

SYNTHESES OF C-GLYCOSIDE NATURAL
PRODUCTS VIA OXOCARBENIUM
CATIONIC INTERMEDIATES

by

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ABSTRACT

This dissertation highlights studies into the total synthesis of C-glycoside natural products via oxocarbenium cationic intermediates with a brief introduction given in the first chapter. The second chapter examines our approach to the first total synthesis and absolute configuration of the antibiotic (+)-bruguierol C. The key step is the diastereoselective capture of an *in situ* generated oxocarbenium cation via an intramolecular Marson-type Friedel-Crafts cyclization, which concomitantly generates the chiral quaternary center. The third chapter illustrates the formal syntheses of (+)-brussonol and (+)-abrotanone, attained in a convergent and concise manner, making these syntheses the shortest to date. The key step, as with (+)-bruguierol C, involves the diastereoselective capture of an *in situ* generated oxocarbenium cation via an intramolecular Marson-type Friedel-Crafts cyclization. A novel methodology that employs catalytic quantities of pyridinium tribromide (Py•Br₃) in methanol to chemoselectively deprotect primary TBS ethers in the presence of a variety of other protecting groups and common functional groups is the subject of the fourth chapter. The formal synthesis of the unnatural (-)-neopeltolide core, whose natural antipode has been found to be extremely cytotoxic and has emerged as a promising anticancer lead is discussed in the fifth chapter. Efficient application of the Evans' protocol for the synthesis of 1,3-*syn* diols via an intramolecular hetero-Michael addition followed by reductive deprotection of the resulting benzylidene acetal allowed for swift access to the δ -lactone. Central to the synthetic approach is a tandem nucleophilic addition-diastereoselective axial reduction of an *in situ* generated oxocarbenium cation to construct the β -C-glycoside moiety of the neopeltolide core. The final chapter of this

dissertation describes the total synthesis of the proposed structure of pochonin J, whose reported structure features a rare α -C-glycoside moiety embedded within a 14-membered macrolactone. Key steps of this convergent synthesis include a chemoselective Wacker oxidation, a stereoselective allylation of an oxocarbenium cation intermediate to assemble the α -C-glycoside fragment, and a ring-closing metathesis (RCM) reaction to forge the 14-membered macrolactone. During our studies directed towards its laboratory synthesis, it was found that the spectroscopic data of the synthesized compound does not correlate to the initially described natural product.

DEDICATION

This manuscript, experiments described, and my doctoral degree are dedicated to my loving parents, el Señor Rosalio Martinez Aguayo y la Señora Elva Solorio Solorio de Martinez, and above all, GOD for blessing me with such wonderful parents. For all the love, patience, and understanding they raised me with, and for always believing in me and never losing hope. Gracias por todo su apoyo que me han brindando, por sus bendiciones que siempre estan conmigo aunque ustedes esten lejos. Los quiero mucho mis queridos padres, que DIOS me los bendiga ahora y siempre!

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LIST OF ABBREVIATIONS AND SYMBOLS

$[\alpha]_D^{24}$	rotation @ 24°C on Na ⁺ D-line
9-BBN	9-borabicyclo[3.3.1.]nonane
Bn	benzyl
Bz	benzoyl
BAIB	[bis(acetoxy)iodo]benzene
CM CSA	camphorsulfonic acid
DCM	dichloromethane
DIBAL-H	diisobutyl aluminum hydride
DIPEA	diisopropyl ethyl amine
DMAP	4-dimethyl amino pyridine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
<i>E</i> -	entgegen (opposite, <i>trans</i> -)
ee	enantiomeric excess
er	enantiomeric ratio
equiv	equivalents

HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	hertz
IBX	<i>o</i> -iodoxybenzoic acid
IC ₅₀	50% median inhibition concentration
Im or Imid	imidazole
Ipc	isopinocampheyl
IR	infrared
<i>J</i>	coupling constant
KHMDS	potassium hexamethyl disilazide
LDA	lithium diisopropylamide
LiHMDS or LHMDS	lithium <i>bis</i> (trimethylsilyl)amide
M	molar
MOM	methoxy methyl
MHz	megahertz
mmol	millimole
mol	mole
MTBE	<i>tert</i> -butyl methyl ether
N	normal
NA	not applicable
<i>n</i> BuLi	<i>n</i> -butyllithium
NMO	<i>N</i> -methylmorpholine oxide
NMR	nuclear magnetic resonance

NOE	nuclear Overhauser enhancement
NR	no reaction
<i>o</i> -	<i>ortho</i> -
-OTf	trifluoromethane sulfonate (triflate)
<i>p</i> -	<i>para</i> -
PPTS	pyridinium <i>p</i> -toluene sulfonate
PTSA (TsOH)	<i>p</i> -toluenesulfonic acid
Py (pyr)	pyridine
(<i>R</i>)-	rectus (clockwise)
RCM	ring closing metathesis
rt	room temperature
(<i>S</i>)-	sinister (counterclockwise)
SAR	structure-activity relationship
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	<i>tert</i> -butyl diphenyl silyl
TBS	<i>t</i> -butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl

TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthanate
Z-	zusammen (together, <i>cis</i> -)

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CHAPTER 1: OXOCARBENIUM CATIONIC INTERMEDIATES IN NATURAL PRODUCT SYNTHESIS

1.1 Introduction and Background

The total synthesis of natural products is a science and art-form that continues to pay off enormous dividends in terms of both, practical applications for human society, and perhaps more importantly, the advancement in our understanding of the fundamental principles of structure and reactivity in organic chemistry. Through the synthesis of a previously unknown molecular entity, chemists are able to develop an intimate familiarity with the chemical properties concealed within the bond framework of a particular molecule and if serendipity permits, the formulation of a new scientific principle extrapolated from careful experimental observations. For example, the total synthesis of Vitamin B₁₂ by the groups of R. B. Woodward at Harvard and A. Eschenmoser at ETH Zürich, stands as a landmark achievement in organic chemistry.¹ Its laboratory construction required more than 12 years of meticulous research by multiple post-docs and graduate students, this effort unknown at the time, was to become the foundation for the principles of orbital symmetry conservation, otherwise known as the Woodward-Hoffmann rules. The following quotations from two of the masters in the field of total synthesis are in order:

“Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as the excuse for his activity is often not of special importance in the general sense; rather, the important things are those that he/she finds out in the course of attempting to reach the objective.”

— R. B. Woodward²

“It is in the course of attack of the most difficult problems, without consideration of eventual applications, that new fundamental knowledge is most certainly garnered.”

— R. Robinson³

As destiny would have in store for me, I was first introduced to the field of total synthesis as an undergraduate while taking organic chemistry at UC Santa Cruz through Mrs. Nancy Cox Konopelski, Director of the ACE Honors Program and a close personal friend. Nancy made me realize that I had an aptitude for organic chemistry, and after a full year of “O-Chem” I switched my major from biology to chemistry. The year was 1998, a year filled with some of the most memorable moments of my life, one of those being Alejandra giving birth of our first daughter, MariaXochitl. Five years later, the same year my bachelor’s degree was awarded, Alejandra gave birth to our second daughter, Luciana while we were living in Seattle. In May of 1998, after unexpectedly excelling in organic chemistry, was when I finally knew what type of scientist I wanted to become, an organic chemist. My mother has said that I have always had an inclination towards the sciences, philosophy, and a relentless curiosity, even as a child. I feel very blessed to have the opportunity to put my childhood dreams into practice through the study of organic chemistry. Like total synthesis, life has beautiful moments filled by joy and happiness, as well as dark moments characterized by setbacks and frustrations. Without the pain and sorrow would we be able to truly experience utmost joy in our lives? Do we learn more through mistakes made and the subsequent pain experienced or through our triumphs and victories? Perhaps, this is the reason for my obsession with the study of total synthesis. I love to learn and the life God has blessed me with. No matter how tough and intimidating the lessons may get, I am grateful He has allowed me to reach this far. What follows is a dissertation of laboratory research compiled during my graduate studies here at the University of Alabama from December of 2006 to September of 2010. The lessons learned from this research have been plentiful, inspiring and have helped me grow not only as a scientist but also as a person. Indeed, the field of total synthesis requires self-discipline, motivation, and the willingness and courage to

pick oneself up after multiple and repeated failures. If taken advantage of, these qualities can be sharpened and applied to all areas of our daily life, perhaps leading to a more auspicious outlook of one's fleeting moment in this universe.

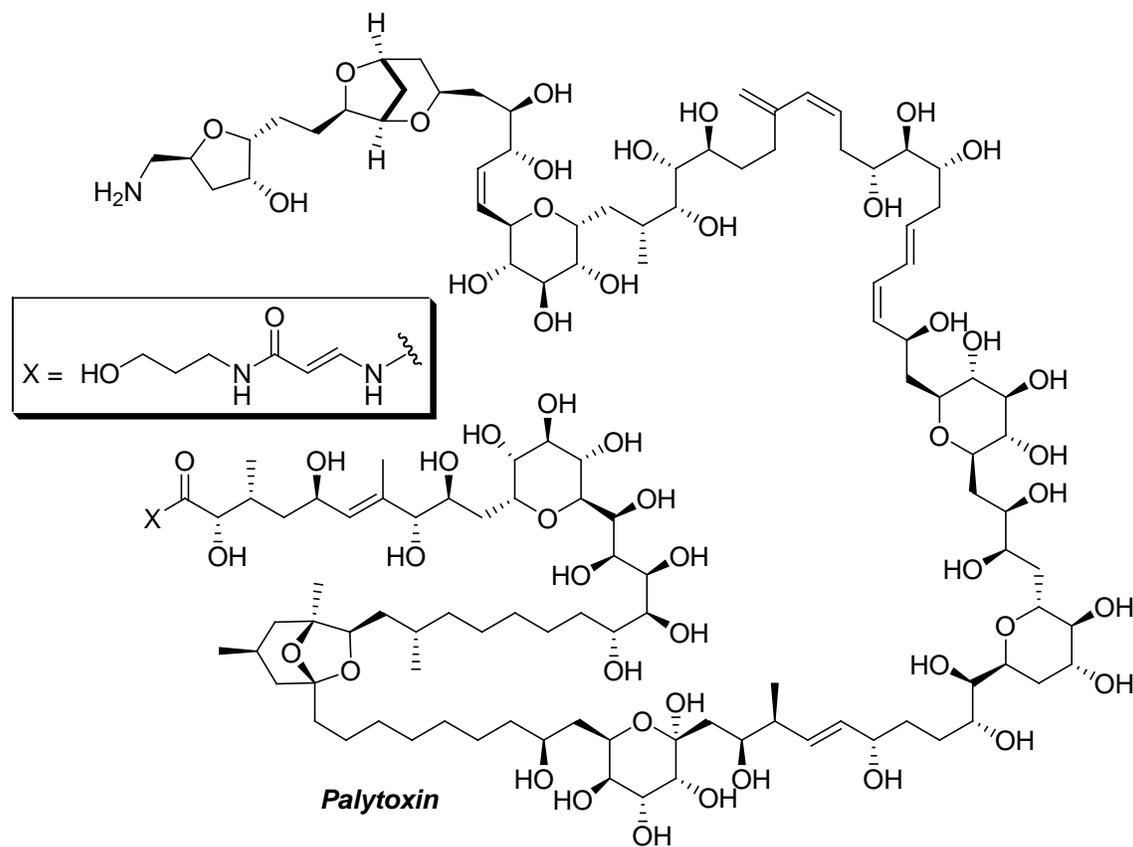
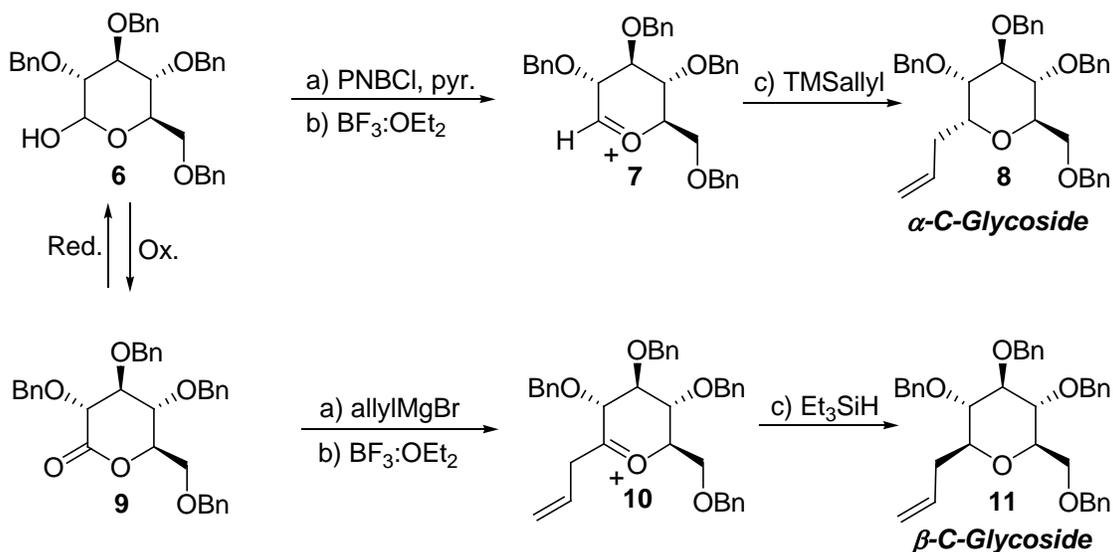


Figure 1.1. Structure of Marine Natural Product Palytoxin

1.2 Kishi's Strategy Towards the Construction of C-Glycosides

C-Glycosides or tetrahydropyrans are ubiquitous motifs found in numerous natural products, of particular prevalence in the polyketide family. In connection with synthetic studies directed towards one of the most structurally complex polyketide secondary metabolites reported to date, palytoxin (Figure 1.1), Professor Kishi at Harvard along with J. K. Cha and M. D. Lewis

reported the synthesis of both, α and β -C-glycosides through a common lactone intermediate.⁴ Such synthetic strategies are highly desirable since they lead the construction of two different compounds with minimal revision to the synthetic plan and/or starting materials. In 1982 Kishi and co-workers published their studies in which they treated tetrabenzylpyranose derivatives such as **6** with allyltrimethylsilane and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to yield the α -C-glycosides such as **8** with a d.r. of 10:1. Conversely, treatment of the tetrabenzylpyranolactone derivative **9** (readily available through oxidation of the tetrabenzylpyranose derivatives) with the allyl Grignard reagent provided the hemiketal intermediate which is then stereoselectively reduced with triethylsilane in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to give β -C-glycoside **11** with equally high diastereoselectivity, as shown in Scheme 1.1. Based on the stereochemical outcome and literature precedent the presumed intermediates were proposed to be reactive oxocarbenium intermediates **7** and **10**.⁴



Scheme 1.1. Kishi's Strategy for the Synthesis of α and β -C-Glycosides⁴

It is well documented that these types of reactions proceed through half-chair like oxocarbenium cation intermediates **15-18**. The oxonium ion preferentially accepts nucleophiles from an axial approach leading to the more favorable chair-like transition state, as well as maximization in overlap of the incoming nucleophile HOMO and the LUMO of the oxocarbenium ion.⁵⁻⁷ Nucleophilic attack via axial approach proceeds through a less hindered more thermodynamically stable intermediate, where the C₅ alkyl side-chain occupies the pseudoequatorial position, such as compounds **15** and **17** (Figure 1.2). As a consequence of the preferred reactive conformers, treatment of a lactol derivative **12** with a Lewis acid generates the oxocarbenium cation conformers **15** and **16**. This is followed by axial attack of the nucleophilic species through the more stable conformer **15** that places the C₅ alkyl side-chain in the pseudoequatorial position thereby forming the α -C-glycoside. Conversely, 1,2-nucleophilic addition to the lactone intermediate **13** by the nucleophile first, generates a hemiketal intermediate **14** that upon treatment with a Lewis acid, generates the presumed oxocarbenium conformers **17** and **18**. Ground-state conformer **17**, where the C₅ alkyl side-chain occupies the pseudoequatorial position, is then stereoselectively reduced with triethylsilane forming the β -C-glycoside. As will be described in the next section, Woerpel's studies have demonstrated that heteroatoms positioned at C₄ or C₃ have a pronounced effect on the stereoselectivity of these types of reactions. However, their studies are based on tetrahydropyrans that are unsubstituted at C₅. As will be described during the syntheses of (-)-neopeltolide (**4**) and "pochonin J" (**5**), while heteroatoms attached to the C₃ or C₄ positions have a pronounced effect on the kinetics these reactions, it is the C₅ alkyl side-chain, positioned in a pseudoequatorial fashion, as in conformers **15** and **17**, that dictates the stereochemical outcome and explains the high diastereoselectivities observed during oxocarbenium alkylations/reductions.

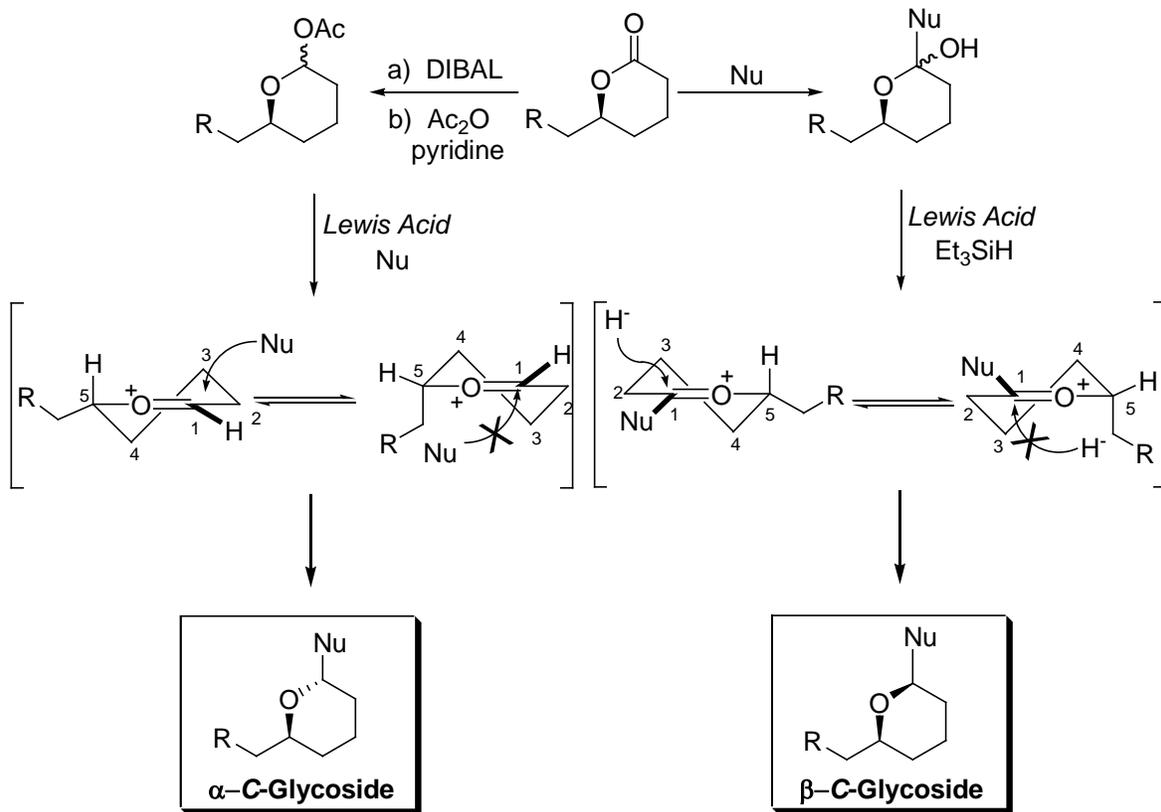


Figure 1.2. Reactive Conformers in the Synthesis of C-Glycosides

The Jennings laboratory has had a long-standing interest in expanding and defining a broader scope of Kishi's strategy for the synthesis of C-glycosides through the use of different nucleophiles and perhaps to include the synthesis of other important classes of natural products besides polyketides. We realized that an intramolecular version of this type of chemistry would be a very efficient process of rapidly building up molecular complexity during a synthesis, and we were very excited when the opportunity arose to test our hypothesis. As will be discussed in chapters two and three, this goal has been in part accomplished with the application of an intramolecular Friedel-Crafts/Marson-type cyclization of an oxocarbenium cation intermediate, a strategy that proved successful for the syntheses of (+)-bruguierol C (**1**), (\pm)-brussonol (**2**), (\pm)-abrotanone (**3**).

1.3 Woerpel's Studies on Oxocarbenium Reactive Conformers

The Woerpel research group has published studies aimed at deciphering the effect of heteroatom substituents on the peripheral of tetrahydropyran rings that are unsubstituted at the C₅ position.⁸ Their pioneering work is summarized in Figure 1.3, nucleophilic attack on the oxocarbenium cation **20** occurs along a pseudoaxial trajectory in order to maximize overlap of the nucleophile HOMO with the LUMO of the oxocarbenium cation. Of the two possible modes of approach by the nucleophilic species, the most favorable pathway of attack for an oxocarbenium intermediate, which adopts a half chair-like conformation such as **20**, is through the lower energy chair-like pathway **b** leading to product **21**, as opposed to the higher energy twist boat pathway **a** that leads to product **19**.⁵⁻⁷

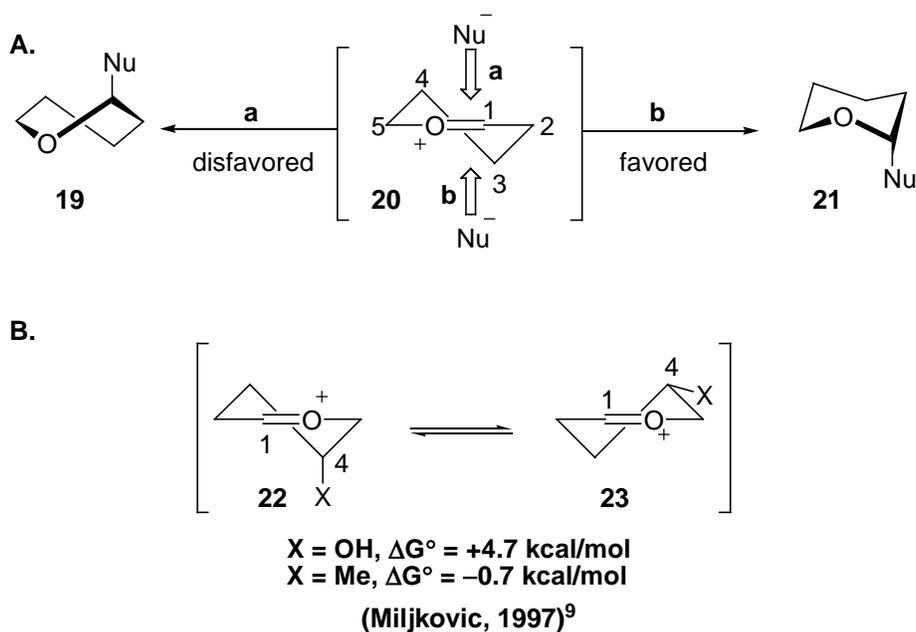


Figure 1.3. Conformational Preference of Oxocarbenium Intermediates

Furthermore, as depicted in part B of Figure 1.3, Woerpel described a stabilizing electrostatic interaction between the partial negative charge of a heteroatom substituent (on C₃ and C₄) and the cationic carbon atom of the oxonium ion. Pseudoaxial conformer **22** should be favored because the opposite charges are brought closer together compared to the equatorial conformer **23**.⁸ This conclusion is further supported by *ab initio* calculations (RHF 6-31G**) performed by Miljkovic, on C₄ alkoxy substituted oxocarbenium ions. They concluded that an electrostatic interaction is responsible for stabilizing the axial conformation **22** by ~5 kcal/mol relative to the equatorial conformer **23**.⁹ Woerpel's experiments demonstrate a dramatic difference in diastereoselectivity between alkyl and heteroatom substituted tetrahydropyrans. Whereas nucleophilic additions of alkyl substituted tetrahydropyrans precede through pseudoequatorially substituted oxocarbenium cations, additions of alkoxy substituted tetrahydropyrans proceed through pseudoaxially oriented oxocarbenium cations, giving rise to opposite stereoselectivities. Once again, it is important to recognize that these studies were conducted on substrates that were unsubstituted at the C₅ position, where steric factors have to be taken into consideration. Experimental observations from the Jennings' laboratory suggest that the C₅ substituent plays a dominant role with respect to reactive oxocarbenium conformation preference during an alkylation and/or reduction process.¹⁵ These factors will be further described in chapters five and six, during the syntheses of (–)-neopeltolide (**4**) and pochonin J (**5**).

1.4 Friedel-Crafts Alkylations of Oxocarbenium Cations by Marson and Wu

In the late 1990's, independent studies by the groups of Marson at the University of Sheffield in the United Kingdom and Wu at Shanghai Institute of Organic Chemistry in China,

led to the rapid assembly of 8-oxabicyclo[3.2.1]octane ring systems **25** and **27** via an acid-catalyzed Friedel-Crafts intramolecular alkylation, as depicted in Figure 1.4.^{10,11}

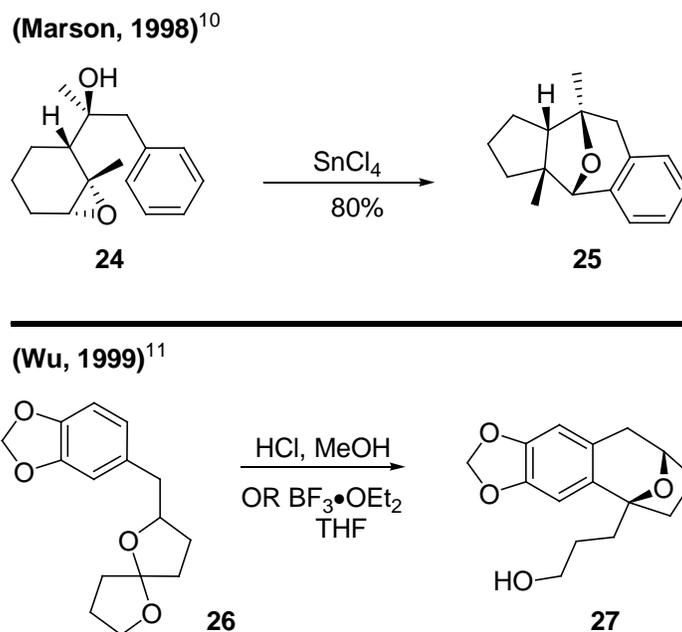


Figure 1.4. Friedel-Crafts Alkylations by Marson¹⁰ and Wu¹¹

Although the basic premise of both strategies is consistent with an intramolecular Friedel-Crafts type alkylation of an incipient oxocarbenium cation intermediate, they were each unique in the manner of which the presumed oxocarbenium cations were formed. In 1998, Marson published his pioneering work which inspired us to apply this methodology as an extension of Kishi's work on the synthesis of *C*-glycosides. In their studies, 3-epoxy alcohols such as **24** (Figure 1.4) were treated with tin tetrachloride to generate ring systems such as **25**, presumably through a proposed oxocarbenium cation intermediate. One year later, Wu and co-workers reported a very similar reaction with the presumed oxocarbenium intermediate derived from cyclic ketals such as **26** to give 8-oxabicyclo[3.2.1]octane cores such as **27**.¹¹ With this precedent in mind, and considering our own interest in constructing *C*-glycoside moieties via

oxocarbenium chemistry, we thought of unifying these concepts through laboratory experimentation, this will be the subject of the next chapter.

1.5 Conclusions

Oxocarbenium intermediates generated from δ -lactone intermediates have been successfully exploited for the construction α and β -*C*-glycoside subunits found in numerous biologically active compounds in the Jennings' laboratory as well as other research groups. Precedent first established by Kishi in the early 1980's and then later studied and refined by Woerpel, have motivated our research group to apply this methodology for the stereoselective synthesis of *C*-glycosides, motifs ubiquitous to the polyketide natural product family. In addition, the chemistry independently discovered by Marson and Wu have inspired the Jennings' laboratory to develop an extension of this methodology via a diastereoselective intramolecular Friedel-Crafts alkylation of an oxocarbenium cation for the construction of the diterpene natural product, brussonol (**2**).

The studies highlighted in this dissertation describe experiments and methods towards the total syntheses of the *C*-glycoside natural products (+)-bruguierol C (**1**), (\pm)-brussonol (**2**), (\pm)-abrotanone (**3**), (-)-neopeltolide (**4**), and pochonin J (**5**). The first chapter is a brief introduction of oxocarbenium chemistry and its use in the construction of natural products, as well as a description of some of the literature precedent used throughout this dissertation. The second chapter will discuss the first total synthesis of the antibiotic (+)-bruguierol C (**1**). The third chapter describes the formal syntheses of both (\pm)-brussonol (**2**) and (\pm)-abrotanone (**3**). The focus will temporarily digress in the fourth chapter where a novel methodology employing catalytic quantities of commercially available pyridinium tribromide to chemoselectively deprotect primary TBS ethers will be described. A formal synthesis of the unnatural (-)-

neopeltolide (**4**) will be the subject of the fifth chapter. Finally, the sixth chapter will conclude this dissertation with the synthesis of the reported structure of pochonin J (**5**).

CHAPTER 2: THE TOTAL SYNTHESIS AND ABSOLUTE CONFIGURATION DETERMINATION OF (+)-BRUGUIEROL C

2.1 Isolation, Characterization, and Initial Biological Studies

If only but a brief moment would suffice to contemplate with what exquisite power Nature carefully balances life throughout the universe. The world's oceans, which cover two-thirds of the Earth's surface are replete with organisms that have evolved in very interesting ways which help them not only to survive, but to thrive in a particular set of environmental pressures. Marine plants are examples of such organisms that have evolved to deal with constant and drastic changes in conditions such as salt exposure and nutrient supply. Mangroves are marine plants that are able to exploit their habitat by developing physiological adaptations to overcome the problems of anoxia, high salinity and frequent tidal inundation. Due to the necessary adaptations brought about by tidal changes, mangroves found along tropical and subtropical coast-lines, are considered to have an exceptionally diverse secondary metabolisms and therefore rich sources of biologically active natural products.¹²

In 2005, Sattler and co-workers disclosed an unusual family of aromatic β -C-glycoside natural products termed bruguierols A-C from the stem of the *Bruguiera gymnorhiza* mangrove tree, which they collected off the southern coast of Xiamen, China.¹² Of the initial 6.1 kg of pulverized plant material submitted to methanolic extraction, 25 mg of bruguierol C (**1**) was isolated, indicating a need for an effective and concise strategy towards its chemical synthesis in the laboratory. In an international collaboration between the Hans-Knöll Institute for Natural

Products Research in Jena, Germany and the National Research Laboratory of Natural and Biomimetic Drugs of Peking University in Beijing, China, the isolation, structural characterization, and biological investigations of these natural products were carefully evaluated. Within this family of natural products, as depicted in Figure 2.1, they had shown that the inclusion of the *meta*-substituted hydroxyl groups is crucial for the antimicrobial activity. Thus, only bruguierol C (**1**) was shown to exhibit modest antimicrobial activities (minimal inhibitory concentration, MIC: 12.5 $\mu\text{g/ml}$) against *Staphylococcus aureus* SG 511, *Micrococcus luteus* ATCC 10240, *Enterococcus faecalis* 1528 (vanA), *Escherichia coli* SG 458, *Mycobacterium vaccae* (MT 10670). Two observations are quite remarkable. The first is that the antimicrobial activity of **1** against the *Enterococcus faecalis* 1528 microorganism is noteworthy, due to its resistance to other antibiotics such as gentamicin, teicoplanin, and vancomycin A.¹³ Secondly, compound **1** shares the same MIC@12.5 $\mu\text{g/ml}$ activity versus *Micrococcus luteus* ATCC 10240 with that of ciprofloxacin.^{12,14} Based on the fact that **1** exhibits activity against both Gram-positive and Gram-negative bacteria, one could envision further investigations of bruguierol C or hybrid analogues thereof as broad spectrum antibiotics. Based not only the biological profile of **1**, we were also attracted to pursuing the total synthesis of bruguierol C due to our own interest¹⁵ in constructing quaternary centered β -C-glycoside moieties via oxocarbenium chemistry.

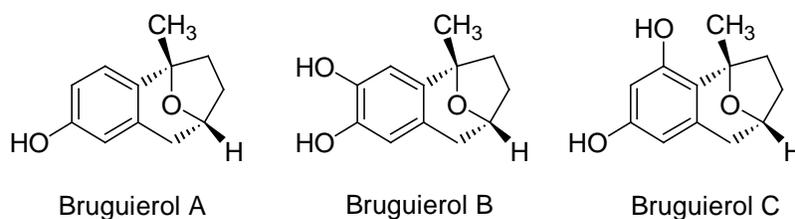
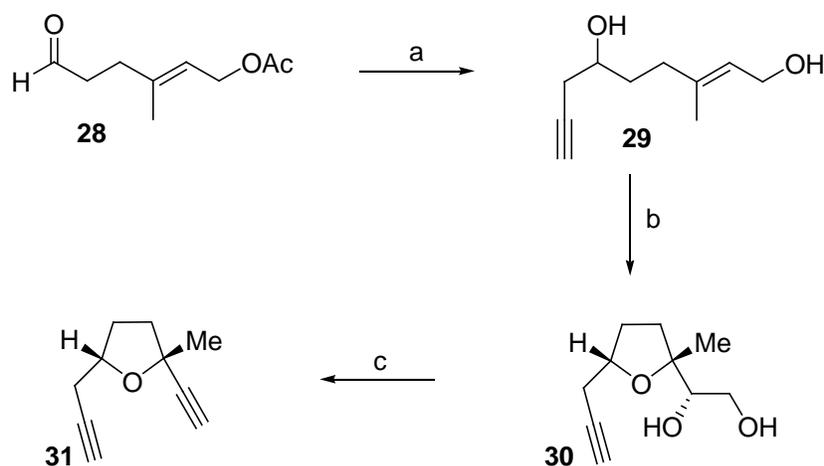


Figure 2.1. Structures of Bruguierols A-C

2.2 Previous Syntheses of Bruguierol A

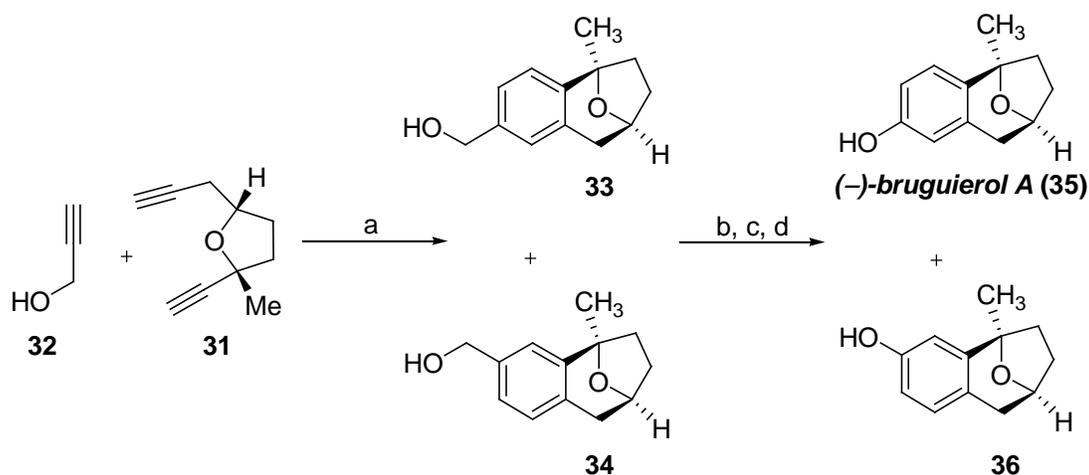
Interest in this family of natural products has given rise to several unique methodologies towards their construction. Although a previous synthesis of bruguierol C has not been reported to date, there have been four reported syntheses of bruguierol A.^{11b,16-18} The first synthesis of bruguierol A was accomplished by Ramana and co-workers where they employed a very elegant [2+2+2] alkyne cyclotrimerization in a late stage installation of the aromatic/bicyclic segment.¹⁶ Described in Scheme 2.1 is the synthesis of the THF diyne segment **31** of bruguierol A, which was obtained in three steps from known aldehyde **28**, starting from geraniol acetate. This sequence of events involved a Barbier alkynylation to give intermediate **29**. This was followed by a Sharpless asymmetric epoxidation (SAE) with concomitant cyclization to yield THF **30**, and finally treatment with the Ohira-Bestmann reagent afforded the requisite diyne scaffold **31**.



Scheme 2.1. Synthesis of the Bruguierol A THF Segment (**31**):¹⁶ a) 1. propargyl bromide, Zn, THF, 87%; 2. K₂CO₃, MeOH:H₂O, 90%; b) L-(+)-DIPT, Ti(OiPr)₄, *t*BuOOH, DCM, 90%; c) 1. silica-supported NaIO₄, DCM, 90%; 2. dimethyl-1-diazo-2-oxopropylphosphonate, K₂CO₃, MeOH, 82%.

With the aliphatic segment completed, Ramana's group was now in position to attempt the key [2+2+2] alkyne cyclotrimerization. Upon treatment of diyne **31** and propargyl alcohol

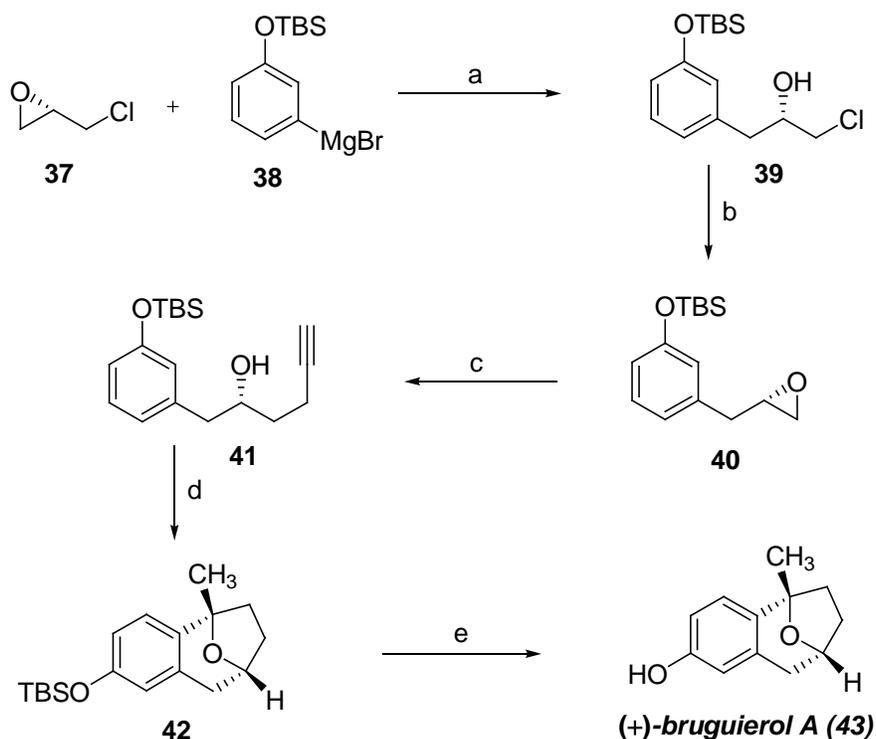
32 with Wilkinson's catalyst the proposed transformation was affected to yield an inseparable 1:1 mixture of regioisomeric products **33** and **34** in an overall yield of 67%. This mixture was then oxidized to obtain the antipode of the natural product, (-)-bruguierol A (**35**) and its isomer **36** in a combined yield of 33%, as summarized in Scheme 2.2. Ramana's contribution established the absolute configuration of bruguierol A while employing a unique and elegant solution towards the late-stage installation of the 8-oxabicyclo[3.2.1]octane ring system.¹⁶



Scheme 2.2. Synthesis of (-)-Bruguierol A (**35**) by Ramana and Co-Workers:¹⁶ a) Rh(PPh₃)₃Cl, toluene, 85%; b) MnO₂, CH₂Cl₂; c) *m*-CPBA, CH₂Cl₂; d) sat. aq. NaOH, THF, 33% yield over 3 steps.

In 2009, Fañanas and his group at the Universidad de Oviedo in Spain, devised a successful strategy towards the natural antipode, (+)-bruguierol A (**43**) in five synthetic operations starting from commercially available (*S*)-epichlorhydrin **37** and aryl Grignard reagent **38** in an overall yield of 69%.¹⁷ Alkynylation of epoxide **40** led to the key precursor **41**. Their innovative strategy involved a Pt-catalyzed tandem intramolecular hydroalkoxylation

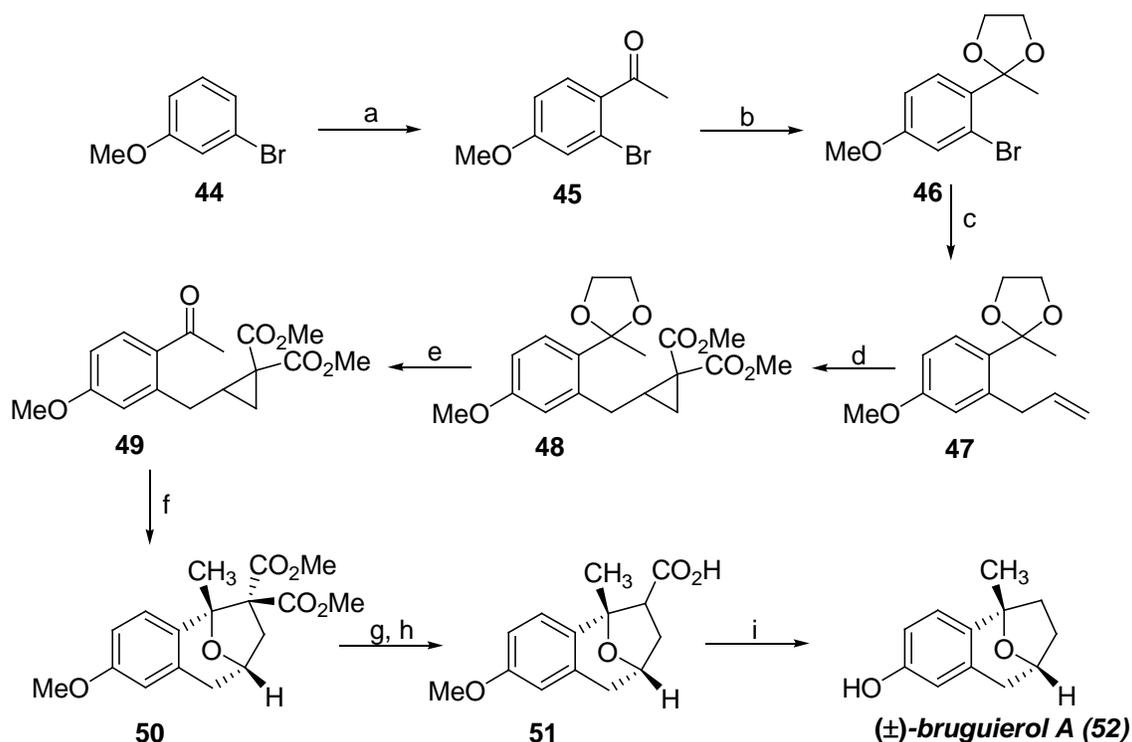
hydroarylation reaction of pentynol derivative **41** and was responsible for the rapid construction of the natural product (+)-bruguierol A (**43**), as summarized in Scheme 2.3.



Scheme 2.3. Synthesis of (+)-Bruguierol A (**43**) by the Fañanas Group:¹⁷ a) Et₂O, 92%; b) MeLi, THF, 92%; c) propargylmagnesium bromide, Et₂O, 90%; d) 5 mol% PtCl₄, CH₂Cl₂, 94%; e) TBAF, THF, 96%, 69% overall yield over 5 steps.

At Nankai University in Tianjin, China, a team of scientists led by Wang realized the racemic synthesis of bruguierol A (**52**) using a Sc(OTf)₃ catalyzed intramolecular [3+2] cycloaddition of the cyclopropane 1,1-diester **49** to yield the 8-oxabicyclo[3.2.1]octane core **50**, starting from commercially available 3-bromoanisole **44**.¹⁸ Final Barton decarboxylation followed by cleavage of the methoxy ether with the sodium thiolate anion in refluxing DMF, afforded racemic bruguierol A (**52**) in 10 steps in an overall yield of 16.8%, as delineated in

Scheme 2.4. Wang's group had previously established precedent with these types of $\text{Sc}(\text{OTf})_3$ catalyzed intramolecular [3+2] cycloadditions with a 2010 synthesis of platensimycin.¹⁹ Their synthesis of racemic bruguierol A (**52**) represents another useful application of this methodology.



Scheme 2.4. Synthesis of *rac*-Bruguierol A (**52**) by Wang:¹⁸ a) AlCl_3 , CH_3COCl , 72%; b) *p*-TsOH, ethylene glycol, 94%; c) *t*-BuLi, Et_2O , allyl bromide, 64%; d) $\text{N}_2=\text{C}(\text{CO}_2\text{Me})_2$, $\text{Rh}_2(\text{esp})_2$, 77%; e) 1M HCl, THF, 95%; f) $\text{Sc}(\text{OTf})_3$, DCE, 98%; g) LiCl, wet DMSO, 88%; h) LiOH, MeOH, H_2O , THF, 88%; i) 1. Barton decarboxylation 2. NaSEt, DMF, 70% over 2 steps.

While living in Seattle, more than 2,500 miles away in the northwest corner of the country, my obsession with the total synthesis of natural products drew me to Dr. Michael P. Jennings' laboratory here at the University of Alabama. Adventurous as we were, Alejandra, MariaXochitl, Luciana and I decided to move Alabama so that I could attend graduate school and further my scientific education. I will be forever grateful that Dr. Jennings allowed me the opportunity to be a part his research group, and as time could only tell, I could not have been

blessed with a better research advisor. In early December of 2006, after my first semester of graduate studies and successful completion of two cumulative examinations, Dr. Jennings approached me with the structure of bruguierol C (**1**) and a very concise strategy towards its synthesis. In my naive and immature scientific mind, I was disappointed at first by the lack of complexity in the natural product. As I would soon learn, it is not necessarily the complexity of a natural product that makes it an interesting synthetic target or the bearer of fruitful science. Hidden from my inexperienced eyes, within the structure of bruguierol C (**1**) was the opportunity to extend the scope of the original Kishi protocol for the synthesis of *C*-glycoside moieties. This chapter will discuss the successful realization of this goal with the first total synthesis and absolute configuration of (+)-bruguierol C (**1**). The key step involved the diastereoselective capture of an *in-situ* generated oxocarbenium ion via an intramolecular Friedel-Crafts alkylation that ultimately delivered the targeted natural product.

2.3 Initial Retrosynthetic Analysis of Bruguierol C (**1**)

Our initial synthetic blueprint of **1** was engineered to feature a domino reaction sequence via an oxidation of the vinylic boronate **55** to provide the γ -hydroxy ketone followed by cyclization to the lactol **54**. Final oxocarbenium formation under acidic conditions and an intramolecular Friedel-Crafts capture of the pseudo C_2 -symmetric cationic intermediate **53** would provide **1** as delineated in Figure 2.2. The success of the intramolecular Friedel-Crafts alkylation to deliver the desired natural product relied on the pseudo C_2 -symmetry of the natural product which was the result of the *meta*-substituted hydroxyl groups, a substitution pattern also responsible for the antimicrobial activity. The synthesis of the vinylic boronate **55** would be derived from a cross-metathesis between isopropenyl pinacol boronate **58** and the homoallylic alcohol **56** which in turn, could be readily obtained from the known aldehyde **57**²⁰ via

asymmetric allylboration.²¹ This aldehyde was to be obtained via a two-step reduction/oxidation sequence from the bis-TBS protected methyl ester **58**.

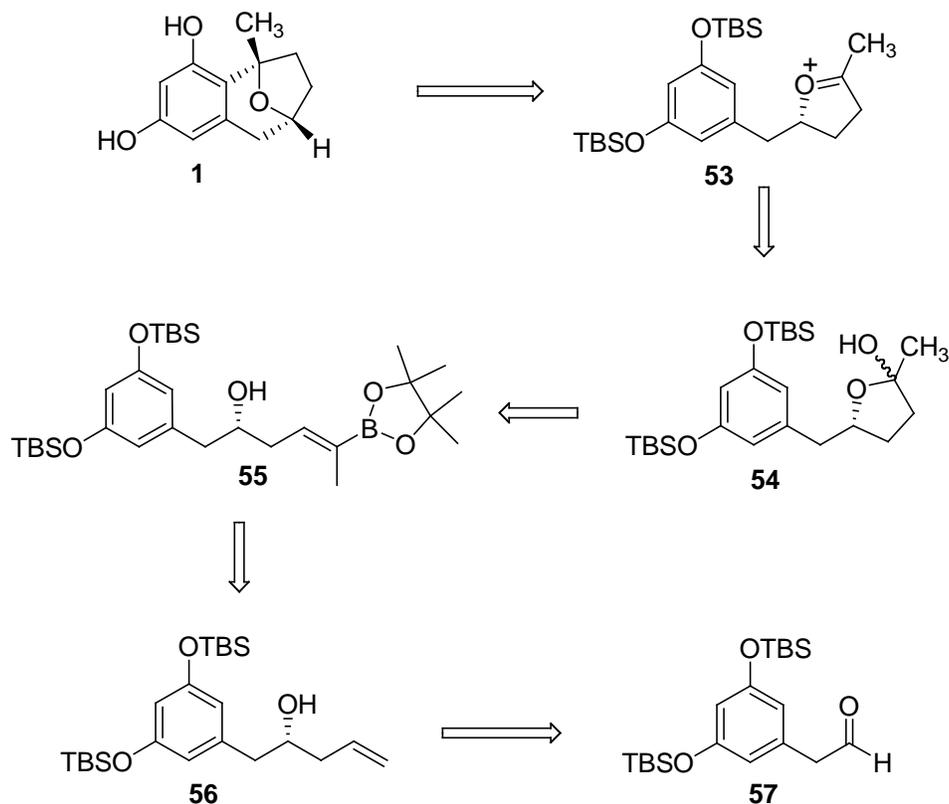
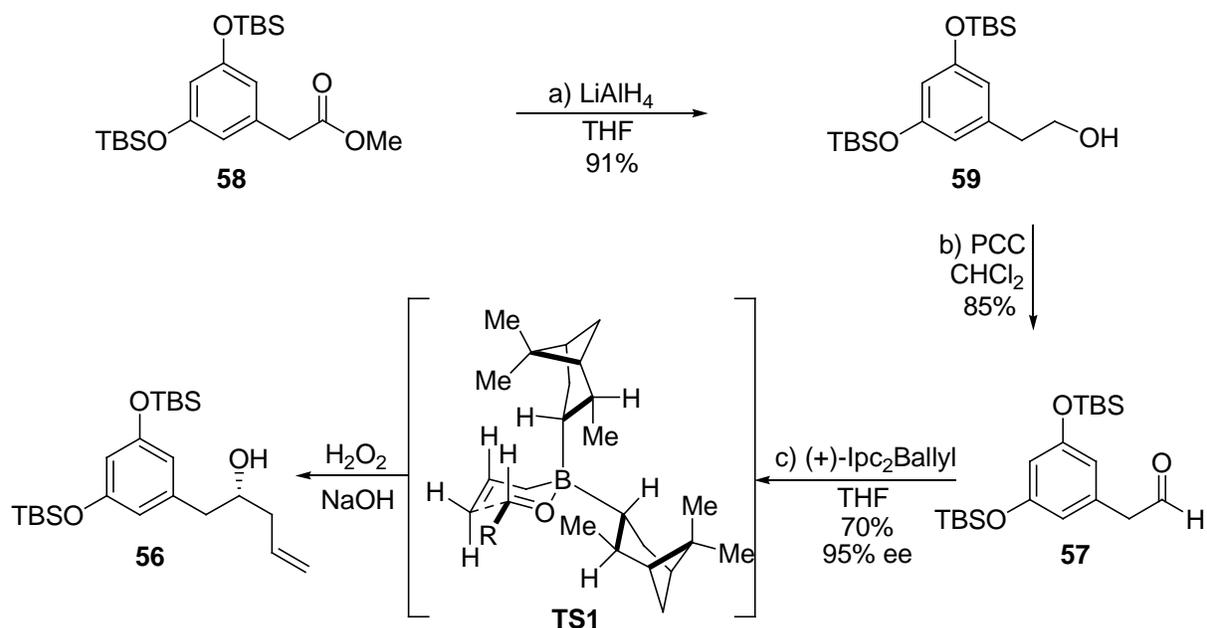


Figure 2.2. Retrosynthetic Analysis of Bruguierol C (**1**)

2.4 Failed Approach to Key Lactol Intermediate

With the initial blueprint in mind, focus was first placed on the synthesis of the required homoallylic alcohol **56** (Scheme 2.5). Unfortunately, partial reduction of the known bis-TBS protected methyl ester **58**²⁰ directly to the aldehyde by means of the electrophilic reducing agent DIBAL, was problematic and over reduction was the principal reaction pathway leading to the primary alcohol **59**. On the basis of this observation, we decided to fully reduce **58** with LAH, the nucleophilic reducing agent, to the primary alcohol **59**. Subsequent oxidation of the primary

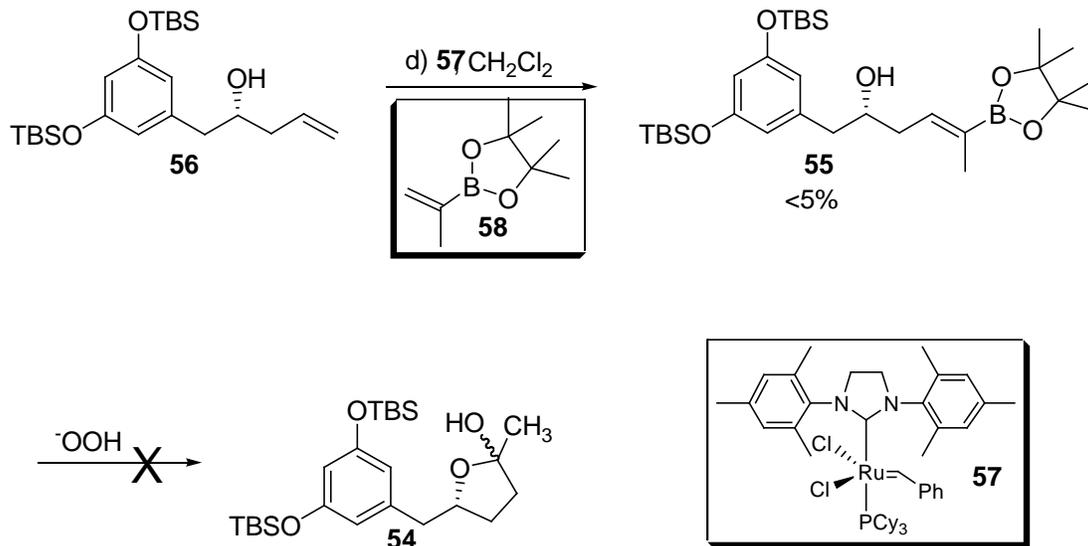
hydroxyl moiety was accomplished with Corey's PCC reagent to provide the desired aldehyde **57** in 77% yield over the two steps as delineated in Scheme 2.5. Several other oxidants such as Dess-Martin periodinane (DMP), TPAP-NMO, Swern protocol, or TEMPO-BAIB failed to provide any of the desired aldehyde and only led to the recovery of the starting material or decomposition. An ensuing asymmetric allylboration of **57** was accomplished utilizing Brown's Ipc based allylborane reagent,²¹ followed by basic oxidation to furnish the homoallylic alcohol **56** in 70% yield with an er of 95:5, as determined by the Mosher ester. As depicted in **TS1**, this type of allylation proceeds through a chair-like TS where the R-group of the aldehyde occupies an equatorial position to reduce 1,3-diaxial ring strain and the aldehyde facial selectivity derives from minimization of steric interactions between the axial Ipc ligand and the allyl group.



Scheme 2.5. Synthesis of Homoallylic Alcohol (**56**) via Brown Allylation

With the desired homoallylic alcohol **56** in hand, the stage was set for the proposed cross-metathesis (CM) between isopropenyl pinacol boronate **58** and **56** in the presence of Grubbs' second-generation catalyst **57** as depicted in Scheme 2.6. Inspired both by the Grubbs' account regarding the CM of type I alkenes with pinacol boronate **58**²² and also the Sulikowski synthesis of apoptolidin in which they elegantly utilized a CM reaction with **58** and a type I olefin,²³ we envisioned little difficulty with a CM reaction sequence between **56** and **58** promoted by catalyst **57**. Much to our dismay, we observed less than 5% conversion of the homoallylic alcohol **56** to the obligatory vinyl pinacol boronate ester **55**. Not surprisingly, further one-pot oxidation of the reaction mixture (pH 7 buffered or basic H₂O₂) of the *in-situ* formed vinyl boronate failed to provide any trace amount of either the γ -hydroxy ketone or the cyclized lactol **54** (Scheme 2.6). In retrospect, the success of the Sulikowski cross-metathesis can be attributed to the protection of the secondary homoallylic alcohol as a TES ether, and even then the group reported a modest 30% yield along with 30% recovered starting material using 18 equivalents pinacol boronate **58**! Unprotected hydroxyl groups, such as the one present in our substrate, have been known to chelate to the ruthenium catalyst, effectively shutting down the metathesis catalytic cycle.

Undaunted by the failure of the cross-metathesis reaction, that very same day Dr. Jennings and I discussed an alternative strategy towards the construction of lactol **54**. Utilizing the previously synthesized homoallylic alcohol **56**, the lactol intermediate was proposed to arise from a three step sequence involving hydroboration/oxidation of the terminal alkene, Ley oxidation of the resulting 1,4-diol to the lactone, and finally 1,2 nucleophilic addition with MeLi to generate lactol **54**. Although this sequence would add an extra step to the overall synthesis, it was a very straightforward strategy to attain the desired lactol. Keeping this in mind we made a slight modification to our synthetic strategy and moved forward.



Scheme 2.6. Failed Approach to Lactol (**54**)

2.5 Second-Generation Retrosynthetic Analysis of Bruguierol C (1)

Disappointed by the failure of the two preceding reactions to provide meaningful quantities of the desired lactol **54**, we reformulated a new approach to **1**. As shown in Figure 2.3, our end game remained consistent with that of the first-generation retrosynthetic analysis. We envisaged that the final natural product would be furnished via the intramolecular trap of the incipient oxocarbenium cation by means of a Friedel-Crafts alkylation. The key distinction between the two strategies lies in the formation of lactol **54**. In the second-generation approach, we envisioned a sequence of reactions that would ultimately form the oxocarbenium cation via a sequential methylation of lactone **60** followed by treatment of lactol **54** with an appropriate Lewis acid. In turn, lactone **60** could be readily derived from the previously prepared homoallylic alcohol **56** via a hydroboration-TPAP oxidation²⁴ sequence (Figure 2.3).

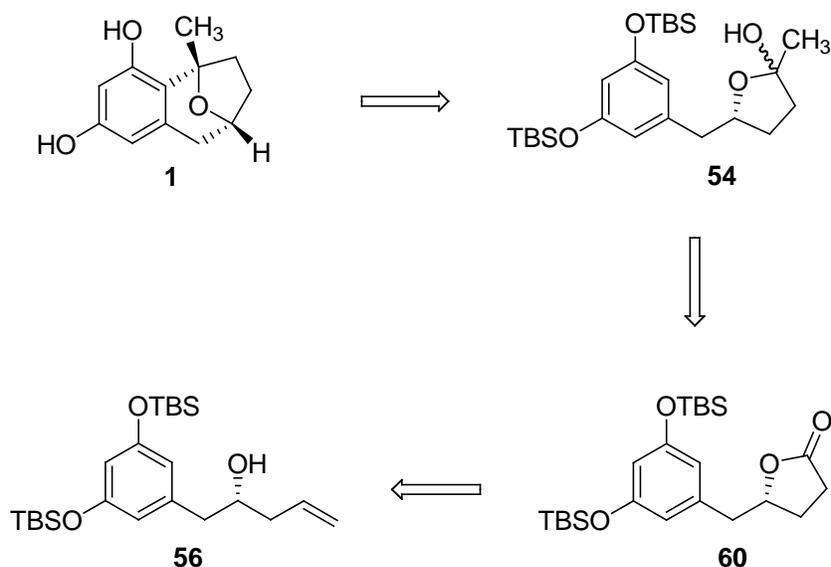
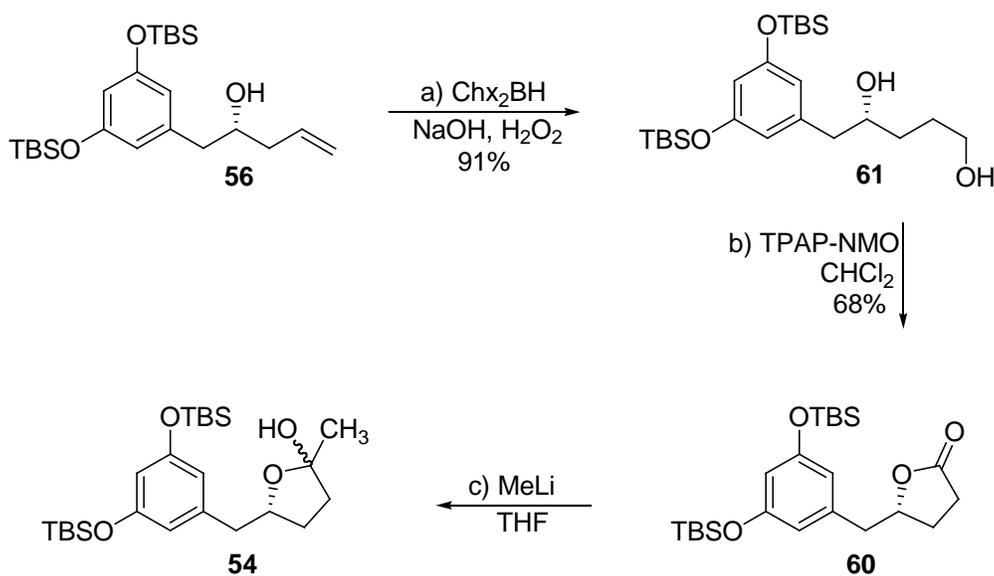


Figure 2.3. Second-Generation Retrosynthetic Analysis of Bruguierol C (**1**)

2.6 Total Synthesis of (+)-Bruguierol C Via a Intramolecular Marson/Friedel-Crafts Cyclization

With the second-generation strategy firmly in place, we focused our initial efforts on the formation of the desired lactone **60** as highlighted in Scheme 2.7. Thus, hydroboration of the olefinic portion of the previously synthesized homoallylic alcohol **56** with three equivalents of dicyclohexyl borane (Chx_2BH) followed by basic oxidation provided the diol **61** in 91% yield. It is worth noting that attempted hydroboration of **56** with $\text{BH}_3\cdot\text{THF}$, $\text{BH}_3\cdot\text{DMS}$, or 9-BBN did not lead to a sufficient amount of the desired diol **61**. The low product formation of diol **61** with these reagents is attributed to the differences in kinetics and reactivity of these particular boranes, as a majority of the alkene starting material was recovered.²⁵ Ensuing selective oxidation of the primary alcohol moiety of diol **61** to the aldehyde followed by intramolecular cyclization to the lactol and further oxidation to the obligatory lactone **60** was accomplished by means of Ley's TPAP-NMO protocol (5 mol%) in 68% yield.²⁶ With the synthesis of lactone **60**, the stage was set for our envisioned sequential reaction that would ultimately form the

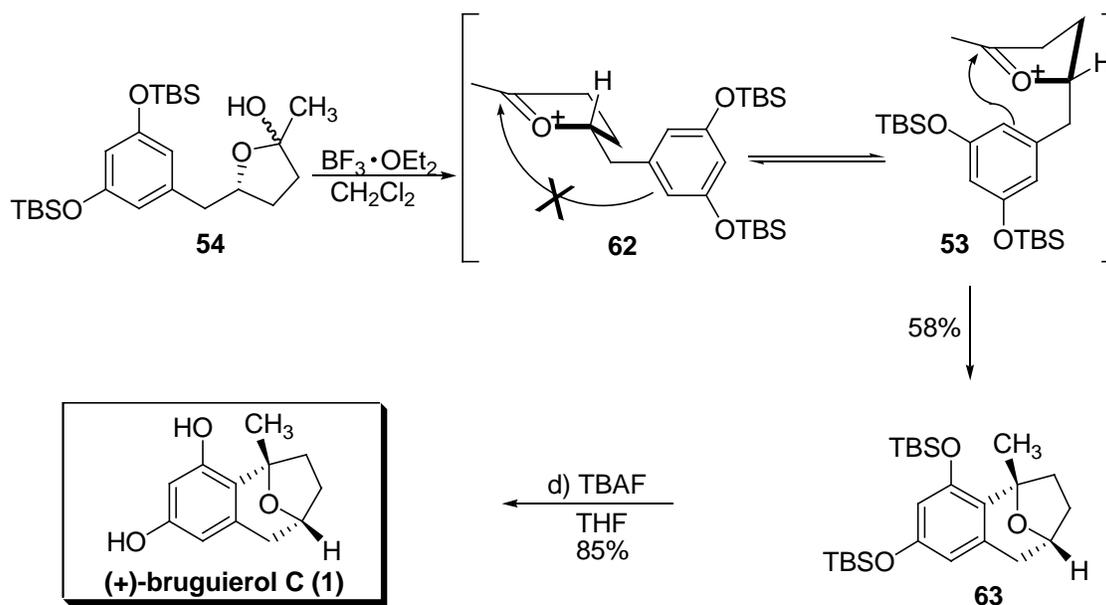
oxocarbenium cation via an ensuing methylation followed by treatment of lactol **54** with an appropriate Lewis acid. Finally, an intramolecular trap of the incipient oxocarbenium cation by means of a Marson-type Friedel-Crafts alkylation^{10,11} should allow for the formation of the protected bruguirol C **63**.



Scheme 2.7. Synthesis of Key Lactol Intermediate (**54**)

With this idea in mind, treatment of lactone **60** with 1.3 equivalents of MeLi in THF quantitatively furnished lactol **54**, the key oxocarbenium precursor, which was then sequentially treated with $\text{BF}_3 \cdot \text{OEt}_2$ and allowed to react at -20°C for 2 hours. As depicted in Scheme 2.8, the product is presumed to arise from oxocarbenium conformer **53**. Of the two reactive conformers **62** and **53**, **53** with the aryl substituent in an axial orientation, is in close proximity to undergo a Friedel-Crafts type alkylation to give the bis-TBS protected natural product **63**. As mentioned earlier the pseudo C_2 -symmetry of the oxocarbenium intermediate was a structural feature that was exploited during this transformation, since alkylation at either of the chemically equivalent

carbon atoms would in fact lead to the same product. Much to our delight, the three step reaction sequence (alkylation, oxocarbenium formation to afford **53**, and final intramolecular Friedel-Crafts alkylation) provided the desired β -C-glycoside product **63** with an overall 58% yield from lactone **60**. Lastly, treatment of **63** with 3 equivalents of TBAF at rt in THF furnished the natural product **1** in a respectable 85% yield. The sequence of events is summarized in Scheme 2.8. The spectral data (^1H NMR, 360MHz; ^{13}C NMR, 125 MHz), optical rotation ($[\alpha]_D^{rt} + 4.2^\circ$, $c = 0.0050$ g/ml MeOH), and HRMS data of synthetic (+)-bruguierol C were in agreement with the natural sample.^{12, 89}



Scheme 2.8. First Total Synthesis of (+)-Bruguierol C (**1**)⁸⁹

2.7 Conclusions

In conclusion, we have completed the total synthesis and determined the absolute configuration of (+)-bruguierol C (**1**) in 7 linear steps from the known *bis*-TBS protected methyl

ester **58**.⁸⁹ The first asymmetric induction was accomplished via a reagent-control Brown allylboration utilizing the commercially available Ipc-based reagent to give a homoallylic alcohol which upon Brown hydroboration/oxidation of the terminal olefin gave the 1,4 diol intermediate. This diol was then oxidized and cyclized to the requisite lactone, which then underwent a 1,2-nucleophilic addition with methyllithium to generate the lactol oxocarbenium precursor. The key step of the synthesis featured a diastereoselective capture of an *in-situ* generated oxocarbenium ion via an intramolecular Marson-type Friedel-Crafts cyclization, which concomitantly generated the chiral quaternary center. Final fluorine-mediated desilylation liberated the phenol moieties, thus producing (+)-bruguierol C (**1**) in a very concise manner.⁸⁹ Through the synthesis of this potential antibiotic, an extension of Kishi's original protocol⁴ to include aromatic nucleophiles in Friedel-Crafts alkylations of electrophilic oxocarbenium intermediates has been accomplished. In addition, the methodology independently developed by Marson¹⁰ and Wu¹¹ has been applied to the synthesis of a natural product representing a "proof of concept."

CHAPTER 3: CONVERGENT FORMAL SYNTHESSES OF (±)-BRUSSONOL AND (±)-ABROTANONE VIA AN INTRAMOLECULAR MARSON TYPE CYCLIZATION

3.1 Introduction, Isolation, and Initial Biological Studies

Virtually every culture has utilized biologically relevant extracts from plants and animals for specific medicinal indications ranging from anti-inflammation to hepatitis.²⁷ Plants belonging to the genus *Salvia* (Lamiaceae) have been recognized worldwide as a valuable medicinal resource since ancient times. Undoubtedly, this recognition is due to the vast diversity of biological functions, such as; antibacterial, antiplasmodial, antituberculosis, antiphlogistic, cardioactive, antidiabetic, anti-inflammatory, analgesic, antipyretic, antispasmodic, anti-tumor, antiviral, hallucinogenic, trypanocidal, antifungal, and antioxidant agent.²⁸ Mexico has a rich diversity of medicinal plants and approximately 3,000 to 5,000 are currently used medicinally by 52 different ethnicities throughout the country. The genus *Salvia* (Lamiaceae) is highly respected in Mexican traditional medicine since the time of the Aztecs, Olmecs, and Mayas who meticulously recorded and catalogued medicinal herbs and their uses. For example, *Salvia elegans* Vahl is a perennial shrub native to Mexico, commonly known as pineapple sage or pineapple-scented sage, and “mirto”, “flor del cerro”, “limoncillo” and “perritos rojos,” in Spanish. It is widely used in Mexican traditional medicine to alleviate central nervous system ailments.²⁹

Today, plants continue to provide biologically active compounds as well as synthetically challenging targets that are essential in the advancement of our understanding in the fundamental

principles of structure and reactivity. Along this line, the icetexane diterpenoids are representative of these types of medicinally relevant and architecturally intriguing compounds.³⁰ Members within this family of natural products, as depicted in Figure 3.1, include brussonol (**2**), abrotanone (**3**), 5,6-dihydro-6 α -hydroxy-salviasperanol (**64**), salviasperanol (**65**), demethylsalvicanol (**66**), and the complex dimer grandione (**67**). Isolated from the root cultures of an endangered species of plant native to the Canary Islands, *Salvia broussoneti*, brussonol (**2**) was reported by Fraga and co-workers in 2005 and was initially shown to be cytotoxic towards insect and mammalian cell lines.²⁸ Fraga's team of scientists at El Instituto de Productos Naturales y Agrobiología in Tenerife, Spain and El Centro de Ciencias Medioambientales in Madrid, Spain performed ethanolic extractions on 45.3 grams of freeze-dried hairy roots and obtained 5 milligrams of brussonol (**2**). Thus, it was clear from the outset that a synthetic plan towards the laboratory syntheses of these secondary metabolites was necessary in order to obtain

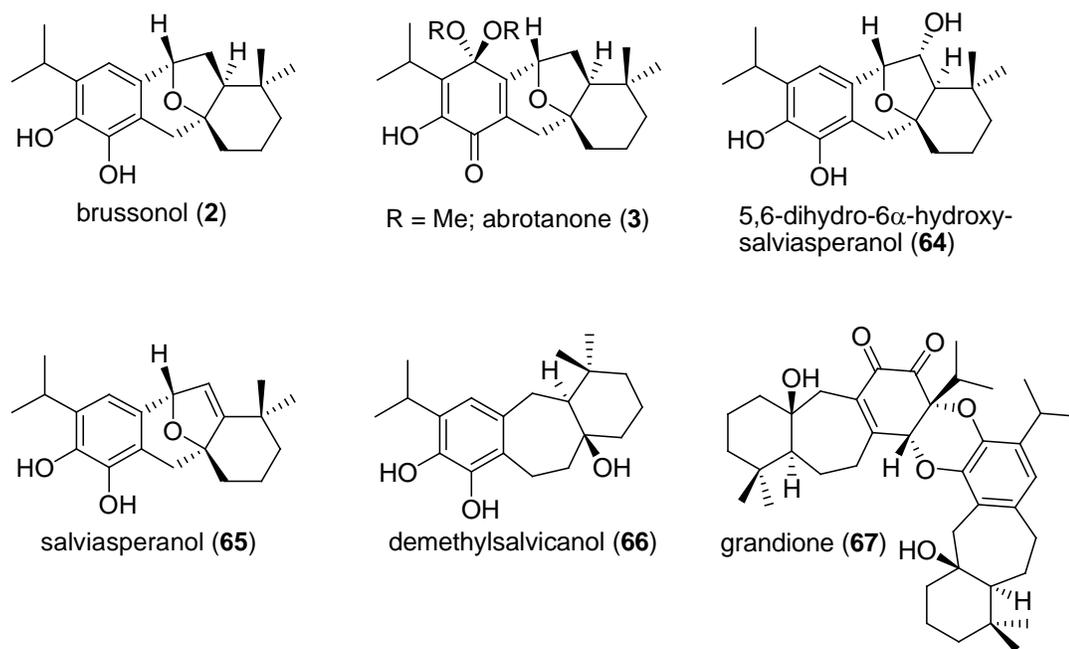


Figure 3.1. Icetexane Natural Products

significant quantities for further biological studies. This task was in part achieved by a Japanese collaboration between the Universities of Tokyo and Josai in which several icetexane diterpene analogues were semi-synthesized from demethylsalvicanol (**66**) and evaluated for their structure activity relationships (SAR) studies. In their published results, Takeya and co-workers found that **2** exhibits moderate cytotoxicity against the P388 murine leukemia cell line with an IC₅₀ value of 1.9 µg/mL.³¹

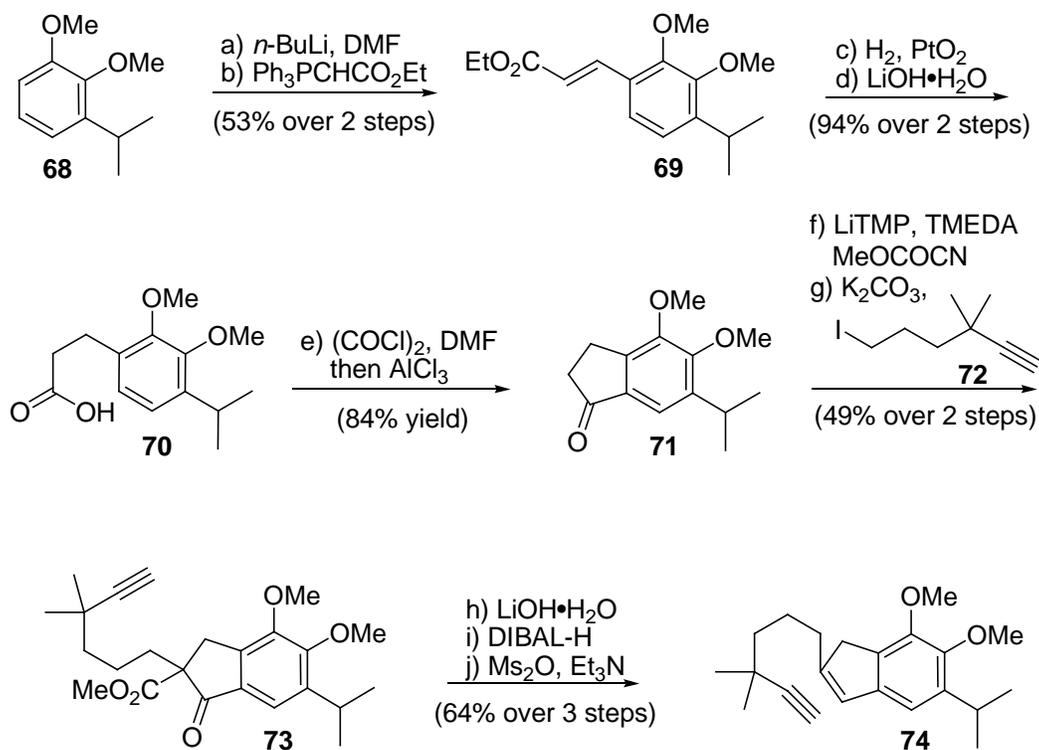
Although the initial biological investigations have led to modest results, the densely functionalized and congested cage-like three-dimensional structures of these molecules have provoked and captivated the imaginations of synthetic chemists leading to innovative solutions towards their synthesis. At the time of our disclosure, there were two reported syntheses of brussonol (**2**), the first by Sarpong at UC Berkeley³³ and a second by Majetich at the University of Georgia.³⁵ Utilizing unique methodologies, both groups have made significant and lasting contributions to the syntheses of icetexane natural products.

The Jennings group became attracted to the synthesis of **2** due to our long-standing interest in constructing highly substituted β-C-glycoside moieties via oxocarbenium cation intermediates¹⁵ and the limited knowledge of its biological profile. Additionally, the benzo-fused 8-octabicyclo[3.2.2] carbon skeleton was a structural feature we were very familiar with. Upon glancing at the structure of **2**, my thoughts were immediately directed towards that of our first target (+)-bruguierol C (**1**) as my heart palpitated with the familiar feeling of excitement and scientific curiosity. Our previous synthesis of bruguierol C featured a diastereoselective capture of an in situ generated oxocarbenium ion via an intramolecular Marson type Friedel-Crafts cyclization as the key step that readily delivered the natural product.⁸⁹ We were hopeful that a similar strategy would allow for the formal syntheses of both (±)-brussonol (**2**) and (±)-

abrotanone (**3**) in a very rapid and efficient manner utilizing inexpensive starting materials and reagents. Our synthetic plan, if realized, would not only be a prime example of a step-economical synthesis but its convergence would insure that it could be amenable to the practical synthesis of analogues in the search of more potent cytotoxic therapeutic leads. In addition, this project would represent an extension of Kishi's original protocol for the synthesis of α and β -C-glycoside moieties⁴ through oxocarbenium intermediates via a Marson-type intramolecular Friedel-Crafts cyclization on a more complex system than our previous "proof of concept" synthesis of bruguierol C.⁸⁹ This chapter will discuss the formal syntheses of both (\pm)-brussonol (**2**) and (\pm)-abrotanone (**3**) via an intramolecular Friedel-Crafts/Marson type cyclization.

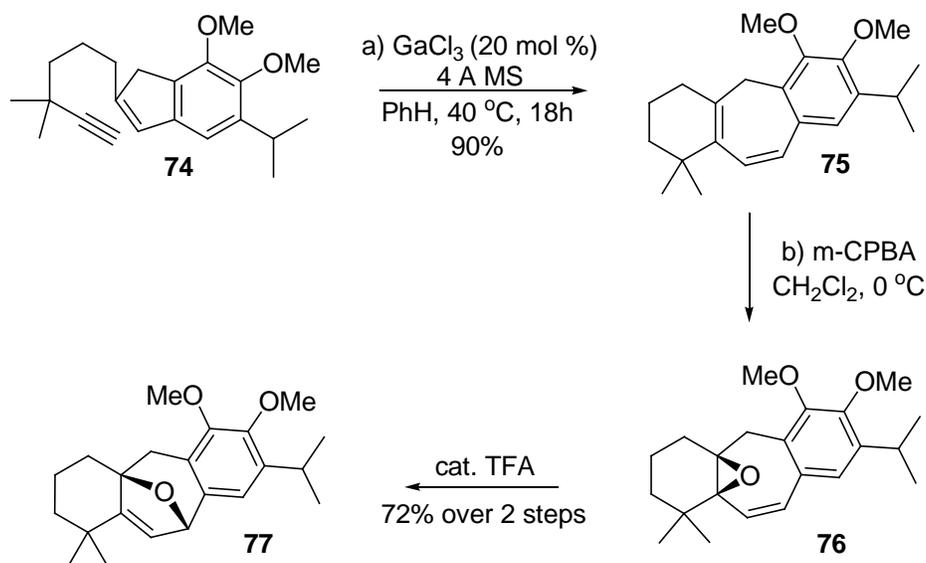
3.2 Previous Synthetic Approaches to Icetexane Natural Products

Due to their novel and intriguing structures, coupled with the limited biological profiles of such icetexane natural products, brussonol (**2**) and abrotanone (**3**) are attractive targets for chemical synthesis. Recently, Sarpong and co-workers achieved the total syntheses of several members of this growing family of secondary metabolites, including; (\pm)-brussonol (**2**), (\pm)-5,6-dihydro-6 α -hydroxysalviasperanol (**64**), (\pm)-abrotanone (**3**), and (\pm)-salviasperanol (**65**) through the use of an innovative Ga(III)-catalyzed cycloisomerization strategy.^{32,33} Summarized in Scheme 3.1 is Sarpong's synthesis of the requisite indene precursor **74**. Following Majetich's three-step protocol for the synthesis of isopropylveratrol **86**,³⁴ the indene precursor was synthesized in ten additional high-yielding steps.³² With the indene precursor **74** constructed, the stage was set for Sarpong's key Ga(III)-catalyzed cycloisomerization reaction, which would efficiently construct the natural product core in a single synthetic operation.

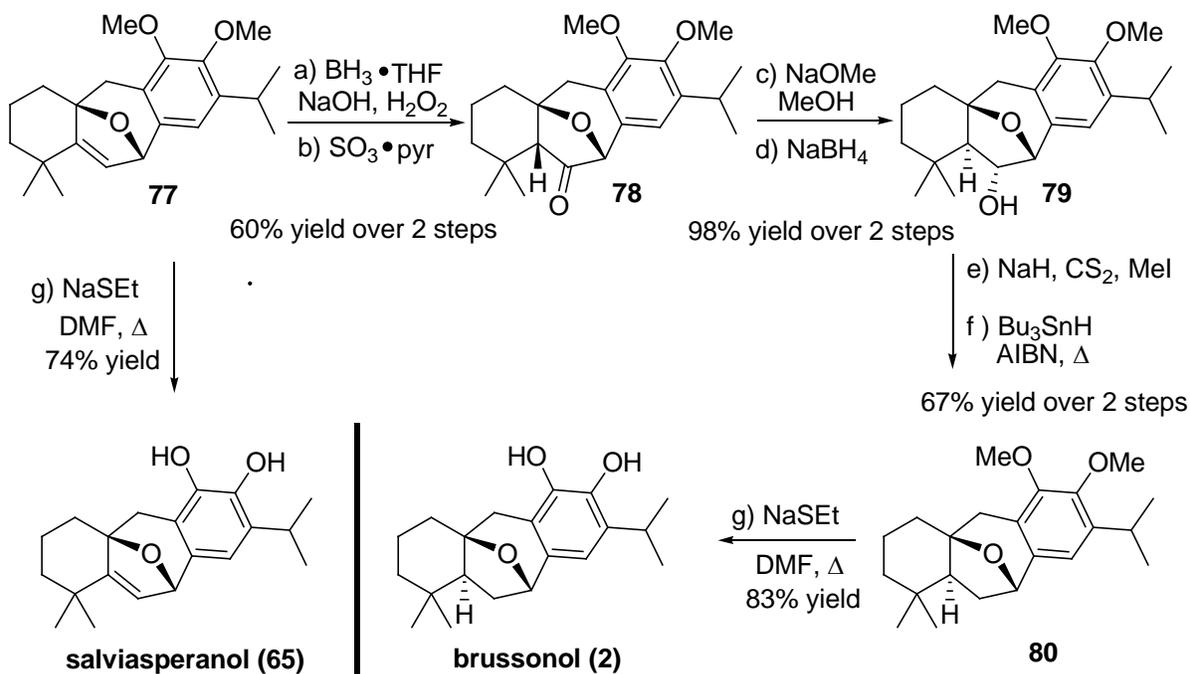


Scheme 3.1. Sarpong's Synthesis of the Indene Cycloisomerization Precursor (**74**)³³

Accordingly, treatment of alkynyl indene **74** with GaCl₃ effected an enyne cycloisomerization reaction that led to the desired cycloheptadiene **75** in an excellent yield of 90%, as shown in Scheme 3.2. With the icetexane core established, chemoselective epoxidation of the more electron rich alkene employing *meta*-chlorobenzoic acid in dichloromethane at ice-cold temperature led to **76**, which upon treatment with catalytic amounts of TFA, cleanly isomerized to the dihydrofuran **77** in a yield of 72% over 2 steps. At this point in their strategy, deprotection of the methoxy ethers with the sodium thiolate anion in refluxing DMF led to the synthesis of salviasperanol **65**,³² while carrying this intermediate forward through a series of synthetic operations led to the production of brussanol (**2**) as depicted in Scheme 3.3.³³

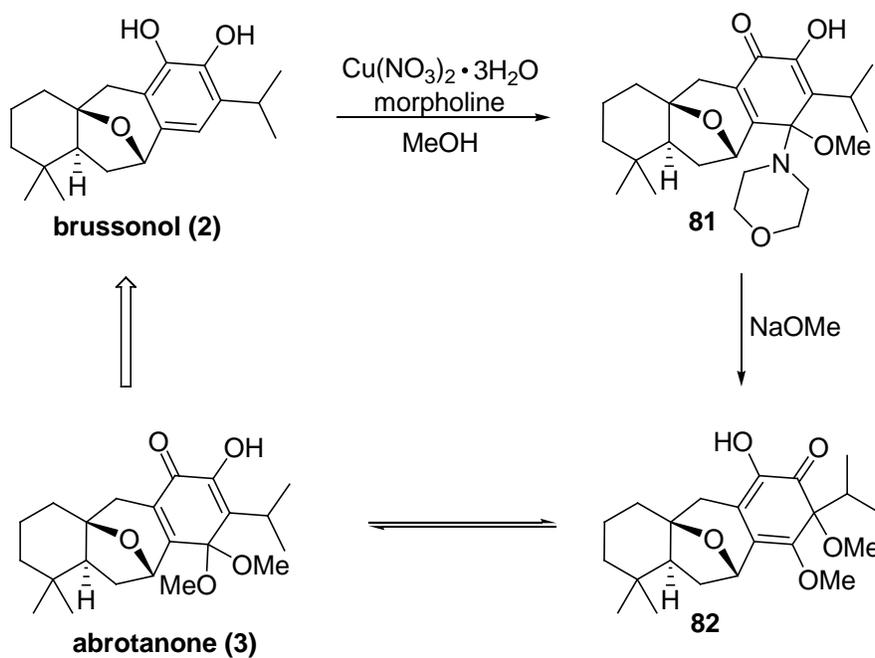


Scheme 3.2. Sarpong's Enyne Cycloisomerization Strategy³²



Scheme 3.3. Total Syntheses of Brussonol (**2**) and Salviasperanol (**65**) by Sarpong^{32,33}

Sarpong and co-workers further reported the revised structure of abrotanone (**3**), which was synthesized from **2** in a process involving a net four-electron oxidation mediated by Cu^{2+} accompanied with regioselective addition of 2 equivalents of methanol as depicted in Scheme 3.4.³³ Thus, treatment of brussonol (**2**) with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ and morpholine in MeOH as solvent, led to hemiaminal **81**. Further treatment with NaOMe in MeOH led to a 2:1 equilibrium mixture of isomeric α -hydroxydieneones **82** and **3** which were separated by column chromatography. The authors reported that α -hydroxydieneone **3** was consistent with spectral data reported for abrotanone, thereby revealing its true structure.³³



Scheme 3.4. Sarpong's Revised Structure of Abrotanone (**3**)³³

Sarpong's work highlights the important role of chemical synthesis in structure elucidation of unknown and misassigned chemical entities. Total synthesis continues to contribute to structural assignments/reassignments where current spectroscopic technologies are

insufficient. Through chemical synthesis, this important work has helped clarify discrepancies in the literature and has led to the structural revisions of abrotanone (**3**) and abrotandiol, the latter was found to be identical to brussonol (**2**). The subject of total synthesis and its role in structure elucidation of natural products will be revisited in chapter six, during our synthesis of pochonin J (**5**).

During the synthesis of the icetexane dimer (+)-grandione (**67**), Majetich identified and reported conditions that lead to the production of (-)-brussonol starting from the *ortho*-quinone form of (+)-demethylsalvicanol (**66**) employing diethyl ether as the solvent.³⁵ Interestingly, when water was used as the solvent, the desired dimer (+)-grandione (**67**) was formed as the major product in a bimolecular Diels-Alder reaction. Majetich explains that brussonol (**2**) can only be formed if the *ortho*-quinone form of (+)-demethylsalvicanol (**66**) tautomerizes to its enol form, and that in enol-keto tautomerizations, enol formation is favored by solvents with low dielectric constants such as diethyl ether (4.335 at 20 °C), thus leading to brussonol as the major product. Furthermore, the keto form usually benefits from solvents having high dielectric constants (water = 78.39 at 25 °C), and it is this keto tautomer which undergoes a Diels-Alder reaction leading to grandione (**67**).³⁵ This explanation nicely correlates with the experimental observations. What follows is our account of the synthetic strategies that were studied and ultimately lead to the successful formal syntheses of both (±)-brussonol (**2**) and (±)-abrotanone (**3**).

3.3 Initial Retrosynthetic Analysis of (±)-Brussonol and (±)-Abrotanone

As delineated in Figure 3.2, our initial approach was based on the successful union of epoxide **87** and isopropylveratrol **86** via an *ortho* directed metallation reaction.³⁶ Synthons **87** and **86** should be both readily obtained starting from commercially available 3-methyl-2-

cyclohexen-1-one **89** and veratrol **91**. Once this coupling was completed, it could be envisioned that hemiketal **84** would arise in a single step from an oxidation of the terminal alkene moiety of **85** via the aldehyde intermediate in the presence of MeOH. Similar to bruguierol C, oxocarbenium formation under Lewis acidic conditions followed by an intramolecular Friedel-Crafts capture of the oxocarbenium cation intermediate should provide **83**, thus constituting a formal synthesis of (\pm)-brussonol (**2**). Subsequent cleavage of the methoxy phenyl ethers should provide **2** and an ensuing oxidation under Sarpong's conditions should ultimately afford **3**.³³

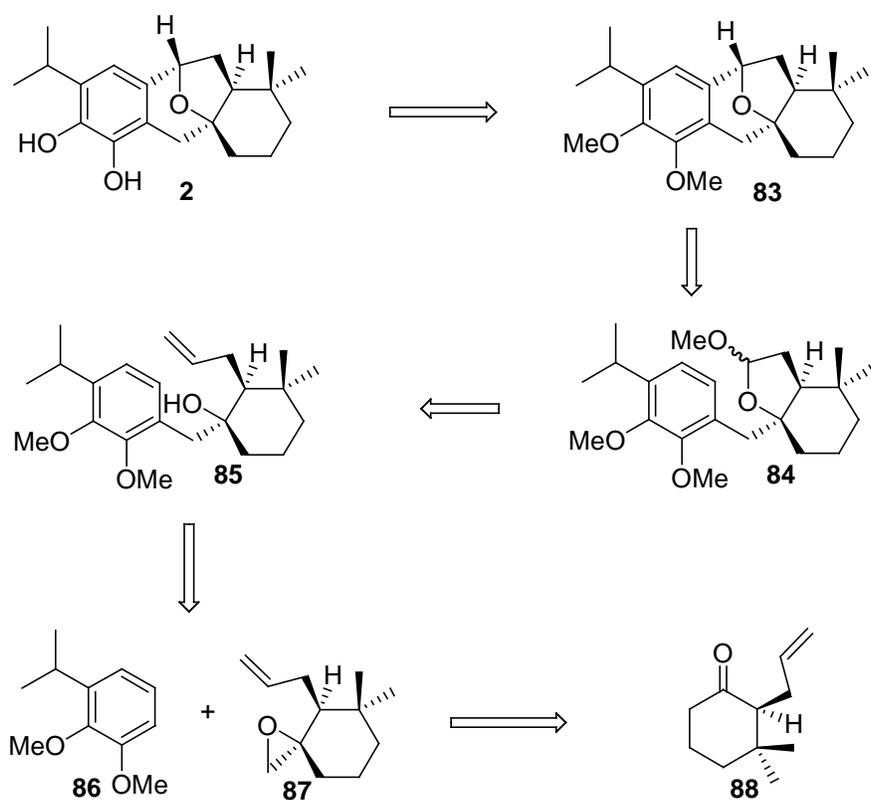
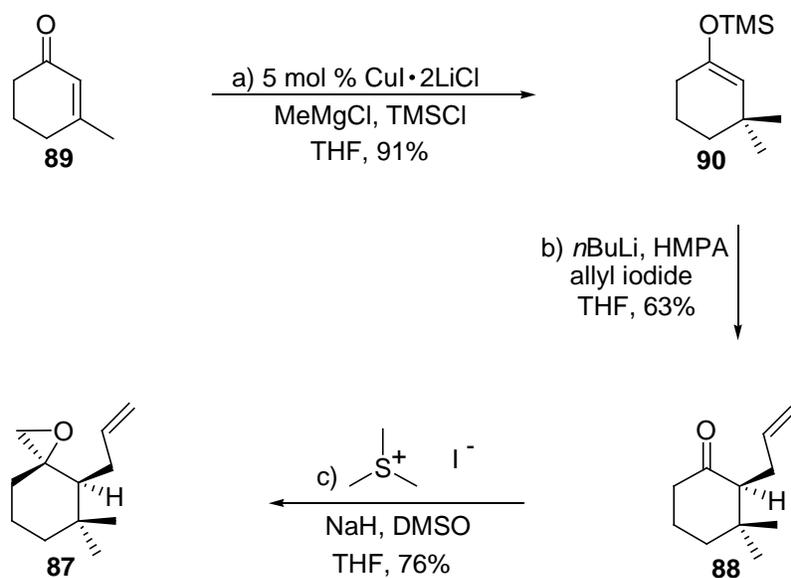


Figure 3.2. First-Generation Retrosynthetic Analysis of Brussonol (**2**)

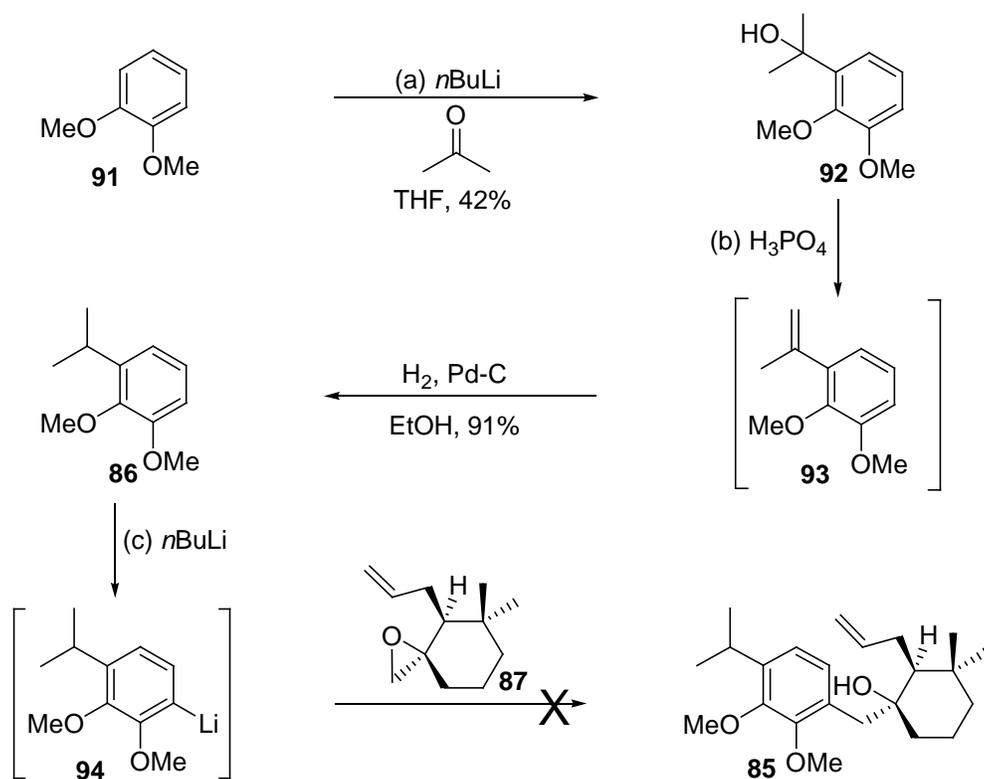
3.4 Failed Approach to Key Tertiary Alcohol (85)

With our initial retrosynthetic plan in mind, focus was placed on the synthesis of the required coupling fragments, **86** and **87**. As shown in Scheme 3.5, the preparation of epoxide **87** commenced with a classical Kharasch type reaction with the α,β -unsaturated ketone **89**.³⁷ Under the conditions described by Reetz,³⁸ copper-catalyzed (5 mol% of CuI•2LiCl) conjugate addition of MeMgCl to ketone **89** in the presence of TMSCl provided silyl enol ether **90** in 91% yield which was used without further purification. Catalytic copper is responsible for the excellent regioselectivity observed during this type of reaction where competitive 1,2-addition reactions can lead to undesired products. Subsequent treatment of latent enolate **90** with *n*BuLi in the presence of HMPA followed by electrophilic quench of the corresponding lithium enolate with allyl iodide provided a mixture of ketone **88** and the *O*-alkylated allylic ether, which was then transformed into the desired product **88** by means of a Claisen rearrangement at elevated temperature with DMSO as the solvent in an overall yield of 63% from enol ether **90**. In retrospect, the use of MeLi without HMPA instead of *n*-BuLi would have probably led to the desired ketone **88** without the formation of the *O*-alkylated allylic ether. The use of HMPA helps to break the O-Li bond thus generating an alkoxide intermediate which can react with allyl iodide in an S_N2 fashion, leading to the undesired *O*-alkylated allylic ether. An ensuing Corey-Chaykovsky epoxidation³⁹ of **88** with the standard reagents (trimethyl sulfonium iodide and the Na salt of the DMSO anion) delivered the desired coupling partner **87** with an overall yield of 44% over three steps from **89**. Much to our delight, nucleophilic addition of the corresponding trimethyl sulfonium anion to ketone **88** led to exclusive formation of the desired epoxide **87** as a single diastereomer, as depicted in Scheme 3.5.



Scheme 3.5. Synthesis of *Exo*-Epoxide (**87**) via a Corey-Chaykovsky Epoxidation

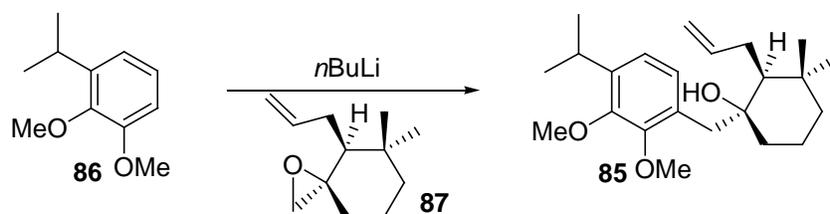
With epoxide **87** in hand, we next turned our attention to the completion of 3-isopropylveratrol **86** using a short and practical two-step sequence as first reported by Majetich and is depicted in Scheme 3.6.³⁴ Thus, treatment of **91** with 1.05 equiv of *n*BuLi at $-78\text{ }^\circ\text{C}$ afforded the intermediate *ortho*-metallated anion which was subsequently trapped with acetone to provide the tertiary benzyl alcohol **92** in 42% yield along with about 50% recovered starting material, which could be resubmitted to the reaction conditions. An ensuing acid promoted dehydration and hydrogenation under atmospheric pressure using 10% Pd/C delivered **86** conveniently in a one-flask operation. Presumably this reaction proceeded through intermediate **93**, the result of an E_1 elimination of the extraneous hydroxyl group via a stabilized tertiary/benzylic carbocation intermediate, in an overall yield of 91% from **92**. It is worth noting that we modified the original Majetich procedure to circumvent the usage of a high-pressure one-pot dehydration/hydrogenation protocol from **92** to **86**.



Scheme 3.6. Attempted Coupling of (**86**) and (**87**) via Directed Lithiation

With our two fragments, **86** and **87**, in hand we were ready to explore conditions which would lead to the formation of the highly desired tertiary alcohol **85**. Unfortunately, as highlighted in Table 3.1, all attempts failed to provide the coupled product **85** in workable yields and purity. Attempted *ortho*-lithiation of **86** under a variety of conditions, solvents, and additives was quite successful (*vide infra*), however quenching of the lithiated arene with epoxide **87** generally lead to little or no desired product **85**. Setbacks such as these are quite common in organic synthesis and one must always be prepared with a back-up plan. Fortunately, our synthetic plan was quite amenable to a very minor but effective modification, whereby the previously electrophilic carbon of the oxirane moiety would now be incorporated onto isopropylveratrol, this time to function as the nucleophile.

Table 3.1. Attempted *Ortho*-Lithiation of **86** and Electrophilic Quench With Epoxide **87**



no.	solvent	T(°C)	time (h)	additive	yield (%)
1	THF	-78 to rt	12	none	trace
2	THF	-78 to rt	24	HMPA	~10 ^a
3	THF	-78 to rt	24	TMEDA	~15 ^a
4	THF	-78 to rt	24	BF ₃ •OEt ₂	trace
5	Et ₂ O	-78 to rt	12	none	trace
6	Et ₂ O	-78 to rt	48	HMPA	~10 ^a
7	Et ₂ O	-78 to rt	48	TMEDA	~10 ^a
8	Et ₂ O	-78 to rt	48	BF ₃ •OEt ₂	trace
9	Et ₂ O	-78 to rt	48	BF ₃ •OEt ₂	trace

^a The quoted yields are a mixture of products (which includes **6**) that coelute from a silica gel column. ^b Reaction ran also with TMEDA as a second additive.

3.5 Second-Generation Retrosynthetic Analysis

With the failure of the initial synthetic blueprint, we reformulated our synthetic plan. As depicted in Figure 3.3, our end-game strategy remained identical to that of our first-generation retrosynthetic analysis. The major difference between the two strategies lies in the formation of tertiary alcohol **85**. In the second-generation approach, we envisaged that a chemoselective directed benzylic lithiation of the methyl moiety of **96** should provide the stabilized organometallic reagent **95** followed by electrophilic quench of our previously synthesized ketone **88** should afford the elusive tertiary alcohol **85**. In turn, **96** could be readily obtained from the previously prepared isopropylveratrol **86** via a directed aromatic lithiation/ alkylation protocol.

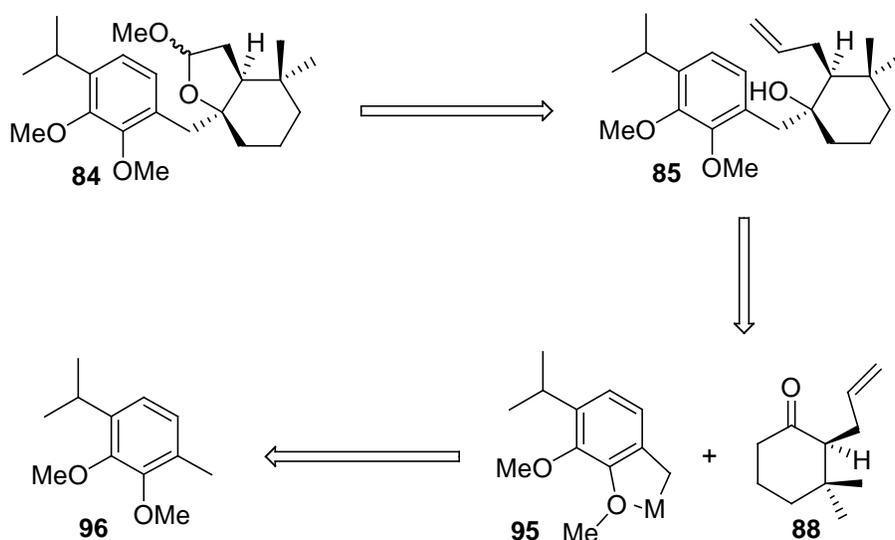
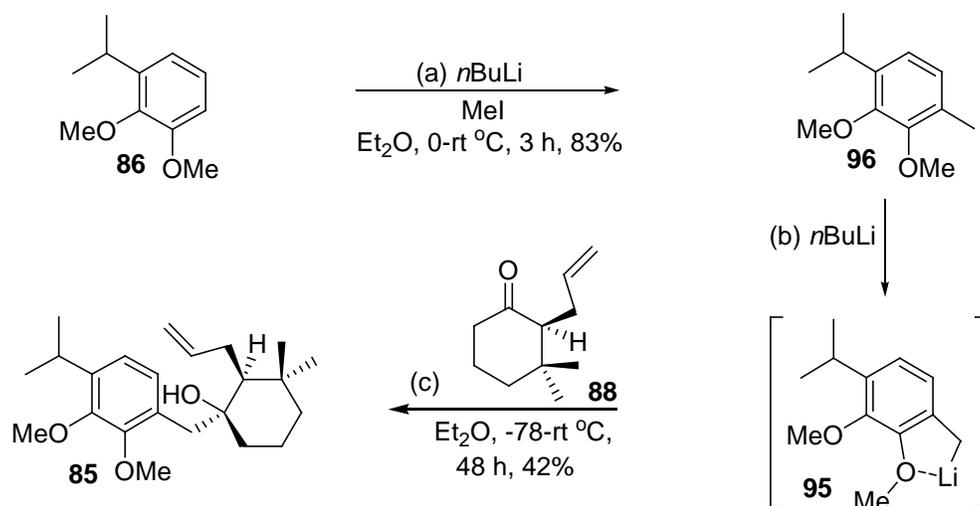


Figure 3.3. Second-Generation Retrosynthetic Analysis of Brussonol (**2**)

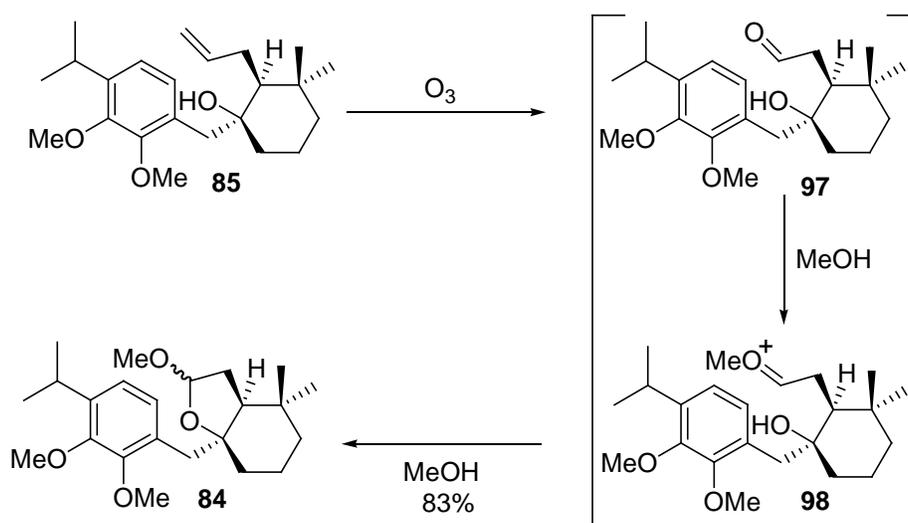
3.6 Completion of the Formal Syntheses of (\pm)-Brussonol and (\pm)-Abrotanone

Armed with our revised strategy, we focused our attention to the formation of **85** via the proposed coupling of **96** and **88** as depicted in Scheme 3.7. Thus, a second *ortho*-directed metallation followed by electrophilic quench with iodomethane provided **96** in an 83% yield. Once again, the stage was set for the attempted coupling of fragments **96** and **88**. Gratifyingly, fragment union was achieved through a chemoselective directed benzylic lithiation of **96** in Et₂O and in the presence of the bidentate ligand TMEDA at -78 °C, which presumably generated the stabilized five-membered chelate intermediate **95**, followed by electrophilic quench with ketone **88** to furnish **85** in 42% yield. It is important to recognize that abstraction of the second acidic proton on the isopropyl group was not observed, perhaps due to the unfavorable steric interactions mandated by the presumed transition state. Much to our delight, the nucleophilic addition of the lithiated intermediate **95** to **88** provided **85** as a single diastereomer via selective axial attack (Scheme 3.7). Although the yield was moderate at best, we were extremely pleased to have obtained this highly sought after intermediate after numerous repeated attempts.



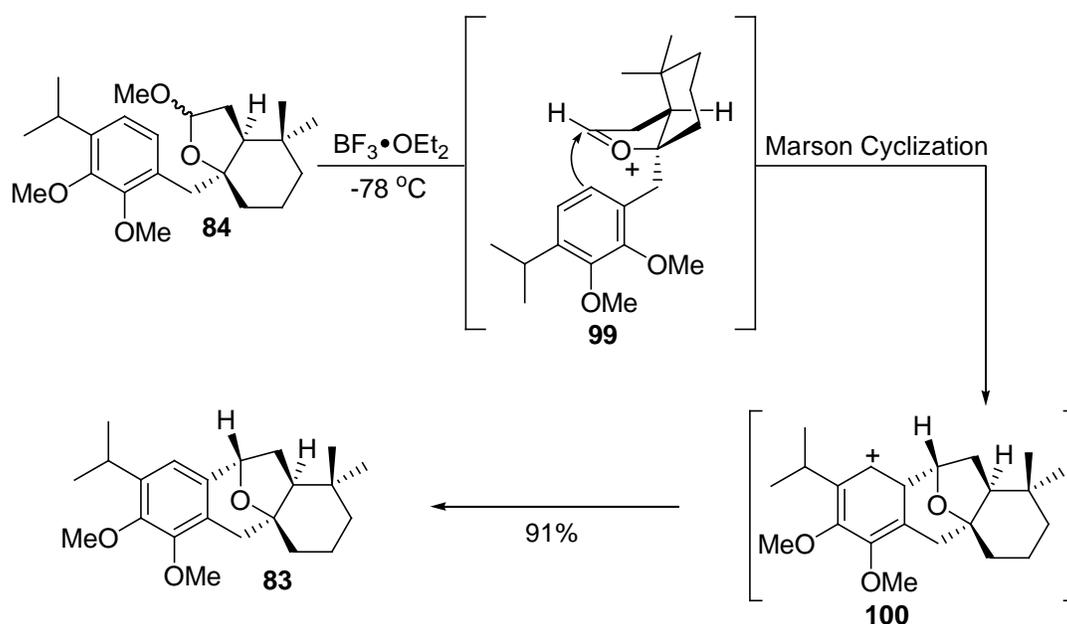
Scheme 3.7. Successful Fragment Union via Benzylic Lithiation

Having worked on the union of these fragments for about six weeks, I was excited to get back into the lab for further experimentation towards the completion of this secondary metabolite. As it turned out, the most difficult hurdles of this project had been cleared, and oxidative cleavage of the terminal alkene followed by a Marson-type cyclization was all that was needed to arrive at our target.



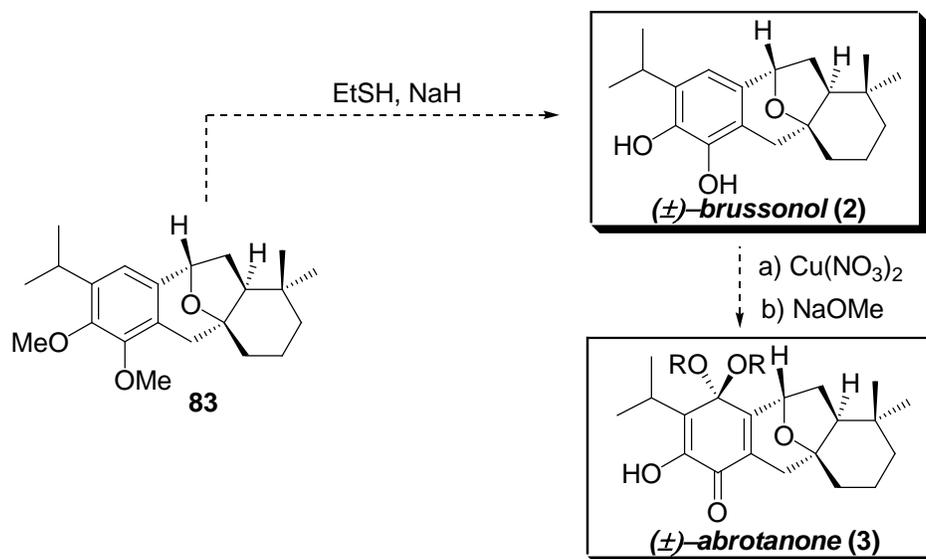
Scheme 3.8. One-Step Synthesis of Methoxy Acetal (**84**) via Ozonolysis

With our fragments successfully coupled, we next turned our attention to the rapid completion of **83** as shown in Scheme 3.8. Thus, terminal olefin oxidation of **85** via ozonolysis in MeOH presumably formed intermediate aldehyde **97**, followed by creation of the methoxy oxonium cation **98** in the presence of MeOH which subsequently cyclized to deliver the methoxy ketal **84** in 83% yield. As shown in Scheme 3.9, final treatment of **84** with 2 equiv. of $\text{BF}_3 \cdot \text{OEt}_2$ at $-20\text{ }^\circ\text{C}$ for 1 h provided the cyclized product **83** in 91% yield apparently via the proposed intermediates **99** and **100**, as with bruguierol C via a Marson-type Friedel-Crafts cyclization.⁹¹ Much to our delight, the spectral data (^1H NMR, 600 MHz; ^{13}C NMR, 125 MHz) and HRMS data of synthetic **83** were in complete agreement with those previously reported.^{28,33,91}



Scheme 3.9. An Intramolecular Marson/Friedel-Crafts Cyclization⁹¹

Finally, **83** could be converted to (\pm)-brussonol (**2**) by cleavage of the two methoxy ethers by means of treatment of **83** with the thiolate anion in DMF.³³ In addition, it has been reported by Sarpong that **2** can be readily converted into (\pm)-abrotanone (**3**) via a copper-mediated oxidation sequence in a solution of NaOMe-MeOH, as demonstrated in Scheme 3.10.³³



Scheme 3.10. Formal Syntheses of (\pm)-Brussonol (**2**) and (\pm)-Abrotanone (**3**)

3.7 Conclusions

In conclusion, we have completed a highly practical and convergent formal synthesis of both (\pm)-brussonol (**2**) and (\pm)-abrotanone (**3**) in 7 steps (longest linear sequence) from veratrol for brussonol, and 9 steps for abrotanone.⁹¹ Key steps in this synthesis include two distinct Snieckus directed-*ortho* metallation reactions to elaborate the aromatic subunit. Chemoselective benzylic lithiation of the aromatic subunit followed by 1,2-addition to the prepared ketone unified the fragments in a highly convergent manner. Oxidation of the terminal alkene in MeOH initiated a 5-exo-trig cyclization that led directly to the methoxy acetal oxocarbenium precursor in a single

flask operation. Treatment of this intermediate with $\text{BF}_3 \cdot \text{OEt}_2$ induced the diastereoselective capture of an *in situ* generated oxocarbenium ion via an intramolecular Friedel-Crafts/Marson-type cyclization. These synthetic studies demonstrate that the Marson-type cyclization^{10,11} has proven effective on a slightly more complex system, as well as representing the first diterpene natural product synthesized utilizing Kishi's protocol⁴ for the construction of C-glycosides subunits, further extending the utility of oxocarbenium protocols.

CHAPTER 4: CHEMOSELECTIVE TBS DEPROTECTION OF PRIMARY ALCOHOLS BY MEANS OF PYRIDINIUM TRIBROMIDE (PY•BR₃) IN MEOH

4.1 Introduction and background

The usage of protecting groups in modern organic chemistry, more specifically, in multi-step natural product synthetic chemistry has become quite ubiquitous over the past 30 years.⁴⁰ While the selective masking and unmasking of precious functional groups plays an important role in many areas of organic synthesis, there remains a great need for the ability to chemoselectively introduce and remove orthogonal protecting groups in multi-functionalized molecules.⁴¹ Since the introduction of the TBS group for the protection of the alcohol moiety by Corey, virtually every polyketide and/or polypropionate natural product synthesis has utilized this or a similar silicon masking group.^{42,43} With the usage of such protecting groups, numerous reagents have been developed for the chemoselective unmasking of a given silyl ether dependent upon its acid or base lability.⁴⁴ For example, the fluoride anion (i.e., TBAF, aq. HF, HF•pyridine, etc.) has been utilized under both acidic and basic conditions for the cleavage of a variety of silyl ethers. In addition, silyl protecting groups can be cleaved under either Lewis or Brönsted acidic conditions. One of the major drawbacks in both of these cases lies in the potential inability to chemoselectively remove silyl ethers in the presence of other protecting groups or functionalities.

In one of our on-going synthetic projects, we had the need to chemoselectively remove a primary TBS ether in the presence of a secondary TES group. We initially investigated the

typical desilylation methods (TBAF, aq. HCl, PPTS in MeOH, etc...), but unfortunately these reaction conditions failed to furnish the desired primary alcohol in workable yields. We next focused our attention on the report of Patel, that tetrabutyl ammonium tribromide (TBATB) in MeOH removed a primary TBS ether within minutes as opposed to hours for the secondary TBS ether counterparts.⁴⁵ Based on this observation, we adopted their protocol for our chemoselective deprotection and found that TBATB did indeed remove the primary TBS ether in the presence of a secondary TES group, however, the yield was modest (~ 45%) due to a competing side reaction which ultimately led to dead-end material. Based on this observation, we decided to investigate if a catalytic amount (5 mol%) of pyridinium tribromide (Py•Br₃) in MeOH at lower temperatures (-20 °C) would mimic the same chemoselectivity as TBATB, but be devoid of the unwanted side-product.

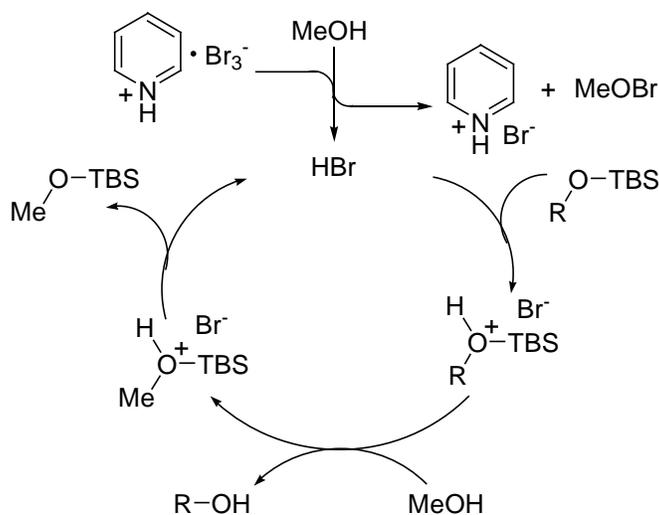


Figure 4.1. Proposed Cycle Generating Catalytic HBr

Our initial working catalytic cycle is highlighted in Figure 4.1. It has been reported that tertalkylammounium tribromides generate HBr in the presence of MeOH.^{45,46} Based on these

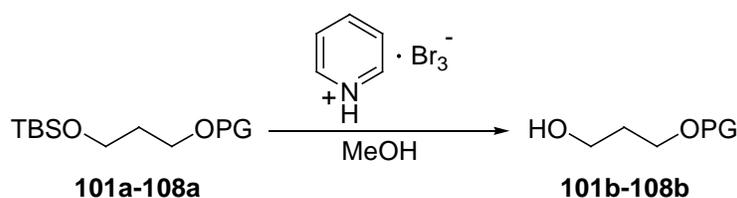
observations, we assumed that $\text{Py}\cdot\text{Br}_3$ would mirror that of the afore mentioned aliphatic tribromides, provide a small amount of HBr , and enter into a catalytic process. Subsequent to the HBr formation, protonation of the TBS ether should provide the oxonium cation, followed by a nucleophilic displacement with MeOH should cleave the silyl ether and furnish the desired alcohol. A final deprotonation (or disproportionation) of the secondary oxonium cation derived from MeOTBS with Br^- should regenerate the acid catalyst, hence making the protocol catalytic in HBr .

4.2 Chemoselective Deprotection of TBS Ethers

With this idea in mind, we decided to investigate the chemoselective deprotection of a TBS ether in the presence of other protecting groups derived from 1,3-propane diol. A series of orthogonally TBS protected diols were synthesized and subjected to differing amounts of $\text{Py}\cdot\text{Br}_3$ in MeOH as shown in Table 4.1. Initially, we chose to investigate the catalyst loading of $\text{Py}\cdot\text{Br}_3$ on the chemoselective deprotection of the TBS ether in the presence of the quite robust TBDPS silyl moiety (**101a**). Thus, treatment of **101a** with a full molar equivalent of $\text{Py}\cdot\text{Br}_3$ at 0°C in MeOH led to a 40% yield for the TBDPS protected diol **101b** while the remaining material balance was the *bis*-desilylated-1,3-propane diol. Lowering the molar equivalents of $\text{Py}\cdot\text{Br}_3$ from 50→5 mol%, while maintaining the reaction temperature at 0°C for **101a**, afforded **101b** in increased yield (from 48 to 77%) as the catalyst loading decreased as shown in table 1. Likewise, a similar trend is also observed when cooling the reaction of **101a** down to -20°C . The optimal yield of **101b** (89%) for the chemoselective TBS deprotection of **101a** with $\text{Py}\cdot\text{Br}_3$ occurred at -20°C with 5 mol% catalyst loading. Similar to that of **101a**, we next investigated the TIPS protected 1,3-propane diol variant **102a**. It is well known that the TIPS ether resident in **102a** is more labile to acidic conditions when compared to the TBDPS group of **101a**.⁴⁷ Thus,

we initially envisioned that the yield for deprotection of **102a** might be inferior to that of **101a**. After scanning a variety of reaction conditions with respect to catalyst loading and temperature, the maximum yield for the chemoselective TBS ether cleavage in the presence of the TIPS group was 86% for the desired compound **102b**. Interestingly, these conditions furnished nearly identical yields (89% vs 86%) for both **101b** and **102b**, respectively.

Table 4.1. Chemoselective Pyridinium Tribromide (Py•Br₃) Deprotection of Primary TBS Ethers in the Presence of Other Protecting Groups



sm #	PG	Mol%	Temp.	T (h)	prod. #	Yield %
101a	TBDPS	100	0	1.5	101b	40
101a	TBDPS	50	0	1.5	101b	48
101a	TBDPS	30	0	1.5	101b	52
101a	TBDPS	10	0	1.5	101b	66
101a	TBDPS	5	0	1.5	101b	77
101a	TBDPS	100	-20	1.5	101b	60
101a	TBDPS	50	-20	1.5	101b	60
101a	TBDPS	10	-20	1.5	101b	52
101a	TBDPS	5	-20	1.5	101b	89
102a	TIPS	30	0	2.0	102b	36
102a	TIPS	10	0	2.0	102b	70
102a	TIPS	100	-20	2.0	102b	36
102a	TIPS	50	-20	2.0	102b	41
102a	TIPS	30	-20	2.0	102b	35
102a	TIPS	10	-20	2.0	102b	81
102a	TIPS	5	-20	2.0	102b	86
103a	TES	5	-20	1.5	103b	0
104a	MOM	5	-20	1.5	104b	93
105a	Bn	5	-20	1.5	105b	80
106a	Bz	5	-20	1.5	106b	94
107a	Ac	5	-20	1.5	107b	82
108a	THP	5	-20	1.5	108b	0

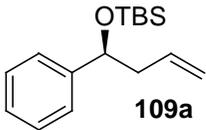
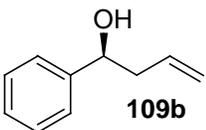
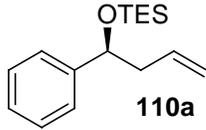
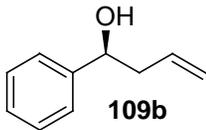
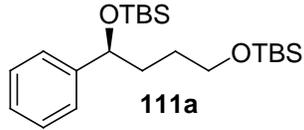
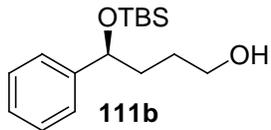
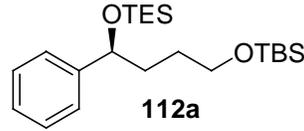
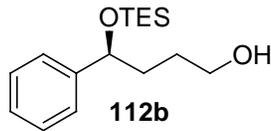
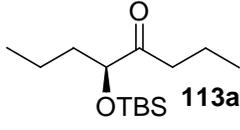
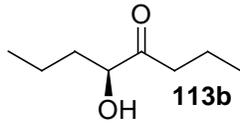
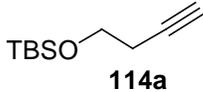
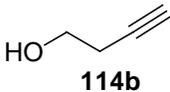
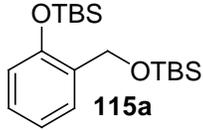
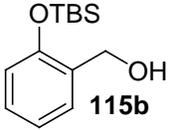
With the standardized reaction condition in hand (5 mol% Py•Br₃ at -20 °C), we chose to investigate the scope and limitations of the selective TBS ether removal in the presence of a variety of other orthogonal protecting groups. Hence, the TES-TBS protected 1,3-propane diol variant (**103a**) unfortunately did not afford the mono protected TES diol **103b**. Not surprising due to the instability of the TES moiety under acidic conditions, the catalytic amount of HBr formed from Py•Br₃ in MeOH at -20 °C cleaved both the TBS and TES ethers and provided 1,3-propane diol as the quantitative product. Similar to that of **103a**, the THP-TBS compound **108a** did not furnish the desired THP protected diol **108b**, but afforded 1,3-propane diol as the sole product due to the lability of the THP moiety under reaction conditions. Much to our delight other orthogonally protected 1,3-propane diol derivatives did undergo chemoselective TBS removal with Py•Br₃ in MeOH at -20 °C. Thus, the Bz (**106a**) and Ac (**107a**)-TBS protected diols underwent silyl ether cleavage and provided the correspond desired products **106b** and **107b** in very goods yields of 94% and 82%, respectively. Likewise, the acyclic acetal MOM-TBS 1,3-propane diol (**104a**) readily afforded the MOM protected alcohol **104b** in 93% yield by means of the chemoselective removal of the silyl ether under the standard reaction conditions. Lastly, the Bn ether derivative **105a** smoothly underwent selective silyl group removal to provide the desired product **105b** in 80% yield.

4.3 Deprotection of TBS Ethers in Presence of a Variety of Functional Groups

While Table 4.1 provided us with an appropriate standardized condition for chemoselective removal of the TBS group and provided some insight into the scope and limitations of the reaction, we decided to shift the focus of our investigation to examining selective silyl group (TES and TBS) removal in the presence of other common function groups as described in Table 4.2. Thus, the removal of both secondary TBS and TES ethers of **109a** and

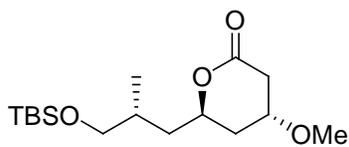
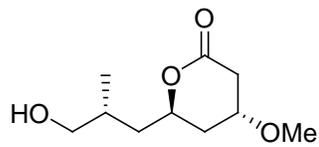
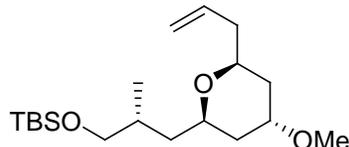
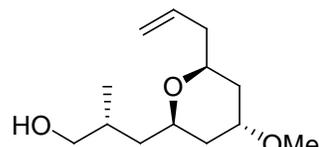
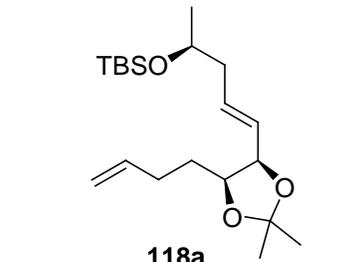
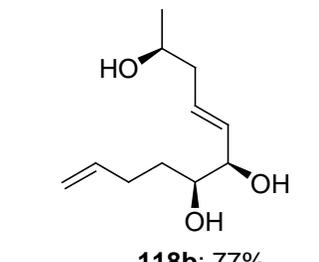
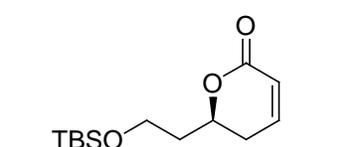
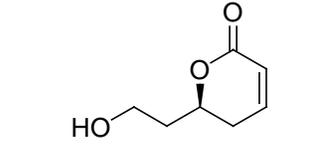
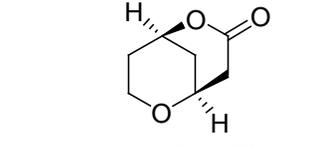
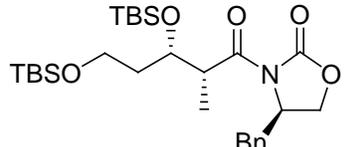
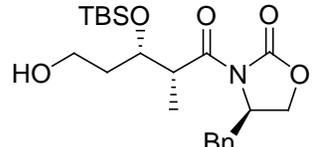
110a in the presence of a terminal alkene proceeded with $\text{Py}\cdot\text{Br}_3$ in MeOH to provide the corresponding homoallylic alcohol **109b** in nearly identical yields of 78% and 76%. However, the catalyst loading was increased from 5 to 10 mol% and the reaction temperature was warmed from -20 to 0 °C to help facilitate the protecting group removal within a few hours. It should be noted that one could utilize the standardized conditions from Table 4.1 for silyl ethers **109a** and **110a**, although the reactions times were much longer (>24 h) for appreciable conversion to **109b**. Based on this observation, we envisioned that lower catalyst loading might allow for a chemoselective removal of a primary TBS (or TES) ether in the presence of a secondary one. Much to our delight, treatment of the *bis*-TBS ether compound **111a** with 5 mol% of $\text{Py}\cdot\text{Br}_3$ in MeOH at 0 °C did indeed undergo chemoselective cleavage of the primary TBS ether in the presence of the secondary one and afforded the mono-protected alcohol **111b** in 74% yield. Likewise, chemoselective removal of the primary TBS moiety resident in **112a** in the presence of a secondary TES ether was also accomplished under the exact reaction conditions for that of **111a** to provide alcohol **112b** in a virtually identical yield of 72% with respect to **111b**. We also examined the chemoselectivity of the TBS ether cleavage in the presence of other typical functional moieties. Thus, the TBS protected α -hydroxy ketone **113a** did undergo silyl cleavage without affecting the carbonyl group to furnish the keto-alcohol **113b** in a modest yield of 55%. However, the reaction was quite sluggish at 0 °C and required warming to rt to drive the reaction to significant conversion with 10 mol% of $\text{Py}\cdot\text{Br}_3$. Likewise, selective deprotection of the TBS group resident in **114a** at 0 °C readily afforded 3-butyn-1-ol (**114b**) in an 81% yield. Similar to that of **110a**, chemoselective removal of the primary TBS ether of **115a** in the presence of a phenolic TBS protecting group furnished the free benzylic alcohol **115b** in an exceptional 93% yield under the standard reaction conditions as described in Table 4.2.

Table 4.2. Py•Br₃ Catalyzed Deprotection of the Silyl Groups in the Presence of a Variety of Functional Groups.^a

Silyl Ether	Product	Yield
 109a	 109b	78% ^b
 110a	 109b	76% ^b
 111a	 111b	74%
 112a	 112b	72%
 113a	 113b	55% ^{b,c}
 114a	 114b	81%
 115a	 115b	93%

(a) reactions were run with 5 mol% of Py•Br₃ and 0.15 mmol of substrate in 2 mL of MeOH at 0 °C until complete by TLC analysis. (b) 10 mol% of Py•Br₃ was employed. (c) reaction run at rt.

Table 4.3. Py•Br₃ Catalyzed Deprotection of the TBS Group Resident in Complex Organic Synthons.^a

Silyl Ether	Product, Yield
 <p>116a</p>	 <p>116b: 70%</p>
 <p>117a</p>	 <p>117b: 65%</p>
 <p>118a</p>	 <p>118b: 77%</p>
 <p>119a</p>	 <p>119b: 41%</p>
	 <p>119c: 49%</p>
 <p>120a</p>	 <p>120b: 89%</p>

(a) reactions were run with 5 mol% of Py•Br₃ and 0.15 mmol of substrate in 2 mL of MeOH at 0 °C until complete by TLC analysis.

As the final component of our investigation, we chose to examine the efficiency of $\text{Py}\cdot\text{Br}_3$ in MeOH for the chemoselective removal of TBS ethers in the presence of other function groups resident in fairly complex organic synthons and/or natural product intermediates as delineated Table 4.3. Thus, treatment of the primary TBS ether β -hydroxy lactone **116a** with 5 mol % of $\text{Py}\cdot\text{Br}_3$ in MeOH at 0 °C swiftly removed the TBS protecting group while not disturbing either the lactone or the β -methoxy moiety and provided the desired free primary alcohol **116b** in 70 % yield. We were initially concerned that the reaction conditions might promote β -elimination of the methoxide anion to provide the corresponding α,β -unsaturated lactenone. However, we were quite pleased that only TBS ether cleavage was observed. Similar to **116a**, $\text{Py}\cdot\text{Br}_3$ mediated chemoselective TBS cleavage of the protected β -C-glycoside compound **117a** readily proceeded to afford the free hydroxyl group of **117b** with a modest yield of 65%. We also examined the selective removal of a secondary TBS ether in the presence of an acetonide protecting. Unfortunately, treatment of **118a**⁴⁸ with $\text{Py}\cdot\text{Br}_3$ in MeOH at 0 °C led to concomitant removal of both the acetonide and silyl ether after 24 h to provide the triol **118b** with a 77% yield. Similar to lactone **116a**, the TBS protected α,β -unsaturated lactenone **117a** was subjected to standard reaction conditions and furnished two products **117b** and **117c** in a combined yield of 90%. The predicted desilylated lactenone **117b** was produced in 41% yield, whereas the bicyclic pyran-lactone **119c** was formed in 49 % yield via an intramolecular cyclization of the free hydroxyl moiety onto the Michael acceptor.^{49,50} Not surprisingly, longer reaction times led selectively to the bicyclic lactone **119c** (via **119b**) in nearly quantitative yields. Thus, $\text{Py}\cdot\text{Br}_3$ in MeOH can catalyze TBS group removal and also facilitate intramolecular Michael additions as well. Lastly, the *bis*-TBS-protected β -hydroxy carbonyl **120a**, derived from an Evans' oxazolidinone aldol reaction,⁵¹ readily underwent primary silyl group cleavage to

afford the free hydroxy compound **120b** in an 89% yield without forming any appreciable amount of the cyclized lactone product. Interestingly, the reaction of **120a** with TBATB not only chemoselectively removed the TBS moiety, but also promoted cyclization to afford the corresponding lactone in approximately 50% yield.

4.4 Conclusions

In conclusion, we have shown that $\text{Py}\cdot\text{Br}_3$ in MeOH chemoselectively deprotects primary TBS (and TES) ethers in the presence of a variety of other protecting and common functional groups in modest to excellent yields when performed at 0 °C and 5 mol% catalyst loading.⁹⁰ Chemoselective deprotection of primary TBS groups in the presence of secondary TBS groups can also be achieved further extending the utility of this methodology. Pyridinium tribromide is a relatively inexpensive commercially available reagent that is used in catalytic quantities in the presented protocol, further minimizing the cost and utility of this transformation. During our investigations it was found that that $\text{Py}\cdot\text{Br}_3$ in MeOH can catalyze TBS group removal as well as facilitating intramolecular Michael additions leading to interesting bicyclic pyran-lactone structures. The substrates tested in this study were relatively advanced organic building blocks with various functionalities present. Based on the various substrates investigated, the described mild and straightforward protocol should be quite useful in the stereoselective synthesis of natural product subunits and/or the production of valuable organic synthons.

CHAPTER 5: FORMAL SYNTHESIS OF (-)-NEOPELTOLIDE FEATURING A HIGHLY STEREOSELECTIVE OXOCARBENIUM FORMATION/REDUCTION SEQUENCE

5.1 Isolation, Characterization, and Initial Biological Studies

Sea-dwelling organisms that lead a sedentary lifestyle have evolved the ability to biosynthesize highly toxic compounds as a chemical defense system against natural predators. These types of organisms produce some of the most toxic substances known to human beings such as the secondary metabolite brevetoxin, produced by the marine algae *Karenia brevis*, which is responsible for the “red tide” phenomena associated with massive coastal sea life poisonings off the coast of Florida, USA. Ironically, marine derived secondary metabolites have also rendered a myriad of molecular architectures that have proven an invaluable source of therapeutically promising leads, as well as valuable molecular probes for investigations of uncharted biochemical pathways. One such compound is (+)-neopeltolide which was first found in 1993 from a deep-water sponge belonging to the family Neopeltidae, collected off the northwest coast of Jamaica and subsequently disclosed in 2007 by Wright as shown in Figure 1.⁵² The sponge was not identified, but it most closely matches the taxonomic description for the genus *Daedalopelta Sollas*, and is described as a close relative of *Callipelta* which is a rich source of biologically active marine compounds. Although (+)-neopeltolide was isolated from a sponge, the authors do not rule out the possibility that neopeltolide could have been produced by epibiotic heterotrophic cyanobacteria living in association with the sponge from which it was isolated. Wright’s team of scientists from Harbor Branch Oceanographic Institution in Fort

Pierce, Florida, collected two samples of *Daedalopelta Sollas* sponge using the Johnson-Sea Link human occupied submersible at depths of 442 and 433 meters. A 105 gram sample of frozen sponge was extracted exhaustively with ethanol and yielded approximately 4 milligrams of (+)-neopeltolide, thus indicating an urgent need for an efficient synthetic approach towards its laboratory synthesis.

Neopeltolide is an extremely potent inhibitor of in vitro proliferation of A-549 human lung adenocarcinoma, NCI/ADR-RES ovarian sarcoma, and P388 murine leukemia cell line with IC_{50} values in the nanomolar range (1.2, 5.1, and 0.56 nM, respectively). This polyketide natural product also demonstrates inhibitory effects in PANC-1 pancreatic and DLD-1 colorectal cell lines as well as potent inhibition (MIC = 0.625 $\mu\text{g}/\text{mL}$) of the fungal pathogen *Candida albicans*, which can greatly threaten the health of advanced AIDS patients.⁵³ Noteworthy is the fact that only 50% cell death was observed over an extended dose range, suggesting a cytostatic rather than cytotoxic effect for these two cell lines. Initially, investigations into the mechanism of action of neopeltolide suggested that it does not act via interaction with tubulin or actin. Additionally, Kozmin's experiments suggested that both, neopeltolide and leucascandrolide A (Figure 5.1) target cytochrome *bc1*, resulting in the inhibition of mitochondrial ATP synthesis.⁵⁴

The structural features of neopeltolide include a β -C-glycoside subunit embedded within the 14-membered macrolactone ring which is adorned with six stereogenic centers. The oxazol- and carbamate-containing side chain, attached through an ester linkage, is identical to the one found in the 18-membered macrolide leucascandrolide A, a structurally homologous marine natural product which displays a similar biological profile (Figure 5.1). The initial relative configuration was assigned on the basis of one- (1D) and two-dimensional (2D) ^1H NMR techniques, including TOCSY, COSY, NOESY, and a series of double-pulsed field gradient spin

echo NOE experiments. However, the lack of available material precluded the assignment of the absolute stereochemistry.⁵² Professor Panek's group at Boston University was the first to complete a laboratory synthesis of (+)-neopeltolide, as well as providing a reassignment of the originally proposed structure.^{55a} This work was later verified with a second total synthesis of (+)-neopeltolide, this time from Professor Scheidt's laboratory at Northwestern University, whose independent studies led them the exact structural reassignment.^{55b} To date, seven total syntheses of (+)-neopeltolide, five formal syntheses, as well as numerous biological studies have been reported in the literature, giving rise to innovative synthetic approaches and ample quantities for further biological assays of this promising anti-proliferative marine macrolide polyketide.⁵⁴⁻⁵⁷

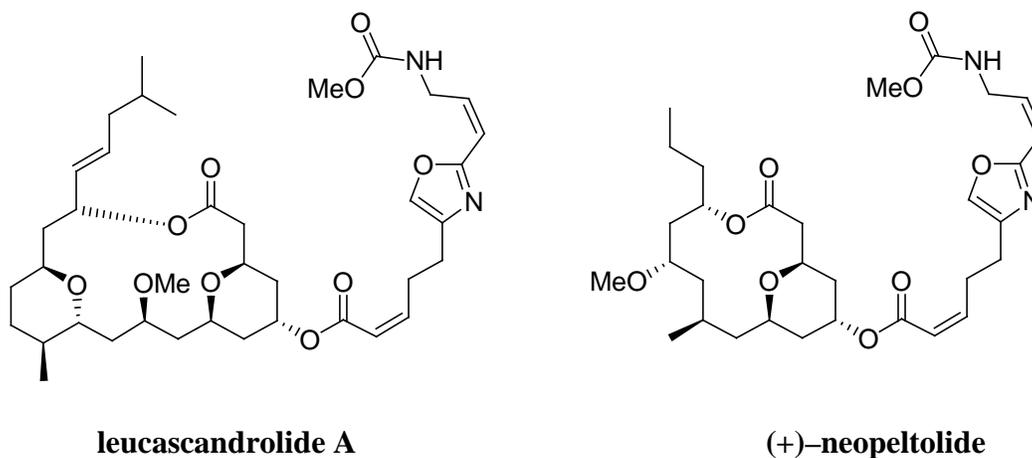
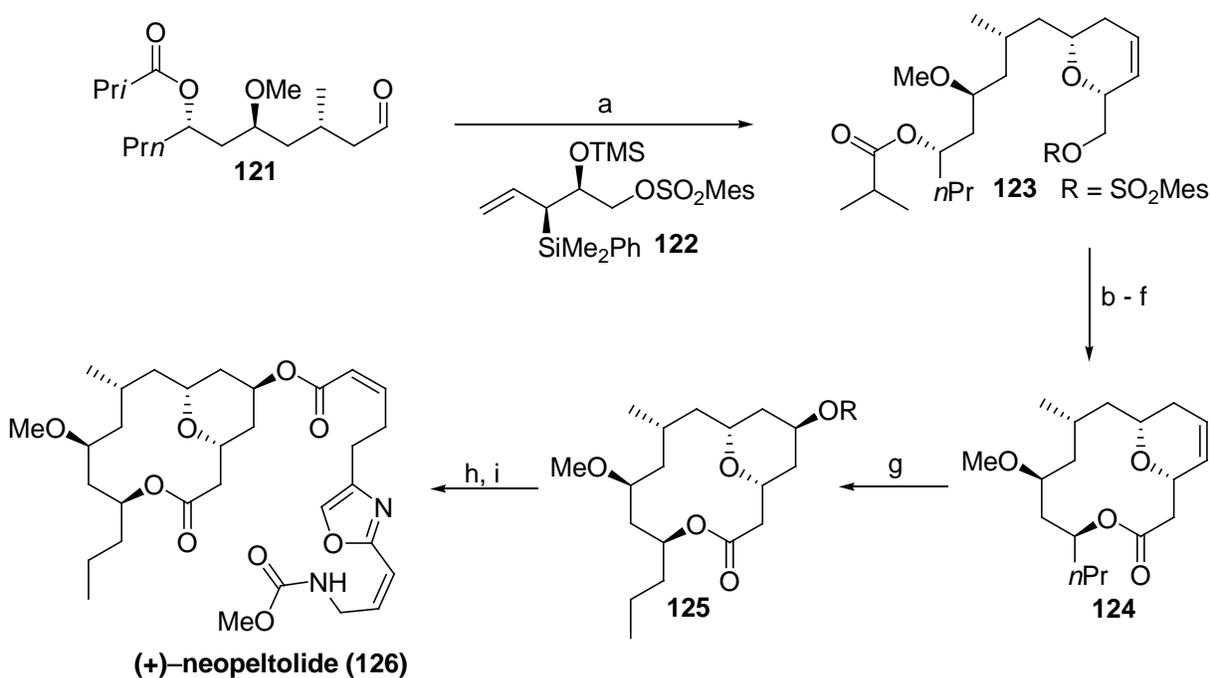


Figure 5.1. Structurally Homologous Anti-Proliferative Sponge Metabolites

5.2 Previous Syntheses of (+)-Neopeltolide

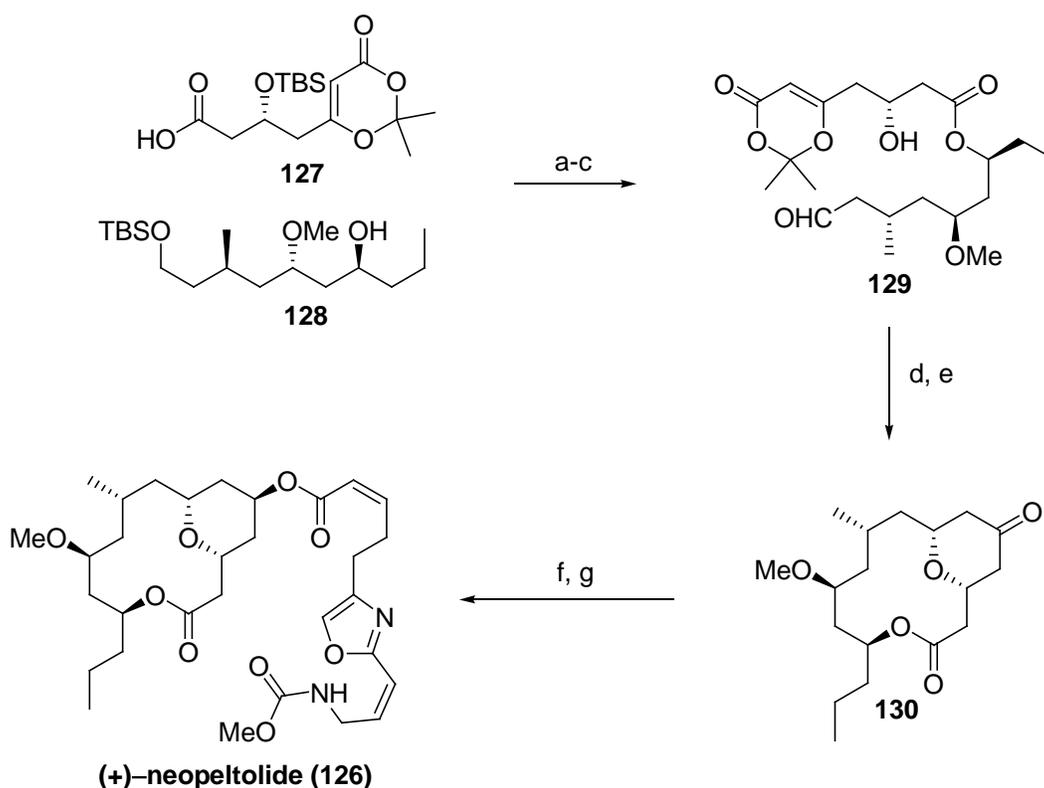
Due to its unique structure, exceptional potency, and line-selective anti-cancer activity, (+)-neopeltolide **126** has been the subject of numerous synthetic studies.⁵⁴⁻⁵⁷ Panek was the first to disclose the total synthesis of (+)-neopeltolide **126** exploiting an elegant [4+2]-allylsilane

annulation as the key step to forge the advanced pyran intermediate **123**, presumably through an oxocarbenium intermediate.^{55a} Macrocyclic ring closure was accomplished via a standard Yamaguchi protocol to give macrolactone **124**. The oxazole containing side-chain was introduced via a two-step procedure involving a Still-Genari olefination, as depicted in Scheme 5.1. In this manner, Panek's longest linear sequence required 19 steps with an overall yield of 1.3%. Panek's work led to the reassignment of stereochemical and absolute configurations, once again highlighting the importance of total synthesis in structural assignment/verification of natural product metabolites.



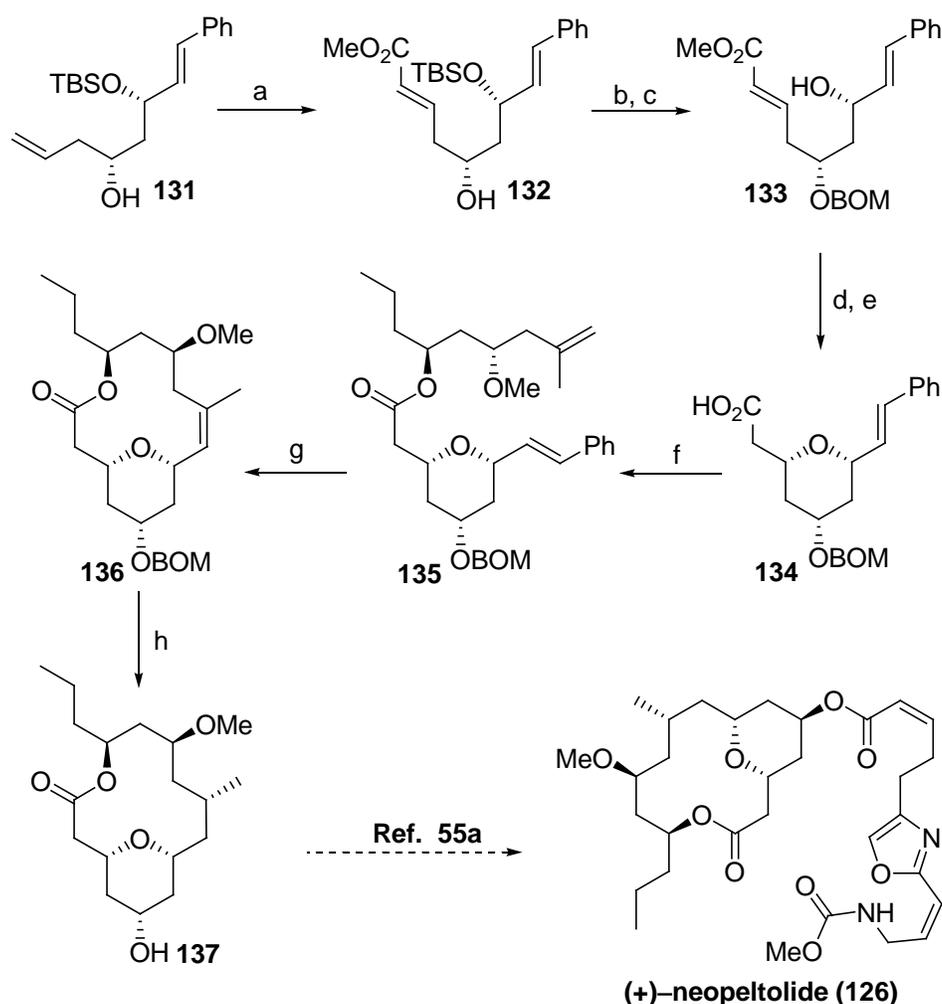
Scheme 5.1. First Total Synthesis of (+)-Neopeltolide (**126**) by Panek:^{55a} a) TfOH, CH₂Cl₂/benzene (3:1), -78 °C, 75% (d.r. 10:1); b) NaCN, DMF, 60 °C, 84%; c) DIBAL-H, diethyl ether, -78 °C, 96%; d) DIBAL-H, CH₂Cl₂, -78 °C, 60%; e) NaClO₂, 2-methyl-2-butene, NaH₂PO₄·H₂O, tBuOH, H₂O, 85%; f) 2,4,6-trichlorobenzoyl chloride, toluene, DMAP, NEt₃, 44%; g) Hg(O₂CCF₃)₂ then NaBH₄, THF:H₂O (1:1), 63% (d.r. >20:1); h) (CF₃CH₂O)₂P(O)CH₂CO₂H, EDCI·HCl, HOBT·H₂O, CH₂Cl₂, 99%; i) [18]crown-6, KHMDS, -78 °C, then oxazole containing side-chain, -85 °C, 62%.

A subsequent report by Scheidt confirmed the stereochemical re-assignments made by Panek and utilized an innovative Lewis acid-catalyzed cyclization to generate the *cis*-tetrahydropyran ring and the macrocycle concomitantly, through a Prins-like reaction of an *in situ* generated oxonium ion, starting from advanced dioxinone intermediate **129**.^{55b} The Northwestern University group's research efforts have led to a unique macrocyclization strategy that builds up complexity in an unprecedented fashion, generating a stereogenic center, the THP ring, and the macrocycle **130** in a single synthetic operation, shown in Scheme 5.2.



Scheme 5.2. Scheidt's Total Synthesis of (+)-Neopeltolide (**126**):^{55b} a) 2,4,6-trichlorobenzoyl chloride, toluene, DMAP, NEt₃; b) HF·pyridine, THF; c) TEMPO, H₅C₆I(OAc)₂, CH₂Cl₂, 76% yield over 3 steps; d) Sc(OTf)₃, CaSO₄, MeCN; e) DMSO, H₂O, 130 °C, 21% yield over 2 steps; f) NaBH₄, MeOH, 0 °C; g) DIAD, Ph₃P, oxazole containing side-chain, benzene, 76% yield over 2 steps.

Most recently, Fuwa reported a very efficient second-generation synthesis (12 steps in 14% yield to the macrocycle) of (+)-neopeltolide **126** featuring a chemo- and diastereoselective cross-metathesis reaction to give **132**, followed by an oxy-Michael addition to forge the β -C-glycoside subunit **134**.^{55g} Fuwa's second-generation synthesis of this important macrolide is the shortest strategy of the macrolactone core reported to date and takes advantage of both cross- and ring-closing metatheses reactions as key bond-forming events, as depicted in Scheme 5.3.



Scheme 5.3. Fuwa's Ten-Step Synthesis of the Neopeltolide Macrolactone (**137**):^{55g} a) Grubbs catalyst II, methyl acrylate, CH₂Cl₂, 82%; b) BOMCl, iPr₂EtN, TBAI, DME; c) TBAF, AcOH, THF, 90% yield over 2 steps. d) DBU, toluene, d.r. >20:1, 73%; e) TMSOK, Et₂O, 99%; f) 2,4,6-trichlorobenzoylchloride, Et₃N, THF; then secondary alcohol, DMAP, toluene, 94%; g) Grubbs catalyst II, 1,4-benzoquinone, toluene, 85%; h) H₂, Pd/C, Pd(OH)₂/C, EtOH, 93%.

In addition to their total synthesis, the Scheidt group has also helped shed light on the structure activity relationships (SAR) of (+)-neopeltolide.^{57b} Their studies determined that both the ester side chain and the macrolide core bound together are needed for biological activity, since neither are active independently. Furthermore, the group found that stereochemistry on the macrolide is crucial for potency as the originally proposed structure for (+)-neopeltolide is 84 to 100-fold less potent than the natural product. Maier's SAR studies have found that shortening the distance between the lactone and the oxazole side-chain greatly reduces the biological activity.^{57c} Further SAR studies of this promising compound should give clues as to the mode of action and what key pharmacophore(s) are crucial for its impressive biological activity.

Having successfully completed two natural products of modest structural and stereochemical complexity, the familiar feeling of excitement took over me when Dr. Jennings approached me with the structure of neopeltolide. As a second-year graduate student, I was extremely anxious to get my "hands wet" attempting the construction of a novel, highly cytotoxic marine macrolide. Notwithstanding its impressive biological profile, our attraction to neopeltolide stemmed from the β -C-glycoside moiety embedded within the macrolactone core. We have successfully demonstrated in a variety of previous synthetic ventures, the efficient formation of these building blocks capitalizing on a stereoselective oxocarbenium cation formation/reduction protocol starting from δ -lactones.¹⁵ We were hopeful that this synthetic approach would deliver the targeted β -C-glycoside, which in principle, could be transformed to the neopeltolide core. To the best of our knowledge, no biological testing of unnatural (-)-neopeltolide (**4**) has been performed and based on our previous experience with (-)-dactylolide,⁵⁸ we thought it might be prudent to synthesize the antipode of the natural product core in order to potentially advance SAR studies of this promising compound. Along this line, recall that the

unnatural (-)-dactylolide is roughly two to three fold more active against the SK-OV-3 line than that of (+)-dactylolide. Also, (-)-dactylolide exhibited GI₅₀ values in the nanomolar (25-99 ng/mL) range against the four cell lines HL-60, K-562, HCC-2998, and SF-539, while displaying modest LC₅₀ values. Our previous results with (-)-dactylolide illustrate the need for synthetic natural product molecules (or in this case the antipode) for the undertaking of more comprehensive *in vitro* biological screening. The following work describes the formal synthesis of **4** utilizing a highly diastereoselective reduction of an *in situ* generated oxocarbenium intermediate that generates the final stereogenic center, as well as establishing the β-C-glycoside core of the natural product.

5.3 Retrosynthetic Analysis of (-)-Neopeltolide (**4**)

Our retrosynthetic analysis of **4** followed Panek's initial disconnection of the oxazole containing side chain in that it could be introduced via a two-step procedure involving a Still-Genari olefination as delineated in Figure 5.2.^{55a} As our key step, we envisaged the β-C-glycoside **139** would emerge from a stereoselective reduction of an endocyclic oxocarbenium cation mediated by the treatment of an appropriate hemi-ketal with a Lewis acid. This hemi-ketal could be derived from a nucleophilic addition of the allyl Grignard reagent to the MOM protected δ-lactone **140**. Working backward, lactone **140** would be derived from acetal **141** and access to **141** was envisioned to arise from the precursor homoallylic alcohol **142** and methyl acrylate via a cross-metathesis reaction employing second-generation Grubbs catalyst **57**. Alcohol **142** would evolve from an asymmetric allylation of the corresponding aldehyde which would be provided by means of partial reduction of the Weinreb amide **143**. Along this line, amide **143** would potentially be furnished via ring-opening of lactone **144** which could be synthesized via a variety of synthetic strategies by way of the previously prepared benzyl

protected β -hydroxy aldehyde **145**. Aldehyde **145** was to be accessed via an asymmetric allylboration of commercially available butyraldehyde, followed by benzyl protection of the resulting secondary alcohol, and finally oxidative cleavage of the terminal alkene.

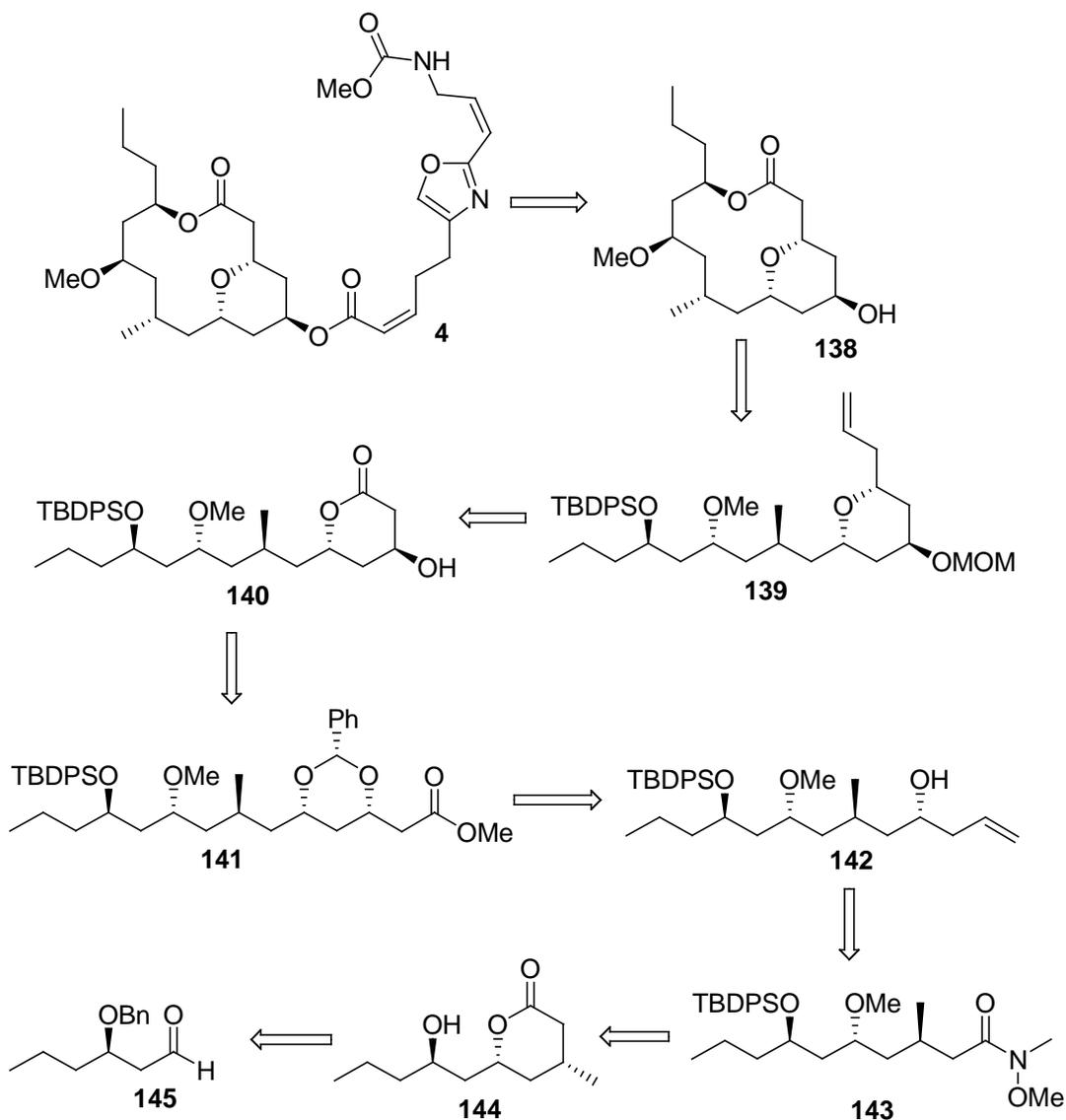
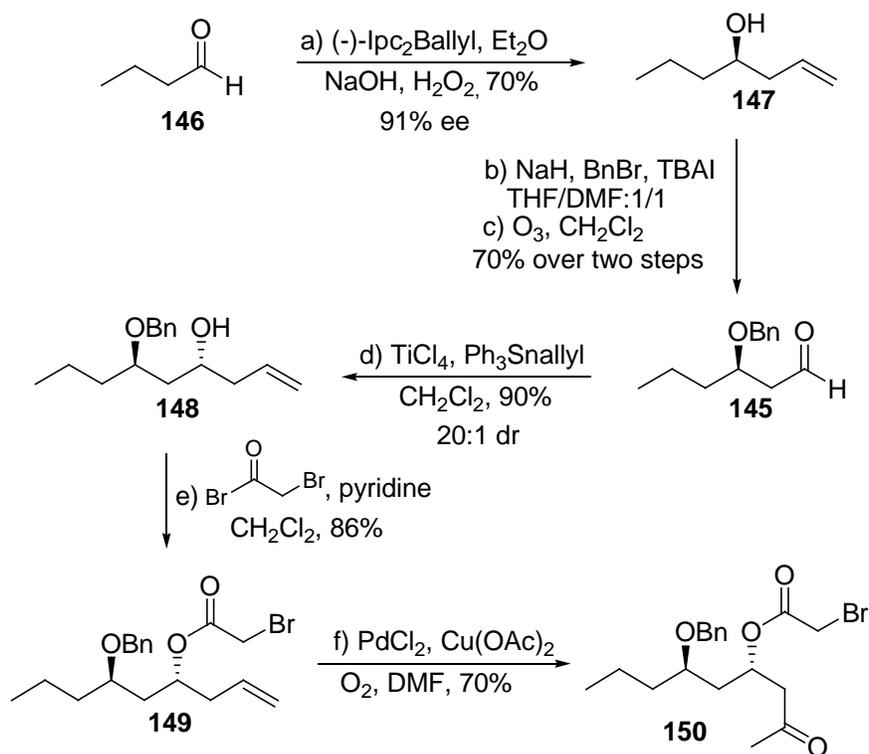


Figure 5.2. Retrosynthetic Analysis of (-)-Neopeltolide (**4**)

5.4 Initial Wacker Oxidation/Intramolecular Reformatsky Sequence

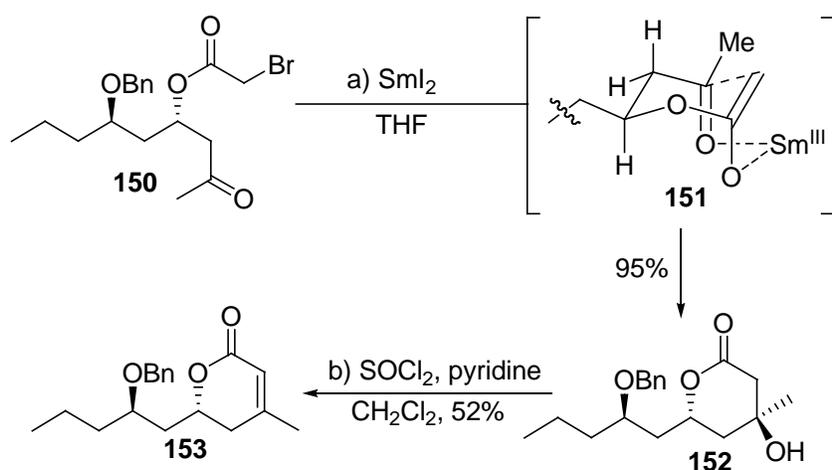
Initially, our synthetic strategy enlisted a Wacker oxidation/intramolecular Molander-Reformatsky sequence en route to the construction of the required hydroxy lactone **144**, as

shown in Scheme 5.4.⁵⁹ Thus, the synthesis commenced with an asymmetric allylation-oxidation of **146** utilizing Brown's (-)-Ipc₂Ballyl reagent to provide the homoallylic alcohol **147** in 70% yield and 91% ee.²¹ Ensuing benzyl protection under basic conditions (NaH, BnBr, and TBAI) of **147**, utilizing TBAI to initiate an *in situ* Finkelstein reaction thus generating the more reactive benzyl iodide, followed by ozonolysis of the corresponding alkene moiety delivered the previously reported aldehyde **145** with a 70% yield over two steps from **11**.^{55e} This benzyl protecting group was crucial for the generation of the next stereogenic center. As first reported by Keck,⁶⁰ chelation-controlled TiCl₄ mediated allylation of **145** was carried out at -78 °C, and a 20:1 d.r. resulted in favor of the desired benzyl protected 1,3-*anti* diol **148** in 90% yield.



Scheme 5.4. Synthesis of the Reformatsky Precursor Ketone (**150**)

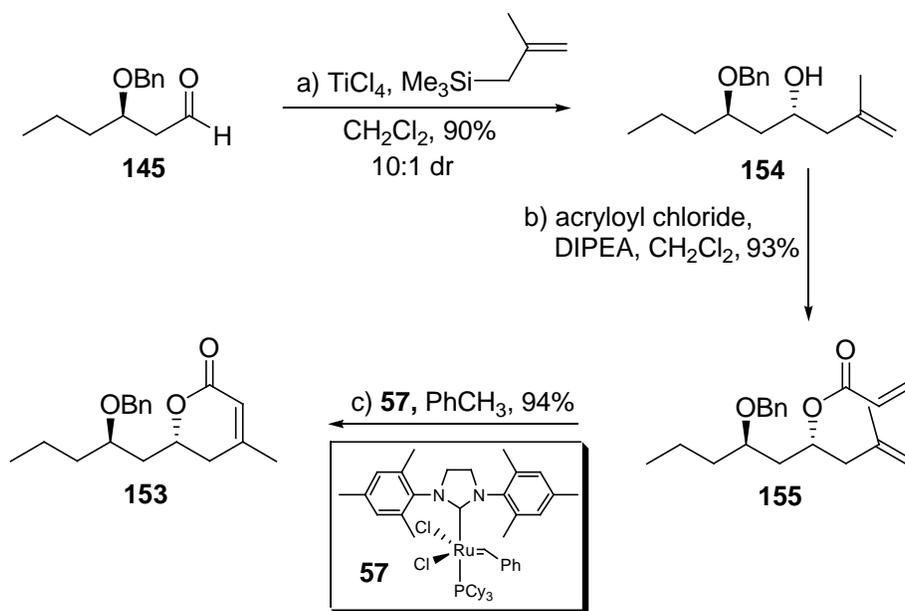
Subsequent treatment of **148** with 2-bromoacetyl bromide and pyridine provided the corresponding ester **149** in 86% yield in anticipation for the intramolecular Molander-Reformatsky reaction. Much to our delight, an ensuing Wacker oxidation of **149** under the standard aerobic O_2 - Pd^{II} - Cu^{II} catalysis protocol in DMF:H₂O (7:1) afforded the desired ketone **150** in 70% yield and set the stage for the intramolecular SmI_2 mediated cyclization. As first described by Molander,⁶¹ treatment of bromo ester **150** with SmI_2 in THF at -78 °C formed a $Sm(III)$ enolate which subsequently underwent an intramolecular aldol reaction with the pendant ketone via the highly ordered double six-membered transition state, depicted as **151** in Scheme 5.5, to provide the β -hydroxy lactone **152** in 95% yield and excellent diastereoselectivity at the newly generated stereocenter (>20:1 by ¹H NMR). In order to arrive at the desired α,β -unsaturated lactone **153**, an elimination of the newly generated stereocenter was then performed. Thus, treatment of **152** with thionyl chloride and pyridine furnished **153** in a 52% yield. Although this synthetic sequence was viable, our necessity for gram quantities of **153** forced us to pursue an alternative and more efficient strategy.



Scheme 5.5. SmI_2 Mediated Molander-Reformatsky Reaction of (**150**)

5.5 Revised Strategy Towards the Construction of Lactenone (153)

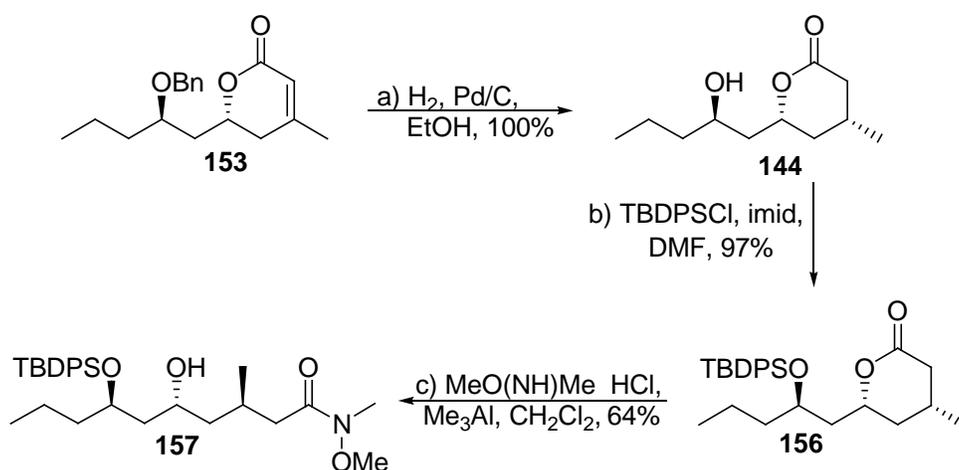
With our reformulated synthetic blueprint as described in Scheme 5.6, previously synthesized aldehyde **145** was subjected to TiCl_4 mediated methallylation and provided the homoallylic alcohol **154** (10:1 d.r. by ^1H NMR) in 90 % yield.^{55e} Ensuing treatment of **154** with acryloyl chloride and Hunig's base furnished acrylate ester **155** which was sequentially treated with Grubbs' second generation catalyst **57** to afford the requisite α,β -unsaturated lactenone **153** in 94% yield via a ring-closing metathesis reaction.⁶² This sequence of reactions proved highly reliable and amenable to scale-up without the slightest deterioration in yield.



Scheme 5.6. RCM Approach Towards the Synthesis of Lactenone Intermediate (**153**)

As skillfully described by Roulland^{55f} on a very similar substrate, diastereoselective reduction of the resulting alkene in **153** with concomitant removal of the benzyl protecting group was accomplished by means of a Pd/C catalyzed hydrogenation and delivered lactone **144** in

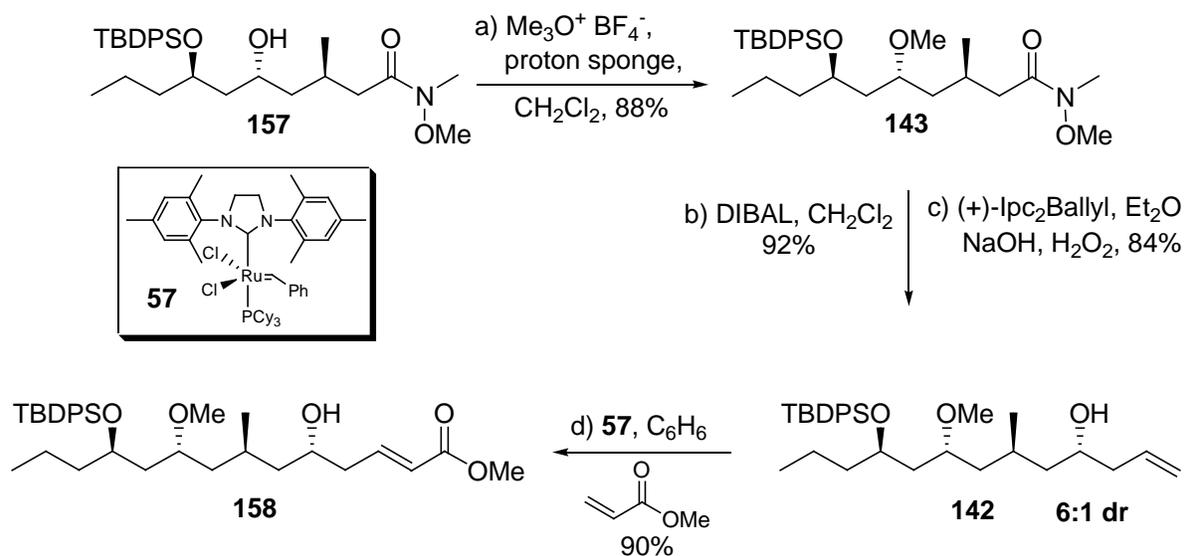
quantitative yield as a single diastereomer, as described in Scheme 5.7. The secondary hydroxyl moiety of **144** was re-protected as a TBDPS ether with imidazole and a catalytic amount of DMAP to afford **156** in 97% yield. Subsequently, lactone **156** was subjected to transamidation conditions (MeO(NH)Me•HCl and Me₃Al)⁶³ and provided the unstable Weinreb amide **157**, which tended to re-lactonize back to **156** during purification.



Scheme 5.7. Weinreb Transamidation of Lactone Intermediate (**153**)

Therefore, the resulting free hydroxyl group of amide **157** was immediately treated with Meerwein's salt (Me₃O⁺ BF₄⁻), 1,8-Bis(dimethylamino)naphthalene (proton sponge), and 4Å molecular sieves to provide methoxy ether **143** in 55% yield over three steps from **144** (Figure 5.8).^{55f} An ensuing partial DIBAL reduction of **143** furnished an aldehyde intermediate in 92% yield and set the stage for chain elongation en route to macrocycle **138**. As shown in Scheme 5.8, a mismatched Brown allylation of the prepared aldehyde afforded the homoallylic alcohol **142** with a 6:1 d.r. at the newly generated stereocenter in 84% yield.²¹ An ensuing highly

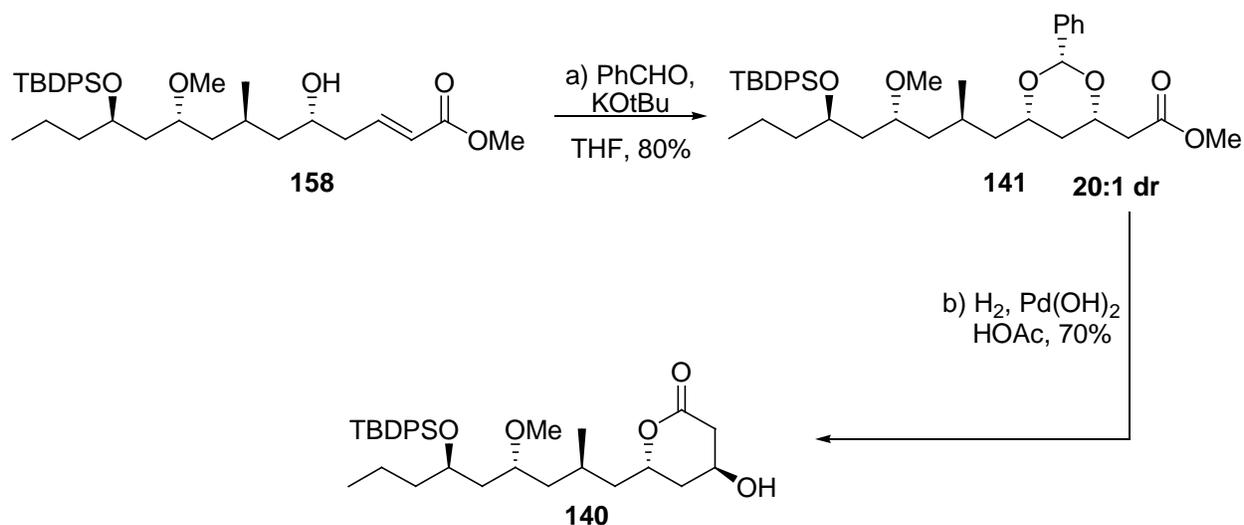
diastereoselective cross-metathesis of the resulting alkene moiety resident in **142** with methyl acrylate and catalyzed by Grubbs' catalyst **57**, as described by Professor O'Doherty, provided the (*E*)- α,β -unsaturated ester **158** in 90% yield.⁶⁴



Scheme 5.8. A Mismatched Brown Allylation & (*E*)-Selective Cross-Metathesis

Following the Evans' protocol for the diastereoselective synthesis of 1,3-*syn* diols, ester **158** was treated with benzaldehyde and catalytic amounts of *Kt*OBu in THF at 0 °C and provided **141** in 80% yield with an excellent level of diastereoselectivity (>20:1) for the *syn*-benzylidene acetal, as depicted in Scheme 5.9.⁶⁵ We surmised that upon reductive deprotection of the benzylidene acetal moiety resident in **141**, coupled with acidic reaction conditions, the ensuing substrate should readily cyclize to the desired β -hydroxy lactone **140**. Upon dissolution of **141** in AcOH and in the presence of Pearlman's catalyst [$\text{Pd}(\text{OH})_2$] under an atmosphere of H₂, deprotection occurred, but cyclization of the resultant diol to lactone **140** was slow. Once the

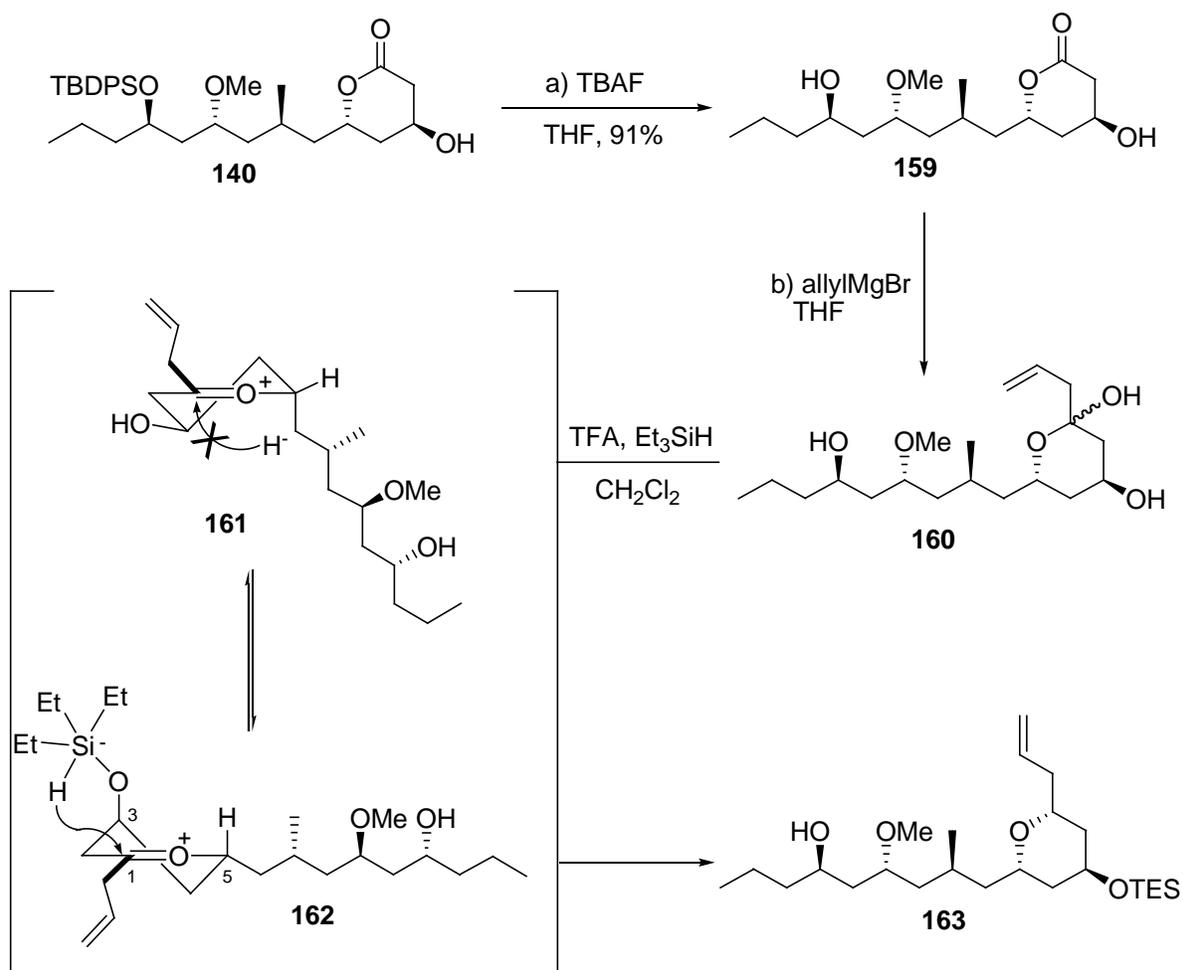
crude material was filtered to remove the catalyst and the filtrate refluxed (70 °C) in AcOH and H₂O (4:1), lactone **140** was isolated in 70% yield from acetal **141**.



Scheme 5.9. Synthesis of Key δ -Lactone Intermediate (**140**)

Desilylation of the secondary TBDPS ether was accomplished with TBAF in THF at room temperature to afford diol **159** in 91 % yield. During Dr. Jesse D. Carrick's, synthesis of the complex macrolide dimer, (–)-clavosolide, the key oxocarbenium formation/reduction step proceeded uneventfully in the presence of a free secondary alcohol on the *ansa* chain of the monomeric lactone.^{15g} In addition to the clavosolide example and concerns of a potential β -elimination to give a lactenone by-product, as observed during the synthesis of (–)-dactylolide, we initially were steered away from protecting the secondary alcohol on the lactone ring.⁵⁸ It was also deemed necessary to initially orthogonally protect the secondary alcohol located on the lactone ring of **159** due to the need of selective access to the hydroxyl group resident in the *ansa* chain for final macrocyclization. Based upon our previous observations of concomitant silylation of a “directing” free hydroxyl moiety during the oxocarbenium reduction via a

presumed siliconate (i.e. intermediate **162**), we decided to attempt our key step on the unprotected lactone **159** (Scheme 5.10). We surmised selective protection of the secondary alcohol resident on the initial lactone ring as a TES ether. Thus, when excess (6-10 equivalents) allylmagnesium bromide was added to a stirring solution of lactone **159** at $-78\text{ }^{\circ}\text{C}$ in THF, lactol **160** was presumably formed by the partial consumption of lactone **159** as indicated by TLC analysis. Attempts to fully consume **159** by differing the amount of added Grignard reagent and altering the reaction temperature, unfortunately did not lead to greater production of **160**.

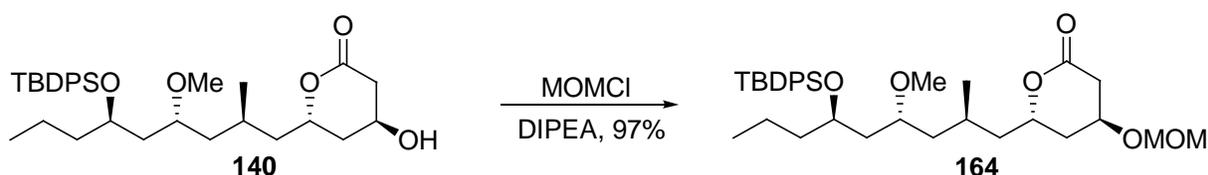


Scheme 5.10. Synthesis of β -C-Glycoside (**163**) via a Siliconate Directed Reduction

Consequently, the *in situ* formation/reduction of the oxocarbenium cation by addition of TFA and Et₃SiH to **160** provided the TES-protected β-C-glycoside **163** in very low yields (~15-22%) via the presumed ground-state siliconate conformer **162** where the C₅ alkyl side-chain is in the pseudoequatorial position, as seen in Scheme 5.10.

5.6 Second Attempt at a Highly Diastereoselective Oxocarbenium Formation/Reduction

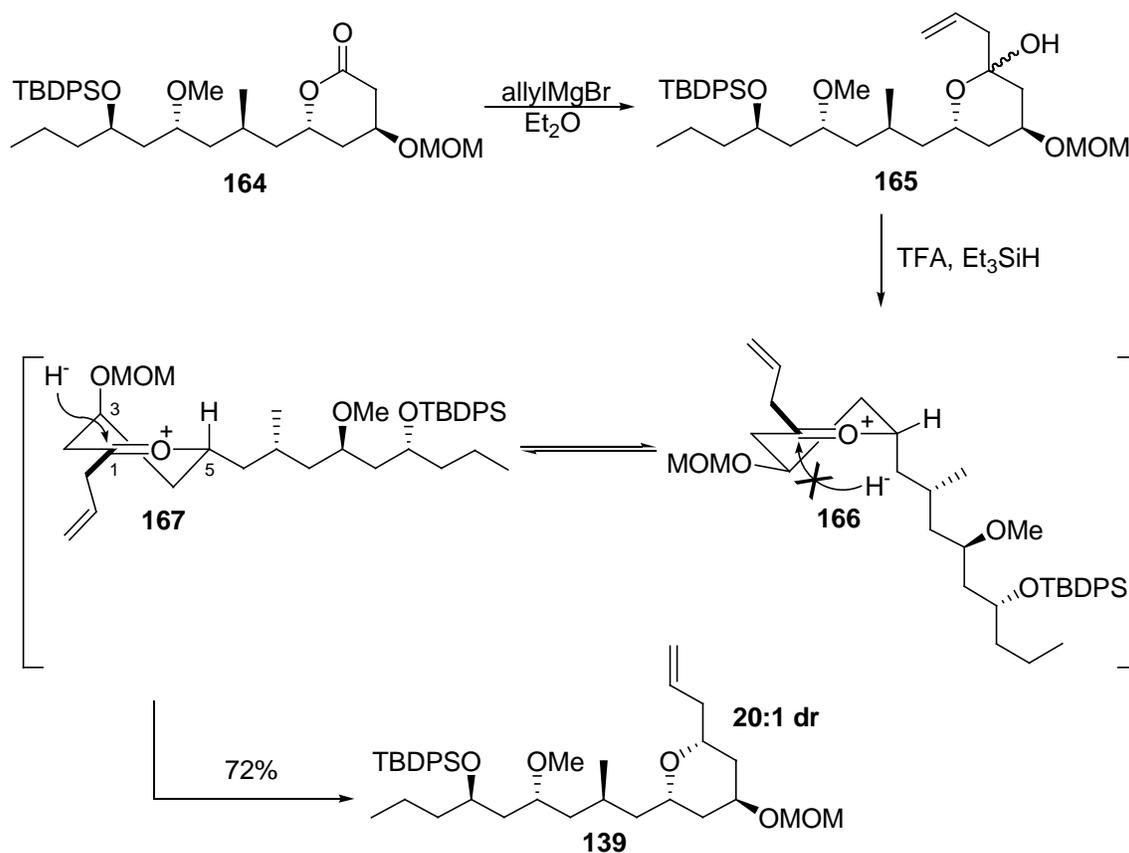
Having constructed the β-C-glycoside subunit **163** in unsatisfactory yields, it was essential to initially orthogonally protect the secondary alcohol located on the lactone ring of **140**. Thus, MOM protection of the free hydroxyl group of **140** using Hunig's base in CH₂Cl₂ furnished the highly desired δ-lactone **164** in near quantitative yield, as depicted in Scheme 5.11.



Scheme 5.11. Requisite MOM Protection of δ-Lactone (**140**)

With the secondary hydroxyl group protected as a MOM ether, the stage was once again set for the oxocarbenium formation-reduction sequence as shown in Scheme 5.12. Upon treatment of **164** with 3 equivalents of allylmagnesium bromide at -78 °C, the resultant lactol **165** was formed as determined by the consumption of **164** by TLC analysis and with the subsequent addition of TFA, **165** presumably was transformed to the corresponding oxocarbenium cation (**166** and **167**) which was consequently reduced stereoselectively (via reactive conformer **167**) with Et₃SiH to deliver the β-C-glycoside subunit **139** in 72% yield and excellent d.r. (> 20:1) in

less than 30 minutes. This result is very similar to Dr. Amanda J. Muller Hendrix's observations during her synthesis of aspergillide B, where the C₄ hydroxyl moiety was placed in the axial position and the C₅ substituent in the pseudoequatorial geometry and the allylation took only 30 min for completion.⁷⁹ The relatively short reaction times can be explained by considering the Woerpel effect.⁸



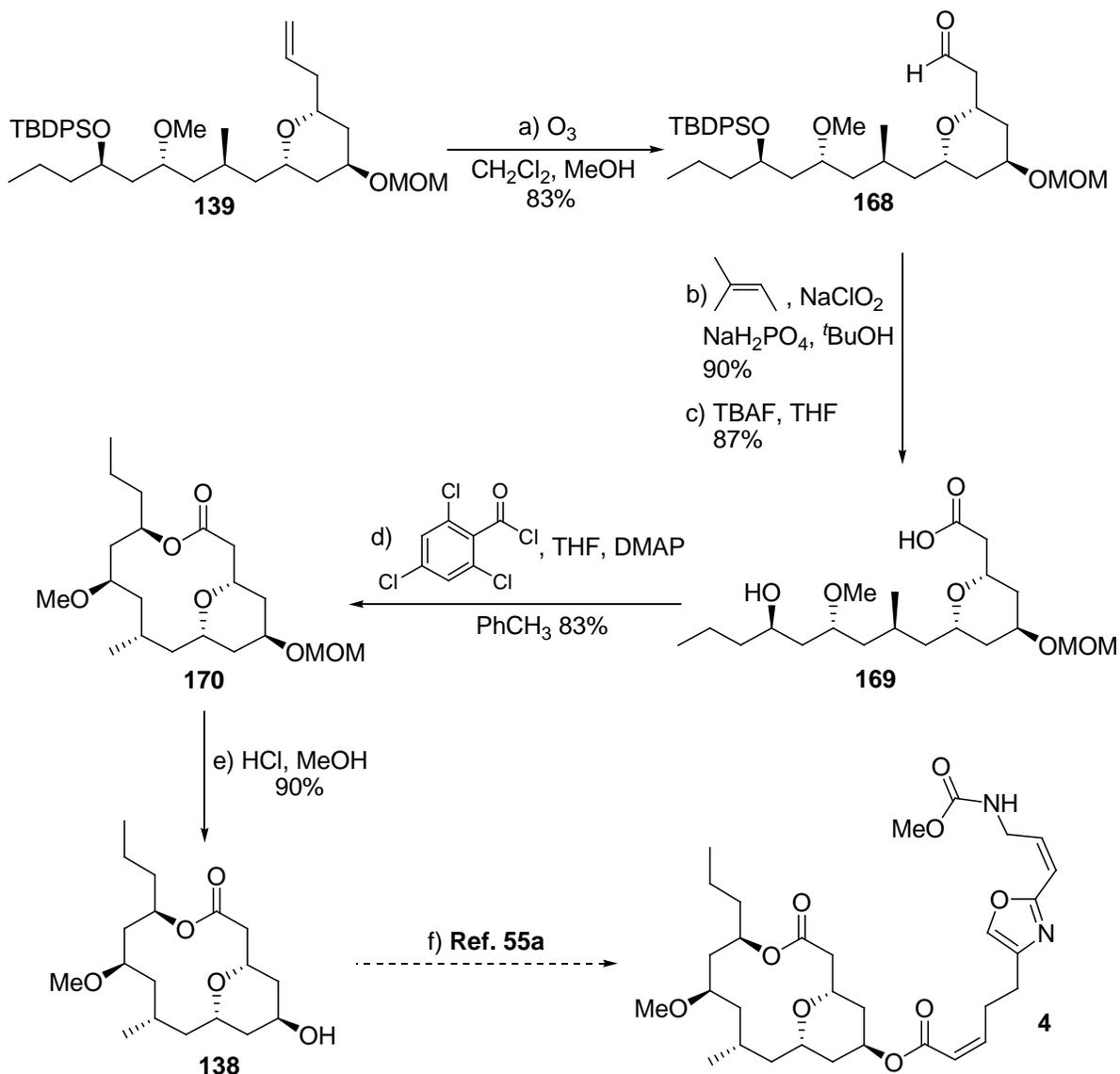
Scheme 5.12. Highly Stereoselective Oxocarbenium Formation/Reduction Sequence

Consistent with our previous observations and based on Woerpel's models, the observed product was assumed to arise from the more reactive conformer (i.e. **167**) that places the alkyl side chain at C₅ in the pseudo-equatorial position and the MOM-protected hydroxyl moiety at C₃

in the axial position.^{8,15} This reactive conformer allows for the stereoselective axial approach of the nucleophilic hydride via a chair-like transition state. Also, the Woerpel effect comes into play with the MOM-protected hydroxyl moiety at C₃ in the axial position, where it can stabilize the cationic carbon of the oxonium ion efficiently in a through-space electrostatic interaction.^{8,9} Based on Woerpel's precedent and our observations on these types of oxocarbenium reductions, these systems tend to represent a "matched" geometry leading to the extremely short reaction times. While heteroatoms positioned in an axial orientation at C₃ and C₄ do indeed stabilize the transition state leading to extremely short reaction times, studies from the Jennings laboratory suggest that it is the alkyl group at C₅ oriented in a pseudoequatorial fashion that dictates the stereochemical outcome of these types of reactions. This point will be readdressed in the following chapter during our synthetic studies of pochonin J, where the both the C₄ and C₅ substituents are placed in a pseudoequatorial orientation, but nonetheless allowed for a highly stereoselective allylation albeit requiring six hours for completion. With **139** in hand, attention was directed to the completion of the formal synthesis of **4** via stepwise transformations analogous to those previously reported.^{55,56}

As shown in Scheme 5.13, ozonolysis of the terminal alkene of **139** followed by reductive work-up with PPh₃ resulted in the production of aldehyde **168** in 83% yield. The corresponding aldehyde moiety of **168** was immediately subjected to a Lindgren-Kraus-Pinnick oxidation to give the carboxylic acid intermediate, followed by TBAF mediated cleavage of the TBDPS ether to furnish the Yamaguchi precursor hydroxy-acid **169**.⁶⁶ The *seco*-acid **169** was then subjected to the previously reported macrolactonization conditions to provide the MOM-protected macrolide ester **170** in 83% yield.⁶⁷

Final deprotection of the MOM acetal of **170** was accomplished using Maier's conditions employing concentrated HCl in MeOH to afford **138** in 90% yield, thus constituting a formal synthesis of (-)-neopeltolide (**4**).^{55a} As previously mentioned, Panek's group had reported the attachment of the oxazole-containing side-chain through a Still-Genari olefination.^{55a}



Scheme 5.13. Formal Synthesis of (-)-Neopeltolide (**4**)⁹²

5.7 Conclusions

In closing, a formal synthesis of (–)-neopeltolide (**4**) has been achieved in 19 linear steps from the previously reported aldehyde **145**^{55e} in a total overall yield of 5.6%.⁹² Key features of the synthesis include a Brown allylboration to establish the first stereogenic center via reagent control. Most of the remaining stereocenters are derived from this initial stereoinduction, including a titanium-mediated methallylation, a stereoselective hydrogenation catalyzed by Pd/C, followed by a second Brown allylboration. An (*E*)-selective cross-metathesis reaction with methyl acrylate sets the stage for the formation of the next stereogenic center. Efficient application of the Evans' protocol for the synthesis of 1,3-*syn* diols via an intramolecular hetero-Michael addition followed by reductive deprotection of the resulting benzylidene acetal allowed for swift access to the δ -lactone **140**. Central to the synthetic approach was a tandem nucleophilic addition-diastereoselective axial reduction of an *in situ* generated oxocarbenium cation to assemble the β -*C*-glycoside moiety of the neopeltolide core. Once the last stereocenter was established via this key step, oxidation of the terminal alkene to the carboxylic acid functionality followed by macrocyclic ring-closure via a Yamaguchi protocol, and final deprotection of the MOM ether with concentrated hydrochloric acid in MeOH allowed for the formal synthesis of the unnatural antipode of the highly cytotoxic/cytostatic marine macrolide, neopeltolide.⁹²

CHAPTER 6: SYNTHESIS OF THE PURPORTED *ENT*-POCHONIN J STRUCTURE FEATURING A STEREOSELECTIVE OXOCARBENIUM ALLYLATION

6.1 Isolation, Characterization, and Initial Biological Studies

Pochonia chlamydosporia is an endoparasitic nematophagous fungus that colonizes the roots of non-host plants and protects them against phytopathogenic fungi. As Nature had intended, this form of symbiotic relationship is not only beneficial to both organisms but further serves to showcase the delicate balance and interconnections of life. Terrestrial derived sources have long since been a repository for biologically relevant natural products.⁶⁸ In 2009, Shinonaga and co-workers at the Taisho Pharmaceutical Co. in Saitama, Japan, disclosed four unique pochonin family structures (pochonins G-J) from the culture broth of *Pochonia chlamydosporia* var. *chlamydosporia*.⁶⁹ These compounds were isolated via bioassay guided fractionation against WNT-5A expression in search of novel hair-growth stimulants. WNT-5A (wingless-type mouse mammary tumor virus integration site family, member 5A) is a secretory glycoprotein that belongs to the WNT family of vital intercellular signaling molecules that regulate organ formation during the fetal stage. This particular strain of *Pochonia chlamydosporia* var. *chlamydosporia*, strain TF-0480, was isolated from a soil sample collected in Fujioka City, Tochigi Prefecture, Japan in 1994. The culture broth prepared was centrifuged, and the supernatant was then washed with H₂O and MeOH and the MeOH eluent extracted with EtOAc. The resulting crude mixture was separated by flash chromatography, yielding 4.3 mg of pochonin J (**5**). The structures of pochonins G-J were elucidated by means of a combination

of 1D and 2D-NMR spectroscopic techniques, including NOESY, NOE, COSY, and HMBC correlations. The entire family of pochonin natural products (A-P) has been shown to share a common structural motif of a 14-membered macrocyclic resorcylic acid lactone core. In addition, all pochonins except F and J are chlorinated at C13 of the aromatic ring analogous to radicicol and monorden.⁷⁰ Similarly, pochonins J (5) and F demonstrate more resemblances to the aigialomycin family of natural products and hypothemycin, due in part to the lack of C13 chlorination as shown in Figure 6.1.^{71,72} Because of their diverse biological functions and curious skeletal connectivities, members of these families of natural products have been met with interest giving rise to innovative synthetic approaches towards their assembly.⁷³

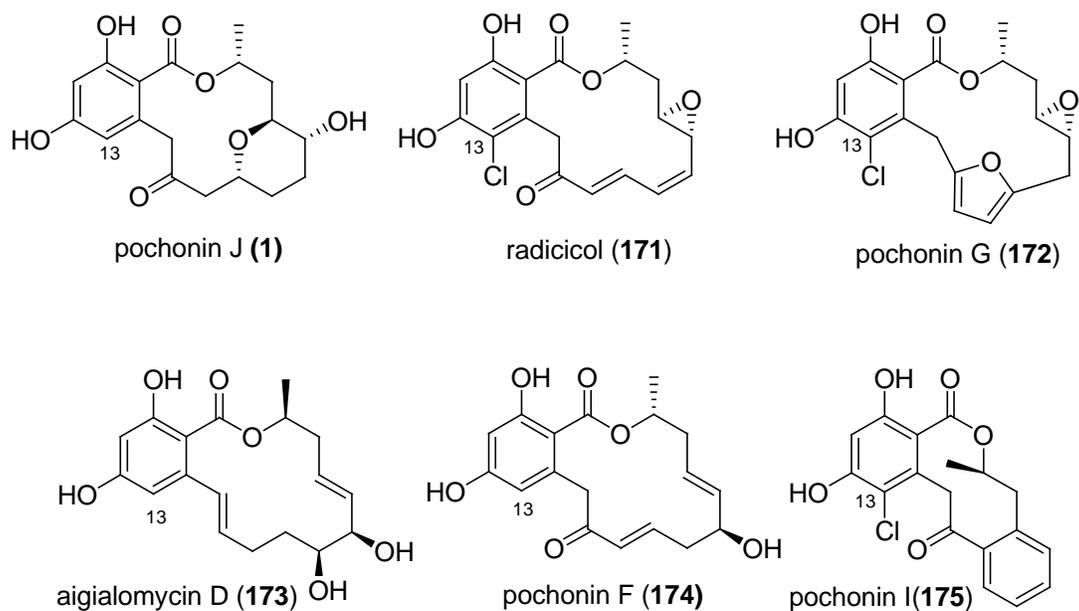


Figure 6.1. Resorcylic Macrolide Natural Products

6.2 Previous Syntheses of Resorcylic Acid Lactones

Resorcylic acid lactones (RALs) of the type shown in Figure 6.1 are secondary metabolites that have been known since 1953 with the isolation of radicicol.⁷⁴ RALs are an important class of natural products that have exhibited a wide range of biological functions. Despite the great leaps forward in structure elucidation and characterization provided by NMR spectroscopy and other analytical methods, it is not uncommon to find errors in structure assignment. Nicolaou and Snyder reported the existence of over 300 structural revisions in the literature published between January 1990 and April 2004.⁷⁵ In over half of these cases, total synthesis of the presumed structure was required to identify a discrepancy and ultimately allowed for the determination of the correct structure. Surprisingly, these errors were not limited to molecules of great complexity as one would initially surmise, but include compounds of varying degrees of size and stereochemical complexity. Thus, total synthesis continues to play a very important role in structure elucidation of chemical entities by overcoming the gaps in technology that exist in the current state of spectroscopy.

As part of a research program aimed at expanding the diversity of RALs beyond the naturally occurring compounds, efforts made by the Winssinger group have also yielded significant contributions to the syntheses and biological studies of RALs. They have successfully synthesized aigialomycin D (**173**), pochonin A, C, and D, and through the application of solid-state chemistry, a library of pochonin and aigialomycin D analogues that have been key in gaining valuable insight into their biological profiles.⁷⁶ Shown in Scheme 6.1 is the Winssinger effort towards the synthesis of aigialomycin D, both in solution and solid phase. Their research revealed that aigialomycin D is a moderate inhibitor of the kinases

Shown in Scheme 6.2, is the synthesis of pochonin D by Winssinger and co-workers.⁷⁴ The practical six step synthesis, requiring a single purification, made it an ideal strategy for combinatorial synthesis. Taking advantage of this combinatorial diversification strategy, the Winssinger group then prepared a library of pochonin-like analogues from which twelve new compounds were found to be kinase inhibitors.⁷⁴ Winssinger's contributions have demonstrated the potential of the "pochonin-like scaffold" and its medicinal value.

"No down-time in between projects!" This was a common phrase that I lived by in graduate school, and this time was no exception. Having successfully completed bruguierol C, brussonol, and a 19-step linear synthesis of the unnatural neopeltolide antipode, my appetite for total synthesis had grown intensely. Knowing that I was anxious to get back into the lab, Dr. Jennings offered me the opportunity to select a natural product from the literature and work out a strategy towards its laboratory synthesis. Such opportunities are extremely rare, and I am very grateful that Dr. Jennings has given me the scientific freedom to allow my ideas to actually come to fruition, of course with his ever-guiding hand leading me towards the right direction.

Our attraction to **5** initially arose from the inclusion of a α -C-glycoside subunit in the 14-membered macrocyclic structure. Such structural motifs are extremely rare and have only been seen in aspergillide B and C.⁷⁷ Based on our previous synthetic work on resorcylic macrolides (i.e. aigialomycin D) and the synthesis of aspergillide B, we sought to merge our interests and investigate the synthesis of **5**.^{78,79} Since we were uncertain of the absolute stereochemistry of **5** and considering its similarity to aigialomycin D, we initiated the synthetic venture towards **5** with the (*S*)-TBDPS protected glycidol starting chiral synthon (similar to our synthetic work with aigialomycin D). We were cognizant that the chiral starting material might lead to the enantiomer of **5** based on the initial disclosure by Shinonaga and co-workers.

6.3 Initial Retrosynthetic Analysis of *ent*-Pochonin J (5)

Our initial retrosynthetic analysis of *ent*-**5** envisioned a late stage oxocarbenium cation formation, followed by intramolecular diastereoselective axial attack by the tethered TMS kinetic enolate **199** derived *in situ* from ketone **200** as delineated in Figure 6.2. This approach was particularly attractive considering that formation of a stereogenic center to forge the α -C-glycoside moiety along with concomitant generation of the macrocycle could be theoretically achieved. If successful, this strategy would further extend the scope of our oxocarbenium protocols as well as providing an alternative methodology for macrocycle construction. With this in mind, the macrocyclic/oxocarbenium precursor **200** was expected to arise from a transesterification reaction of the aromatic subunit **201** with methoxy ketal **202**. Aromatic precursor **201** was envisioned to be the product of a Wacker oxidation of the terminal alkene **209**. In turn, terminal alkene **209** would arise from the previously reported aromatic subunit **208** by means of a Pd-catalyzed cross coupling. The required methoxy ketal **202** could, in principle, be derived from oxidative cleavage of the terminal alkene resident in triol **203**, leading to a 6-*exo*-trig cyclization followed by treatment with PPTS in MeOH to generate the methoxy ketal **202**. Compound **203** would be ultimately derived from diol **204** via a chemoselective Wacker oxidation of the least sterically hindered olefin and a subsequent intramolecular 1,3-*anti* reduction of the corresponding ketone moiety. In turn, diol **204** would be the result of an asymmetric allylboration of an aldehyde intermediate resulting from TBDPS ether **205**. Lastly, **205** would arise from the union of the prenyl derived Grignard reagent **206** and TBDPS protected (*S*)-glycidol **207**, by regioselective attack at the less sterically hindered carbon atom of the oxirane moiety in **207**.

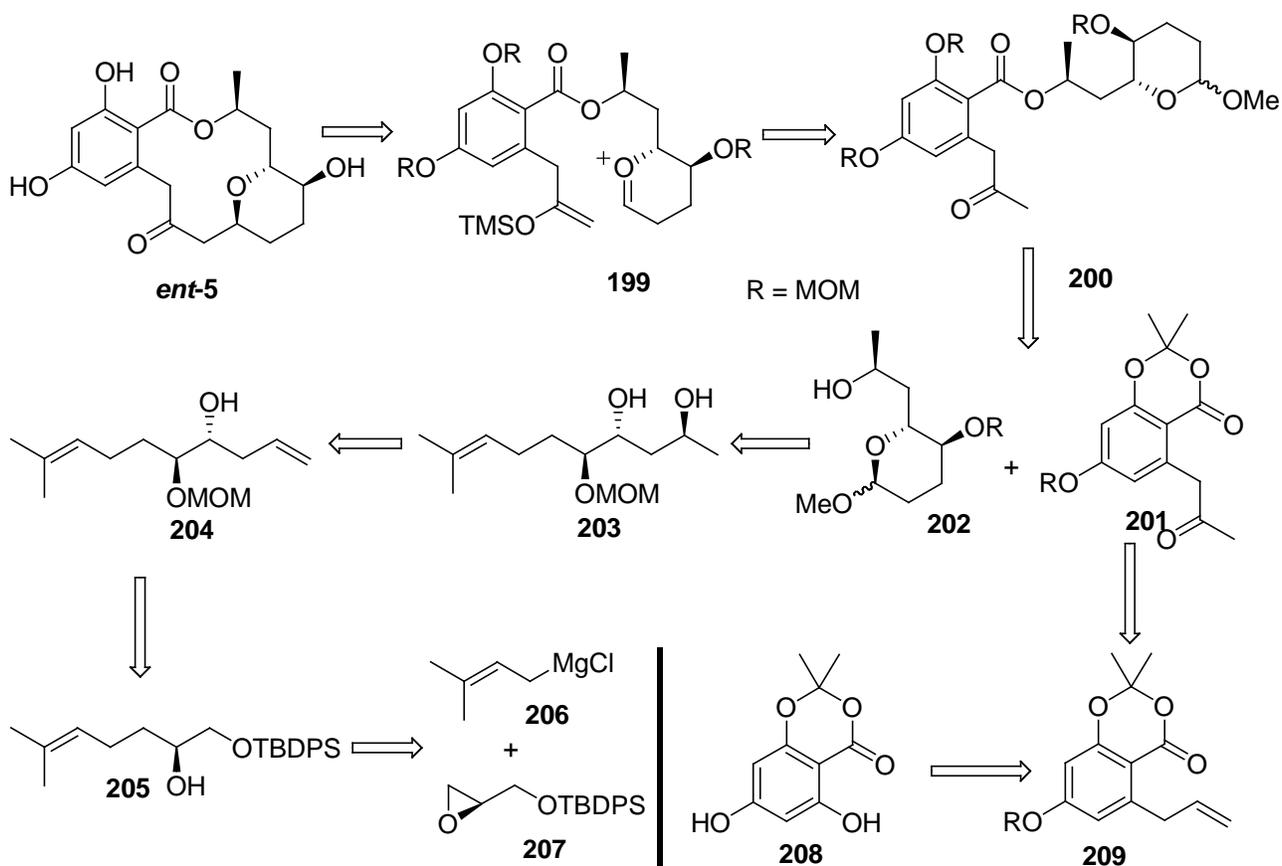
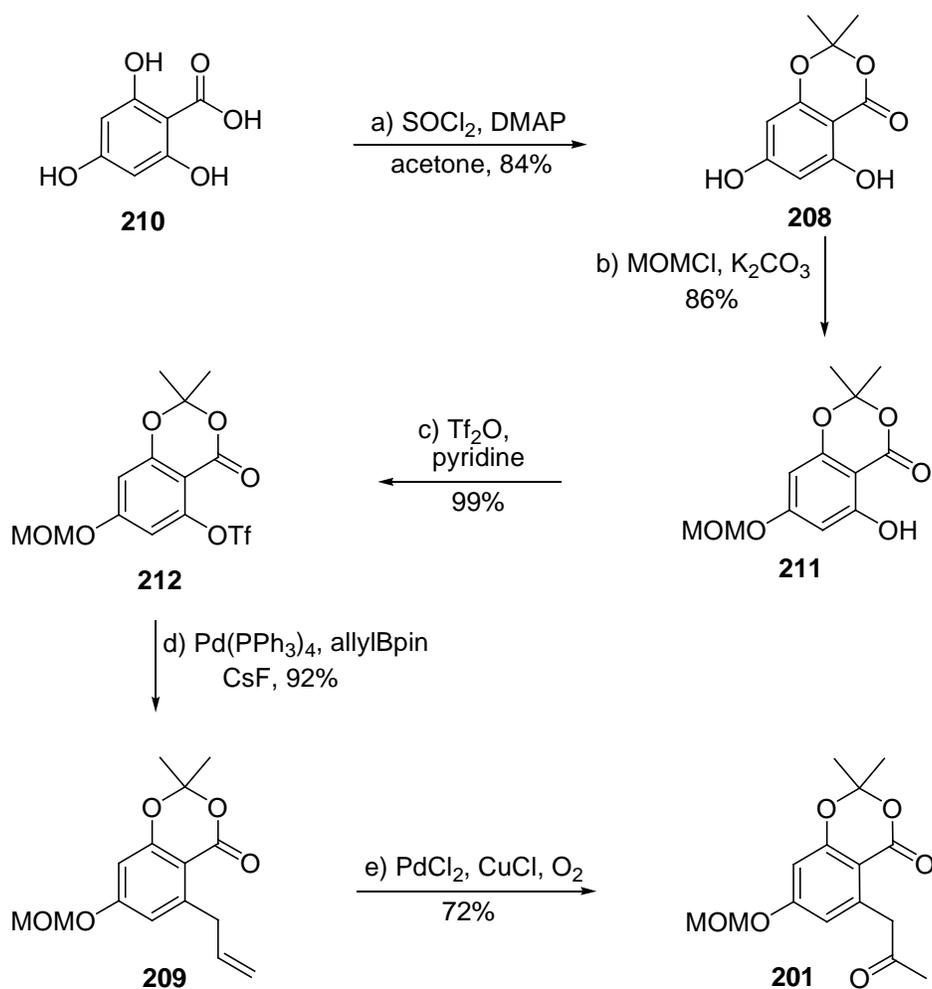


Figure 6.2. First-Generation Retrosynthetic Analysis of *ent*-Pochonin J (5)

6.4 Substituted Styrene Precursor and Attempted Kinetic Enolization

With the original retrosynthetic blueprint in mind, our initial focus was on the construction of aromatic subunit **201** which commenced with acetonide formation of commercially available 2,4,6-trihydroxybenzoic acid **210** in the presence of SOCl_2 , DMAP, and acetone to give aryl acetonide **208** in 84% yield as shown in Scheme 6.3.⁸⁰ This procedure was found to be far superior to the previously reported conditions employing TFA and TFAA, in which the product **208** was formed in a 32% yield along with about 50% recovered starting material **210**. Subsequent chemoselective protection of the more reactive phenol moiety as a MOM ether by employing MOMCl and K_2CO_3 in acetone afforded the desired product **211** in

86% yield. Interestingly, employing standard MOM protecting group conditions (MOMCl, DIPEA, DMAP) led to the exclusive protection of the phenol involved in a hydrogen bonding interaction with the acetonide carbonyl functionality. Next, aryl triflate **212** was obtained in near quantitative yield and an ensuing Pd-catalyzed Suzuki-Miyaura allylation provided aromatic subunit **209** in a 92% yield.⁸¹ Lastly, treatment of **209** under stoichiometric Wacker conditions, employing 50 mol% of PdCl₂ and excess quantities of CuCl (2.0 equiv.) under an atmosphere of O₂ provided the desired aryl ketone **201** in 72% yield.⁸²

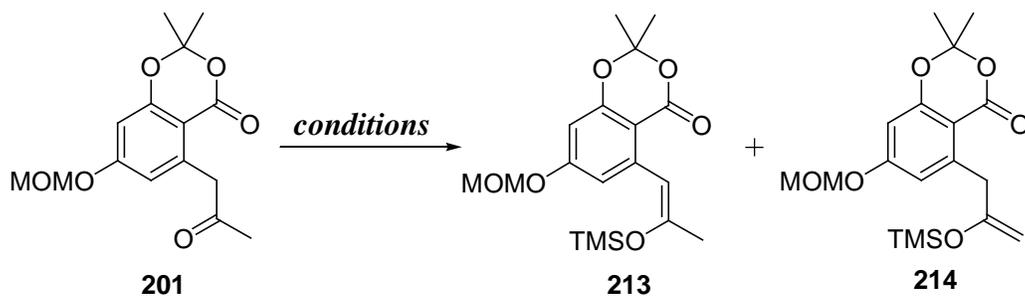


Scheme 6.3. Synthesis of Aromatic Subunit (**201**) via a Wacker Oxidation

Prior to the attempted unification of fragments **201** and **202**, en route to the coveted trimethylsilyl enol ether **199** intermediate, we chose to explore conditions which would hopefully lead to the desired kinetic silyl enol ether **214** from ketone **201**. Based on early studies on the kinetic deprotonation of benzyl methyl ketone conducted by Dr. Masaaki Yoshifuji and co-workers, we reasoned that it might be possible to obtain kinetic silyl enol ether **214** by using a sterically hindered lithium base, such as 1-lithio-2,4,6-tri-*tert*-butylbenzene, at low temperatures.⁸³ More recently, Kozlowski's group has also demonstrated that kinetic enolization at the least hindered position of highly substituted benzyl methyl ketones was indeed possible utilizing sterically hindered LiHMDS/Ph₃N adducts in toluene at -78 °C.⁸⁴ Despite the initial promise provided by these examples, careful implementation of literature procedures lead exclusively to the undesired thermodynamic silyl enol ether **213**. Summarized in Table 6.1 are the various attempts made to attain the desired kinetic silyl enol ether **214**.

In retrospect, aryl ketone **201** possesses a carbonyl moiety that is locked in position through the cyclic acetonide subunit, a functionality not present in the substrates studied by Yoshifuji or Kozlowski. As shown in Figure 6.3, one could envision a scenario where deprotonation at the more acidic benzylic position would lead to a lithiated stabilized 6-membered chelate intermediate **215**, somewhat similar to the one proposed during our synthesis of brussanol.⁹¹ This scenario would account for the funneling of material through this stabilized tautomer leading to the exclusive formation of **213**, despite the stringent kinetic conditions employed. Unfortunately, the recalcitrant TMS enol ether **214** eluded all attempts towards its synthesis and we were forced to abandon our initial synthetic strategy.

Table 6.1. Attempted Kinetic Enolization of Aromatic Ketone (**201**)^a



entry	solvent	Time (h)	Base	additive	TMSCl (equiv.)	213:214
1	THF	0.5	ArLi (1.2 equiv.) ^b	NEt ₃ (2.3 equiv.)	2	>97:3
2	THF	1	ArLi (1.5 equiv.) ^b	NEt ₃ (6.0 equiv.)	5	>97:3
3	PhCH ₃	1	LiHMDS (1.25 equiv.)	Ph ₃ N (5.0 equiv.)	3	>97:3
4	PhCH ₃	1	LiHMDS (1.25 equiv.)	Ph ₃ N (10.0 equiv.)	4	>97:3
5	PhCH ₃	1	LiHMDS (1.5 equiv.)	Ph ₃ N (10.0 equiv.)	5	>97:3
6	PhCH ₃	1	LiHMDS (1.25 equiv.)	Ph ₃ N (40.0 equiv.)	5	>97:3
7	PhCH ₃	1	LiHMDS (1.25 equiv.)	Ph ₃ N (80.0 equiv.)	5	>97:3

a) All reactions were run at $-78\text{ }^{\circ}\text{C}$. b) ArLi = 1-lithio-2,4,6-tri-*tert*-butylbenzene

Figure 6.3. Rationale for the Thermodynamic Enolate Formation of (**201**)

Fortunately our synthetic plan was quite flexible, a designed feature from the beginning, and amenable towards the unexpected obstacles so often encountered in the laboratory. Keeping in mind that there is always “more than one way to skin a cat”, we redesigned a second synthetic blueprint. This time taking advantage of a highly diastereoselective intermolecular oxocarbenium allylation reaction, which has been successfully employed in numerous synthetic ventures in our laboratory.¹⁵

6.5 Second-Generation Retrosynthetic Analysis of Pochonin J (5)

Disappointed, yet undaunted by the failure to obtain the key kinetic silyl enol ether **214**, we proceeded to revise our synthetic strategy. The second-generation retrosynthetic analysis envisioned a late stage alcohol oxidation of **217** which would be derived from the macrocyclic olefin **218** as delineated in Figure 6.4. Synthesis of macrocycle **218** would be obtained from a ring-closing metathesis reaction of the acyclic diene **219**, followed by MOM protection of the free phenol moiety involved in a hydrogen bonding interaction with the carbonyl functionality. In turn, a trans-esterification of the aromatic subunit **220** with α -C-glycoside **221** should provide diene **219**. Aromatic subunit **220** should be accessed starting from the previously synthesized aryl triflate **212** via a Pd-catalyzed coupling with potassium vinyl trifluoroborate. The required alcohol **221** could, in principle, be derived from a highly stereoselective oxocarbenium allylation reaction process between precursor **222** and allyl trimethylsilane. Thus, acetal **222** would be envisioned to arise from an oxidative cleavage of the olefin resident in **203** followed by cyclization and capping of both hydroxyl moieties with acetic anhydride. Olefin **203**, had been previously synthesized during our first-generation attempt.

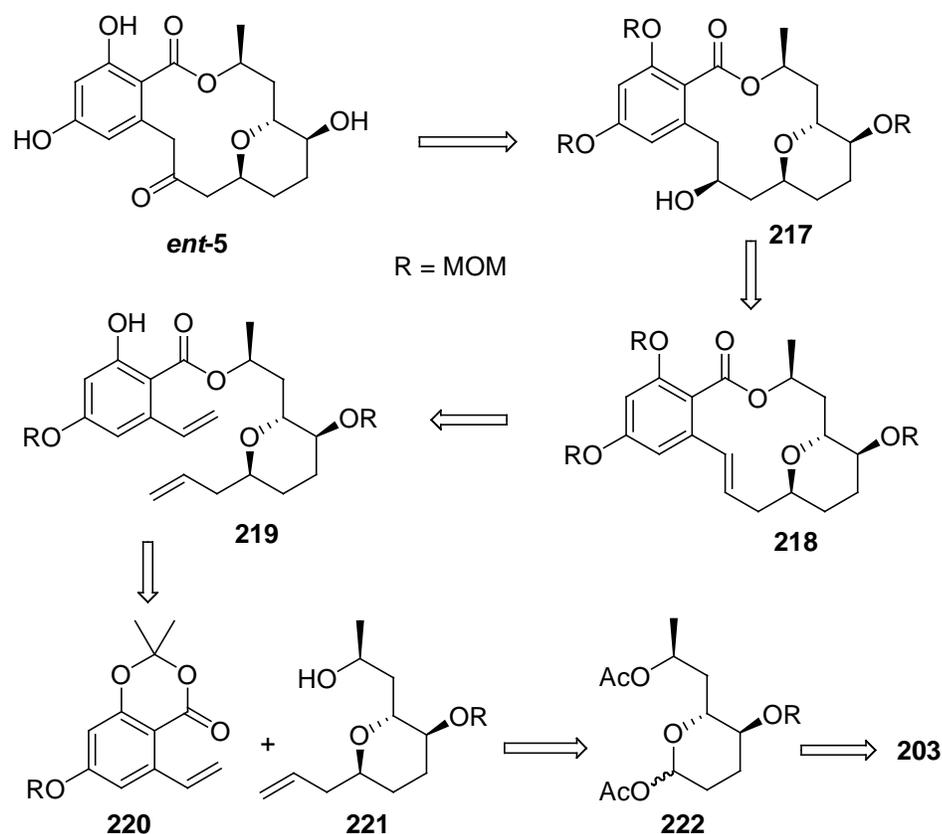
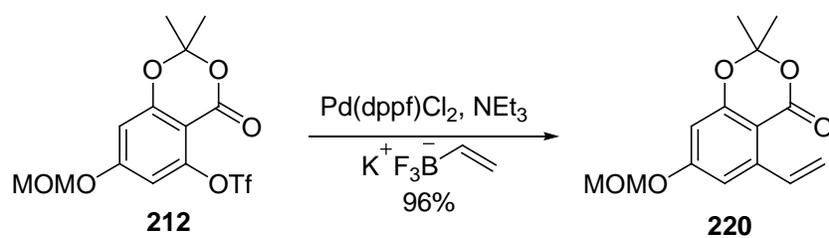


Figure 6.4. Second-Generation Synthetic Blueprint of *ent*-Pochonin J (5)

As presented in Scheme 6.4, our revised synthetic blueprint required the synthesis of substituted styrene **220**. By analogy to Dr. Naval Bajwa's, synthesis of *epi*-aigialomycin D, treatment of aryl triflate **212** with potassium vinyl trifluoroborate and Pd(dppf)Cl₂ under conditions reported by Molander, readily provided compound **220** in an excellent 96% yield.^{78,85}

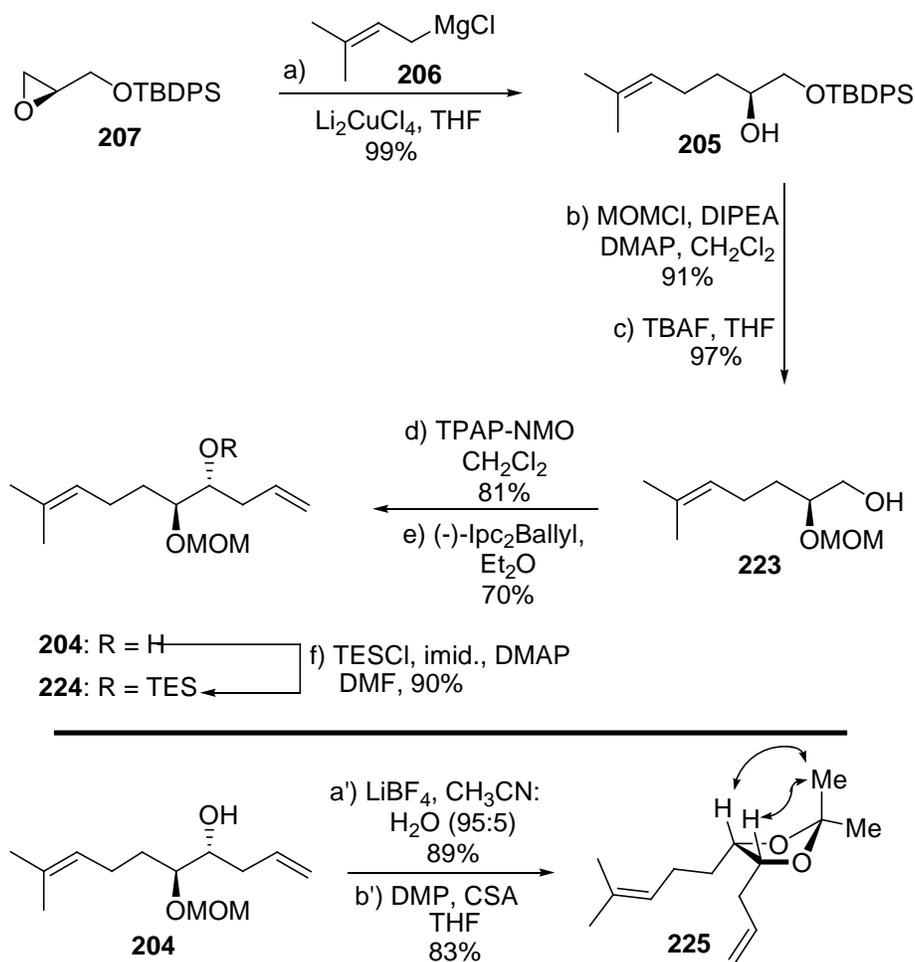


Scheme 6.4. Synthesis of Substituted Styrene (**220**) via a Suzuki Cross-Coupling

6.6 Synthesis of the Aliphatic Framework of Pochonin J (5)

With the aromatic segment **220** readily in hand, we proceeded with the synthesis of the α -C-glycoside segment of *ent*-**5**. Thus, the addition of prenyl derived Grignard reagent **206** to TBDPS protected (*S*)-glycidol **207** readily proceeded with a catalytic amount of Li_2CuCl_4 to provide diol **205** in virtually a quantitative yield as shown in Scheme 6.5. Of particular note, this reaction can be carried out on a 30 gram scale without the slightest deterioration in yield, a feature of this reaction that proved very fortuitous, being the first step in a linear synthetic sequence. An ensuing protection of the resulting free hydroxyl moiety in **205** as a MOM ether utilizing standard conditions (MOMCl, DMAP, and DIPEA) followed by fluorine mediated desilylation of the corresponding primary TBDPS ether furnished diol **223** in 88% yield over two steps from **205**. Subsequent oxidation of the primary alcohol with Ley's TPAP reagent afforded the requisite aldehyde which followed a matched asymmetric allylation with Brown's (+)- $\text{Ipc}_2\text{Ballyl}$ reagent provided homoallylic alcohol **204** in 57% yield over the two step sequence with a >20:1 d.r in favor of the desired diastereomer.²¹

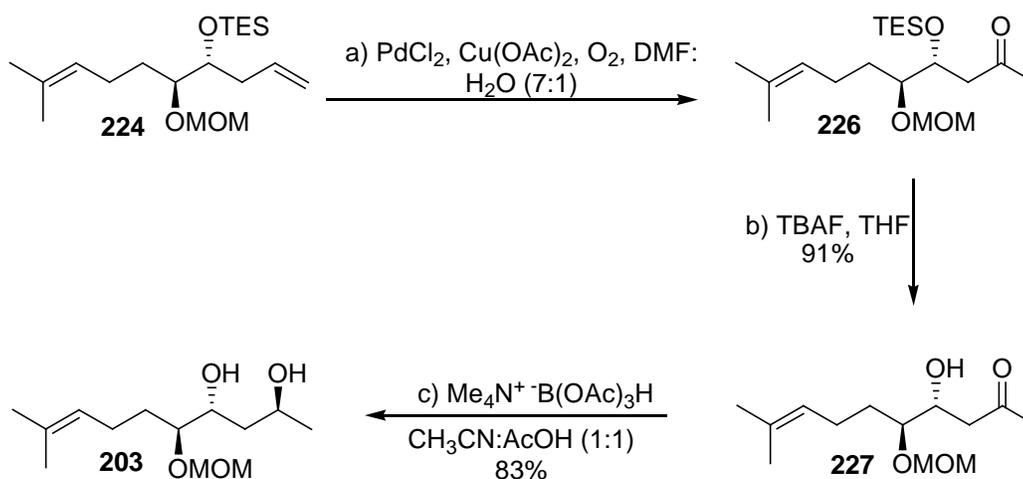
At this point in the synthesis, we deemed it prudent to verify the 1,2-*anti* relationship of the diol moiety resident in **204**. Thus, removal of the MOM ether with LiBF_4 furnished the free diol which was immediately submitted to acetonide formation utilizing 2,2-dimethoxypropane (DMP) and CSA to afford compound **225** in 74% yield over the two steps. As depicted in Scheme 6.5, we observed very strong nOe crosspeak signals between the hydroxyl-methine signals and the axial methyl group which strongly supports the notion that the stereochemistry of the 1,2-diol unit was indeed *anti* as expected.



Scheme 6.5. Synthesis of Diene Wacker Precursor (**224**)

With **204** in hand, the stage was set for what we envisioned would be a chemoselective Wacker oxidation of the terminal olefin in the presence of the trisubstituted alkene. Initial attempts at terminal alkene oxidation in the presence of a free secondary alcohol, led to diminished yields of the desired product (~10%). Along this line, the hydroxyl group of **204** was protected as a TES ether under standard silylation conditions (TESCl, imidazole, and DMAP) and furnished **224** in 90% yield. Much to our delight, treatment of **224** with 10 mol% of PdCl₂ and 0.2 equiv of Cu(OAc)₂ under an atmosphere of O₂ chemoselectively provided the desired

TES protected β -hydroxy ketone **226** in 77% yield. This was accompanied by ~15 % of the TES deprotected β -hydroxy ketone, presumably the result of desilylation due to the formation of AcOH during the Wacker oxidation catalytic cycle. Complete removal of the TES protecting group was readily accomplished with TBAF and afforded ketone **227**. As first reported by Professor Evans at Harvard, an ensuing hydroxyl directed intramolecular 1,3-*anti* reduction of **227** with $\text{H}(\text{OAc})_3\text{B}^-\text{NMe}_4^+$ provided the MOM protected triol **203** with a d.r. of >20:1 in 76% yield over two steps from ketone **226**.⁸⁶

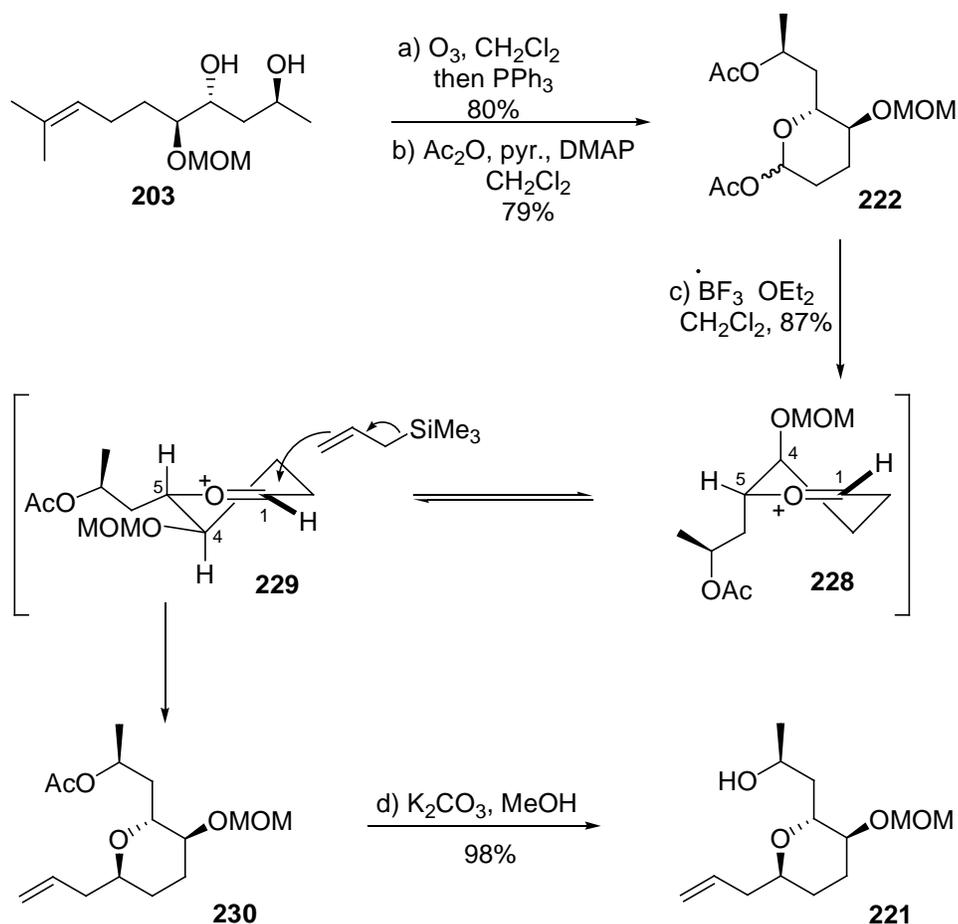


Scheme 6.6. Chemoselective Wacker Oxidation & Evans Antireduction

With protected triol **203** readily in hand, we were in position to proceed and cyclize the linear fragment through an oxidative cleavage reaction process as shown in Scheme 6.7. Hence, treatment of **203** under standard ozonolysis conditions allowed for oxidative cleavage of the alkene moiety followed by a 6-*exo*-trig cyclization of the corresponding *bis*-hydroxy aldehyde intermediate to afford the resultant hemi-acetal product, which when directly treated with excess Ac_2O and pyridine with catalytic amounts of DMAP provided the desired *bis* acetyl hemi-ketal **222** as a mixture of diastereomers in a modest yield of 79% over two steps from triol **203**. With

222 in hand, addition of $\text{BF}_3 \cdot \text{OEt}_2$ at $-78\text{ }^\circ\text{C}$ readily generated the endocyclic oxocarbenium cation and stereoselective allylation of reactive intermediate conformer **229** with allyltrimethylsilane provided the desired α -C-glycoside **230** in 87% yield as a single diastereomer.

Presumably, alkylations of oxocarbenium cations occur via axial addition of the allyl silane to afford the α -C-glycoside via a chair-like transition state.⁴ Of the two possible reactive conformers (**228** and **229**) and based on the isolated α -C-glycoside, the proposed conformer **229** placed the substituents at C_4 and C_5 in pseudo-equatorial positions. During our prior examination of stereoselective endocyclic oxocarbenium alkylation with respect to the synthesis of aspergillide B, the C_4 hydroxyl moiety was placed in the axial position and the C_5 substituent in the pseudo equatorial geometry and the allylation took only 30 min for completion.⁷⁹ Based on Woerpel's observations and in conjunction with our prior investigations, these C_4 axial and C_5 pseudo-equatorial oxocarbenium conformations tend to represent a "matched" geometry,^{8,79} as in the previous chapter during synthetic studies towards the antipode of neopeltolide. However, the current reactive oxocarbenium conformer **229** placed both the C_4 and C_5 substituents in the pseudo-equatorial positions. Interestingly, the highly stereoselective oxocarbenium formation/alkylation reaction required ~ 6 hours for completion at $-78\text{ }^\circ\text{C}$. Hence, it is alleged that conformer **229** represents a "mismatched" geometry that nonetheless allows for a highly stereoselective oxocarbenium allylation. Time and time again, our results have suggested that the C_5 substituent plays a dominant role with respect to reactive oxocarbenium conformation preference during an alkylation and/or reduction process.¹⁵ Final hydrolysis of the acetate resident in **230** with K_2CO_3 and MeOH provided the requisite aliphatic portion **221** of *ent*-**1** in nearly quantitative yield as delineated in Scheme 6.7.



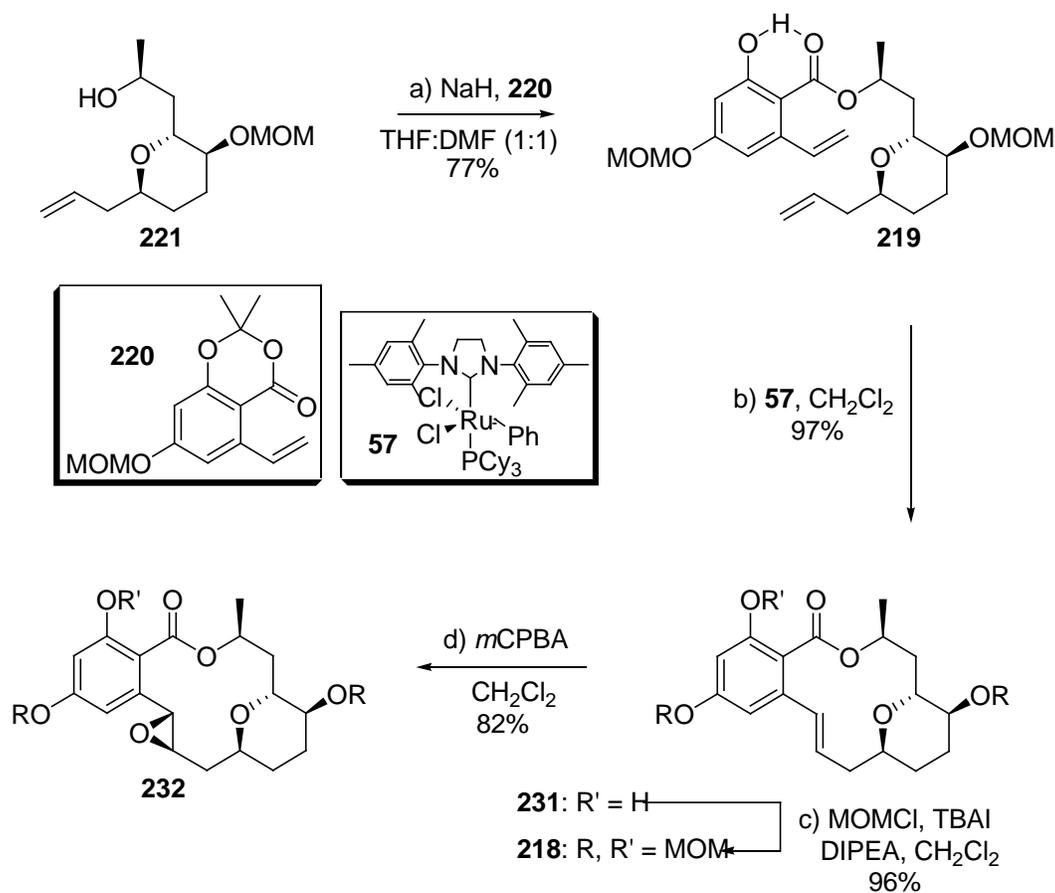
Scheme 6.7. Highly Stereoselective Oxocarbenium Allylation

6.7 Convergent Union via Transesterification and Completion of the Synthesis

With the aliphatic α -C-glycoside subunit **221** readily in hand, our focus turned towards the completion of *ent-5* as summarized in Schemes 6.8 and 6.9. Following precedent established by Dr. Naval Bajwa during her synthesis of *epi*-aigialomycin D in 2008,⁷⁸ convergent transesterification of **220** with the alkoxide anion derived from the treatment of **221** with NaH in a 1:1 THF/DMF solvent mixture proceeded to provide diene **219** in 77% yield. Interestingly, this transesterification reaction required rigorous optimization in order to achieve good yields. Addition of substituted styrene **220** at five hour intervals was necessary in order for complete

consumption of the α -C-glycoside subunit **221** to be observed via TLC analysis. Similar to our previous work on *epi*-aigialomycin D, we envisaged a macrocyclization to the 14-membered ring via a ring closing metathesis at C₁₀-C₁₁.⁷⁸ Thus, treatment of **219** with Grubbs' second generation catalyst **57** in refluxing CH₂Cl₂ led to the formation of the desired 14-membered macrocycle **231** in an excellent 97% yield. With the crude framework in place, we sought to install the final carbon-oxygen bond by means of an *m*-CPBA mediated epoxidation of the newly formed olefin in **231**. Since epoxidation of this intermediate proved problematic and led only to degradation of the starting material, we chose to protect the free phenol of **231** as a MOM ether and the said reaction furnished the fully protected macrocycle **218** in 96% yield. Much to our surprise, treatment of **218** with *m*-CPBA, buffered in a 1:1 bi-phasic solvent mixture of CH₂Cl₂ and 1M aqueous solution of NaHCO₃, stereoselectively oxidized the olefin to afford epoxide **232** in a good yield of 82% as a single diastereomer. Although the generation of this stereogenic center is extraneous, as it is later oxidized to the requisite ketone, it is noteworthy that the epoxidation took place with such remarkable stereoselectivity. The stereochemistry of the epoxide **232** was determined via nOe correlation spectroscopy.

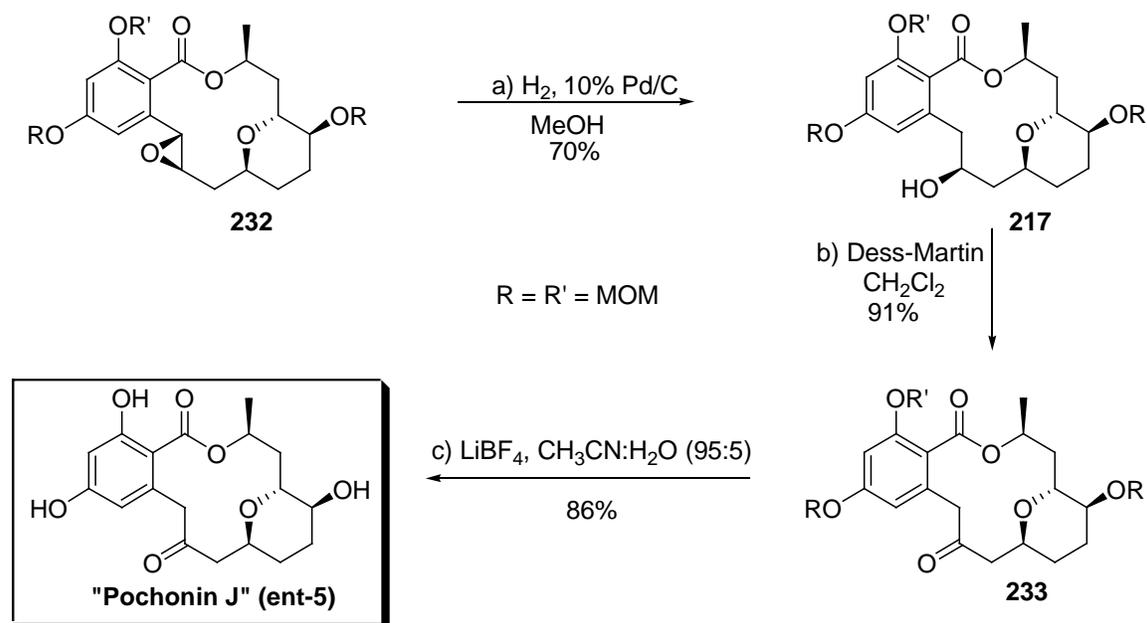
As summarized in Scheme 6.9, after meticulous experimentation and optimization of reaction parameters, reductive benzylic hydrogenolysis of the oxirane moiety of **232** with H₂ and 10% Pd/C in MeOH furnished the homobenzylic alcohol **217** in 70% yield. If excess Pd/C was used or the reaction was too concentrated, this caused an unexpected deprotection of the phenolic residue which is hydrogen bonding to the carbonyl functionality. This outcome proved to be problematic since the desired product turned out to have an equal R_f value as this by-product, thereby complicating flash chromatography.



Scheme 6.8. Fragment Union via Transesterification and Further Oxidation

Initial screening of several oxidants (TPAP, IBX, and Swern) failed to provide the desired ketone **233** and led only to starting material decomposition. Fortunately, the Dess-Martin periodinane reagent proved competent for the required oxidation of the secondary alcohol.⁸⁷ Ensuing global deprotection of the three MOM ether groups with LiBF₄ in refluxing aqueous acetonitrile provided *ent*-**5** in 78% yield over two steps from **217**. Unfortunately, the spectral (¹H NMR, 500MHz; ¹³C NMR, 125 MHz) and optical rotation data of synthetic (+)-pochonin J did not agree with the natural sample.^{69,93} This result is not surprising considering that Nicolaou and Snyder reported over 300 structural revisions in the literature from 1990 to 2004.

Total synthesis continues to play a very important role in the structure elucidation of unknown chemical compounds, and aids in the clarification of discrepancies in the scientific literature.



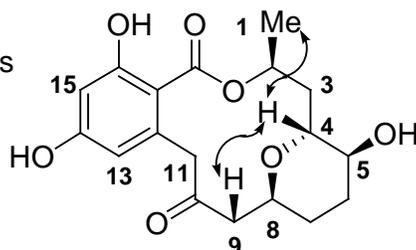
Scheme 6.9. Synthesis of the Reported Structure of Pochonin J (**5**)⁹³

The key nOe enhancements in Table 6.2 strongly suggest that *ent-5* is indeed an α -C-glycoside and the C₁ methyl group has the presumed stereochemistry as illustrated. As shown in Table 6.2, many of the signals of *ent-5* in the ¹H NMR do not match that of the reported structure. A couple of significant ¹H NMR discrepancies lie at both C₉ and C₁₁ and these results might provide valuable insight into the true structure of pochonin J. One theory is that pochonin J might truly be a β -C-glycoside instead of the reported α -C-glycoside. As previously stated, 14-membered macrolides containing α -C-glycoside subunits are extremely rare. If one considers the biogenesis of these types of natural products, perhaps arising from the radicicol-like epoxide, an

intramolecular oxy-Michael addition to open this epoxide would theoretically form the β -C-glycoside instead of the reported α -C-glycoside.

Table 6.2. ^1H NMR Chemical Shift Comparison of Natural vs Synthetic Pochonin J (ref. Peak = 3.31 ppm) in CD_3OD .

Key nOe
Enhancements
of **ent-5**



Natural pochonin J ppm, mult., <i>J</i> in Hz	Carbon	Synthetic <i>ent</i> -pochonin J ppm, mult., <i>J</i> in Hz
1.34, d, (6.7)	1	1.34, d, (6.0)
5.32, m	2	5.27, m
2.18, dd, (15.5, 2.4)	3a	2.04, m
1.58, ddd, (15.5, 7.3, 4.3)	3b	1.93, m
3.42, ddd, (10.0, 7.3, 2.4)	4	3.81, m
3.58, m	5	3.31, m
2.05, m	6a	1.96, m
1.94, m	6b	1.77, m
1.91, m	7a	1.83, m
1.74, m	7b	1.68, m
4.38, m	8	4.33, m
2.65, dd, (15.5, 10.0)	9a	3.21, dd, (13.9, 11.9)
2.40, dd, (15.5, 4.0)	9b	2.34, dd, (13.9, 3.8)
4.27, d, (18.3)	11a	4.44, d, (18.9)
3.85, d, (18.3)	11b	4.27, d, (18.9)
5.98, d, (2.4)	13	6.11, d, (2.5)
6.14, d, (2.4)	15	6.26, d, (2.5)

6.8 Conclusions

In summary, an efficient synthesis of the reported structure of pochonin J *ent-5* has been achieved but unfortunately does not match the spectroscopic data initially reported.⁹³

Construction of the α -C-glycoside subunit is highlighted by a highly diastereoselective oxocarbenium cation formation/allylation sequence of a hemi-ketal intermediate. Results from the Jennings' laboratory demonstrate that while the Woerpel effect has a profound effect on the kinetics of these reactions, it is the C₅ alkyl substituent positioned in a pseudoequatorial orientation that plays the dominant role with respect to reactive oxocarbenium conformation preference during an alkylation and/or reduction process.¹⁵ Other key reactions of the synthesis for the aliphatic portion of pochonin J include, a Brown asymmetric allylboration, a chemoselective Wacker oxidation of the terminal alkene in the presence of a tri-substituted alkene, and an Evans anti-reduction of the resulting ketone moiety. Convergent union of the elaborated sub-units, through a trans-esterification reaction and subsequent ring-closing metathesis reaction, forged the 14-membered macrolactone. Final oxidation of the resulting alkene provided "pochonin J" which did not spectroscopically correlate to the initially disclosed natural product.⁹³

CONCLUSIONS

This dissertation describes experimental studies directed towards the synthesis of natural products containing *C*-glycosides via oxocarbenium cationic intermediates. The first total synthesis of (+)-bruguierol C has been achieved involving the diastereoselective capture of an *in situ* generated oxocarbenium cation via an intramolecular Friedel-Crafts/Marson-type cyclization. Similarly, the formal syntheses of (±)-brussonol and (±)-abrotanone were completed in a step-economical strategy, representing an extension of oxocarbenium methodology, as well as the first diterpene natural products constructed utilizing this type of synthetic strategy. A useful methodology for the chemoselective removal of primary TBS groups in the presence of a variety of other protecting groups and functional groups has been discovered by employing commercially available pyridinium tribromide and methanol as the solvent. The formal synthesis of unnatural (-)-neopeltolide has been attained. Central to the synthetic approach is a tandem nucleophilic addition-diastereoselective axial reduction of an *in situ* generated oxocarbenium cation to construct the β-*C*-glycoside moiety. Finally, the synthesis of the proposed structure of pochonin J has been completed utilizing a diastereoselective oxocarbenium allylation to construct the α-*C*-glycoside fragment as the key step. Unfortunately, the spectral (¹H NMR, 500MHz; ¹³C NMR, 125 MHz) and optical rotation data of synthetic (+)-pochonin J did not agree with the natural sample.

EXPERIMENTAL

General Procedure. The NMR spectra were recorded with either a 360 or 500 MHz Bruker spectrometer. ^1H and ^{13}C NMR spectra were obtained using CDCl_3 as the solvent with either tetramethylsilane (TMS: $\delta = 0.00$ ppm) or chloroform (CHCl_3 : $\delta = 7.26$ ppm) as the internal standard. Chemical shifts are given in δ (ppm) and coupling constants (J) in Hz. FTIR spectra were recorded on a BIO-RAD FTS-40 spectrometer. HRMS determination was performed in the laboratory of mass spectrometry at the University of Alabama. A JASCO P-1030 Polarimeter at the University of Alabama was used for optical rotations ($[\alpha]_D^{24}$). Column chromatography was performed using 60-200 μm silica gel. Analytical thin layer chromatography was performed on silica coated glass plates with F-254 indicator. Visualization was accomplished by UV light (254 nm) and KMnO_4 or Cerium Sulfate. All starting materials and solvents were commercially available (Aldrich or Alfa Aesar) and were used without further purification.

2-[3,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-phenyl]-ethanol (59): To a solution of methyl ester **58** (3.50 g, 8.53 mmol) dissolved in anhydrous ether (30.0 mL) was added LAH (17.1 mL, 1.00 M in Et_2O , 2.00 equiv) at 0 °C under argon. The reaction was left stirring for three hours until the starting material was consumed as checked by TLC. The reaction was then quenched with Rochelle salt and left stirring overnight. The aqueous layer was then extracted (40.0 mL \times 3) with Et_2O . The organic layers were combined, dried with anhydrous MgSO_4 , filtered, and

concentrated under reduced pressure. Flash chromatography (silica, 20% ethyl acetate in hexanes) afforded **59** as a yellowish oil (3.12 g, 91%). $^1\text{H NMR}$ (360 MHz, CDCl_3), δ 6.34 (d, 2H, $J = 2.2$ Hz), 6.22 (t, 1H, $J = 2.2$ Hz), 3.8 (t, 2H, $J = 6.5$ Hz), 2.74 (t, 2H, $J = 6.5$ Hz), 1.52 (br s, 1H), 0.97 (s, 18H), 0.19 (s, 12H). $^{13}\text{C NMR}$ (90MHz, CDCl_3) δ 156.6, 140.3, 114.1, 110.2, 63.5, 39.1, 25.6, 18.2, -4.4. **IR** (CHCl_3): 3606, 3056, 2957, 2932, 2859, 1589, 1451, 1264, 1166, 836, 743 cm^{-1} . **R_f** at 30% ethyl acetate in hexanes: 0.4. **HRMS** (EI) calculated for $\text{C}_{20}\text{H}_{38}\text{O}_3\text{Si}_2$ (M⁺): 382.2360, found: 382.2351.

[3,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-phenyl]-acetaldehyde (57): To a solution of primary alcohol **59** (100 mg, 0.262 mmol) dissolved in anhydrous CH_2Cl_2 (10.0 mL) was added PCC (70.6 mg, 1.25 equiv) at room temperature. The reaction was left stirring for two hours until starting material was consumed at which time the mixture was filtered through a plug of silica gel and rinsed with Et_2O . The resulting solution was then concentrated under reduced pressure. Flash chromatography (silica, 5% ethyl acetate in hexanes) afforded aldehyde **57** as a colorless oil (85.0 mg, 85%). $^1\text{H NMR}$ (360 MHz, CDCl_3), δ 9.67 (t, 1H, $J = 2.5$ Hz), 6.32 (d, 2H, $J = 2.2$ Hz), 6.27 (t, 1H, $J = 2.2$ Hz), 3.53 (d, 2H, $J = 2.5$ Hz), 0.97 (s, 18H), 0.19 (s, 12H).

1-[3,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-phenyl]-pent-4-en-2-ol (56): To a solution of (+)- $(\text{Ipc})_2\text{BOMe}$ (406 mg, 1.28 mmol) dissolved in anhydrous Et_2O (6.00 mL) was added allylmagnesium bromide (1.20 mL, 1.00 M in Et_2O , 1.30 equiv) at -78 °C under argon. The dry ice bath was removed after 10 minutes and the solution was allowed to reach room temperature for 1 hour. The solution was then re-cooled to -78 °C and aldehyde **57** (385 mg, 1.01 mmol) was added drop wise as a solution in Et_2O (8.00 mL). The reaction was stirred at -78 °C for 2 hours

then warmed to 0 °C and was oxidized with 8 ml of 3M NaOH and 4 ml of 30% H₂O₂ (added drop wise under argon). The solution was stirred for 20 minutes at 0 °C, and then allowed to reach rt while stirring for 12 h. The aqueous layer was extracted (20.0 mL × 3) with Et₂O. The combined organic extracts were dried with anhydrous MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded **56** as a colorless oil (270 mg, 70%). ¹H NMR (360 MHz, CDCl₃), 6.33 (d, 2H, *J* = 2.2 Hz), 6.22 (t, 1H, *J* = 2.2 Hz), 5.83 (m, 1H), 5.17 (m, 1H), 5.12 (m, 1H), 3.83 (m, 1H), 2.68 (dd, 1H, *J* = 13.7, 4.7 Hz), 2.60 (dd, 1H, *J* = 13.3, 7.9), 2.33 (m, 1H), 2.21 (m, 1H), 1.71 (br s, 1H) 0.97 (s, 18H), 0.18 (s, 12H). ¹³C NMR (90MHz, CDCl₃) δ 156.6, 140.1, 134.7, 117.9, 114.6, 110.3, 71.6, 43.3, 41.1, 25.7, 18.2, -4.41. IR (CHCl₃): 3429, 2929, 2861, 1590, 1453, 1341, 1260, 1161, 1024, 831, 783 cm⁻¹. R_f at 20% ethyl acetate in hexanes: 0.5. [α]_D²⁵: -1.58 (c 0.06, CH₂Cl₂). HRMS (EI) calculated for C₂₃H₄₂O₃Si₂ (M⁺): 422.2673, found: 422.2681.

5-[3,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-phenyl]-pentane-1,4-diol (61): To a solution of BH₃•S(CH₃)₂ (0.360 mL, 10.0 M in Et₂O, 3.00 equiv) dissolved in anhydrous Et₂O (50.0 mL) was added cyclohexene (0.770 mL, 7.59 mmol, 6.40 equiv) drop wise at 0 °C. The reaction was allowed to reach room temperature and stirred for 2 hours. The solution was then re-cooled to 0 °C and followed by drop wise addition of the homoallylic alcohol **56** (500 mg, 1.18 mmol, 1.00 equiv) as a 5.00 ml solution in Et₂O. The reaction was allowed to reach room temperature and left stirring for 10 h. The reaction was re-cooled to 0 °C and oxidized with 10.0 ml of 3M NaOH and 5.00 ml of 30% H₂O₂ and the reaction mixture was allowed to reach room temperature and stirred for 4 hours. The aqueous layer was extracted (20.0 mL × 3) with Et₂O. The combined organic extracts were dried with anhydrous MgSO₄, filtered, and concentrated under reduced

pressure. Flash chromatography (silica, 40% ethyl acetate in hexanes) afforded diol **61** as a colorless oil (455 mg, 91%). $^1\text{H NMR}$ (360 MHz, CDCl_3), δ 6.32 (d, 2H, $J = 2.5$ Hz), 6.22 (t, 1H, $J = 2.2$ Hz), 3.79 (m, 1H), 3.66 (m, 2H), 2.68 (dd, 1H, $J = 13.3, 4.3$ Hz) 2.57 (dd, 2H, $J = 13.7, 7.9$ Hz), 2.37 (broad s, 2H), 1.71 (m, 3H), 1.51 (m, 1H), 0.97 (s, 18H), 0.18 (s, 12H). $^{13}\text{C NMR}$ (90MHz, CDCl_3) δ 156.6, 140.2, 114.5, 110.4, 72.5, 62.9, 44.1, 33.6, 29.3, 25.6, 18.2, -4.4. **IR** (CHCl_3): 3733, 3627, 3333, 2953, 2857, 2341, 1586, 1540, 1449, 1389, 1333, 1251, 1159, 1005, 939, 828, 778 cm^{-1} . R_f at 40% ethyl acetate in hexanes: 0.24. $[\alpha]_D^{25}$: -4.8 (c 0.02, CH_2Cl_2). **HRMS** (EI) calculated for $\text{C}_{23}\text{H}_{44}\text{O}_4\text{Si}_2$ (M+): 440.2778, found: 440.2786.

5-[3,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-benzyl]-dihydro-furan-2-one (60): To a solution of diol **61** (740 mg, 1.68 mmol) dissolved in anhydrous CH_2Cl_2 (8.00 mL) was added NMO (790 mg, 6.74 mmol, 4.00 equiv), TPAP (30.0 mg, 0.084 mmol, 0.05 equiv), and 4 Å MS (500 mg) at room temperature. The reaction mixture was left stirring until the starting material was consumed by TLC (~12 h). The reaction mixture was filtered through a plug of silica gel and rinsed with Et_2O to give the crude product. The resulting solution was then concentrated under reduced pressure. Flash chromatography (silica, 5% ethyl acetate in hexanes) afforded lactone **60** as a yellowish oil (500 mg, 68%). $^1\text{H NMR}$ (360 MHz, CDCl_3), δ 6.32 (d, 2H, $J = 1.8$ Hz), 6.24 (t, 1H, $J = 2.2$ Hz), 4.68(m, 1H), 2.99 (dd, 1H, $J = 13.3, 5.8$ Hz), 2.75 (d, 1H, $J = 13.7, 6.8$ Hz), 2.43 (m, 2H), 2.21 (m, 1H), 1.92 (m, 1H), 0.97 (s, 18H), 0.18 (s, 12H). $^{13}\text{C NMR}$ (90MHz, CDCl_3) δ 176.9, 156.7, 137.6, 114.6, 110.8, 80.6, 41.2, 28.6, 27.1, 25.7, 18.2, -4.4. **IR** (CHCl_3): 2956, 2930, 2858, 1775, 1590, 1452, 1338, 1265, 1167, 1022, 832, 782, 741, 704 cm^{-1} . R_f at 20% ethyl acetate in hexanes: 0.4. $[\alpha]_D^{25}$: -5.6 (c 0.05, CH_2Cl_2). **HRMS** (EI) calculated for $\text{C}_{23}\text{H}_{40}\text{O}_4\text{Si}_2$ (M+): 436.2465, found: 436.2456.

3,5-Bis-(tert-butyl-dimethyl-silanyloxy)-1-methyl-12-oxa-tricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (63): To a solution of lactone **60** (250 mg, 0.570 mmol, 1.00 equiv) dissolved in anhydrous Et₂O (5.00 ml) was added MeLi (0.480 ml, 0.770 mmol, 1.30 equiv) drop wise under argon at -78 °C. The reaction was left stirring for 1.5 hours until starting material was consumed at which time the reaction was quenched with NH₄⁺Cl⁻. The aqueous layer was then extracted (20.0 mL × 3) with Et₂O. The combined organic extracts were dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure which afforded the crude lactol product. To a solution of crude lactol dissolved in 5.00 ml of CH₂Cl₂ was added BF₃•OEt₂ (0.140 mL, 1.14 mmol, 2.00 equiv) drop wise under argon at -20 °C. The solution was left stirring for 2 h and the reaction was quenched with sat. NH₄⁺Cl⁻. The aqueous layer was then extracted (20.0 mL × 3) with Et₂O. The combined organic extracts were dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford the crude product. Flash chromatography (silica, 5% diethyl ether in hexanes) afforded the bis-TBS protected bruguierol C (**63**) as a colorless oil (143 mg, 58% over two steps). ¹H NMR (360 MHz, CDCl₃), δ 6.17 (d, 1H, *J* = 2.5 Hz), 6.12 (d, 1H, *J* = 2.2 Hz), 4.61 (dddd, 1H, *J* = 7.2, 5.4, 2.5, 1.8 Hz), 3.31 (dd, 1H, *J* = 16.2, 5.0), 2.34 (d, 1H, *J* = 16.2), 2.21 (m, 1H), 2.09 (dddd, 1H, *J* = 10.8, 9.4, 2.2, 1.4 Hz) 1.84 (s, 3H), 1.76 (m, 1H), 1.63 (m, 1H), 1.01 (s, 9H), 0.96 (s, 9H), 0.30 (s, 3H), 0.24 (s, 3H), 0.17 (s, 6H). ¹³C NMR (90MHz, CDCl₃) δ 154.1, 152.2, 135.1, 126.8, 113.4, 108.5, 80.4, 73.1, 42.0, 37.8, 26.0, 25.6, 24.2, 18.5, 18.1, -3.5, -3.9, -4.4, -4.4. IR (CHCl₃): 2954, 2930, 2897, 2355, 1601, 1571, 1424, 1372, 1279, 1190, 1082, 894, 830, 778cm⁻¹. R_f at 30% ethyl acetate in hexanes: 0.4. [α]_D²⁵: +16.2 (*c* 0.03, CH₂Cl₂). HRMS (EI) calculated for C₂₄H₄₂O₃Si₂ (M⁺): 434.2673, found: 434.2674.

(+)-**Bruguierol C (1)**: To a solution of protected natural product **63** (90.0 mg, 0.210 mmol, 1.00 equiv) dissolved in THF (5.00 ml) was added TBAF (0.630 mL, 0.630 mmol, 3.00 equiv) drop wise at rt. The reaction was left stirring for 1.5 h and the reaction was quenched with sat. NH_4^+Cl^- . The aqueous layer was then extracted (20.0 mL \times 3) with EtOAc. The combined organic extracts were dried with anhydrous MgSO_4 , filtered, and concentrated under reduced pressure which afforded the crude product. Flash chromatography (silica, 40% ethyl acetate in hexanes) afforded (+)-bruguierol C (**1**) as a white solid (37.0 mg, 85%). $^1\text{H NMR}$ (360 MHz, CD_3OD), δ 6.08 (d, 1H, $J = 2.2$ Hz), 6.02 (d, 1H, $J = 2.5$ Hz), 4.58 (dddd, 1H, $J = 7.2, 5.4, 2.2, 1.8$ Hz), 3.20 (dd, 1H, $J = 16.2, 5.0$), 2.35 (d, 1H, $J = 16.2$), 2.20 (m, 1H), 2.10 (m, 1H), 1.81 (s, 3H), 1.74 (m, 1H), 1.63 (m, 1H). $^{13}\text{C NMR}$ (125MHz, CD_3OD) δ 157.5, 155.5, 136.0, 122.3, 108.1, 102.0, 82.3, 75.0, 42.9, 38.8, 31.0, 24.4. **IR** (CHCl_3): 3735, 3633, 3326, 2923, 2854, 2360, 1608, 1464, 1348, 1296, 1161, 1028, 997, 836 cm^{-1} . **R_f** at 50% ethyl acetate in hexanes: 0.4. $[\alpha]_D^{25}$: +4.2 (c 0.005, MeOH). **HRMS** (EI) calculated for $\text{C}_{12}\text{H}_{14}\text{O}_3$ (M⁺): 206.0943, found: 206.0947.

Silyl enol ether (90). LiCl (0.039 g, 0.905 mmol) and CuI (0.088 g, 0.454 mmol) were dissolved in anhydrous THF (55.0 mL) under argon at rt. The resulting mixture was cooled to -40 °C at which time (**89**) (1.00g, 9.07 mmol, 1.00 equiv) and TMSCl (1.30 mL, 9.99 mmol) were added and the solution was stirred for 10 min. MeMgCl (4.63 mL, 13.6 mmol, 22% wt in THF) was added dropwise and left stirring at -40 °C for 45 min. The reaction mixture was then poured onto 150 mL of saturated aqueous ammonium chloride and the aqueous layer was extracted (3 \times 100 mL) with EtOAc. The combined organic extracts were dried with anhydrous MgSO_4 ,

filtered, and concentrated under reduced pressure to afford silyl enol ether **90** as a dark orange oil (1.64 g, 91 %) which was used without further purification.

Ketone (88). To a solution of silyl enol ether **90** (0.688 g, 3.47 mmol, 1.00 equiv) dissolved in anhydrous THF (14.0 mL) was added *n*-BuLi (1.40 mL, 3.47 mmol, 2.50 M in hexanes) dropwise and stirred for 2 h under argon at rt. The reaction mixture was then cooled to -20 °C at which time HMPA (5.00 mL) and allyl iodide (0.350 mL, 3.82 mmol, 1.10 equiv) were added dropwise as a solution in anhydrous THF (5.00 mL). The reaction was allowed to slowly reach rt and stirred for 5 h until complete consumption of starting material was observed by TLC analysis. The reaction was then quenched with saturated aqueous ammonium chloride (20.0 mL) and the aqueous layer was extracted (3 × 30.0 mL) with EtOAc. The combined organic extracts were dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography (silica, 100% hexanes) afforded ketone (**88**) as a yellow oil (0.443 g, 77%).

Epoxide (87). A mixture of sodium hydride (0.058 g, 2.40 mmol, 2.00 equiv) and dry DMSO (2.00 mL) was stirred at 75-80 °C for 45 min under argon. A dark green solution was observed. The reaction was allowed to cool to rt and dry THF (2.00 mL) was added at which time the reaction was further cooled to -5 °C. A solution of trimethylsulfonium iodide (0.490 g, 2.40 mmol, 2.00 equiv) in dry dimethyl sulfoxide (2.50 mL) was added rapidly and the mixture was stirred for 5 min. A solution of ketone **88** (0.200 g, 1.20 mmol, 1.00 equiv) in THF (2.00 mL) was added dropwise and the reaction mixture was stirred for 10 min at 0 °C, then 2.5 h at rt until complete consumption of starting material was observed by TLC analysis. The reaction mixture was then quenched with H₂O and the aqueous layer was extracted (3 × 15.0 mL) with EtOAc.

The combined organic extracts were dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography (silica, 100% hexanes) afforded epoxide **87** as a clear colorless oil (0.165 g, 76%). **R_f** at 5% ethyl acetate in hexanes: 0.58. **¹H NMR** (500 MHz, CDCl₃), δ 5.85 (m, 1H), 4.99 (dq, 1H, *J* = 17.0, 1.9 Hz), 4.93 (dq, 1H, *J* = 10.1, 1.9 Hz), 2.65 (d, 1H, *J* = 5.1 Hz), 2.48 (d, 1H, *J* = 4.7 Hz), 2.19 (m, 1H), 2.09 (m, 1H), 1.73 (m, 1H), 1.61 (m, 2H), 1.49 (m, 1H), 1.36 (m, 1H), 1.26 (m, 2H), 1.00 (s, 3H), 0.92 (s, 3H). **¹³C NMR** (125 MHz, CDCl₃), δ 140.0, 114.2, 59.5, 53.6, 49.8, 39.6, 36.0, 32.6, 31.7, 30.3, 28.7, 20.8. **IR** (CHCl₃) 2926, 2859, 1734, 1640, 1458, 1363, 1259, 1098, 1014, 905, 806 cm⁻¹. **HRMS** (EI) calcd for C₁₂H₂₀O (M⁺) 180.1514, found 180.1513.

2-[2,3-dimethoxyphenyl]-propan-2-ol (92). To a solution of veratrol (**91**) (10.3 g, 74.5 mmol, 1.00 equiv) dissolved in anhydrous THF (50.0 mL) was added *n*-BuLi (31.4 mL, 2.50 M in hexanes, 78.4 mmol, 1.05 equiv) dropwise at -78 °C under argon. The mixture was stirred at 0 °C for a three hour period. A light yellow precipitate was observed. The mixture was then cooled to -60 °C and anhydrous acetone (5.50 mL, 74.5, 1.00 equiv) was added dropwise. The reaction was allowed to reach room temperature and stirred overnight (~10 h). The reaction was quenched with saturated aqueous ammonium chloride, the aqueous layer was then extracted (3 × 100 mL) with EtOAc. The combined organic extracts were dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Gradient flash chromatography, 5% ethyl acetate in hexanes to recover starting material (50%), then 20% ethyl acetate in hexanes afforded alcohol **92** as a pale yellow viscous oil (6.10 g, 42%). **R_f** at 5% ethyl acetate in hexanes: 0.15.

3-isopropylveratrol (86). A mixture of benzyl alcohol (**92**) (2.01 g, 10.2 mmol, 1.00 equiv), 85% phosphoric acid (1.50 mL) and Pd, 10 wt. % on activated carbon (0.204 g) dissolved in ethanol (20.0 mL) was hydrogenated under one atmosphere of H₂ (balloon pressure) at 60 °C until complete consumption of starting material was observed by TLC analysis (~24 h). The catalyst was removed by filtration over Celite and concentrated under reduced pressure. The residue was extracted (3 × 30.0 mL) with EtOAc and H₂O. The combined organic extracts were washed with saturated aqueous sodium carbonate, dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography (silica, 100% hexanes) afforded **86** as a pale yellow oil (1.61 g, 91%). **R_f** at 5% ethyl acetate in hexanes: 0.60.

6-Methyl-3-isopropylveratrol (96). To a solution of 3-isopropylveratrol (**86**) (0.100 g, 0.554 mmol, 1.00 equiv) and N,N,N',N'-tetramethylethylenediamine (0.130 mL, 0.830 mmol, 1.50 equiv) dissolved in anhydrous Et₂O (0.800 mL) was added *n*-BuLi (0.341 mL, 2.50 M in hexanes, 0.831 mmol, 1.50 equiv) dropwise under argon at 0 °C. After addition was complete, the mixture was stirred at rt for a two hour period. A light yellow precipitate was observed. The solution was re-cooled to 0 °C and MeI (0.075 mL, 1.11 mmol, 2.00 equiv) was added dropwise. A white precipitate immediately formed. The reaction mixture was then stirred at rt until complete consumption of starting material was observed by TLC analysis (~3 h) at which time the reaction was quenched with saturated aqueous sodium thiosulfate. The aqueous layer was then extracted (3 × 5.00 mL) with EtOAc. The combined organic extracts were dried with anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography (silica, 100% hexanes) afforded **96** as a clear colorless oil (0.089 g, 83 %). **R_f** at 5% ethyl acetate in hexanes: 0.70. **¹H NMR** (360 MHz, CDCl₃), δ 6.90 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.32

(septet, 1H, $J = 6.8$ Hz), 2.26 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (90 MHz, CDCl_3), δ 151.3, 150.5, 140.5, 129.5, 125.7, 121.0, 60.8, 60.0, 26.7, 23.7, 15.7. IR (CHCl_3) 2963, 2932, 2870, 2828, 1494, 1463, 1406, 1333, 1281, 1218, 1077, 1057, 1031, 916, 853, 812, 656 cm^{-1} . HRMS (EI) calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$ (M^+) 194.1307, found 194.1312.

Tertiary alcohol (85). To a solution of **96** (0.101 g, 0.511 mmol, 1.00 equiv) and *N,N,N',N'*-tetramethylethylenediamine (0.124 mL, 0.772 mmol, 1.50 equiv) dissolved in anhydrous Et_2O (0.750 mL) was added *n*-BuLi (0.340 mL, 2.50 M in hexanes, 0.831 mmol, 1.50 equiv) dropwise under argon at -78 °C. The reaction mixture was then stirred at rt for a four hour period and a bright yellow solution was observed. The solution was then re-cooled to -78 °C followed by dropwise addition of ketone **88** (0.135 g, 7.73 mmol, 1.50 equiv) as a 2.00 mL solution in Et_2O . The reaction was allowed to reach rt and stirred for 48 h. The resulting dark red mixture was then quenched with H_2O . The aqueous layer was then extracted (3×5.00 mL) with EtOAc. The combined organic extracts were dried with anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was left *in vacuo* for an eight hour period to remove the excess ketone **88**. Flash chromatography (silica, 0.5% Et_2O in hexanes) afforded the desired compound **85** as an opaque colorless viscous oil (0.075 g, 42%). R_f at 10% ethyl acetate in hexanes: 0.72. ^1H NMR (500 MHz, CDCl_3), δ 6.89 (d, 1H, $J = 7.9$ Hz), 6.80 (d, 1H, $J = 8.2$ Hz), 5.98 (m, 1H), 5.08 (d, 1H, $J = 18.6$ Hz), 4.94 (d, 1H, $J = 9.8$ Hz), 3.87 (s, 3H), 3.83 (s, 3H), 3.33 (d, 1H, $J = 13.9$ Hz), 3.27 (septet, 1H, $J = 6.9$ Hz), 2.52 (m, 1H), 2.26 (m, 2H), 1.64 (m, 2H), 1.36 (m, 4H), 1.20 (m, 8H), 1.00 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3), δ 150.8, 150.4, 142.6, 141.5, 129.0, 127.5, 121.2, 113.5, 75.4, 60.7, 60.0, 54.3, 43.5, 42.2, 38.1, 35.3, 32.3, 30.6, 26.7, 23.4, 21.5, 18.1. IR (CHCl_3) 3490, 3073, 2963, 2932, 2870, 1640, 1463, 1411, 1389, 1337,

1276, 1218, 1057, 1020, 910, 853, 801 cm^{-1} . **HRMS** (EI) calcd for $\text{C}_{23}\text{H}_{36}\text{O}_3$ (M^+) 360.2664, found 360.2678.

Ketal (84). An ozone stream was bubbled through a suspension of tertiary alcohol (**85**) (0.048 g, 0.130 mmol, 1.00 equiv) dissolved in MeOH (10.0 mL) at $-78\text{ }^\circ\text{C}$ until complete consumption of starting material was observed by TLC analysis (~ 2 h). The reaction mixture was then quenched with PPh_3 (0.180 g, 0.670 mmol, 5.00 equiv) at $-78\text{ }^\circ\text{C}$ for 30 min. then stirred for an additional 2.5 h at rt. The reaction was then concentrated under reduced pressure. Flash chromatography (0.5% Et_2O in hexanes) afforded hemiketal (**84**) as a viscous opaque colorless oil (0.043 g, 89%). R_f in 5% ethyl acetate in hexanes: 0.380. **^1H NMR (major)** (500 MHz, CDCl_3), δ 7.18 (d, 1H, $J = 8.2$ Hz), 6.92 (d, 1H, $J = 8.2$ Hz), 4.87 (d, 1H, $J = 4.4$ Hz), 3.83 (s, 3H), 3.81 (s, 3H), 3.46 (d, 1H, $J = 13.6$ Hz), 3.40 (s, 3H), 3.29 (septet, 1H, $J = 6.9$ Hz), 2.62 (d, 1H, $J = 13.2$ Hz), 2.04 (m, 2H), 1.92 (dd, 1H, $J = 11.7, 6.3$ Hz), 1.62 (m, 3H), 1.44 (m, 1H), 1.33 (m, 2H), 1.21 (dd, 7H, $J = 6.9, 2.5$ Hz), 1.16 (s, 3H), 0.94 (s, 3H). **^{13}C NMR (major)** (125 MHz, CDCl_3), δ 151.8, 150.1, 140.8, 129.6, 127.2, 120.7, 102.8, 85.4, 60.5, 54.6, 51.0, 39.5, 36.2, 34.8, 32.9, 32.1, 31.0, 29.7, 29.3, 26.7, 23.5, 19.5. **IR** (CHCl_3) 2958, 2926, 2865, 1729, 1458, 1406, 1276, 1109, 1036, 947, 864, 806 cm^{-1} . **HRMS** (EI) calcd for $\text{C}_{23}\text{H}_{36}\text{O}_4$ (M^+) 376.2614, found 376.2610.

Brussonol dimethyl ether (83). To a solution of hemiketal (**84**) (0.015 g, 0.043 mmol, 1.00 equiv) dissolved in CH_2Cl_2 (0.450 mL) was added $\text{BF}_3 \cdot \text{OEt}_2$ (11.0 μL , 0.085 mmol, 2.00 equiv) dropwise under argon at $-20\text{ }^\circ\text{C}$ until complete consumption of starting material was observed by TLC analysis (~ 1 h). The reaction was then quenched with saturated aqueous ammonium chloride. The aqueous layer was then extracted (3×5.00 mL) with EtOAc. The combined

organic extracts were dried with anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. Flash chromatography (silica, 1% Et_2O in hexanes) afforded **83** as clear colorless oil (0.014 g, 91%). R_f at 5% ethyl acetate in hexanes: 0.45. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 6.63 (s, 1H), 4.85 (d, 1H, $J = 6.6$ Hz), 3.82 (s, 3H), 3.81 (s, 3H), 3.27 (septet, 1H, $J = 6.9$ Hz), 2.78 (d, 1H, $J = 16.9$ Hz), 2.49 (d, 1H, $J = 16.9$ Hz), 2.11 (td, 1H, $J = 12.3, 6.9$ Hz), 1.98 (m, 1H), 1.91 (dd, 1H, $J = 12.3, 8.4$ Hz), 1.81 (m, 3H), 1.62 (m, 1H), 1.52 (m, 1H), 1.19 (m, 7H), 0.96 (s, 3H), 0.84 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 150.8, 148.8, 140.0, 137.7, 124.1, 116.4, 80.1, 75.9, 60.7, 59.7, 50.9, 39.6, 39.4, 32.1, 31.8, 30.6, 30.6, 26.7, 26.6, 23.8, 23.5, 16.2. **IR** (CHCl_3) 3416, 2958, 2932, 2865, 2354, 1729, 1634, 1458, 1415, 1333, 1259, 1092, 1051, 1014, 801 cm^{-1} . **HRMS** (EI) calcd for $\text{C}_{22}\text{H}_{32}\text{O}_3$ (M^+) 344.2351, found 344.2363.

General Experimental Procedure for the synthesis of (101b-120b): To a solution of TBS protected products **101a-120a** (67.0 mg, 0.200 mmol) dissolved in methanol (2.00 mL) was added $\text{Py}\cdot\text{Br}_3$ (3.00 mg, 0.010 mmol, 0.050 equiv) at 0 °C. The reaction was left stirring until the starting material was consumed according to TLC analysis (30 min - 1.5 h). The reaction was then quenched with sodium bicarbonate (1.00 mL). The aqueous layer was then extracted (3 x 10.0 mL) with EtOAc. The combined organic extracts were dried with anhydrous MgSO_4 , filtered and concentrated under reduced pressure. Flash chromatography (silica) afforded the products **101b-120b**.

R-Hept-1-en-4-ol (147): To a stirred solution of (-)-Ipc₂BOMe (8.20 g, 25.9 mmol, 1.40 equiv) in Et_2O (75.0 mL) at -78 °C under Ar was added allylmagnesium bromide (1.00 M in Et_2O , 24.1 mL, 1.30 equiv). The reaction mixture was allowed to reach rt and stirred for 1 hour after which

the mixture was re-cooled to $-78\text{ }^{\circ}\text{C}$. Butanal **146** (1.67 mL, 18.5 mmol, 1.00 equiv) was the added dropwise to the reaction mixture and allowed to stir for 2 h. The reaction was warmed to $0\text{ }^{\circ}\text{C}$. To this mixture was added 3M NaOH (5.40 mL) and 30% aq. H_2O_2 (9.40 mL) sequentially. The reaction mixture was allowed to stir at rt for 6 h after which the aqueous layer was extracted with Et_2O (3 x 75.0 mL). The organic extracts were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude material was distilled to give homoallylic alcohol **147** as clear oil (1.48 g, 70% yield). R_f at 10% ethyl acetate in hexanes: 0.30. $^1\text{H NMR}$ (360 MHz, CDCl_3), δ 5.80 (m, 1H), 5.11 (m, 1H), 5.07 (m, 1H), 3.62 (m, 1H), 2.25 (m, 1H), 1.87 (s, 1H), 1.39 (m, 4H), 0.90 (t, 3H, $J = 7.1\text{ Hz}$).

3R-Benzyloxy-hexanal (145): NaH (60 % disp. in mineral oil, 820 mg, 34.2 mmol, 3.00 equiv) was suspended in a 1:1 mixture of DMF:THF (40.0 mL) and cooled to $0\text{ }^{\circ}\text{C}$ under argon. To this mixture, alcohol **147** (1.30 g, 11.4 mmol, 1.00 equiv) dissolved in THF (9.00 mL), was added dropwise and stirred for 30 min. Benzyl bromide was then added (2.05 mL, 17.1 mmol, 1.50 equiv) followed by tetrabutylammonium iodide (421 mg, 1.14 mmol, 0.100 equiv). The reaction mixture was allowed to reach rt and stirred for 16 h. An aqueous solution of NH_4Cl (50.0 mL) was added to the reaction mixture at $0\text{ }^{\circ}\text{C}$. The aqueous layer was extracted with EtOAc (3 x 50.0 mL) and the organic extracts were dried over Na_2SO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica, 1 % ethyl acetate in hexanes) afforded the benzyl ether as yellowish oil (2.15 g, 92 % yield). R_f at 1% ethyl acetate in hexanes: 0.35.

A stream of ozone was bubbled through a solution of the benzyl ether (2.15 g, 10.5 mmol, 1.00 equiv) dissolved in a 4:1 mixture of CH_2Cl_2 :MeOH (100 mL) at $-78\text{ }^{\circ}\text{C}$ until complete consumption of starting material was observed by TLC analysis (30 min.). The

reaction mixture was added PPh₃ (8.30 g, 31.6 mmol, 3.00 equiv) at -78 °C stirred initially for 30 min. and then for an additional 2.5 h at rt. The solution was concentrated in vacuo and flash chromatography (silica, 5 % ethyl acetate in hexanes) afforded aldehyde **145** as a yellow oil (1.74 g, 80 % yield).^{55e} **R_f** at 5% ethyl acetate in hexanes: 0.30. **¹H NMR** (360 MHz, CDCl₃), δ 9.81 (t, 1H, *J* = 2.1 Hz), 7.32 (m, 5H), 4.56 and 4.52 (ABq, 2H, *J* = 11.3 Hz), 3.95 (m, 1H), 2.68 (dd, 1H, *J* = 7.1, 7.3 Hz), 2.56 (dd, 1H, *J* = 4.7, 5.1 Hz), 1.68 (m, 1H), 1.54 (m, 1H), 1.41 (m, 2H), 0.93 (t, 3H, *J* = 7.3 Hz).

6R-Benzyloxy-non-1-en-4R-ol (148): To a stirred solution of aldehyde **145** (700 mg, 3.39 mmol, 1.00 equiv) in CH₂Cl₂ (17.0 mL) at -78 °C under Ar was slowly added TiCl₄ (1.00 M solution in CH₂Cl₂, 3.39 mmol, 1.00 equiv). The resulting yellow solution was allowed to stir for 10 min. To this mixture was added allyltriphenylstannane (2.66 g, 6.79 mmol, 2.00 equiv) dissolved in CH₂Cl₂ (4.00 mL) dropwise over a 15 min. period. After 4 h, the reaction was quenched at -78 °C by a dropwise addition of a saturated solution of NaHCO₃ (20.0 mL) and allowed to reach rt. The mixture was then diluted with CH₃CN (50.0 mL) and stirred with the addition of KF (1.23 g, 20.9 mmol, 6.15 equiv) for 12 h. The suspension was then filtered through a pad of celite and the aqueous layer was extracted with EtOAc (3 x 75.0 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 5 % ethyl acetate in hexanes) afforded the homoallylic alcohol **148** as a clear viscous oil (750 mg, 90 % yield). **R_f** at 10% ethyl acetate in hexanes: 0.25. **¹H NMR** (500 MHz, CDCl₃), δ 7.30 (m, 5H), 5.83 (m, 1H), 5.12 (m, 1H), 5.08 (t, 1H, *J* = 1.2 Hz), 4.57 and 4.53 (ABq, 2H, *J* = 11.2 Hz), 3.97 (m, 1H), 3.72 (m, 1H), 2.77 (d, 1H, *J* = 3.4 Hz), 2.22 (m, 2H), 1.67 (m, 3H), 1.51 (m, 1H), 1.36 (m, 2H), 0.93 (t, 3H, *J* = 7.3 Hz).

Bromo-acetic acid 1R-(2R-benzyloxy-pentyl)-but-3-enyl ester (149): To a solution of alcohol **148** (750 mg, 3.02 mmol, 1.00 equiv) in CH₂Cl₂ (12.0 mL) at 0 °C under Ar was slowly added pyridine (0.200 mL, 2.42 mmol, 2.00 equiv) and bromoacetyl bromide (0.210 mL, 2.42 mmol, 2.00 equiv). After 6 h, the reaction was quenched with a saturated aqueous solution of NH₄Cl (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 30.0 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 1 % ethyl ether in hexanes) afforded bromoacetyl bromide **149** as a yellow oil (940 mg, 86 % yield). *R_f* at 5 % ethyl acetate in hexanes: 0.15. ¹H NMR (500 MHz, CDCl₃), δ 7.35 (m, 4H), 7.28 (m, 1H), 5.75 (m, 1H), 5.26 (m, 1H), 5.10 (d, 1H, *J* = 5.1 Hz), 5.07 (s, 1H), 4.53 and 4.40 (ABq, 2H, *J* = 11.1 Hz), 3.72 (s, 2H), 3.47 (m, 1H), 2.37 (m, 2H), 1.75 (m, 2H), 1.56 (m, 2H), 1.38 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz). ¹³C NMR (125 MHz, CDCl₃), δ 166.7, 138.5, 132.9, 128.3, 128.1, 127.6, 118.2, 74.9, 72.6, 71.2, 39.1, 38.6, 35.9, 26.1, 18.1, 14.2. IR (CH₂Cl₂) 696, 734, 920, 993, 1106, 1278, 1357, 1456, 1734, 2874, 2928, 2958, 3030, 3065 cm⁻¹. [*α*]_D²⁰ = +131 (*c* 0.43, CH₂Cl₂). HRMS (EI) calcd for C₁₈H₂₅ Br O₃ (M⁺) 368.0987, found 368.0983.

Bromo-acetic acid 3-benzyloxy-1-(2-oxo-propyl)-hexyl ester (150): A suspension of bromoacetyl bromide **149** (73.0 mg, 0.198 mmol, 1.00 equiv), PdCl₂ (3.50 mg, 0.020 mmol, 0.100 equiv) and Cu(OAc)₂ (7.30 mg, 0.0400 mmol, 0.200 equiv) in DMF:H₂O (7:1, 2.00 mL) was placed under O₂ balloon pressure and stirred at rt for 48 h. The reaction was then diluted with Et₂O (10.0 mL) and water (10.0 mL). The aqueous layer was extracted with Et₂O (3 x 10.0 mL) and the combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 10 % ethyl acetate in hexanes) afforded ketone **150** as a yellow viscous oil (51.0 mg, 70 % yield). *R_f* at 10 % ethyl acetate in hexanes: 0.20. ¹H NMR

(500 MHz, CDCl₃), δ 7.33 (m, 4H), 7.27 (m, 1H), 5.49 (m, 1H), 4.55 and 4.39 (ABq, 2H, $J = 11.3$ Hz), 3.90 (m, 2H), 3.48 (m, 1H), 2.74 (m, 2H), 2.12 (s, 3H), 1.80 (m, 2H), 1.56 (m, 2H), 1.36 (m, 2H), 0.93 (t, 3H, $J = 7.3$ Hz). ¹³C NMR (125 MHz, CDCl₃), δ 205.1, 166.7, 138.4, 128.4, 127.6, 74.9, 70.8, 70.2, 48.2, 40.9, 38.8, 35.7, 30.3, 18.1, 14.2. IR (CH₂Cl₂) 453, 696, 742, 977, 1073, 1183, 1293, 1357, 1411, 1453, 1723, 1742, 2870, 2958. $[\alpha]_D^{20} = -77.2$ (c 0.3, CH₂Cl₂). HRMS (EI) calcd for C₁₈H₂₅ Br O₄ (M – H⁺) 384.0936, found 384.0922.

6-(2-Benzyloxy-pentyl)-4-hydroxy-4-methyl-tetrahydro-pyran-2-one (152): To a stirred solution of ketone **150** (720 mg, 1.87 mmol, 1.00 equiv) in deoxygenated THF (18.7 mL) at –78 °C under Ar was added a SmI₂ solution (0.100 M solution in THF, 9.34 mmol, 93.5 mL, 5.00 equiv) dropwise. The dark blue mixture was allowed to stir at –78 °C for 6 h at which time the reaction was quenched with a saturated aqueous solution of NH₄Cl (150 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 x 75.0 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 30 % ethyl acetate in hexanes) afforded β -hydroxy lactone **152** as a white crystalline solid (530 mg, 95 % yield). R_f at 50 % ethyl acetate in hexanes: 0.40. ¹H NMR (500 MHz, CDCl₃), δ 7.33 (m, 4H), 7.27 (m, 1H), 4.86 (m, 1H), 4.62 and 4.49 (ABq, 2H, $J = 11.3$ Hz), 3.82 (m, 1H), 2.61 (d, 1H, $J = 17.4$ Hz), 2.42 (d, 1H, $J = 17.4$ Hz), 1.86 (dt, 1H, $J = 2.8, 14.1$ Hz), 1.76 (m, 1H), 1.68 (m, 2H), 1.58 (m, 2H), 1.51 (m, 1H), 1.39 (m, 2H), 1.33 (s, 3H), 0.94 (t, 3H, $J = 7.3$ Hz). ¹³C NMR (125 MHz, CDCl₃), δ 170.5, 138.7, 128.4, 127.9, 127.6, 75.1, 73.9, 71.9, 68.3, 44.1, 42.5, 41.3, 36.7, 30.3, 18.2, 14.3. IR (CH₂Cl₂) 457, 703, 738, 1057, 1122, 1267, 1376, 1453, 1723, 2870, 2928, 2962, 3053, 3410 cm⁻¹. $[\alpha]_D^{20} = -155.1$ (c 0.13, CH₂Cl₂). HRMS (EI) calcd for C₁₈H₂₆O₄ (M + H⁺) 306.1831, found 306.1838.

6-(2-Benzyloxy-pentyl)-4-methyl-5,6-dihydro-pyran-2-one (153): To a stirred solution of β -hydroxy lactone **152** (65.0 mg, 0.213 mmol, 1.00 equiv) in CH_2Cl_2 (2.20 mL) under Ar at 0 °C was added pyridine (0.350 mL, 4.24 mmol, 20.0 equiv) and SOCl_2 (0.003 mL, 0.424 mmol, 2.00 equiv) dropwise. The reaction mixture was allowed to stir for 2 h and then quenched with a saturated solution of aqueous NaHCO_3 (10.0 mL). The aqueous layer was extracted with EtOAc (3 x 10.0 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica, 10 % ethyl acetate in hexanes) afforded lactenone **153** as a clear oil (32.0 mg, 52 % yield). R_f at 10 % ethyl acetate in hexanes: 0.2. $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 7.29 (m, 4H), 7.24 (m, 1H), 5.75 (s, 1H), 4.59 and 4.43 (ABq, 2H, $J = 11.3$ Hz), 4.55 (m, 1H), 3.80 (m, 1H), 2.25 (m, 1H), 2.13 (m, 1H), 1.90 (s, 3H), 1.85 (m, 1H), 1.68 (m, 1H), 1.59 (m, 1H), 1.48 (m, 1H), 1.37 (m, 2H), 0.93 (t, 3H, $J = 7.3$ Hz). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 165.1, 157.2, 138.6, 128.3, 127.8, 127.6, 116.4, 74.8, 74.2, 71.8, 40.5, 36.5, 35.2, 22.8, 18.1, 14.3. **IR** (CH_2Cl_2) 691, 739, 849, 1020, 1066, 1150, 1250, 1307, 1389, 1452, 1723, 2874, 2952, 3031, 3505 cm^{-1} . $[\alpha]_D^{20} = -10.8$ (c 0.3, CH_2Cl_2). **HRMS** (EI) calcd for $\text{C}_{18}\text{H}_{24}\text{O}_3$ (M^+) 288.1725, found 288.1723

6R-Benzyloxy-2-methyl-non-1-en-4R-ol (154): To a solution of aldehyde **145** (3.81 g, 18.5 mmol, 1.00 equiv) in CH_2Cl_2 (50.0 mL) at -78 °C under Ar was added TiCl_4 (1.00 M in CH_2Cl_2 , 20.3 mL, 1.10 equiv) dropwise. The solution was allowed to stir for 0.5 h. The methylallylating reagent, $\text{CH}_2\text{C}(\text{CH}_3)\text{CH}_2\text{TMS}$, (16.2 mL, 92.4 mmol, 5.00 equiv) was then added dropwise. The reaction mixture was stirred for 8 h at -78 °C at which time the reaction was carefully quenched with a saturated NaHCO_3 solution (50.0 mL) and then allowed to reach rt. The aqueous layer was extracted with CH_2Cl_2 (3 x 50.0 mL) and the organic extracts were dried

over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 3 % ethyl acetate in hexanes) afforded homomethallylic alcohol **154** as a clear viscous oil (4.35 g, 90 % yield). *R_f* at 10 % ethyl acetate in hexanes: 0.35. ¹H NMR (500 MHz, CDCl₃), δ 7.31 (m, 5H), 4.82 (s, 1H), 4.76 (s, 1H), 4.57 and 4.52 (ABq, 2H, *J* = 11.3 Hz), 4.06 (m, 1H), 3.74 (m, 1H), 2.69 (s, 1H), 2.17 (m, 2H), 1.75 (s, 3H), 1.65 (m, 3H), 1.51 (m, 1H), 1.38 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz). ¹³C NMR (125 MHz, CDCl₃), δ 142.8, 138.5, 128.3, 127.8, 127.6, 112.9, 76.8, 71.3, 65.9, 46.3, 40.1, 35.9, 22.4, 18.6, 14.2. IR (CH₂Cl₂) 700, 736, 891, 1071, 1201, 1376, 1454, 1650, 2869, 2931, 3034, 3070, 3458 cm⁻¹. [*α*]_D²⁰ = - 88.7 (*c* 0.14, CH₂Cl₂). HRMS (EI) calcd for C₁₇H₂₆O₂ (M⁺) 262.1933, found 262.1937.

Acrylic acid 1*R*-(2*R*-benzyloxy-pentyl)-3-methyl-but-3-enyl ester (155): To a stirred solution of homomethallylic alcohol **154** (8.74 g, 33.3 mmol, 1.00 equiv) in CH₂Cl₂ (166 mL) was added DMAP (814 mg, 6.66 mmol, 0.200 equiv), DIPEA (29.0 mL, 166 mmol, 5.00 equiv), and acryloyl chloride (8.01 mL, 99.9 mmol, 3.00 equiv) at 0 °C under Ar. The reaction mixture was stirred for 18 hr at rt at which time the reaction temperature was lowered to 0 °C and carefully quenched with a saturated NaHCO₃ solution (200 mL) and then allowed to reach rt. The aqueous layer was extracted with Et₂O (3 x 150 mL) and the organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 1 % ethyl acetate in hexanes) afforded acrylate ester **155** as a clear viscous oil (9.77 g, 93 % yield). *R_f* at 1 % ethyl acetate in hexanes: 0.30. ¹H NMR (500 MHz, CDCl₃), δ 7.33 (m, 4H), 7.25 (m, 1H), 6.36 (dd, 1H, *J* = 1.3, 17.4 Hz), 6.08 (dd, 1H, *J* = 10.4, 17.3 Hz), 5.77 (dd, 1H, *J* = 1.7, 10.4 Hz), 5.41 (m, 1H), 4.81 (s, 1H), 4.72 (s, 1H), 4.49 and 4.41 (ABq, 2H, *J* = 11.1 Hz), 3.44 (m, 1H), 2.36 (m, 1H), 2.24 (m, 1H), 1.75 (m, 5H), 1.53 (m, 2H), 1.37 (m, 2H), 0.92 (t, 3H, *J* = 7.3 Hz). ¹³C

NMR (125 MHz, CDCl₃), δ 165.6, 141.5, 138.6, 130.2, 128.8, 128.2, 127.9, 127.7, 127.4, 112.5, 75.5, 71.5, 69.8, 43.6, 39.2, 36.3, 22.4, 18.2, 14.2. **IR** (CH₂Cl₂) 700, 741, 813, 901, 988, 1066, 1190, 1268, 1299, 1407, 1459, 1634, 1727, 2874, 2925, 2967, 3034, 3076 cm⁻¹. $[\alpha]_D^{20} = -141.3$ (c 0.22, CH₂Cl₂). **HRMS** (EI) calcd for C₂₀H₂₈O₃ (M⁺) 316.2038, found 316.2029.

6-(2-Benzyloxy-pentyl)-4-methyl-5,6-dihydro-pyran-2-one (153): To a refluxing solution of acrylate ester **155** (410 mg, 1.30 mmol, 1.00 equiv) in toluene (130 mL, 80 °C) under Ar was added a solution of Grubbs' second-generation catalyst **57** (165 mg, 0.194 mmol, 0.150 equiv) in toluene (19.5 mL) dropwise over a period of 2 hr. The reaction mixture was allowed to stir at 80 °C for 18 hr at which time the reaction was concentrated in vacuo. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded lactenone **153** as a clear viscous oil (352 mg, 94% yield).

6-(2-Hydroxy-pentyl)-4-methyl-tetrahydro-pyran-2-one (144): To a solution of lactenone **153** (90.0 mg, 0.312 mmol, 1.00 equiv) in EtOH (1.60 mL) was added Pd/C (45.0 mg) in one portion. The reaction vessel was evacuated under vacuum and placed under atmospheric H₂ balloon pressure. The reaction mixture was allowed to stir at rt for 48 hr until complete consumption of the starting material was observed via TLC analysis. The reaction was filtered through a plug of celite and concentrated in vacuo. Flash chromatography (silica, 40 % ethyl acetate in hexanes) afforded lactone **144** as a clear viscous oil (60.0 mg, 100 % yield). R_f at 35 % ethyl acetate in hexanes: 0.20. **¹H NMR** (500 MHz, CDCl₃), δ 4.55 (m, 1H), 3.93 (m, 1H), 2.62 (m, 1H), 2.46 (s, 1H), 2.02 (m, 2H), 1.86 (m, 1H), 1.68 (ddd, 1H, $J = 2.1, 9.7, 14.5$ Hz), 1.55 (ddd, 1H, $J = 2.6, 14.2, 17.1$ Hz), 1.36 (m, 4H), 1.19 (m, 1H), 0.98 (d, 3H, $J = 7.1$ Hz), 0.88 (t, 3H, $J = 7.3$ Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 171.6, 77.4, 66.7, 43.5, 40.1, 37.8, 37.4,

26.6, 21.6, 18.6, 13.9. **IR** (CH₂Cl₂) 572, 634, 791, 931, 984, 1025, 1092, 1233, 1380, 1458, 1729, 2874, 2958, 3432 cm⁻¹. $[\alpha]_D^{20} = -76.4$ (*c* 1.23, CH₂Cl₂). **HRMS** (EI) calcd for C₁₁H₂₀O₃ (M + H) 201.1484, found 201.1484.

6-[2-(tert-Butyl-diphenyl-silanyloxy)-pentyl]-4-methyl-tetrahydro-pyran-2-one (156): To a solution of lactone **144** (4.20 g, 21.0 mmol, 1.00 equiv) in DMF (105 mL) under Ar at 0 °C was added imidazole (4.30 g, 62.9 mmol, 3.00 equiv), DMAP (512 mg, 4.19 mmol, 0.200 equiv), and TBDPSCl (8.00 mL, 31.5 mmol, 1.50 equiv). The reaction mixture was allowed to stir at rt for 48 hr, quenched with H₂O (200 mL), and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 5 % ethyl acetate in hexanes) afforded the TBDPS protected lactone **156** (8.76 g, 95 % yield). *R_f* at 5 % ethyl acetate in hexanes: 0.20. **¹H NMR** (500 MHz, CDCl₃), δ 7.70, (m, 4H), 7.38 (m, 6H), 4.23 (m, 1H), 4.12 (m, 1H), 4.46 (m, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.69 (m, 3H), 1.43 (m, 2H), 1.26 (m, 3H), 1.06 (s, 9H), 0.94 (d, 3H, *J* = 6.3 Hz), 0.74 (t, 3H, *J* = 7.2 Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 171.1, 135.8, 129.5, 127.4, 69.4, 43.3, 39.8, 37.6, 37.3, 27.0, 26.4, 21.7, 19.4, 17.6, 13.9. **IR** (CH₂Cl₂) 509, 619, 713, 739, 817, 931, 1072, 1114, 1239, 1380, 1426, 1468, 1739, 2865, 2958, 3073, 3442. $[\alpha]_D^{20} = -66.2$ (*c* 0.7, CH₂Cl₂). **HRMS** (EI) calcd for C₂₃H₂₉O₃Si (M – C₄H₉) 381.1886, found 381.1890.

7-(tert-Butyl-diphenyl-silanyloxy)-5-hydroxy-3-methyl-decanoic acid methoxy-methyl-amide (157): To a solution of MeO(NH)Me•HCl (116 mg, 1.19 mmol, 5.00 equiv) in CH₂Cl₂ (2.65 mL) at -78 °C was added Me₃Al (0.600 mL, 1.11 mmol, 5.10 equiv) dropwise. The reaction mixture was allowed to warm to rt and stirred to 2 hr before the solution was re-cooled

to 0 °C and the TBDPS protected lactone **156** (95.0 mg, 0.217 mmol, 1.00 equiv) was added dropwise as a solution in CH₂Cl₂ (1.45 mL). The reaction mixture was allowed to stir for 18 hr at rt before it was carefully quenched at 0 °C with a 1M solution of Rochelle's salt (10.0 mL). After 1 hr, the mixture was extracted with ethyl acetate (3 x 20.0 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (silica, 35 % ethyl acetate in hexanes) afforded the hydroxy Weinreb amide **157** (65.1 mg, 64 % yield) along with the recovered starting material **156** (30.4 mg). *R_f* at 35 % ethyl acetate in hexanes: 0.20. ¹H NMR (500 MHz, CDCl₃), δ 7.69, (m, 4H), 7.39 (m, 6H), 3.95 (m, 2H), 3.66 (s, 3H), 3.17 (s, 3H), 2.39 (m, 1H), 2.28 (m, 1H), 2.18 (m, 1H), 1.51 (m, 5H), 1.15 (m, 2H), 1.06 (s, 10H), 0.91 (d, 3H, *J* = 6.7 Hz), 0.67 (t, 3H, *J* = 7.4 Hz). ¹³C NMR (125 MHz, CDCl₃), δ 135.9, 133.9, 133.6, 129.7, 127.5, 77.3, 76.7, 71.8, 66.0, 61.1, 45.1, 42.7, 38.5, 27.0, 26.5, 19.9, 19.2, 18.3, 13.9. IR (CH₂Cl₂) 615, 705, 737, 823, 906, 1008, 1110, 1386, 1427, 1466, 1650, 2859, 2935, 2957, 3434. [*α*]_D²⁰ = +26.1 (*c* 0.4, CH₂Cl₂).

7-(tert-Butyl-diphenyl-silanyloxy)-5-methoxy-3-methyl-decanoic acid methoxy-methyl-amide (143): To a solution of hydroxy amide **157** (1.21 g, 2.40 mmol, 1.00 equiv) in CH₂Cl₂ (30.0 mL) protected from light, was added Me₃OBF₄ (1.25 g, 8.40 mmol, 3.50 equiv), proton sponge (2.57 g, 12.0 mmol, 5.00 equiv) and 4Å molecular sieves (2.50 g) at rt under Ar. The reaction mixture was allowed to stir for 8 hr at which time the reaction was transferred to a separatory funnel, diluted with CH₂Cl₂ (70.0 mL), and washed with a 1M HCl solution (6 x 100 mL) and saturated NaHCO₃ (100 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 10 % ethyl acetate in hexanes) afforded methyl ether-amide **143** as a yellow viscous oil (1.05 g, 88 % yield). *R_f* at 10 % ethyl

acetate in hexanes: 0.25. **¹H NMR** (500 MHz, CDCl₃), δ 7.69, (m, 4H), 7.37 (m, 6H), 3.88 (m, 1H), 3.65 (s, 3H), 3.36 (m, 1H), 3.17 (s, 3H), 3.11 (s, 3H), 2.35 (m, 1H), 2.17 (m, 2H), 1.69 (m, 1H), 1.50 (m, 1H), 1.40 (m, 3H), 1.26 (m, 2H), 1.05 (s, 9H), 0.90 (d, 3H, *J* = 7.1 Hz), 0.71 (t, 3H, *J* = 7.3 Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 135.9, 135.9, 134.9, 134.4, 129.4, 129.4, 127.4, 127.3, 75.5, 70.5, 61.0, 55.4, 41.9, 41.5, 39.5, 27.0, 26.6, 20.1, 19.4, 17.7, 13.9. **IR** (CH₂Cl₂) 622, 710, 823, 999, 1108, 1382, 1428, 1464, 1671, 2859, 2947, 3070. [α]_D²⁰ = + 15.1 (*c* 0.2, CH₂Cl₂). **HRMS** (EI) calcd for C₂₆H₃₈NO₄Si (M – C₄H₉) 456.2570, found 456.2574.

10R-(tert-Butyl-diphenyl-silanyloxy)-8R-methoxy-6S-methyl-tridec-1-en-4R-ol (142): To a solution of compound **143** (1.05 g, 2.04 mmol, 1.00 equiv) in CH₂Cl₂ (13.6 mL) at - 78 °C was added a solution of DIBAL-H (1.00 M in toluene, 3.20 mL, 1.55 equiv) dropwise. The resulting solution was stirred at - 78 °C for 1 hr and quenched carefully with MeOH (3.00 mL). The reaction was poured into CH₂Cl₂ (20.0 mL) and washed with 1M HCl (50.0 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 5 % ethyl acetate in hexanes) afforded an aldehyde intermediate as a clear viscous oil (860 mg, 92 % yield). **R_f** at 20 % ethyl acetate in hexanes: 0.65. **¹H NMR** (500 MHz, CDCl₃), δ 9.67 (t, 1H, *J* = 2.1 Hz), 7.71 (m, 4H), 7.39 (m, 6H), 3.86 (m, 1H), 3.28 (m, 1H), 3.10 (s, 3H), 2.30 (m, 1H), 2.14 (m, 2H), 1.72 (m, 1H), 1.45 (m, 3H), 1.31 (m, 3H), 1.23 (m, 1H), 1.06 (s, 9H), 0.90 (d, 3H, *J* = 7.1 Hz), 0.76 (t, 3H, *J* = 7.3 Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 202.4, 135.9, 134.5, 129.5, 127.4, 75.5, 70.5, 55.6, 51.2, 41.8, 41.3, 39.4, 26.9, 24.9, 19.9, 19.3, 17.7, 13.9. **IR** (CH₂Cl₂) 611, 700, 746, 819, 1113, 1422, 1454, 1733, 2709, 2859, 2941, 3070 cm⁻¹. [α]_D²⁰ = + 27.3 (*c* 1.01, CH₂Cl₂). **HRMS** (EI) calcd for C₂₄H₃₃O₃Si (M – C₄H₉) 397.2199, found 397.2211.

To a stirred solution of (+)-Ipc₂Ballyl (1.00 M solution in pentane, 0.320 mL, 1.20 equiv) in Et₂O (0.200 mL) at - 78 °C under argon was added a solution of the previously prepared aldehyde (120 mg, 0.264 mmol, 1.00 equiv) in Et₂O (1.30 mL) dropwise. The reaction mixture was stirred for 2 hr at which time a solution of 3 M NaOH (0.500 mL) and 30% aqueous H₂O₂ were added slowly at 0 °C. The mixture was allowed to stir for 12 hr at rt. The aqueous layer was extracted with Et₂O (3 x 10.0 mL) and the combined extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 5 % ethyl acetate in hexanes) afforded homoallylic alcohol **142** as a clear viscous oil (110 mg, 84 % yield). *R_f* at 5 % ethyl acetate in hexanes: 0.25. ¹H NMR (500 MHz, CDCl₃), δ 7.69 (m, 4H), 7.39 (m, 6H), 5.82 (m, 1H), 5.14 (s, 1H), 5.12 (d, 1H, *J* = 3.6 Hz), 3.87 (m, 1H), 3.70 (m, 1H), 3.32 (m, 1H), 3.12 (s, 3H), 2.24 (m, 1H), 2.13 (m, 1H), 1.75 (m, 1H), 1.68 (m, 1H), 1.52 (m, 2H), 1.32 (m, 6H), 1.16 (m, 1H), 1.05 (s, 9H), 0.97 (m, 1H), 0.85 (d, 3H, *J* = 7.1 Hz), 0.72 (t, 3H, *J* = 7.3 Hz). ¹³C NMR (125 MHz, CDCl₃), δ 135.9, 134.9, 134.4, 129.4, 127.4, 117.9, 75.8, 70.5, 68.4, 55.8, 44.7, 42.7, 42.4, 42.0, 39.5, 26.1, 19.6, 19.4, 17.8, 14.1. IR (CH₂Cl₂) 619, 702, 827, 901, 1114, 1380, 1432, 1473, 2219, 2932, 3067, 3453, 3693 cm⁻¹. [*α*]_D²⁰ = + 16.1 (*c* 0.062, CH₂Cl₂). HRMS (EI) calcd for C₂₇H₃₉O₃Si (M – C₄H₉) 439.2668, found 439.2657.

11R-(tert-Butyl-diphenyl-silanyloxy)-5S-hydroxy-9R-methoxy-7S-methyl-tetradec-2-enoic acid methyl ester (158): To a stirred solution of homoallylic alcohol **142** (100 mg, 0.201 mmol, 1.00 equiv) in benzene (1.00 mL) at rt under Ar was added methyl acrylate (0.060 mL, 0.403 mmol, 3.00 equiv) and Grubbs' second-generation catalyst **57** (3.40 mg, 0.004 mmol, 0.020 equiv). The reaction mixture was allowed to stir at rt for 24 hr at which time the reaction was concentrated in vacuo. Flash chromatography (silica, 10 % ethyl acetate in hexanes) afforded

ester **158** as a clear viscous oil (100 mg, 90% yield). R_f at 15 % ethyl acetate in hexanes: 0.20. $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 7.69 (m, 4H), 7.38 (m, 6H), 6.98 (m, 1H), 5.89 (dt, 1H, $J = 15.7$ Hz), 3.82 (m, 2H), 3.73 (s, 3H), 3.29 (m, 1H), 3.11 (s, 3H), 2.32 (m, 2H), 1.86 (s, 1H), 1.71 (m, 2H), 1.31 (m, 9H), 1.05 (s, 9H), 0.94 (m, 1H), 0.83 (d, 3H, $J = 7.1$ Hz), 0.73 (t, 3H, $J = 7.3$ Hz). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 166.7, 145.9, 135.9, 134.5, 129.5, 127.4, 123.2, 75.9, 70.6, 67.7, 55.9, 51.4, 44.8, 42.4, 41.8, 40.9, 40.4, 39.2, 27.1, 26.2, 20.9, 19.6, 17.8, 14.1. IR (CH_2Cl_2) 699, 820, 1040, 1108, 1427, 1654, 1722, 2858, 2935, 2958, 3439 cm^{-1} . $[\alpha]_D^{20} = + 11.2$ (c 0.14, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{29}\text{H}_{41}\text{O}_5\text{Si}$ ($M - \text{C}_4\text{H}_9$) 497.2723, found 497.2720.

{6-[6-(tert-Butyl-diphenyl-silanyloxy)-4-methoxy-2-methyl-nonyl]-2-phenyl-[1,3]dioxan-4-yl}-acetic acid methyl ester (141**):** To a solution of ester **158** (100 mg, 0.180 mmol, 1.00 equiv) in THF (2.00 mL) at 0 °C under Ar were added freshly distilled benzaldehyde (0.020 mL, 0.198 mmol, 1.10 equiv) followed by $\text{KO}t\text{-Bu}$ (2.00 mg, 0.018 mmol, 0.100 equiv). The addition of base and benzaldehyde was repeated (three times for benzaldehyde and eight times for $\text{KO}t\text{-Bu}$) at 15-minute intervals until consumption of the starting material was complete as observed by TLC analysis. The reaction was then quenched with a solution of pH 7 buffered phosphate solution (5.00 mL). The aqueous layer was extracted with Et_2O (3 x 10.0 mL) and the combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica, 5 % ethyl acetate in hexanes) afforded benzylidene acetal **141** as a yellow viscous oil (95.0 mg, 80% yield). R_f at 20 % ethyl acetate in hexanes: 0.60. $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 7.70 (t, 4H, $J = 6.9$ Hz), 7.40 (m, 11H), 5.55 (m, 1H), 4.32 (m, 1H), 3.89 (m, 2H), 3.72 (s, 3H), 3.56 (m, 1H), 3.11 (s, 3H), 2.74 (m, 1H), 2.52, (m, 1H), 1.87 (m, 1H), 1.66 (m, 3H), 1.52 (m, 1H), 1.40 (m, 4H), 1.26 (m, 4H), 1.06 (s, 9H), 0.98 (m, 1H), 0.89 (d, 3H, $J =$

6.7 Hz), 0.72 (t, 3H, $J = 6.9$ Hz). ^{13}C NMR (125 MHz, CDCl_3), δ 171.2, 138.6, 134.4, 129.4, 128.1, 127.4, 126.1, 100.1, 75.6, 74.4, 73.2, 70.5, 55.7, 51.7, 43.4, 41.9, 40.8, 39.5, 37.1, 27.1, 25.4, 19.4, 17.7, 14.1. IR (CH_2Cl_2) 460, 517, 609, 700, 738, 818, 901, 1026, 1110, 1210, 1349, 1384, 1426, 1456, 1738, 2856, 2932, 2954, 3042, 3068 cm^{-1} . $[\alpha]_{\text{D}}^{20} = -10.6$ (c 0.6, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{36}\text{H}_{47}\text{O}_6\text{Si}$ (M - C_4H_9) 603.3142, found 603.3129.

6-[6-(tert-Butyl-diphenyl-silanyloxy)-4-methoxy-2-methyl-nonyl]-4-hydroxy-tetrahydro-pyran-2-one (140): A stirred solution of benzylidene acetal **141** (780 mg, 1.18 mmol, 1.00 equiv) in HOAc (11.8 mL) was hydrogenated over 10 % Pd(OH)₂ on carbon (780 mg) for 24 hr under H₂ at atmospheric pressure. Once complete, the catalyst was filtered off over a pad of celite and the filtrate was concentrated under vacuo to afford a mixture of lactone **140** and straight-chained diol. The crude mixture was re-dissolved in HOAc (9.00 mL) and H₂O (3.00 mL) and refluxed (70 °C) for 4 hr until complete consumption of the diol was observed by TLC analysis. The mixture was concentrated under reduced pressure and redissolved in EtOAc (40.0 mL). The organic layer was then quenched at 0 °C with a saturated solution of NaHCO₃ (20.0 mL) and the aqueous layer was extracted with EtOAc (3 x 30.0 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 40 % ethyl acetate in hexanes) afforded lactone **140** as a clear viscous oil (450 mg, 70% yield). R_f at 40 % ethyl acetate in hexanes: 0.20. ^1H NMR (500 MHz, CDCl_3), δ 7.69 (t, 4H, $J = 7.5$ Hz), 7.39 (m, 6H), 4.74 (m, 1H), 4.34 (m, 1H), 3.85 (m, 1H), 3.30 (m, 1H), 3.11 (s, 3H), 2.70 (dd, 1H, $J = 7.2, 15.8$ Hz), 2.59, (dd, 1H, $J = 6.3, 15.7$ Hz), 1.89 (m, 2H), 1.67 (m, 3H), 1.35 (m, 8H), 1.04 (s, 9H), 0.94 (m, 1H), 0.87 (d, 3H, $J = 6.7$ Hz), 0.72 (t, 3H, $J = 6.5$ Hz). ^{13}C NMR (125 MHz, CDCl_3), δ 170.7, 135.9, 134.3, 129.4, 127.4, 75.7, 73.6, 70.5, 62.5, 55.9, 43.2, 41.9, 39.4, 38.6, 36.4, 26.9, 25.3,

19.3, 17.8, 13.9. **IR** (CH₂Cl₂) 611, 698, 732, 819, 1076, 1105, 1253, 1385, 1427, 1461, 1714, 2855, 2931, 2957, 3047, 3071, 3425 cm⁻¹. [α]_D²⁰ = - 9.8 (c 0.65, CH₂Cl₂). **HRMS** (EI) calcd for C₂₈H₃₉O₅Si (M - C₄H₉) 483.2567, found 483.2576.

6-[6-(tert-Butyl-diphenyl-silanyloxy)-4-methoxy-2-methyl-nonyl]-4-methoxymethoxy-

tetrahydro-pyran-2-one (164): To a stirred solution of lactone **140** (200 mg, 0.370 mmol, 1.00 equiv) in CH₂Cl₂ (1.85 mL) at 0 °C under Ar was added DMAP (14.0 mg, 0.111 mmol, 0.300 equiv), DIPEA (0.390 mL, 2.22 mmol, 6.00 equiv), and MOMCl (0.110 mL, 1.48 mmol, 4.00 equiv). The reaction mixture was allowed to stir at rt for 18 hr at which time the reaction was re-cooled to 0 °C and quenched with a solution of saturated NaHCO₃ (10.0 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10.0 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 20 % ethyl acetate in hexanes) afforded MOM/TBDPS lactone **164** as a yellow viscous oil (210 mg, 97% yield). **R_f** at 40 % ethyl acetate in hexanes: 0.55. **¹H NMR** (500 MHz, CDCl₃), δ 7.68 (t, 4H, *J* = 7.3 Hz), 7.37 (m, 6H), 4.66 (s, 3H), 4.13 (m, 1H), 3.86 (m, 1H), 3.35 (s, 3H), 3.31 (m, 1H), 3.11 (s, 3H), 2.68 (m, 2H), 1.99 (d, 1H, *J* = 14.3 Hz), 1.90 (m, 1H), 1.68 (m, 3H), 1.47 (m, 1H), 1.38 (m, 2H), 1.27 (m, 4H), 1.04 (s, 9H), 0.94 (m, 2H), 0.87 (d, 3H, *J* = 6.3 Hz), 0.72 (t, 3H, *J* = 6.6 Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 169.9, 135.9, 134.6, 129.4, 127.4, 95.1, 75.5, 73.8, 70.5, 68.0, 55.8, 55.6, 43.3, 41.9, 39.5, 36.4, 34.6, 27.0, 25.4, 19.4, 17.8, 13.9. **IR** (CH₂Cl₂) 607, 700, 744, 817, 917, 1039, 1102, 1146, 1235, 1361, 1375, 1424, 1464, 1738, 2935, 2961, 3049, 3072 cm⁻¹. [α]_D²⁰ = - 19.1 (c 0.43, CH₂Cl₂). **HRMS** (EI) calcd for C₃₀H₄₃O₆Si (M - C₄H₉) 527.2829, found 527.2830.

[6-(6-Allyl-4-methoxymethoxy-tetrahydro-pyran-2-yl)-3-methoxy-5-methyl-1-propyl-hexyloxy]-tert-butyl-diphenyl-silane (139): To a solution of lactone **164** (100 mg, 0.171 mmol, 1.00 equiv) in Et₂O (1.70 mL) was added allylmagnesium bromide (1.00 M solution in Et₂O, 0.550 mL, 3.10 equiv) at - 78 °C under Ar. The reaction mixture was stirred until the starting material had been consumed as indicated by TLC analysis and was quenched with a saturated solution of NH₄Cl (5.00 mL) and extracted with Et₂O (3 x 10.0 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated in vacuo and used directly in the next step without further purification.

The resultant crude hemiketal **165** (130 mg, 0.208 mmol, 1.00 equiv) was dissolved in CH₂Cl₂ (2.10 mL) and cooled to - 78 °C under argon. To the solution was added Et₃SiH (0.330 mL, 2.08 mmol, 10.0 equiv) and TFA (0.100 mL, 1.04 mmol, 5.00 equiv). The temperature was allowed to warm to - 40 °C and the reaction mixture stirred for 0.5 h. The reaction was quenched with NaHCO₃ (10.0 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 10.0 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 2% ethyl acetate in hexanes then 10 % ethyl acetate in hexanes) afforded β-C-glycoside **139** as a yellow viscous oil (74.0 mg, 72% yield). **R_f** at 15 % ethyl acetate in hexanes: 0.55. **¹H NMR** (500 MHz, CDCl₃), δ 7.70 (t, 4H, *J* = 7.2 Hz), 7.39 (m, 6H), 5.85 (m, 1H), 5.07 (dd, 1H, *J* = 17.2 Hz), 4.99 (dd, 1H, *J* = 10.2 Hz), 4.67 (s, 2H), 4.02 (m, 1H), 3.90 (m, 1H), 3.73 (m, 2H), 3.38 (m, 1H), 3.37 (s, 3H), 3.11 (s, 3H), 2.28 (m, 1H), 2.12 (m, 1H), 1.73 (m, 4H), 1.36 (m, 9H), 1.06 (s, 9H), 0.96 (m, 1H), 0.85 (d, 3H, *J* = 6.3 Hz), 0.70 (t, 3H, *J* = 6.6 Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 135.9, 135.2, 134.8, 134.5, 129.4, 127.4, 116.3, 94.9, 75.6, 71.7, 70.5, 70.3, 69.8, 55.5, 55.3, 43.9, 41.9, 40.7, 39.6, 36.9, 36.1, 27.1, 25.8, 19.7, 19.4, 17.7, 13.9. **IR** (CH₂Cl₂) 611, 700, 740, 825, 847, 917, 1039, 1098, 1146, 1357, 1383, 1428, 1460, 2821, 2932, 3049, 3072, 3452

cm⁻¹. $[\alpha]_{\text{D}}^{20} = + 24.8$ (*c* 0.23, CH₂Cl₂). **HRMS** (EI) calcd for C₃₃H₄₉O₅Si (M – C₄H₉) 553.3349, found 553.3343.

{6-[6-(tert-Butyl-diphenyl-silanyloxy)-4-methoxy-2-methyl-nonyl]-4-methoxymethoxy-tetrahydro-pyran-2-yl}-acetaldehyde (168): A solution of β-C-glycoside **139** (74.0 mg, 0.121 mmol, 1.00 equiv) in CH₂Cl₂/MeOH (1:1, 2.00 mL) was cooled to -78 °C and a stream of O₃ was bubbled through the reaction mixture for 15 min. until the starting material had been consumed as indicated by TLC analysis. The reaction was then quenched by the addition of SMe₂ (0.050 mL, 0.604 mmol, 5.00 equiv) and allowed to stir at rt for 4 h at which time the reaction was concentrated in vacuo. Flash chromatography (silica, 15 % ethyl acetate in hexanes) afforded aldehyde **168** as a clear viscous oil (61.0 mg, 83 % yield). **R_f** at 15 % ethyl acetate in hexanes: 0.20. **¹H NMR** (500 MHz, CDCl₃), δ 9.78 (t, 1H, *J* = 2.1 Hz), 7.69 (m, 4H), 7.38 (m, 6H), 4.68 (s, 2H), 4.25 (m, 1H), 4.03 (m, 1H), 3.89 (m, 1H), 3.82 (m, 1H), 3.35 (m, 5H), 3.09 (s, 3H), 2.52 (ddd, 1H, *J* = 2.4, 8.4, 16.1 Hz), 2.37 (ddd, 1H, *J* = 2.2, 4.4, 16.0 Hz), 1.71 (m, 4H), 1.47 (m, 2H), 1.35 (m, 4H), 1.23 (m, 2H), 1.05 (s, 10H), 0.95 (m, 1H), 0.83 (d, 3H, *J* = 6.3 Hz), 0.69 (t, 3H, *J* = 7.3 Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 201.6, 135.9, 134.8, 134.4, 129.4, 127.3, 94.9, 75.5, 70.5, 69.9, 69.7, 67.8, 55.6, 55.4, 49.6, 43.6, 42.1, 39.6, 36.7, 36.2, 27.1, 25.6, 19.6, 19.4, 17.7, 13.9. **IR** (CH₂Cl₂) 609, 701, 737, 821, 914, 1038, 1106, 1155, 1375, 1431, 1467, 1728, 2723, 2932, 3048, 3073, 3438 cm⁻¹. $[\alpha]_{\text{D}}^{20} = + 28.1$ (*c* 0.05, CH₂Cl₂). **HRMS** (EI) calcd for C₃₂H₄₇O₆Si (M – C₄H₉) 555.3142, found 555.3135.

[6-(6-Hydroxy-4-methoxy-2-methyl-nonyl)-4-methoxymethoxy-tetrahydro-pyran-2-yl]-acetic acid (169): To a solution of aldehyde **168** (60.0 mg, 0.098 mmol, 1.00 equiv) in *t*-butyl

alcohol (1.20 mL) and H₂O (0.500 mL) cooled to 0 °C was added 2-methyl butene (1.01 mL, 9.80 mmol, 100 equiv) in one portion. A freshly prepared solution of NaClO₂ (53.0 mg, 0.588 mmol, 6.00 equiv) and NaH₂PO₄ (118 mg, 0.980 mmol, 10.0 equiv) in *t*-butyl alcohol (0.500 mL) and H₂O (0.500 mL) was then added dropwise. The reaction mixture was then allowed to stir at rt for 5 hr at which time the reaction was quenched by addition of a saturated solution of NH₄Cl (10.0 mL) and extracted with EtOAc (3 x 10.0 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo. Flash chromatography (silica, 25 % ethyl acetate in hexanes and 1 % acetic acid) afforded the TBDPS acid as a yellow viscous oil (55.0 mg, 90 % yield). **R_f** at 30 % ethyl acetate in hexanes: 0.25.

To a stirred solution of the TBDPS acid (55.0 mg, 0.088 mmol, 1.00 equiv) in THF (0.300 mL) at 0 °C was added TBAF (1.00 M solution in THF, 0.900 mL, 10.0 equiv). The reaction mixture was allowed to stir at rt for 72 h at which time the mixture was quenched with H₂O (5.00 mL) and extracted with EtOAc (3 x 10.0 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 60 % ethyl acetate in hexanes and 1 % acetic acid) afforded acid **169** as yellow viscous oil (27.0 mg, 87 % yield). **R_f** at 60 % ethyl acetate in hexanes: 0.20. **¹H NMR** (500 MHz, CDCl₃), δ 4.66 (s, 2H), 4.18 (m, 1H), 4.01 (m, 1H), 3.94 (m, 1H), 3.84 (t, 1H, *J* = 9.7 Hz), 3.53 (m, 1H), 3.36 (s, 3H), 3.34 (s, 3H), 2.43 (d, 2H, *J* = 6.2 Hz), 1.76 (m, 5H), 1.40 (m, 9H), 1.14 (m, 2H), 0.90 (m, 7H). **¹³C NMR** (125 MHz, CDCl₃), δ 174.4, 95.0, 78.2, 71.6, 69.8, 69.5, 68.9, 56.8, 55.3, 43.7, 41.3, 40.9, 40.1, 39.1, 36.9, 35.8, 27.3, 20.6, 18.8, 14.2. **IR** (CH₂Cl₂) 696, 734, 920, 993, 1106, 1278, 1357, 1456, 1734, 2874, 2928, 2958, 3030, 3065 cm⁻¹. **[α]_D²⁰** = - 72.3 (*c* 0.05, CH₂Cl₂). **HRMS** (EI) calcd for C₂₀H₃₉O₇ (M + H) 391.2696, found 391.2701.

7-Methoxy-13-methoxymethoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (170): To a stirred solution of acid **169** (19.0 mg, 0.049 mmol, 1.00 equiv) in THF (0.500 mL) at 0 °C under Ar was added Hunig's base (0.060 mL, 0.300 mmol, 6.00 equiv) followed by 2,4,6-trichlorobenzoyl chloride (0.040 mL, 0.250 mmol, 5.00 equiv). The reaction mixture was stirred at rt for 4 h, after which toluene was added (1.22 mL). This solution was added over 8 h by syringe pump to a refluxing solution of DMAP (150 mg, 1.22 mmol, 25.0 equiv) in toluene (38.0 mL). Upon addition, stirring was continued for an additional 16 h. The mixture was then allowed to cool to ambient temperature and concentrated in vacuo. The crude product was filtered over a pad short pad of silica using 60 % ethyl acetate in hexanes and then concentrated in vacuo. Flash chromatography (silica, 10 % ethyl acetate in hexanes) provided macrolactone **170** as a clear oil (27.0 mg, 87 % yield). R_f at 10 % ethyl acetate in hexanes: 0.20. $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 5.18 (m, 1H), 4.67 (s, 2H), 4.12 (m, 1H) 4.02 (t, 1H, $J = 2.9$ Hz), 3.59 (m, 2H), 3.37 (s, 3H), 3.30 (s, 3H), 2.57 (dd, 1H, $J = 4.1, 14.5$ Hz), 2.33 (dd, 1H, $J = 10.9, 14.5$ Hz), 1.71 (m, 5H), 1.40 (m, 8H), 1.22 (m, 1H), 1.13 (m, 1H), 0.97 (d, 3H, $J = 6.6$ Hz), 0.90 (t, 3H, $J = 7.2$ Hz). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 171.0, 94.9, 75.6, 75.4, 72.9, 69.9, 69.6, 56.2, 55.4, 44.2, 42.5, 42.3, 40.2, 37.2, 36.9, 35.9, 31.3, 25.6, 18.9, 13.9. **IR** (CH_2Cl_2) 727, 793, 922, 984, 992, 1039, 1087, 1150, 1197, 1249, 1274, 1345, 1440, 1458, 1656, 1730, 2927, 3441 cm^{-1} . $[\alpha]_{\text{D}}^{20} = -98.1$ (c 0.1, CH_2Cl_2). **HRMS** (EI) calcd for $\text{C}_{19}\text{H}_{33}\text{O}_6$ ($\text{M} - \text{CH}_3$) 357.2277, found 357.2290.

(-)-Neopeltolide macrocyclic core (138): To a stirred solution of macrolactone **170** (12.0 mg, 0.032 mmol, 1.00 equiv) in MeOH (0.500 mL) at 0 °C was added concentrated HCl (0.020 mL). The reaction mixture was allowed to stir at rt for 24 h at which time the reaction was cooled to 0

°C and quenched with a saturated solution of NaHCO₃ (5.00 mL). The aqueous layer was extracted with EtOAc (3 x 10.0 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 25% ethyl acetate in hexanes) afforded (-)-neopeltolide core **138** as a clear viscous oil (9.00 mg, 90% yield). *R_f* at 30 % ethyl acetate in hexanes: 0.30. **¹H NMR** (500 MHz, CDCl₃), δ 5.19 (m, 1H), 4.24 (t, 1H, *J* = 2.9 Hz), 4.19 (m, 1H), 3.68 (m, 1H), 3.59 (t, 1H, *J* = 9.8 Hz), 3.31 (s, 3H), 2.57 (m, 1H), 2.34 (m, 1H), 1.85 (1H), 1.65 (m, 2H), 1.51 (m, 5H), 1.37 (m, 4H), 1.24 (m, 2H), 0.97 (d, 3H, *J* = 7.1 Hz), 0.90 (t, 3H, *J* = 7.3 Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 171.1, 75.6, 74.8, 72.8, 69.1, 64.9, 56.2, 44.2, 42.5, 42.3, 40.1, 39.4, 38.3, 36.9, 31.4, 25.7, 18.9, 13.9. **IR** (CH₂Cl₂) 734, 797, 988, 1032, 1079, 1164, 1197, 1274, 1345, 1381, 1432, 1461, 1730, 2872, 2920, 3438 cm⁻¹. [*α*]_D²⁰ = - 48.4 (*c* 0.05, CH₂Cl₂). **HRMS** (EI) calcd for C₁₈H₃₂O₅ (M +) 328.2250, found 328.2246.

1-(tert-Butyl-diphenyl-silanyloxy)-6-methyl-hept-5-en-2-ol (205): 1-Chloro-3-methyl-2-butene (1.10 mL, 9.60 mmol, 3.00 equiv) was added dropwise to a stirred suspension of pre-activated Mg powder (466 mg, 19.2 mmol, 6.00 equiv) in THF (9.60 mL) at 0 °C under Ar and stirred for 1.5 h. Meanwhile to a solution of **207** (1.00 g, 3.20 mmol, 1.00 equiv) in THF (16.0 mL) at -40 °C under Ar, was added Li₂CuCl₄ (0.100 M solution in THF, 0.160 mmol, 0.050 equiv). The previously made Grignard reagent **206** was then added dropwise to the reaction mixture and allowed to stir for 1 h at -40 °C, at which time the reaction temperature was warmed to 0 °C and quenched with sat. NH₄Cl (50.0 mL). The reaction mixture was then allowed to reach rt. The aqueous layer was extracted with EtOAc (3 × 30.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 2 % ethyl acetate in hexanes) afforded **205** as a clear viscous oil (1.21 g, 99% yield): *R_f* at 5% ethyl

acetate in hexanes 0.30; **¹H NMR** (500 MHz, CDCl₃), δ 7.72 (m, 4H), 7.44 (m, 6H), 5.13 (m, 1H), 3.77 (m, 1H), 3.71 (dd, 1H, *J* = 10.1, 3.5 Hz), 3.55 (dd, 1H, *J* = 10.1, 7.3 Hz), 2.11 (m, 2H), 1.71 (s, 3H), 1.62 (s, 3H), 1.54 (m, 1H), 1.46 (m, 1H), 1.12 (s, 9H). **¹³C NMR** (125 MHz, CDCl₃), δ 135.5, 135.5, 133.2, 133.1, 131.8, 129.7, 127.7, 123.9, 71.4, 68.0, 32.8, 26.8, 25.6, 24.0, 19.2, 17.6. **IR** (CH₂Cl₂) 610, 703, 736, 825, 1006, 1109, 1427, 1471, 2857, 2928, 3050, 3068, 3456, 3578 cm⁻¹. **[α]_D²⁰** = + 17.8 (*c* 0.40, CH₂Cl₂). **HRMS** (EI) calcd for C₂₄H₃₄O₂Si (M – C₄H₉) 325.1624, found 325.1623.

2-Methoxymethoxy-6-methyl-hept-5-en-1-ol (223): To a stirred solution of **205** (300 mg, 0.78 mmol, 1.00 equiv) in CH₂Cl₂ (4.00 mL) was added DMAP (29.0 mg, 0.240 mmol, 0.300 equiv), DIPEA (0.680 mL, 3.92 mmol, 5.00 equiv), and MOMCl (0.180 mL, 2.35 mmol, 3.00 equiv) at 0 °C under Ar. The reaction mixture was stirred for 18 h at rt, at which time the temperature was lowered to 0 °C and quenched with a saturated aqueous solution of NaHCO₃ (10.0 mL) and deionized H₂O (10.0 mL) and then allowed to reach rt. The aqueous layer was extracted with Et₂O (3 × 20.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 1% ether in hexanes) afforded the MOM protected diol as a light yellow oil (304 mg, 91% yield): **R_f** at 1% ether in hexanes 0.30;

To a solution of the MOM-protected diol (1.60 g, 3.75 mmol, 1.00 equiv) in THF (18.8 mL) was added TBAF (1.00 M solution in THF, 5.63 mmol, 1.50 equiv) at 0 °C under Ar. The reaction mixture was stirred for 6 h at rt, at which time the reaction temperature was lowered to 0 °C and quenched with deionized H₂O (50.0 mL) and then allowed to reach rt. The aqueous layer was extracted with EtOAc (3 × 25.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 20 % ethyl acetate in hexanes)

afforded **223** as a yellow viscous oil (680 mg, 97 % yield): R_f at 20 % ethyl acetate in hexanes 0.20; $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 5.08 (m, 1H), 4.74 (d, 1H, $J = 6.9$ Hz), 4.68 (d, 1H, $J = 6.9$ Hz), 3.54 (m, 3H), 3.43 (s, 3H), 3.13 (dd, 1H, $J = 3.20, 8.8$ Hz), 2.07 and 2.04 (ABq, 2H, $J = 7.3$ Hz), 1.68 (s, 3H), 1.60 (s, 3H), 1.56 (m, 1H), 1.46 (m, 1H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 132.2, 123.6, 97.1, 82.0, 65.8, 55.6, 31.7, 25.7, 23.9, 17.7. **IR** (CH_2Cl_2) 833, 917, 1035, 1105, 1146, 1213, 1375, 1453, 2932, 3445 cm^{-1} . $[\alpha]_{\text{D}}^{20} = +228$ (c 0.33, CH_2Cl_2). **HRMS** (EI) calcd for $\text{C}_{10}\text{H}_{20}\text{O}_3$ (M - H) 187.1334, found 187.1335.

5-Methoxymethoxy-9-methyl-deca-1,8-dien-4-ol (204): To a stirred solution of **223** (2.00 g, 10.6 mmol, 1.00 equiv) in CH_2Cl_2 (106 mL) containing preactivated 4 Å molecular sieves (1.00 g/ mmol) was added NMO (3.74 g, 31.9 mmol, 3.00 equiv), and TPAP (374 mg, 1.06 mmol, 0.100 equiv) at rt under Ar. The reaction mixture was allowed to stir for 1 h at rt, at which time the mixture was filtered through a plug of silica (*ca.* 3 mm) to afford the corresponding aldehyde as a clear oil (1.60 g, 81% yield): R_f at 40 % ethyl acetate in hexanes 0.85.

To a stirred solution of (+)-Ipc₂BOMe (9.51 g, 30.1 mmol, 1.40 equiv) in Et_2O (75.0 mL) at -78 °C under Ar was added allylmagnesium bromide (1.00 M solution in Et_2O , 27.9 mmol, 1.30 equiv). The reaction mixture was allowed to reach rt and stirred for 1 h, after which time the mixture was re-cooled to -78 °C. The previously synthesized aldehyde (4.00 g, 21.5 mmol, 1.00 equiv) was then added dropwise to the reaction mixture, which was allowed to stir for 2 h. The reaction was warmed to 0 °C. To this mixture were added 3 M NaOH (7.50 mL) and 30% aqueous H_2O_2 (15.0 mL) and deionized H_2O (50.0 mL) sequentially. The reaction mixture was allowed to stir at rt for 6 h, after which the aqueous layer was extracted with Et_2O (3 × 50.0 mL). The organic extracts were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash

chromatography (silica, 10 % ethyl acetate in hexanes) afforded **204** as a clear oil (3.43 g, 70% yield): R_f at 10% ethyl acetate in hexanes 0.20; $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 5.87 (m, 1H), 5.10 (m, 3H), 4.72 (d, 1H, $J = 6.6$ Hz), 4.62 (d, 1H, $J = 6.9$ Hz), 3.64 (m, 1H), 3.54 (m, 1H), 3.42 (s, 3H), 2.85 (m, 1H), 2.22 (m, 2H), 2.11 (m, 1H), 2.02 (m, 1H), 1.67 (s, 3H), 1.62 (m, 1H), 1.56 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 135.4, 132.1, 123.8, 117.1, 97.4, 83.2, 72.5, 55.8, 36.5, 30.6, 25.6, 24.2, 17.6. **IR** (CH_2Cl_2) 735, 915, 1033, 1263, 1446, 1641, 1686, 2927, 3060, 3438 cm^{-1} . $[\alpha]_{\text{D}}^{20} = +150$ (c 0.14, CH_2Cl_2). **HRMS** (EI) calcd for $\text{C}_{13}\text{H}_{24}\text{O}_3$ (M^+) 228.1725, found 228.1728.

(1-Allyl-2-methoxymethoxy-6-methyl-hept-5-enyloxy)-triethyl-silane (224): To a solution of **204** (400 mg, 1.74 mmol, 1.00 equiv) in DMF (8.60 mL) was added DMAP (65.0 mg, 0.520 mmol, 0.300 equiv), imidazole (475 mg, 6.95 mmol, 4.00 equiv), and TESCOI (0.750 mL, 4.34 mmol, 2.50 equiv) at 0 °C under Ar. The reaction mixture was stirred for 24 h at rt, at which time the reaction temperature was lowered to 0 °C and quenched with deionized H_2O (50.0 mL) and then allowed to reach rt. The aqueous layer was extracted with Et_2O (3×25.0 mL), and the organic extracts were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica, 1% ether in hexanes) afforded **224** as a light yellow oil (540 mg, 90% yield): R_f at 1% ether in hexanes 0.35; $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 5.83 (m, 1H), 5.11 (m, 1H), 5.05 (m, 2H), 4.76 (d, 1H, $J = 6.6$ Hz), 4.62 (d, 1H, $J = 6.6$ Hz), 3.73 (m, 1H), 3.51 (m, 1H), 3.39 (s, 3H), 2.26 (m, 2H), 2.13 (m, 1H), 2.02 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.58 (m, 1H), 1.47 (m, 1H), 0.95 (t, 9H, $J = 7.6$ Hz), 0.59 (q, 6H, $J = 7.8$ Hz). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 135.7, 131.7, 124.3, 116.7, 96.3, 80.2, 74.4, 55.7, 37.7, 30.8, 25.6, 24.5, 17.7, 6.9, 5.1. **IR** (CH_2Cl_2) 738, 915, 1006, 1036, 1102, 1150, 1238, 1381, 1414, 1458, 1642, 2880, 2912, 2953

cm⁻¹. $[\alpha]_D^{20} = -133$ (*c* 0.33, CH₂Cl₂). **HRMS** (EI) calcd for C₁₉H₃₈O₃Si (M⁺) 342.2590, found 342.2595.

4-Hydroxy-5-methoxymethoxy-9-methyl-dec-8-en-2-one (226): To a solution of **224** (75.0 mg, 0.220 mmol, 1.00 equiv) in DMF:H₂O (2.20 ml, 7:1) was added PdCl₂ (4.00 mg, 0.020 mmol, 0.100 equiv) and Cu(OAc)₂ (8.00 mg, 0.040 mmol, 0.200 equiv). The reaction mixture was allowed to stir under O₂ (1.00 atm) at rt for 48 h. The reaction was then diluted with EtOAc (10.0 mL) and water (20.0 mL). The aqueous layer was extracted with EtOAc (3 × 15.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 10 % ethyl acetate in hexanes) afforded **226** as a yellow oil (60.0 mg, 77 % yield): **R_f** at 10 % ethyl acetate in hexanes 0.20; **¹H NMR** (500 MHz, CDCl₃), δ 5.10 (m, 1H), 4.80 (d, 1H, *J* = 6.3 Hz), 4.64 (d, 1H, *J* = 6.3 Hz), 4.23 (m, 1H), 3.53 (m, 1H), 3.39 (s, 3H), 2.70 (dd, 1H, *J* = 16.4, 7.6 Hz), 2.49 (dd, 1H, *J* = 16.4, 3.8 Hz), 2.16 (s, 3H), 2.11 (m, 1H), 2.02 (m, 1H), 1.68 (s, 3H), 1.61 (s, 3H), 1.48 (m, 1H), 1.37 (m, 1H), 0.93 (t, 9H, *J* = 7.9 Hz), 0.59 (q, 6H, *J* = 8.1 Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 207.5, 132.1, 123.9, 96.5, 80.7, 71.1, 55.7, 46.5, 31.6, 31.4, 25.6, 24.4, 17.7, 6.8, 6.5, 5.8, 4.8. **IR** (CH₂Cl₂) 736, 839, 1032, 1098, 1150, 1239, 1357, 1375, 1412, 1460, 1719, 2880, 2912, 2957, 3438 cm⁻¹. $[\alpha]_D^{20} = -76.9$ (*c* 0.13, CH₂Cl₂). **HRMS** (EI) calcd for C₁₉H₃₈O₄Si (M⁺) 358.2539, found 358.2556.

4-Hydroxy-5-methoxymethoxy-9-methyl-dec-8-en-2-one (227): To a solution of **226** (480 mg, 1.34 mmol, 1.00 equiv) in THF (14.0 mL) was added TBAF (1.00 M solution in THF, 1.34 mmol, 1.00 equiv) at 0 °C under Ar. The reaction mixture was stirred for 6 h at rt, at which time the reaction temperature was lowered to 0 °C and quenched with deionized H₂O (25.0 mL) and

then allowed to reach rt. The aqueous layer was extracted with EtOAc (3 × 25.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 25 % ethyl acetate in hexanes) afforded **227** as a clear viscous oil (297 mg, 91 % yield): **R_f** at 25 % ethyl acetate in hexanes 0.20; **¹H NMR** (500 MHz, CDCl₃), δ 5.04 (m, 1H), 4.69 (d, 1H, *J* = 6.6 Hz), 4.58 (d, 1H, *J* = 6.6 Hz), 4.02 (m, 1H), 3.52 (m, 1H), 3.37 (s, 3H), 2.59 (dd, 1H, *J* = 16.7, 9.20 Hz), 2.52 (dd, 1H, *J* = 16.7, 3.20 Hz), 2.20 (s, 3H), 2.07 (m, 1H), 1.99 (m, 1H), 1.63 (s, 3H), 1.56 (s, 3H), 1.50 (m, 1H), 1.38 (m, 1H). **¹³C NMR** (125 MHz, CDCl₃), δ 208.6, 131.9, 123.5, 97.1, 82.1, 69.4, 55.6, 45.2, 31.1, 30.5, 25.4, 23.8, 17.4. **IR** (CH₂Cl₂) 921, 1032, 1073, 1150, 1213, 1265, 1361, 1375, 1442, 1712, 2924, 3449 cm⁻¹. [**α**]_D²⁰ = + 277 (*c* 0.14, CH₂Cl₂). **HRMS** (EI) calcd for C₁₃H₂₄O₄ (M⁺) 244.1675, found 244.1668.

5-Methoxymethoxy-9-methyl-dec-8-ene-2,4-diol (203): To a solution of tetramethylammonium triacetoxyborohydride (11.8 g, 44.6 mmol, 10.0 equiv) in anhydrous CH₃CN (25.0 mL) was added anhydrous HOAc (25.0 mL) and the mixture was stirred at rt for 0.5 h under Ar. The mixture was cooled to -40 °C and a solution of **227** (1.09 g, 4.46 mmol, 1.00 equiv) in anhydrous CH₃CN (45.0 mL) was added dropwise. The reaction mixture was then allowed to stir at -20 °C for 48 h. The reaction was quenched with a 0.5 M aqueous solution of sodium potassium tartrate (25.0 mL) and the mixture was allowed to warm to rt. The reaction mixture was then carefully neutralized with a saturated aqueous solution of NaHCO₃ (100 mL) at 0 °C and then allowed to warm to rt. The aqueous layer was extracted with CH₂Cl₂ (3 × 50.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 40 % ethyl acetate in hexanes) afforded **203** as a clear viscous oil (910 mg, 83 % yield): **R_f** at 40 % ethyl acetate in hexanes 0.20; **¹H NMR** (500 MHz, CDCl₃), δ 5.00

(m, 1H), 4.65 (d, 1H, $J = 6.9$ Hz), 4.53 (d, 1H, $J = 6.6$ Hz), 4.01 (m, 1H), 3.79 (m, 1H), 3.67 (d, 1H, $J = 6.9$ Hz), 3.44 (m, 1H), 3.34 (m, 1H), 3.32 (s, 3H), 3.22 (broad s, 1H), 2.02 (m, 1H), 1.94 (m, 1H), 1.59 (s, 3H), 1.51 (s, 3H), 1.50 (m, 2H), 1.37 (m, 2H), 1.14 (d, 3H, $J = 6.3$ Hz). ^{13}C NMR (125 MHz, CDCl_3), δ 131.8, 123.7, 97.3, 83.8, 69.7, 64.5, 55.6, 39.3, 30.8, 25.5, 24.1, 23.5, 17.5. IR (CH_2Cl_2) 833, 917, 1035, 1150, 1209, 1375, 1446, 1642, 1723, 2924, 3408 cm^{-1} . $[\alpha]_{\text{D}}^{20} = +115$ (c 0.28, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{13}\text{H}_{26}\text{O}_4$ (M^+) 246.1831, found 246.1831.

4-Allyl-2,2-dimethyl-5-(4-methyl-pent-3-enyl)-[1,3]dioxolane (225): To a solution of **204** (67.0 mg, 0.290 mmol, 1.00 equiv) in 95:5 solvent mixture of $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (5.87 mL) was added LiBF_4 (1.00 M solution in CH_3CN , 2.93 mmol, 10.0 equiv). The reaction mixture was then heated to reflux (75 °C) and allowed to stir for 1 h. After cooling, the reaction was quenched with a saturated aqueous solution of NaHCO_3 (10.0 mL). The aqueous layer was extracted with EtOAc (3×10.0 mL), and the organic extracts were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica, 15% ethyl acetate in hexanes) afforded the corresponding diol as a white crystalline solid (48.0 mg, 89% yield): R_f at 20% ethyl acetate in hexanes 0.20.

To a stirred solution of the synthesized diol (25.0 mg, 0.140 mmol, 1.00 equiv) in THF (2.70 mL) was added CSA (3.20 mg, 0.020 mmol, 0.100 equiv), and 2,2-dimethoxypropane (0.170 mL, 1.36 mmol, 10.0 equiv) at 0 °C under Ar. The reaction mixture was allowed to stir at rt for 5 h, at which time the reaction was quenched with a saturated aqueous solution of NaHCO_3 (5.00 mL). The aqueous layer was extracted with Et_2O (3×5.00 mL), and the organic extracts were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica, 1%

ether in hexanes) afforded **225** as a yellow oil (25.0 mg, 83% yield): R_f at 1% ether in hexanes 0.40; $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 5.84 (m, 1H), 5.10 (m, 3H), 4.08 (m, 2H), 2.28 (m, 1H), 2.18 (m, 2H), 2.04 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.57 (m, 1H), 1.45 (s, 3H), 1.40 (m, 1H), 1.34 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 134.9, 132.3, 123.7, 117.0, 107.6, 77.4, 77.3, 34.6, 29.8, 28.5, 25.9, 25.7, 24.7, 17.7. IR (CH_2Cl_2) 911, 1059, 1214, 1377, 1449, 1639, 1729, 2858, 2927 cm^{-1} . $[\alpha]_D^{20} = +56.7$ (c 0.03, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{24}\text{O}_2$ (M^+) 224.1776, found 224.1781.

Acetic acid 6-(2-acetoxy-propyl)-5-methoxymethoxy-tetrahydro-pyran-2-yl ester (222): A stream of ozone was bubbled through a solution of **203** (750 mg, 3.05 mmol, 1.00 equiv) dissolved in CH_2Cl_2 (60.0 mL) at $-78\text{ }^\circ\text{C}$ until complete consumption of starting material was observed by TLC analysis (30 min). To the reaction mixture was added PPh_3 (4.00 g, 15.3 mmol, 5.00 equiv) at $-78\text{ }^\circ\text{C}$, and the resulting mixture was stirred initially for 0.5 h and then for an additional 2.5 h at rt. The solution was concentrated in vacuo, and flash chromatography (silica, 70% ethyl acetate in hexanes) afforded the hemiacetal as a clear viscous oil (535 mg, 80% yield): R_f at 70 % ethyl acetate in hexanes 0.20.

To a solution of the synthesized hemiacetal (700 mg, 3.18 mmol, 1.00 equiv) in CH_2Cl_2 (16.0 mL) was added DMAP (117 mg, 0.950 mmol, 0.300 equiv), pyridine (0.780 mL, 9.54 mmol, 3.00 equiv), and Ac_2O (0.750 mL, 7.95 mmol, 2.50 equiv) at $0\text{ }^\circ\text{C}$ under Ar. The reaction mixture was stirred for 12 h at rt, at which time the reaction temperature was lowered to $0\text{ }^\circ\text{C}$ and quenched with saturated aqueous solution of NaHCO_3 (25.0 mL) and then allowed to warm to rt. The aqueous layer was extracted with EtOAc ($3 \times 25.0\text{ mL}$), and the organic extracts were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica, 20% ethyl

acetate in hexanes) afforded **222** as a yellow oil (765 mg, 79% yield): R_f at 20% ethyl acetate in hexanes 0.20; $^1\text{H NMR}$ (500 MHz, CDCl_3), **Minor diastereomer:** δ 5.59 (dd, 1H, $J = 8.5, 1.3$ Hz), 5.04 (m, 1H), 4.59 (d, 2H, $J = 6.9$ Hz), 3.45 (m, 1H), 3.34 (d, 3H, $J = 1.0$ Hz), 3.26 (m, 1H), 2.21 (m, 1H), 2.08 (m, 1H), 1.99 (s, 3H), 1.98 (s, 3H), 1.78 (m, 2H), 1.53 (m, 2H), 1.20 (d, 3H, $J = 6.30$ Hz). **Major diastereomer:** δ 5.99 (s, 1H), 5.05 (m, 1H), 4.70 (dd, 2H, $J = 6.9, 1.0$ Hz), 3.64 (t, 1H, $J = 10.1$ Hz), 3.36 (d, 3H, $J = 1.0$ Hz), 3.26 (m, 1H), 2.08 (m, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.78 (m, 2H), 1.53 (m, 2H), 1.19 (d, 3H, $J = 6.3$ Hz). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 142.8, 138.5, 128.3, 127.8, 127.6, 112.9, 76.8, 71.3, 65.9, 46.3, 40.1, 35.9, 22.4, 18.6, 14.2. **IR** (CH_2Cl_2) 944, 1043, 1109, 1249, 1374, 1443, 1737, 2938, 3452 cm^{-1} . $[\alpha]_D^{20} = +463$ (c 0.40, CH_2Cl_2). **HRMS** (EI) calcd for $\text{C}_{14}\text{H}_{24}\text{O}_7$ (M^+) 305.1600, found 305.1602.

Acetic acid 2-(6-allyl-3-methoxymethoxy-tetrahydro-pyran-2-yl)-1-methyl-ethyl ester (230):

To a stirred solution of **222** (550 mg, 1.81 mmol, 1.00 equiv) in CH_2Cl_2 (11.0 mL) was added allylTMS (1.20 mL, 7.24 mmol, 4.00 equiv), and $\text{BF}_3 \cdot \text{OEt}_2$ (0.450 mL, 3.62 mmol, 2.00 equiv) at -78 °C under Ar. The reaction mixture was stirred for 3 h, at which time the reaction was quenched with a saturated aqueous solution of NaHCO_3 (25.0 mL) at -78 °C and slowly allowed to reach rt. The aqueous layer was extracted with CH_2Cl_2 (3×25.0 mL), and the organic extracts were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded **230** as a light yellow oil (440 mg, 87% yield): R_f at 10% ether in hexanes 0.20; $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 5.76 (m, 1H), 5.02 (m, 3H), 4.71 (d, 1H, $J = 6.9$ Hz), 4.63 (d, 1H, $J = 6.9$ Hz), 3.68 (m, 2H), 3.37 (s, 3H), 3.32 (m, 1H), 2.40 (m, 1H), 2.16 (m, 1H), 2.00 (s, 3H), 1.86 (m, 2H), 1.69 (m, 2H), 1.61 (m, 2H), 1.24 (d, 3H, $J = 6.3$ Hz). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 170.3, 134.8, 116.5, 94.7, 73.9, 70.6, 70.3, 67.8, 55.3,

37.3, 37.2, 26.0, 24.3, 21.1, 20.5. **IR** (CH₂Cl₂) 607, 917, 1035, 1106, 1150, 1242, 1375, 1442, 1642, 1734, 2935, 3072, 3534 cm⁻¹. [α]_D²⁰ = + 288 (*c* 0.40, CH₂Cl₂). **HRMS** (EI) calcd for C₁₅H₂₆O₅ (M – C₃H₅) 245.1389, found 245.1397.

1-(6-Allyl-3-methoxymethoxy-tetrahydro-pyran-2-yl)-propan-2-ol (221): To a stirred solution of **230** (300 mg, 1.05 mmol, 1.00 equiv) in MeOH (21.0 mL) was added K₂CO₃ (872 mg, 6.29 mmol, 6.00 equiv) in four portions at 5 min intervals at 0 °C. The reaction mixture was allowed to stir at rt for 5 h, at which time the reaction was quenched with deionized H₂O (50.0 mL) and then allowed to reach rt. The aqueous layer was extracted with EtOAc (3 × 75.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 30% ethyl acetate in hexanes) afforded **221** as a clear viscous oil (250 mg, 98% yield): **R_f** at 30% ethyl acetate in hexanes 0.20; **¹H NMR** (500 MHz, CDCl₃), δ 5.80 (m, 1H), 5.08 (m, 2H), 4.72 (d, 1H, *J* = 6.9 Hz), 4.62 (d, 1H, *J* = 6.9 Hz), 4.03 (m, 1H), 3.88 (m, 1H), 3.80 (m, 1H), 3.39 (m, 1H), 3.36 (s, 3H), 2.60 (broad s, 1H), 2.51 (m, 1H), 2.19 (m, 1H), 1.92 (m, 1H), 1.76 (m, 2H), 1.65 (m, 3H), 1.20 (d, 3H, *J* = 6.3 Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 135.2, 117.0, 94.8, 73.9, 71.4, 70.8, 64.6, 55.5, 39.0, 36.9, 26.4, 24.5, 23.3. **IR** (CH₂Cl₂) 917, 1035, 1102, 1220, 1368, 1446, 1642, 2355, 2942, 3083, 3430 cm⁻¹. [α]_D²⁰ = + 242 (*c* 0.60, CH₂Cl₂). **HRMS** (EI) calcd for C₁₃H₂₄O₄ (M - OH) 227.1647, found 227.1646.

5-Hydroxy-7-methoxymethoxy-2,2-dimethyl-benzo[1,3]dioxin-4-one (211): To a stirred solution of 2,4,6-trihydroxybenzoic acid **210** (5.00 g, 26.6 mmol, 1.00 equiv) in DME (66.0 mL) were added DMAP (325 mg, 2.66 mmol, 0.100 equiv), anhydrous acetone (2.93 mL, 39.9 mmol, 1.50 equiv), and thionyl chloride (2.90 mL, 39.9 mmol, 1.50 equiv) at 0 °C under Ar. The

reaction mixture was stirred for 3 h at rt, at which time the reaction temperature was lowered to 0 °C and quenched with a saturated aqueous solution of NaHCO₃ (100 mL) and then allowed to reach rt. The aqueous layer was extracted with EtOAc (3 × 75.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 20% ethyl acetate in hexanes) afforded aryl acetonide compound as a light yellow solid (4.64 g, 83% yield): **R_f** at 20% ethyl acetate in hexanes 0.20; **¹H NMR** (360 MHz, CDCl₃), δ 10.5 (s, 1H), 9.78 (broad s, 1H), 6.10 (d, 1H *J* = 2.3 Hz), 6.03 (d, 1H, *J* = 2.3 Hz), 1.74 (s, 6H).

To a stirred solution of aryl acetonide (2.10 g, 10.1 mmol, 1.00 equiv) in anhydrous acetone (50.0 mL) were added K₂CO₃ (4.17 g, 30.1 mmol, 3.00 equiv), and MOMCl (1.53 mL, 20.1 mmol, 2.00 equiv) at 0 °C under Ar. The reaction mixture was stirred for 18 h at rt, at which time the reaction temperature was lowered to 0 °C and quenched with a saturated aqueous solution of NaHCO₃ (50.0 mL) and then allowed to reach rt. The aqueous layer was extracted with EtOAc (3 × 50.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 5% ethyl acetate in hexanes) afforded **211** as a white crystalline solid (2.30 g, 90% yield): **R_f** at 5% ethyl acetate in hexanes 0.20; **¹H NMR** (500 MHz, CDCl₃), δ 10.4 (s, 1H), 6.28 (d, 1H *J* = 2.2 Hz), 6.12 (d, 1H, *J* = 2.2 Hz), 5.17 (s, 2H), 3.47 (s, 3H), 1.73 (s, 6H). **¹³C NMR** (125 MHz, CDCl₃), δ 165.2, 165.1, 162.8, 156.8, 119.9, 106.9, 97.9, 95.8, 94.1, 93.7, 56.4, 25.6. **IR** (CH₂Cl₂) 747, 847, 906, 1142, 1279, 1320, 1512, 1627, 1678, 2337, 2362, 2954, 3001, 3105 cm⁻¹. **HRMS** (EI) calcd for C₁₂H₁₄O₆ (M⁺) 254.0790, found 254.0799.

Trifluoro-methanesulfonic acid 7-methoxymethoxy-2,2-dimethyl-4-oxo-4H

benzo[1,3]dioxin-5-yl ester (212): To a stirred solution of **211** (2.14 g, 8.42 mmol, 1.00 equiv)

in anhydrous pyridine (42.0 mL) was added triflate anhydride (2.13 mL, 12.6 mmol, 1.50 equiv) at 0 °C under Ar. The reaction mixture was stirred for 18 h at rt, at which time the reaction temperature was lowered to 0 °C and quenched with a saturated aqueous solution of NaHCO₃ (50.0 mL) and deionized water (50.0 mL) and then allowed to reach rt. The aqueous layer was extracted with EtOAc (3 × 75.0 mL), and the combined organic extracts were washed with a saturated aqueous solution of CuSO₄ (300 mL) to remove excess pyridine, dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 15% ethyl acetate in hexanes) afforded **212** as a white crystalline solid (3.22 g, 99% yield): *R_f* at 15% ethyl acetate in hexanes 0.20; ¹H NMR (500 MHz, CDCl₃), δ 6.67 (d, 1H *J* = 2.2 Hz), 6.64 (d, 1H, *J* = 2.2 Hz), 5.21 (s, 2H), 3.49 (s, 3H), 1.73 (s, 6H). ¹³C NMR (125 MHz, CDCl₃), δ 163.2, 158.5, 157.0, 149.6, 106.5, 106.3, 103.6, 101.5, 94.6, 56.5, 25.3. IR (CH₂Cl₂) 588, 731, 815, 863, 1010, 1083, 1138, 1201, 1377. 1428, 1572, 1627, 1737, 2835, 2960, 3008, 3100 cm⁻¹. HRMS (EI) calcd for C₁₃H₁₃O₈F₃S (M⁺) 386.0283, found 386.0274.

5-allyl-7-(methoxymethoxy)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (209): To a stirred solution of **212** (5.73 g, 14.8 mmol, 1.00 equiv) in THF (926 mL) was added CsF (4.50 g, 29.7 mmol, 2.00 equiv), Pd(PPh₃)₄ (1.72 g, 1.48 mmol, 0.100 equiv), and stirred for 30 minutes at room temperature under Ar. Allyl boronic acid pinacol ester (5.60 mL, 29.7 mmol, 2.00 equiv) was then added and the reaction mixture was stirred for 18 h at reflux (40 °C) and allowed to reach rt, at which time the reaction was quenched with deionized H₂O (400 mL). The aqueous layer was extracted with EtOAc (3 × 250 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 1% ethyl ether in hexanes) afforded **209** as a white solid (3.80 g, 92% yield): *R_f* at 1% ethyl ether in hexanes 0.35; ¹H

NMR (500 MHz, CDCl₃), δ 6.59 (d, 1H, $J = 2.52$ Hz), 6.49 (d, 1H, $J = 2.52$ Hz), 6.00 (m, 1H), 5.18 (s, 2H), 5.07 (m, 1H), 5.05 (m, 1H), 3.85 (s, 1H), 3.84 (s, 1H), 3.47 (s, 3H), 1.68 (s, 6H). **¹³C NMR** (125 MHz, CDCl₃), δ 162.5, 158.9, 147.2, 136.4, 116.2, 113.4, 105.6, 104.9, 101.8, 94.1, 56.4, 38.4, 25.6. **IR** (CH₂Cl₂) 858, 910, 1017, 1079, 1147, 1209, 1279, 1438, 1580, 1612, 1734, 2828, 2943, 2998, 3080 cm⁻¹. **HRMS** (EI) calcd for C₁₅H₁₈O₅ (M⁺) 278.1154, found 278.1161.

7-(methoxymethoxy)-2,2-dimethyl-5-(2-oxopropyl)-4H-benzo[d][1,3]dioxin-4-one (201): To a solution of **209** (300 mg, 1.08 mmol, 1.00 equiv) in DMF:H₂O (10.8 ml, 7:1) was added PdCl₂ (48.0 mg, 0.270 mmol, 0.500 equiv) and CuCl (160 mg, 1.62 mmol, 2.00 equiv). The reaction mixture was allowed to stir under O₂ (1.00 atm) at rt for 48 h. The reaction was then diluted with EtOAc (10.0 mL) and water (20.0 mL). The aqueous layer was extracted with EtOAc (3 \times 15.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 10 % ethyl acetate in hexanes) afforded **201** as a pale yellow solid (230 mg, 72 % yield): **R_f** at 10 % ethyl acetate in hexanes 0.30; **¹H NMR** (360 MHz, CDCl₃), δ 6.51 (s, 1H), 6.47 (s, 1H), 5.15 (s, 2H), 4.09 (s, 2H), 3.44 (s, 3H), 2.27 (s, 3H), 1.67 (s, 6H). **¹³C NMR** (125 MHz, CDCl₃), δ 204.8, 162.5, 160.6, 158.6, 140.6, 115.1, 105.4, 102.6, 94.1, 56.3, 49.2, 30.0, 25.5. **IR** (CH₂Cl₂) 727, 913, 1010, 1081, 1153, 1209, 1286, 1353, 1442, 1581, 1611, 1723, 2252, 2826, 2941, 2997 cm⁻¹. **HRMS** (EI) calcd for C₁₅H₁₈O₅ (M⁺) 294.1103, found 294.1117.

7-Methoxymethoxy-2,2-dimethyl-5-vinyl-benzo[1,3]dioxin-4-one (220): To a stirred solution of **212** (3.08 g, 8.03 mmol, 1.00 equiv) in EtOH (54.0 mL) were added triethylamine (1.45 mL,

10.4 mmol, 1.30 equiv), PdCl₂(dppf)·CHCl₃ (655 mg, 0.810 mmol, 0.100 equiv), and potassium vinyltrifluoroborate (1.20 g, 8.83 mmol, 1.10 equiv) at rt under Ar. The reaction mixture was stirred for 18 h at reflux (75 °C) at which time the reaction was concentrated in vacuo. The crude solid was re-dissolved in EtOAc (50.0 mL) and deionized water (50.0 mL) and allowed to stir for 30 min at rt. The aqueous layer was then extracted with EtOAc (3 × 50.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 2% ethyl acetate in hexanes) afforded **220** as a white solid (2.08 g, 98% yield): **R_f** at 2% ethyl acetate in hexanes 0.25; **¹H NMR** (500 MHz, CDCl₃), δ 7.63 (dd, 1H, *J* = 10.7, 17.3 Hz), 6.83 (d, 1H, *J* = 1.9 Hz), 6.49 (d, 1H, *J* = 2.5 Hz), 5.63 (dd, 1H, *J* = 1.26, 17.3 Hz), 5.33 (dd, 1H, *J* = 1.26, 11.1 Hz), 5.15 (s, 2H), 3.42 (s, 3H), 1.64 (s, 6H). **¹³C NMR** (125 MHz, CDCl₃), δ 162.5, 160.1, 158.4, 144.0, 135.3, 117.7, 109.8, 105.1, 104.7, 102.9, 94.1, 56.4, 25.6. **IR** (CH₂Cl₂) 862, 910, 988, 1039, 1150, 1209, 1275, 1386, 1430, 1575, 1605, 1730, 2828, 2994, 3090 cm⁻¹. **HRMS** (EI) calcd for C₁₄H₁₆O₅ (M⁺) 264.0998, found 264.0989.

2-Hydroxy-4-methoxymethoxy-6-vinyl-benzoic acid 2-(6-allyl-3-methoxymethoxy tetrahydro-pyran-2-yl)-1-methyl-ethyl ester (219): To a stirred solution of **221** (300 mg, 1.23 mmol, 1.00 equiv) in a 1:1 mixture of DMF/THF (54.0 mL) was added NaH (60% dispersion in mineral oil, 210 mg, 4.30 mmol, 3.50 equiv) at 0 °C under Ar. To this mixture was added **220** (422 mg, 1.60 mmol, 1.25 equiv) and the resulting mixture was allowed to stir at rt. At 5 h intervals, additional (4 times) **220** (80.0 mg, 0.310 mmol, 0.250 equiv) was added to the reaction mixture. After 30 h, the resulting suspension was cooled to 0 °C, and quenched with deionized H₂O (100 mL). The mixture was allowed to stir at rt for 30 min, at which time the aqueous layer was extracted with EtOAc (3 × 75.0 mL), and the organic extracts were dried over MgSO₄,

filtered, and concentrated in vacuo. Flash chromatography (silica, 15% ethyl acetate in hexanes) afforded **219** as a yellow viscous oil (425 mg, 77% yield): R_f at 15% ethyl acetate in hexanes 0.20; $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 11.7 (s, 1H), 7.30 (dd, 1H, $J = 17.1, 10.7$ Hz), 6.56 (s, 2H), 5.72 (m, 1H), 5.41 (d, 1H, $J = 17.1$ Hz), 5.30 (m, 1H), 5.20 (m, 1H), 5.18 (s, 2H), 4.95 (m, 2H), 4.71 (d, 1H, $J = 6.9$ Hz), 4.61 (d, 1H, $J = 6.9$ Hz), 3.74 (m, 2H), 3.46 (s, 3H), 3.36 (s, 3H), 3.32 (m, 1H), 2.40 (m, 1H), 2.09 (m, 2H), 1.89 (m, 1H), 1.75 (m, 1H), 1.64 (m, 3H), 1.38 (d, 3H, $J = 6.3$ Hz). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 170.4, 164.5, 161.4, 143.8, 138.7, 134.8, 116.7, 115.4, 109.0, 105.2, 102.9, 94.8, 93.9, 74.2, 70.7, 70.3, 70.1, 56.2, 55.4, 37.5, 36.8, 26.3, 24.5, 20.8. IR (CH_2Cl_2) 813, 921, 1024, 1146, 1261, 1323, 1375, 1571, 1612, 1652, 2938, 3397 cm^{-1} . $[\alpha]_{\text{D}}^{20} = +288$ (c 0.08, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{24}\text{H}_{34}\text{O}_8$ (M^+) 450.2254, found 450.2265.

7,9,16-Tris-methoxymethoxy-13-methyl-12,19-dioxa-tricyclo[13.3.1.0^{5,10}]nonadeca 3,5,7,9-tetraen-11-one (231): To a refluxing solution of **219** (310 mg, 0.690 mmol, 1.00 equiv) in CH_2Cl_2 (68.8 mL, 40 °C) under Ar was added a solution of Grubbs' second-generation catalyst (**57**) (59.0 mg, 0.070 mmol, 0.100 equiv) in CH_2Cl_2 (7.00 mL) dropwise over a period of 2 h. The reaction mixture was allowed to stir at 40 °C for 18 h at which time the reaction was concentrated in vacuo. Flash chromatography (silica, 15% ethyl acetate in hexanes) afforded **231** as a viscous oil (280 mg, 97% yield): R_f at 15% ethyl acetate in hexanes 0.15; $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 11.2 (s, 1H), 6.83 (d, 1H, $J = 15.5$ Hz), 6.49 (d, 1H, $J = 2.5$ Hz), 6.41 (d, 1H, $J = 2.5$ Hz), 5.63 (dd, 1H, $J = 10.4, 4.1$ Hz), 5.28 (m, 1H), 5.15 (s, 2H), 4.75 (d, 1H, $J = 6.9$ Hz), 4.61 (d, 1H, $J = 6.9$ Hz), 3.98 (m, 1H), 3.80 (m, 1H), 3.43 (s, 3H), 3.38 (s, 3H), 3.25 (m, 1H), 2.91 (q, 1H, $J = 12.3$ Hz), 2.09 (m, 1H), 2.00 (m, 1H), 1.90 (m, 3H), 1.72 (m, 1H), 1.59 (m, 1H), 1.37 (d, 3H, $J = 6.3$ Hz). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 170.7, 163.8, 161.3, 143.8,

134.6, 127.9, 108.6, 106.0, 102.2, 95.2, 93.9, 76.0, 71.3, 70.2, 67.7, 56.1, 55.6, 37.7, 33.4, 27.6, 25.9, 19.9. **IR** (CH₂Cl₂) 736, 851, 950, 1028, 1146, 1213, 1261, 1317, 1453, 1575, 1612, 1649, 2935 cm⁻¹. [α]_D²⁰ = - 44.0 (*c* 0.25, CH₂Cl₂). **HRMS** (EI) calcd for C₂₂H₃₀O₈ (M⁺) 422.1941, found 422.1945.

7,9,16-Tris-methoxymethoxy-13-methyl-12,19-dioxa-tricyclo[13.3.1.0^{5,10}]nonadeca-3,5,7,9-tetraen-11-one (218): To a stirred solution of **231** (43.0 mg, 0.110 mmol, 1.00 equiv) in CH₂Cl₂ (1.00 mL) was added TBAI (8.00 mg, 0.020 mmol, 0.200 equiv), DIPEA (0.060 mL, 0.310 mmol, 3.00 equiv), and MOMCl (0.020 mL, 0.210 mmol, 2.00 equiv) at 0 °C under Ar. The reaction mixture was stirred for 24 h at rt, at which time the reaction temperature was lowered to 0 °C and quenched with a saturated aqueous solution of NaHCO₃ (5.00 mL) and deionized H₂O (5.00 mL) and then allowed to reach rt. The aqueous layer was extracted with CH₂Cl₂ (3 × 10.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 25% ether in hexanes) afforded **218** as a light yellow oil (45.0 mg, 96% yield): **R_f** at 25% ethyl acetate in hexanes 0.15; **¹H NMR** (500 MHz, CDCl₃), δ 6.69 (d, 1H, *J* = 2.2 Hz), 6.50 (m, 1H), 5.89 (dd, 1H, *J* = 10.7, 2.8 Hz), 5.41 (m, 1H), 5.19 (d, 1H, *J* = 6.6 Hz), 5.13 (s, 3H), 4.69 (d, 1H, *J* = 6.9 Hz), 4.56 (d, 1H, *J* = 6.9 Hz), 4.13 (m, 1H), 3.56 (m, 1H), 3.46 (s, 3H), 3.44 (s, 3H), 3.34 (s, 3H), 3.18 (m, 1H), 2.76 (m, 1H), 2.30 (m, 1H), 2.15 (m, 1H), 2.04 (m, 1H), 1.84 (m, 1H), 1.69 (m, 1H), 1.48 (m, 2H), 1.26 (d, 3H, *J* = 6.3 Hz), 1.25 (m, 1H). **¹³C NMR** (125 MHz, CDCl₃), δ 167.2, 158.3, 155.6, 138.5, 131.1, 130.3, 118.2, 108.6, 102.6, 95.2, 94.8, 94.3, 77.4, 69.1, 66.9, 66.7, 56.2, 56.1, 55.5, 39.2, 34.8, 27.6, 25.2, 20.8. **IR** (CH₂Cl₂) 925, 977, 1032, 1098, 1150, 1223, 1267, 1447, 1597, 1723, 2935, 3430 cm⁻¹. [α]_D²⁰ = + 120 (*c* 0.40, CH₂Cl₂). **HRMS** (EI) calcd for C₂₄H₃₄O₉ (M⁺) 466.2203, found 466.2192.

Epoxy-macrocycle (232): To a stirred solution of **218** (260 mg, 0.560 mmol, 1.00 equiv) in a 1:1 biphasic mixture of CH₂Cl₂ (5.60 mL) and a 1 M NaHCO₃ aqueous solution (5.60 mL) was added *m*CPBA (77% max., 275 mg, 1.12 mmol, 2.00 equiv) at 0 °C under Ar. The reaction mixture was stirred for 3 h at rt, at which time the reaction temperature was quenched with saturated aqueous solutions of NaHCO₃ (10.0 mL) and Na₂S₂O₃ (10.0 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 25.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 35% ethyl acetate in hexanes) afforded **232** as a clear viscous oil (220 mg, 82% yield): **R_f** at 35% ethyl acetate in hexanes 0.20; **¹H NMR** (500 MHz, CDCl₃), δ 6.78 (d, 1H, *J* = 2.2 Hz), 6.71 (d, 1H, *J* = 2.2 Hz), 5.17 (m, 5H), 4.73 (d, 1H, *J* = 6.6 Hz), 4.60 (d, 1H, *J* = 6.9 Hz), 4.11 (m, 1H), 4.04 (s, 1H), 3.69 (m, 1H), 3.49 (s, 3H), 3.44 (s, 3H), 3.38 (s, 3H), 3.26 (m, 1H), 2.89 (m, 1H), 2.02 (m, 4H), 1.90 (m, 2H), 1.61 (m, 2H), 1.37 (d, 3H, *J* = 6.3 Hz). **¹³C NMR** (125 MHz, CDCl₃), δ 165.6, 159.6, 156.9, 138.9, 116.3, 105.9, 103.9, 95.3, 95.2, 94.2, 76.3, 70.4, 69.3, 67.9, 60.6, 57.6, 56.3, 56.2, 55.6, 37.3, 33.6, 27.9, 25.5, 20.0. **IR** (CH₂Cl₂) 732, 921, 1032, 1150, 1265, 1446, 1605, 1723, 2935, 3527 cm⁻¹. [**α**]_D²⁰ = + 278 (*c* 0.04, CH₂Cl₂). **HRMS** (EI) calcd for C₂₄H₃₄O₁₀ (M⁺) 482.2152, found 482.2151.

3-Hydroxy-7,9,16-tris-methoxymethoxy-13-methyl-12,19-dioxa-

tricyclo[13.3.1.0^{5,10}]nonadeca-5,7,9-trien-11-one (217): To a solution of **232** (65.0 mg, 0.140 mmol, 1.00 equiv) in MeOH (13.5 mL) was added 10% Pd/C (20.0 mg). The reaction vessel was evacuated under vacuum and placed under atmospheric H₂ balloon pressure. The reaction mixture was allowed to stir at rt for 12 h, at which time additional 10% Pd/C (20.0 mg) was added. After 12 h, additional 10% Pd/C (20.0 mg) was added and the suspension was stirred for

12 h. The reaction was then filtered through a plug of Celite and concentrated in vacuo. Flash chromatography (silica, 60% ethyl acetate in hexanes) afforded **217** as a clear viscous oil (45.0 mg, 70% yield): R_f at 60% ethyl acetate in hexanes 0.25; $^1\text{H NMR}$ (500 MHz, CDCl_3), δ 6.71 (d, 1H, $J = 2.2$ Hz), 6.54 (d, 1H, $J = 2.2$ Hz), 5.35 (m, 1H), 5.15 (s, 4H), 4.71 (d, 1H, $J = 6.9$ Hz), 4.61 (d, 1H, $J = 6.9$ Hz), 4.09 (m, 2H), 3.83 (m, 1H), 3.47 (m, 6H), 3.37 (m, 4H), 3.07 (dd, 1H, $J = 13.9, 6.0$ Hz), 2.92 (dd, 1H, $J = 13.9, 8.5$ Hz), 2.25 (broad s, 1H), 2.10 (m, 2H), 1.88 (m, 1H), 1.81 (dd, 1H, $J = 8.8, 2.5$ Hz), 1.68 (m, 2H), 1.60 (m, 2H), 1.38 (d, 3H, $J = 6.3$ Hz), 1.34 (m, 1H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3), δ 167.8, 158.7, 155.9, 138.6, 118.9, 111.4, 102.1, 94.9, 94.8, 94.4, 75.7, 69.2, 69.0, 68.8, 68.6, 56.2, 56.1, 55.5, 42.5, 37.9, 35.7, 26.9, 25.4, 19.7. IR (CH_2Cl_2) 843, 924, 1035, 1150, 1265, 1438, 1605, 1719, 2938, 3430 cm^{-1} . $[\alpha]_{\text{D}}^{20} = +205$ (c 0.10, CH_2Cl_2). HRMS (EI) calcd for $\text{C}_{24}\text{H}_{36}\text{O}_{10}$ (M^+) 484.2308, found 484.2320.

ent-Pochonin J (ent-5): To a stirred solution of **217** (33.0 mg, 0.070 mmol, 1.00 equiv) in CH_2Cl_2 (1.00 mL) was added Dess-Martin periodinane (58.0 mg, 0.140 mmol, 2.00 equiv) at 0 °C. The reaction mixture was allowed to stir at rt for 5 h, at which time the reaction was quenched with saturated aqueous solutions of NaHCO_3 (5.00 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (5.00 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10.0 mL), and the organic extracts were dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (silica, 40% ethyl acetate in hexanes) afforded the ketone macrocycle **233** as a light yellow oil (28.0 mg, 91% yield): R_f at 50% ethyl acetate in hexanes 0.25.

To a stirred solution of the corresponding ketone **233** (30.0 mg, 0.060 mmol, 1.00 equiv) in 95:5 solvent mixture of $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (1.30 mL) was added LiBF_4 (1.00 M solution in CH_3CN , 1.25 mmol, 20.0 equiv). The reaction mixture was then heated to reflux (75 °C) and allowed to

stir for 1.5 h. After cooling, the reaction was quenched with a saturated aqueous solution of NaHCO₃ (10.0 mL). The aqueous layer was extracted with EtOAc (3 × 10.0 mL), and the organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Flash chromatography (silica, 60% ethyl acetate in hexanes) afforded **ent-1** as a white solid (19.0 mg, 86% yield): **R_f** at 70% ethyl acetate in hexanes 0.25; **¹H NMR** (500 MHz, CD₃OD), δ 6.26 (d, 1H, *J* = 2.5 Hz), 6.11 (d, 1H, *J* = 2.5 Hz), 5.27 (m, 1H), 4.44 (d, 2H, *J* = 18.9 Hz), 4.35 (m, 1H), 4.27 (d, 2H, *J* = 18.9 Hz), 3.81 (m, 1H), 3.31 (m, 1H), 3.21 (dd, 1H, *J* = 13.9, 11.9 Hz), 2.34 (dd, 1H, *J* = 14.2, 3.80 Hz), 1.97 (m, 3H), 1.83 (m, 1H), 1.76 (m, 1H), 1.68 (m, 1H), 1.34 (d, 3H, *J* = 6.0 Hz). **¹³C NMR** (125 MHz, CD₃OD), δ 210.1, 173.6, 166.8, 164.6, 140.7, 114.3, 108.5, 103.7, 73.6, 72.9, 71.4, 71.1, 52.3, 46.0, 37.1, 29.8, 29.3, 20.0. **IR** (CH₂Cl₂) 1026, 1255, 1373, 1453, 1646, 1730, 2832, 2946, 3376 cm⁻¹. **[α]_D²⁰** = + 144 (*c* 0.08, MeOH). **HRMS** (EI) calcd for C₁₈H₂₂O₇ (M⁺) 350.1366, found 350.1375.

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APPENDIX

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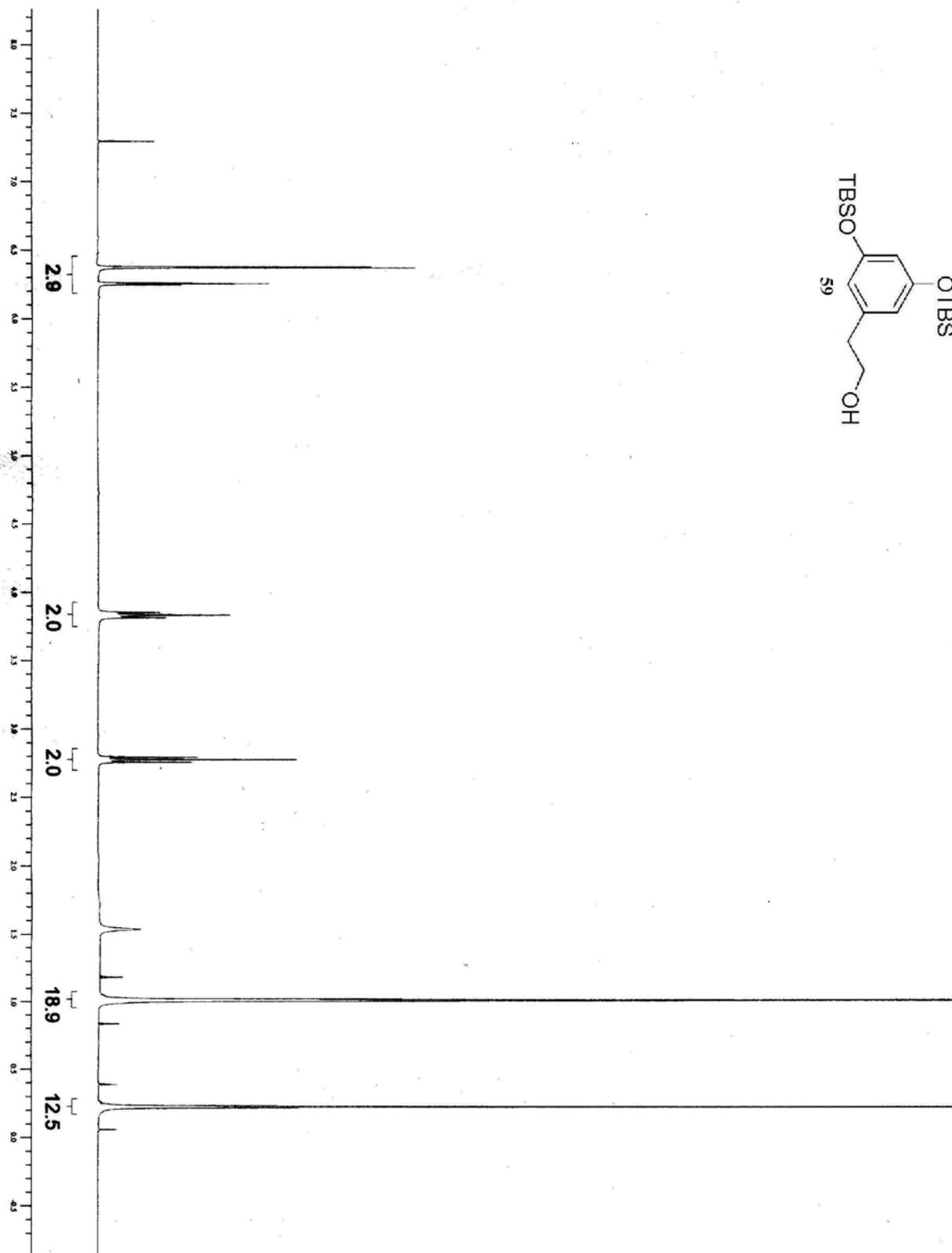
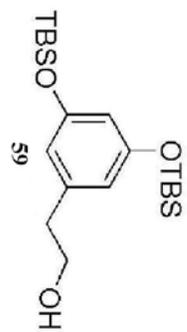
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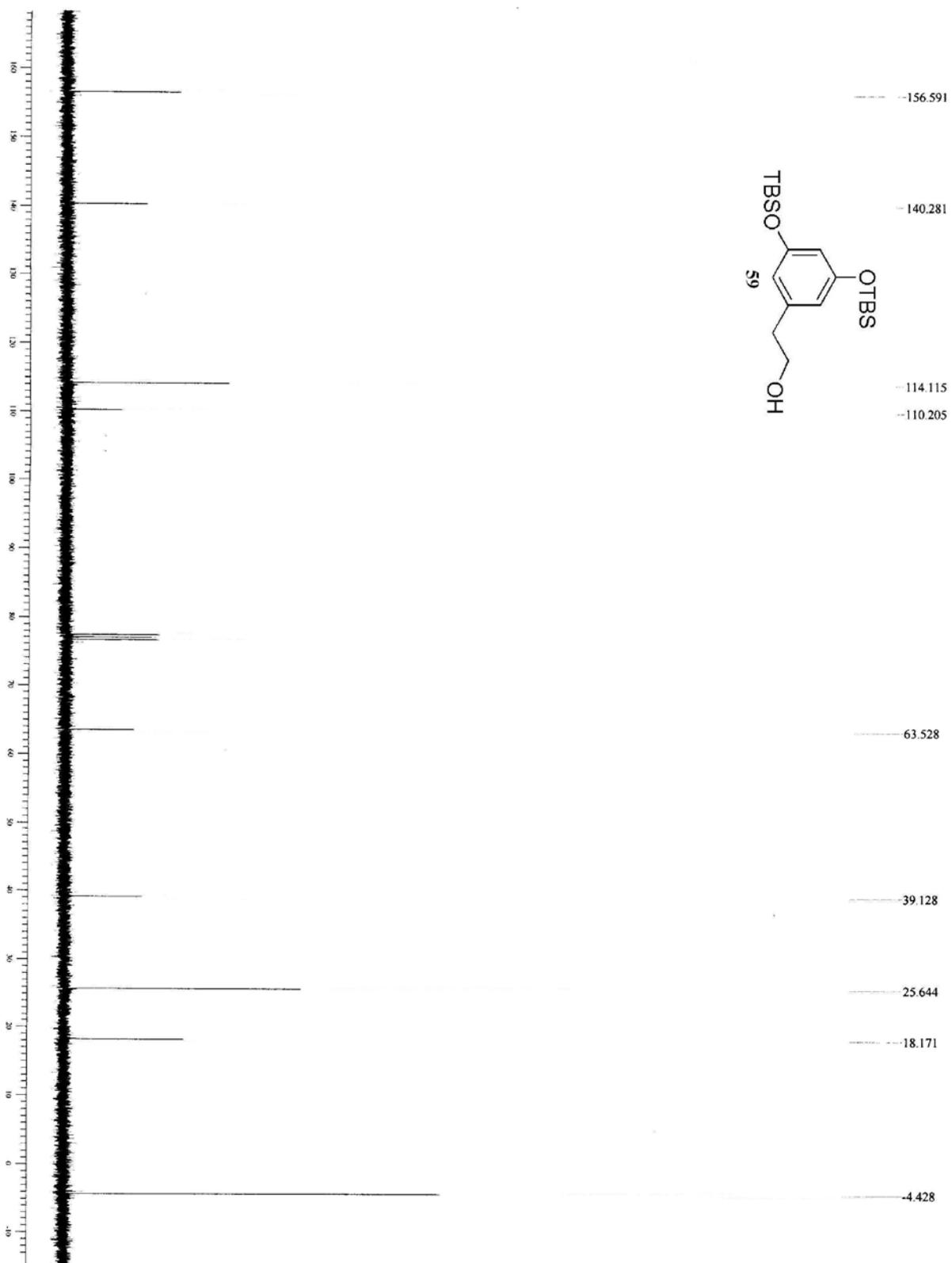
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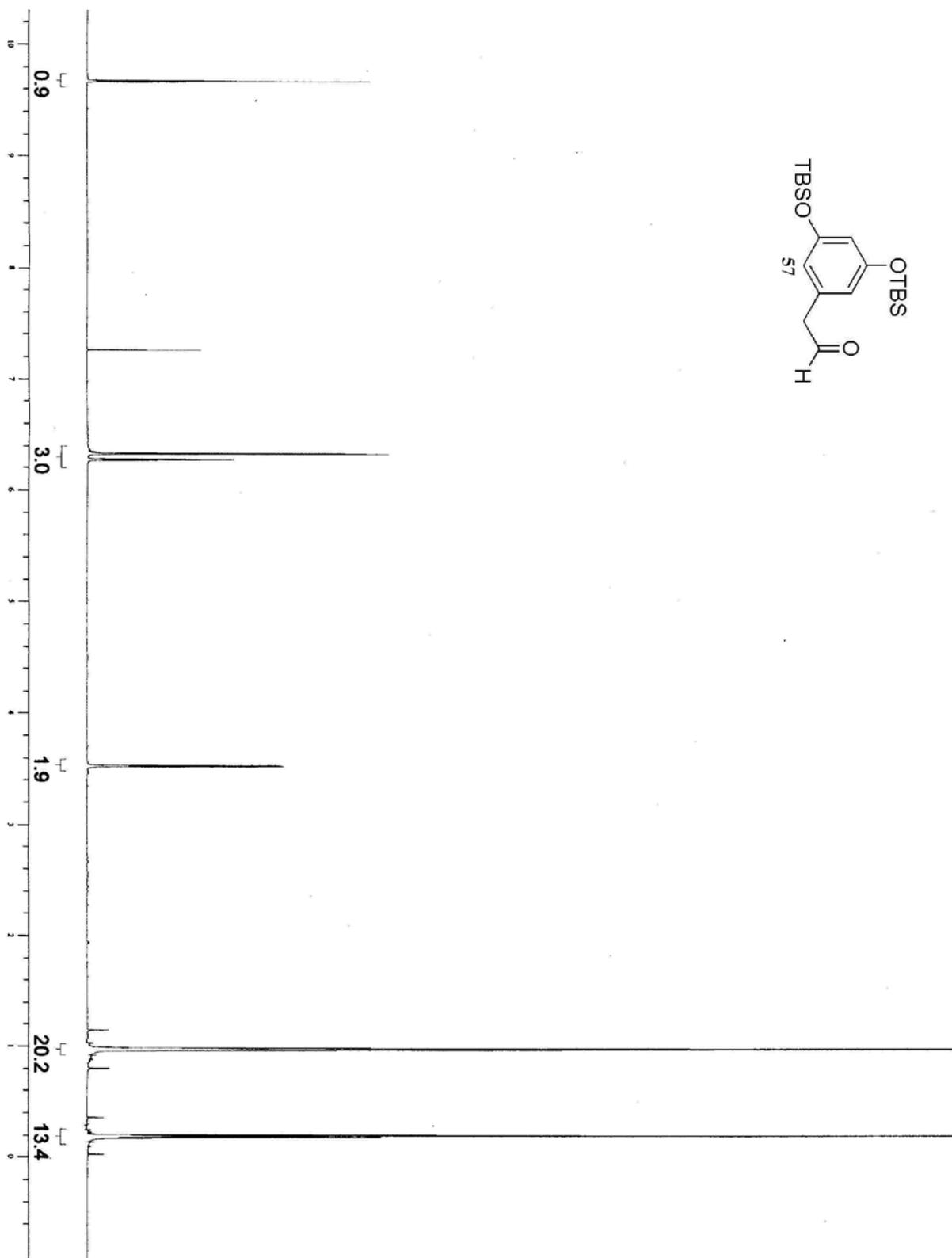
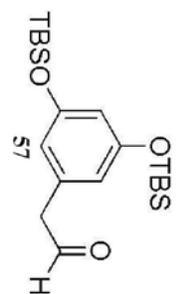
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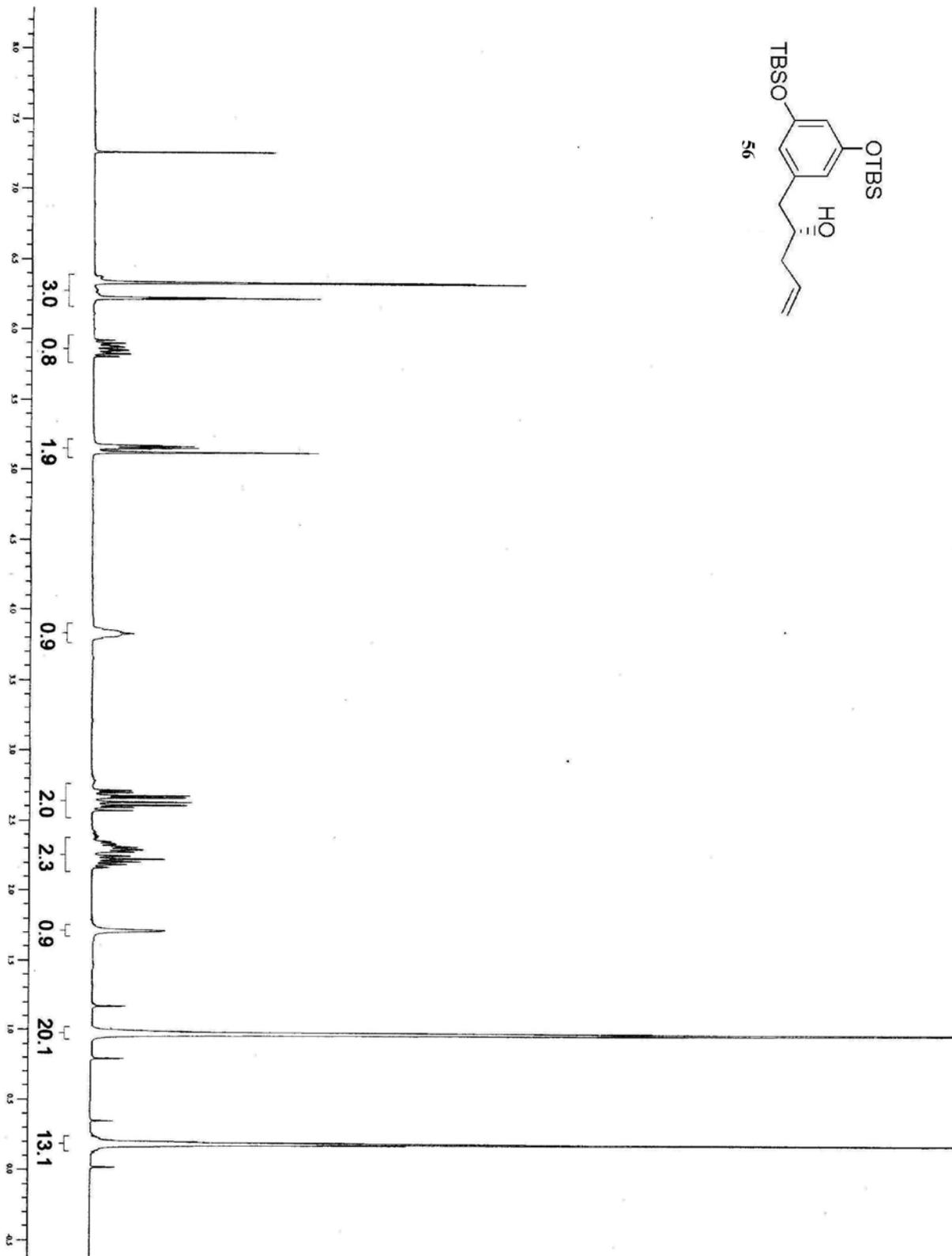
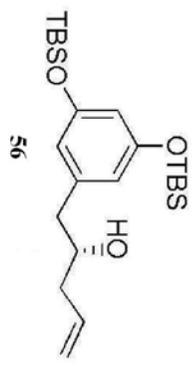
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **59**



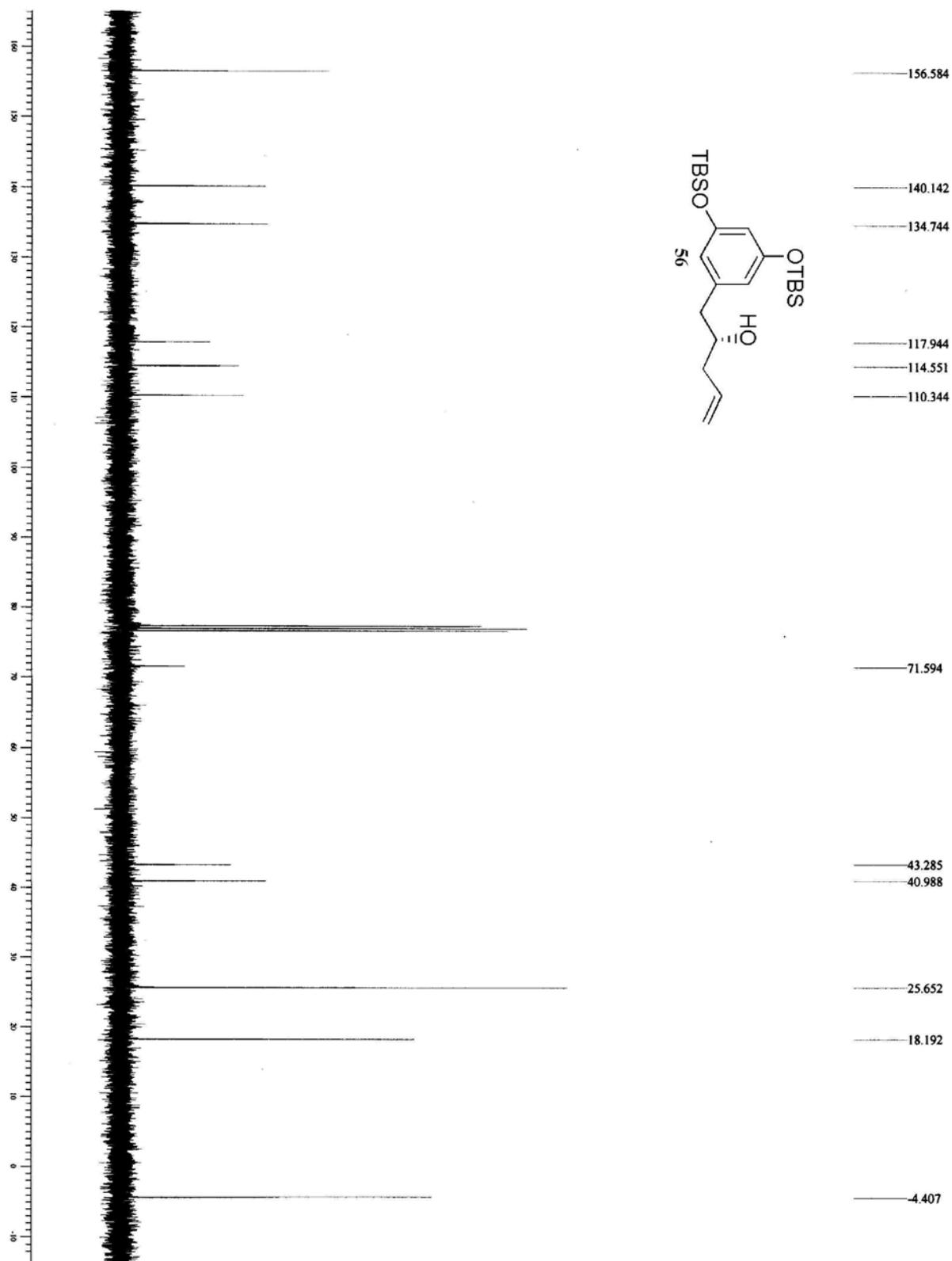
The ^{13}C NMR Spectrum (90 MHz, CDCl_3) of Compound **59**



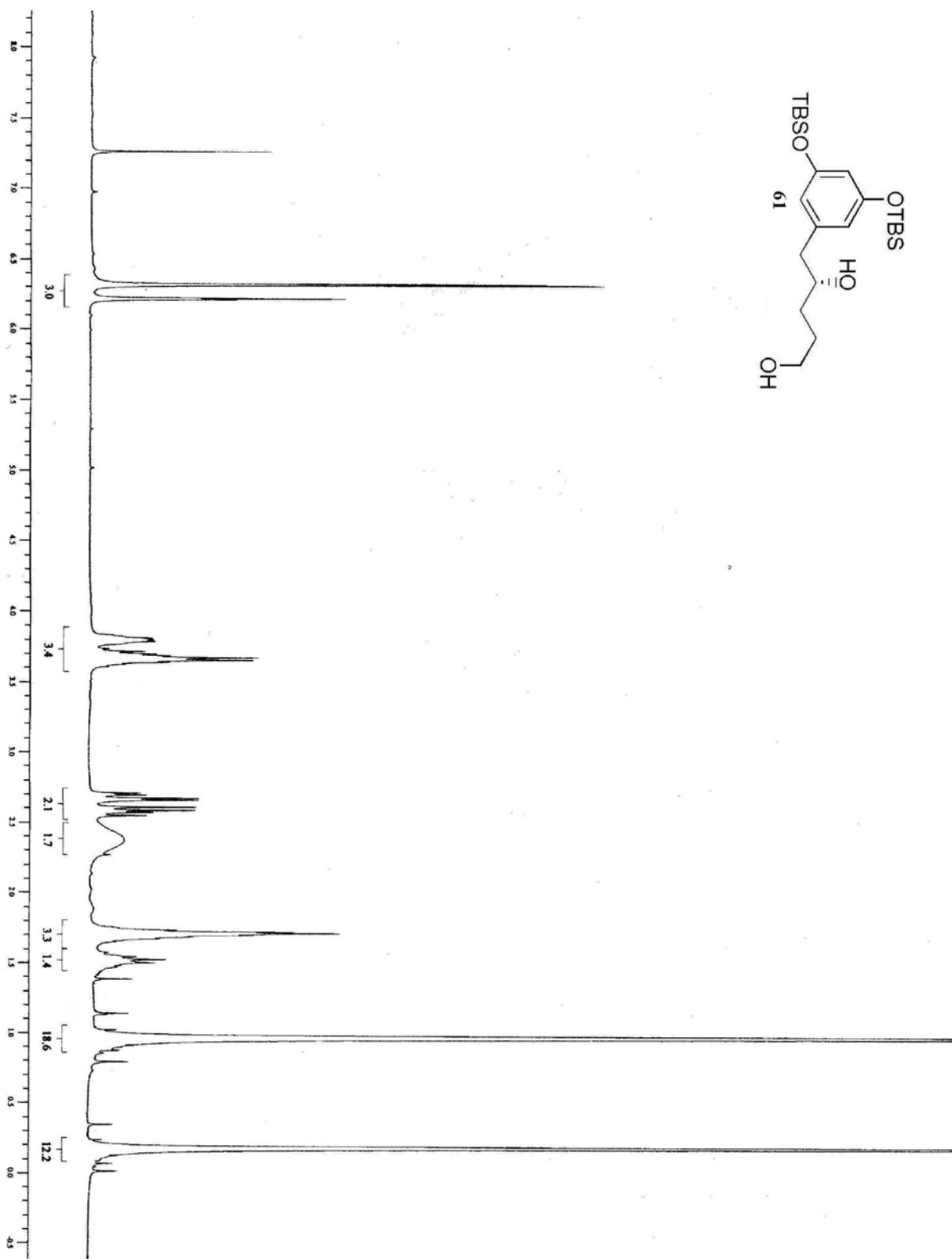
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **57**



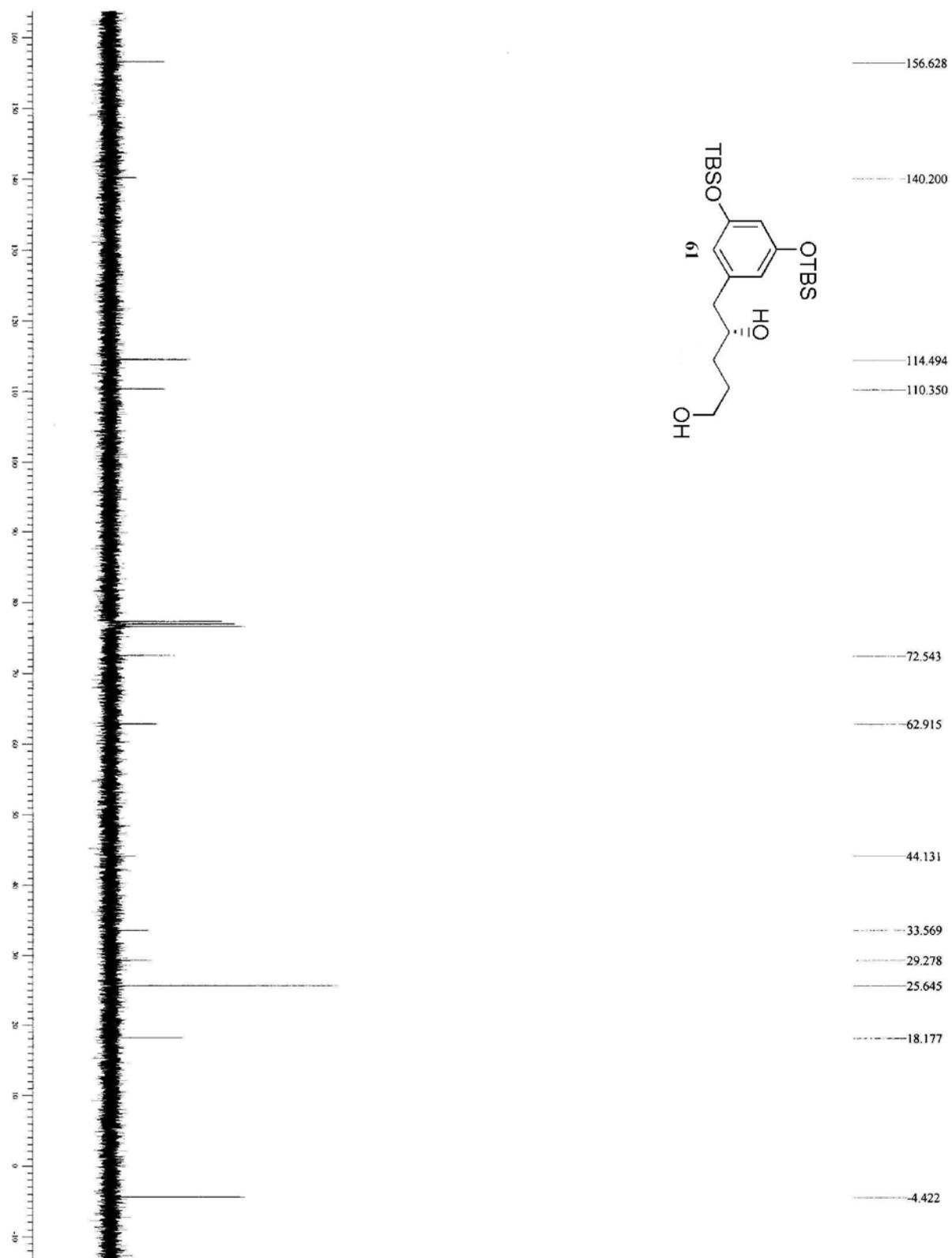
The ¹H NMR Spectrum (360 MHz, CDCl₃) of Compound **56**



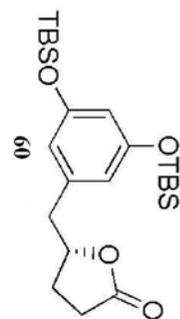
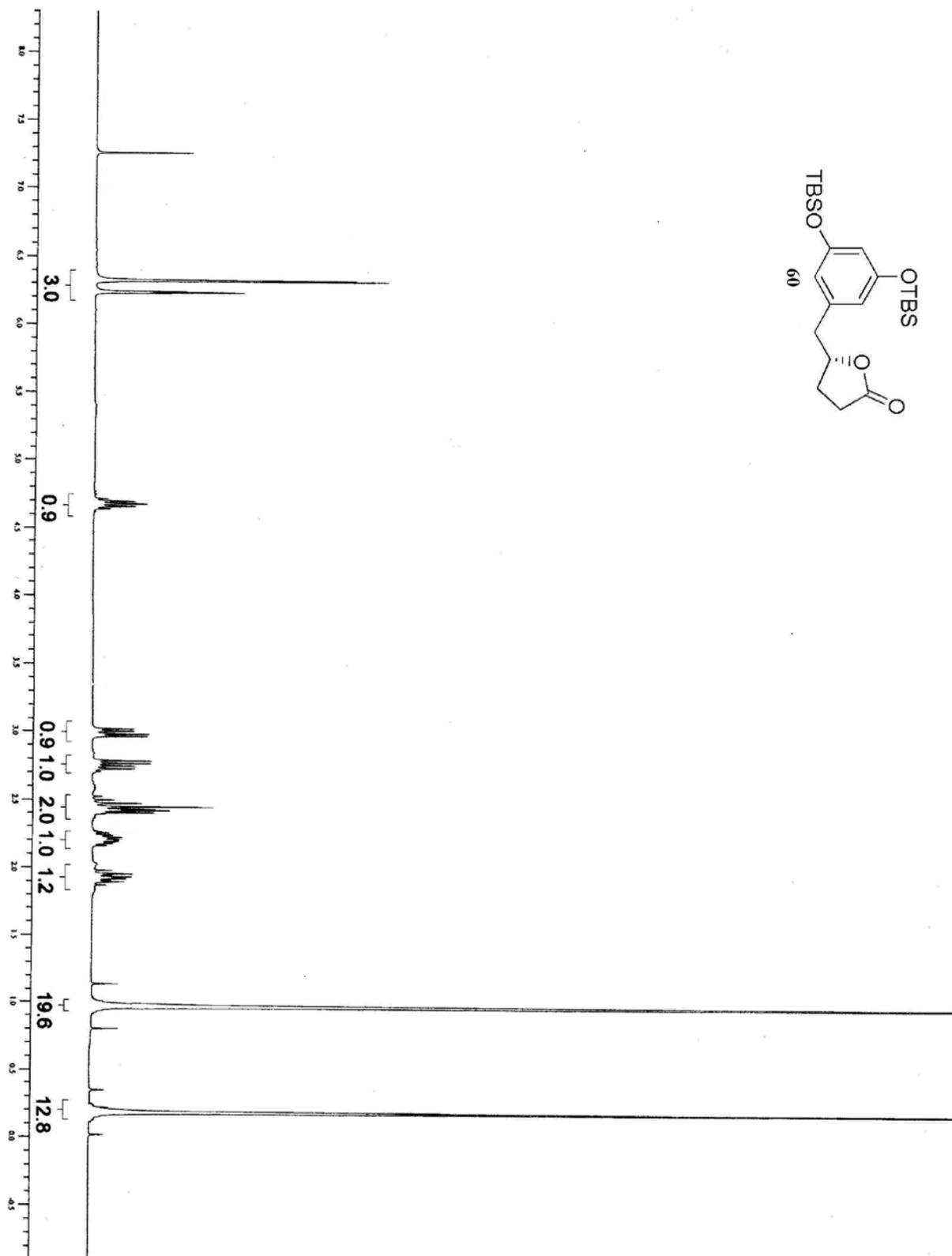
The ^{13}C NMR Spectrum (90 MHz, CDCl_3) of Compound **56**



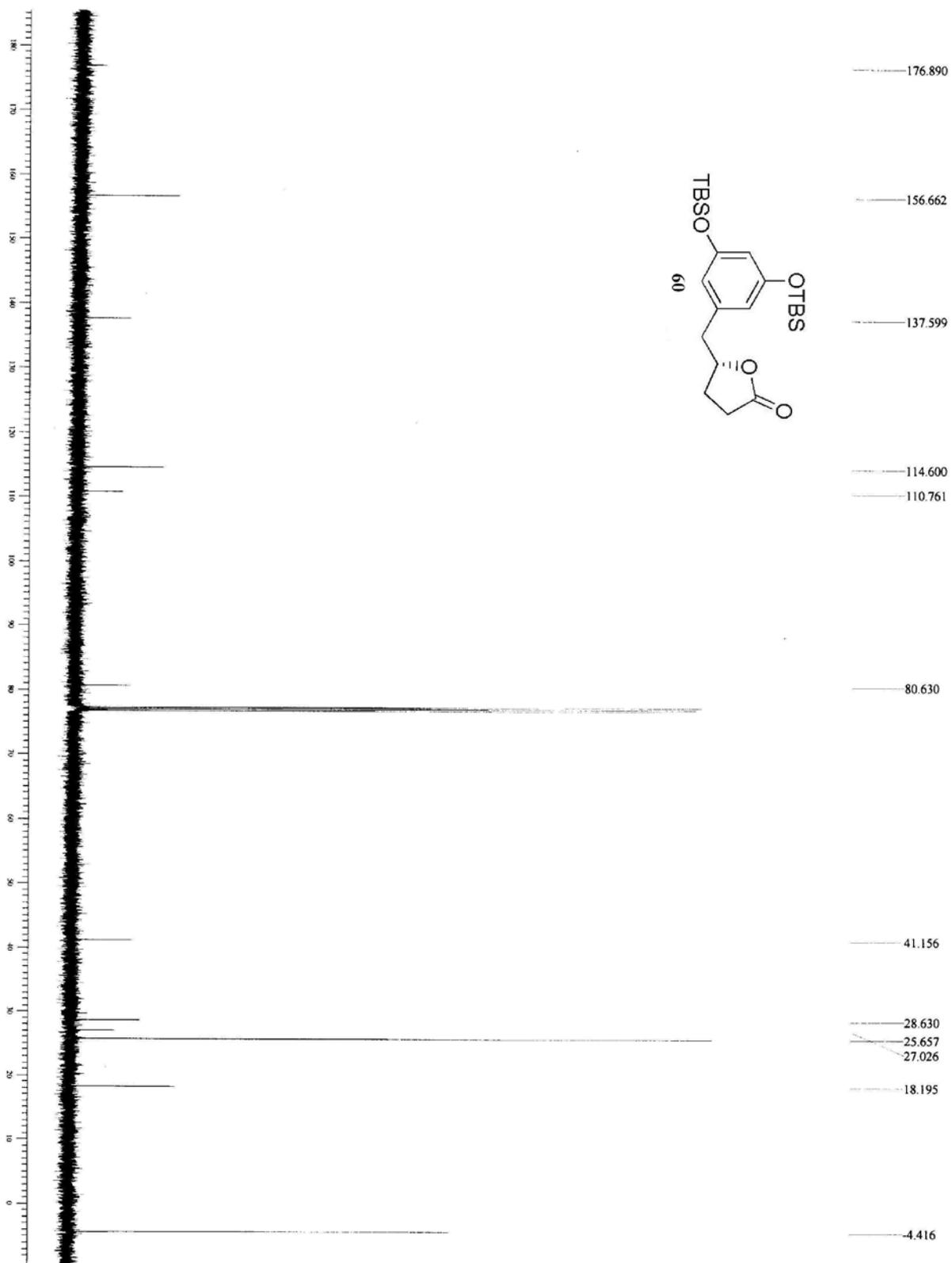
The ¹H NMR Spectrum (360 MHz, CDCl₃) of Compound **61**



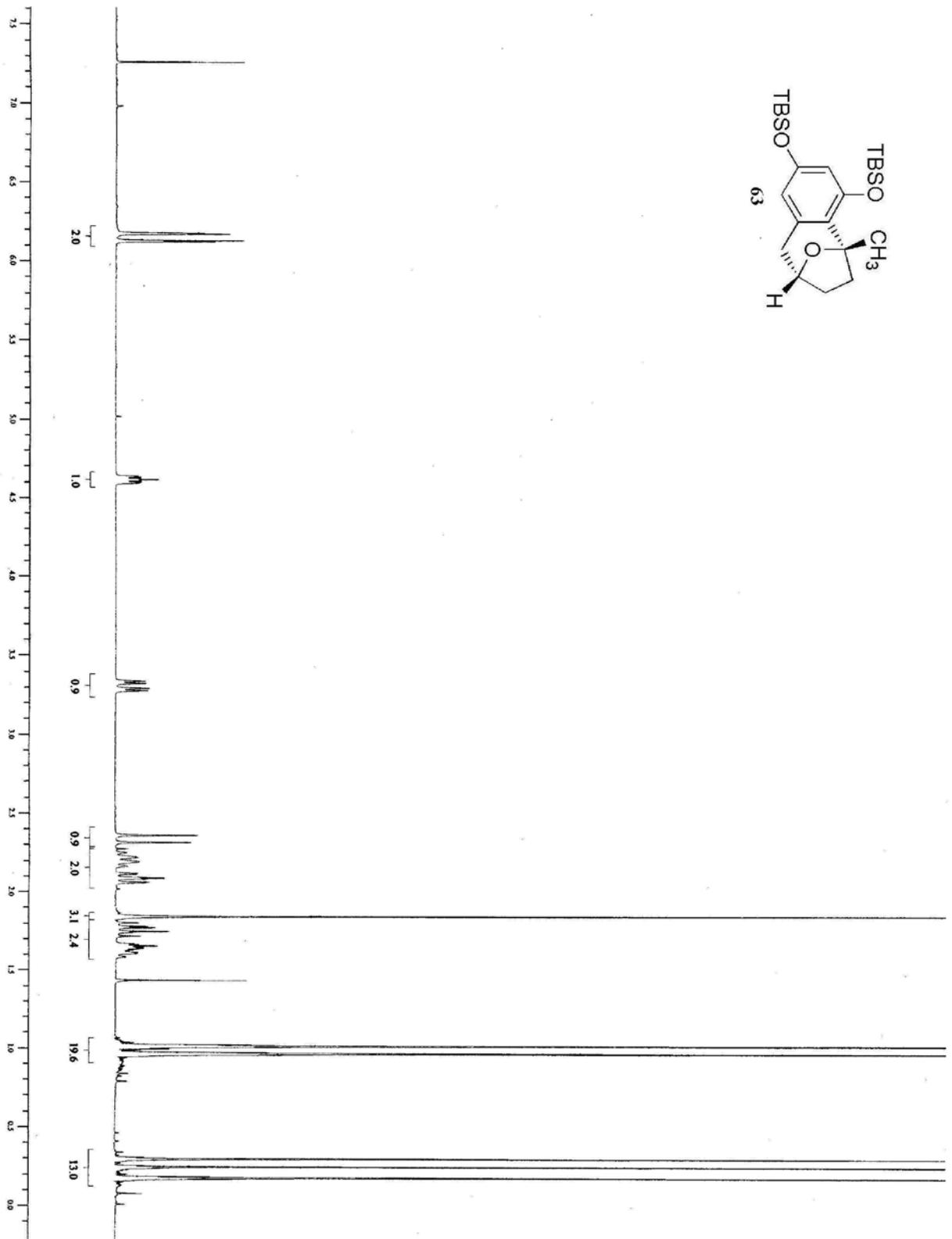
The ^{13}C NMR Spectrum (90 MHz, CDCl_3) of Compound **61**



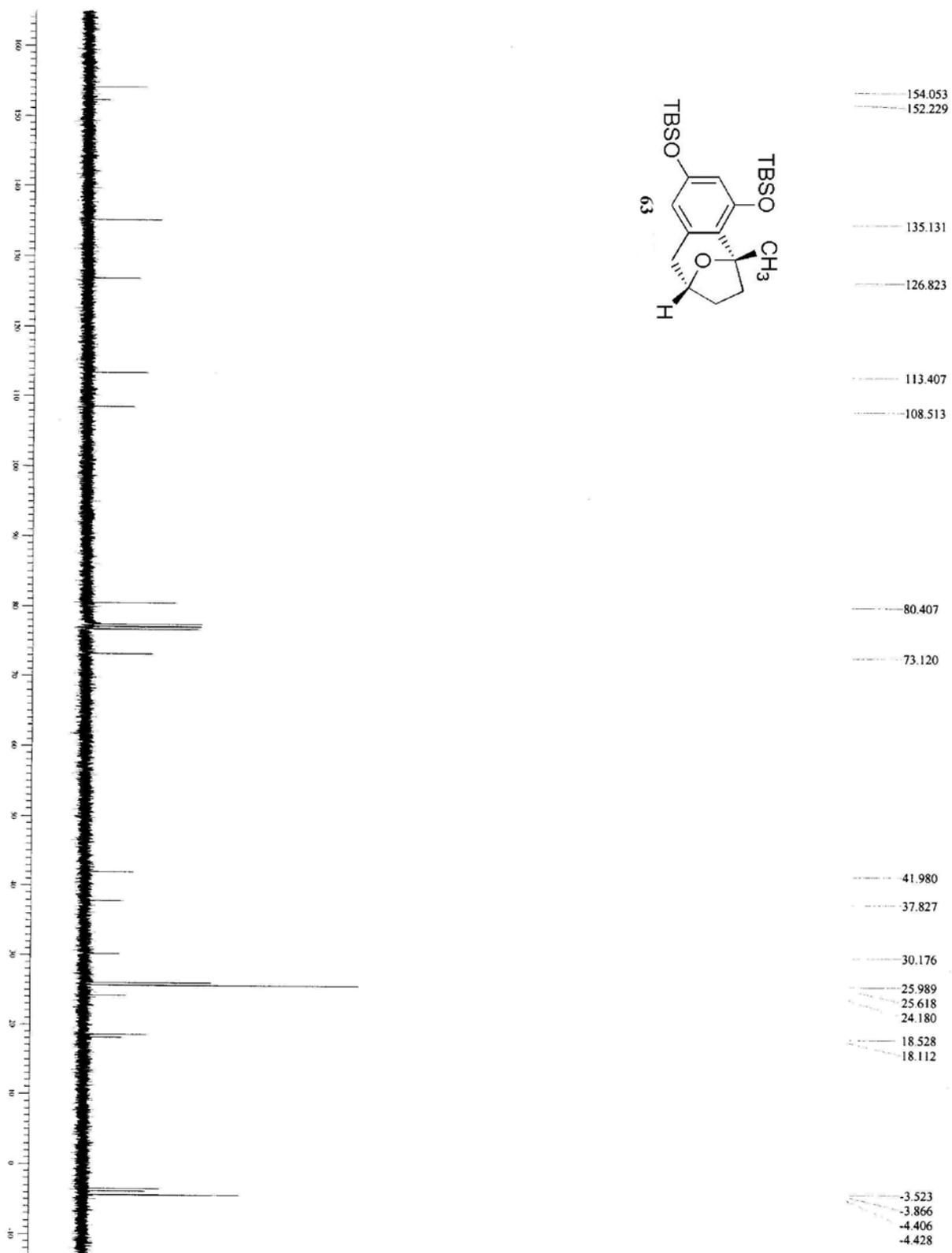
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **60**



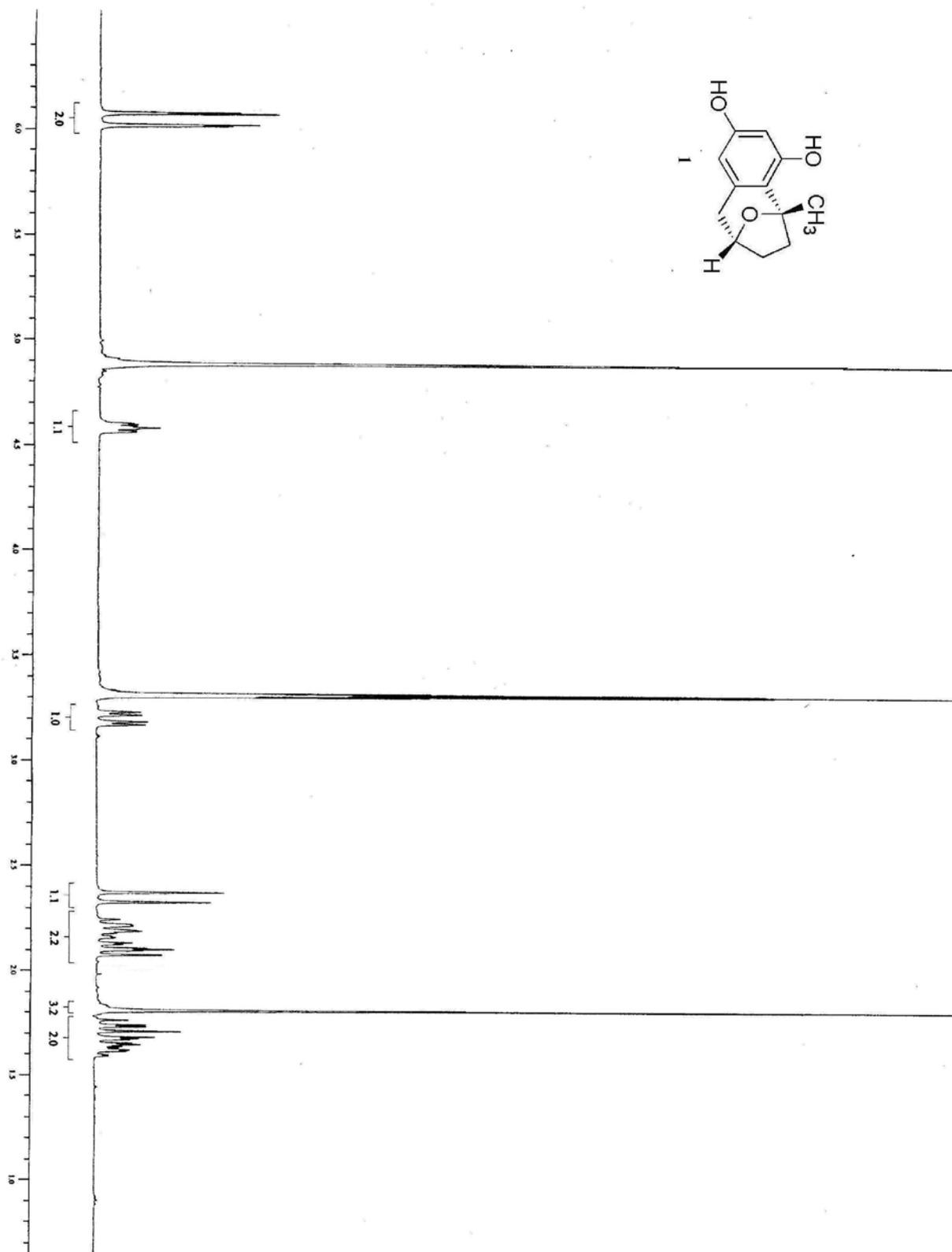
The ^{13}C NMR Spectrum (90 MHz, CDCl_3) of Compound **60**



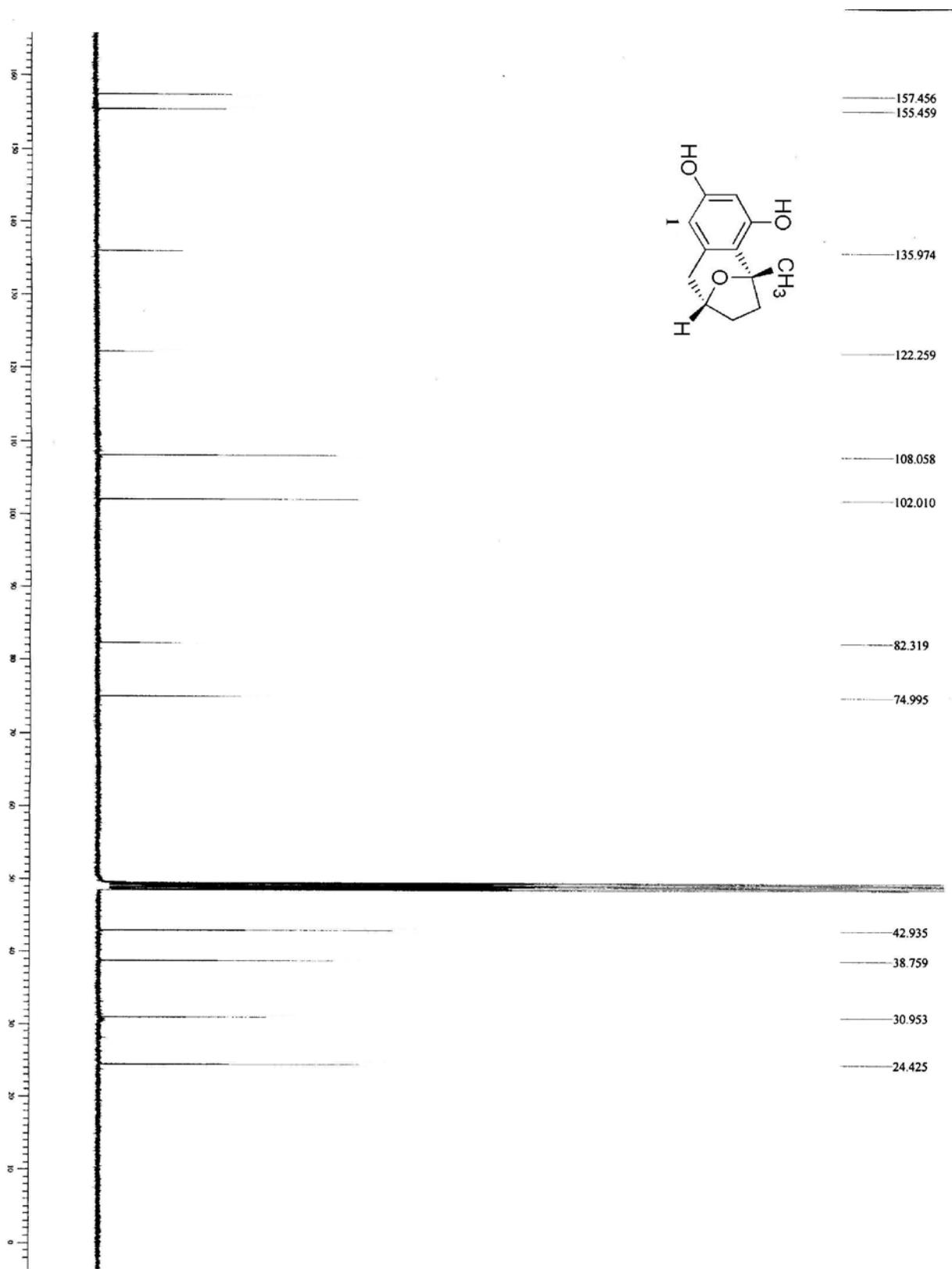
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **63**



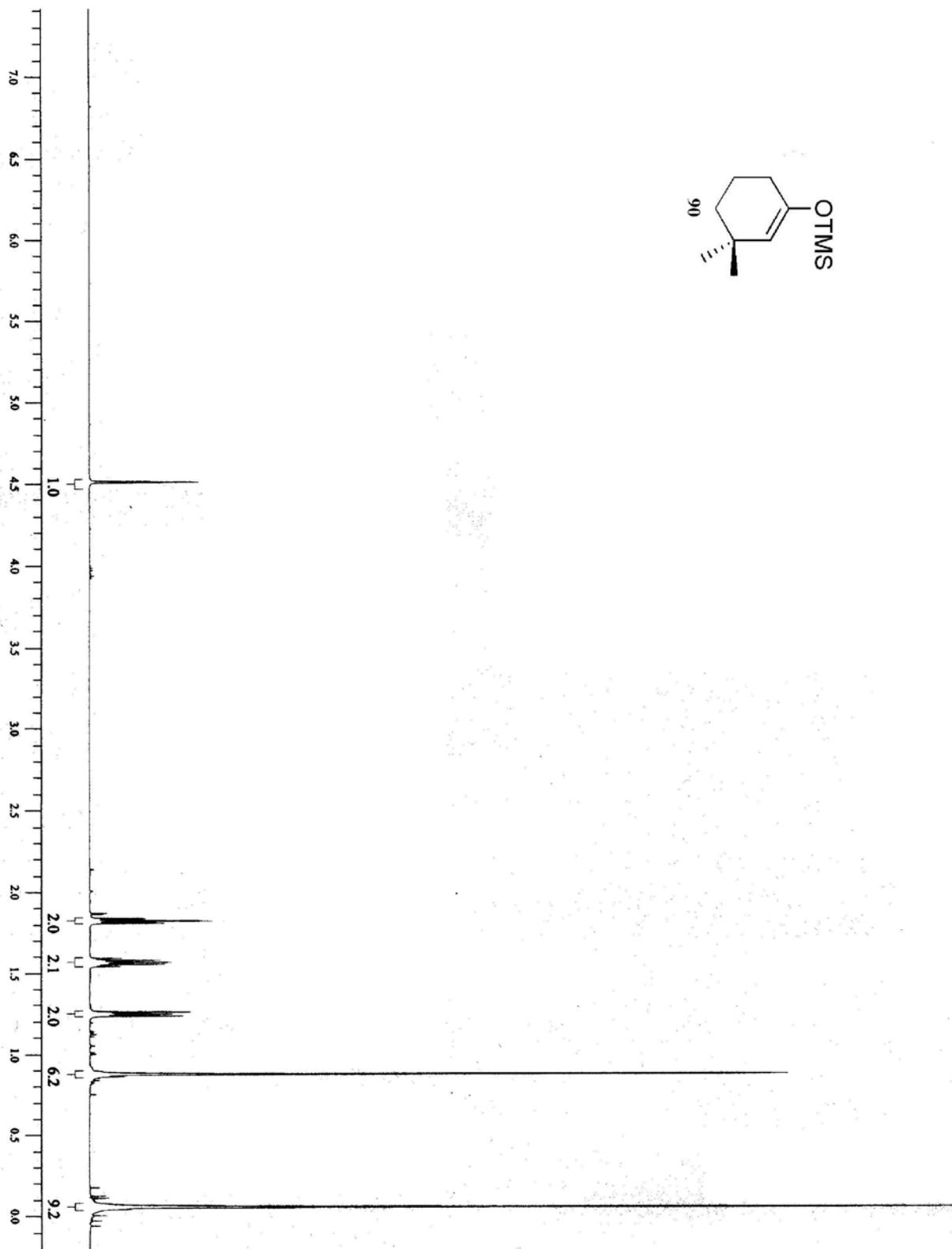
The ^{13}C NMR Spectrum (90 MHz, CDCl_3) of Compound **63**



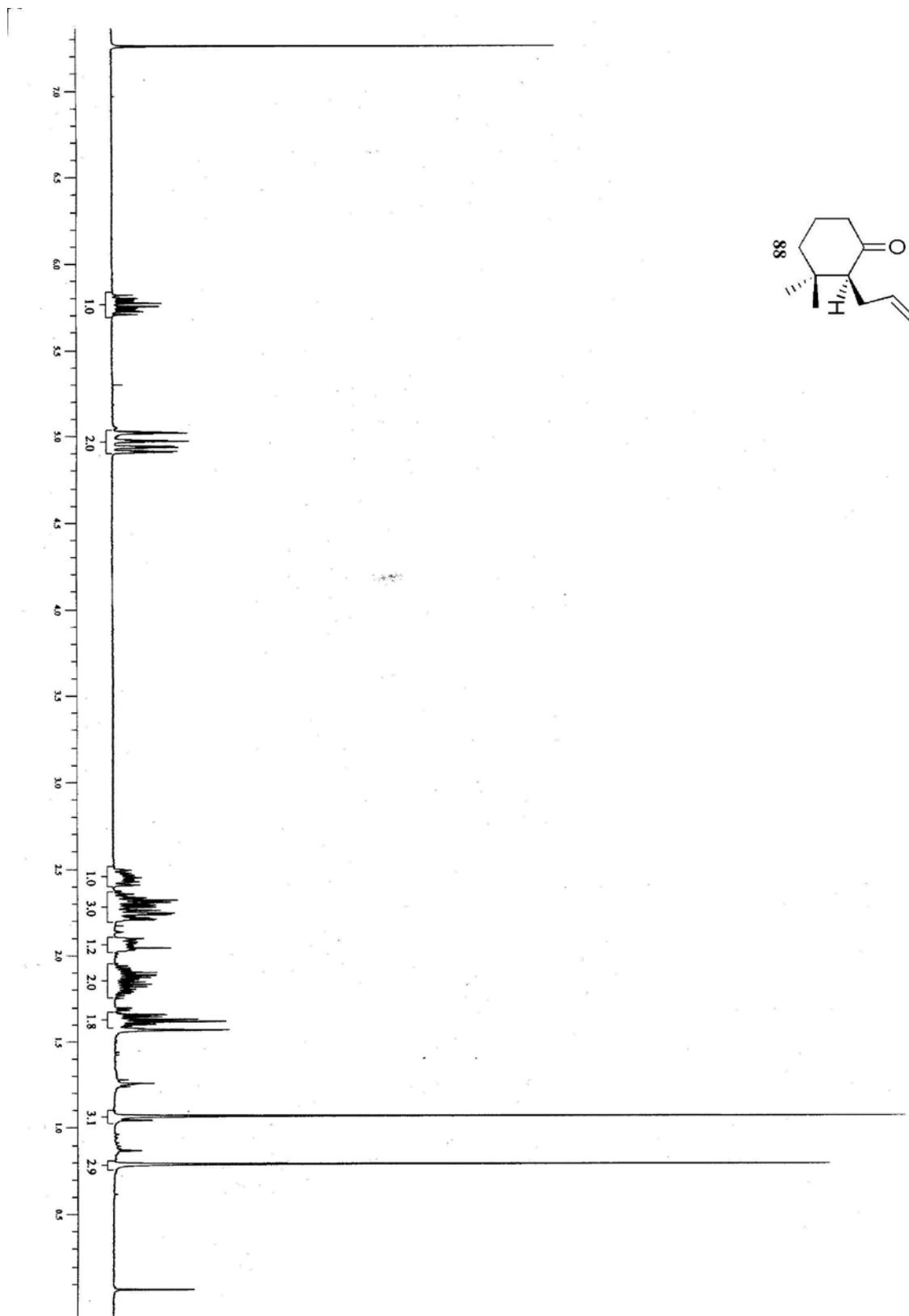
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **1**



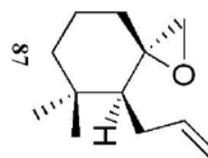
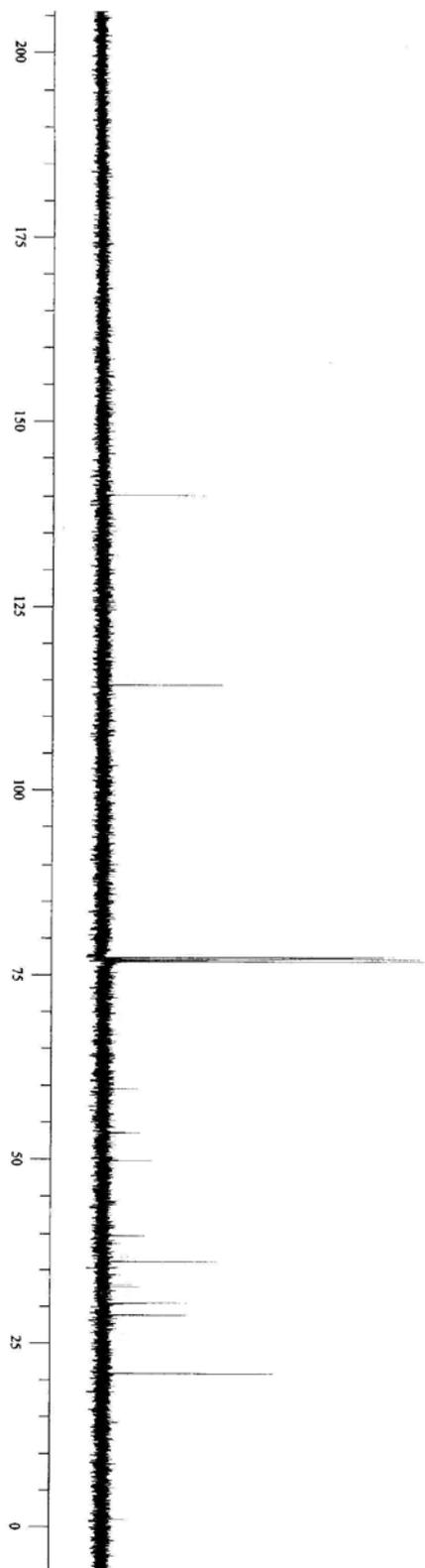
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound 1



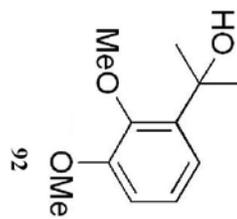
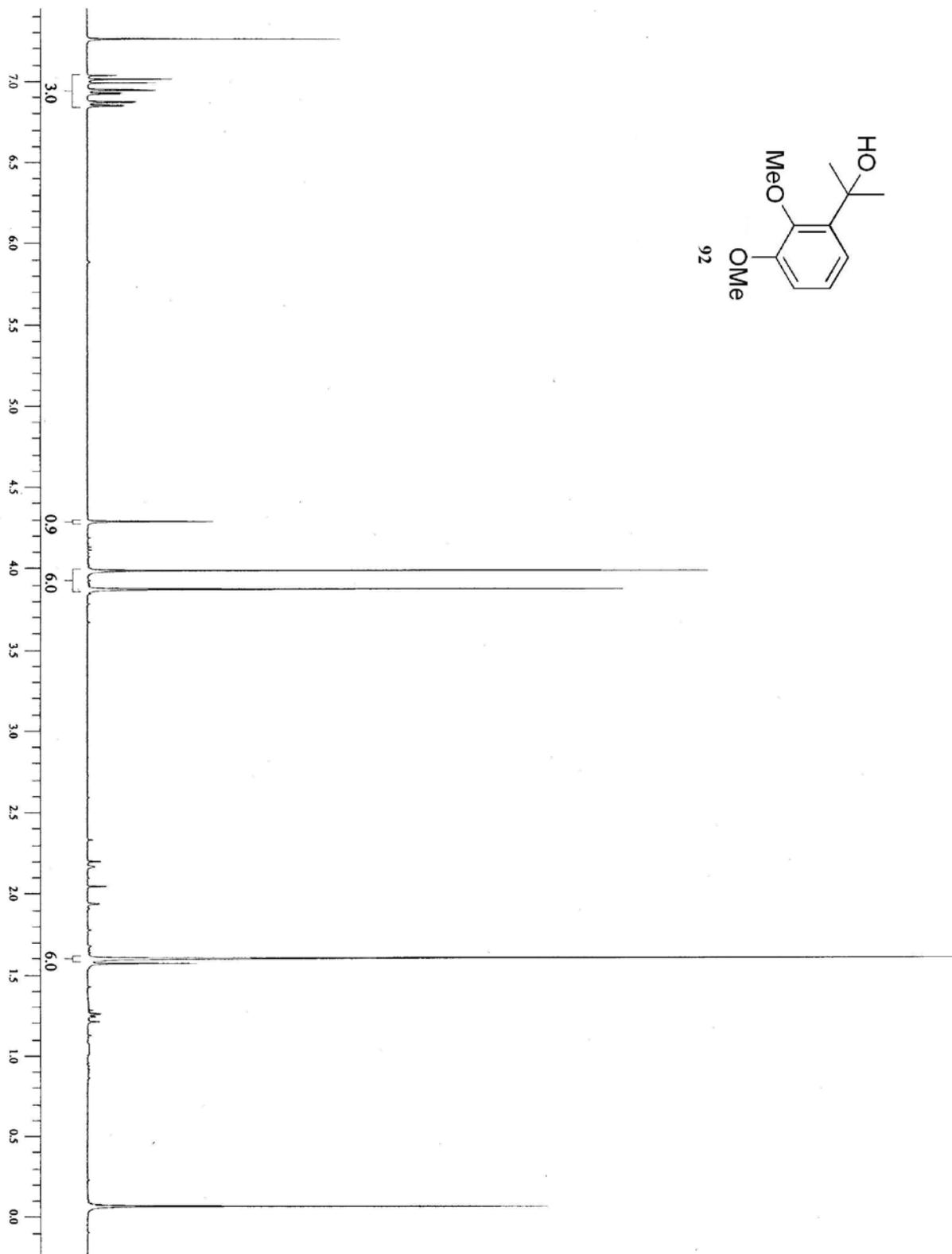
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **90**



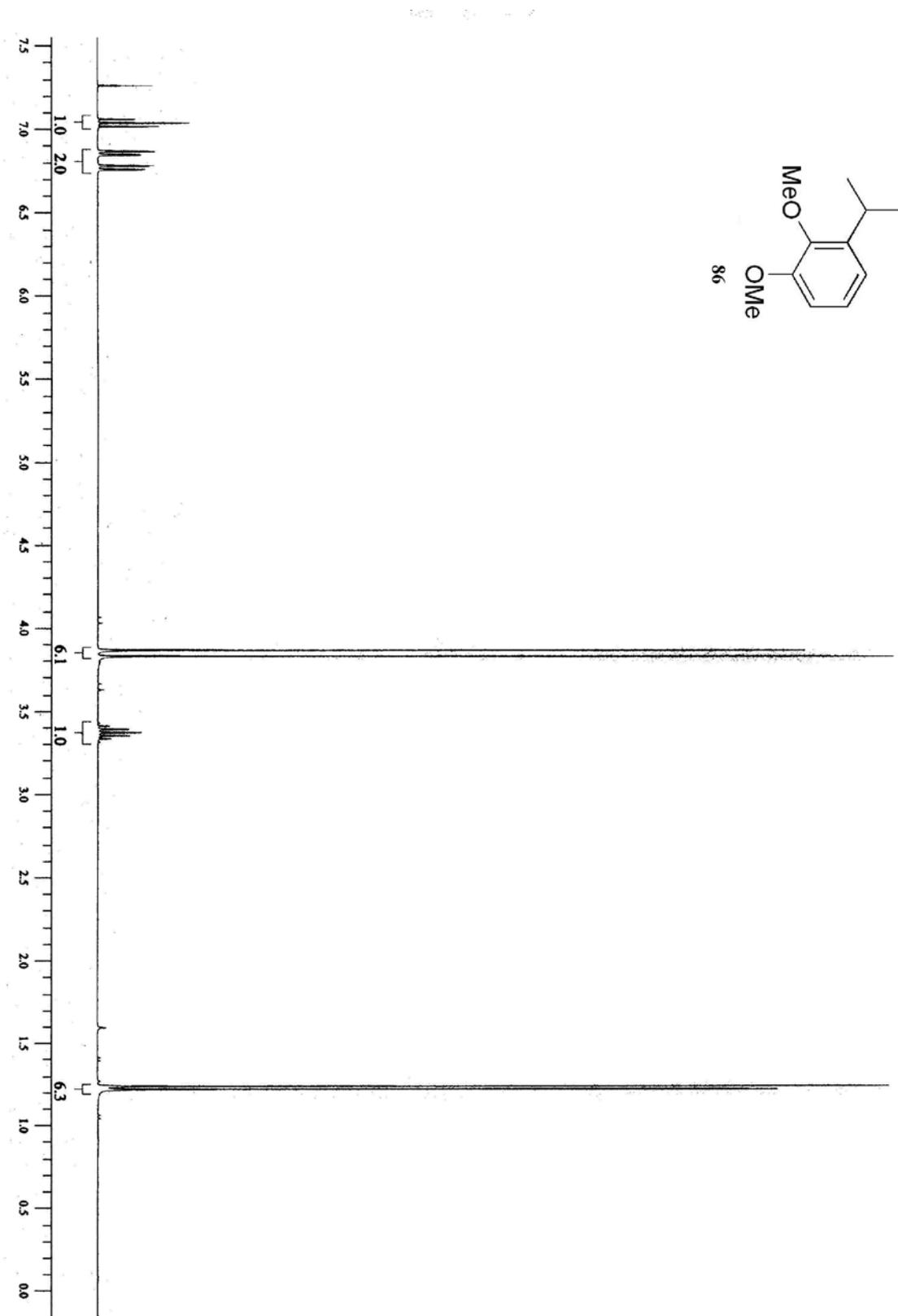
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **88**



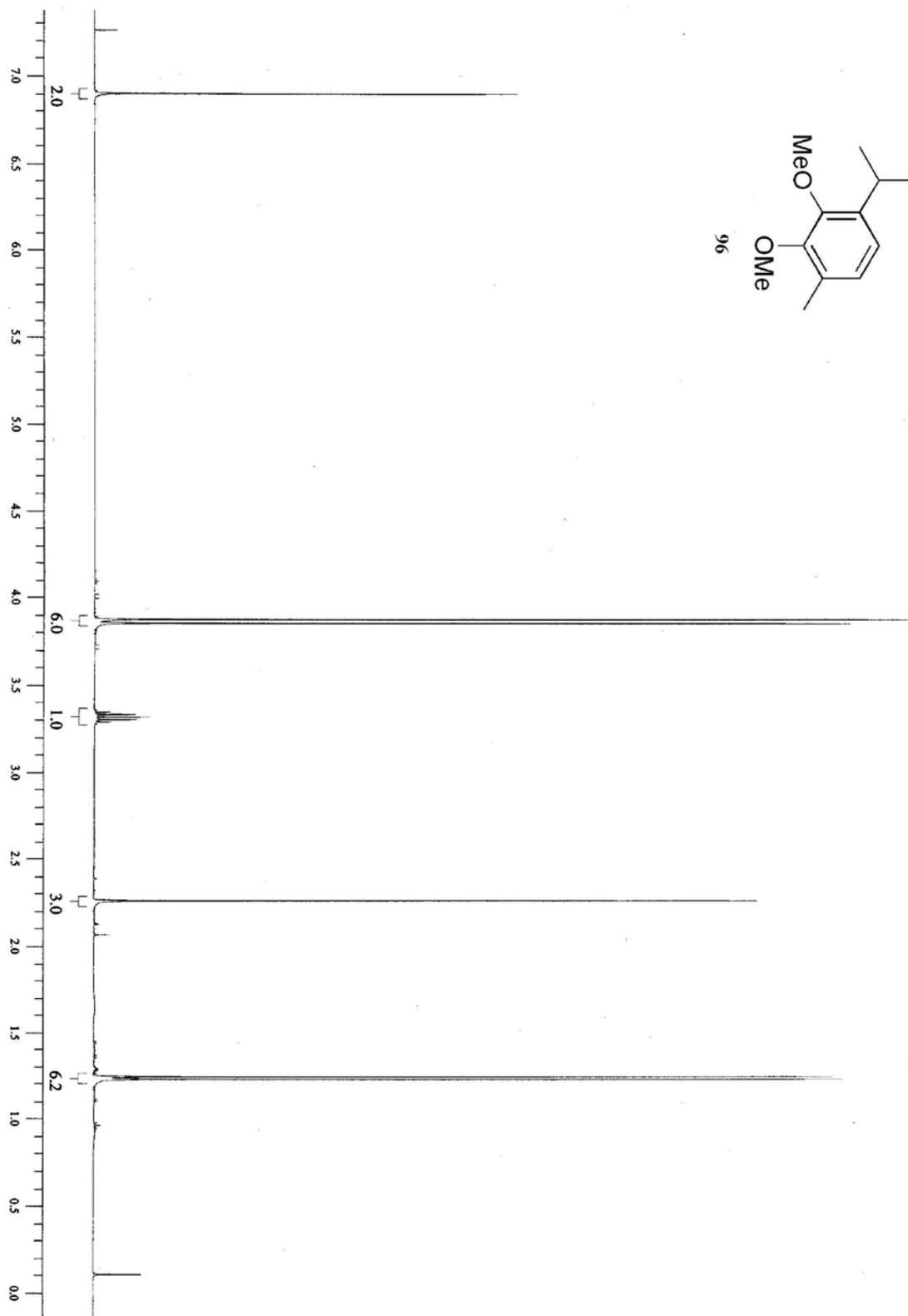
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **87**



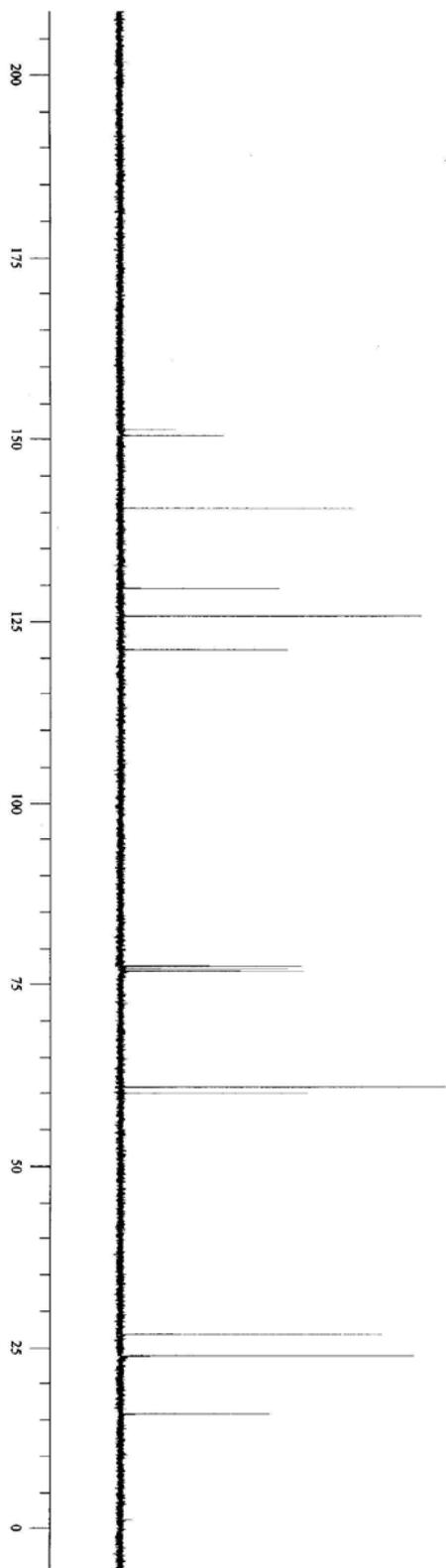
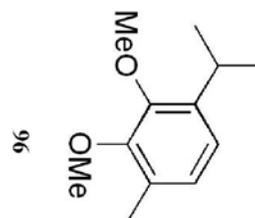
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound 92



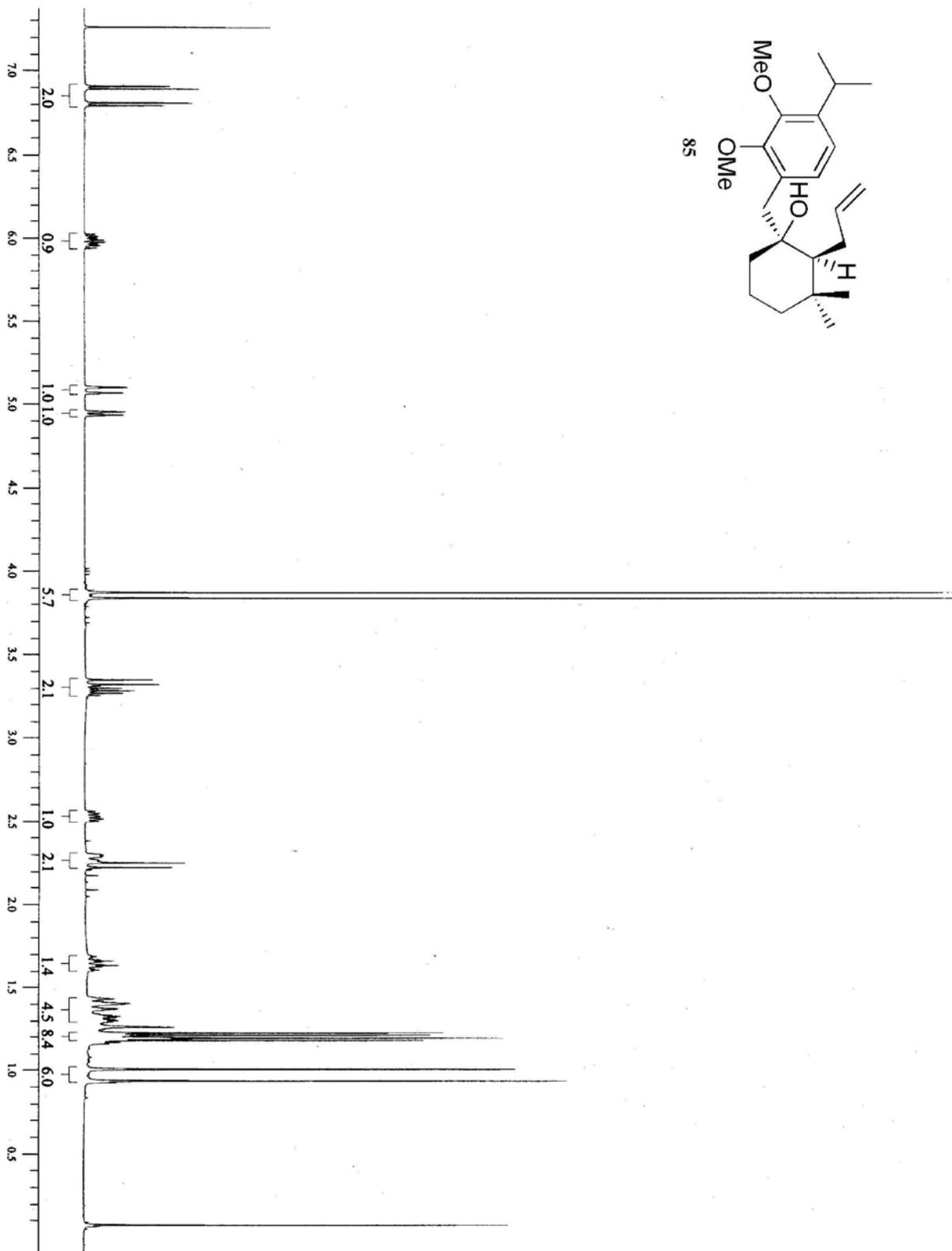
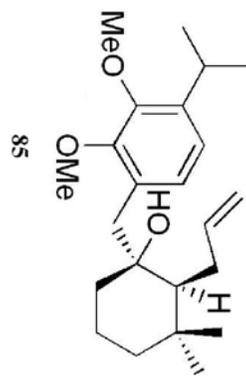
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **86**



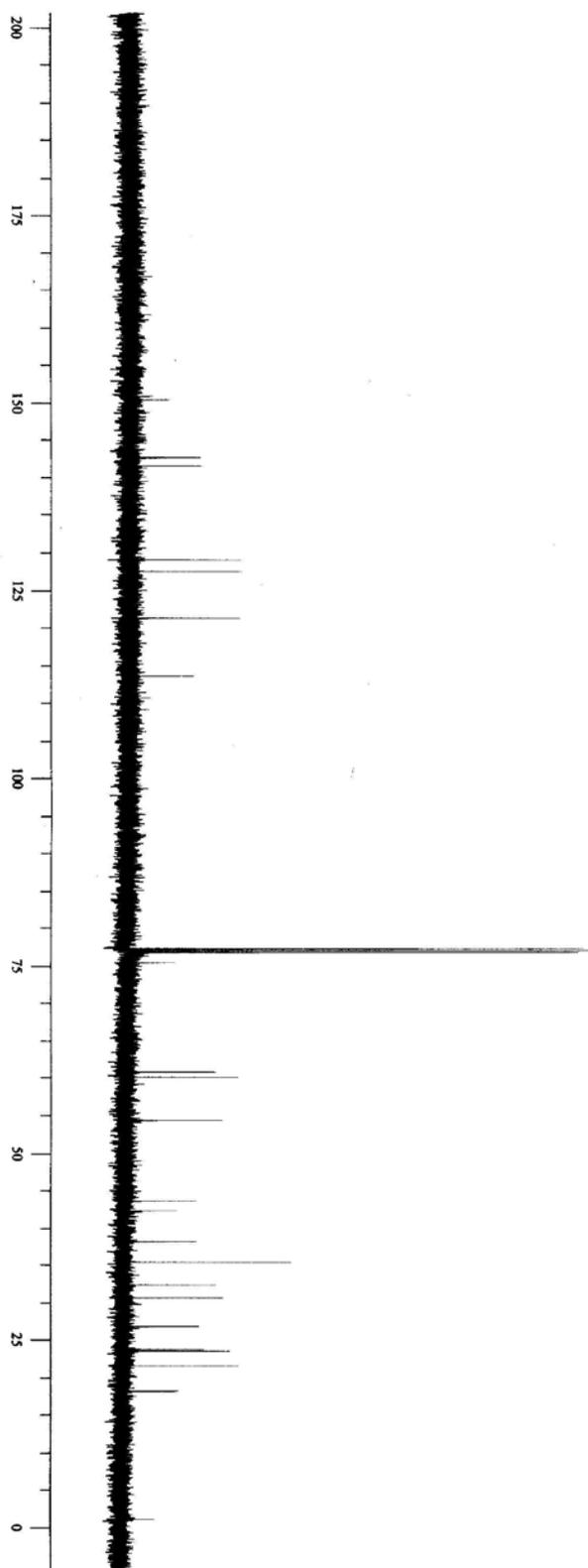
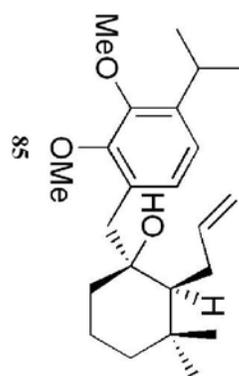
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **96**



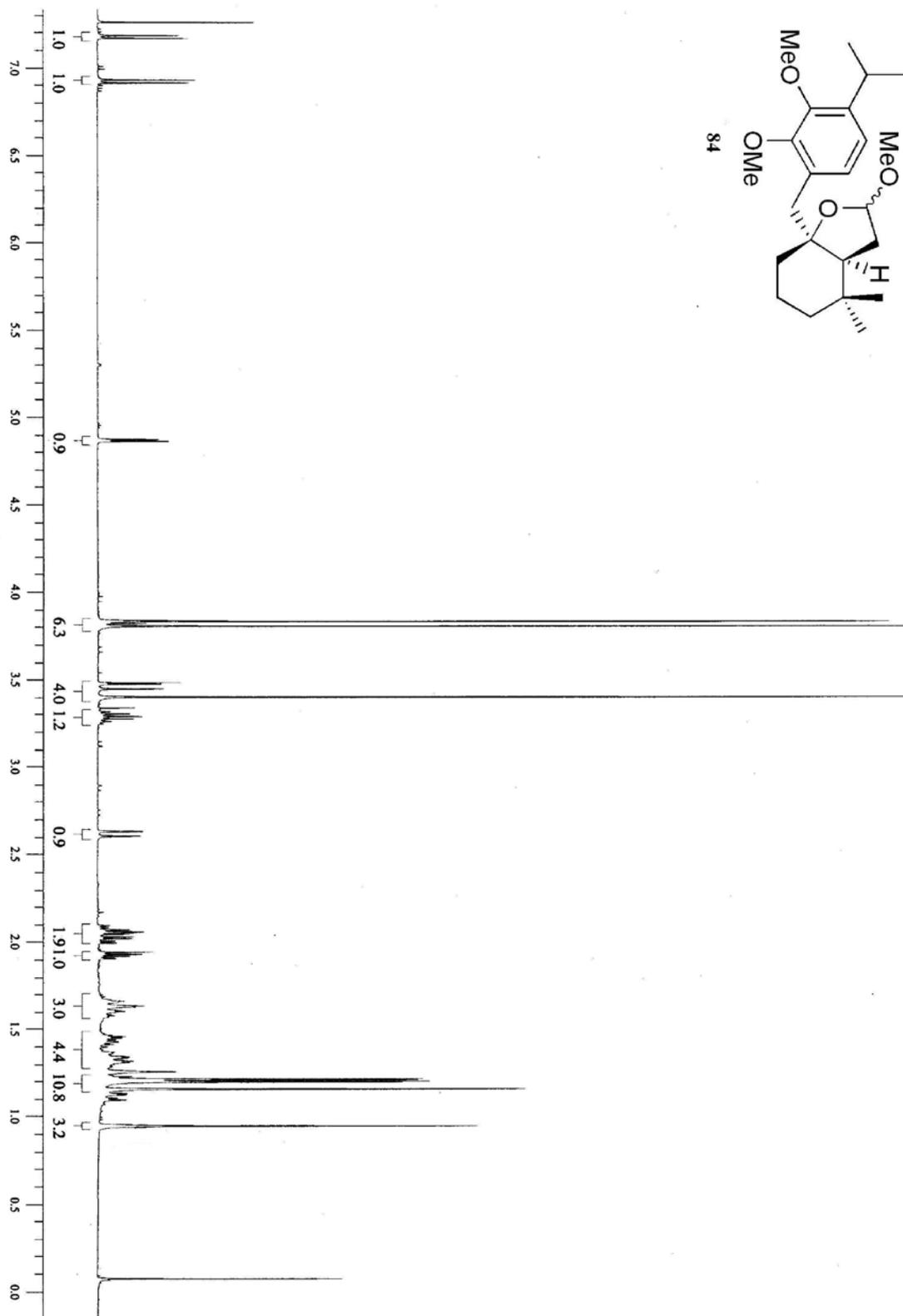
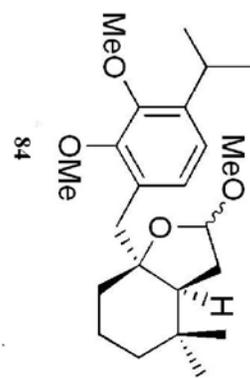
The ^{13}C NMR Spectrum (90 MHz, CDCl_3) of Compound **96**



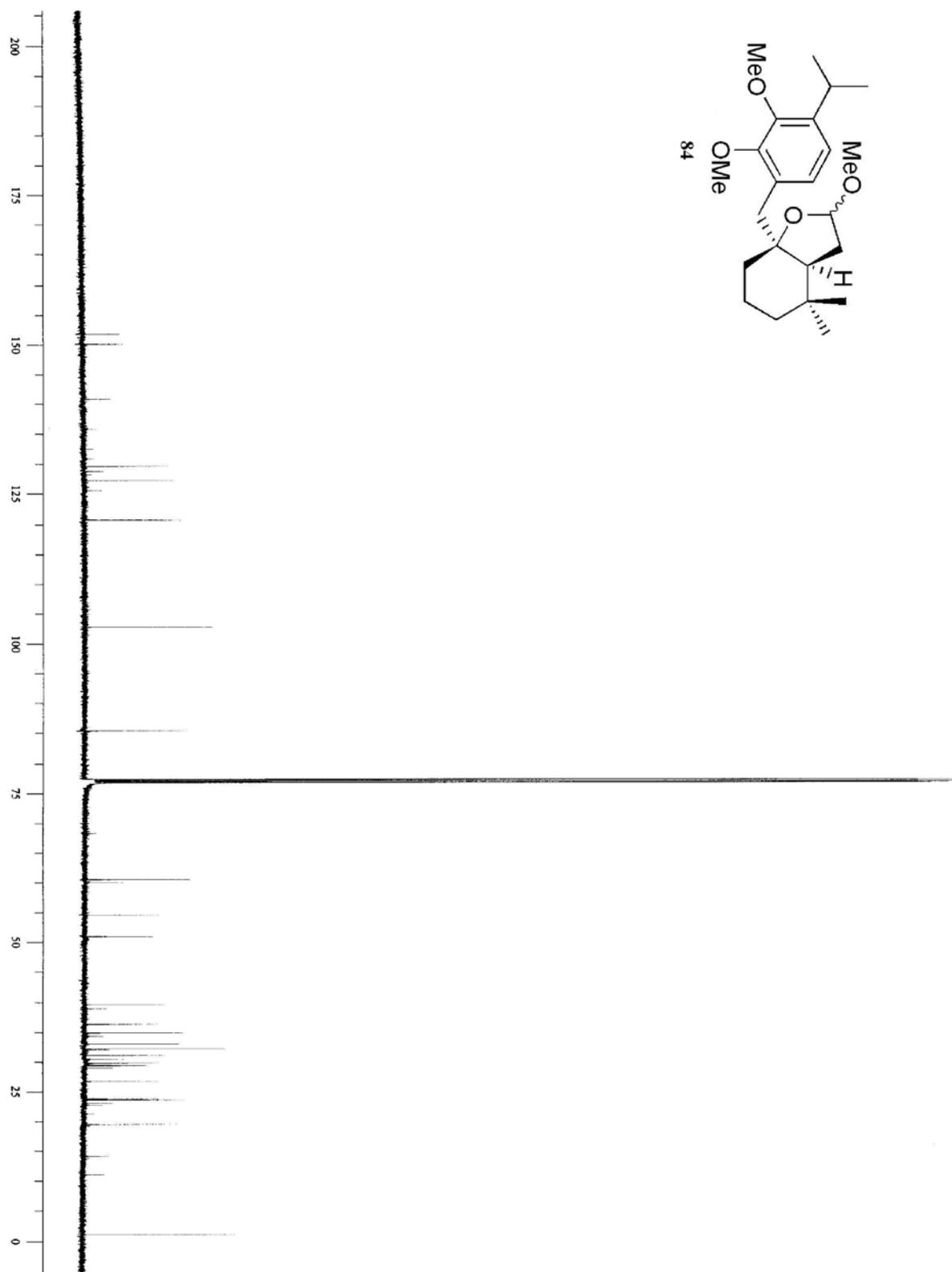
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **85**



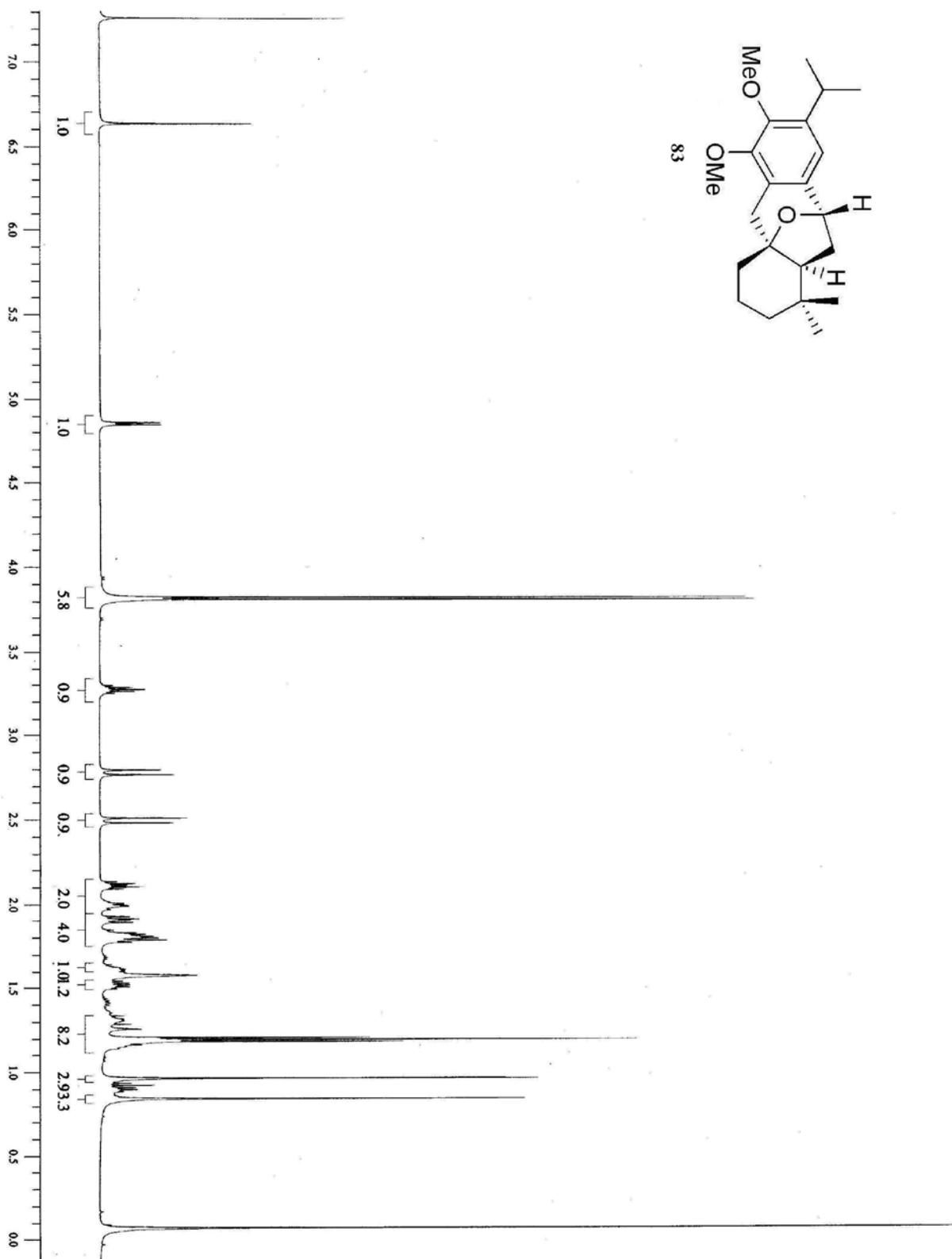
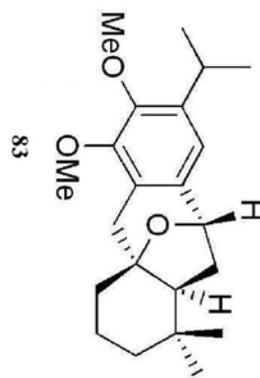
The ¹³C NMR Spectrum (125 MHz, CDCl₃) of Compound 85



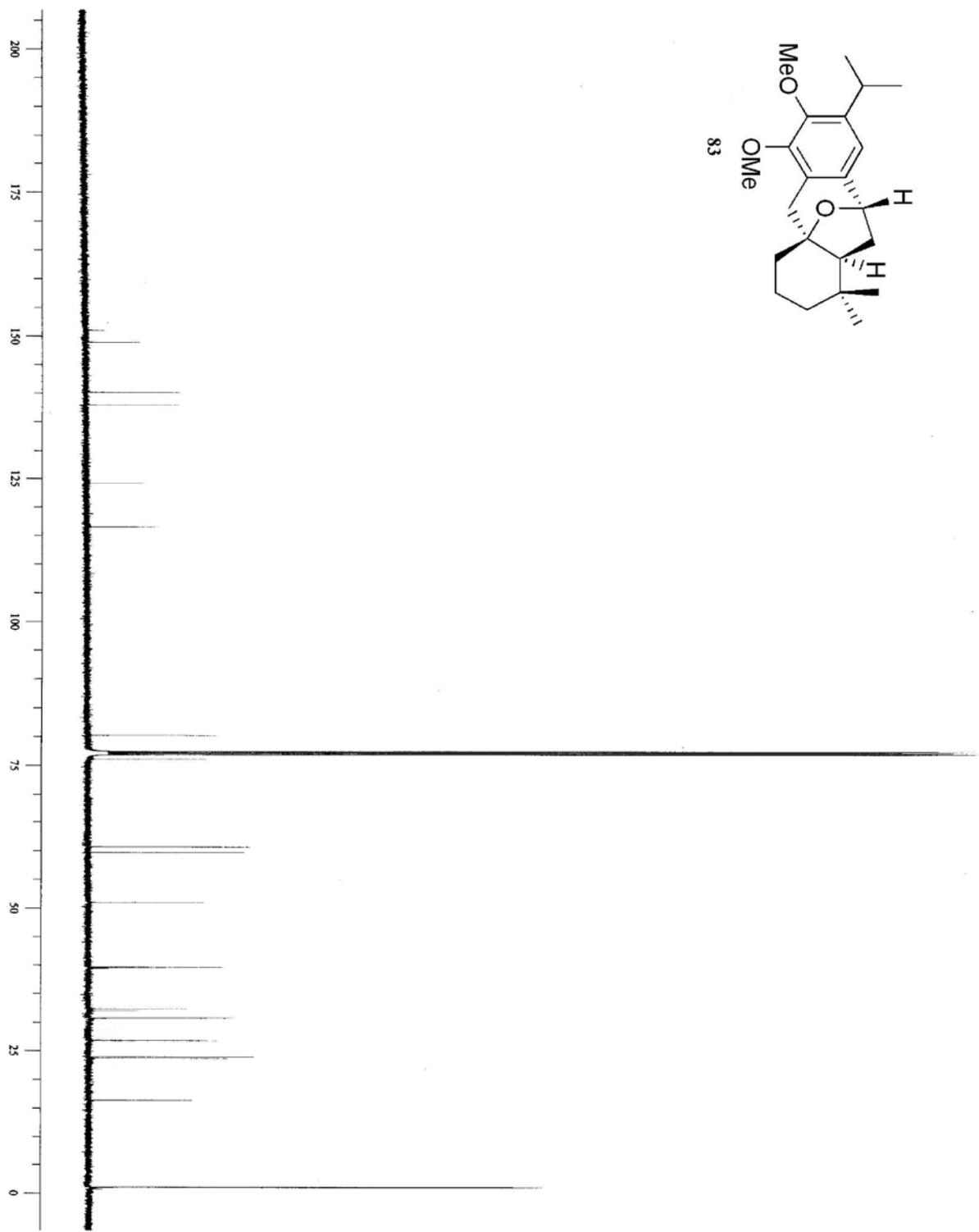
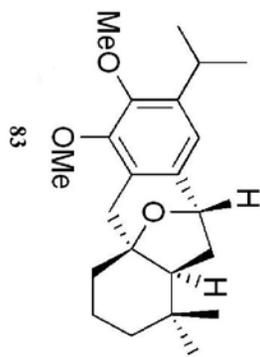
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **84**



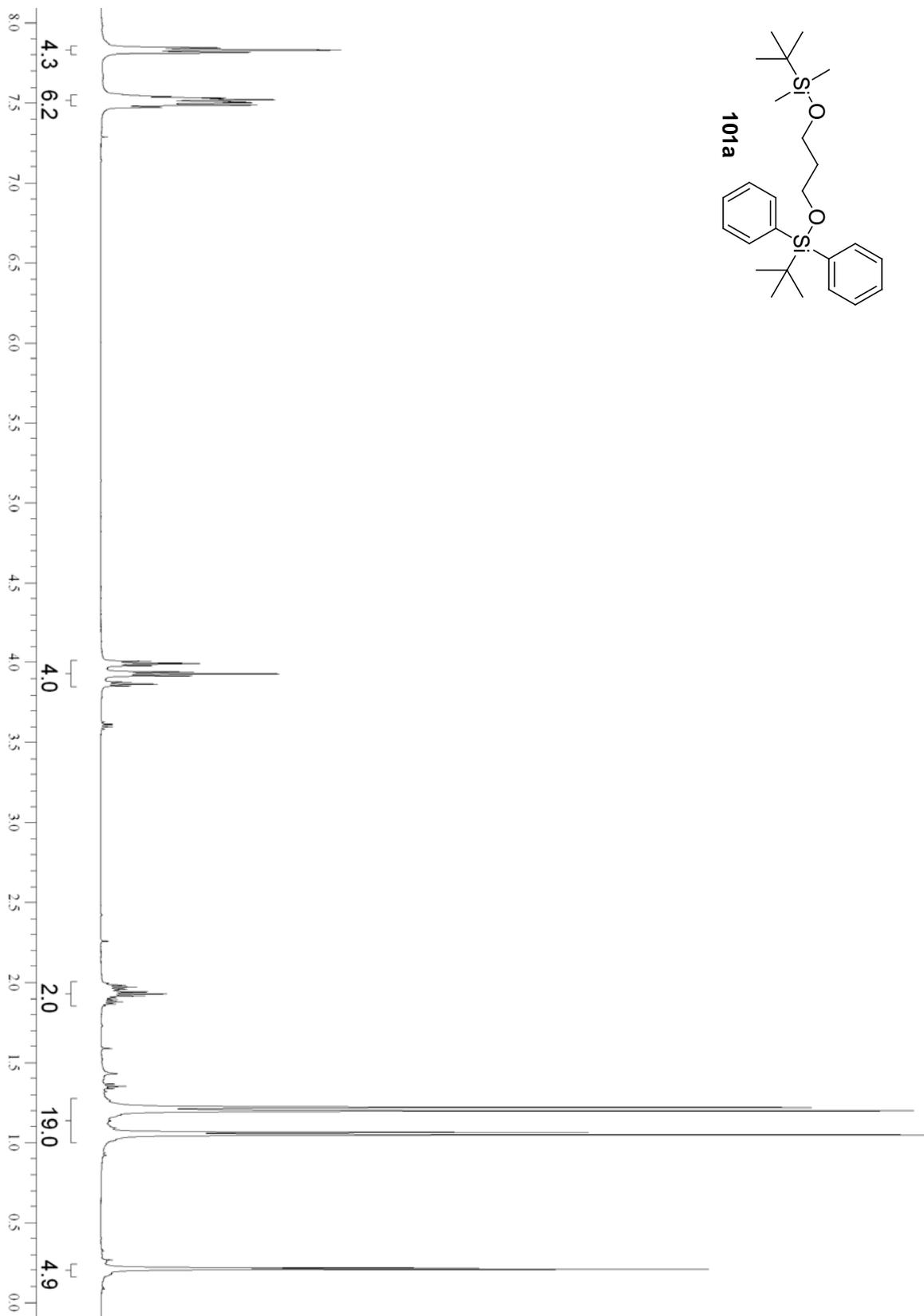
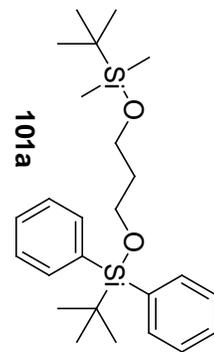
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **84**



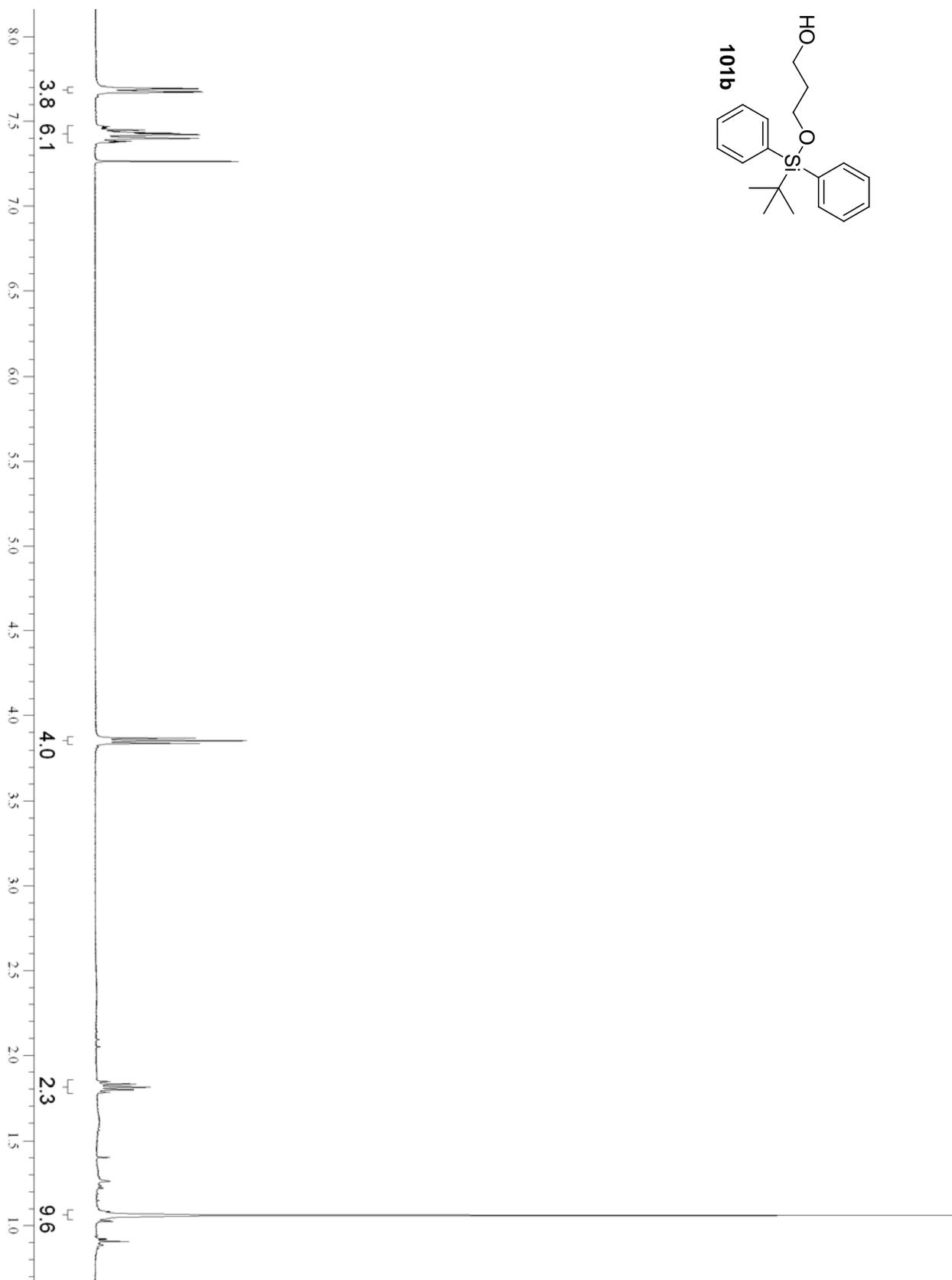
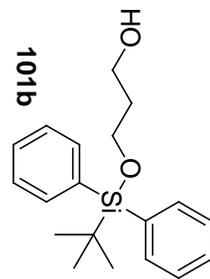
The ^1H NMR Spectrum (600 MHz, CDCl_3) of Compound **83**



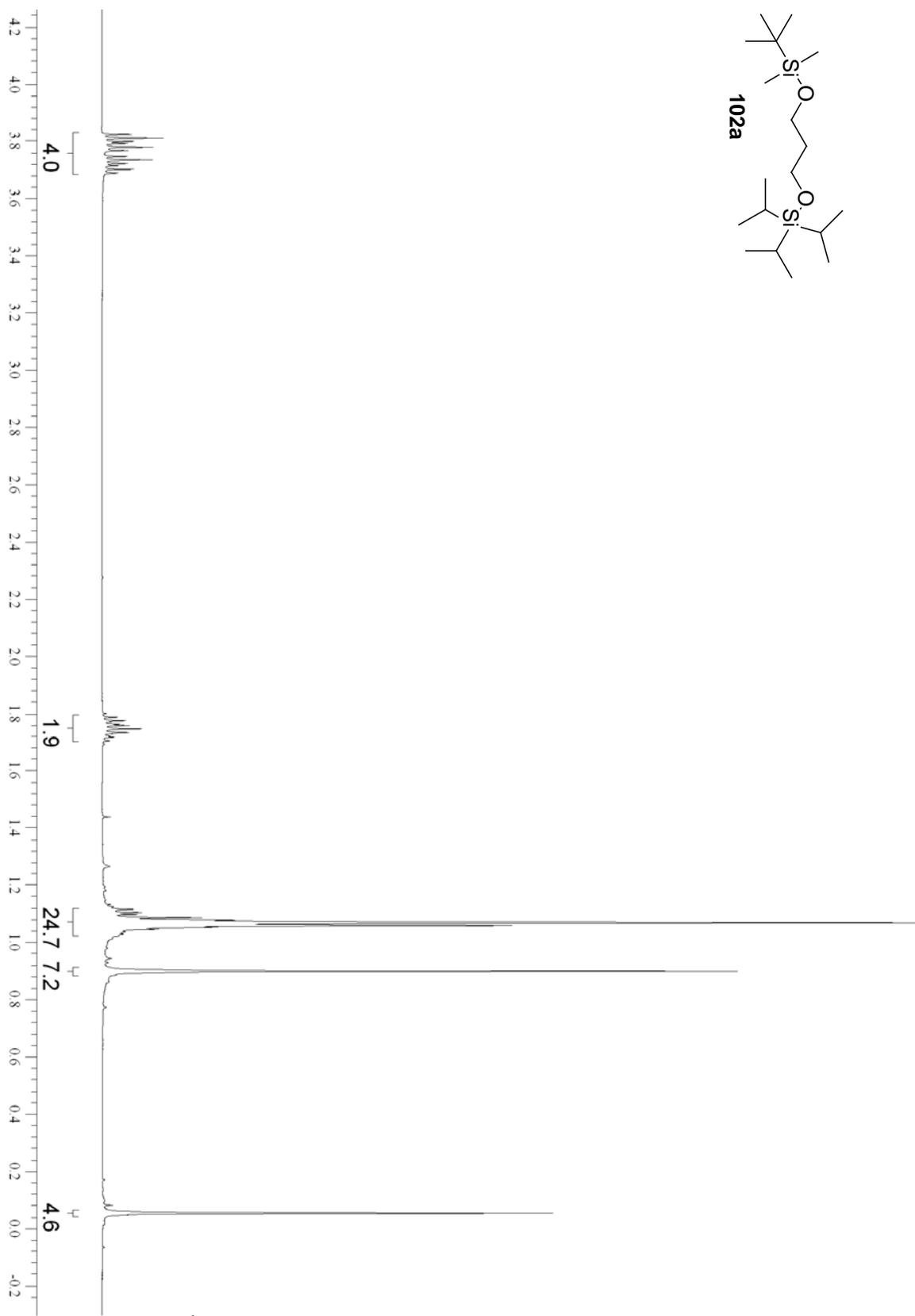
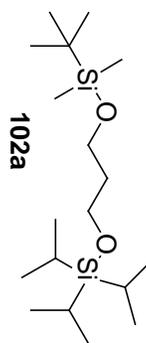
The ¹³C NMR Spectrum (125 MHz, CDCl₃) of Compound **83**



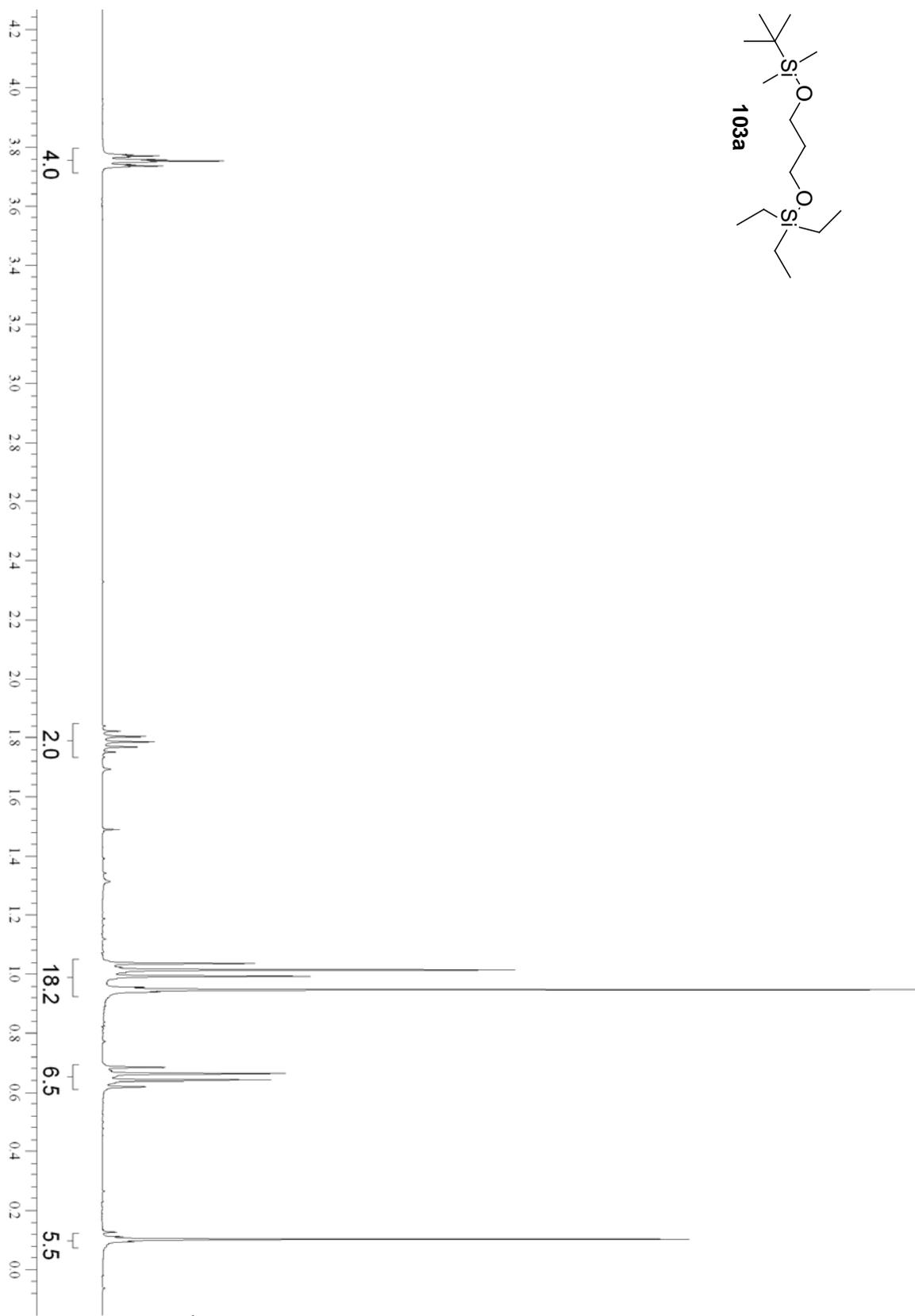
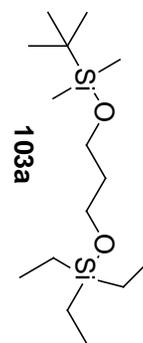
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **101a**



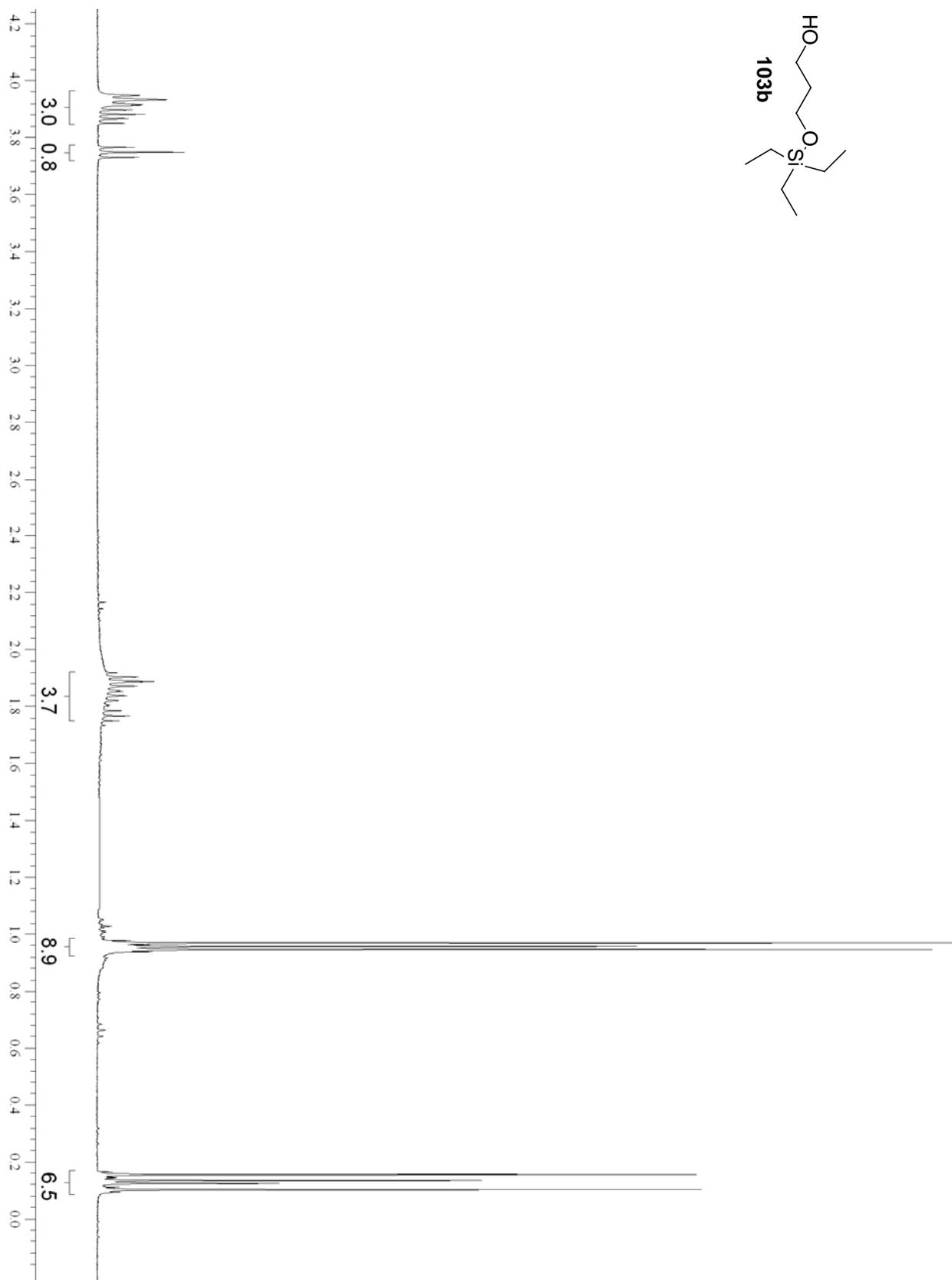
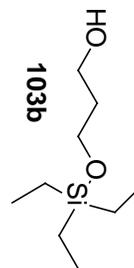
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **101b**



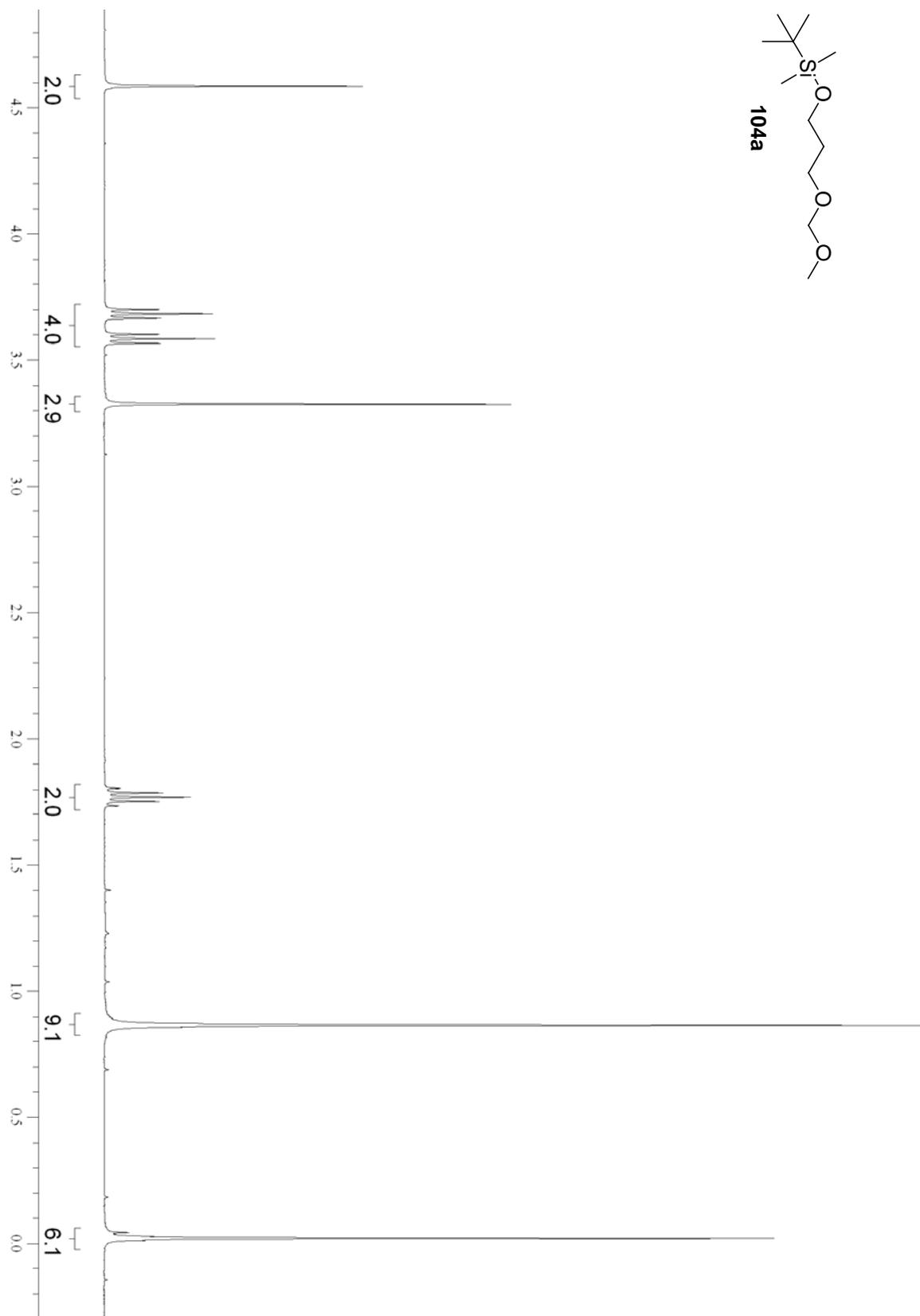
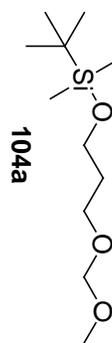
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **102a**



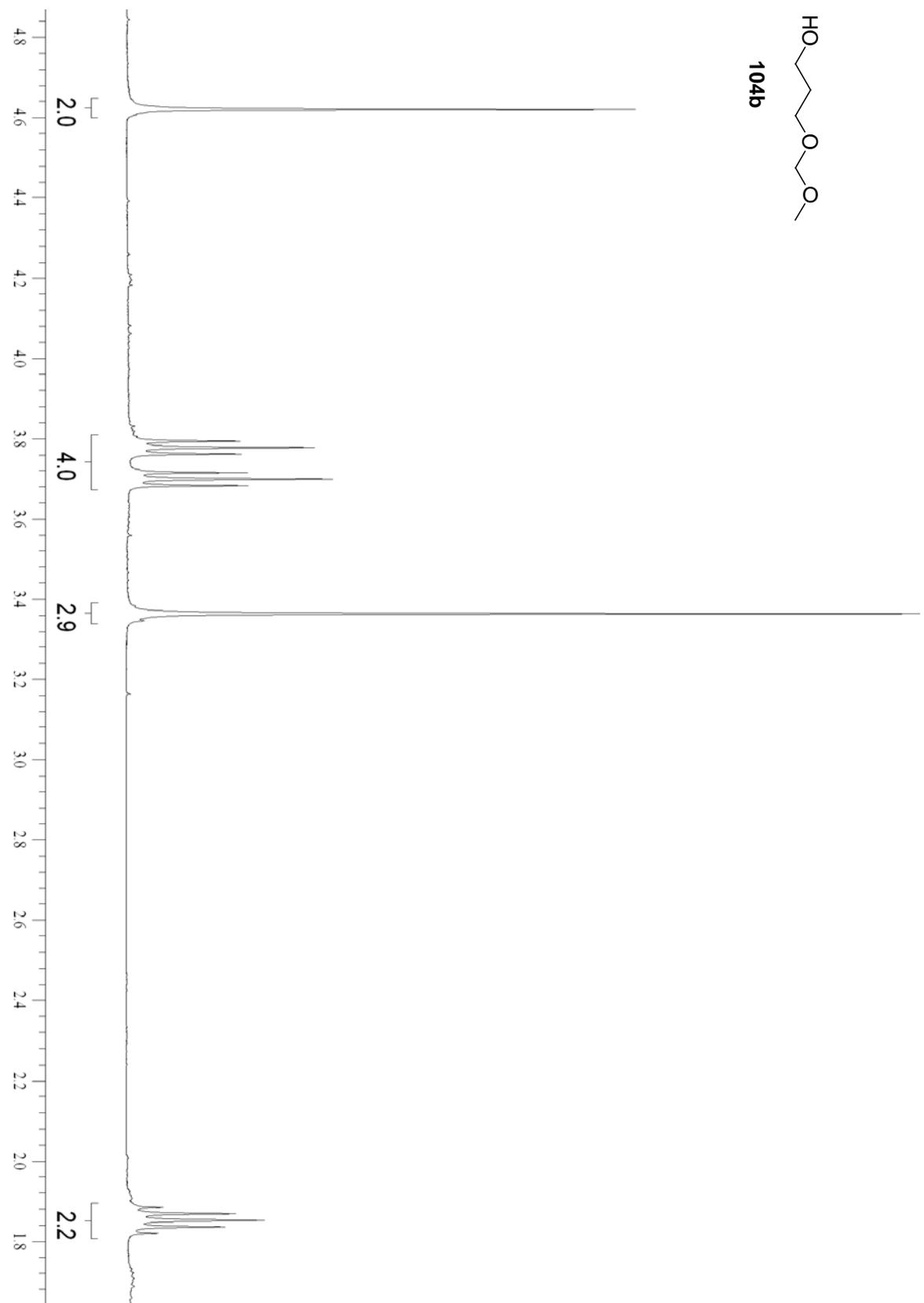
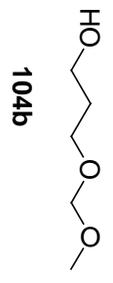
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **103a**



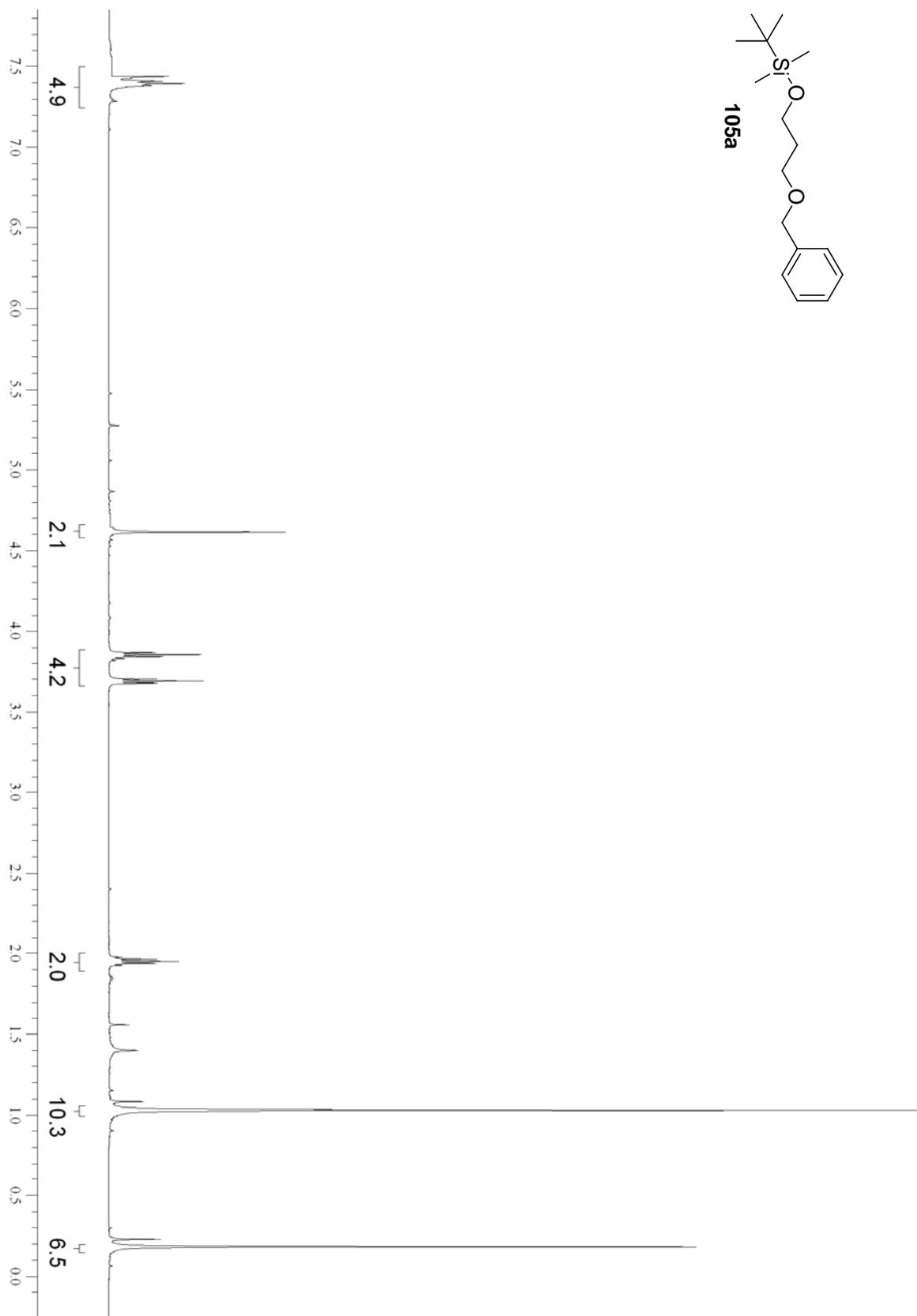
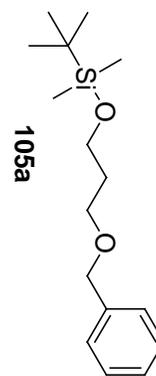
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **103b**



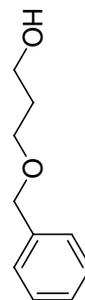
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **104a**



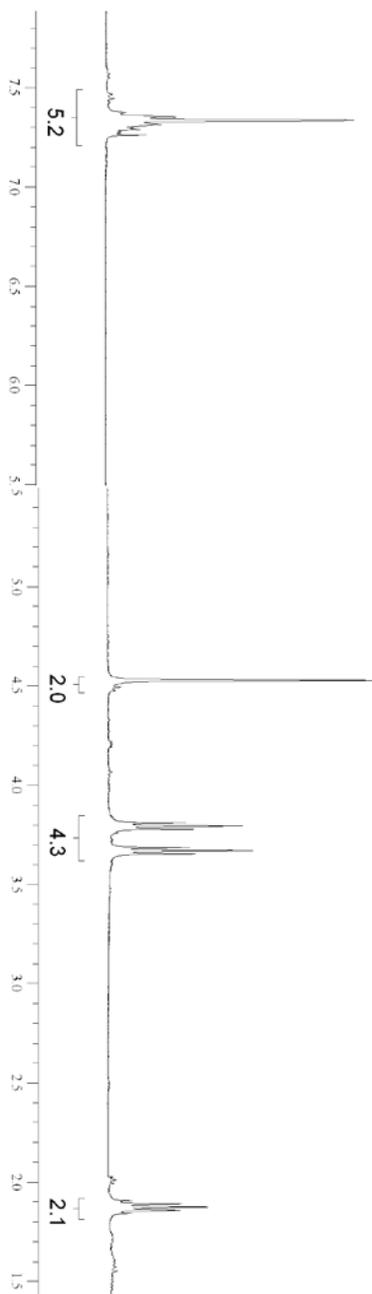
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **104b**



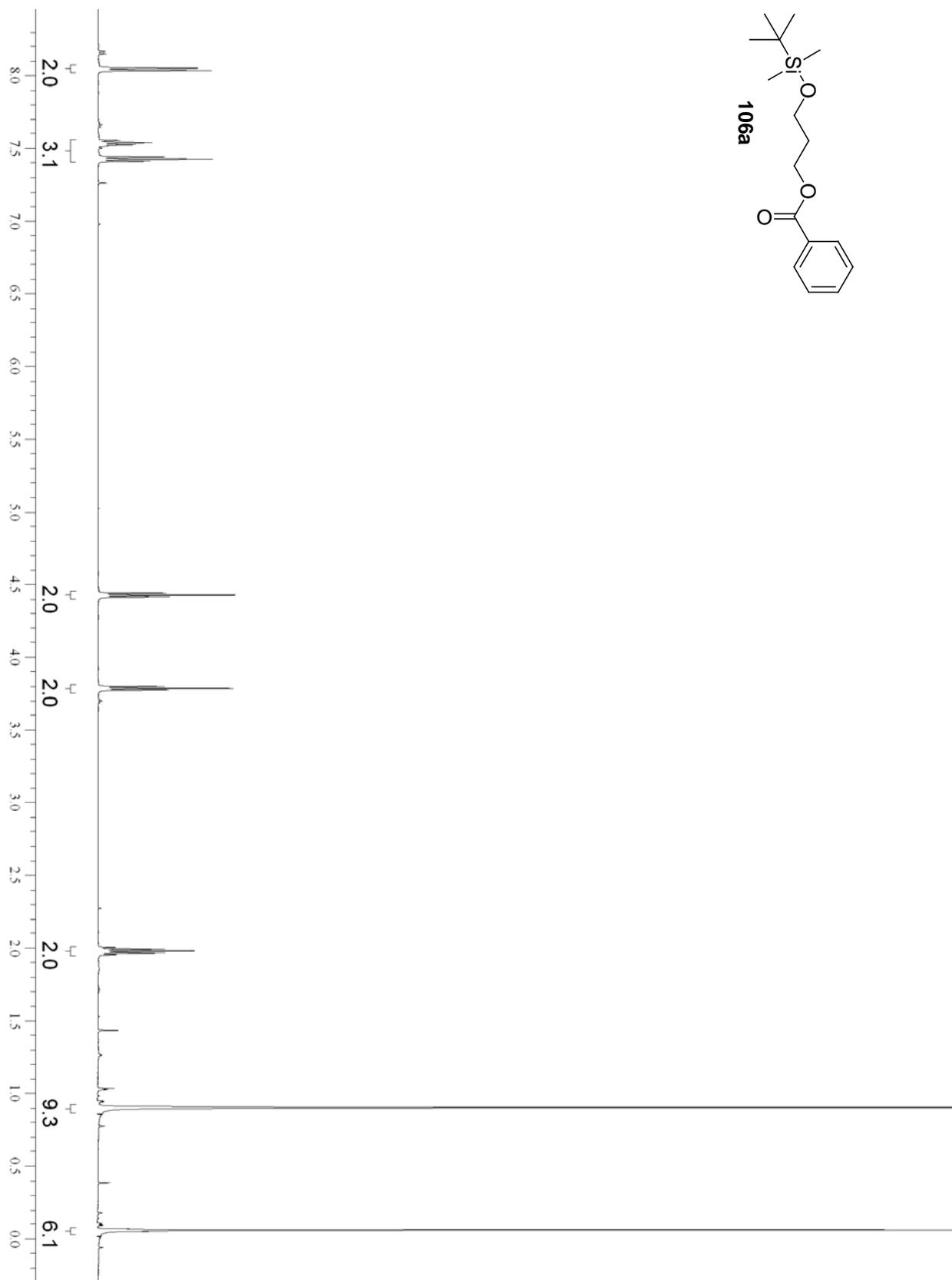
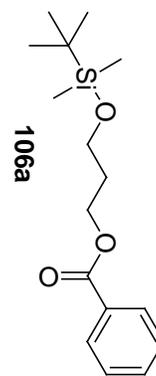
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **105a**



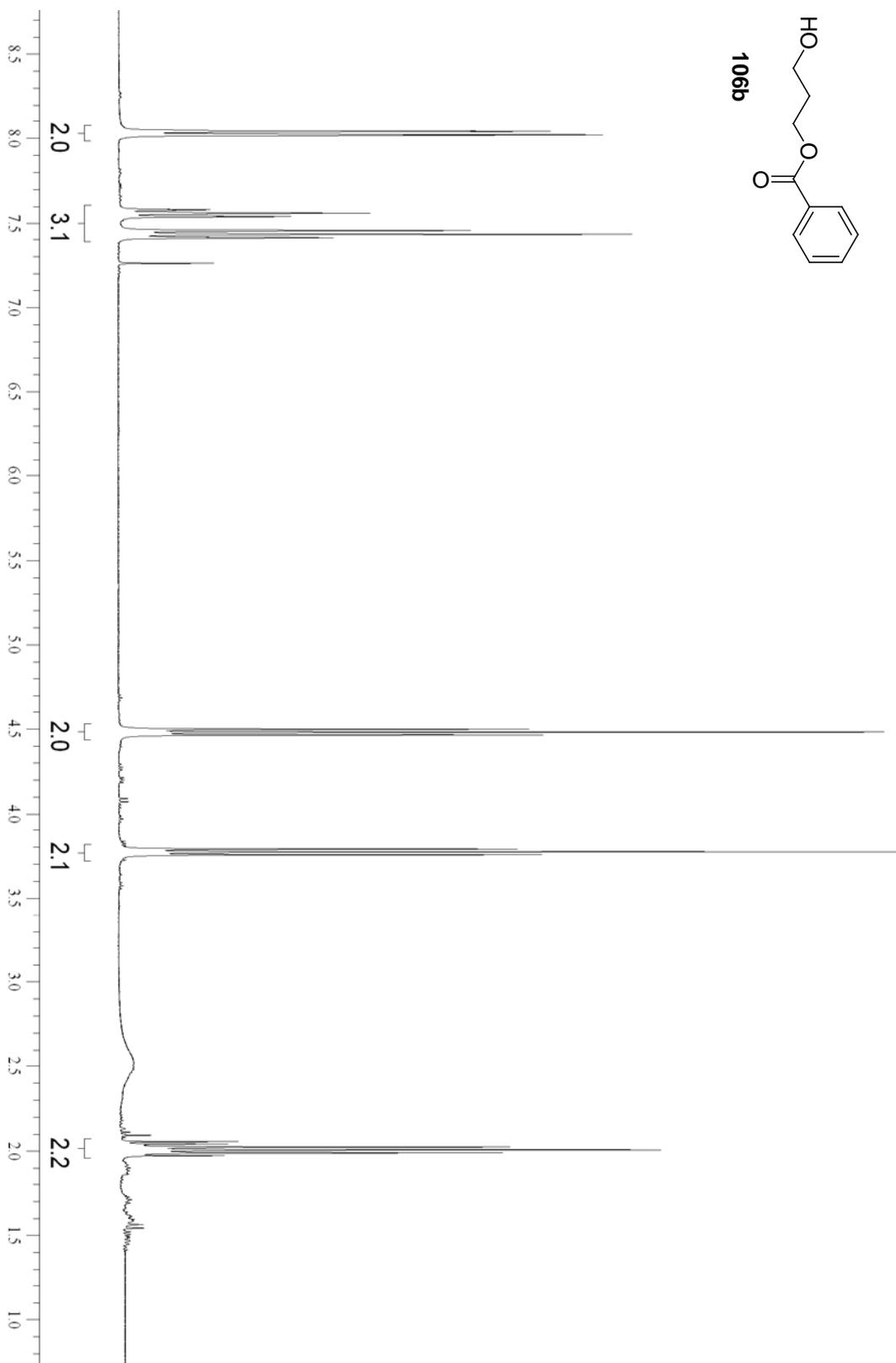
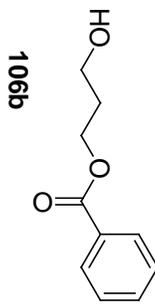
105b



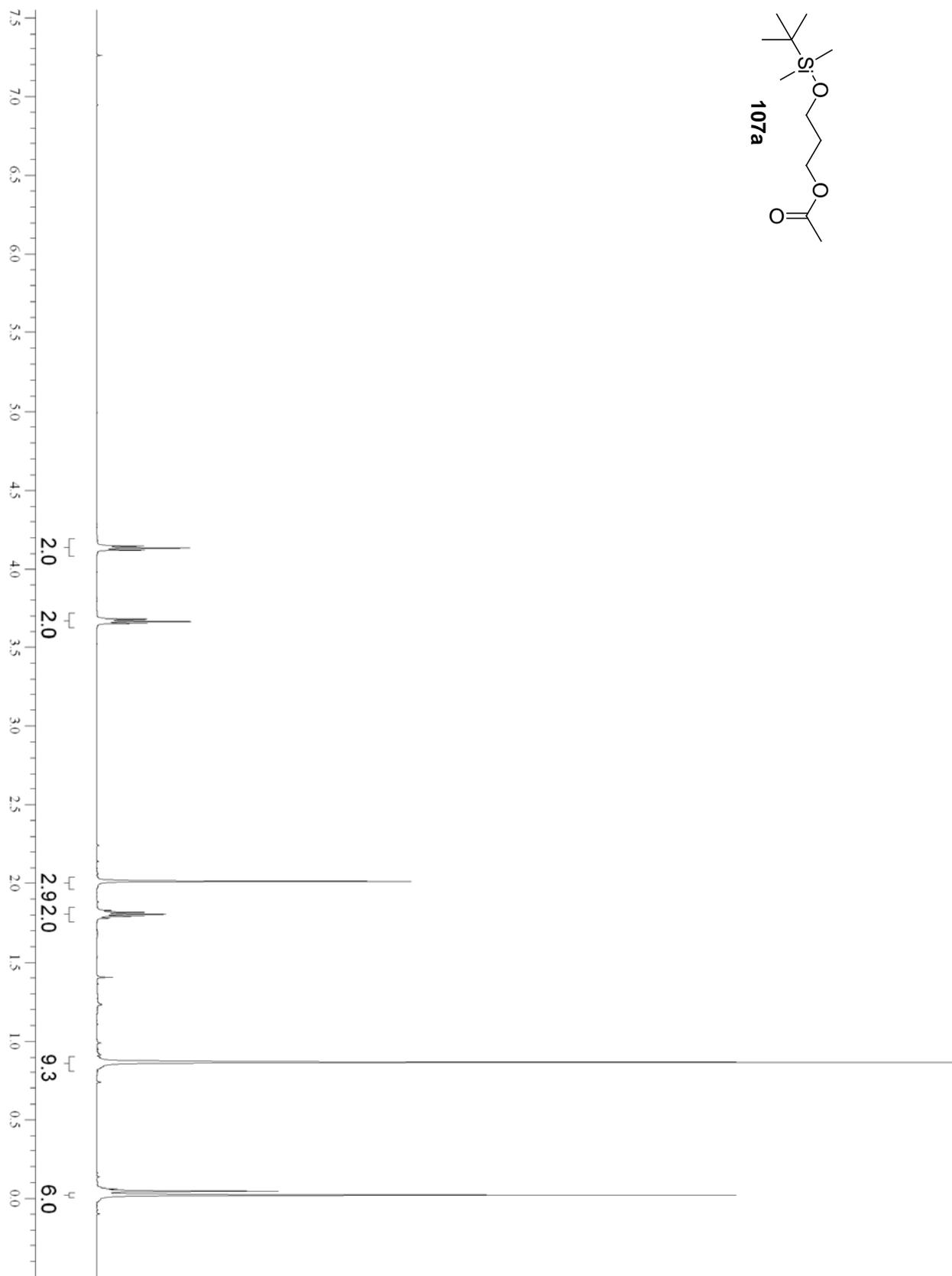
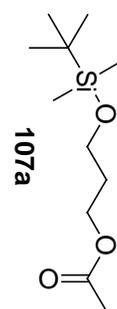
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **105b**



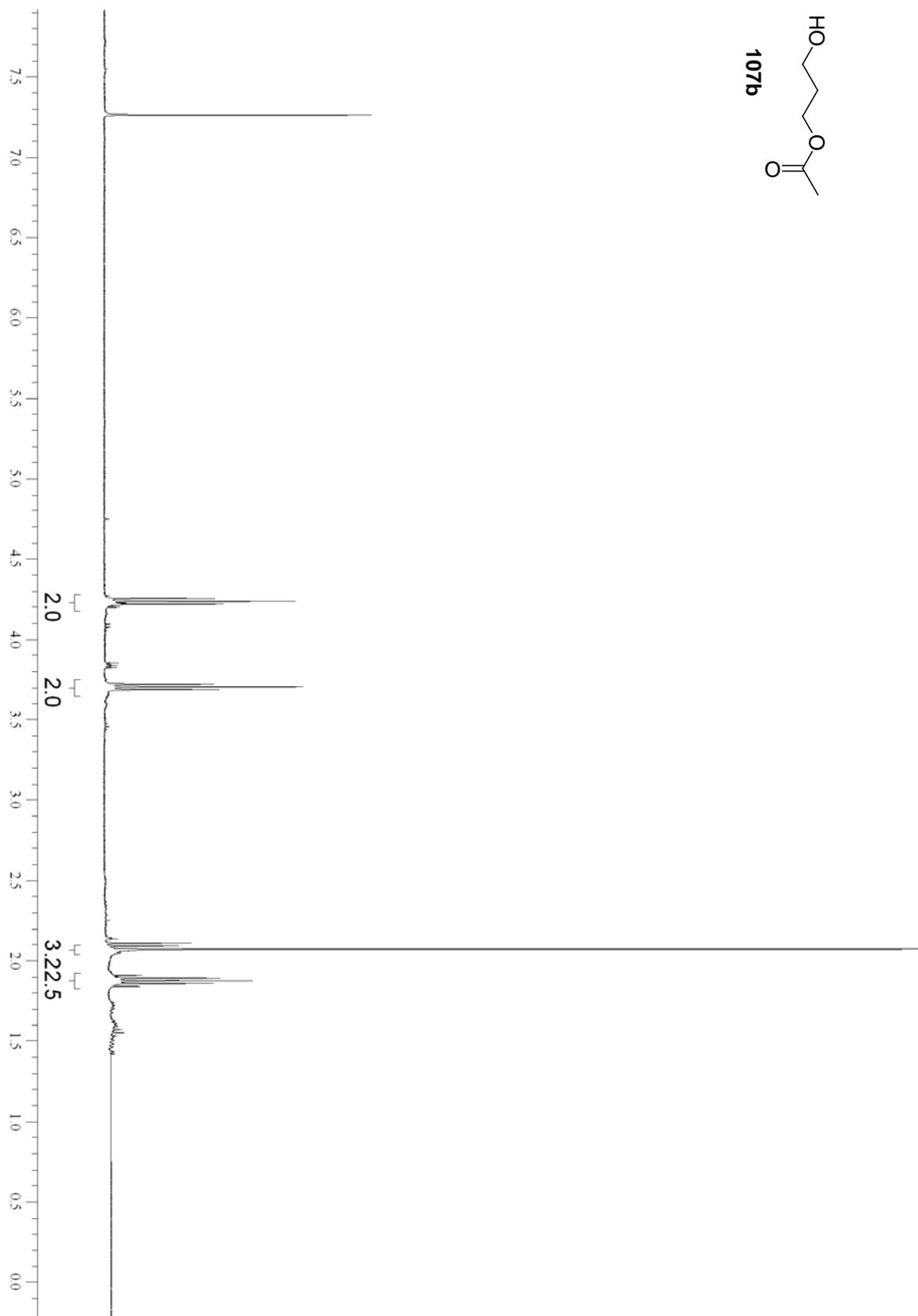
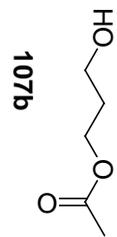
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **106a**



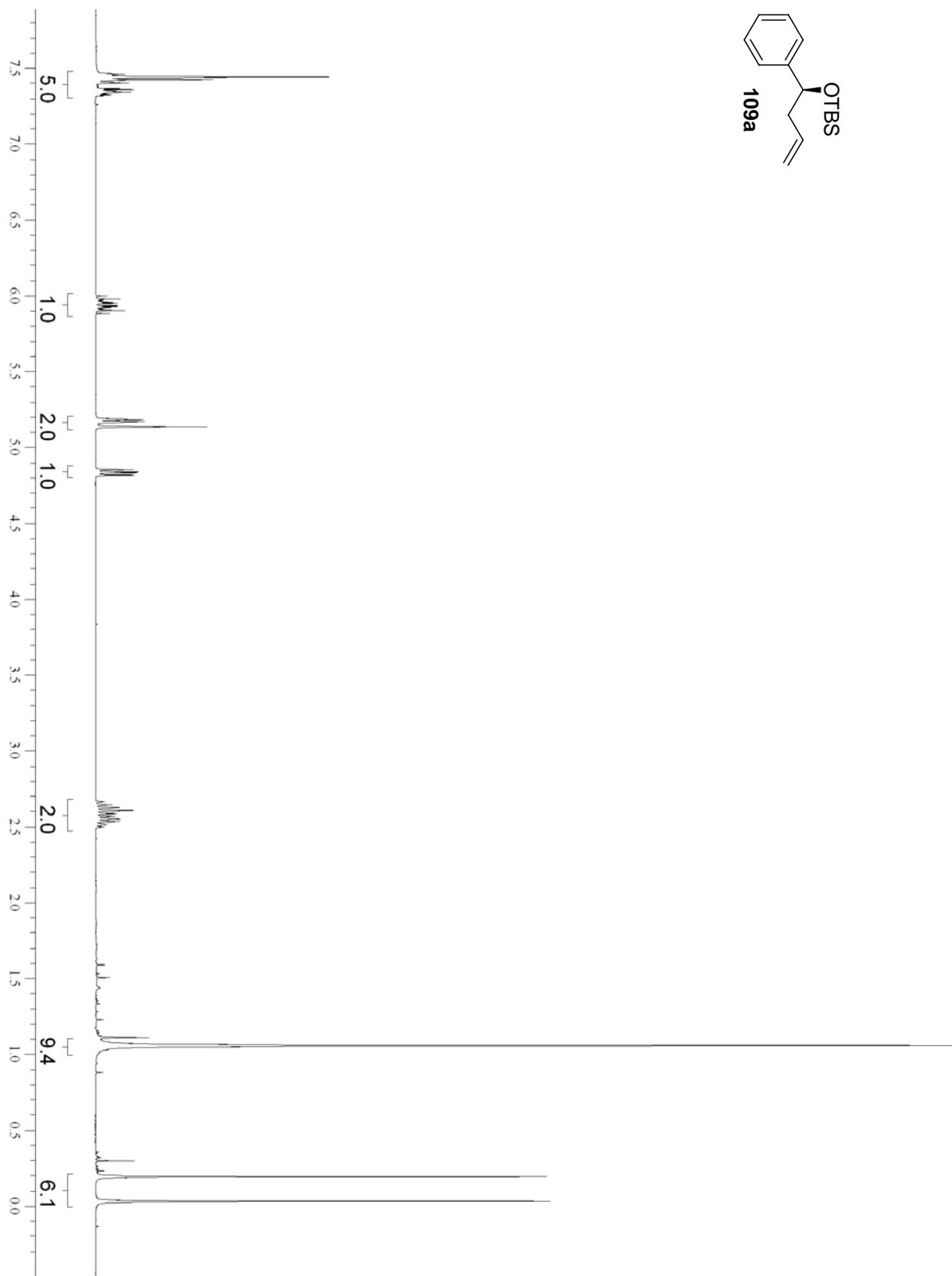
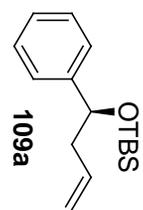
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **106b**



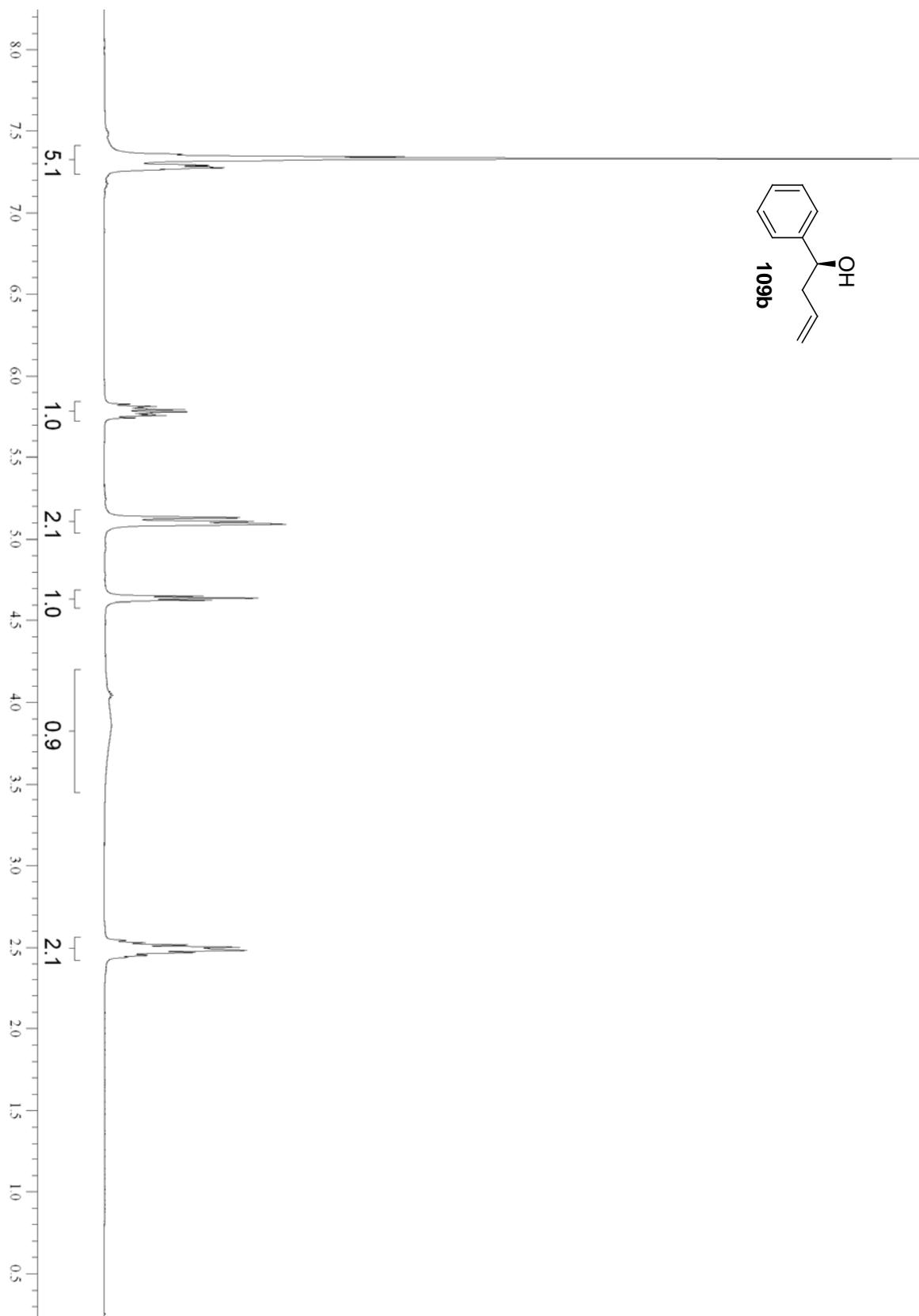
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **107a**



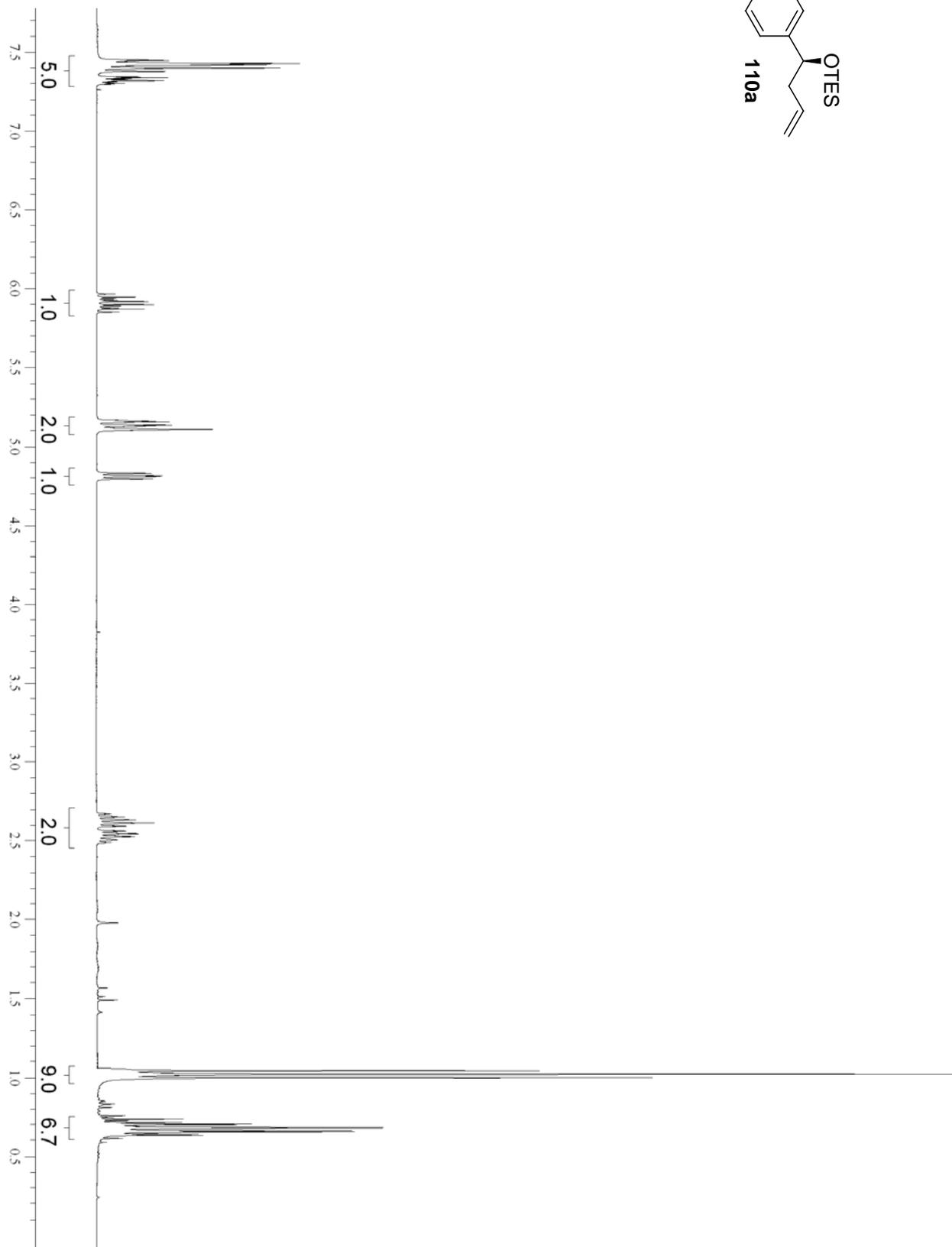
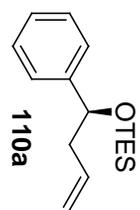
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **107b**



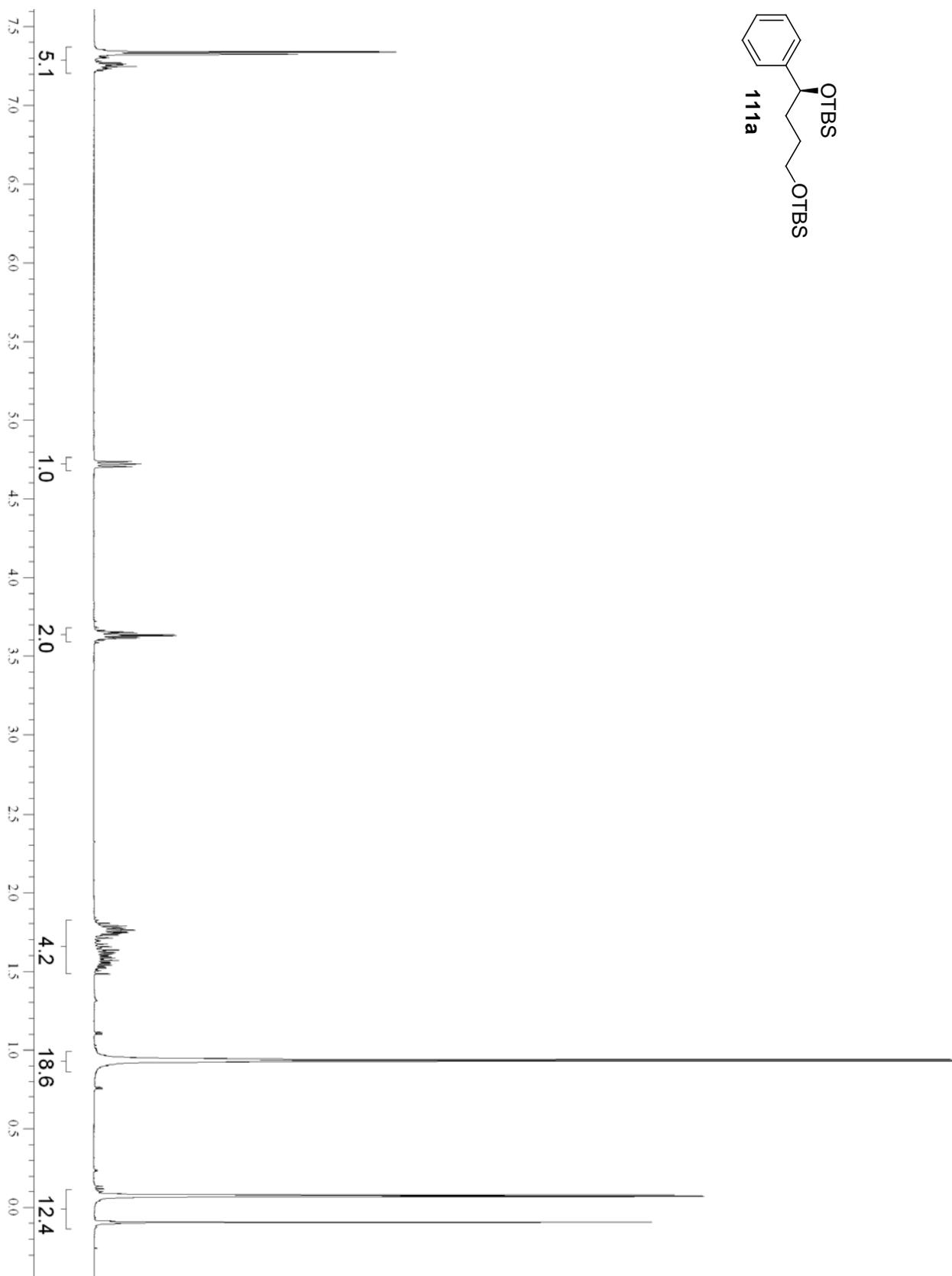
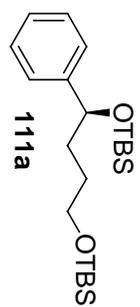
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **109a**



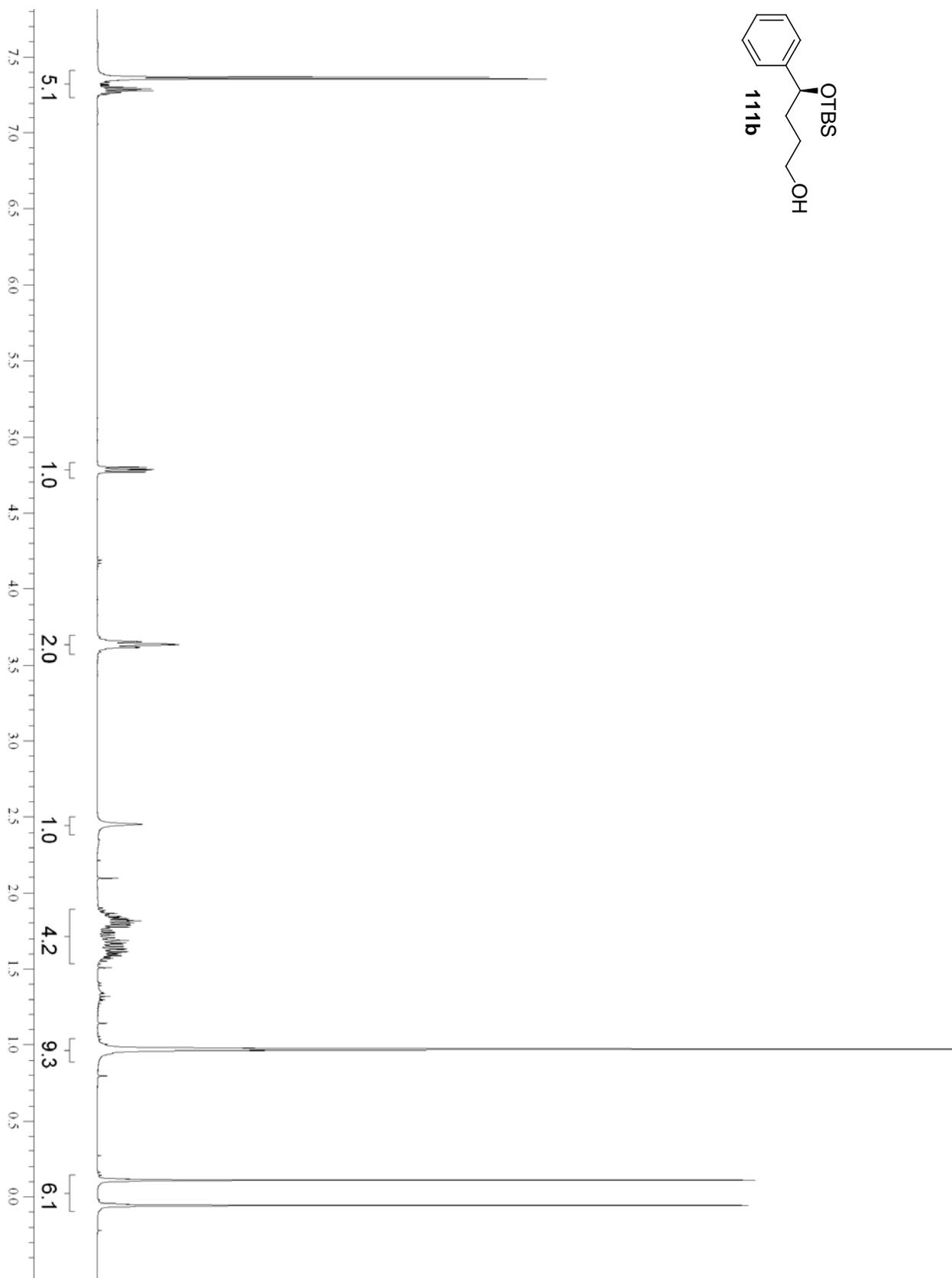
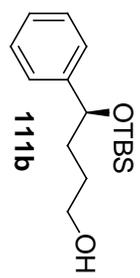
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **109b**



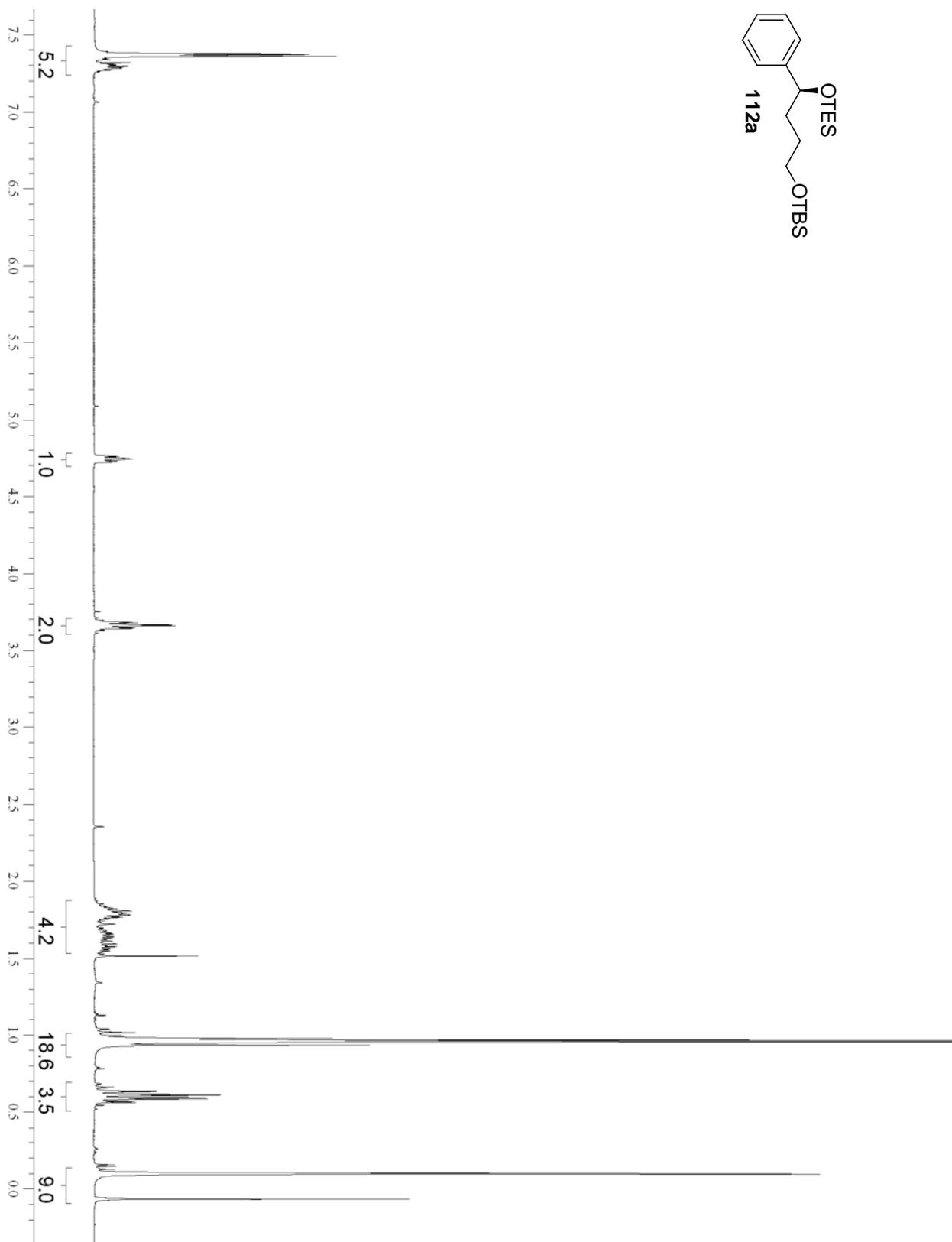
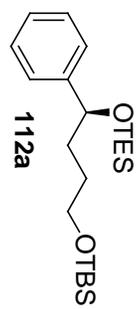
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **110a**



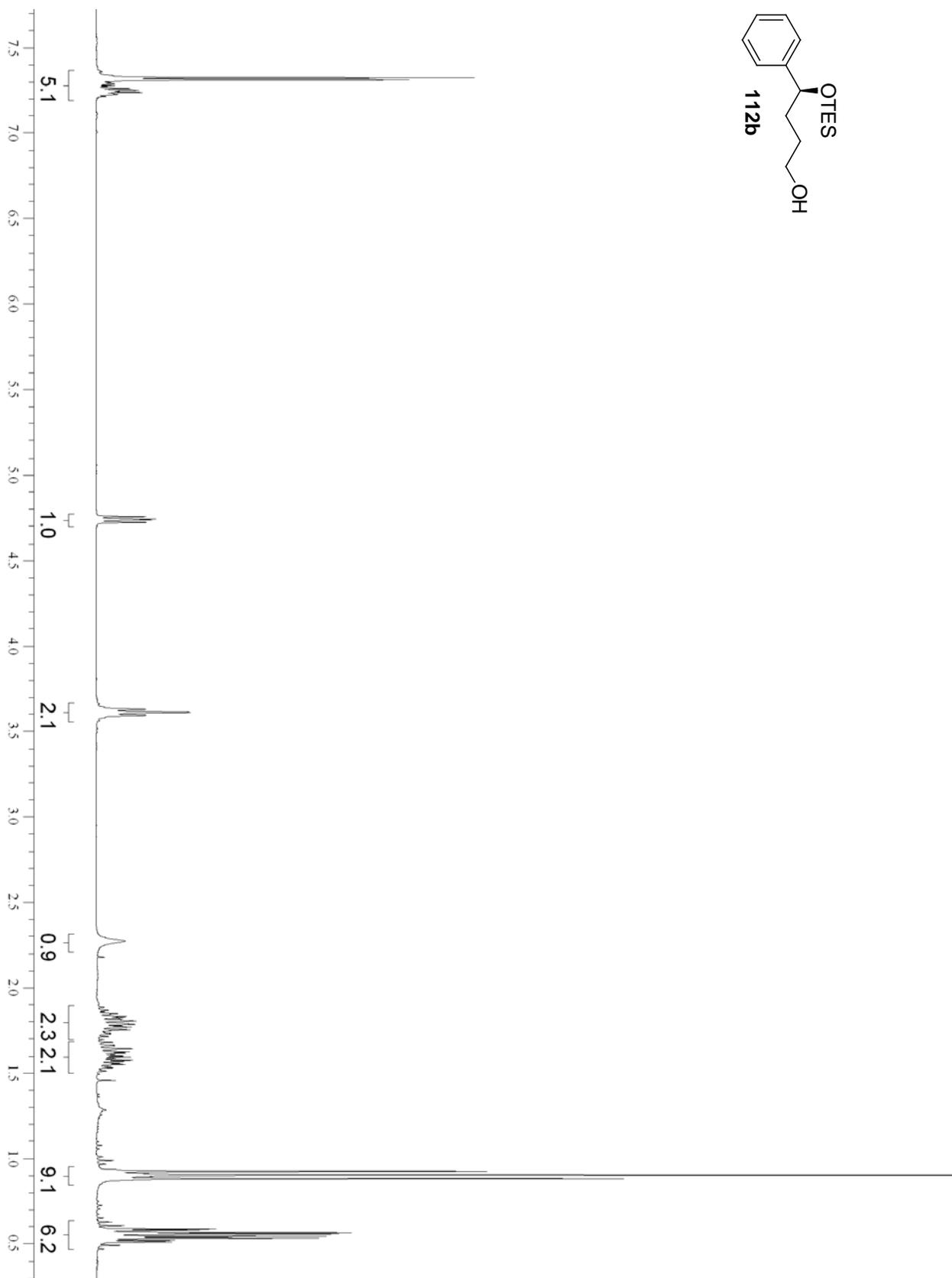
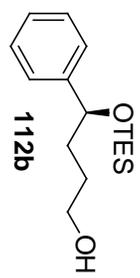
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **111a**



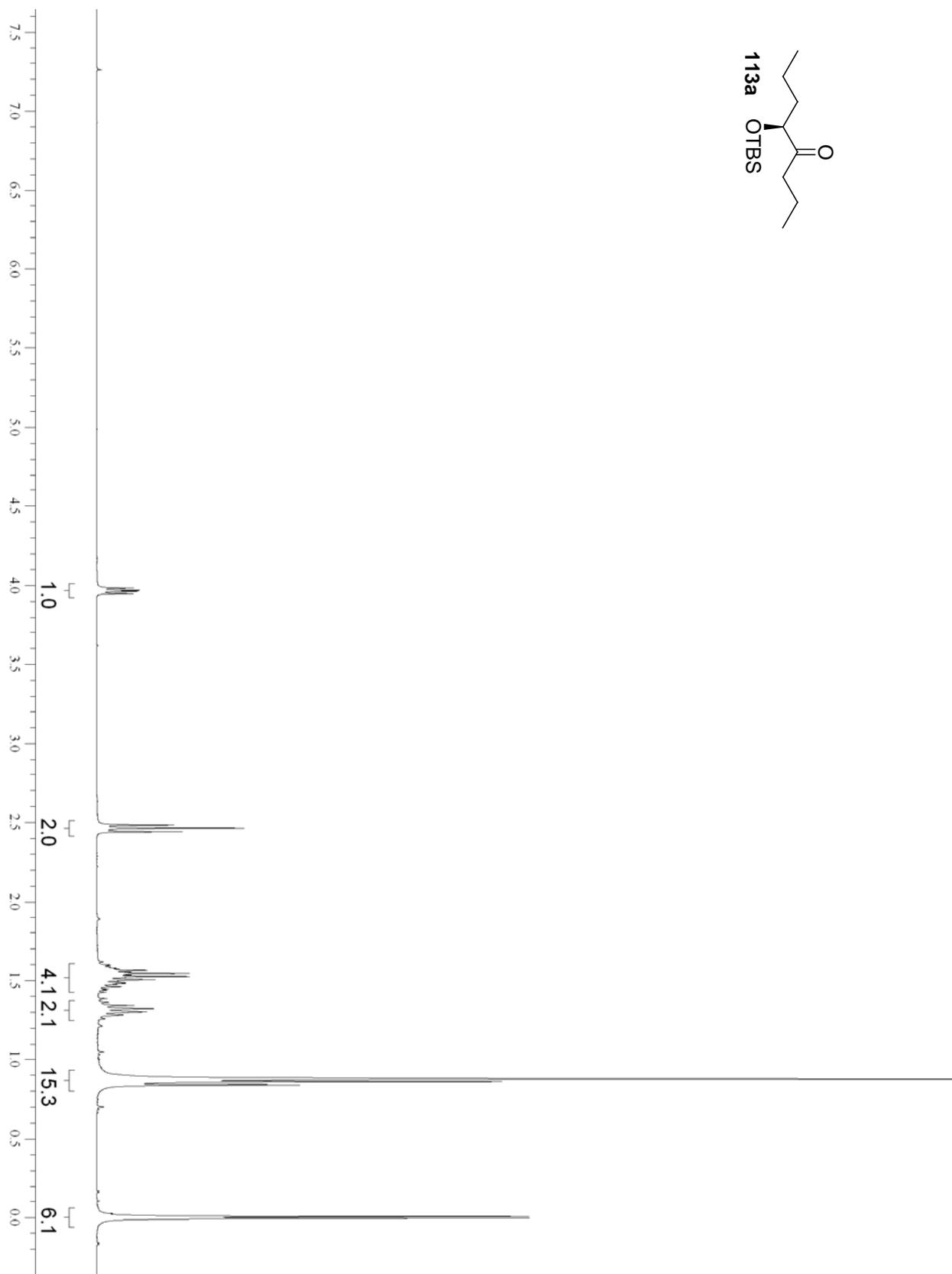
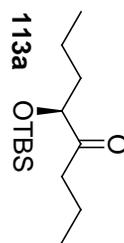
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **111b**



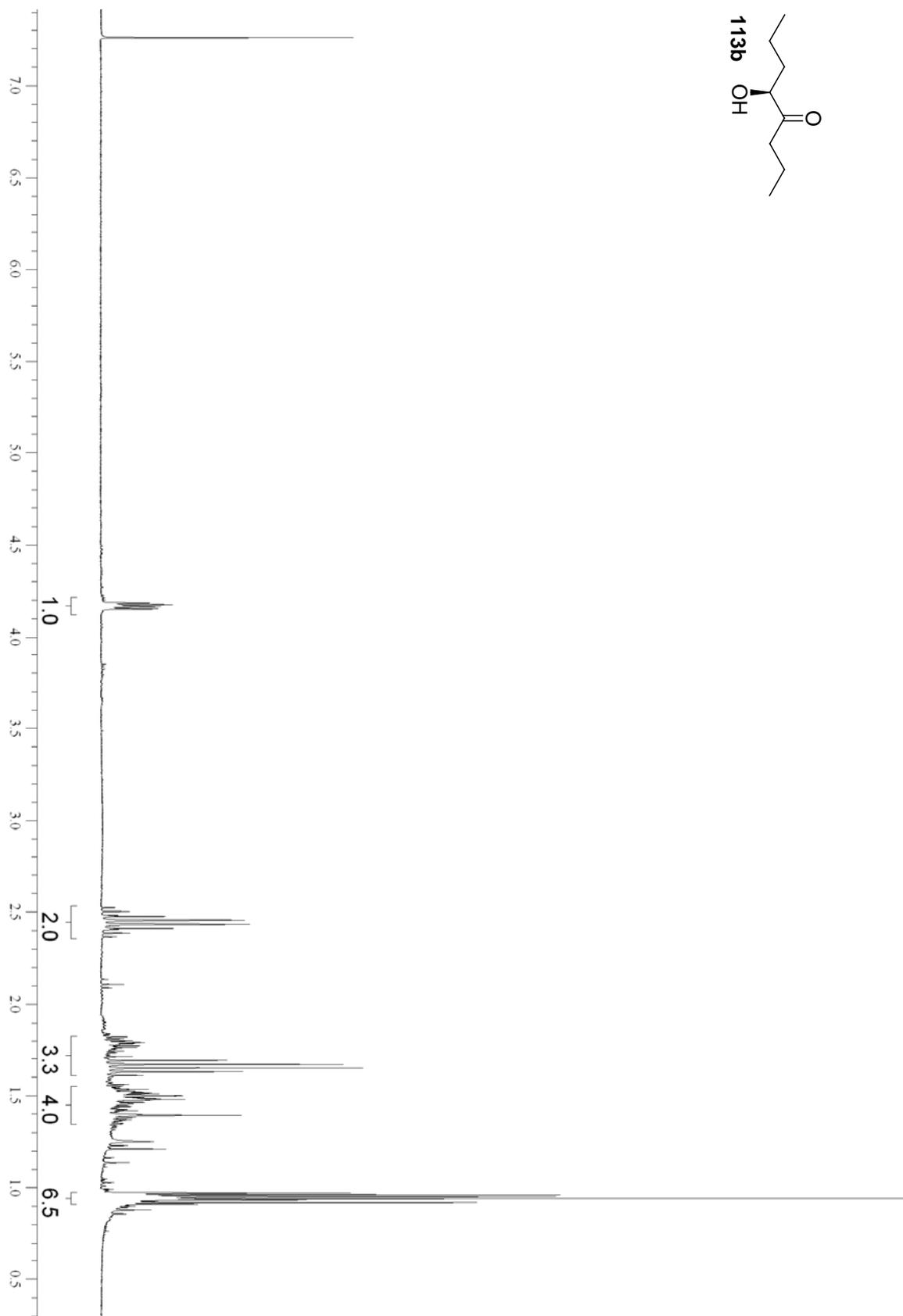
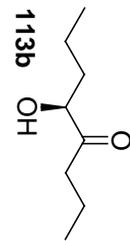
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **112a**



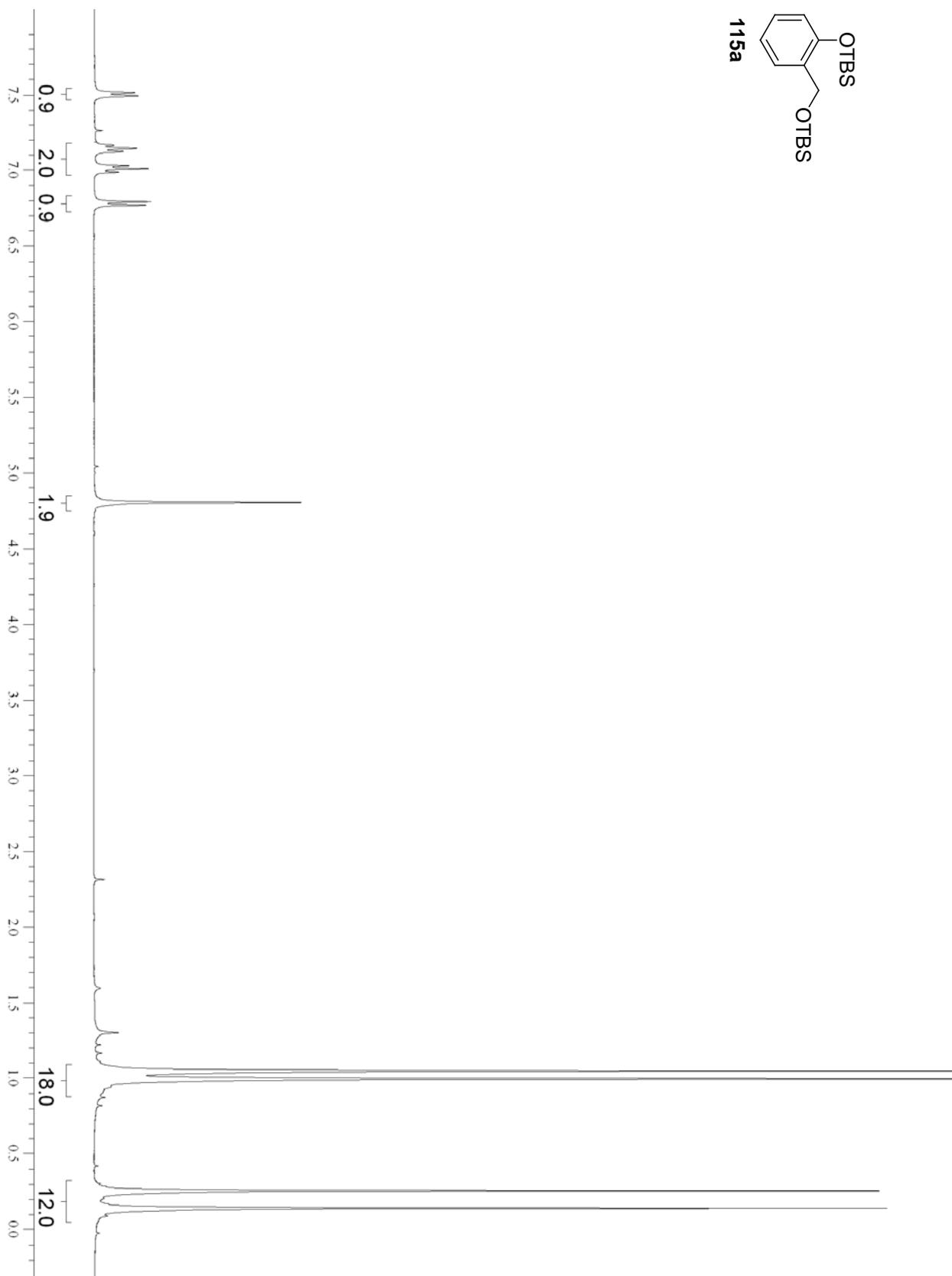
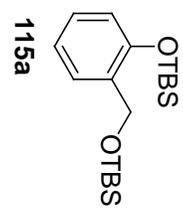
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **112b**



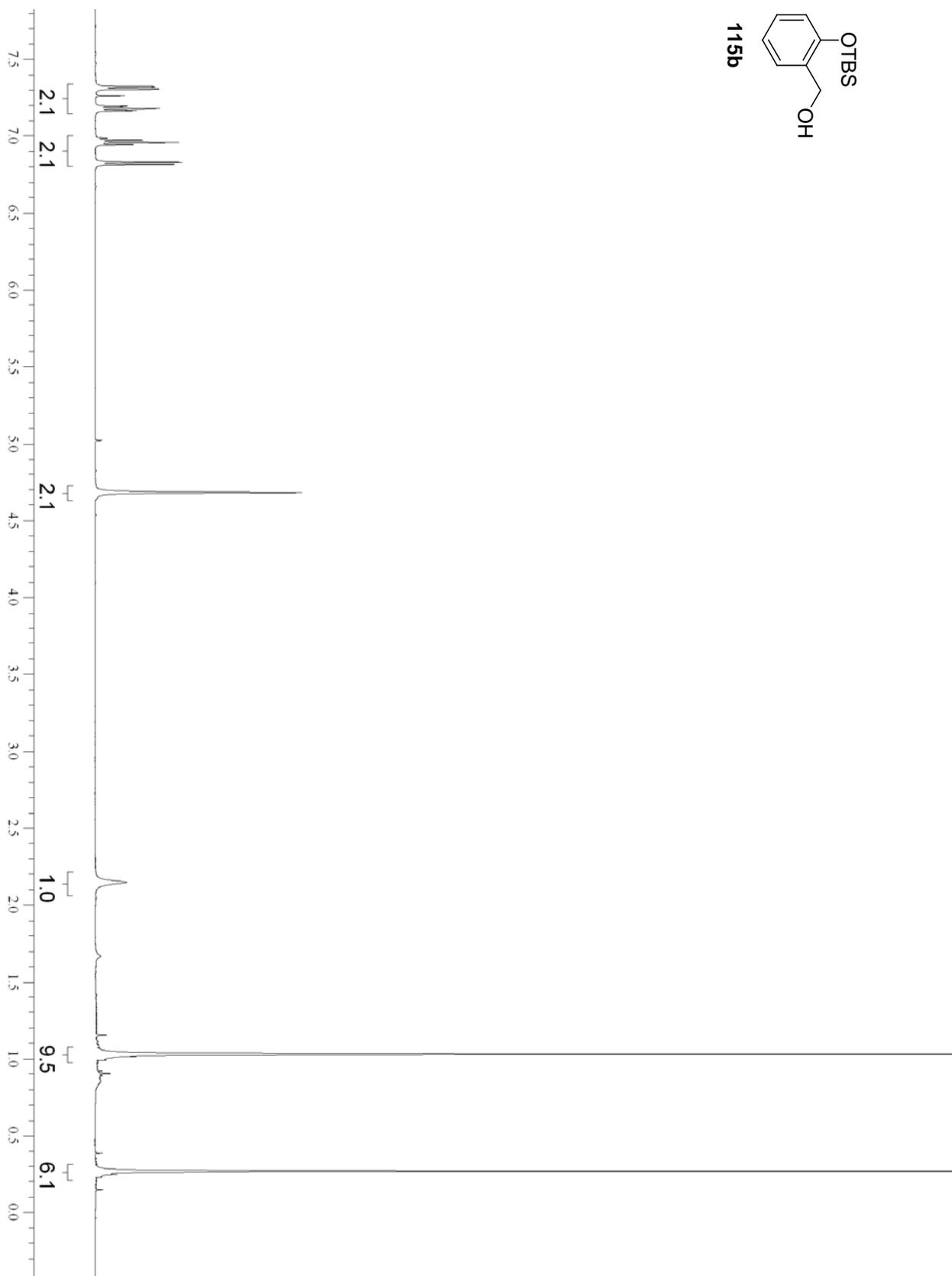
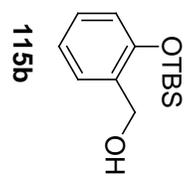
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **113a**



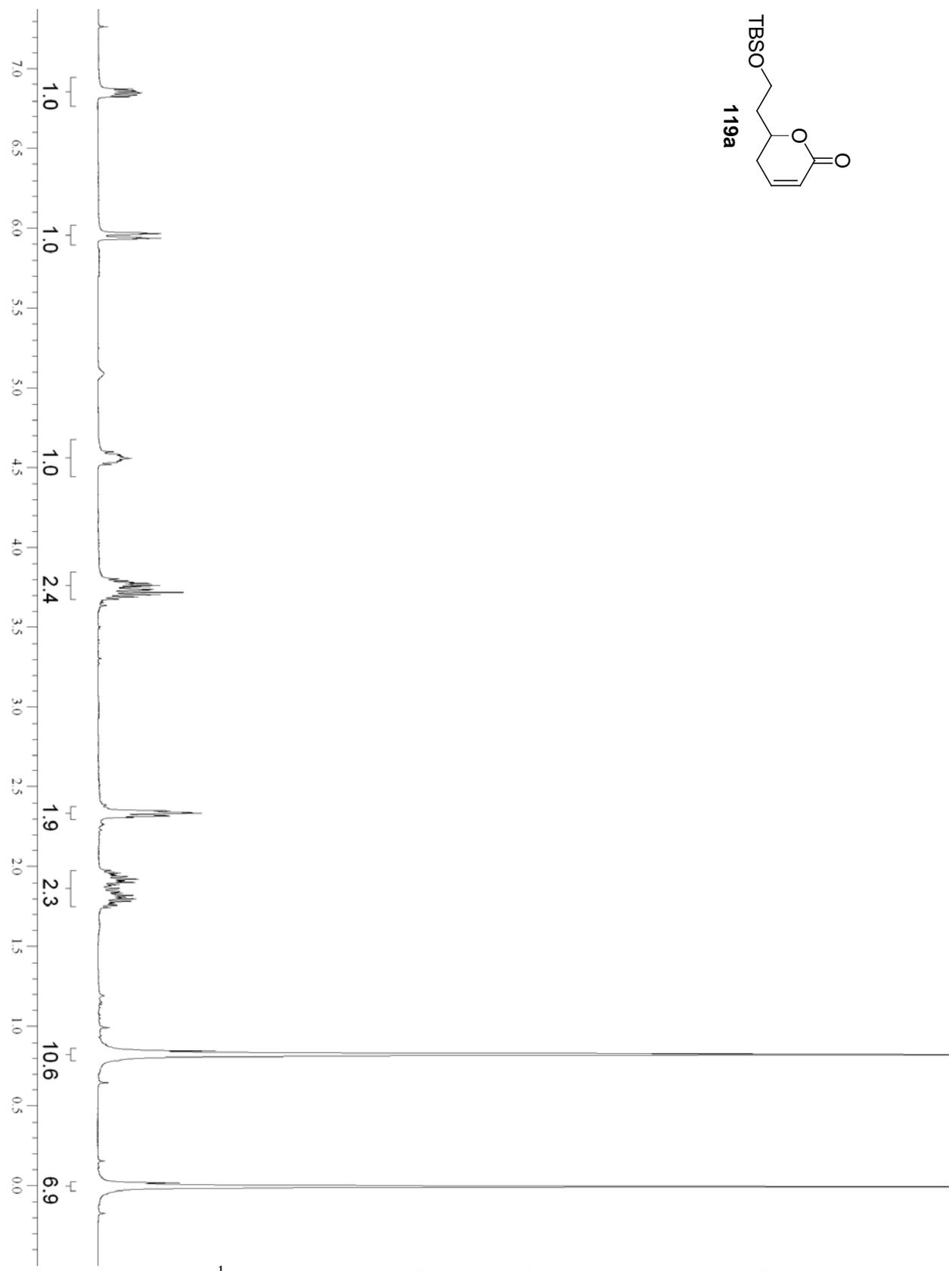
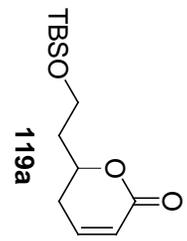
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **113b**



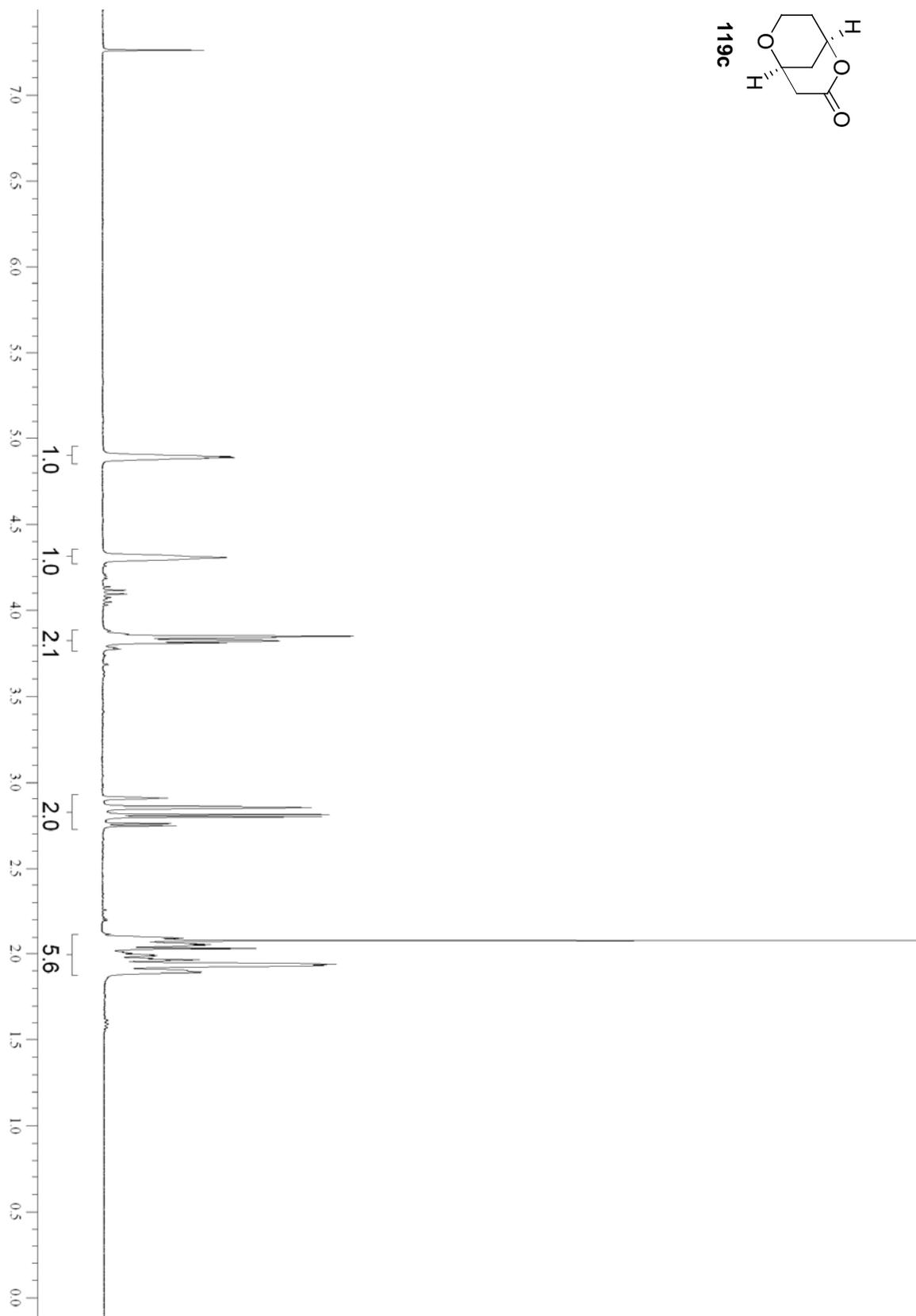
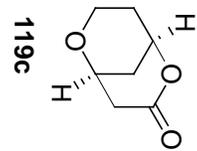
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **115a**



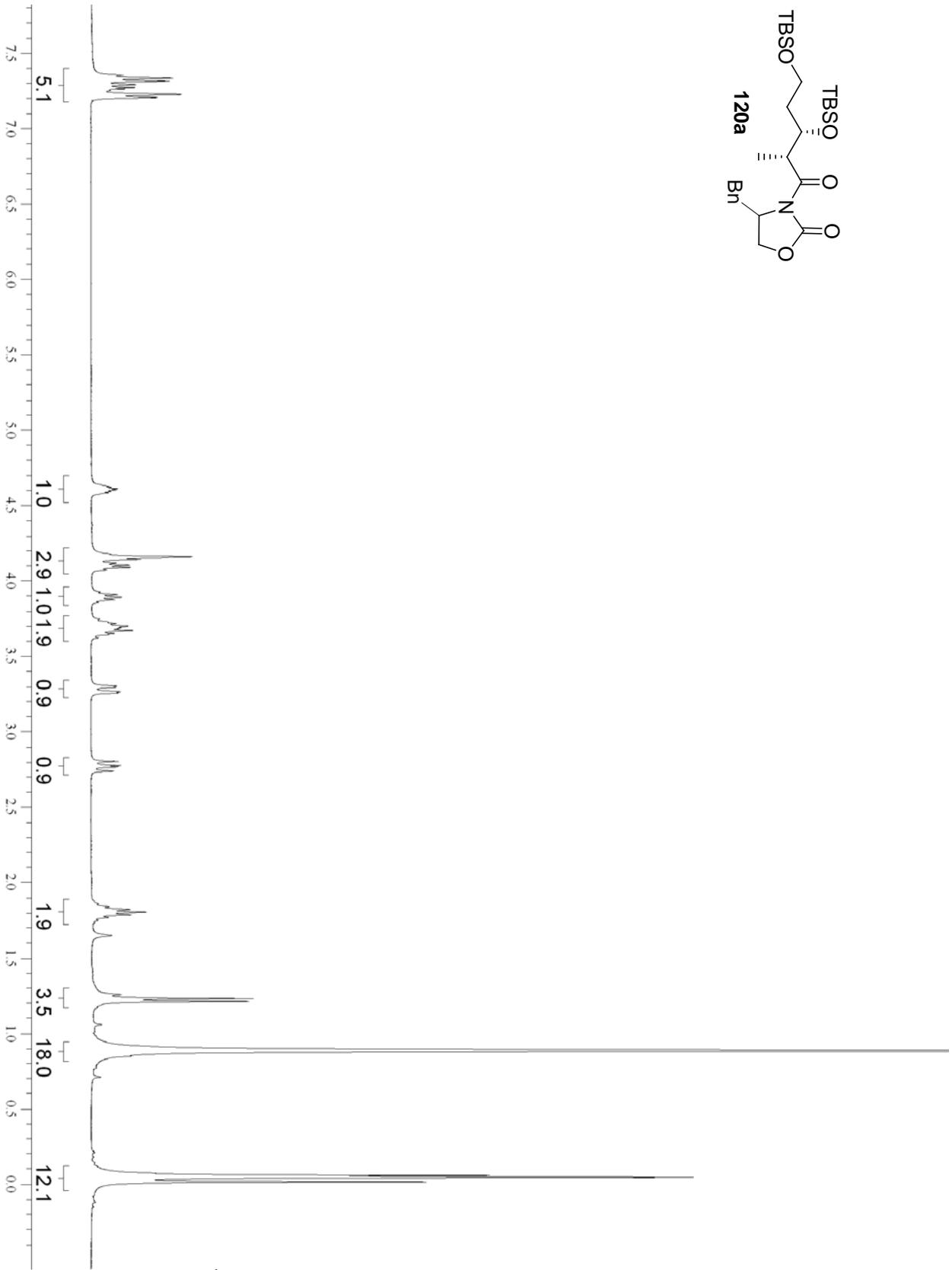
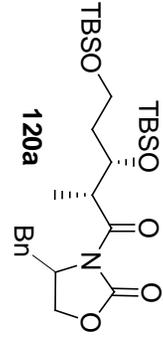
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **115b**



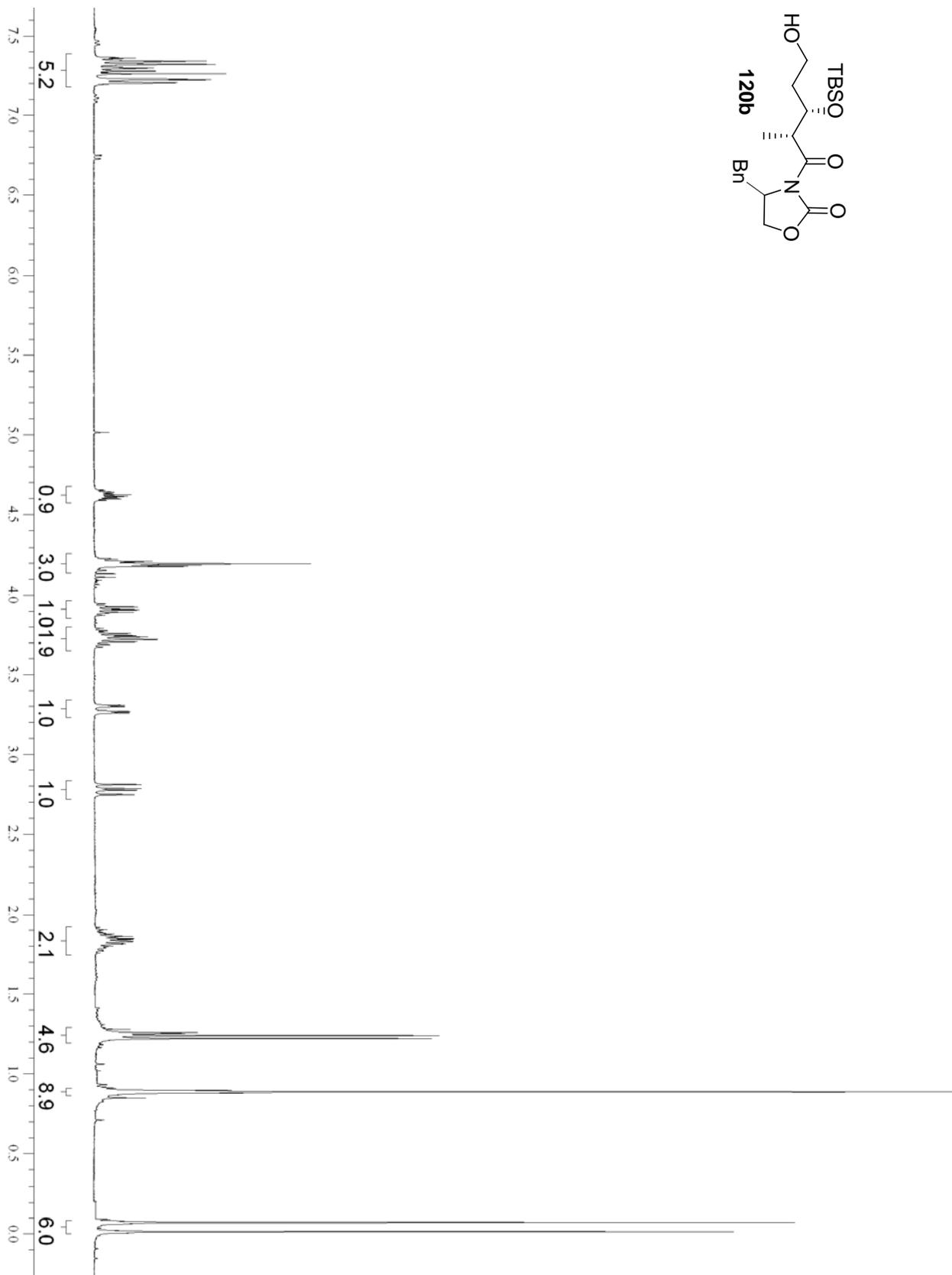
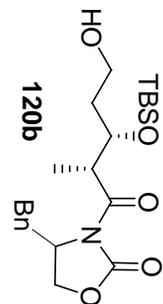
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **119a**



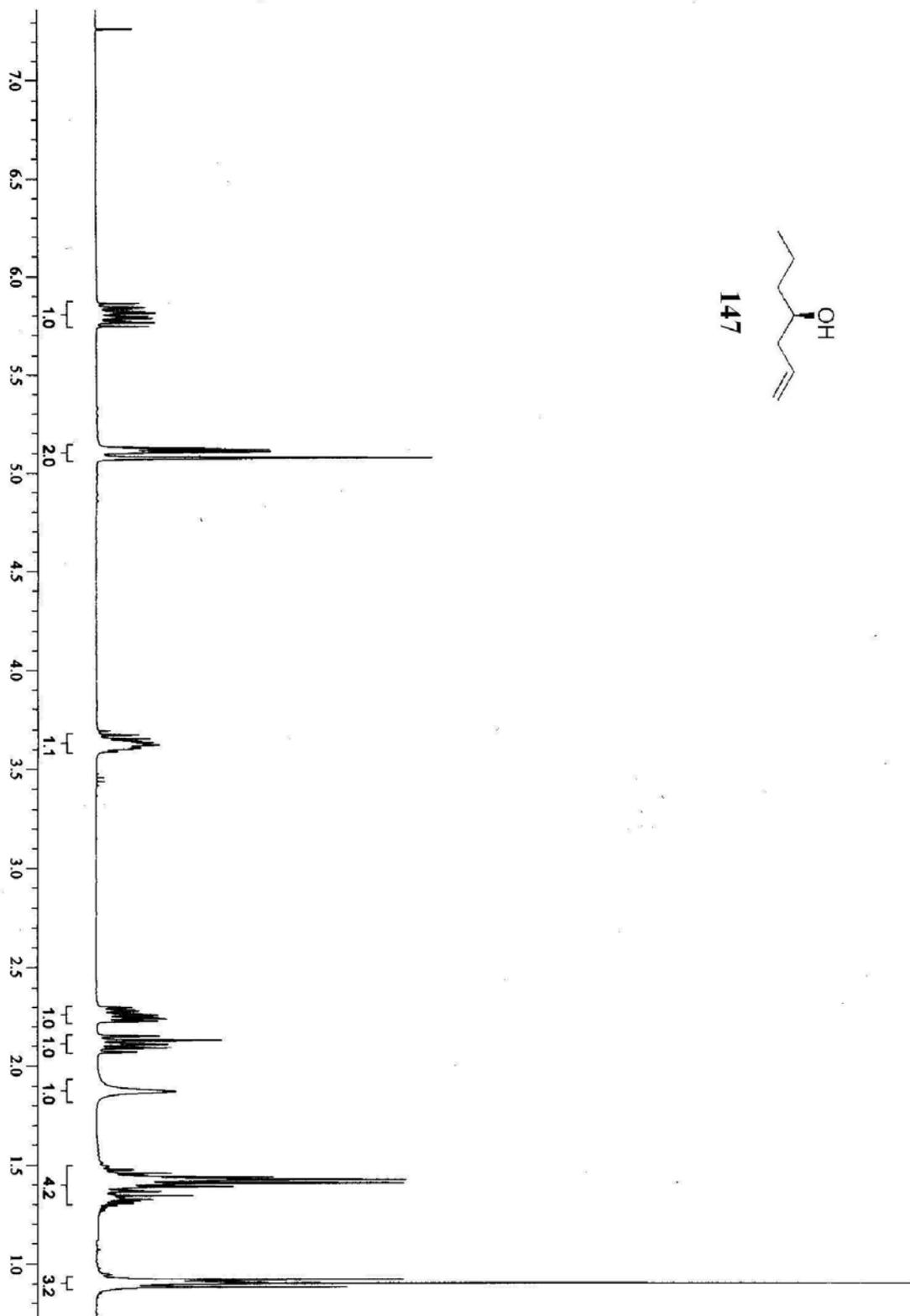
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **119c**



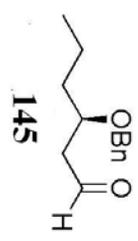
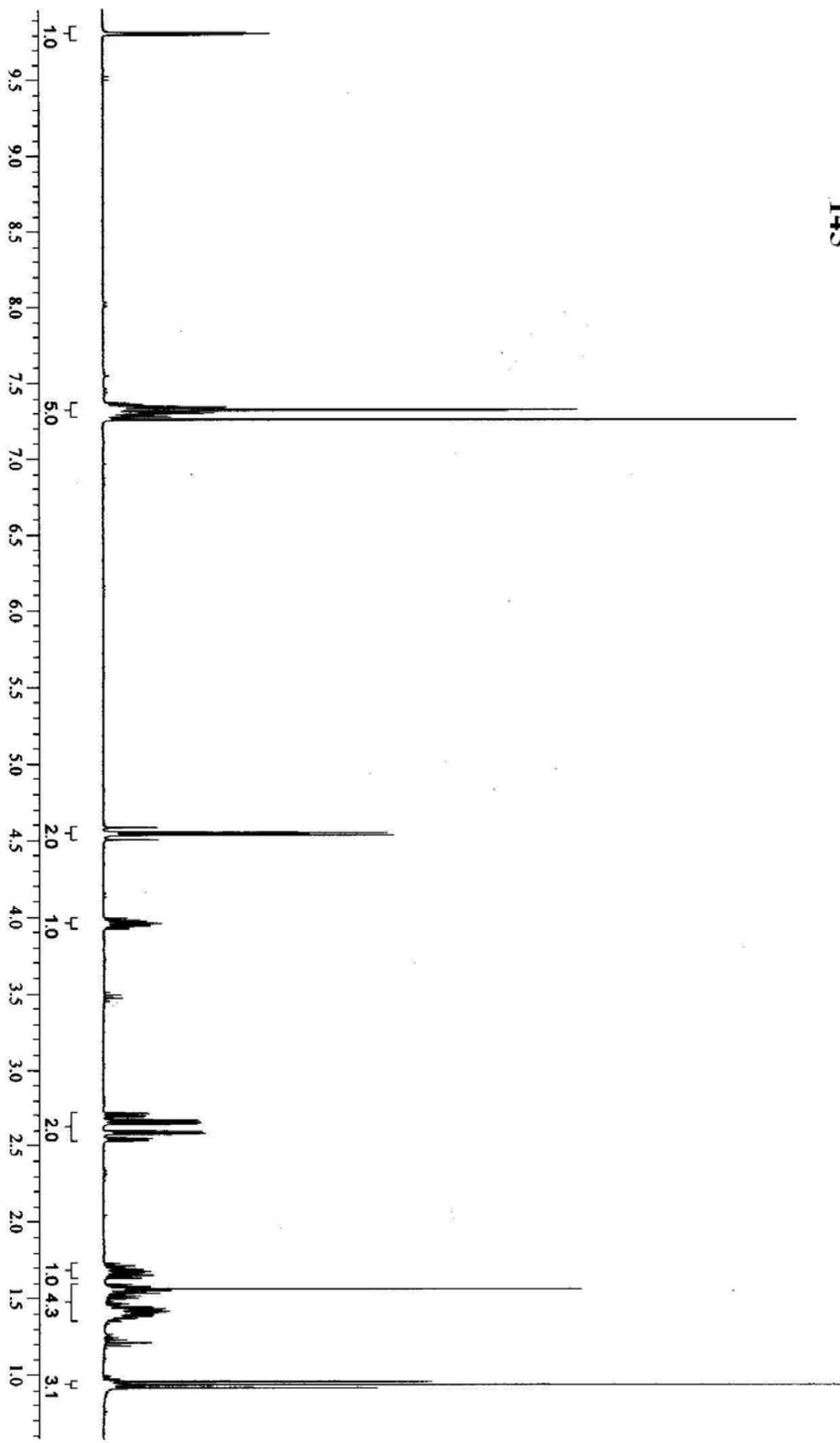
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **120a**



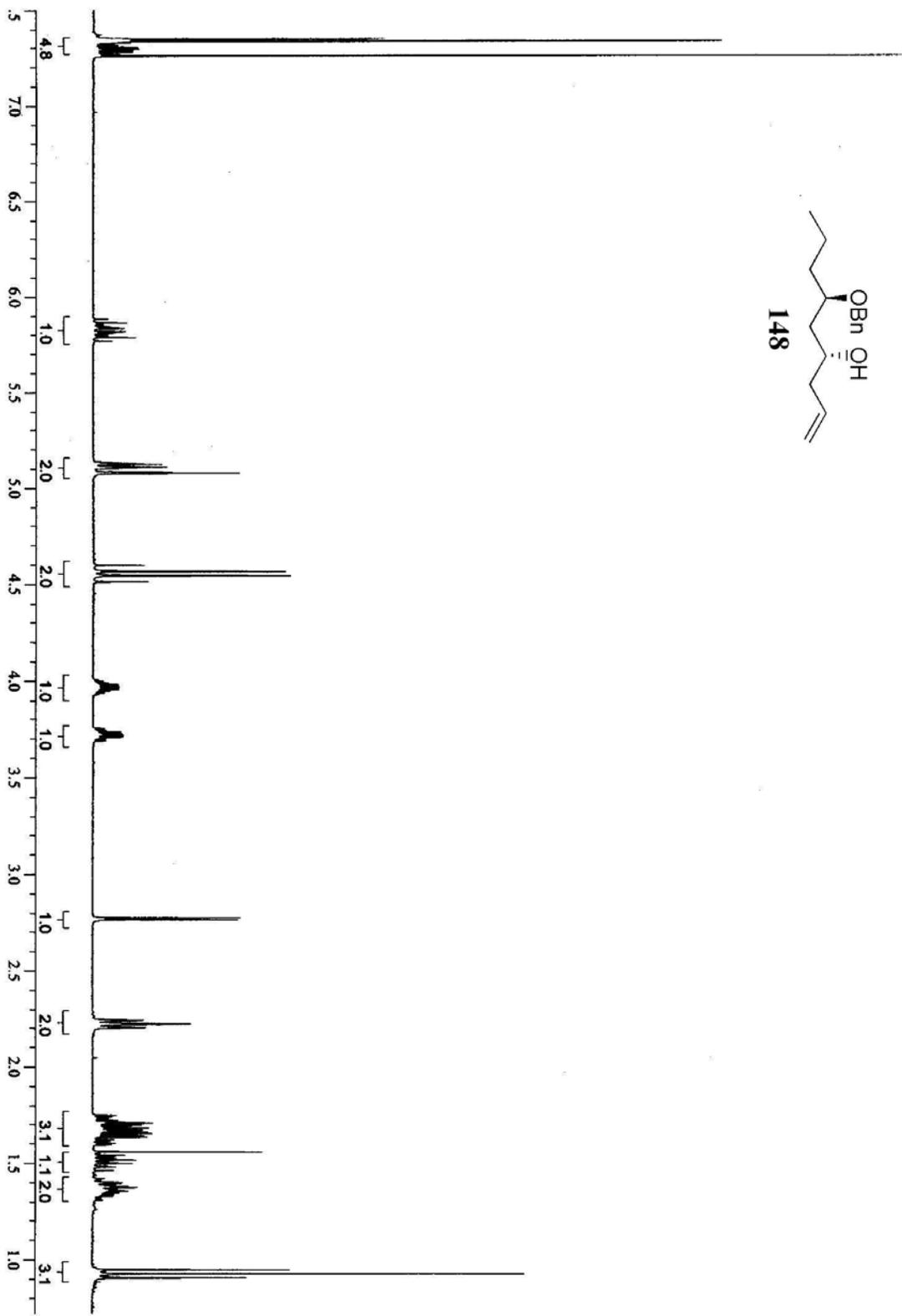
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **120b**



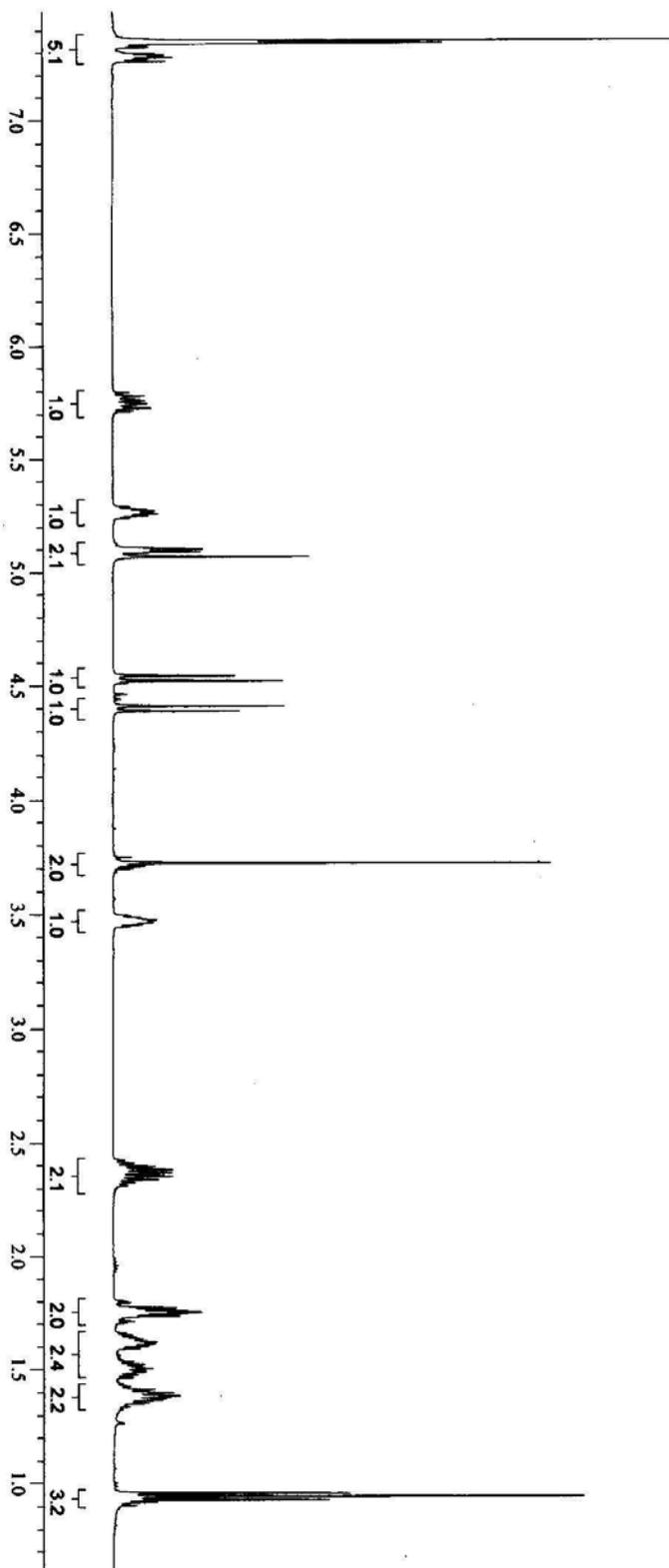
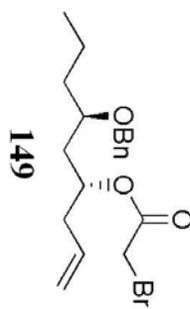
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **147**



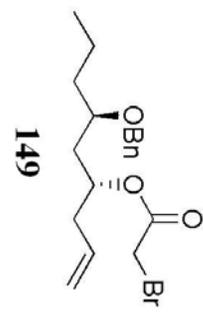
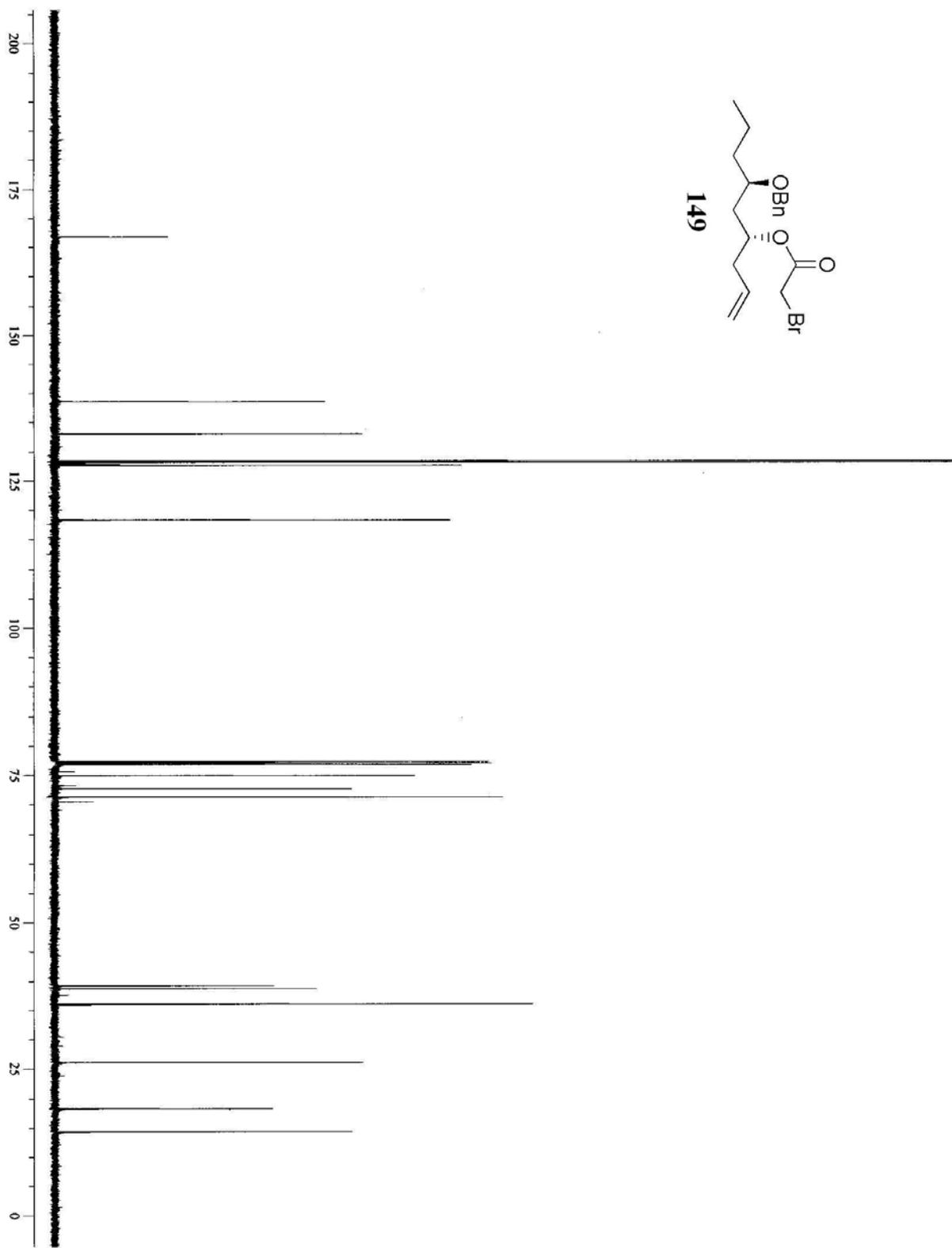
The ¹H NMR Spectrum (360 MHz, CDCl₃) of Compound **145**



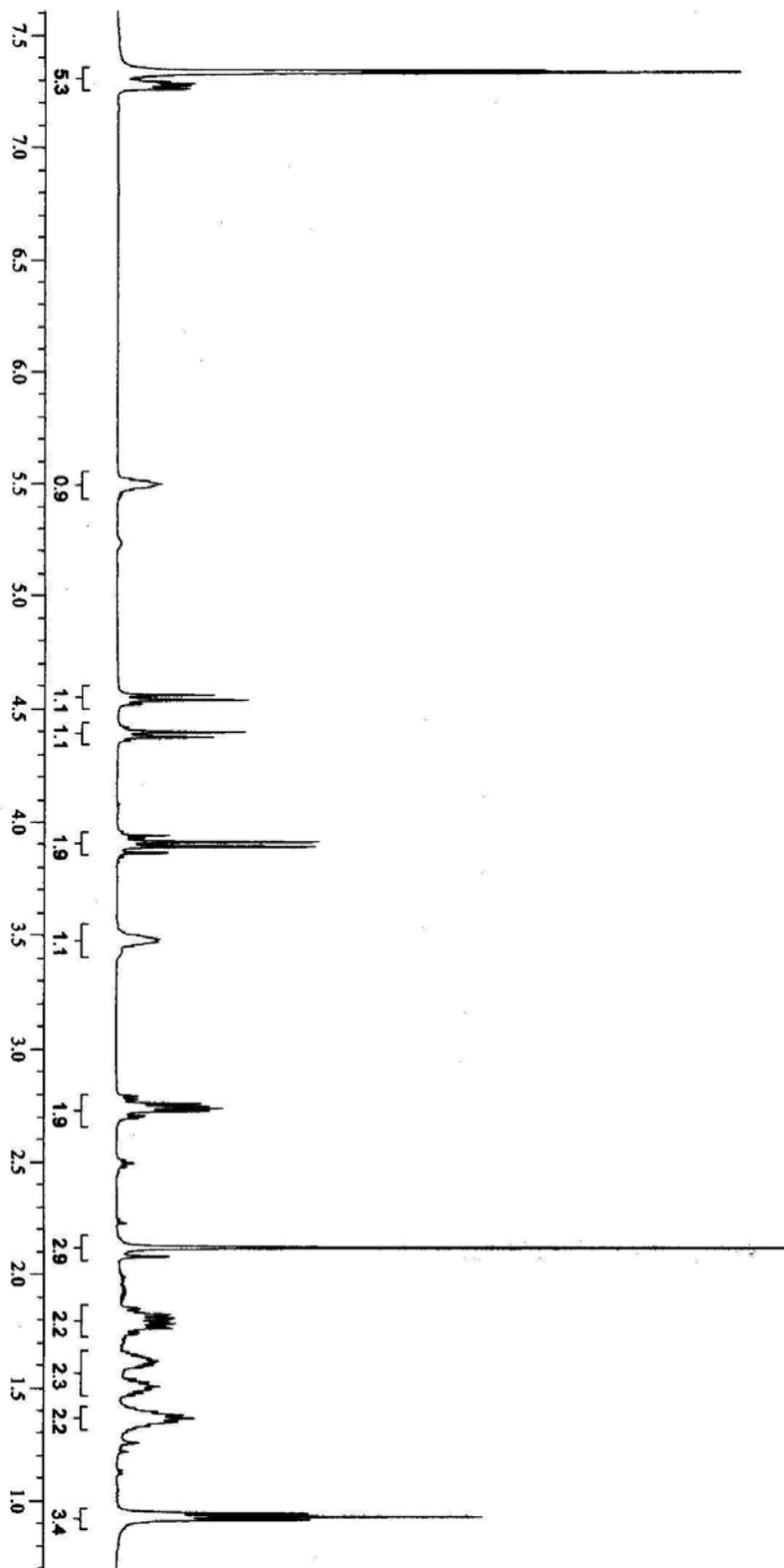
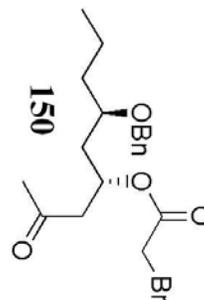
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **148**



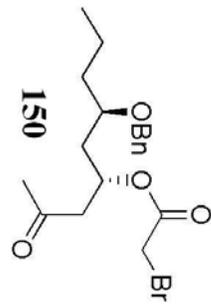
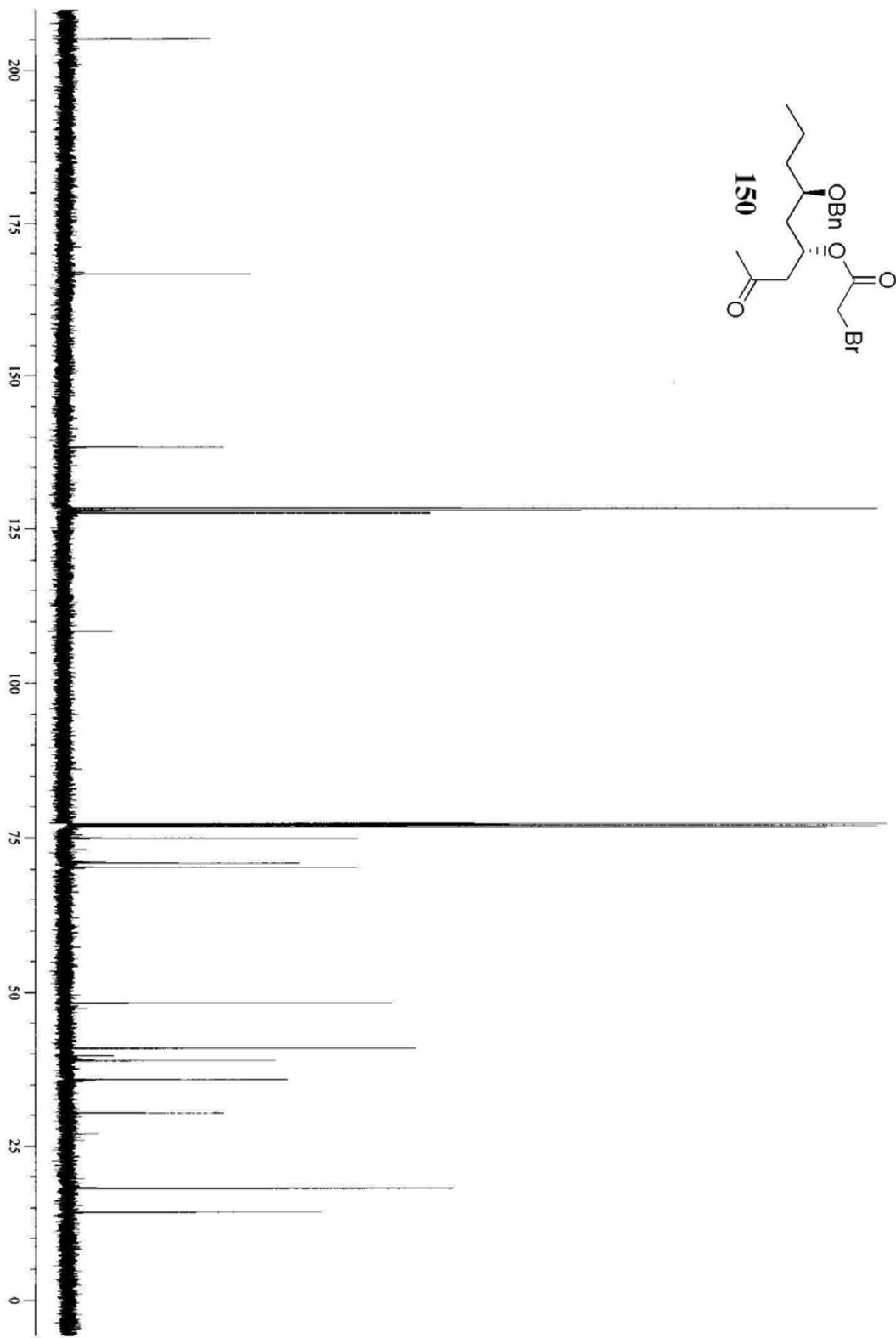
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **149**



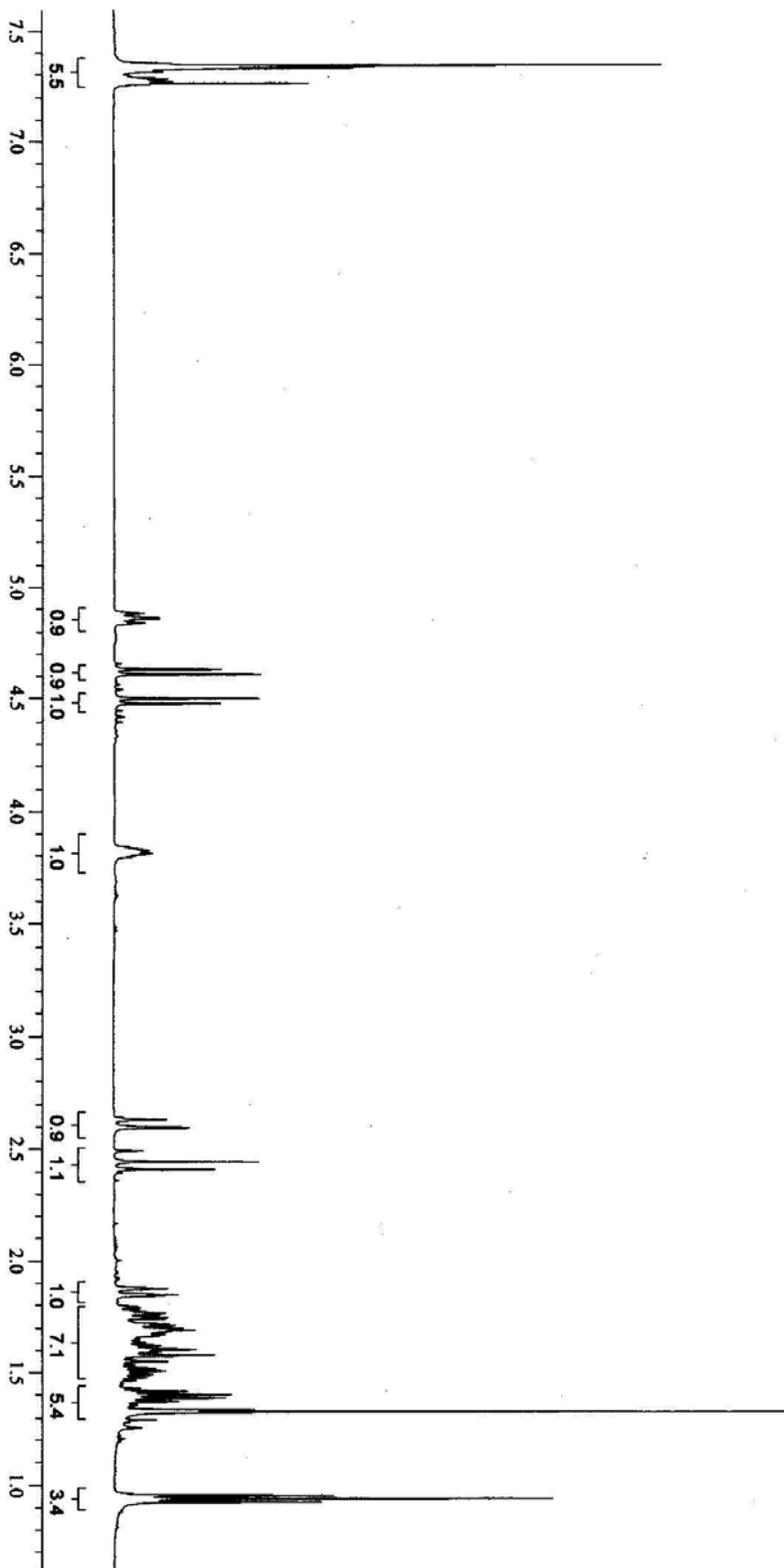
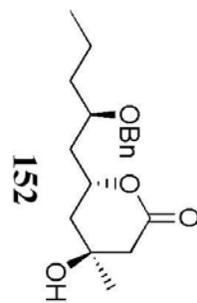
The ^{13}C NMR Spectrum (125 MHz, CDCl₃) of Compound **149**



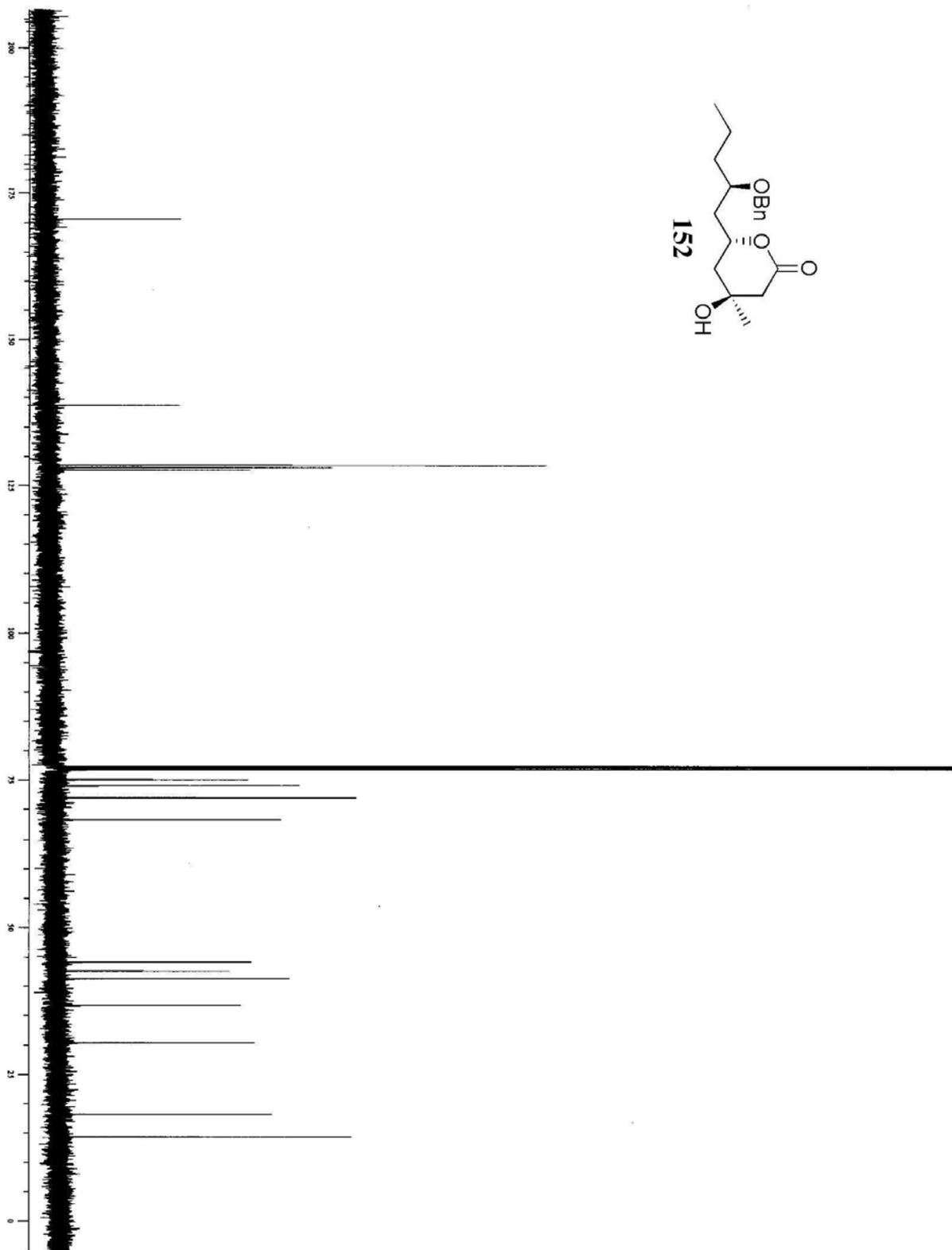
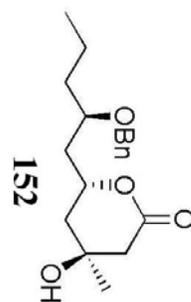
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **150**



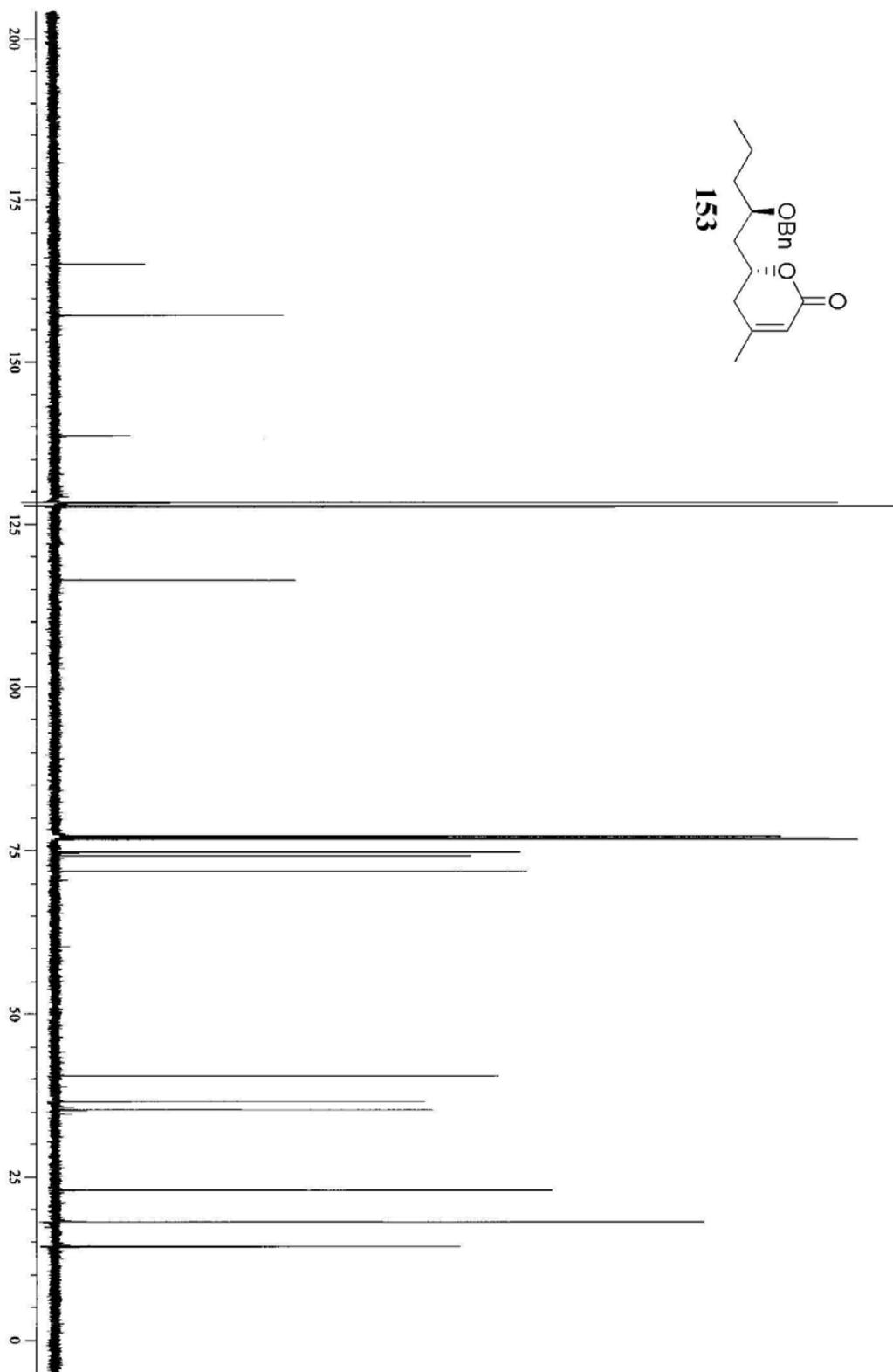
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound 150



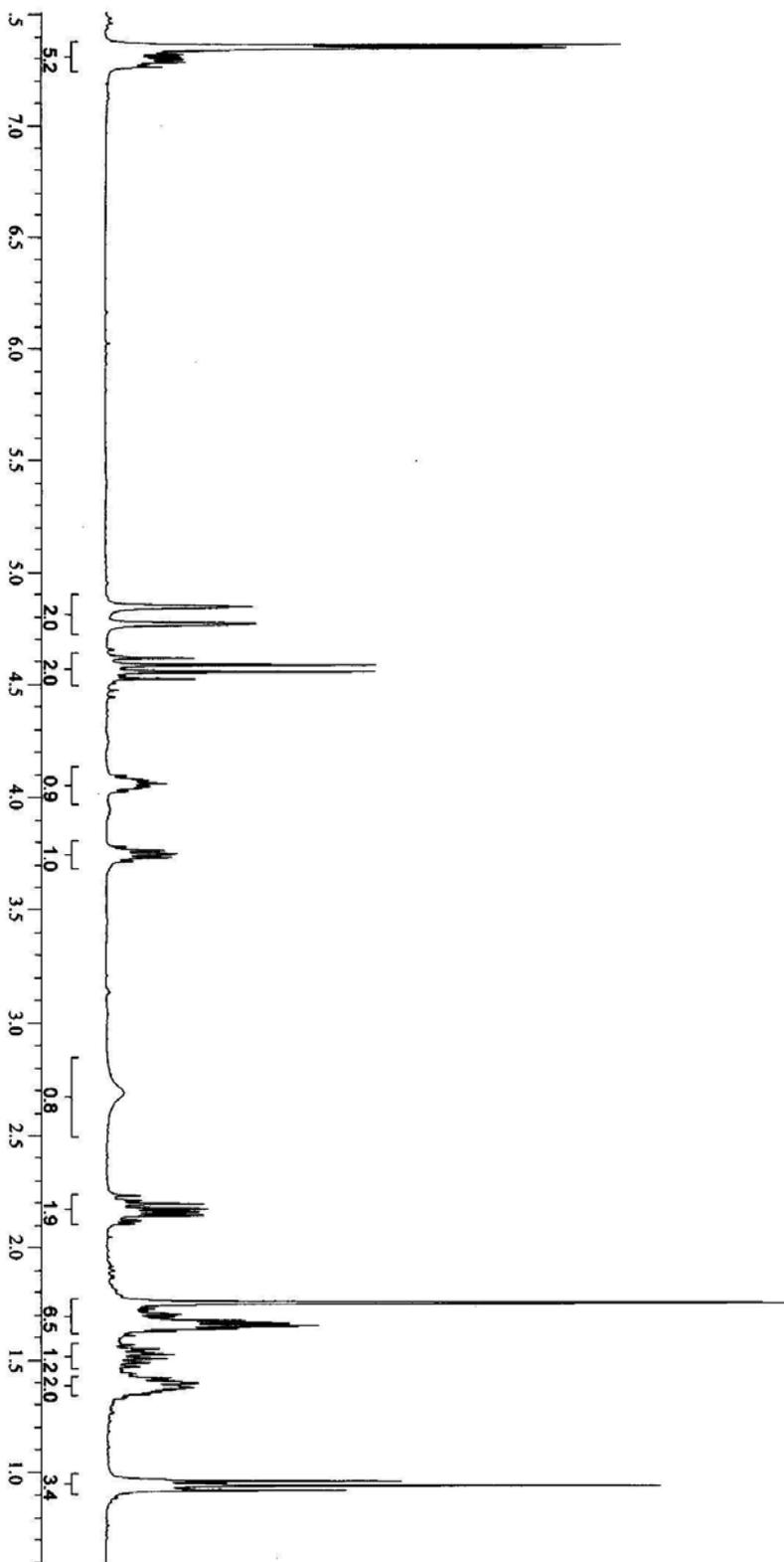
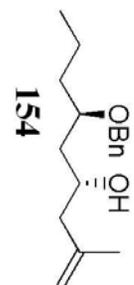
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **152**



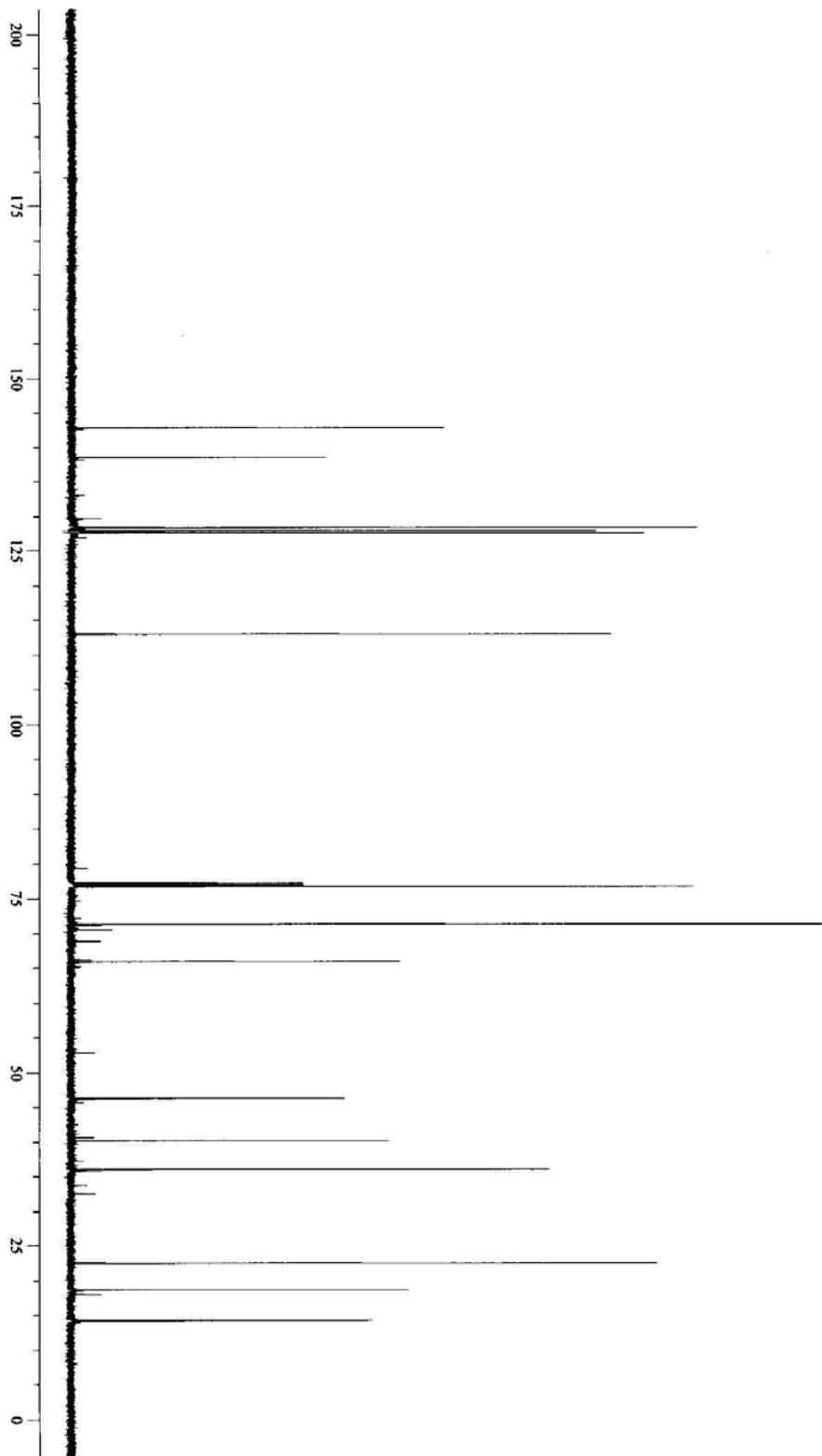
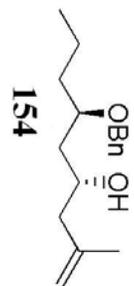
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **152**



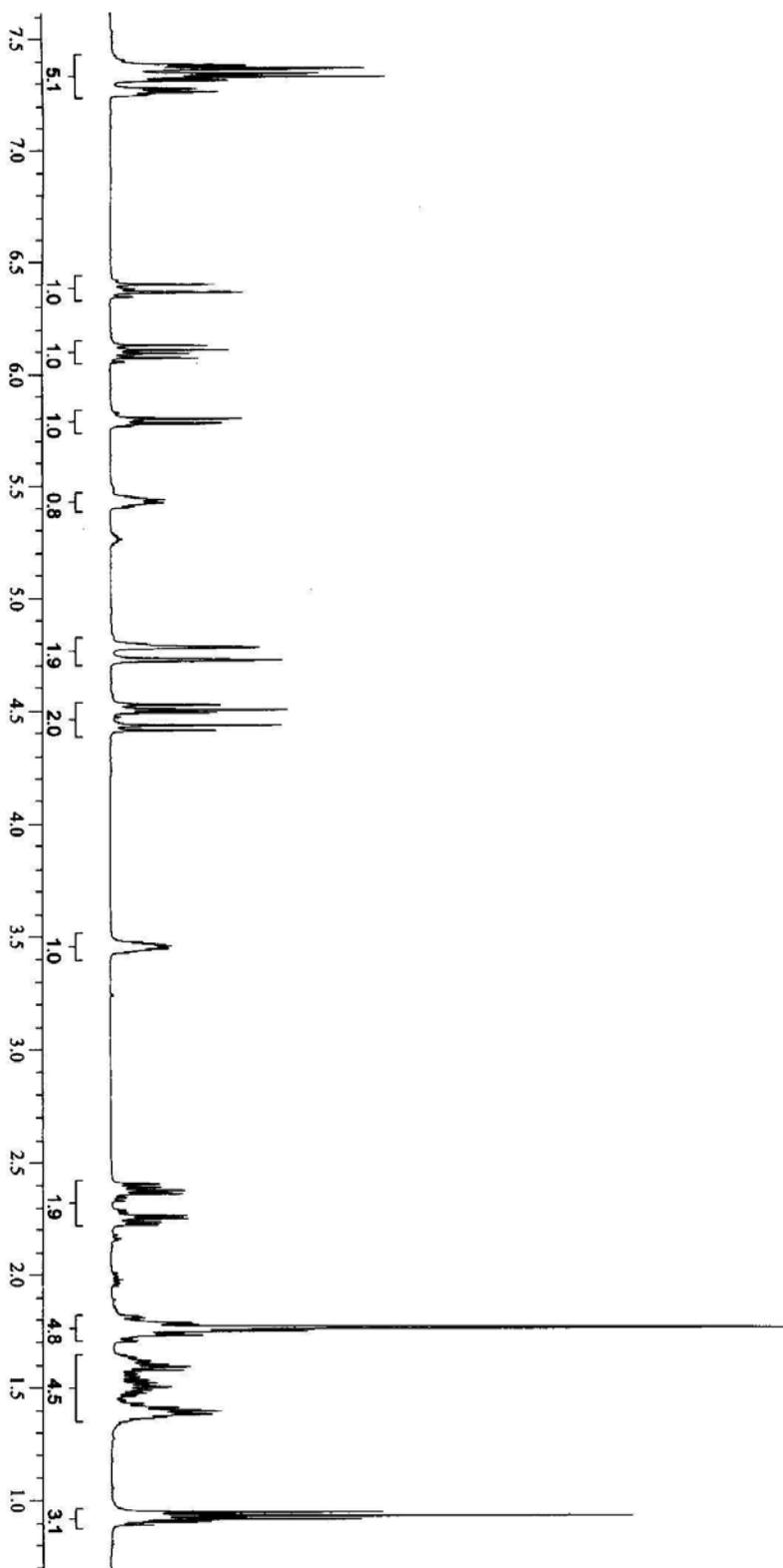
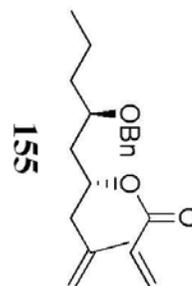
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **153**



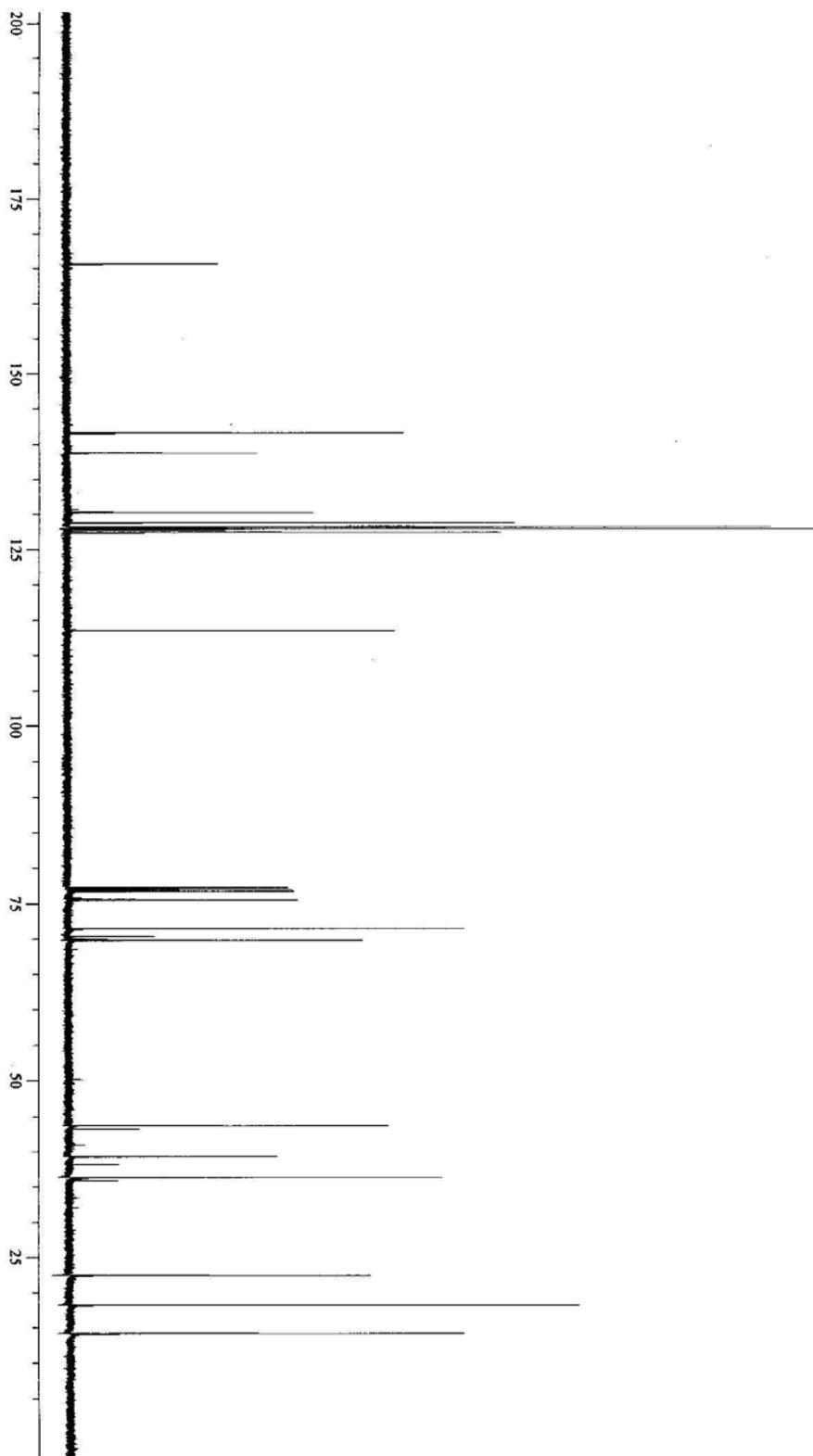
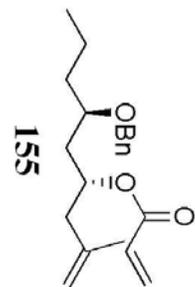
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **154**



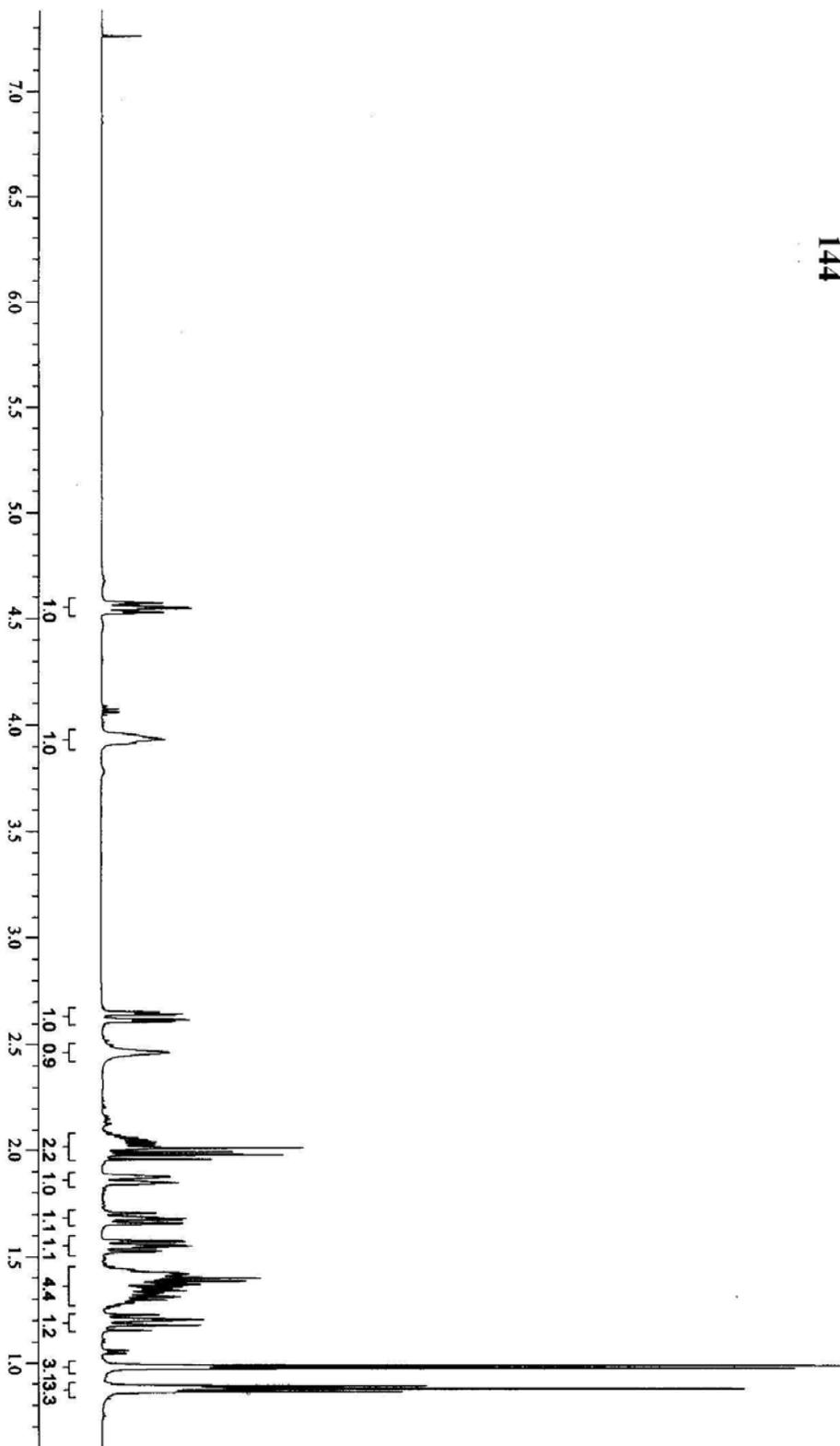
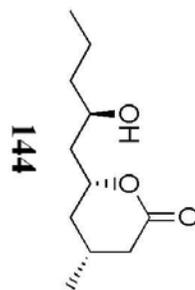
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **154**



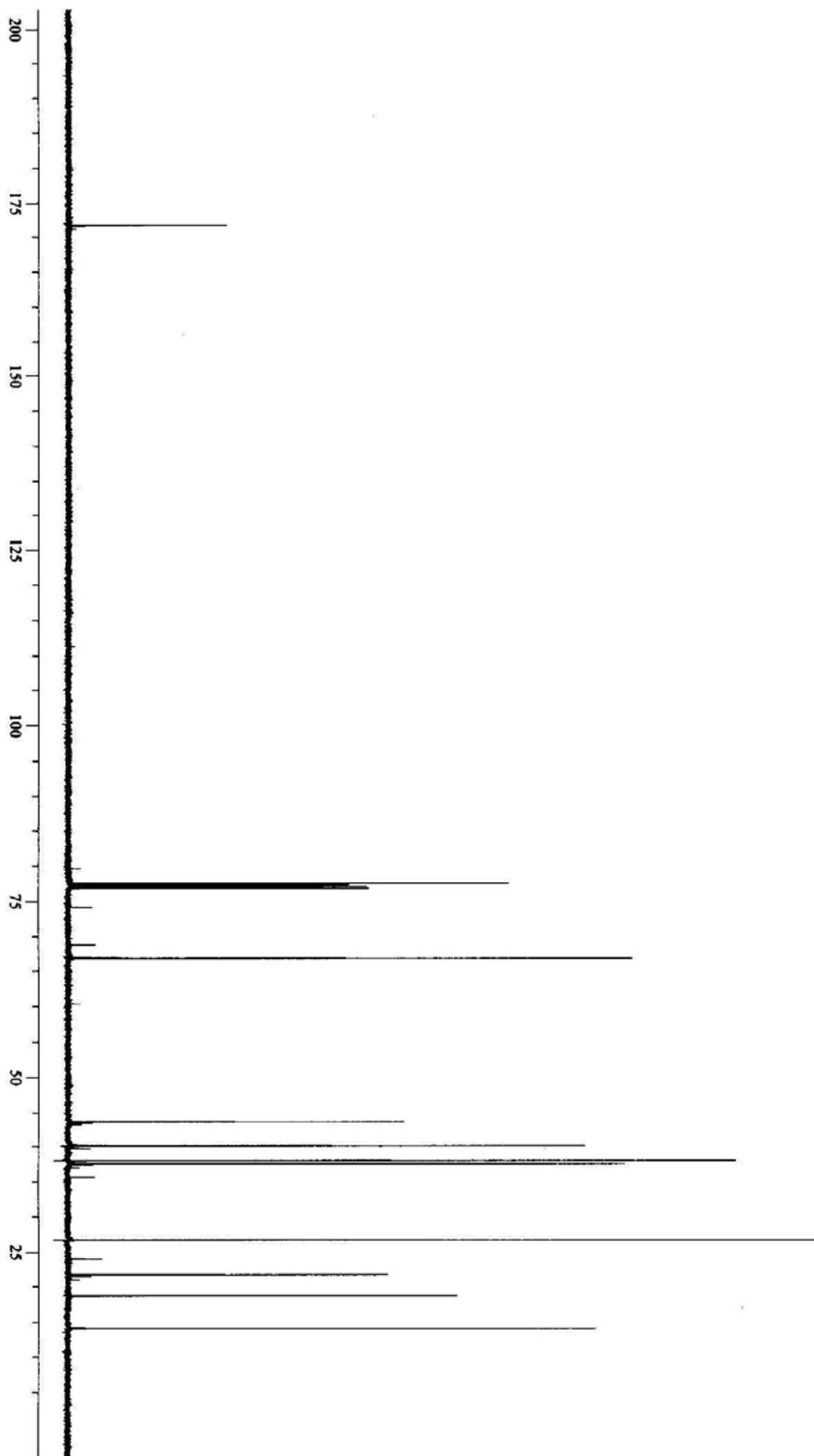
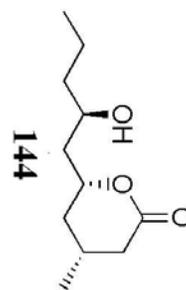
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **155**



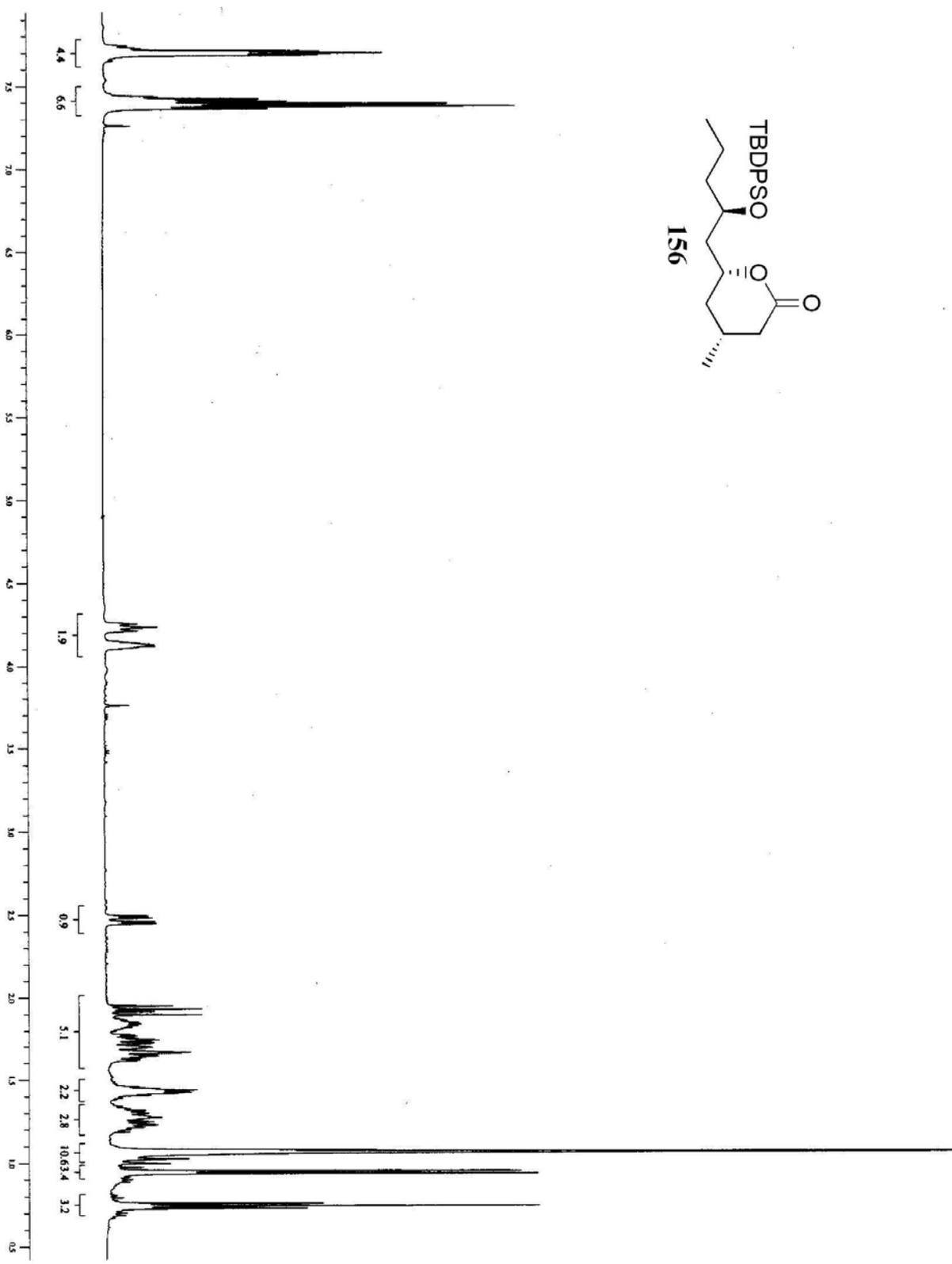
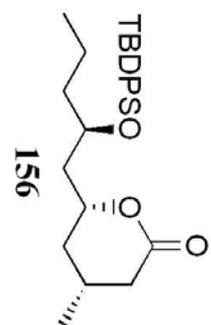
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **155**



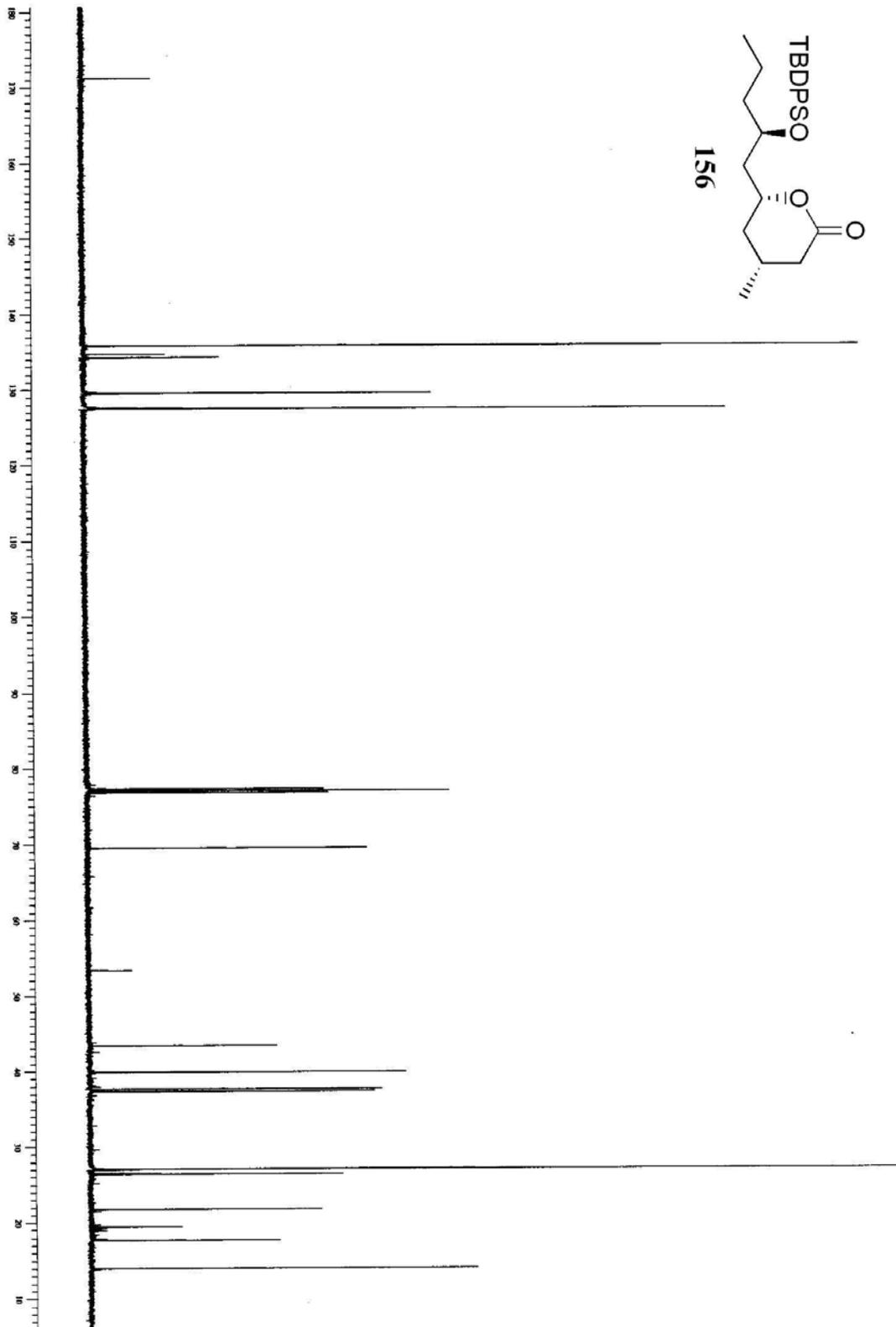
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **144**



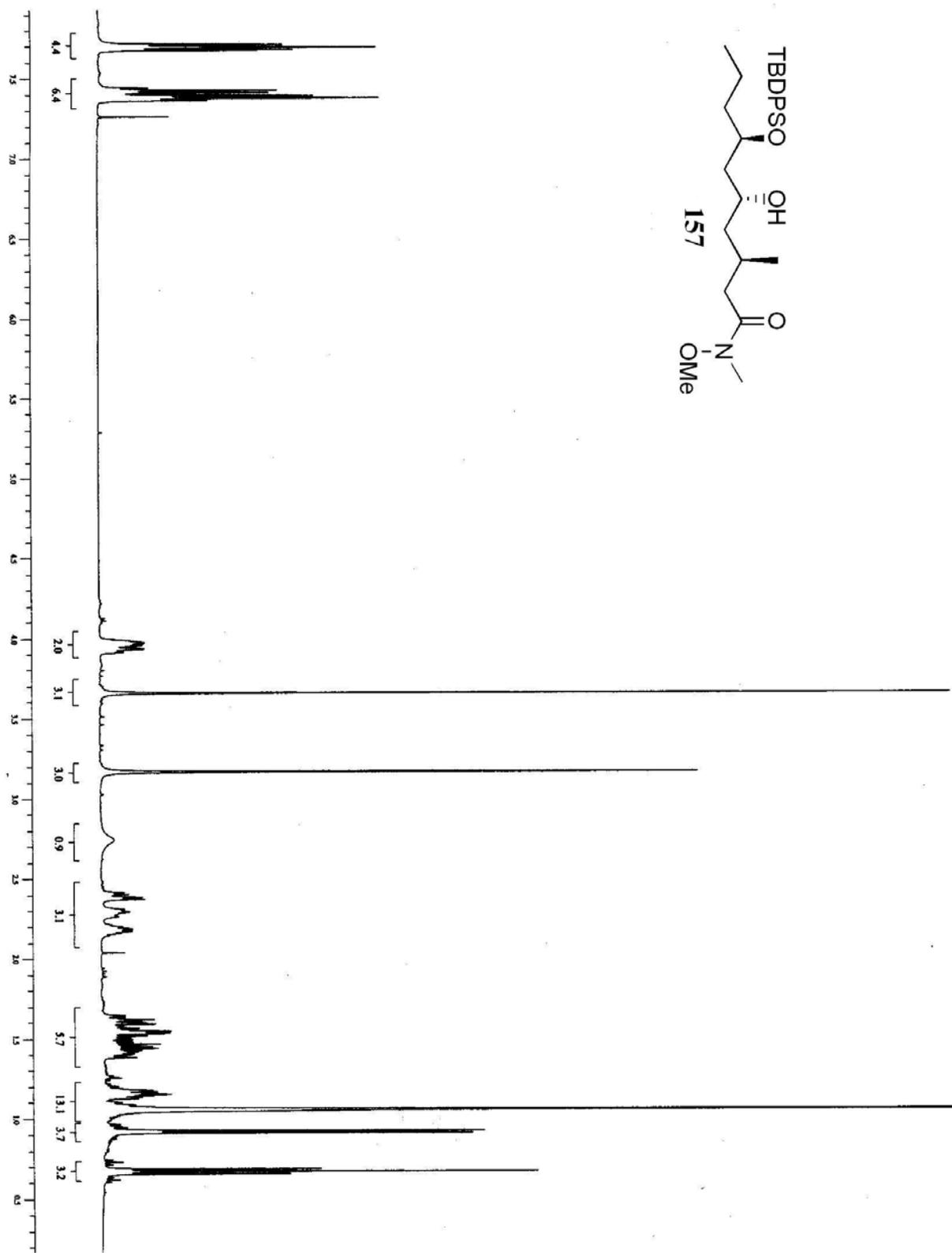
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **144**



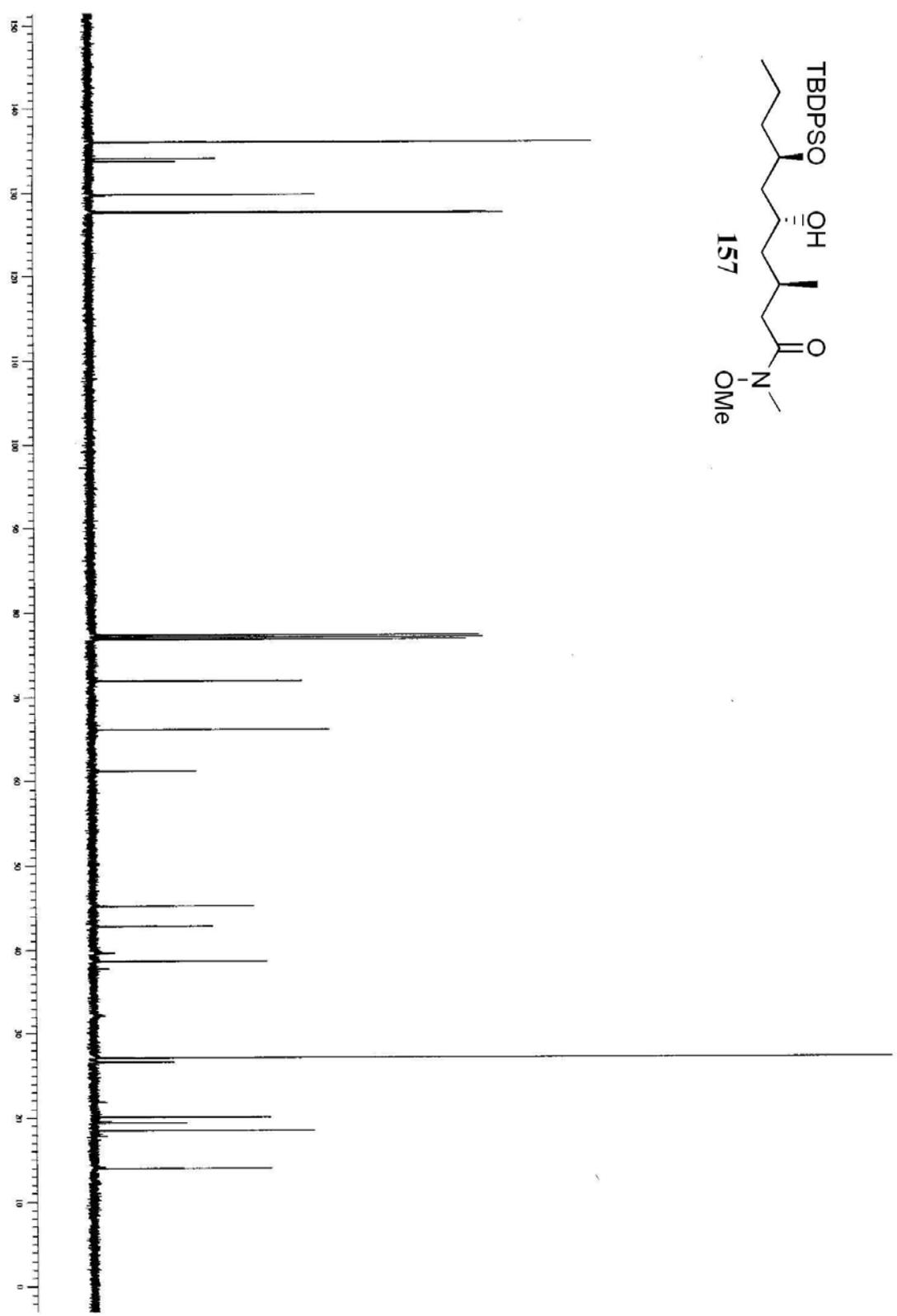
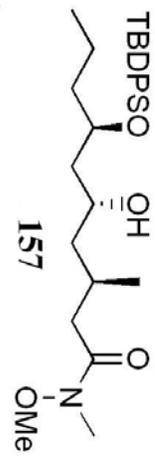
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **156**



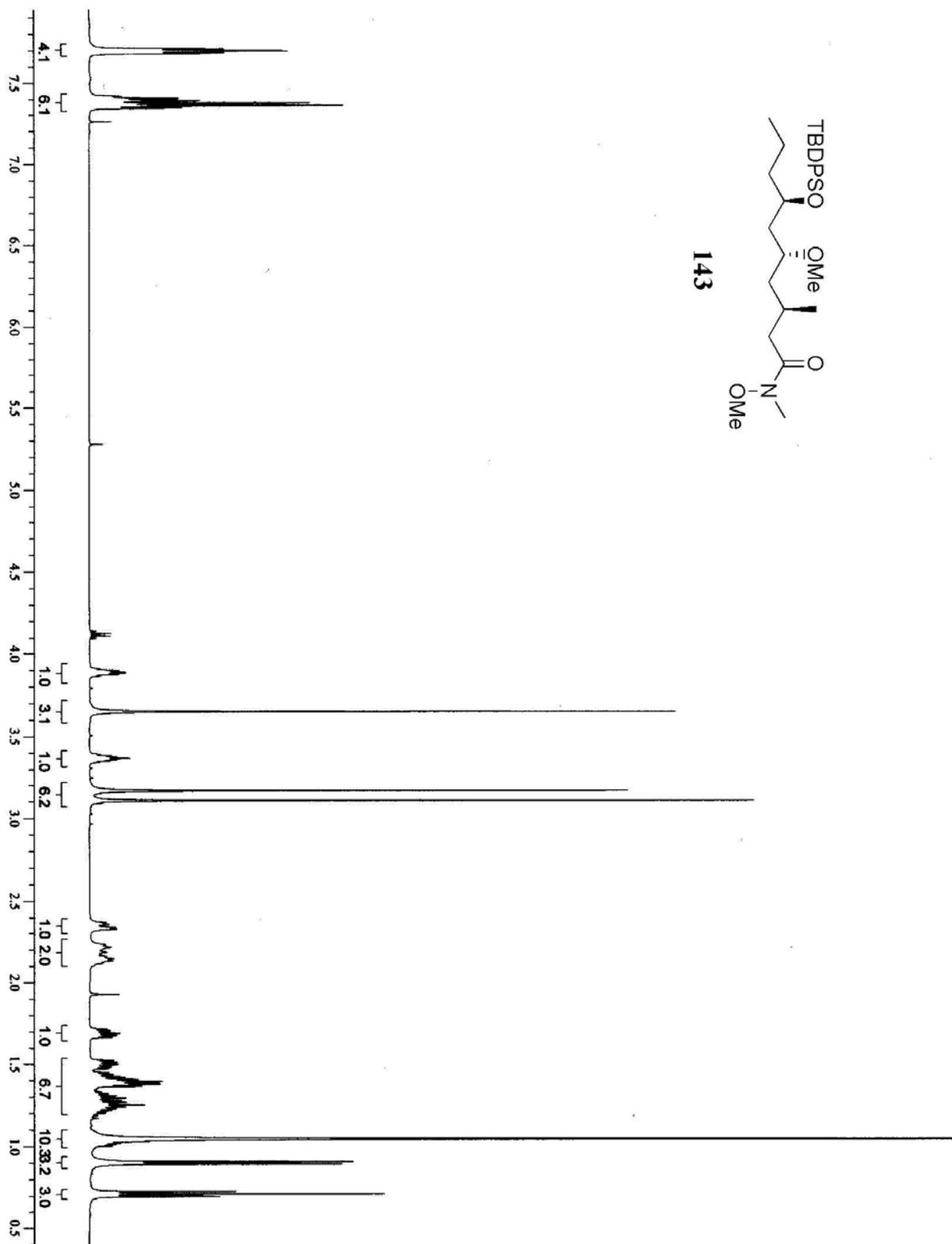
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **156**



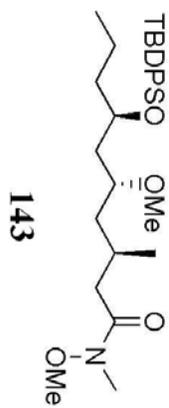
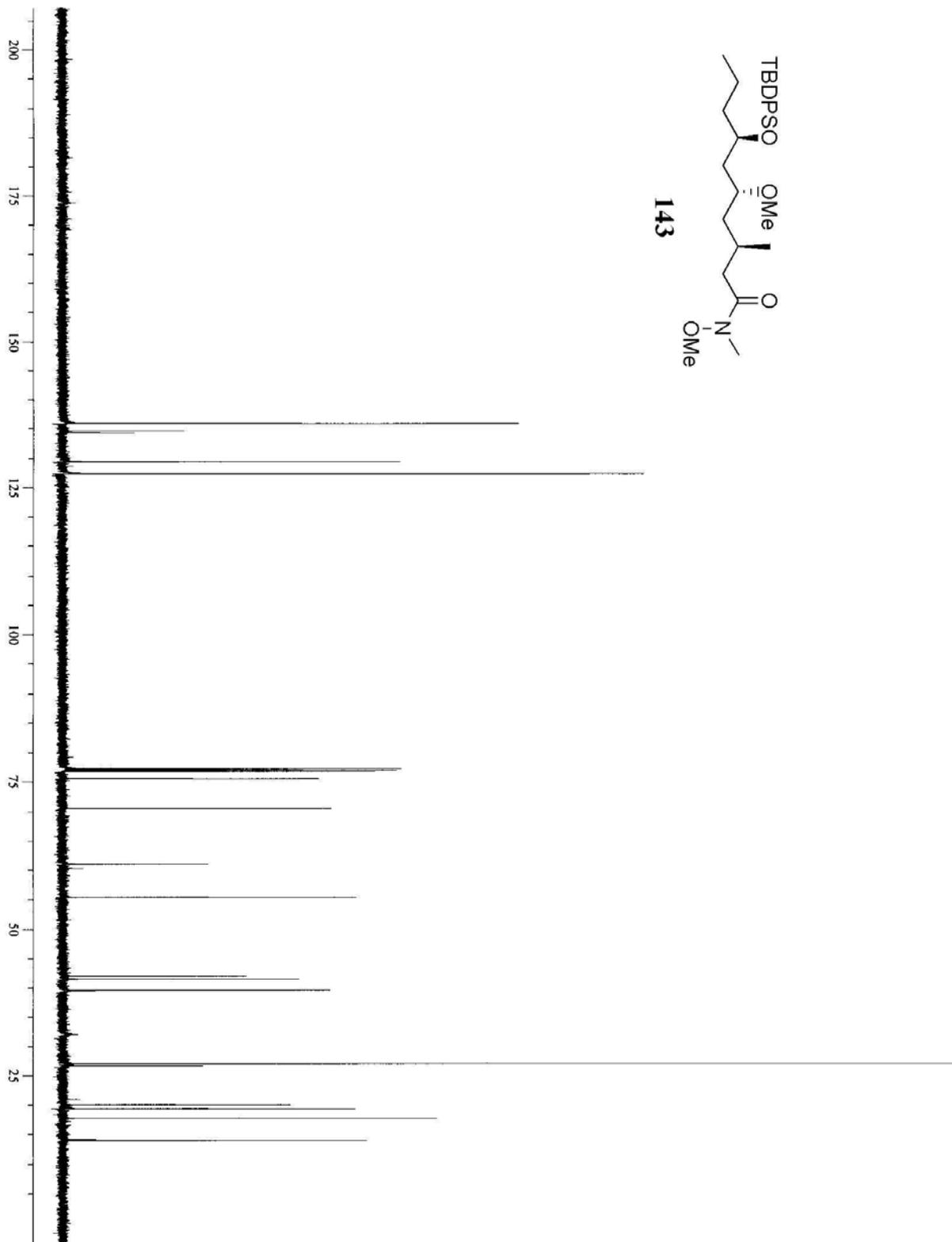
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **157**



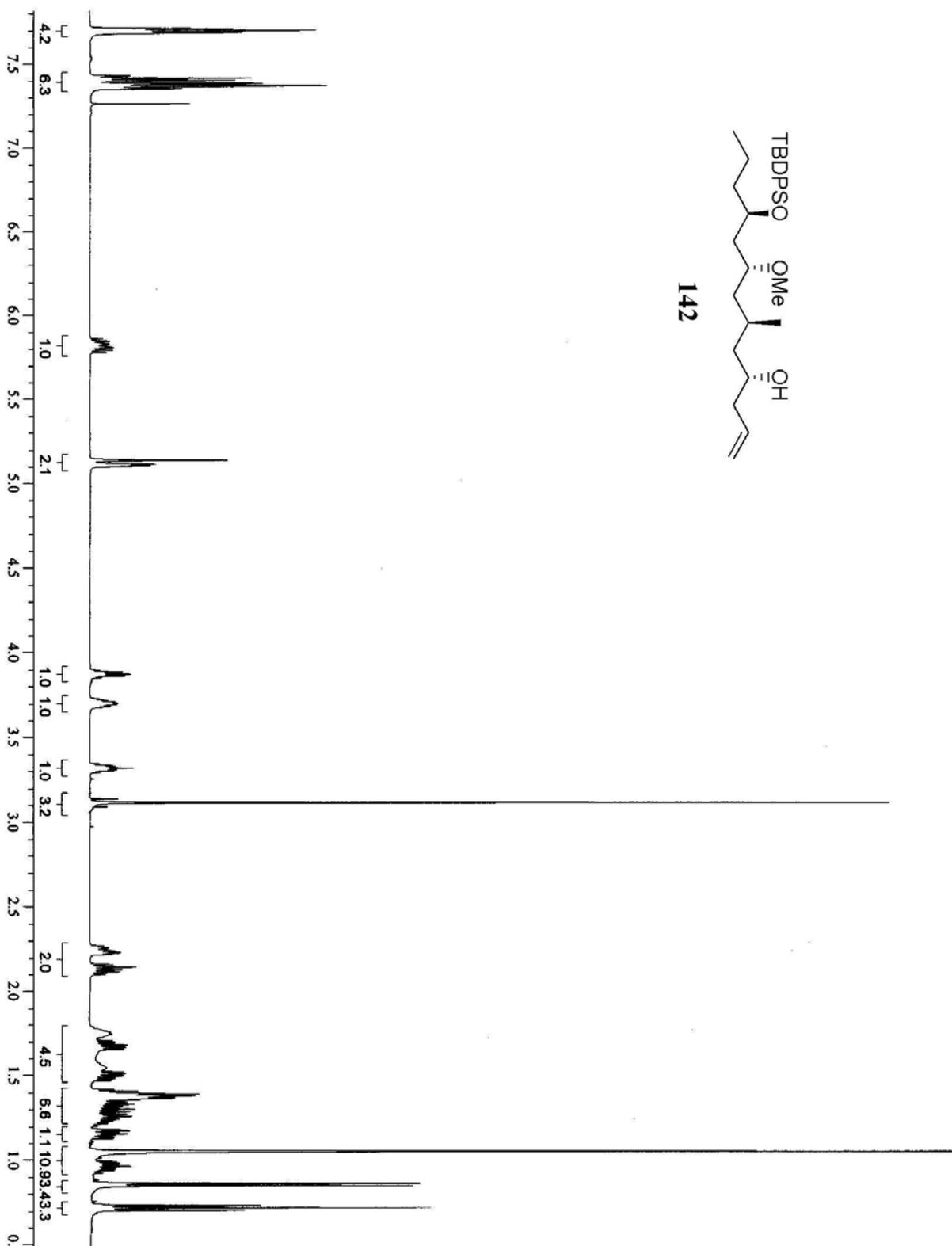
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound 157



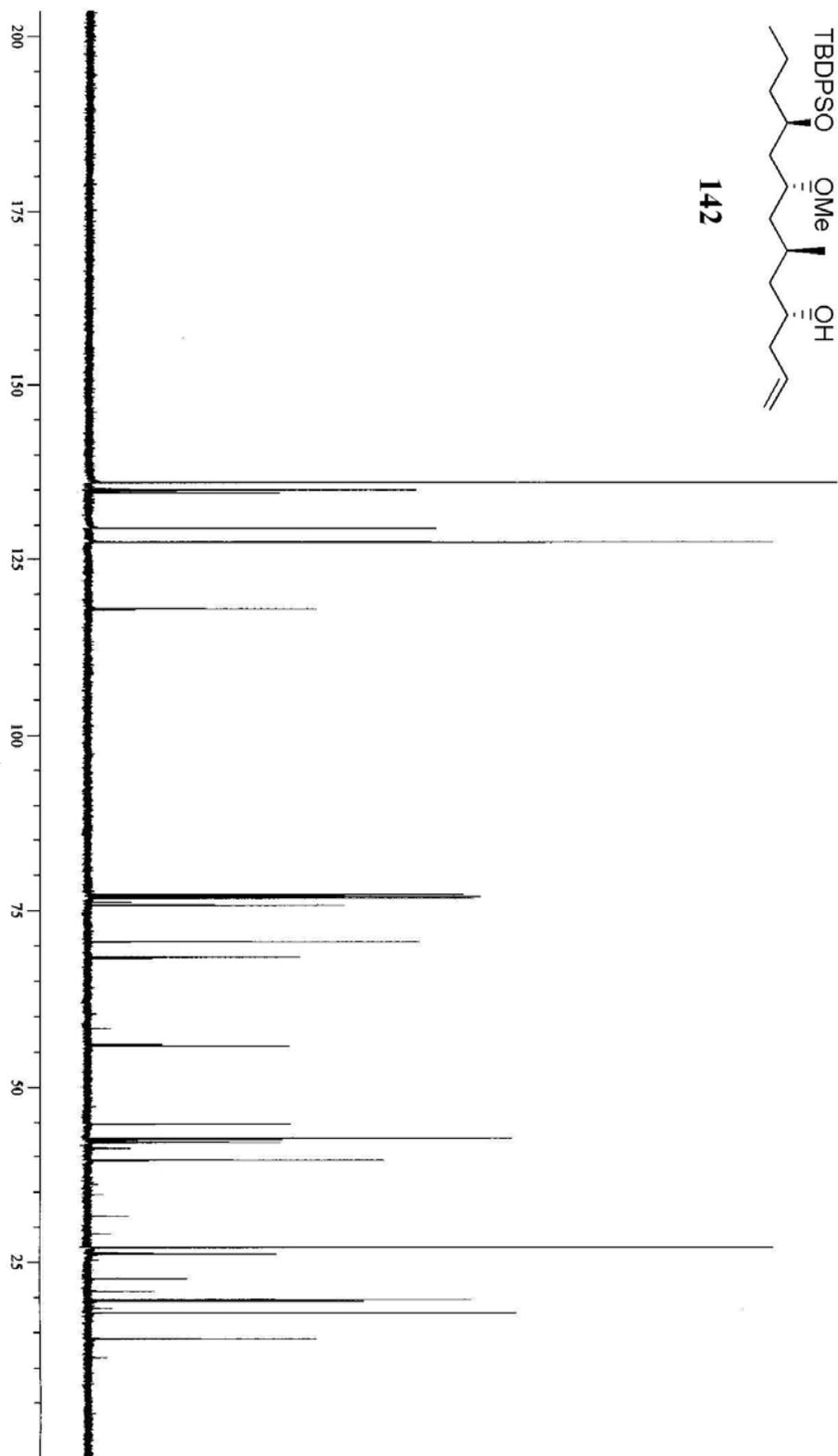
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **143**



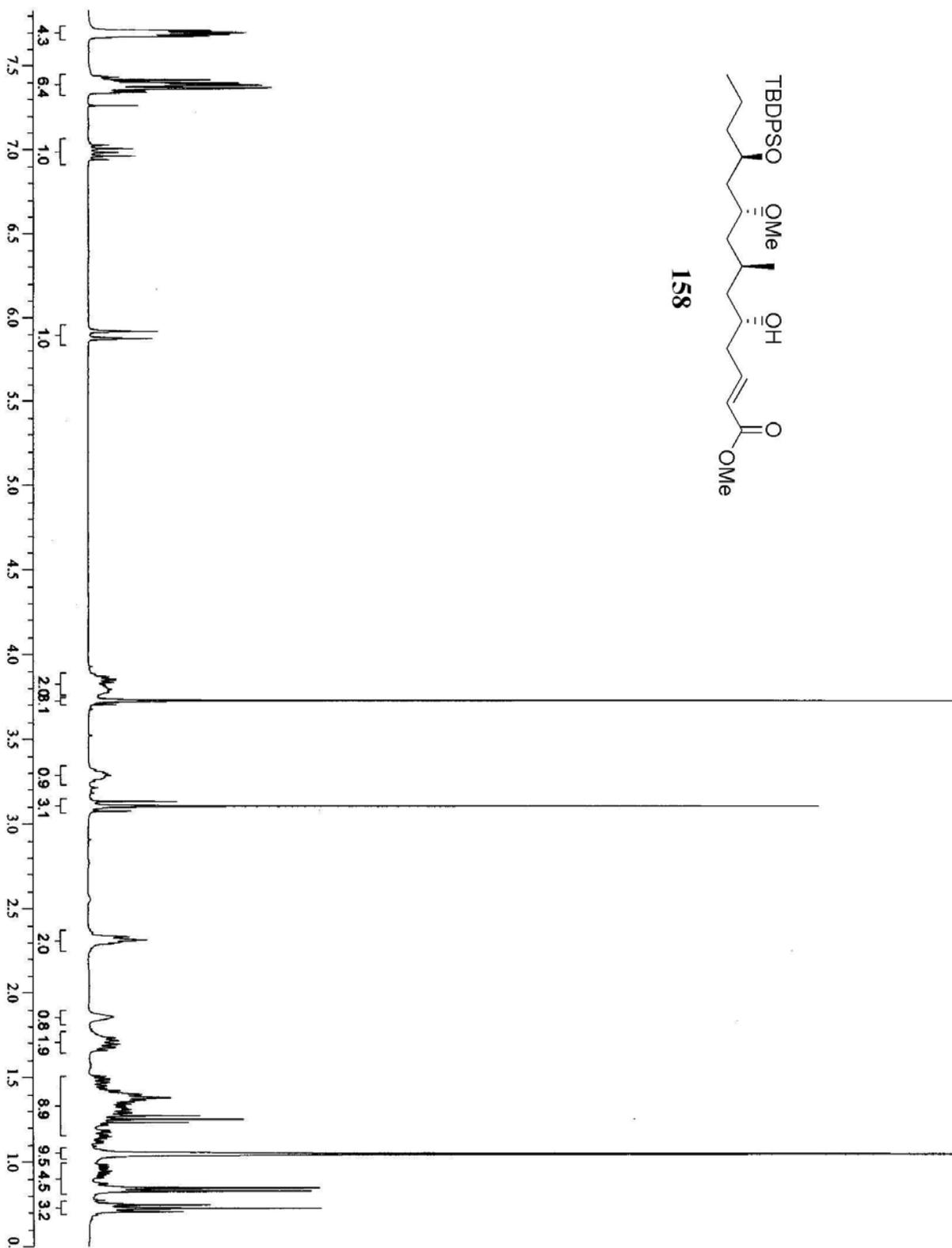
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **143**



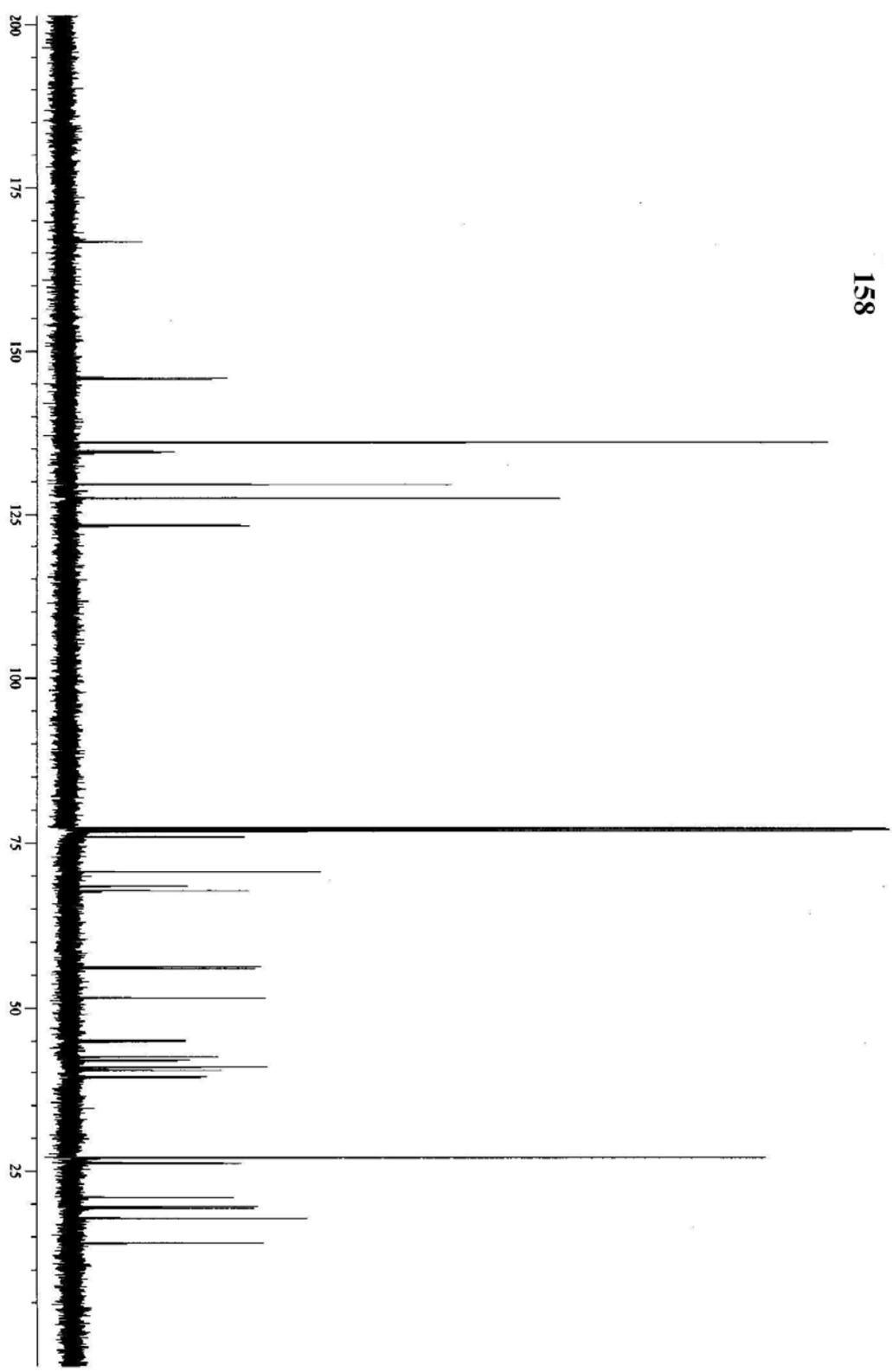
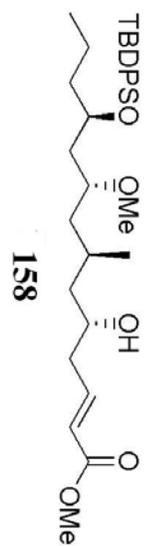
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **142**



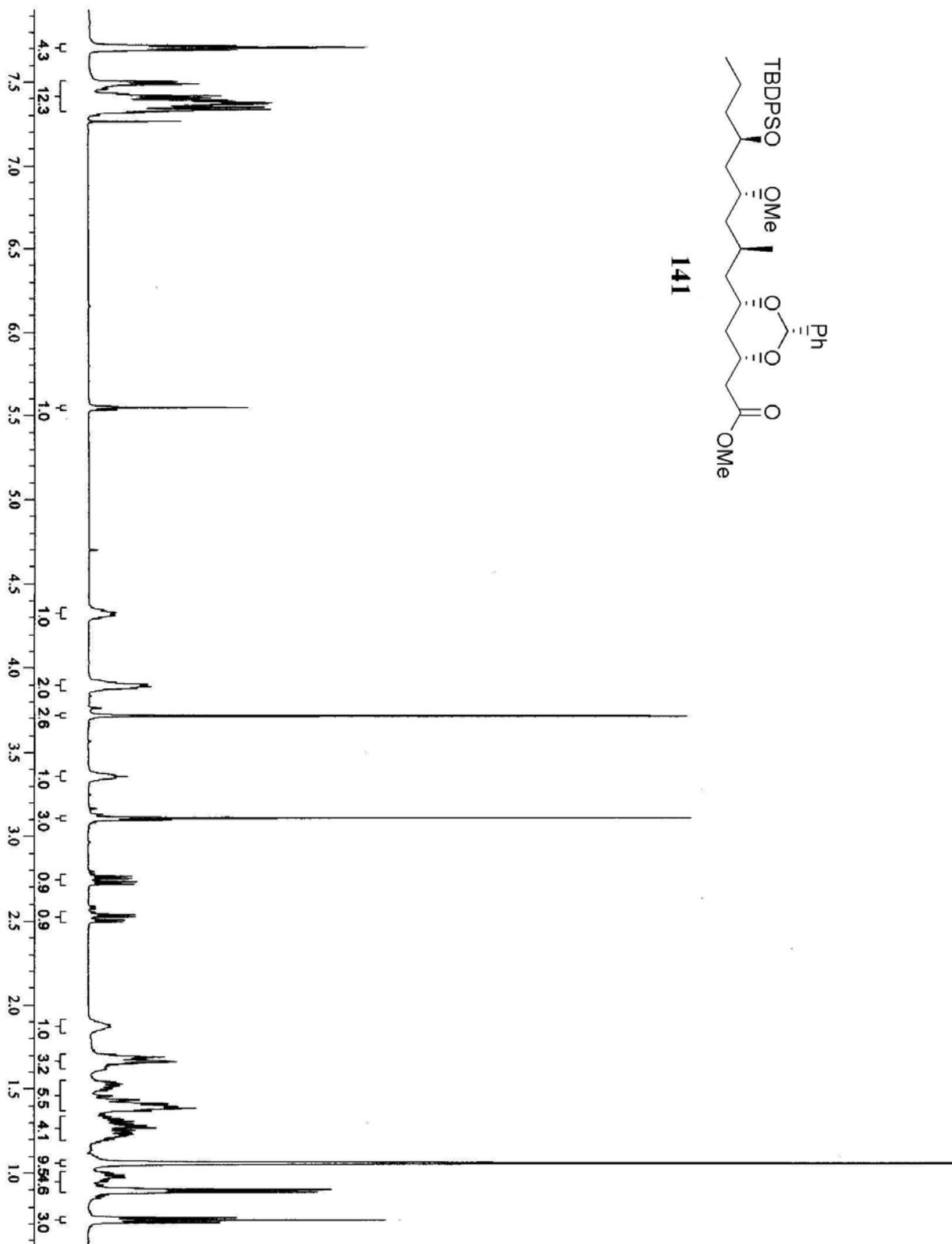
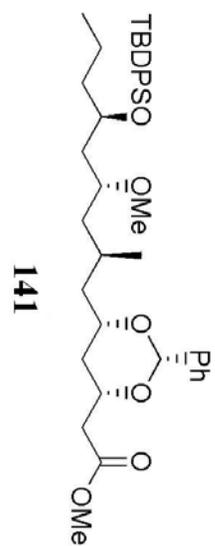
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **142**



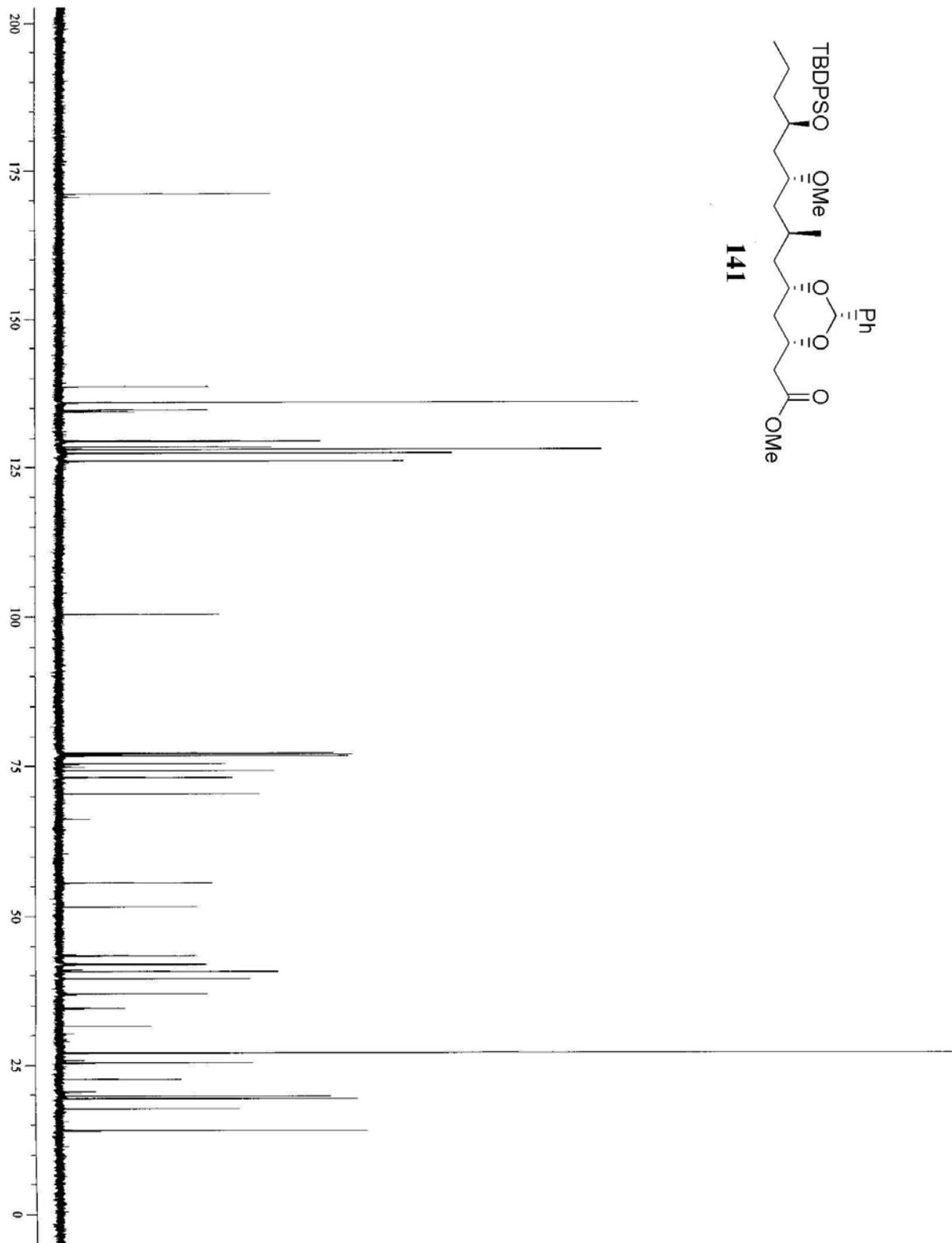
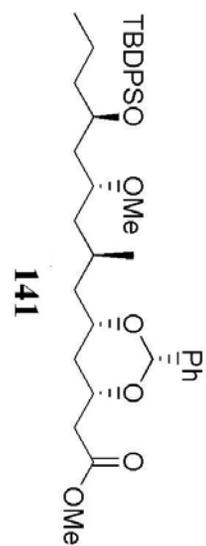
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **158**



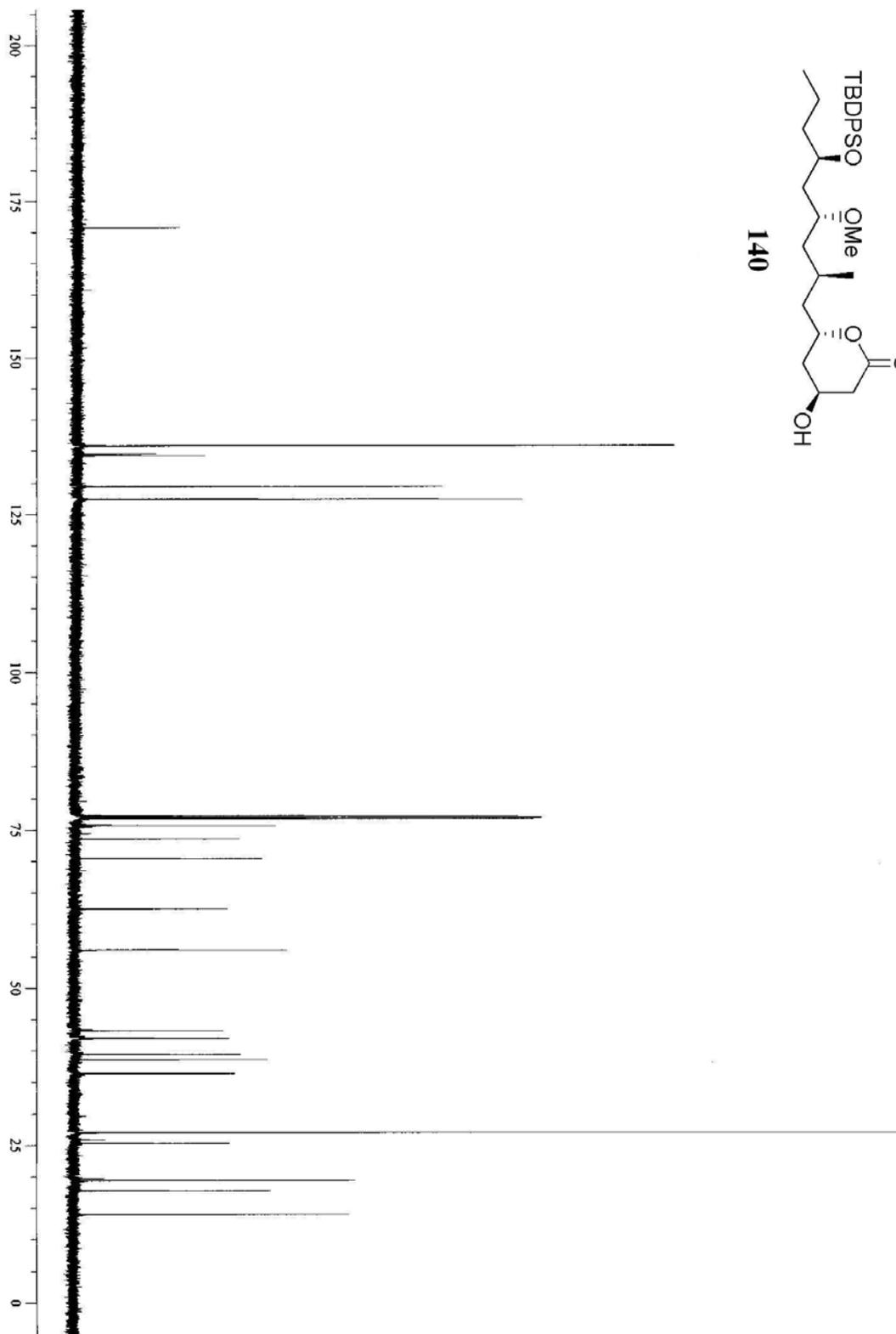
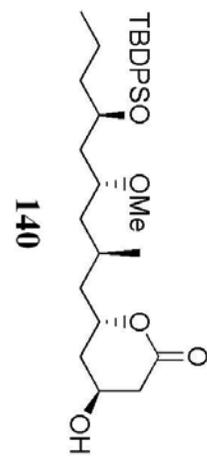
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **158**



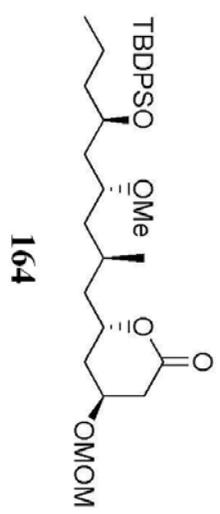
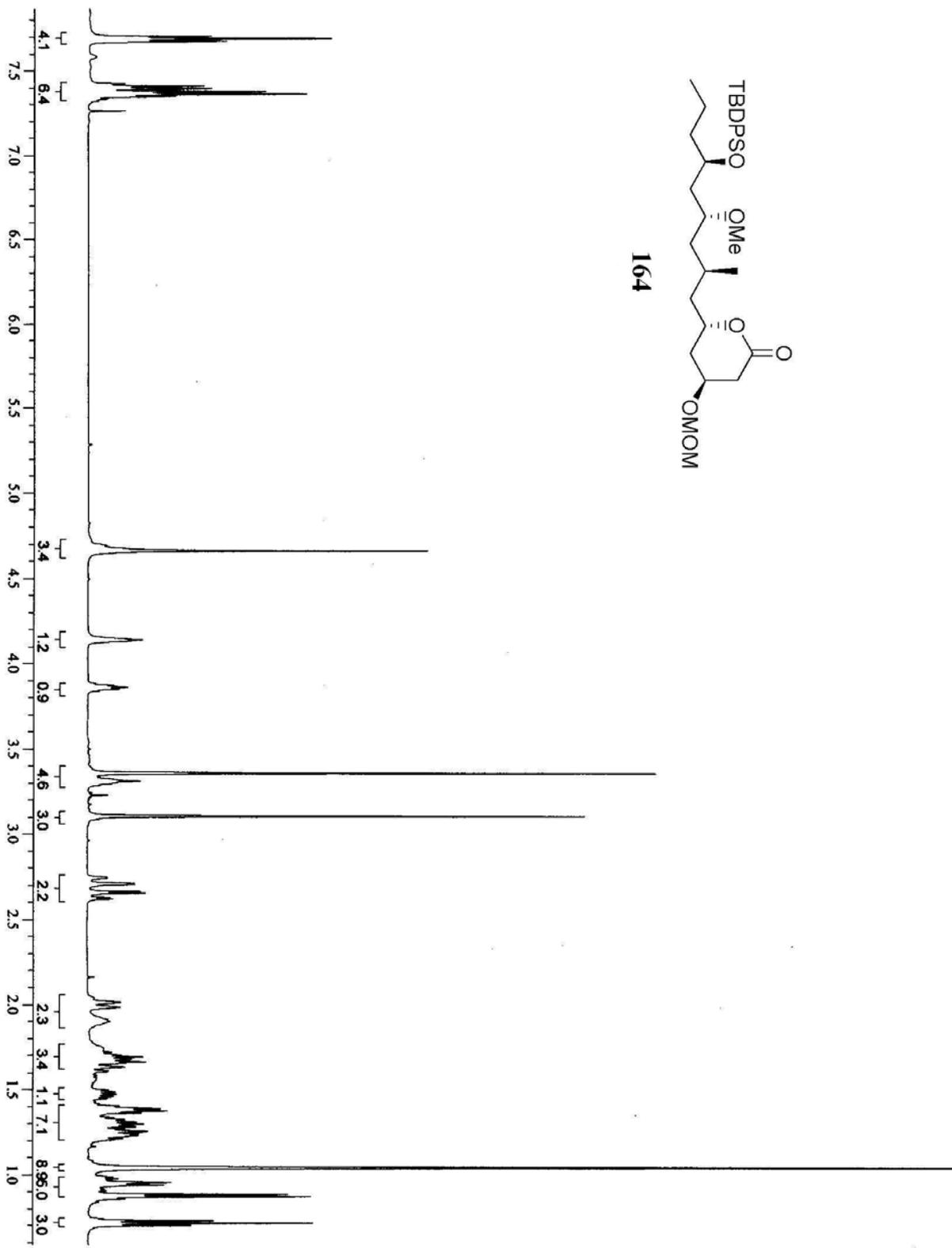
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **141**



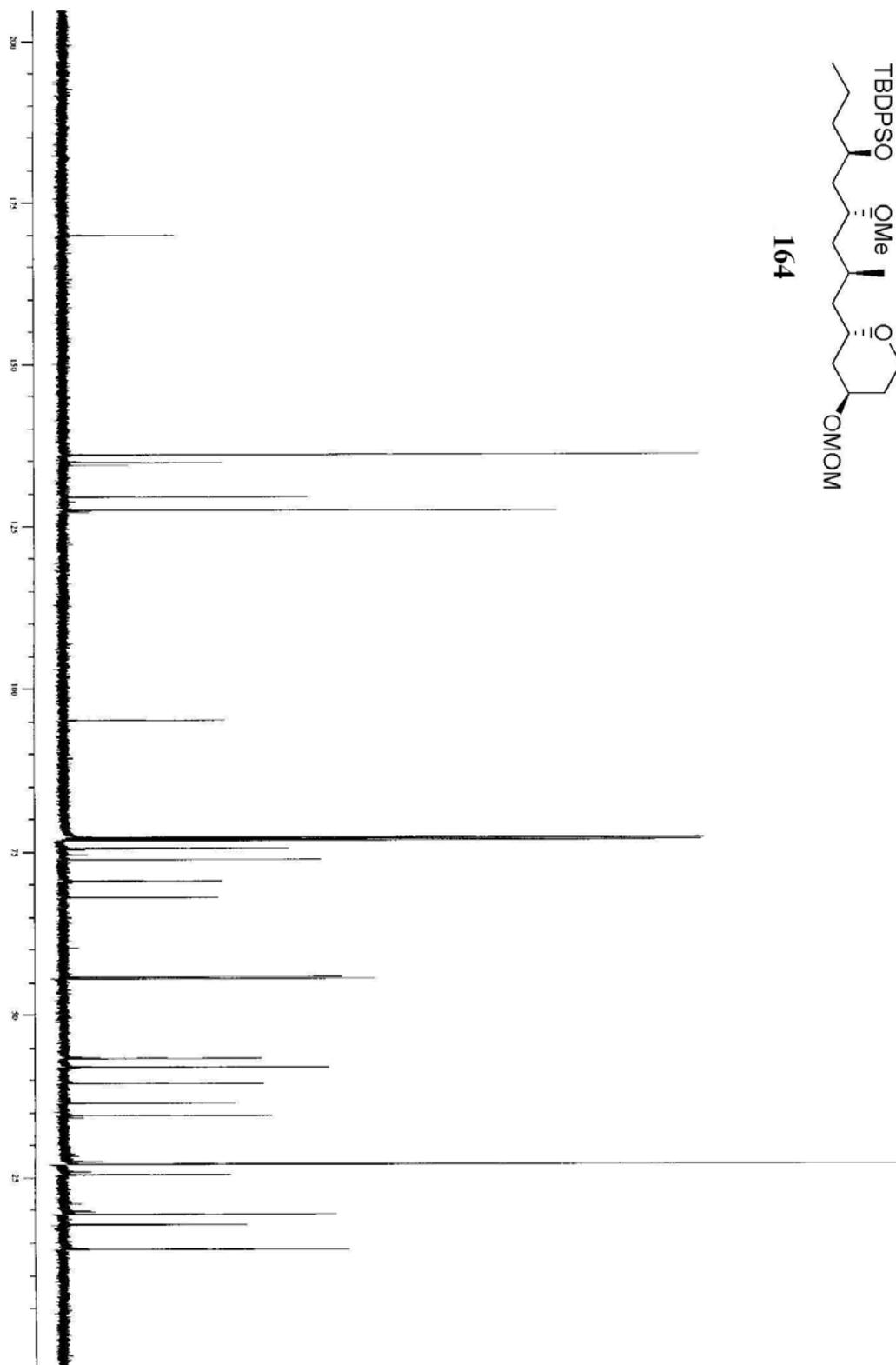
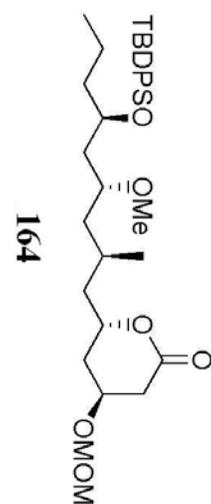
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **141**



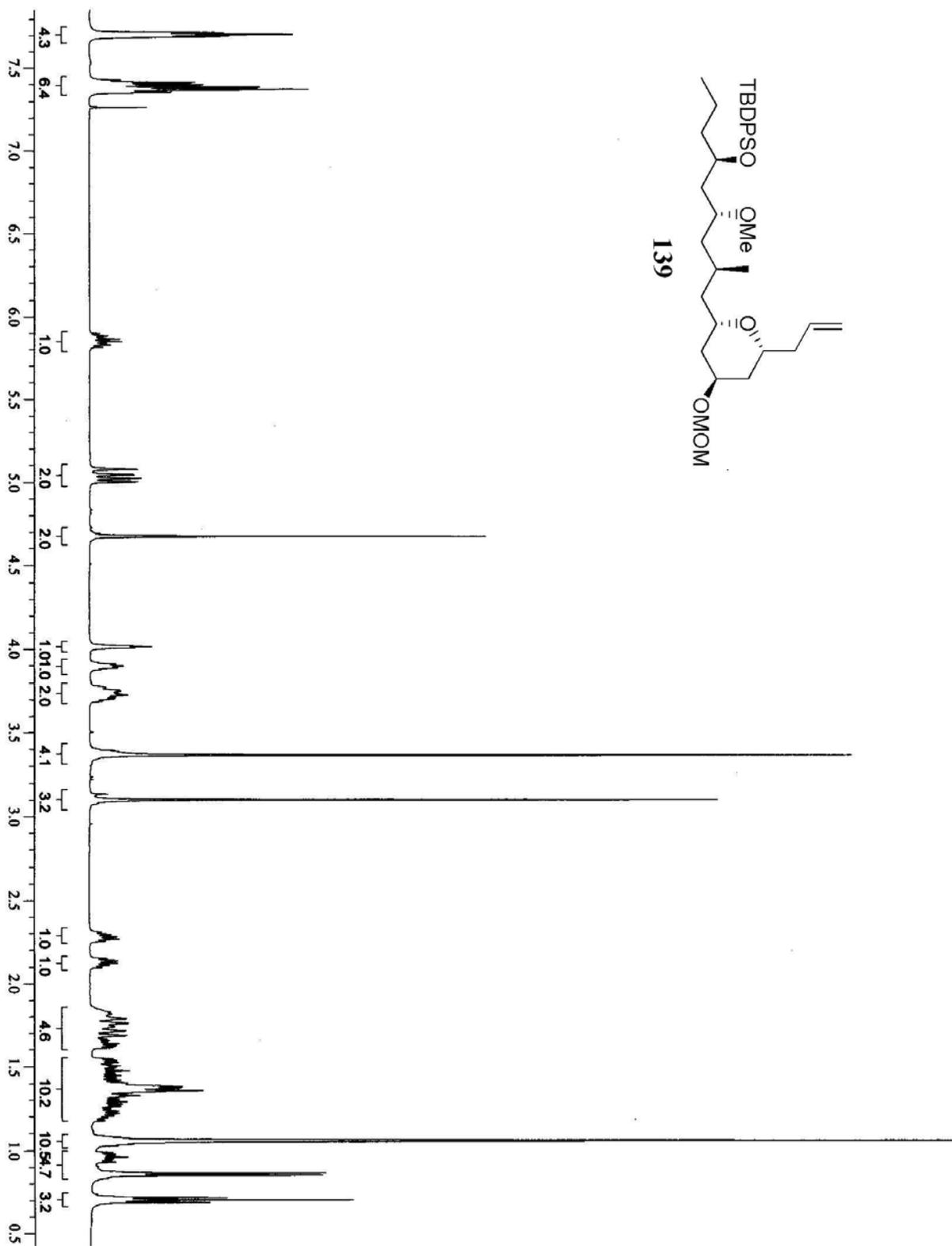
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **140**



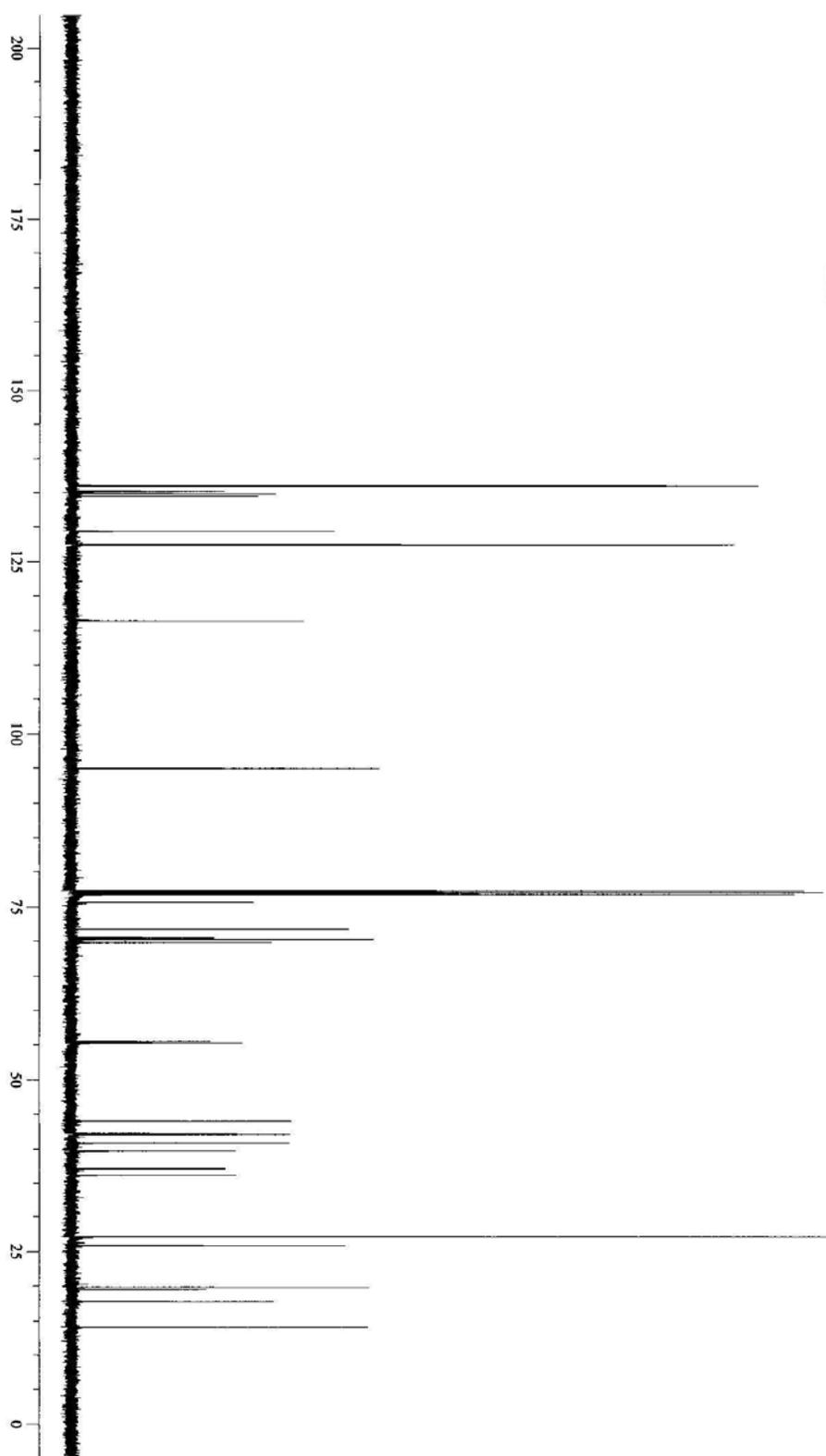
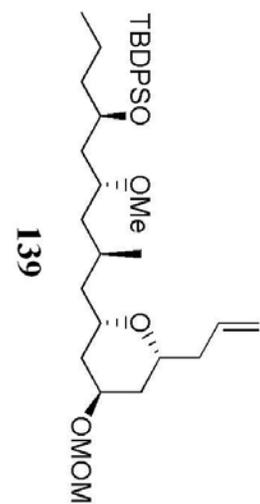
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **164**



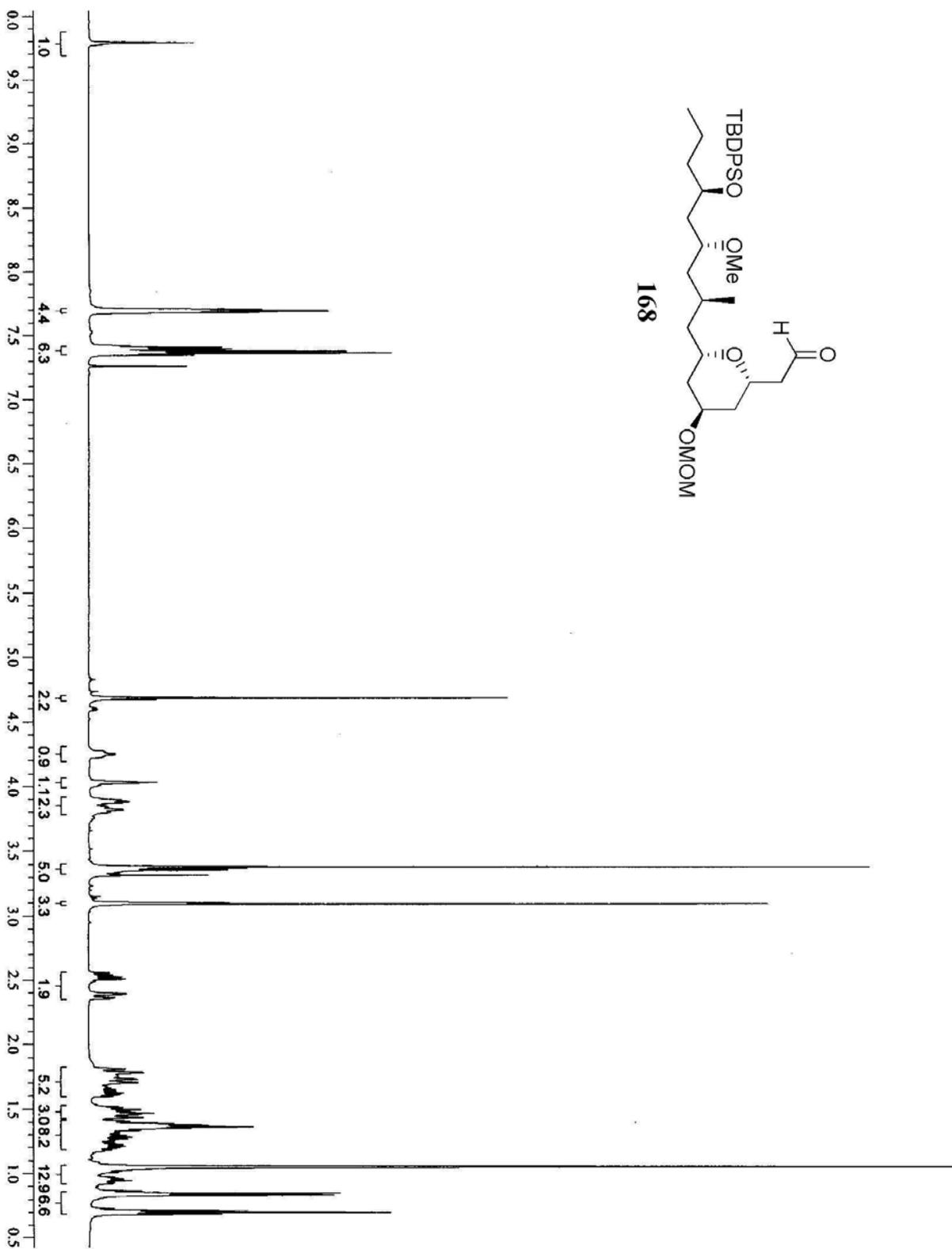
The ¹³C NMR Spectrum (125 MHz, CDCl₃) of Compound **164**



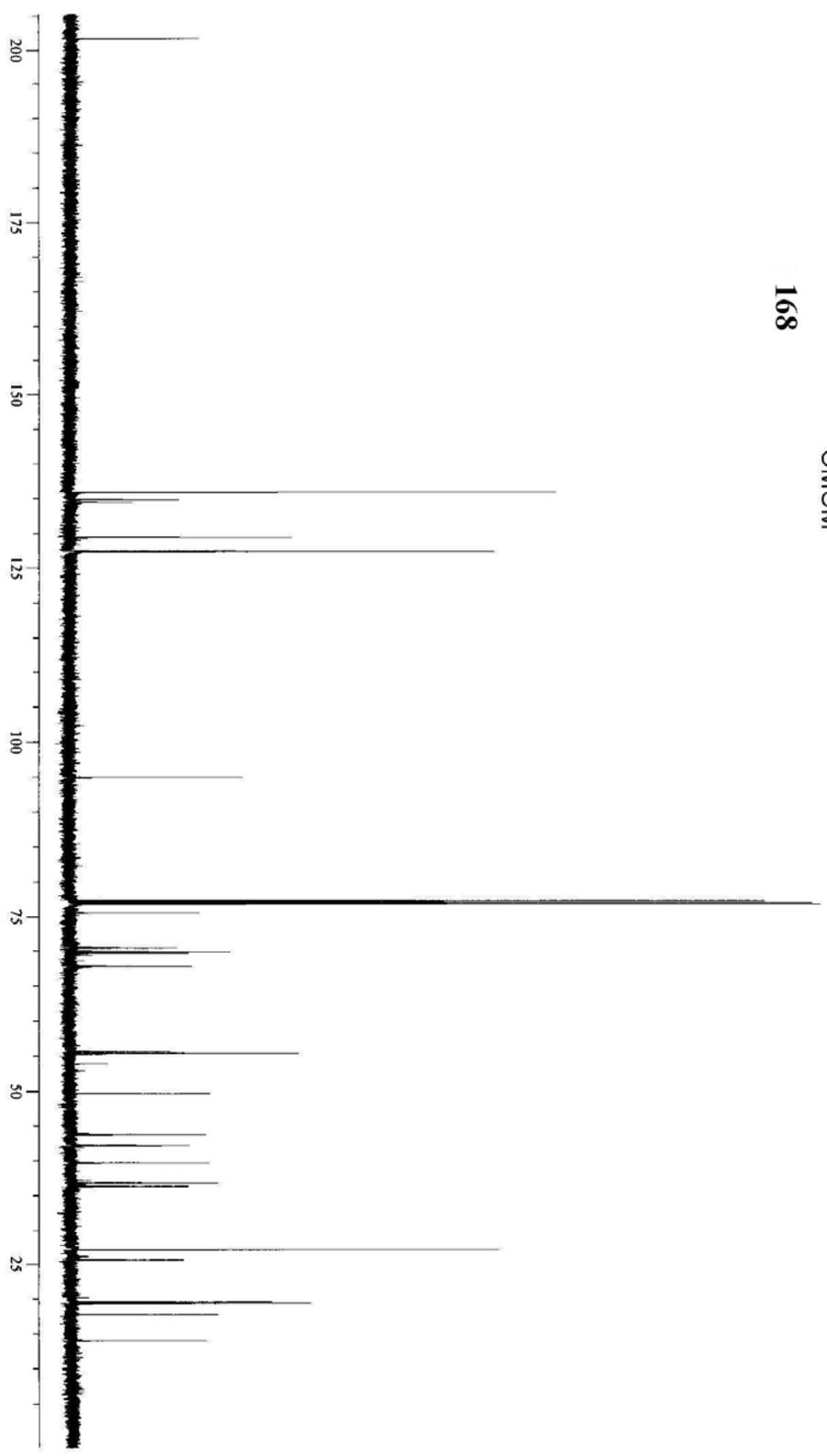
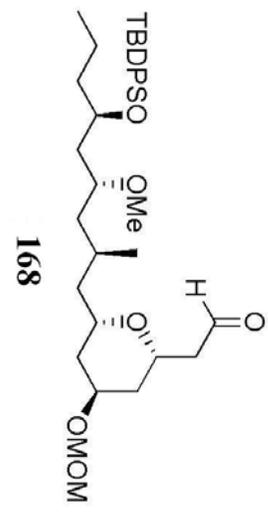
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **139**



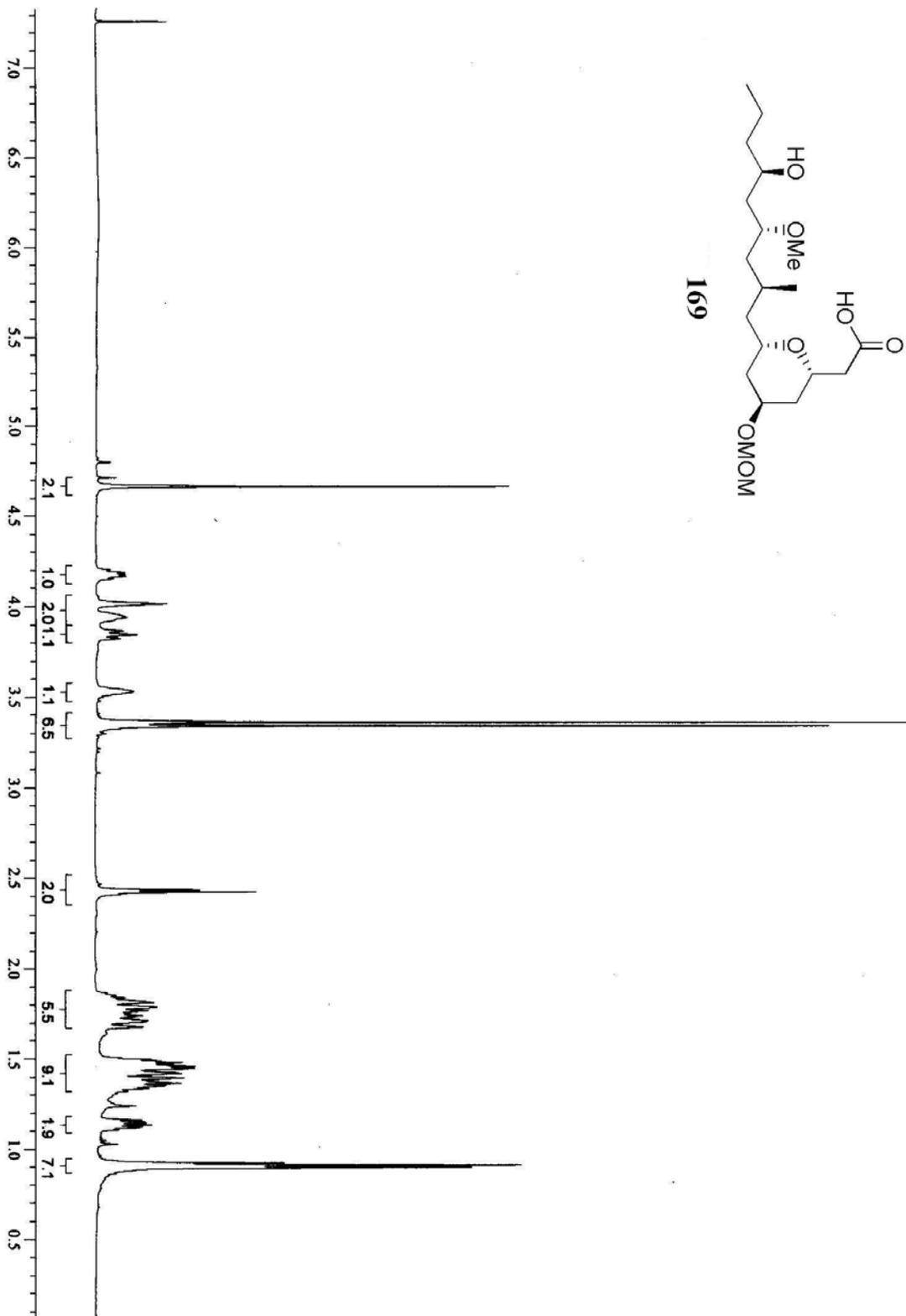
The ¹³C NMR Spectrum (125 MHz, CDCl₃) of Compound 139



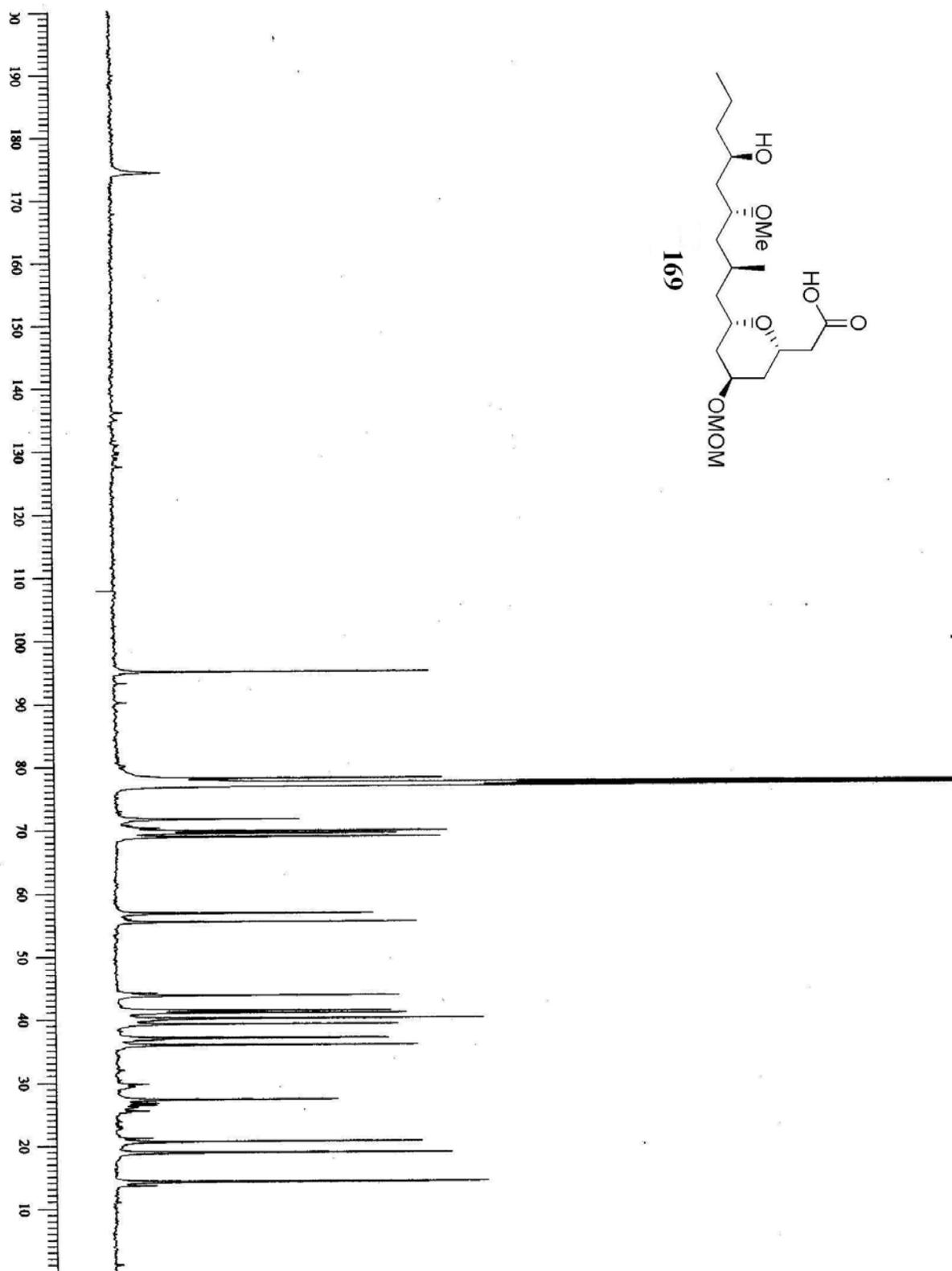
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **168**



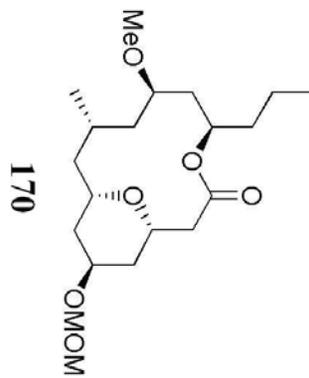
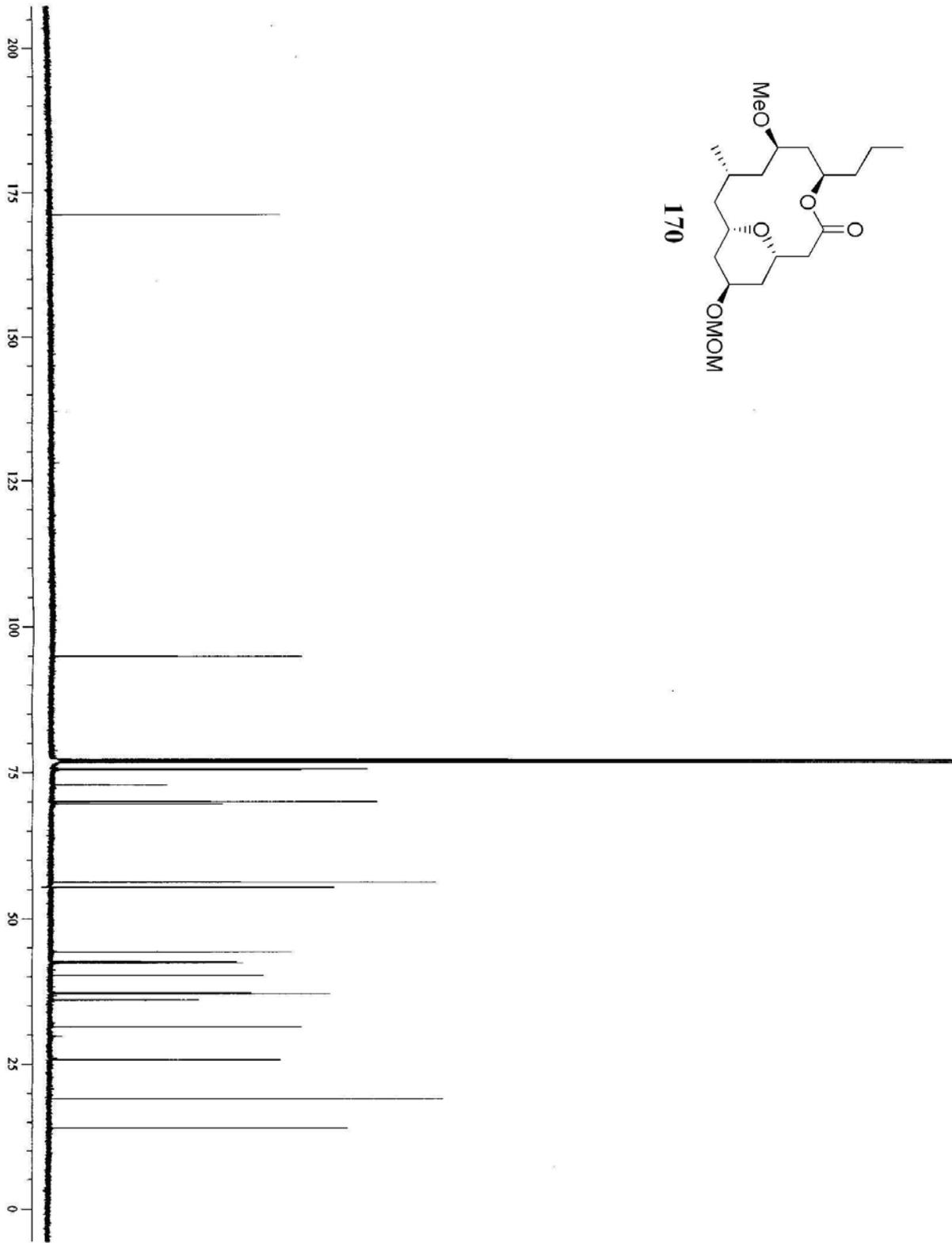
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **168**



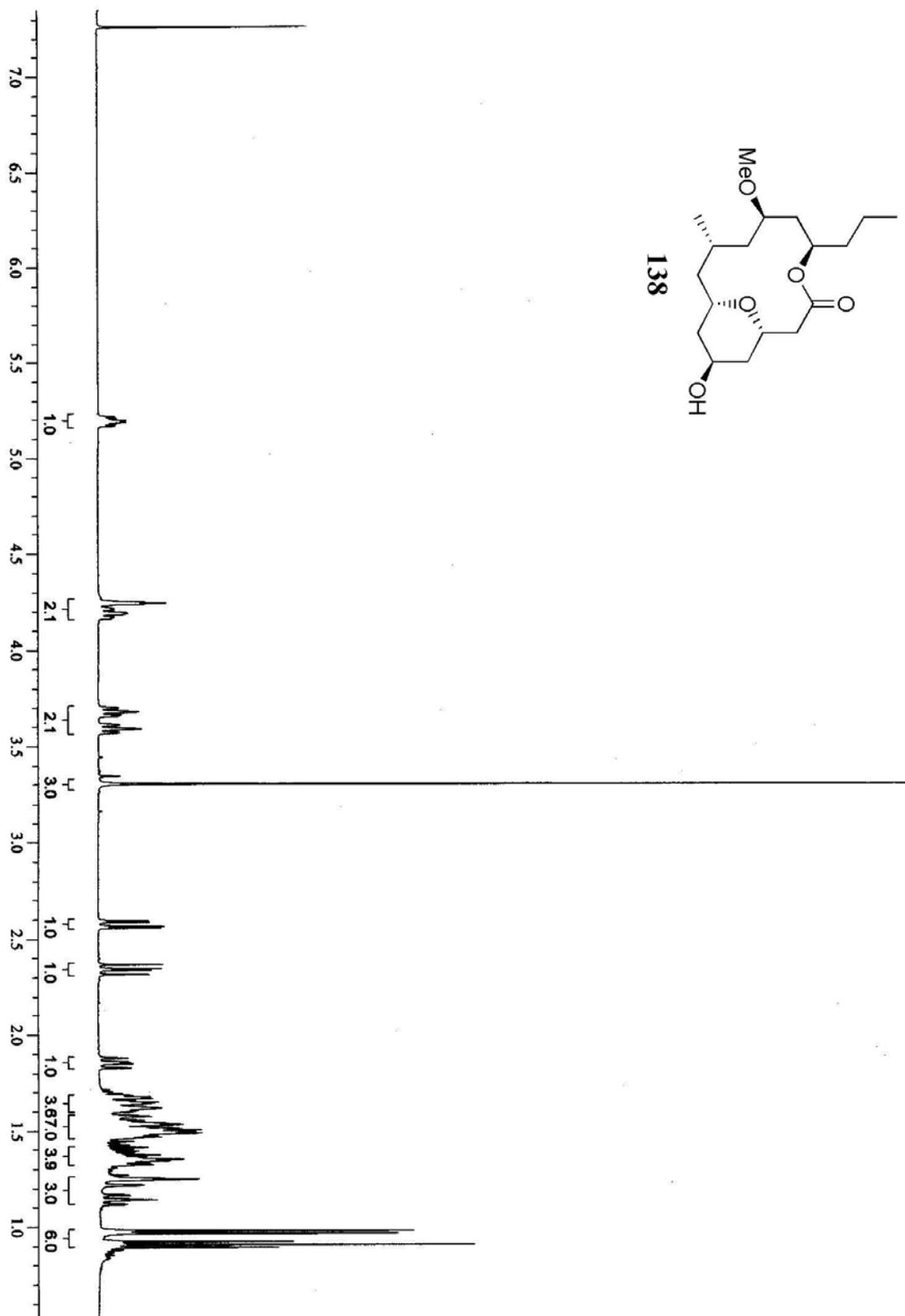
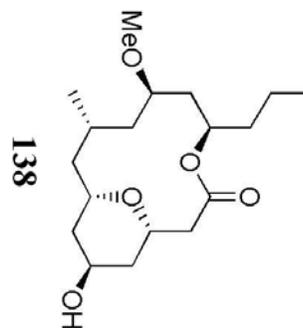
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **169**



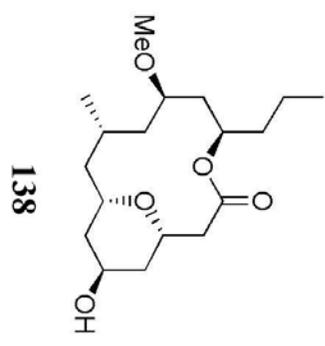
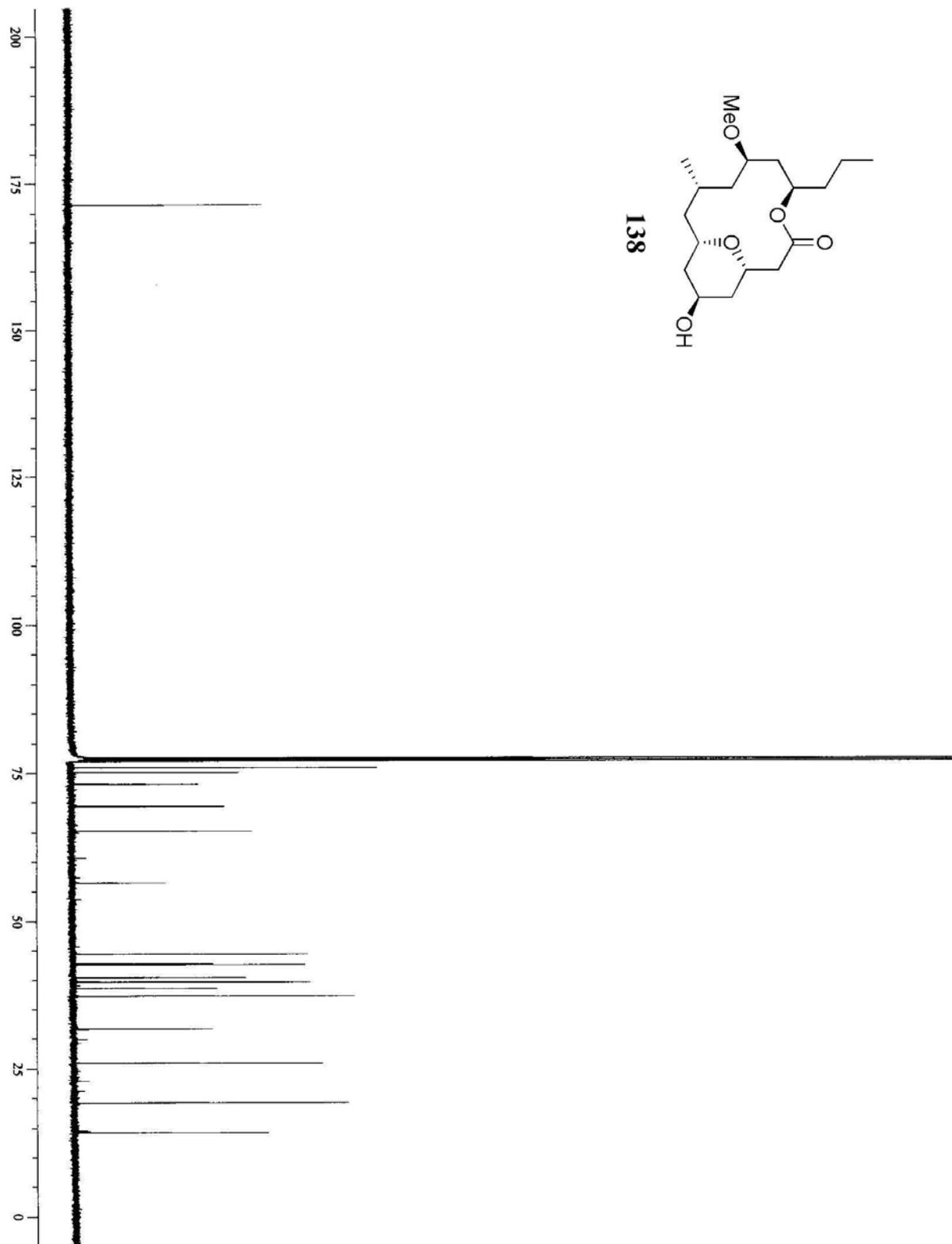
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **169**



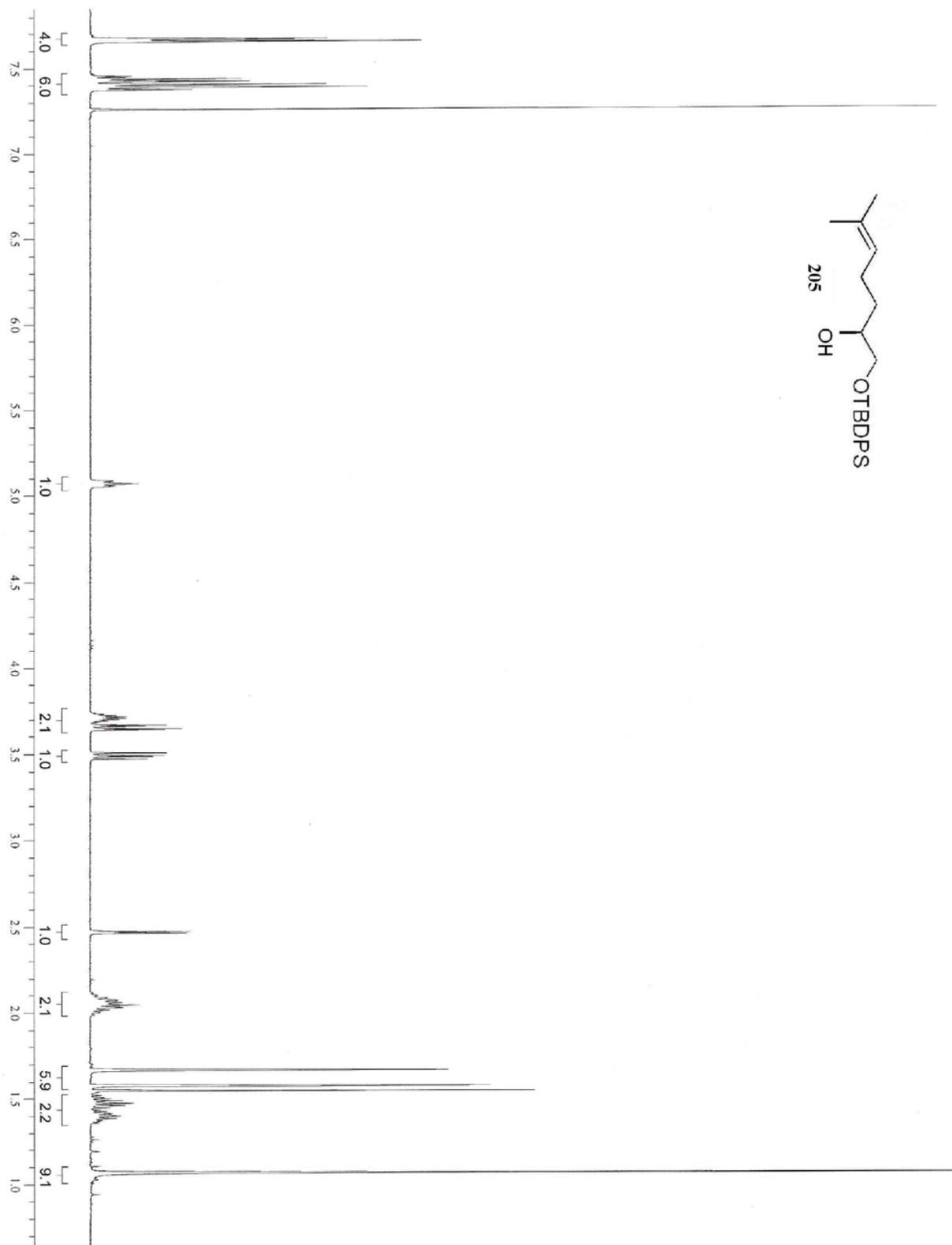
The ^{13}C NMR Spectrum (125 MHz, CDCl₃) of Compound **170**



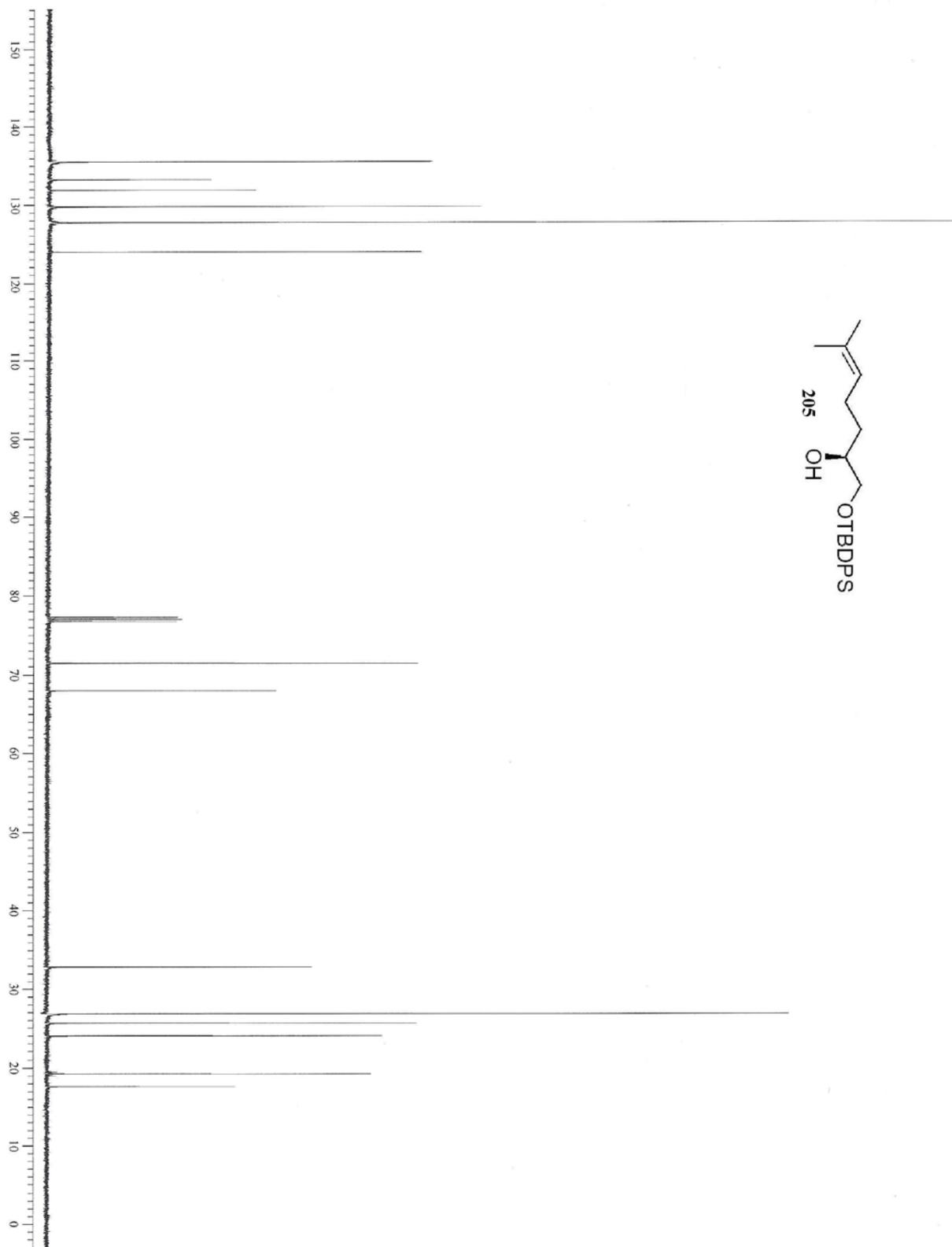
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **138**



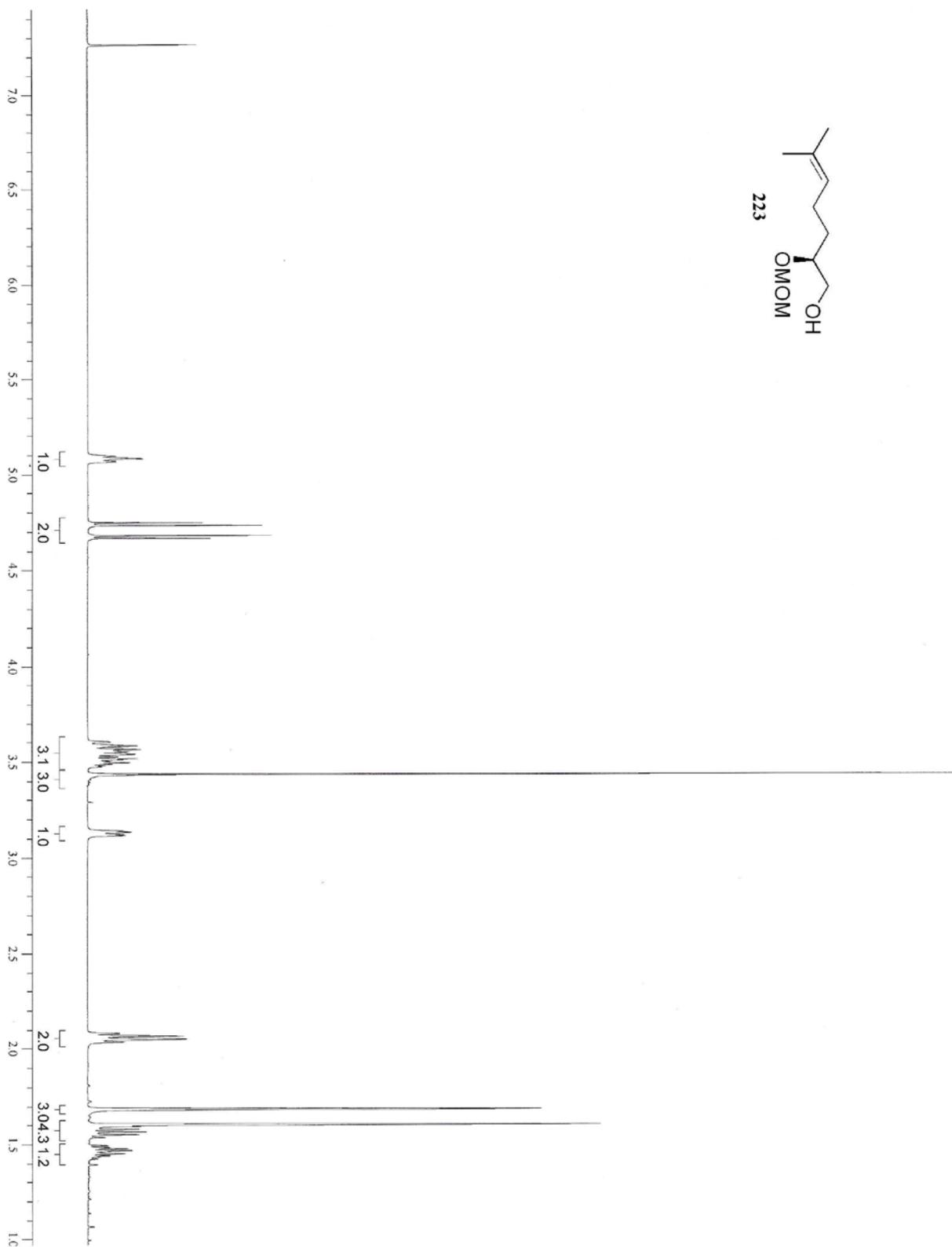
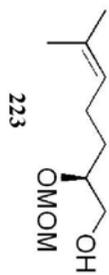
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **138**



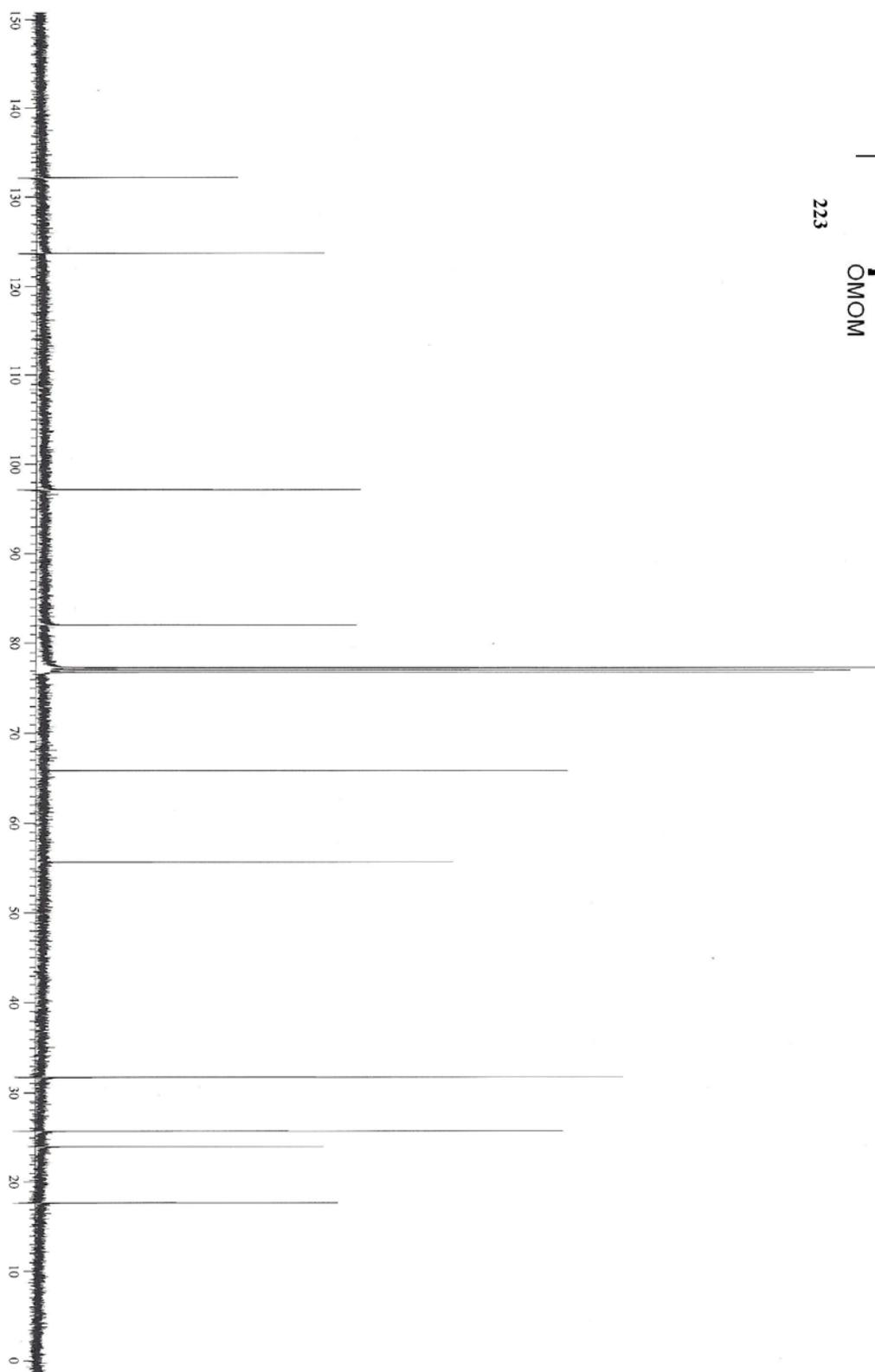
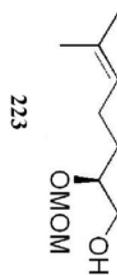
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **205**



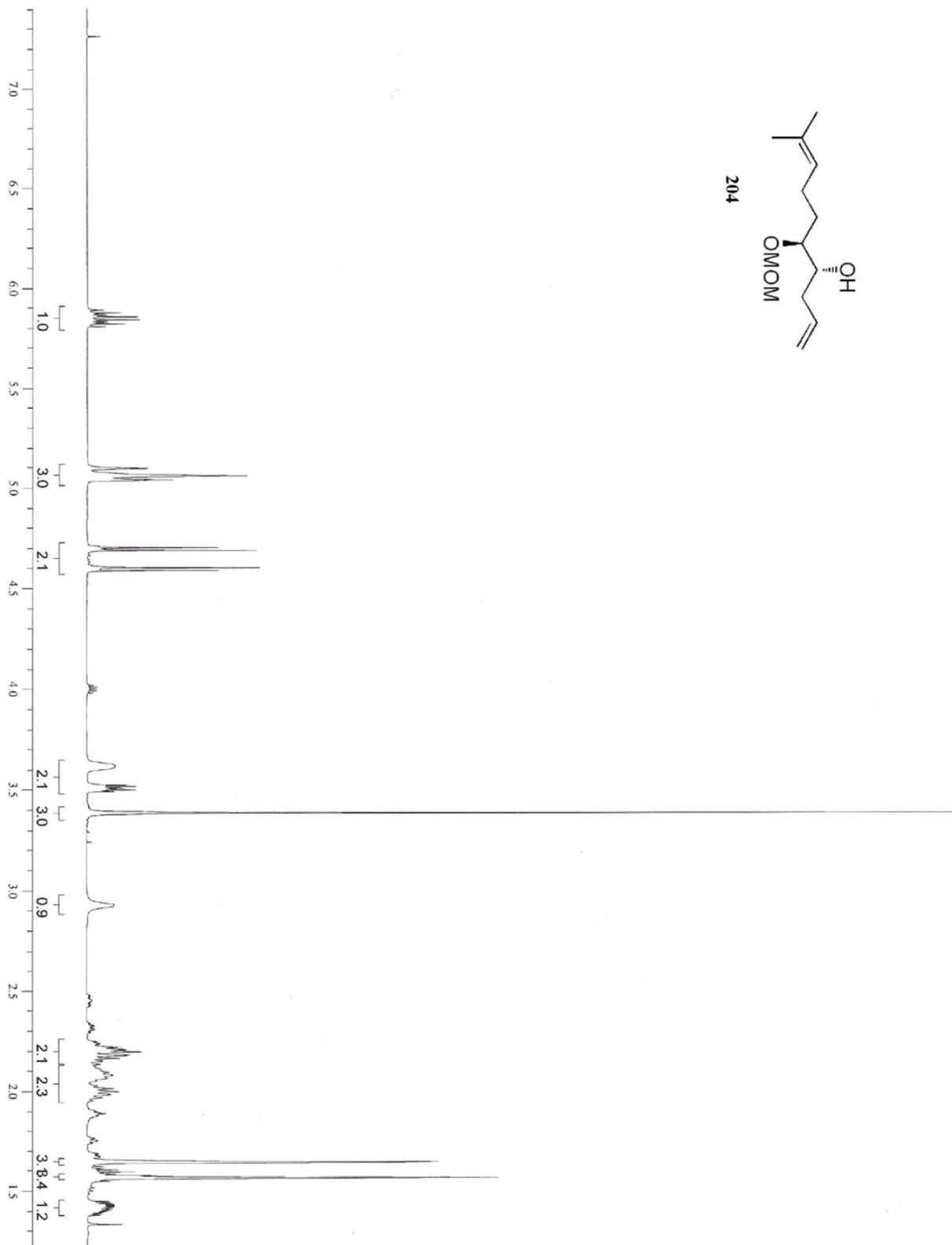
The ¹³C NMR Spectrum (125 MHz, CDCl₃) of Compound **205**



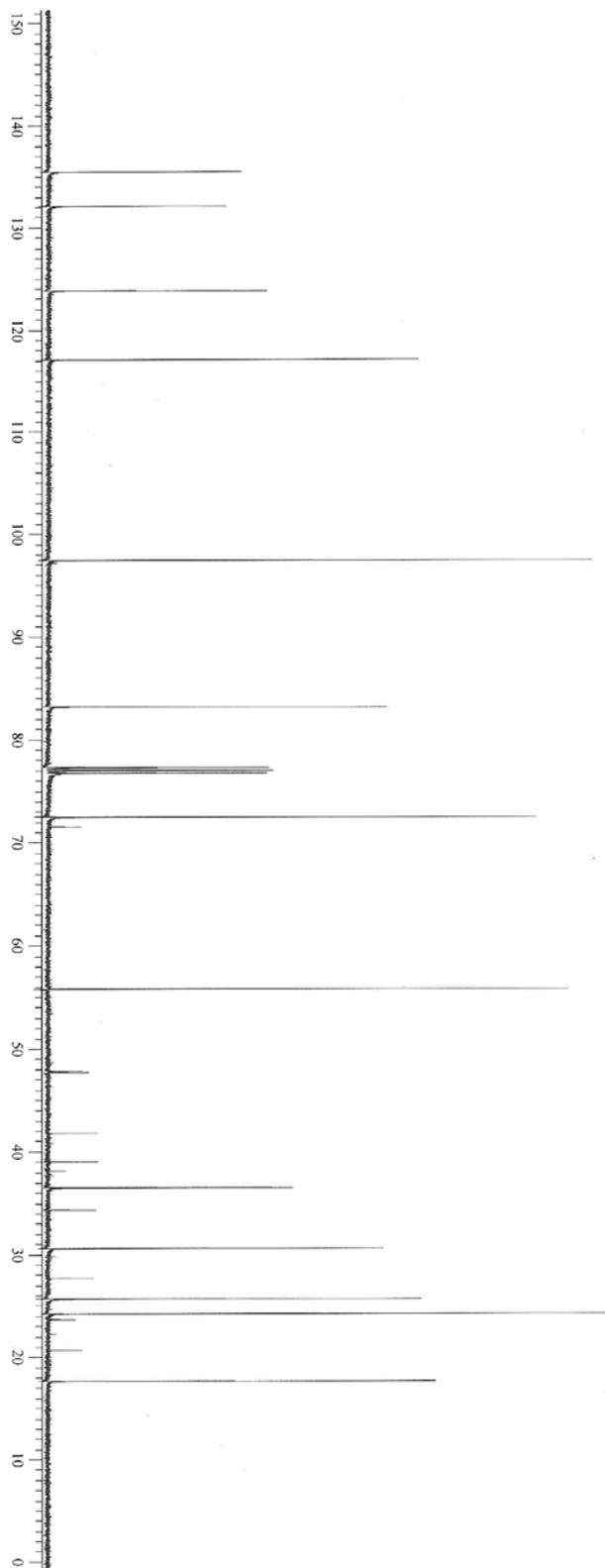
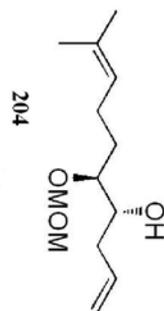
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **223**



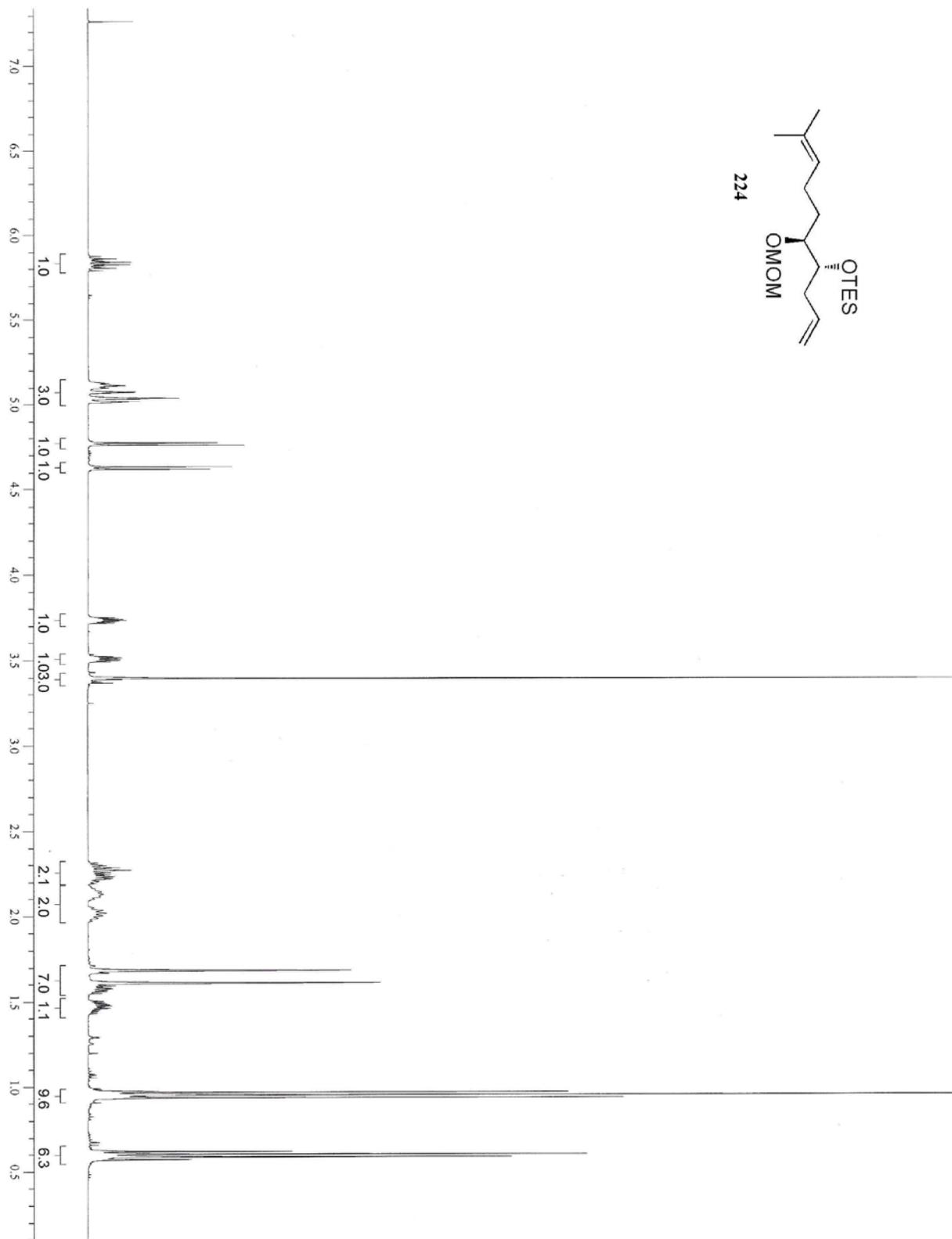
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **223**



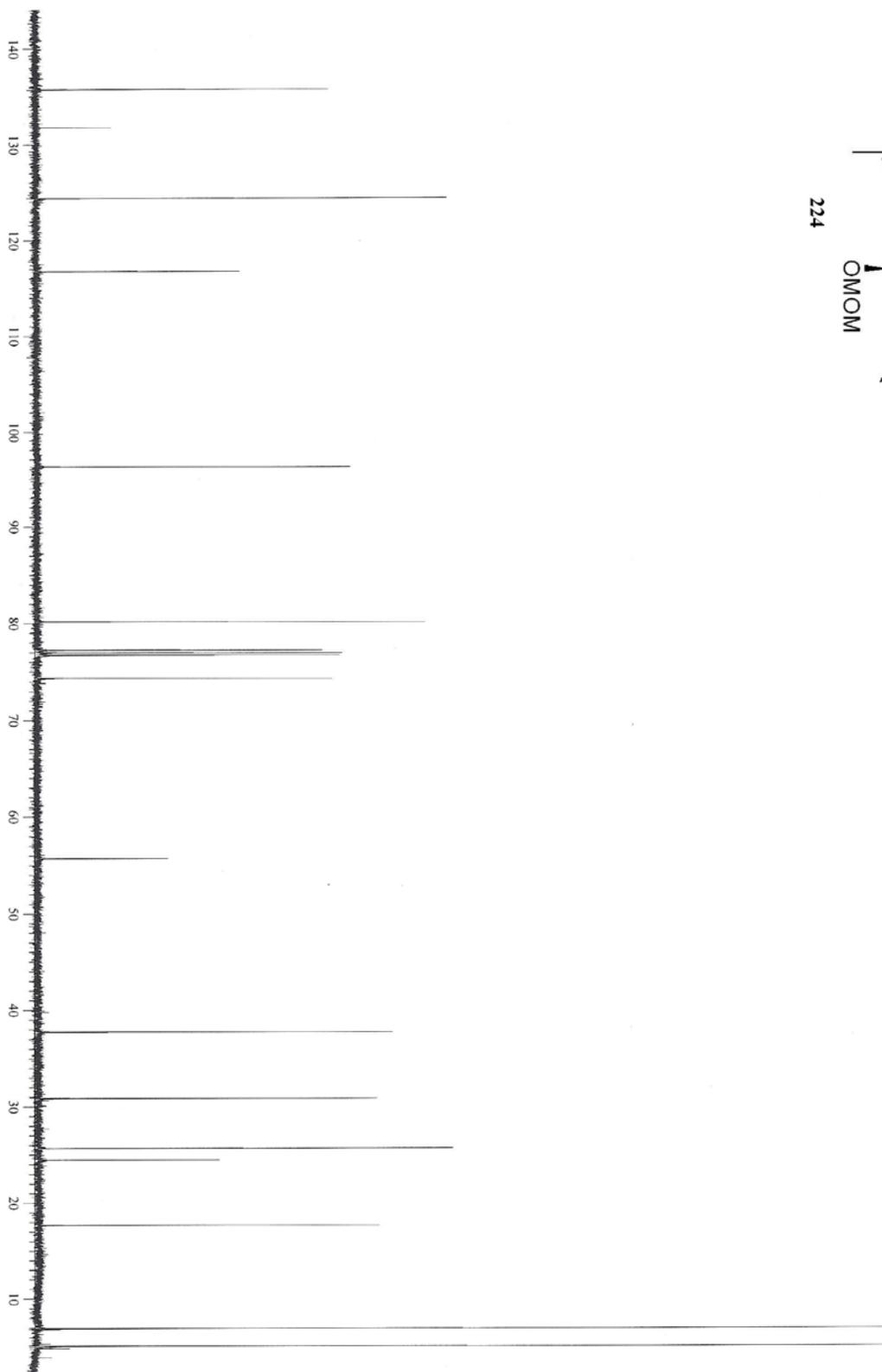
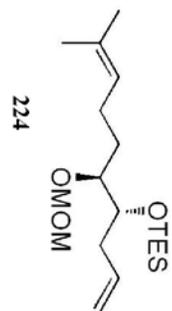
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **204**



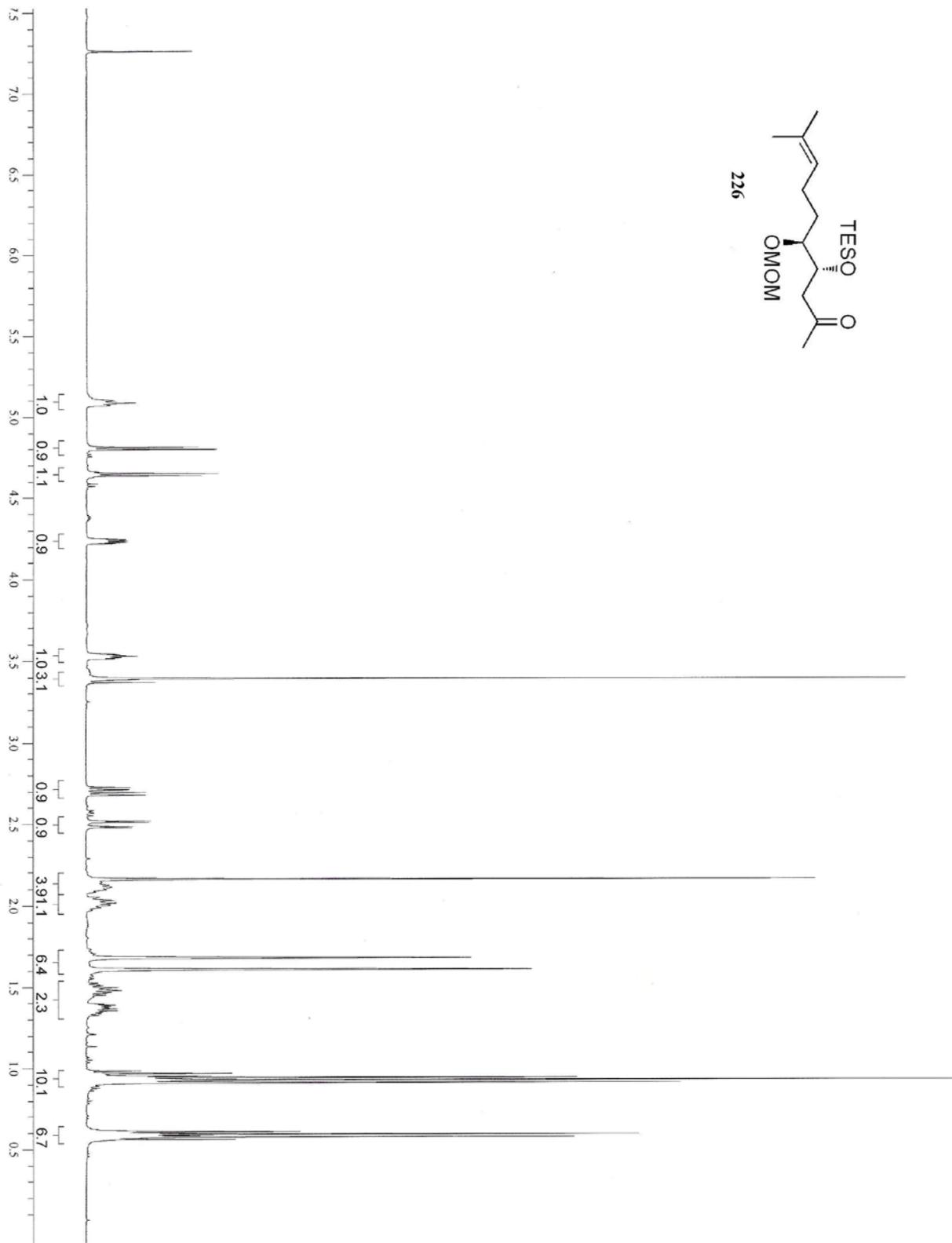
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **204**



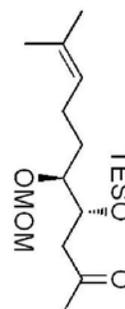
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **224**



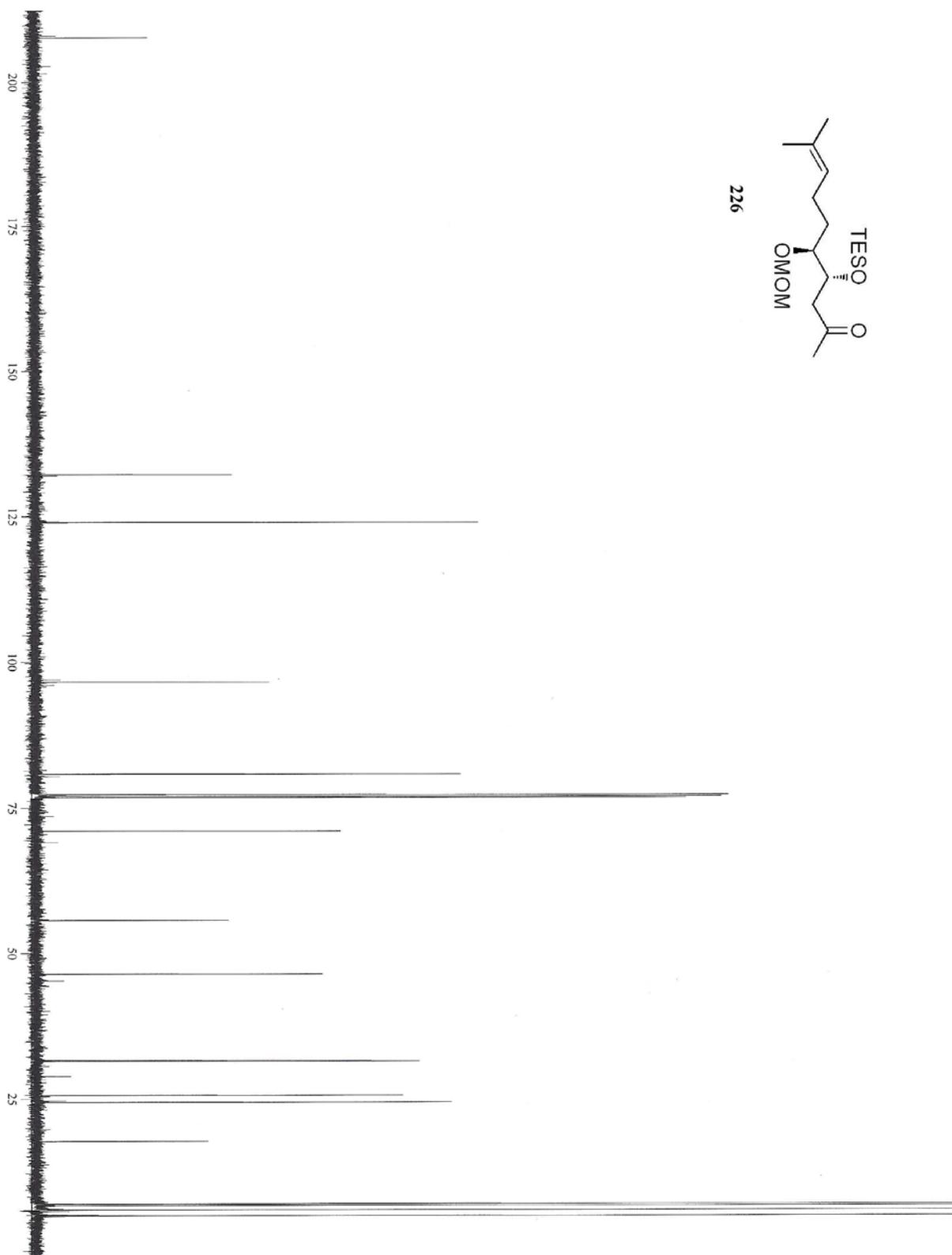
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **224**



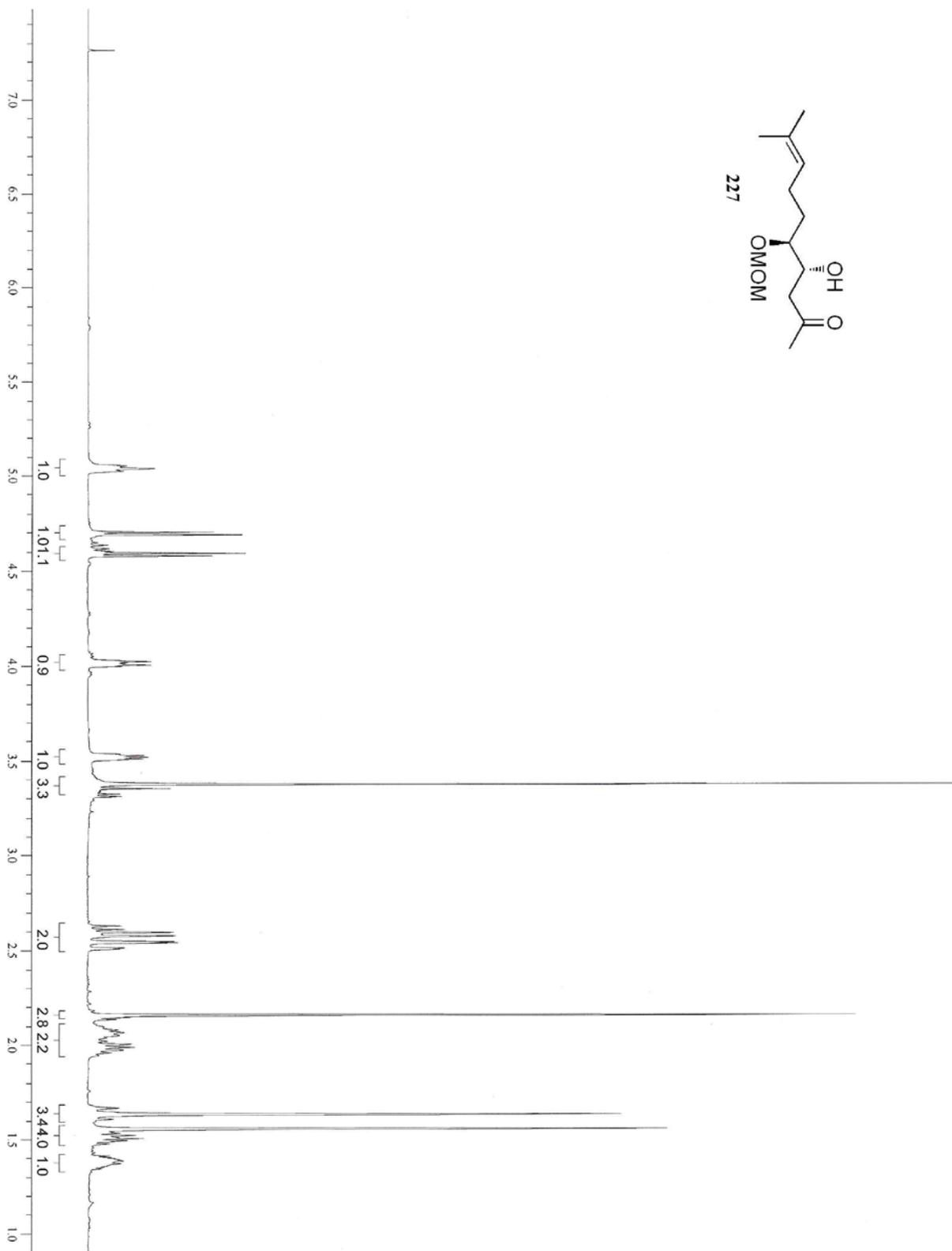
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **226**



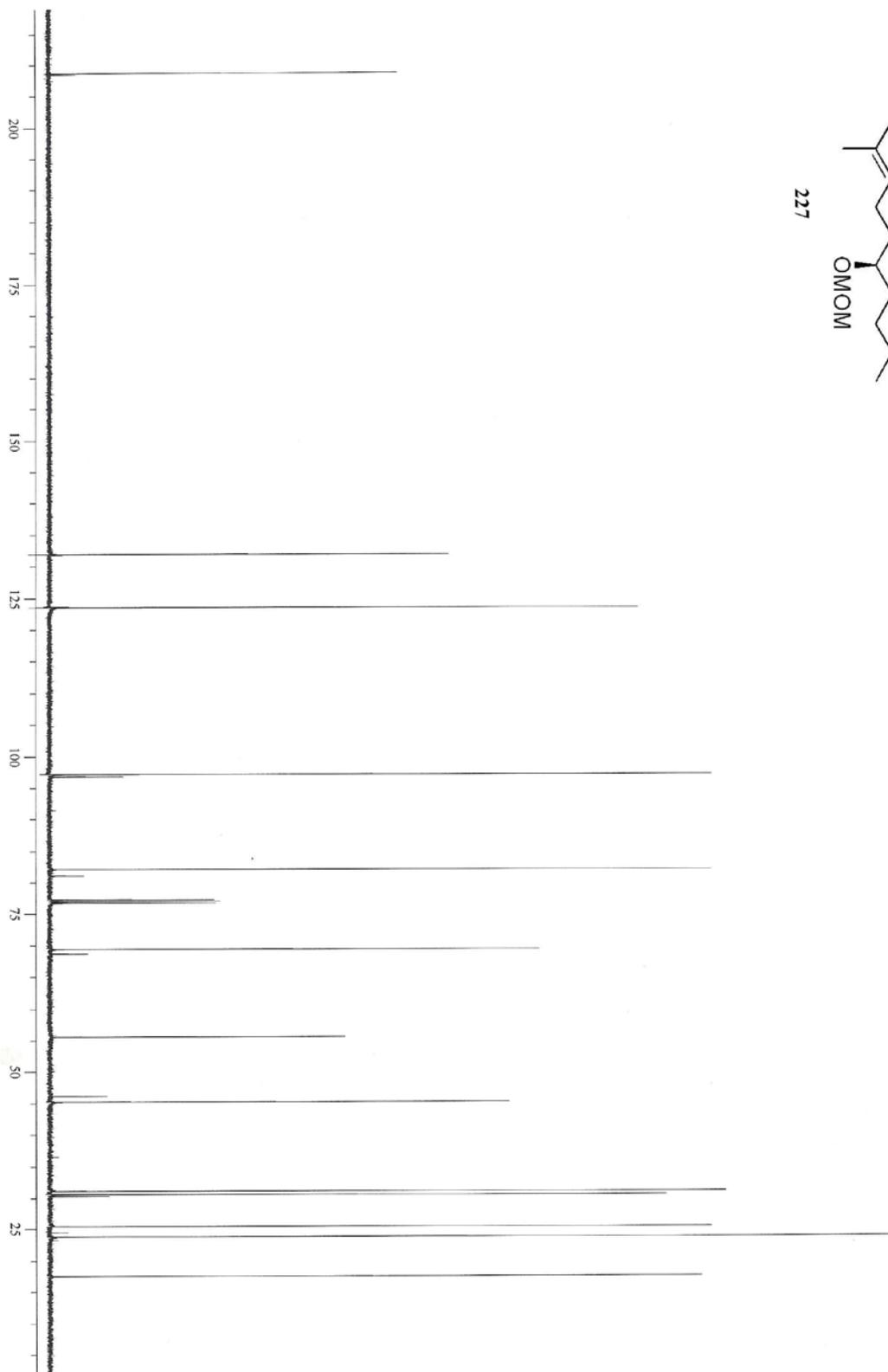
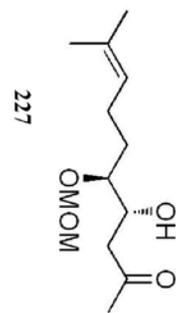
226



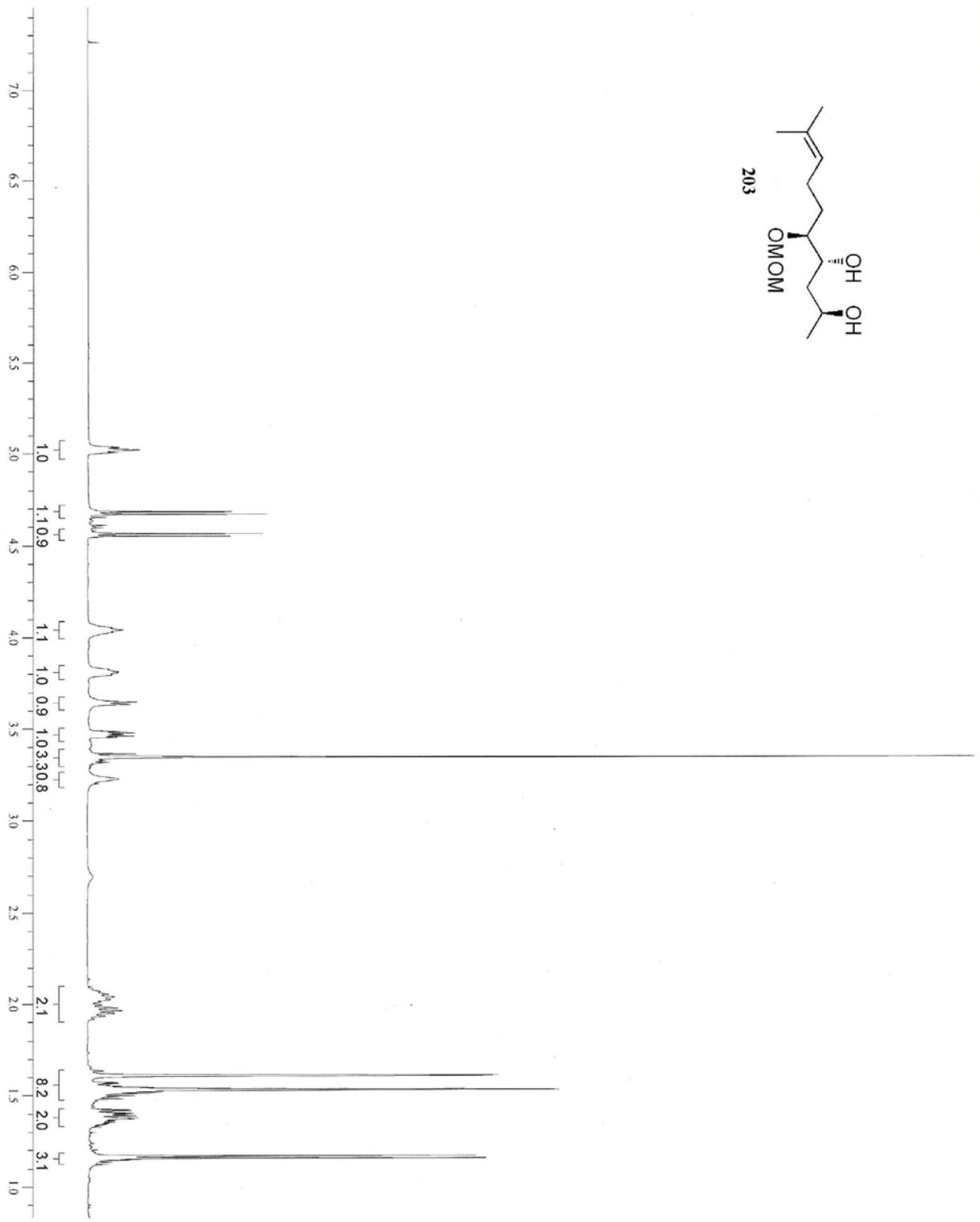
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound 226



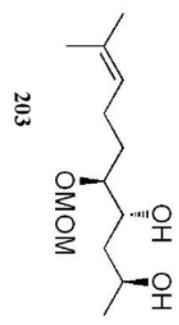
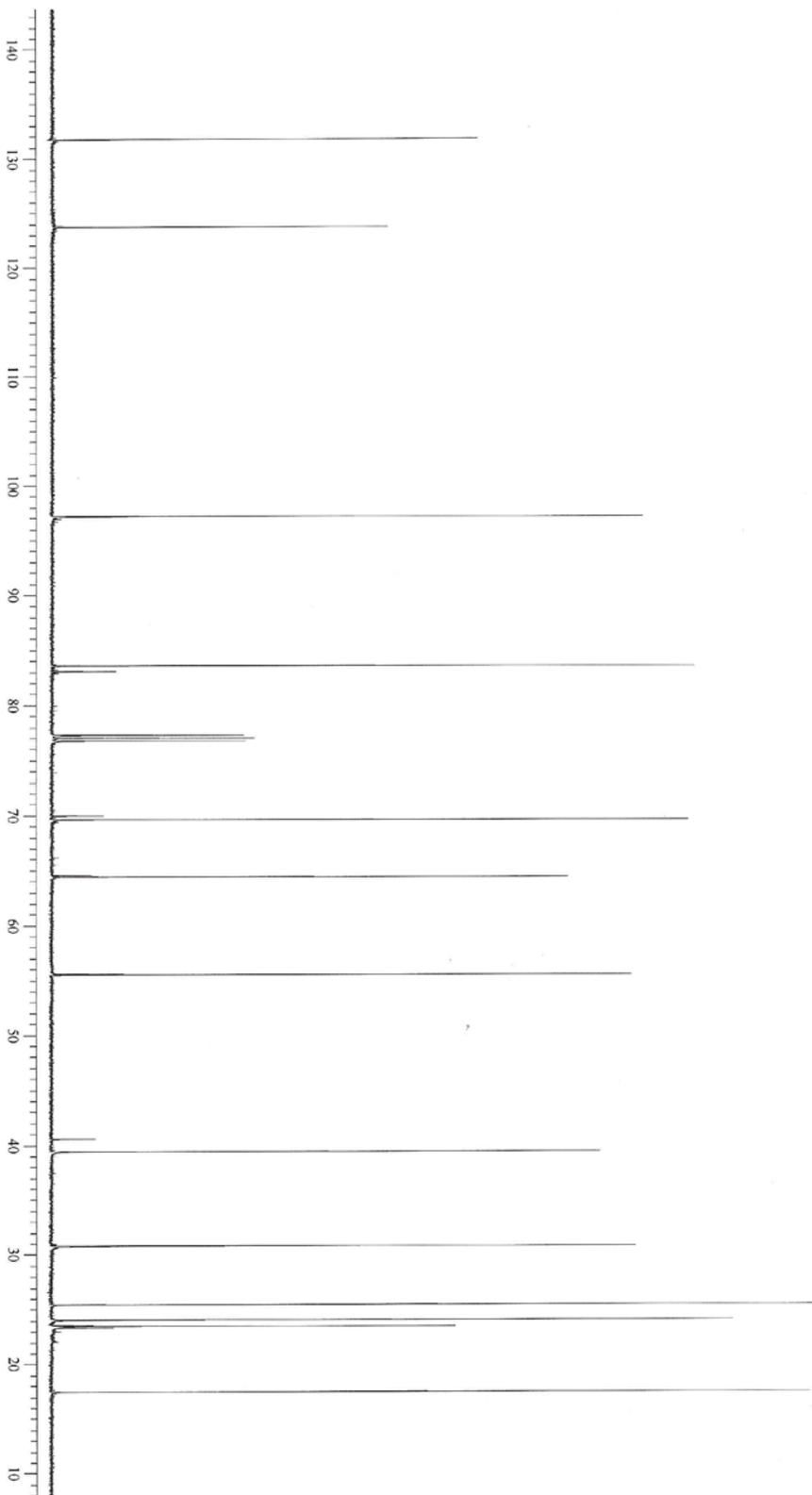
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **227**



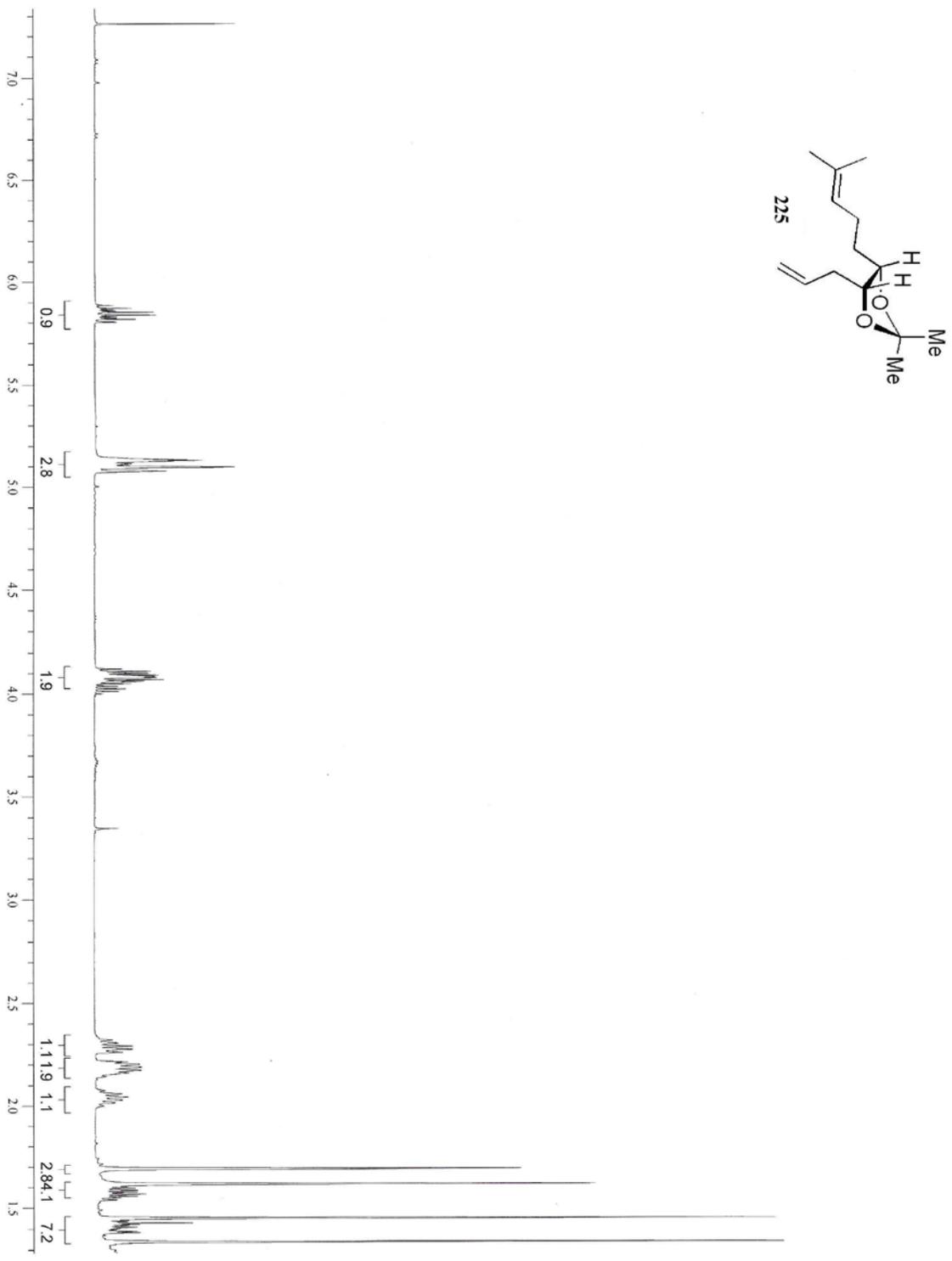
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **227**



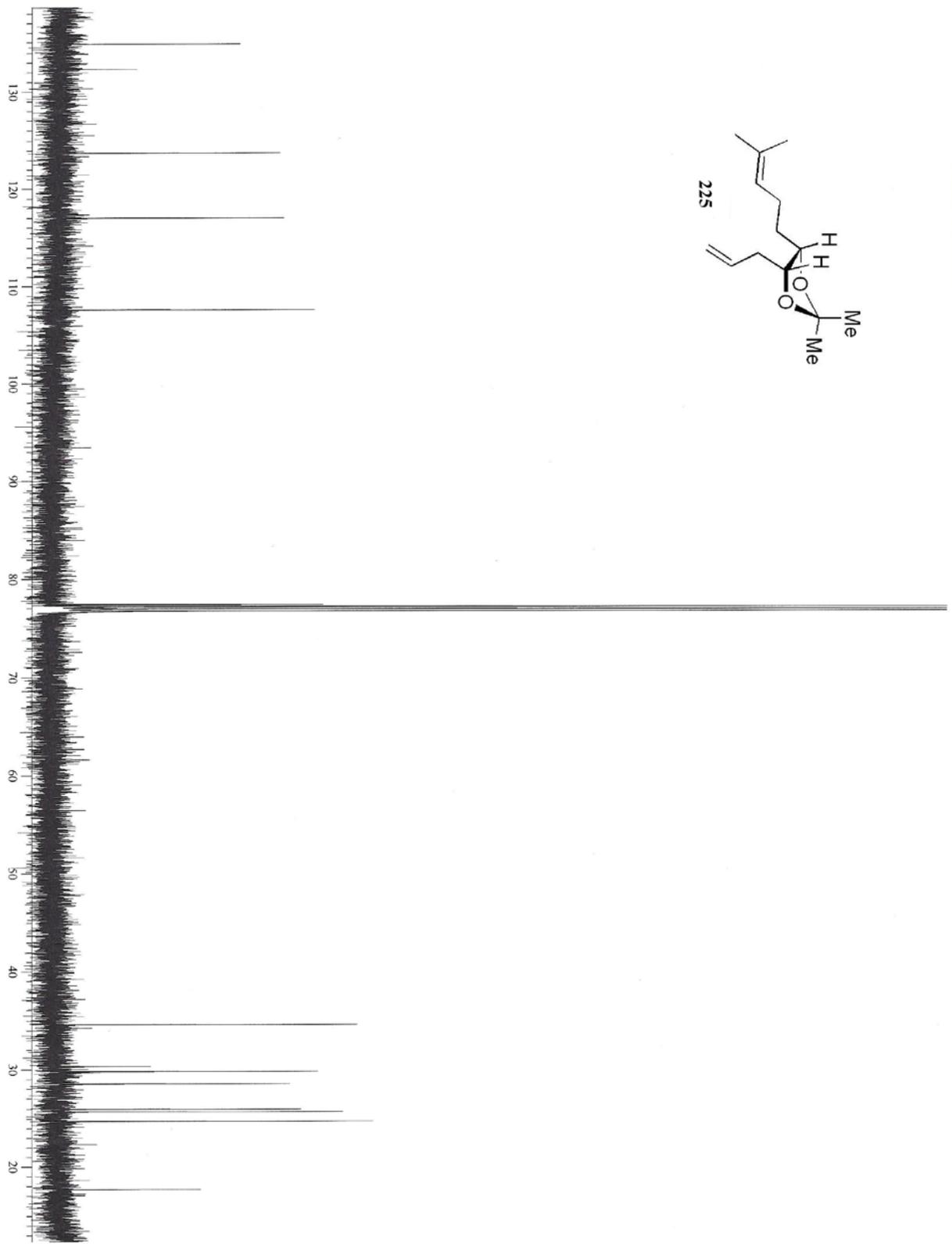
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **203**



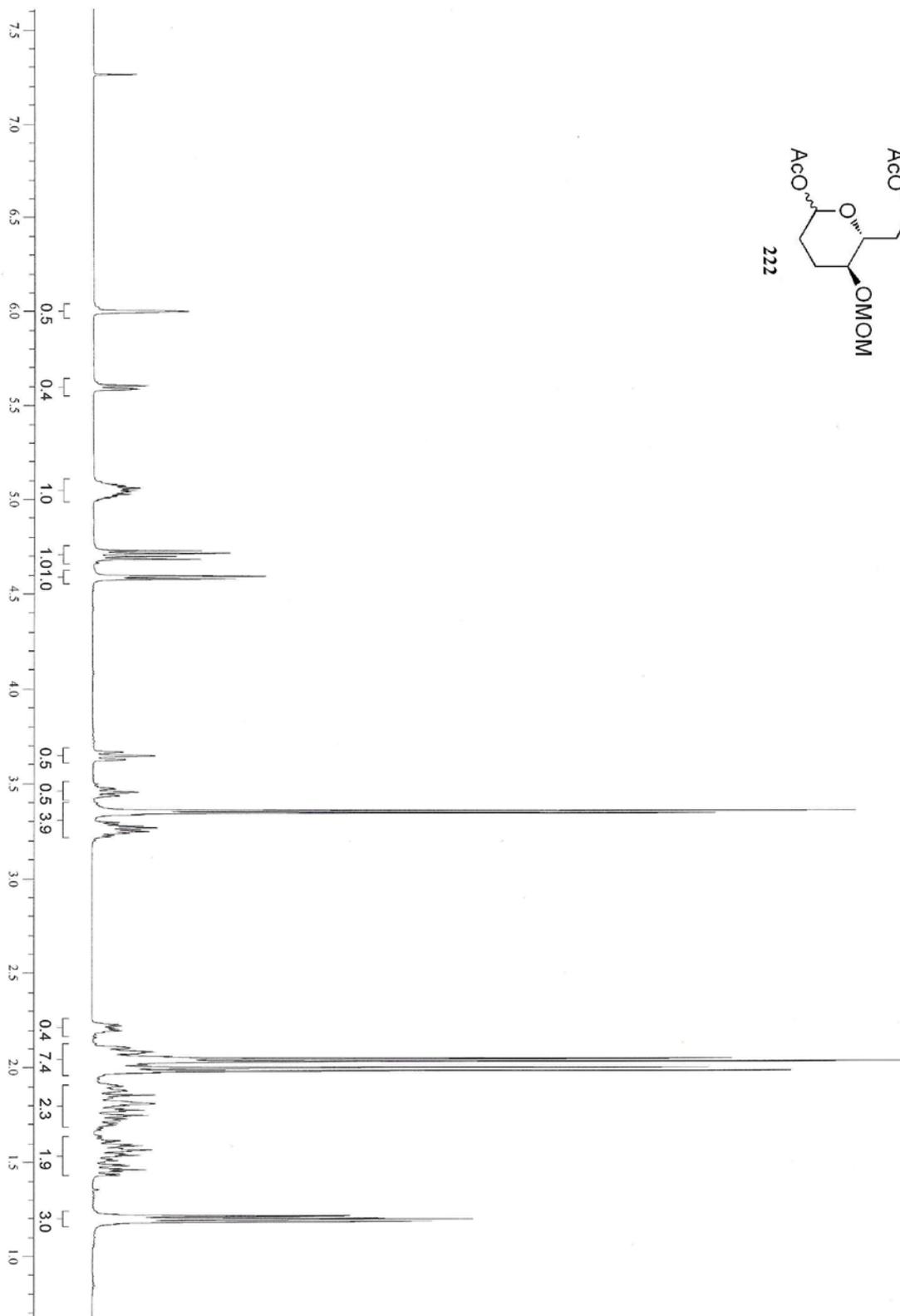
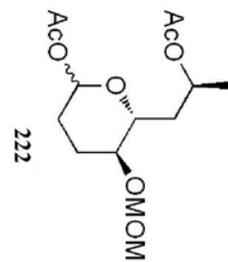
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **203**



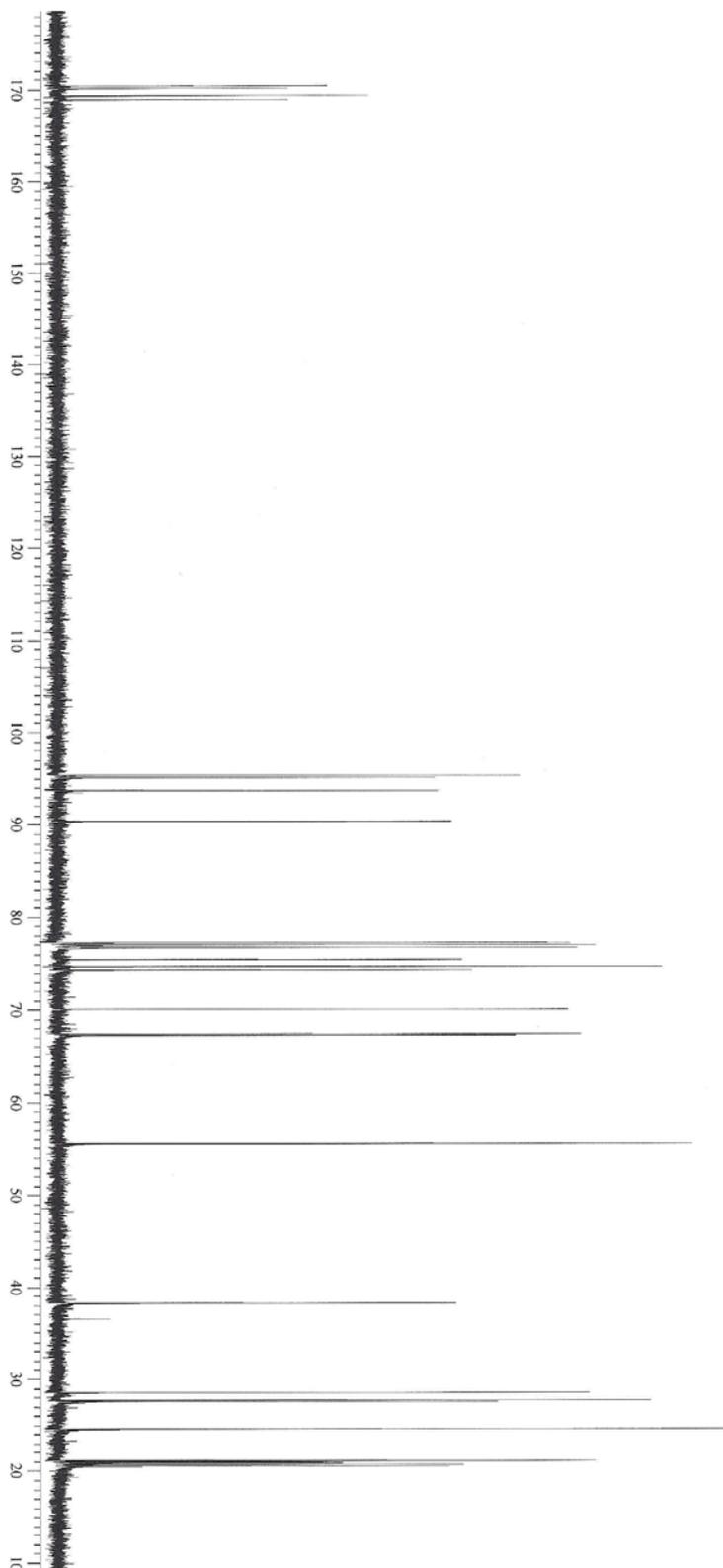
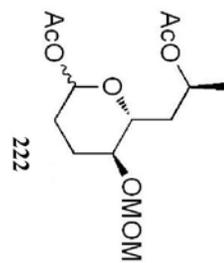
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **225**



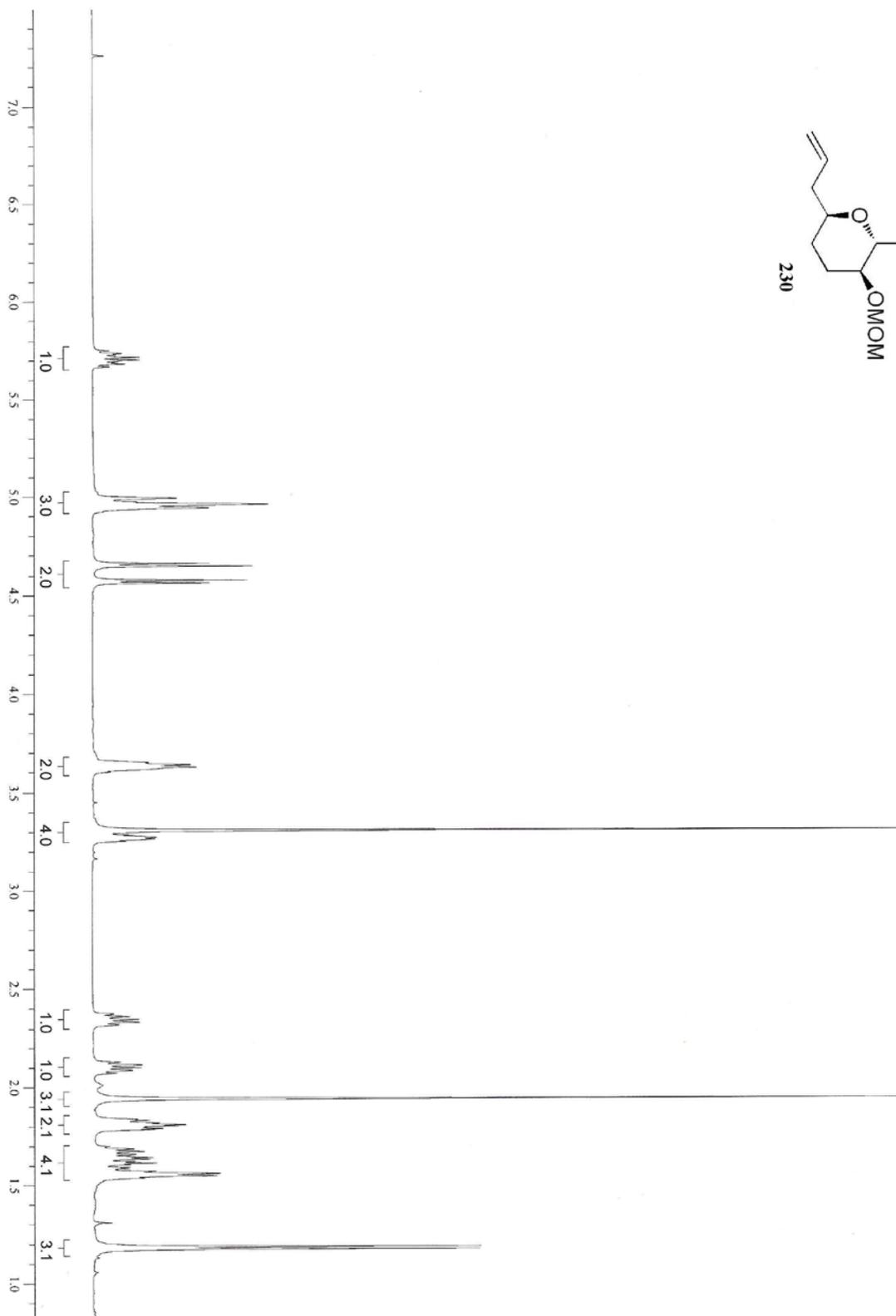
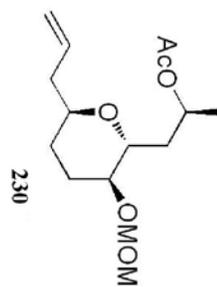
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **225**



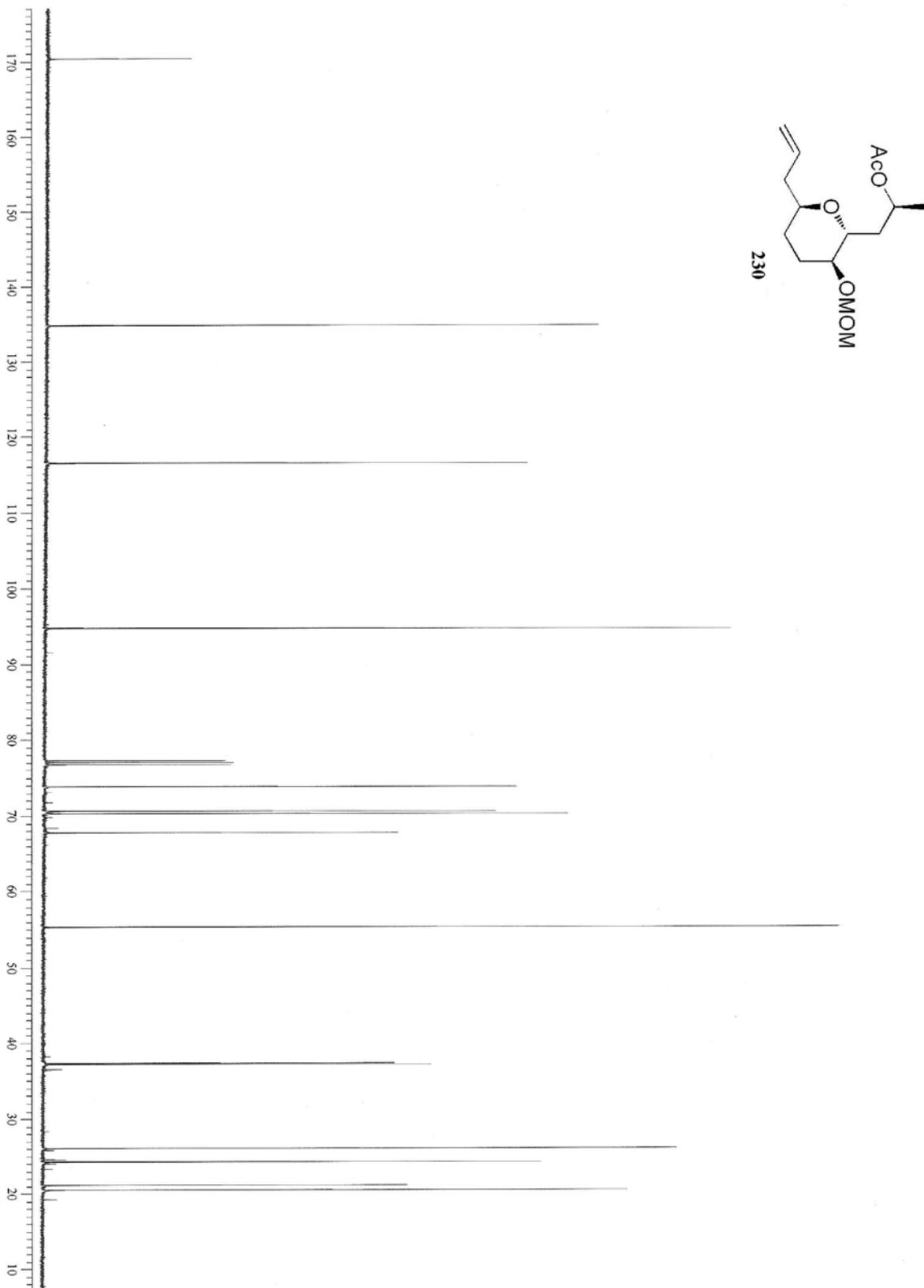
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **222**



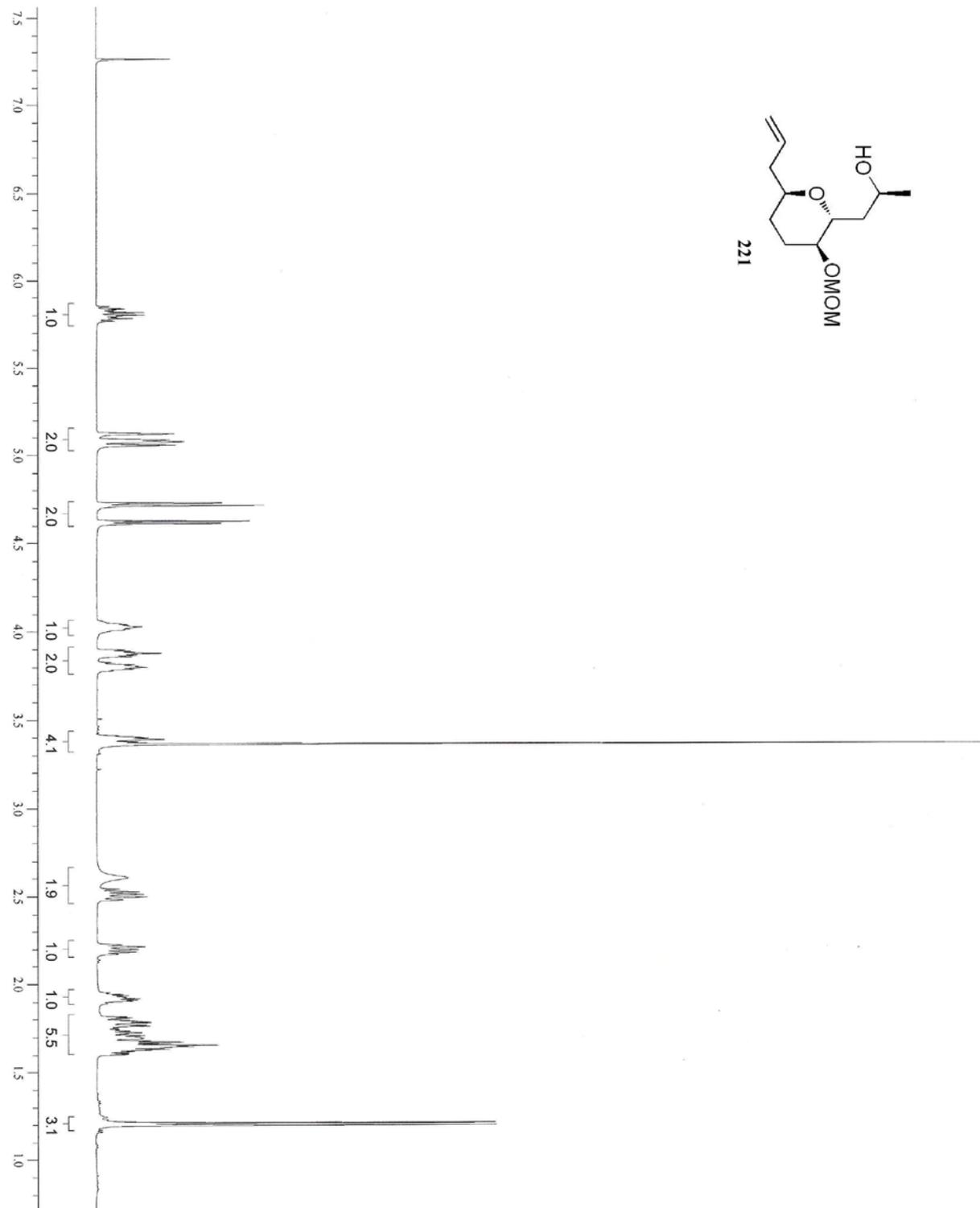
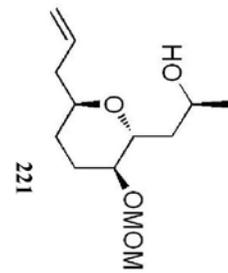
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **222**



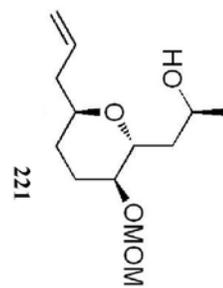
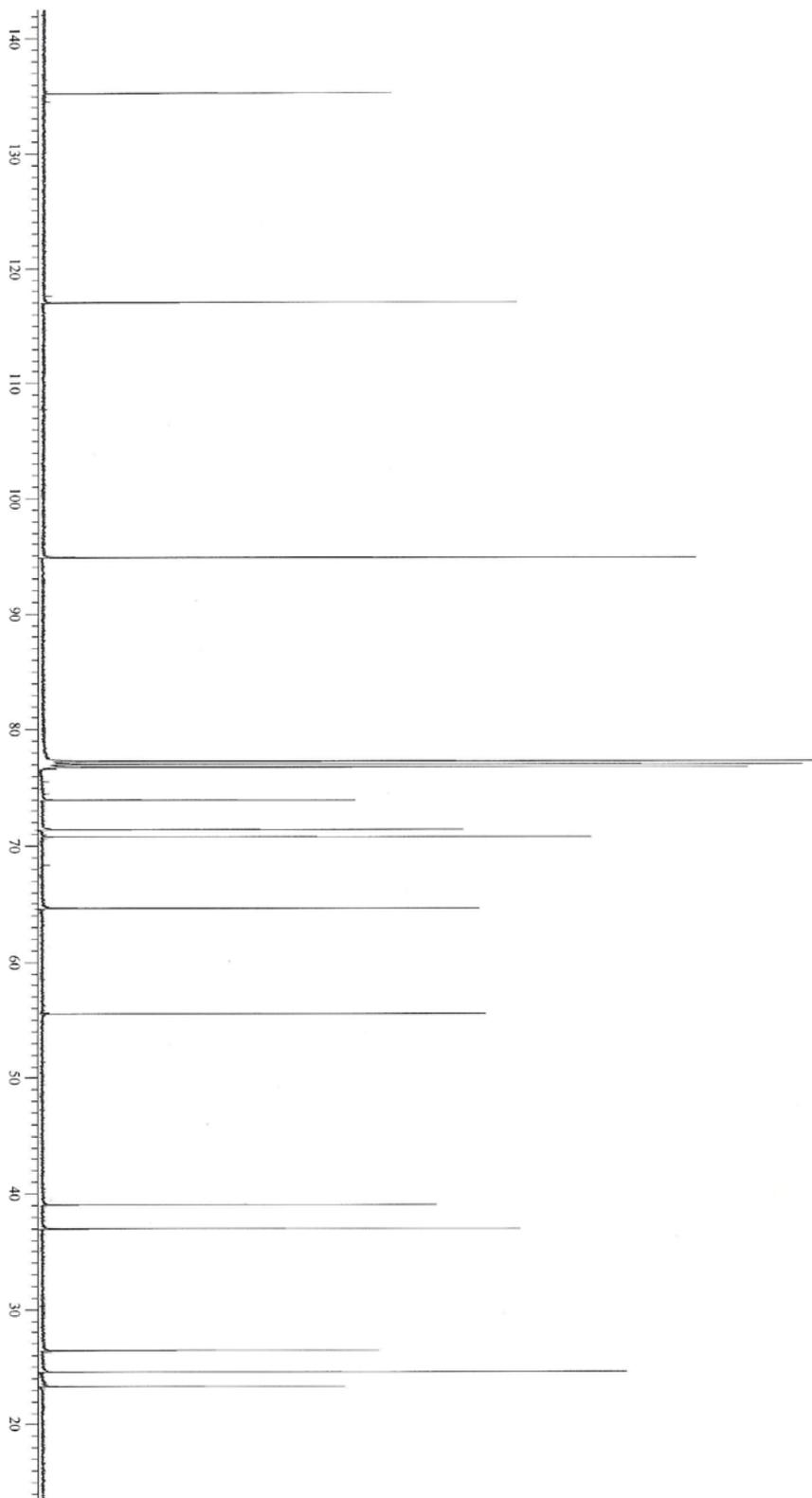
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **230**



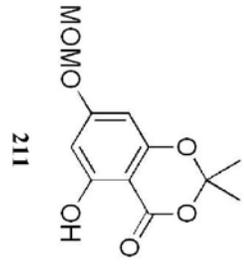
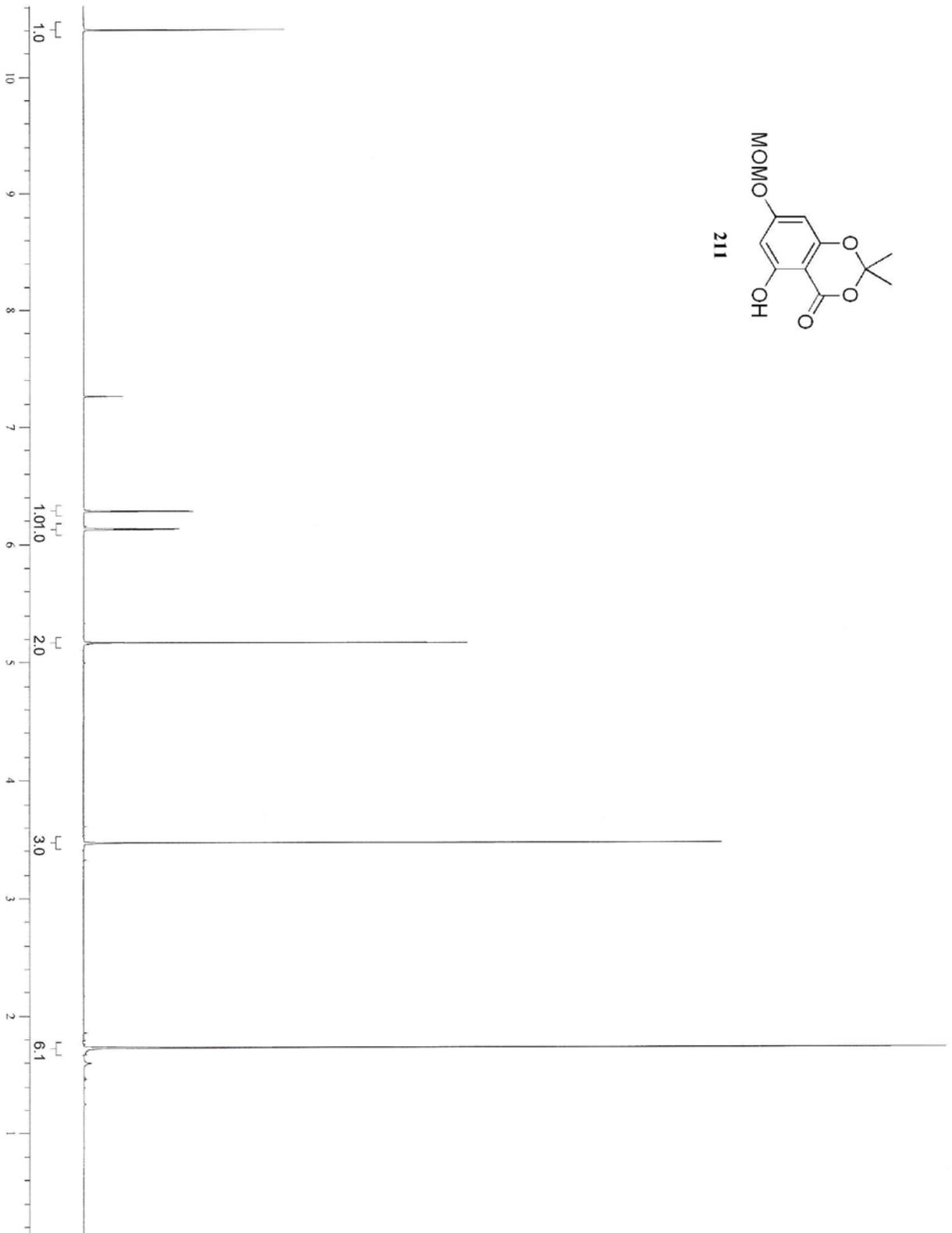
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **230**



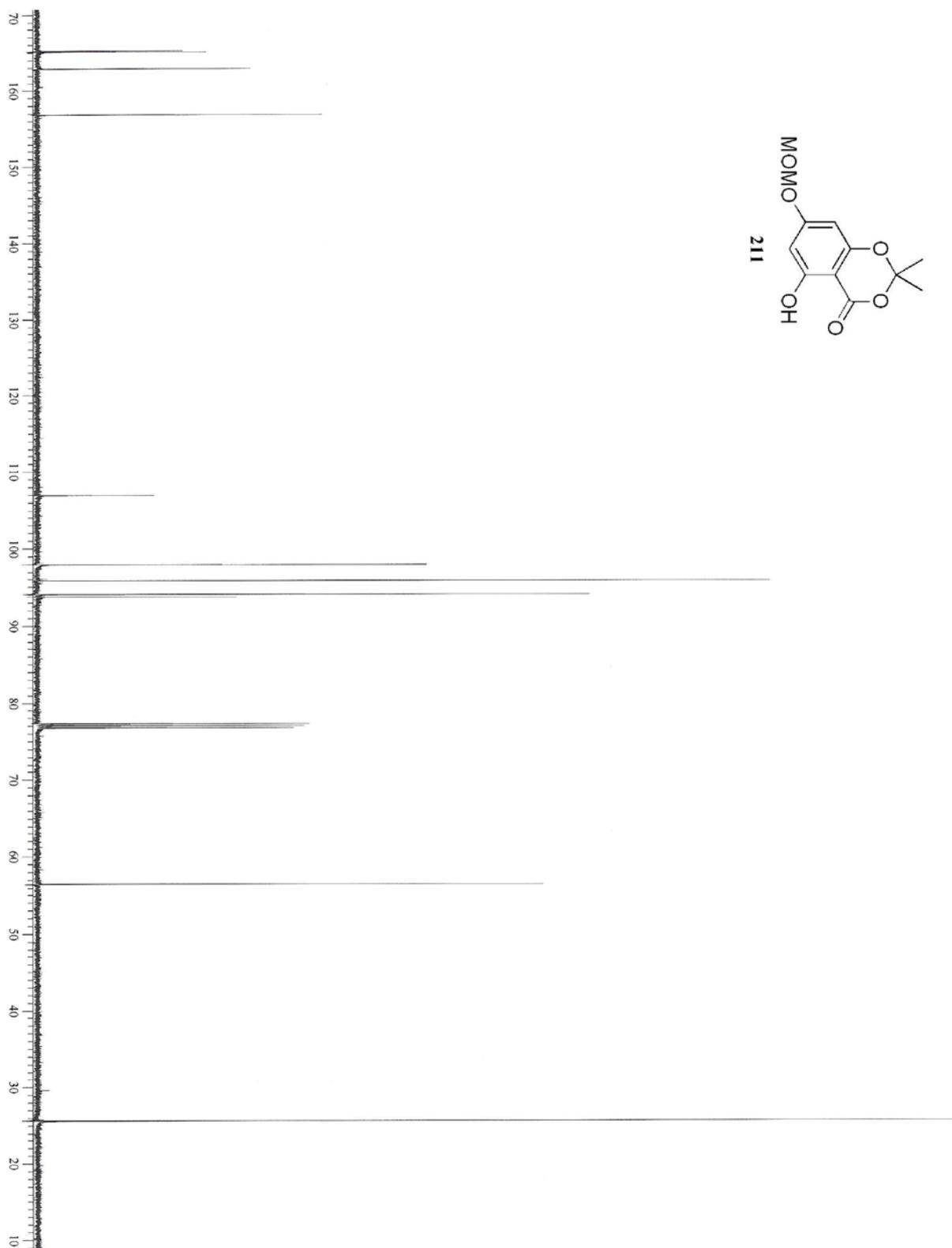
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **221**



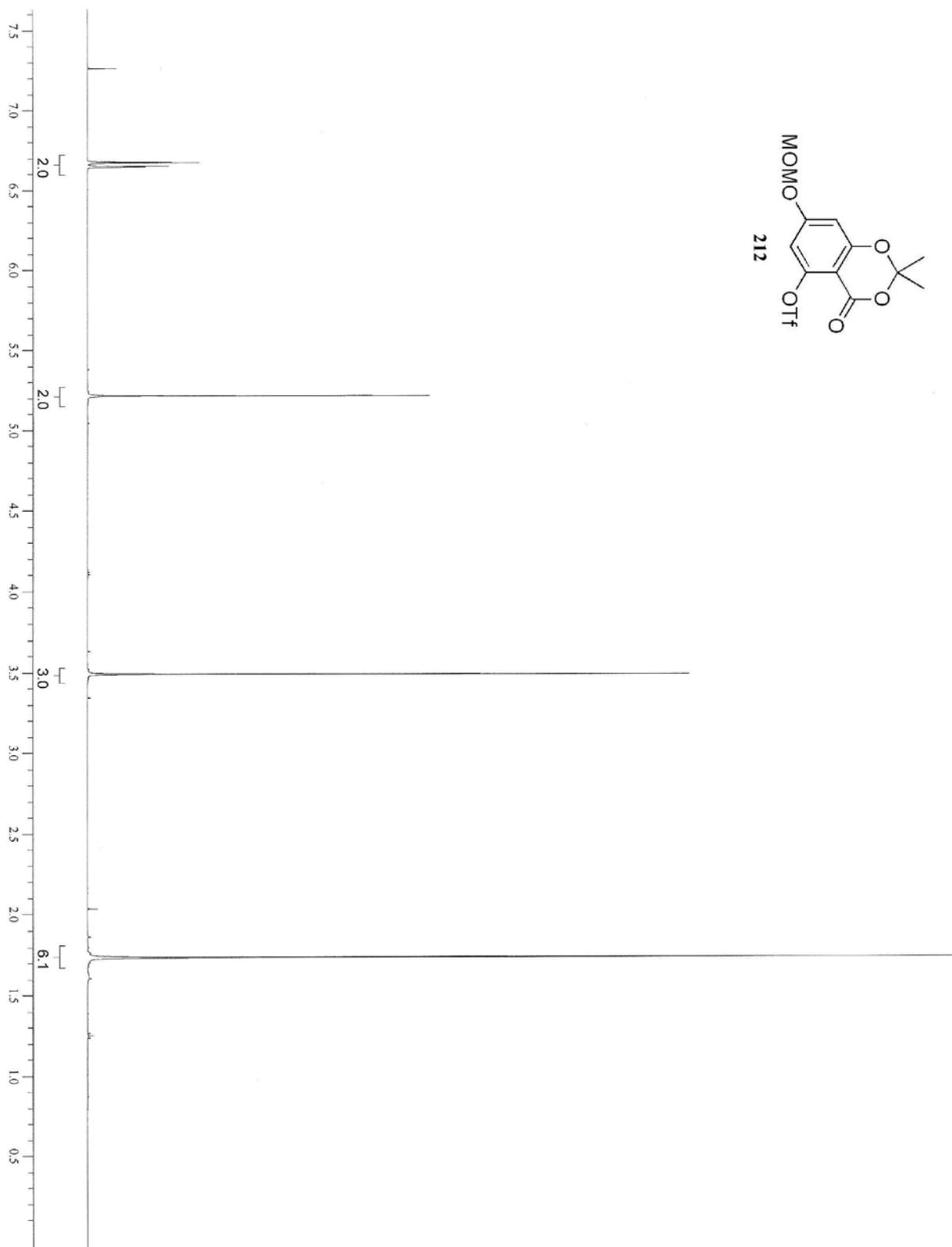
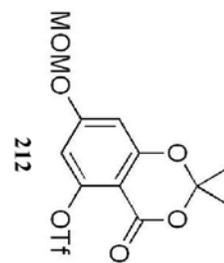
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **221**



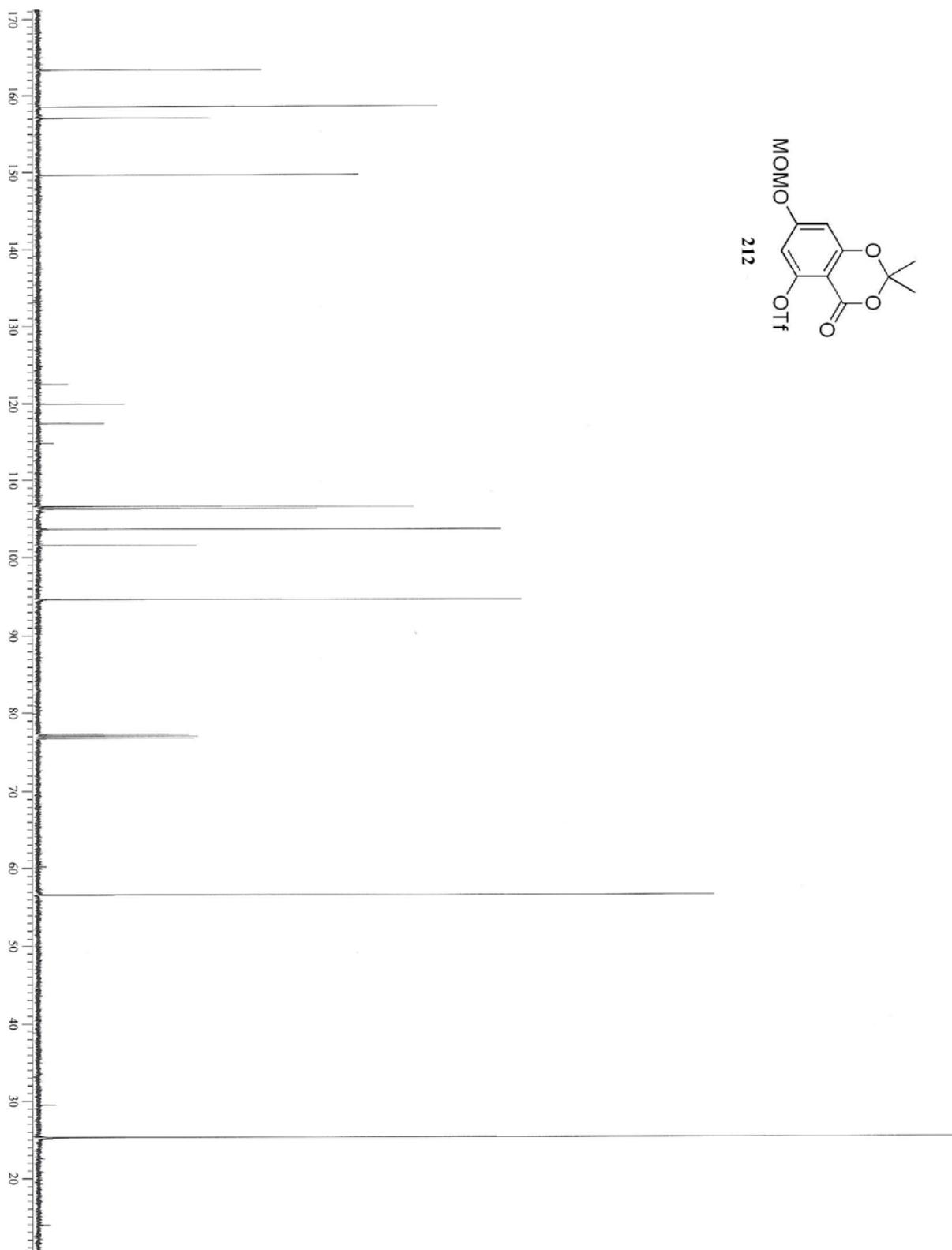
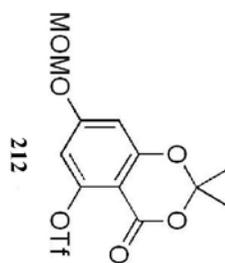
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **211**



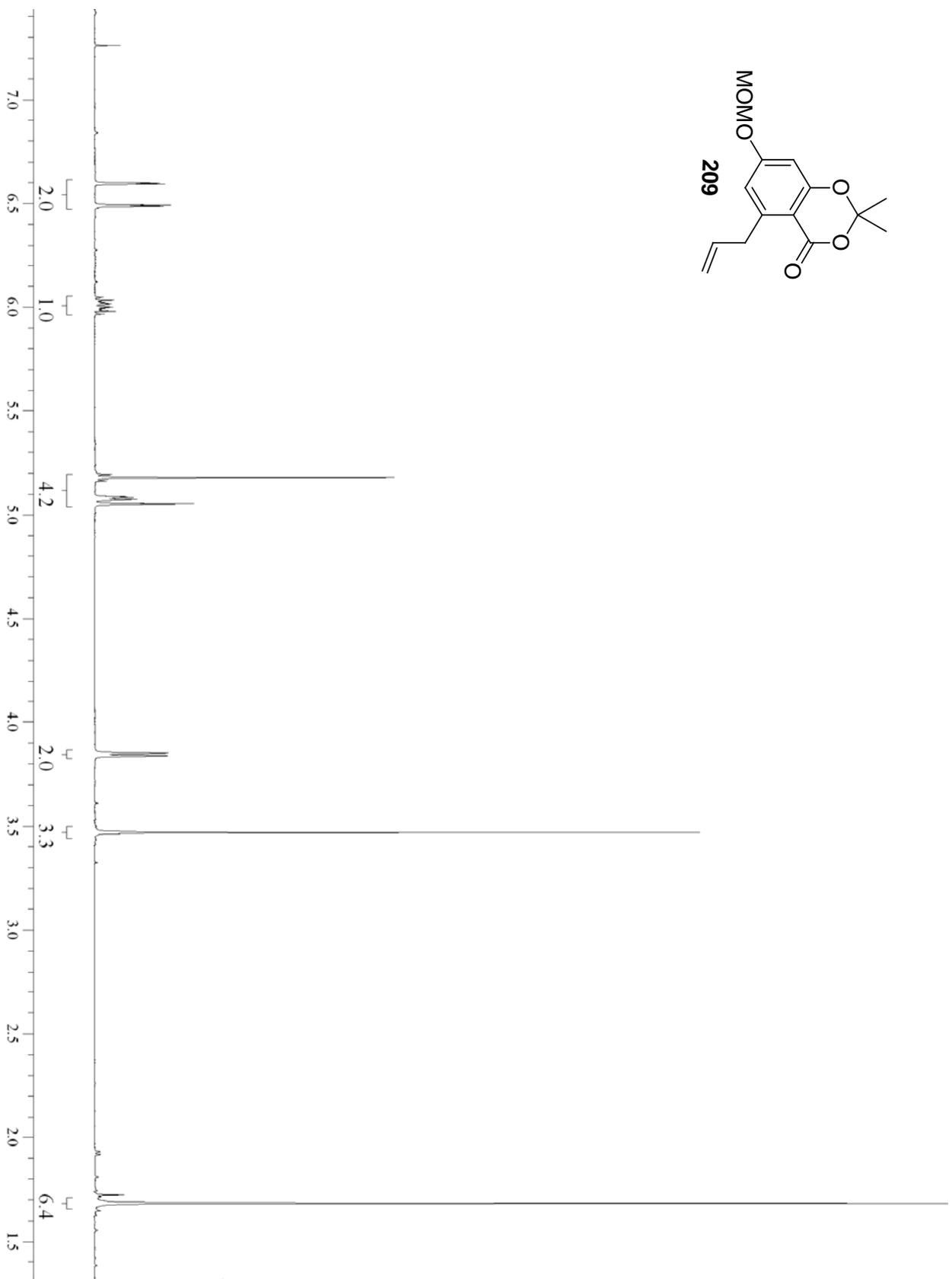
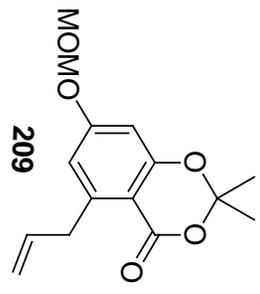
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **211**



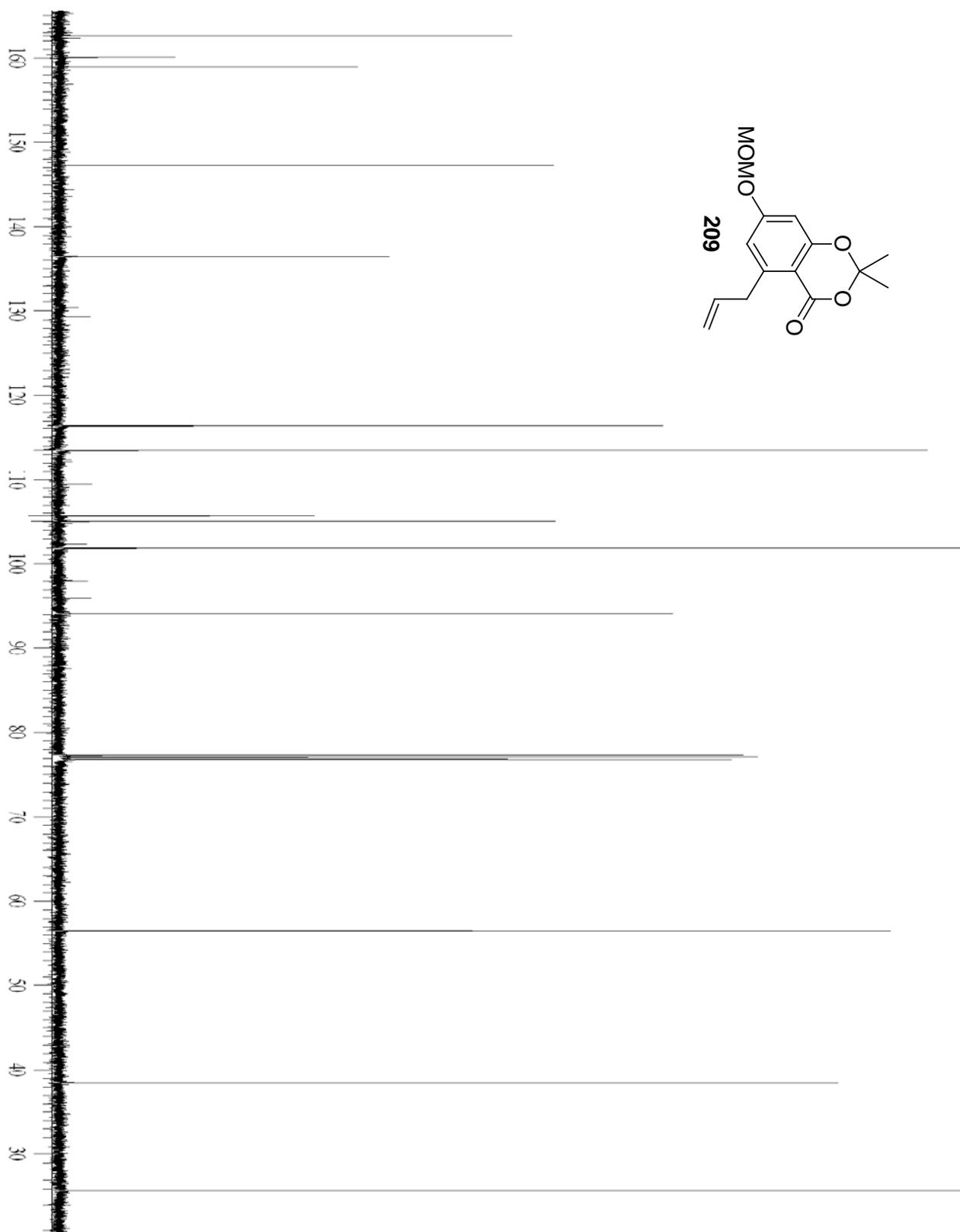
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **212**



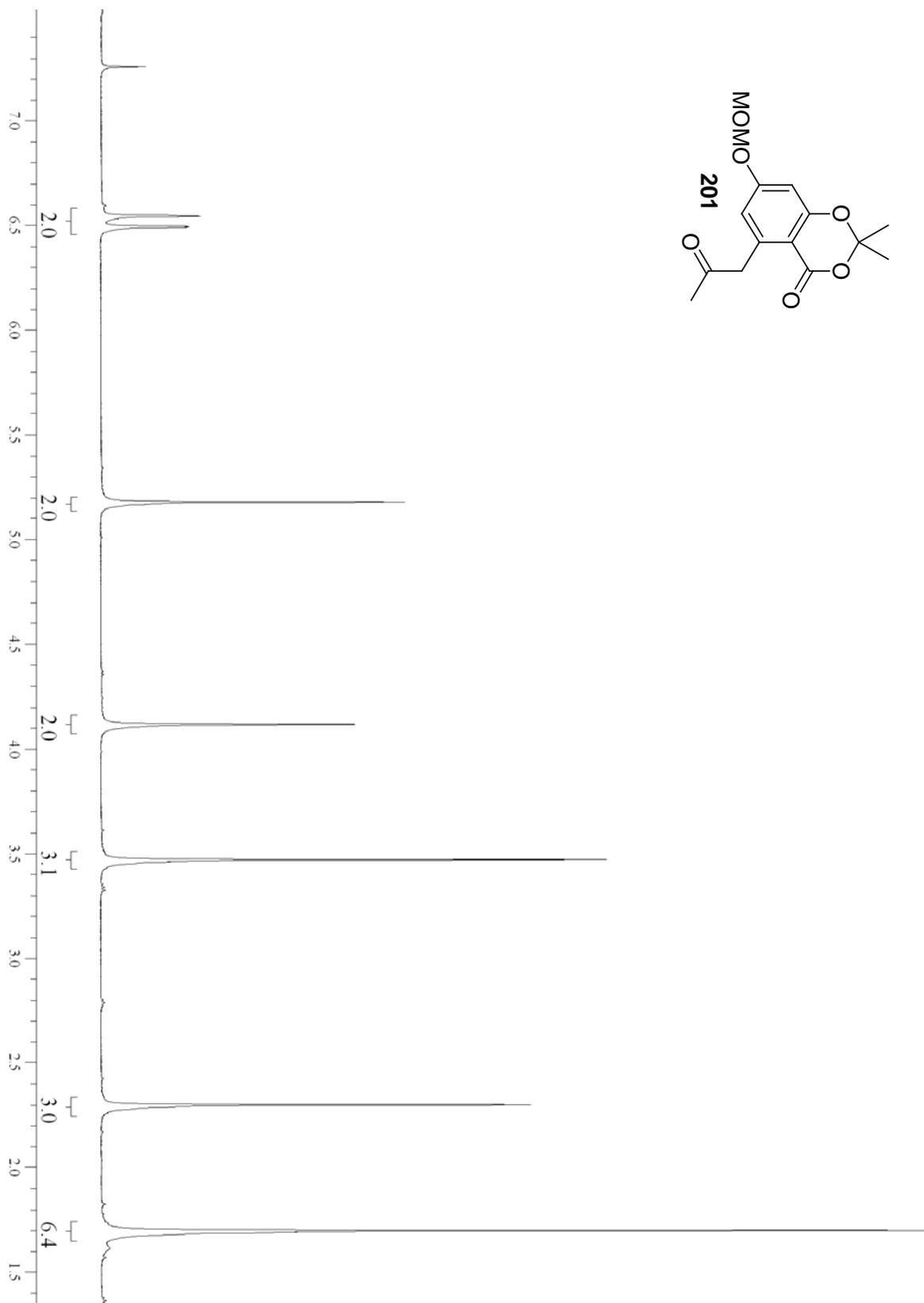
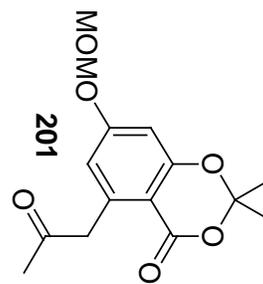
The ¹³C NMR Spectrum (125 MHz, CDCl₃) of Compound **212**



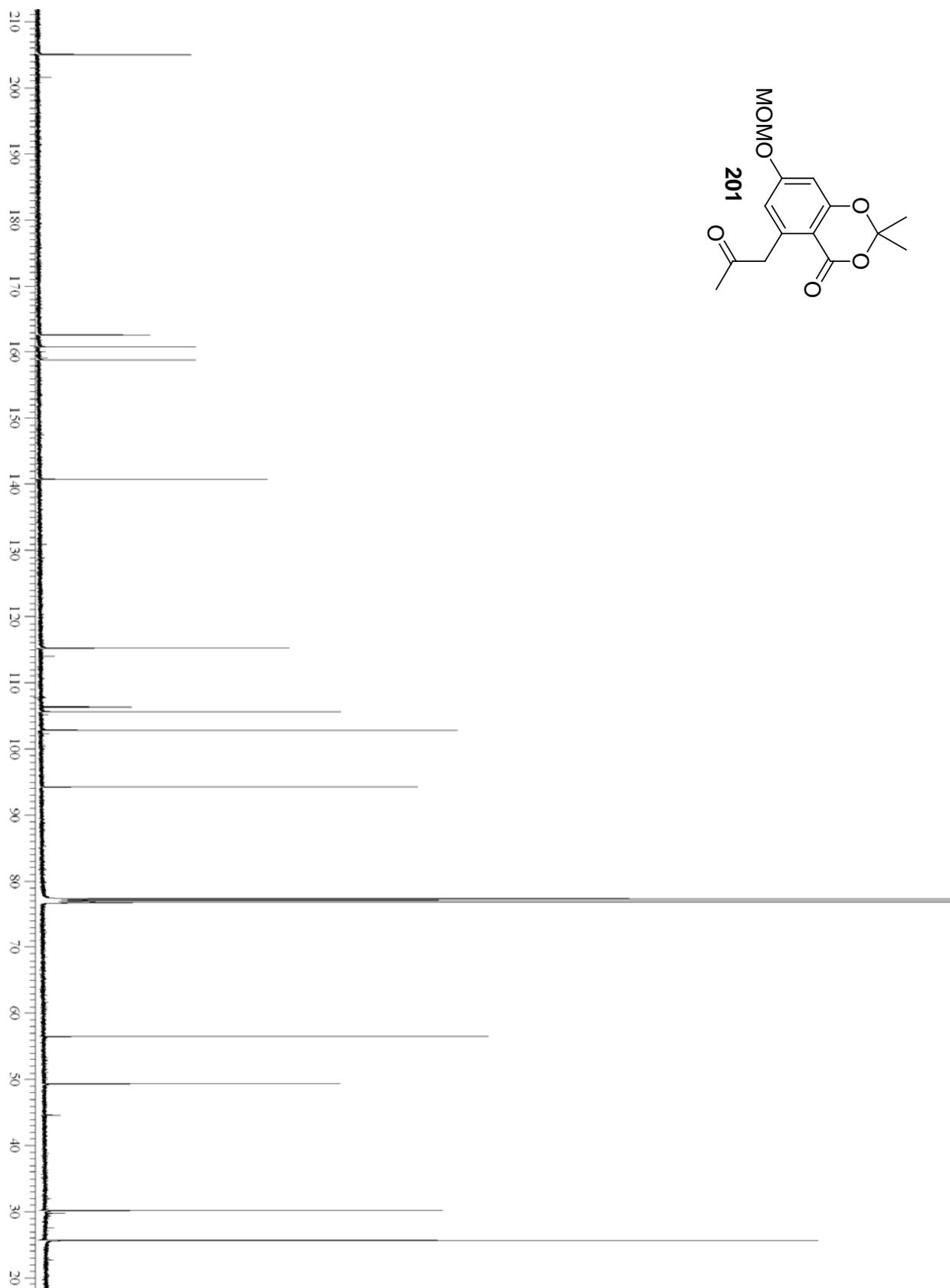
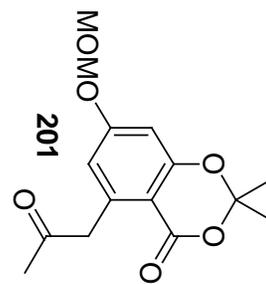
The ¹H NMR Spectrum (500 MHz, CDCl₃) of Compound **209**



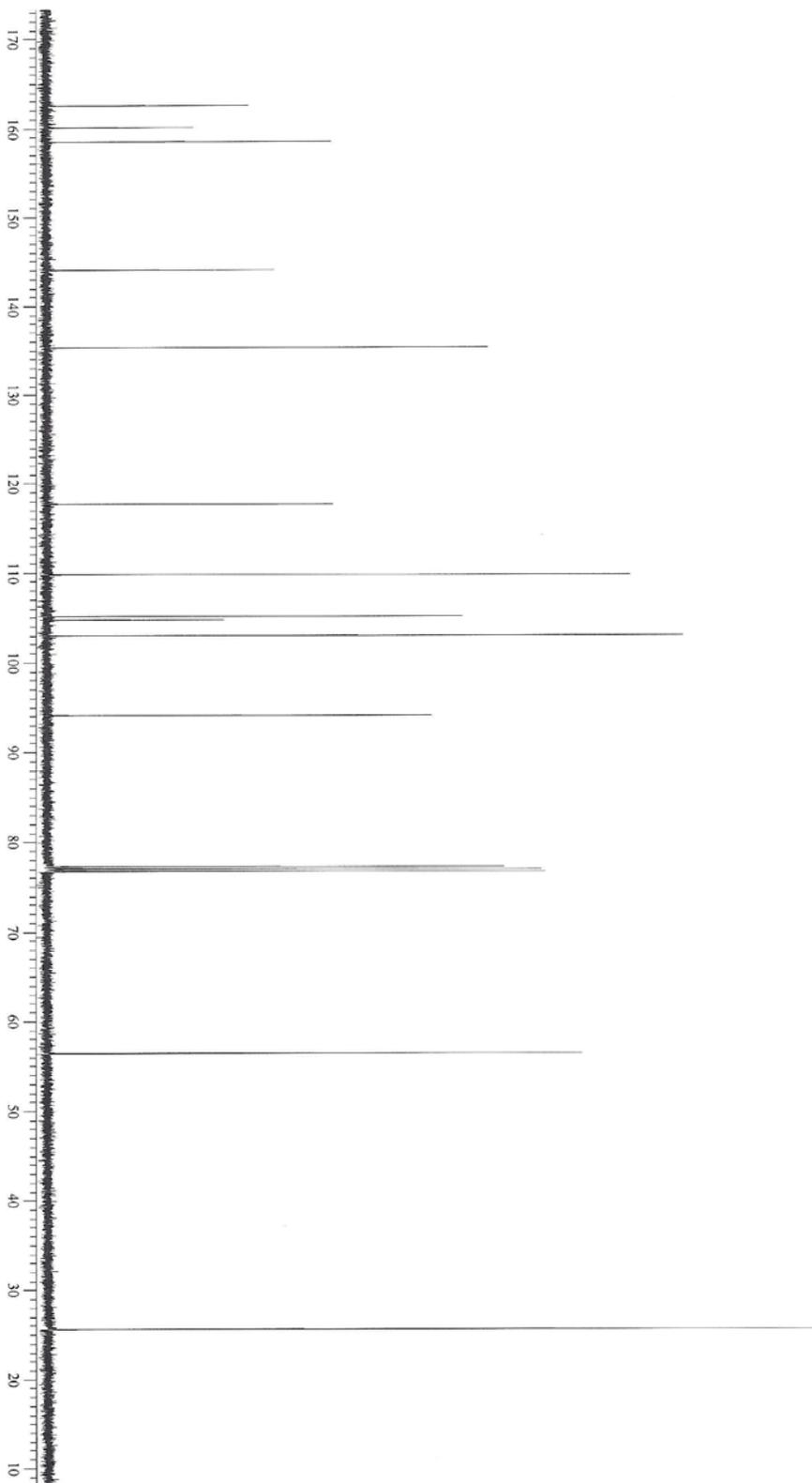
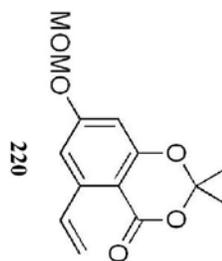
The ^{13}C NMR Spectrum (125 MHz, CDCl₃) of Compound **209**



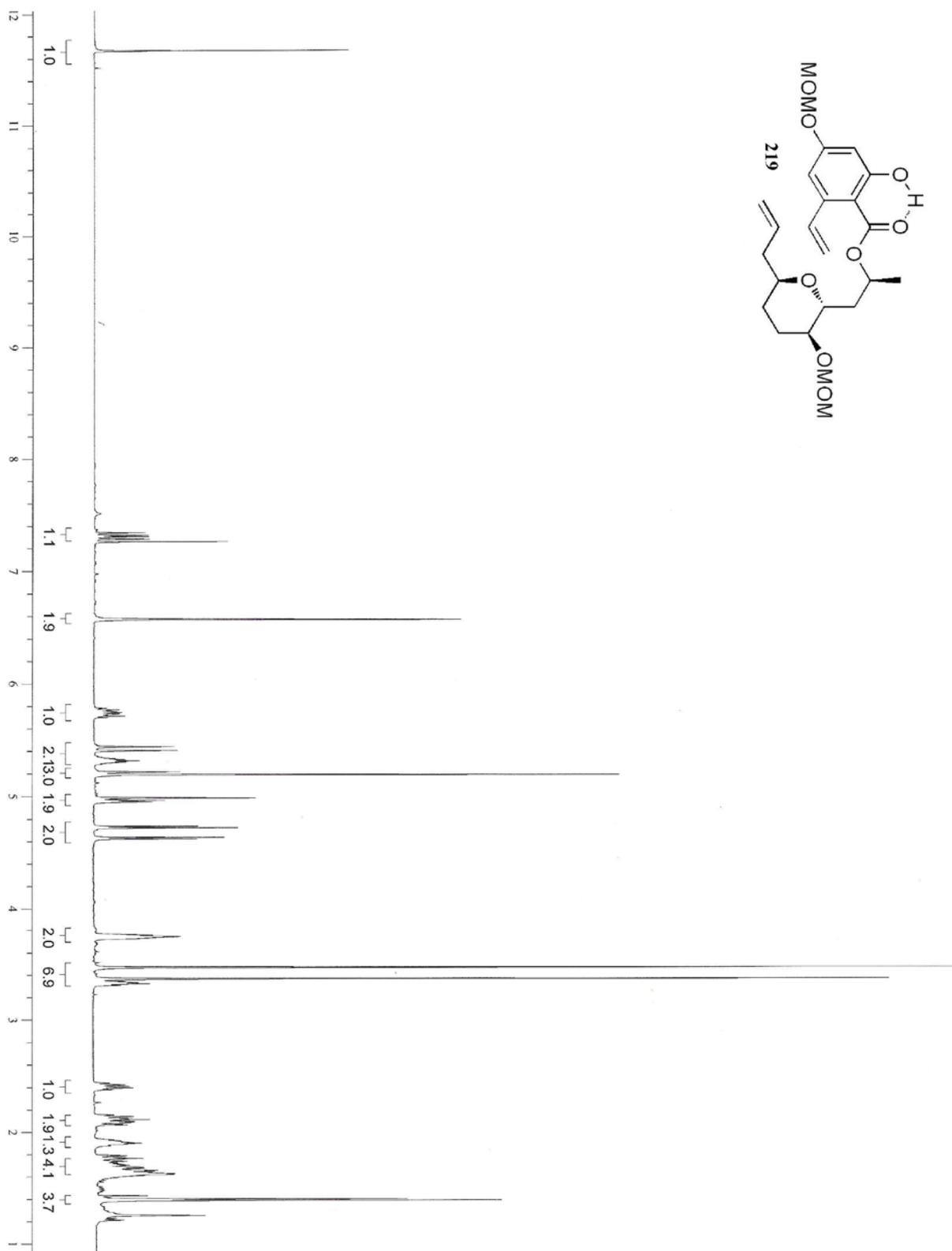
The ^1H NMR Spectrum (360 MHz, CDCl_3) of Compound **201**



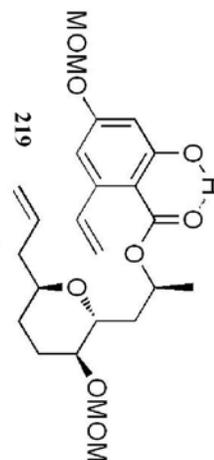
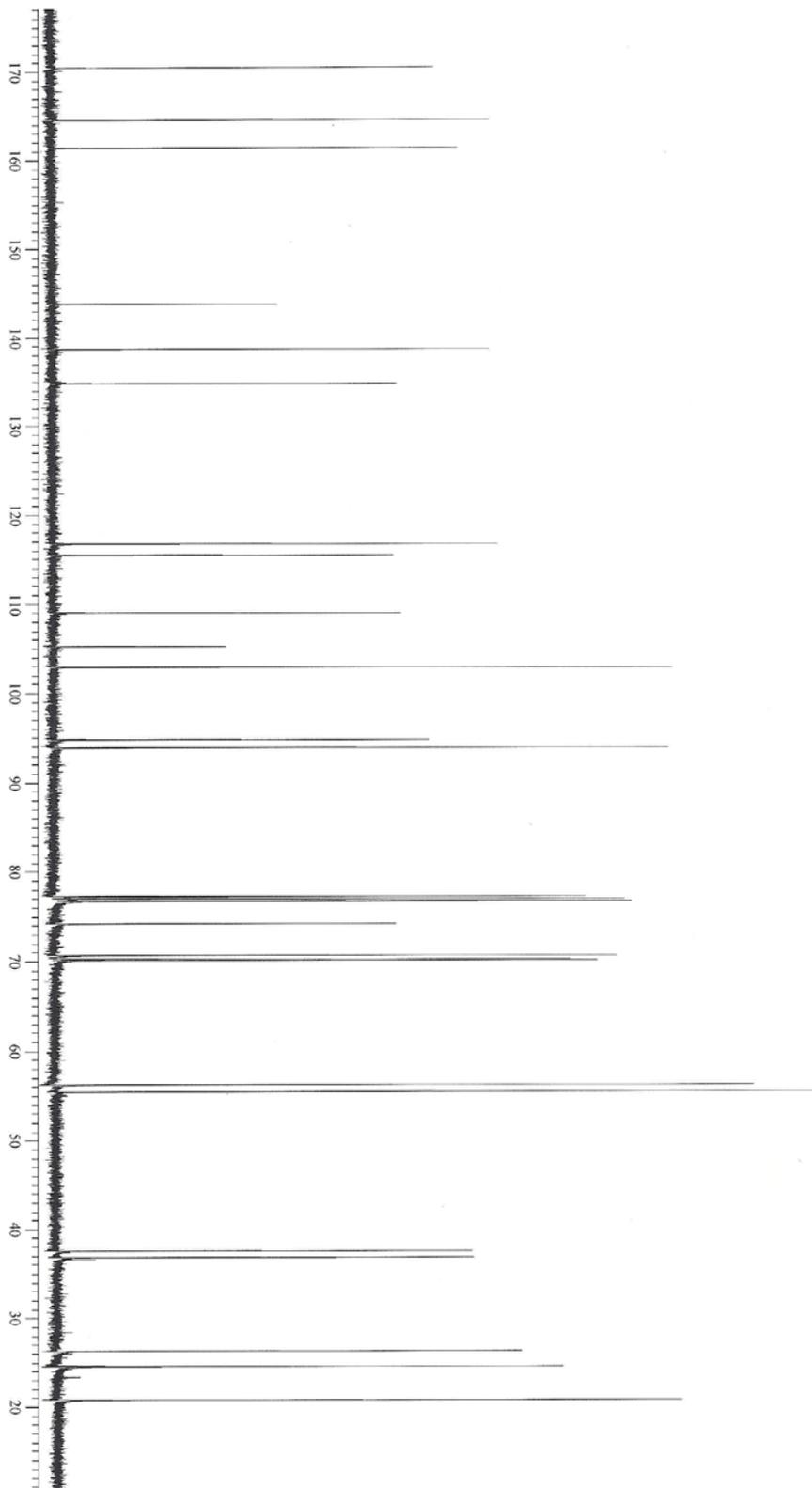
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **201**



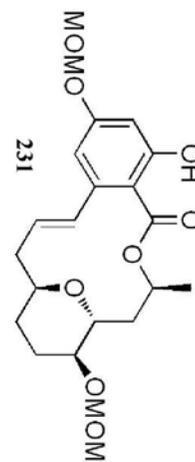
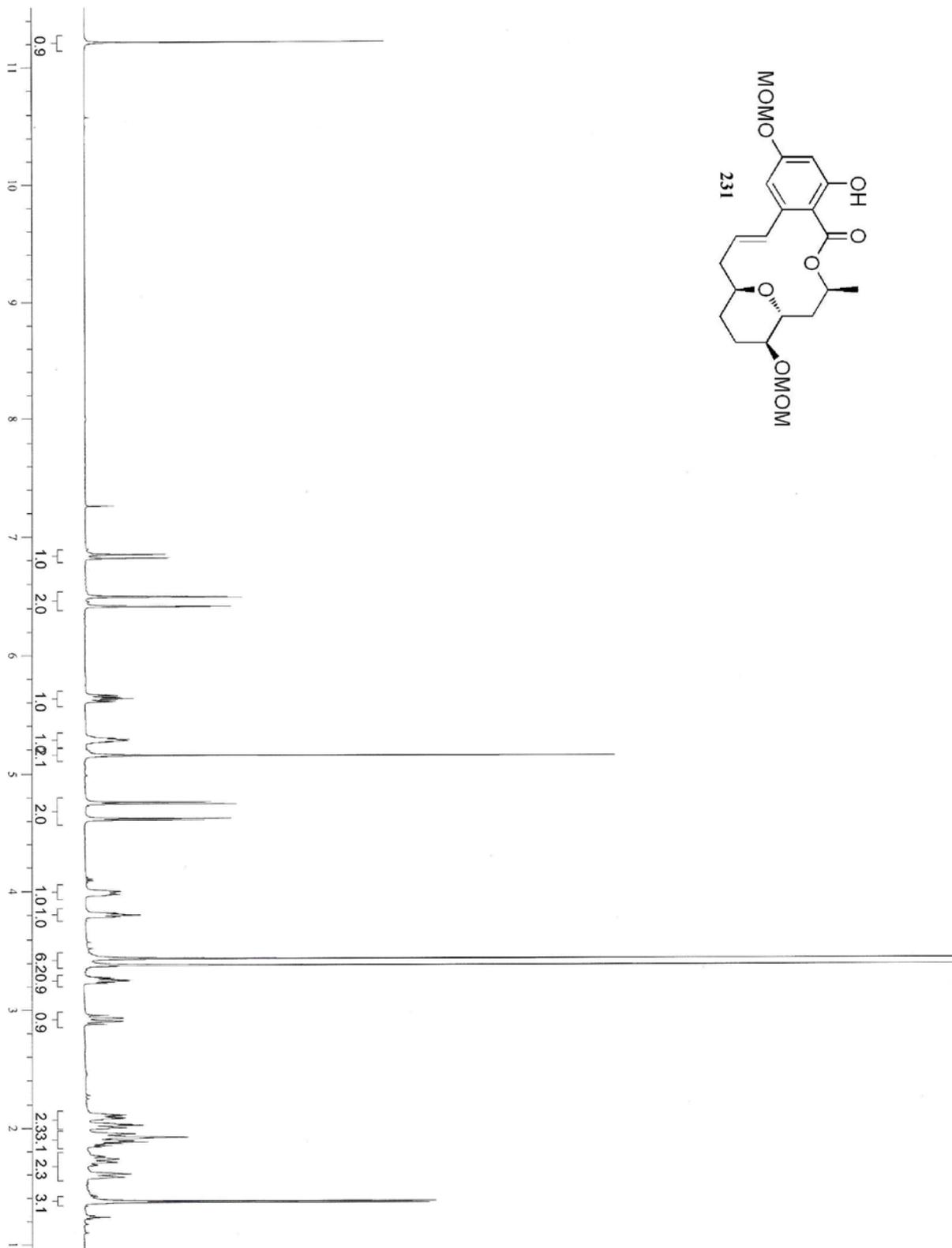
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **220**



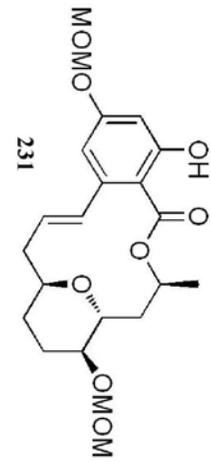
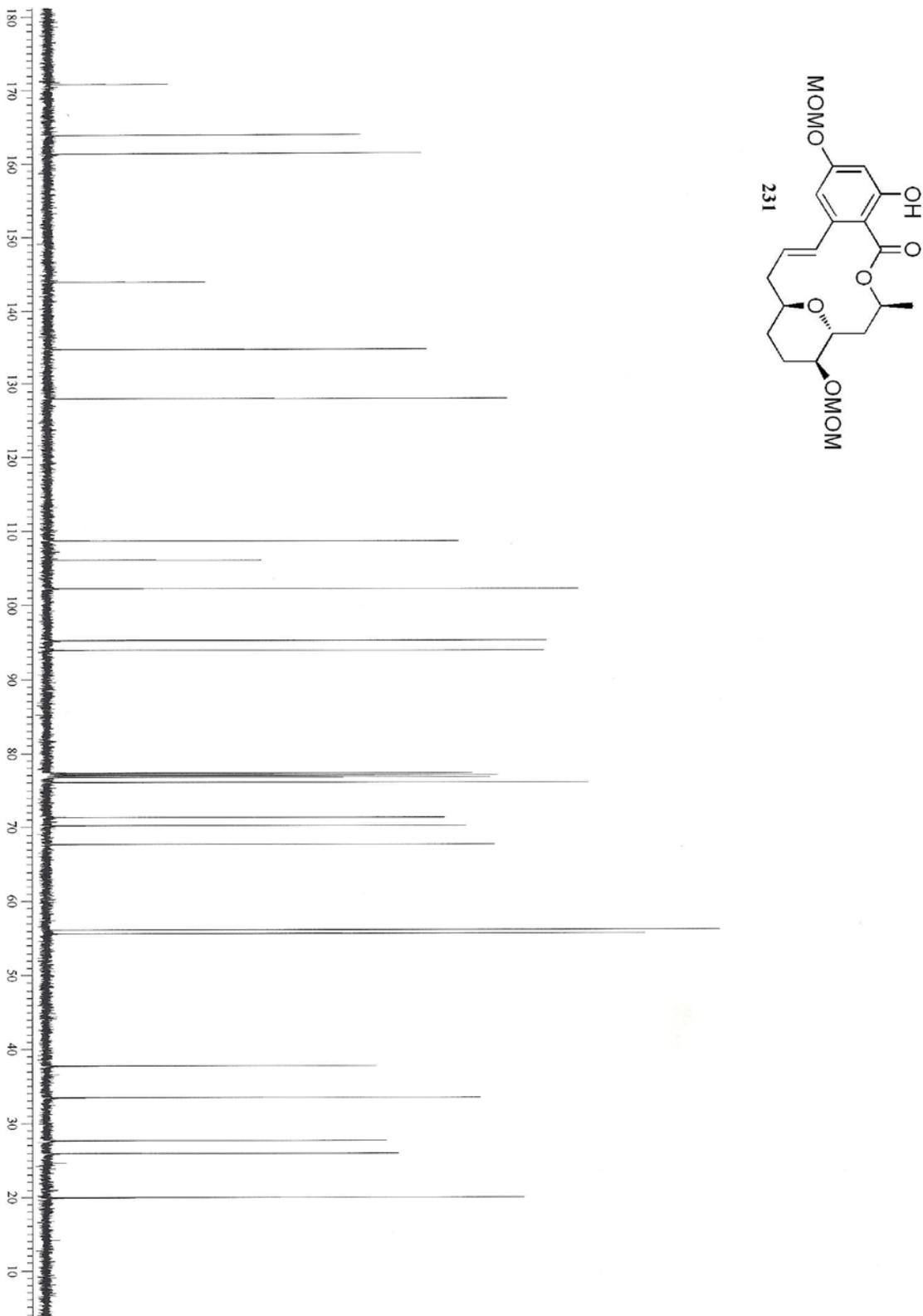
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **219**



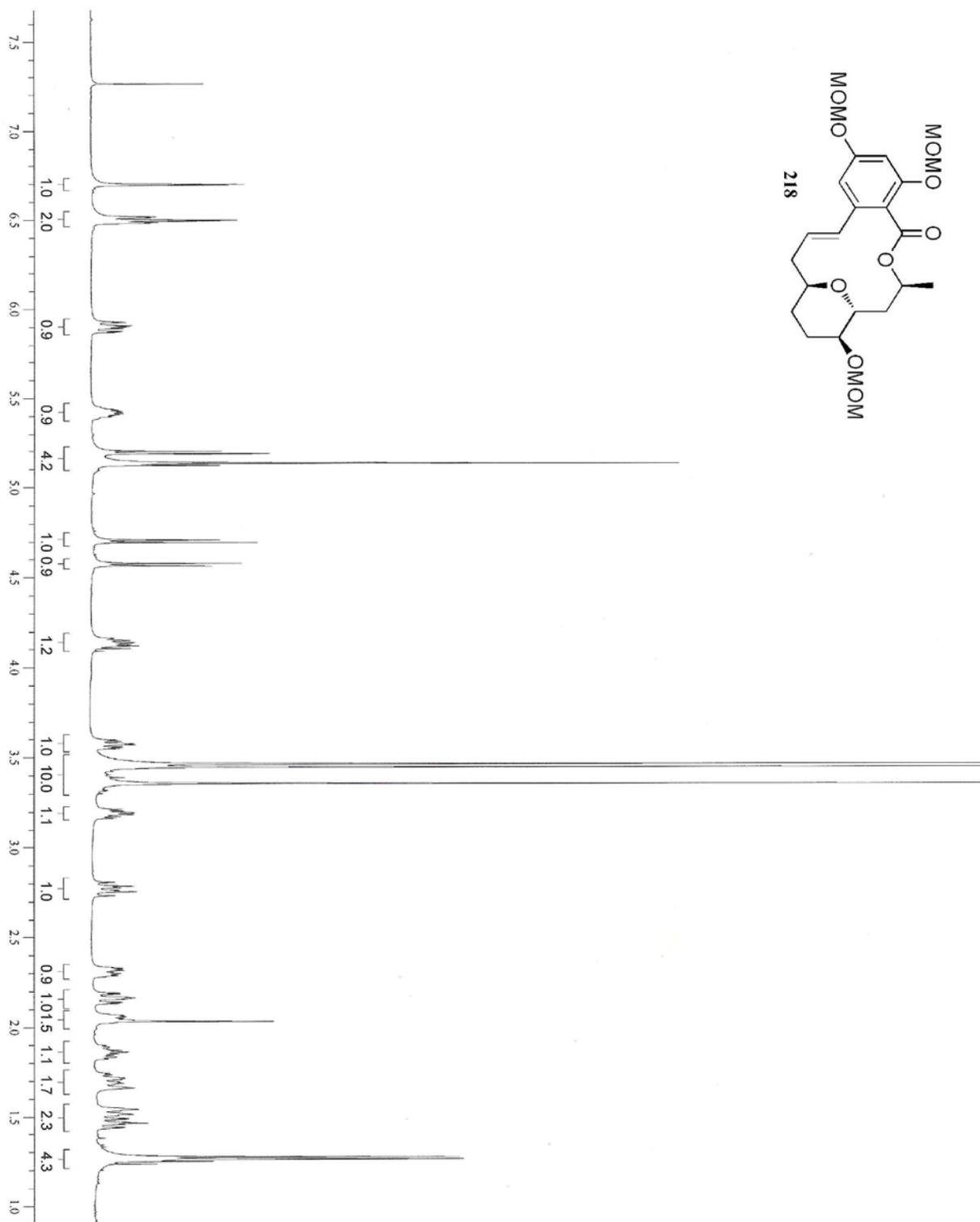
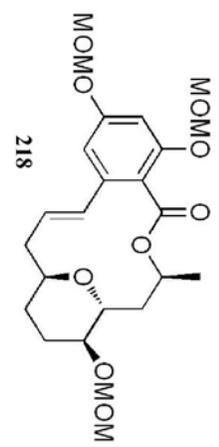
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **219**



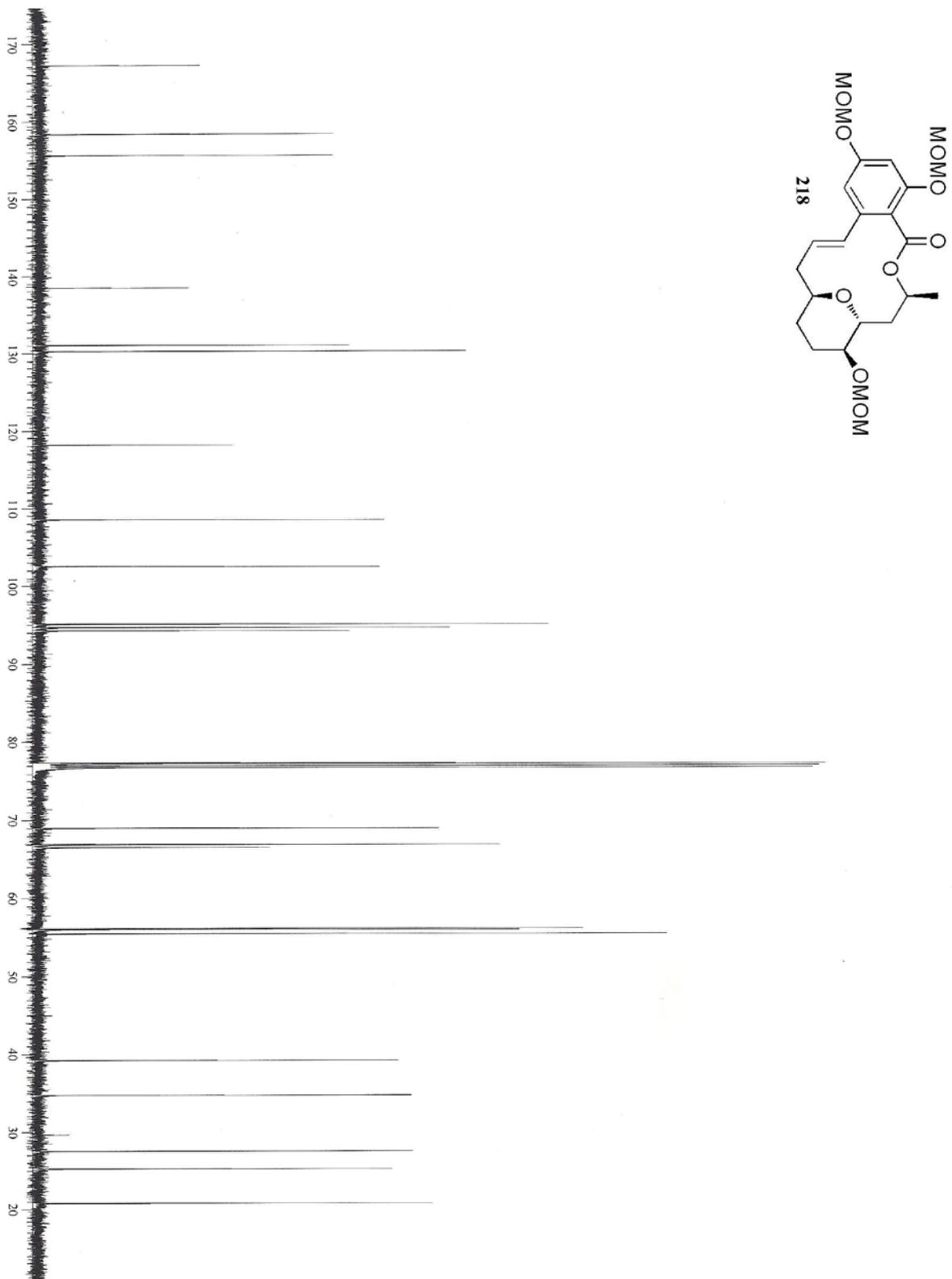
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **231**



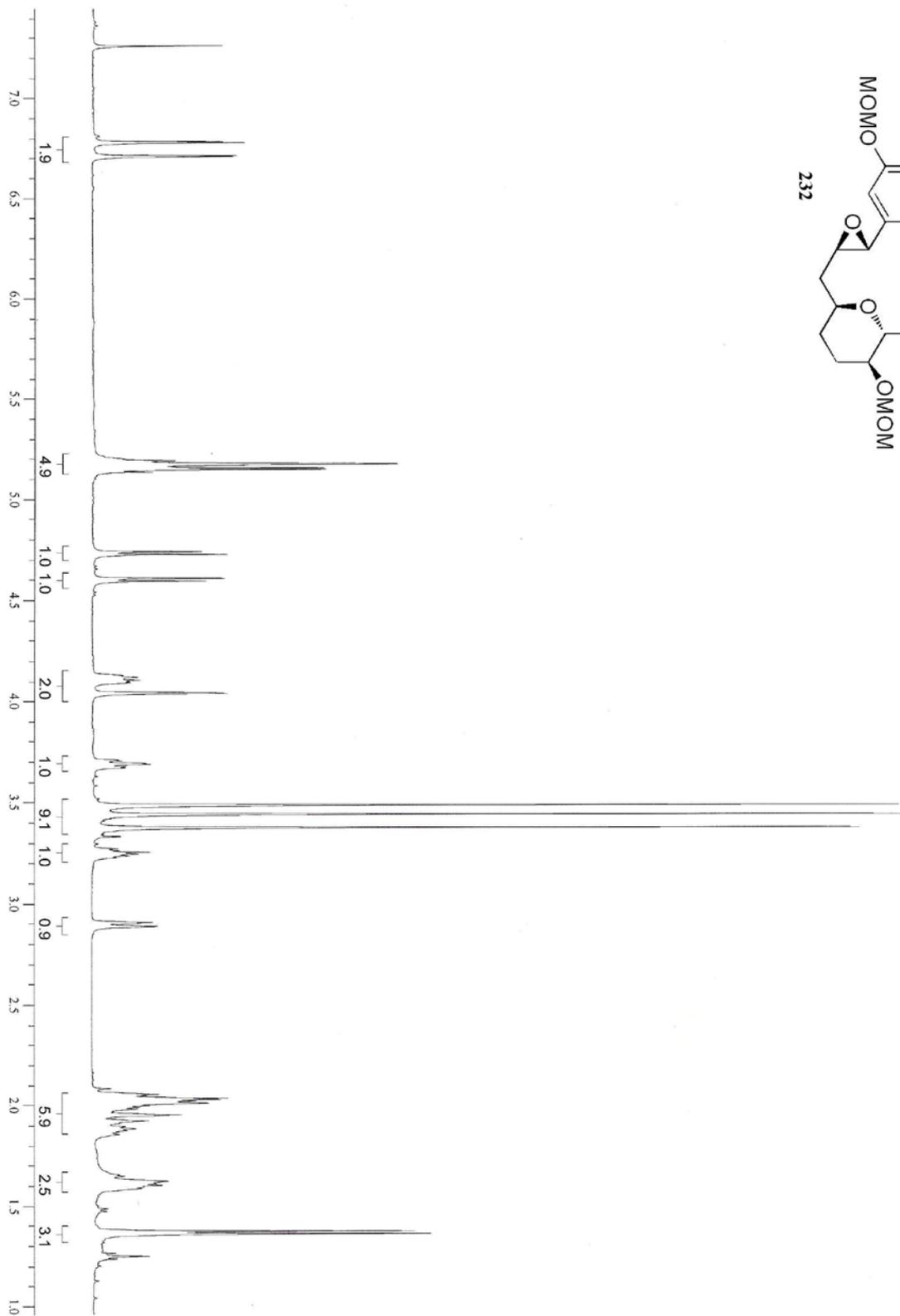
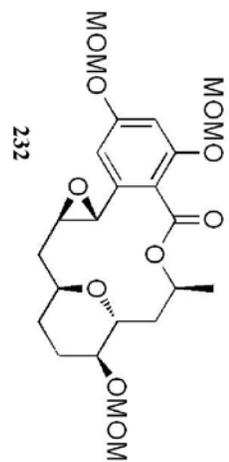
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **231**



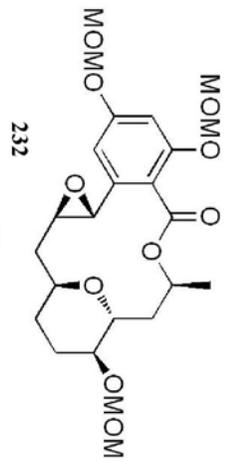
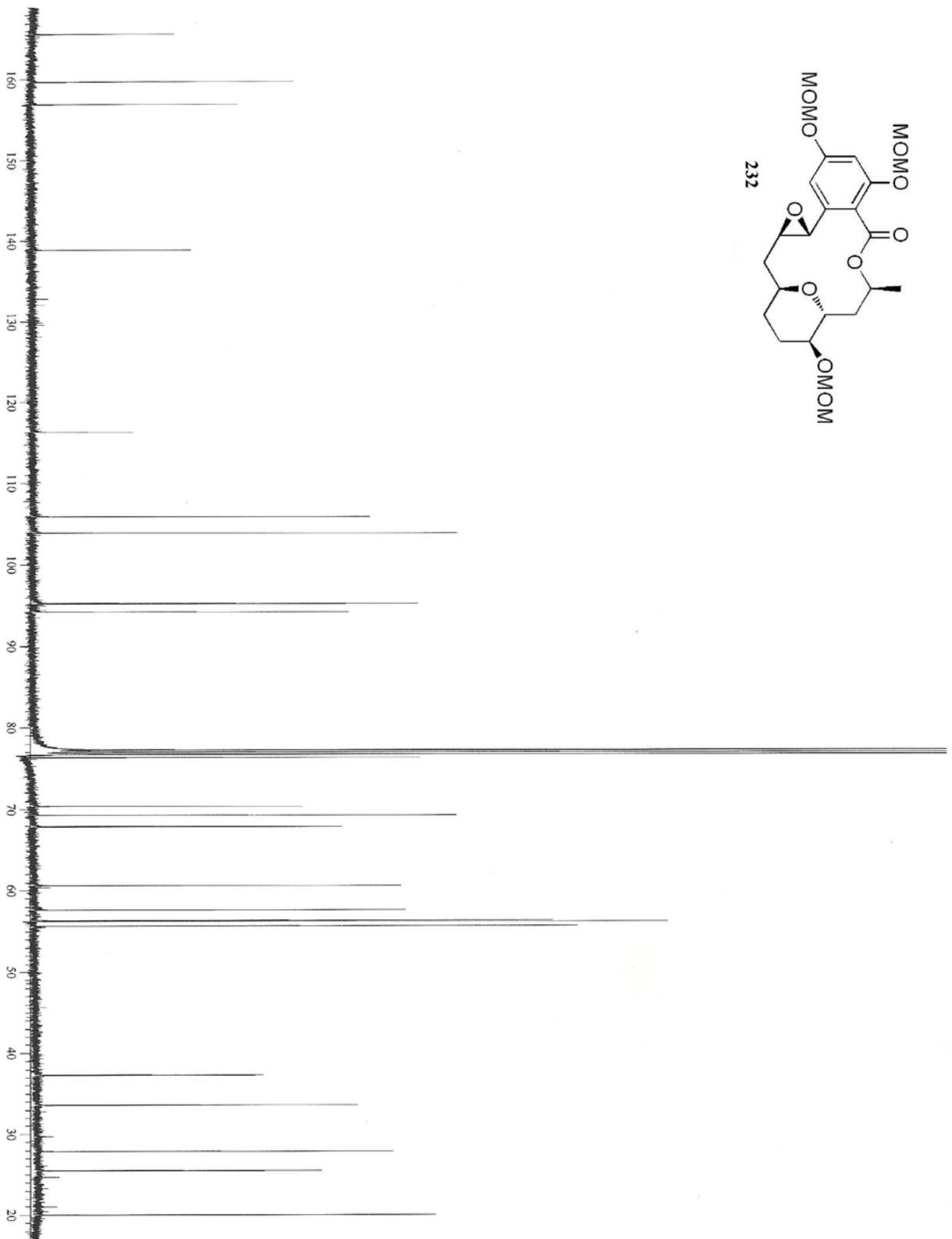
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **218**



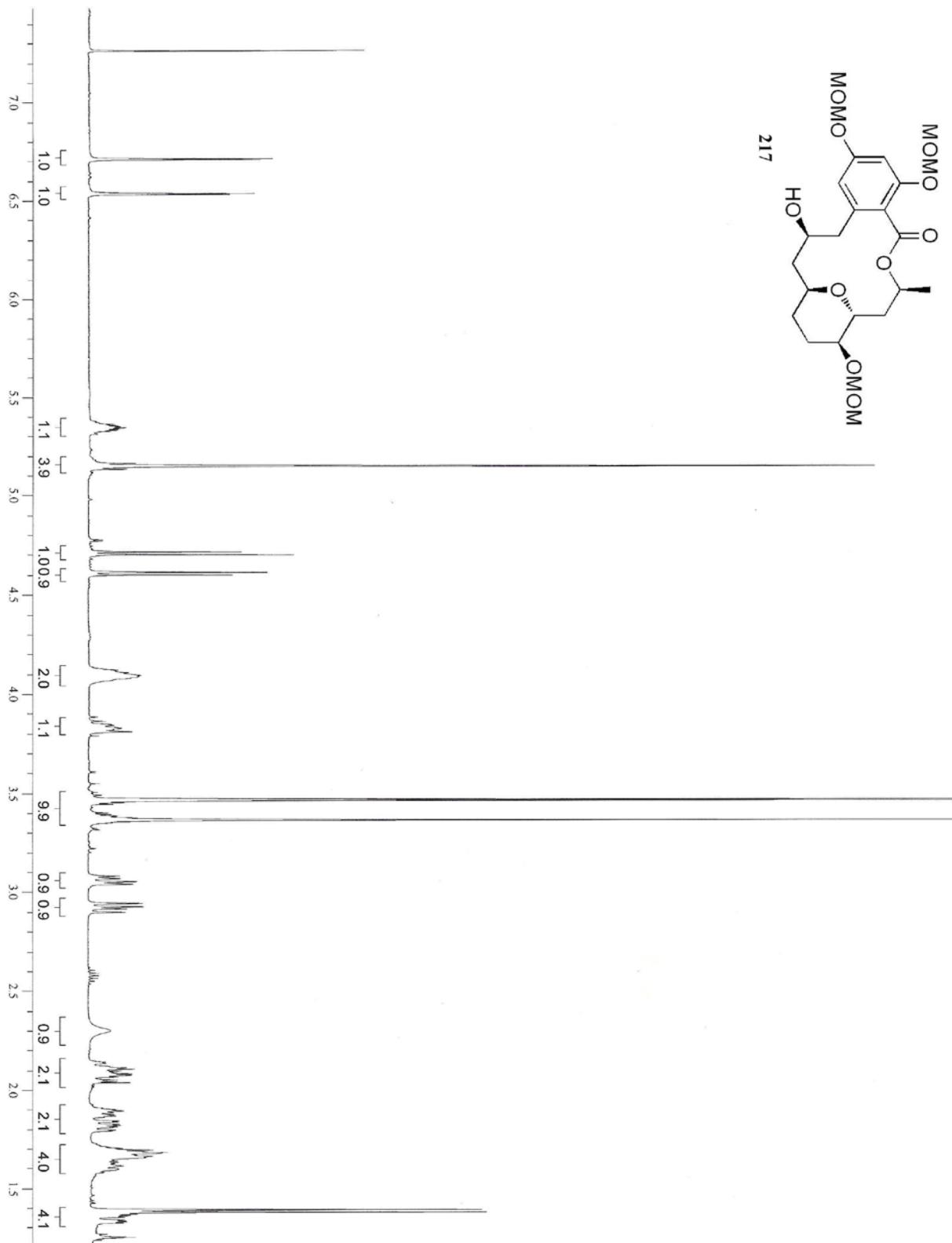
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **218**



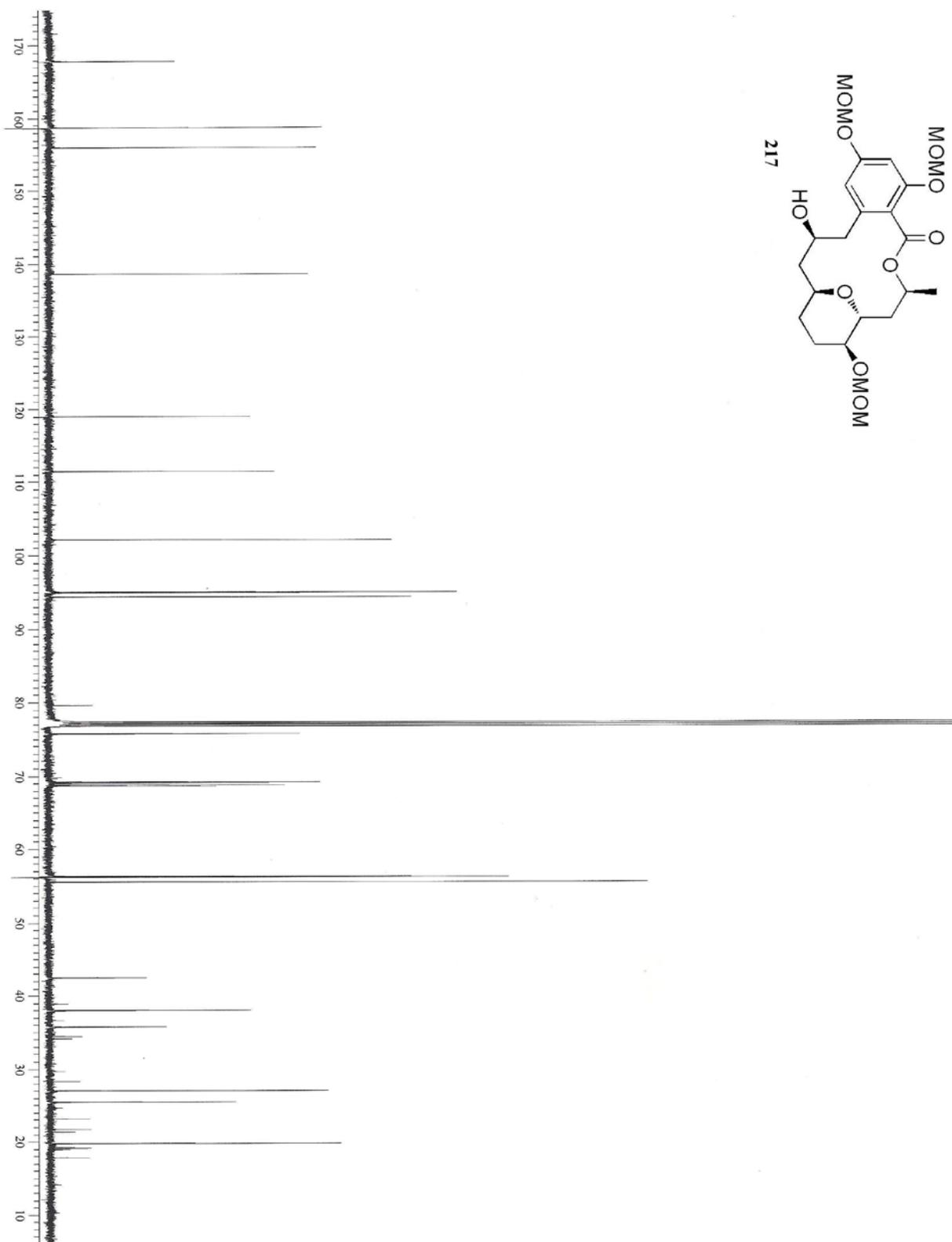
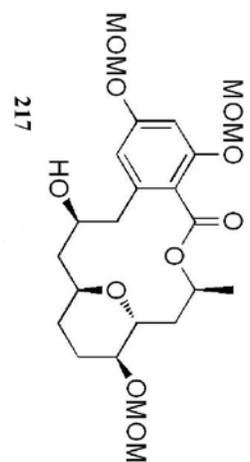
The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **232**



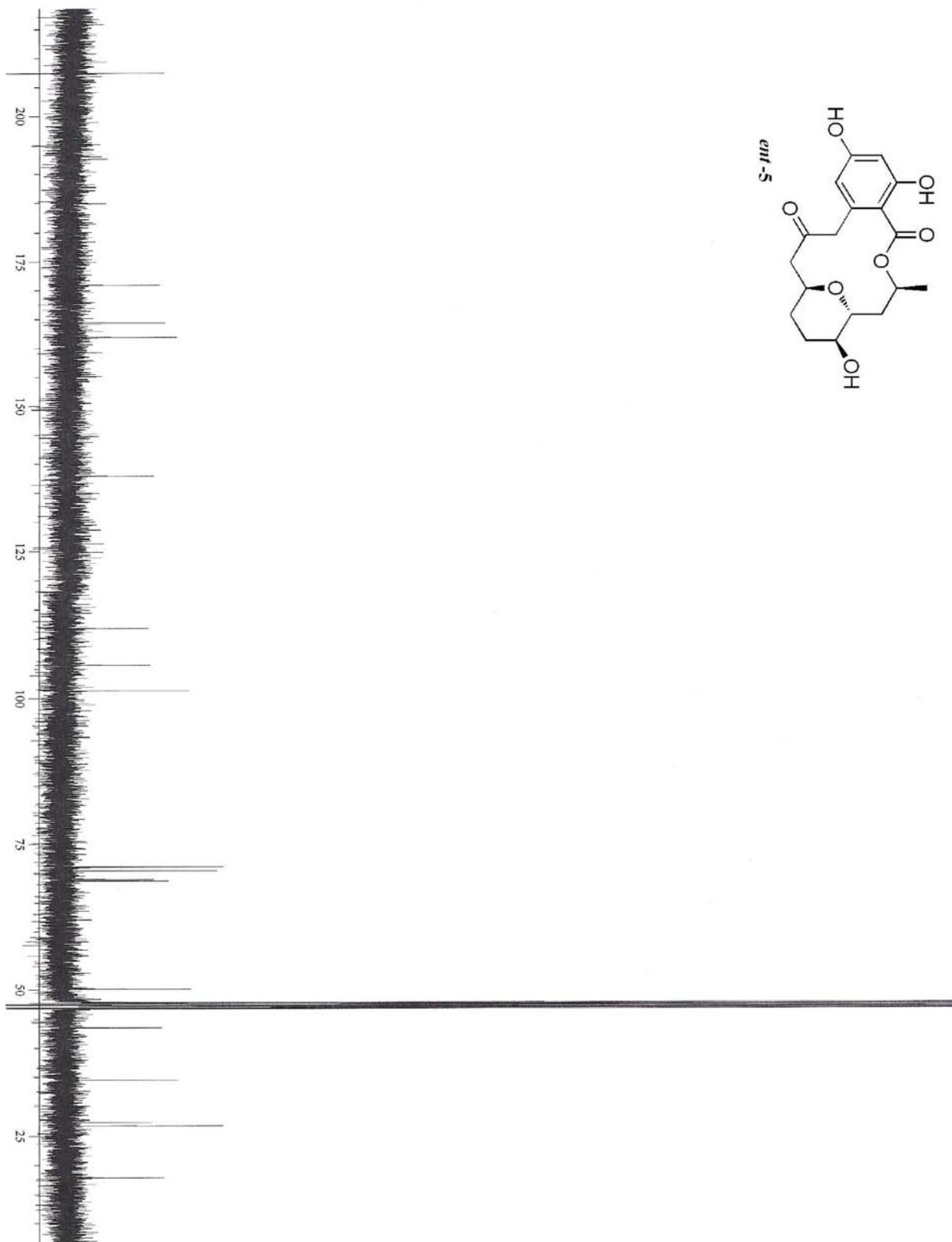
The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **232**



The ^1H NMR Spectrum (500 MHz, CDCl_3) of Compound **217**



The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound **217**



The ^{13}C NMR Spectrum (125 MHz, CDCl_3) of Compound *ent-5*