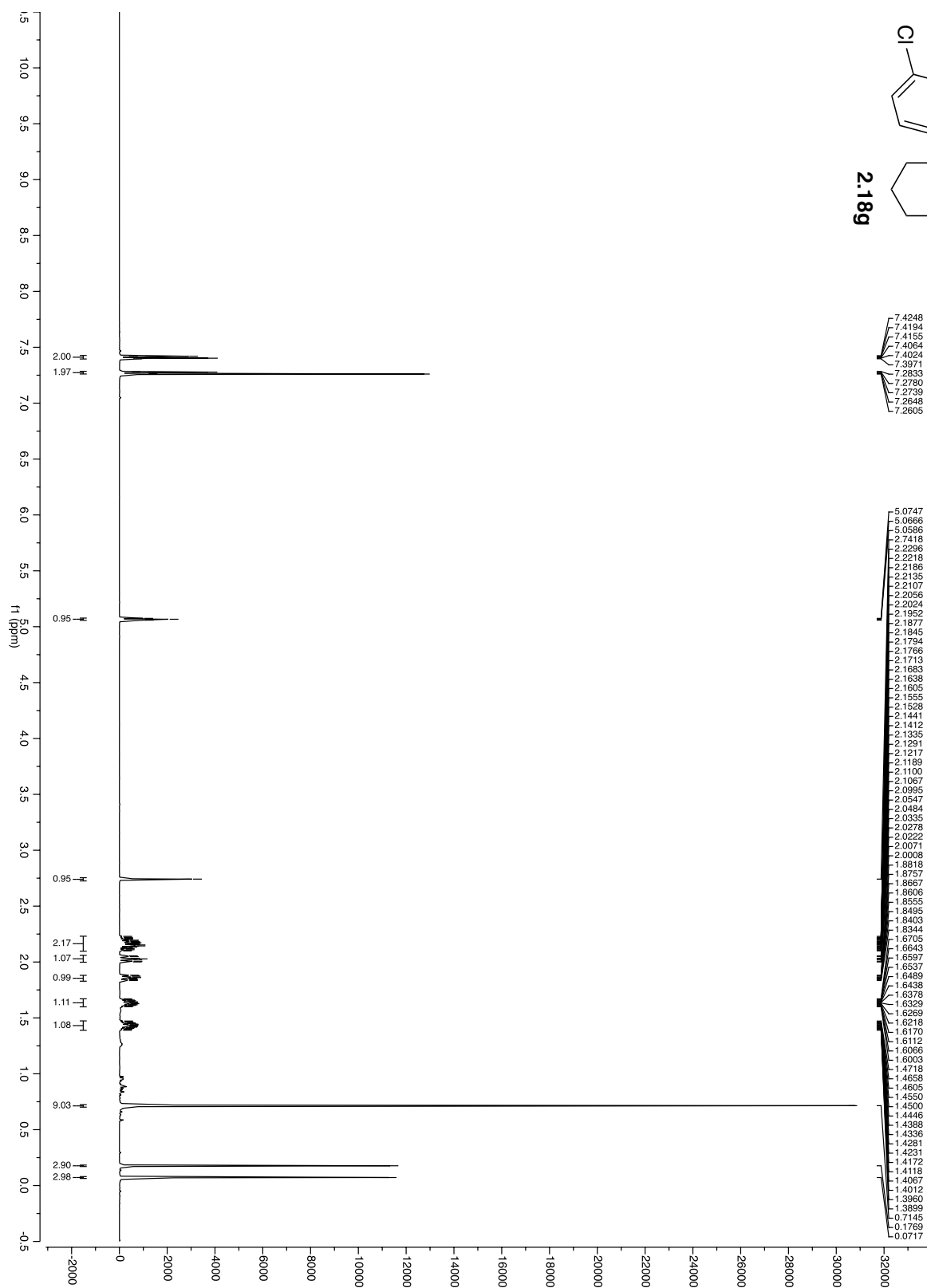
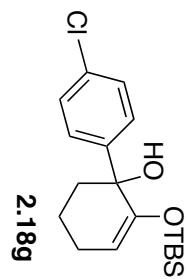


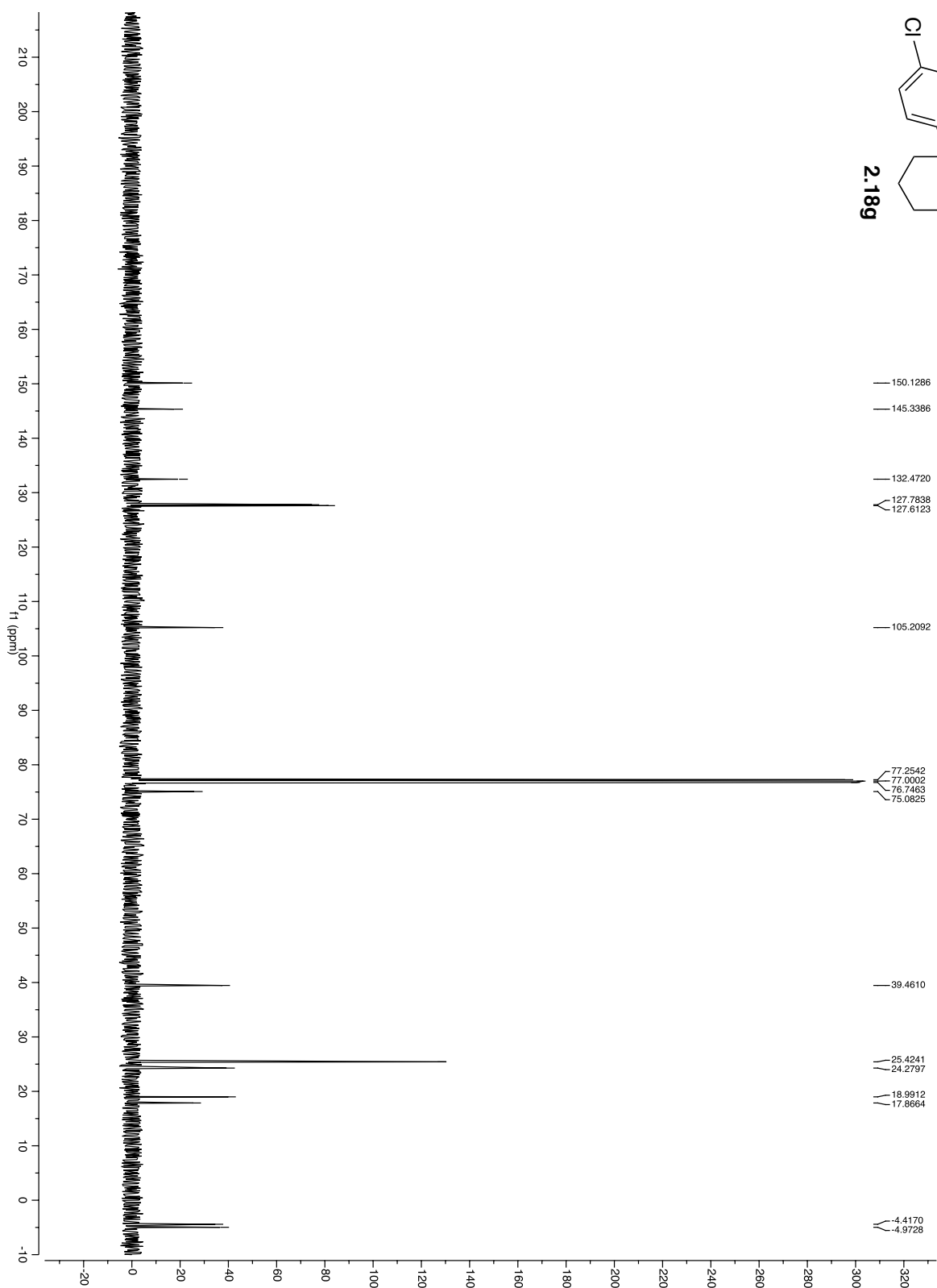
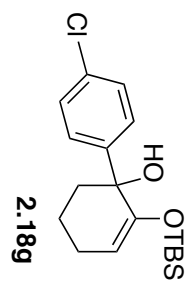


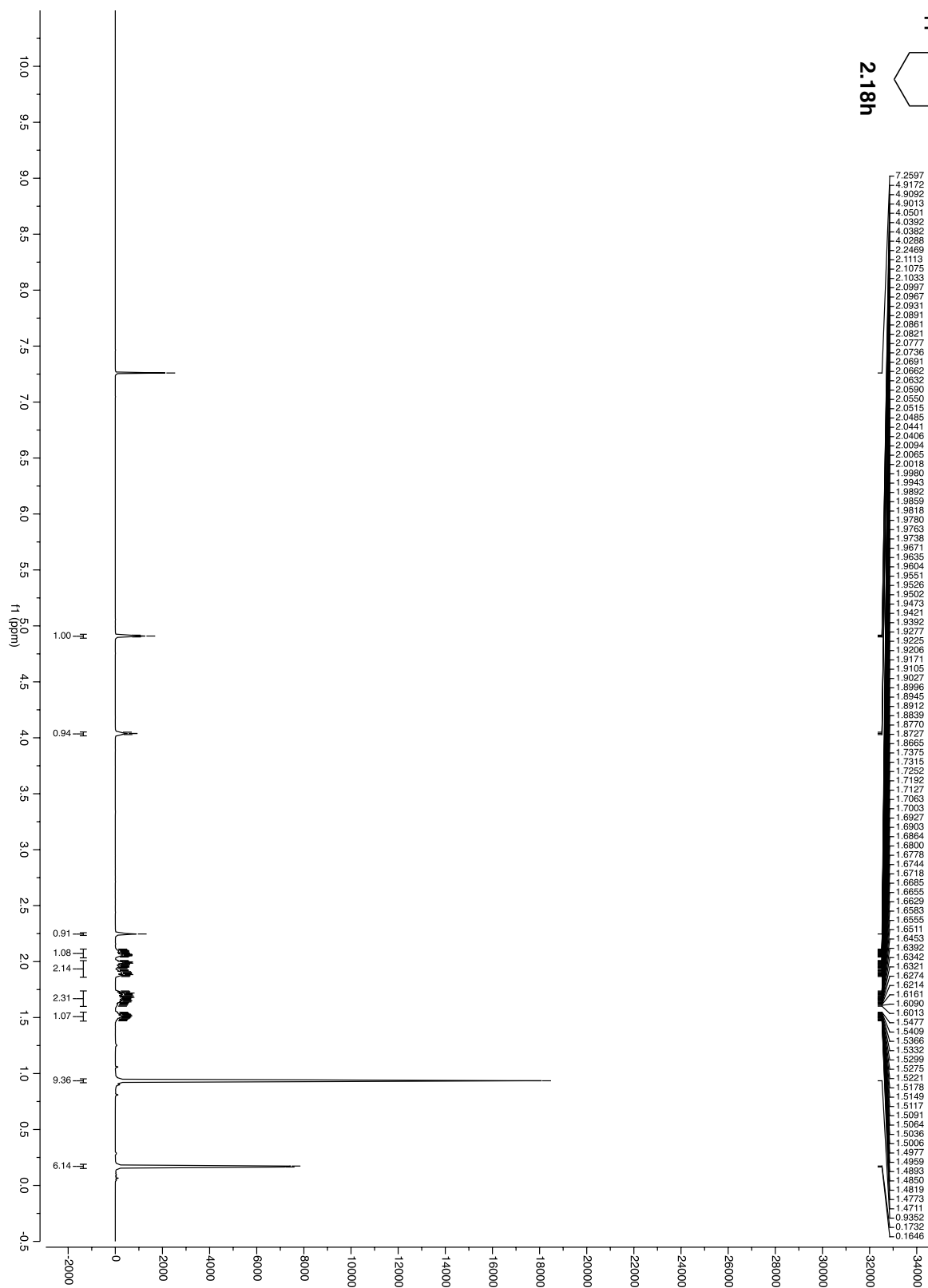
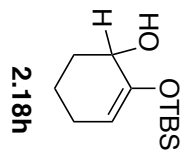


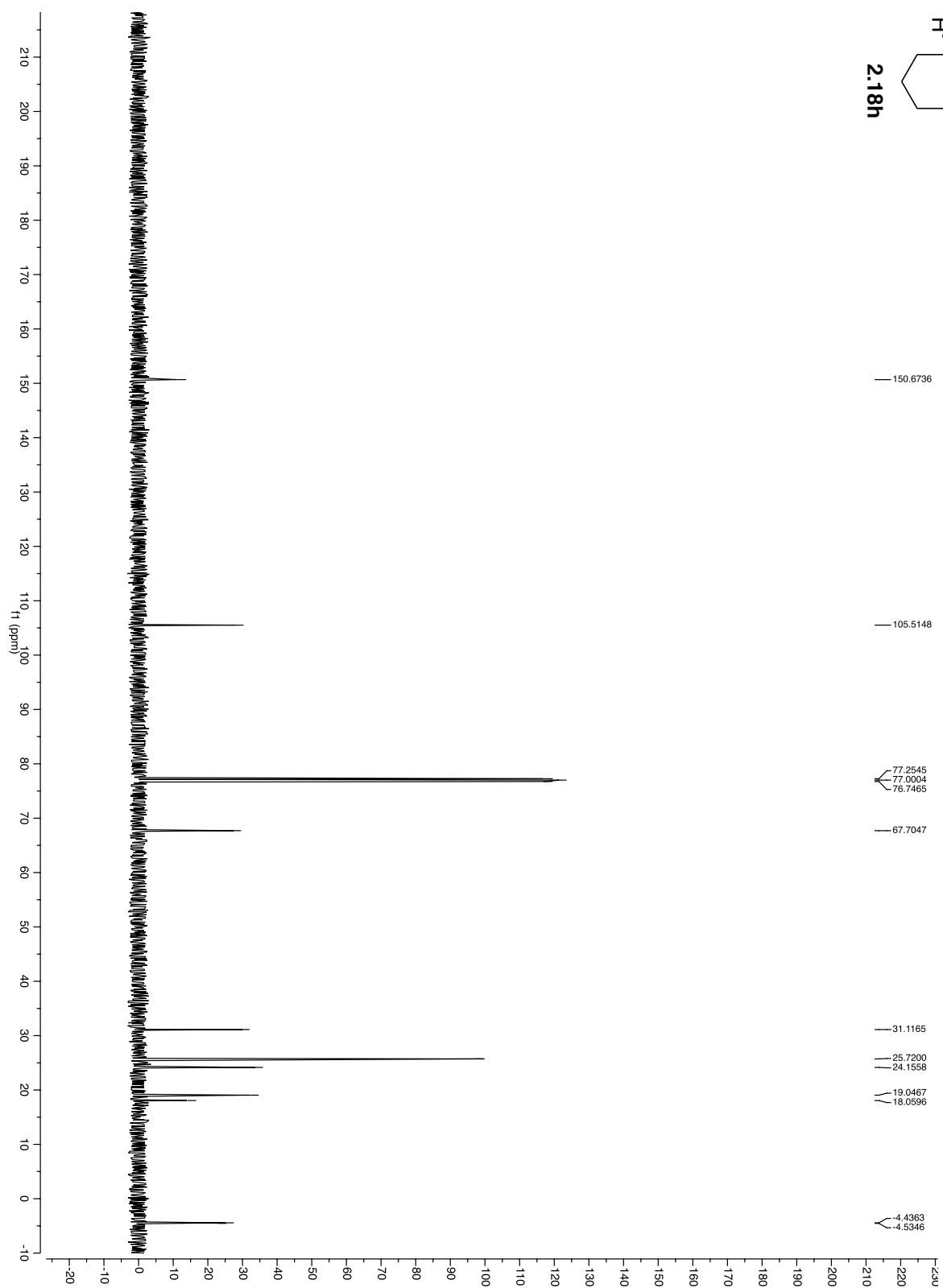
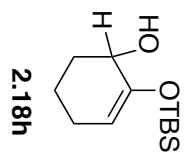


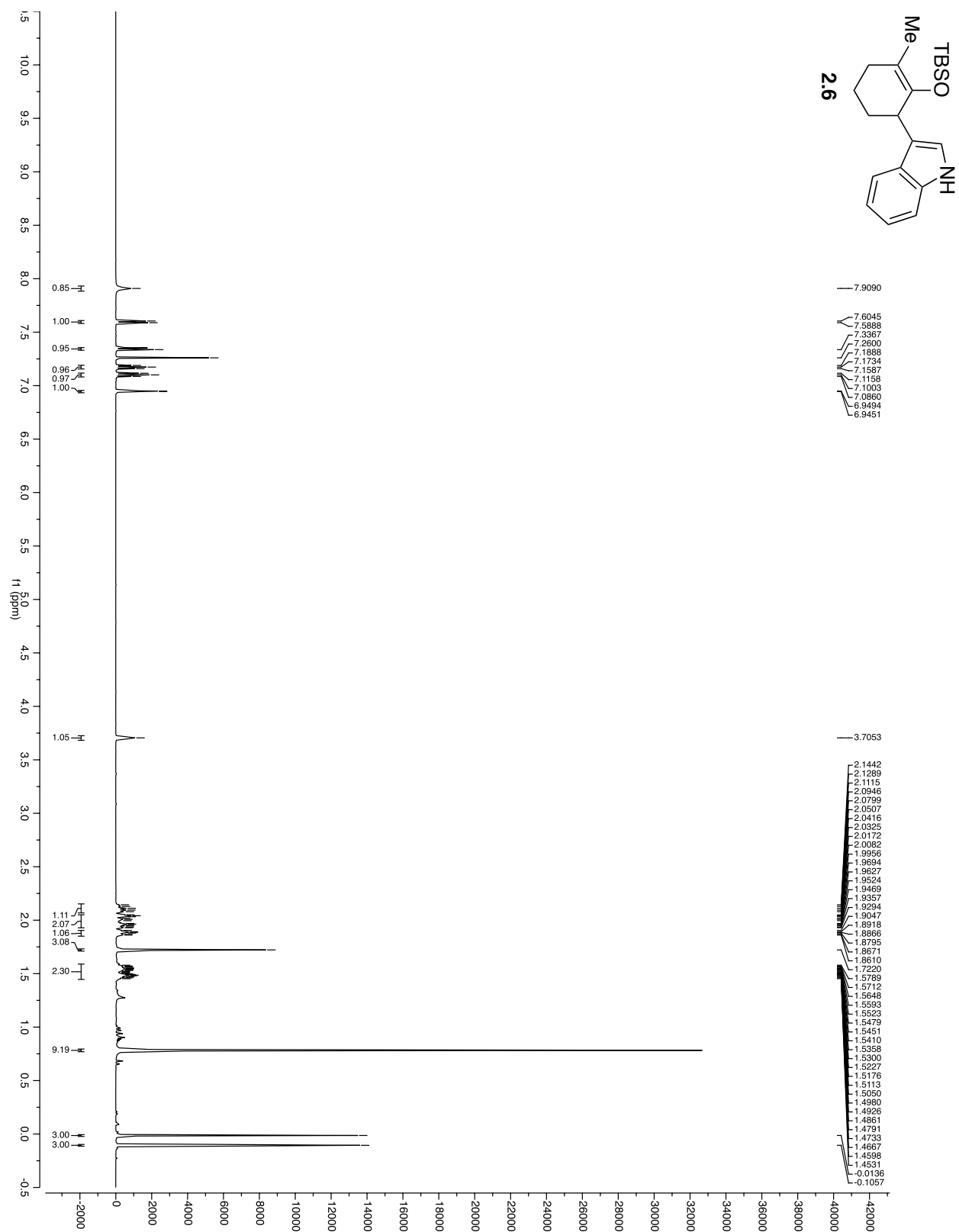




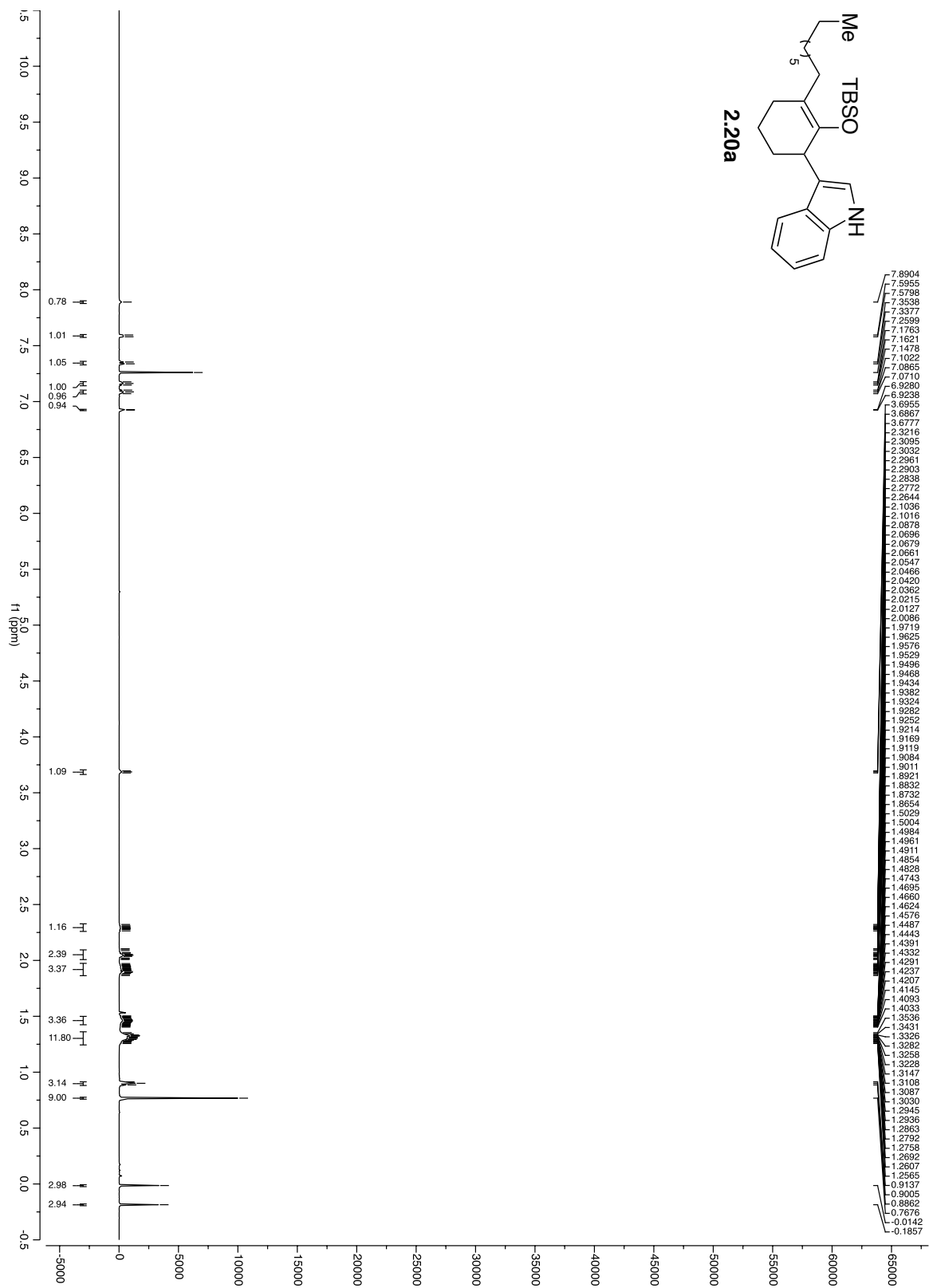
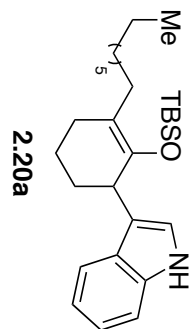


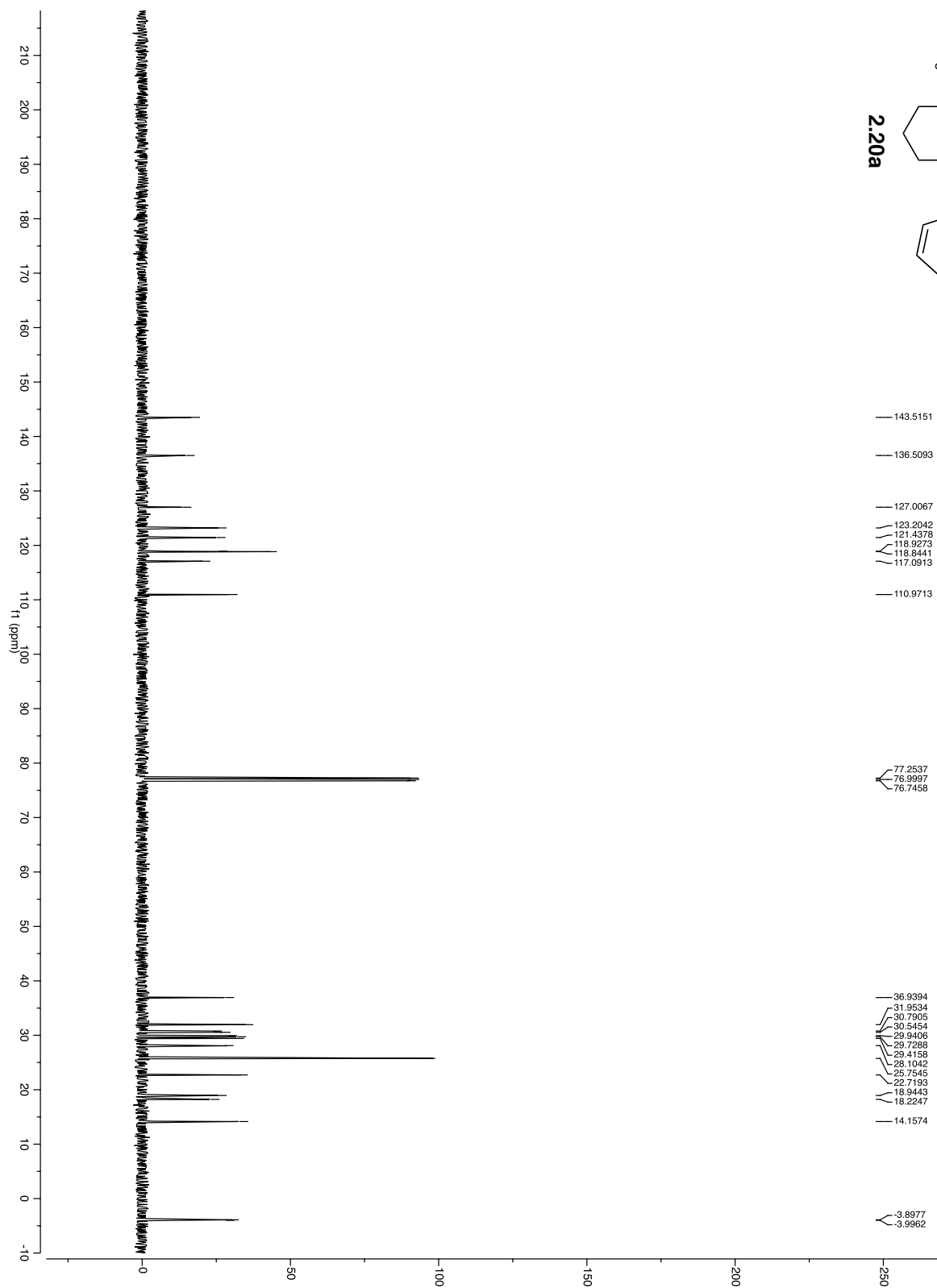
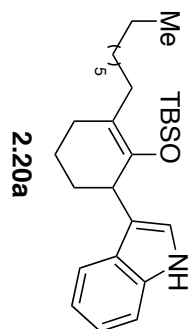


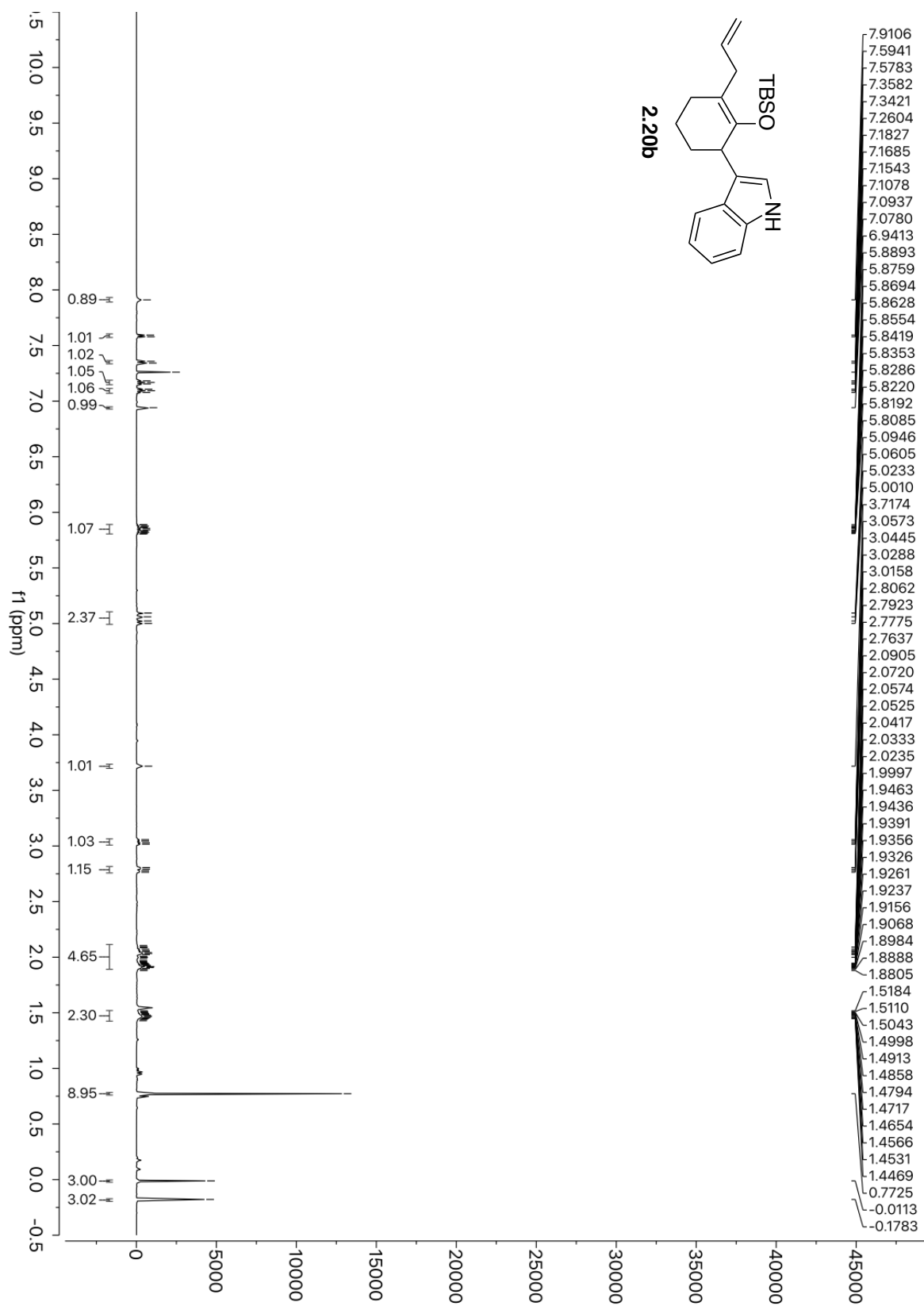


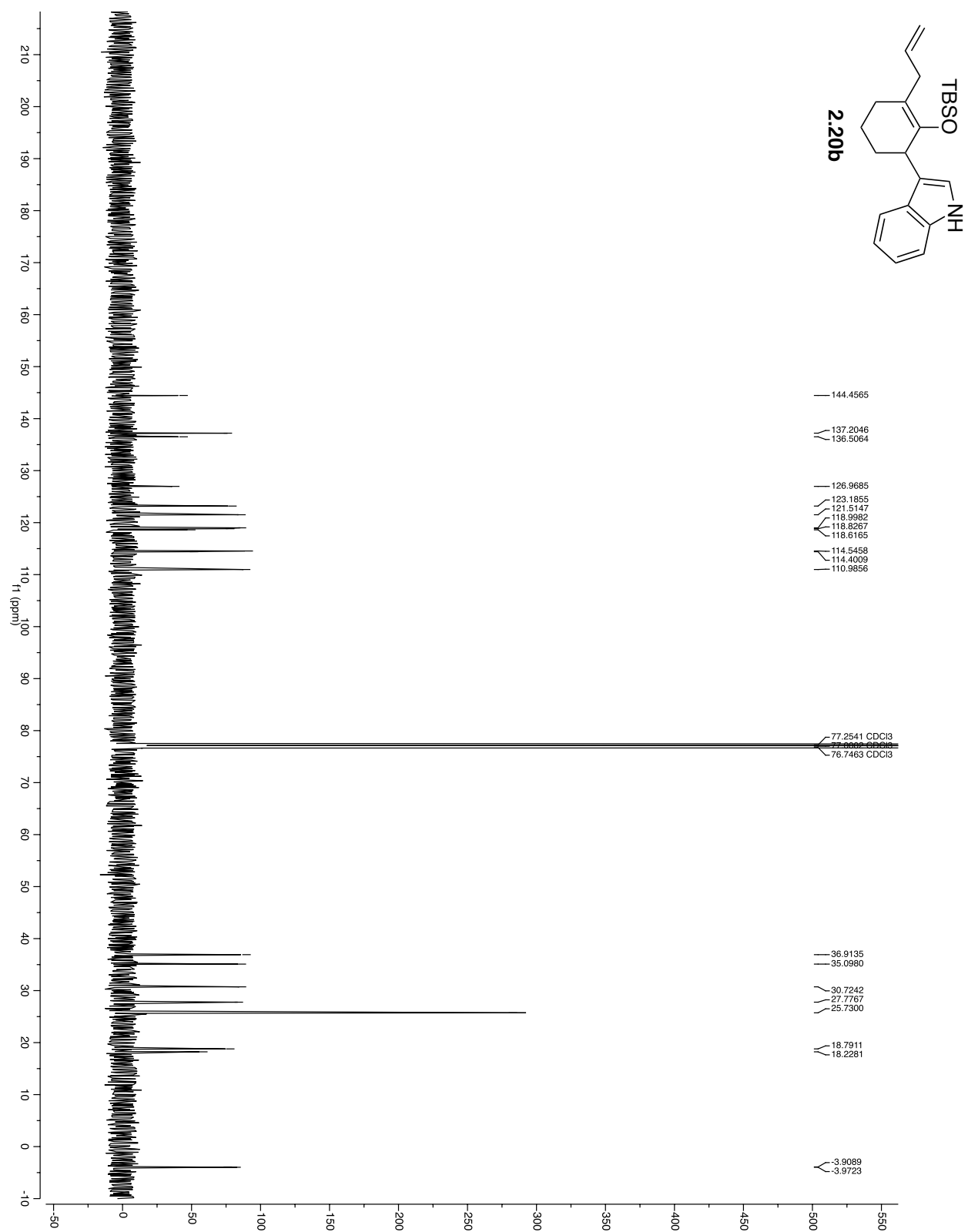


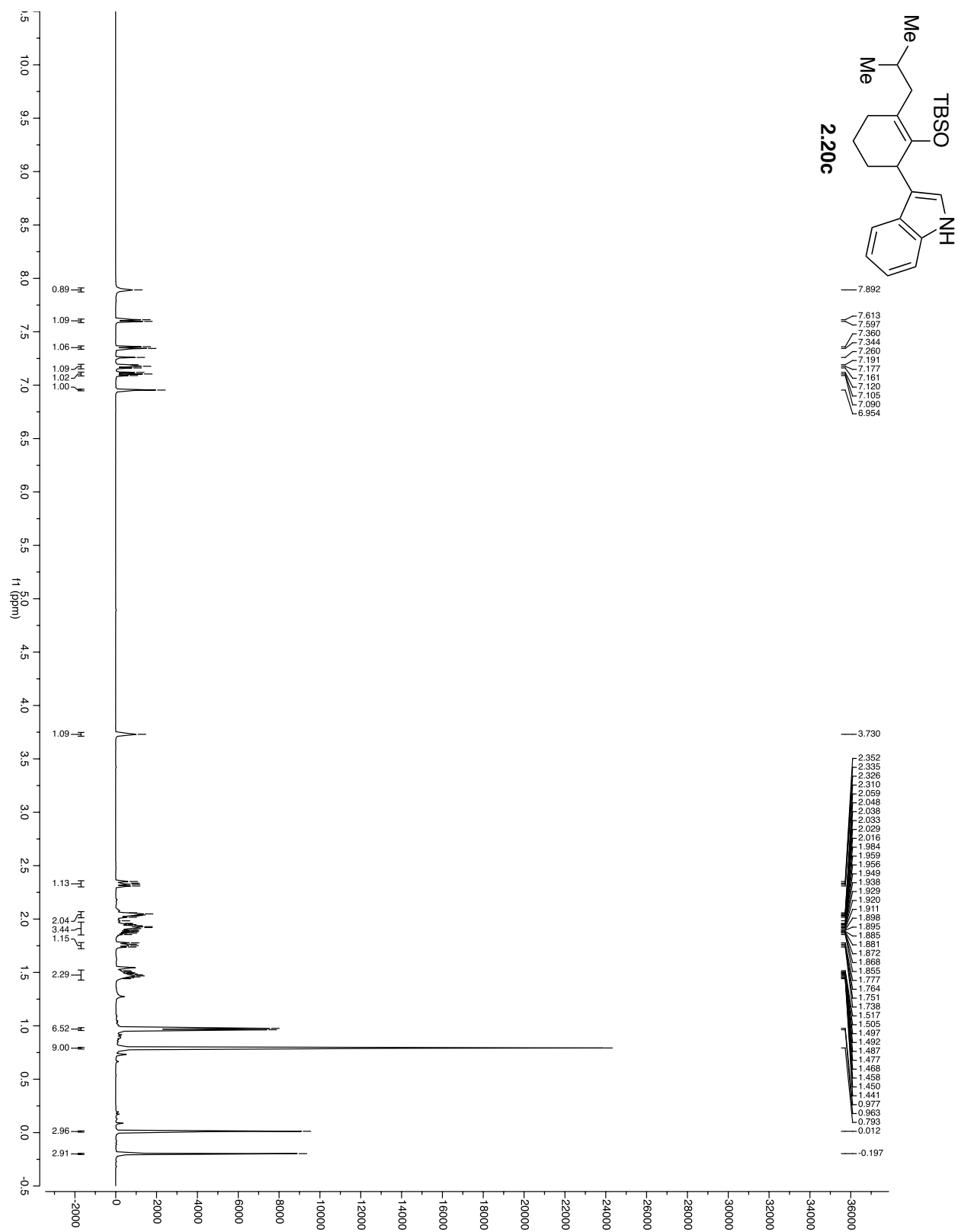


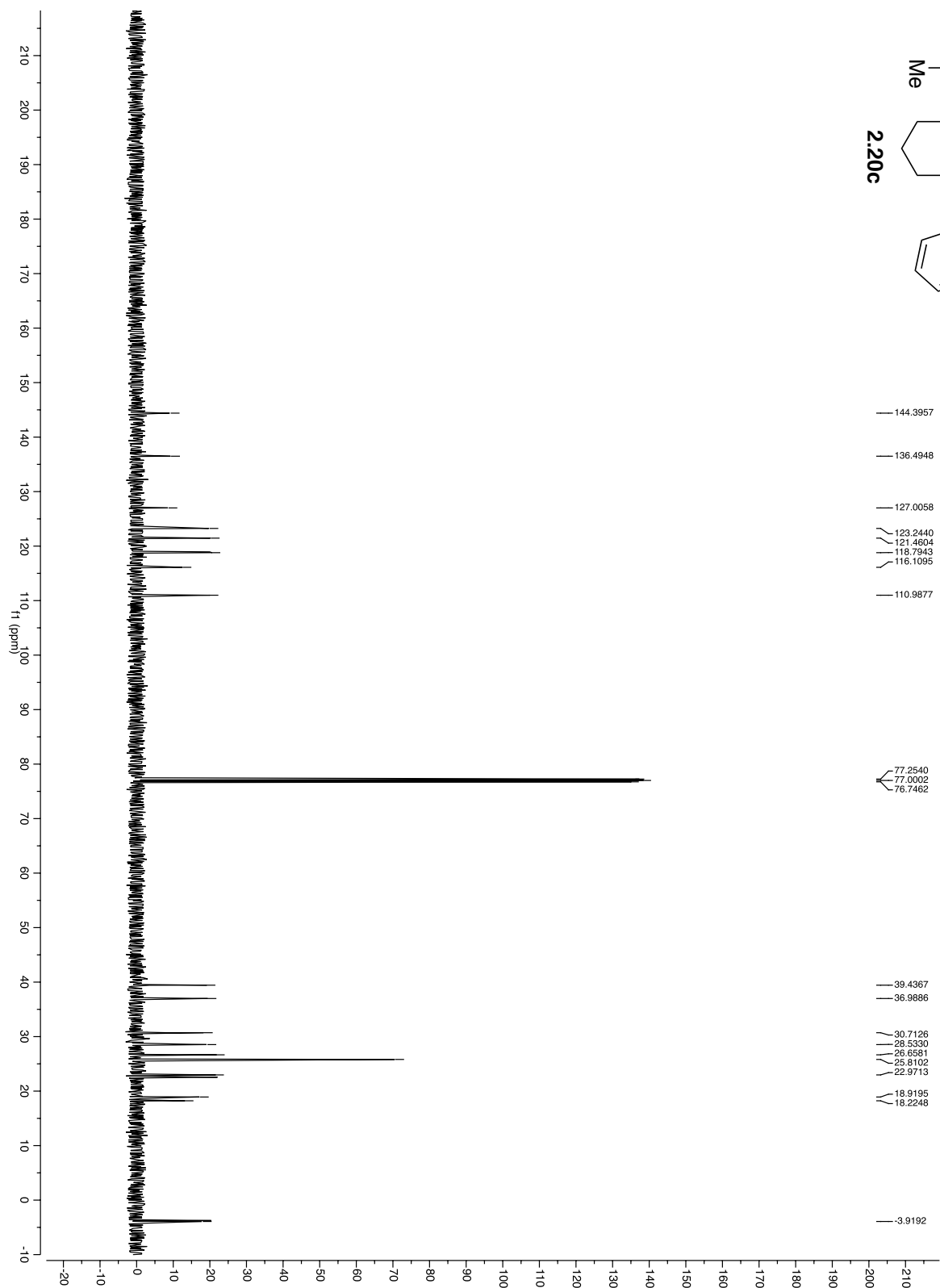
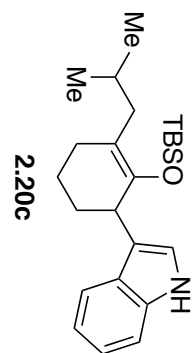


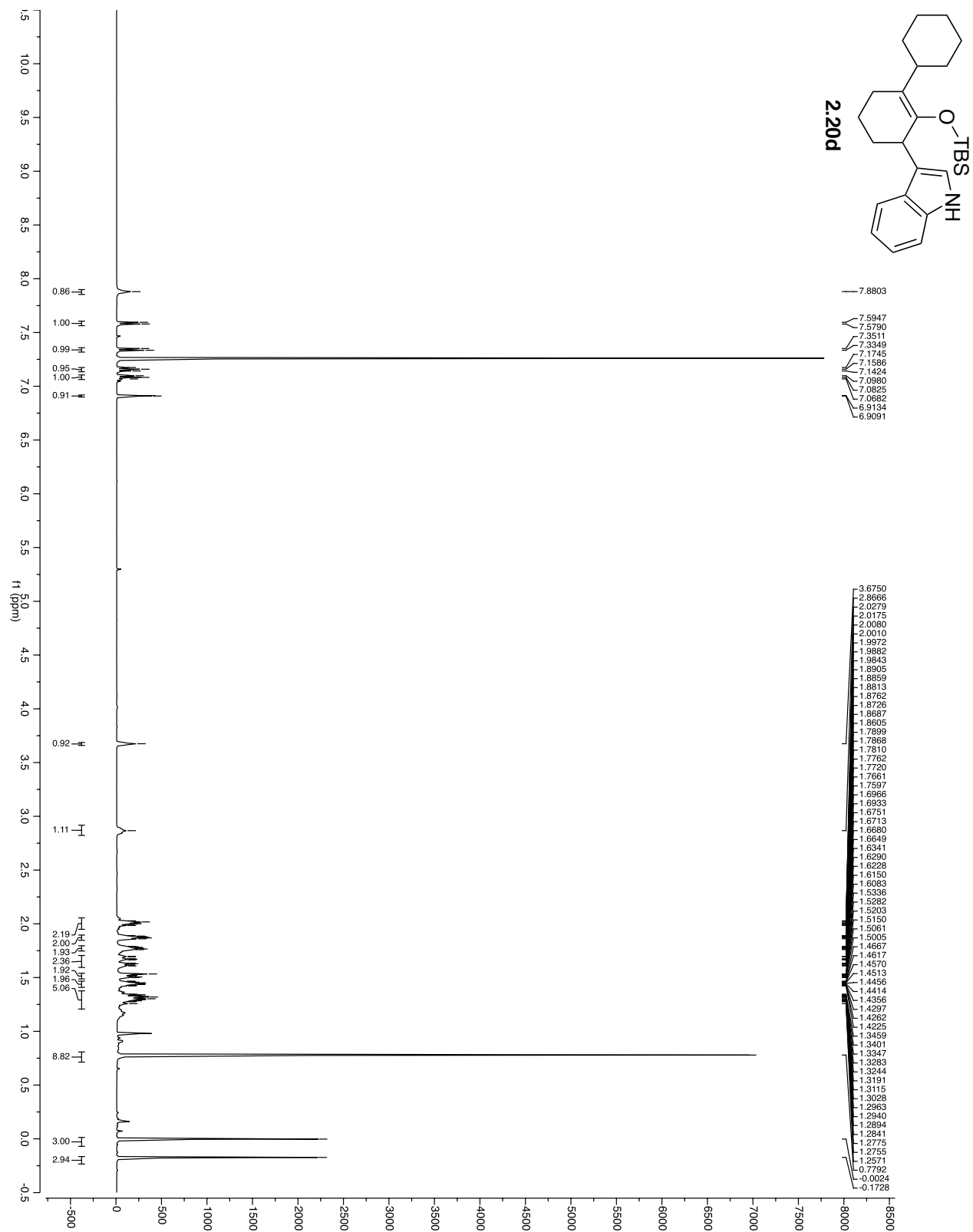


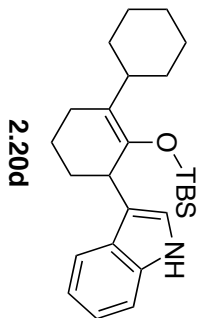


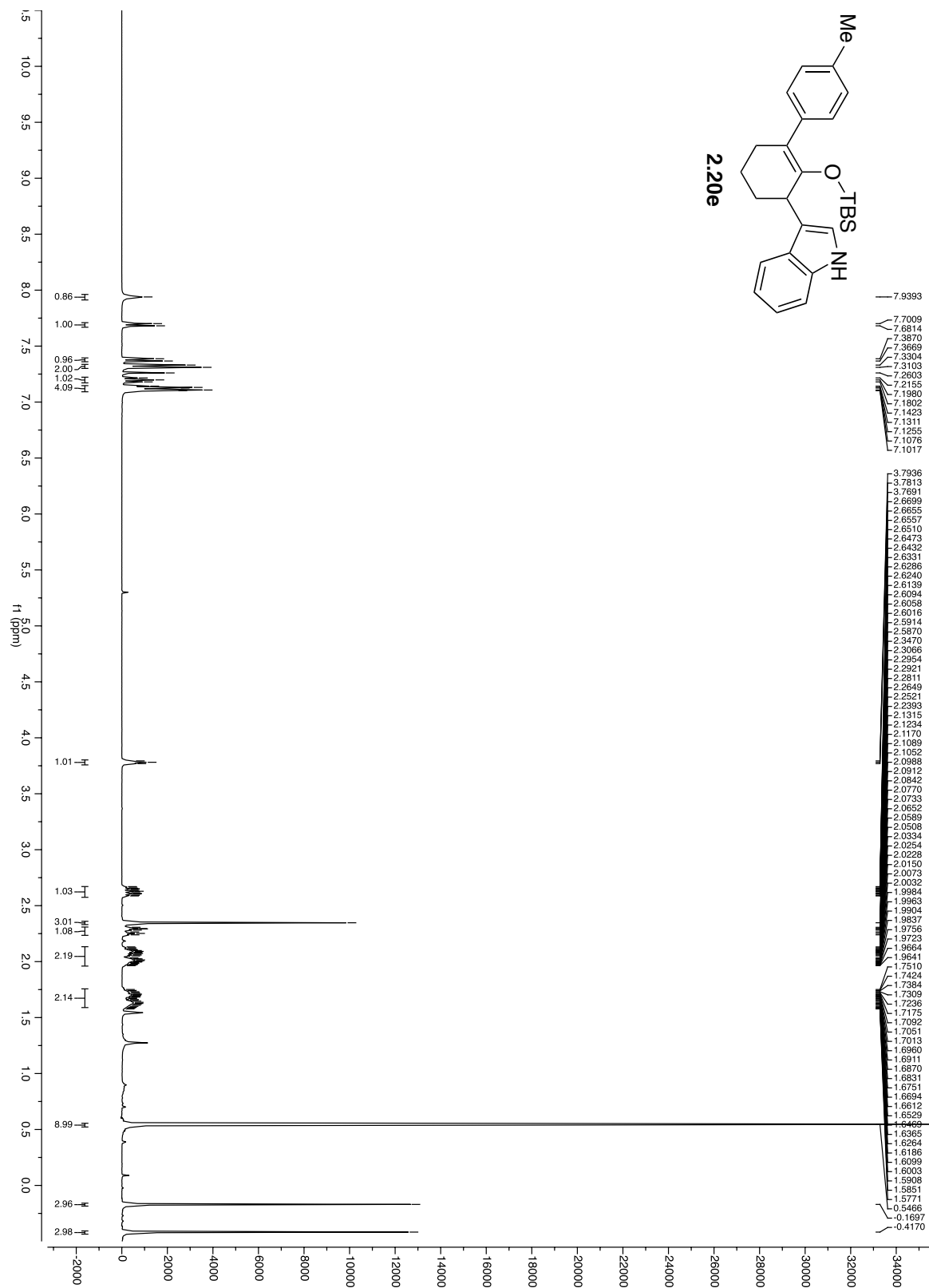


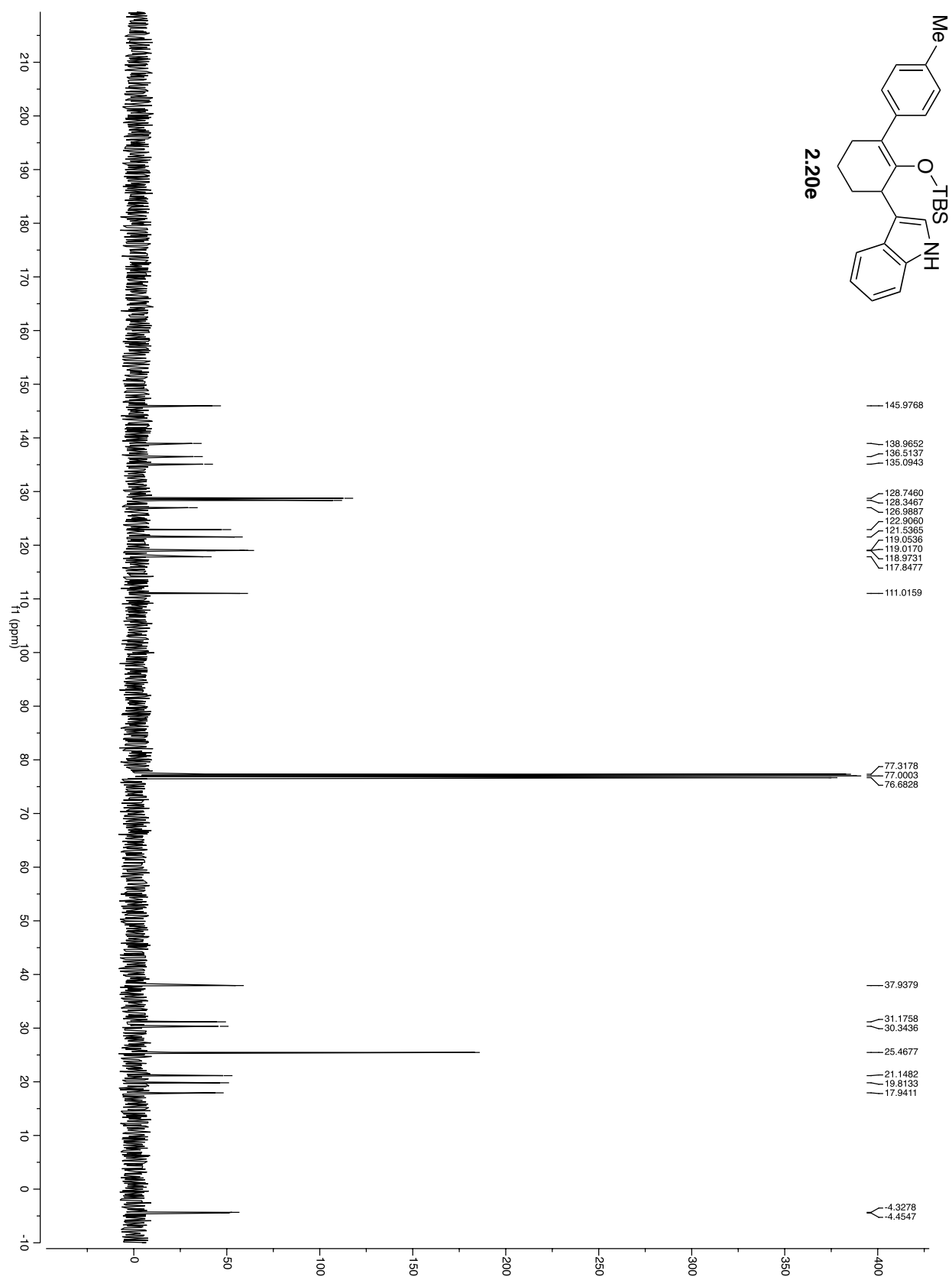


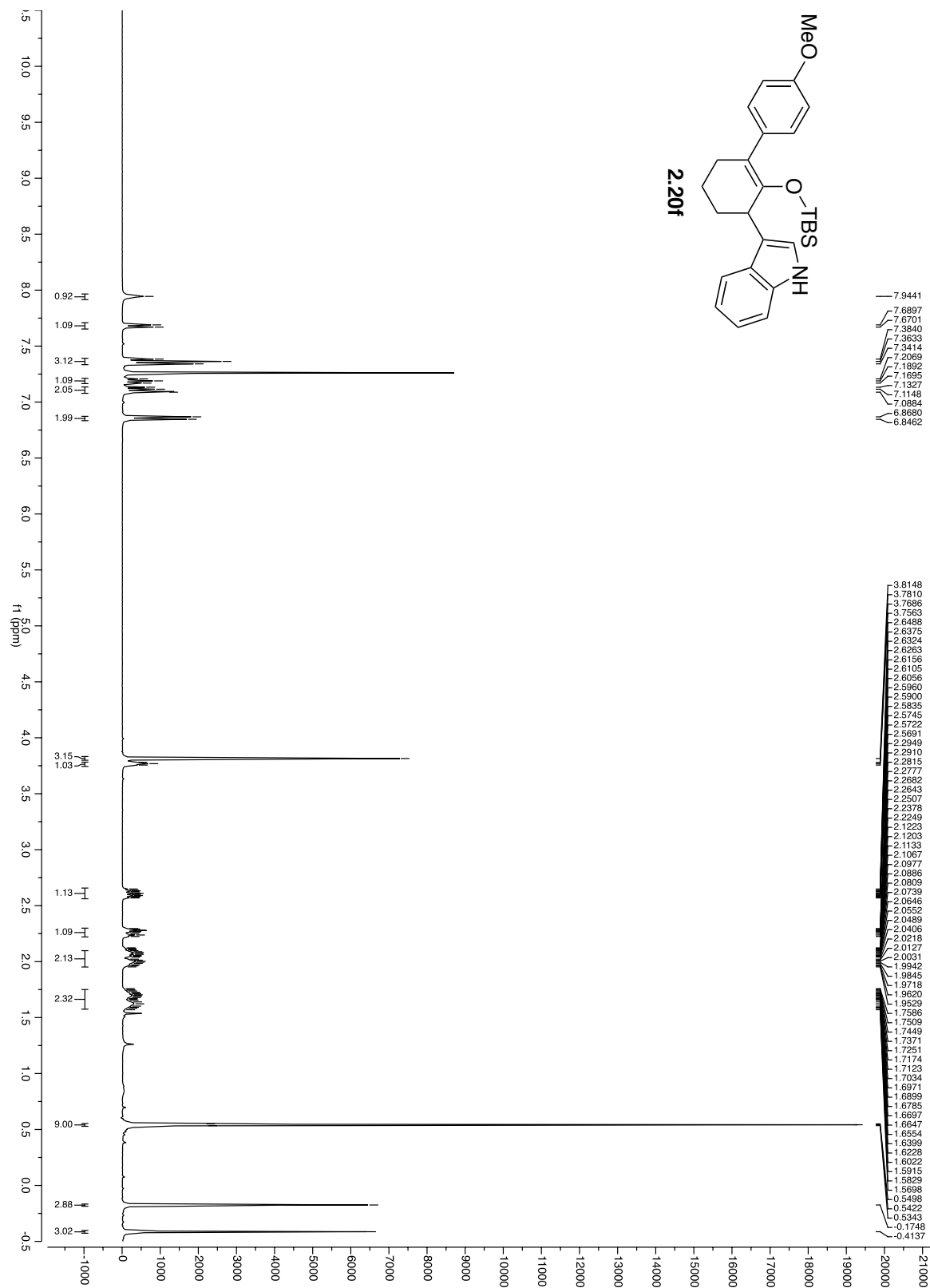


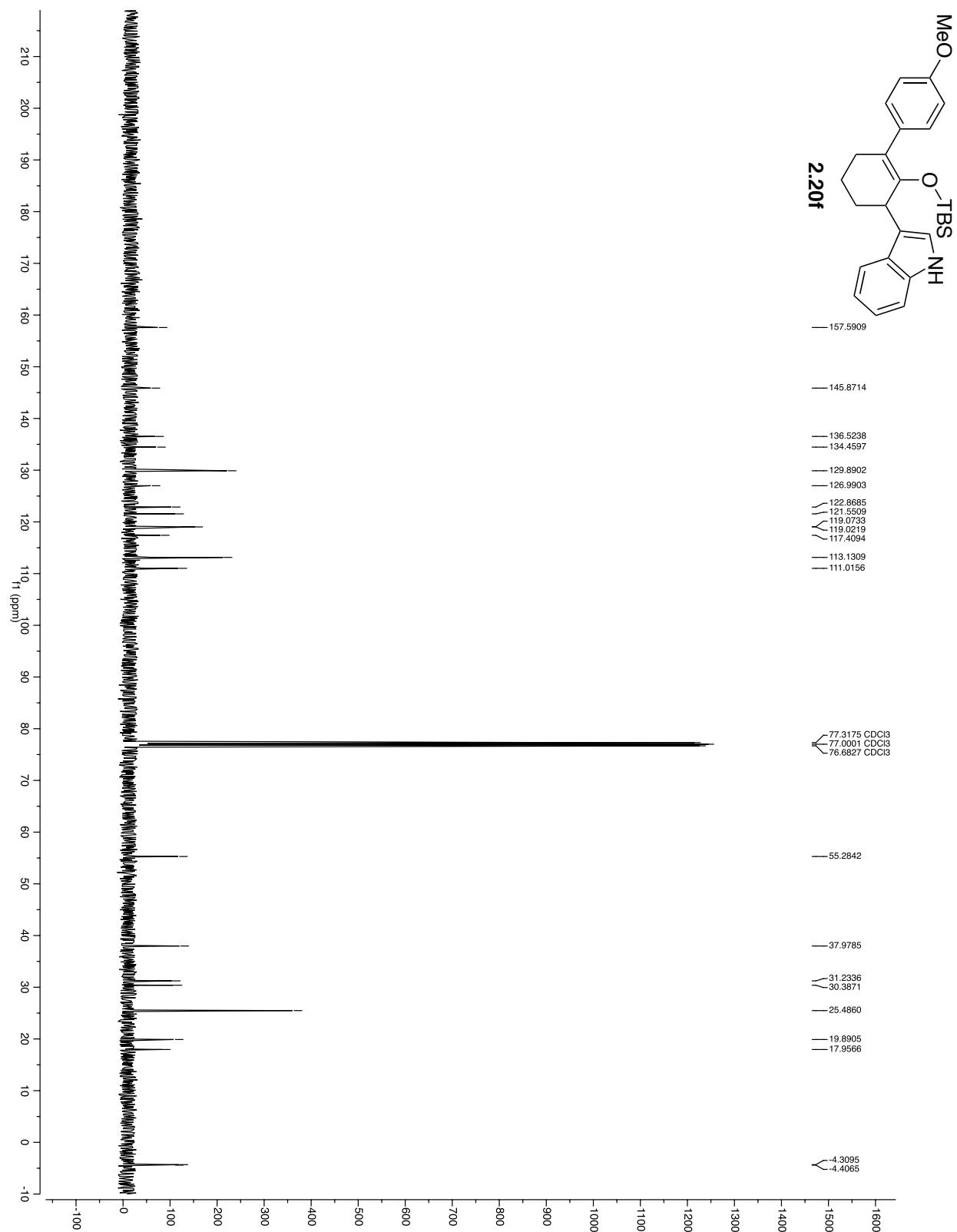


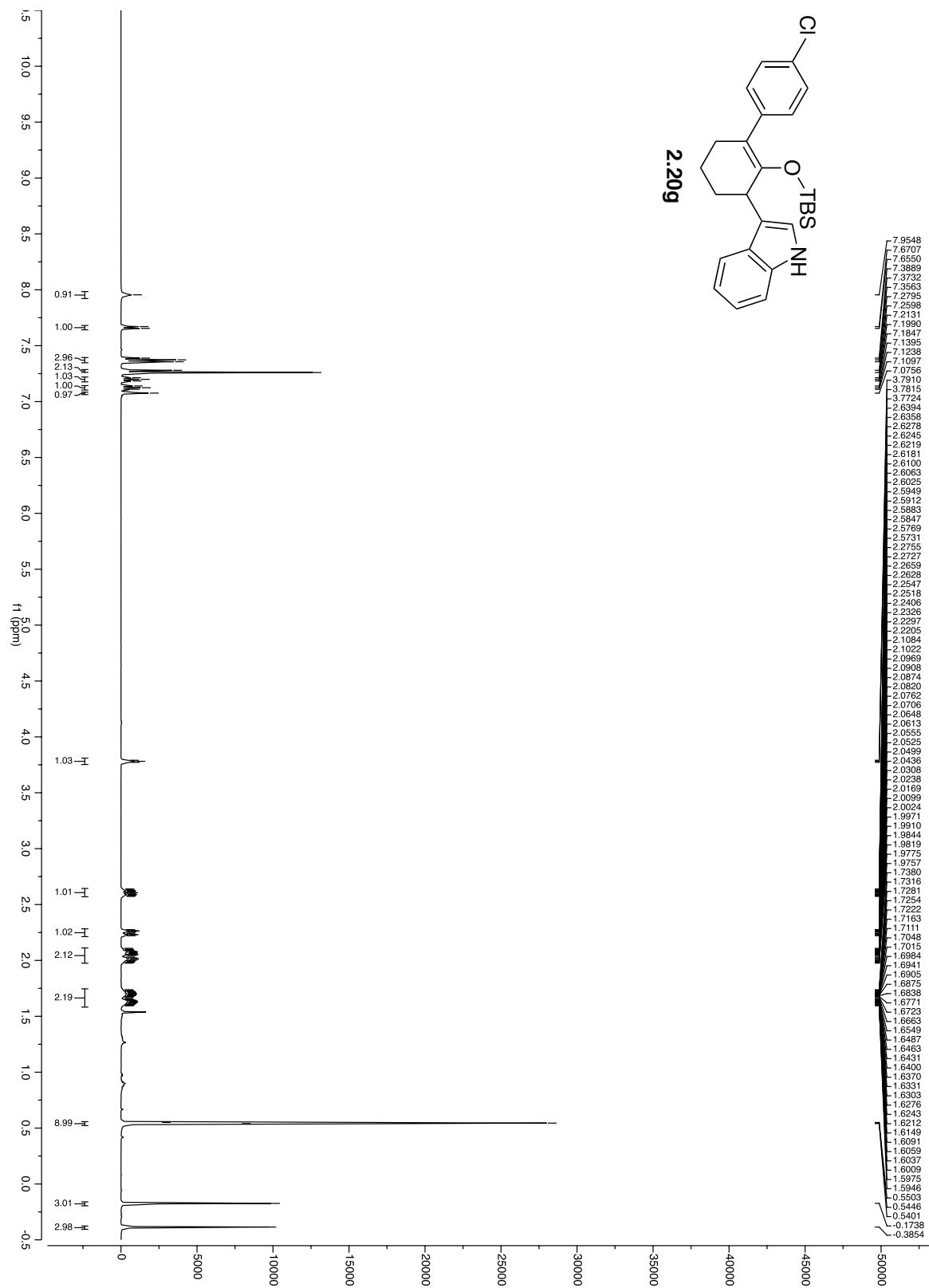


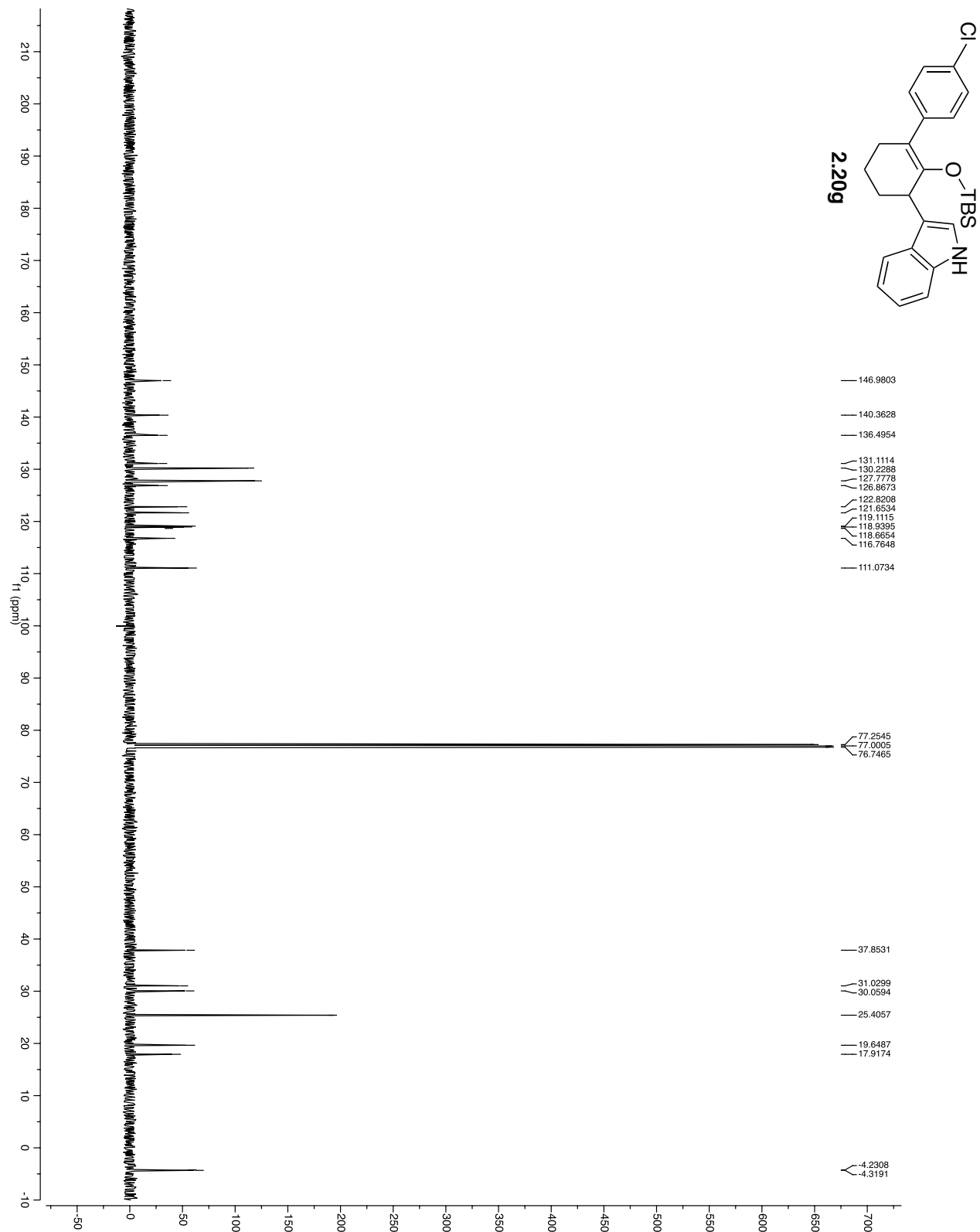




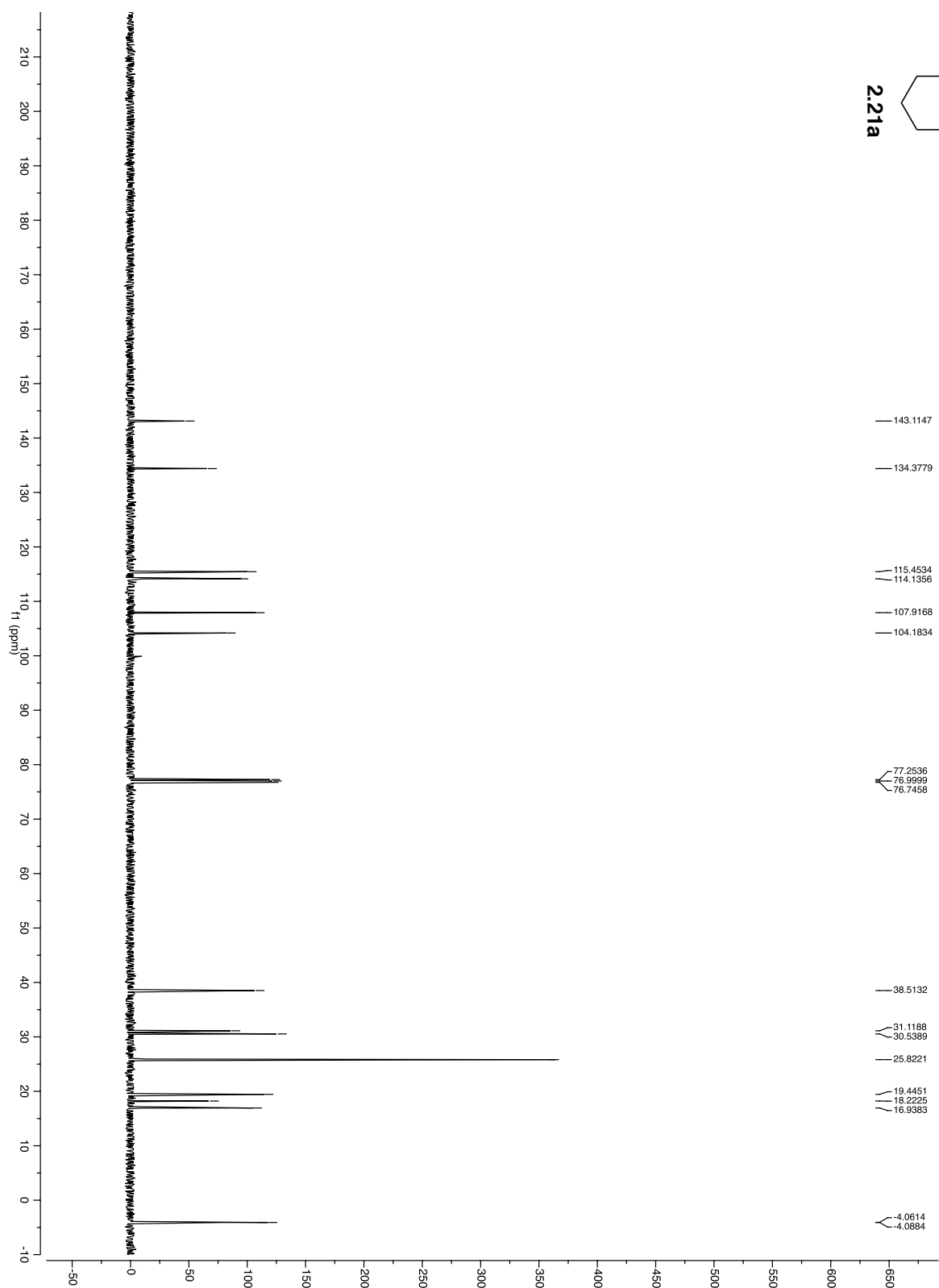
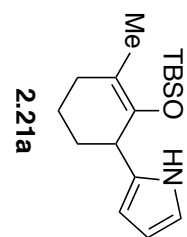


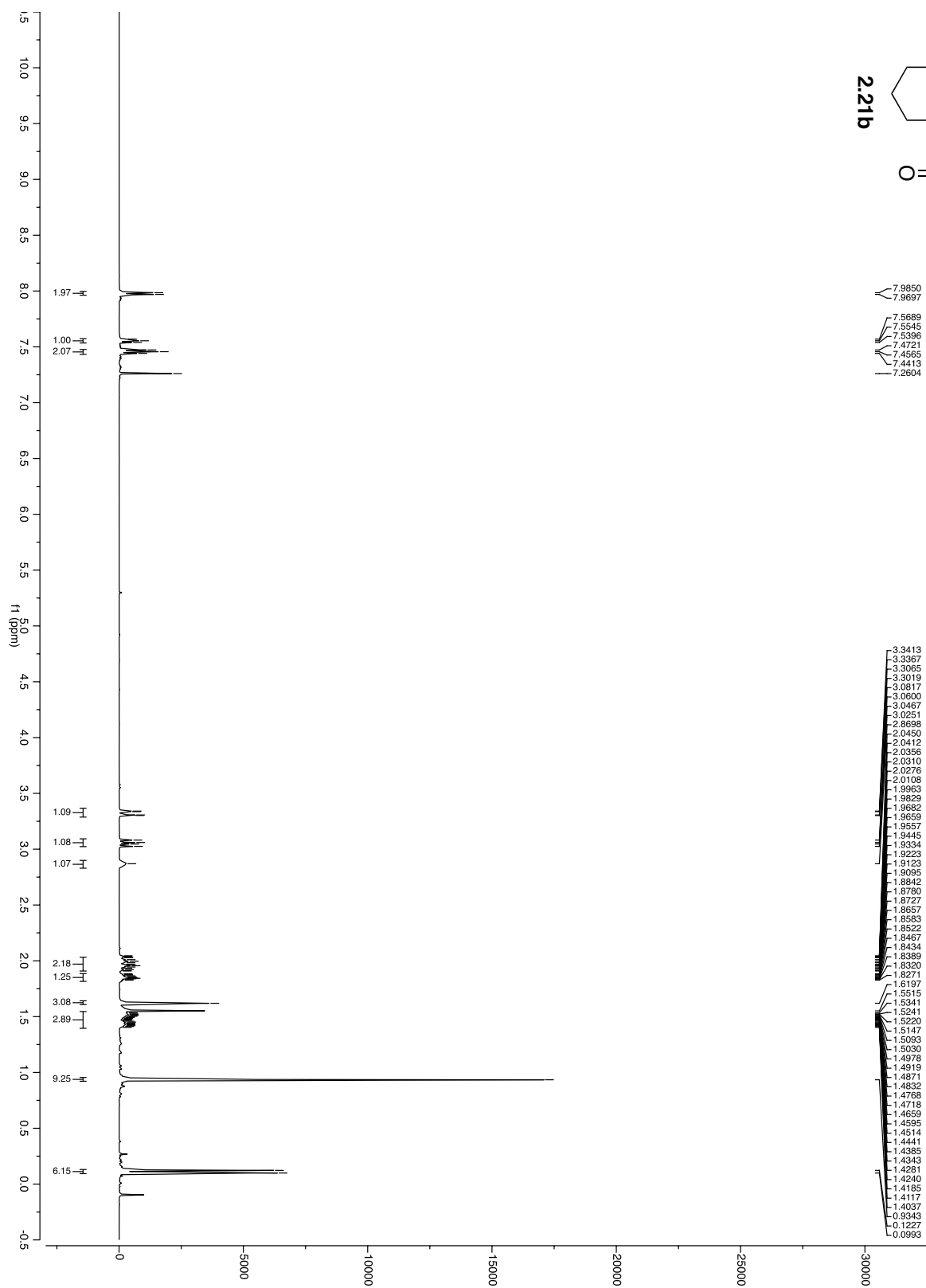
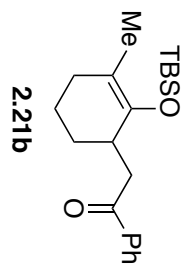


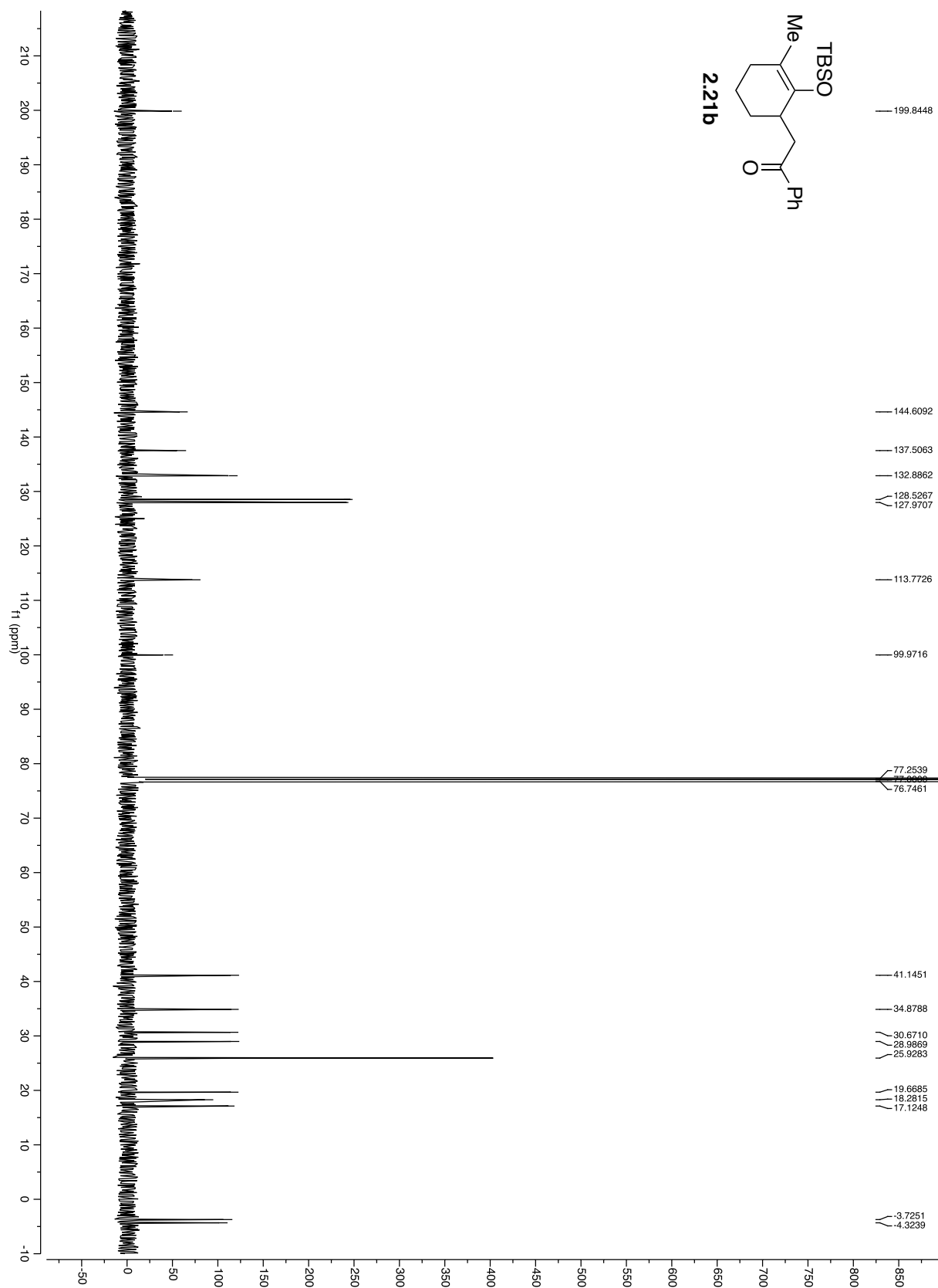


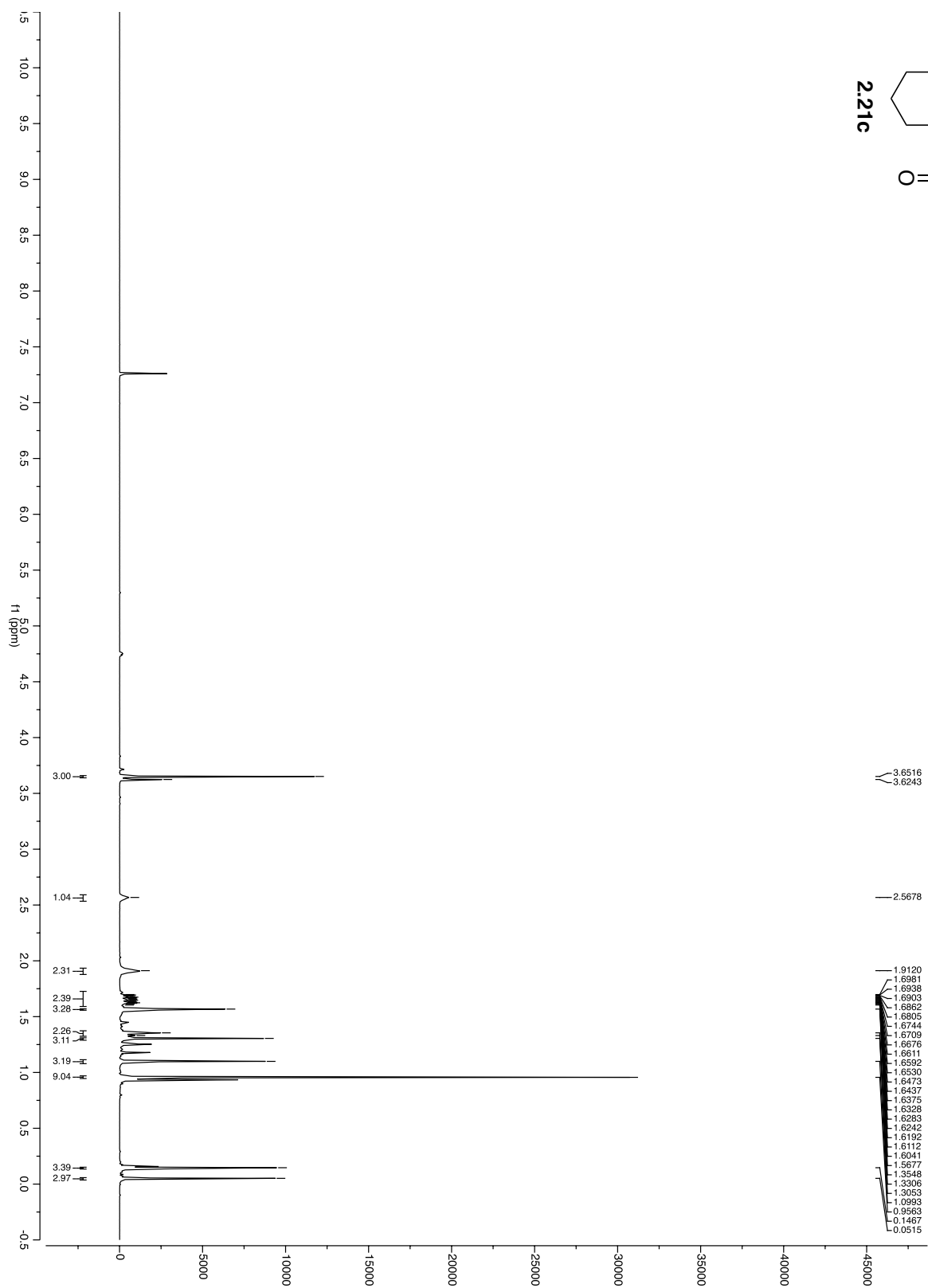
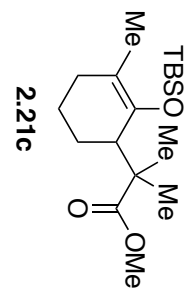


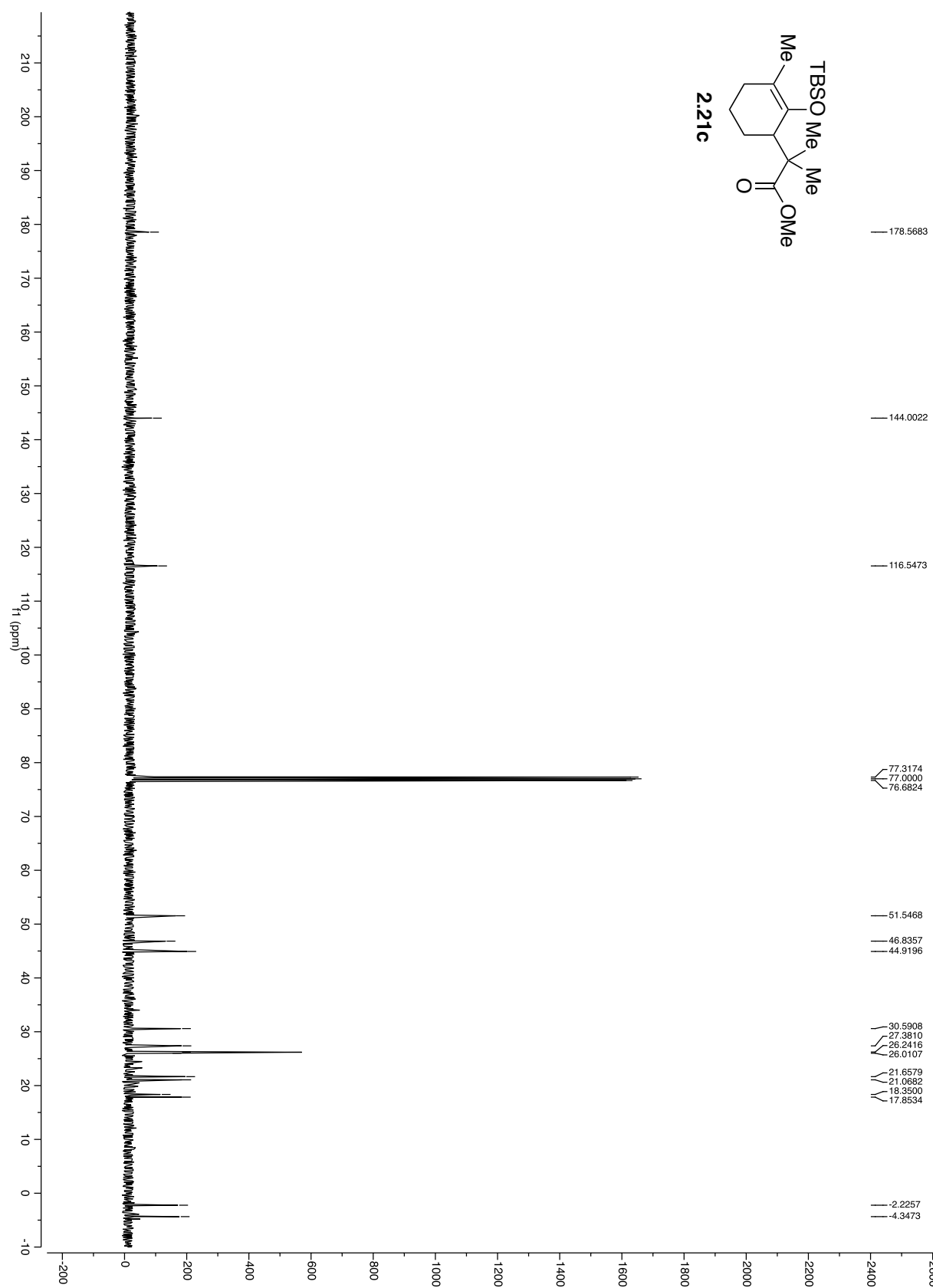




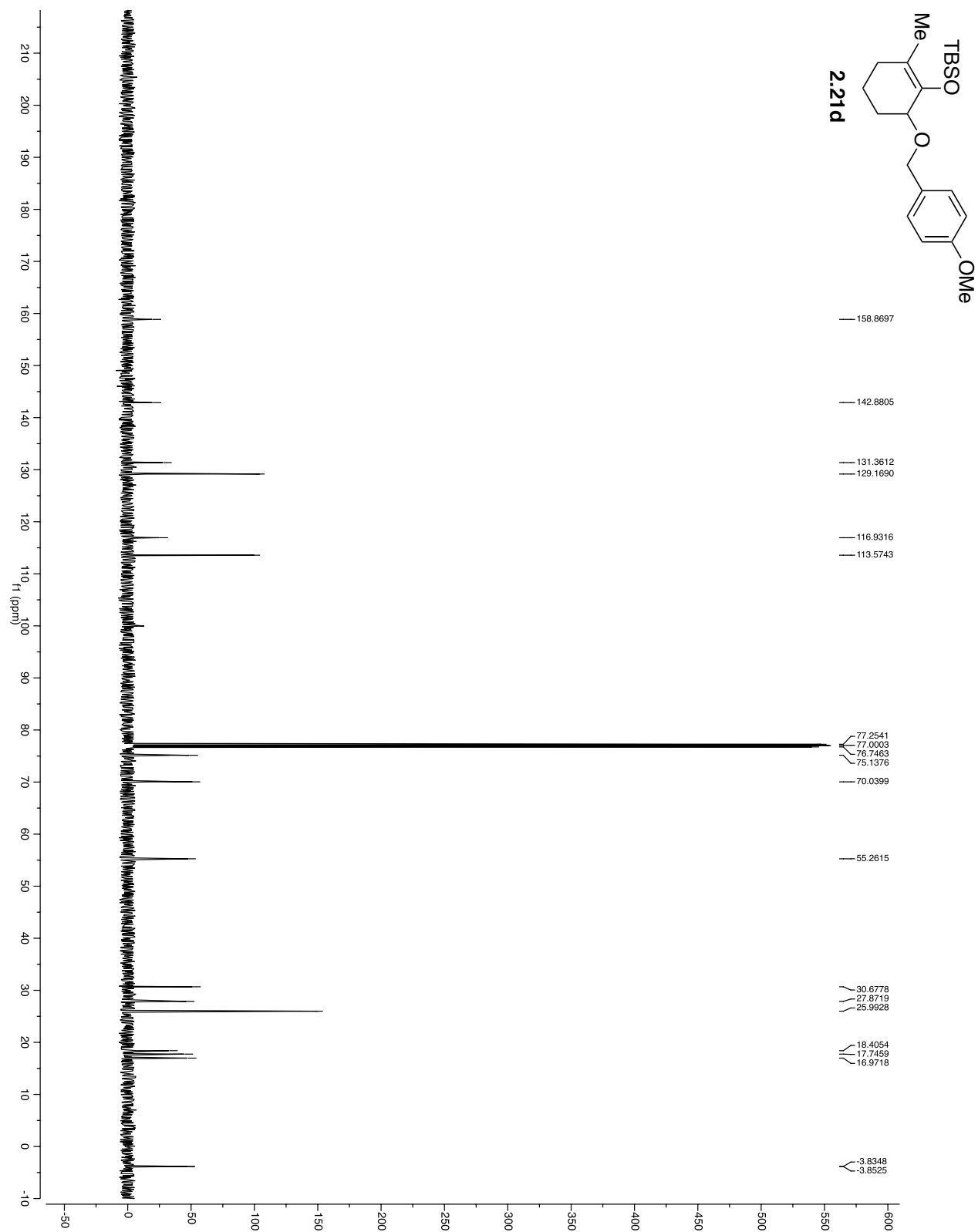


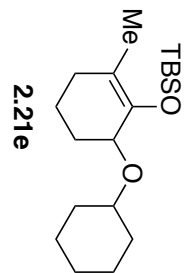


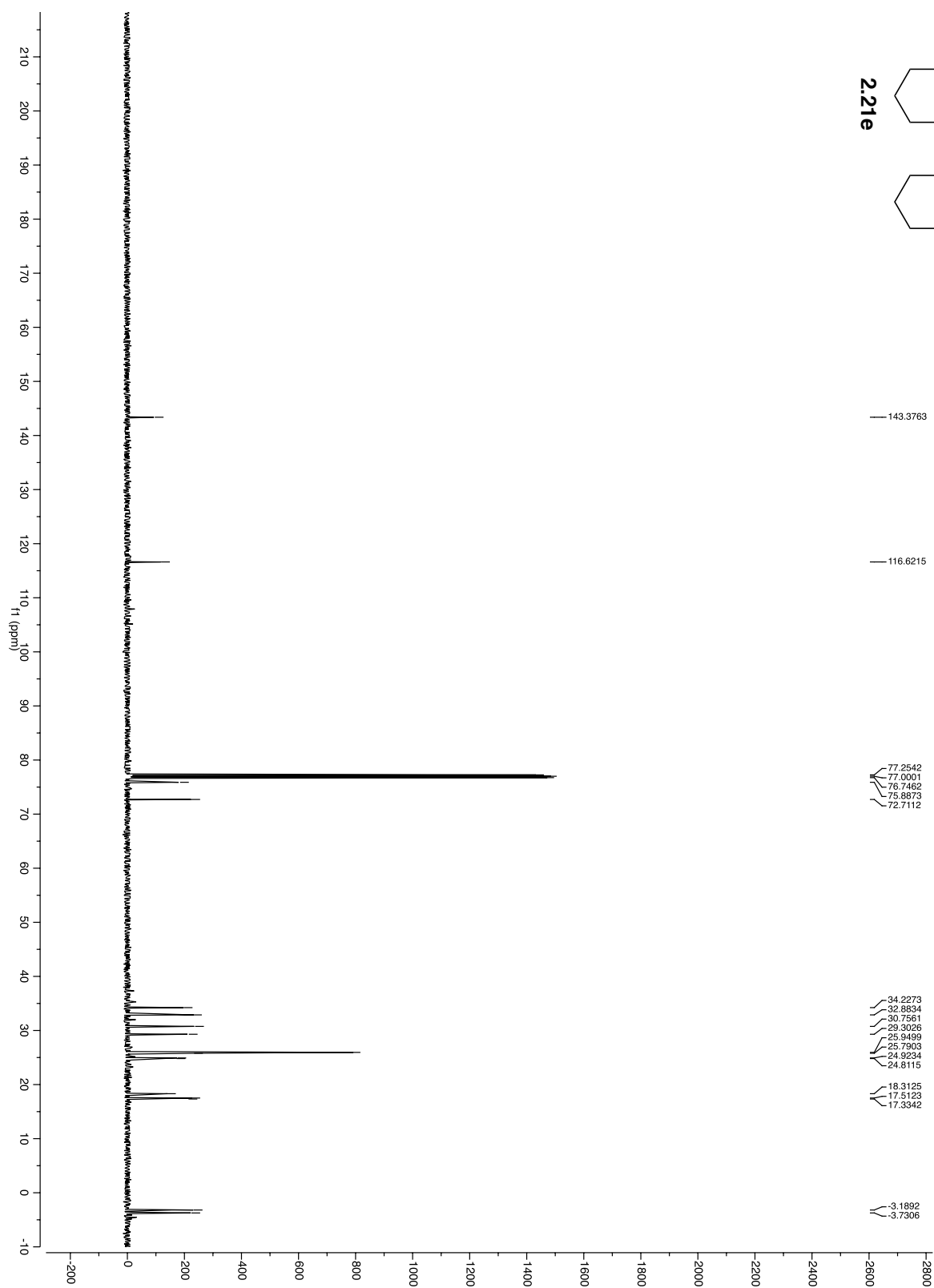
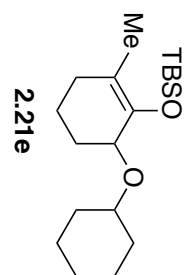


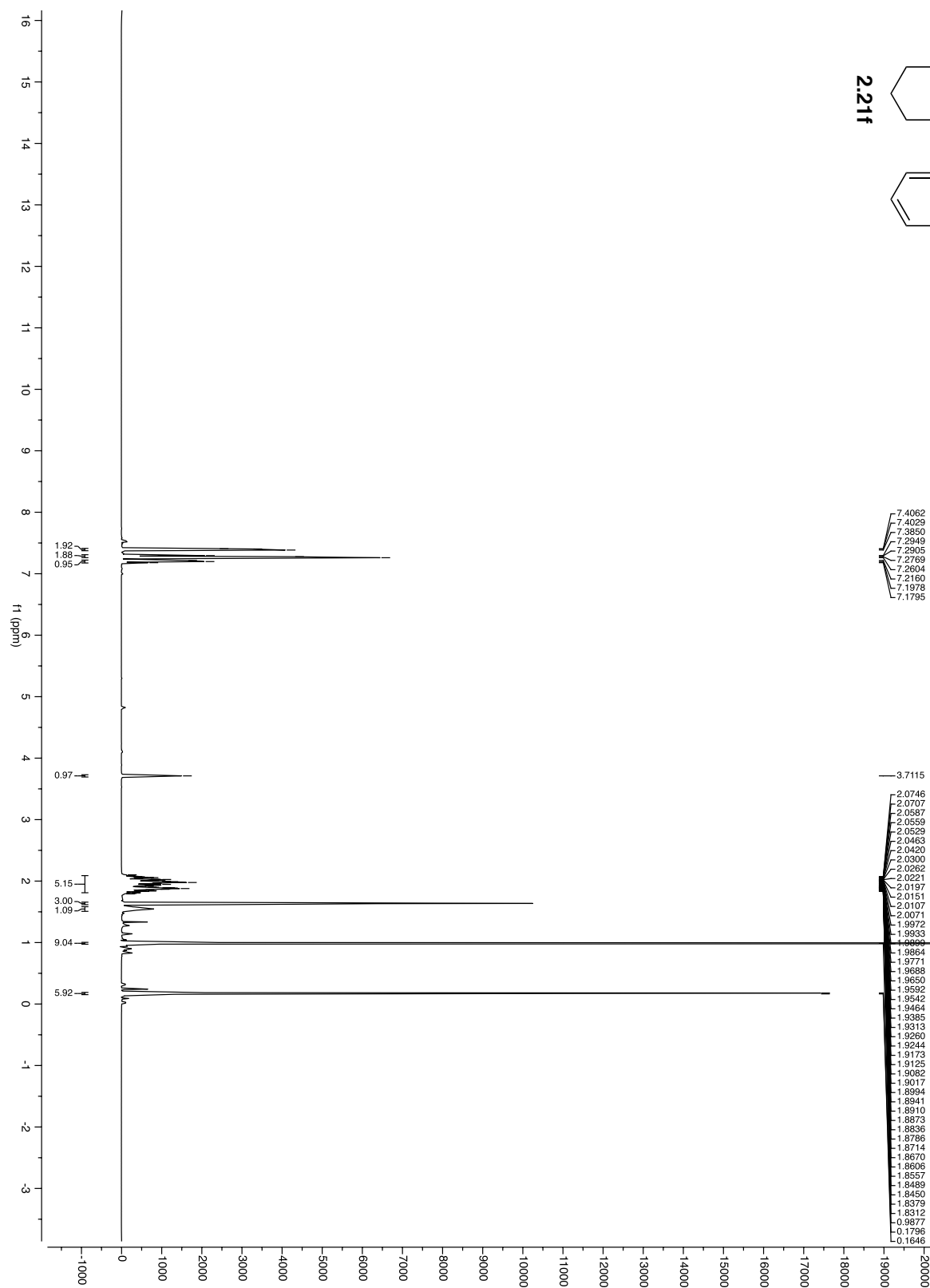
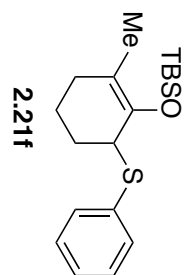


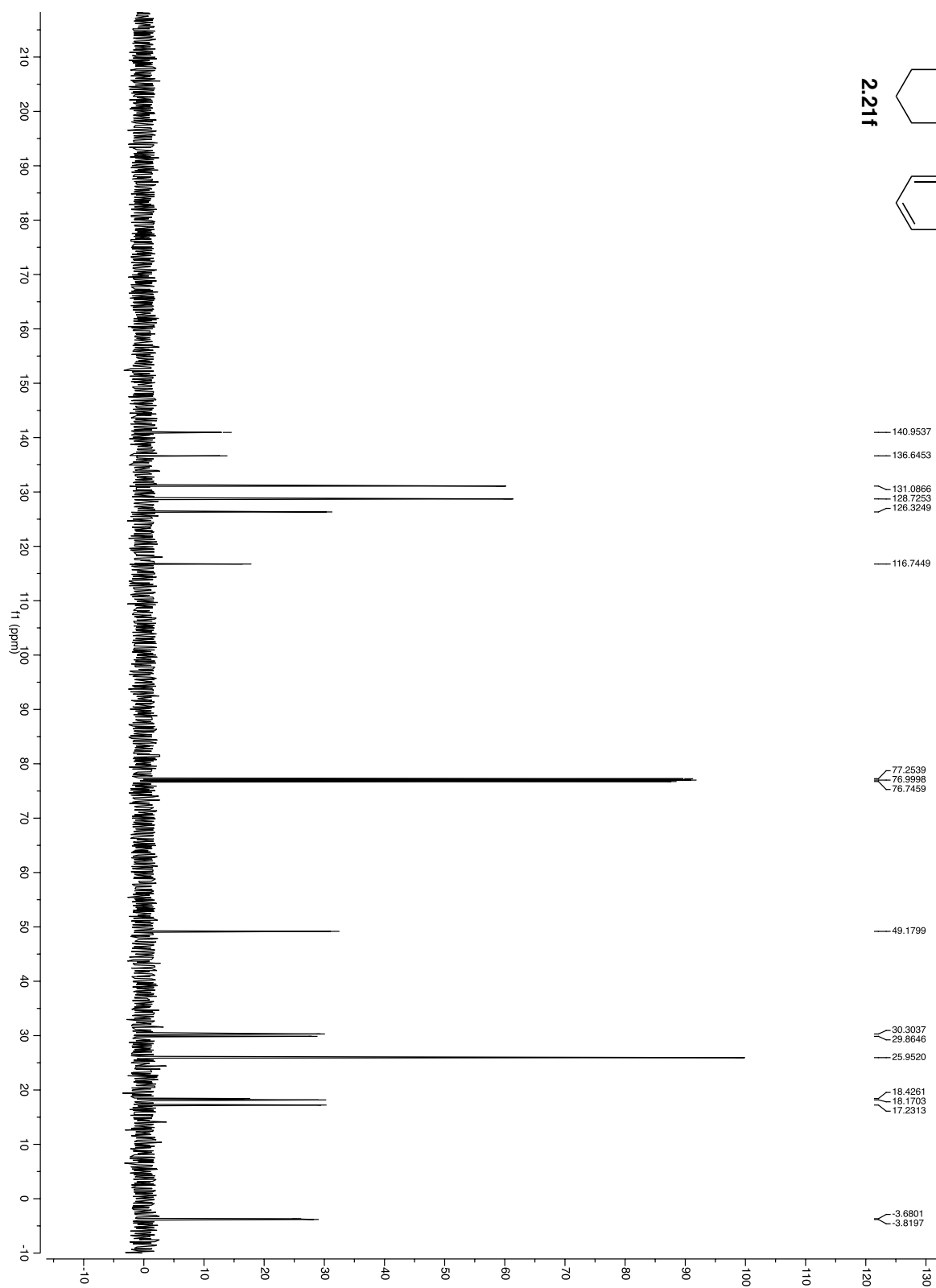
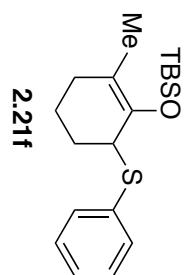




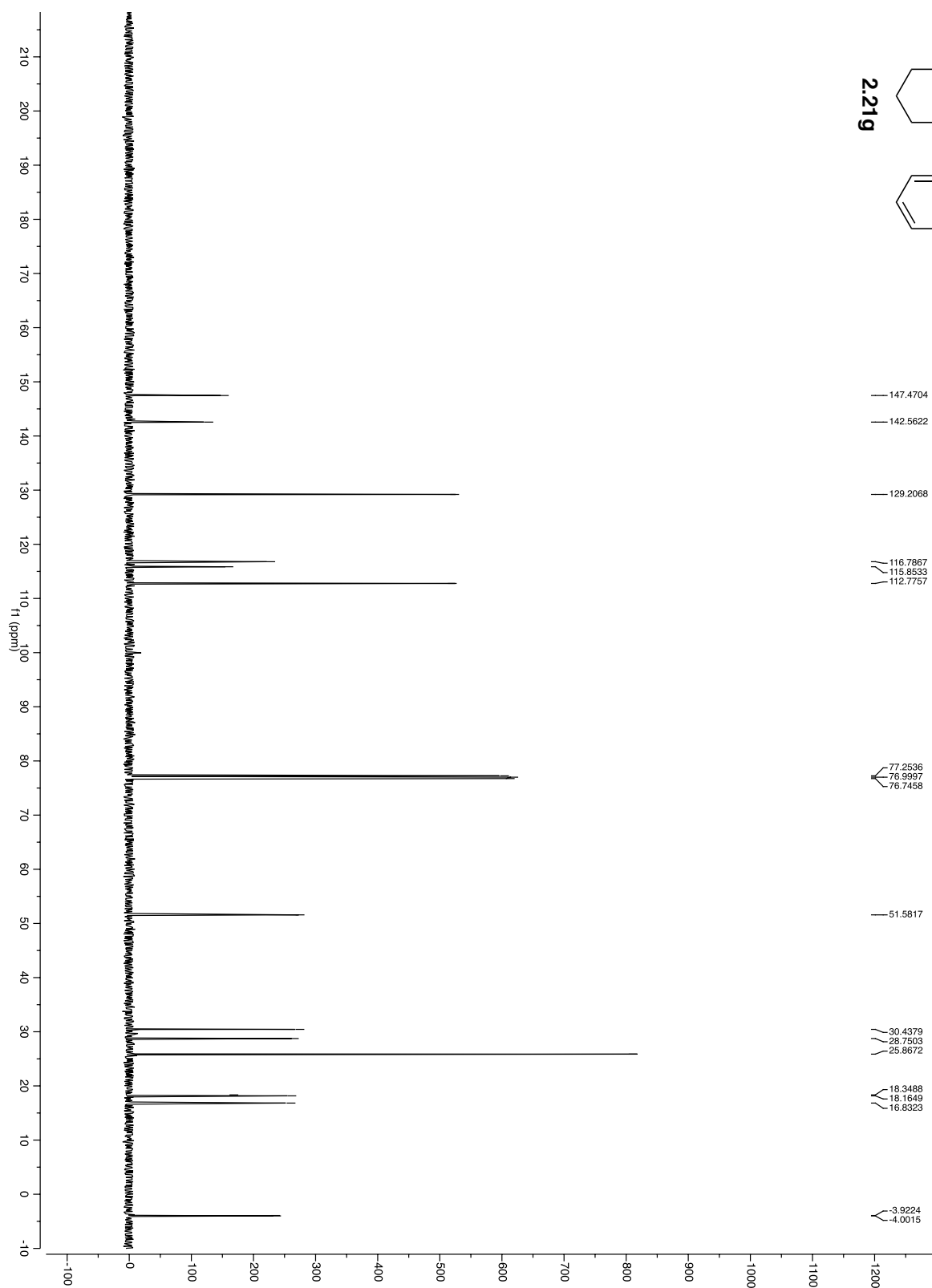
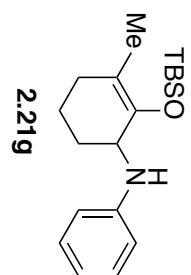


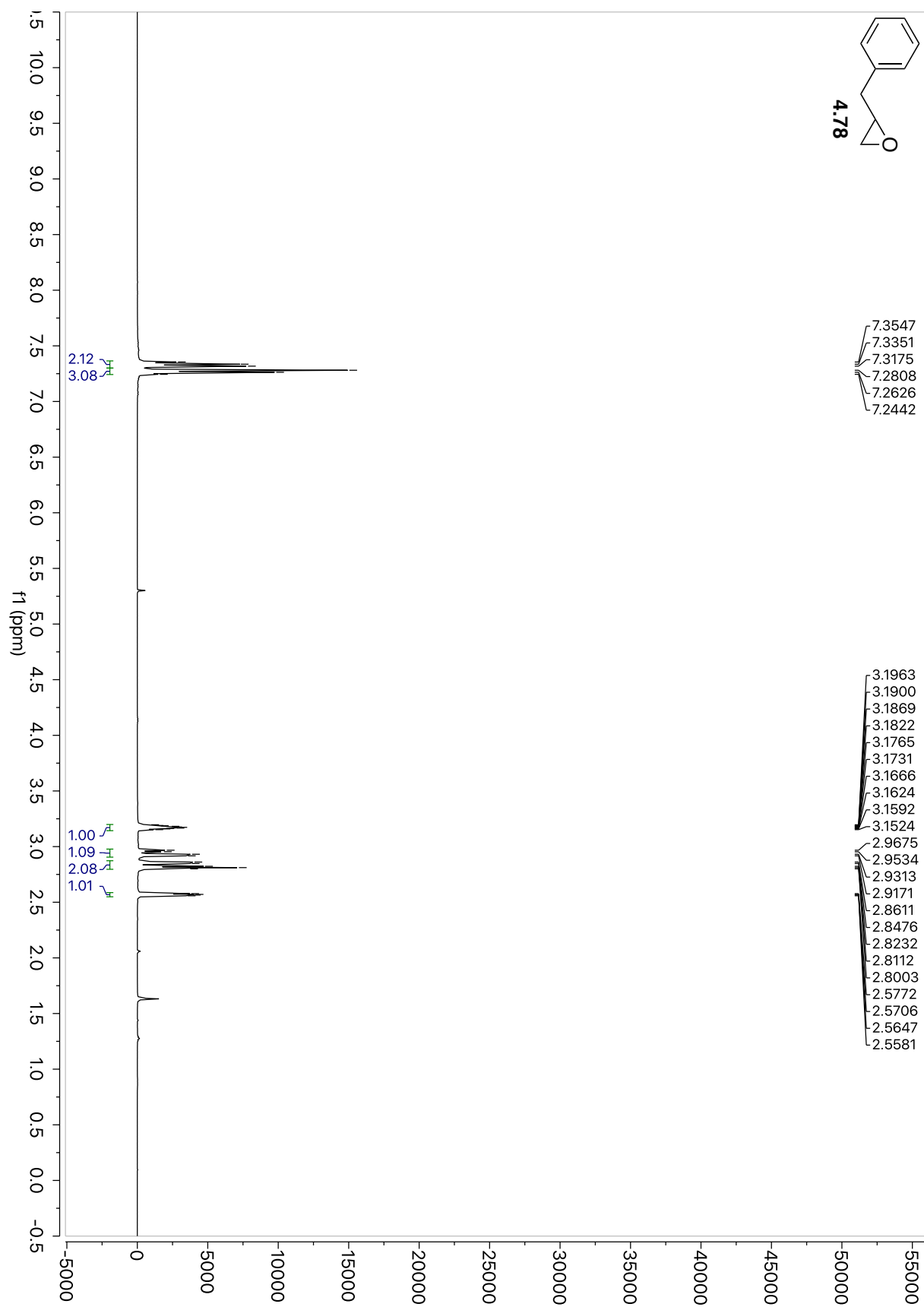


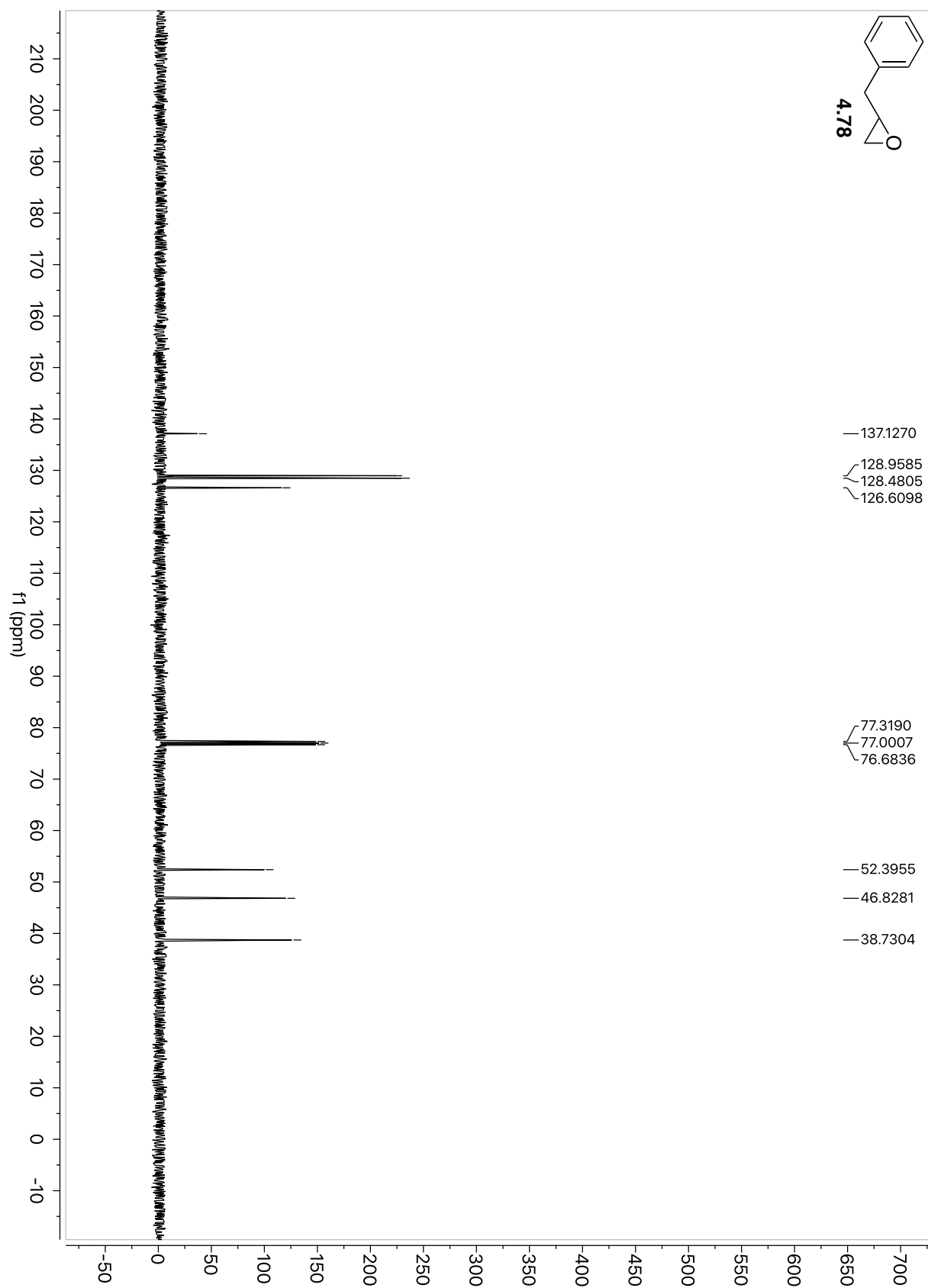


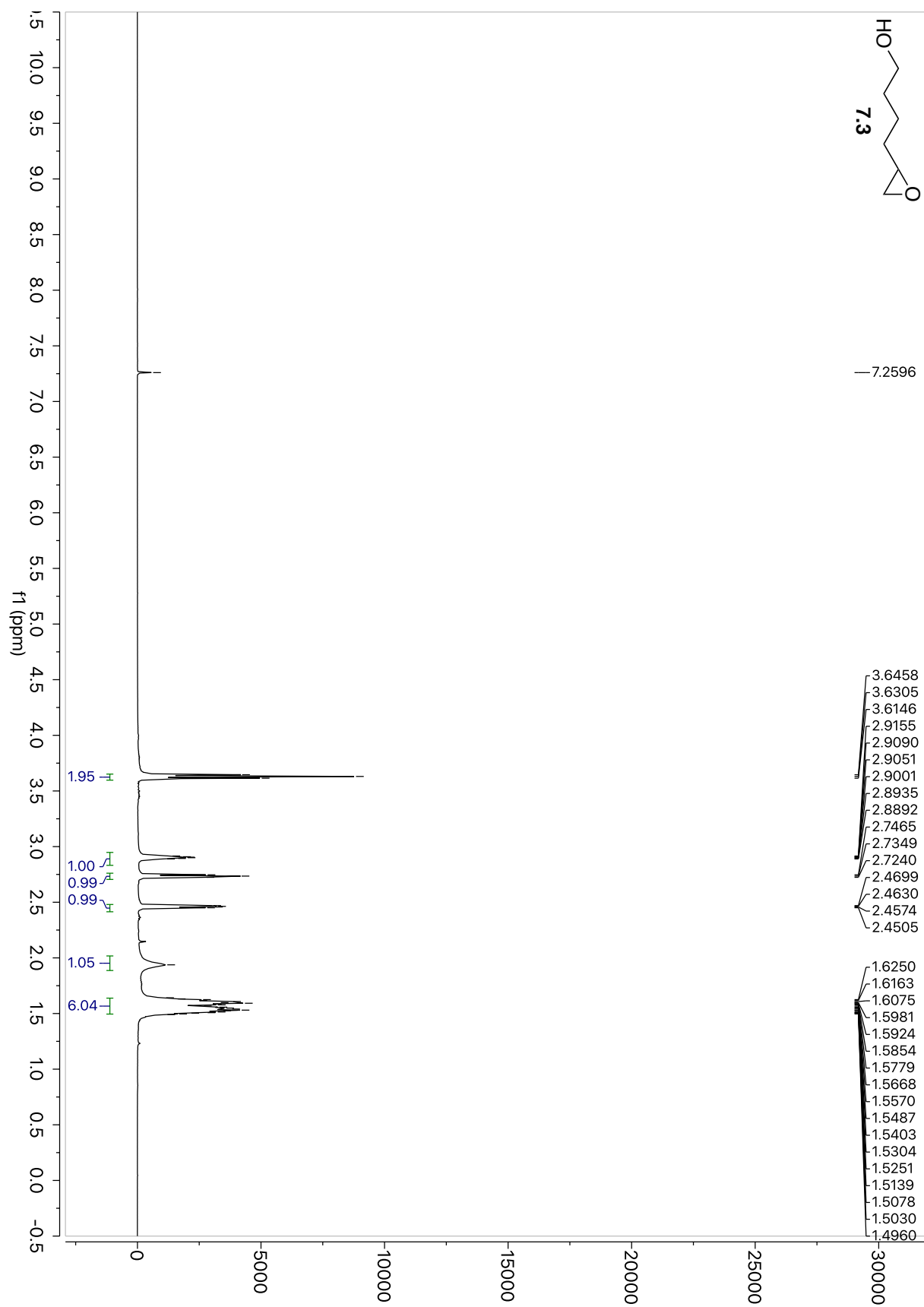


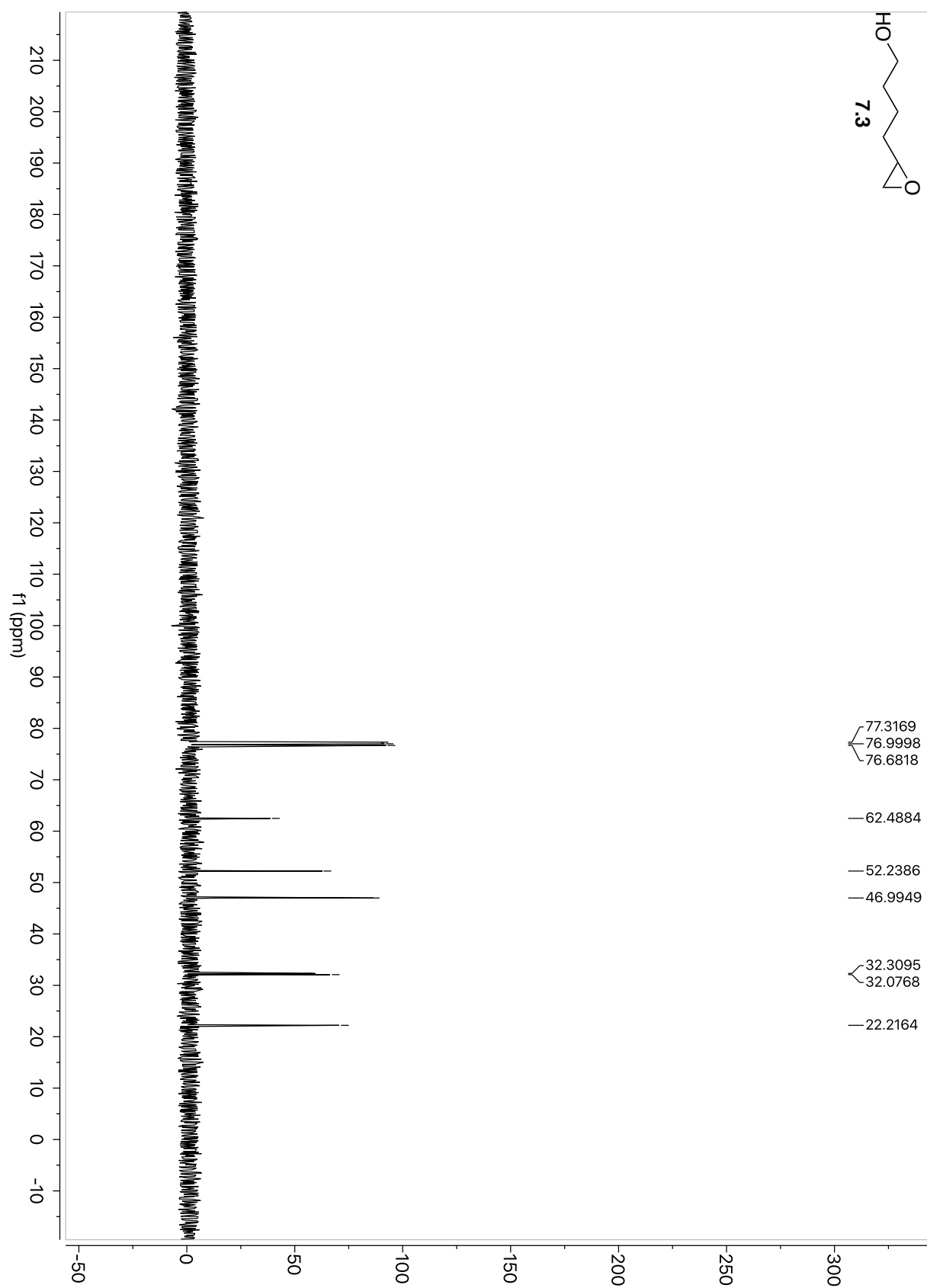


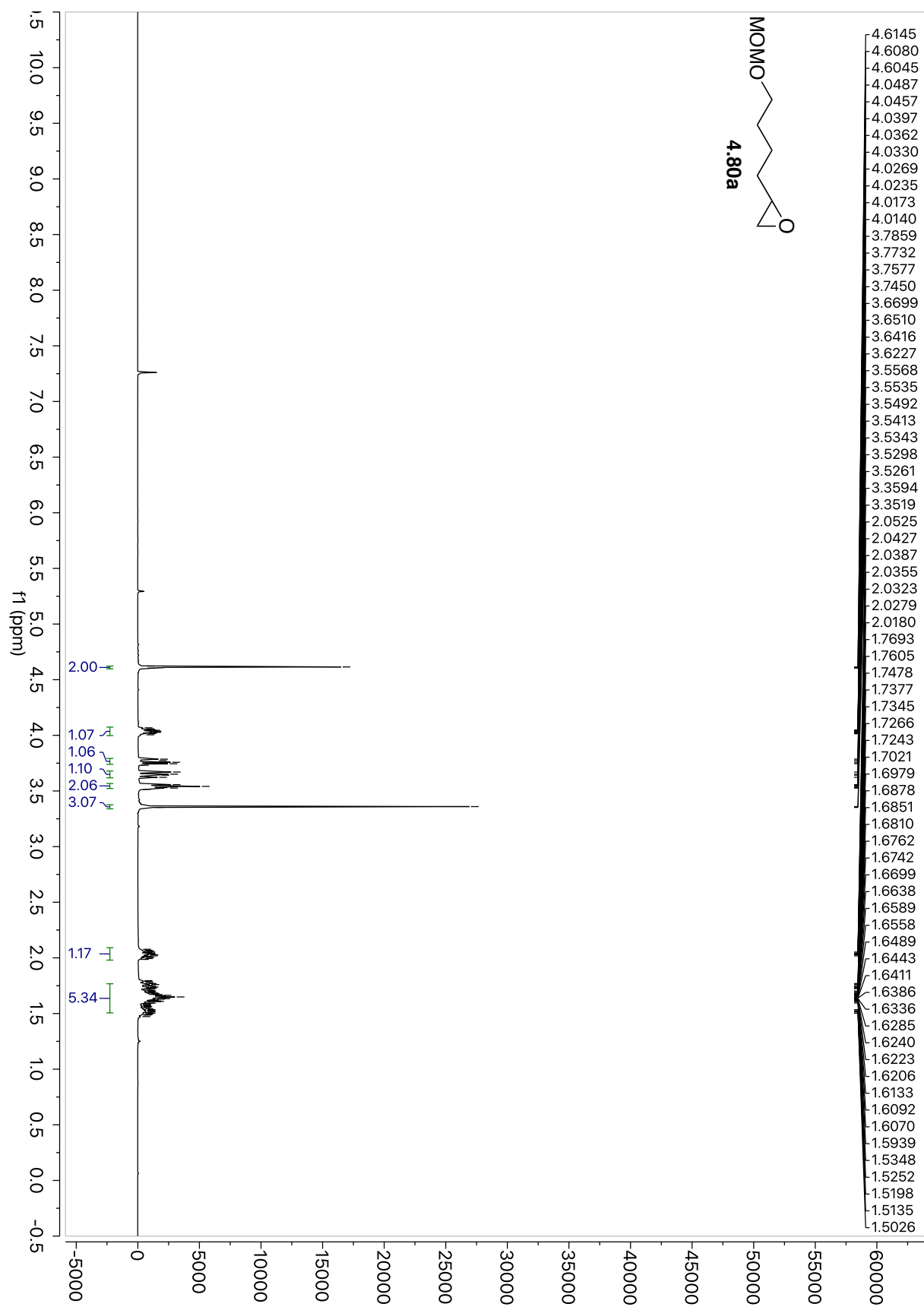


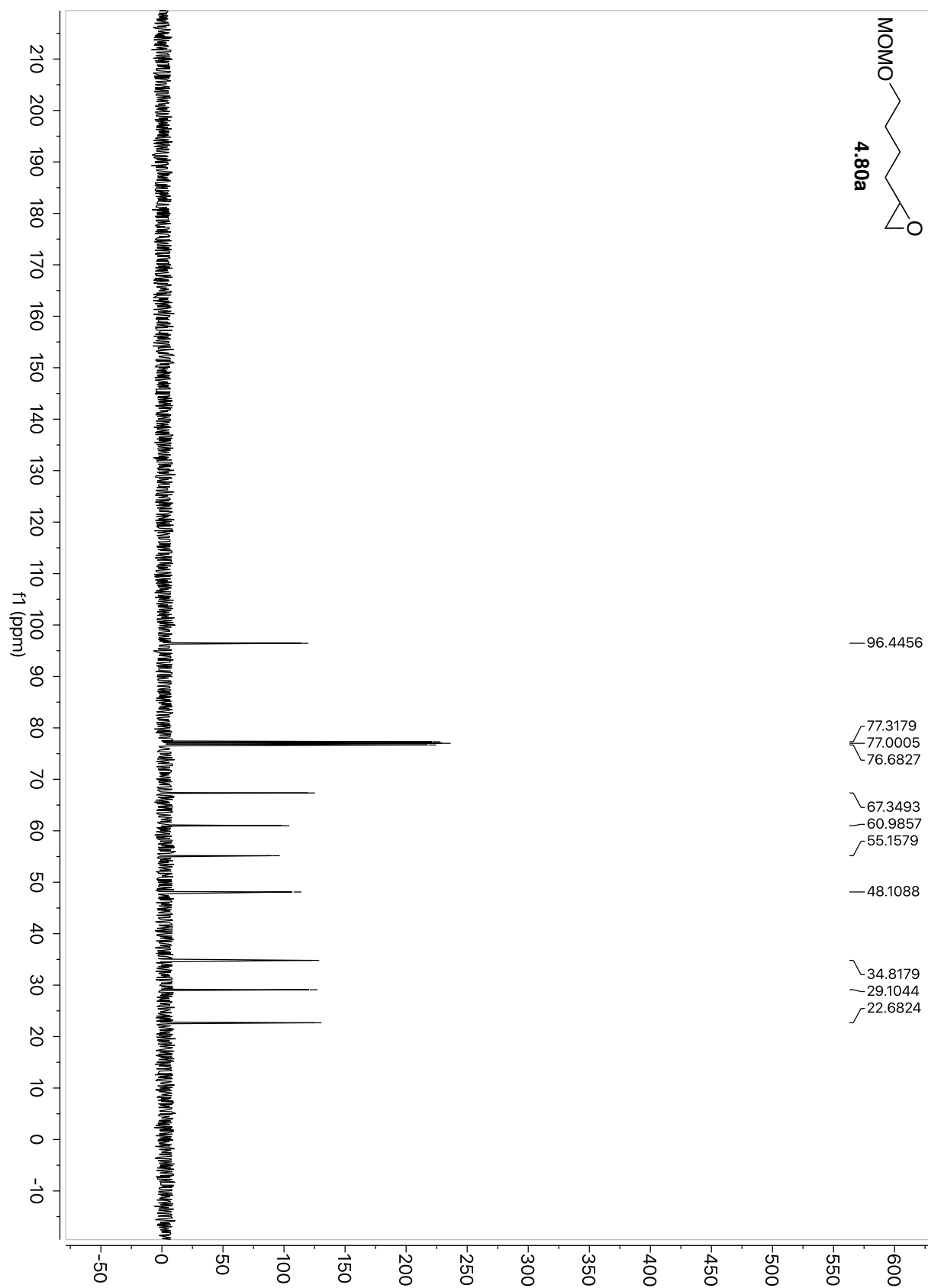


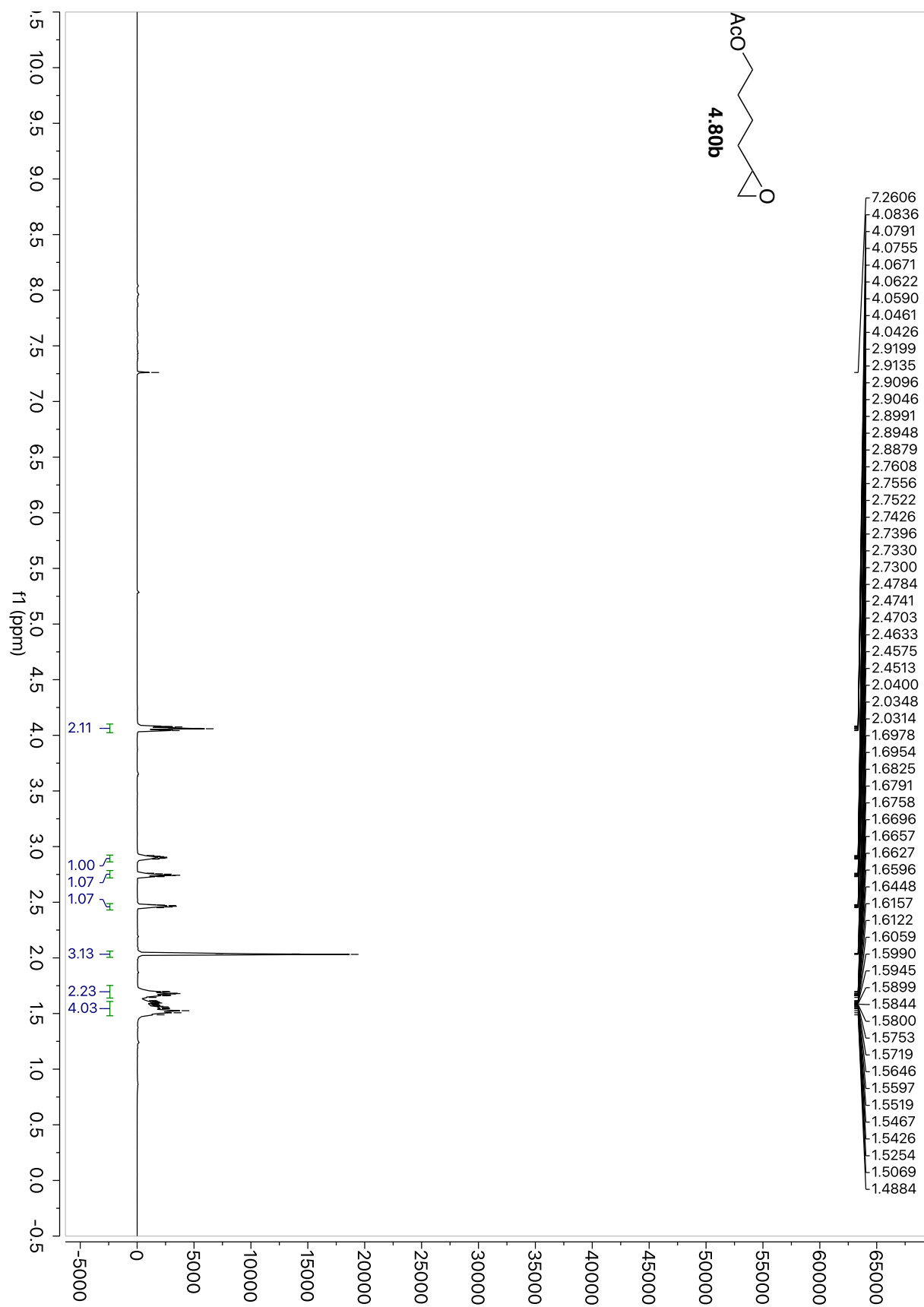


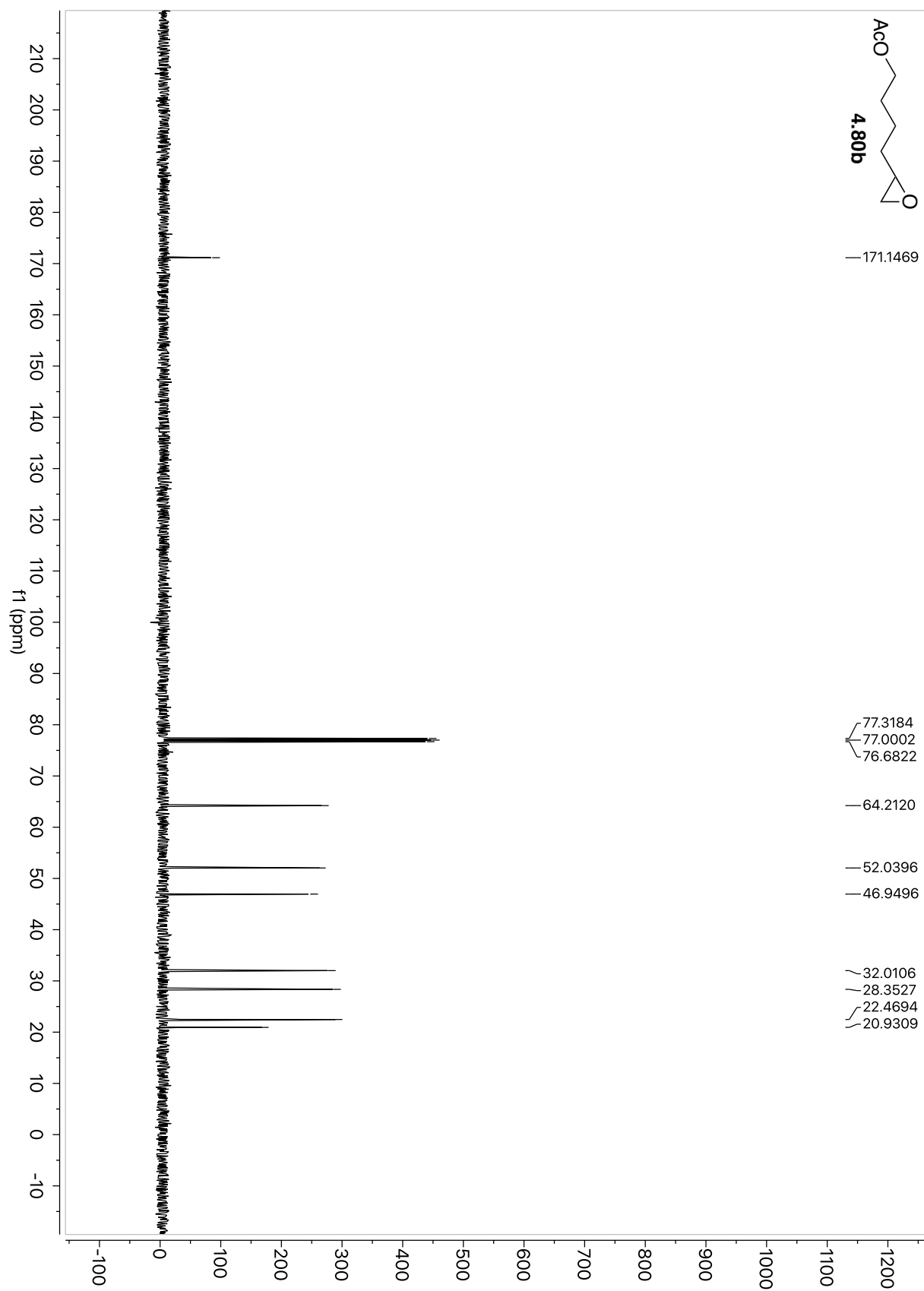


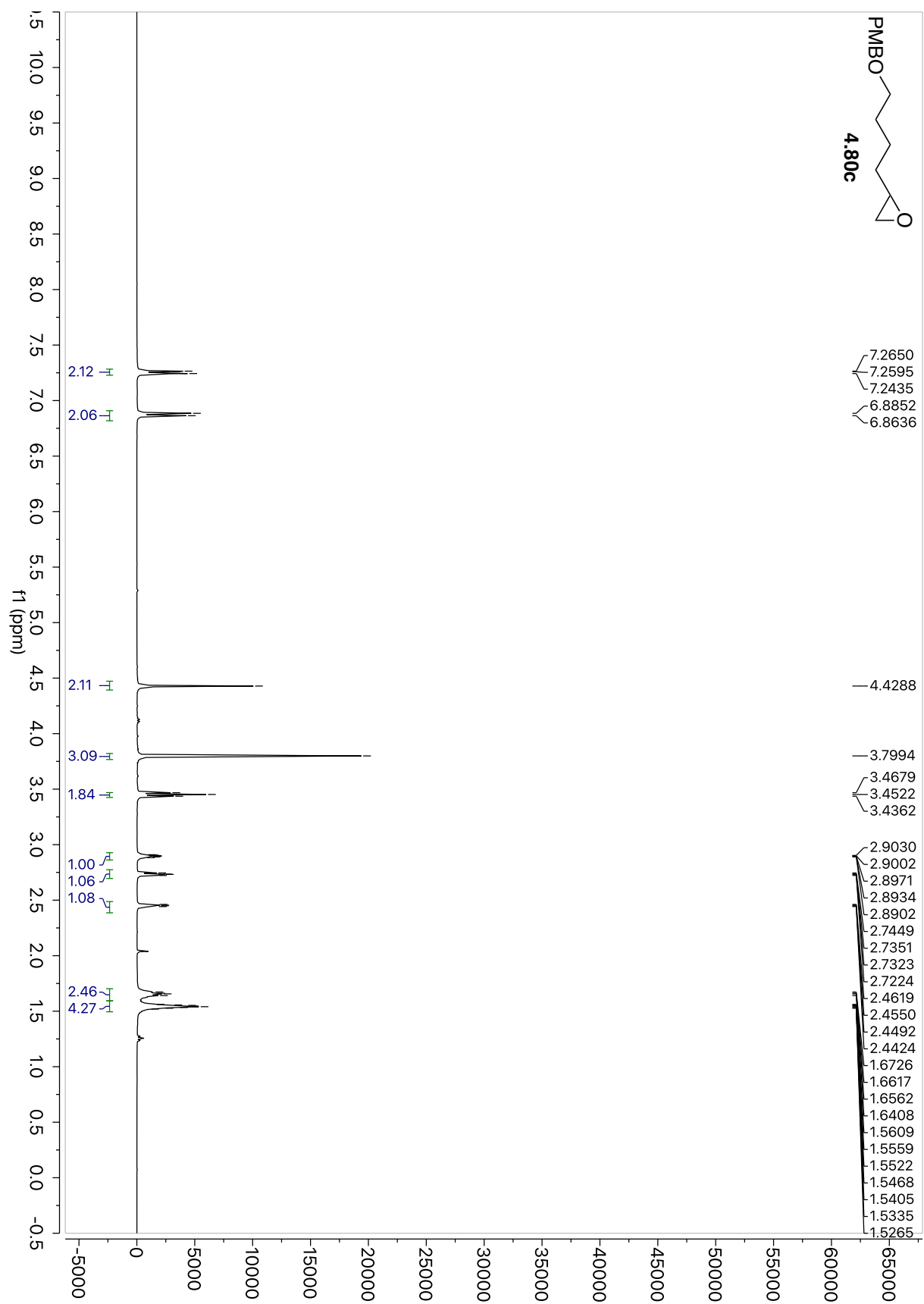




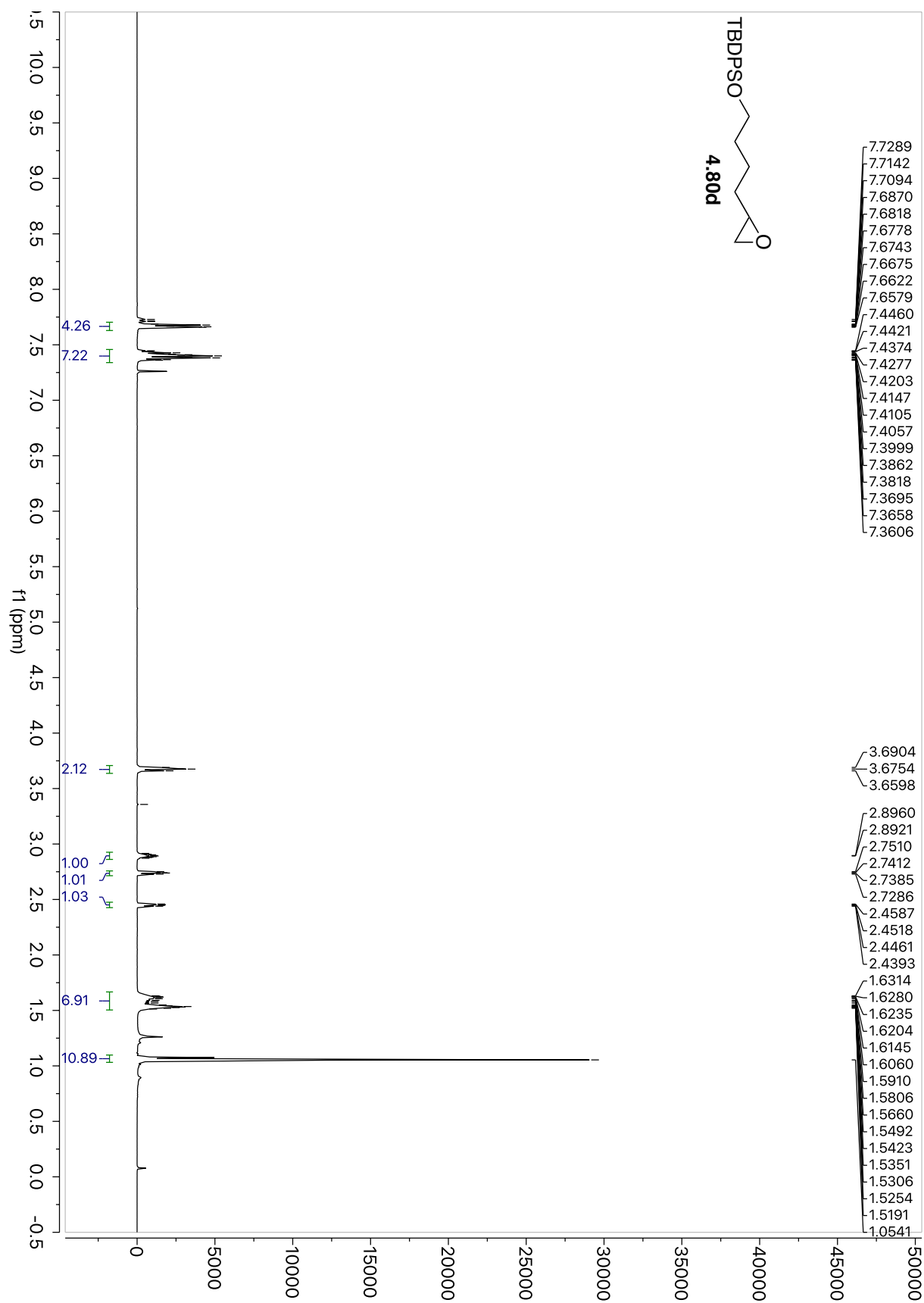




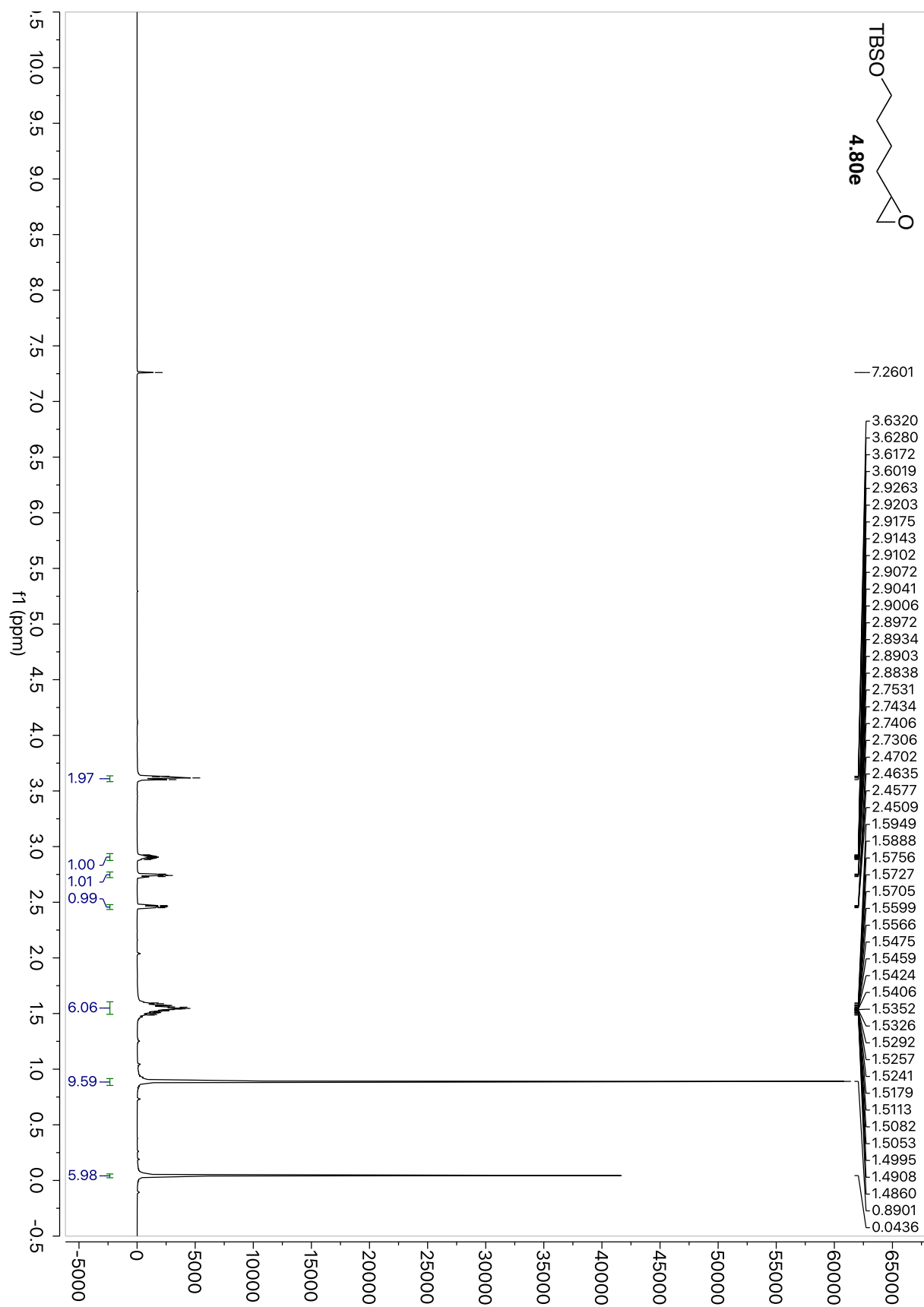


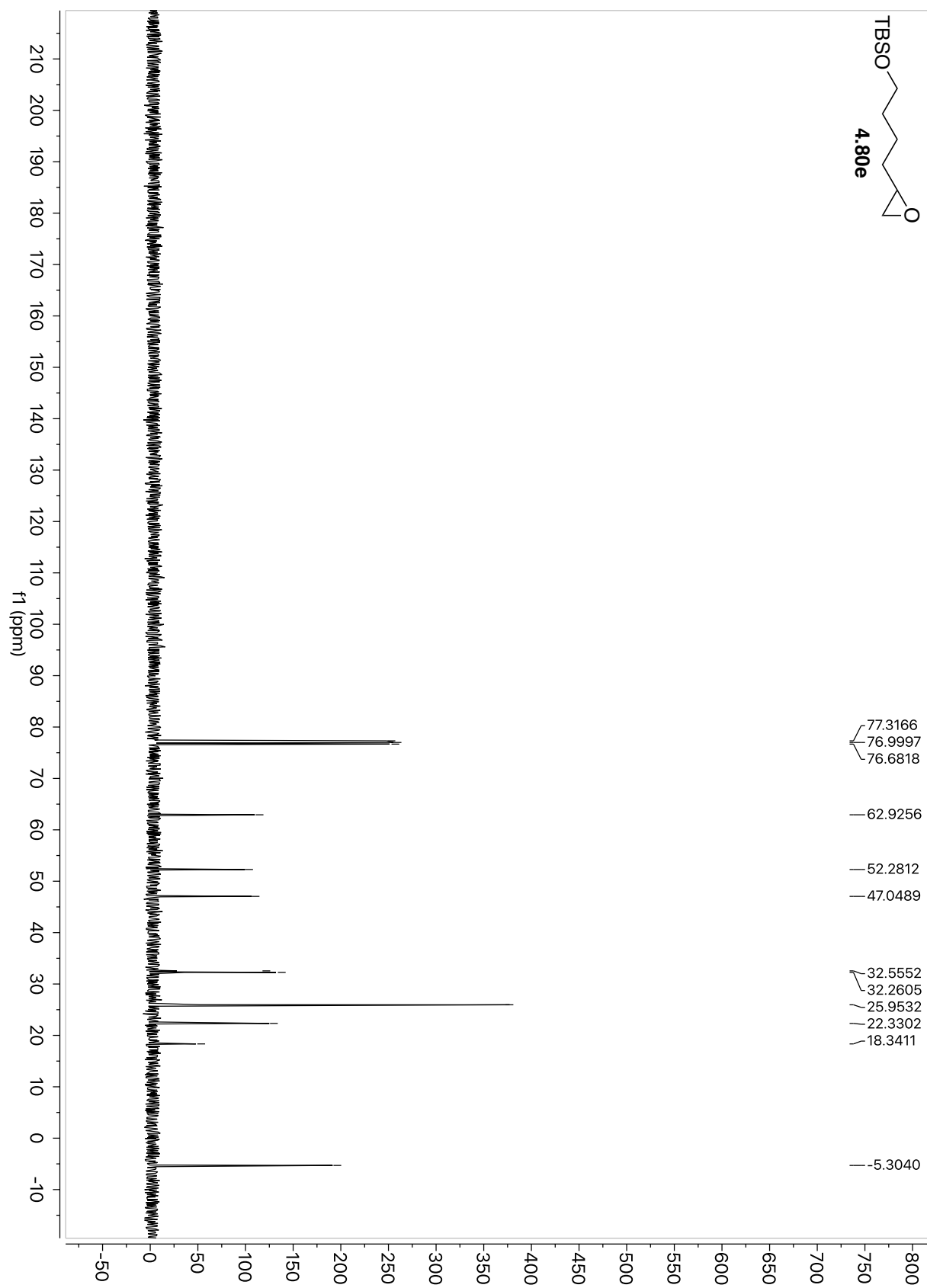


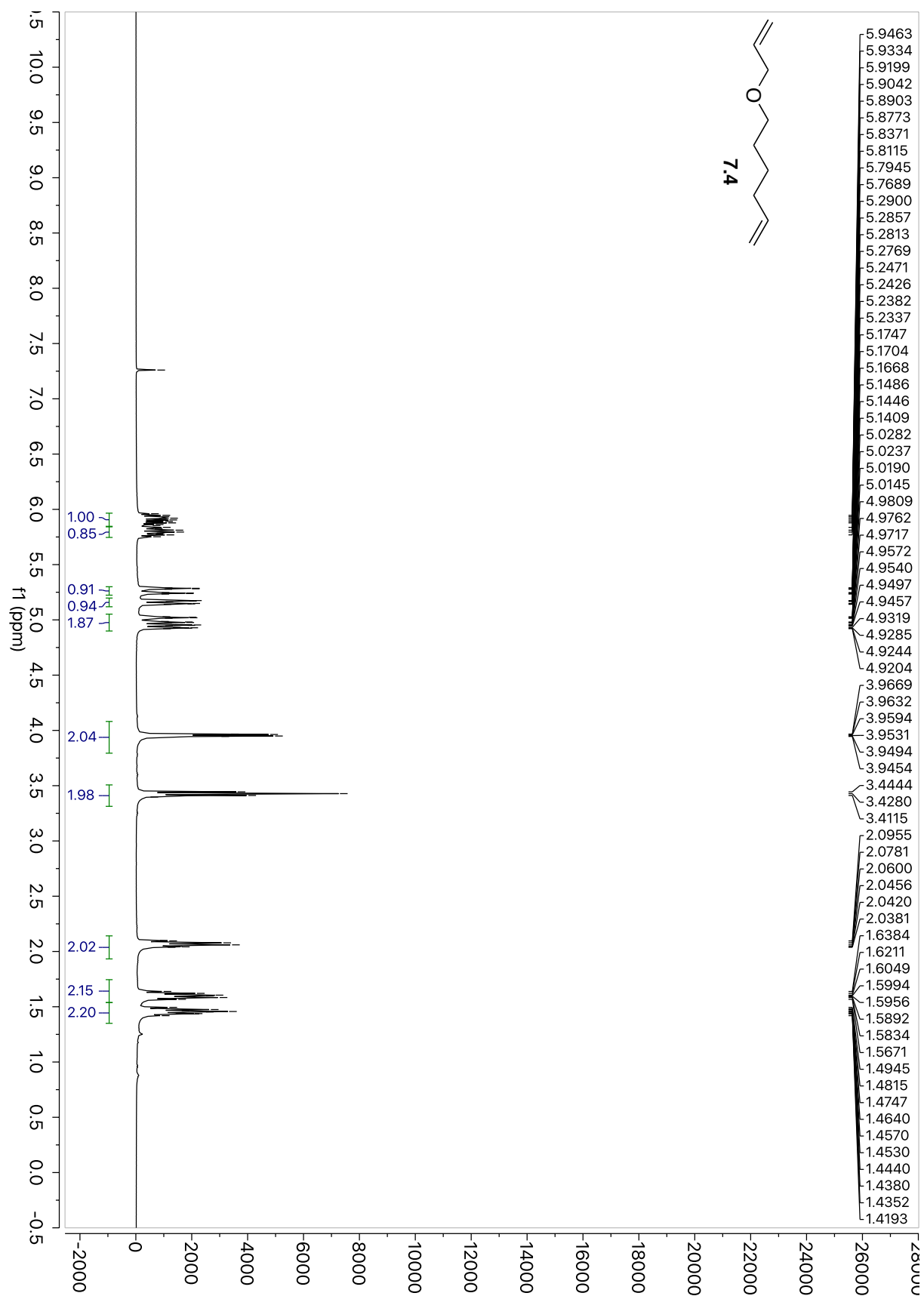


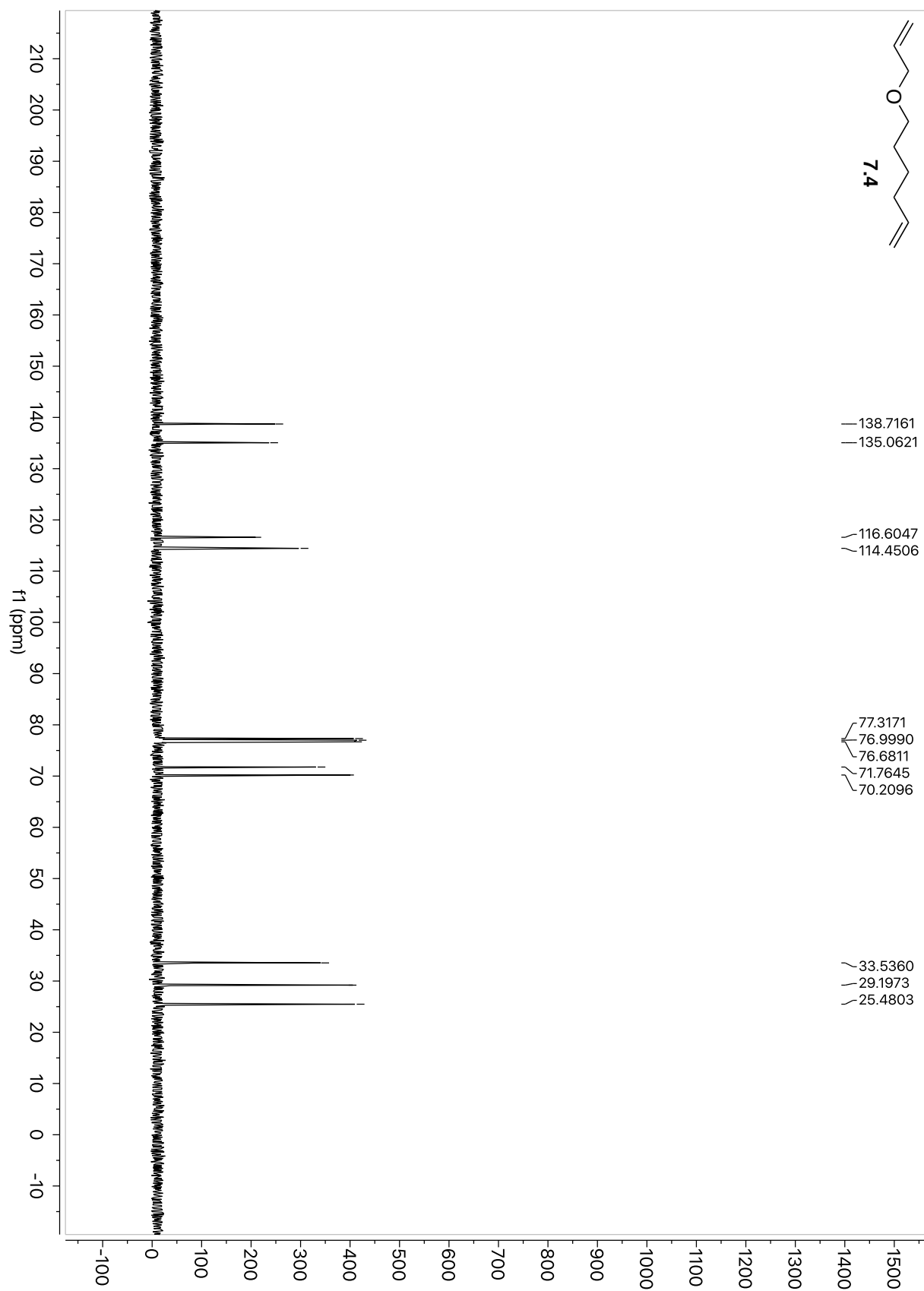


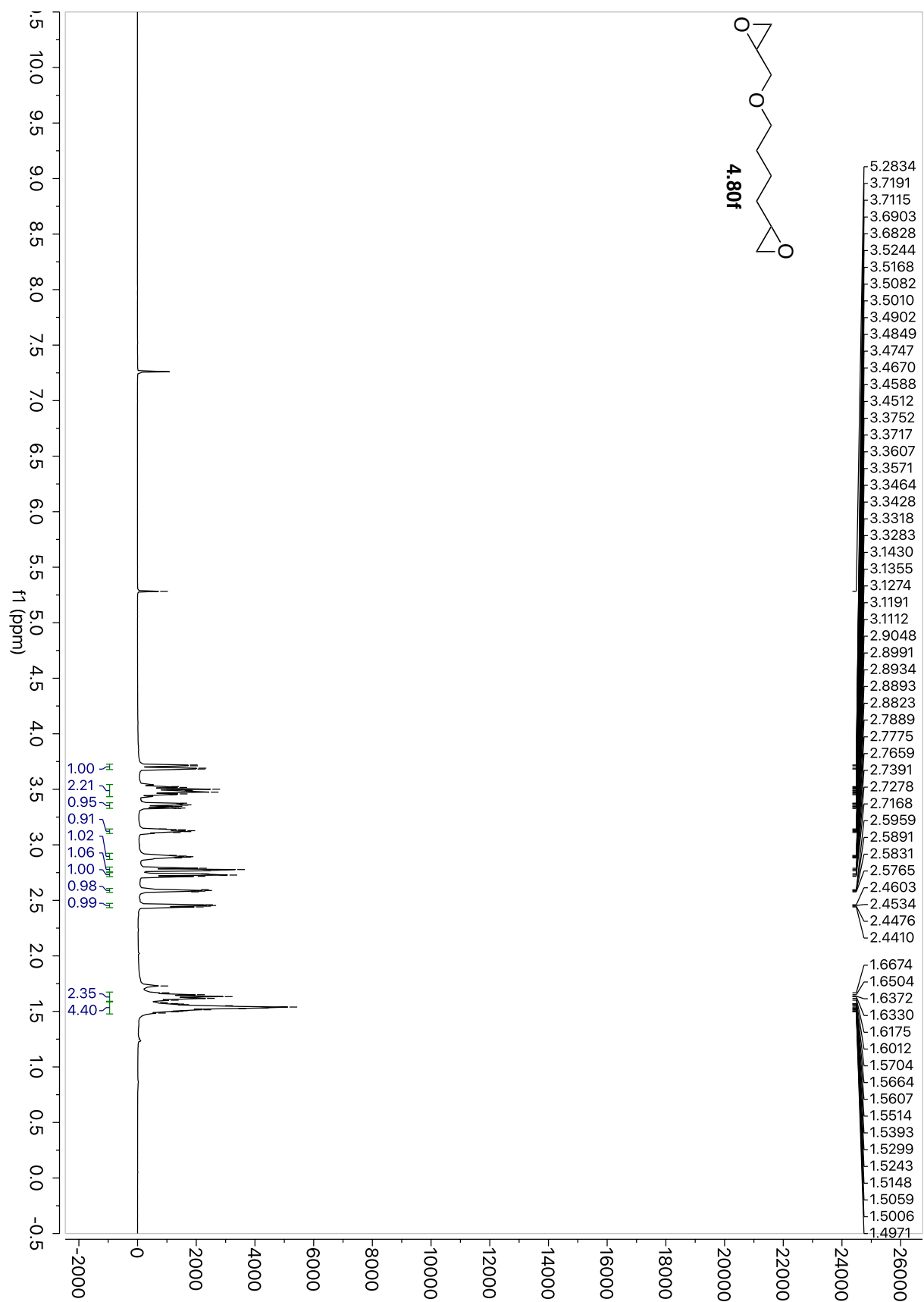


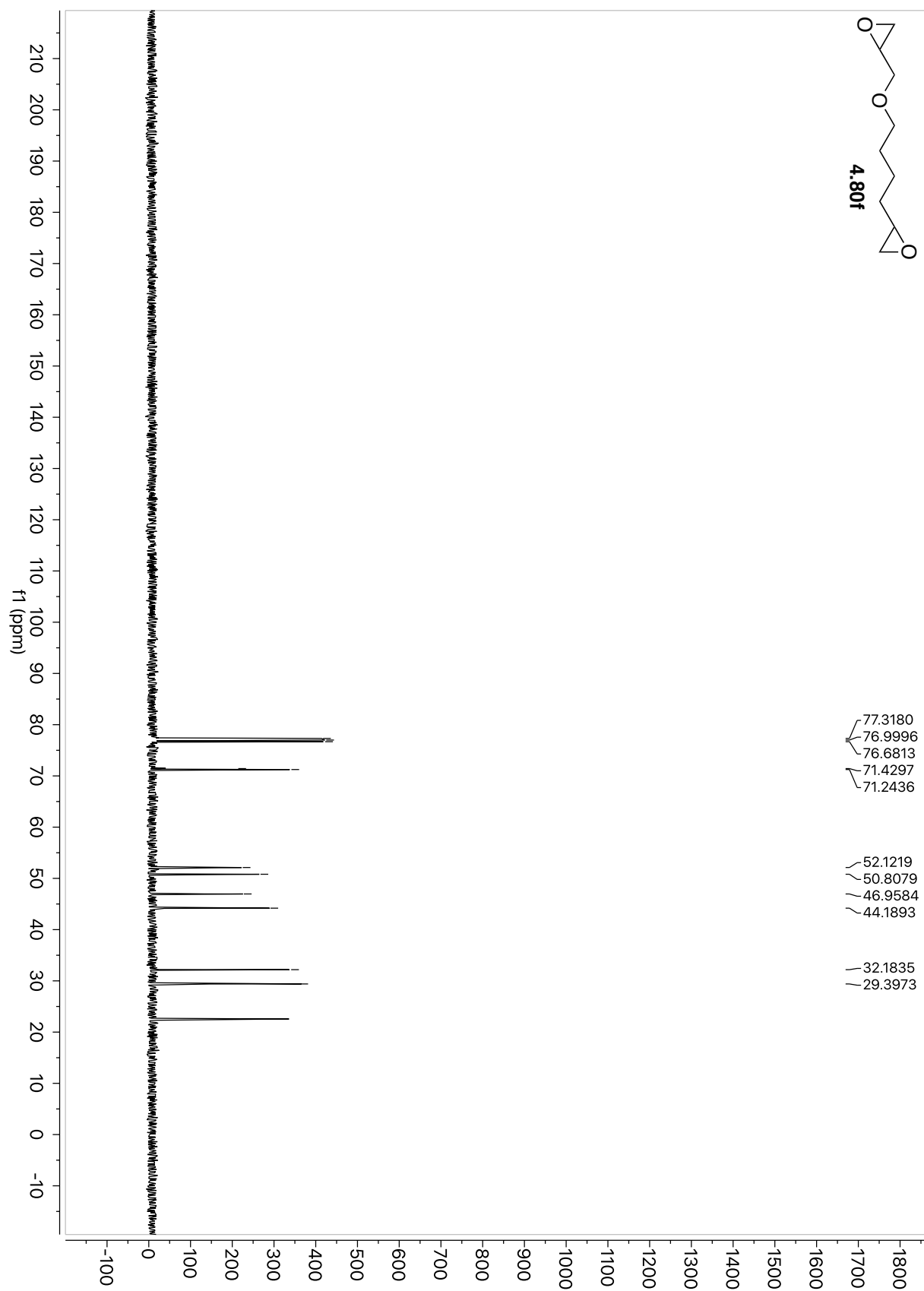


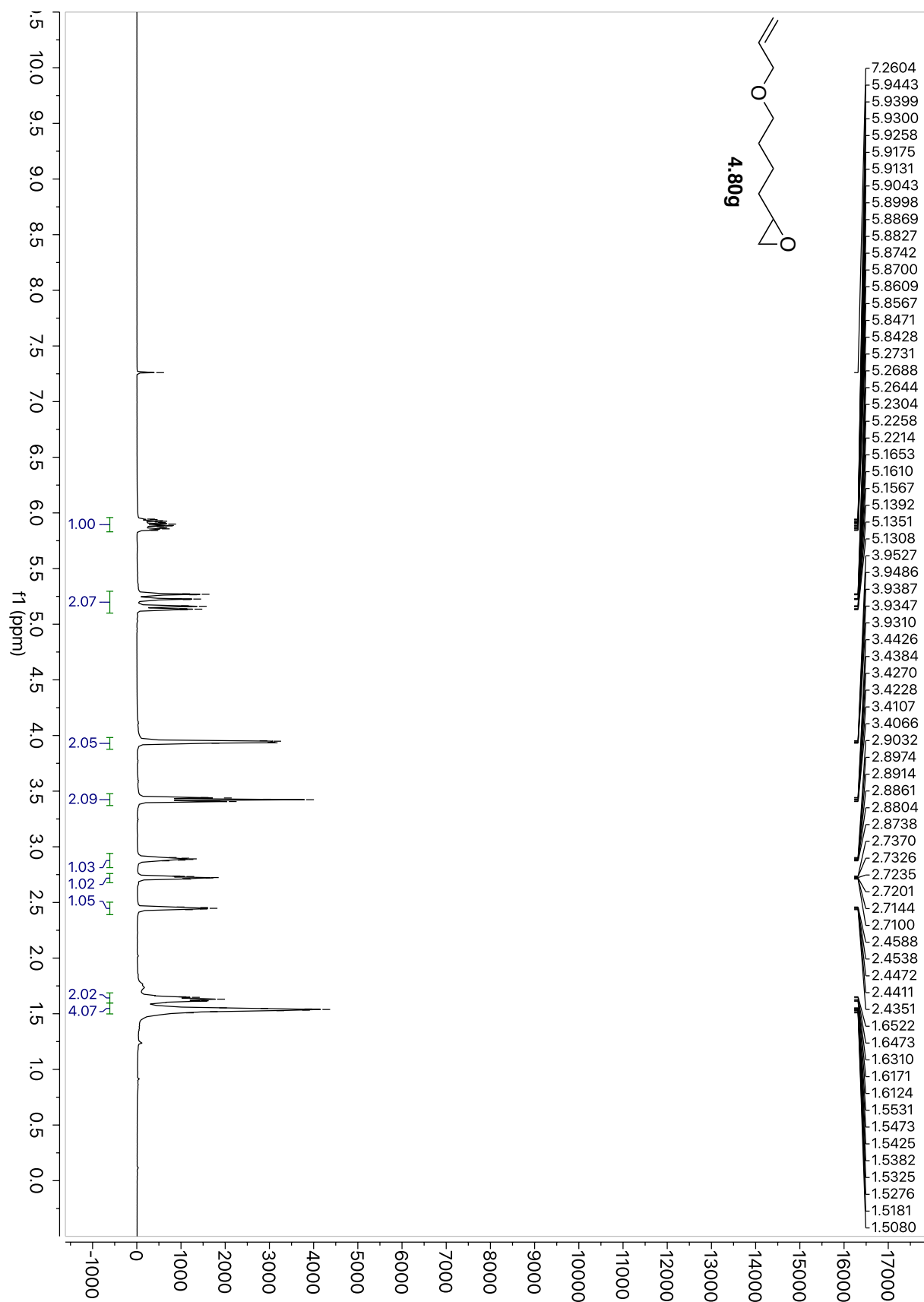


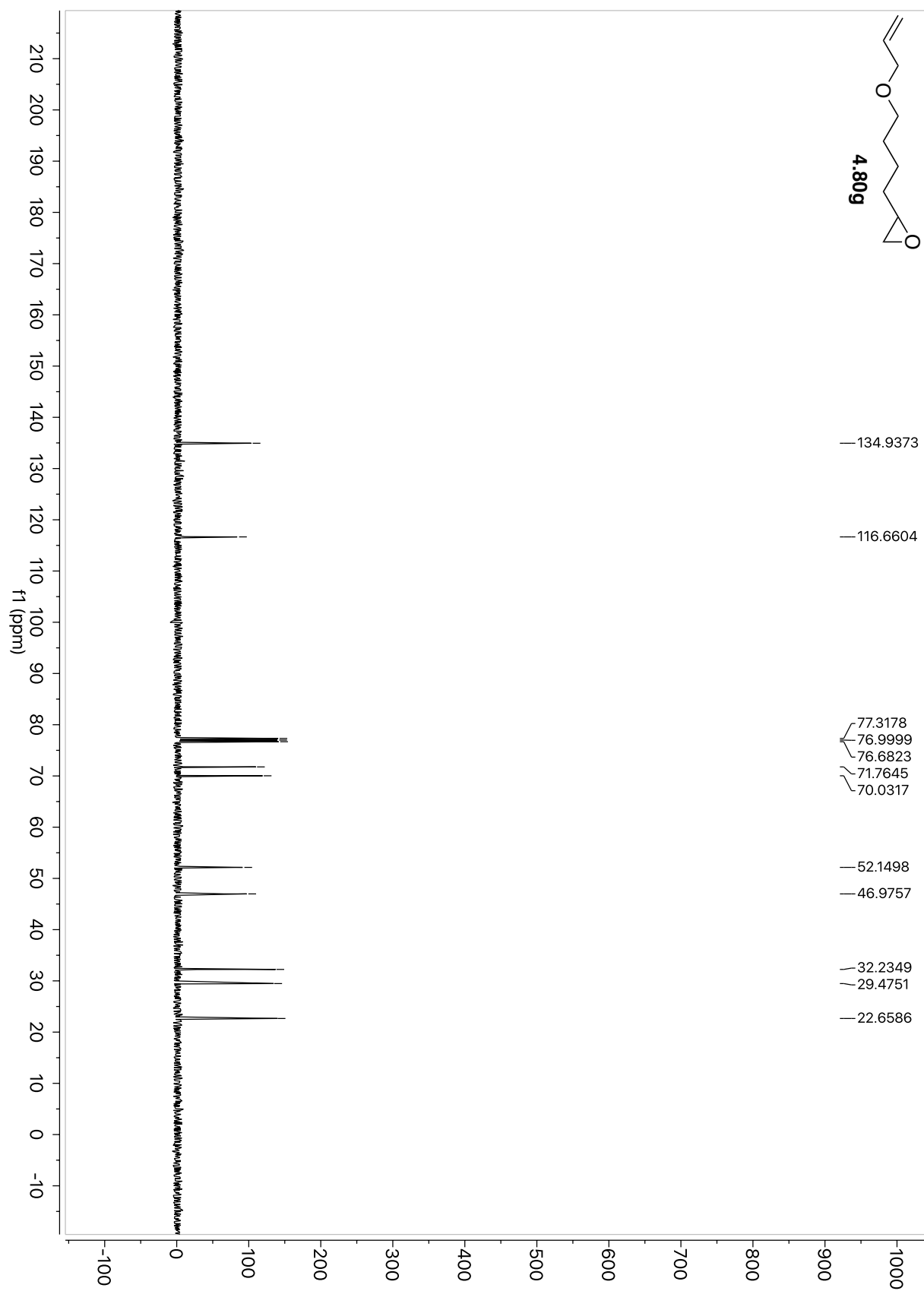


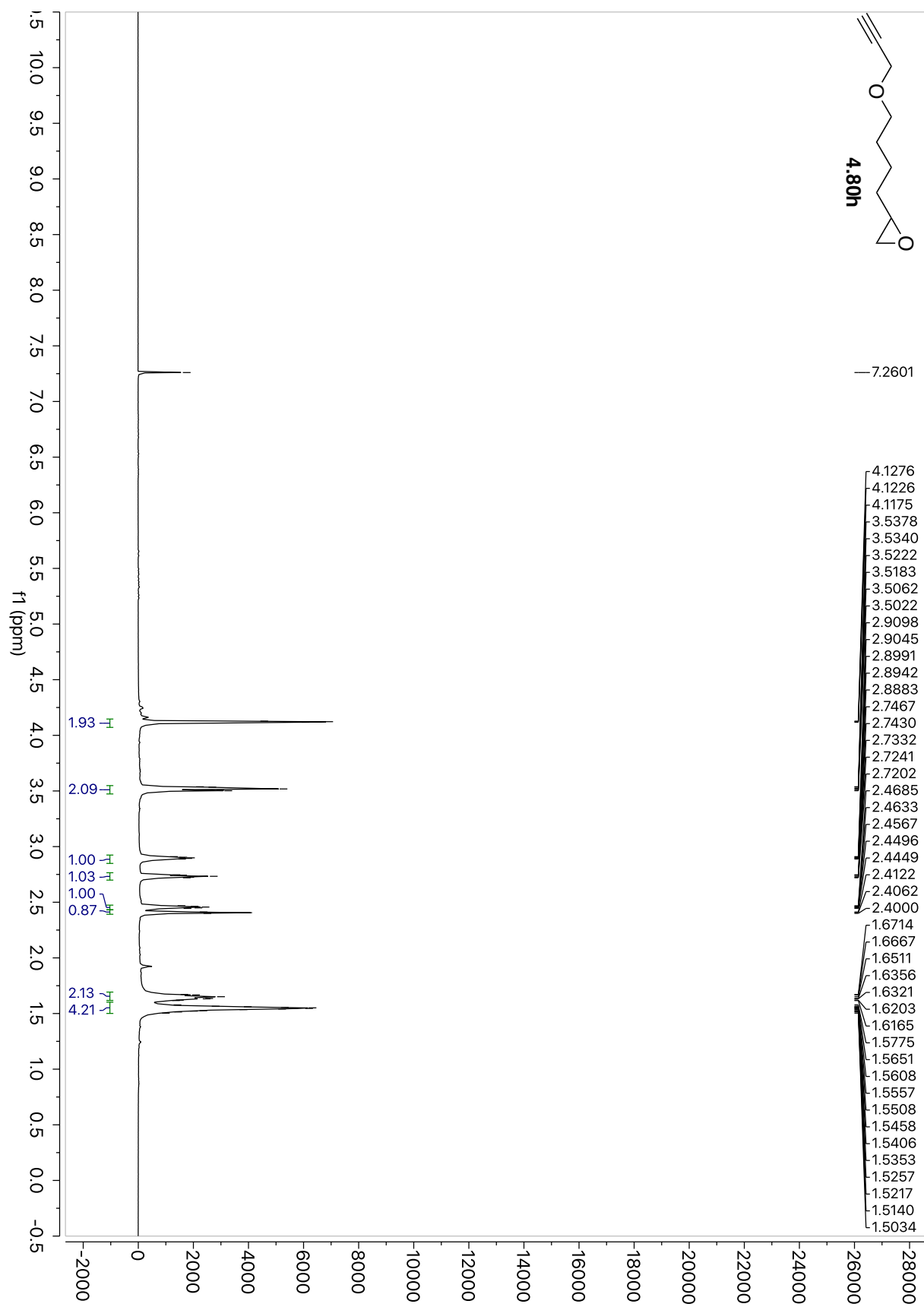


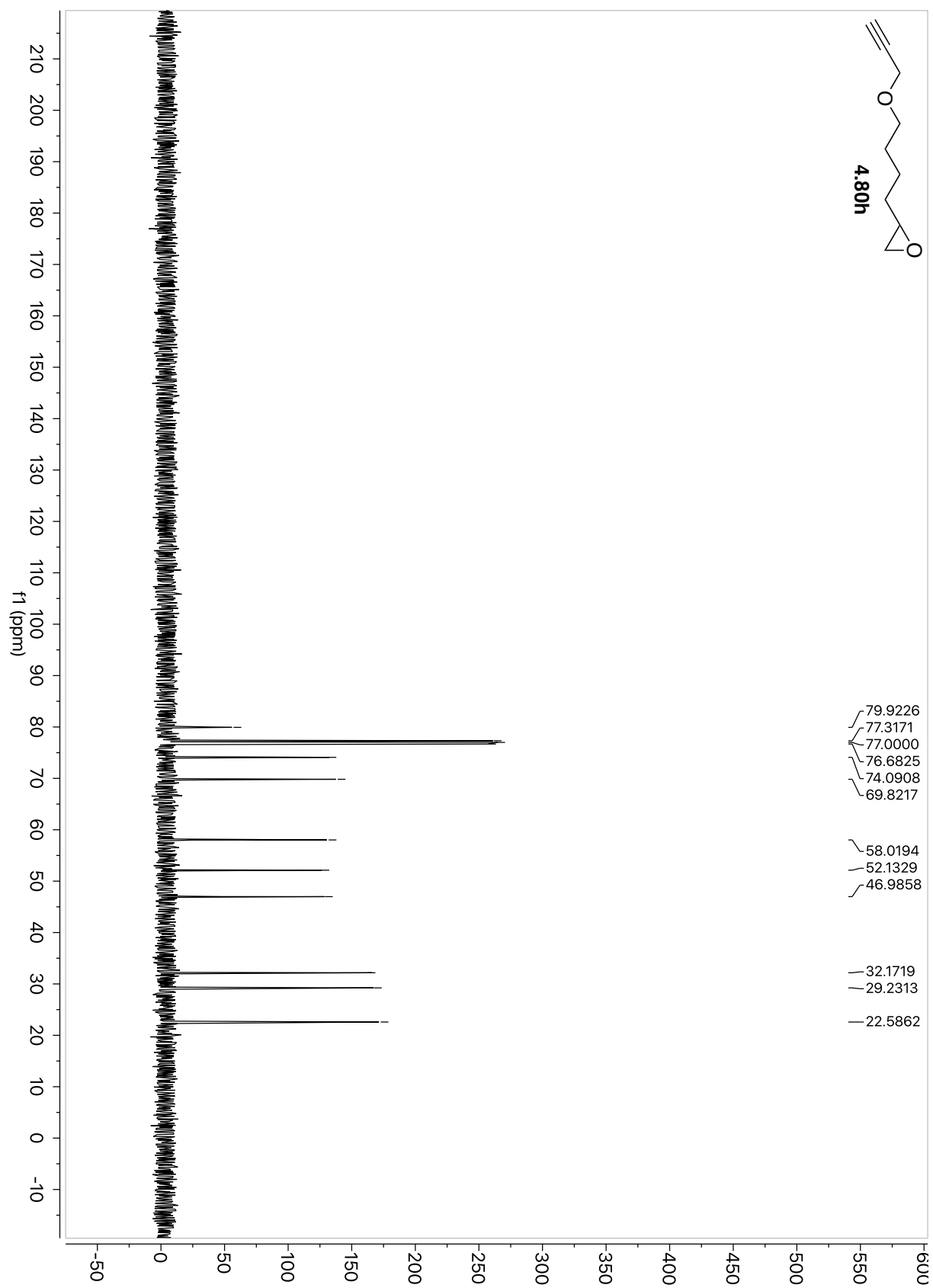


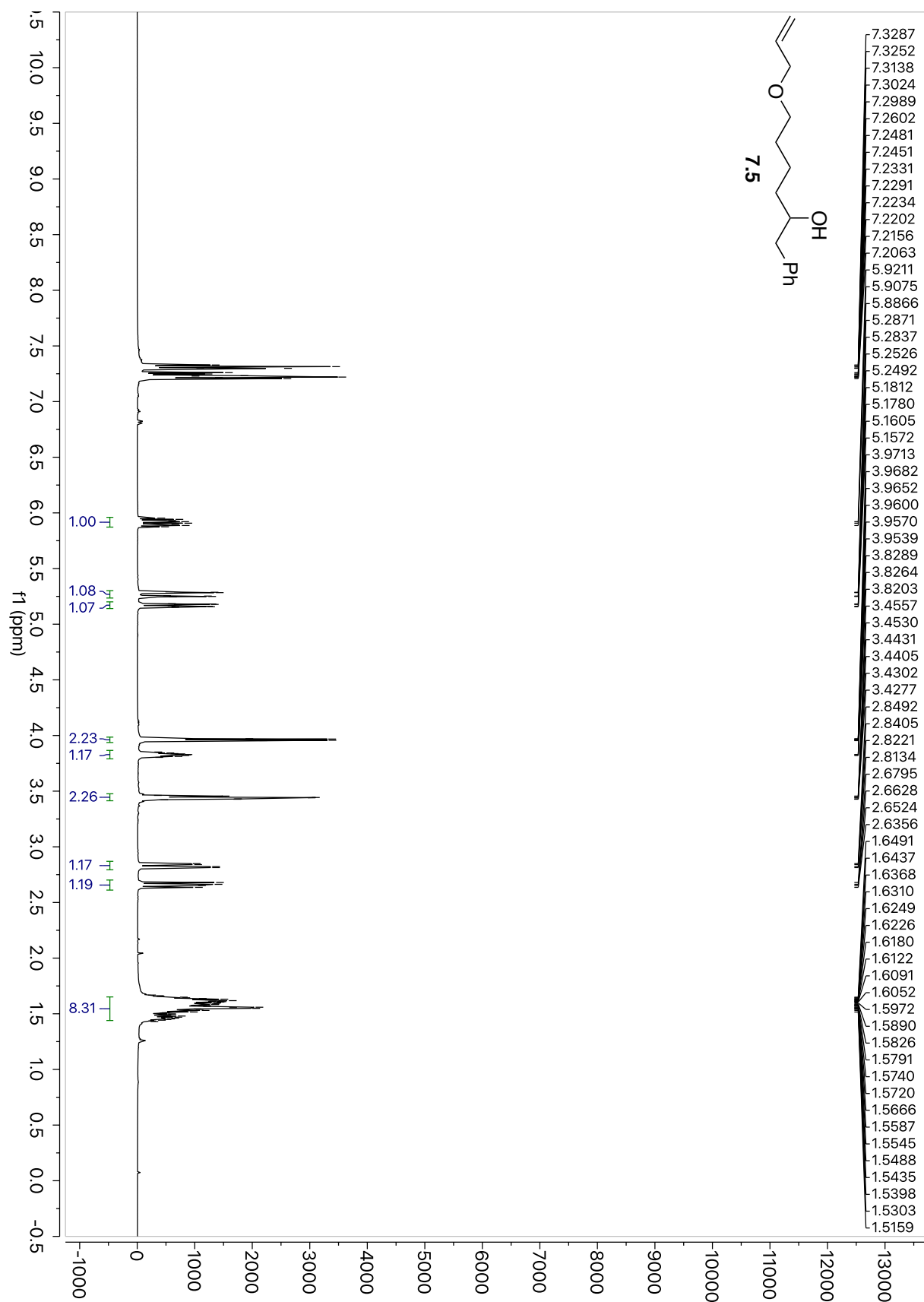


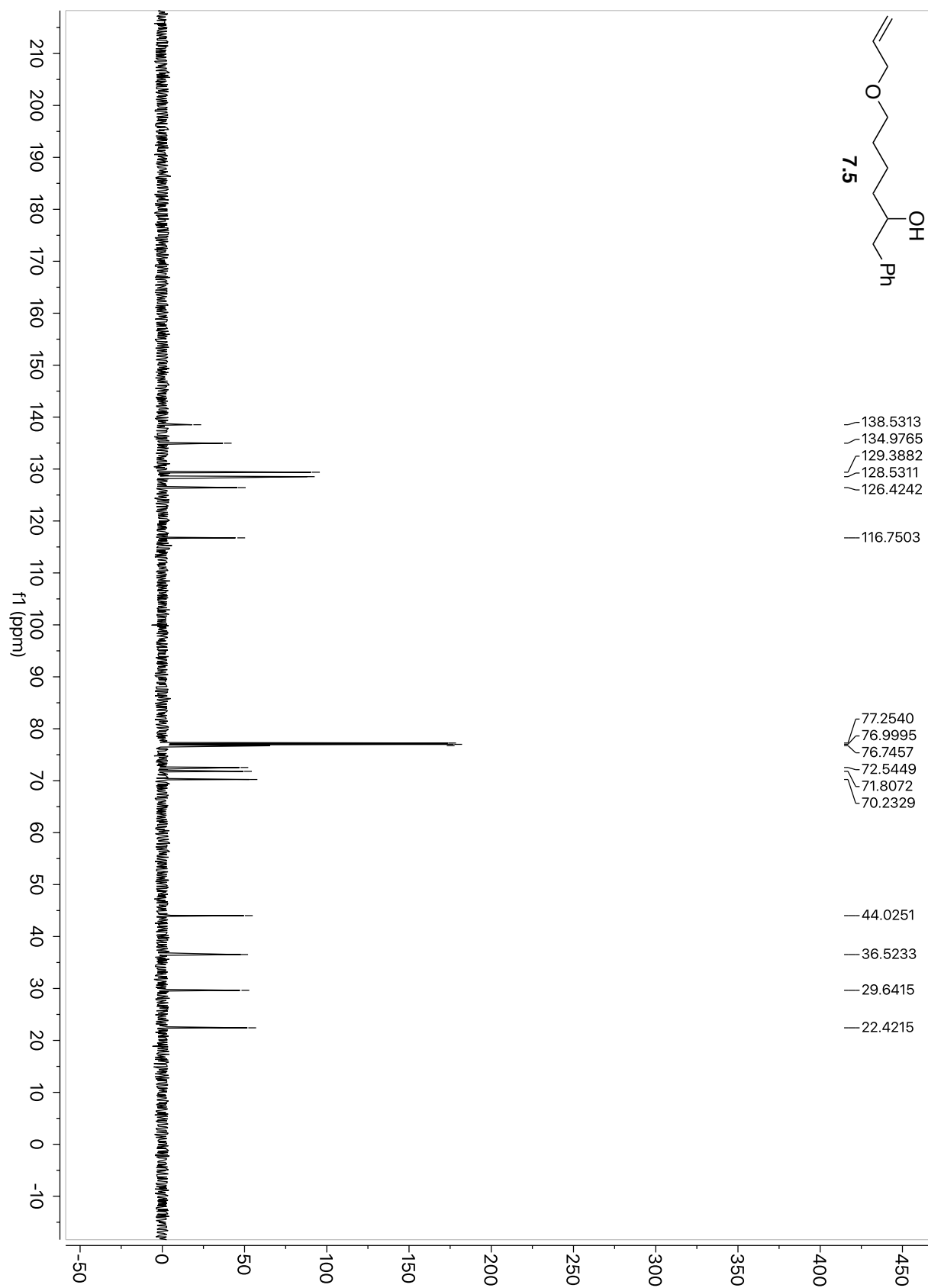


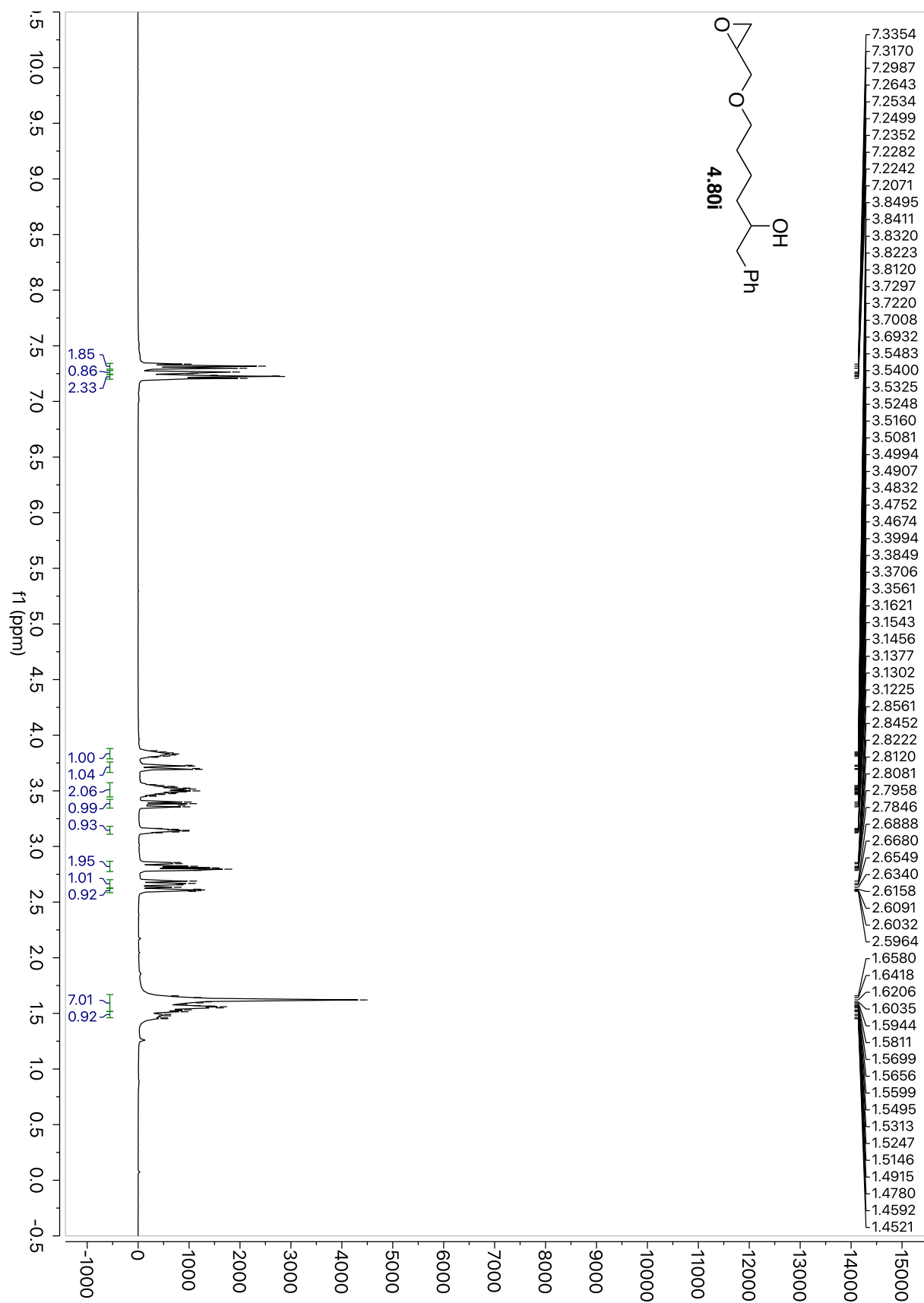


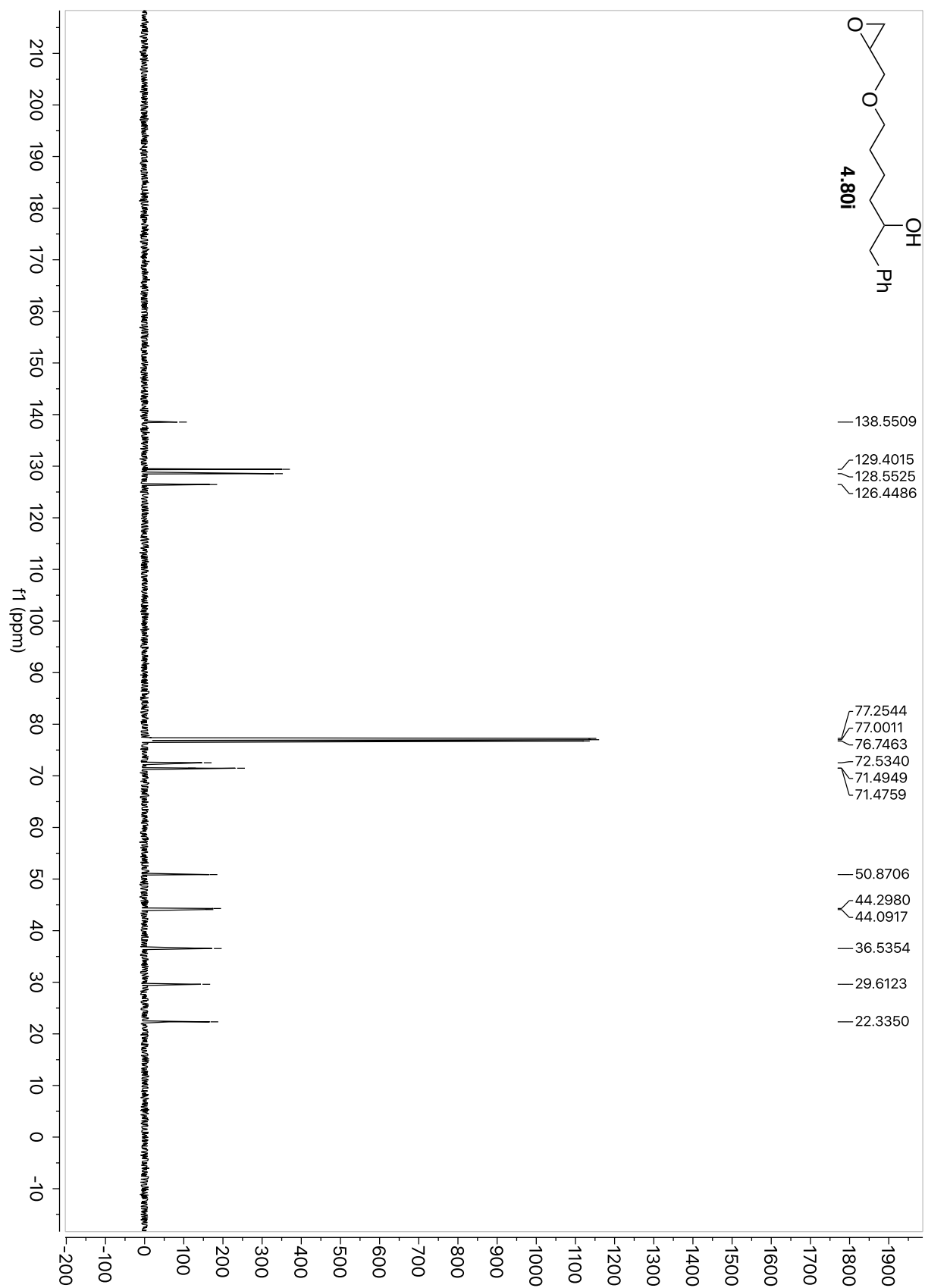


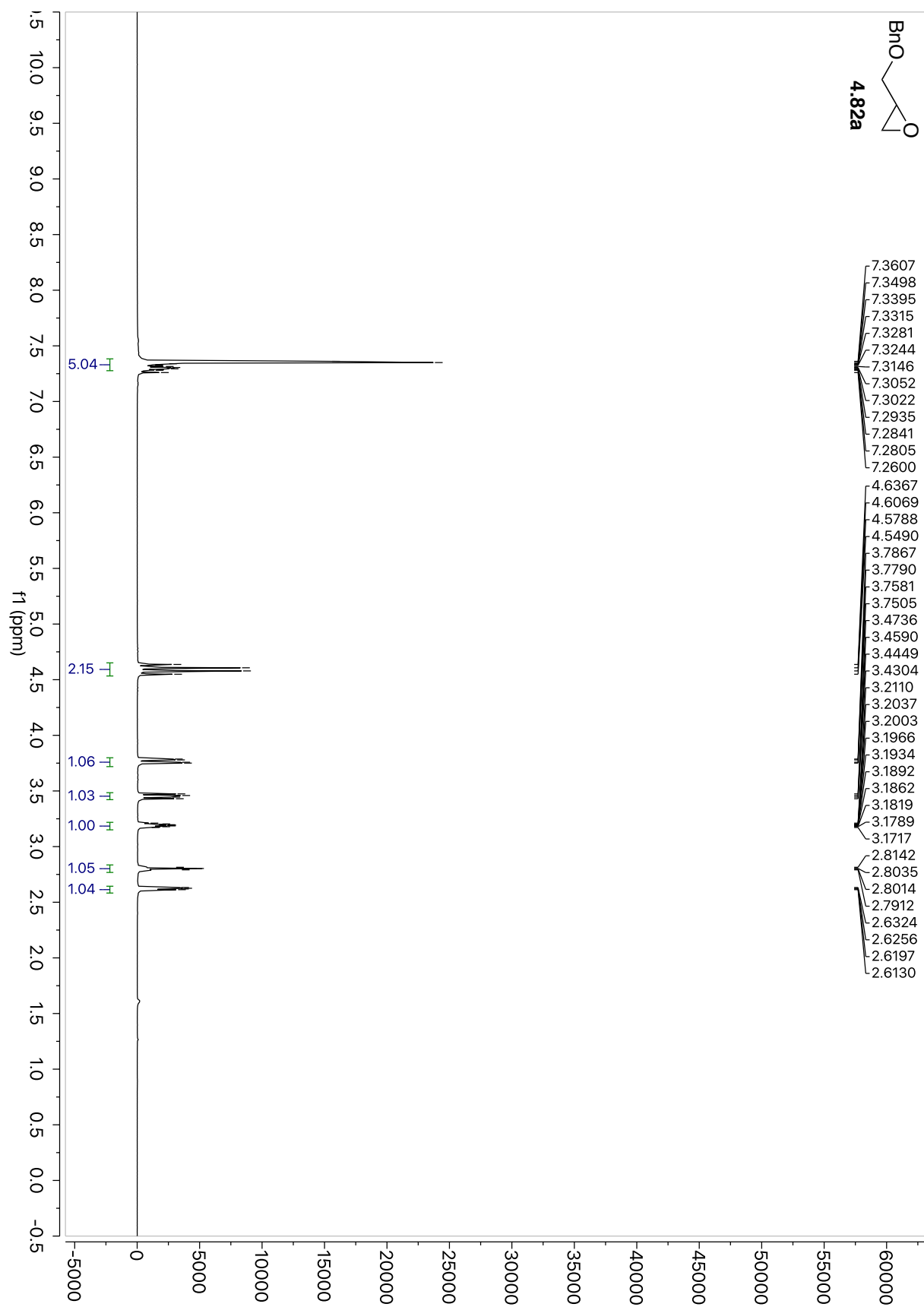


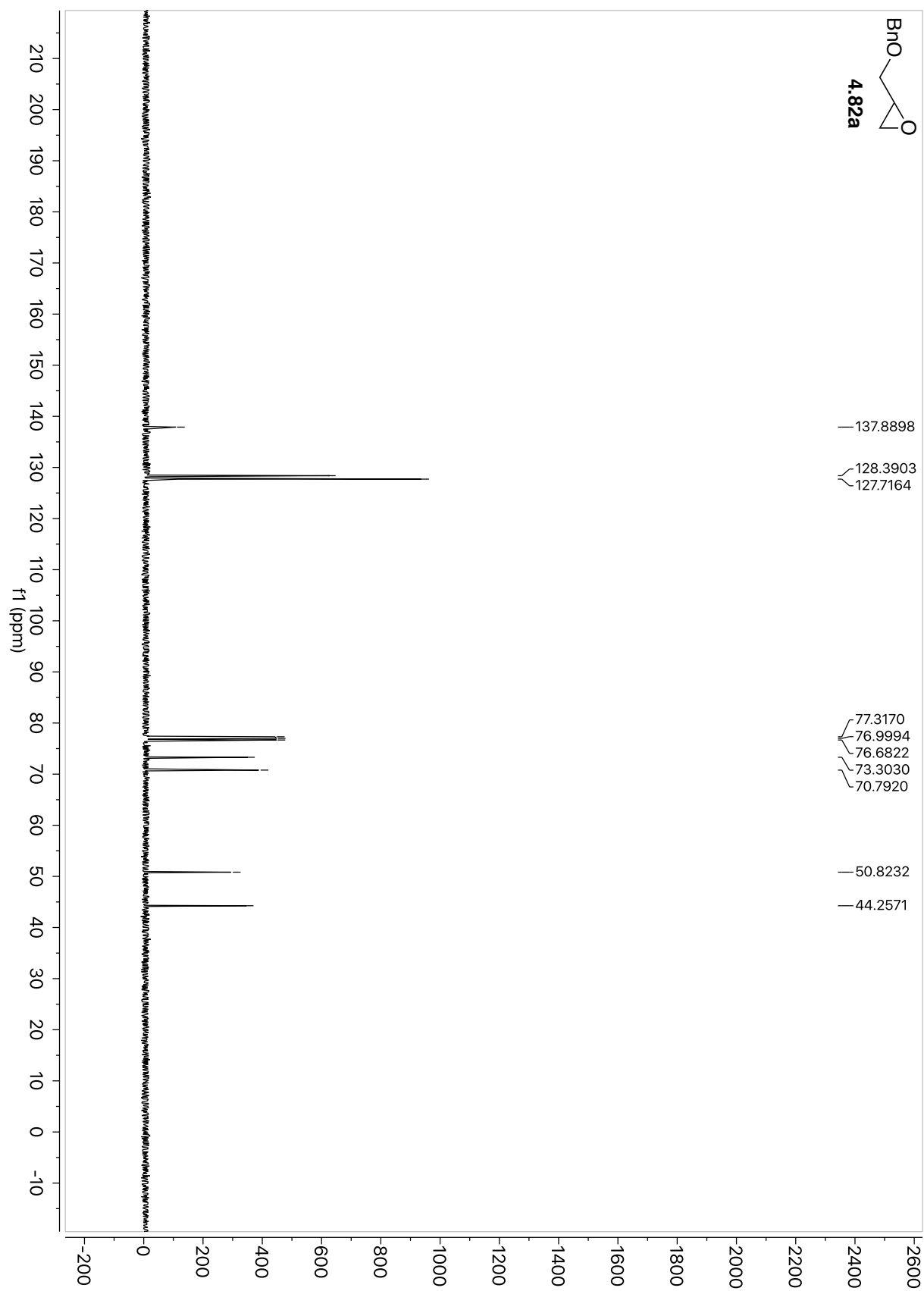


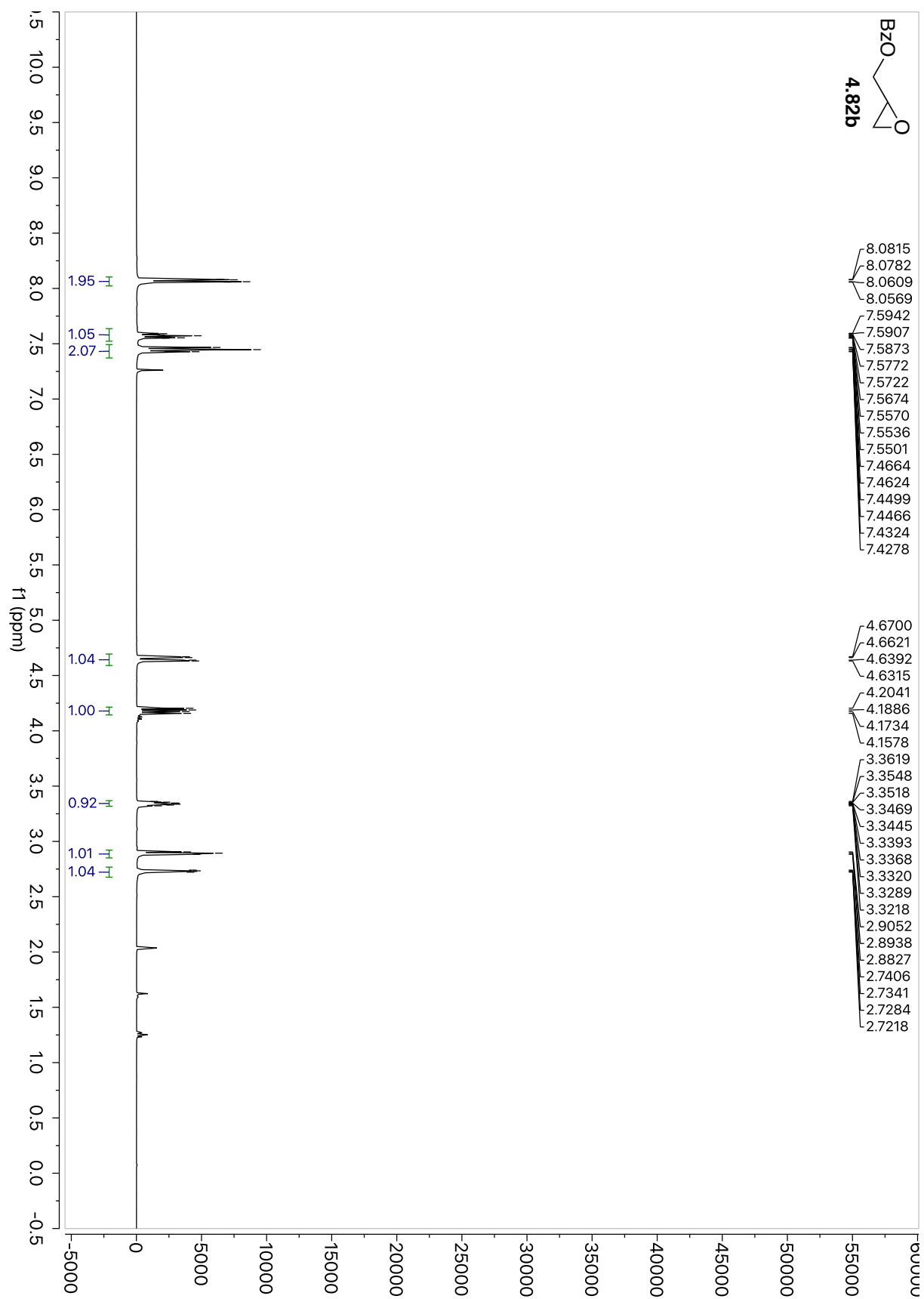


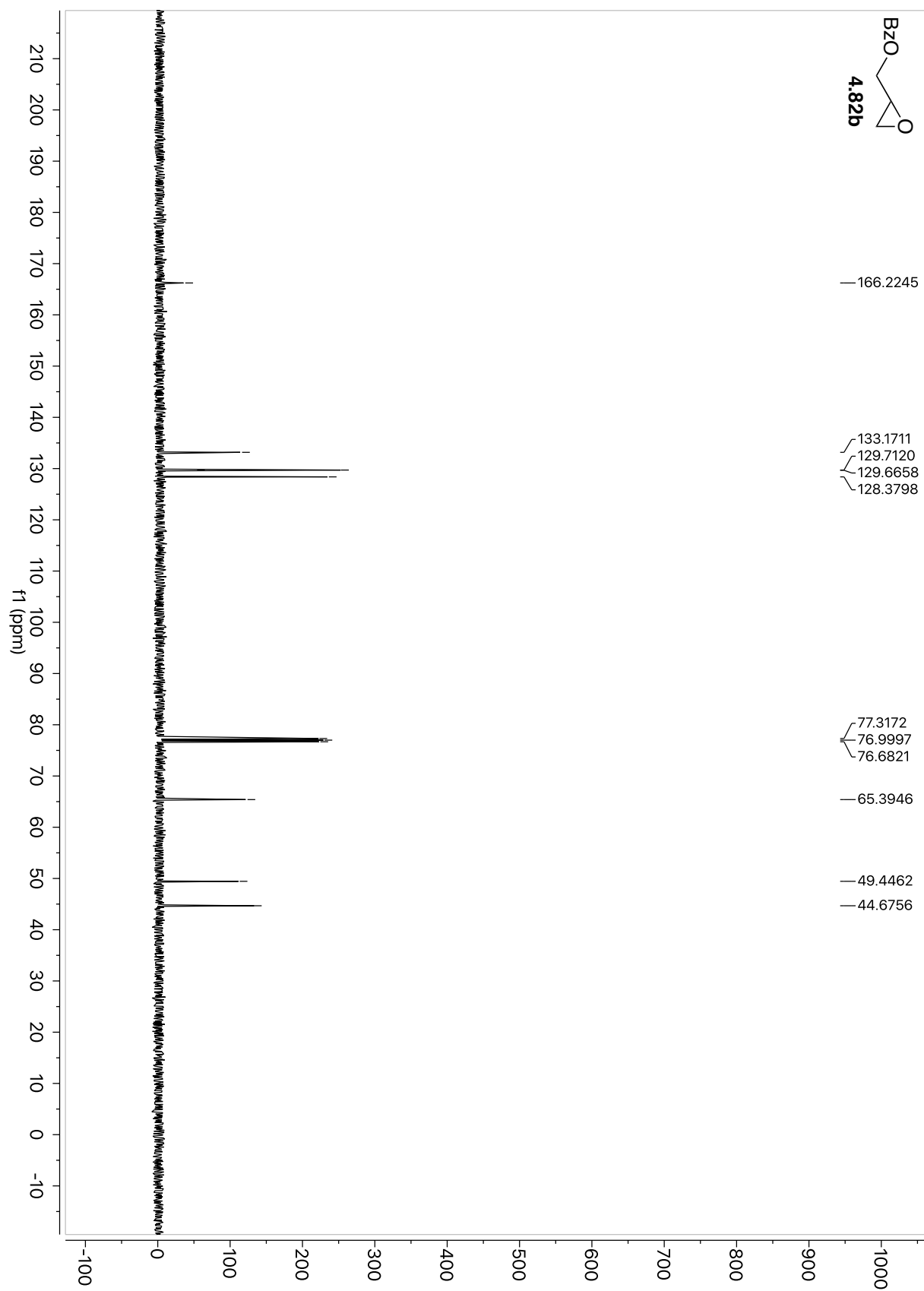


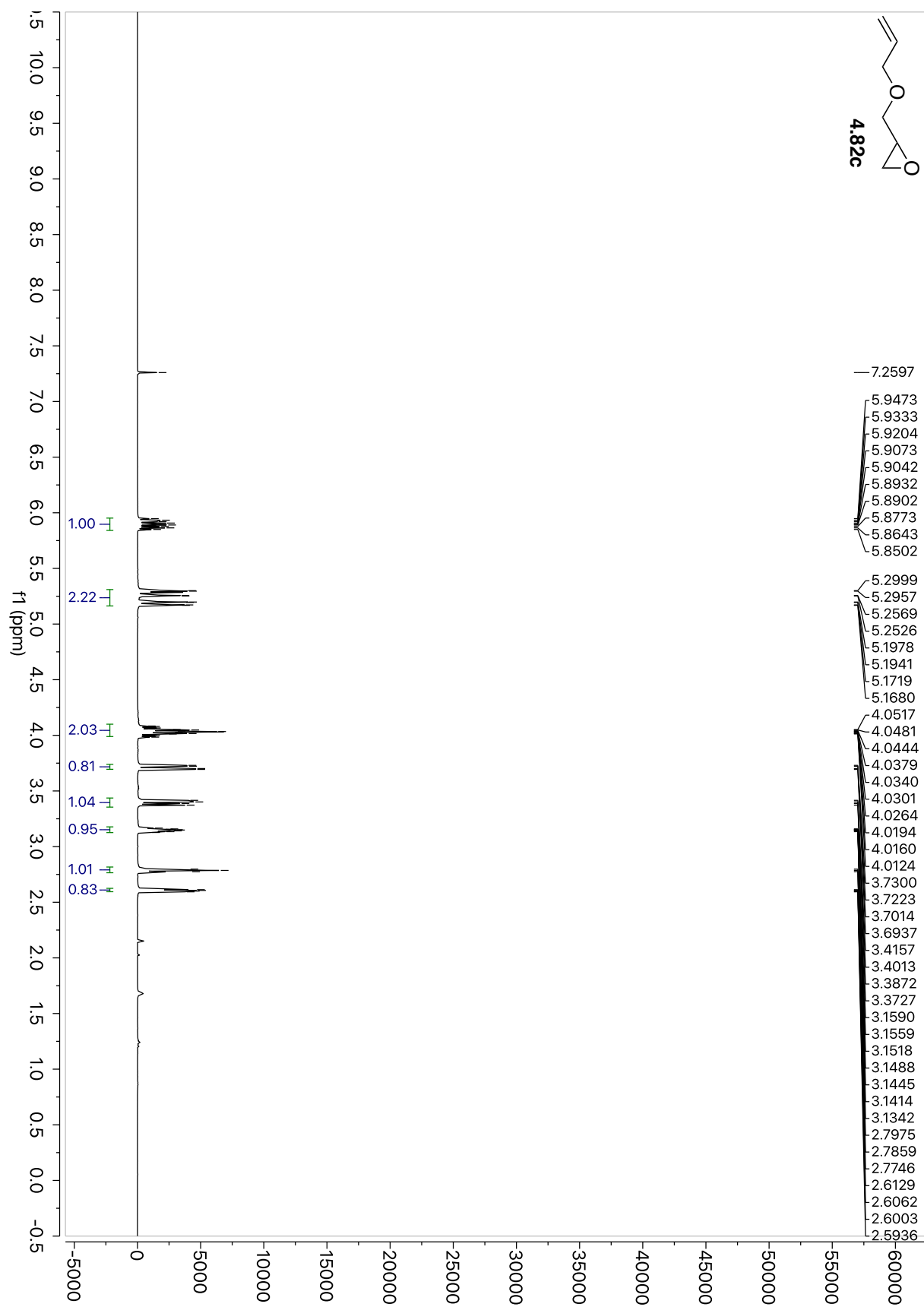


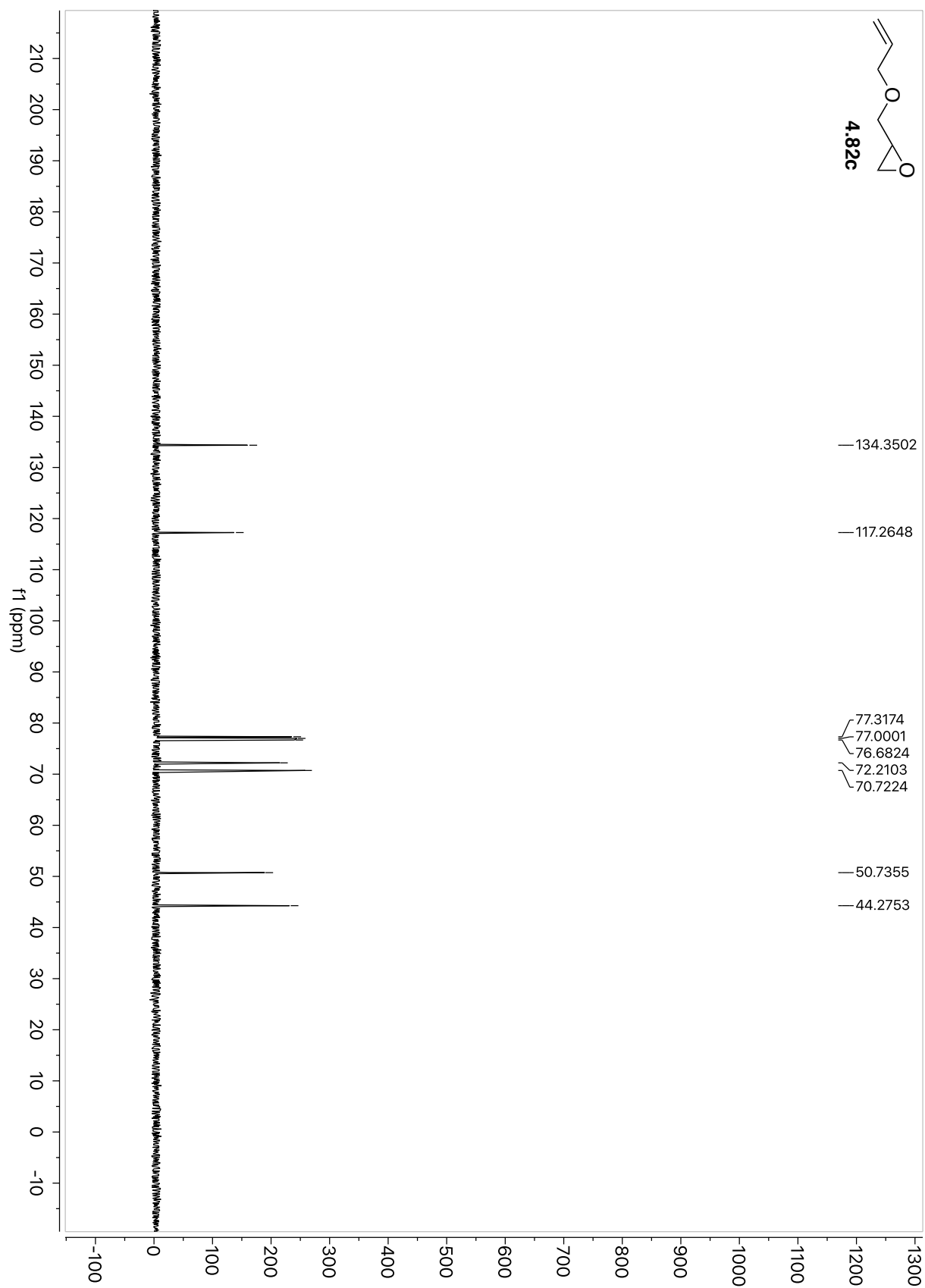


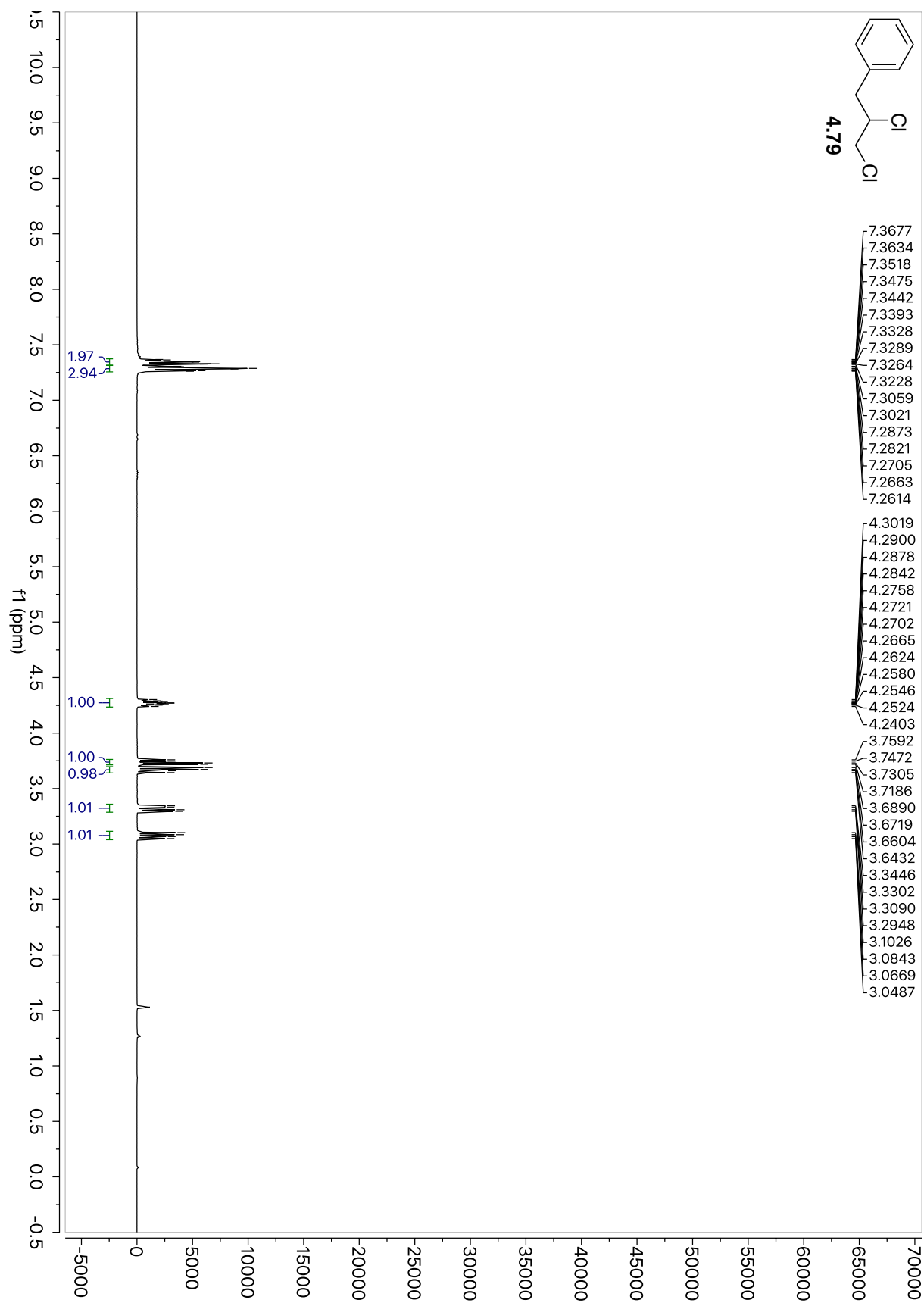


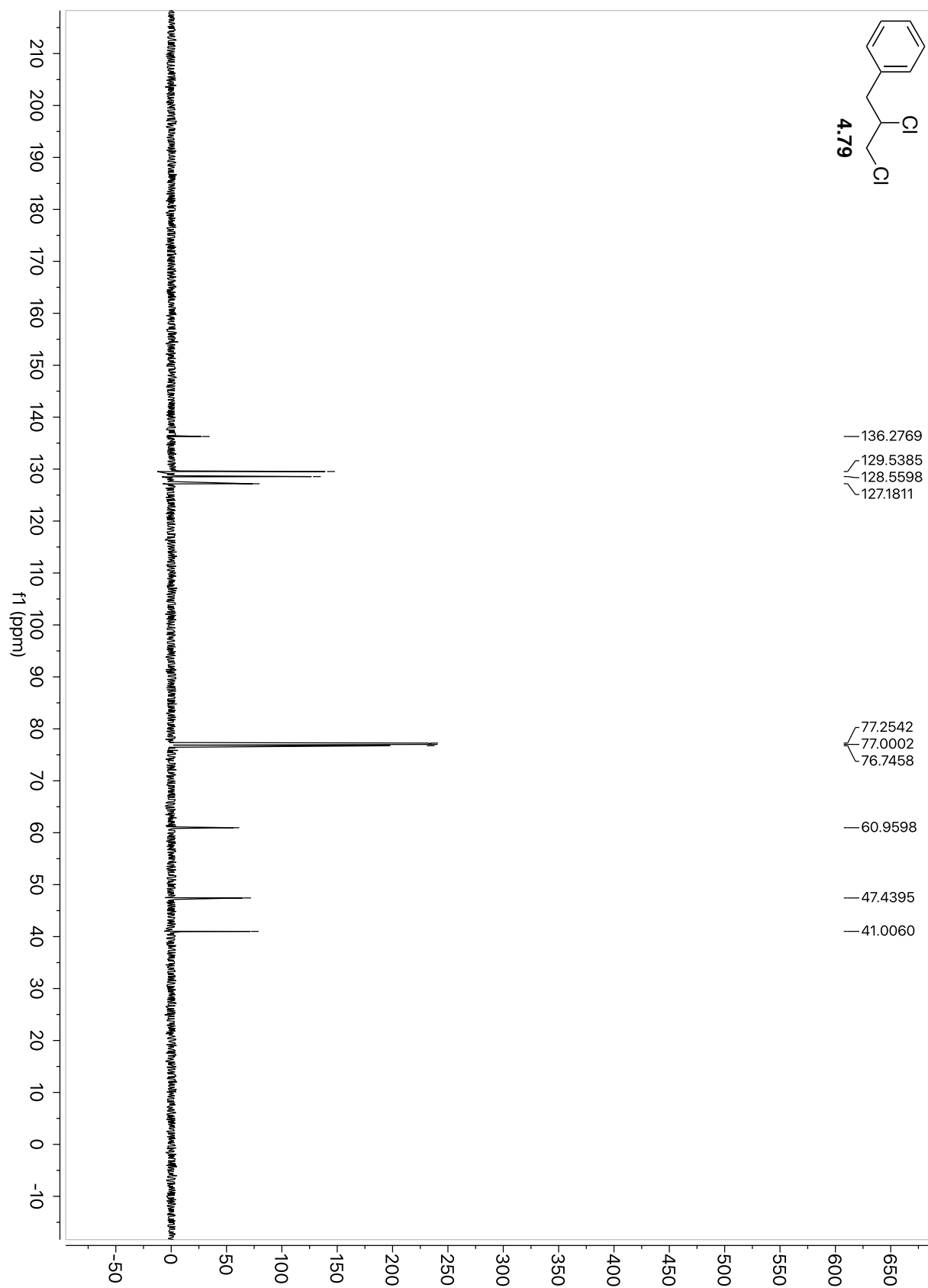


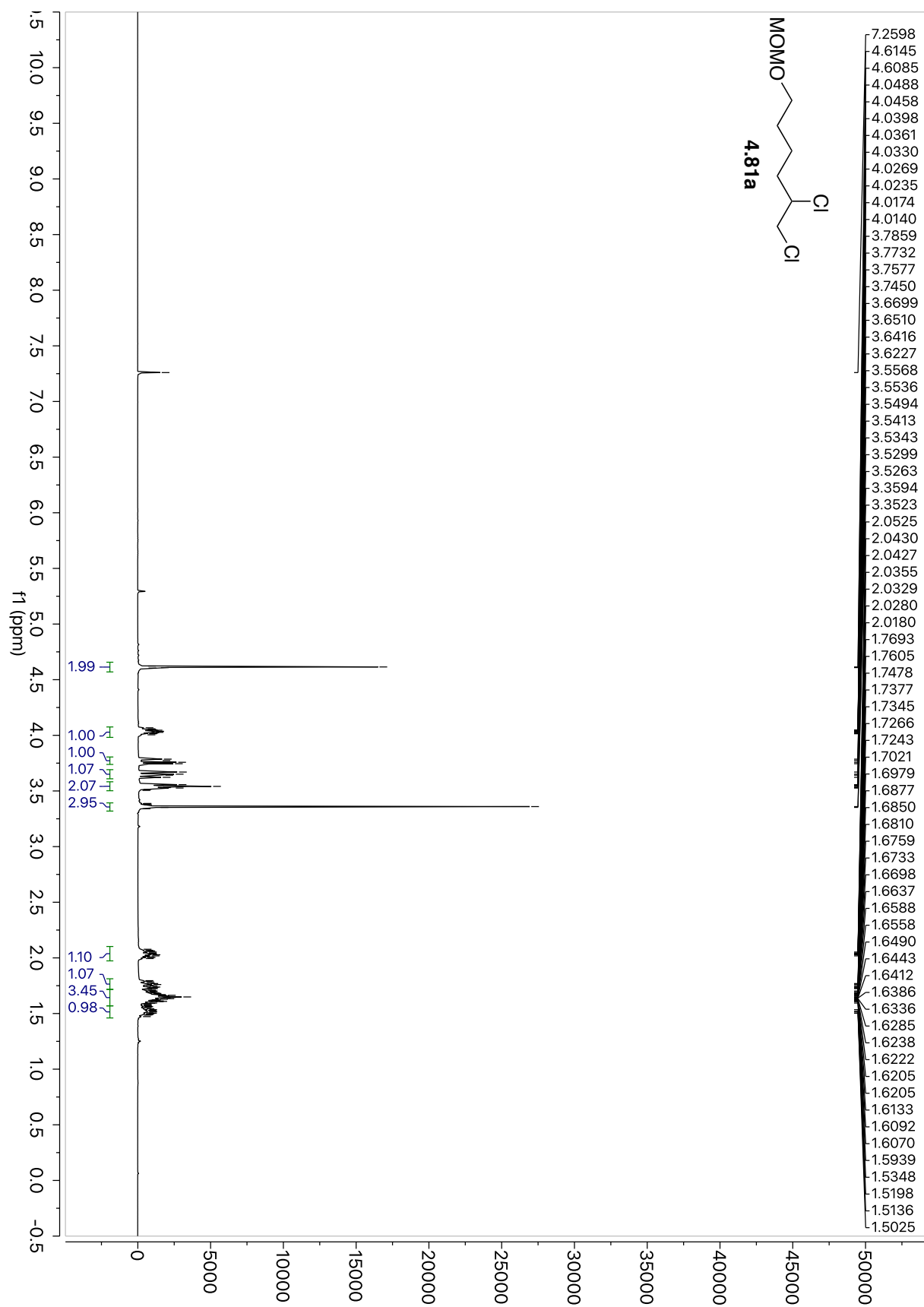


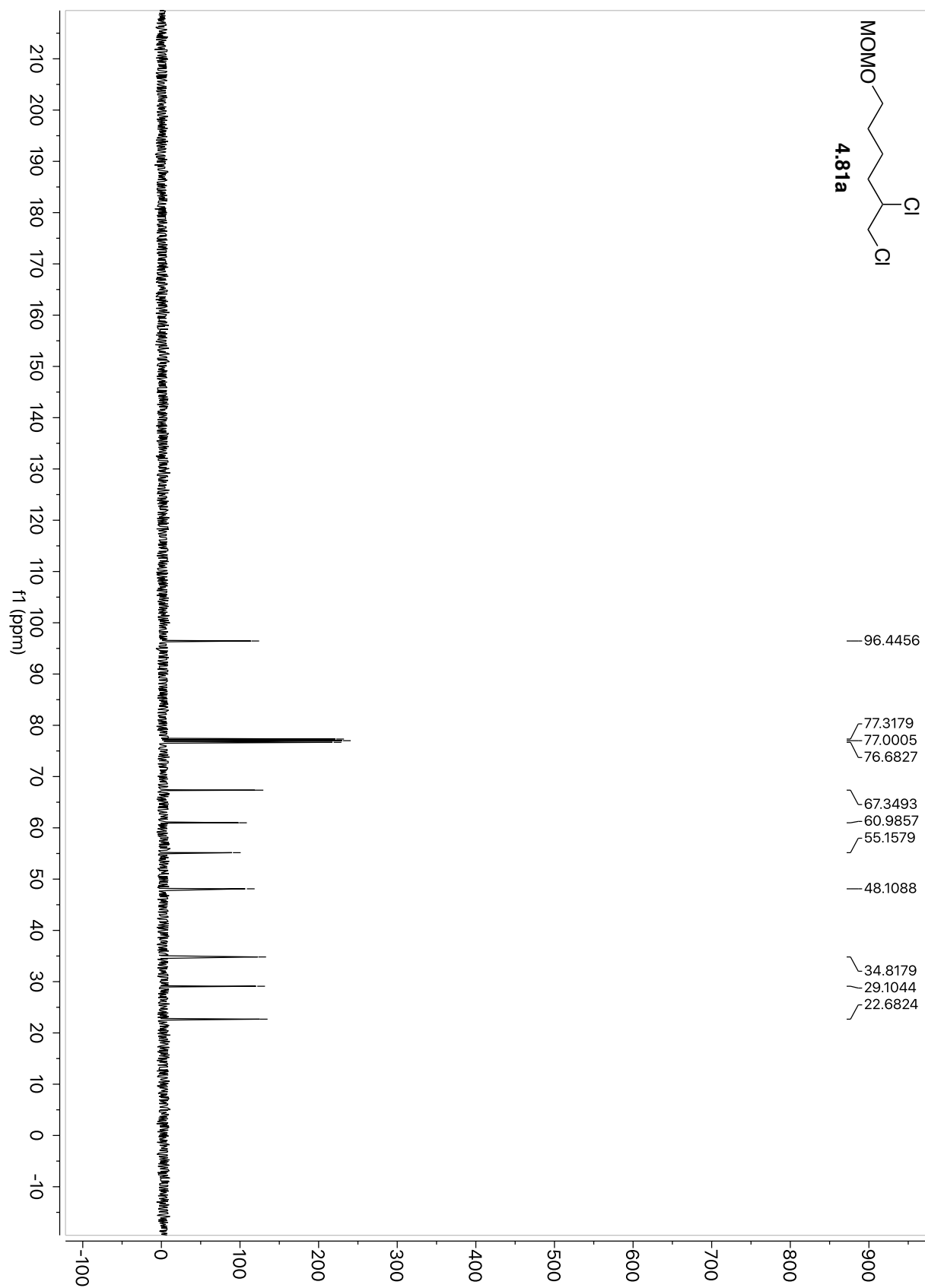


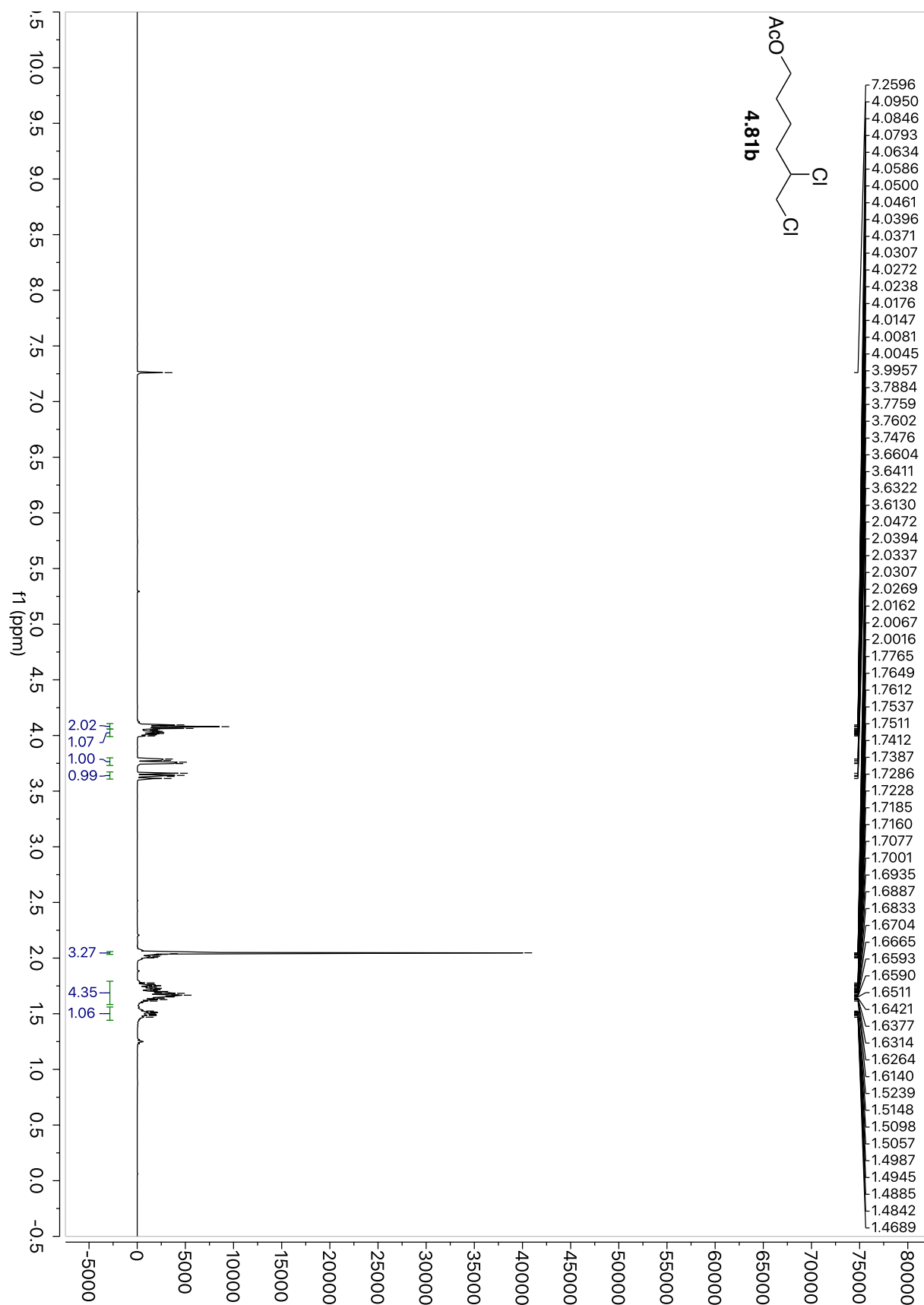


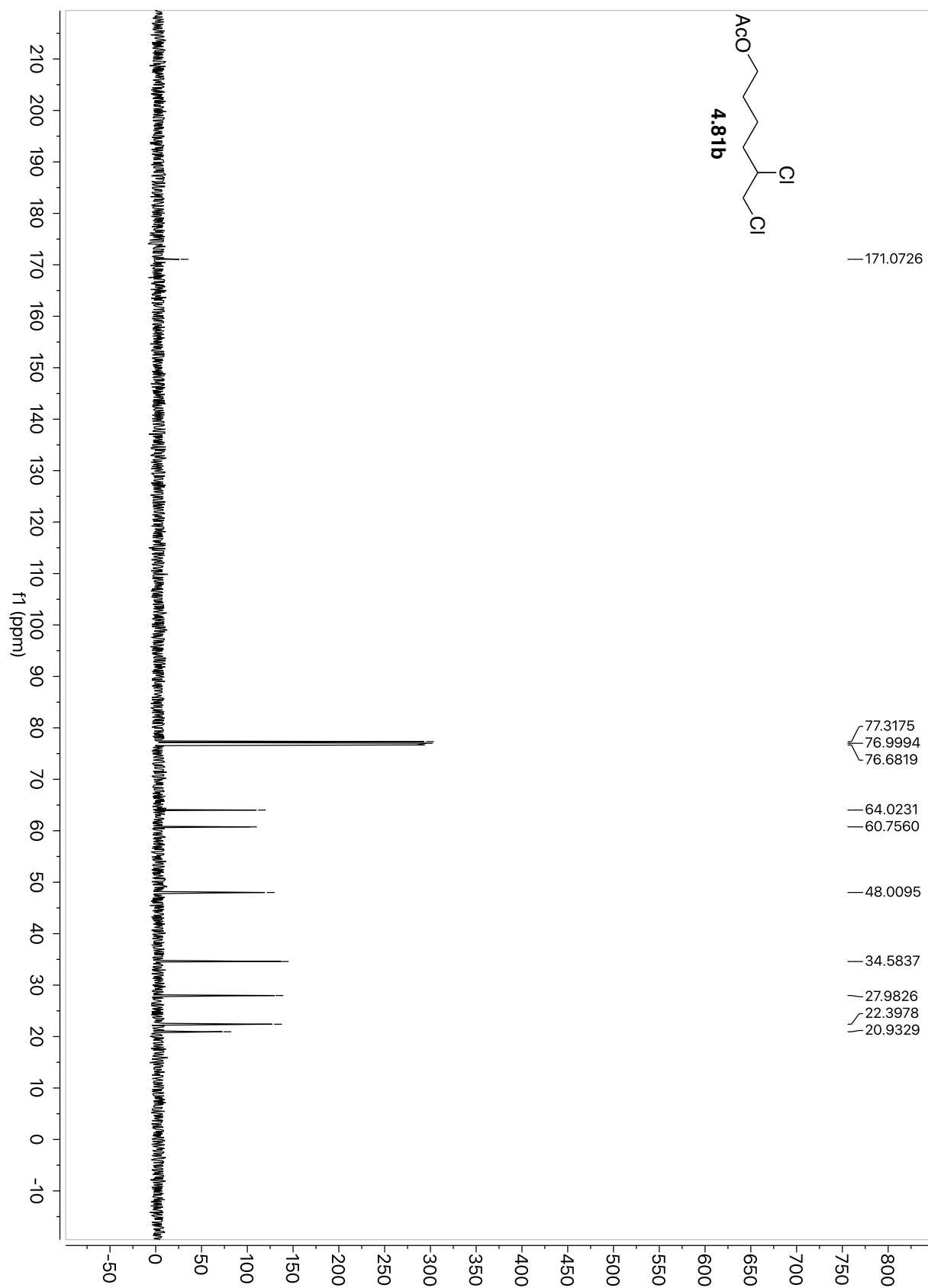


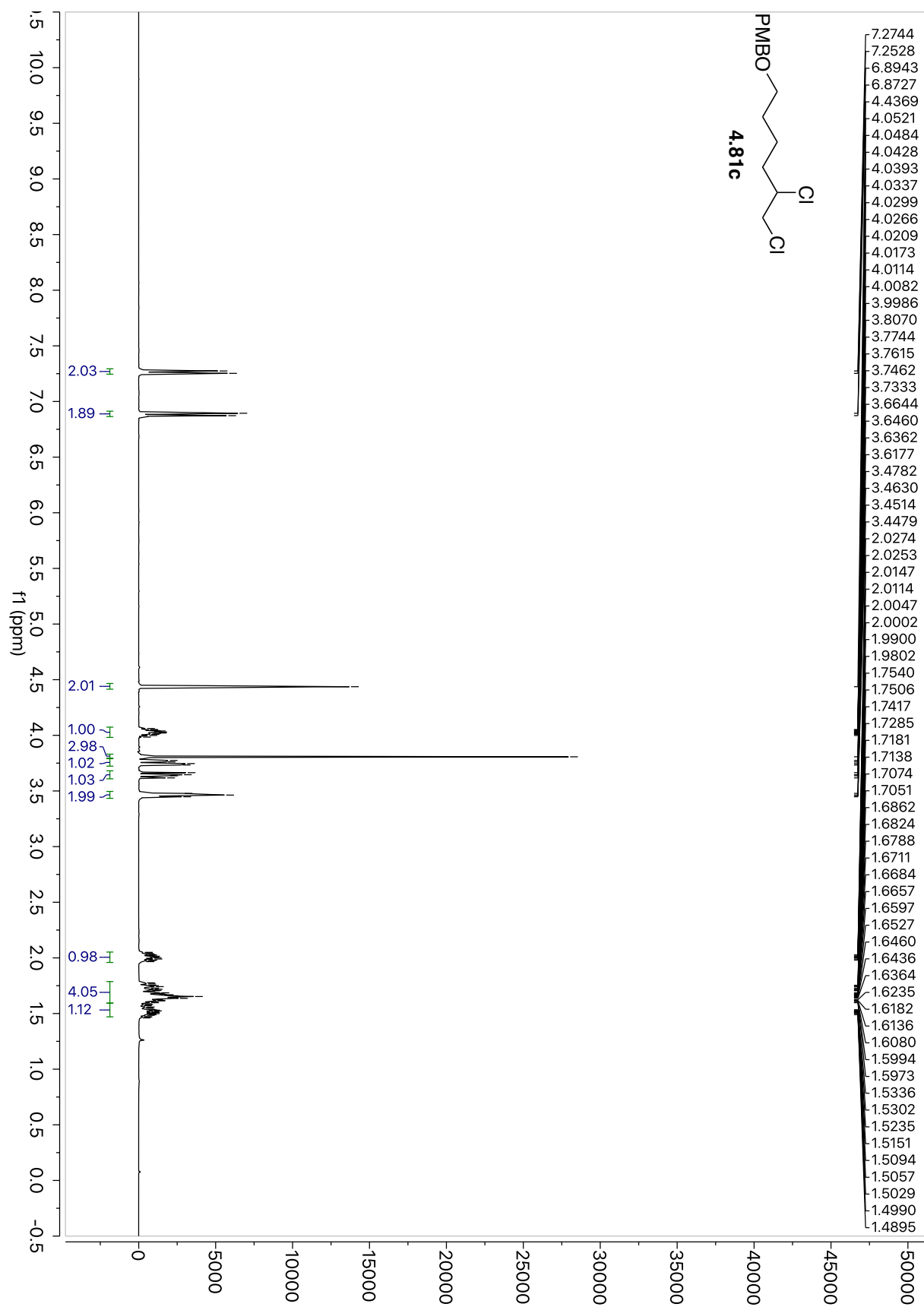


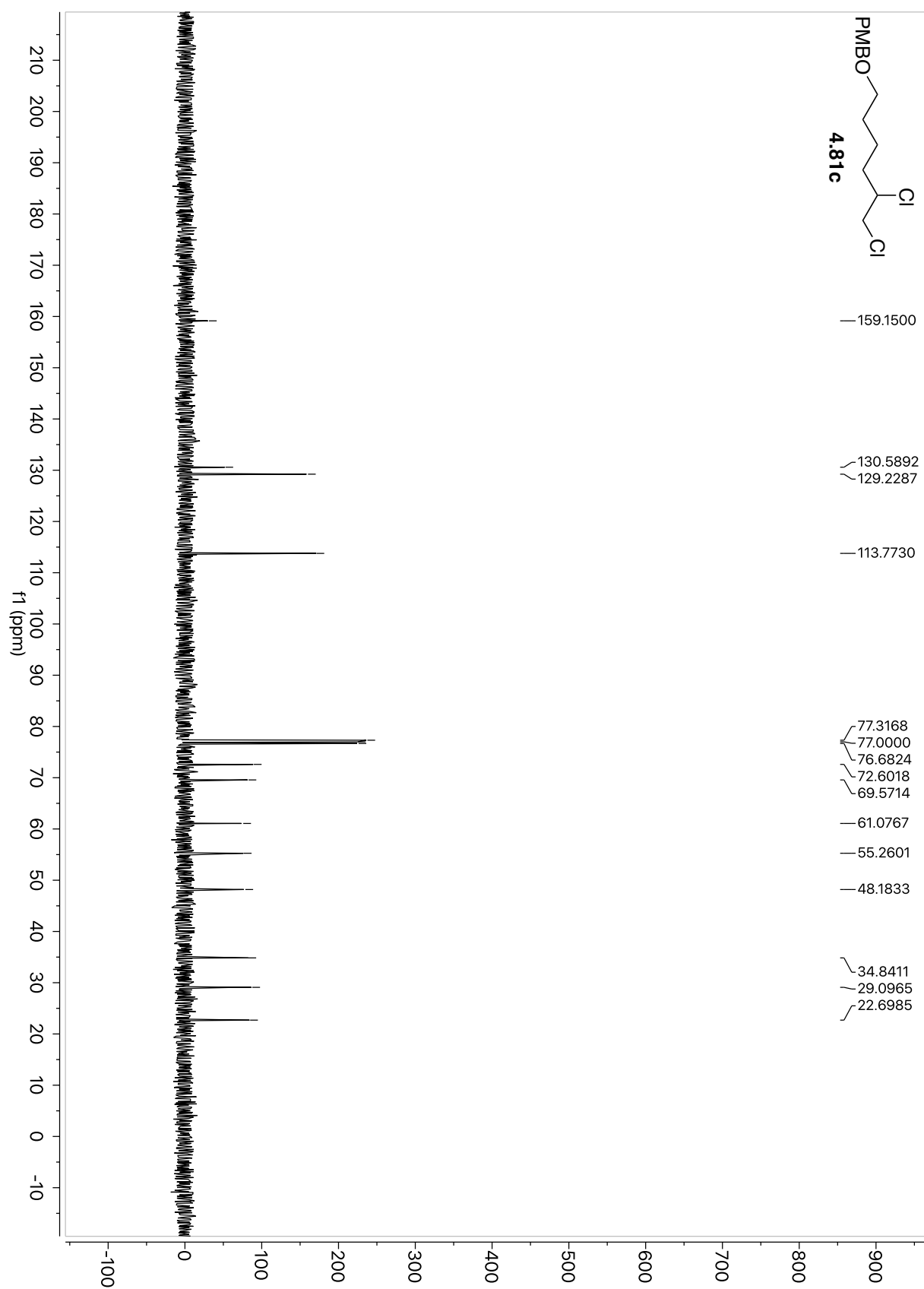


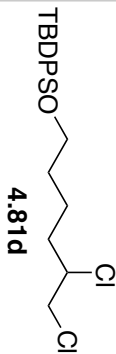




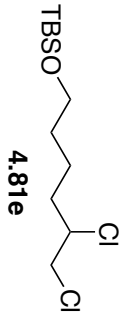


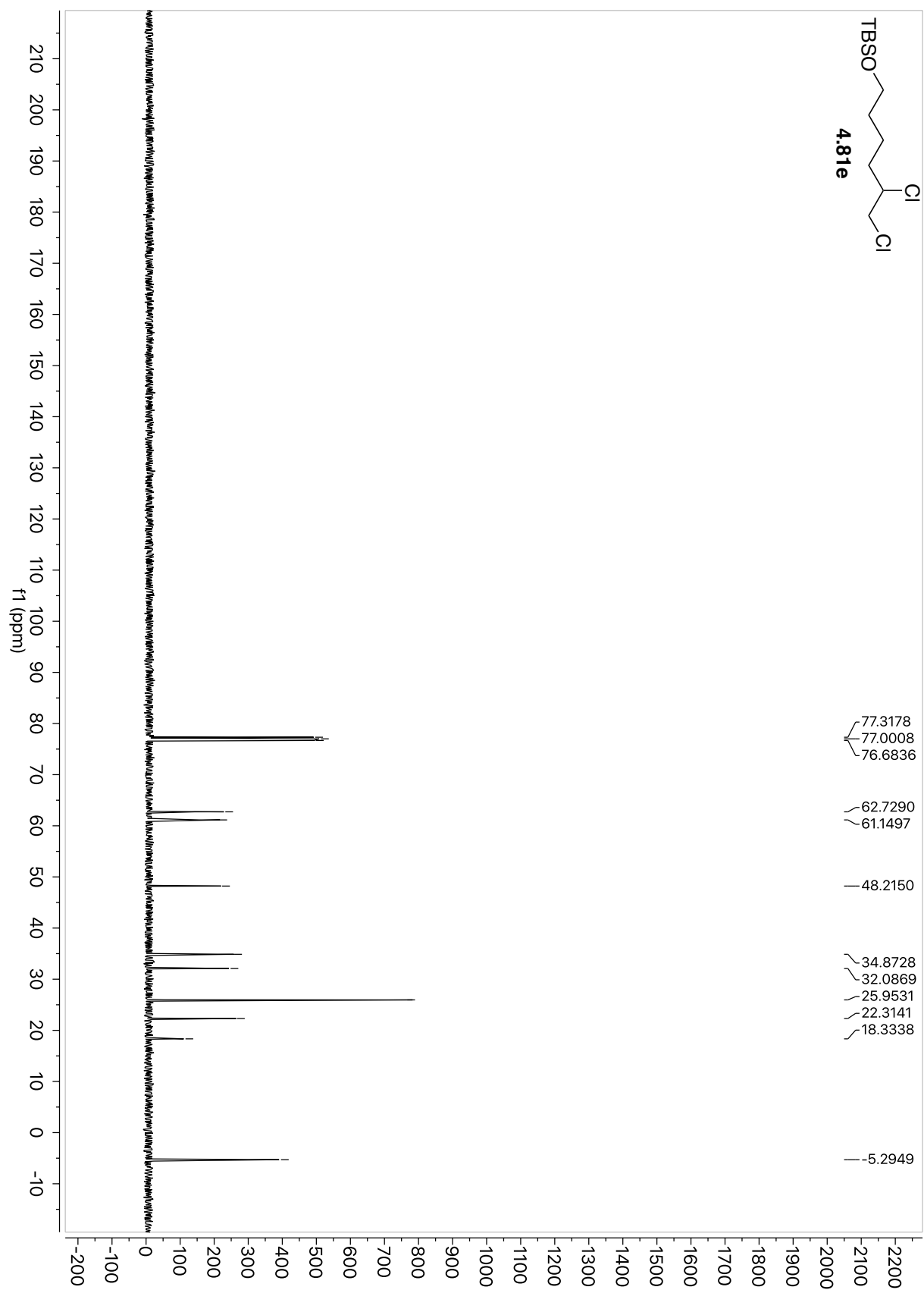


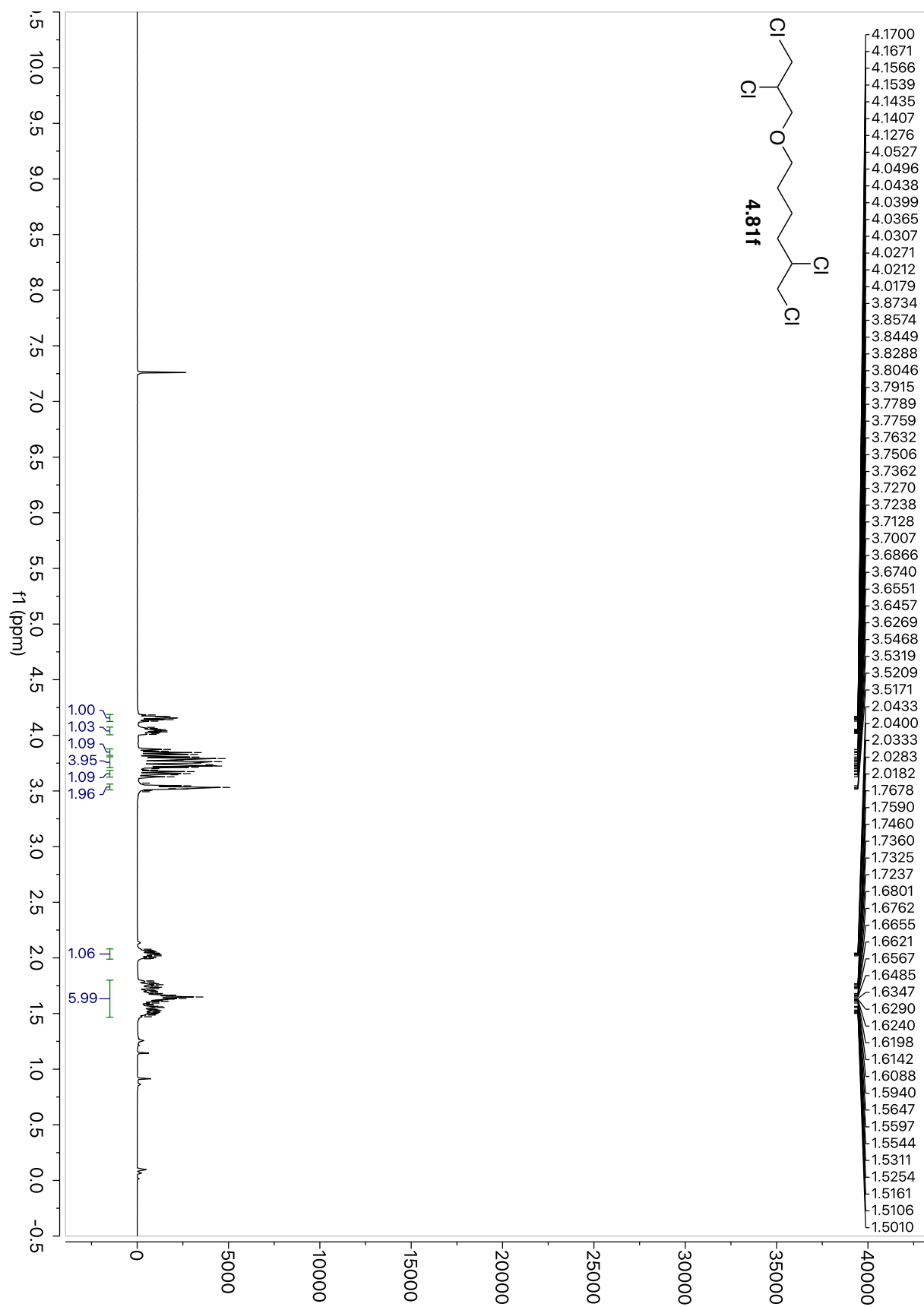


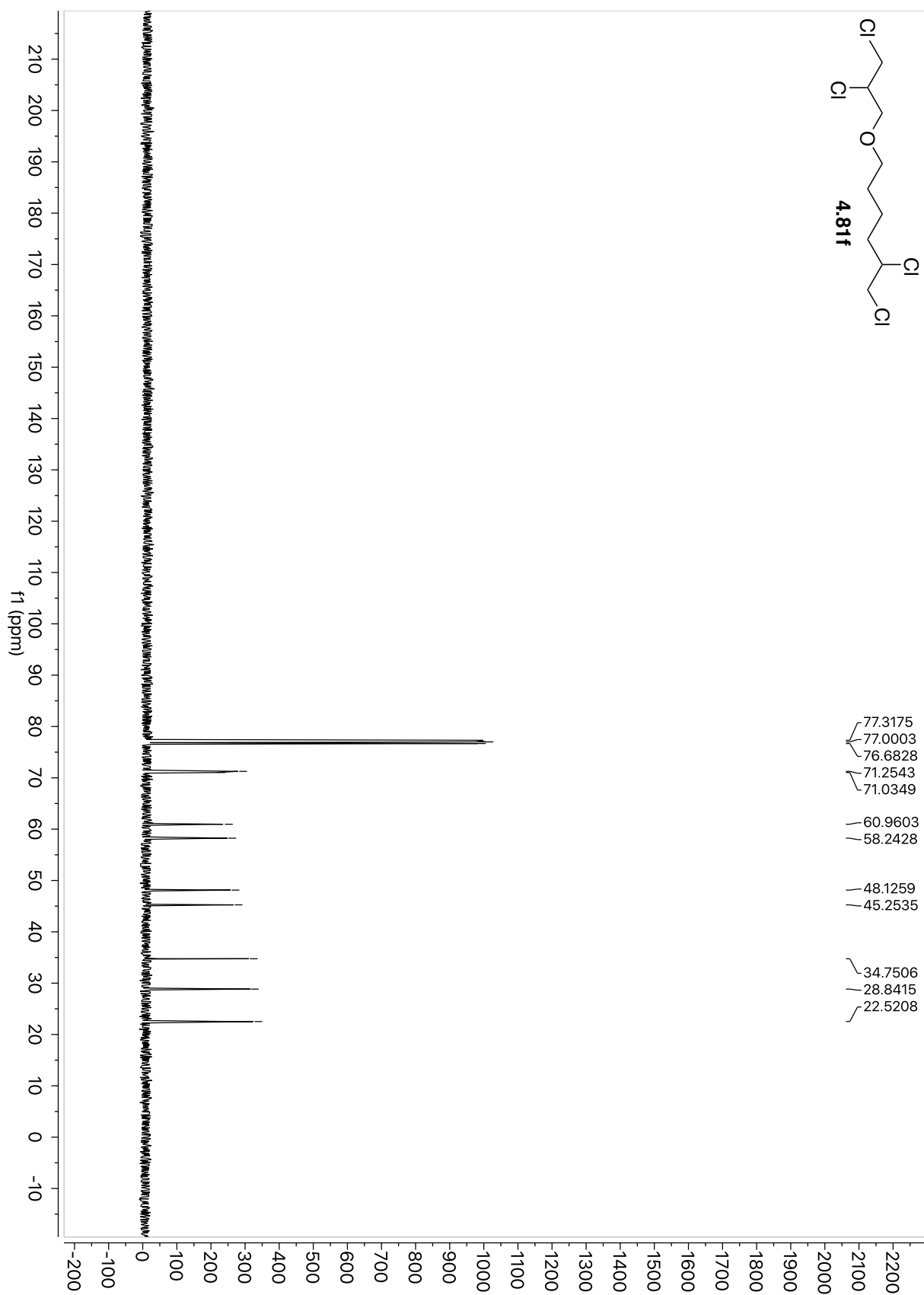
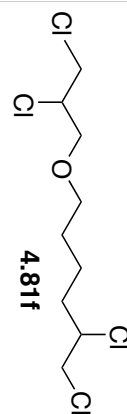


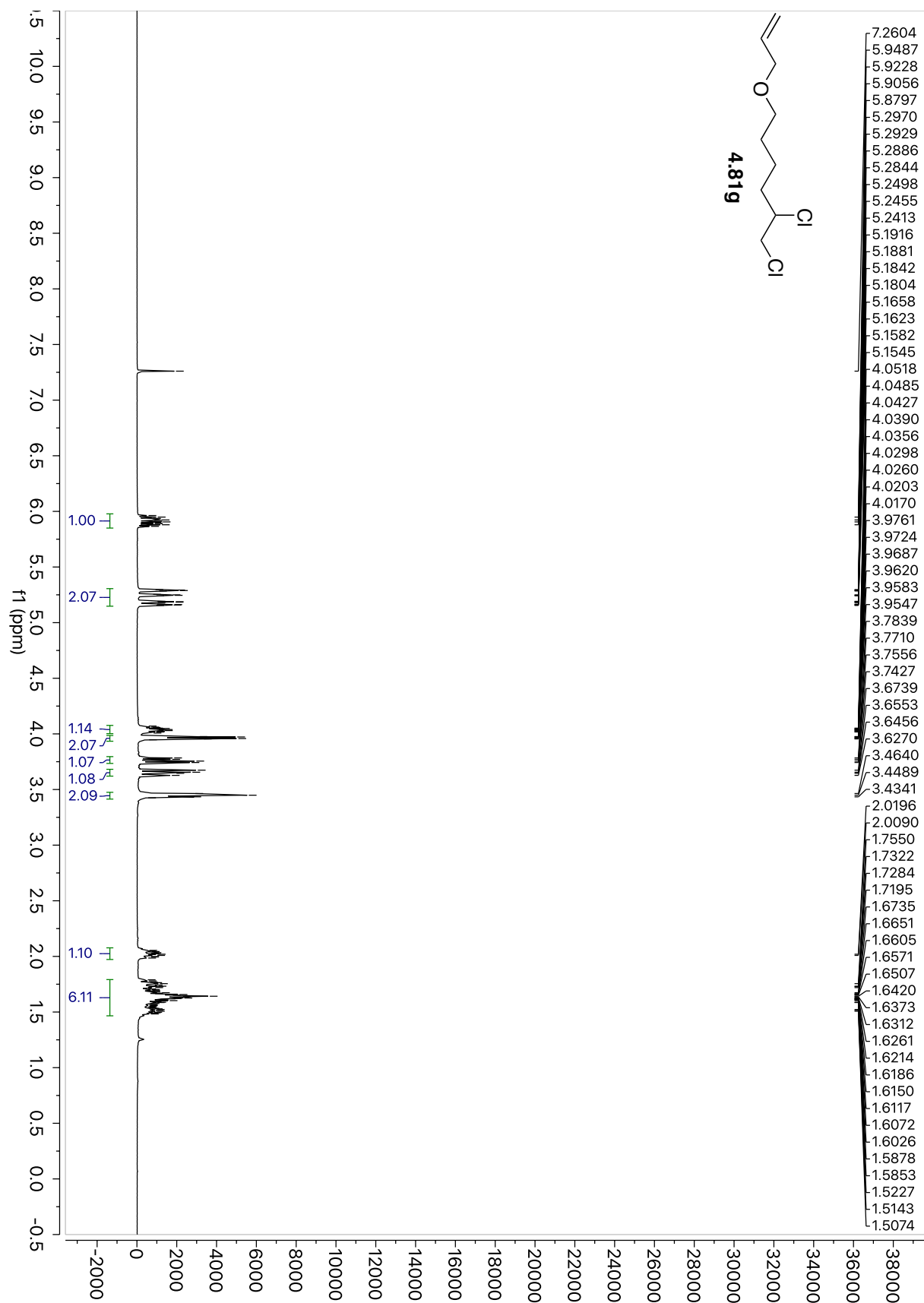


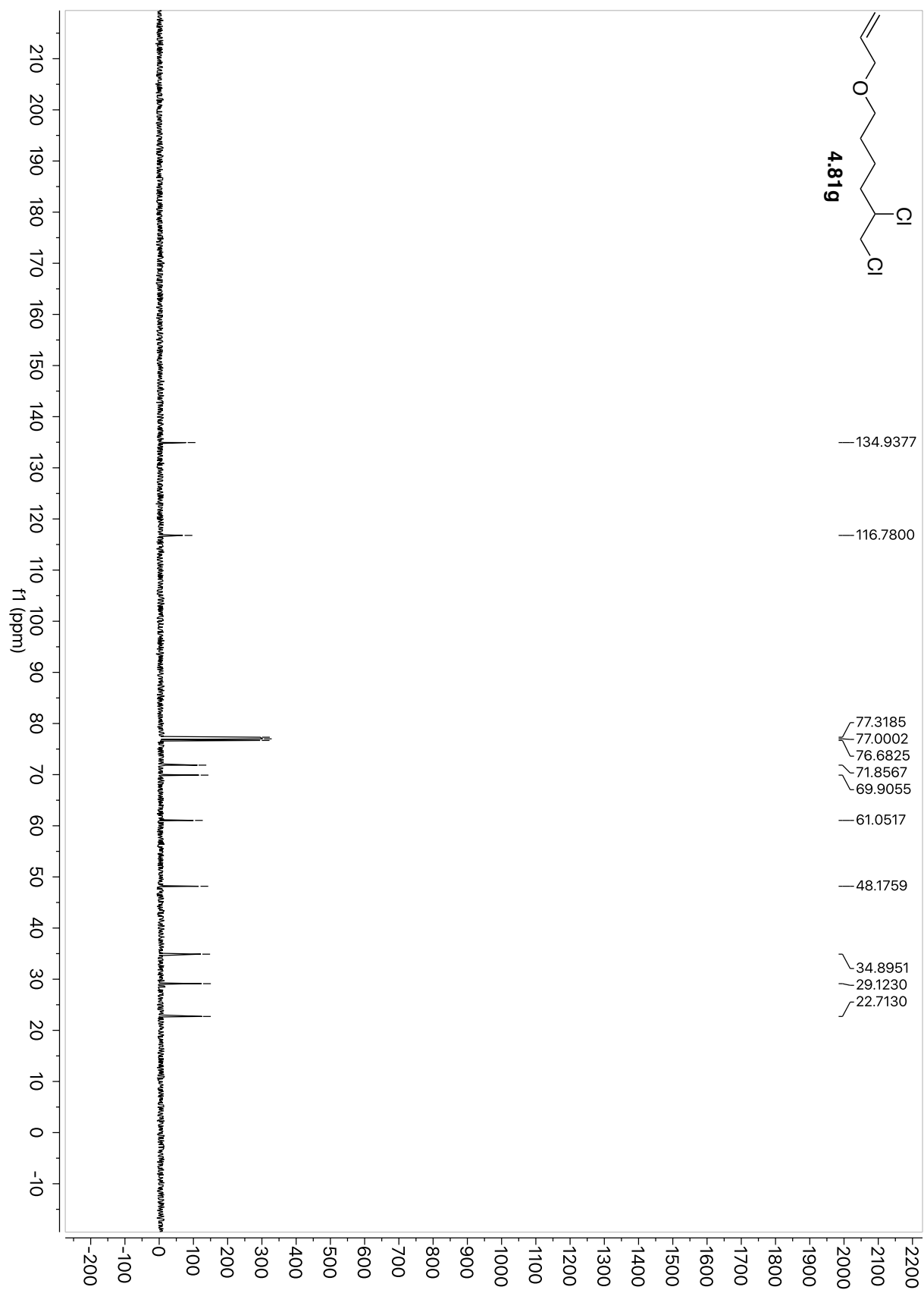


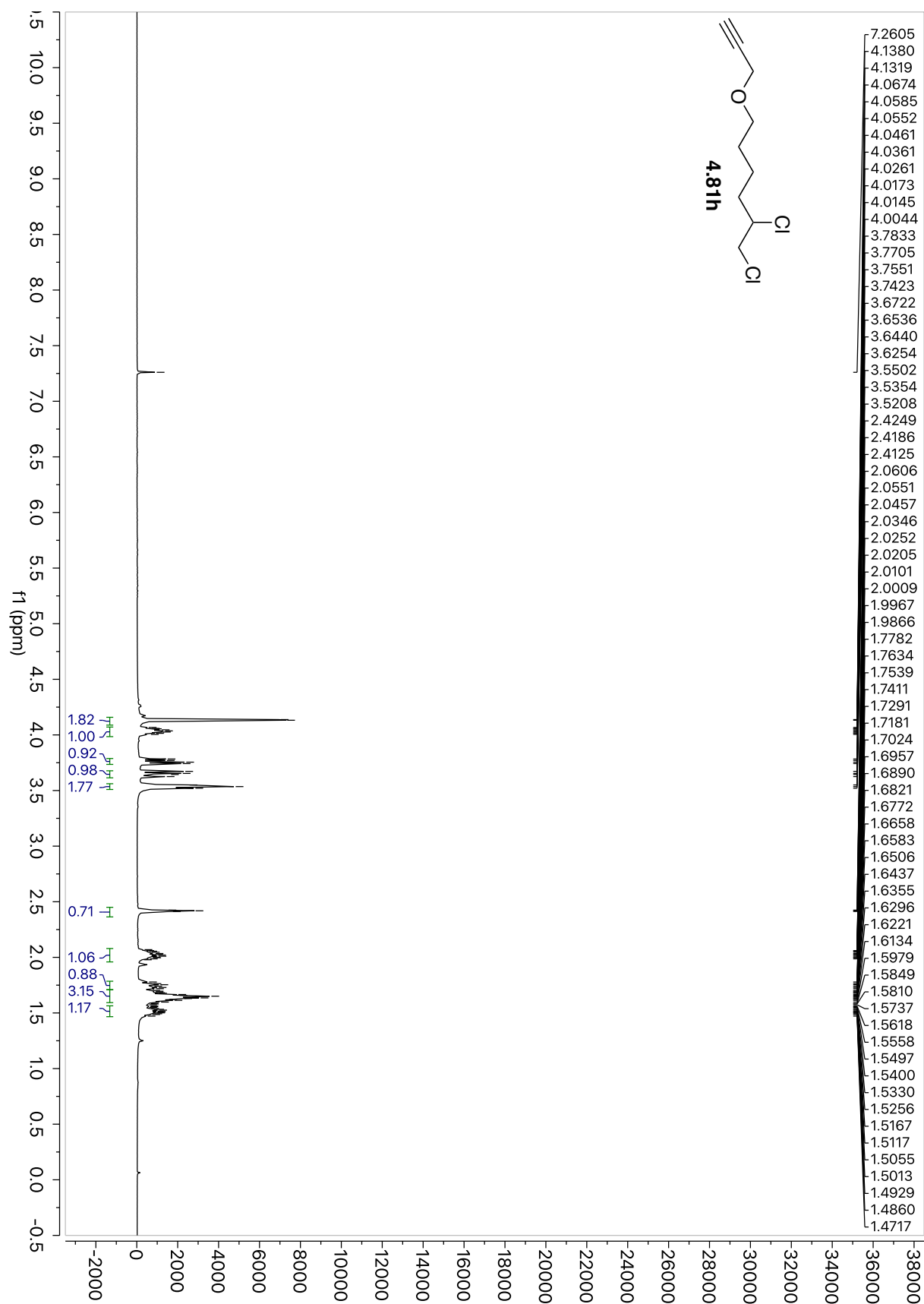


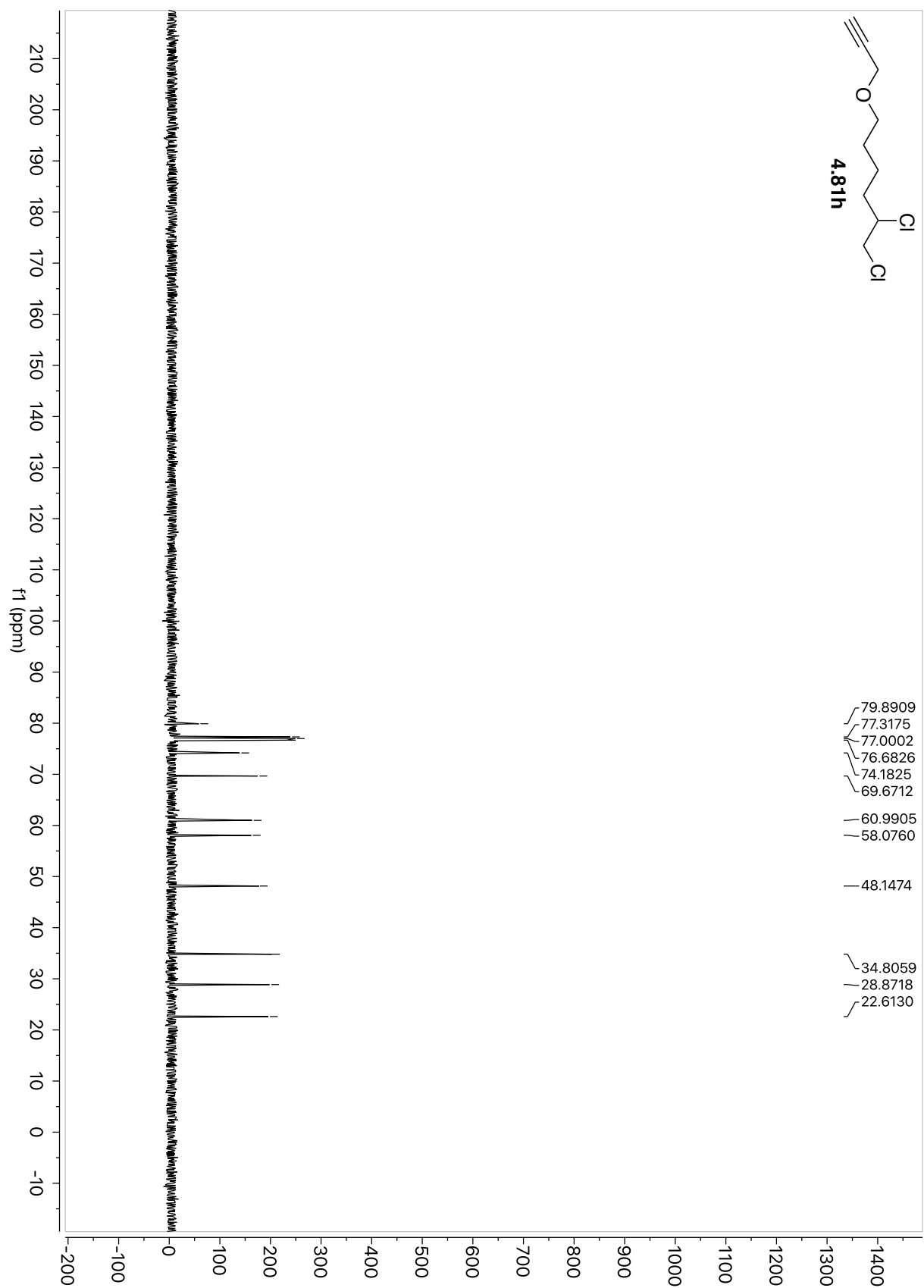


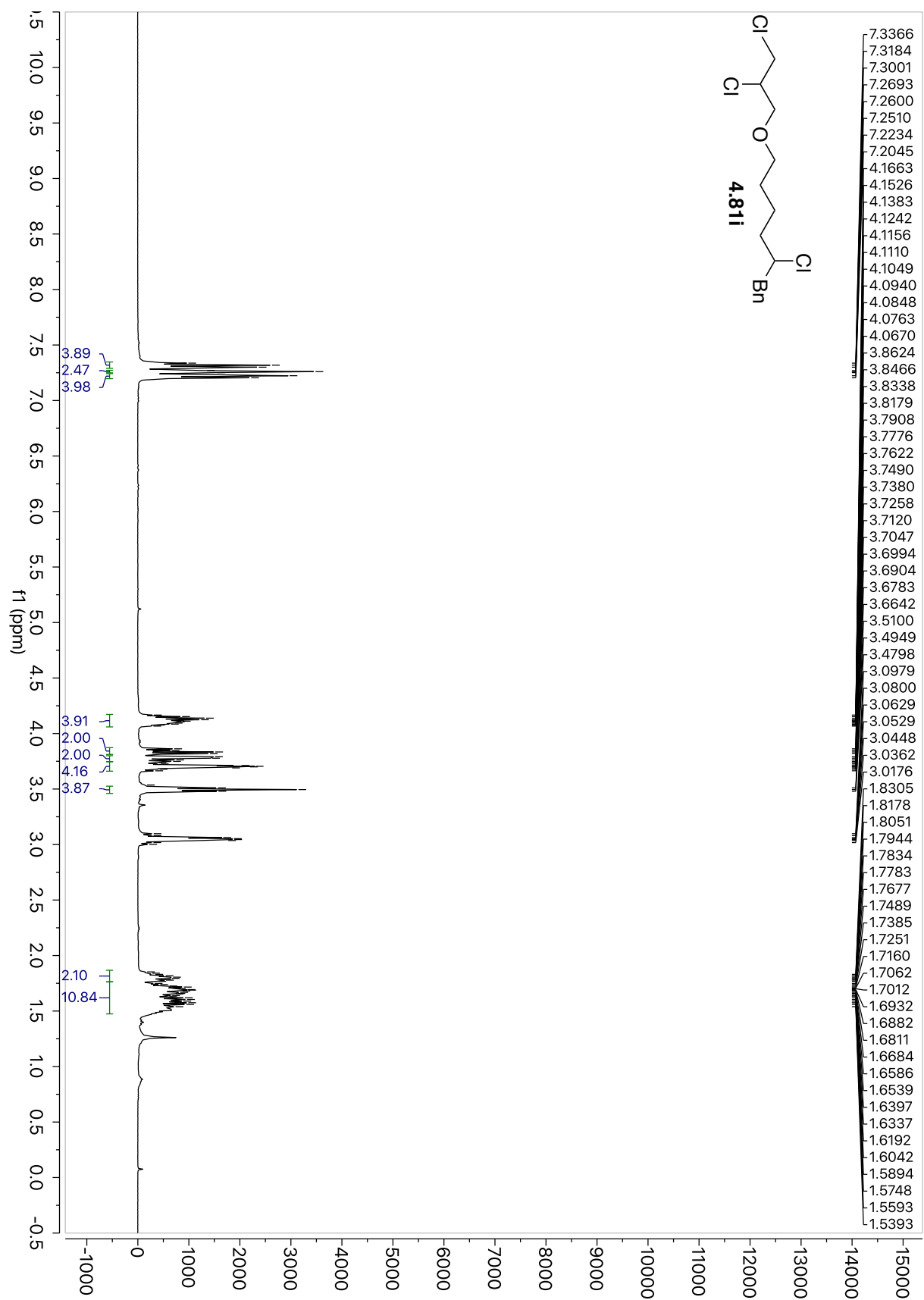


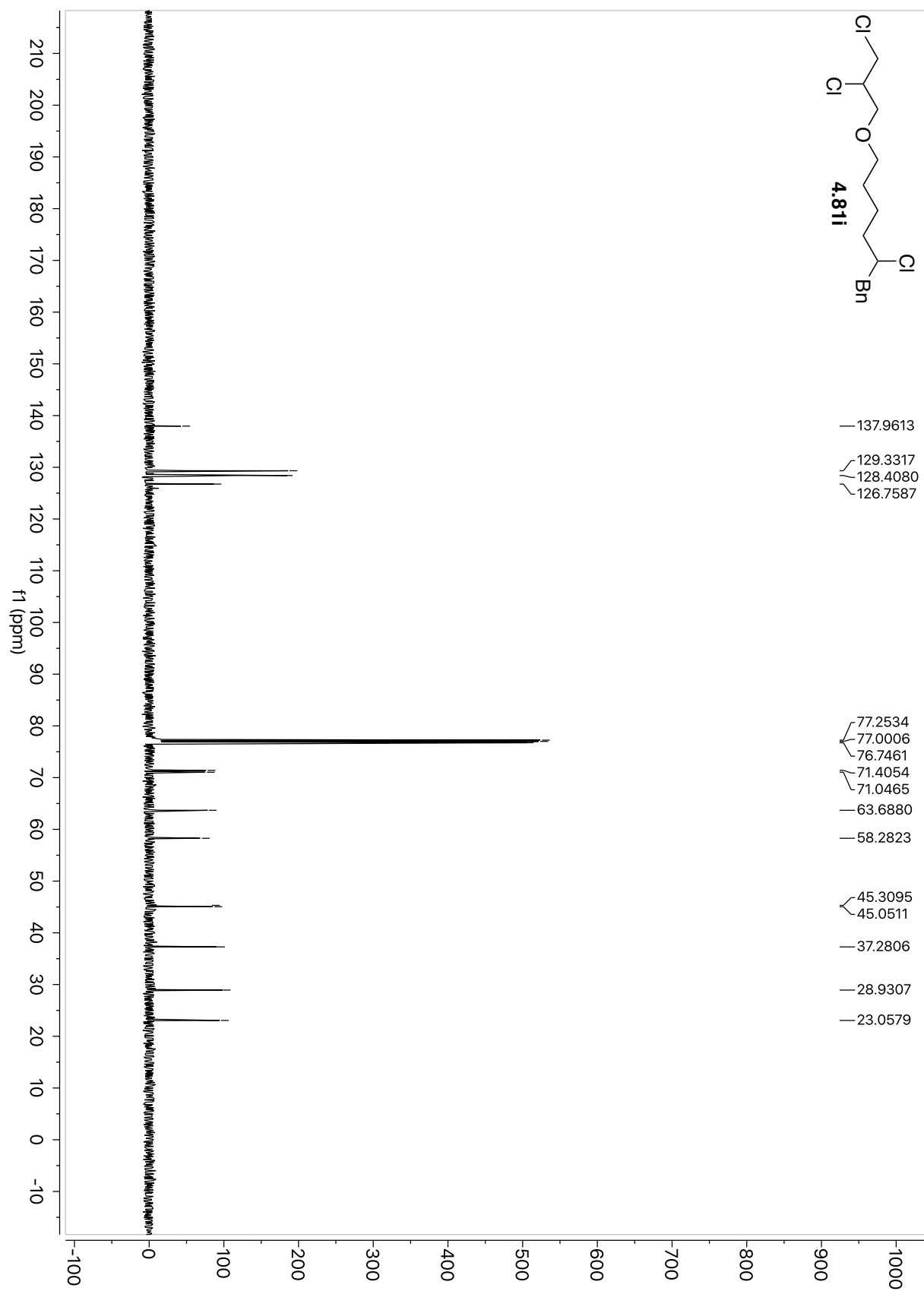


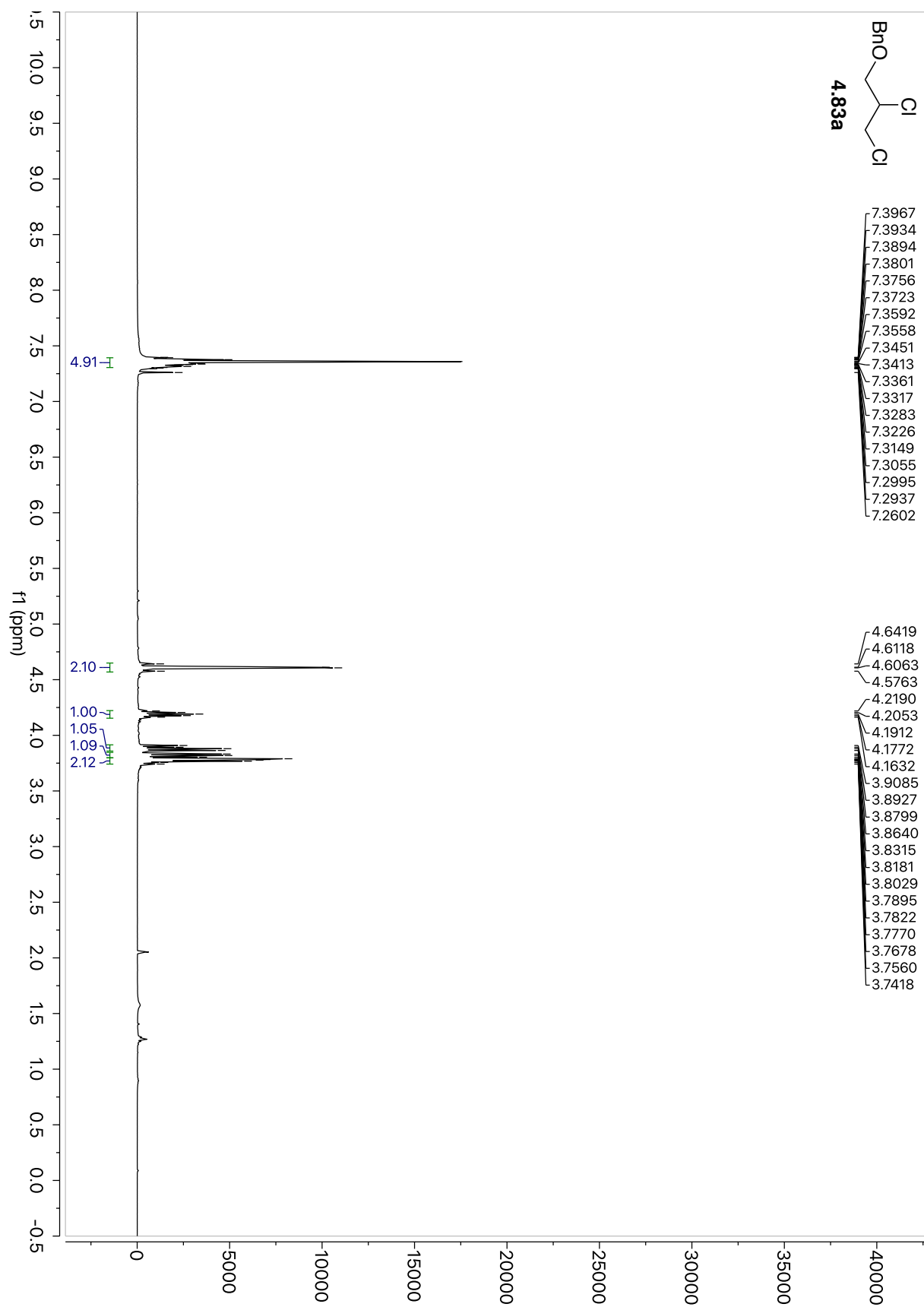


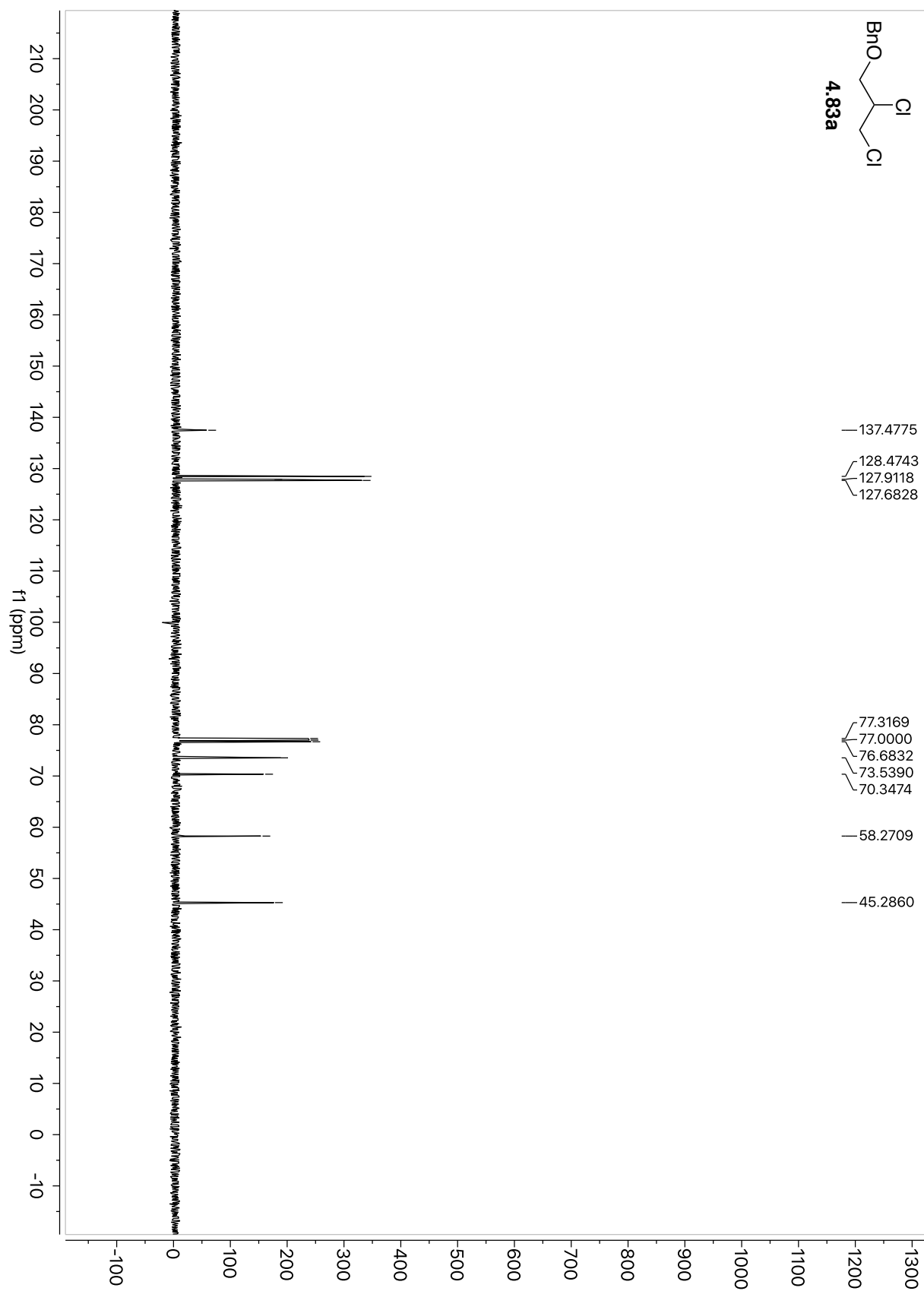


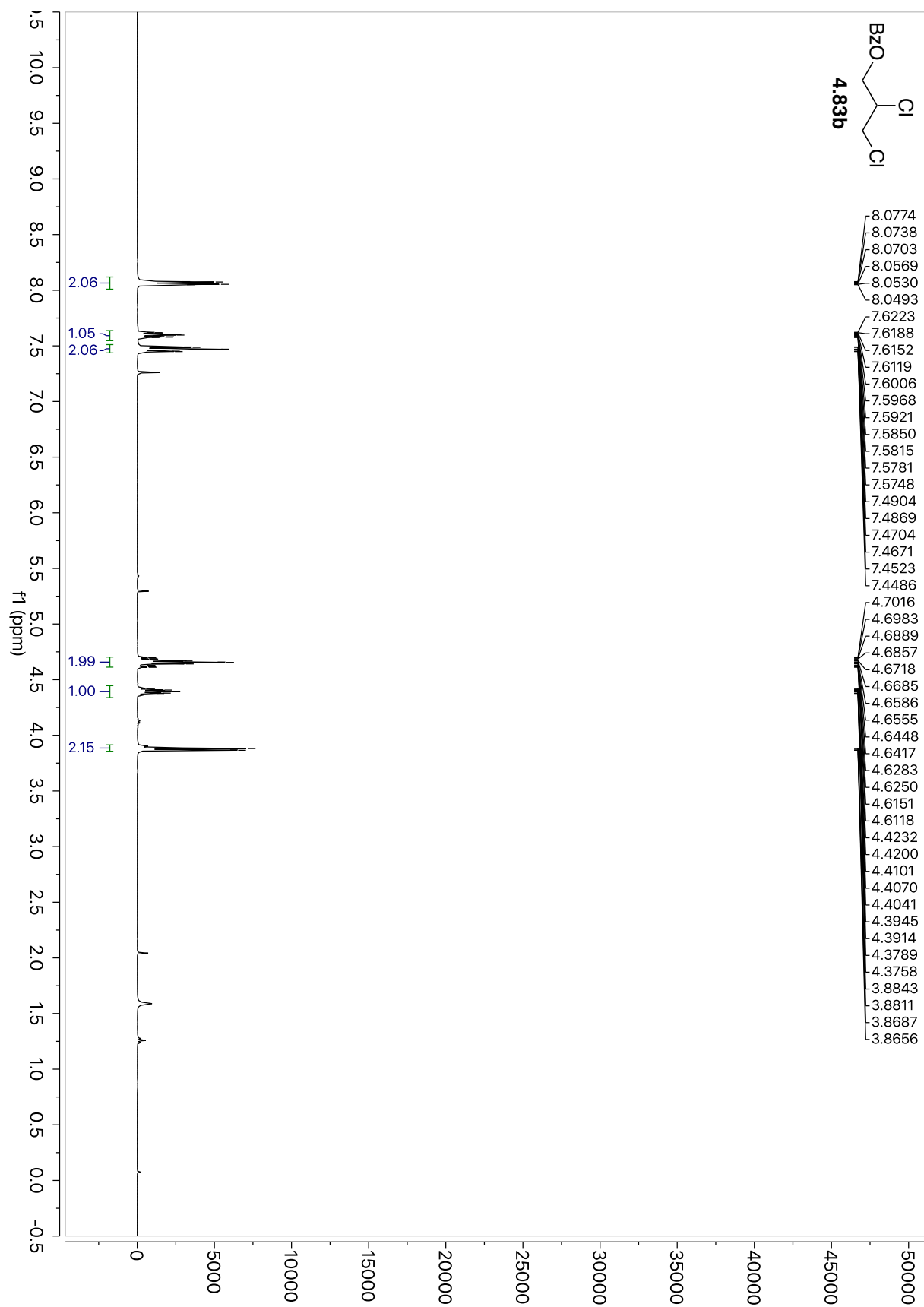


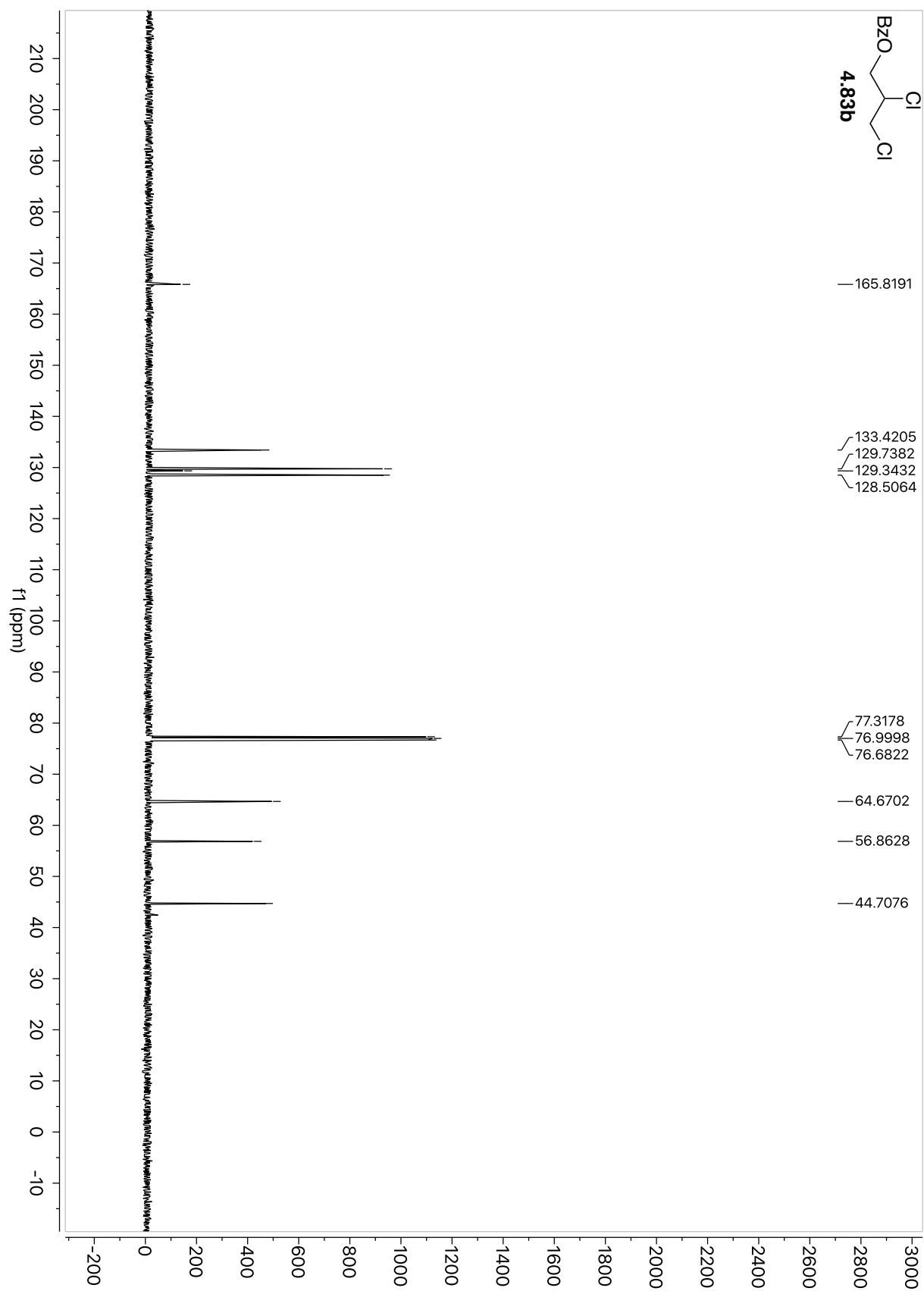


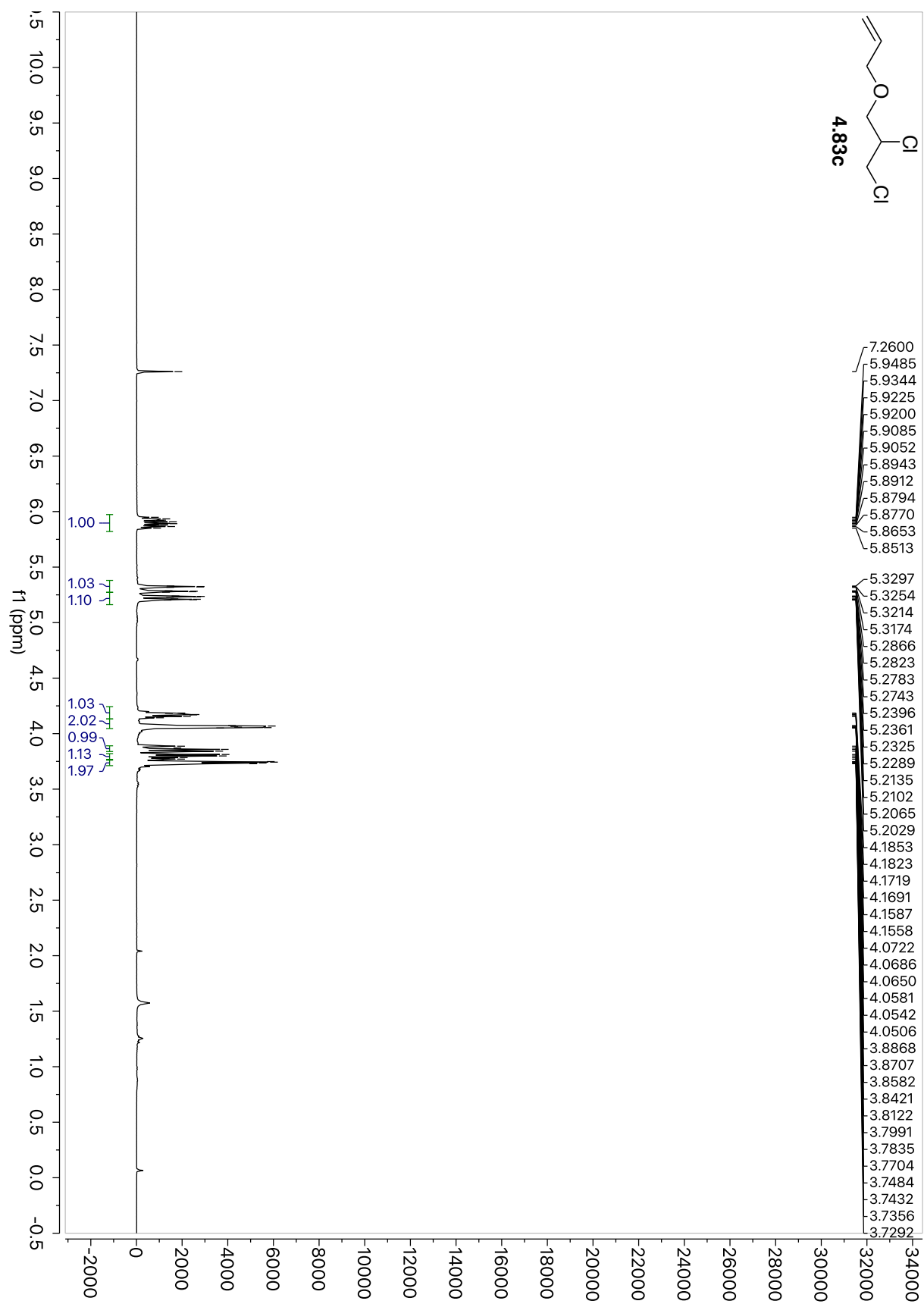


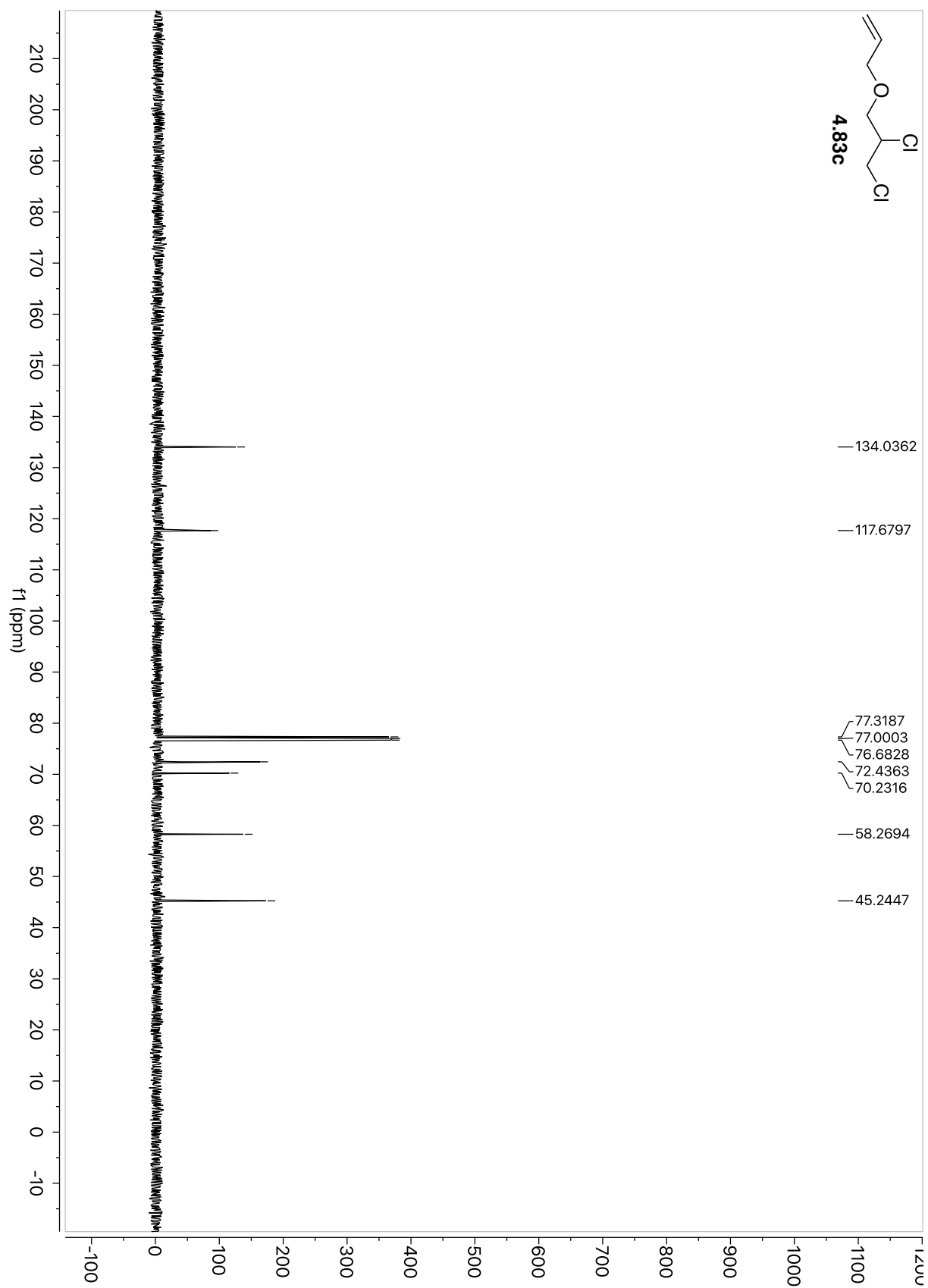


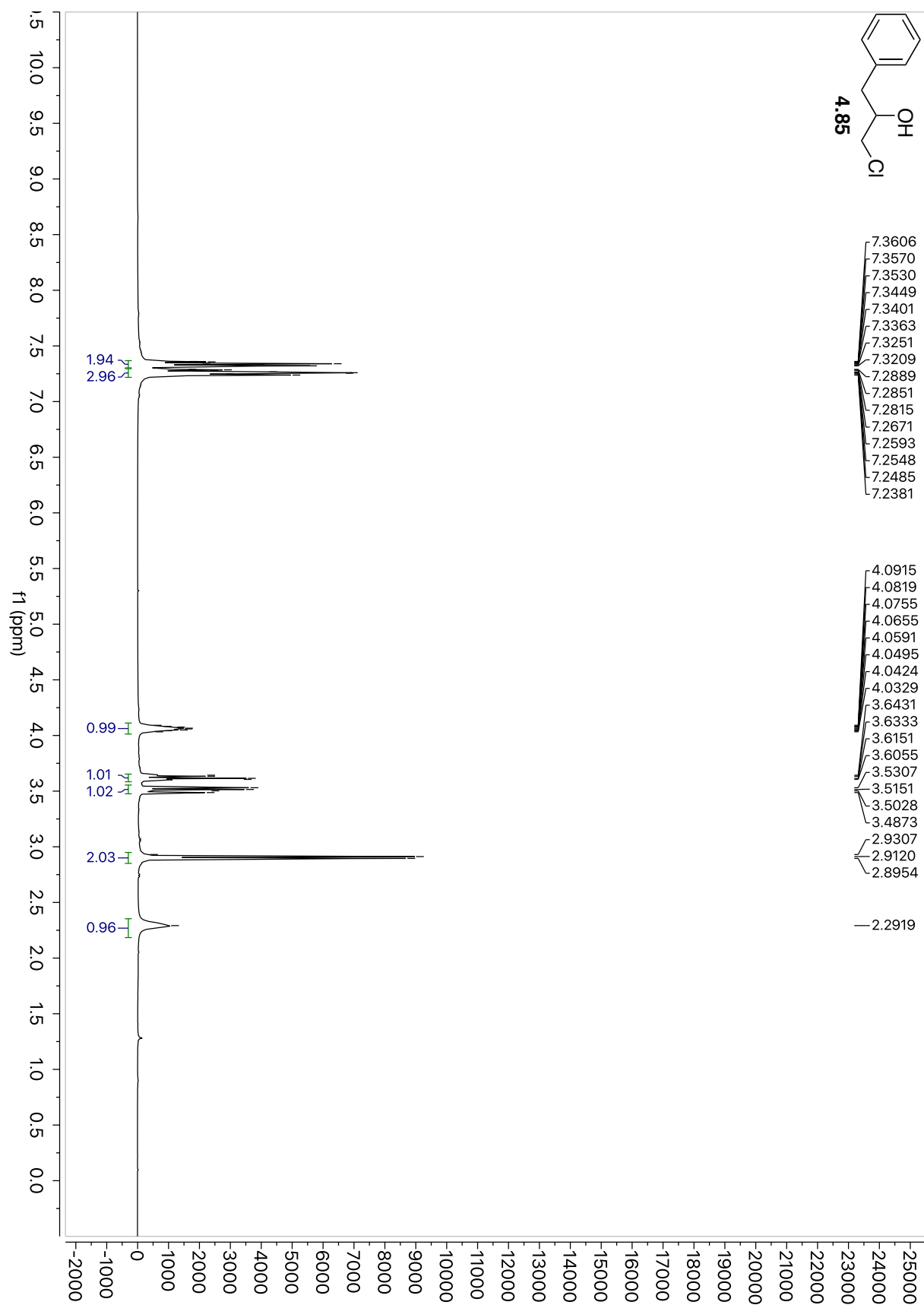


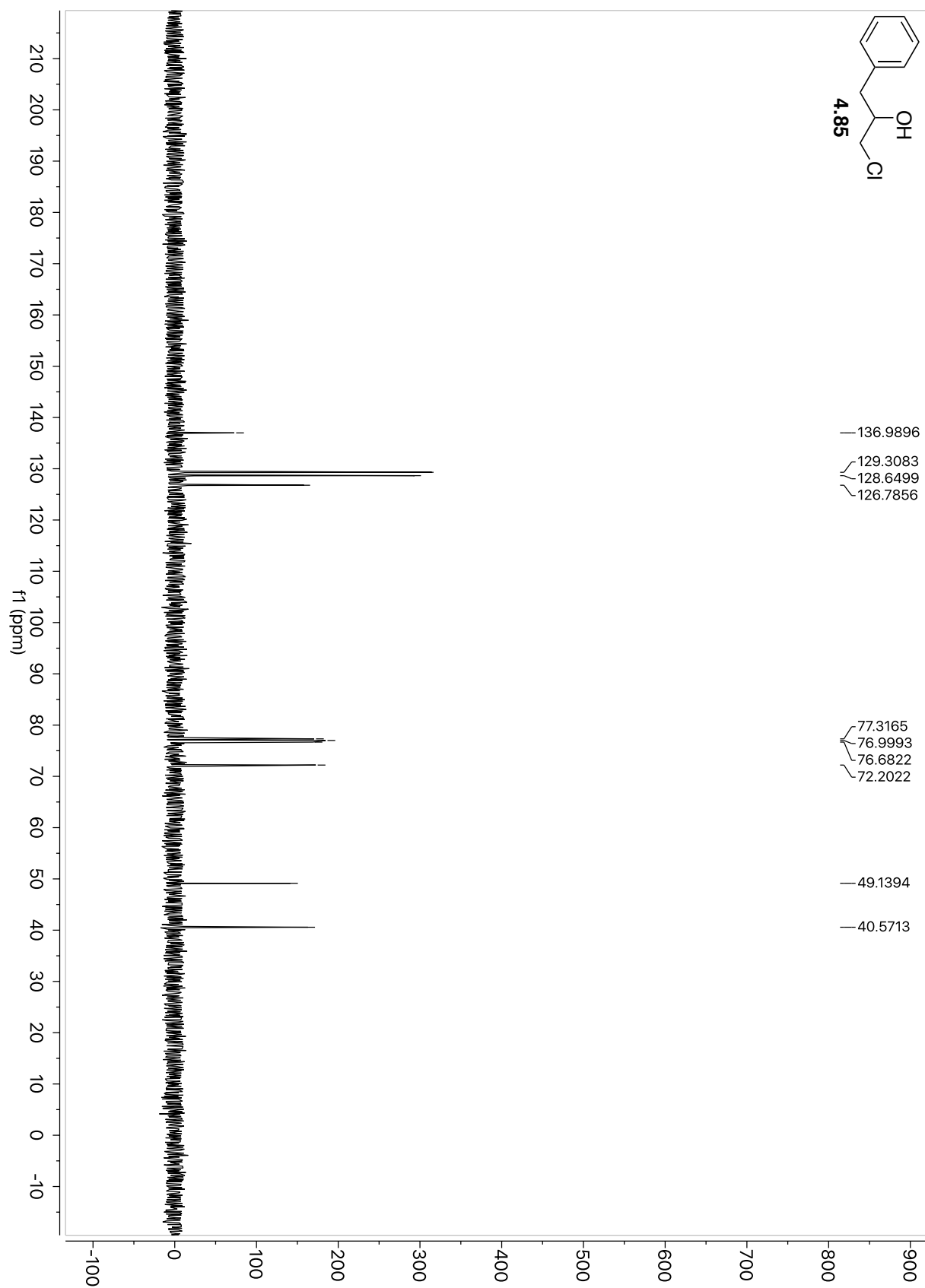


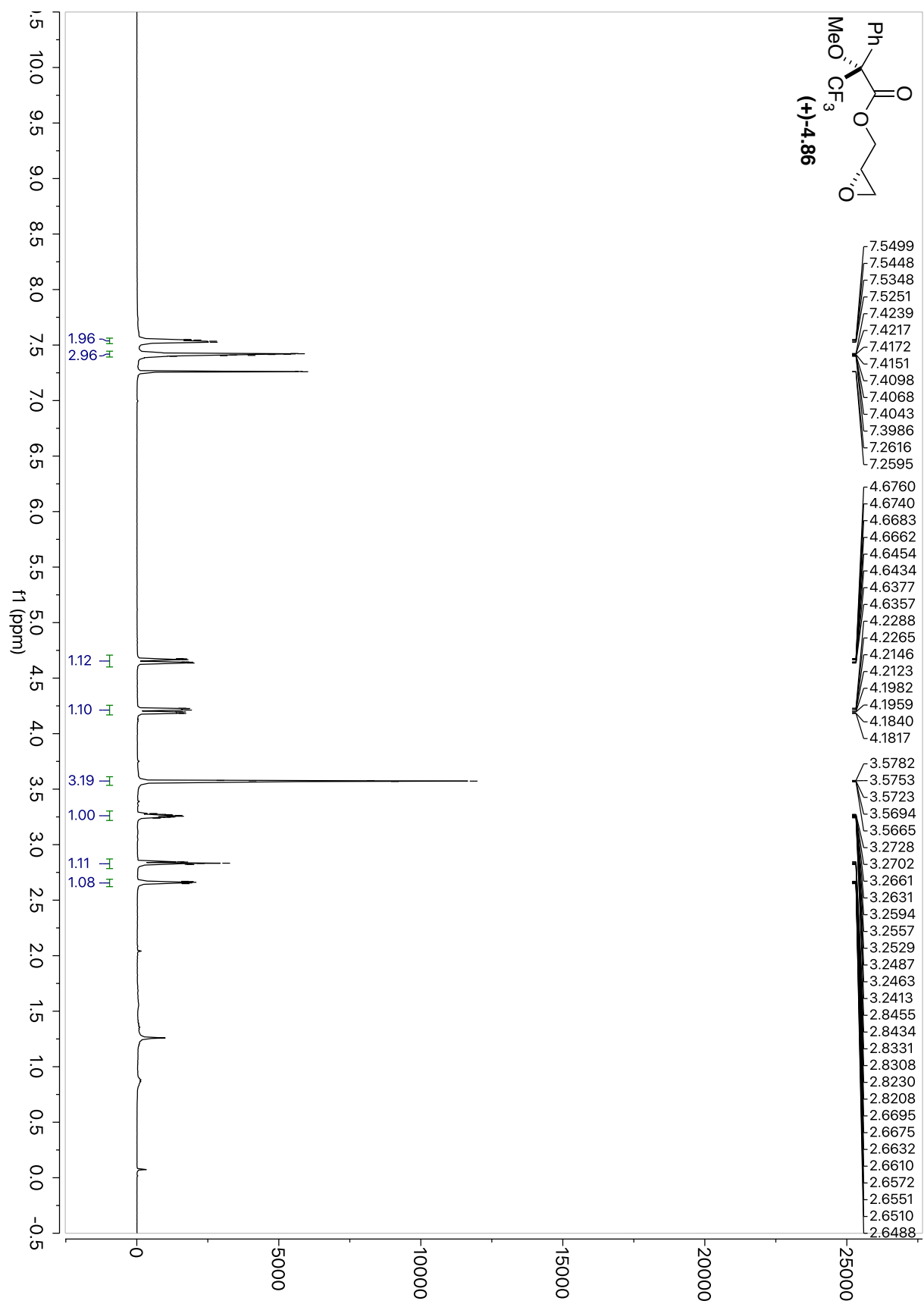


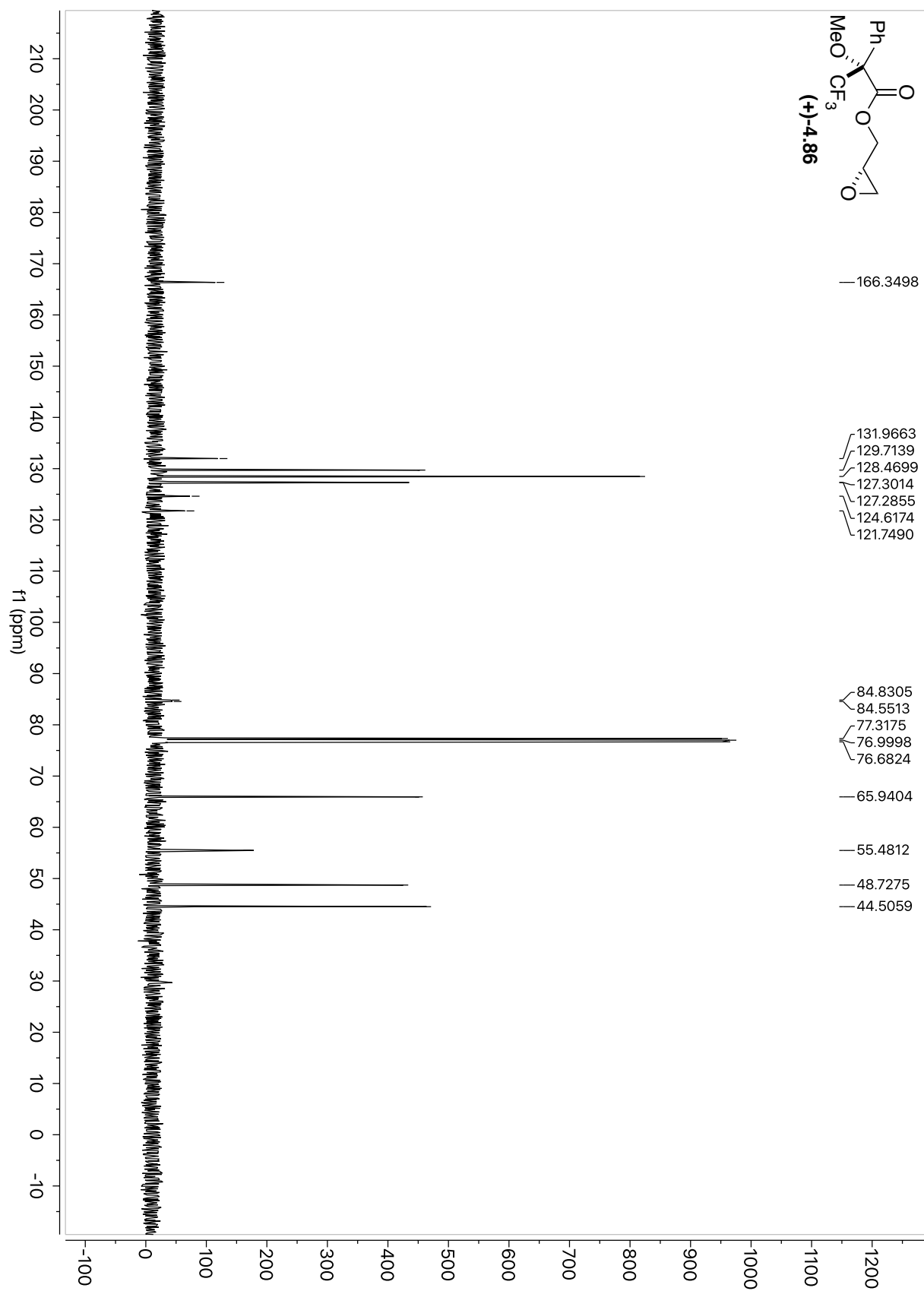


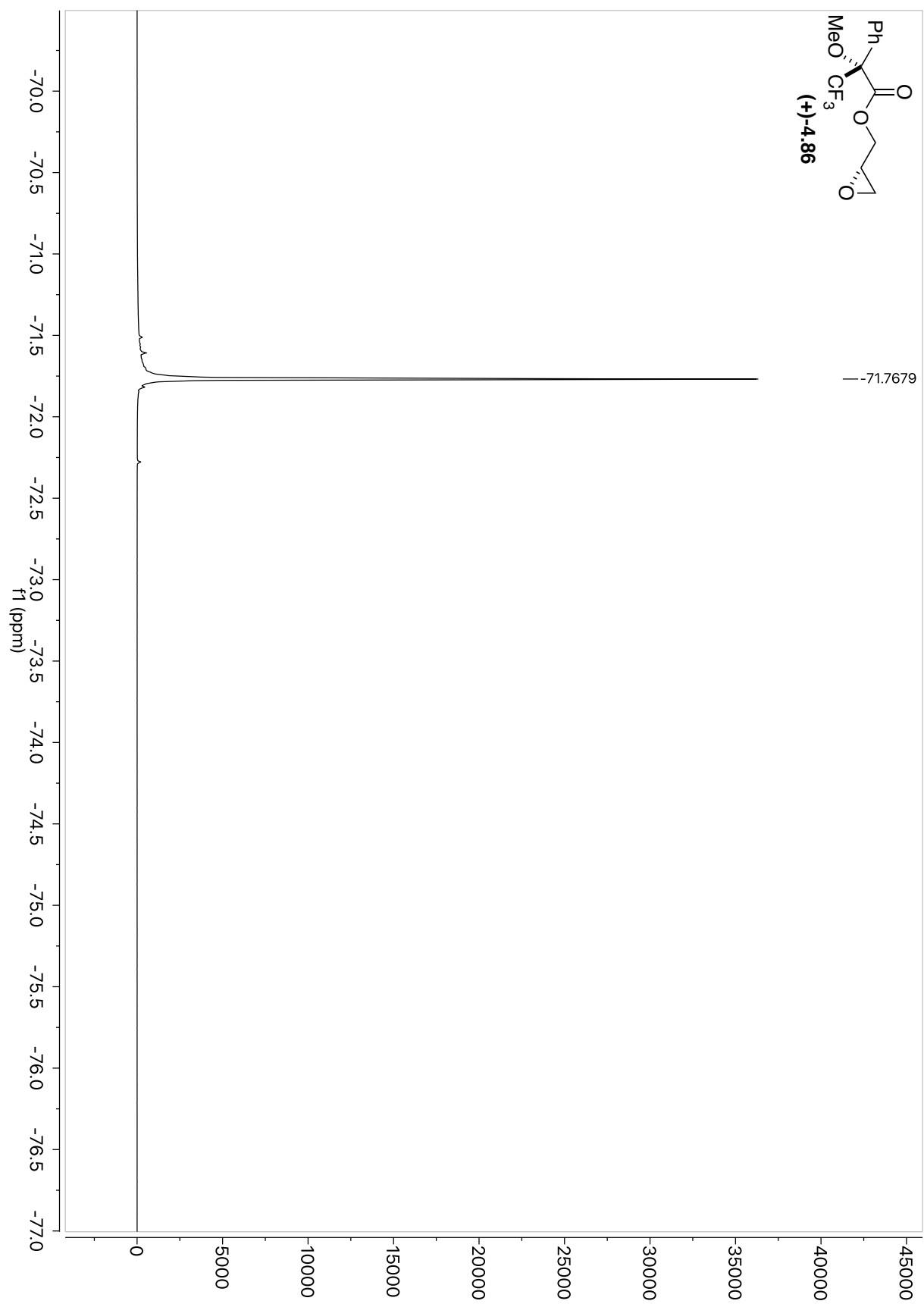


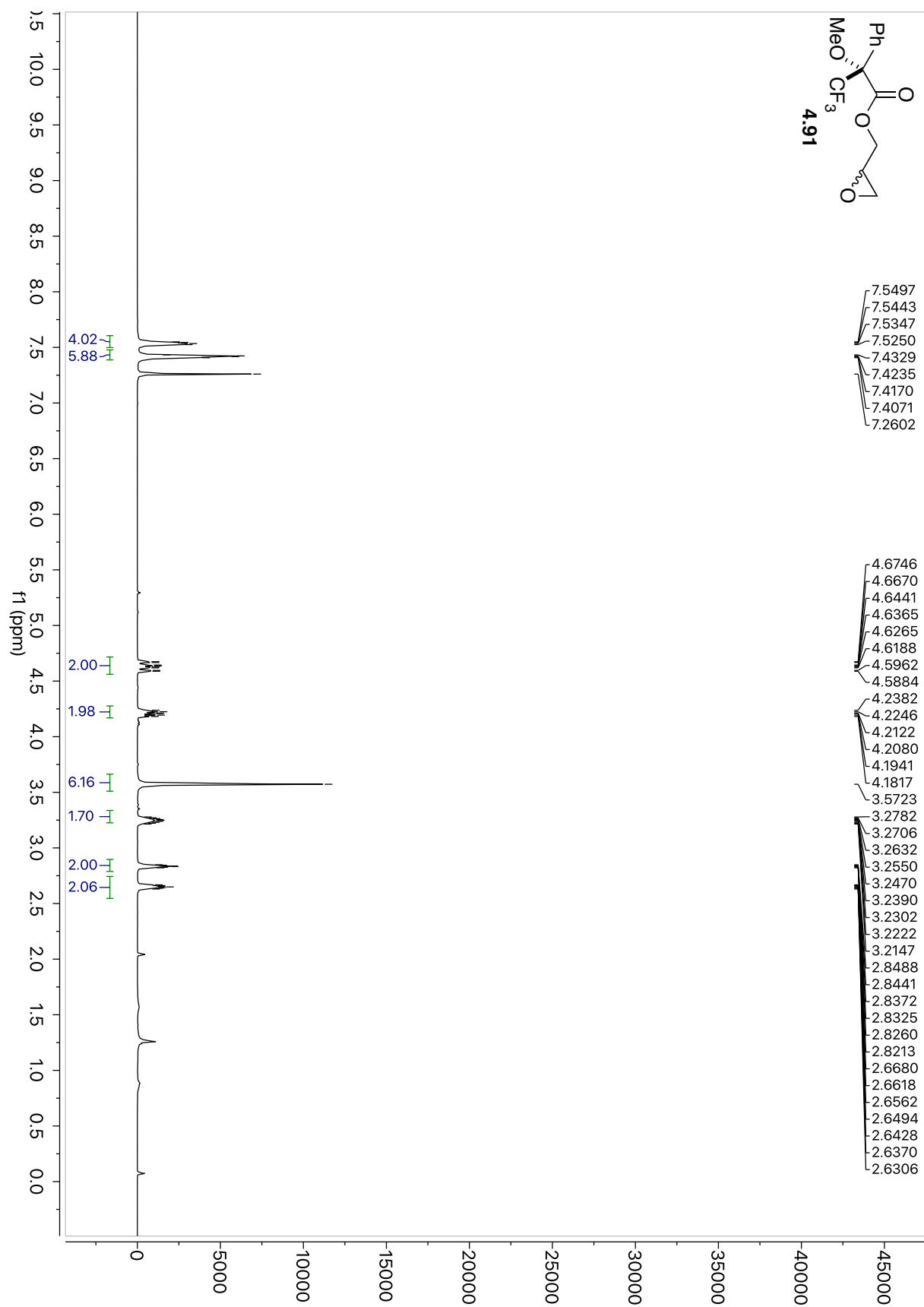


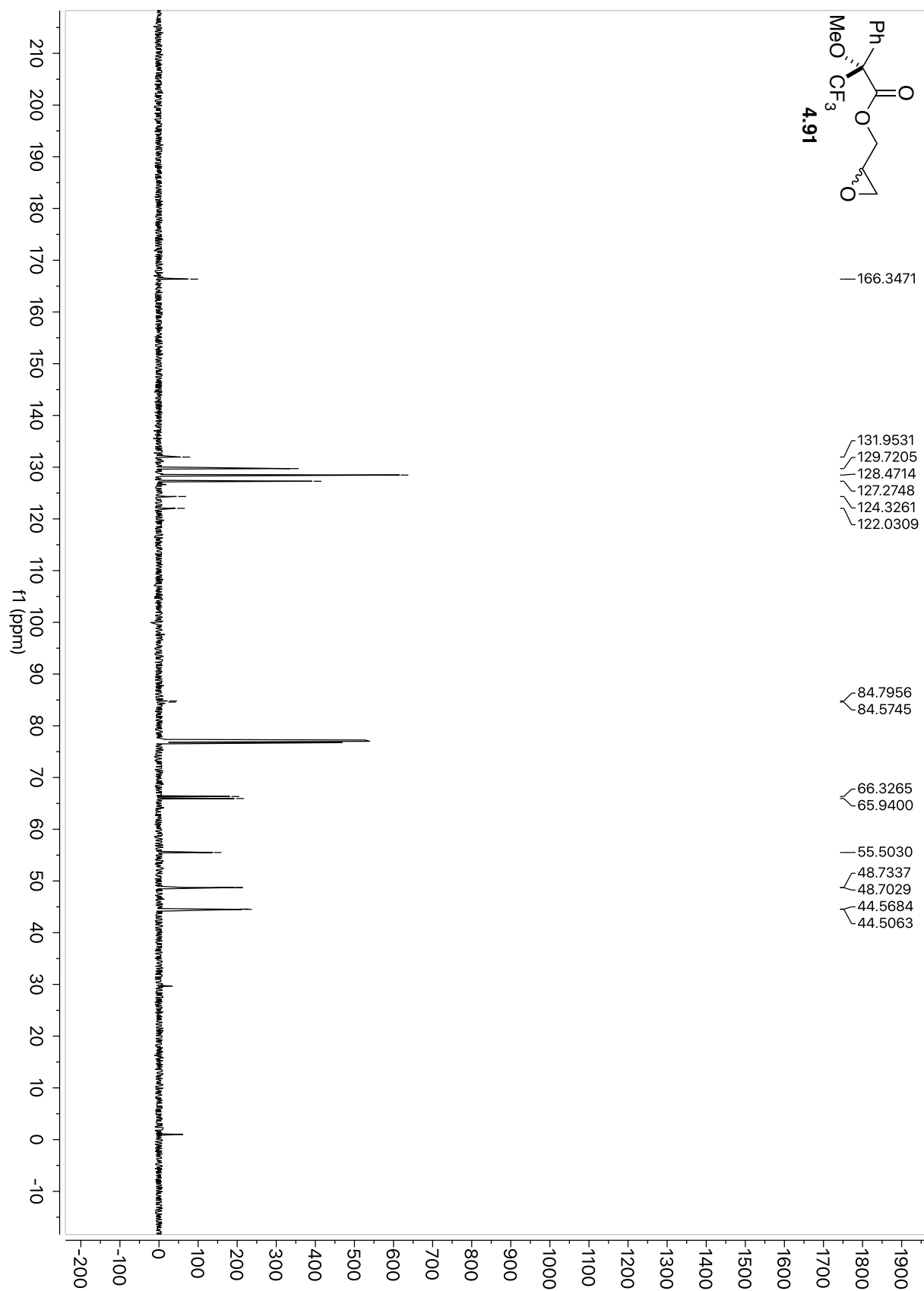


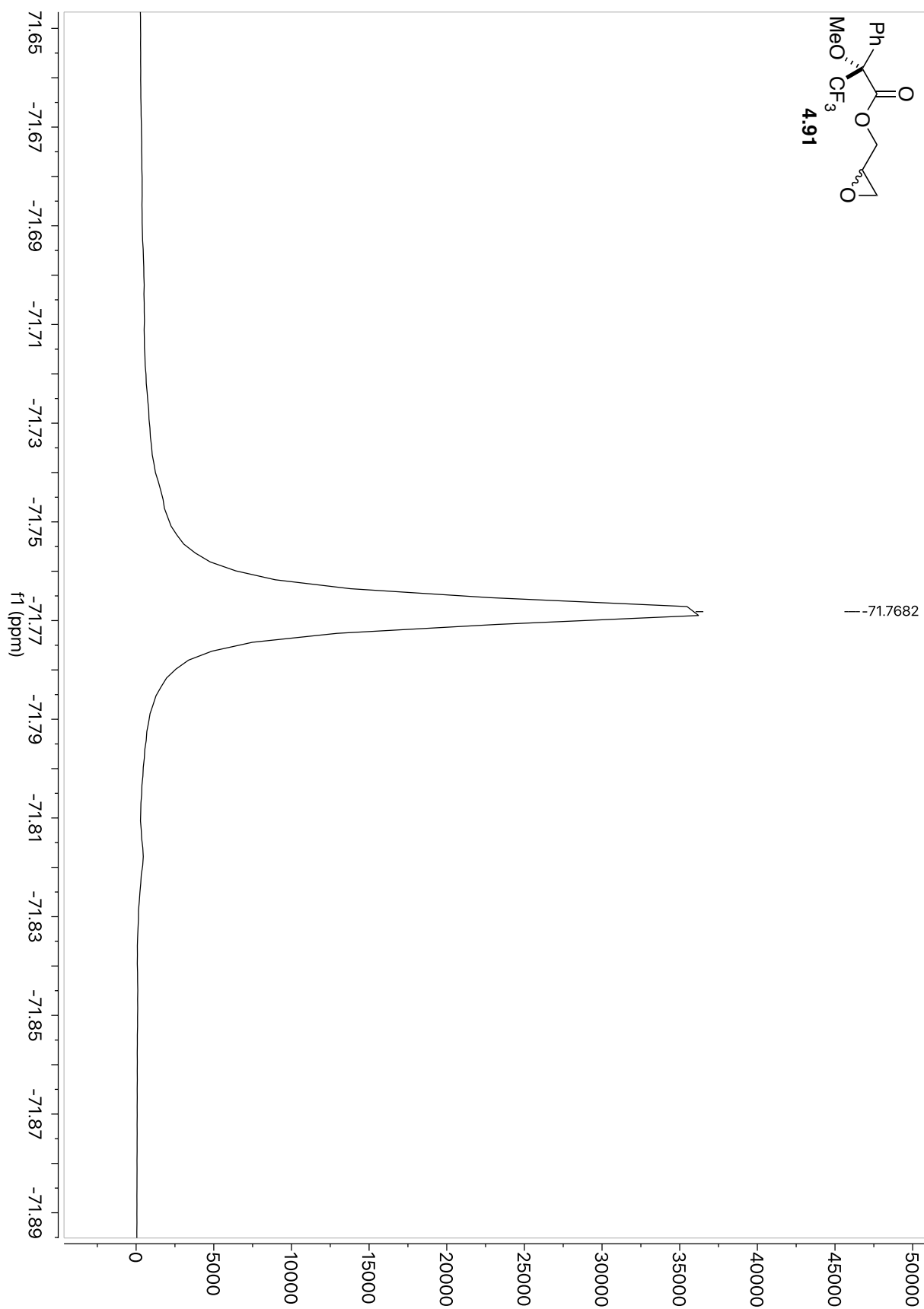
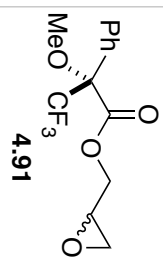


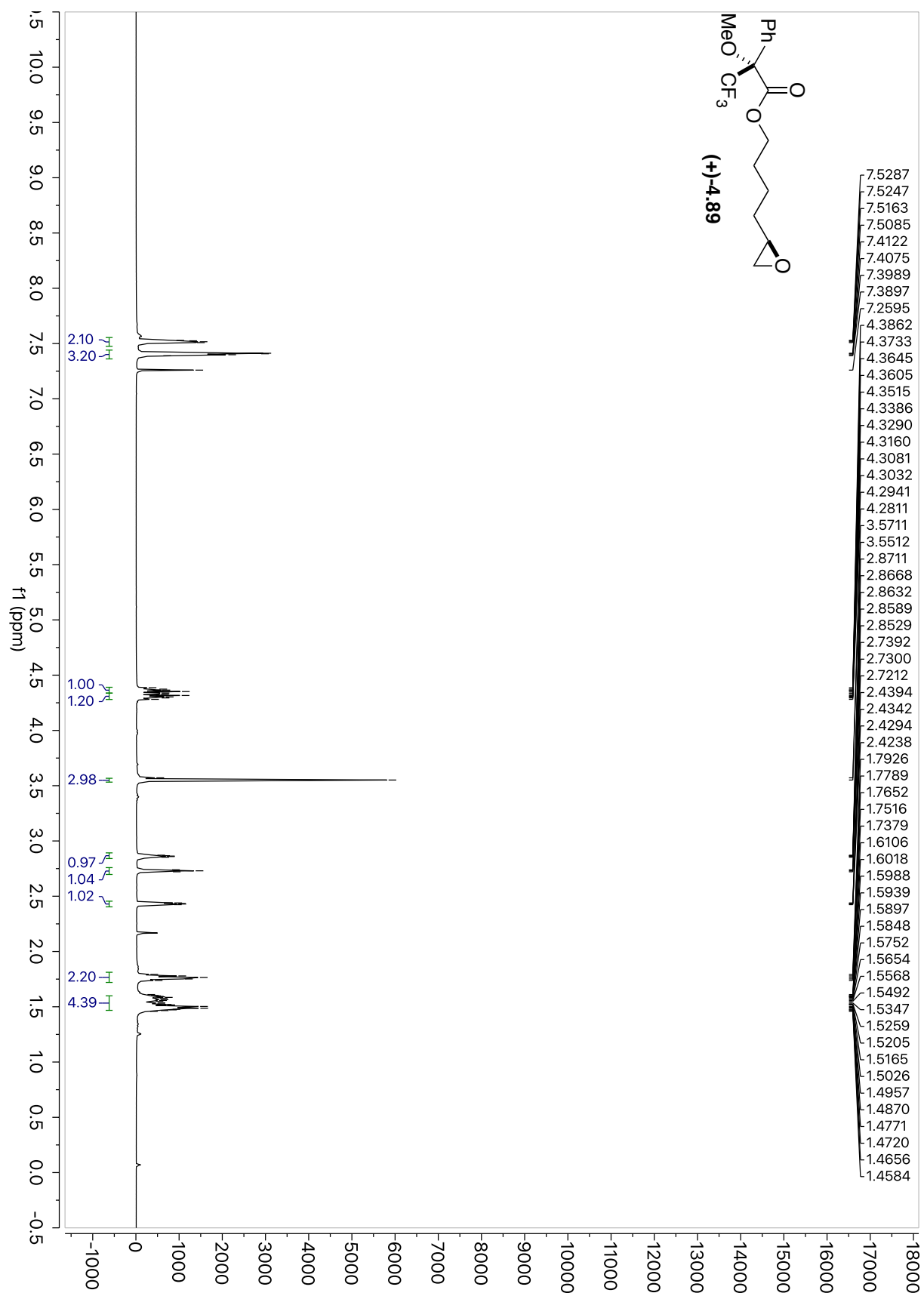


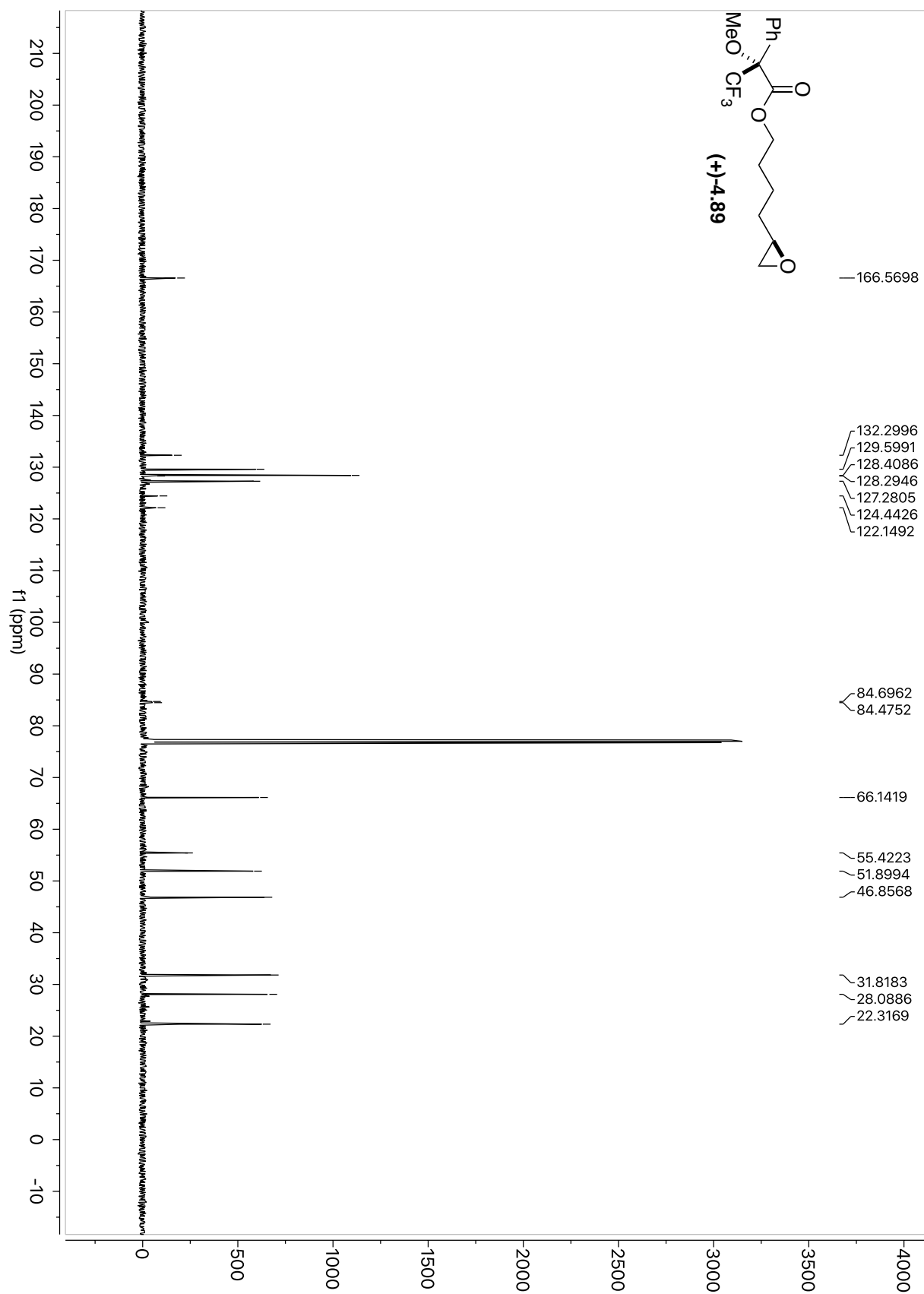


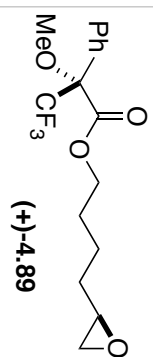




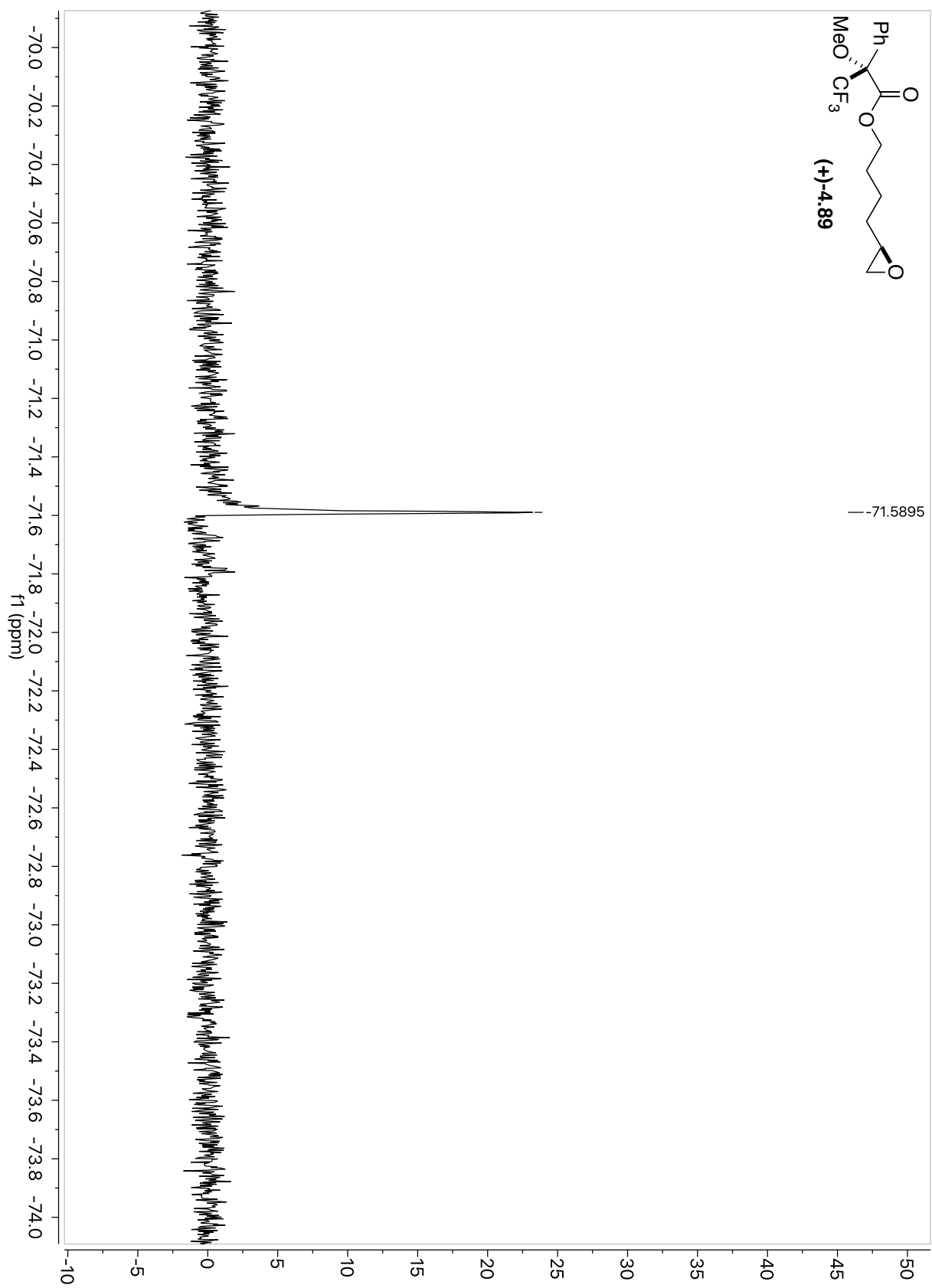


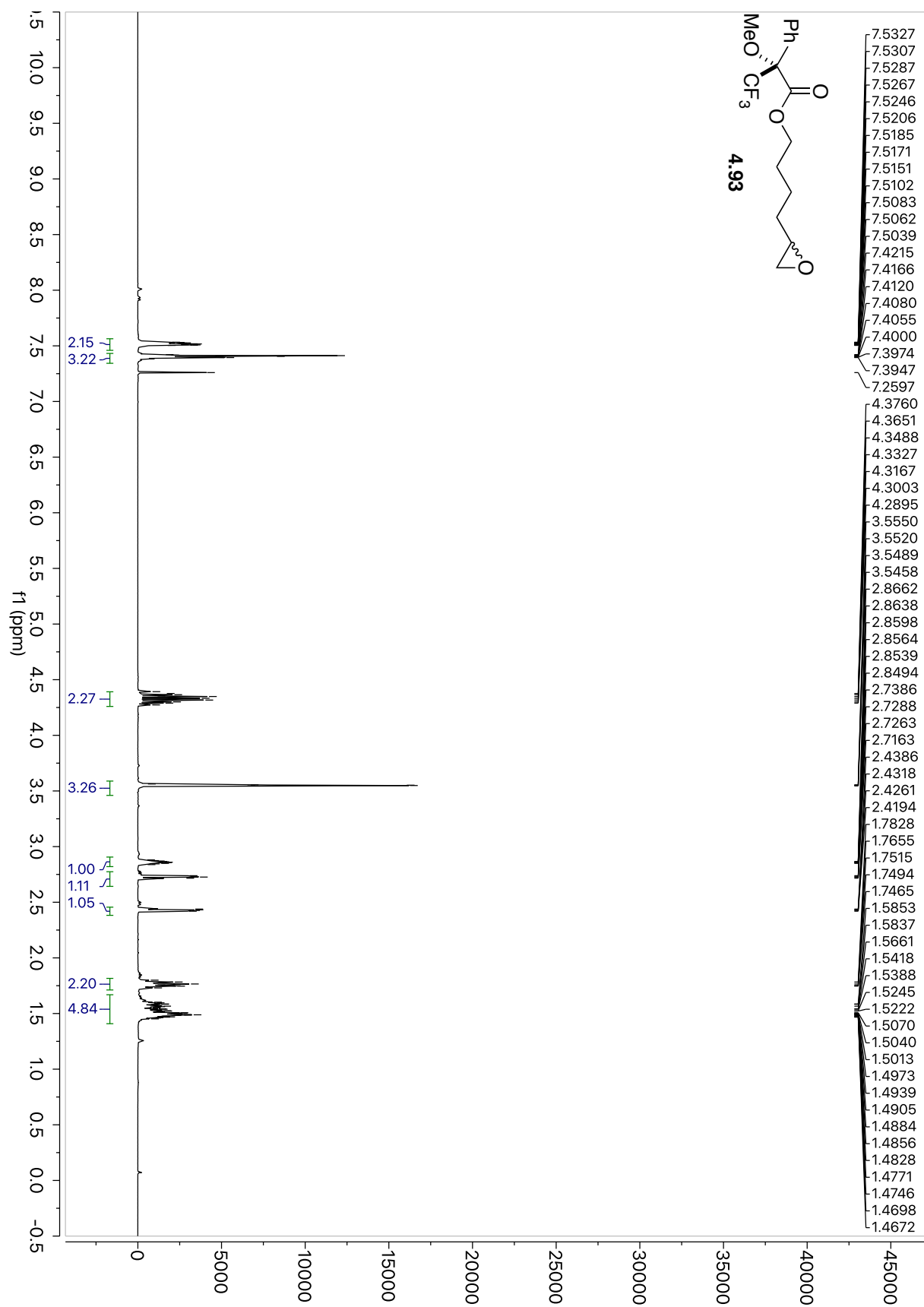


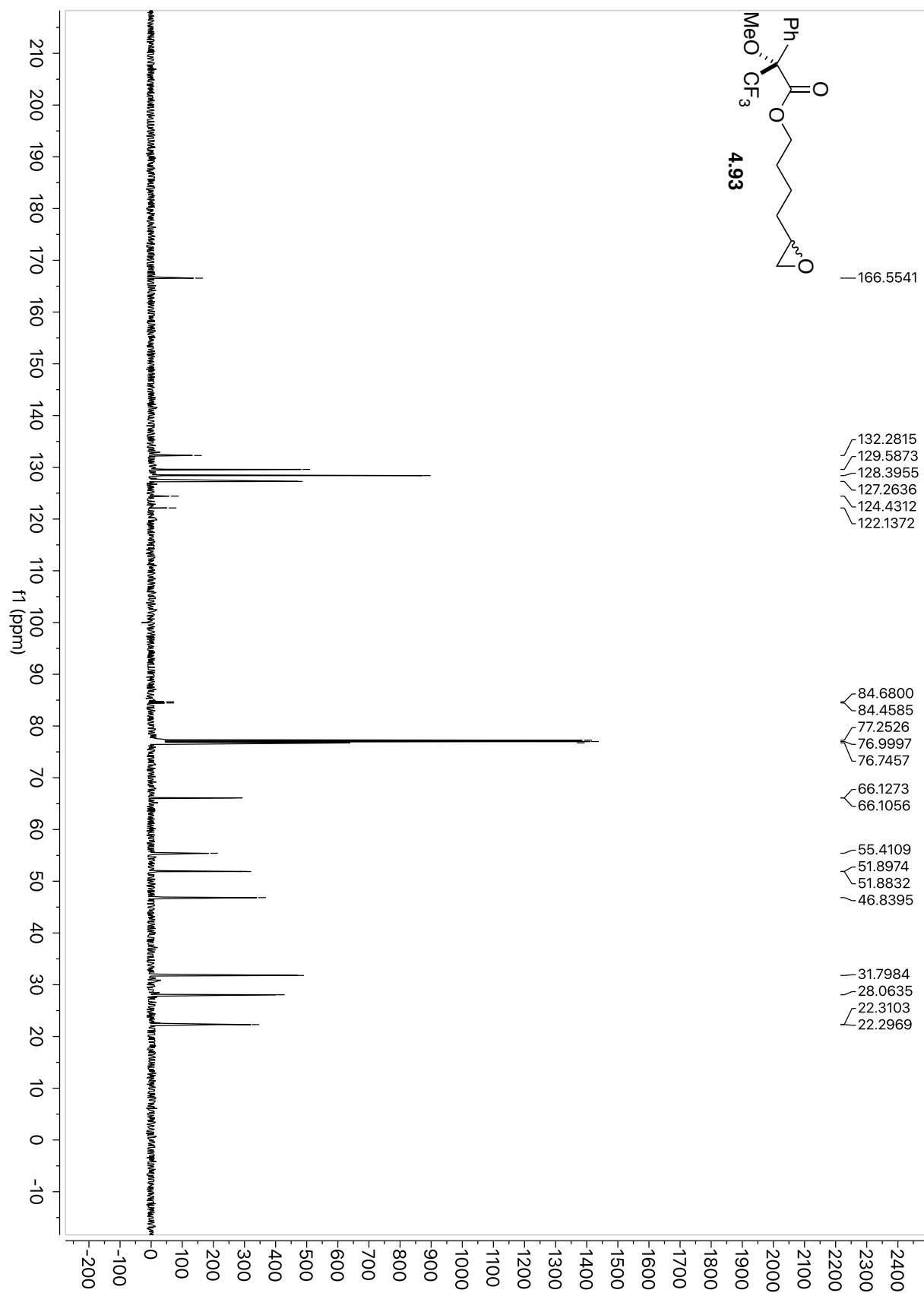


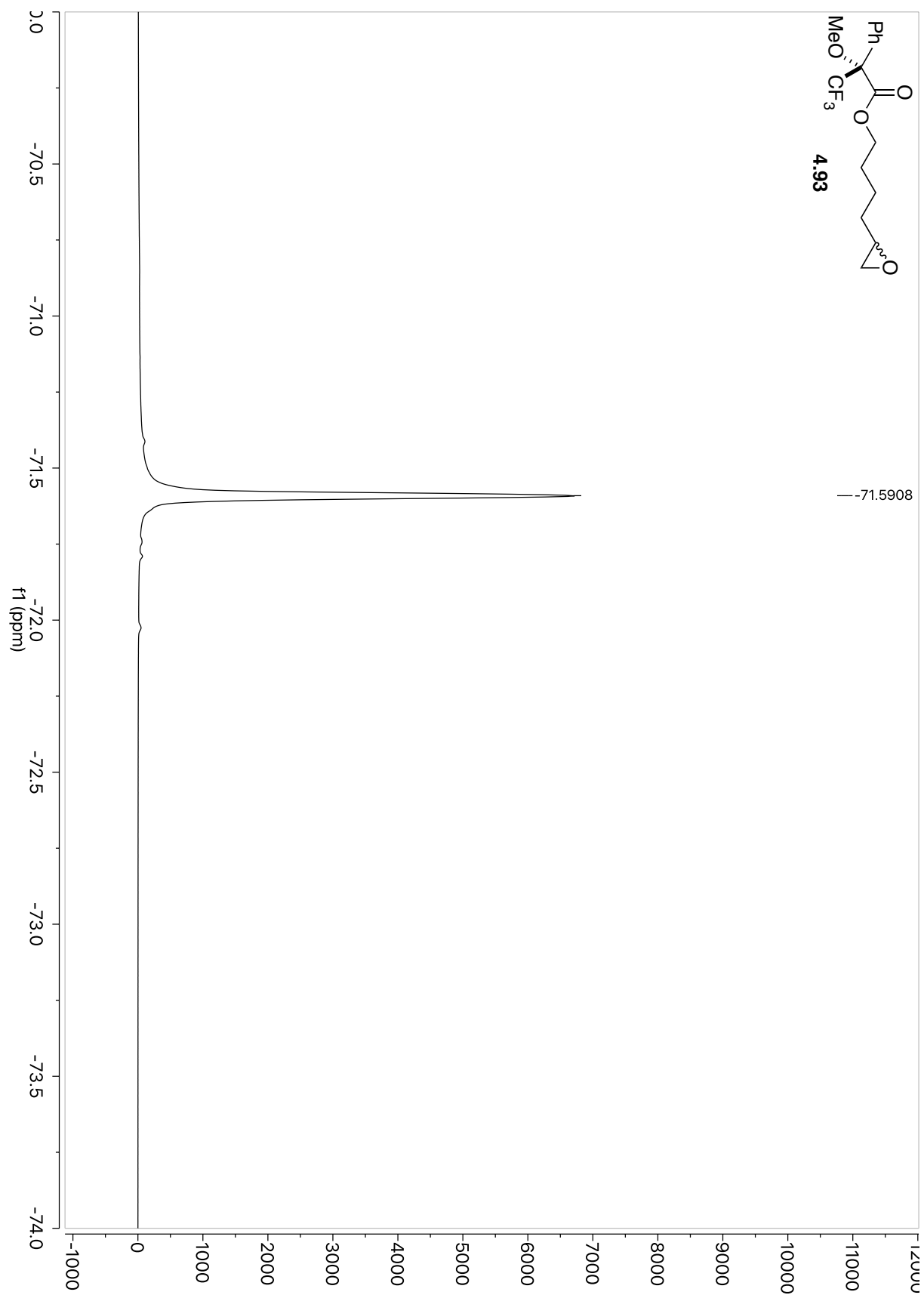


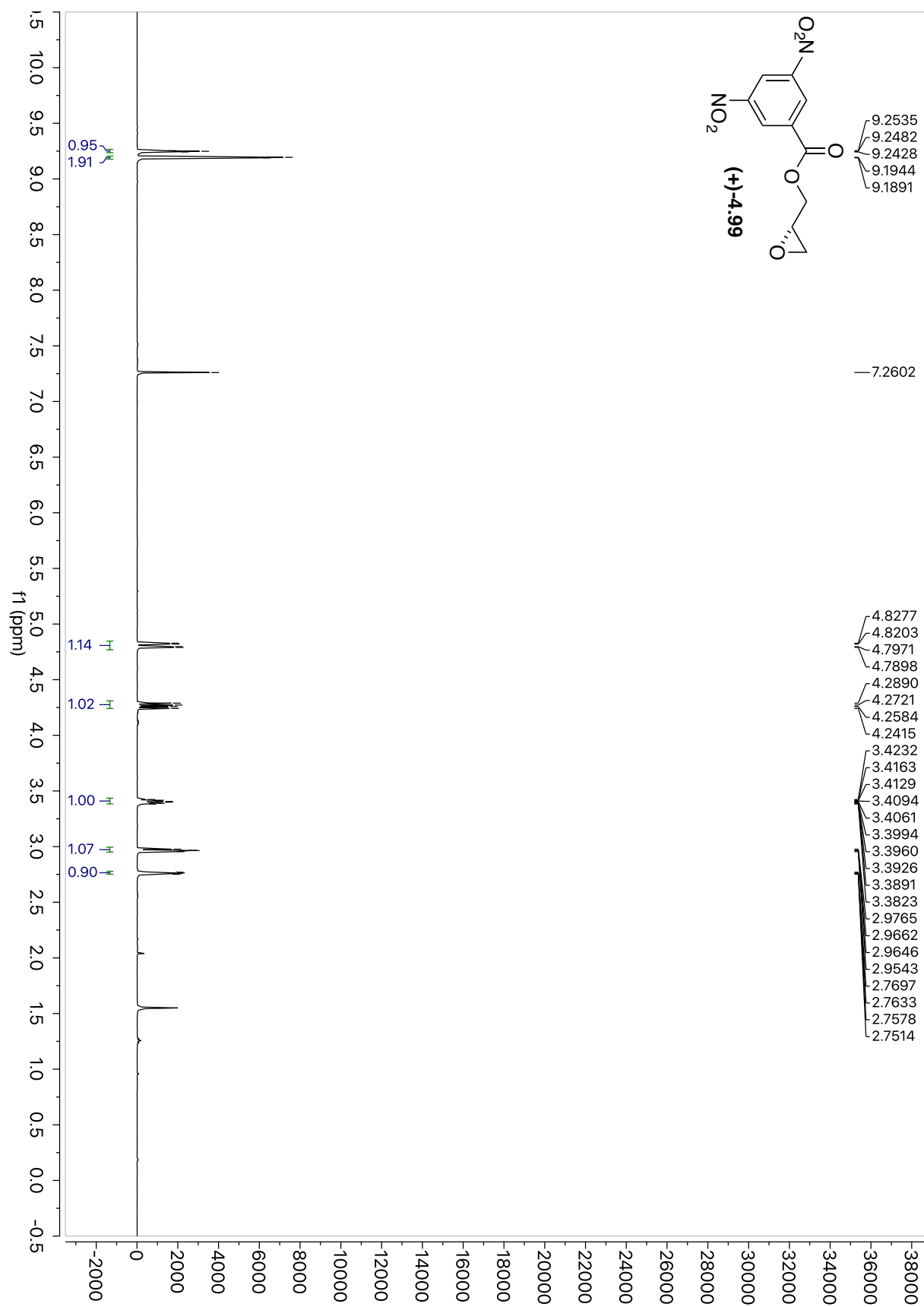
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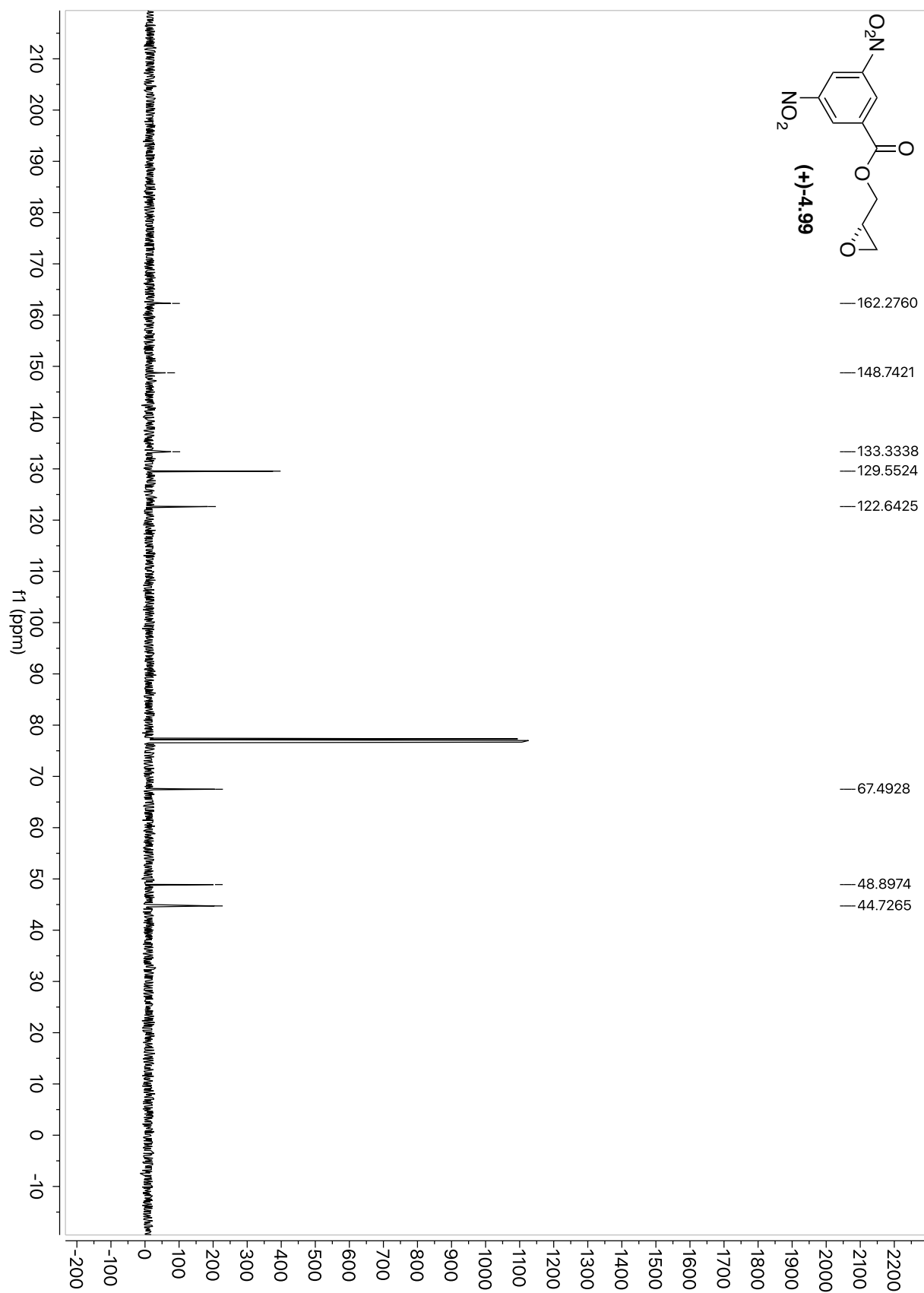


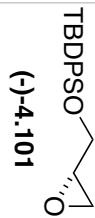


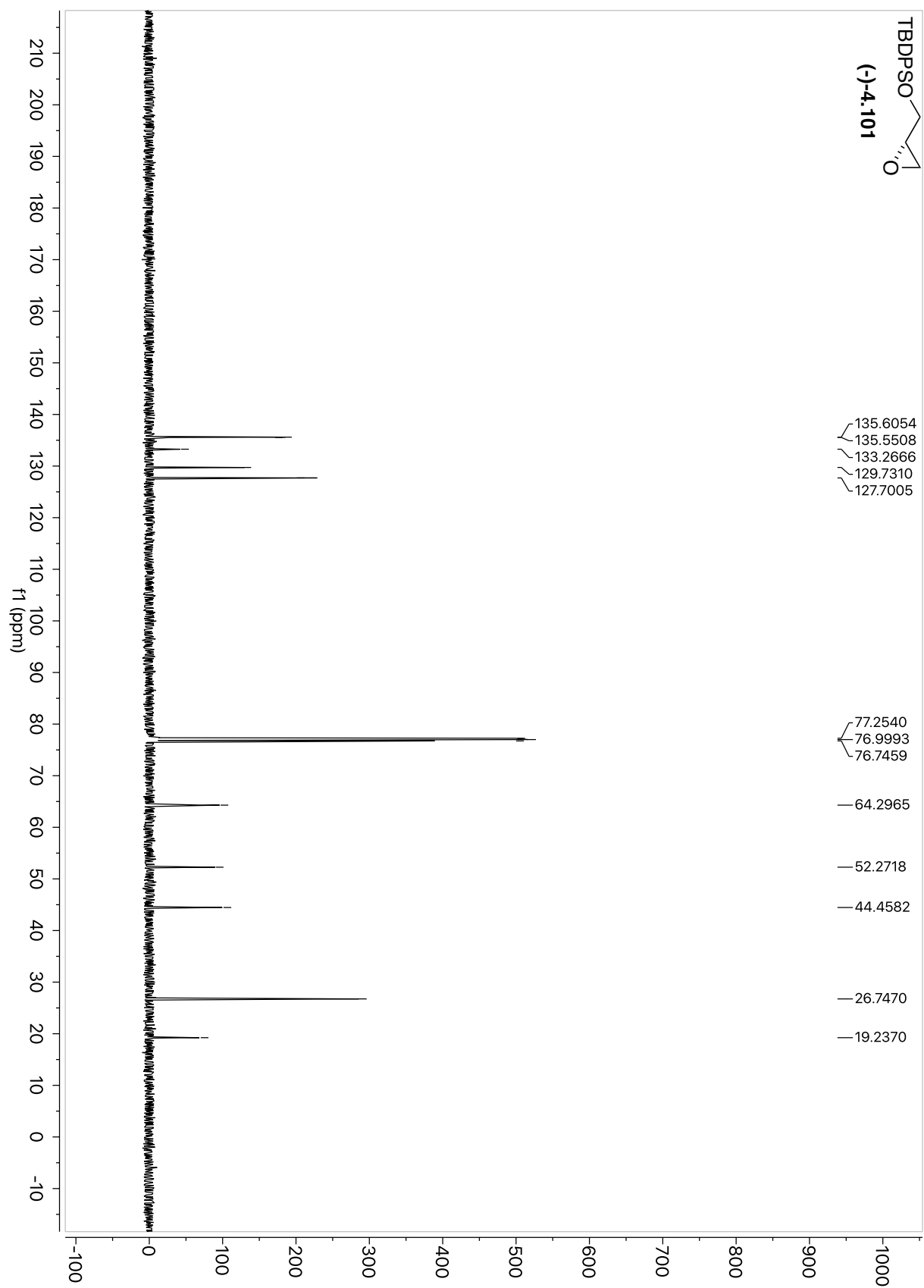


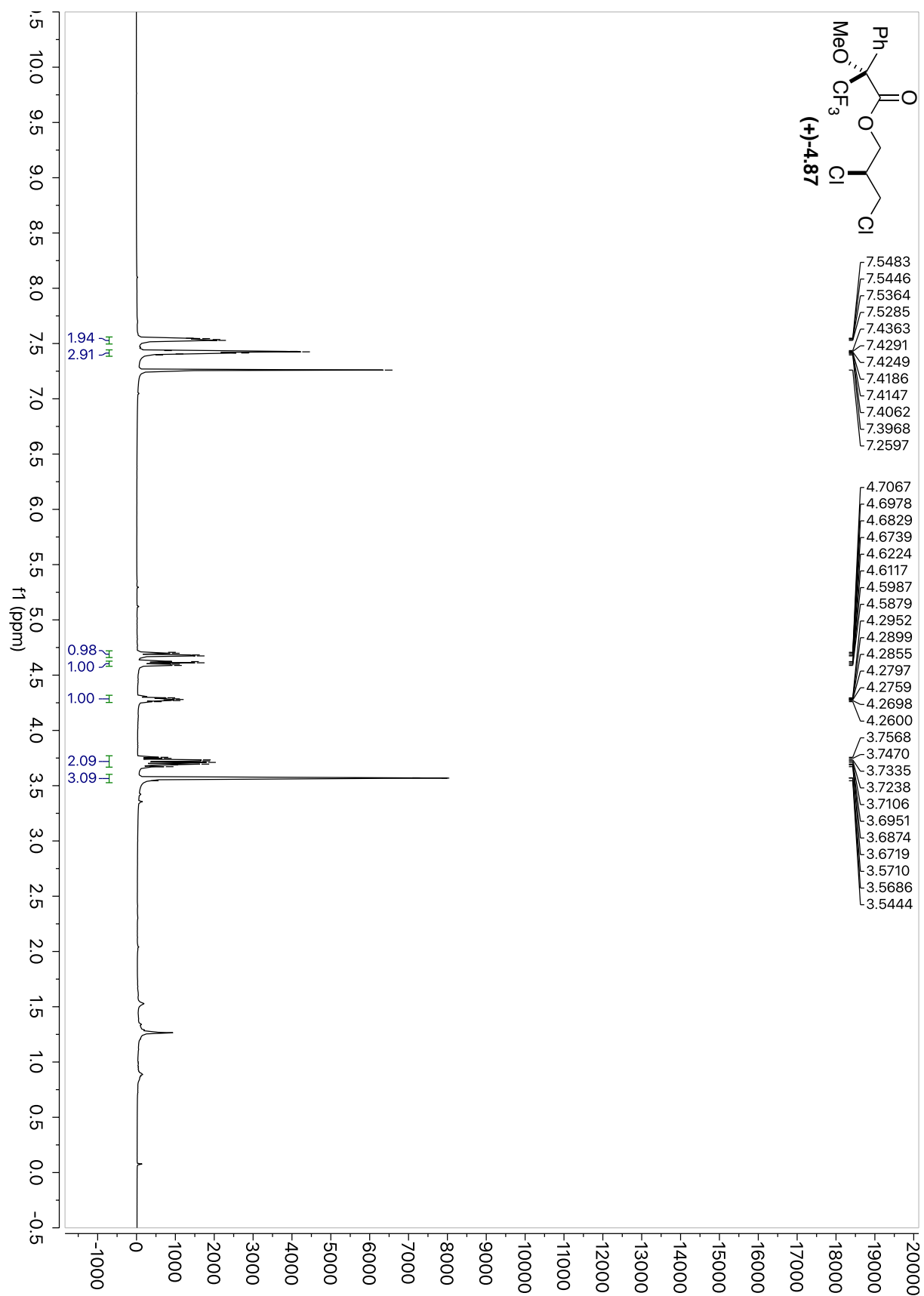


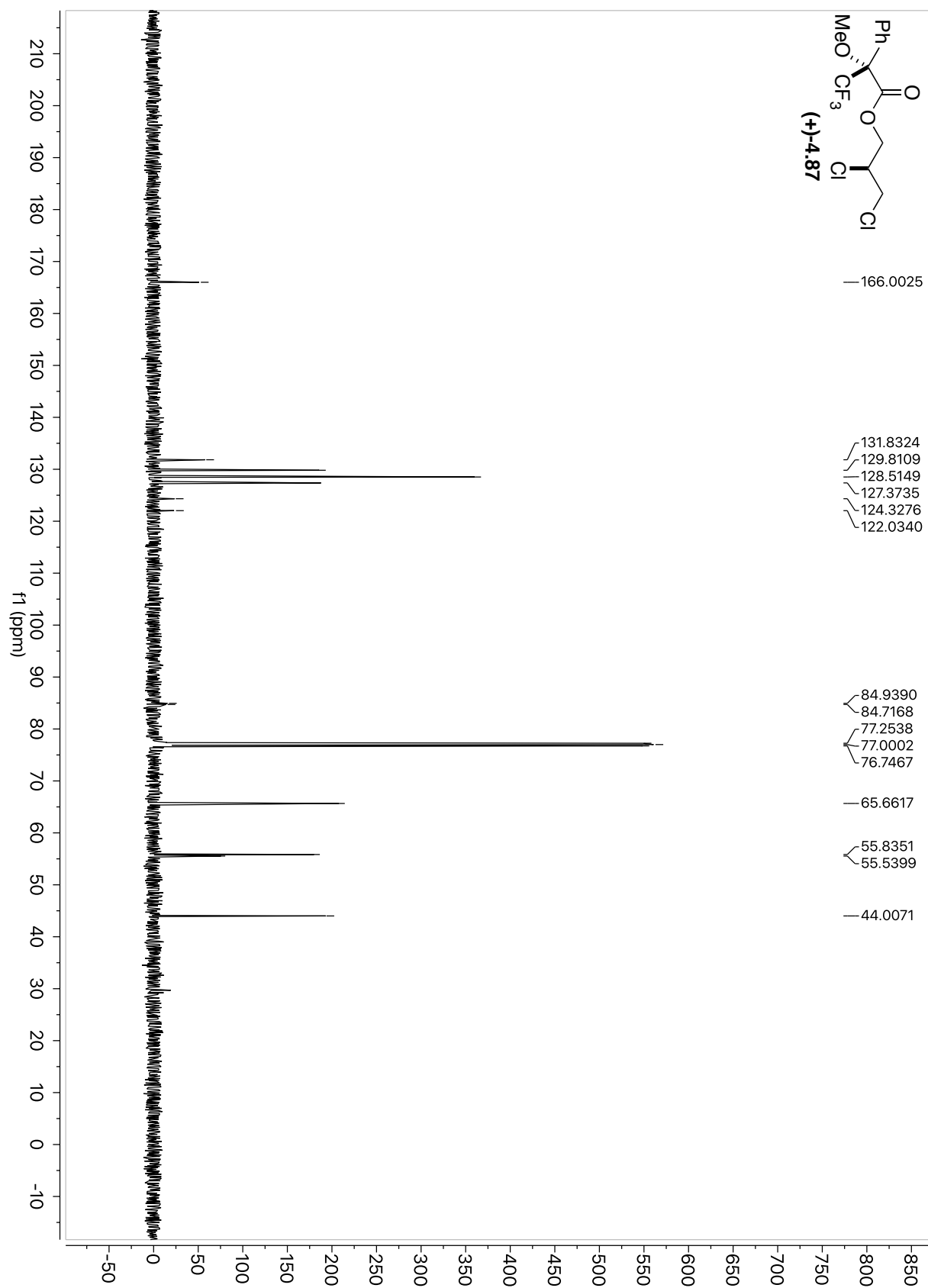


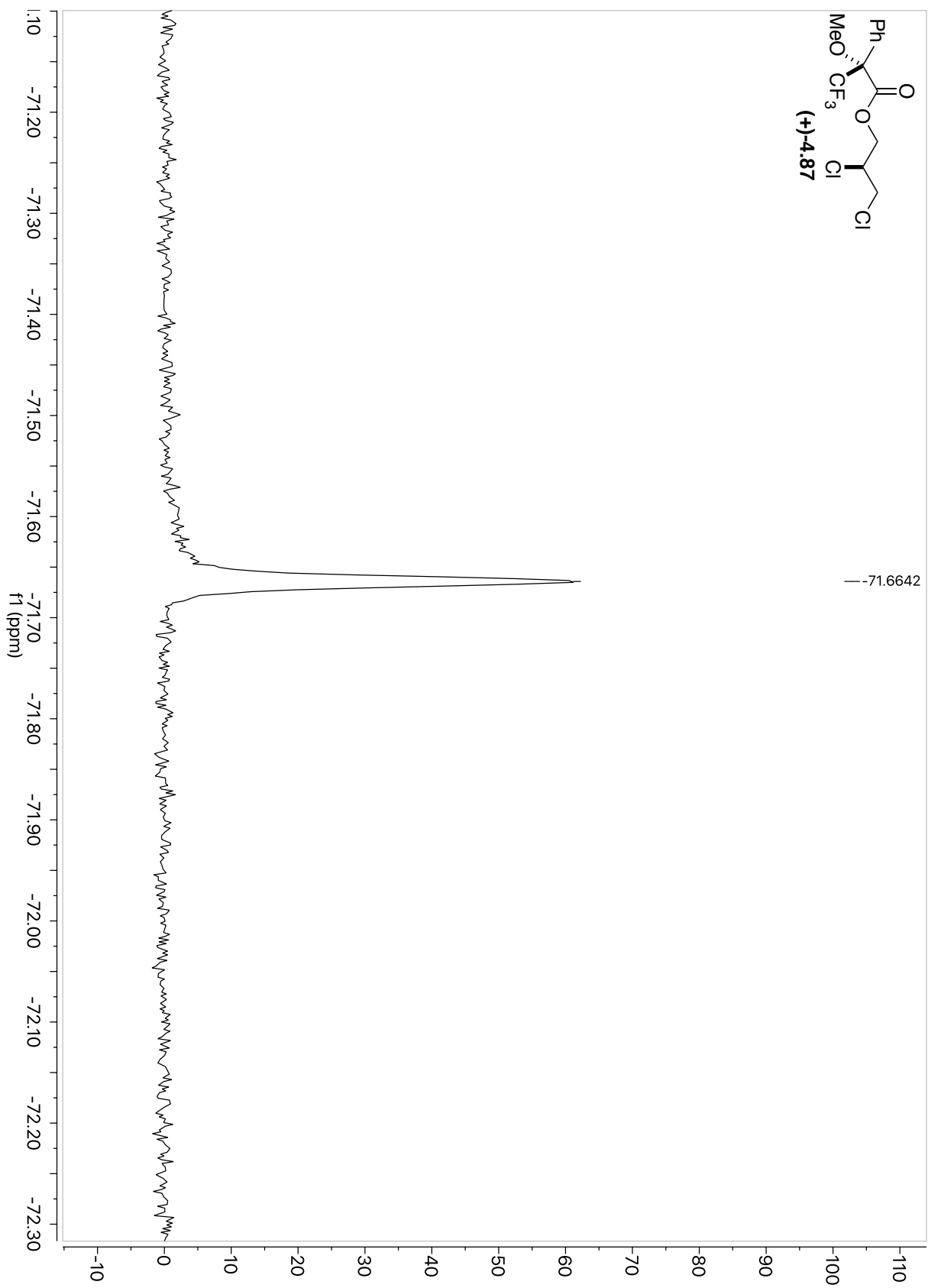
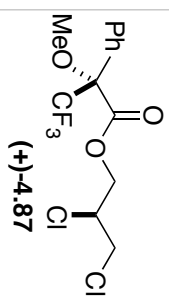


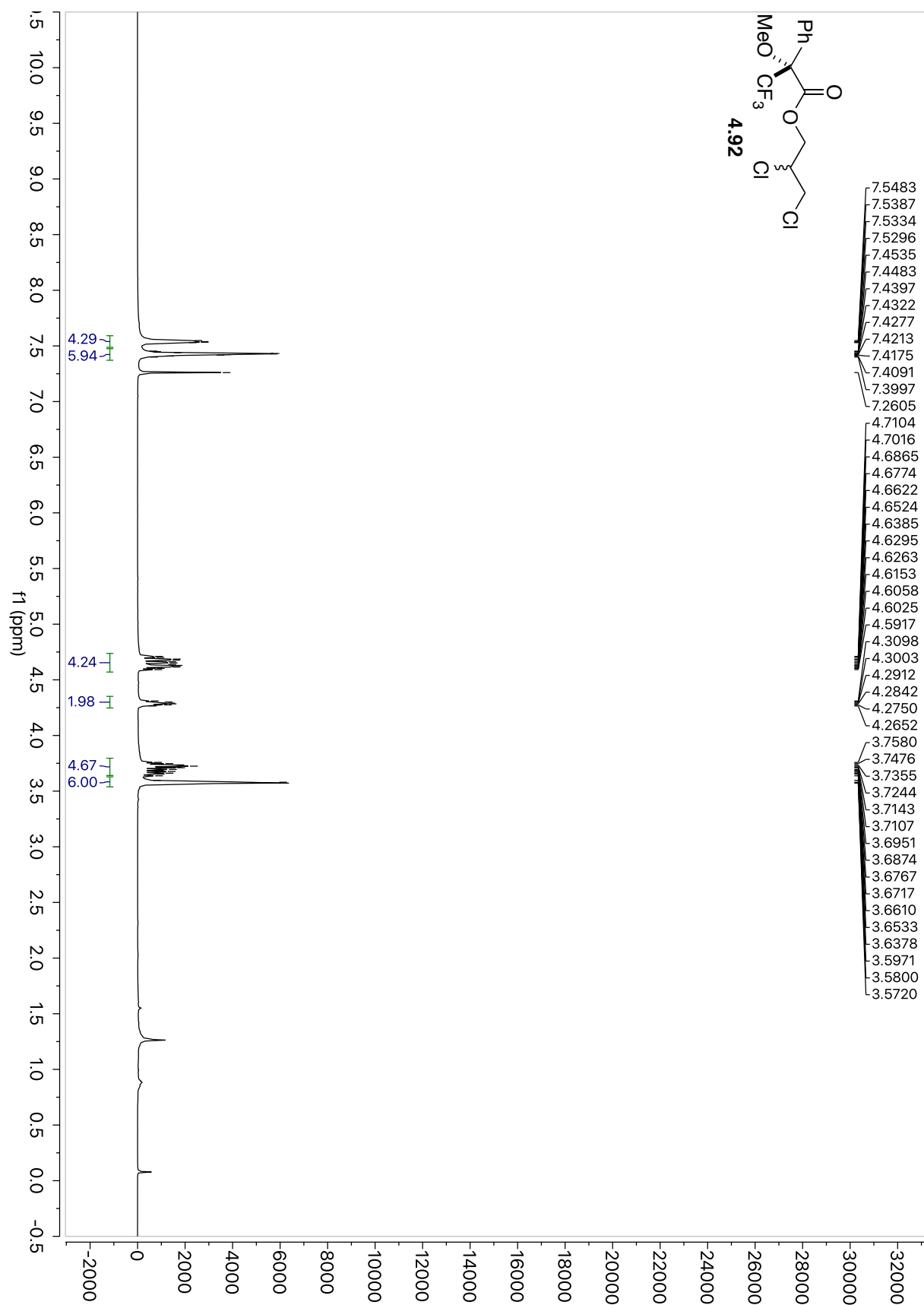


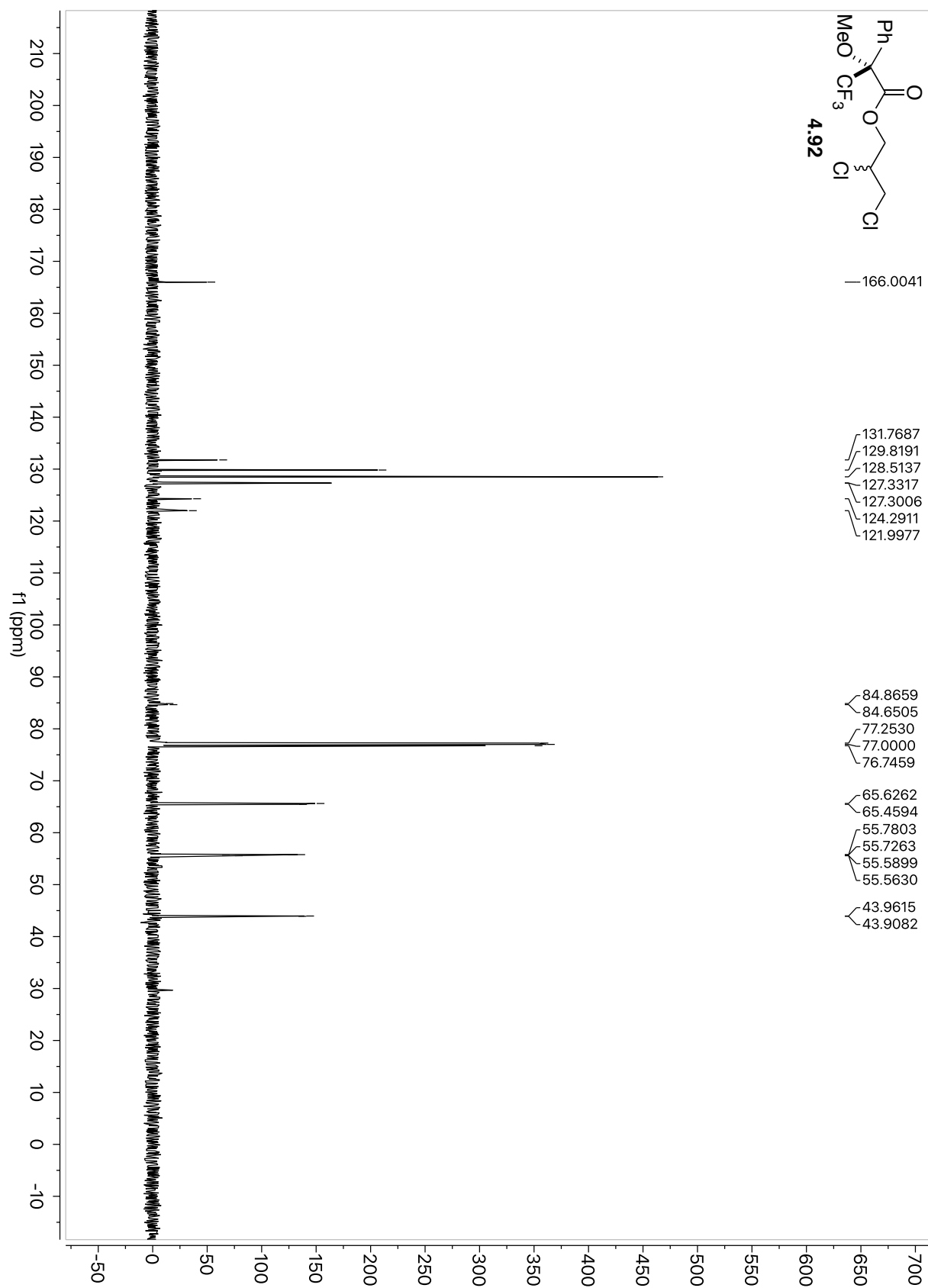


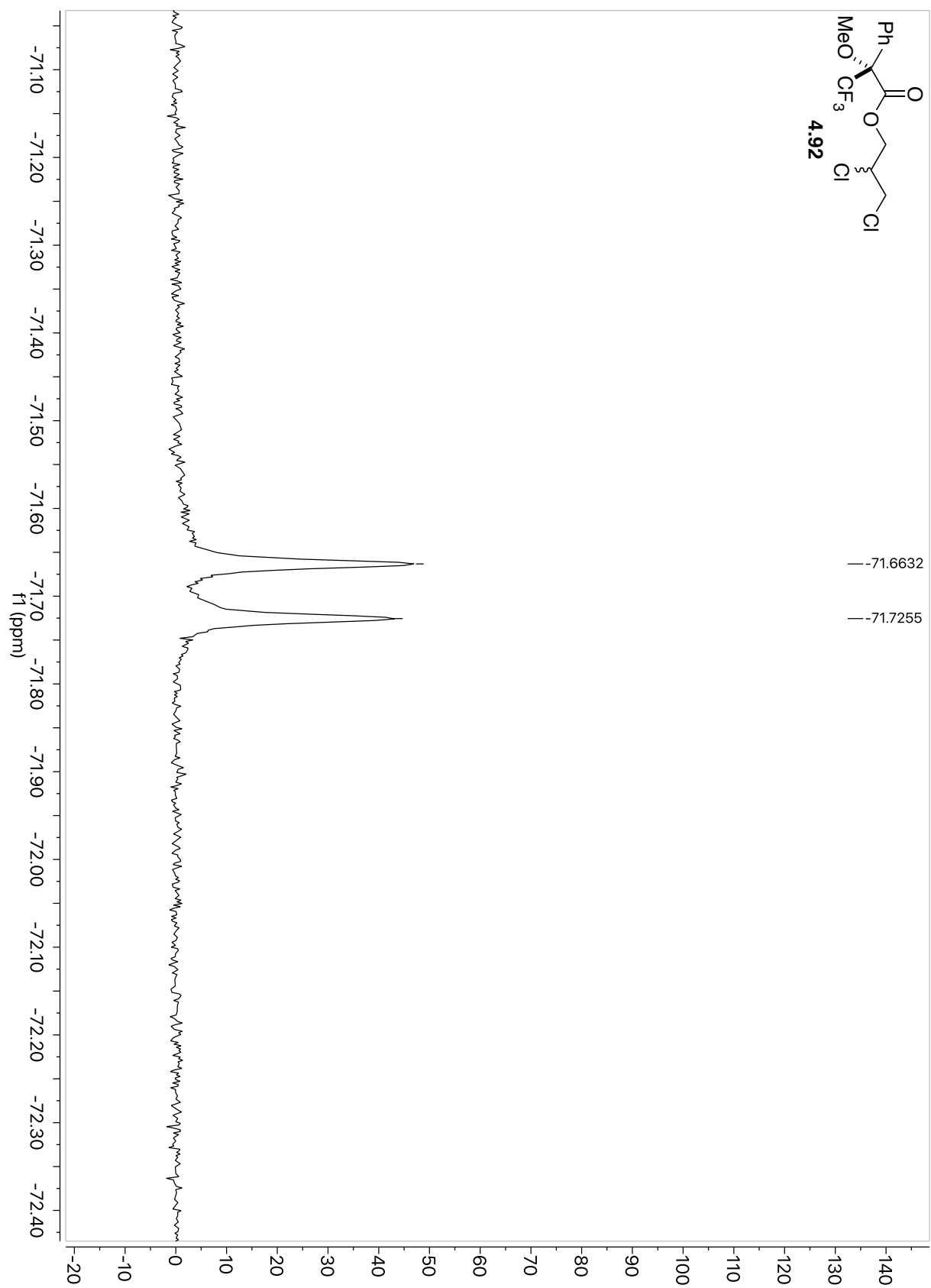


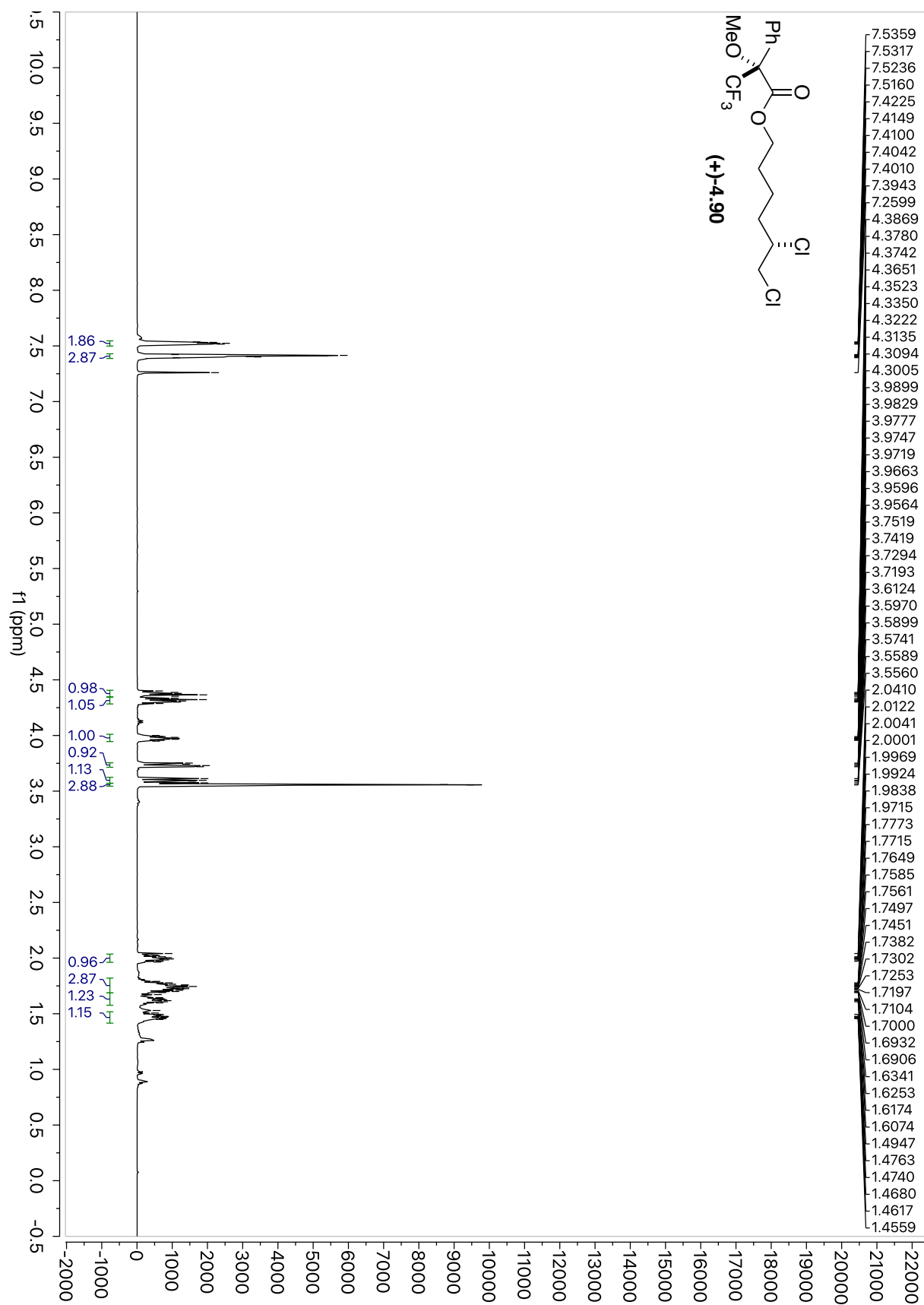


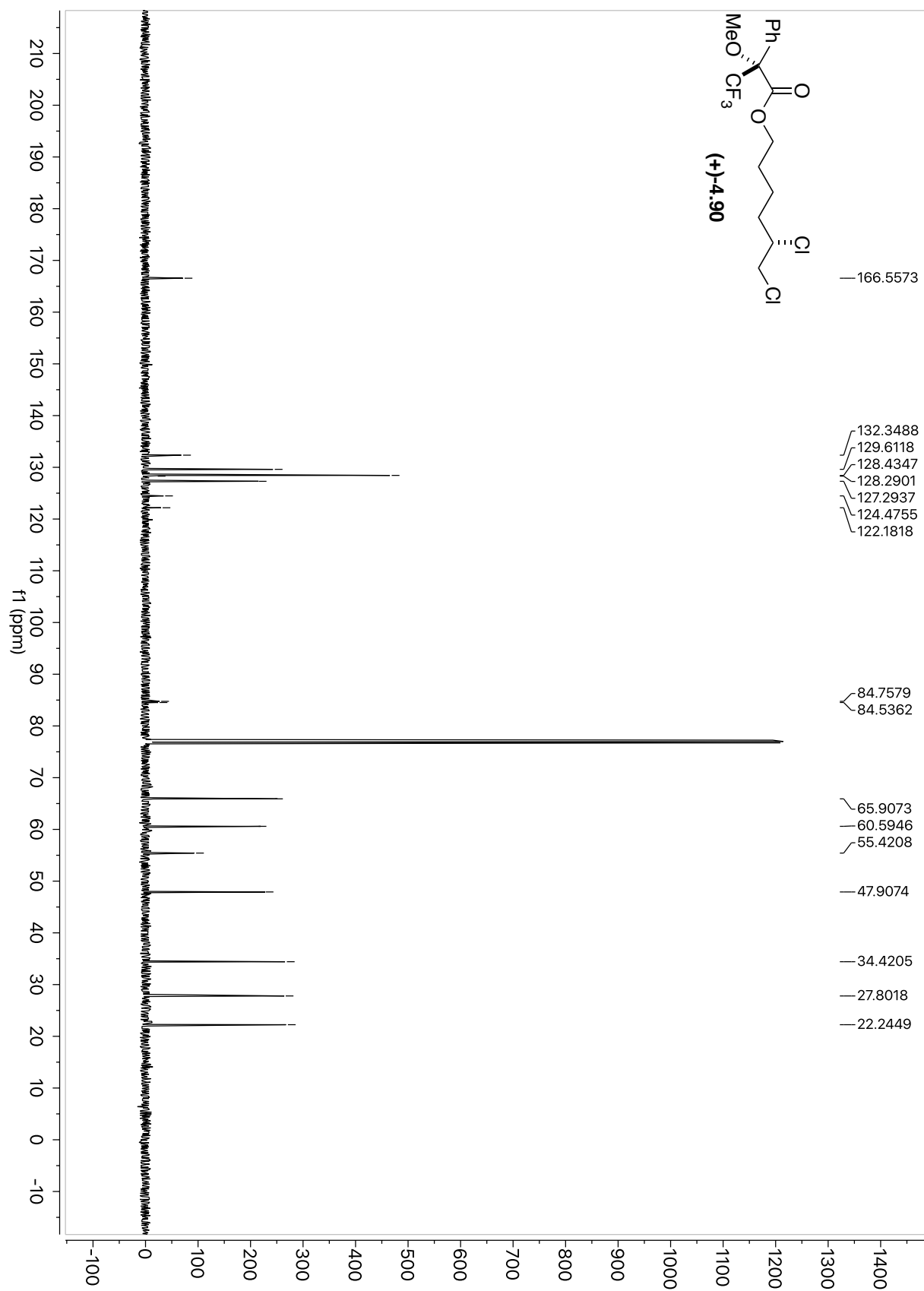


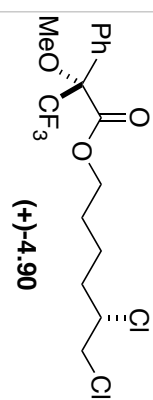




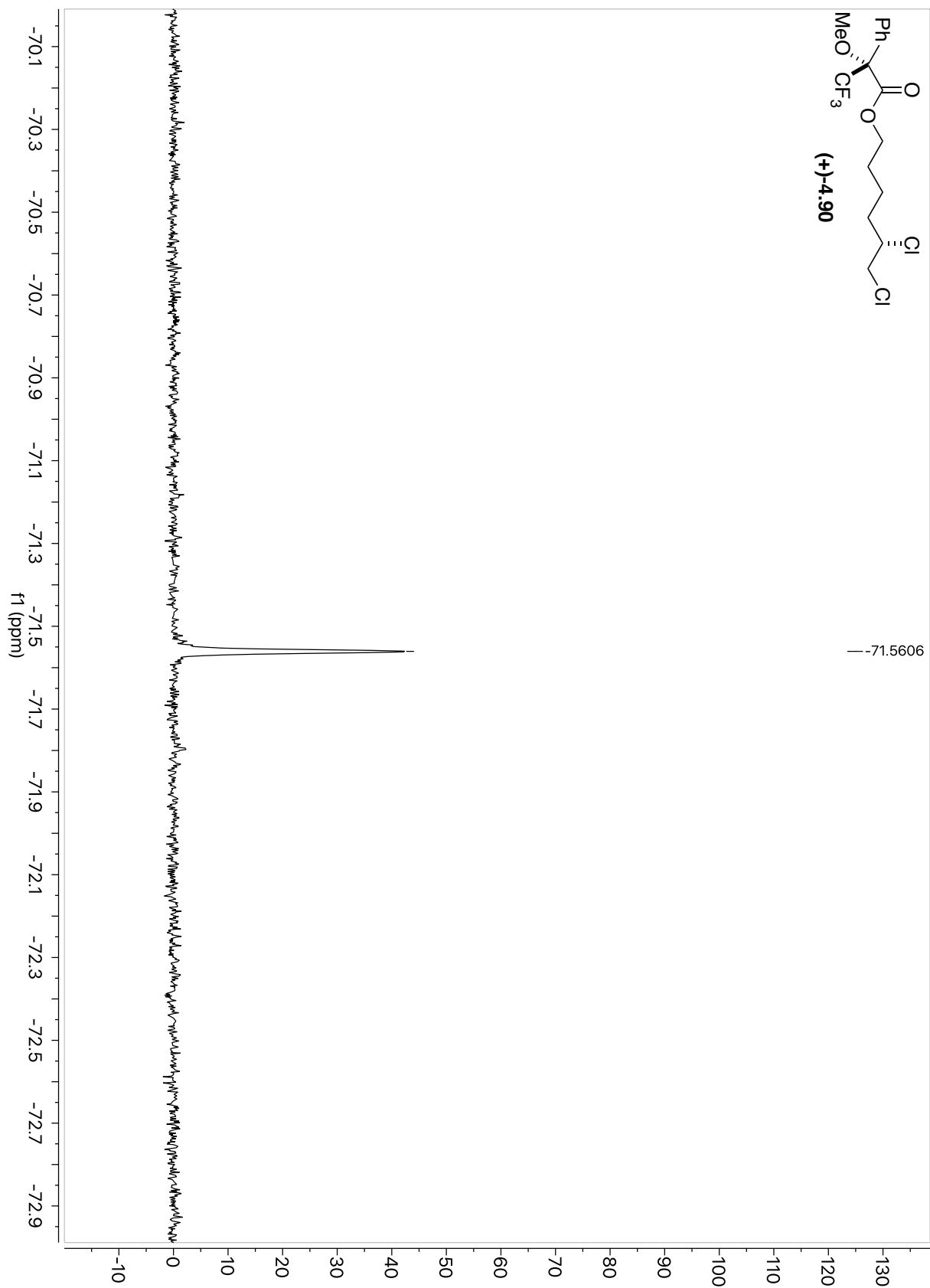


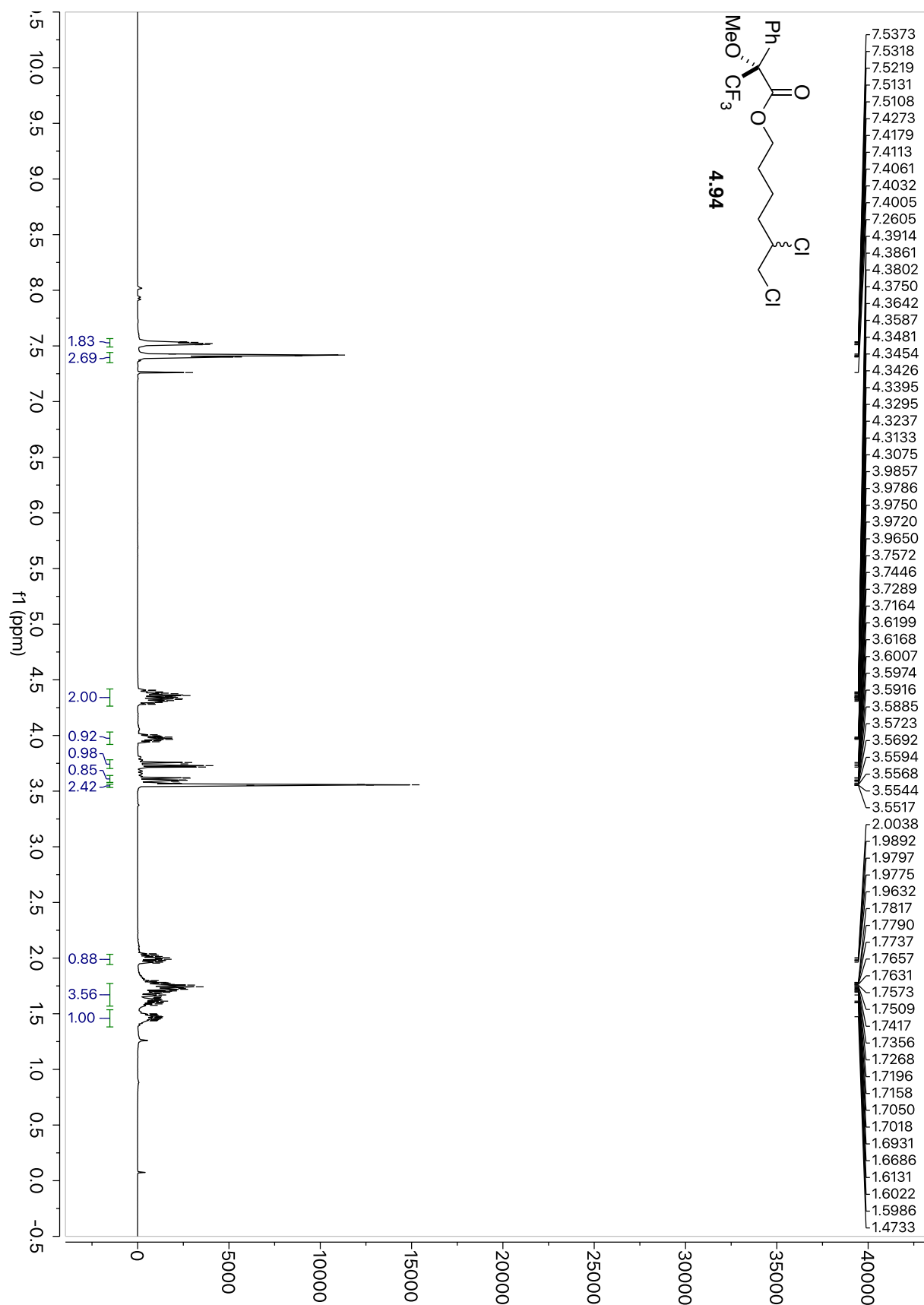


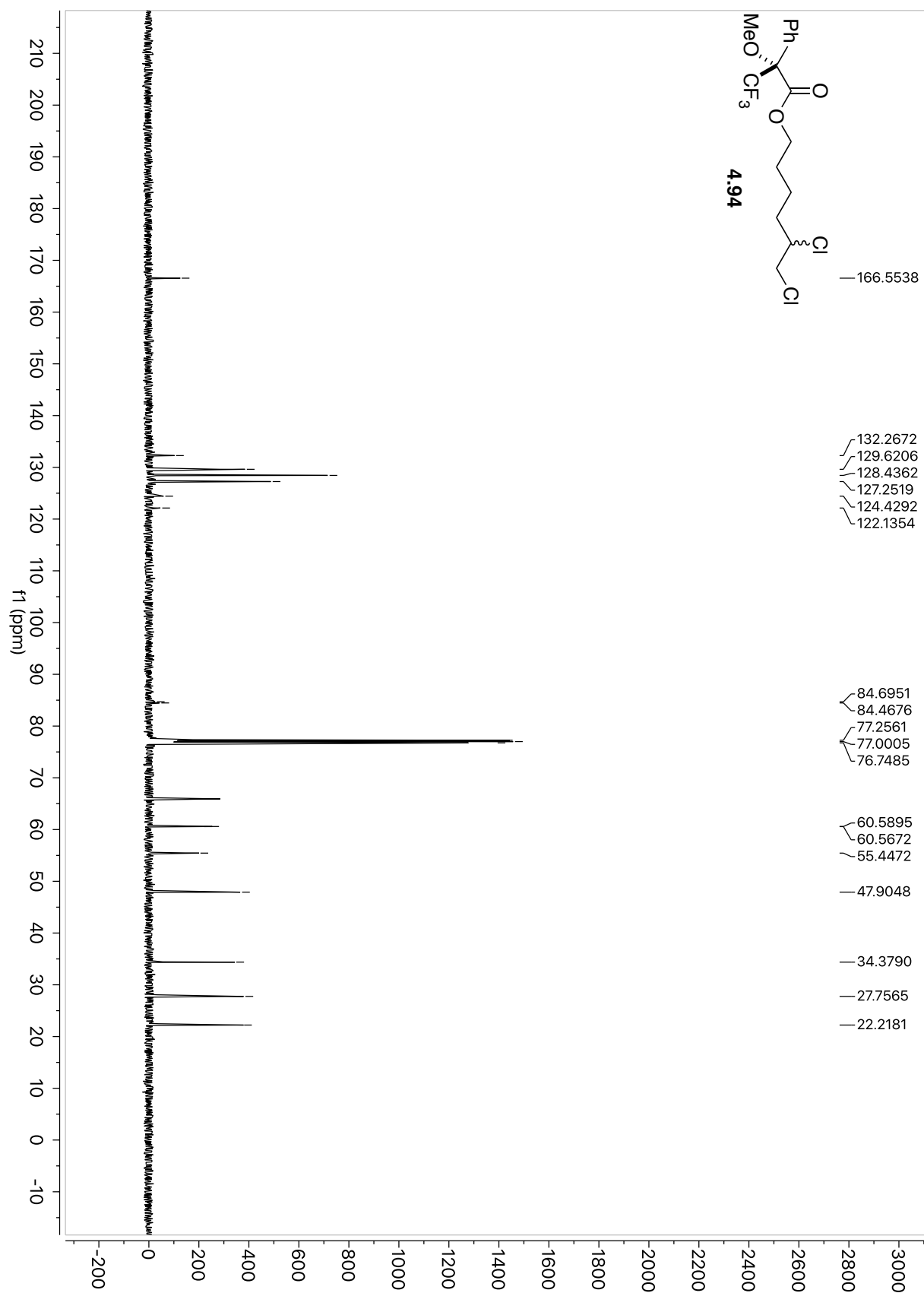


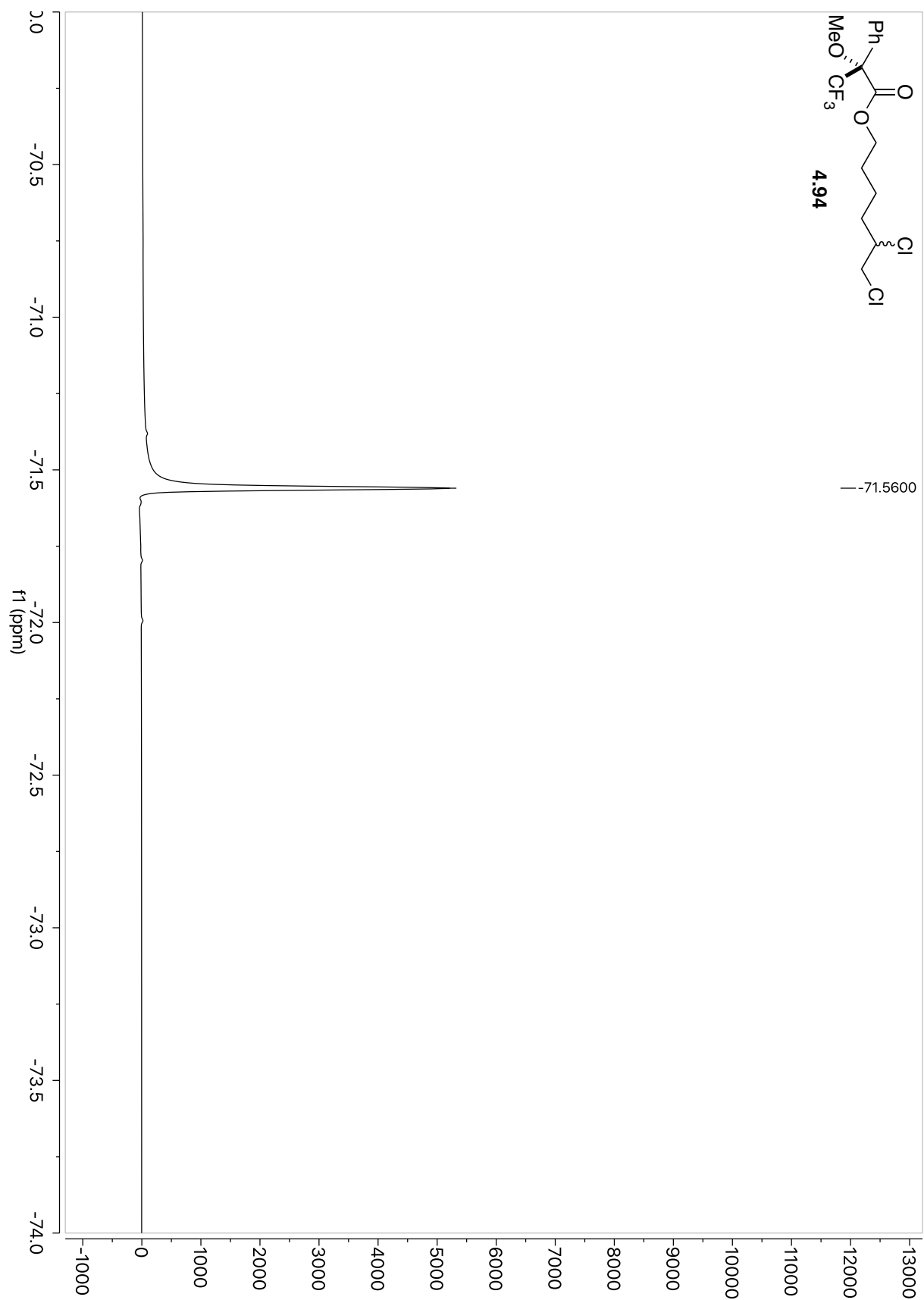


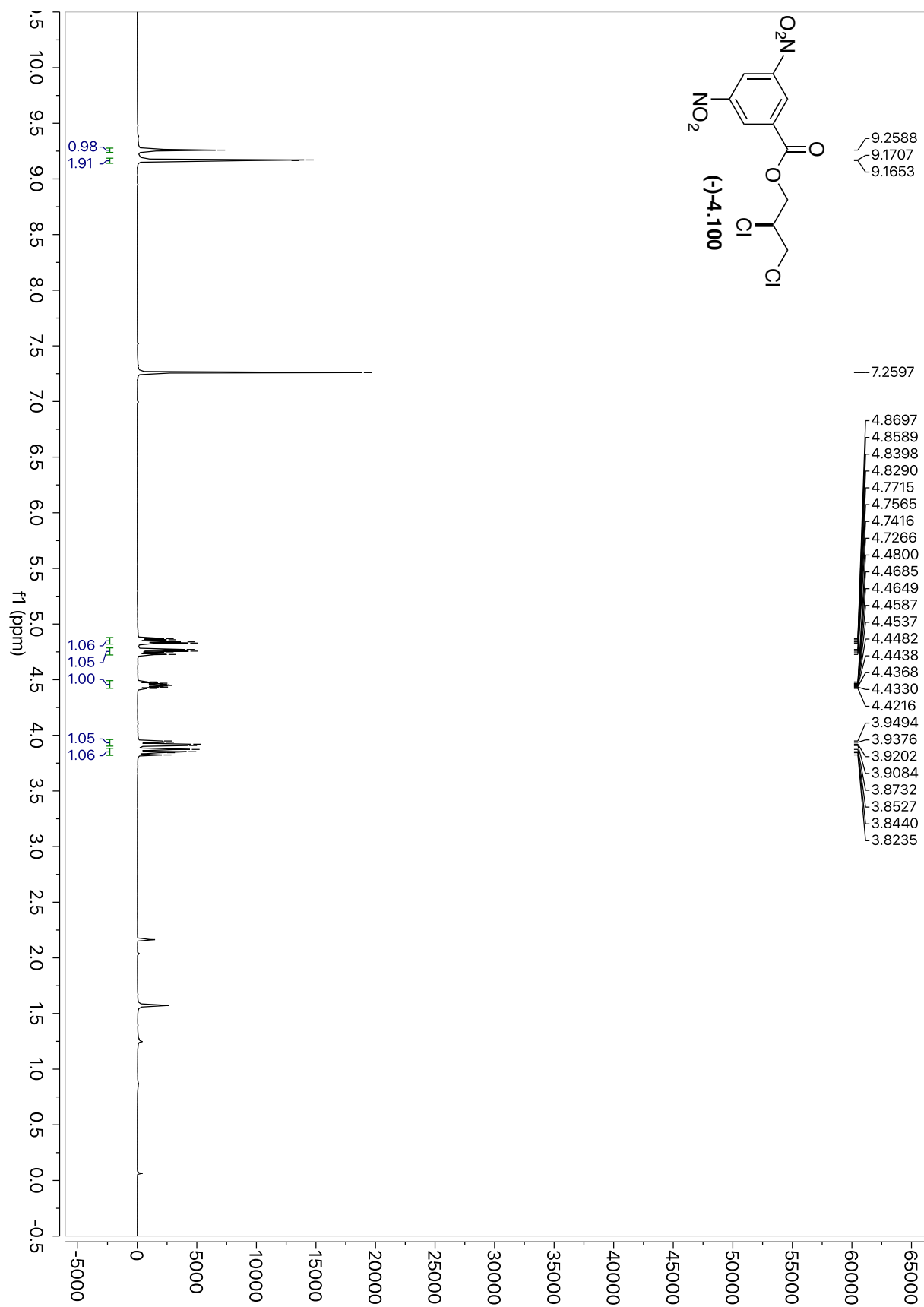
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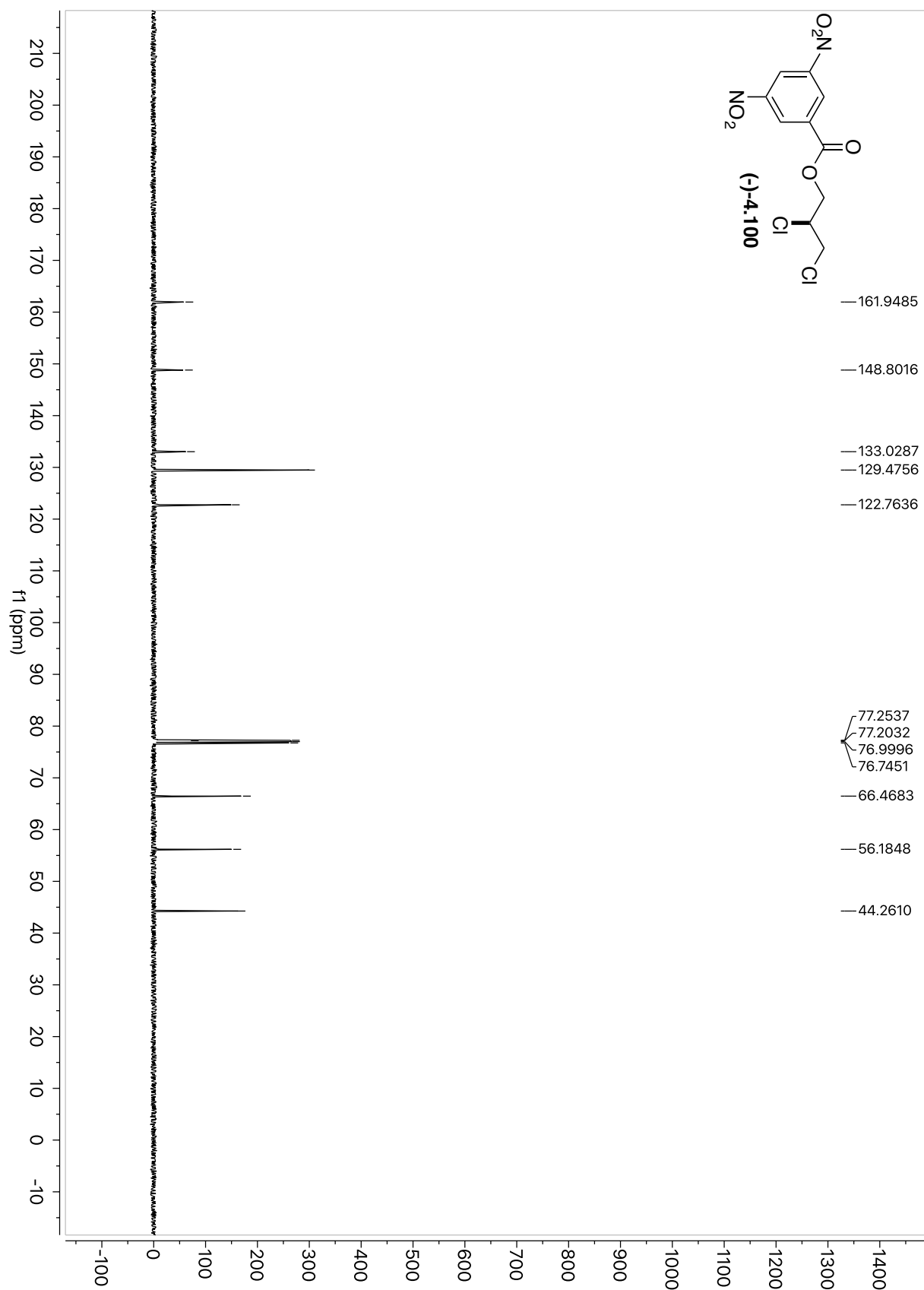


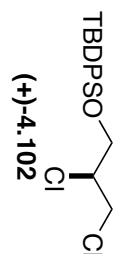




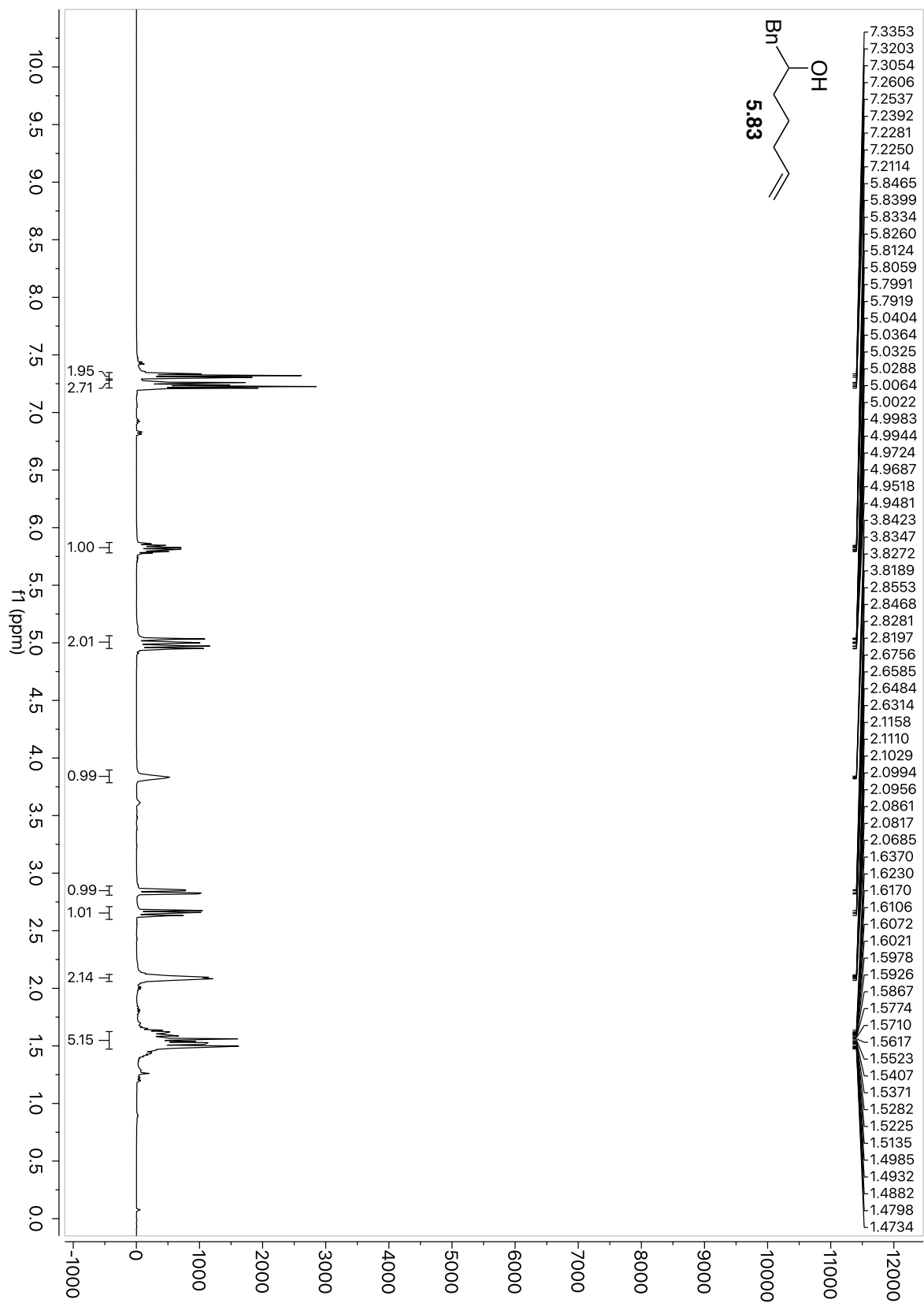


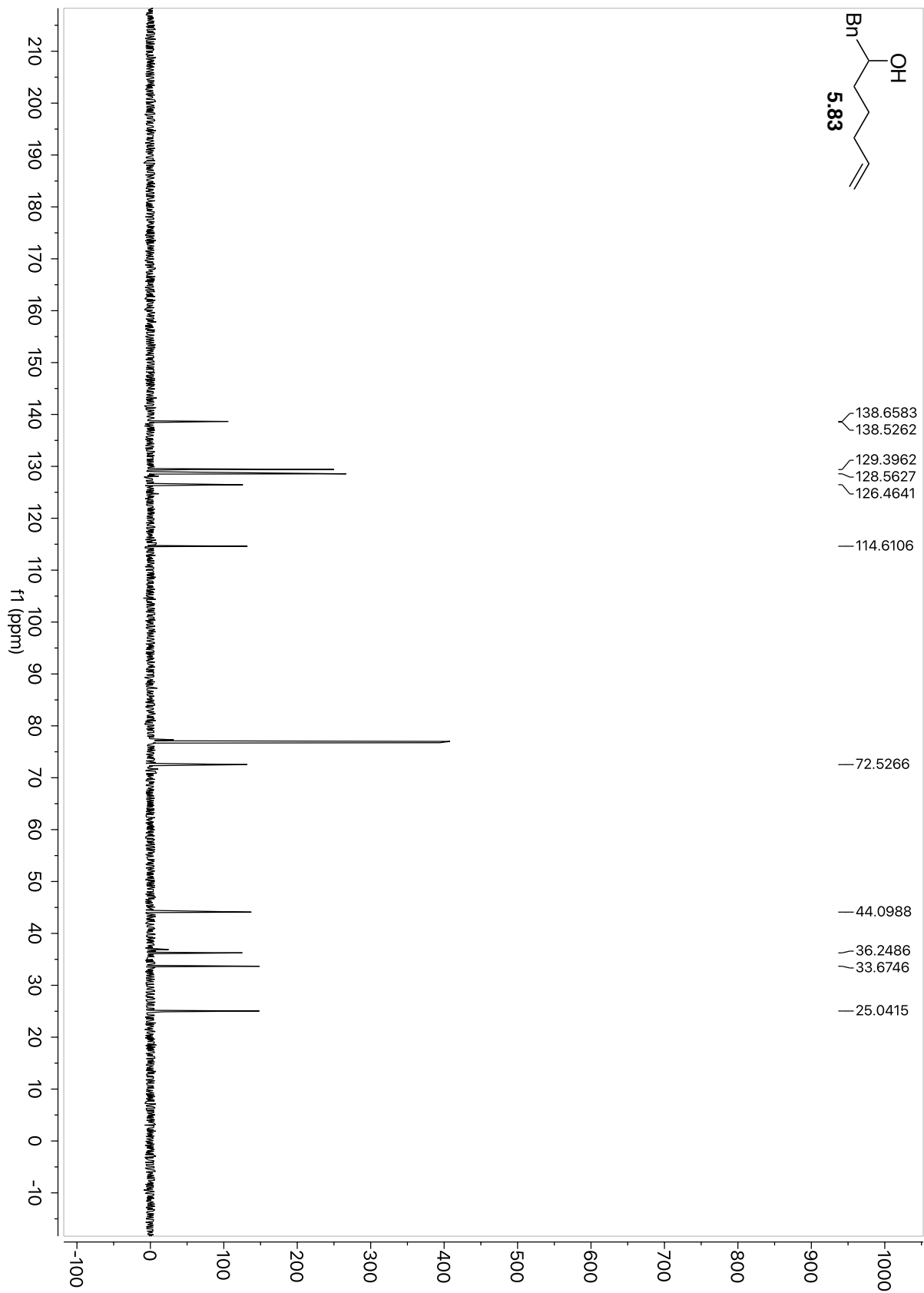


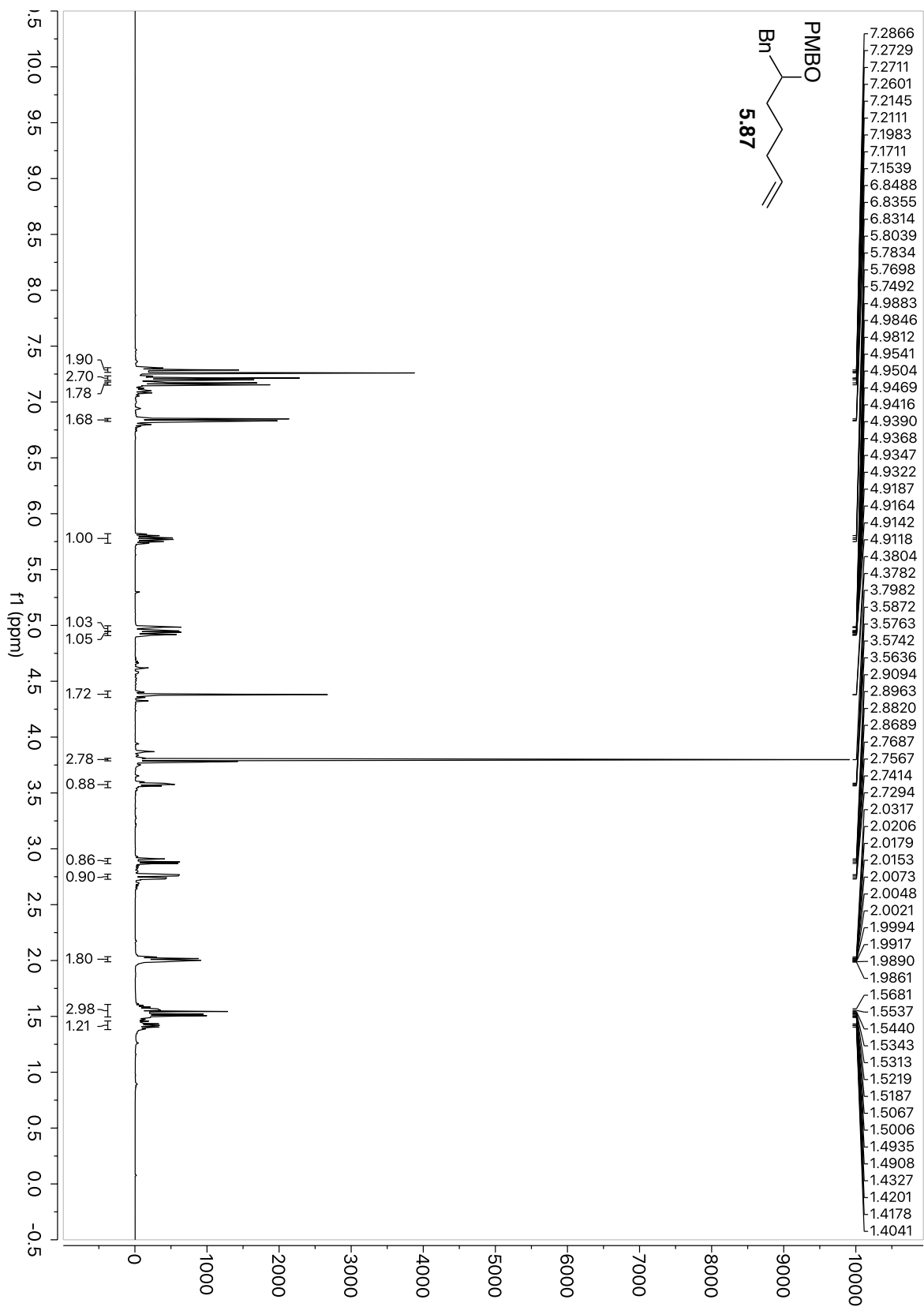


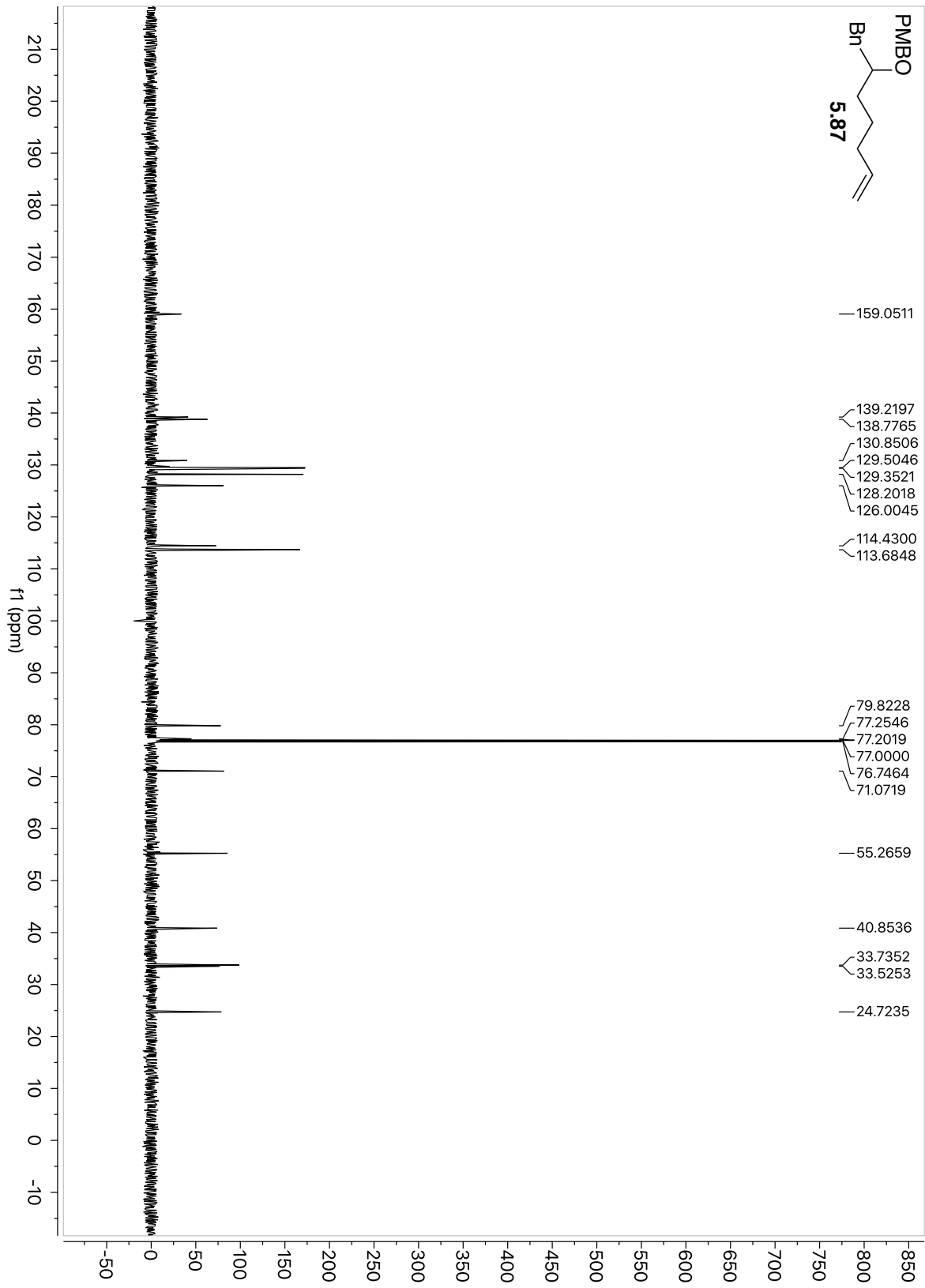


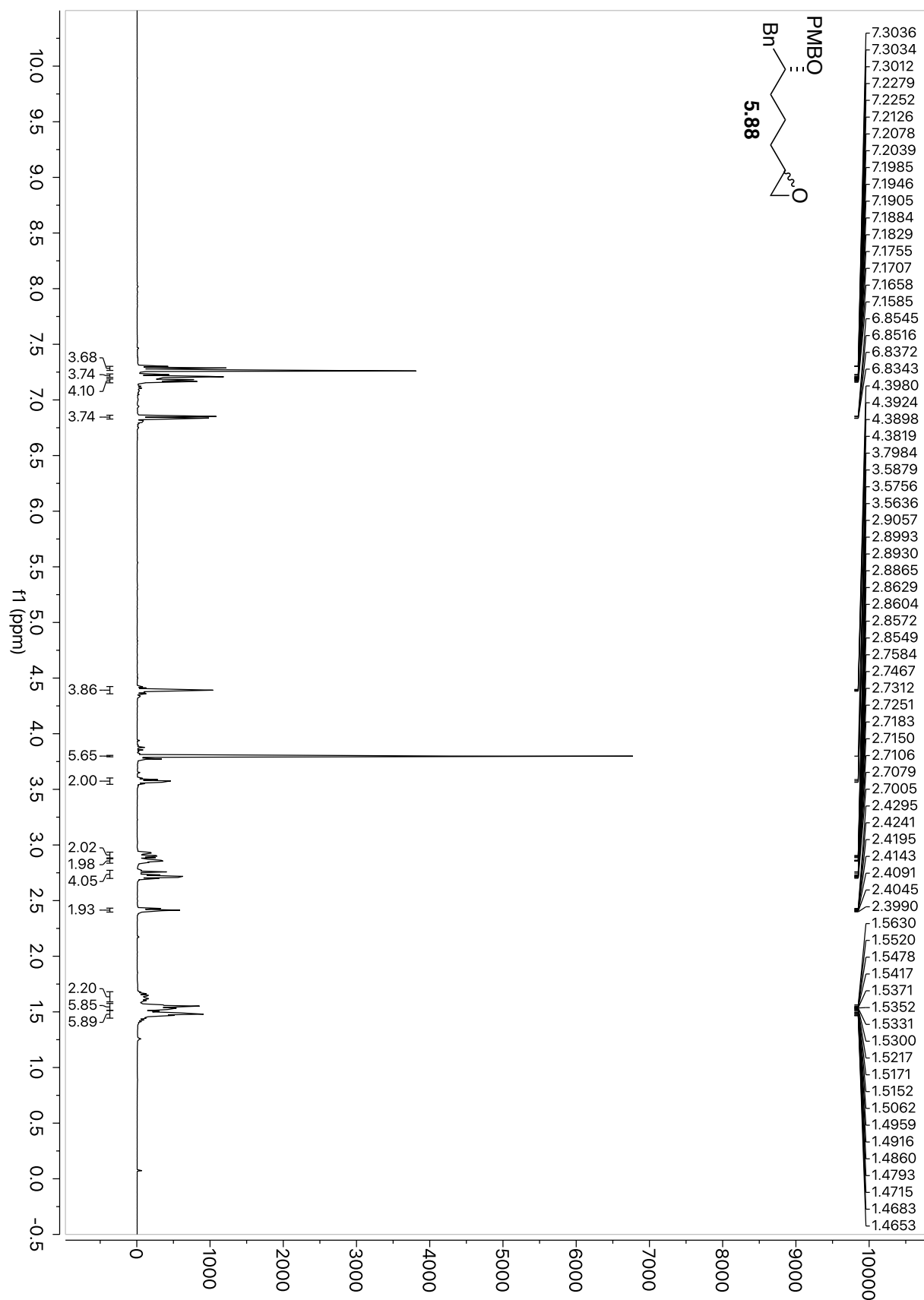


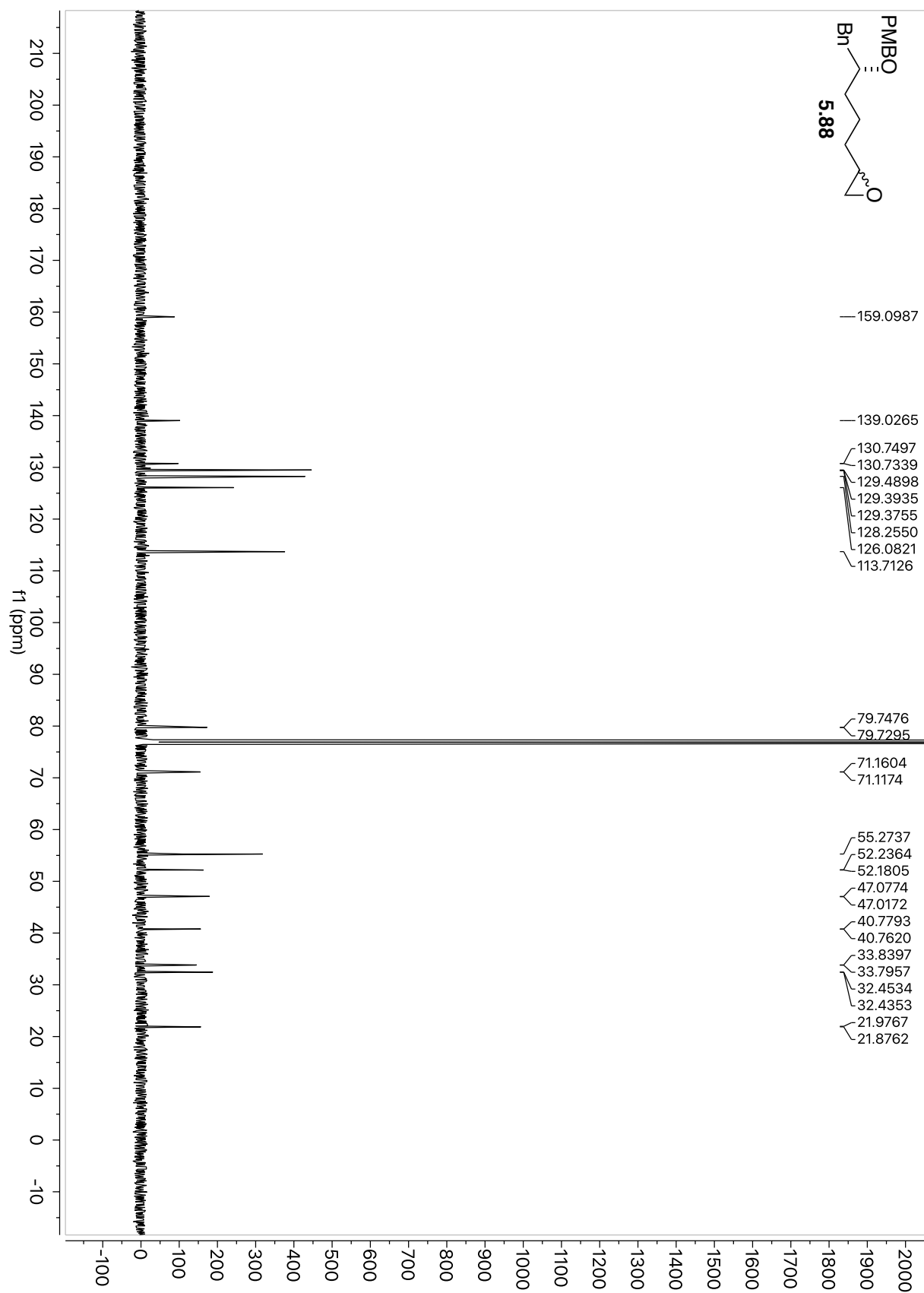


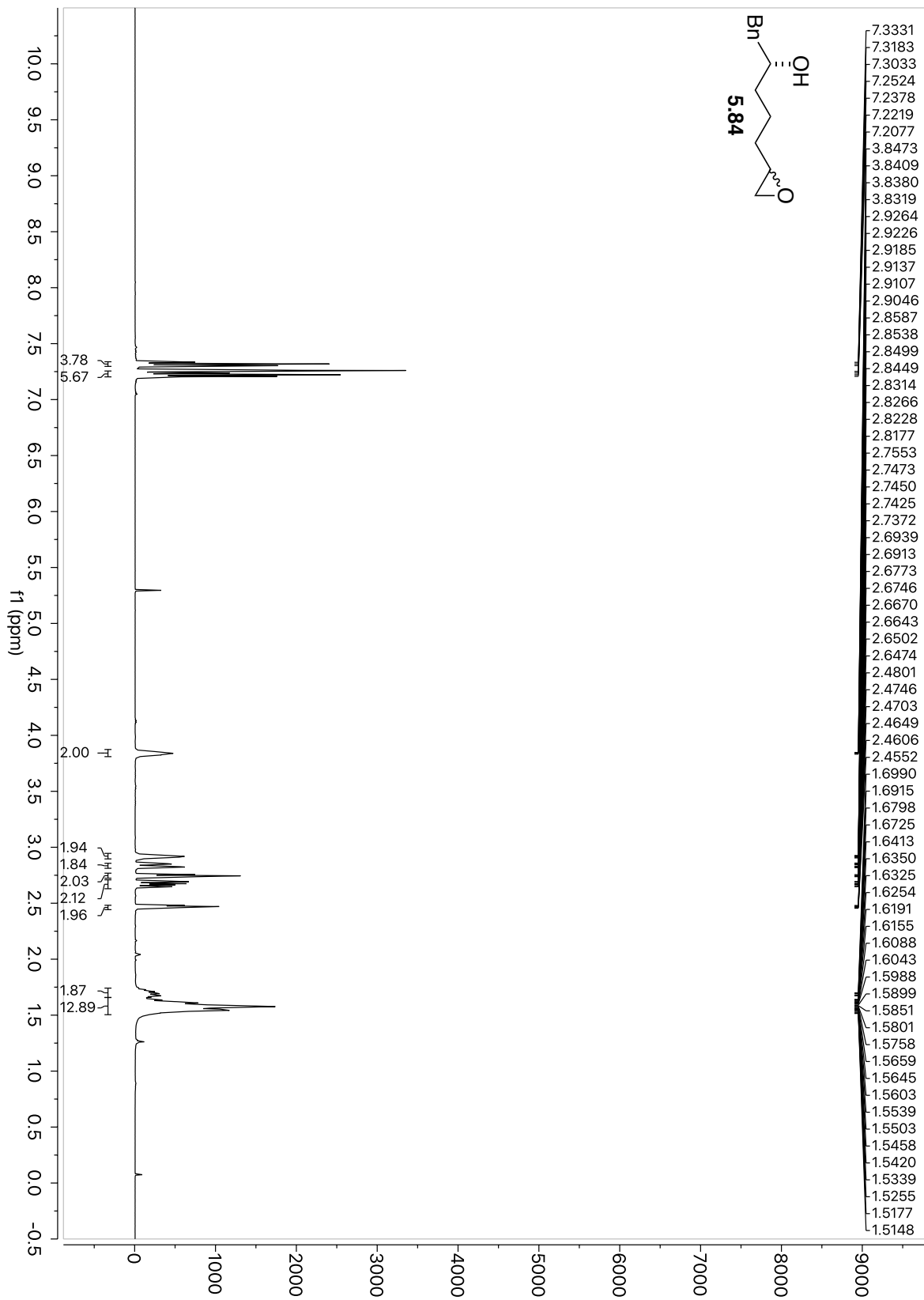


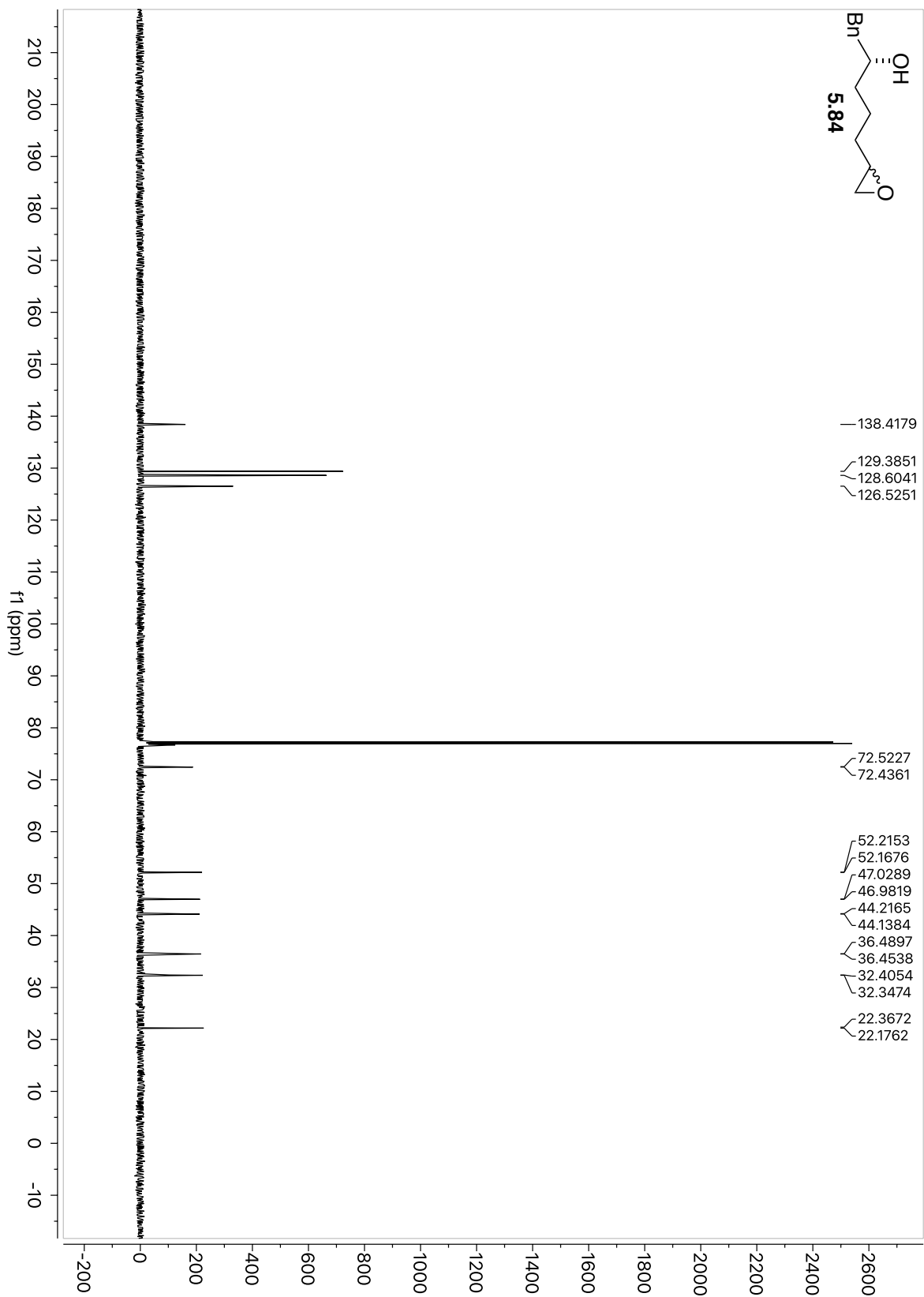


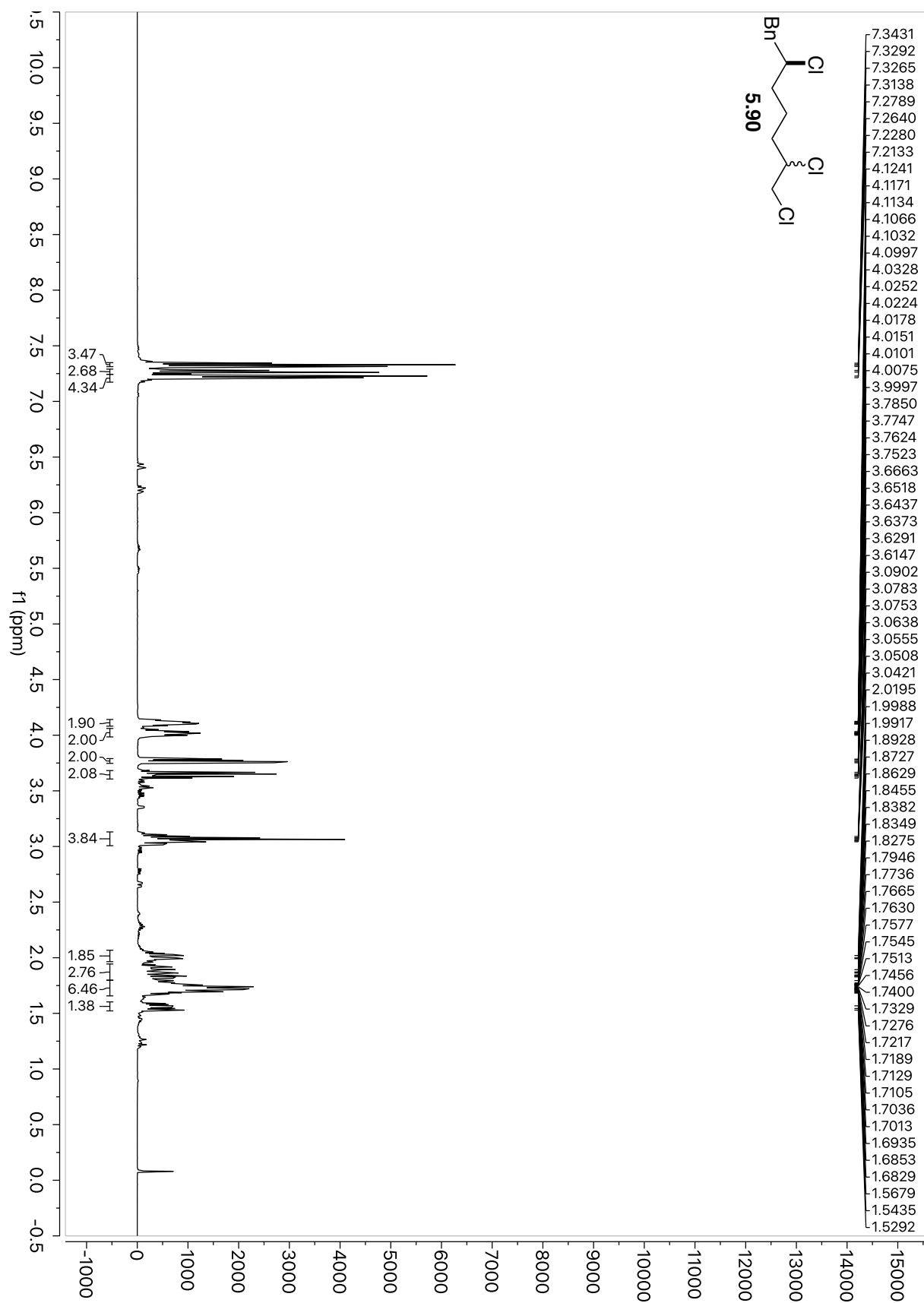


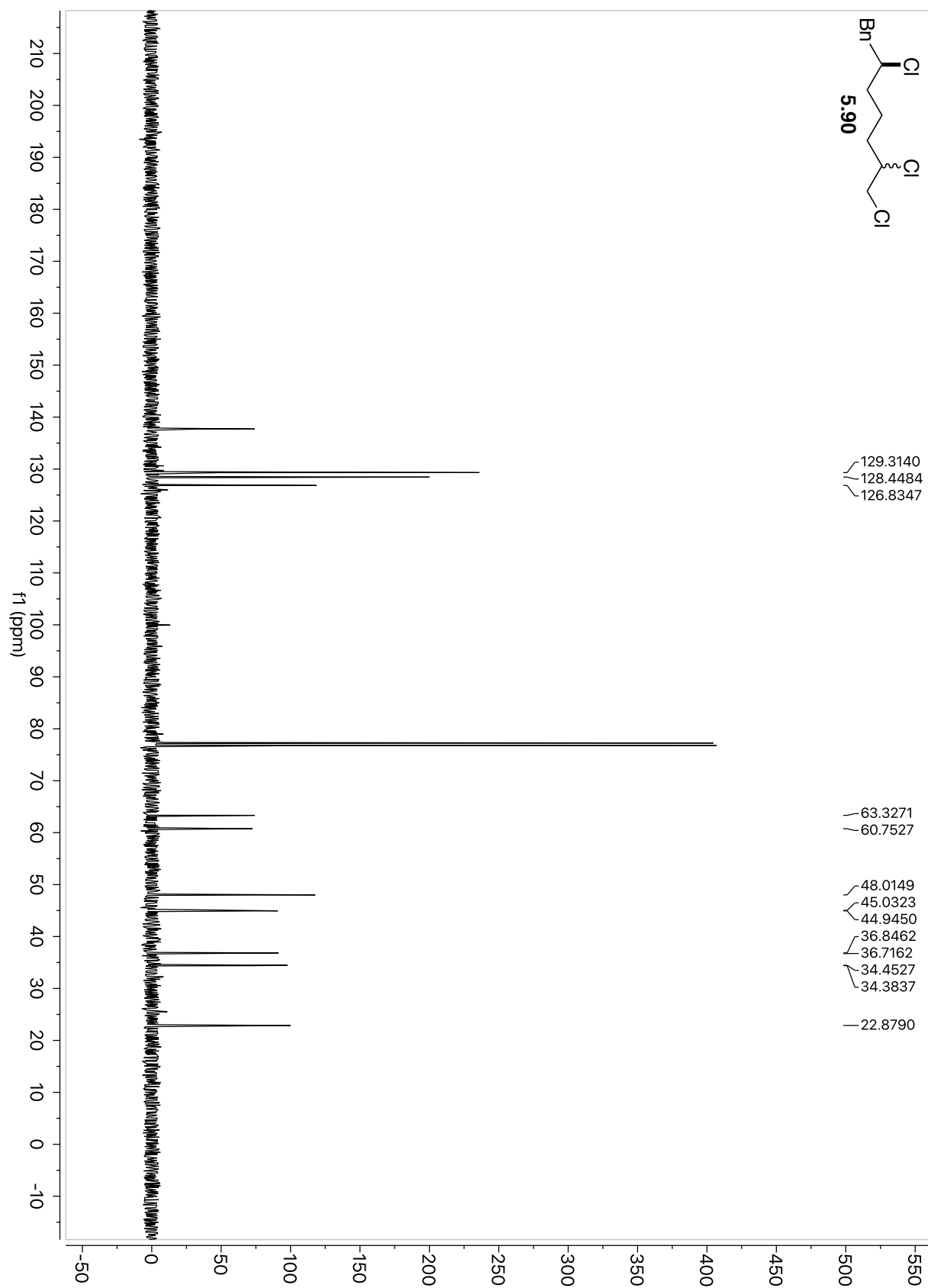


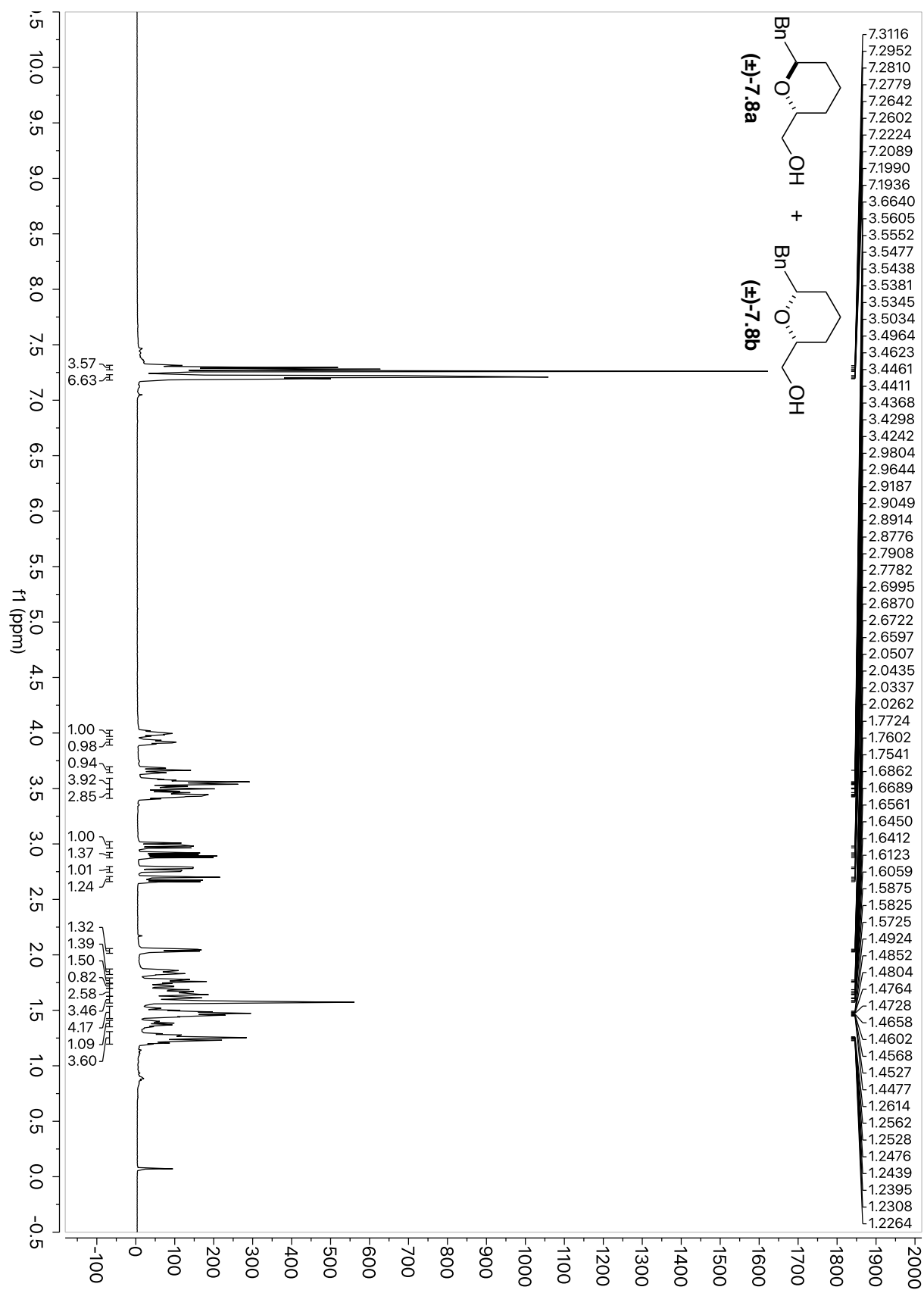


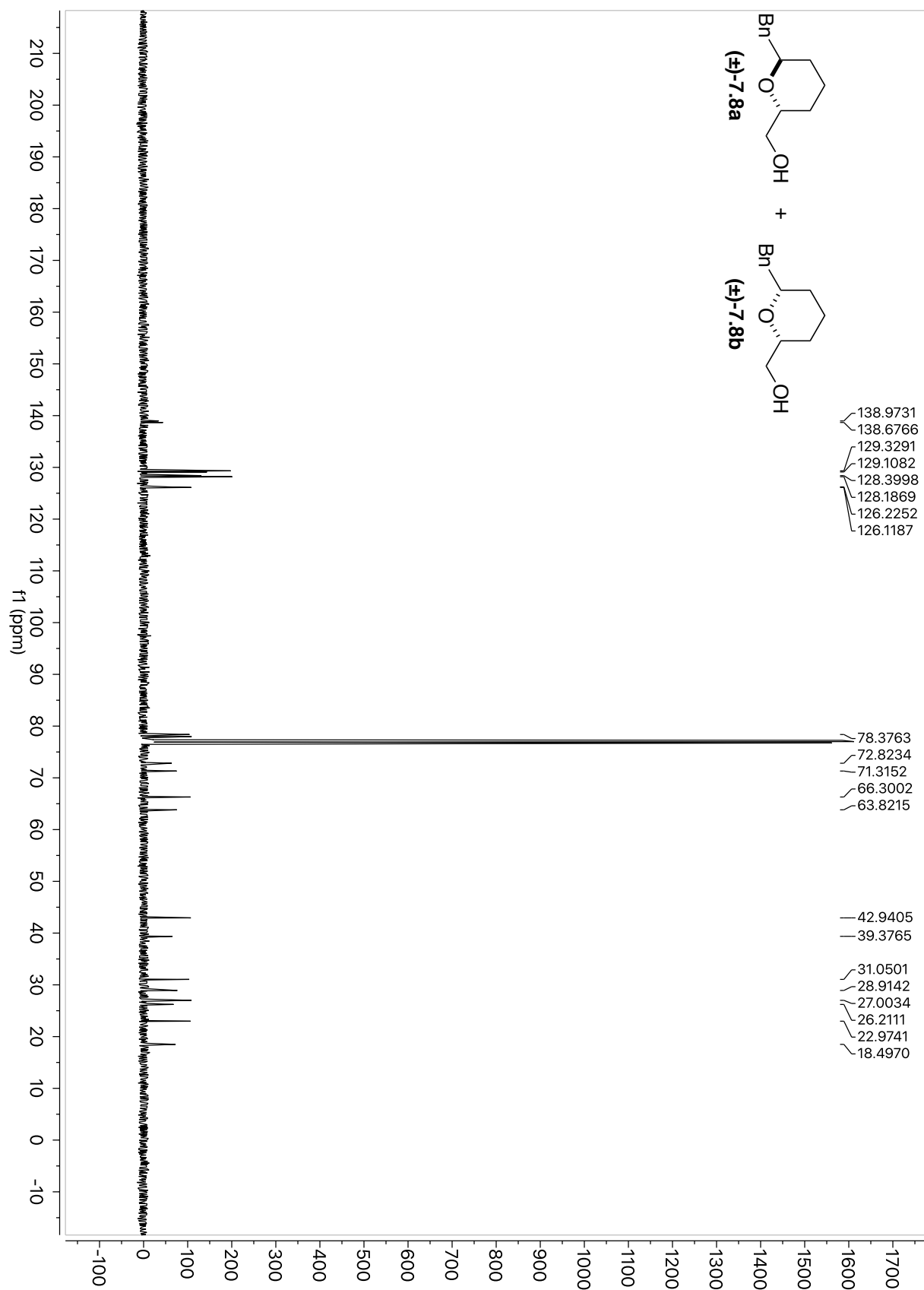


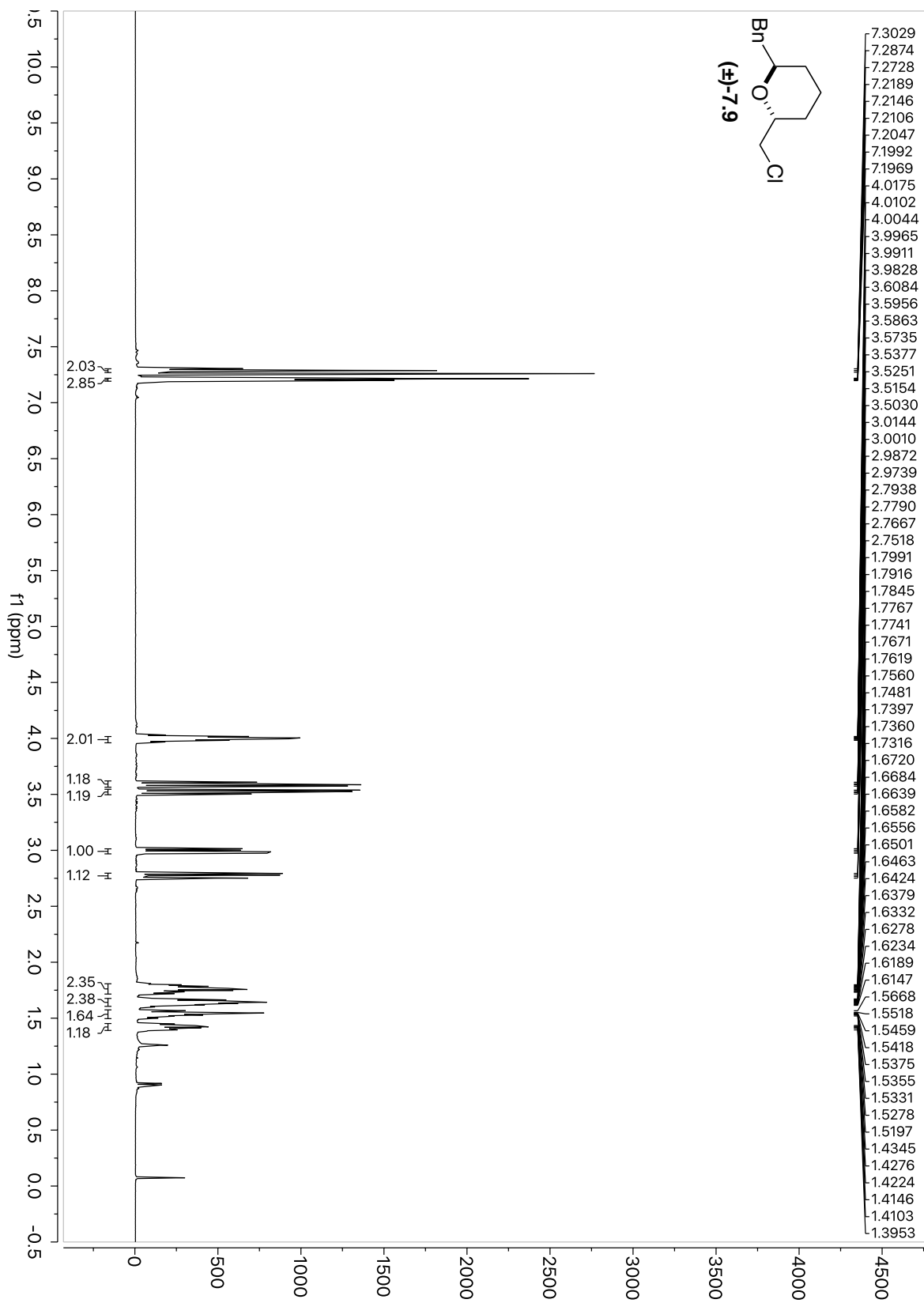


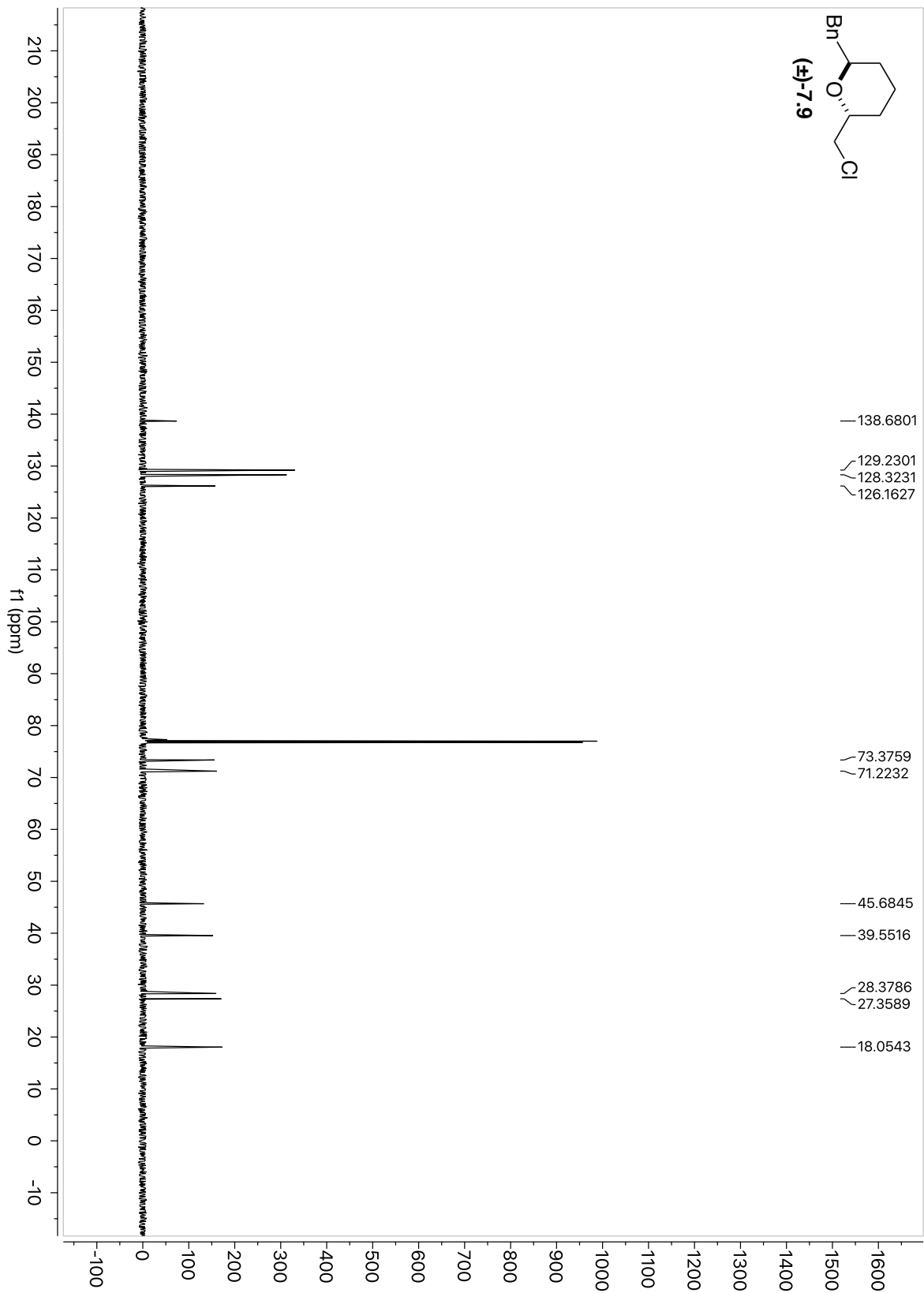


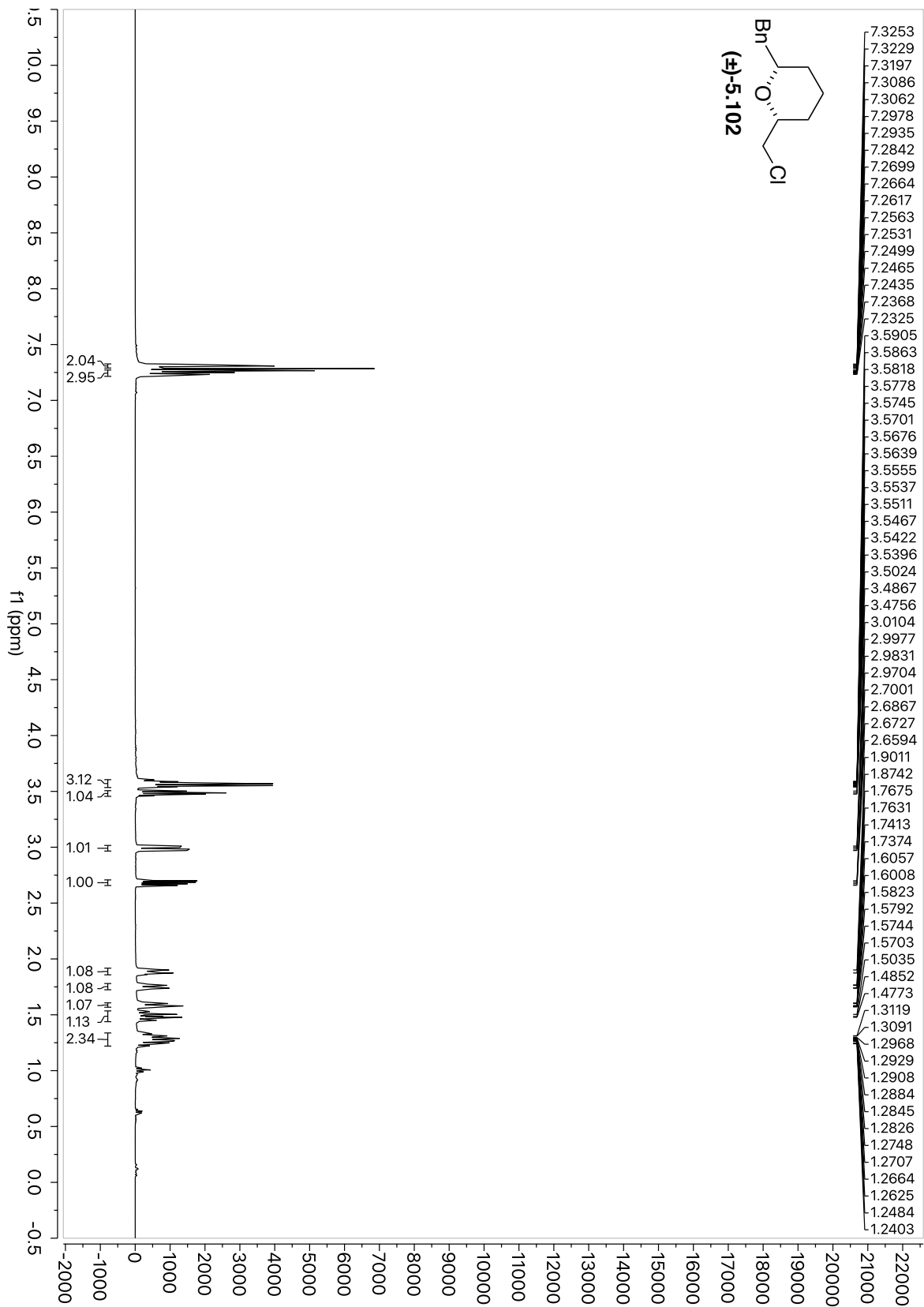


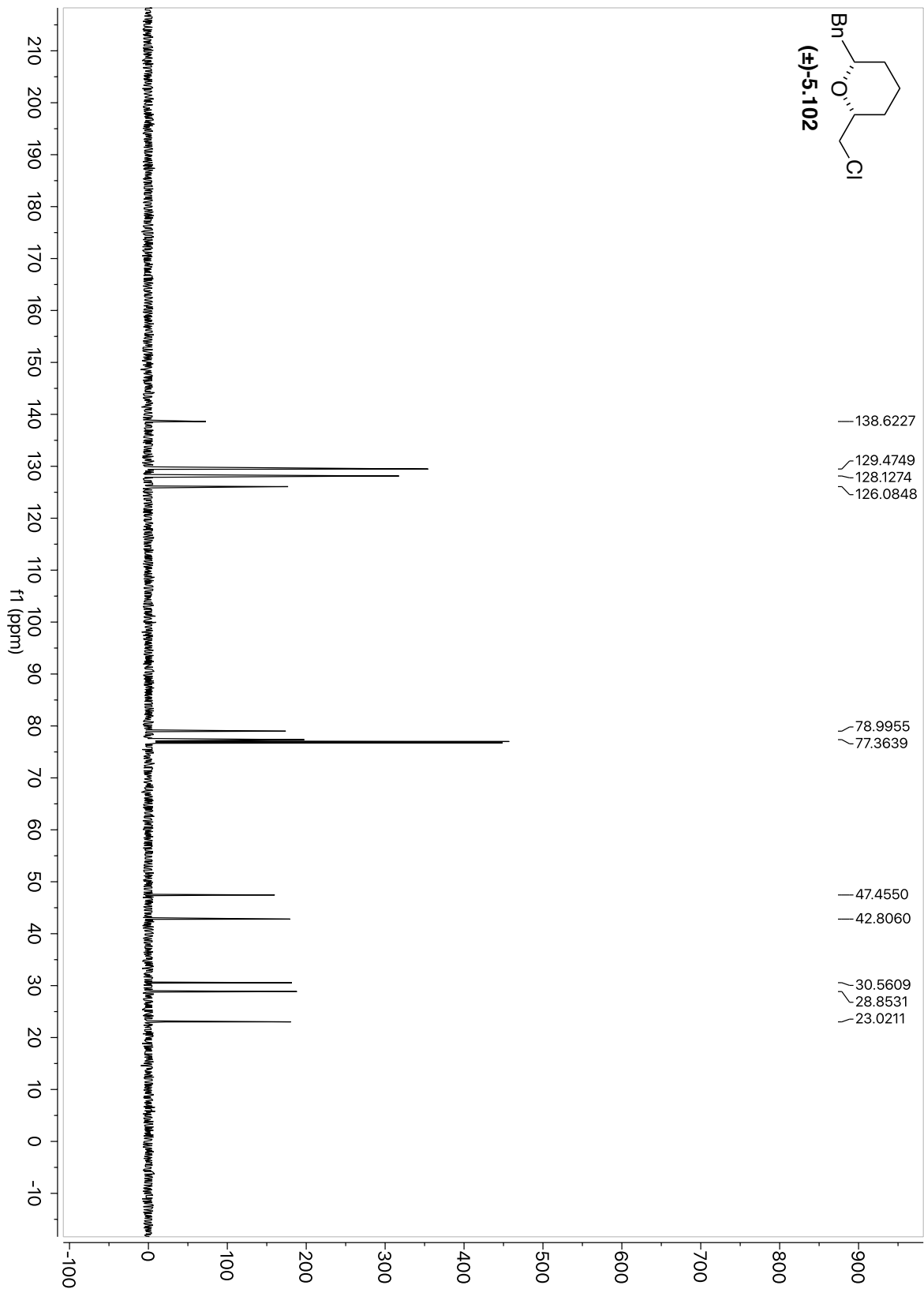


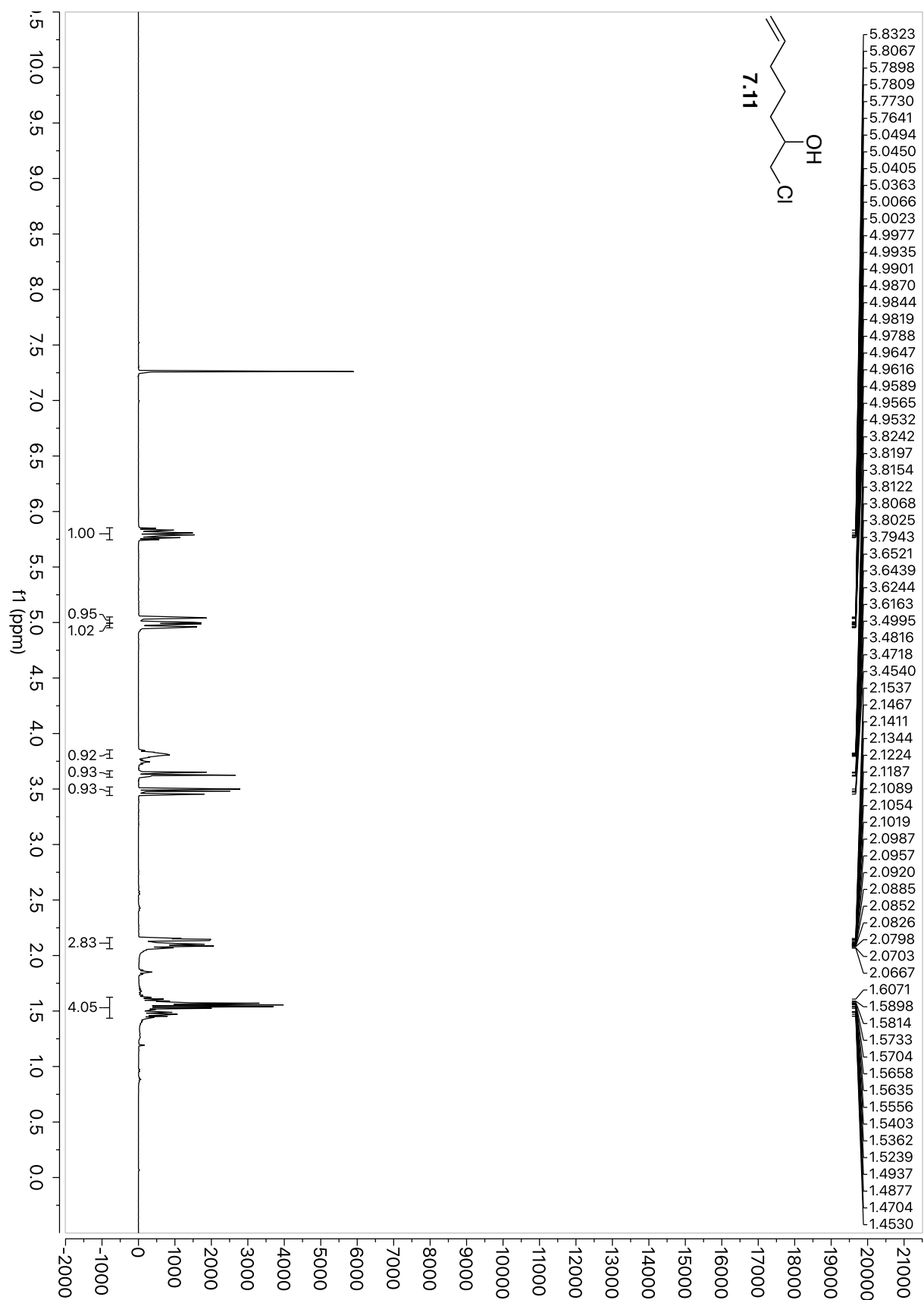


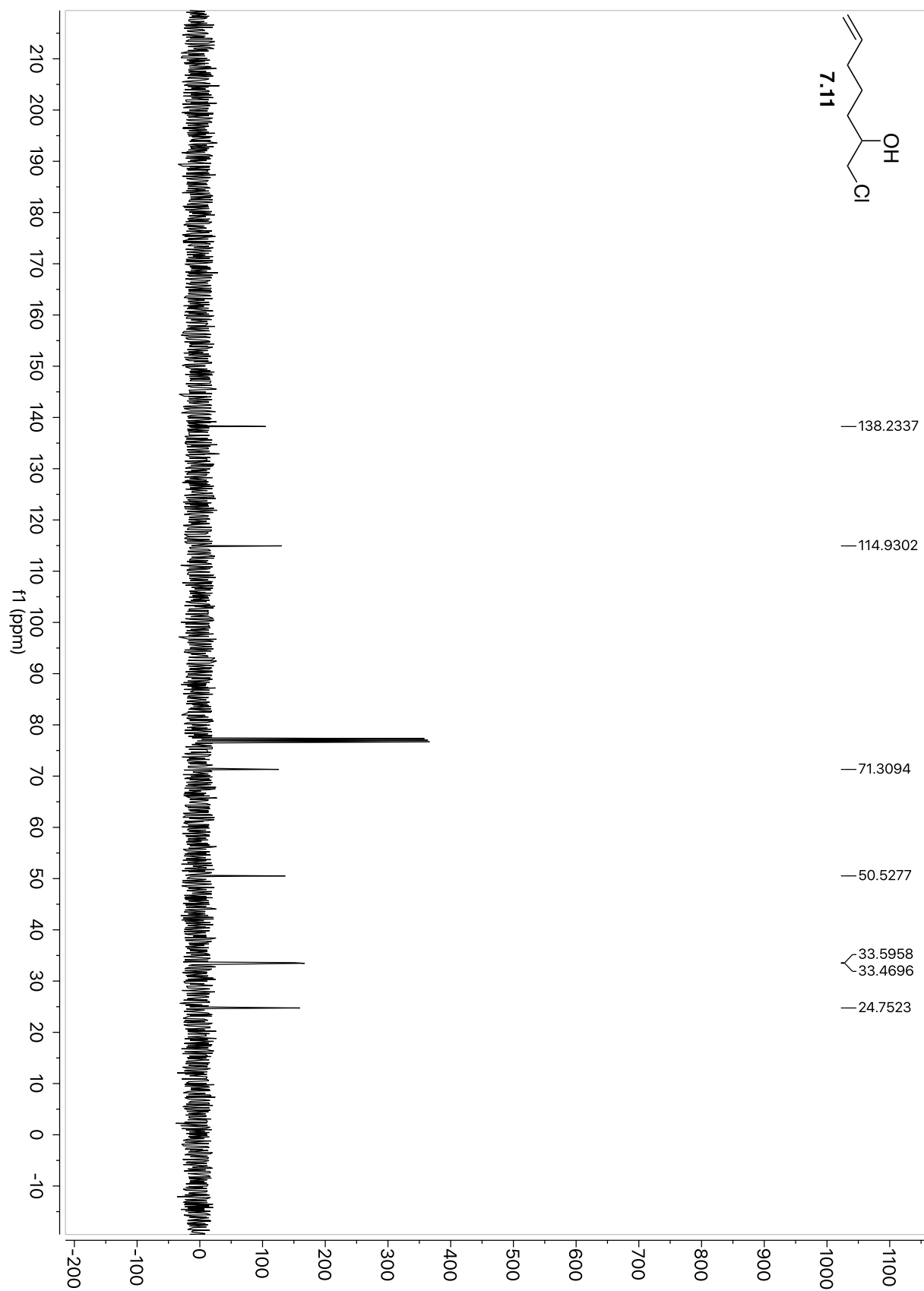


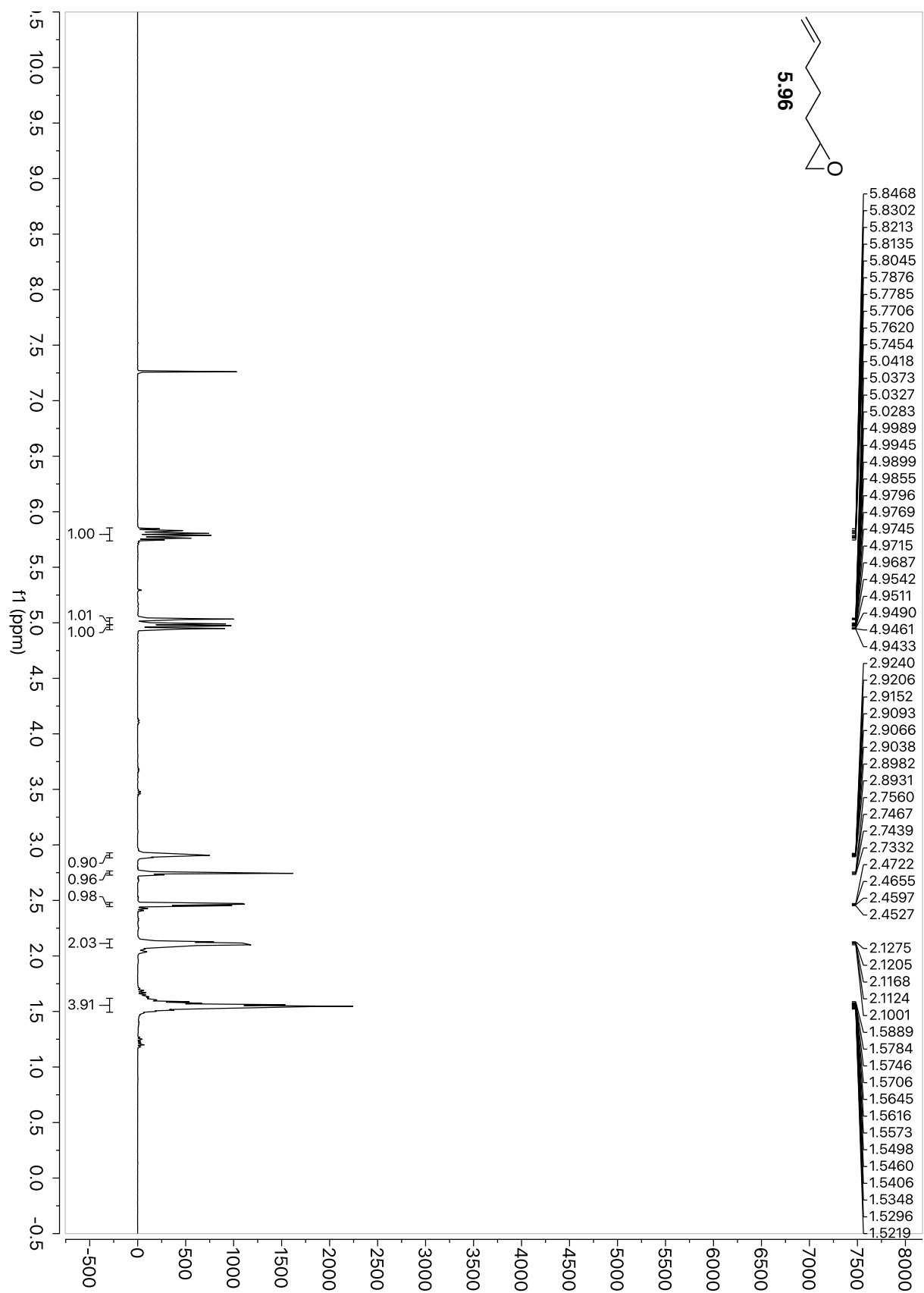


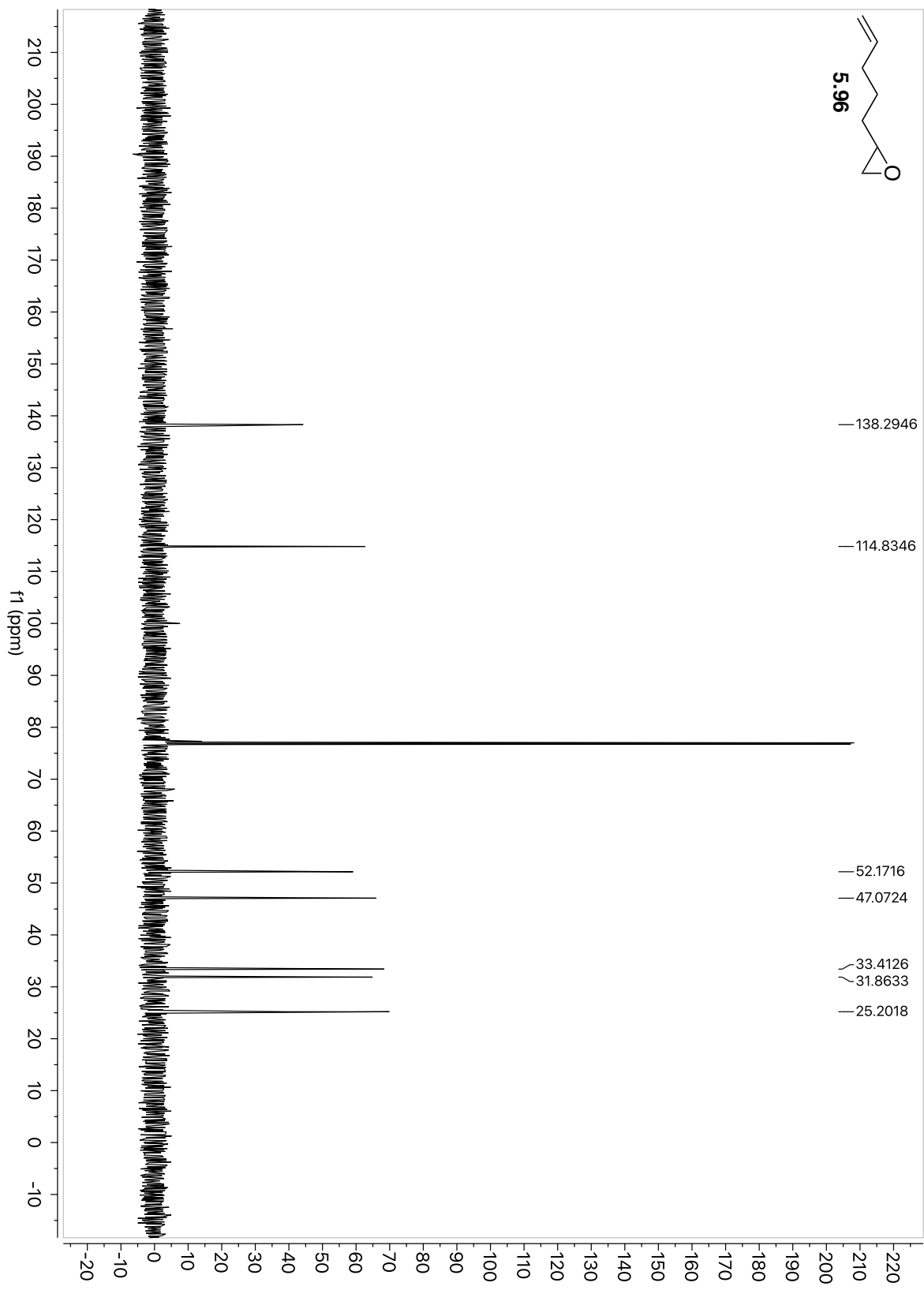


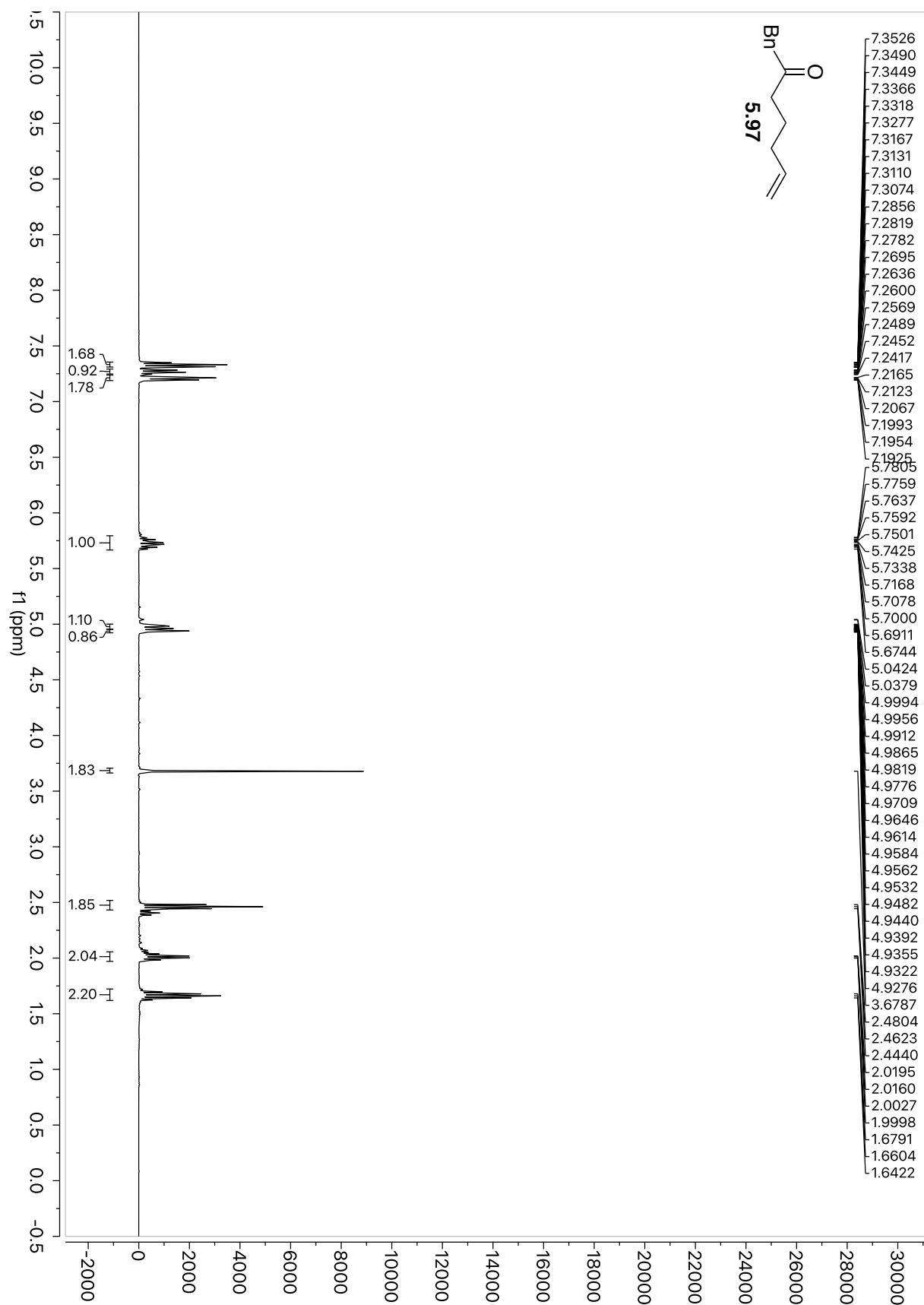


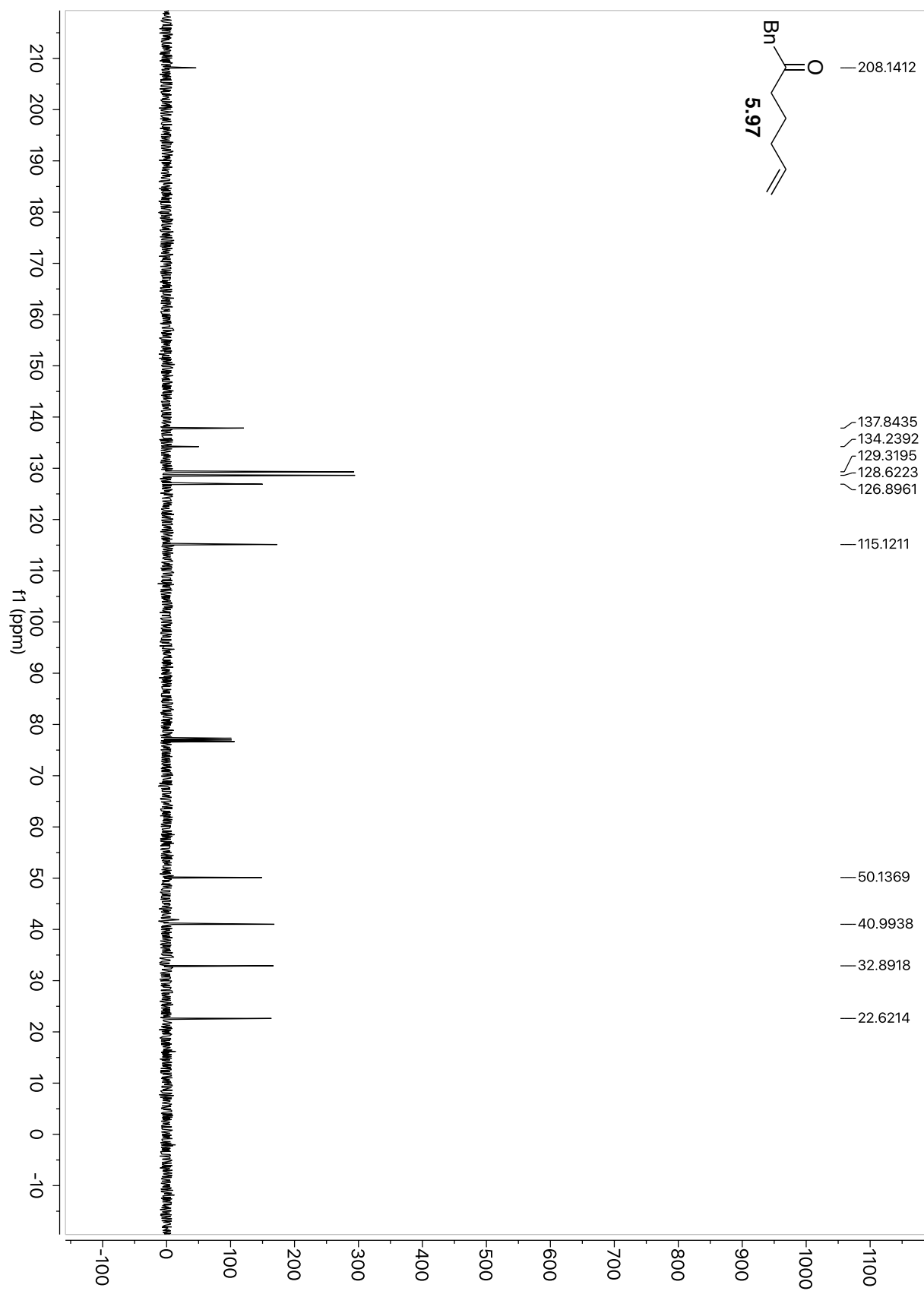


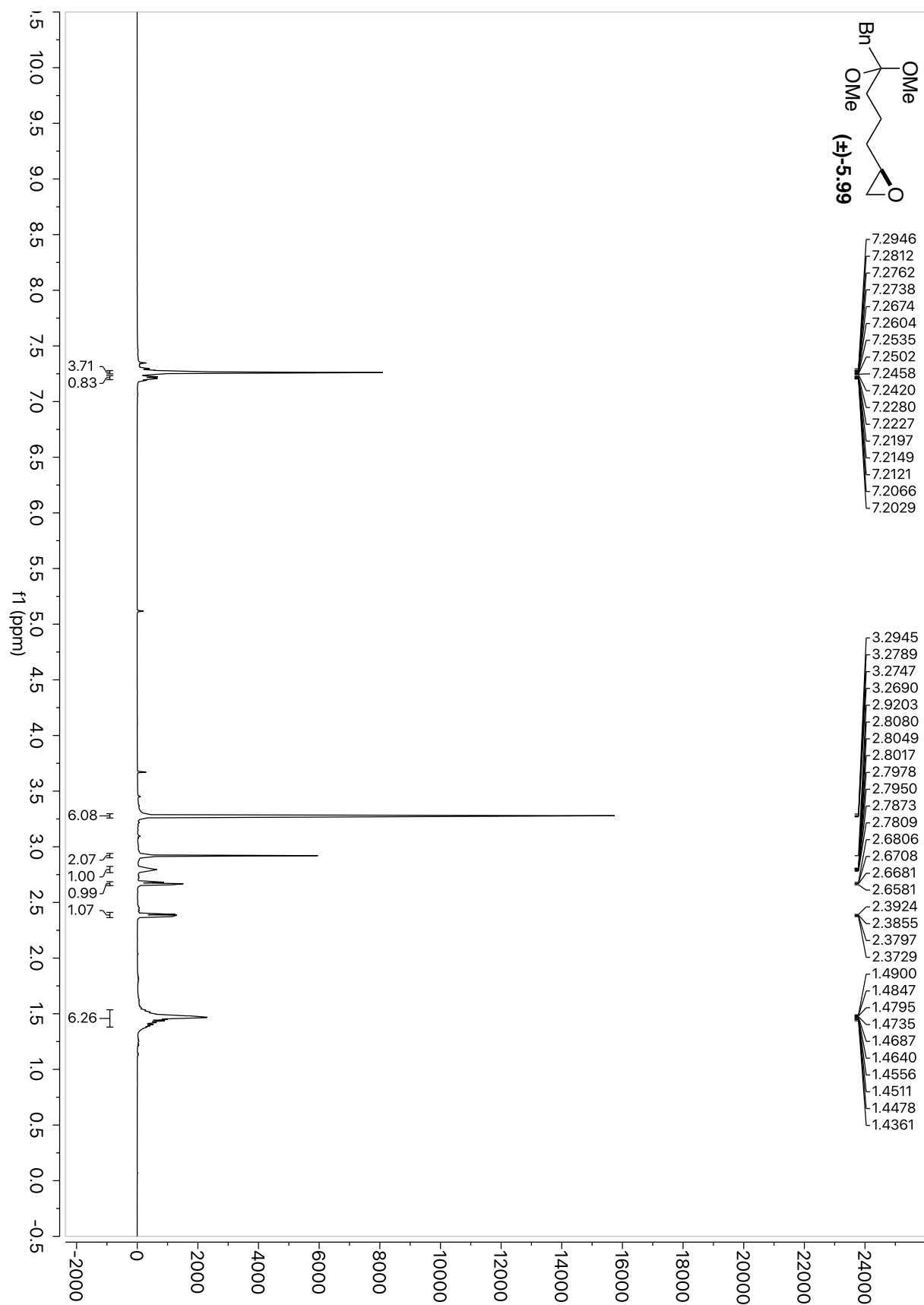


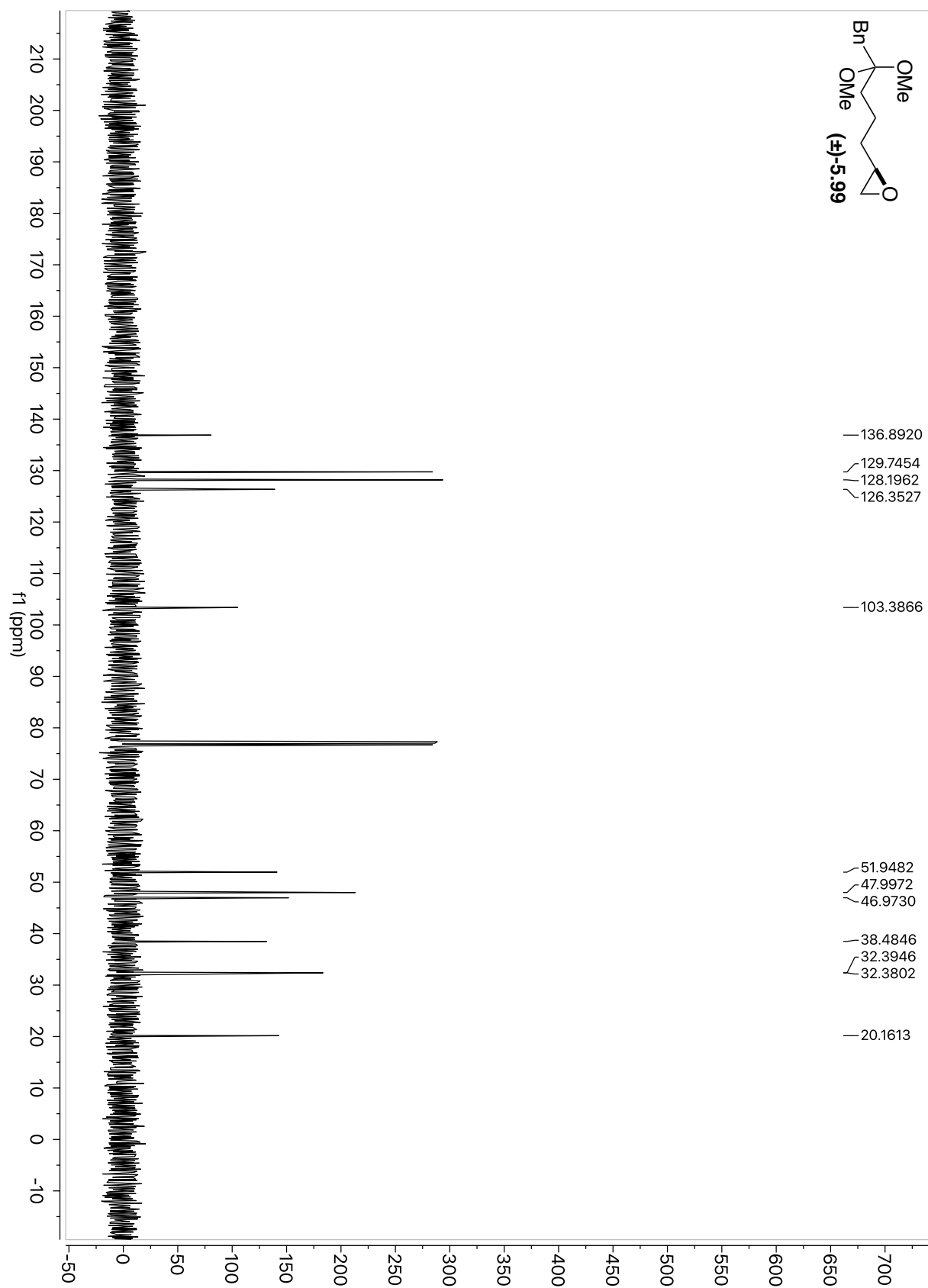


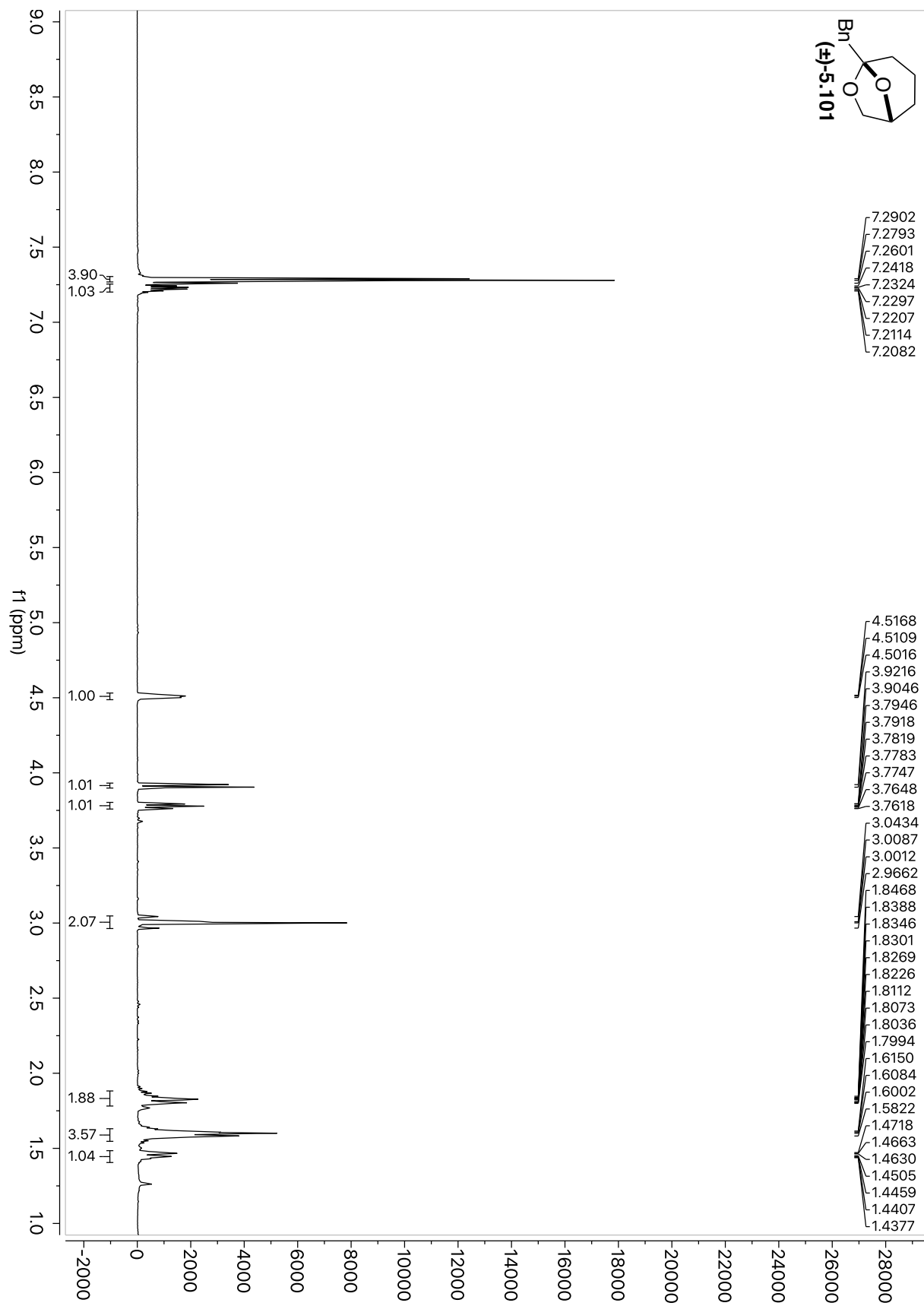


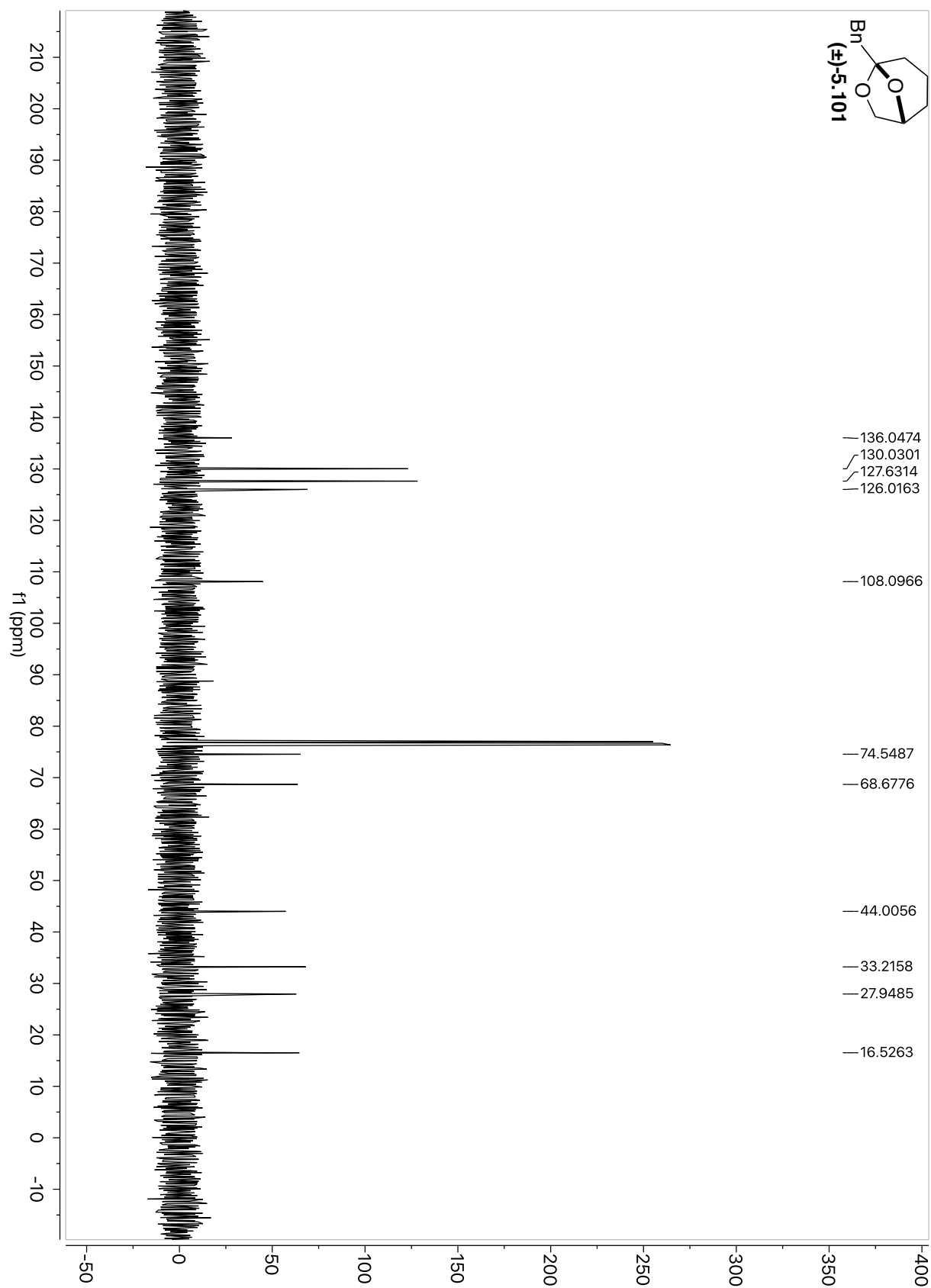


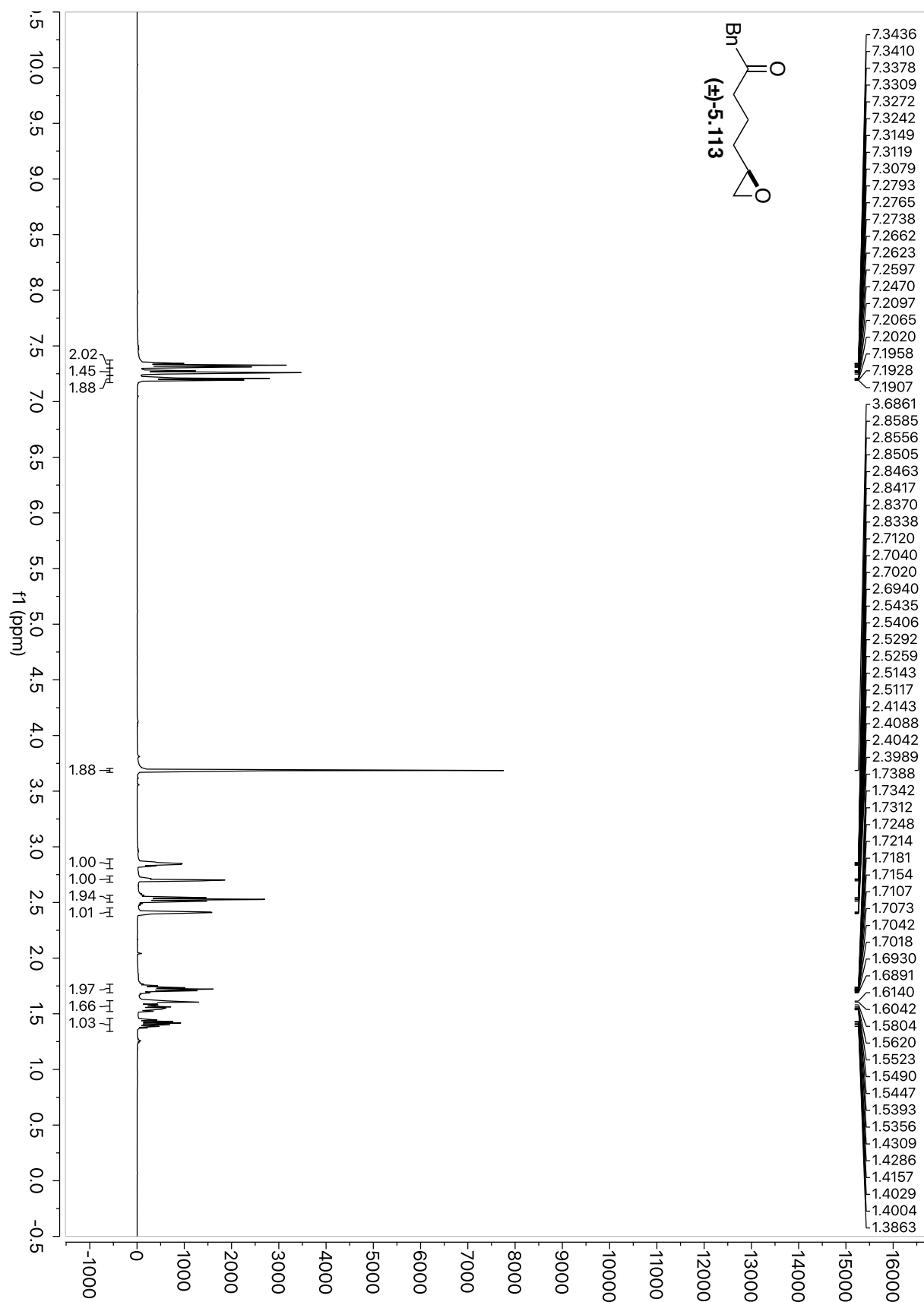


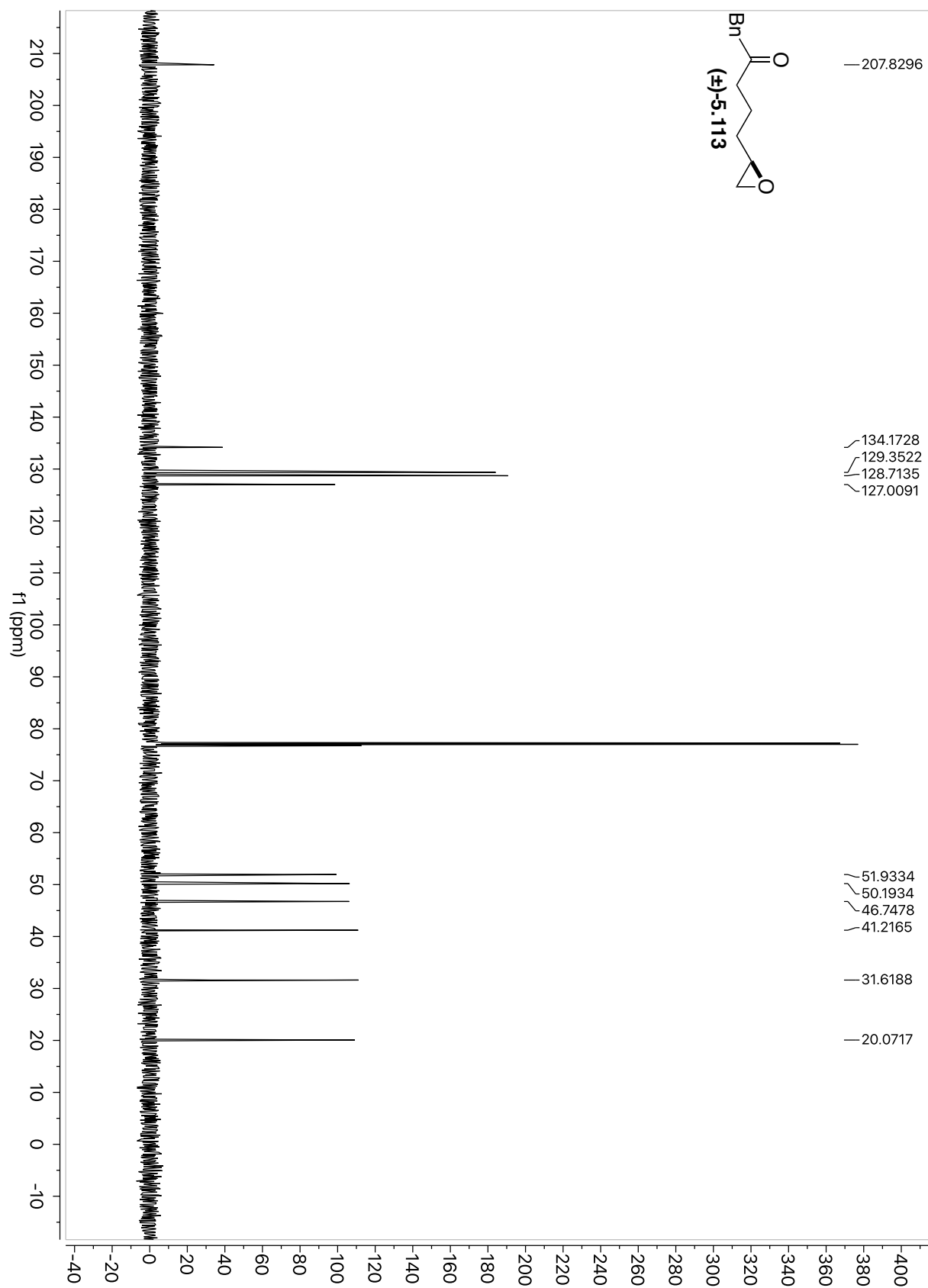


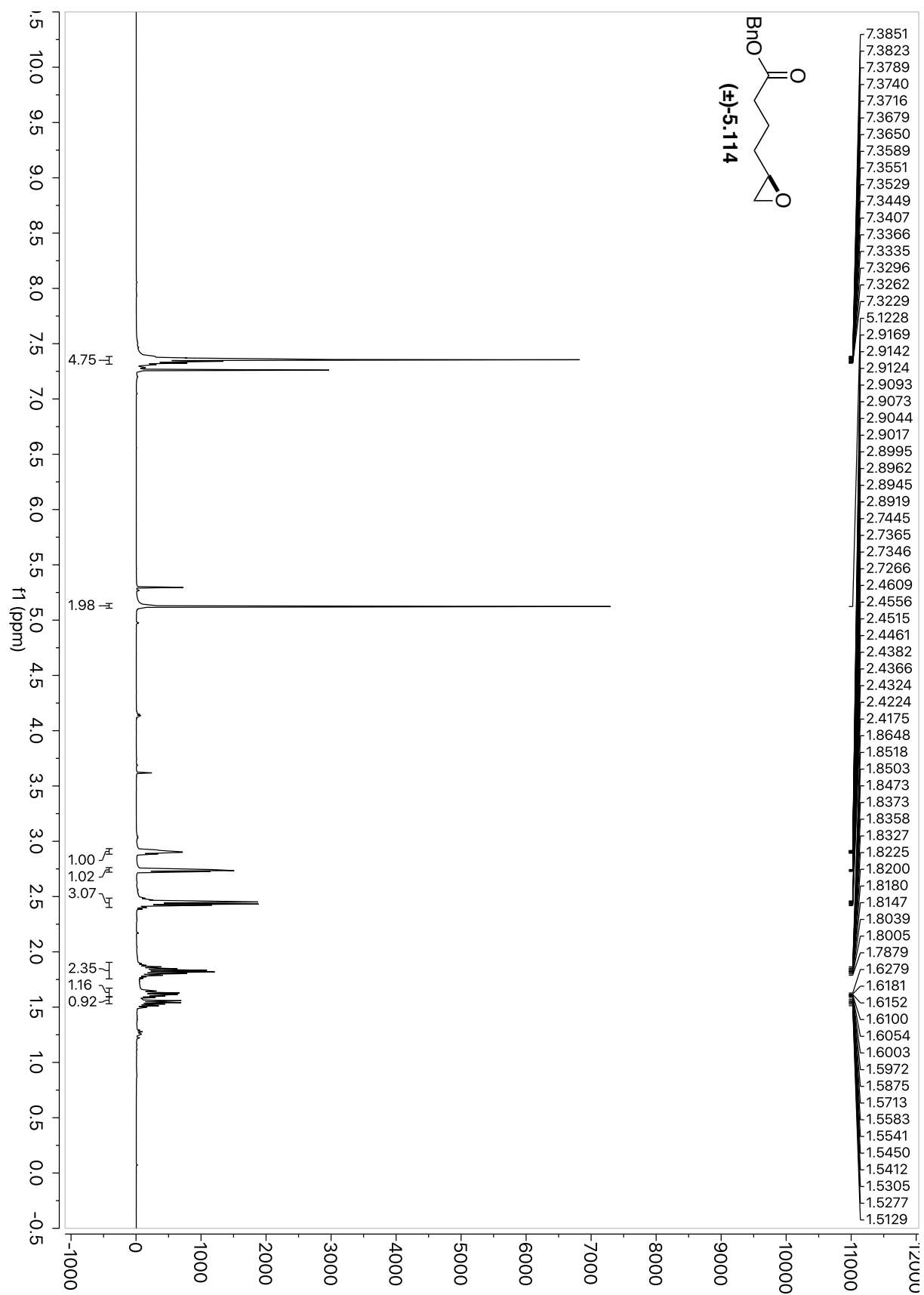


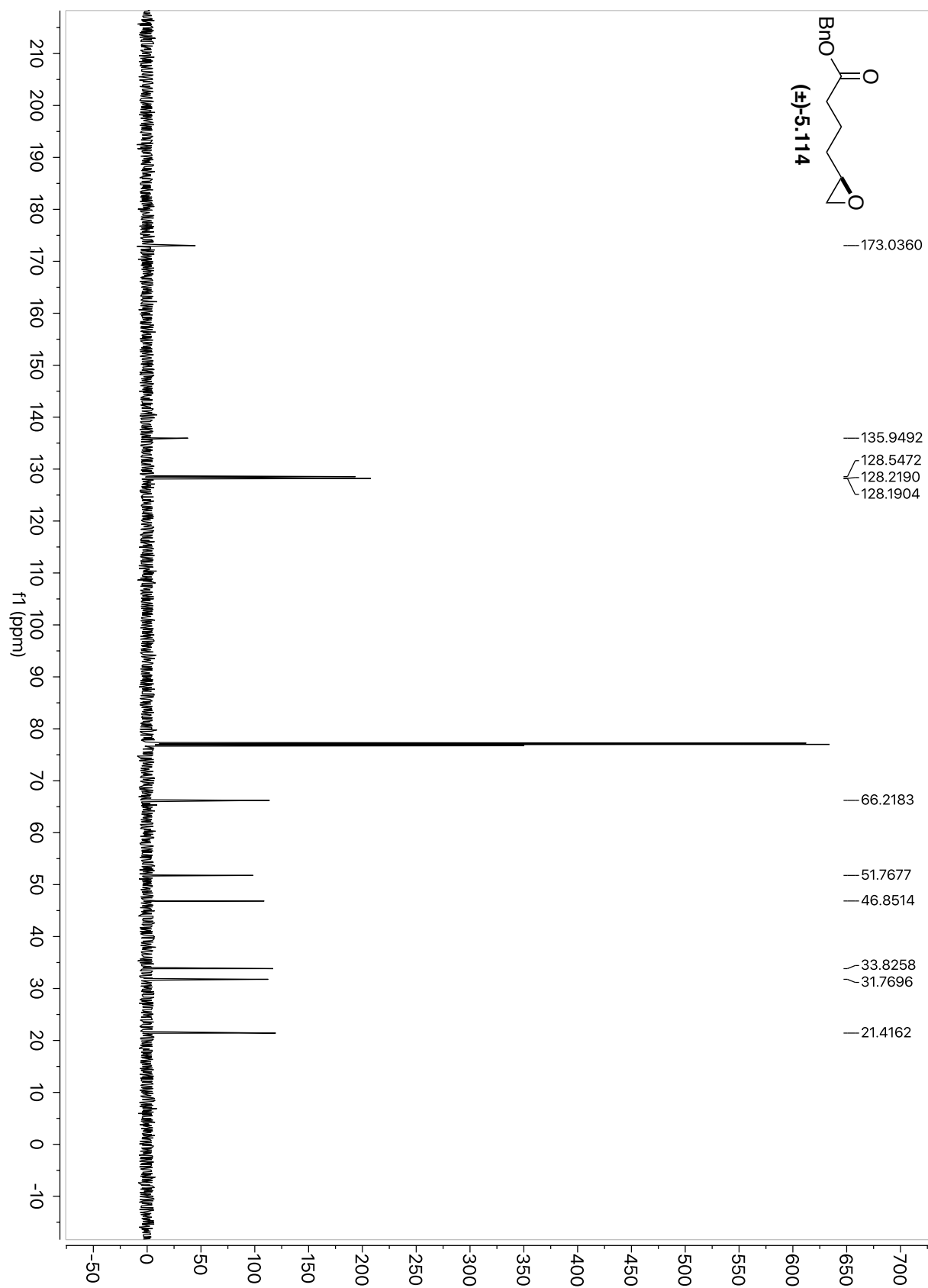


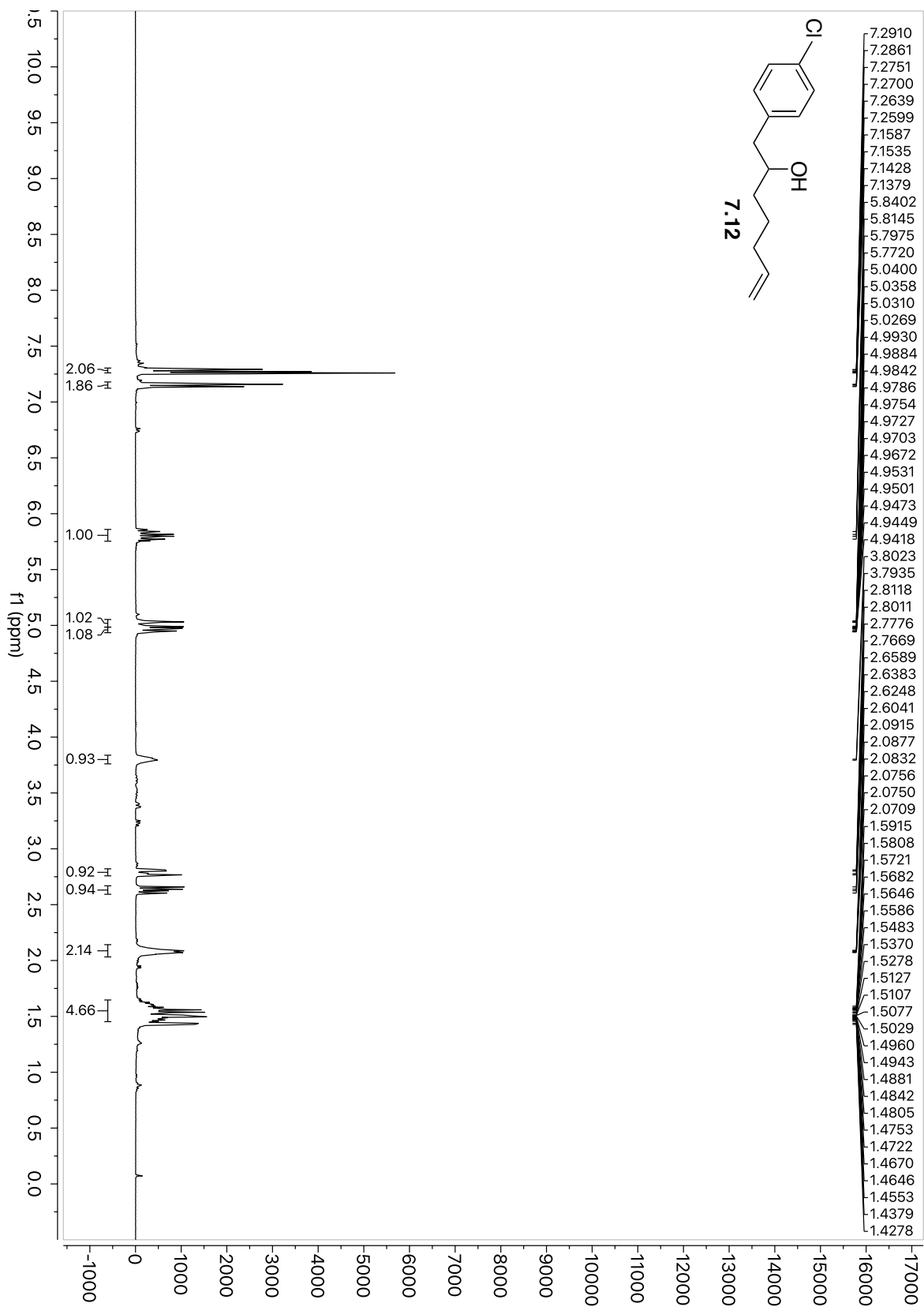


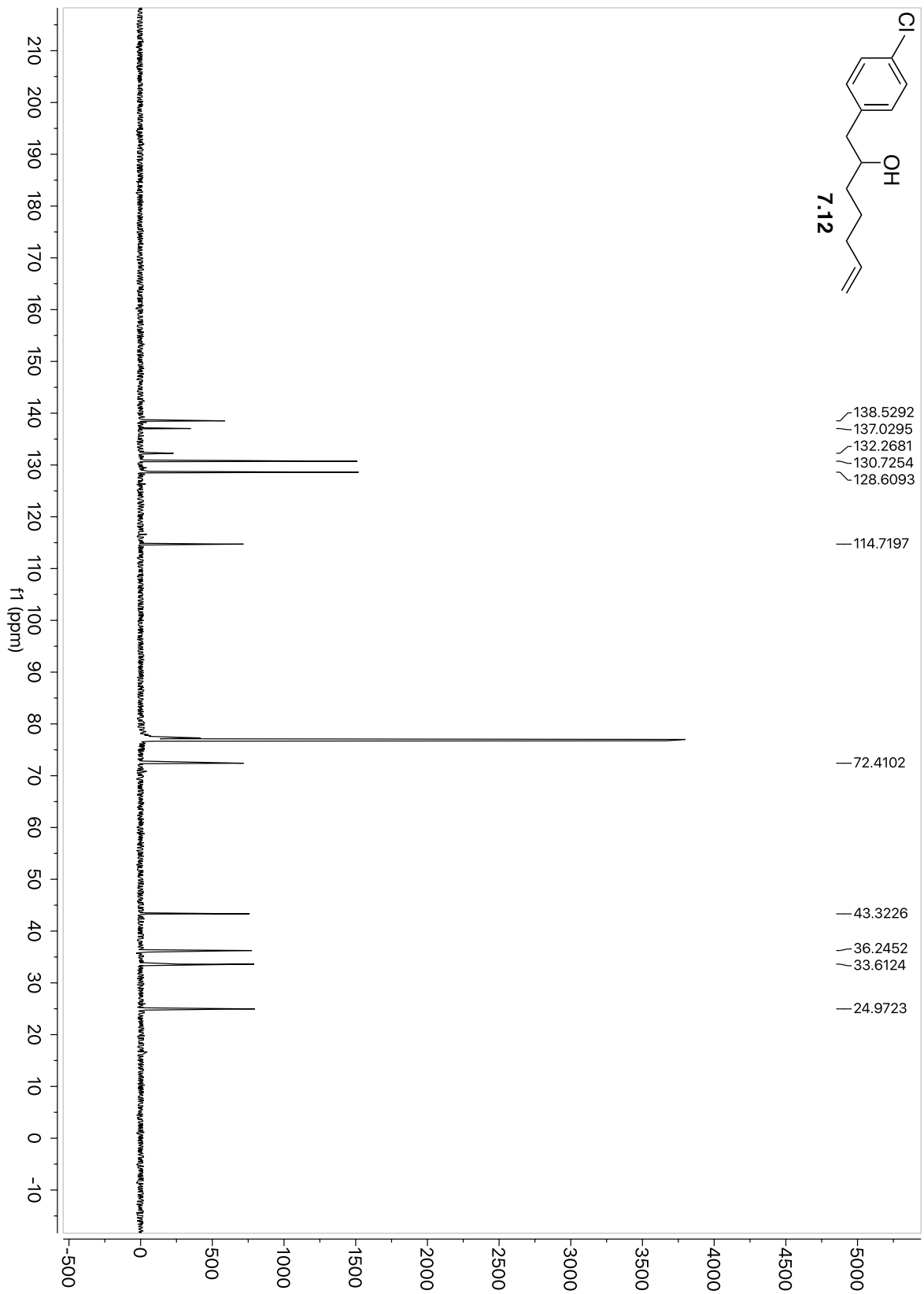


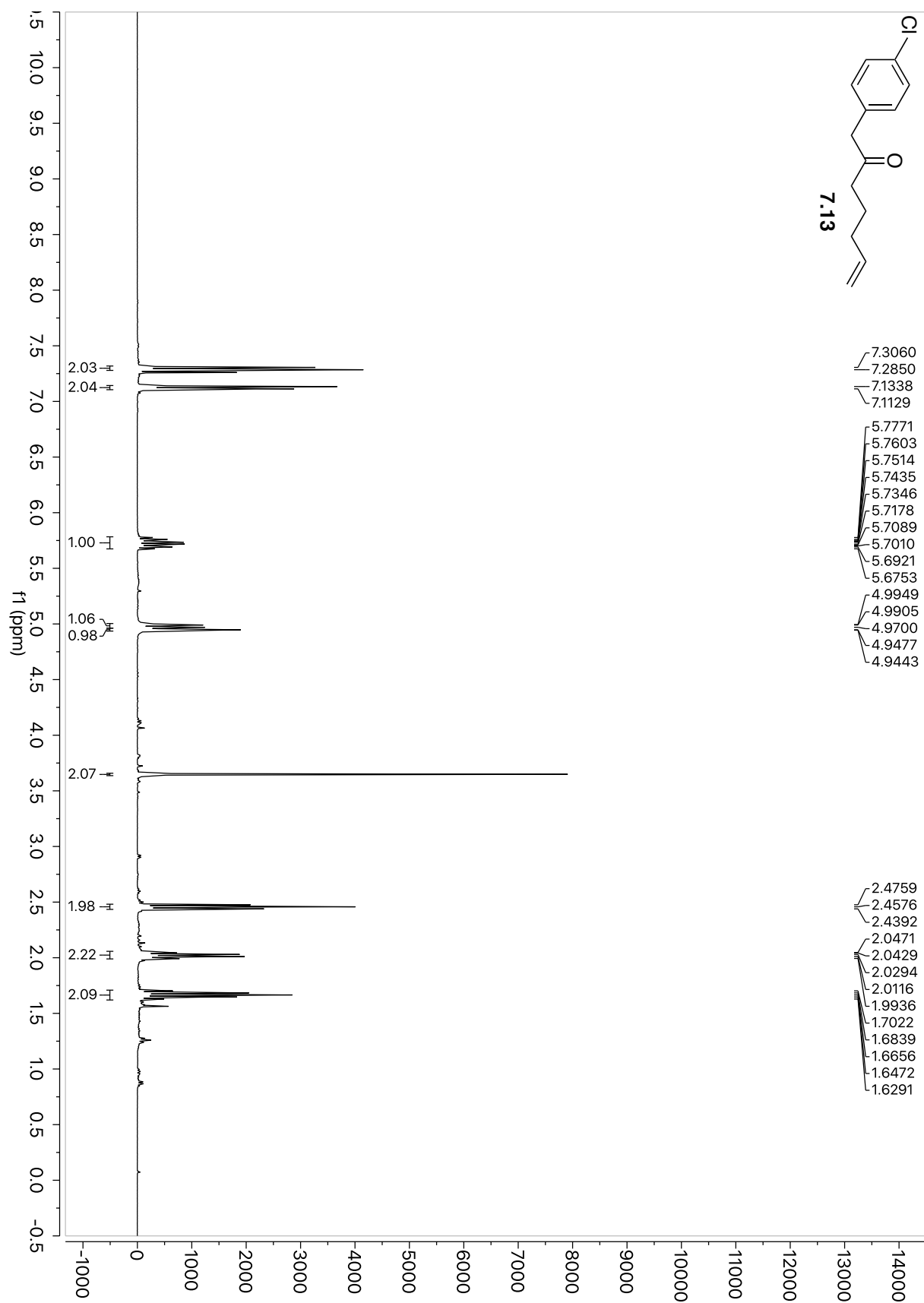


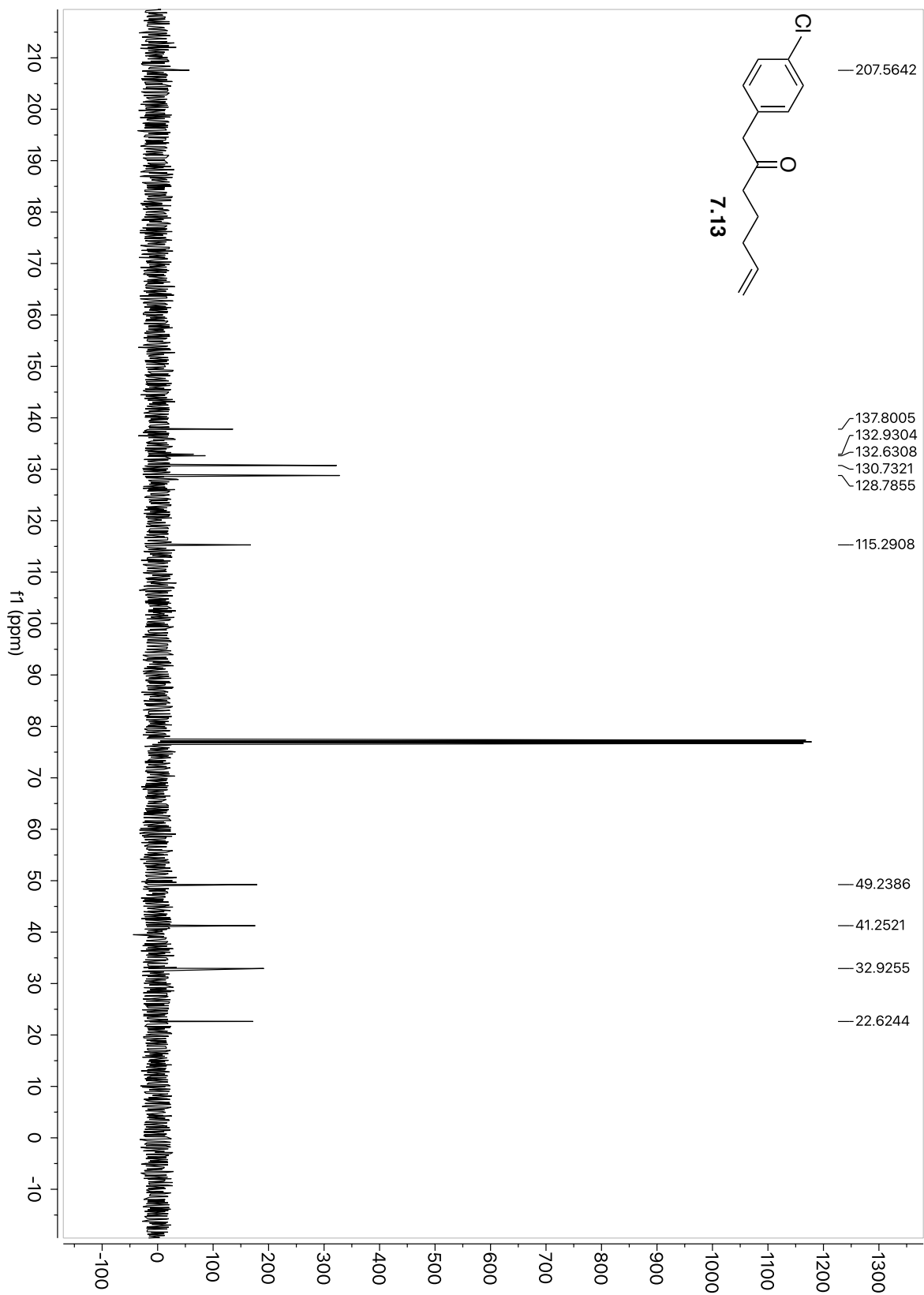


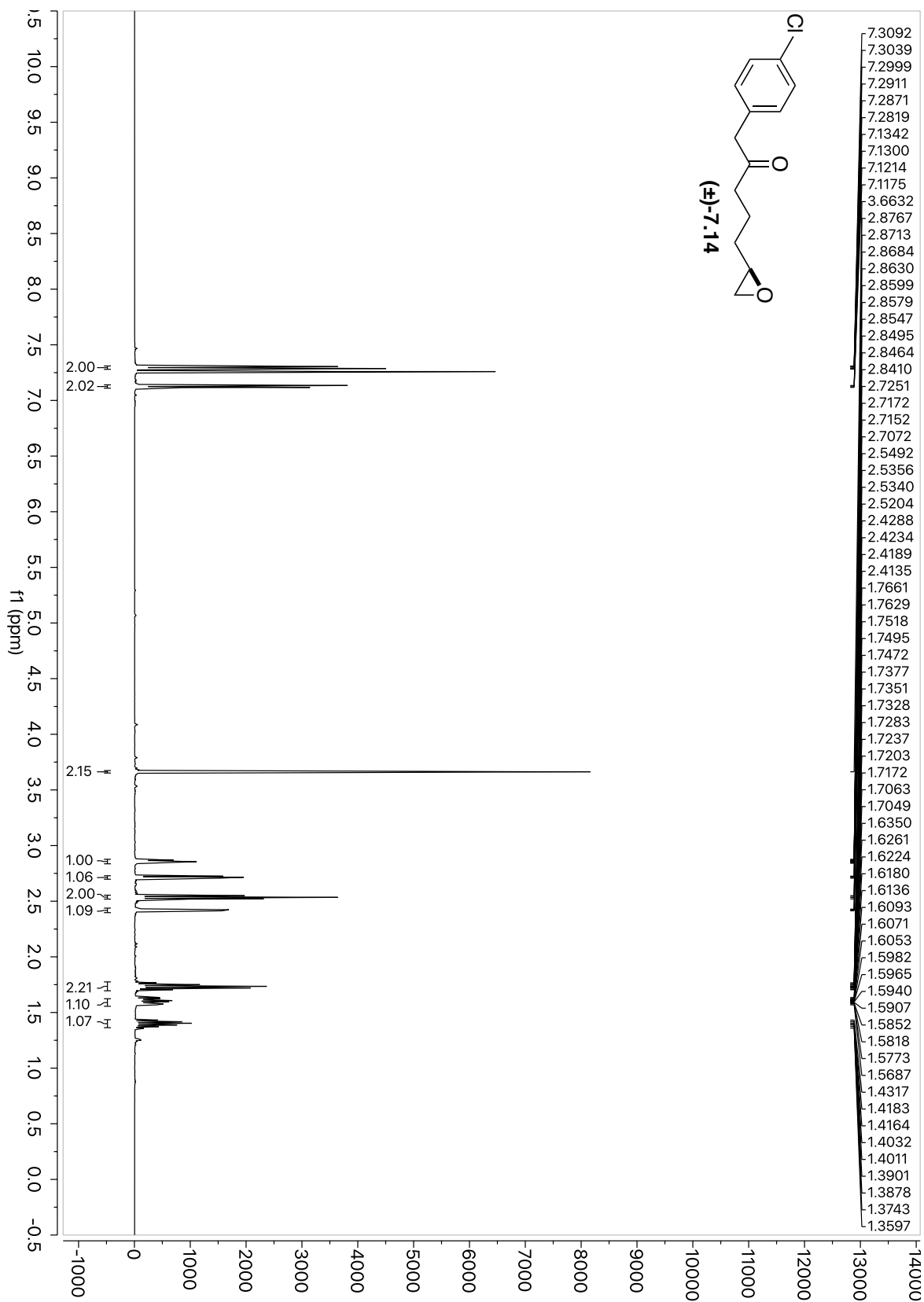


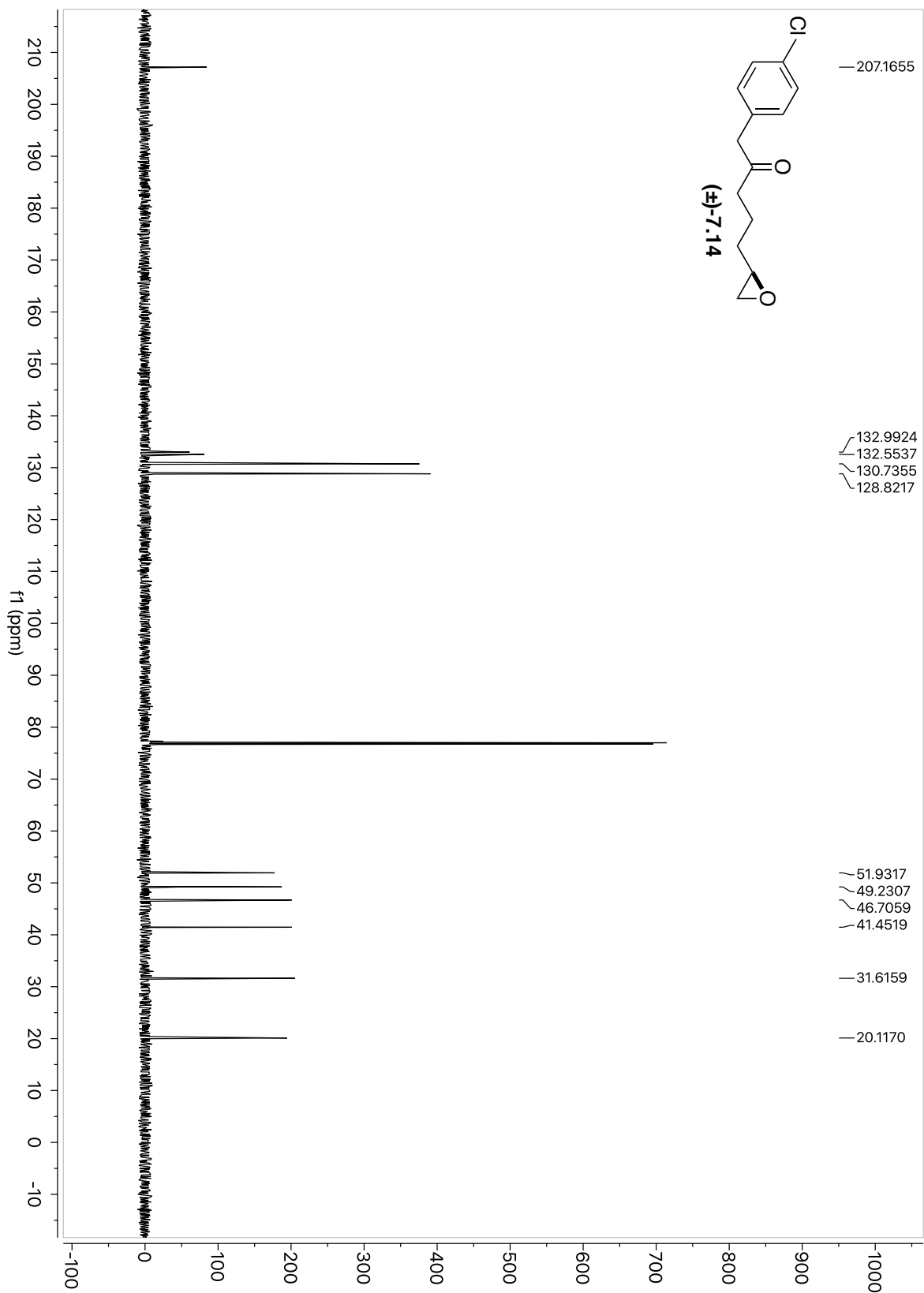


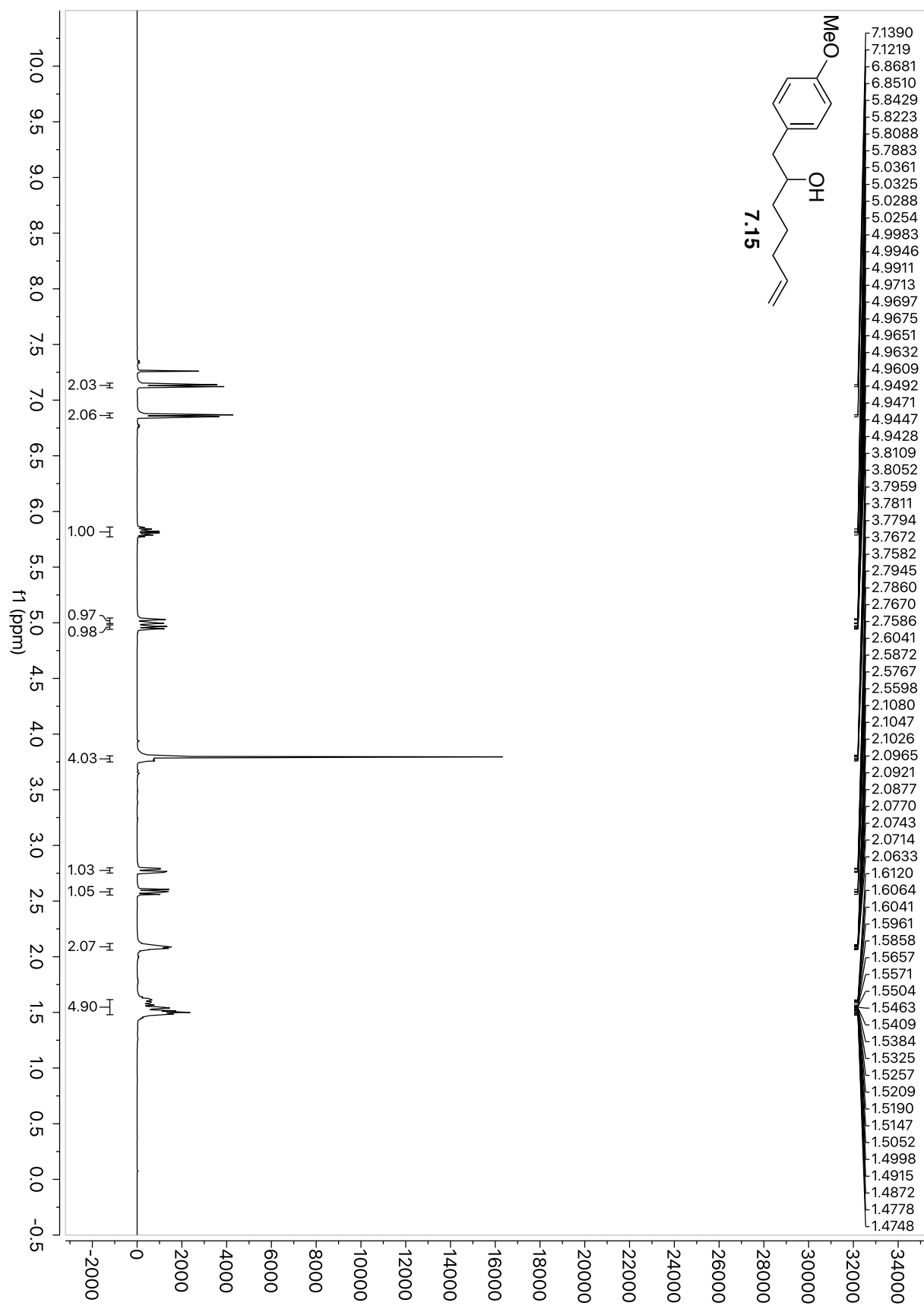


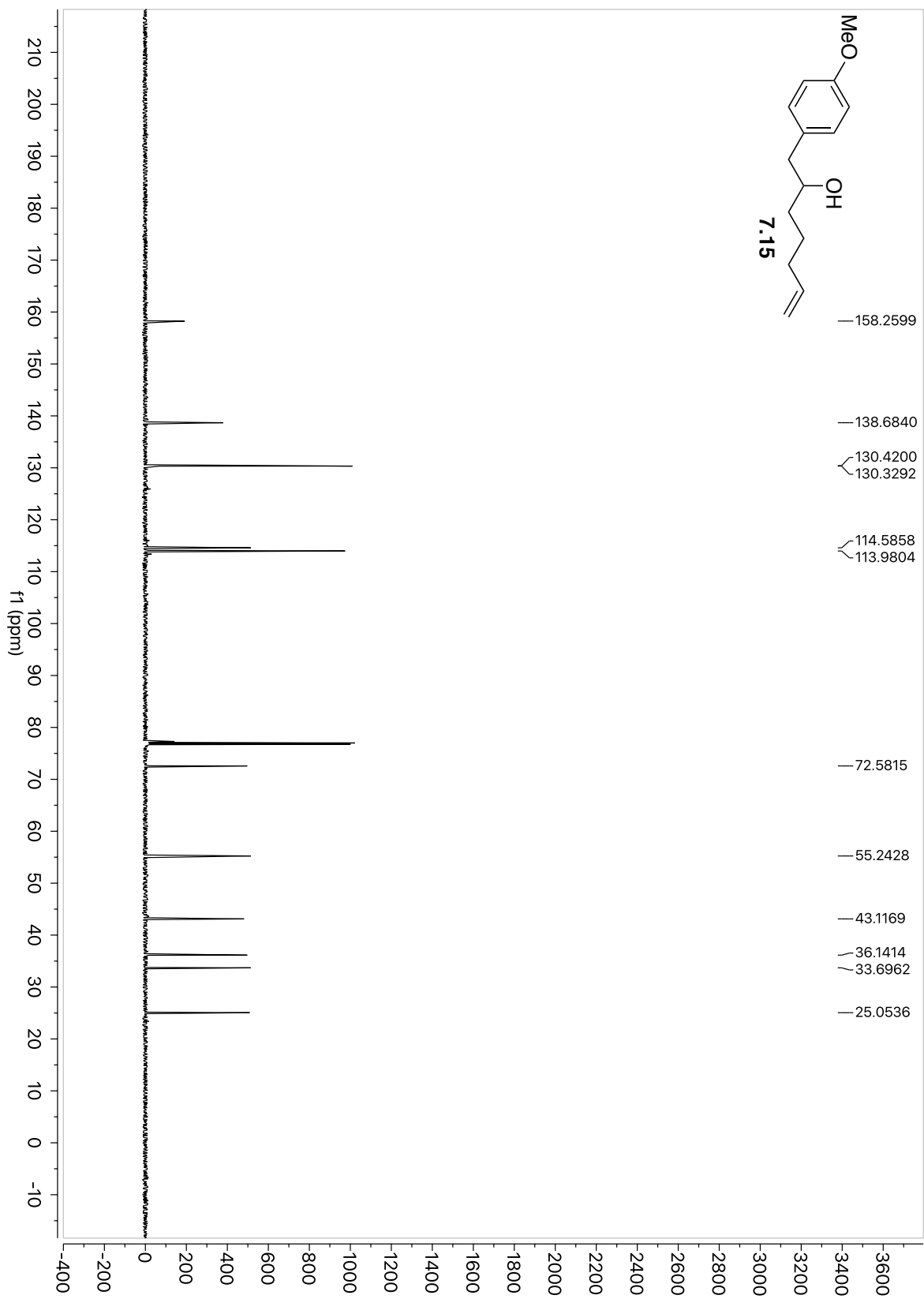


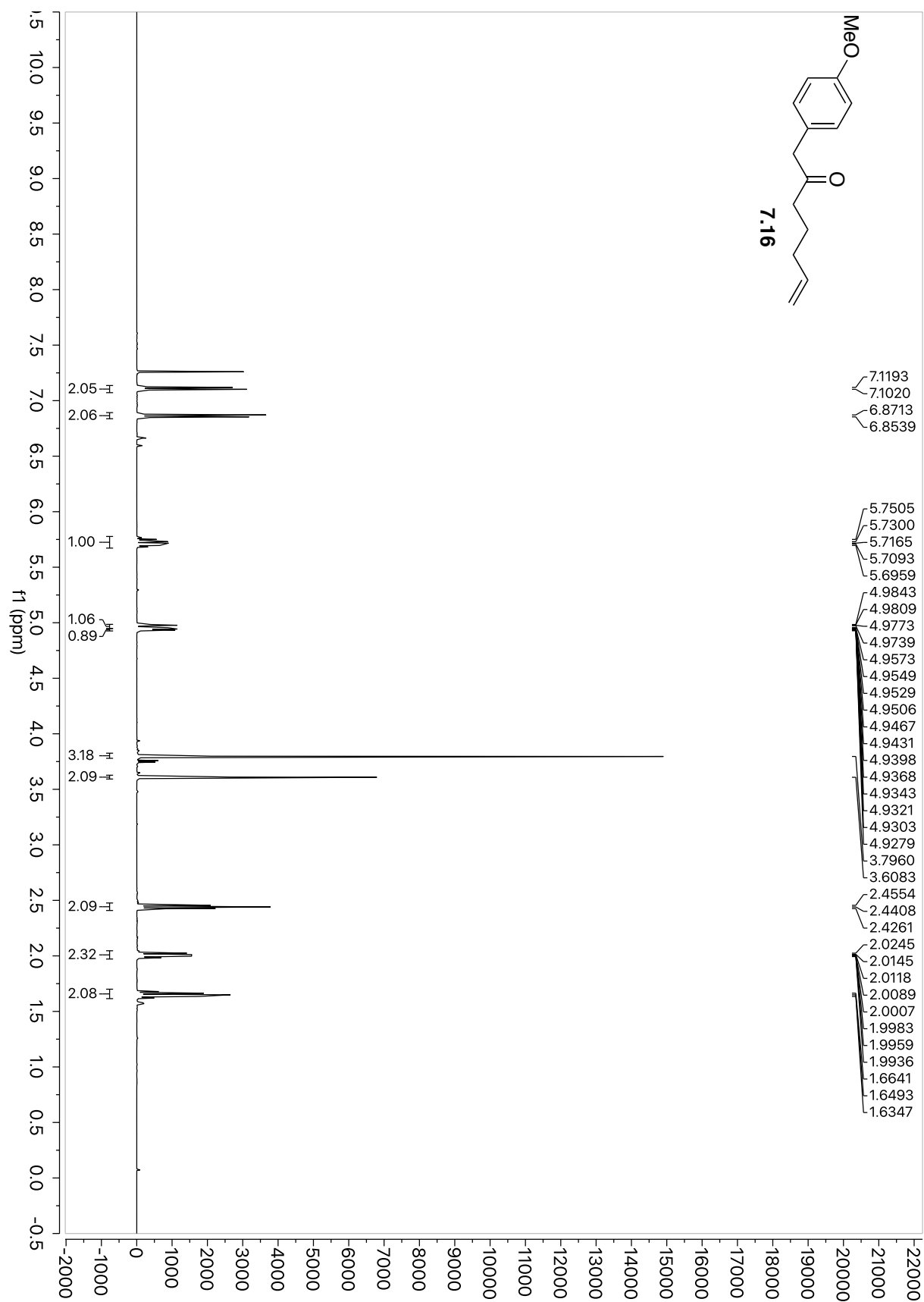


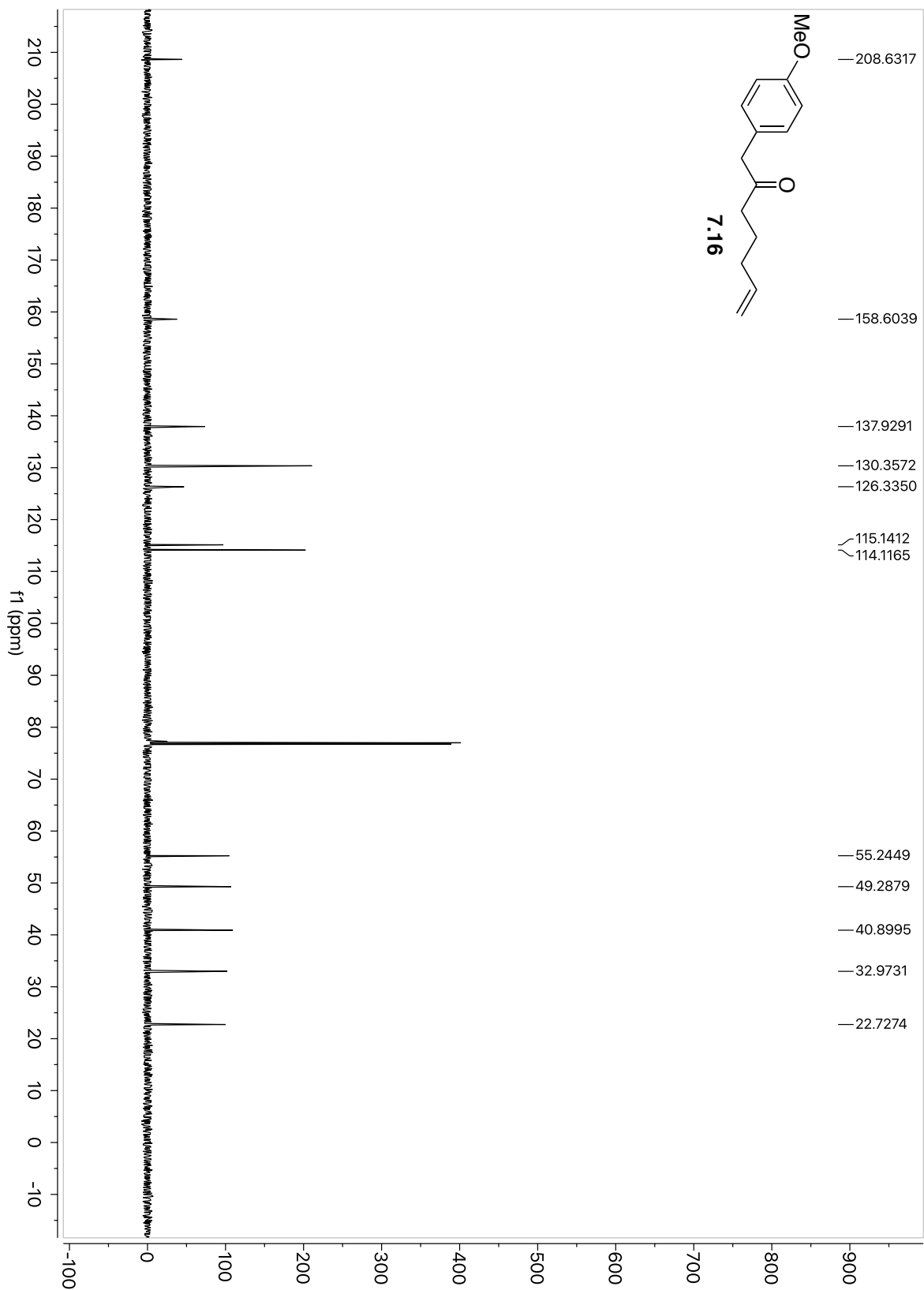


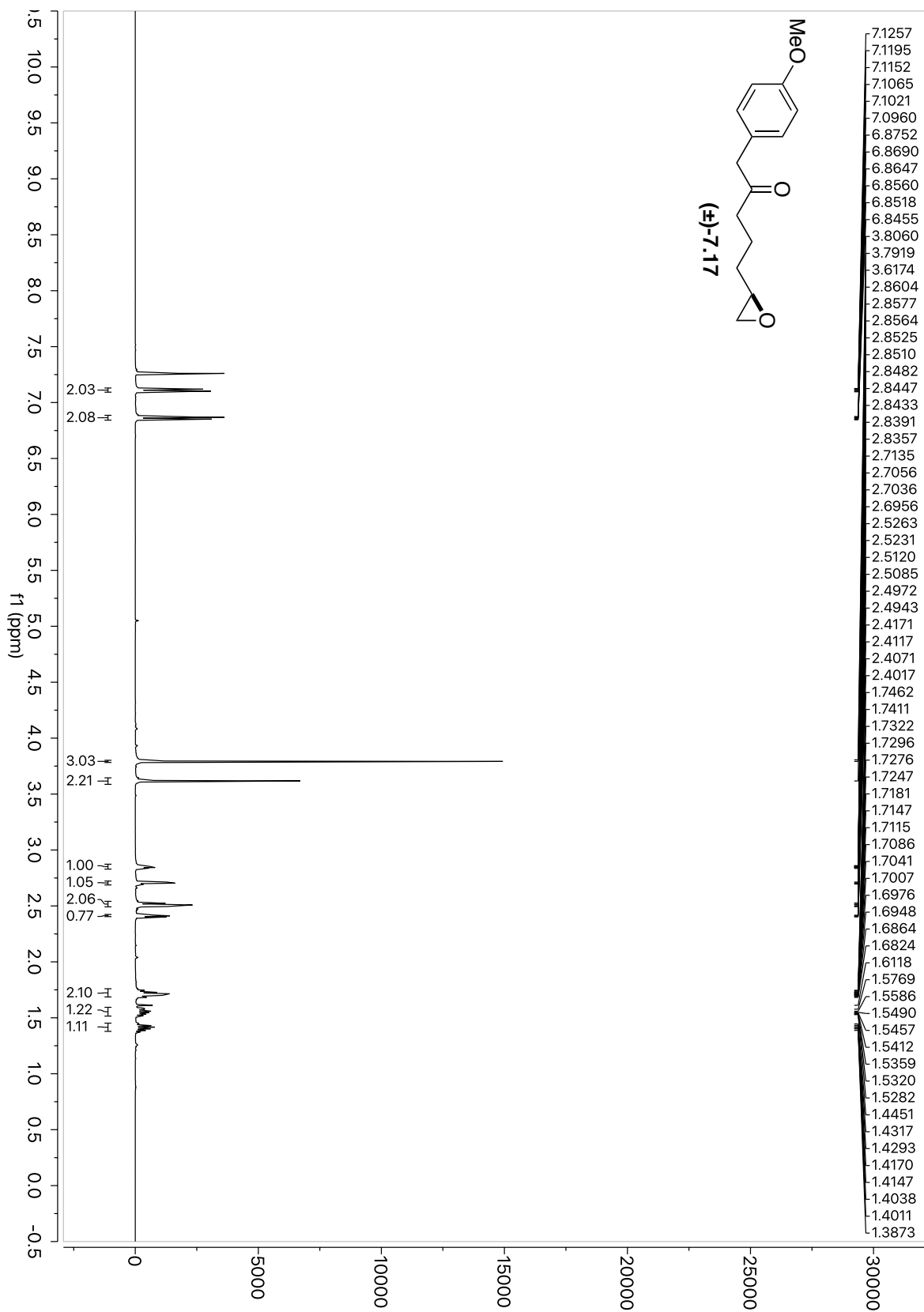


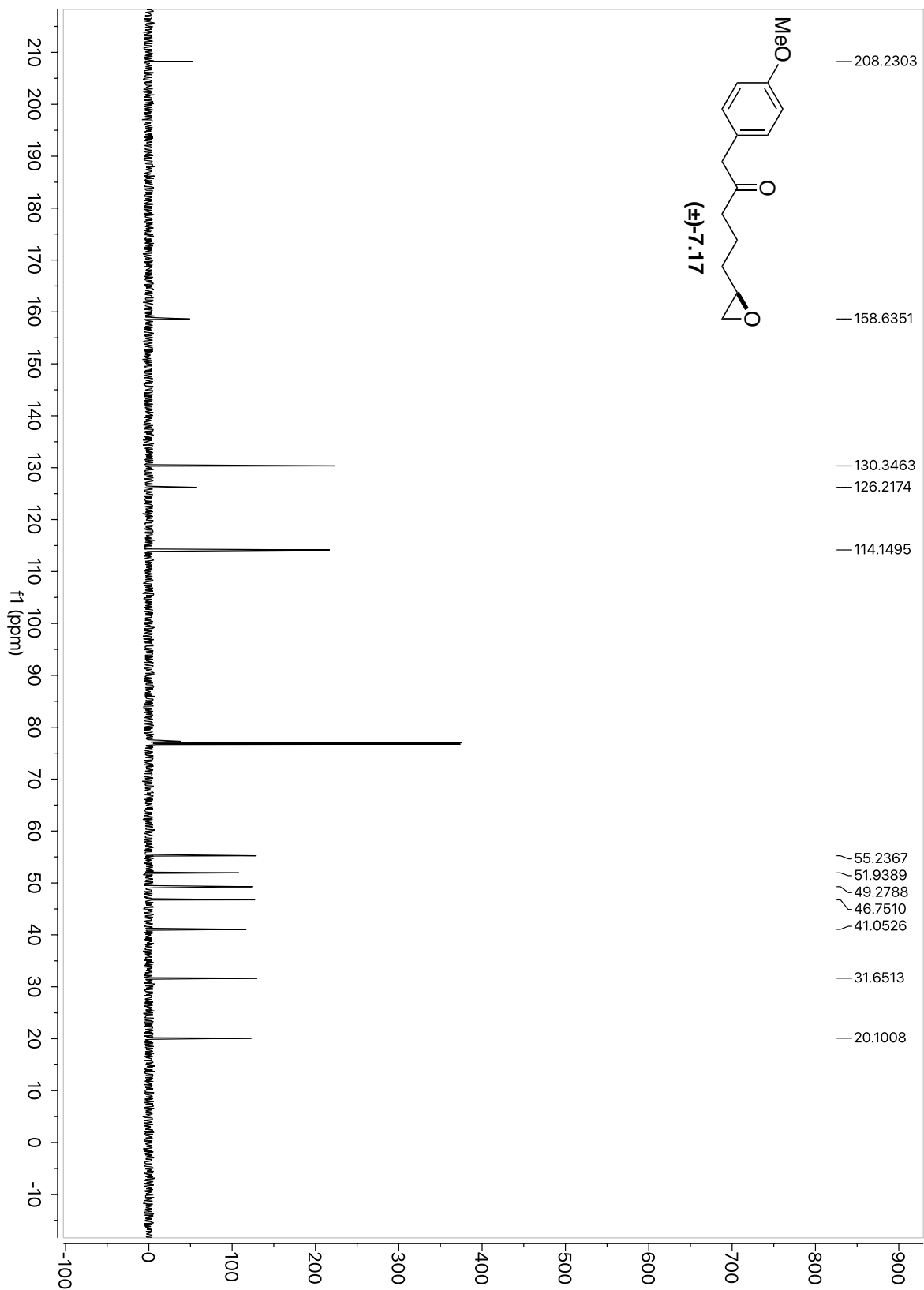


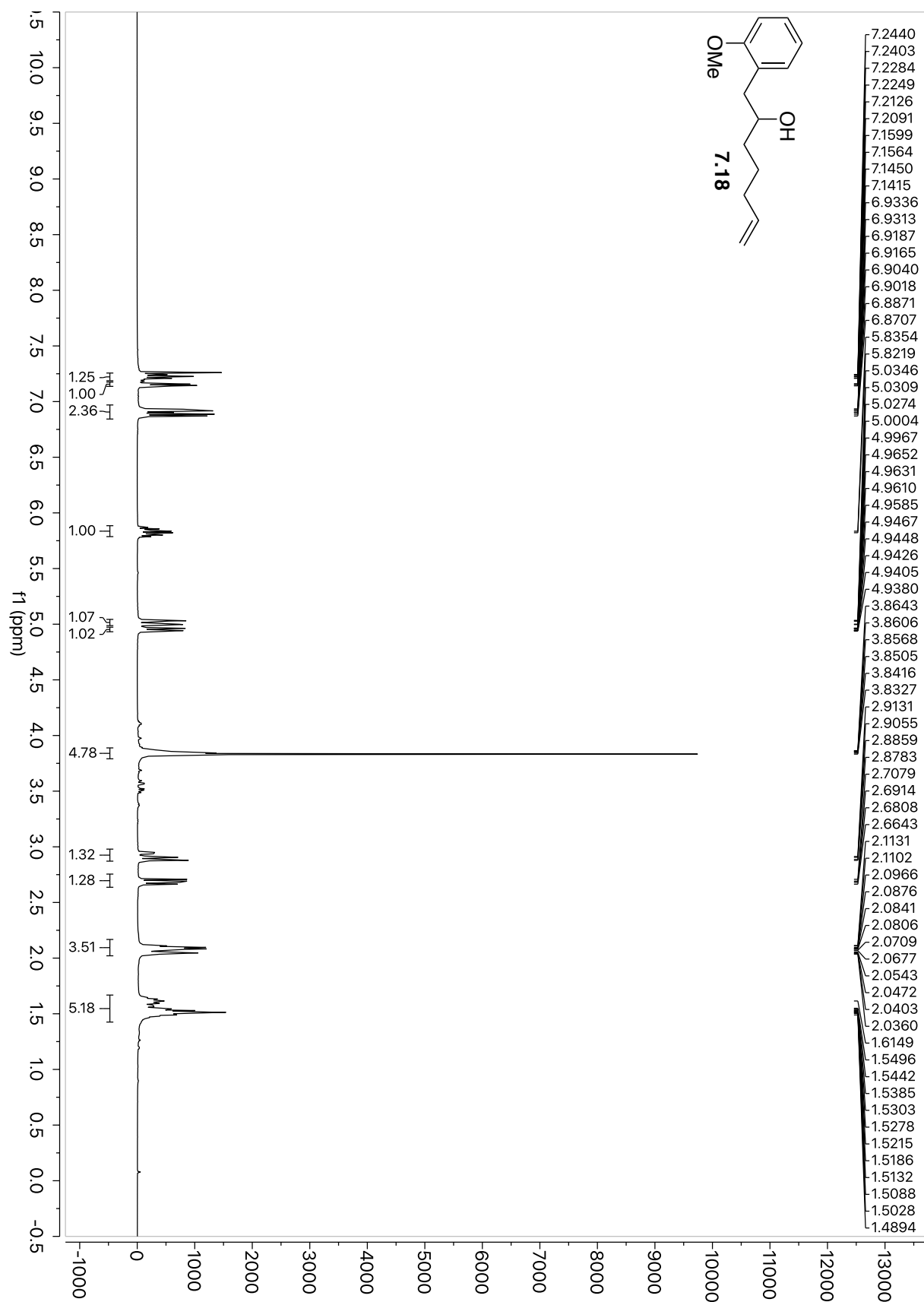


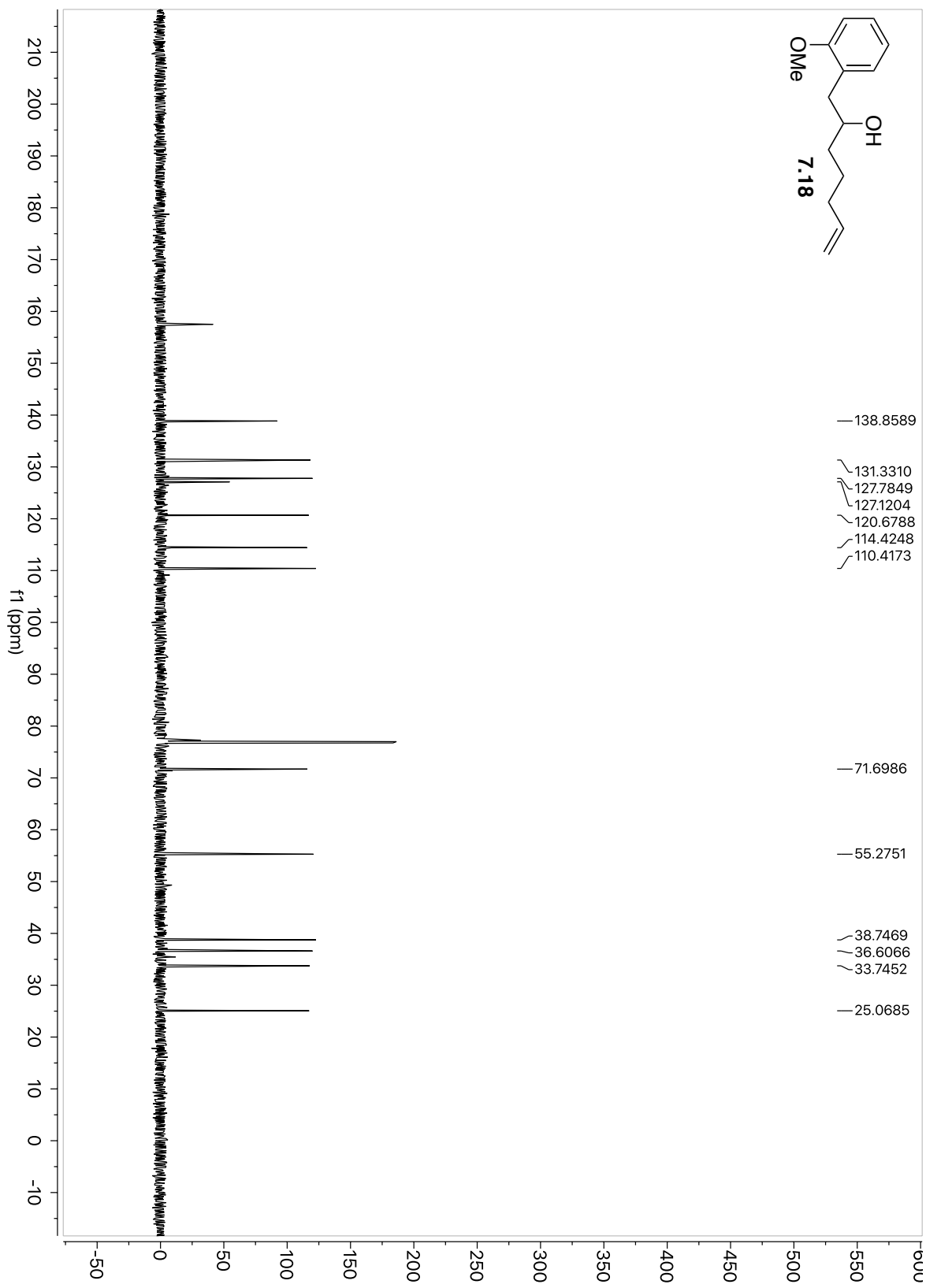


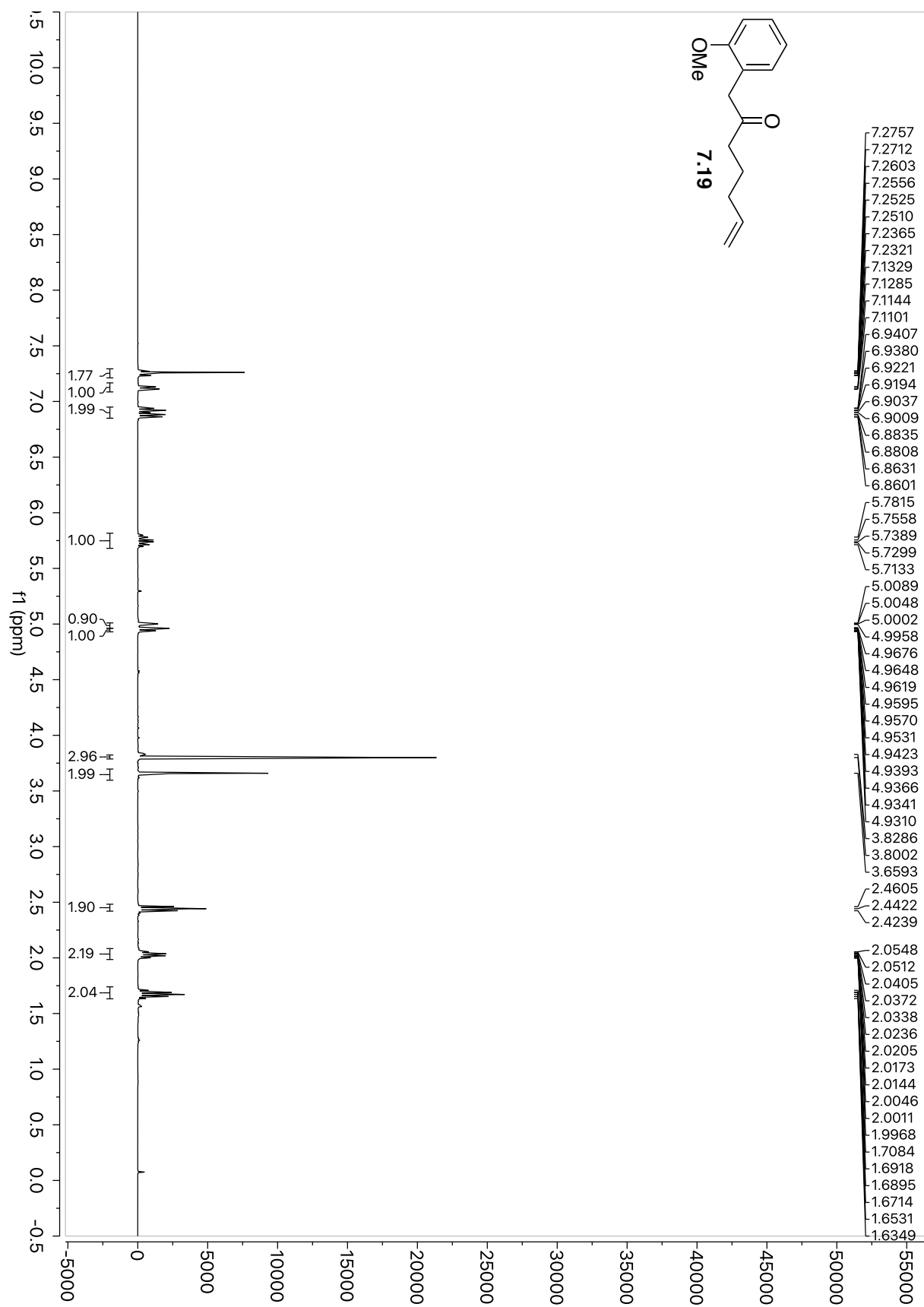


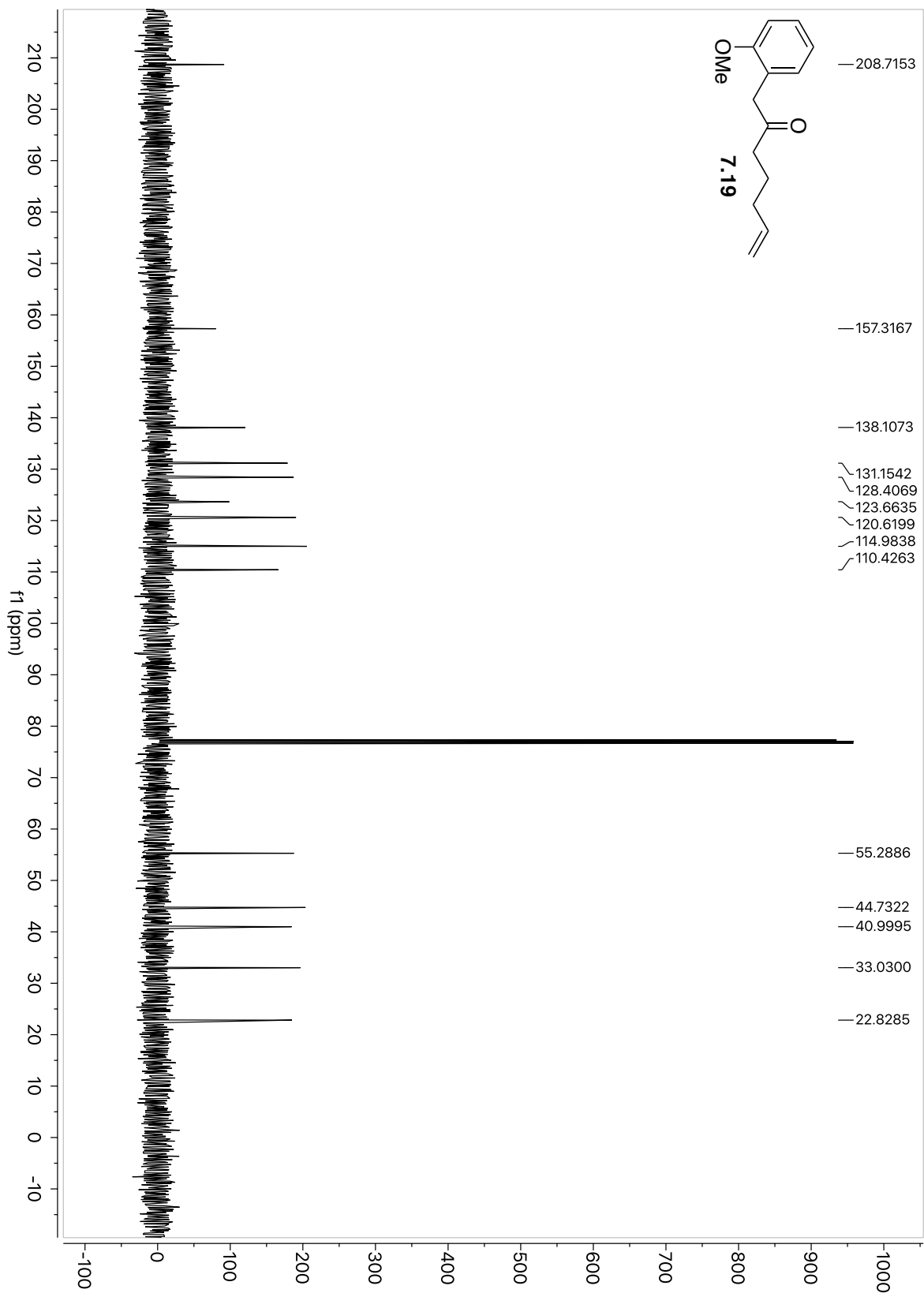


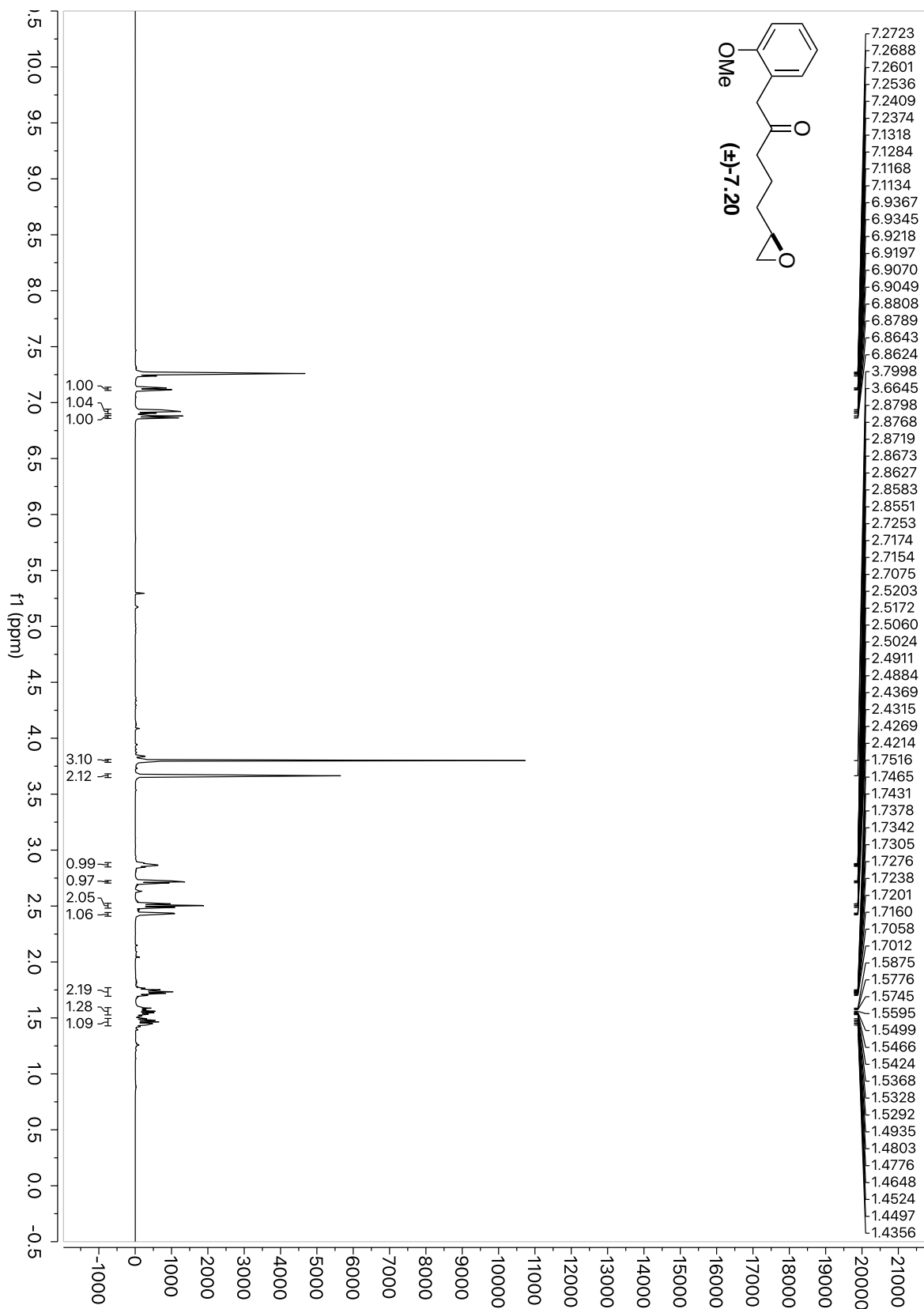


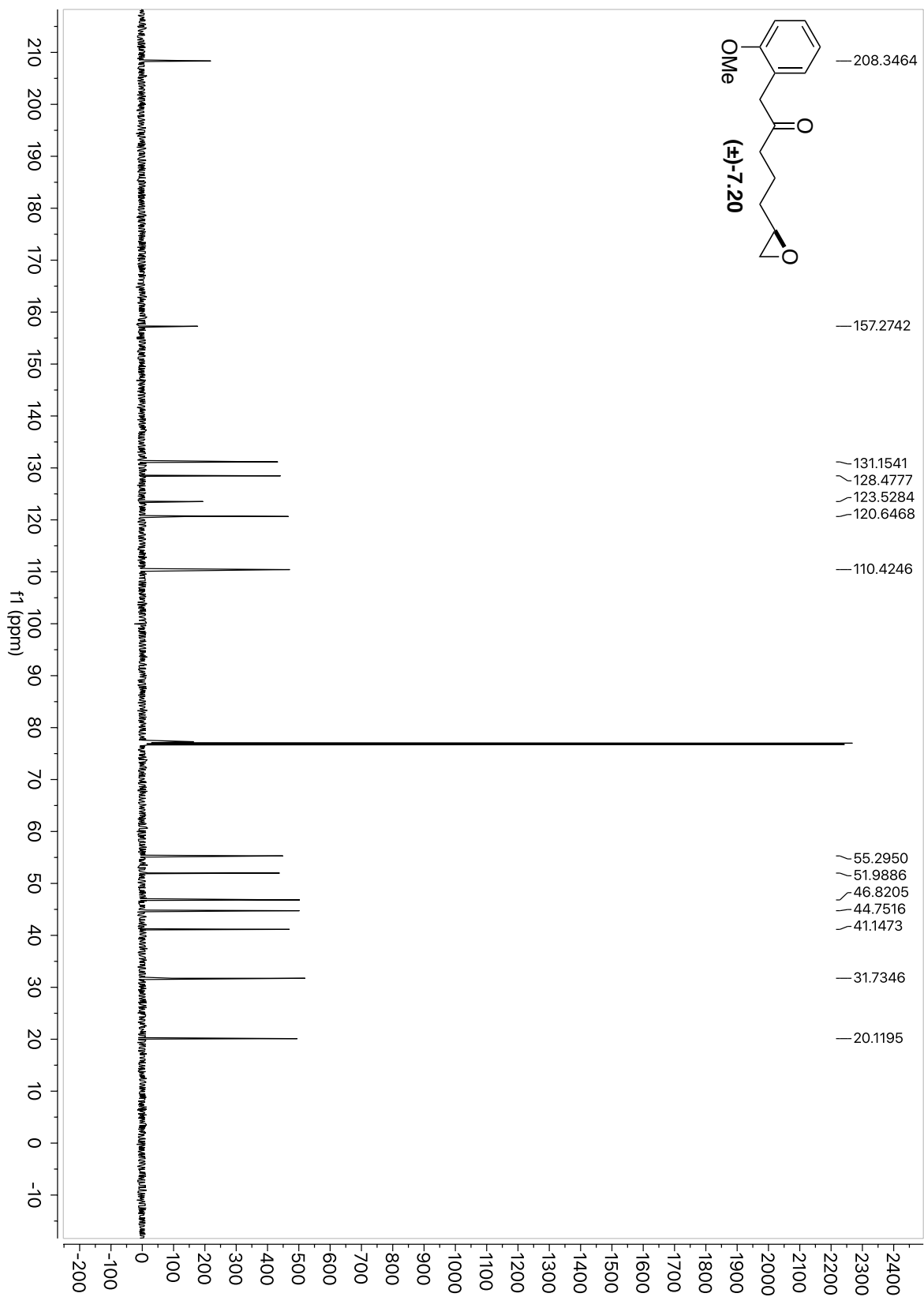


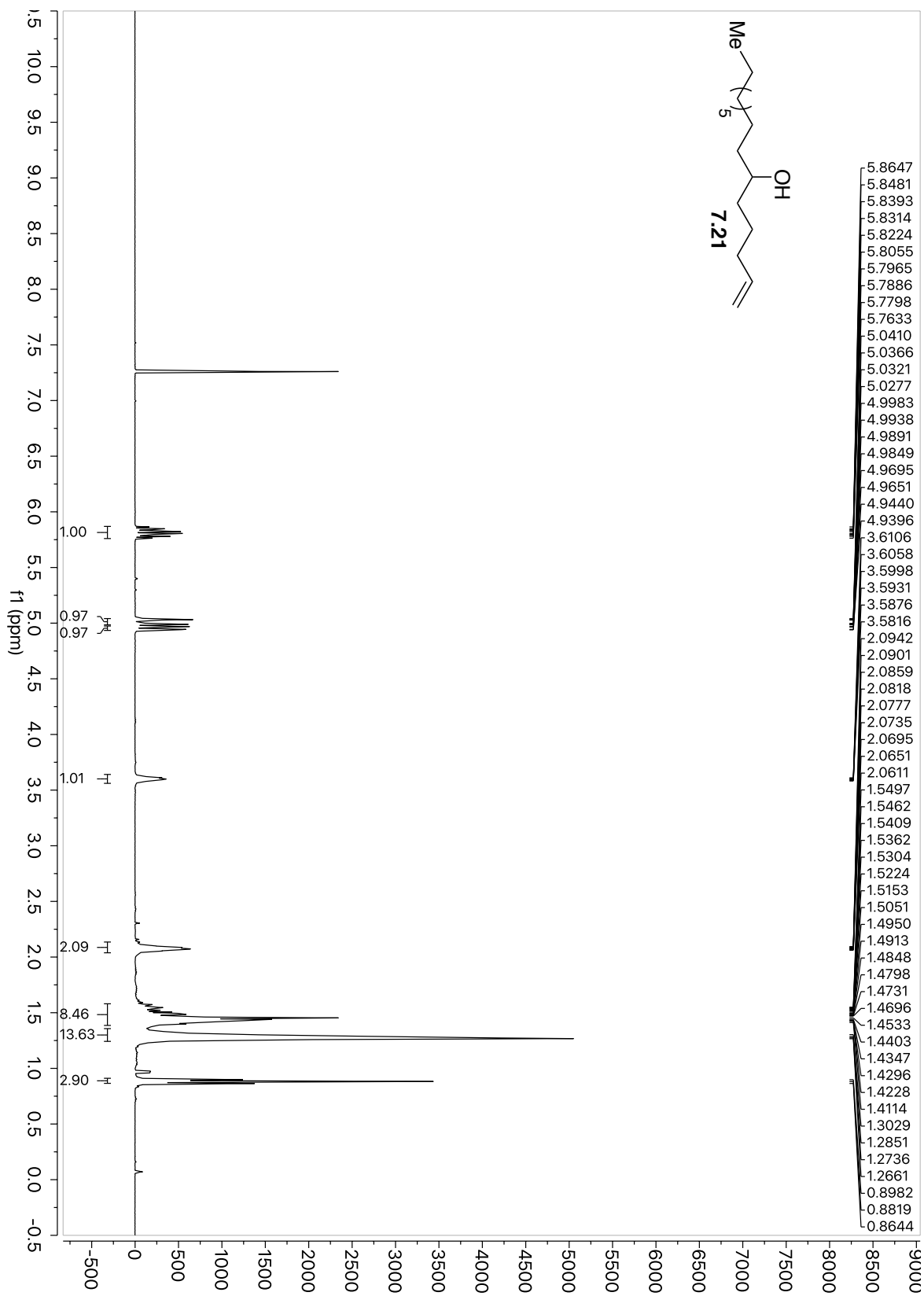


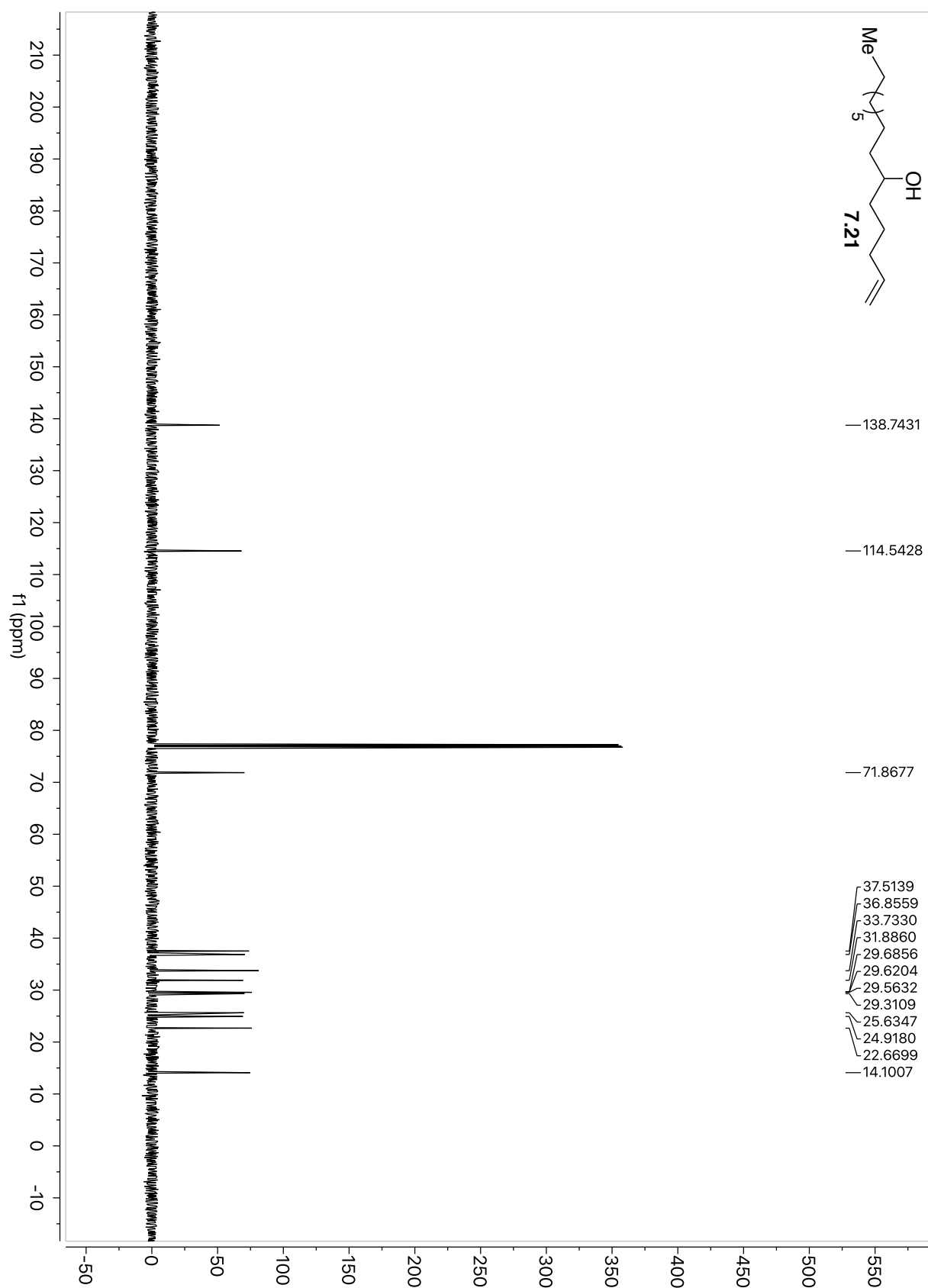


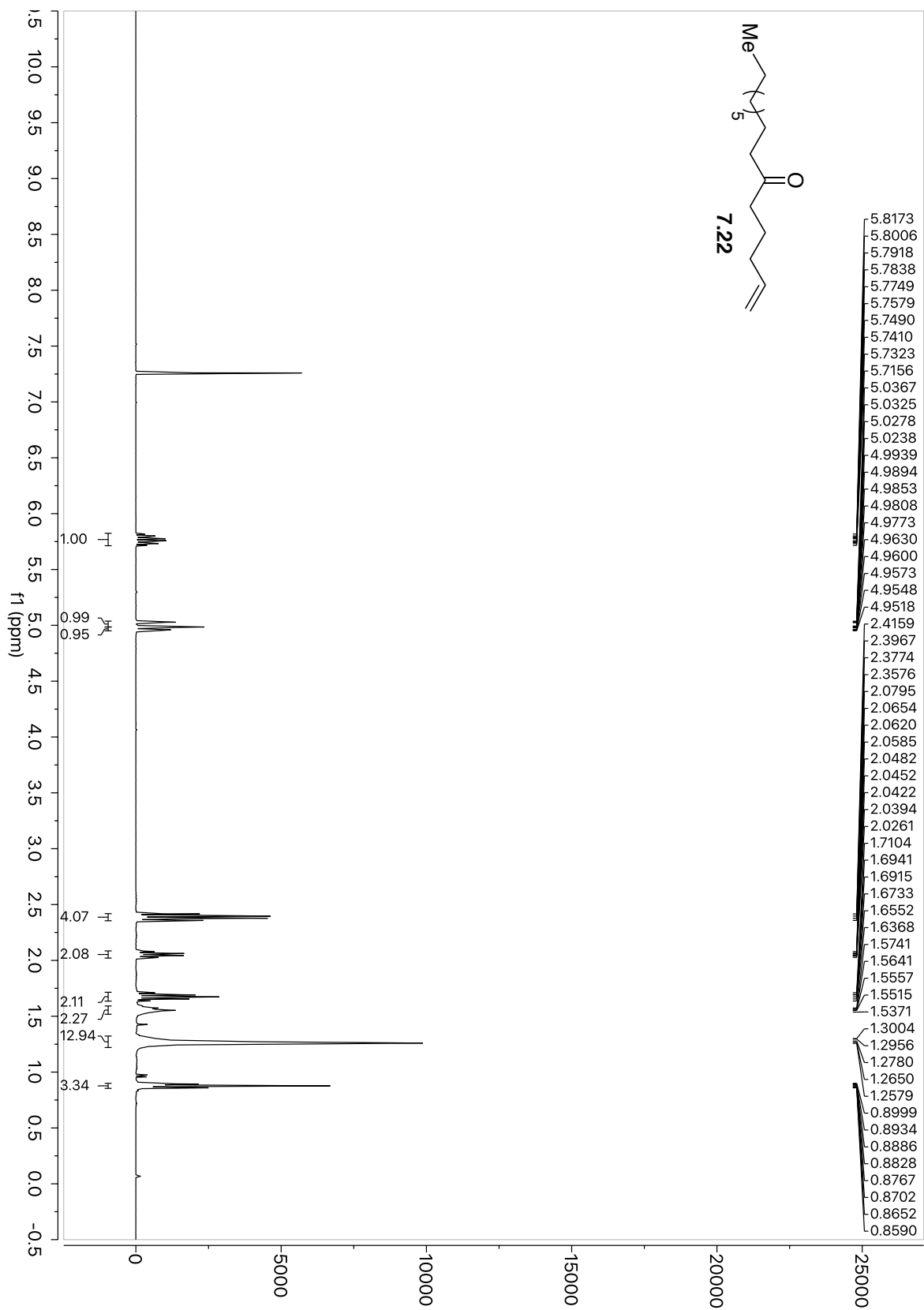


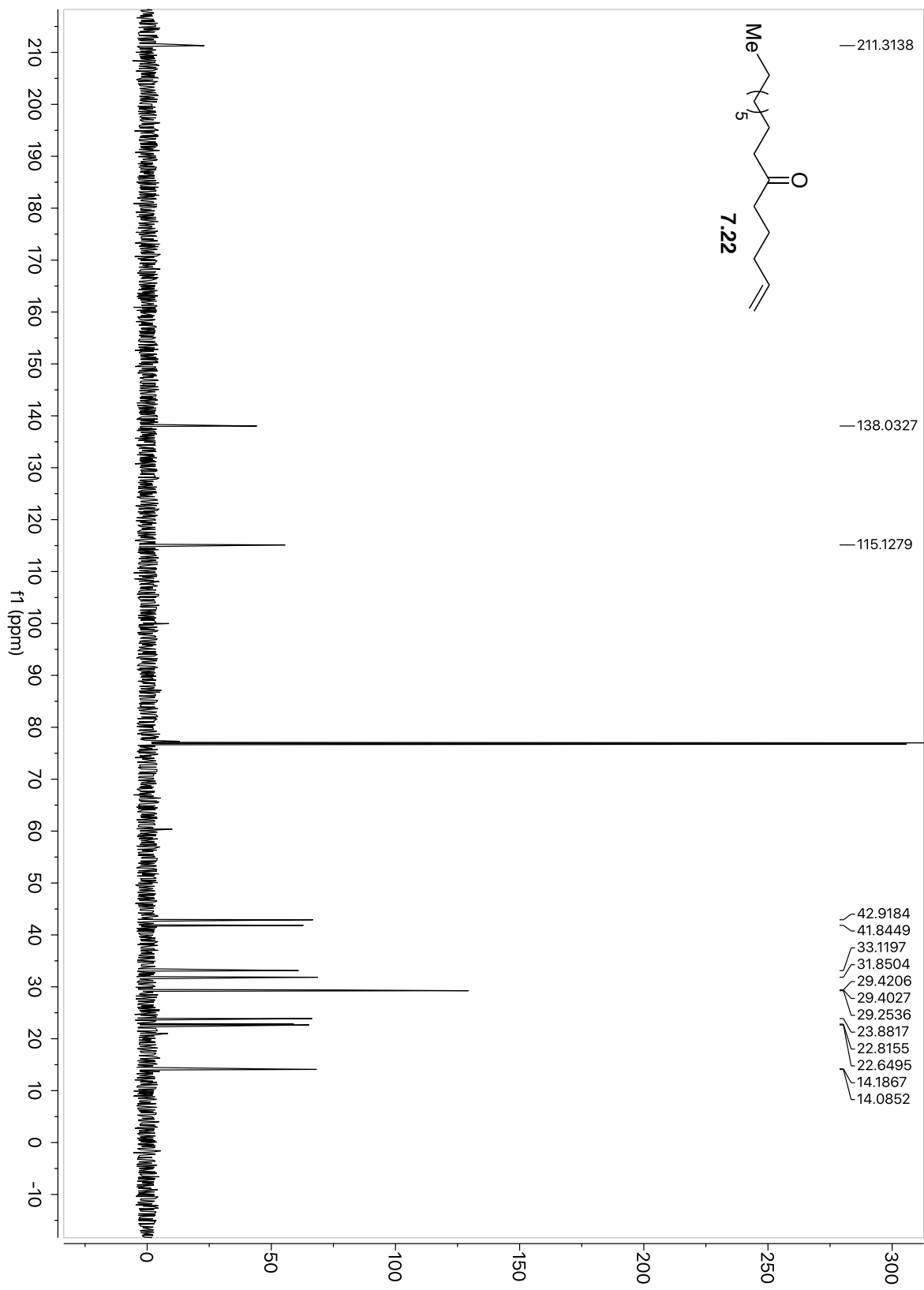


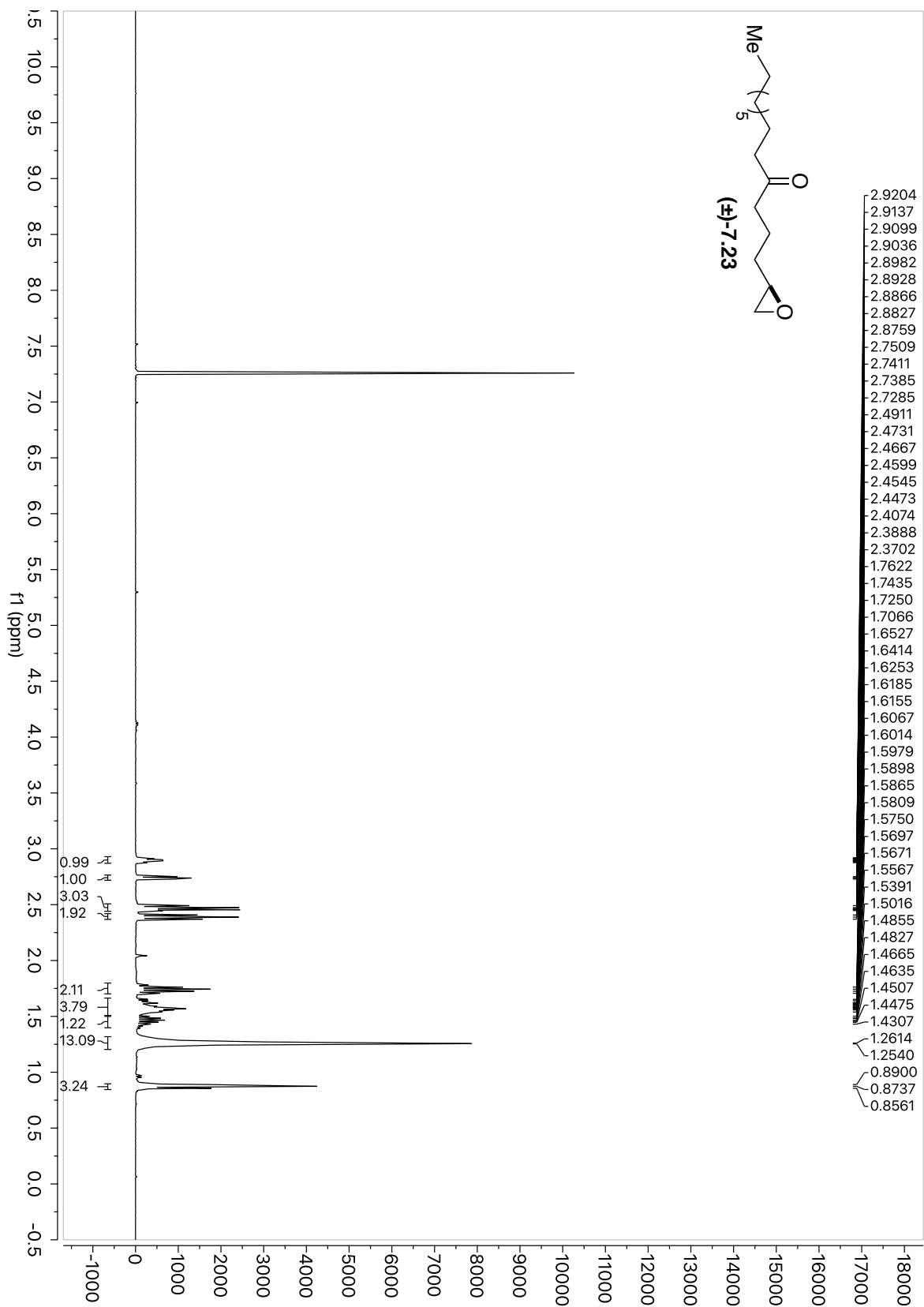


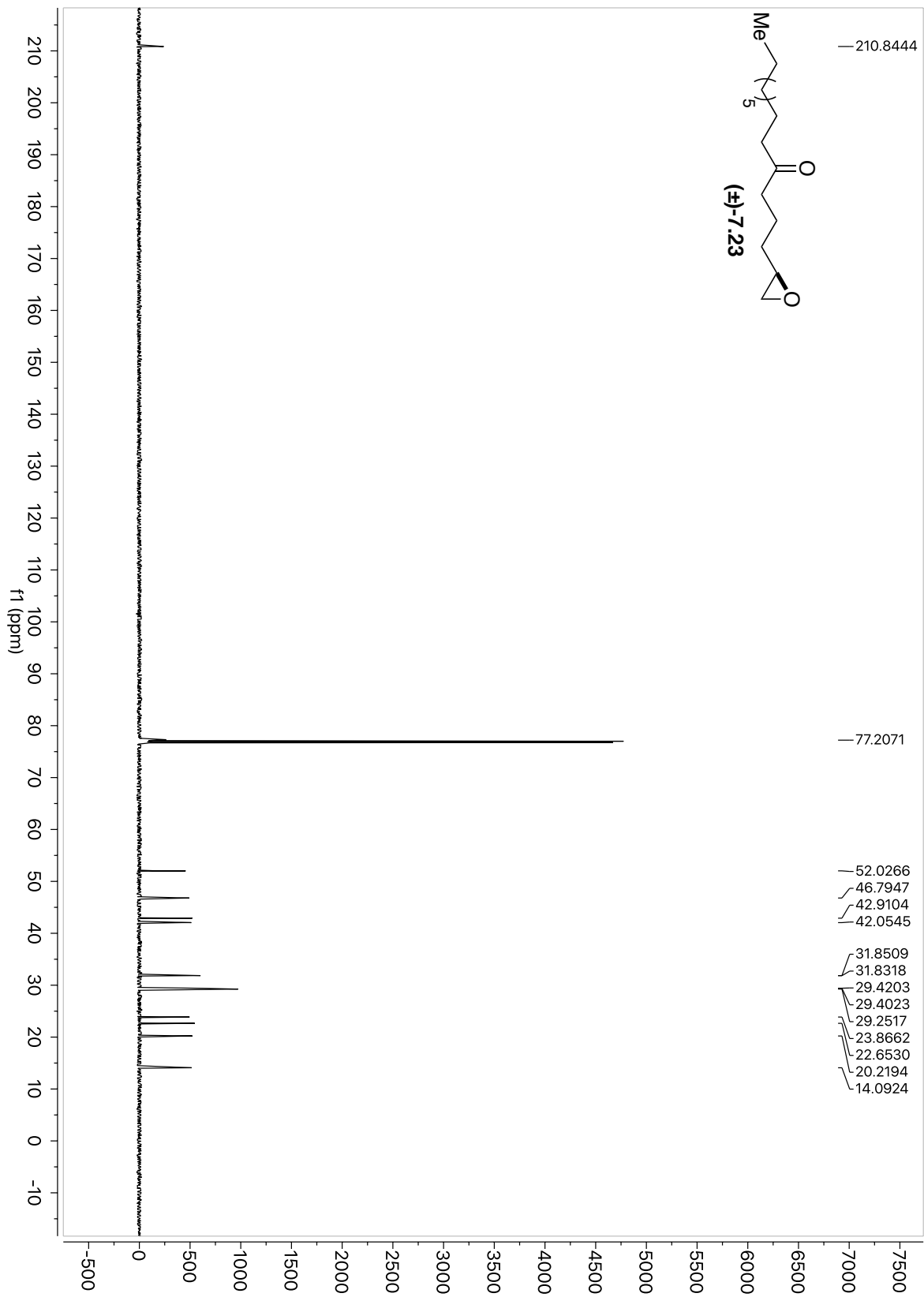


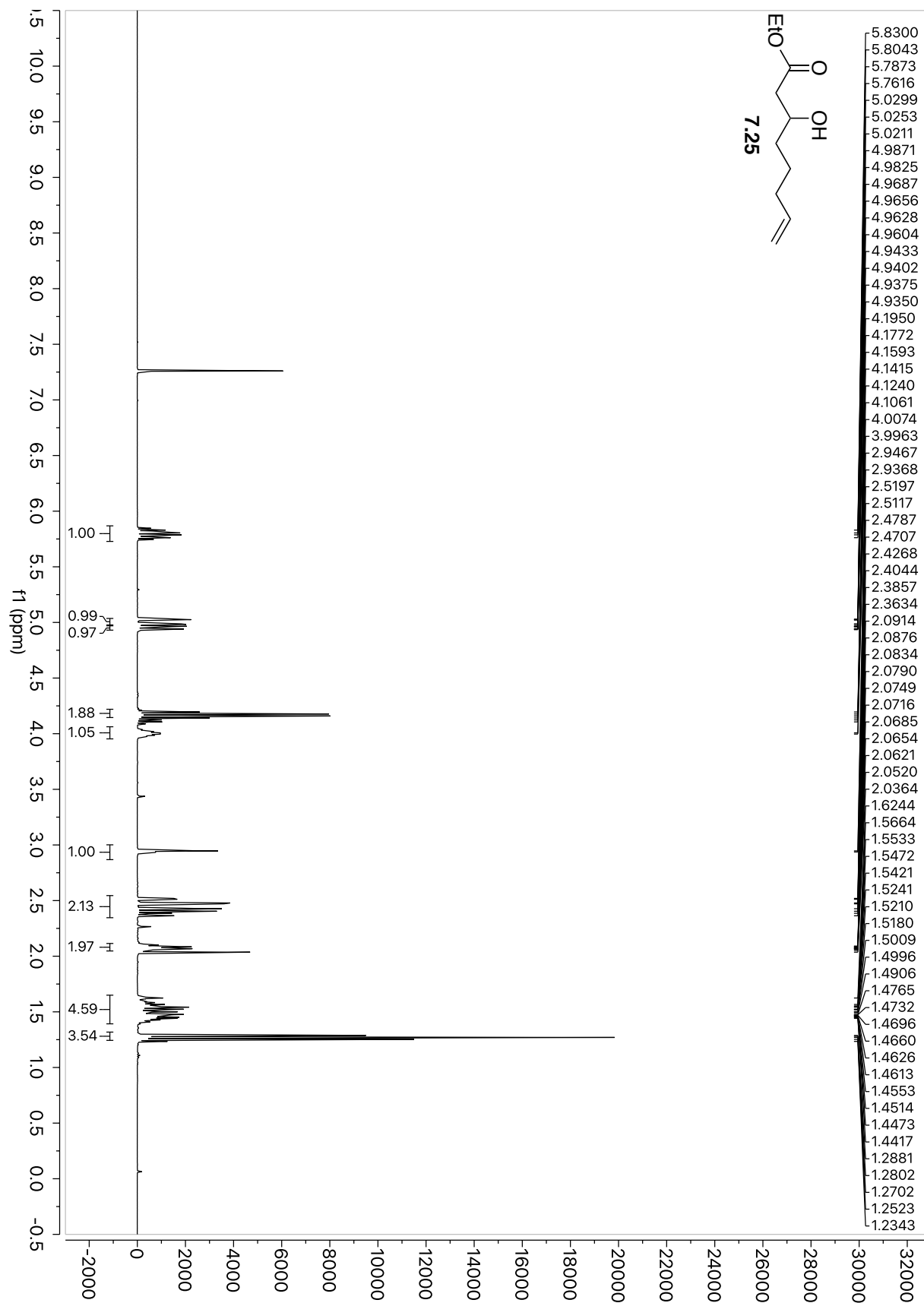


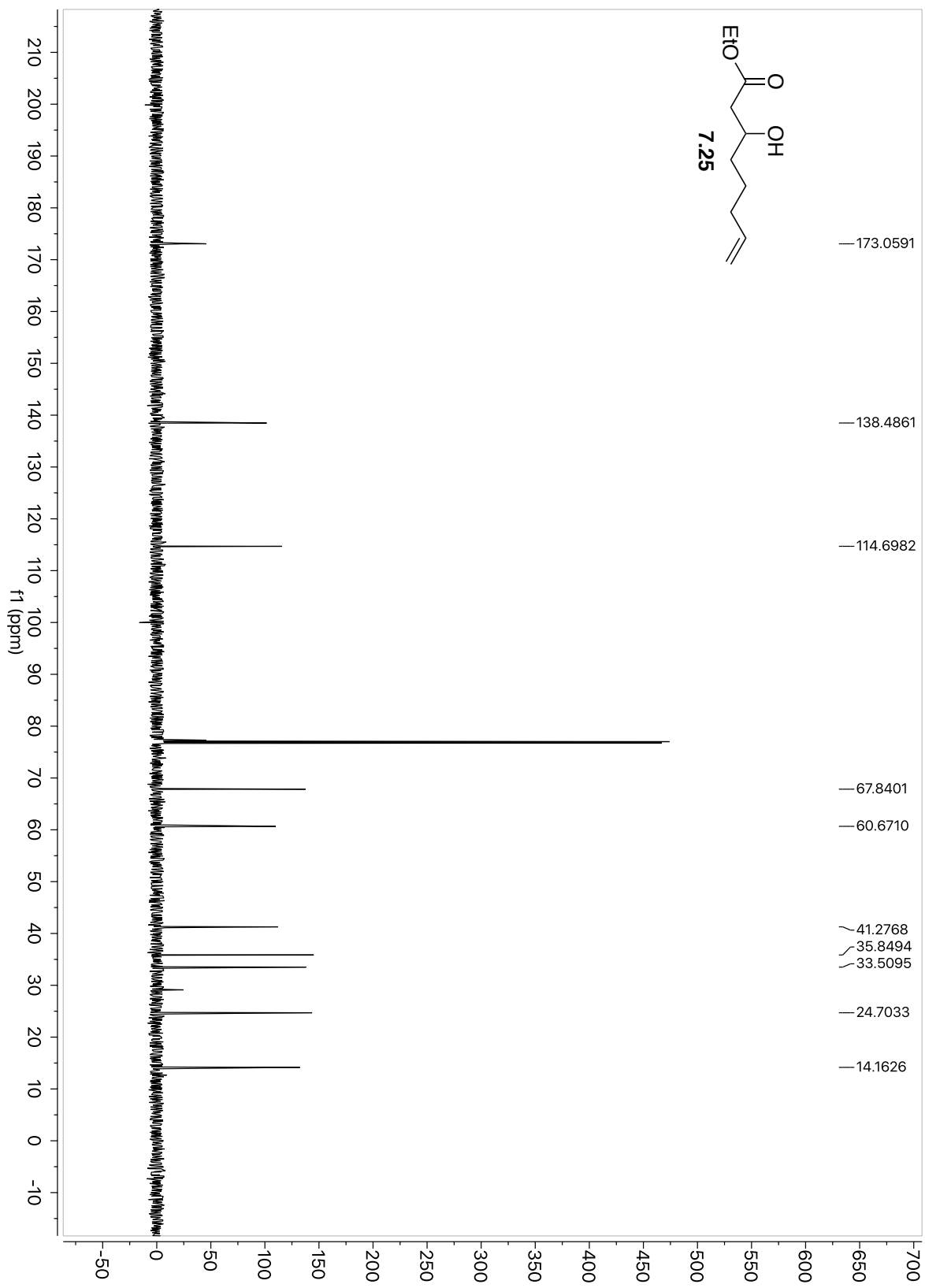


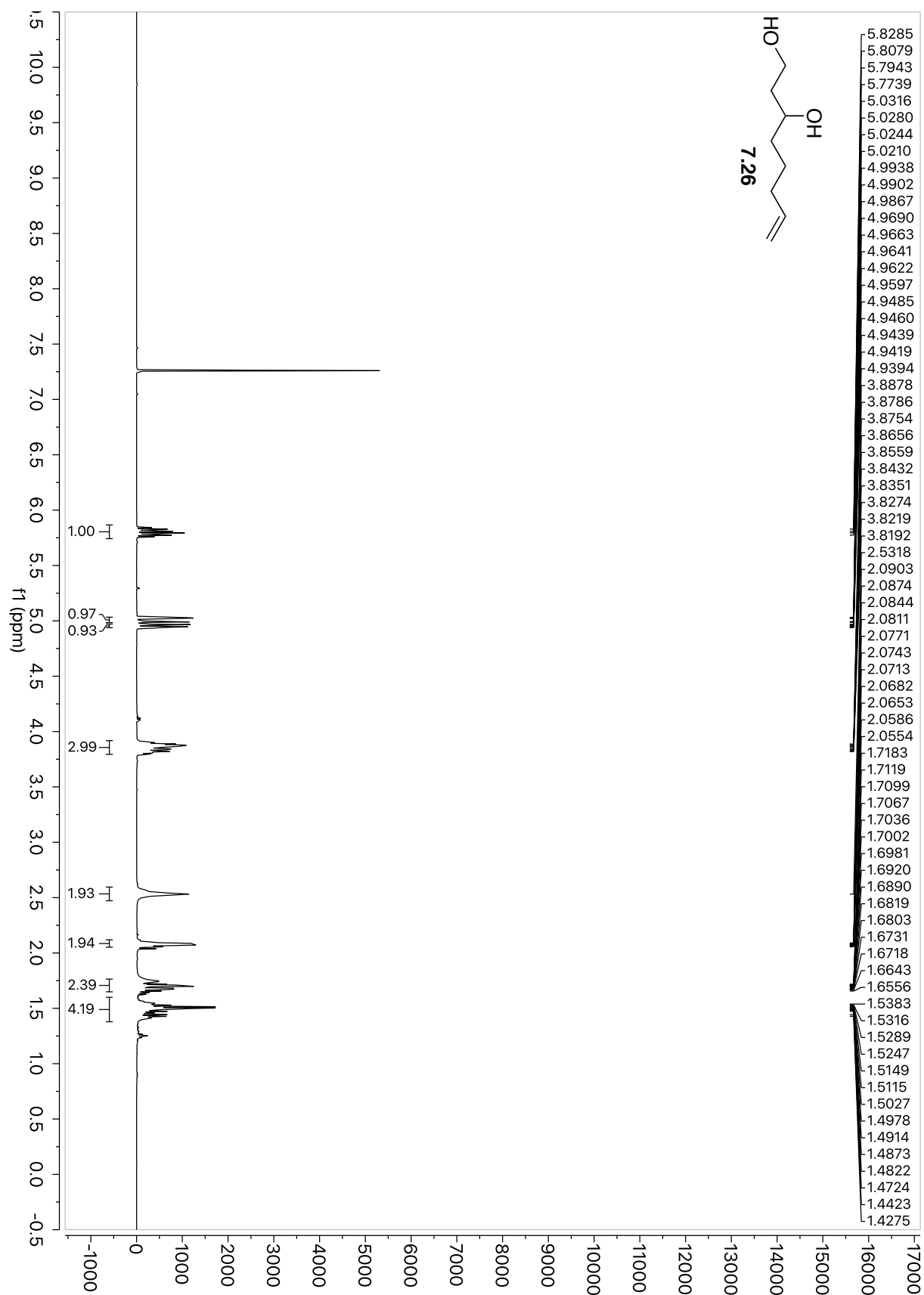


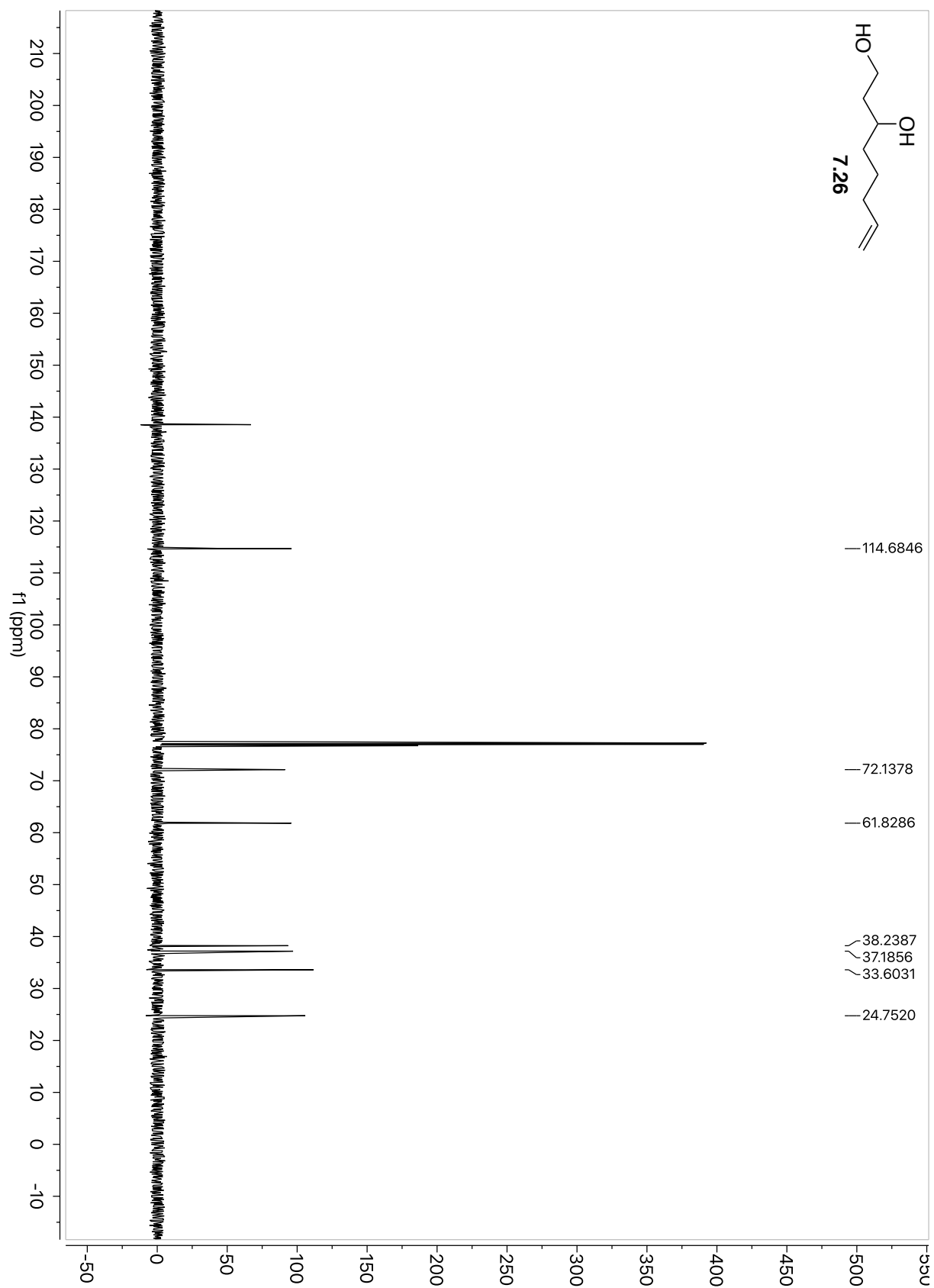


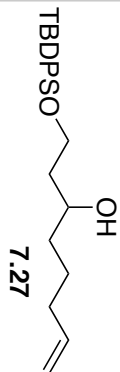


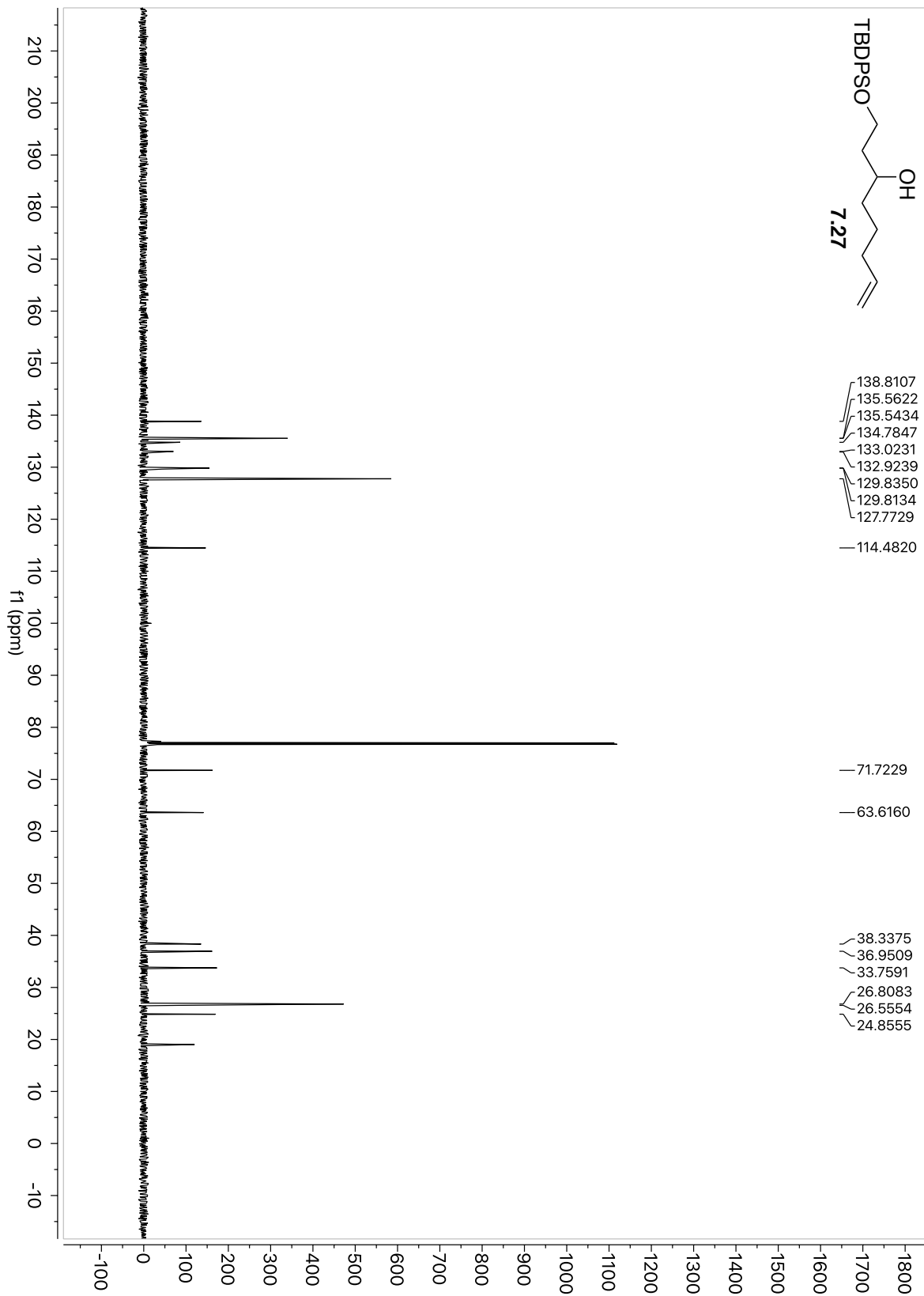


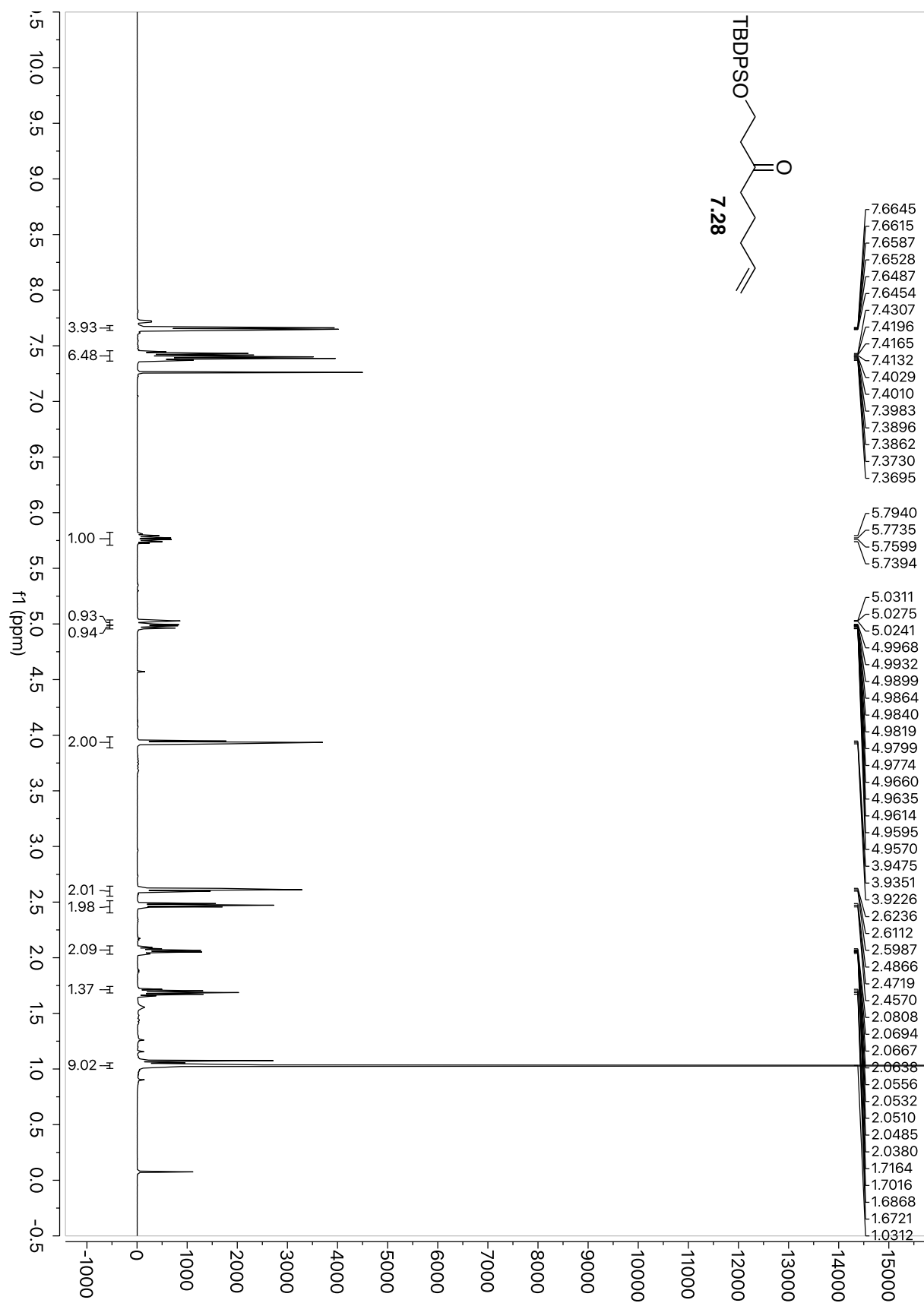


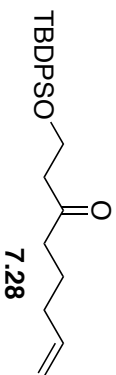


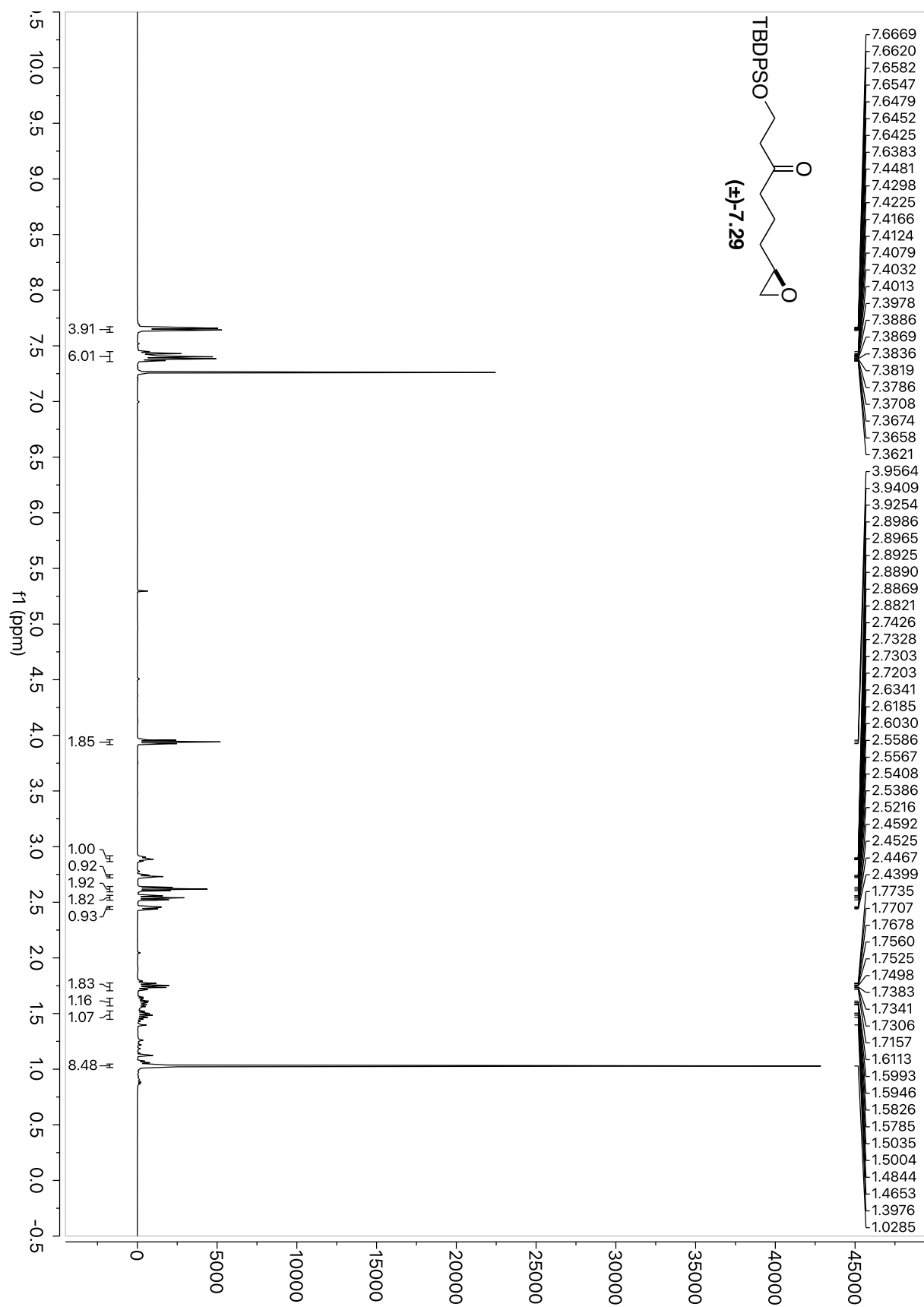


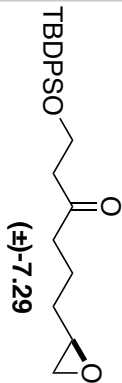


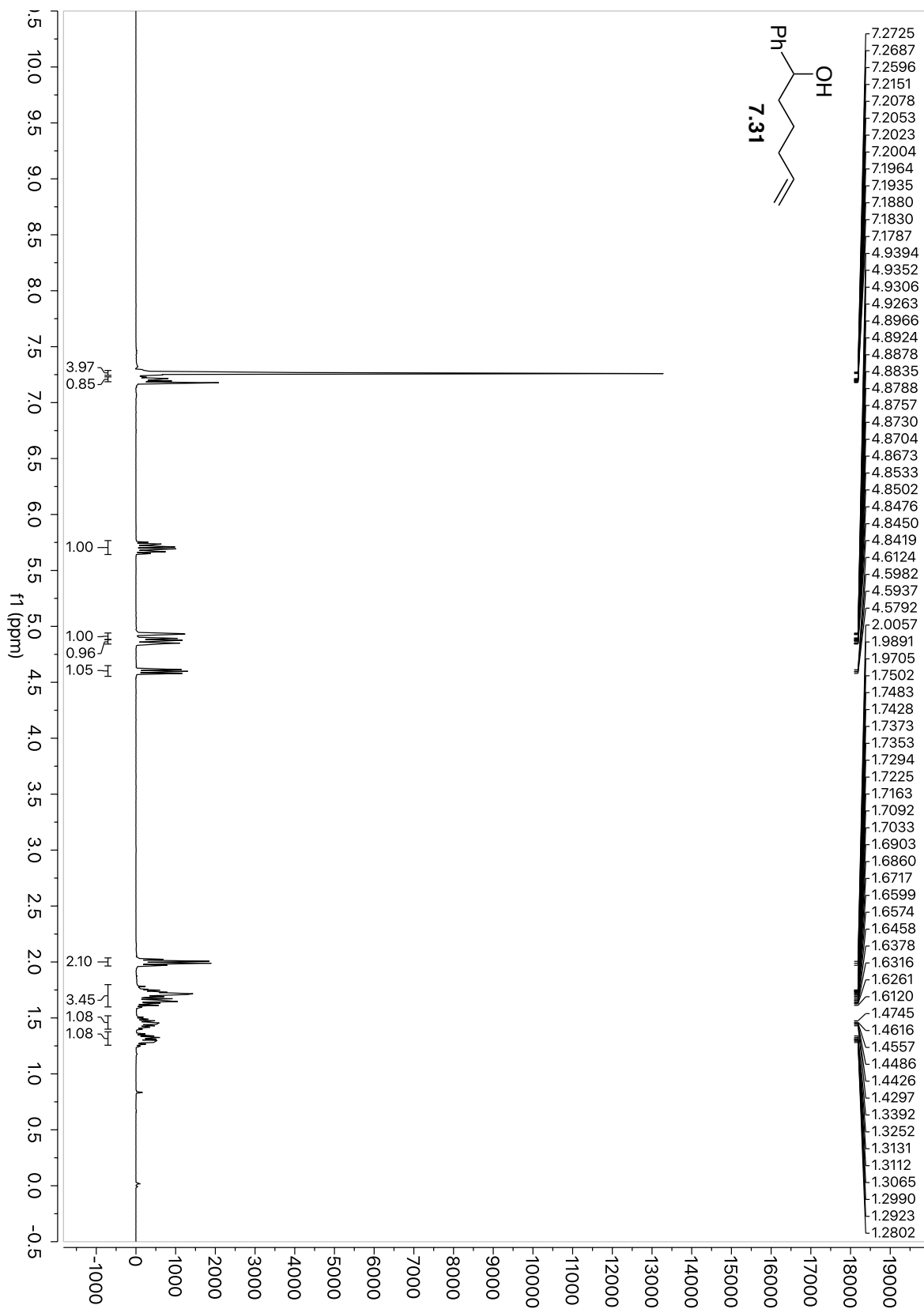


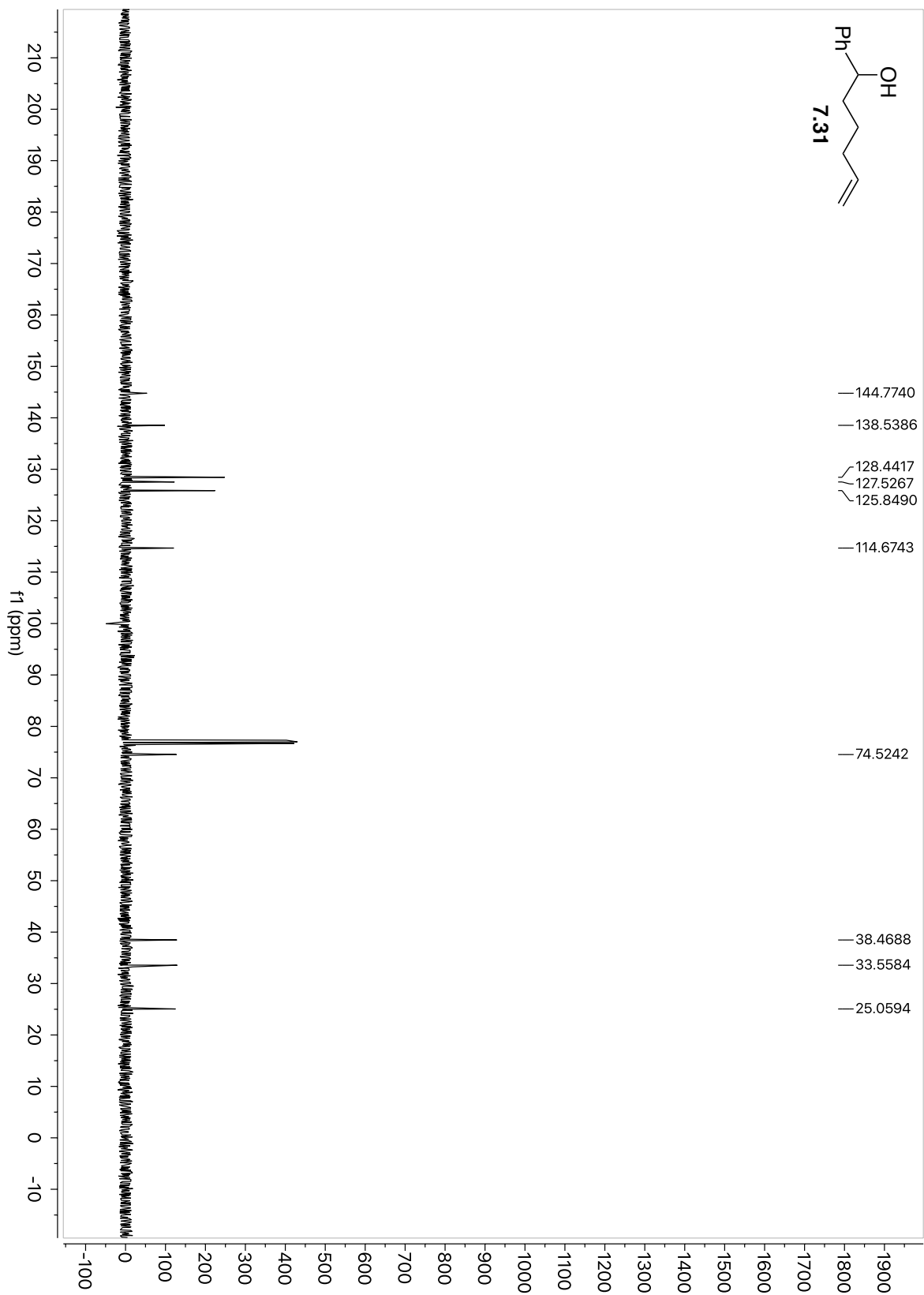


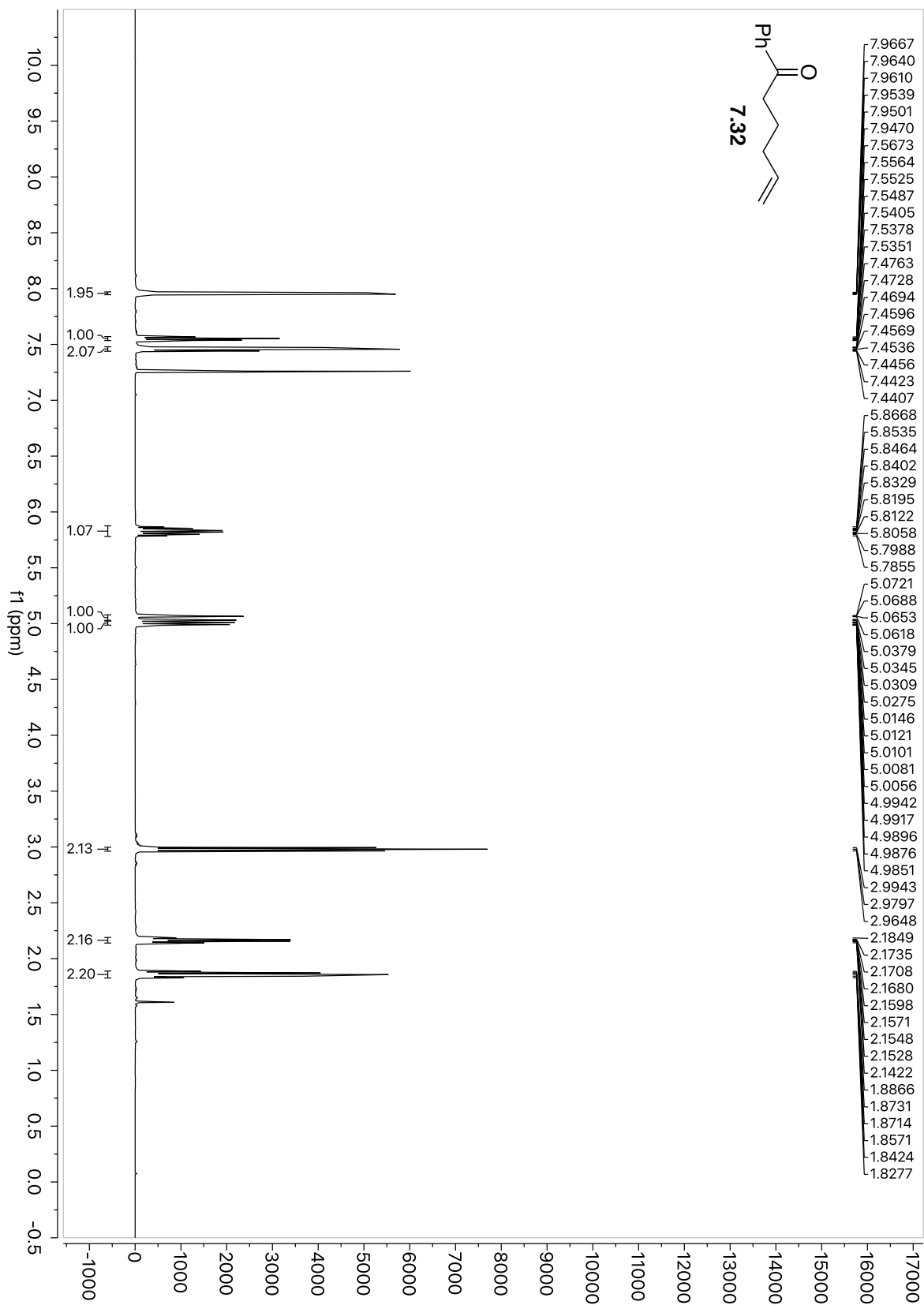


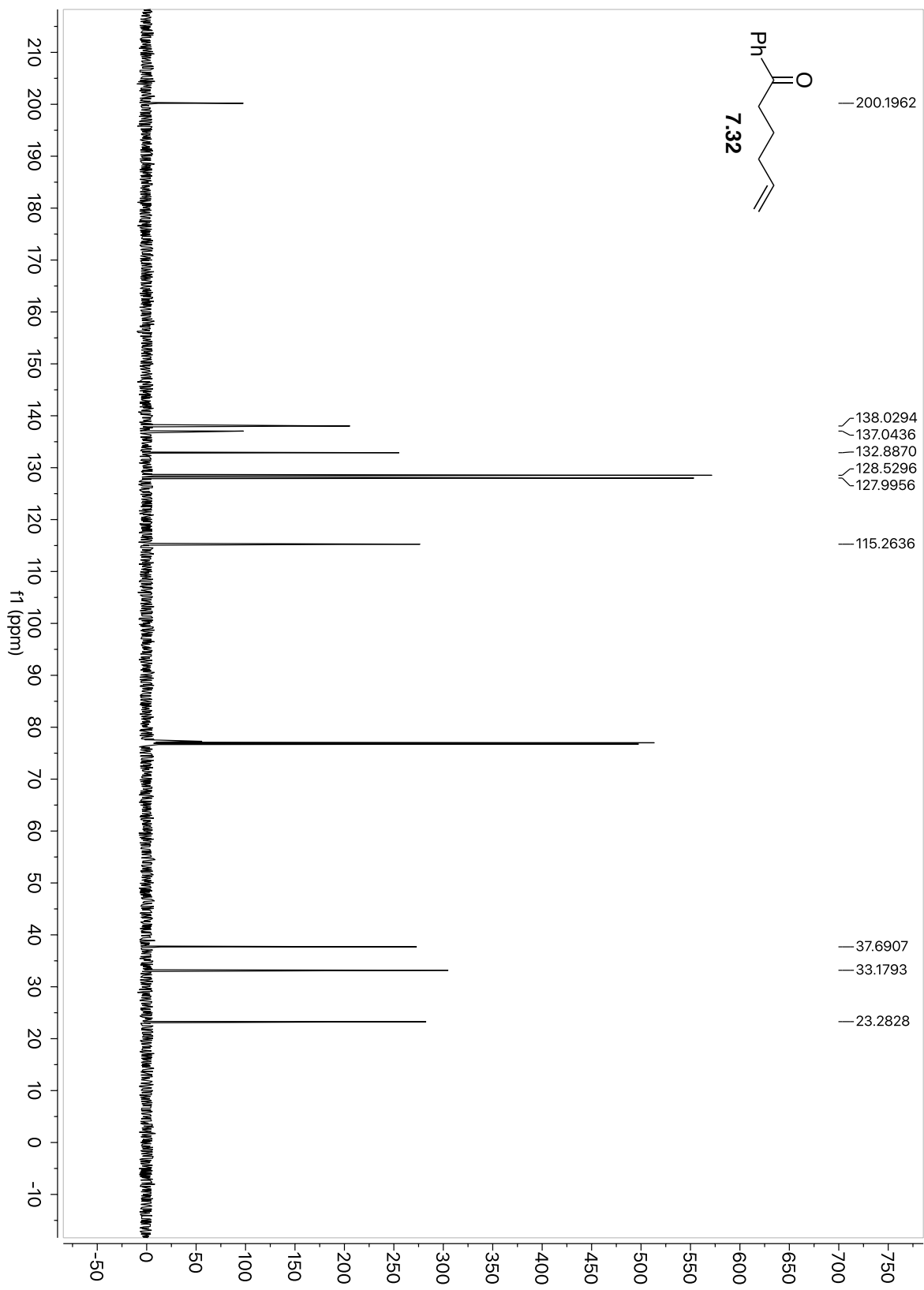


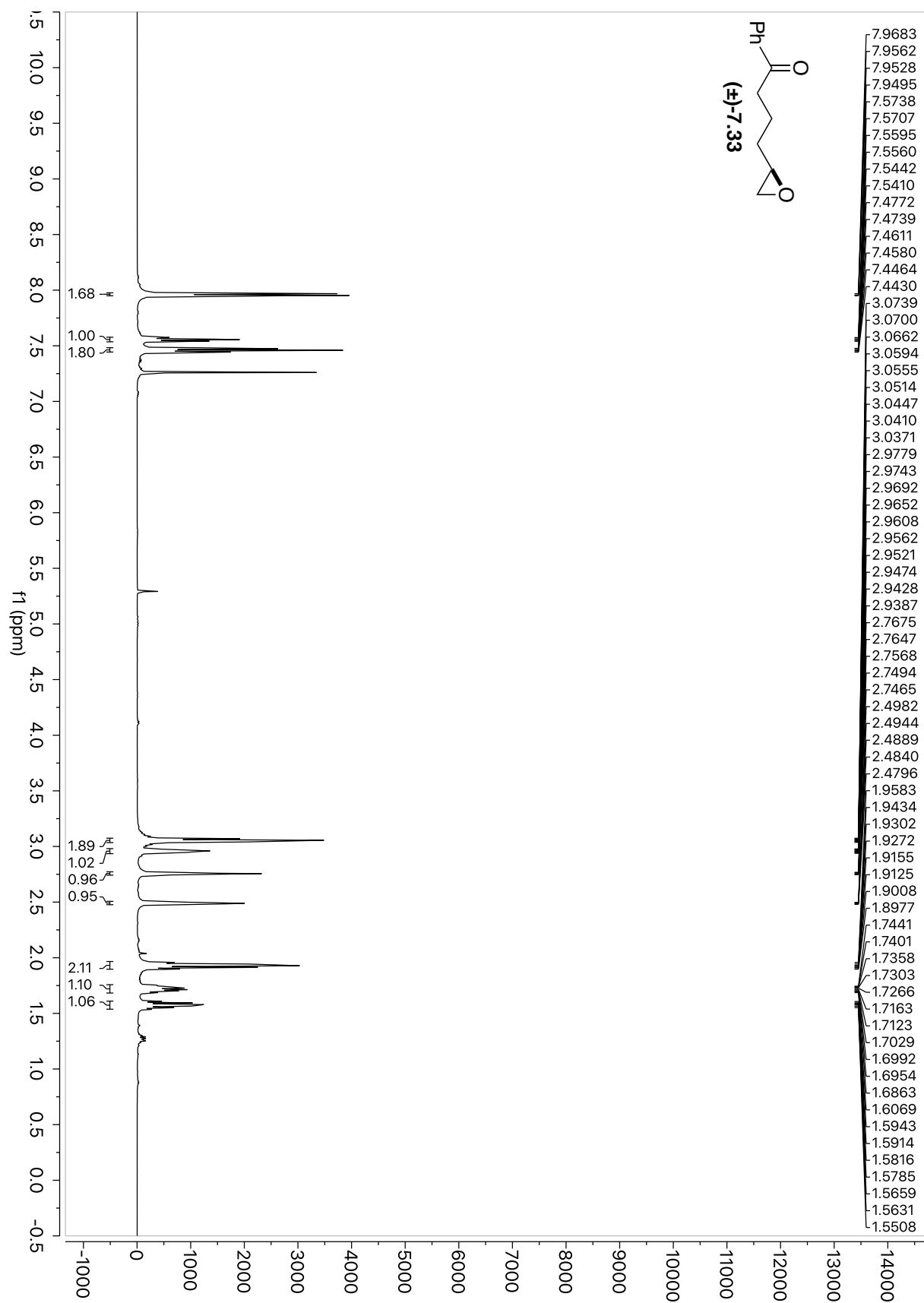


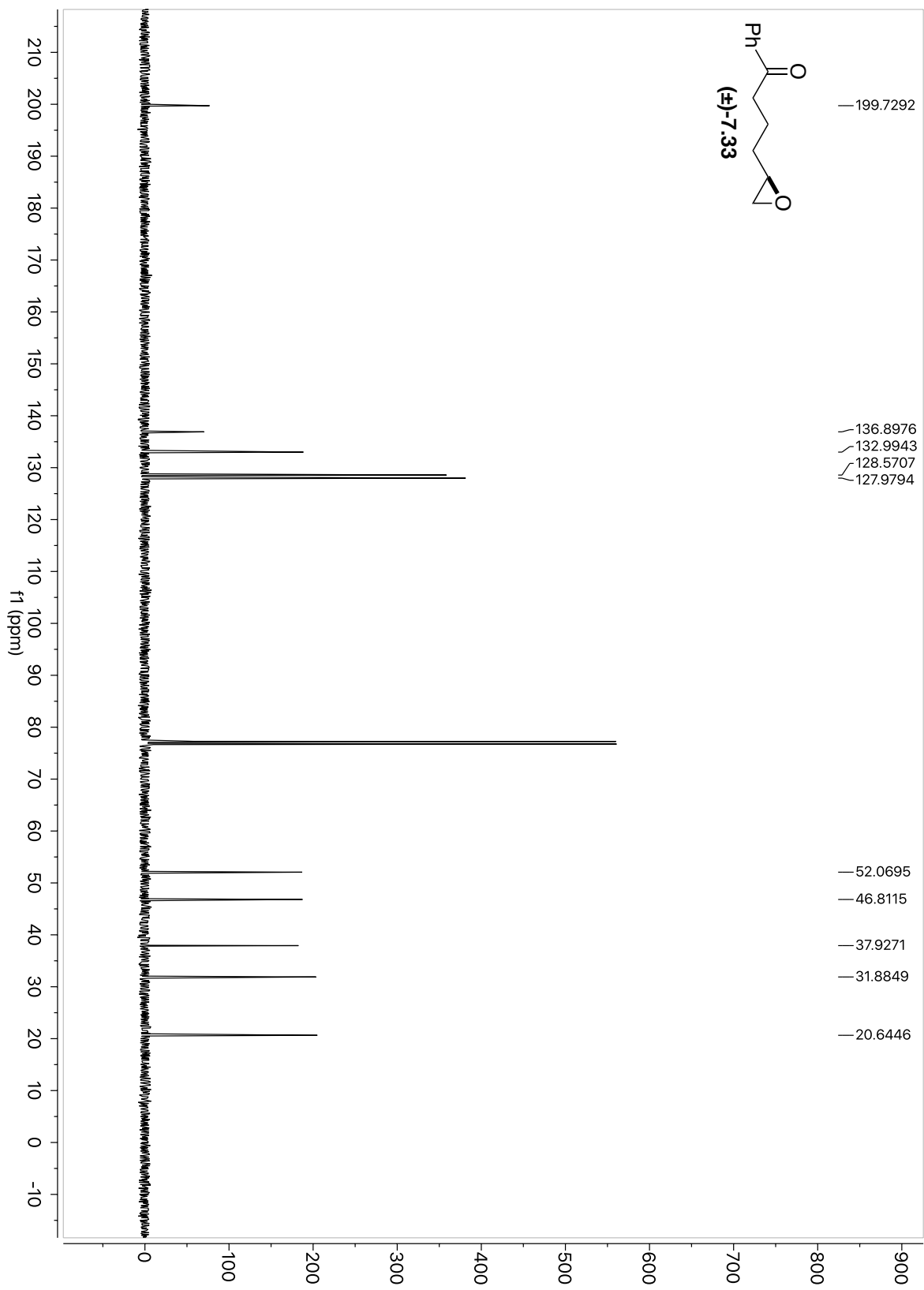


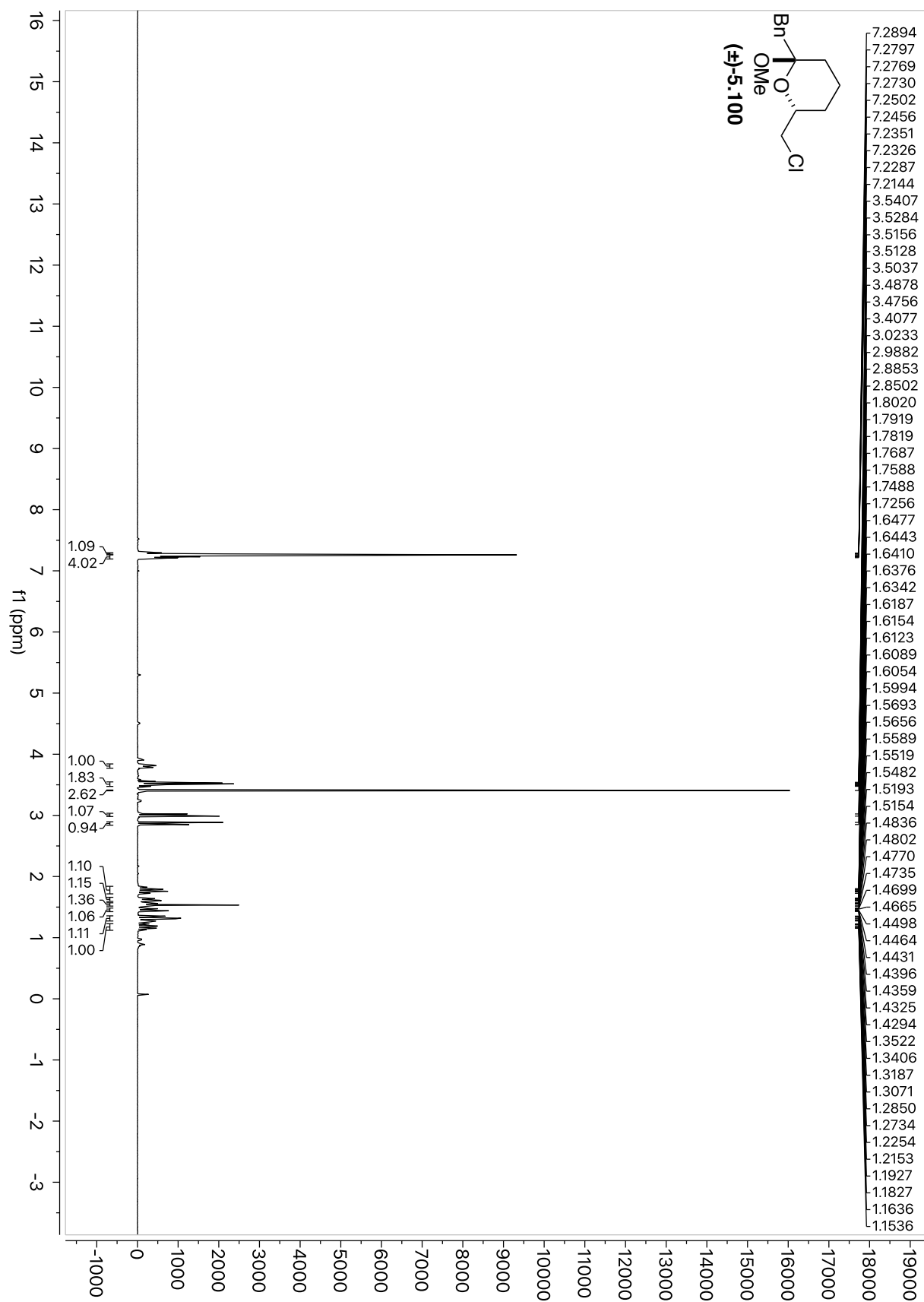


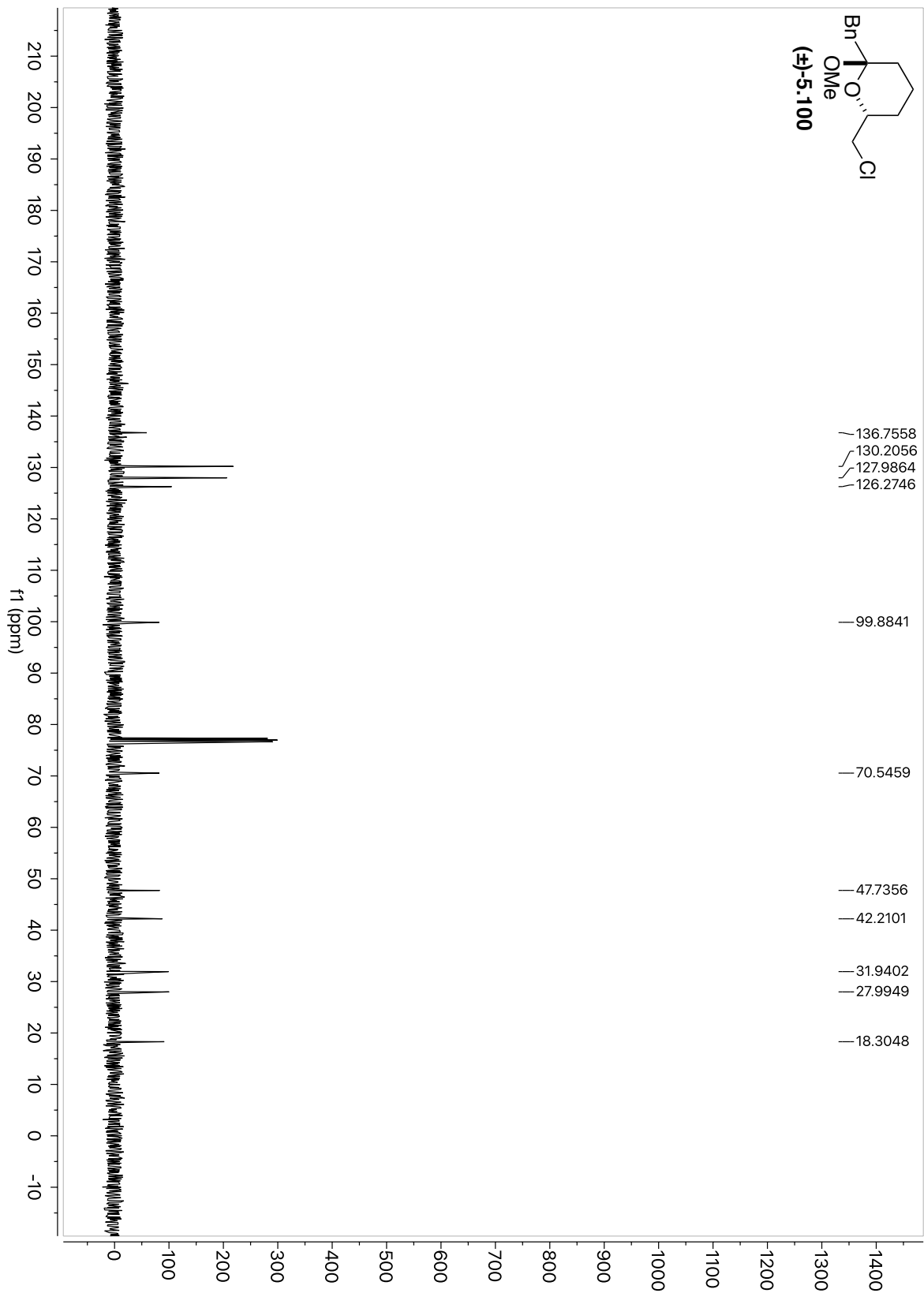


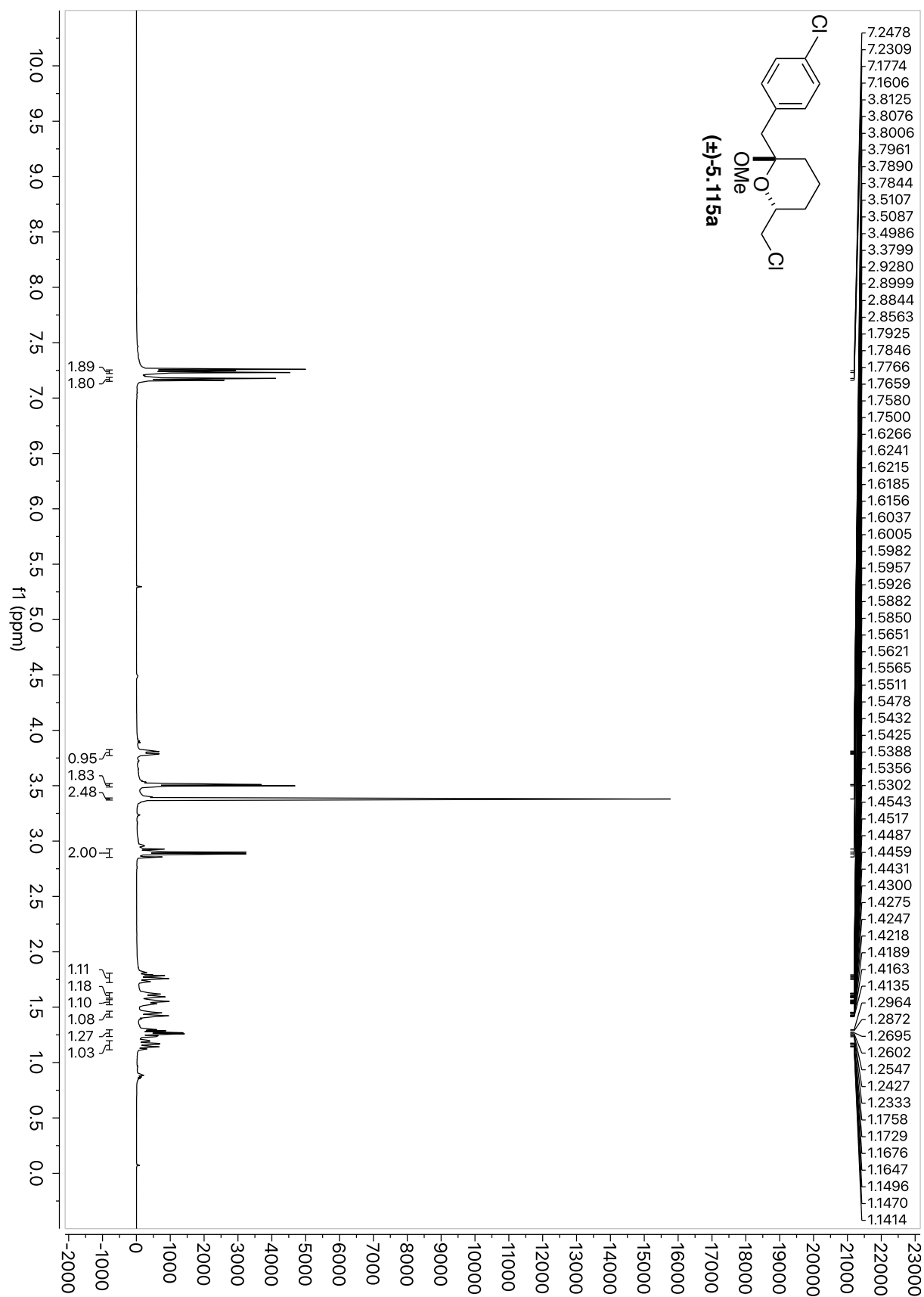


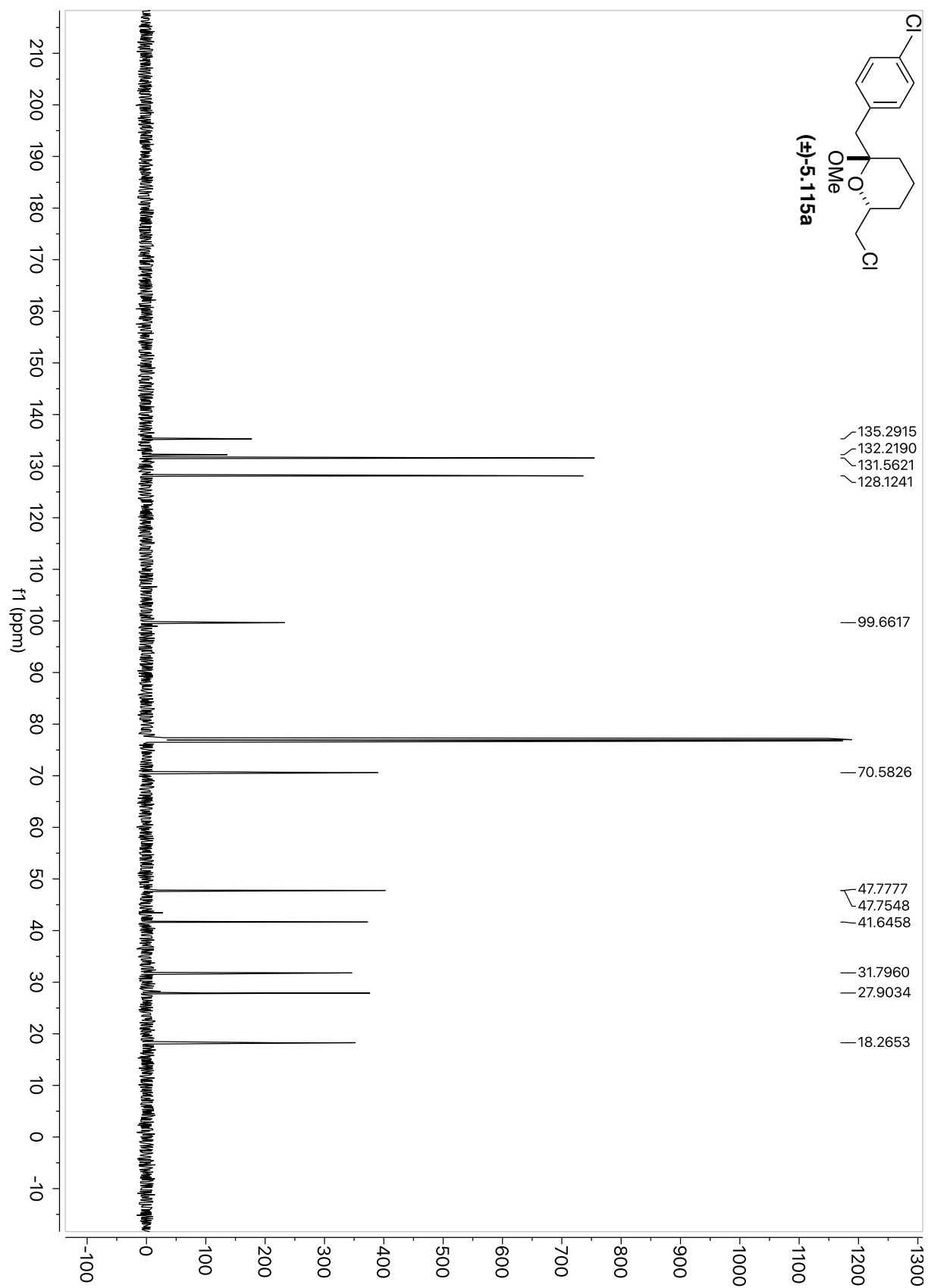


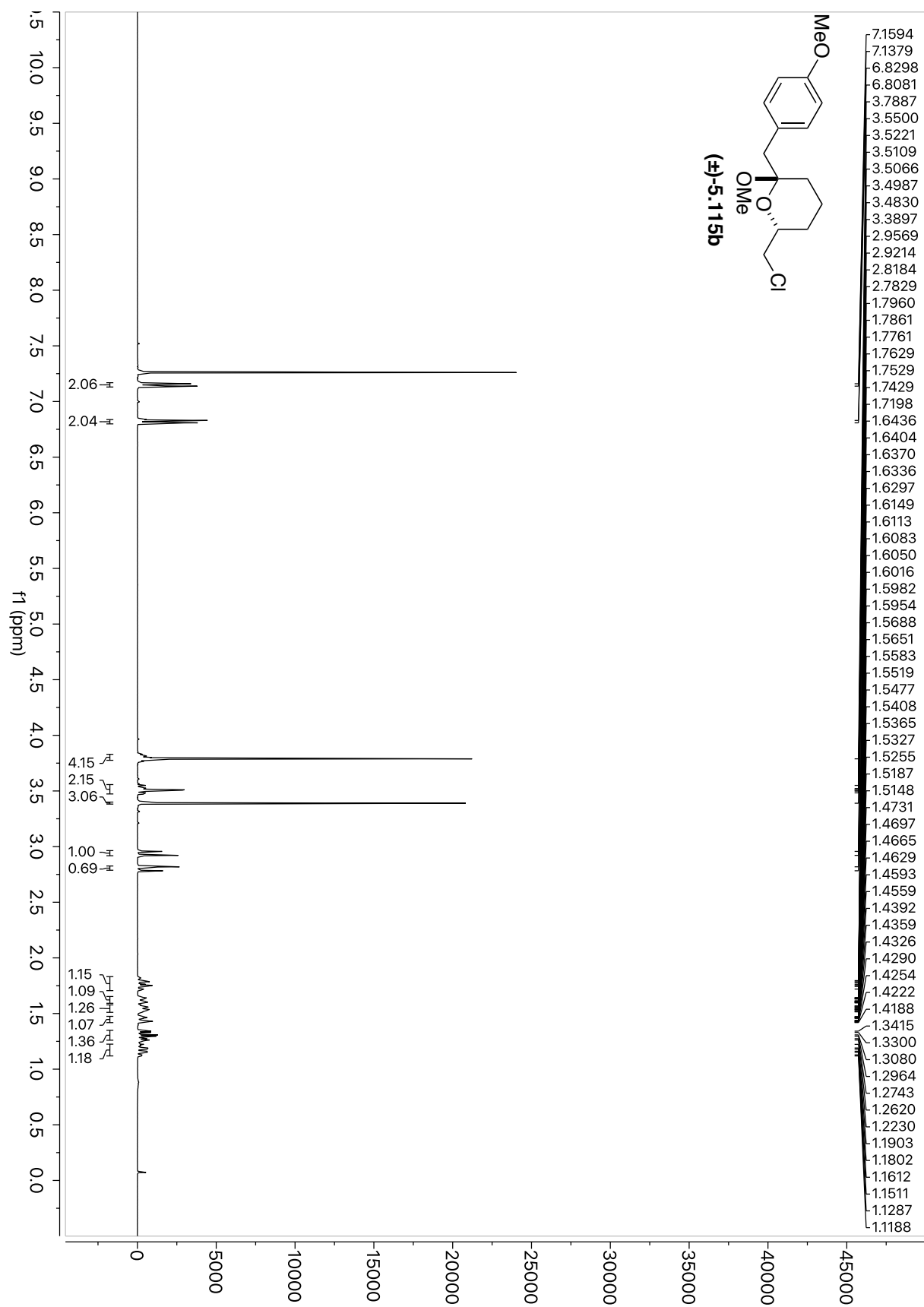


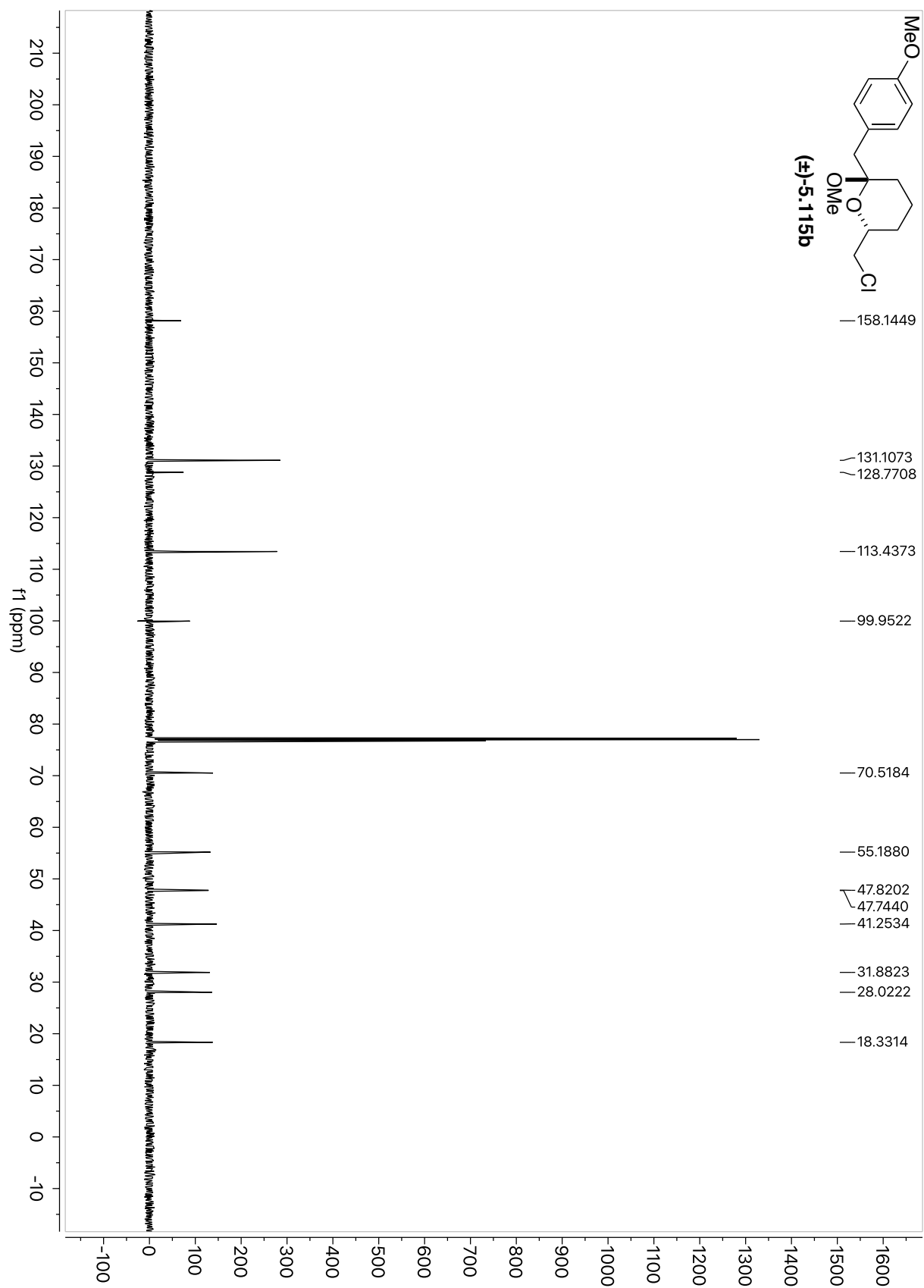


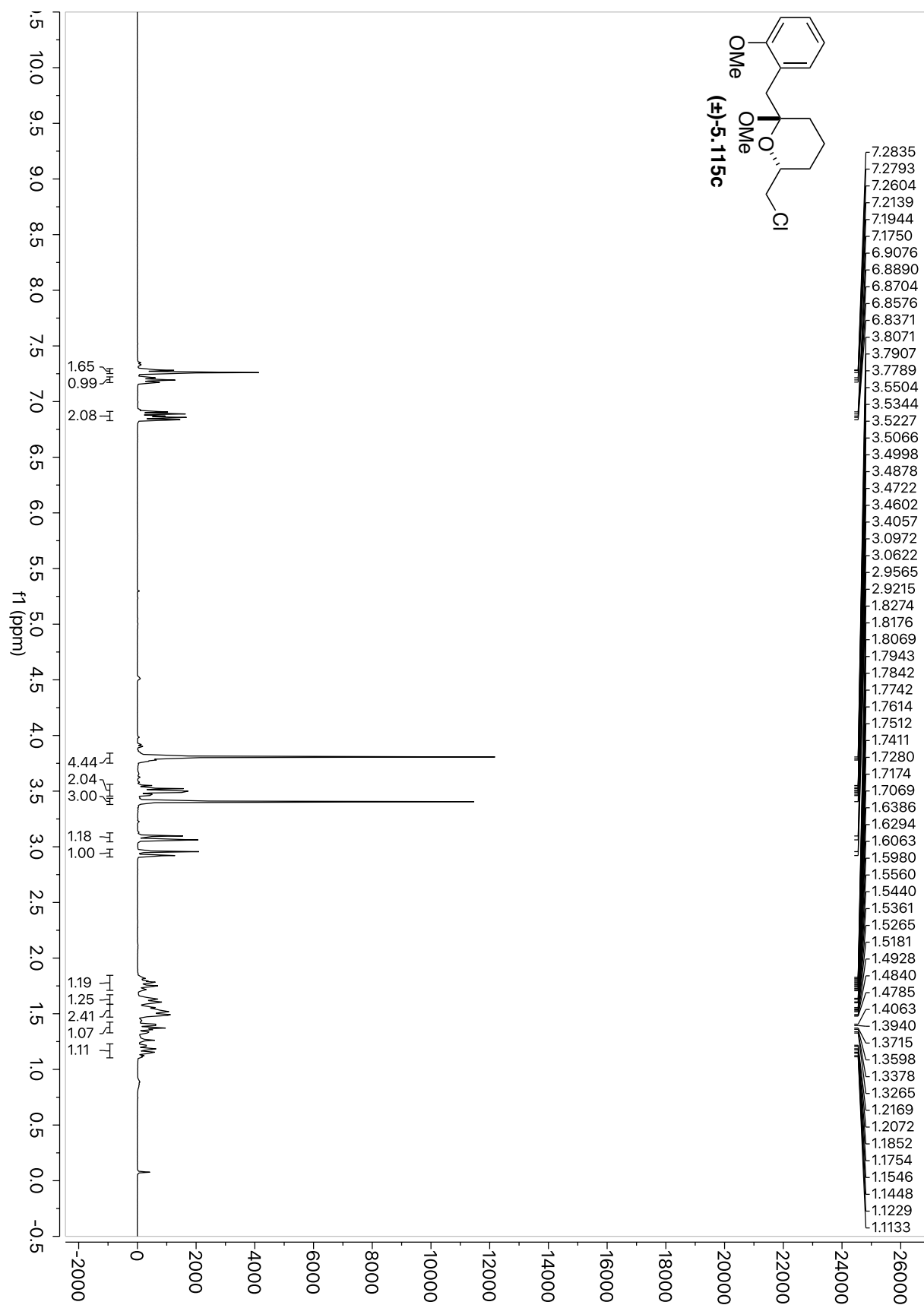


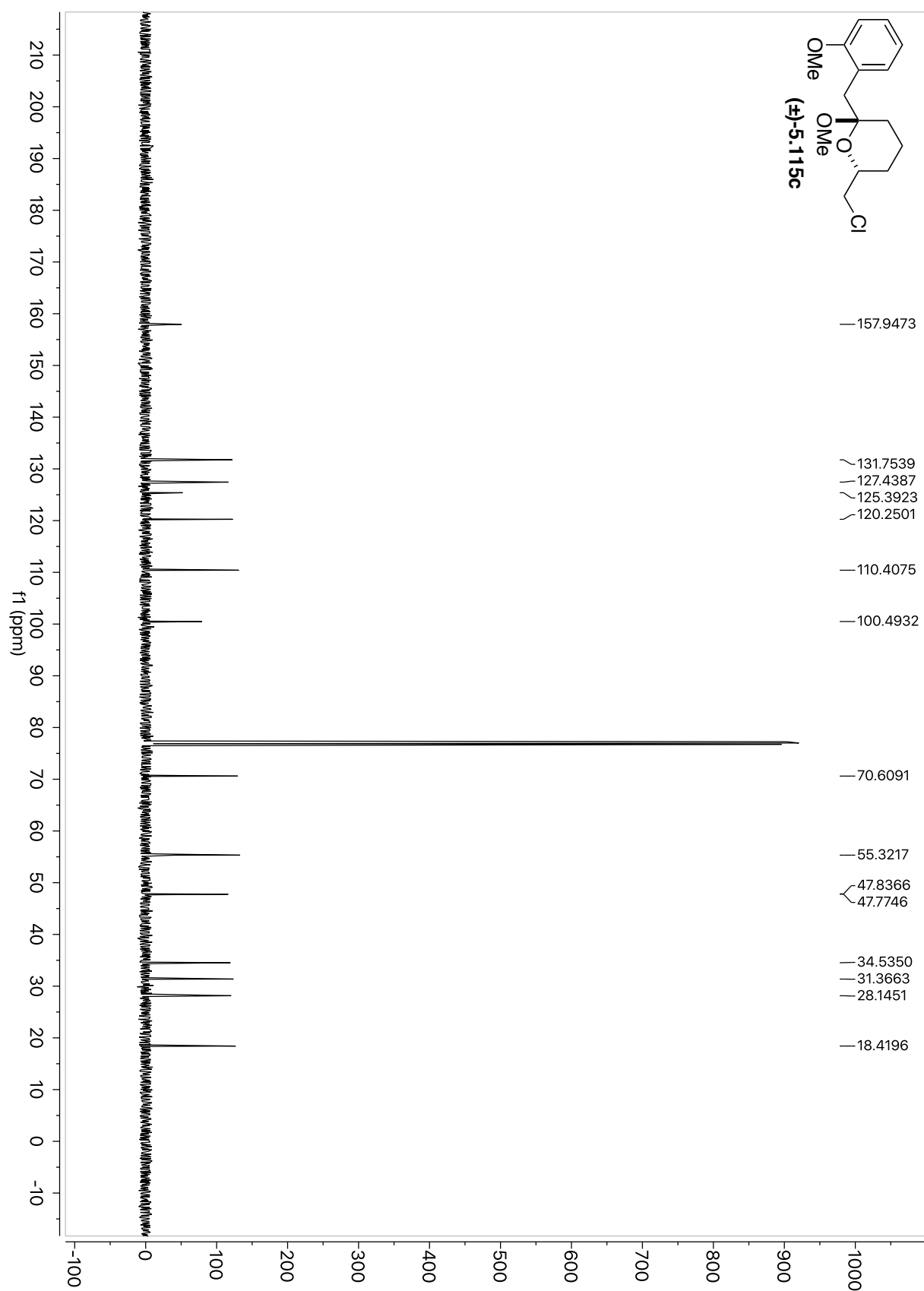


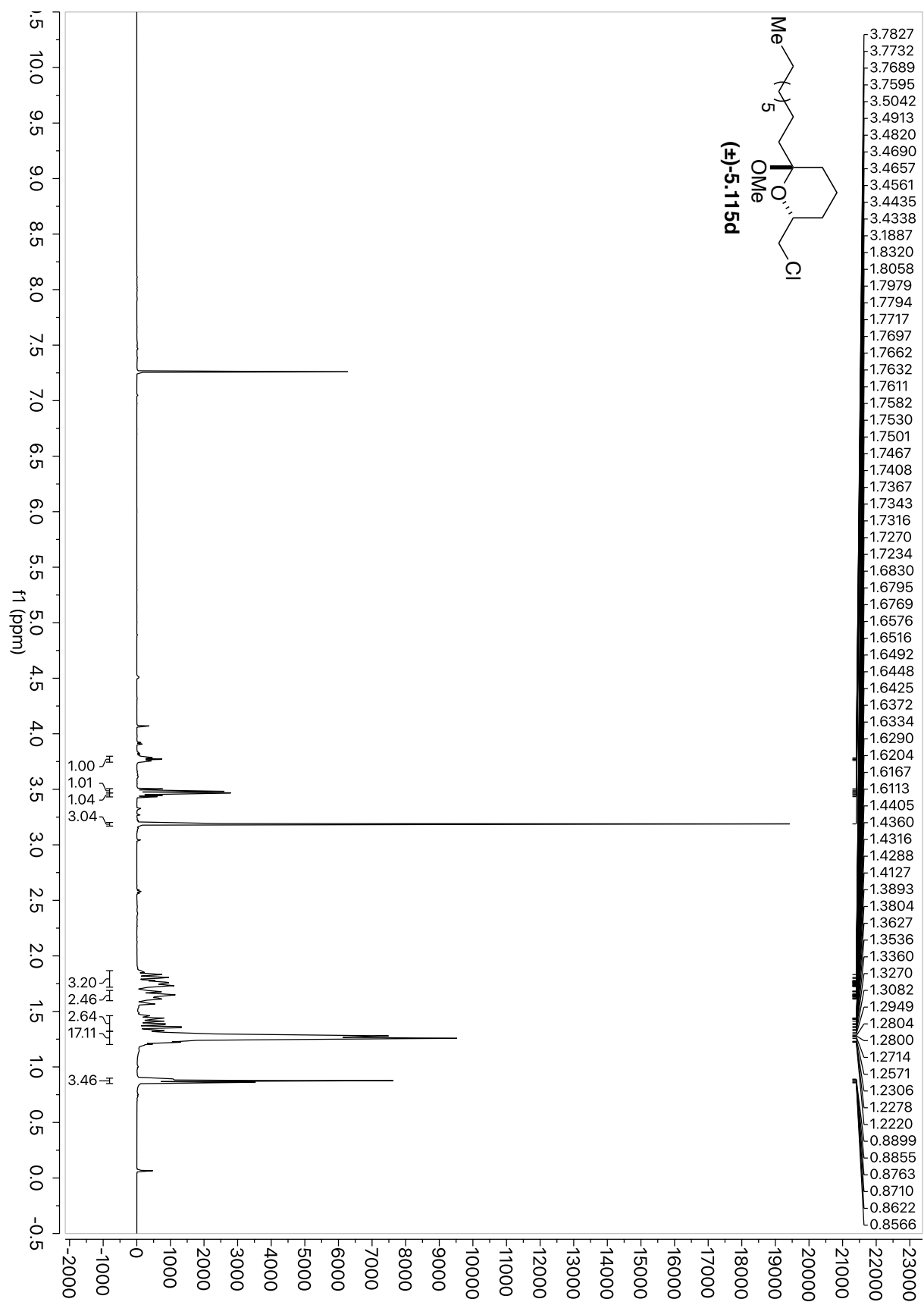


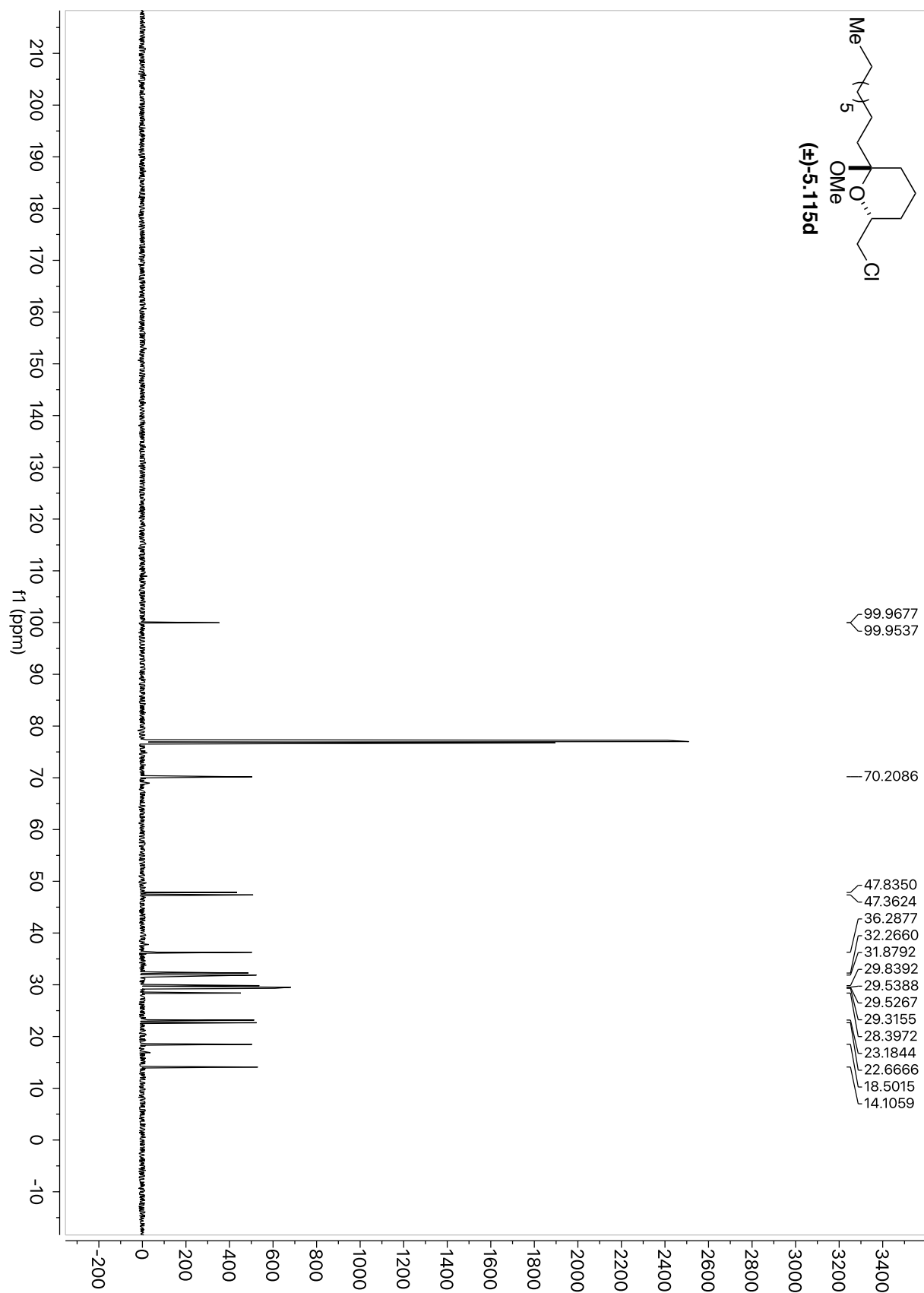




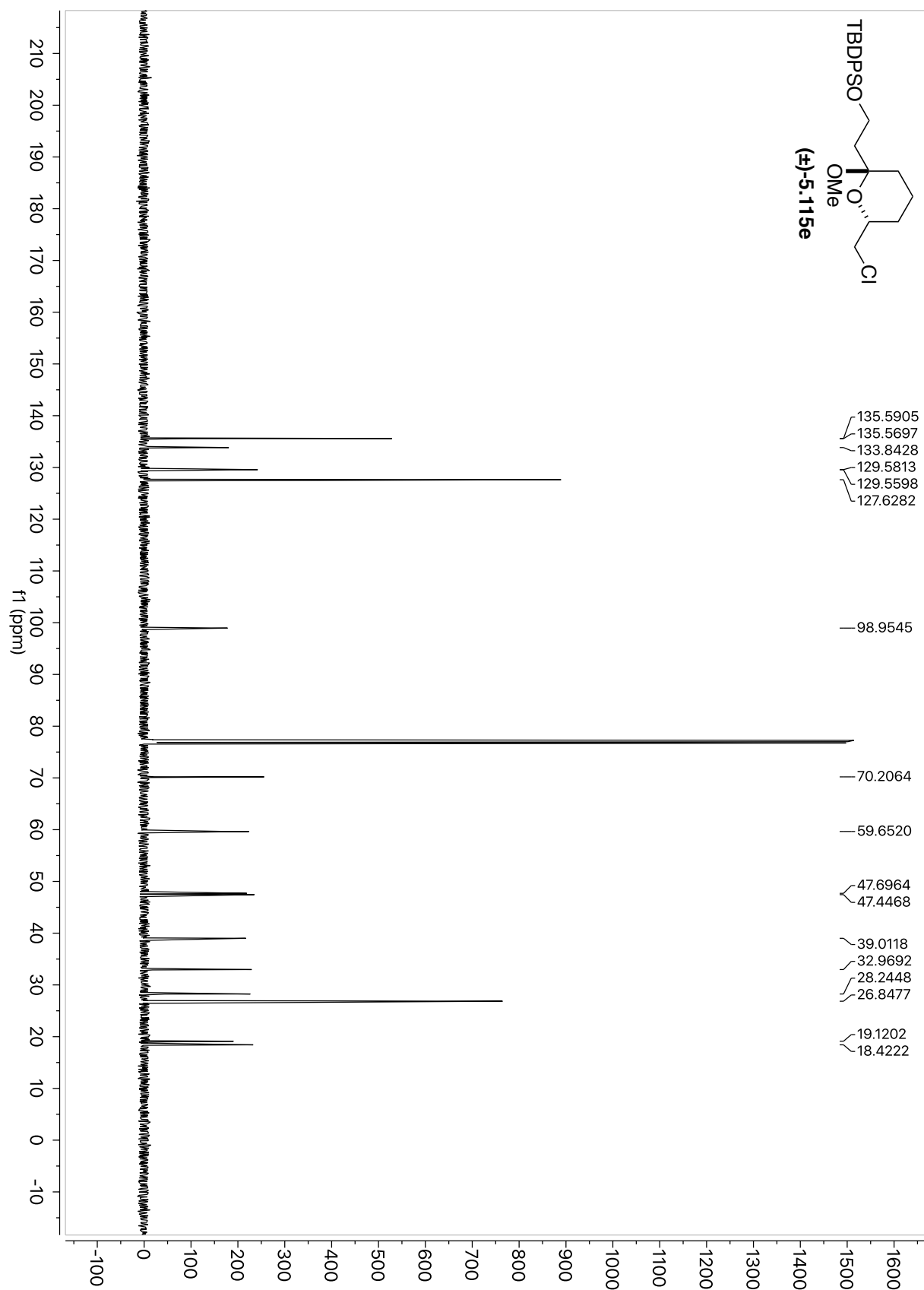


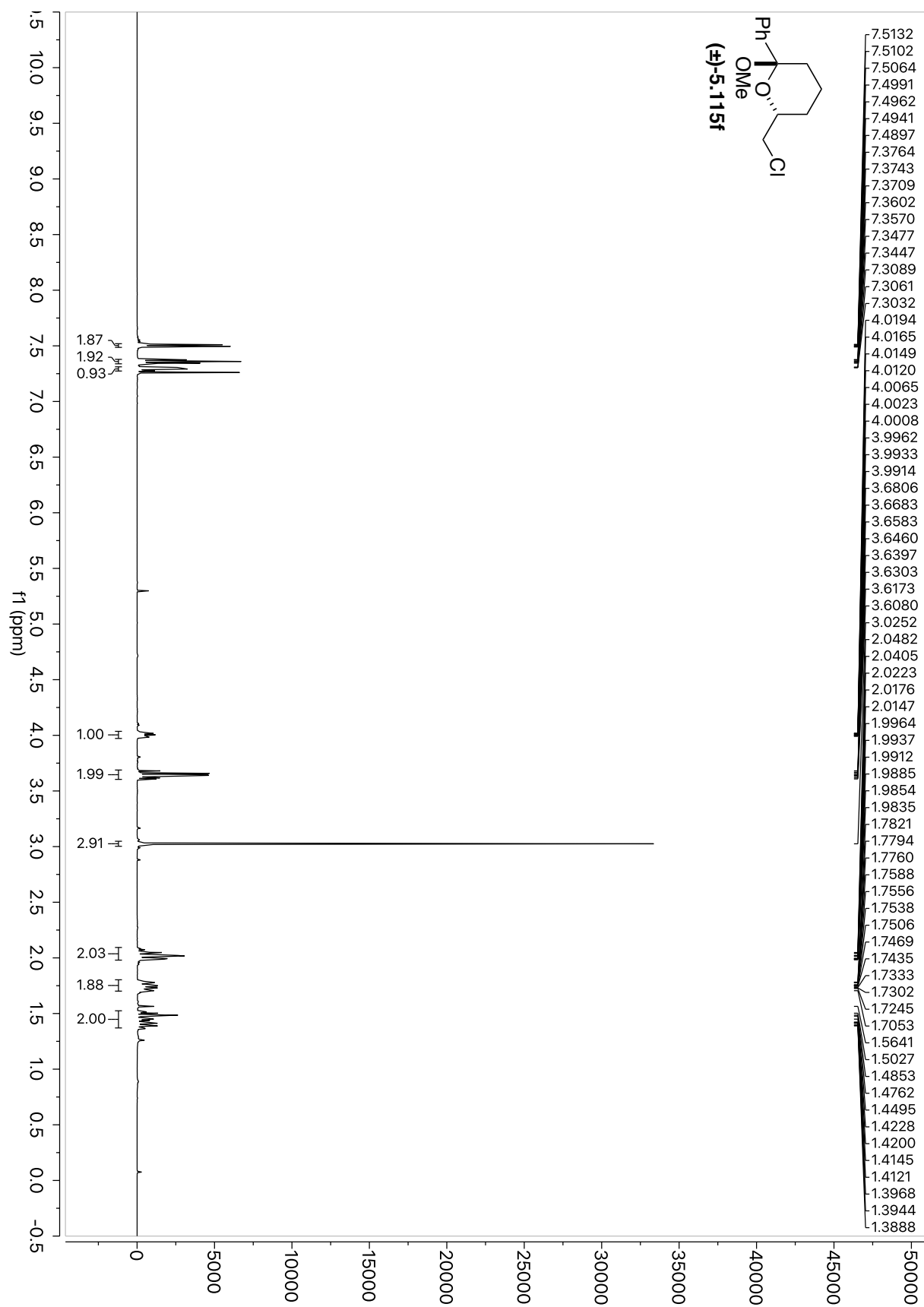


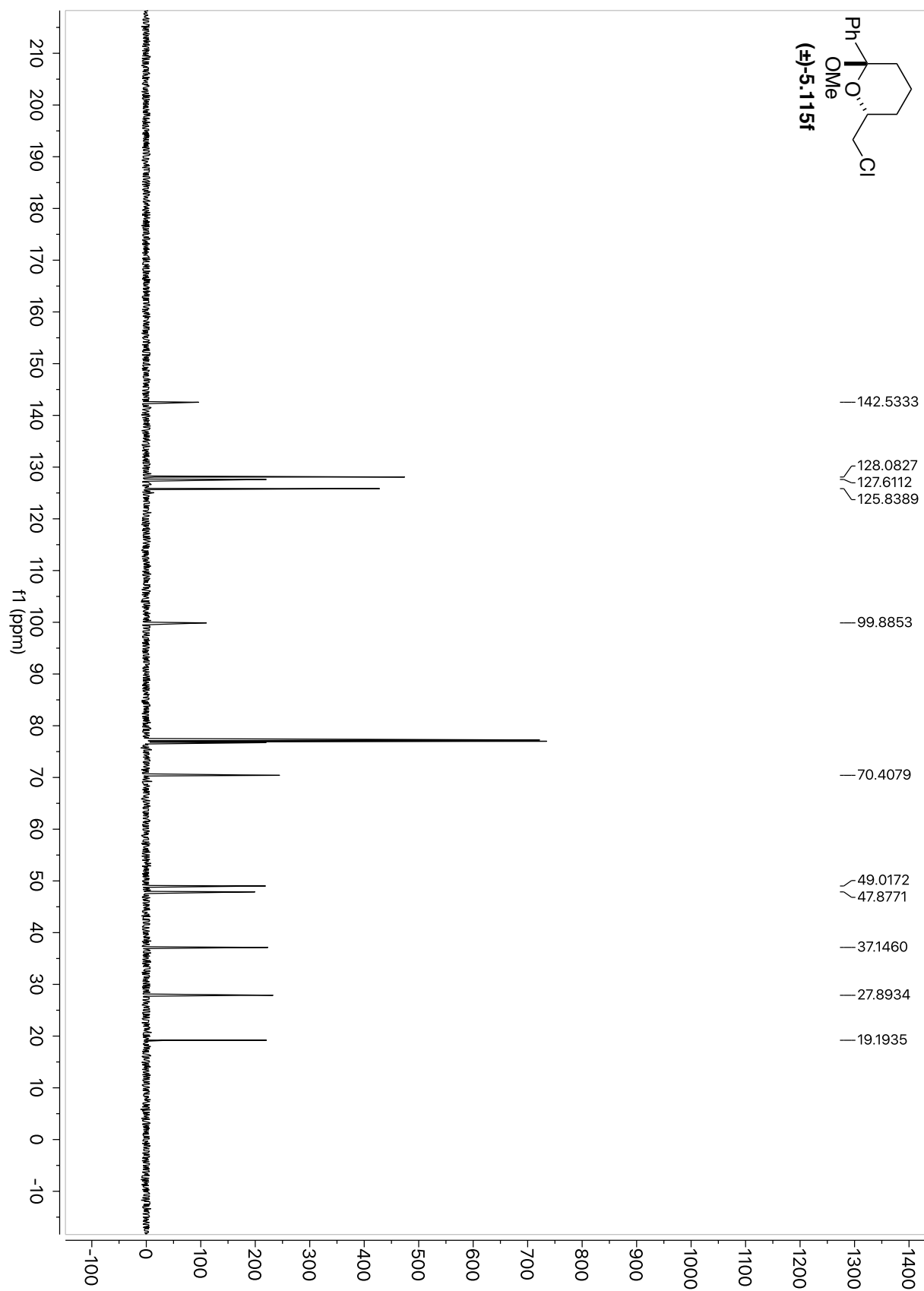


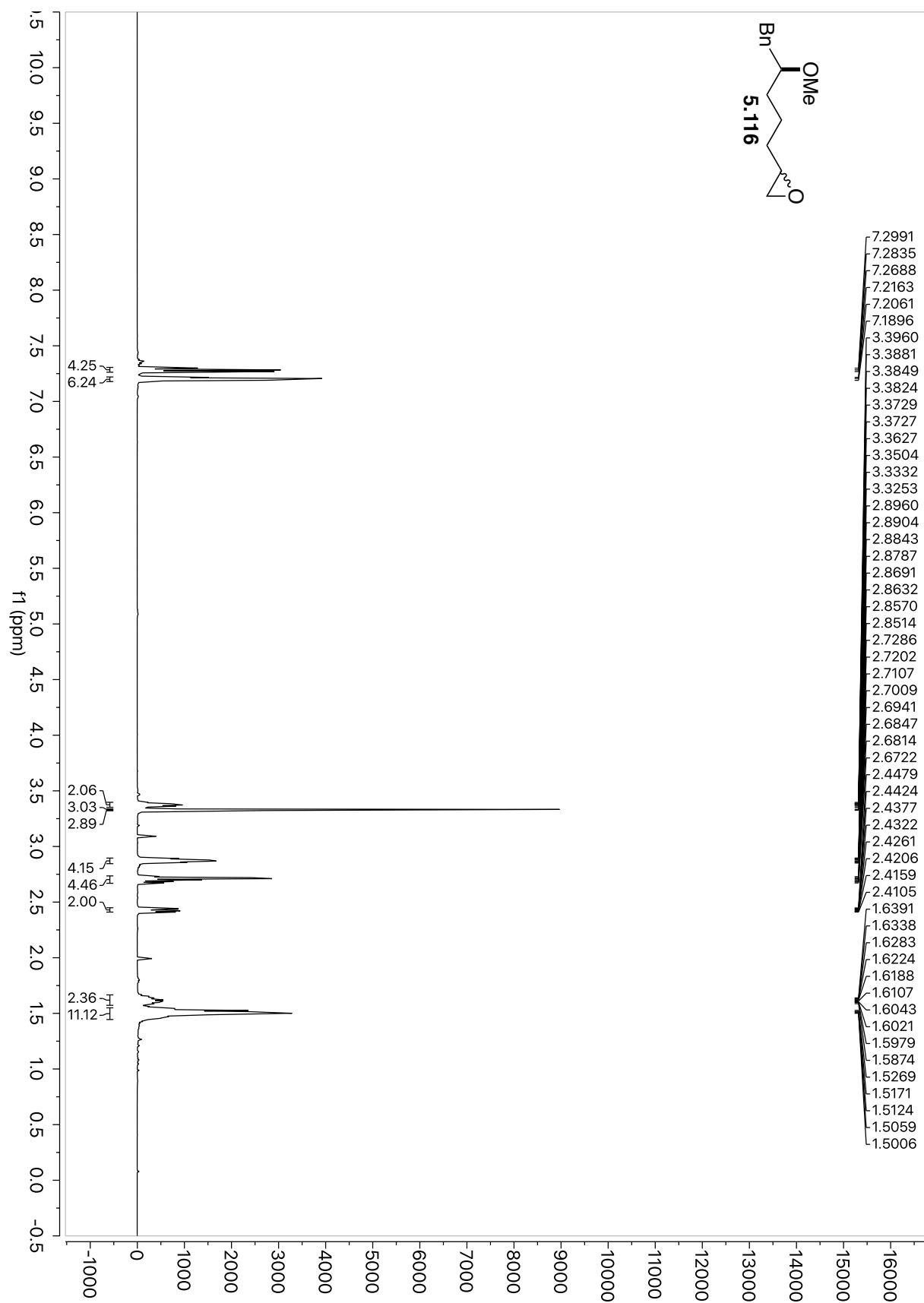


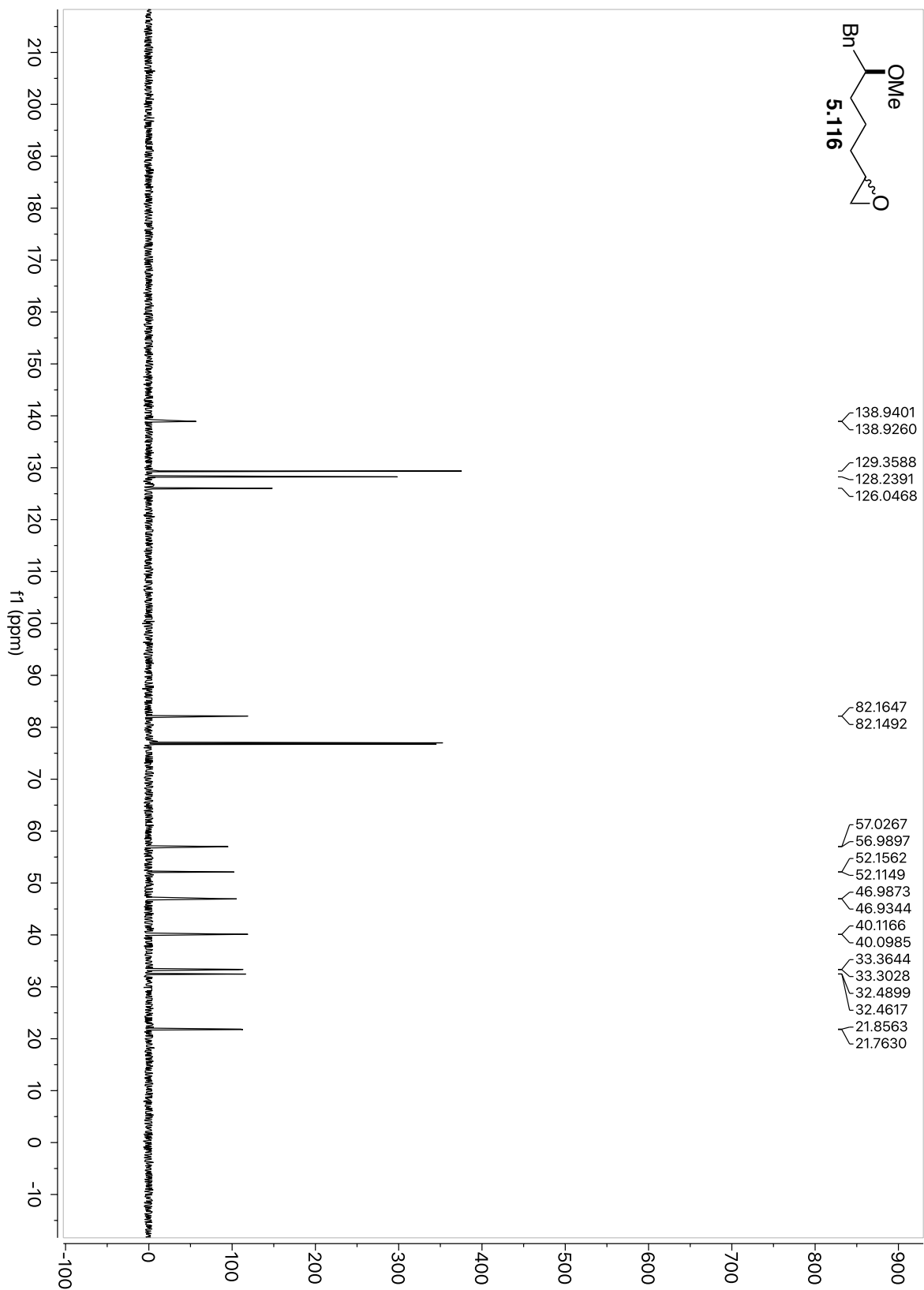


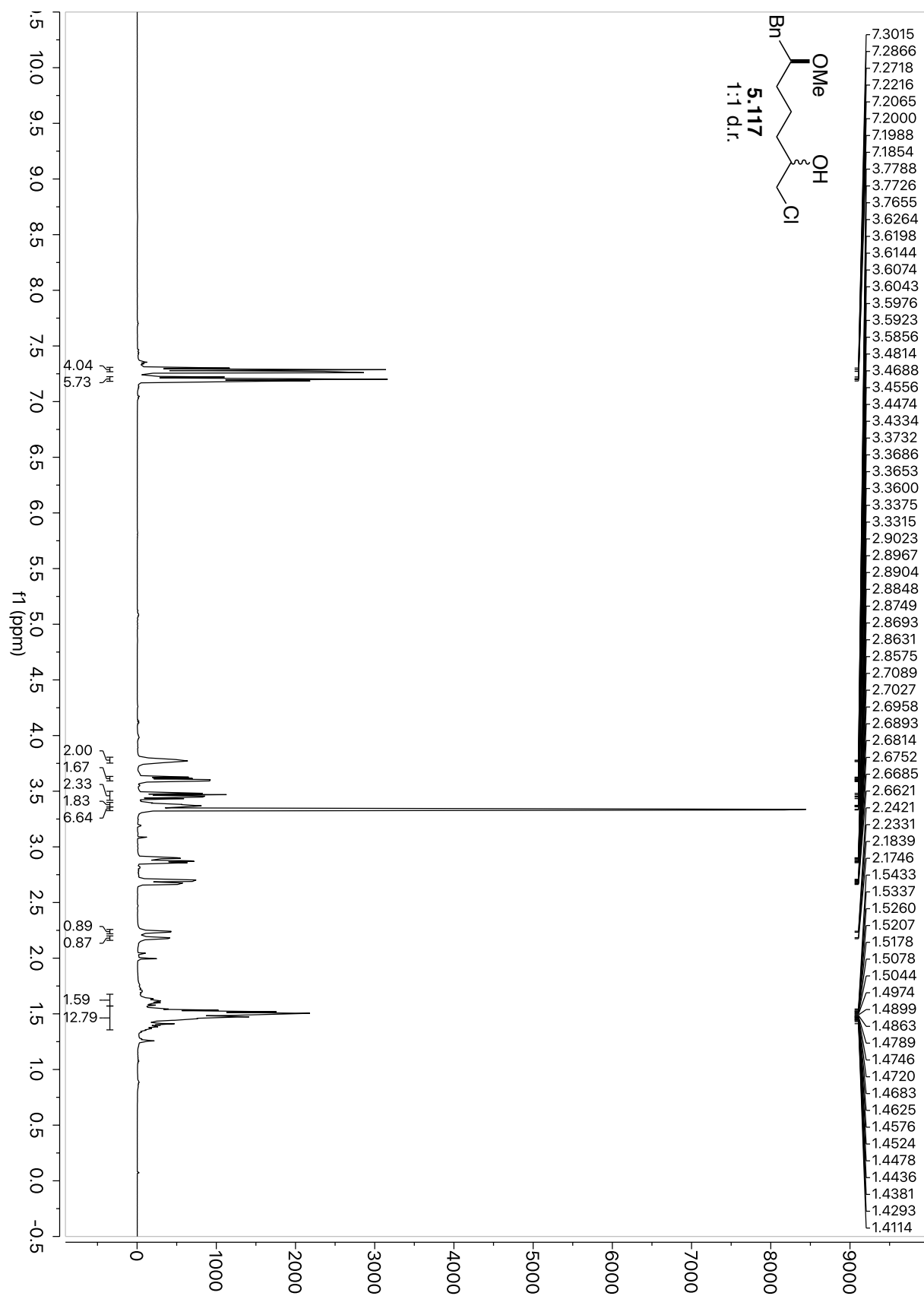


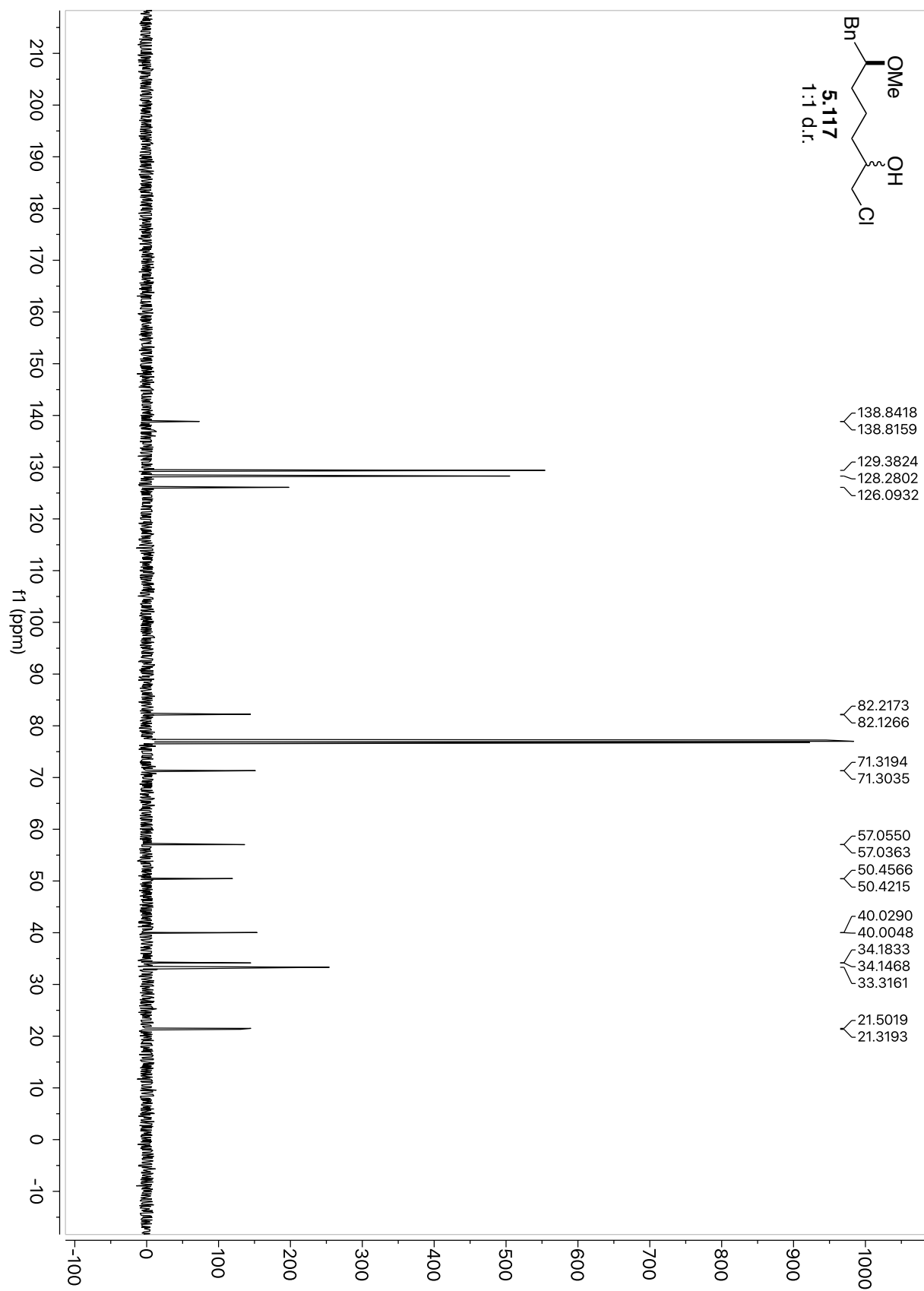


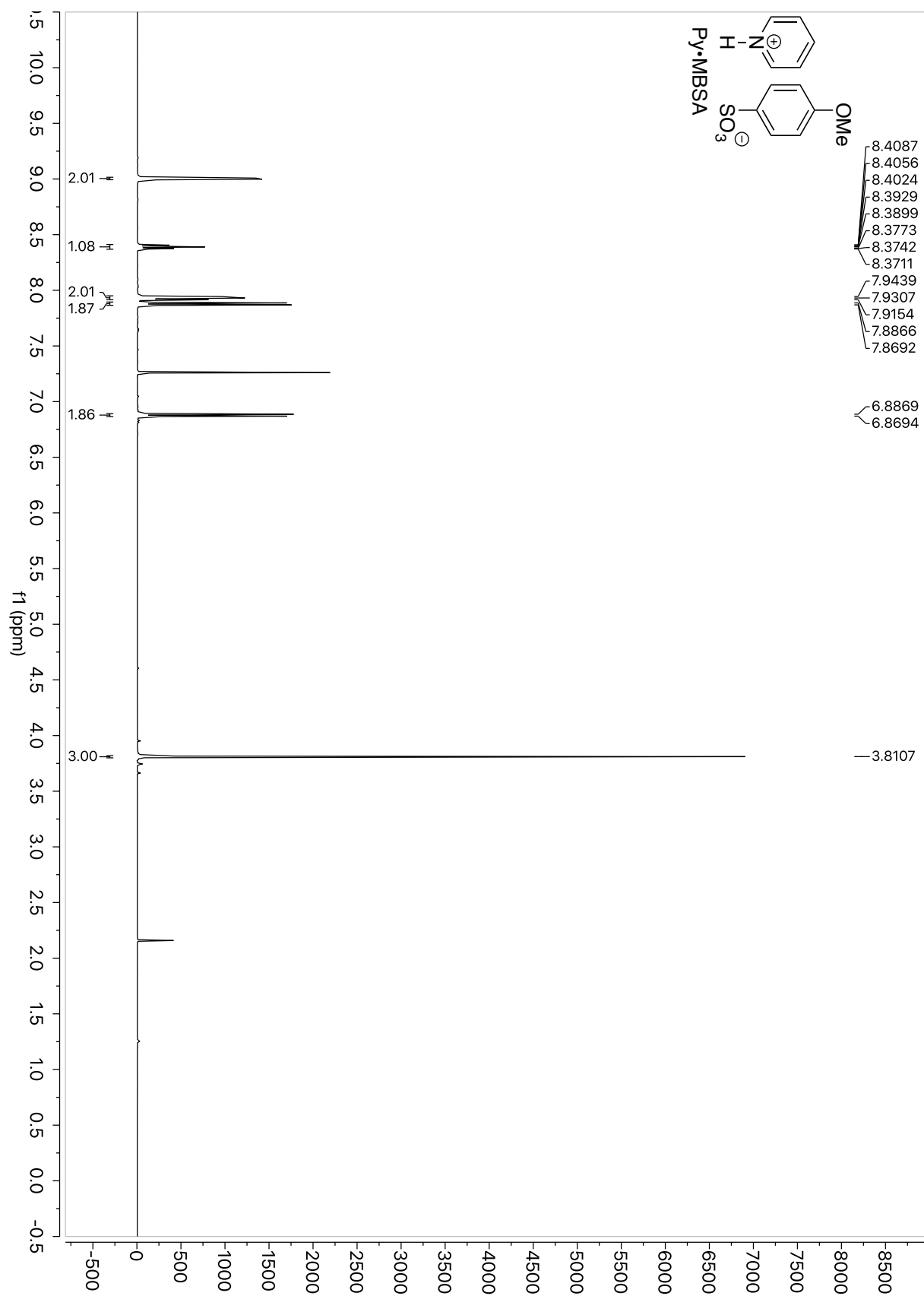


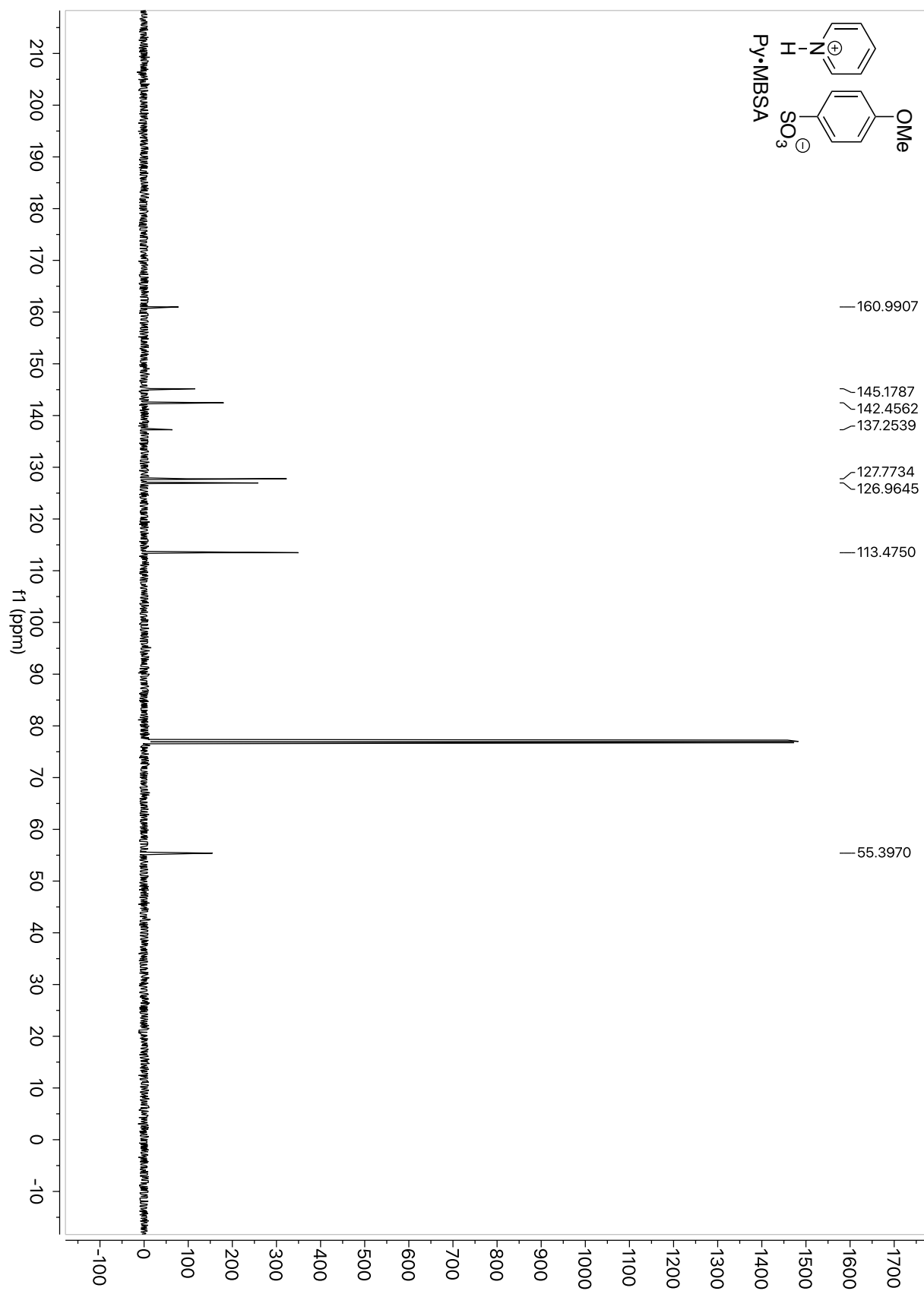












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Vita

Alexander “Alex” Cleveland was born in Kingsport, TN and grew up in rural East Tennessee. Alex enrolled at Tennessee Tech University in the Fall of 2011 and was originally planning to study microbiology. However after one semester of introductory biology courses, Alex changed his major to chemistry and quickly became enamored by organic chemistry. After graduating TTU in the Spring of 2015, Alex enrolled at LSU in the Department of Chemistry to continue his studies in pursuit of his Ph.D. He joined the lab of Prof. Rendy Kartika that Spring Semester and has since coauthored six manuscripts. Alex is a doctoral candidate in chemistry and plans to receive his degree by August 2020.