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Cobalt Mediated Oxidative Cyclizations: The Diastereoselective Synthesis of trans-Tetrahydrofuran Rings

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Graduate Program in Chemistry
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Abstract and Key Words

This thesis details the development of a novel cobalt catalyst for the Mukaiyama oxidative cyclization of THF (tetrahydrofuran) rings. The Mukaiyama cyclization has been an effective methodology for the formation of *trans*-THF rings and has been utilized in the synthesis of several natural products. The first Chapter in this document outlines the development of a water soluble Co(nmp)₂ catalyst and its improved performance in the Mukaiyama cyclization.

The second chapter details further applications of the Co(nmp)₂ catalyst. These applications include failed attempts at alkyne cyclizations and the successful application to trisubstituted 2,2,5-THF products. Applications of Co(nmp)₂ in total synthesis and synthetic methodology are also discussed.

Key Words:

Mukaiyama

cobalt

oxidative cyclization

trans-tetrahydrofuran

NMP

catalyst

heterocycle

synthesis

Co – Authorship Statement

It is explicitly noted that the vast majority of work presented in this document was done collaboratively. Major contributions were made by Dr. Andrew C. Stevens to all aspects of the $\text{Co}(\text{nmp})_2$ projects described. Several substrate examples in the original cobalt catalyst project can be attributed to Dr. Nick Morra, Dr. Ben Machin, and Dr. Barb Morra. Every effort has been made to identify and give appropriate acknowledgment to all contributions. Although not described in this document, preliminary work was conducted by Dr. Nick Morra and Dr. Mark McFarland.

“You don't get what you deserve, you get what you earn”

-Tom Brands

Acknowledgments

I have had the privilege of working with many amazing people throughout my time at Western. Being immersed in a culture of hard work and dedication was an amazing opportunity. It has taught me to strive to become the best version of myself every day. I truly believe that every individual you encounter in your life has something positive they can show you about yourself. My first experience in a research lab was during my fourth-year honors project in the Pagenkopf Lab. I owe many thanks to Dr. Brian Pagenkopf for both the opportunity to work on various research projects and his continued support and encouragement during my time away from school. I would not be accomplishing this goal without him. My time spent in the lab during fourth year and graduate school was made an incredibly enjoyable experience by Andrew Stevens. The Albertan helped teach through mockery, insults, and shaming. Needless to say, we didn't have a hard time getting along and later worked together on several projects during graduate school. I can say without a doubt I would not have succeeded without him in my corner. I can only hope that I somehow made his time in the group more enjoyable.

I am also grateful for the friendship that was shown to me by my fellow group members; Nick Morra, Barb Morra, Ben Machin and Mahmoud Moustafa. The mentorship that I received from Nick and Barb during my time in the lab will not be forgotten and was greatly appreciated. Ben and Mahmoud created an amazing atmosphere in the lab. Their big hearts and genuine love for life are greatly missed.

I would like to thank the members of the Kerr Group for their both for their guidance and friendship. The senior members of the group proved to be incredible role

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As we wander through life there are very few things that remain constant. There are very few things that we can count on to be the same when we come back a day, a month or years later. My family's unconditional love and support has been the key to any successes in life. Thank you to my parents Dan and Cindy and my siblings Danny and Kayla.

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Table of Contents

Certificate of Examination.....	Error! Bookmark not defined.
Abstract and Key Words.....	ii
Co – Authorship Statement.....	iii
Acknowledgments.....	v
List of Tables	ix
List of Figures.....	x
List of Schemes.....	xi
List of Abbreviations	xiii
1. The Synthesis of Tetrahydrofuran Derivatives	1
1.1 S _N 2 THF Cyclization Methods.....	2
1.1.0 General mechanism	2
1.1.1 Chlorohydrin cyclization	2
1.2 THF Formal Cycloaddition Methods	7
1.2.0 Formal Cycloaddition General Mechanism.....	7
1.2.1 Johnson’s Donor-Acceptor Cyclopropane THF Synthesis.....	7
1.2.2 Prins Cyclization.....	10
1.3 Radical Cyclizations of Substituted THF Rings	12
1.3.0 Carbon Centred Radical THF Cyclization.....	13
1.3.1 Sammis Oxygen Centred Radical Cyclization	13
1.4 Transition Metal Catalyzed THF Synthesis	14
1.4.0 Cross Metathesis.....	14
1.4.1 Metal Catalyzed Trost Annulation	16
2. Cobalt Catalyzed Oxidative Cyclization.....	20
2.1 The Mukaiyama Discovery	20
2.3 Applications	28
2.4 The Pagenkopf Group	29
2.4.0 Natural Product Synthesis – Bullatacin and Aplysiallene	29
2.4.1 “Revamped” Synthesis of The Mukaiyama Ligands.....	31
2.4.2 Crystal Structures	32

2.4.3 Substrate Scope Exploration.....	33
2.5 Objectives of the Current Research.....	36
2.6 Results & Discussion	37
2.7 Applications of Co(nmp) ₂ in Total Synthesis.....	43
2.8 Summary and Conclusions.....	45
3. Application of Co(NMP) ₂ in Expanded THF Substitution Patterns	49
3.1 Initial Scope Expansion for Co(nmp) ₂	49
3.2 Synthesis of 2,2,6 – Trisubstituted THF Methanols	50
3.3 Initial Studies with Co(nmp) ₂	52
3.4 Applications of Co(nmp) ₂ in the Synthesis of Cyclocapitelline.....	57
3.5 Oxime Synthesis with Co(nmp) ₂	57
3.6 Summary and Conclusion	58
4. Experimental Procedures	60
Synthesis of Co (nmp) ₂	61
Synthesis of Pentenol substrates and products.....	63
General Grignard Procedure:	63
Synthesis of Hexenol substrates	73
General Procedure for Grignard Addition to Ketones:	73
Images of Co(modp) ₂ Column.....	84
5. Appendices.....	86
6. Curriculum Vitae	157

List of Tables

TABLE 1. MUKAIYAMA SILYLPEROXIDE OXIDATION OF ALKENES	21
TABLE 2. MUKAIYAMA'S INITIAL CYCLIZATION OPTIMIZATION	22
TABLE 3. MUKAIYAMA'S SUBSTRATE SCOPE FOR THE OXIDATIVE CYCLIZATION	23
TABLE 4. SUBSTITUTION EFFECT ON D.R.	35
TABLE 5. PRELIMINARY CATALYST COMPARISON	39
TABLE 6. CATALYST LOADING STUDIES	40
TABLE 7. SUBSTRATE SCOPE.....	42
TABLE 8. OPTIMIZATION STUDY ON METHYL SUBSTITUTED THFS.....	54
TABLE 9. PRELIMINARY SUBSTRATE SCOPE FOR METHYL SUBSTITUTED THFS	56

List of Figures

FIGURE 1. SAMMIS' TRANSITION STATES	14
FIGURE 2. MUKAIYAMA'S LIGANDS	20
FIGURE 3. LIGAND USED IN THE HARTUNG STUDIES	26
FIGURE 4. DIASTEREOSELECTIVITY OF THE MUKAIYAMA CYCLIZATION	26
FIGURE 5. MUCOCIN.....	28
FIGURE 6. BULLATACIN	29
FIGURE 7. APLYSIALLENE	31
FIGURE 8. X-RAY CRYSTAL STRUCTURES OF CO(DIBN) ₂	33
FIGURE 9. SULPHONATED PHOSPHINE.....	36
FIGURE 10. SEVERAL CO ₂ LIGANDS	37
FIGURE 11. COBALT NMP CATALYST	38
FIGURE 12. AMPHIDINOLIDE C AND F	43
FIGURE 13. PROPOSED CHIRAL NMP LIGANDS	50
FIGURE 14. MONENSIN	50
FIGURE 15. IONOMYCIN	51
FIGURE 16. CONDITIONS FOR METHYL THF CYCLIZATION.....	56
FIGURE 17. THE VARYING BANDS OF DECOMPOSED COBALT CATALYST (MODP AND PIPER LIGANDS).	84

List of Schemes

SCHEME 1. WILLIAMSON ETHER SYNTHESIS	2
SCHEME 2. BRITTON BF ₃ THF SYNTHESIS	3
SCHEME 3. MECHANISM OF BRITTON'S BF ₃ THF SYNTHESIS.....	4
SCHEME 4. SILVER TRIFLATE MEDIATED <i>TRANS</i> THF SYNTHESIS.....	5
SCHEME 5. BRITTON CHLOROXYDRIN THF SYNTHESIS.....	5
SCHEME 6. JAMISON EPOXIDE CASCADES.....	5
SCHEME 7. HOYE BIS-THF SYNTHESIS	6
SCHEME 8. GENERAL [3+2] FORMAL CYCLOADDITION MECHANISM.....	7
SCHEME 9. JOHNSON CYCLOPROPANE ANNULATION WITH ALDEHYDES.....	8
SCHEME 10. JOHNSON ANNULATION MECHANISM	8
SCHEME 11. ENANTIOSELECTIVE CYCLOPROPANE ANNULATION	9
SCHEME 12. DYKAT (DYNAMIC KINETIC ASYMMETRIC TRANSFORMATION) PATHWAYS FOR ALDEHYDE CYCLOADDITION.....	10
SCHEME 13. GENERAL PRINZ CYCLIZATION	11
SCHEME 14. PANEK THF SYNTHESIS.....	12
SCHEME 15. GENERAL RADICAL CYCLIZATION MECHANISM.....	13
SCHEME 16. RADICAL MEDIATED SYNTHESIS OF A <i>BIS</i> -THF	13
SCHEME 17. SAMMIS' RADICAL CYCLIZATION	14
SCHEME 18. GRUBBS RING CLOSING METATHESIS	15
SCHEME 19. RCM MECHANISM.....	16
SCHEME 20. TROST ANNULATION.....	17
SCHEME 21. TROST ANNULATION MECHANISM.....	17
SCHEME 22. INTRAMOLECULAR TROST ANNULATION	17
SCHEME 23. SYNTHESIS OF A THF FRAGMENT OF AMPHIDINOLIDE K	18
SCHEME 24. MUKAIYAMA TRIMETHYLSILYLPEROXIDE SYNTHESIS.....	20
SCHEME 25. MUKAIYAMA'S INITIAL DISCOVERY	22
SCHEME 26. MUKAIYAMA OXIDATIVE CYCLIZATION.....	23
SCHEME 27. MUKAIYAMA'S PROPOSED MECHANISM	24
SCHEME 28. COBALT ACTIVATION OF O ₂	25
SCHEME 29. HARTUNG'S PROPOSED MECHANISM	25
SCHEME 30. CATALYST REGENERATION	27
SCHEME 31. HARTUNG REDUCTIVE TERMINATION OF AN OXIDATIVE CYCLIZATION.....	28
SCHEME 32. OXIDATIVE CYCLIZATION OF MUCOCIN PRECURSOR	29
SCHEME 33. UNPROTECTED CYCLIZATION ATTEMPT	30
SCHEME 34. KEY STEPS IN THE SYNTHESIS OF BULLATAACIN	30
SCHEME 35. KEY STEPS IN THE SYNTHESIS OF APLYSIALLENE	31
SCHEME 36. MODP LIGAND SYNTHESIS.....	32
SCHEME 37. SYNTHESIS OF CO(MODP) ₂	32
SCHEME 38. ISOMERIZATION EXPERIMENT	34
SCHEME 39. MUKAIYAMA OXIDATIVE CYCLIZATION.....	35
SCHEME 40. SYNTHESIS OF CO(NMP) ₂	38
SCHEME 41. INITIAL CO(NMP) ₂ REACTION CONDITIONS.....	39
SCHEME 42. CO(L) ₂ CATALYST AND CATALYTIC LOADING CONDITIONS	40

SCHEME 43. SUBSTRATE SCOPE REACTION CONDITIONS	42
SCHEME 44. THE GRAM SCALE SYNTHESIS OF THE C(18)-C(34) FRAGMENT OF AMPHIDINOLIDE C.....	44
SCHEME 45. THE GRAM SCALE SYNTHESIS OF C(1) – C(9) FRAGMENT OF AMPHIDINOLIDE C	44
SCHEME 46. FURSTNER’S SYNTHESIS OF THE C(18)-C(28) FRAGMENT OF AMPHIDINOLIDE F	45
SCHEME 47. ALKYNE OXIDATIVE CYCLIZATION	49
SCHEME 48. PROPOSED RESOLUTION USING CO(NMP) ₂	50
SCHEME 49. LAUTENS THF SYNTHESIS OF IONOMYCIN	52
SCHEME 50. METHYL SUBSTITUTED <i>TRANS</i> -THF RING FORMATION.....	52
SCHEME 51. 2,2,5 SUBSTITUTED THF CYCLIZATION CONDITIONS.....	54
SCHEME 52. THE SYNTHESIS OF CYCLOCAPITELLINE.....	57
SCHEME 53. YU CYCLIZATION OF OXIMES	58

List of Abbreviations

Ac	acetate
Acac	acetylacetone
AIBN	azobisisobutyronitrile
Atm	atmosphere
Bis	the second or two instances of something
Bn	benzyl
BrCCl ₃	trichlorobromomethane
brsm	based on recovered starting material
Bu ₃ SnH	tributyltin hydride
<i>s</i> BuOH	sec-Butyl Alcohol
Calc'd	calculated
CAM	cerium molybdate
CHD	cyclohexadiene
CHP	cumene hydrogen peroxide
D-A	donor - acceptor
DCE	Dichloroethane
dig	digonal
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalents
er	enantiomeric ratio
Et ₃ SiH	triethyltin hydride
exo	substituent farthest from or opposite another group

endo	substituent closest to or adjacent another group
eV	electron volt
eq	equivalent
<i>i</i> PrOH	isopropanol
modp	morpholine functionalized ligand used in the Mukaiyama oxidative cyclization (2.01)
Mol %	mole percentage
MOM	methoxymethyl
MS4Å	4 Angstrom molecular sieves
nmp	N-methyl piperazine functionalized ligand used in the Mukaiyama oxidative cyclization (2.37)
NMR	nuclear magnetic resonance
Ph	phenyl
Phth	phthalimide
PMP	<i>para</i> -methoxyphenol
R group	referring to a general position in a molecule not pertaining to the key functionality of discussion
rt	room temperature
S _N 2	bimolecular nucleophilic substitution
Sn(OTf) ₂	tin (II) trifluoromethanesulfonate
TBS	<i>tert</i> -butyldimethylsilyl
TBDPSCI	<i>tert</i> -butyldiphenylsilyl chloride
<i>t</i> Bu	<i>tert</i> -butyl
<i>t</i> BuOOH	<i>tert</i> -butyl hydrogen peroxide
THF	tetrahydrofuran
THP	tetrahydropyran

TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
TMS	trimethylsilyl

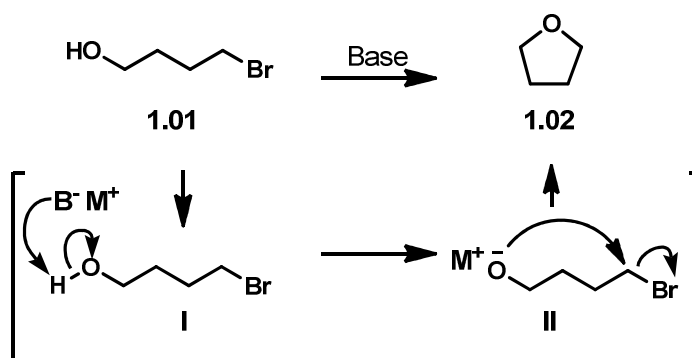
1. The Synthesis of Tetrahydrofuran Derivatives

Tetrahydrofuran (THF) ring systems have attracted considerable attention as synthetic targets due to their prevalence in naturally occurring molecules demonstrating significant biological activity.¹ The discovery of a new class of polyketide natural products, known as acetogenins, derived from plants in the *Annonaceae* family, in recent years has only served to strengthen the field of study.² These and many other compounds containing THF ring structures are often part of fused and/or macrocyclic ring systems. THF natural product's potent bioactivity has been shown to produce potential anti-cancer properties. To explore these properties for pharmaceutical application, it is necessary to produce the molecules on a large scale. As a direct result of the need for large scale synthesis of THF rings and natural products, many innovative methods have been developed to facilitate their synthesis. These methods use a diverse array of strategies, which include radical cyclization,³ chlorohydrin displacement,⁴ donor-acceptor cyclopropane annulations⁵ and many others.⁶

1.1 S_N2 THF Cyclization Methods

1.1.0 General mechanism

A THF ring is a cyclic 5-membered ether and the C – O bond of this structure is the predominant retrosynthetic disconnection. There are various ways in which the C – O bond can be formed but the most straightforward is an S_N2 reaction between an alcohol and a leaving group. As a fundamental reaction in organic chemistry, the Williamson ether synthesis provides a simple illustration of THF synthesis via an S_N2 pathway.⁷ Alcohol **1.01** can be treated with base to form an alkoxide species. This can undergo backside attack displacing the bromide leaving group. This is a clean and simple illustration of how an S_N2 pathway would proceed but in actual application it can produce side products through an elimination pathway. Several methods have been developed to avoid the elimination product.



Scheme 1. Williamson Ether Synthesis

1.1.1 Chlorhydrin cyclization

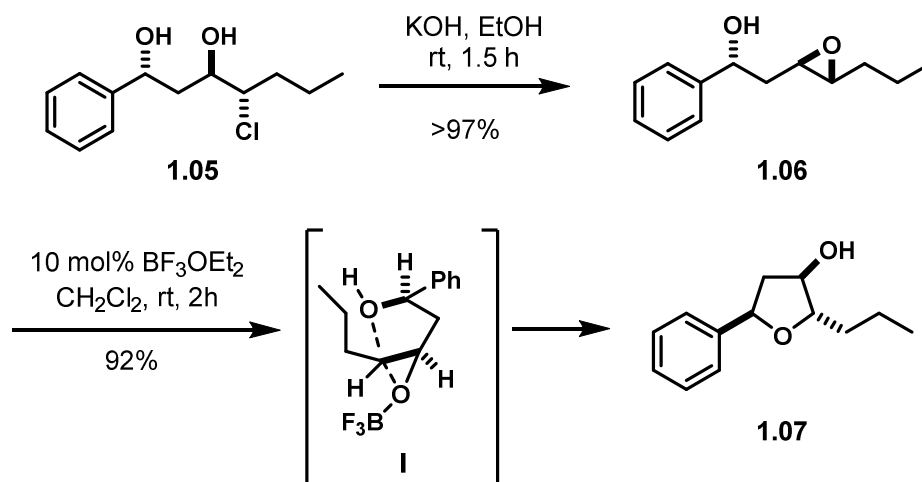
The Britton group has applied chlorhydrin cyclization to the formation of THF rings and have adapted it to oxygenated THF rings (Scheme 2).⁴ The ability to control and

modify the stereochemical outcome of this reaction makes this methodology very interesting. Various reaction conditions can be applied to a single starting material to access all of the possible stereoisomers of the product THF. These modes of reactivity include epoxide formation and opening, direct cyclization and Lewis acid mediated cyclization. These reactions occur in good yield and with diastereomeric ratios (dr) up to 20 :1. This strategy is very robust and is limited only by the synthesis of the starting material.

Synthesis of the THF products can be achieved via treatment of chlorodiols **1.05** with KOH in ethanol to afford epoxide **1.06** in 97% yield (Scheme 3). Epoxide **1.06** can be treated with 10 mol % $\text{BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 to afford THF **1.07** in 92% yield. Chlorodiols **1.03** reacted under the same conditions producing a 96% yield over 2 steps (Scheme 2). The epoxide intermediate allows for retention of stereoconfiguration at the chloride position into the THF product. This occurs as the epoxide inverts the stereocentre and subsequent attack re-establishes the previous configuration.

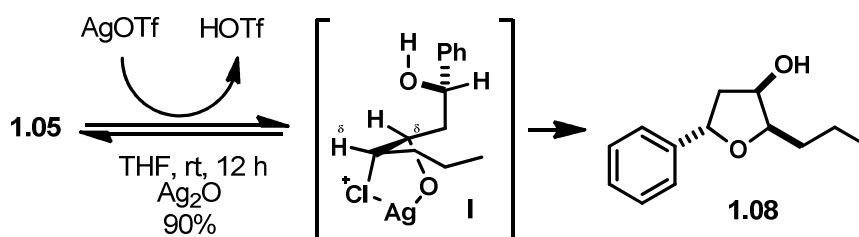
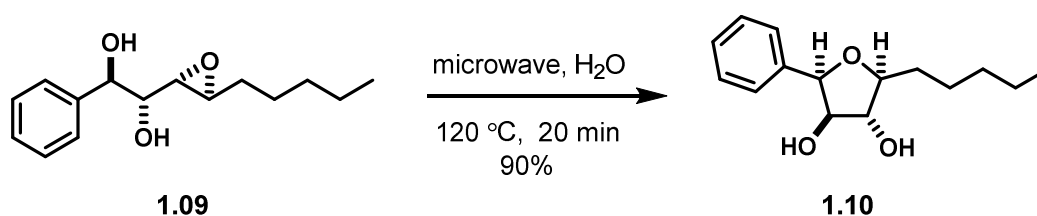


Scheme 2. Britton BF_3 THF Synthesis



Scheme 3. Mechanism of Britton's BF_3 THF Synthesis

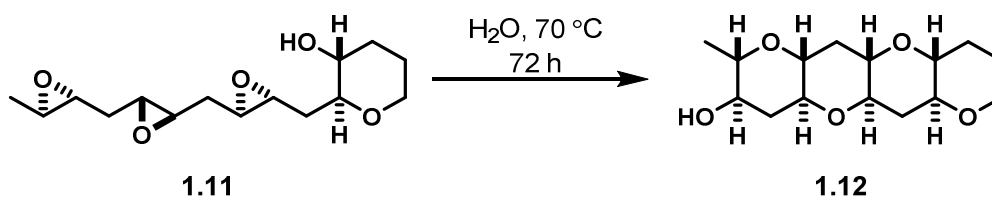
Britton's initial conditions allow for the synthesis of 4,5-*trans* THF products with both 2,5-*cis* and *trans* relative diastereoselectivity based on the correct chlorodiol. An alternative set of conditions were necessary to invert the stereochemistry of the 5 position in the THF product. Britton found that AgOTf was able to coordinate the chloride and adjacent alcohol together to both activate the chloride position and discourage epoxide formation (Scheme 4). The conformation of the silver complex allowed for attack of the pendant alcohol and access to the desired 4,5-*trans* products. The reaction required stoichiometric amounts of AgOTf and Ag_2O , which were found to decrease decomposition, presumably by scavenging TfOH . In addition to Britton's original reaction conditions, it was found that microwave assisted transformations gave excellent yields of the dihydroxylated THF product (**1.10**, Scheme 5).⁴

Scheme 4. Silver Triflate Mediated *trans*THF Synthesis

Scheme 5. Britton Chlorohydrin THF Synthesis

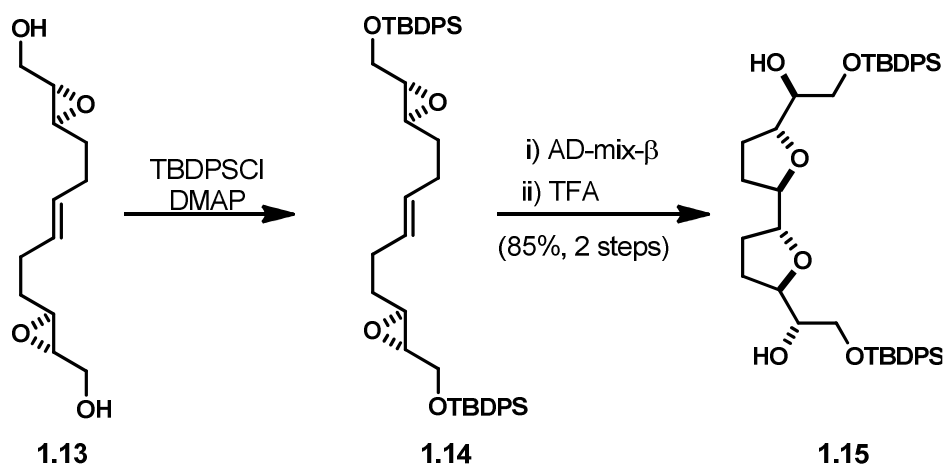
1.1.2 Epoxide Opening Synthesis

Epoxide cascade reactions are an efficient method for forming several cyclic ethers in a single reaction pot.⁸ By strategically placing epoxide and alcohol moieties, many ring systems can cyclize under the same conditions. Jamison and co-workers used this method to access tetrahydropyran (THP) moieties. The Jamison method allows for a pendant alcohol to attack a single epoxide, creating a newly formed THP with an alcohol functionality (Scheme 6). This alcohol can then undergo the same reaction and is propagated through several tethered epoxide centres.



Scheme 6. Jamison Epoxide Cascades

While the Jamison method selectively produces 6 membered rings, it is also possible to access multiple THF rings in a one-pot synthesis. Hoyer used an epoxide opening strategy for the bis-THF (+)-parviflorin.⁹ Diepoxide **1.14** was subjected to Sharpless asymmetric dihydroxylation conditions to provide the diol precursor for an “inside-out” epoxide opening cascade (Scheme 7). Treatment with TFA afforded the THF product (**1.15**) in 85% yield over two steps.

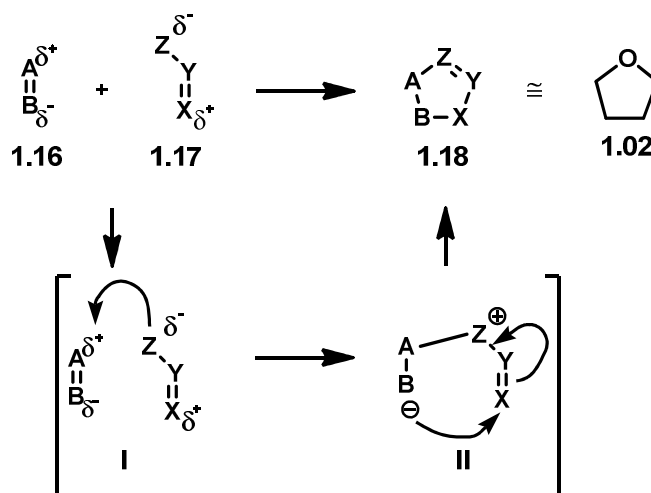


Scheme 7. Hoyer bis-THF Synthesis

1.2 THF Formal Cycloaddition Methods

1.2.0 Formal Cycloaddition General Mechanism

A cycloaddition is the addition of two unsaturated compounds to form a cyclic molecule with a lower bond order than the precursor and the reaction occurs in a concerted fashion. A *formal* cycloaddition gives the cycloaddition product without a concerted reaction mechanism. The general mechanism shown in Scheme 8 depicts a dipolarophile undergoing a nucleophilic attack to create zwitterionic intermediate **I**, which can then form the cycloadduct. This concept has been explored in many unique transformations^{5,12} and several will be discussed in further detail below.

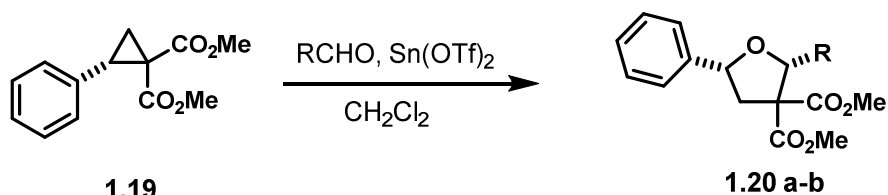


Scheme 8. General [3+2] Formal Cycloaddition Mechanism

1.2.1 Johnson's Donor-Acceptor Cyclopropane THF Synthesis

Donor-acceptor cyclopropanes have been adapted to form an extensive array of cycloaddition products arising from a wide array of dipolarophiles.¹⁰ The Johnson cyclopropane annulation with aldehydes can selectively give *cis*THF products. The addition of Sn(OTf)₂ to cyclopropane **1.19** and an aldehyde gave near quantitative yields

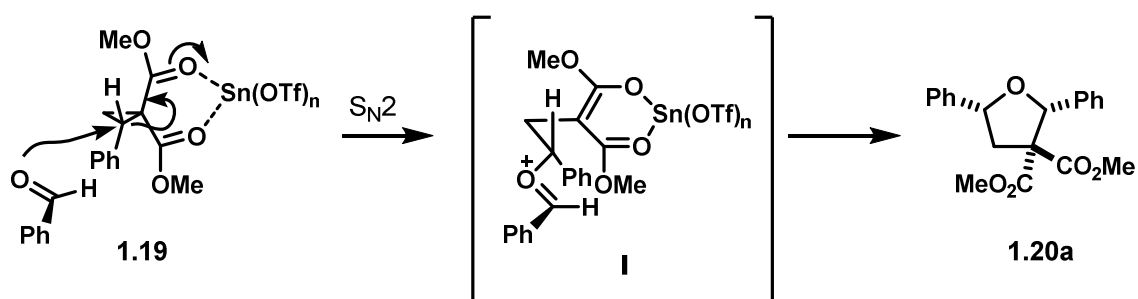
for almost all examples. The reaction shows excellent diastereoselectivity for larger R groups (Ph, *i*Pr) and almost full retention of stereochemistry from the starting cyclopropane (Scheme 9).



- a) R = Ph: 100%, >100:1 d.r., 96% ee
 b) R = *i*Pr: 98%, >56:1, 96% ee

Scheme 9. Johnson Cyclopropane Annulation with Aldehydes

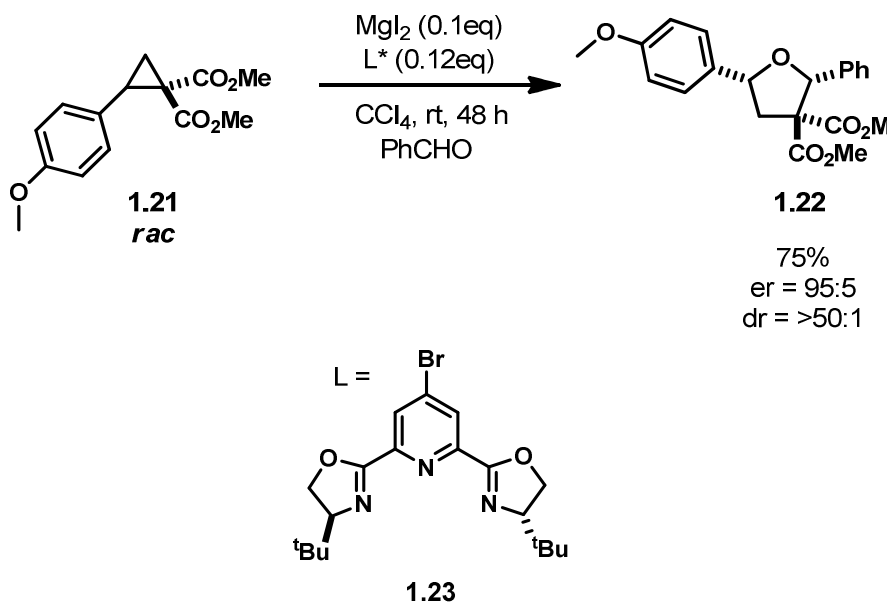
Retention of the enantiomeric purity of the cyclopropane occurs through an S_N2 attack of the chiral centre (Scheme 10). After the initial attack, the zwitterionic species (Scheme 10, **I**) will rotate to allow attack of the aldehyde carbon by the malonate. Bond rotation in intermediate **I** will force the molecule into a *cis* configuration as this puts both phenyl groups in the more stable equatorial positions in the final product (**1.20a**).



Scheme 10. Johnson Annulation Mechanism

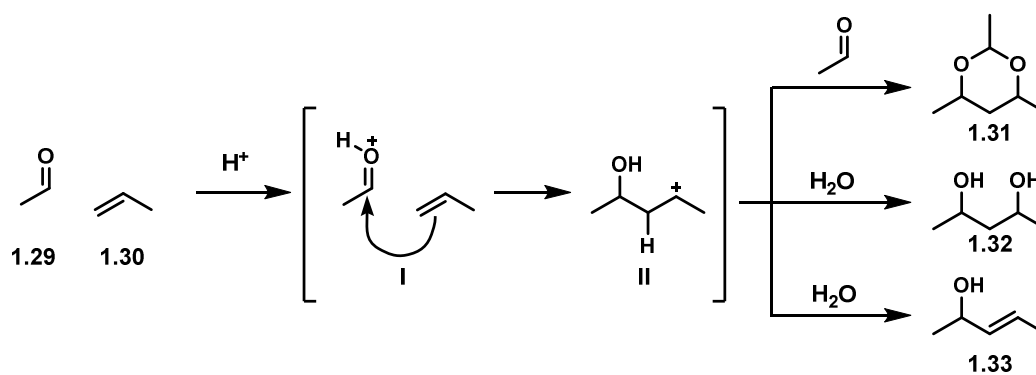
A unique variation on this reaction occurs with the use of a MgI_2 Lewis acid and an equivalent amount of chiral ligand (Scheme 11). These reaction conditions allow the use of a racemic cyclopropane (**1.21**) starting material, which is resolved to a highly

enantioenriched product (**1.22**). Good yield and high diastereoselectivity are conserved from the previous Sn(OTf)₂ catalyzed reactions.



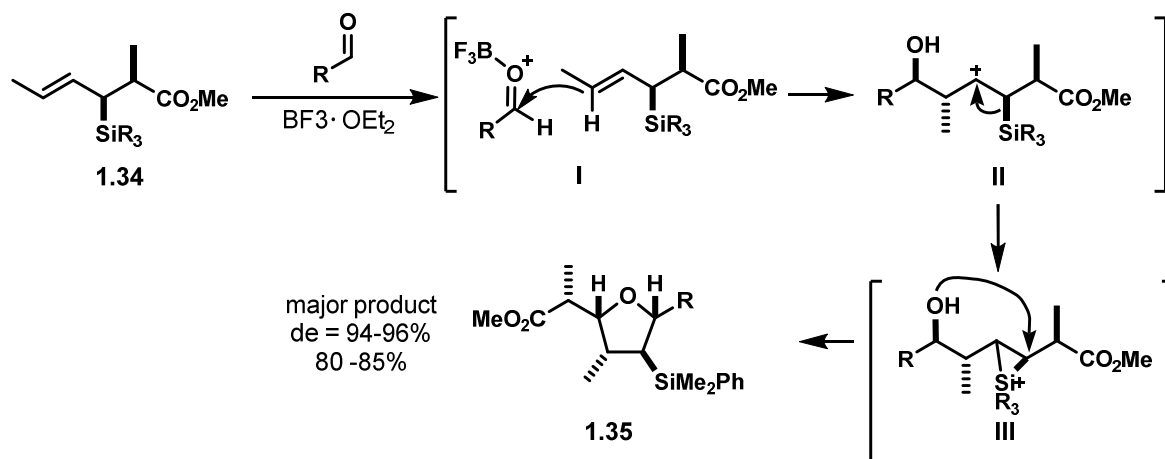
Scheme 11. Enantioselective Cyclopropane Annulation

Two major factors contribute to the enantioenriched product produced from a racemic mixture. The first is background reactivity of the cyclopropane. Magnesium iodide is able to open a donor-acceptor cyclopropane ring and subsequently reform the same compound (Scheme 12). Given no preference to the reformation of a single enantiomer, the cyclopropane will always revert back to a 1:1 er of the starting material. Secondly, the chiral PyBOX (**1.23**) catalyst causes a dynamic kinetic resolution, resulting in excellent er of the THF products. The addition of the PyBOX ligand causes a single enantiomer of the racemic mixture to react at a higher rate than the other. These conditions are able to deplete one enantiomer of the starting material through selectively reacting with a single enantiomer and then converting the other to the kinetically favoured starting material.



Scheme 13. General Prins Cyclization

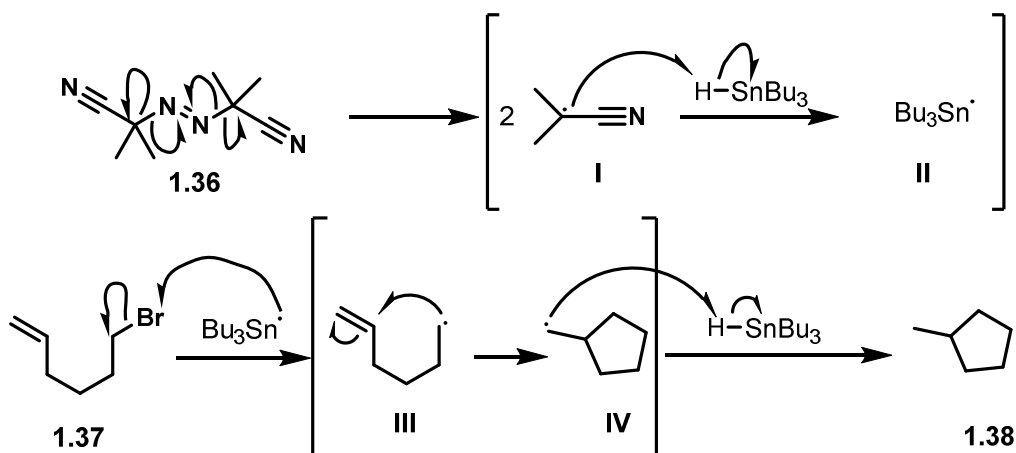
Panek and coworkers were able to use the carbocation intermediate of the Prins cyclization for the synthesis of THF rings.¹² Their strategy begins with a $\text{BF}_3 \cdot \text{OEt}_2$ catalyzed addition of a (E)-crotylsilane (**1.34**) into various aldehydes (Scheme 14). Transition state **I** produces the *anti*-product as the major diastereomer allowing for high diastereoselectivity in the final THF. Where the Panek method differs from a standard Prins reaction is in quenching the carbocation intermediate **II**; by strategically placing a silyl group, which can stabilize the carbocation, they are able to “lock” the structural conformation of the molecule. This unstable intermediate (**III**) can then be attacked by the newly formed alcohol to give the final THF product (**1.35**). Panek’s method allows for the creation of three stereocentres and a THF ring in highly diastereoselective fashion.



Scheme 14. Panek THF Synthesis

1.3 Radical Cyclizations of Substituted THF Rings

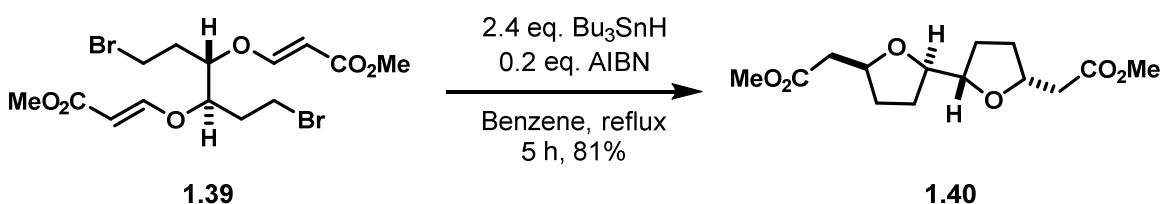
Radical reactions provide an efficient way to produce cyclic compounds and have been utilized in the production of THF rings.¹³ Radical cyclizations require an initiation step to form a radical species, and a classic initiator is AIBN (**1.36**), which under high temperature or light stimulus decomposes into two equivalents of *isobutyl*nitrile radical (**I**) (Scheme 15). This radical can then be transferred to Bu_3SnH , which will go on to react with the cyclization substrate (**II**). The tin radical selectively attacks halogen species **1.37** to form a carbon radical on the substrate (**III**). The radical then cyclizes forming the 5-membered ring, as Baldwin's rules favour 5-exo-tet over 6-endo-tet. Finally, the resultant radical (**IV**) is quenched by Bu_3SnH to form the product (**1.38**) and propagate the reaction.



Scheme 15. General Radical Cyclization Mechanism

1.3.0 Carbon Centred Radical THF Cyclization

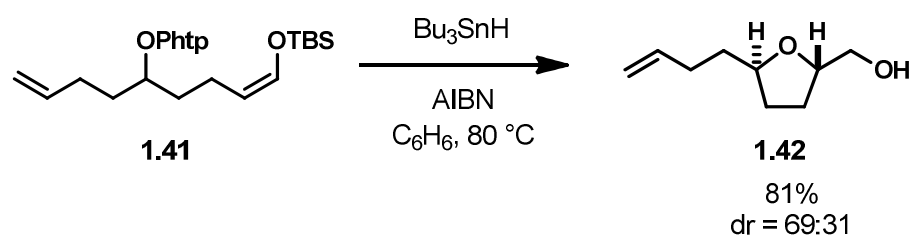
Carbon-centred radical cyclizations have been used to create THF compounds in natural product synthesis.¹⁴ The Kim group used a diethyl tartrate-derived cyclization precursors (**1.39**) to access bis-THF structures (Scheme 16). When precursor **1.39** was submitted to radical cyclization conditions it afforded 81% of the desired product (**1.40**). Kim's cyclization conditions produced the *cis* product exclusively and was extended to include the synthesis of THP rings.

Scheme 16. Radical Mediated Synthesis of a *bis*-THF

1.3.1 Sammis Oxygen Centred Radical Cyclization

Radical cyclizations have been applied in the synthesis of *trans*-THF rings. The Sammis group has developed conditions for generation of an oxygen-centred radical that cyclizes onto strategically placed silyl enol ethers (Scheme 17).³ This reaction selectively forms the THF *exo* addition product over the *endo*-pyran, conforming to Baldwin's rules.

These reaction conditions produce good yields with up to 9:1 diastereoselectivity (Scheme 17). Diastereoselectivity arises from transition state **1.43** as transition state **1.44** is disfavoured due to steric interactions of the silyl group (Figure 1). Placing a sterically bulky group at R³ helps force the silyl enol ether into the desired transition state (**1.43**) improving dr (diastomeric ratio). THF products with little substitution about the ring show a lower dr of 3:1 but maintain high yields.



Scheme 17. Sammis' Radical Cyclization

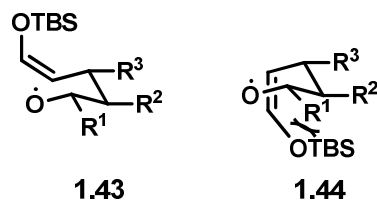


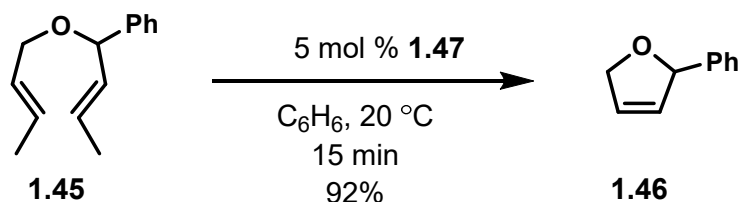
Figure 1. Sammis' Transition States

1.4 Transition Metal Catalyzed THF Synthesis

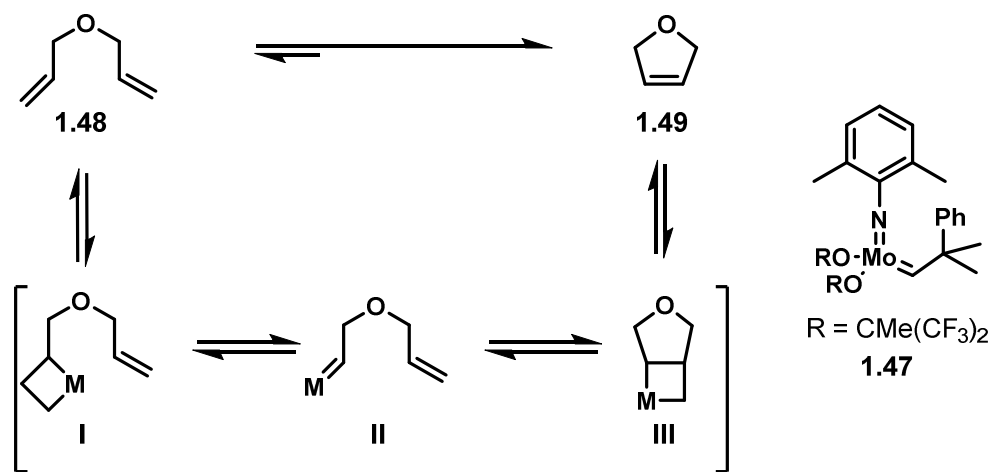
1.4.0 Cross Metathesis

Transition metal-catalyzed reactions have played a major role in expanding the scope of organic synthesis. Many of these reactions have been applied to the formation of cyclic compounds including THF rings. One such transition metal-catalyzed reaction is olefin metathesis – discovered by Zeigler¹⁵ in the 1950's and made synthetically versatile by Grubbs in 1992 - it has become a staple in synthesis.¹⁶ Grubbs along with Schrock and

Chauvin were awarded the Nobel prize in chemistry in 2005 for their contributions in alkene metathesis. Cross metathesis allows for the combination of various olefins to add substituents to an alkene effectively. When used in the synthesis of cyclic molecules this process is referred to as ring closing metathesis (RCM). Ring-closing metathesis requires the use of Mo or Ru complexes (**1.47**).¹⁷ These complexes are able to form a metallocycle (**I**) by cycloaddition to an alkene, which then eliminates a waste alkene and forms a carbene complex (**II**) (Scheme 19). The carbene is now able to undergo an intramolecular formation of a carbocycle intermediate (**III**). This intermediate can eliminate the catalyst to afford a DHF (dihydrofuran) product (**1.46**), which can be reduced under subsequent reaction conditions to afford a THF. Grubbs demonstrated this reactivity using Schrock catalyst **1.47** at 5 mol % loading in benzene.¹⁸ Precursor **1.45** cyclizes selectively to the *cis* alkene due to ring constraint in good yield.



Scheme 18. Grubbs Ring Closing Metathesis



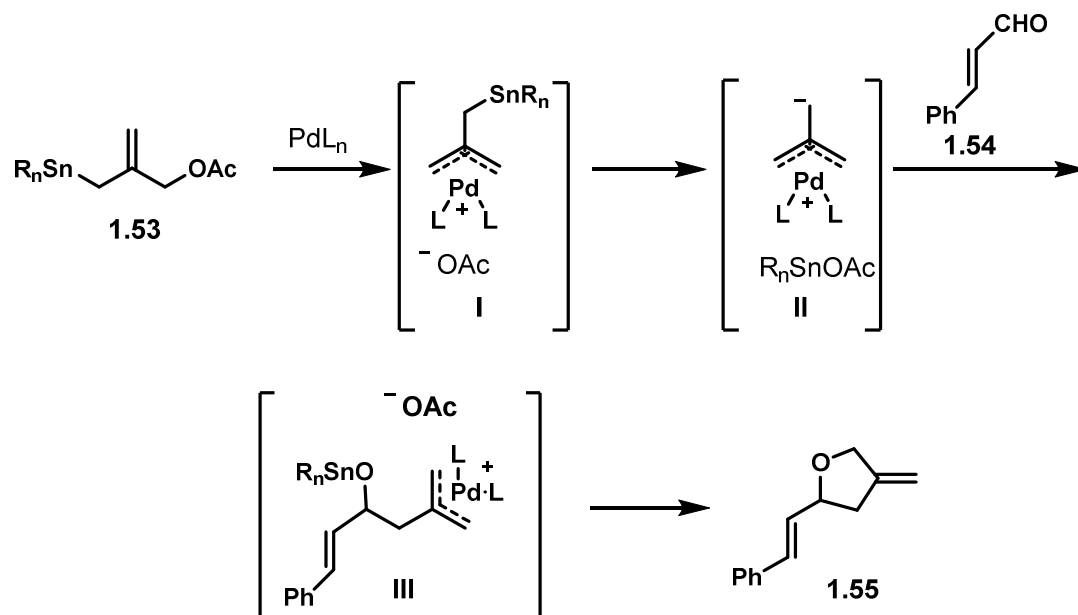
Scheme 19. RCM Mechanism

1.4.1 Metal Catalyzed Trost Annulation

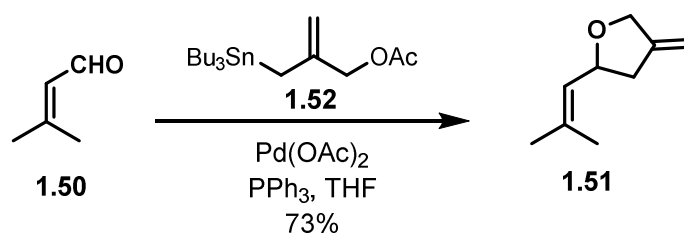
Palladium catalysis has been utilized by Trost to form THF rings with aldehydes.¹⁹ Trost synthesized THF rings using allyl acetate with a pendant metal functionality (**1.53**) (Scheme 20). The palladium catalyst undergoes oxidative addition to the allyl acetate forming a π -allyl complex (**I**) and the pendant tin species is removed, by nucleophilic attack of acetate, allowing the nucleophilic reactivity of the trimethylenemethane species (**II**). Aldehyde is added to the reaction mixture and is attacked by the nucleophilic trimethylenemethane leaving a newly formed alkoxide species, which undergoes cyclization with the π -allyl complex to form the exomethylene THF product (**1.55**). Trost was able to form the desired THF product (**1.51**) in 73% yield when using aldehyde **1.50** (Scheme 21).

The stereochemical outcome of the Trost cyclization reaction is *cis* and the *er* is conserved from the nucleophilic alcohol (Scheme 22). When the benzoate starting material **1.56** is displaced by Pd^0 , it forms complex (**I**). This transition state allows backside attack on the palladium complex to form the *cis* product. Steric interactions of the oxygen centre

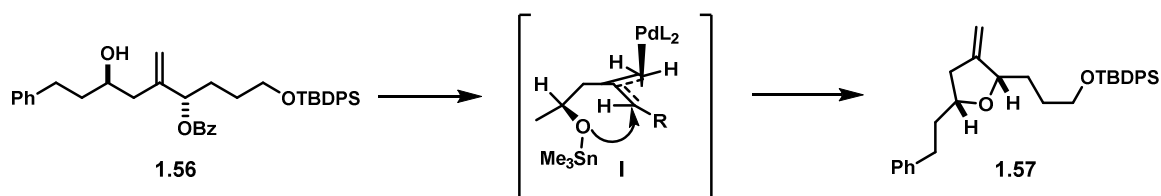
are cited as the predominant reason for the facial selectivity but further studies also incorporate 1,3 interactions as an integral factor in the resultant dr.



Scheme 20. Trost Annulation Mechanism

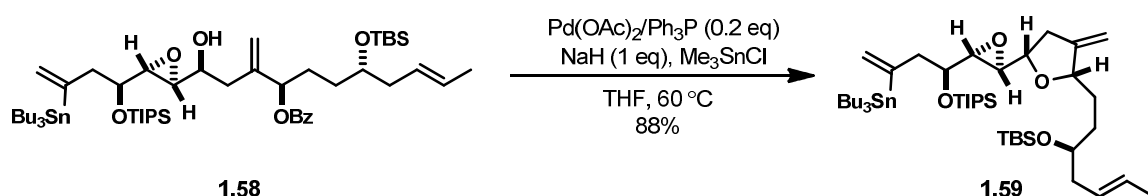


Scheme 21. Trost Annulation



Scheme 20. Intramolecular Trost Annulation

Meyer and co-workers used Trost's strategy to form the C7-C22 fragment of amphidinolide K.²⁰ Under their cyclization conditions THF precursor **1.58** forms both the tin alkoxide and palladium complex which undergoes cyclization to afford THF fragment **1.59** in 88% yield (Scheme 23).



Scheme 21. Synthesis of a THF Fragment of Amphidinolide K

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2. Cobalt Catalyzed Oxidative Cyclization

The use of molecular oxygen as an oxidizing agent is the most cost effective and atom economical choice for oxidation reactions (akin to H_2 in reductions). Unfortunately, molecular oxygen reactivity is typically not high enough to allow for it to be a useful reagent for most chemical transformations. A number of methods have been developed to allow the use of oxygen as the stoichiometric oxidant in conjunction with a catalytic transition metal complex.¹ Such oxidation reactions include, but are not limited to, epoxidation,² olefin dehydrogenation,³ peroxygenation⁴ and alcohol oxidation.⁵

2.1 The Mukaiyama Discovery

In 1989 the Mukaiyama group was studying the use of molecular oxygen with cobalt catalysts to perform various oxidations of alcohols and alkenes.⁶ One such oxidation was the use of $Co(L)_2$ type complexes (Figure 2) to produce trimethylsilylperoxides in good yield (Scheme 24).⁷

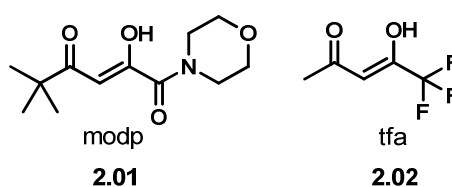
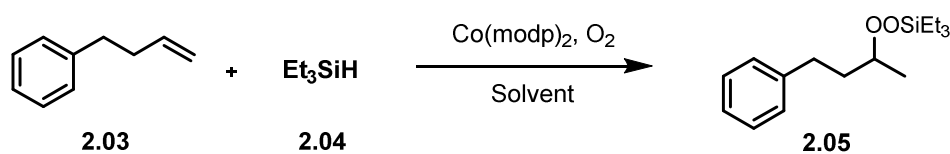

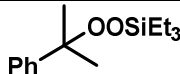
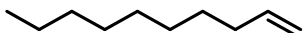
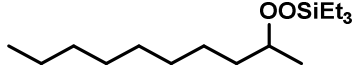
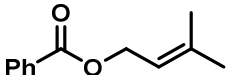
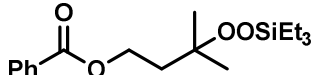
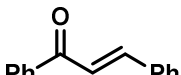
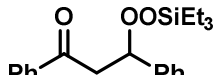


Figure 2. Mukaiyama's Ligands



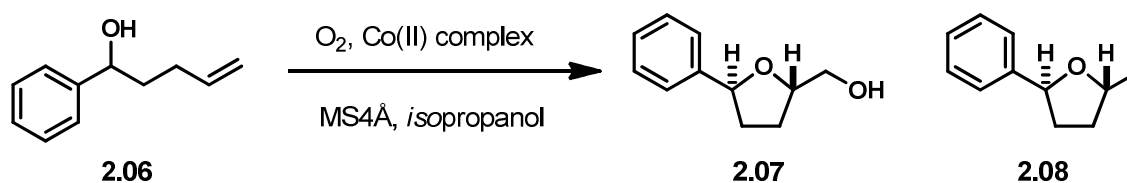
Scheme 22. Mukaiyama Trimethylsilylperoxide Synthesis

Entry	Alkene	Time/h	Product	Yield
1		5		95
2		12		80
3		10		99
4		12		75

a) Reaction conditions: Triethylsilane, alkene and Co(modp)₂ reacted under O₂ atmosphere in DCE.

Table 1. Mukaiyama Silylperoxide Oxidation of Alkenes

This was accompanied by the use of an extended set of similar catalysts to perform oxidation, reduction, or hydrations of alkenes.⁸ Further extension of this work revealed that when subjecting a pent-4-ene-1-ol to the hydration reaction conditions, cyclization and oxidation occurred rather than olefin hydration (Scheme 24, Table 1)). Various Co(II) complexes were examined from Co(tfa)₂ (**2.02**) to Co(modp)₂(**2.01**) (Figure 2).⁶ It was shown that the oxidative activity was present only in cobalt species with a reduction potential from approximately 0 and 0.5 eV relative to Ag/Ag⁺ in acetonitrile.⁹ This reactive range was demonstrated in Mukaiyama's hydration chemistry and the trend holds true for the oxidative cyclization. Electron withdrawing groups, located on the cobalt ligand, such as amides, esters, and trifluoromethyl groups, have been shown to produce cobalt species with reduction potentials in the 0.4 to 0.5 eV. This range of cobalt species has produced the highest yields and selectivity towards to the cyclized THF product. In Mukaiyama's case, the Co(modp)₂ (**2.01**) catalyst proved to be the most effective and continued as the catalyst of choice. The reaction conditions were optimized and it was found that moderate temperatures such as 50 °C were optimal as opposed to 75 °C, which resulted in lower yields and an increase in undesired side products with Co(tfa)₂ (Table 2). The addition of peroxides decreased reaction times and increased yields (Entries 5-7, Table 2).

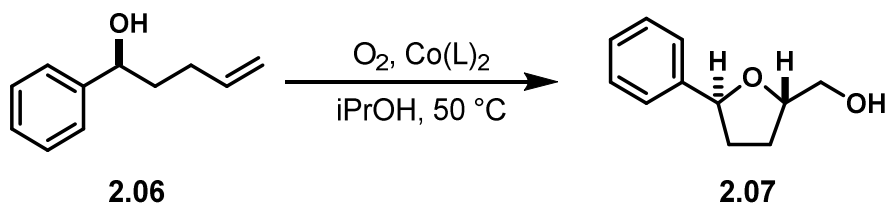


Scheme 23. Mukaiyama's Initial Discovery

Entry	Catalyst	Temperature (°C)	Additive (mol %)	Time (h)	Yield (%)	
					2.07	2.08
1	Co(tfa) ₂	75	-	4	21	24
2	Co(tfa) ₂	50	-	8	55	0
3	Co(acac) ₂	50	-	1	29	0
4	Co(modp) ₂	50	-	0.5	62	0
5	Co(modp) ₂	50	<i>t</i> BuOOH (50)	0.5	64	0
6	Co(modp) ₂	50	<i>t</i> BuOOH (100)	0.5	73	0
7	Co(modp) ₂	50	CHP (100)	0.5	71	0

Table 2. Mukaiyama's Initial Cyclization Optimization

While providing good yields and excellent dr, the examples do not include any oxidatively sensitive functional groups or acid sensitive functional groups. Other major limitations of this study are substitution being limited to differentiation of the C2 position on the tetrahydrofuran ring and only terminal alkenes were explored (Table 3). It was shown that electron donating and withdrawing groups had little effect on the reaction (Table 3, Entries 2 and 3), as did steric bulk (Table 3, Entry 8). A decrease in yield was observed in substrates with bulky groups at the two position with dr remaining greater than 97:3 *trans:cis* selectivity at the C2 and C5 positions.

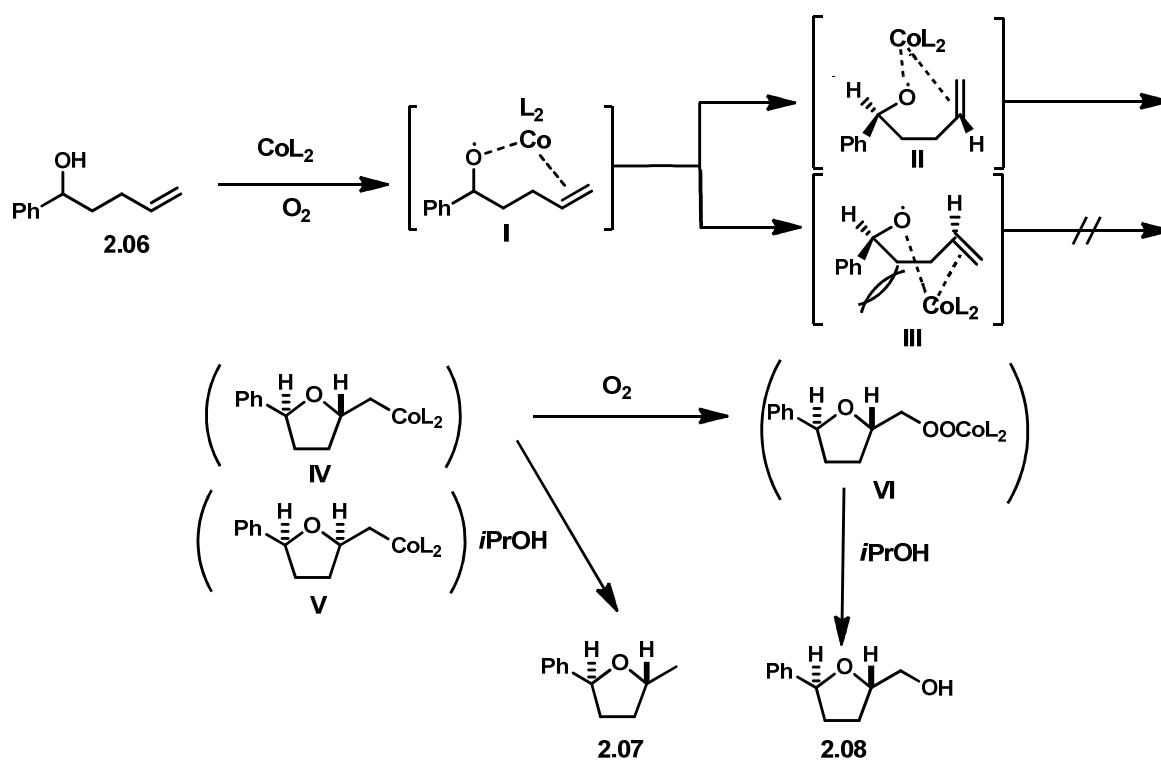


Scheme 24. Mukaiyama Oxidative Cyclization

Entry	Substrate	Product	Yield (%)	dr (trans %)
1			73	99
2			69	99
3			60	99
4			79	99
5			62	99
6			69	97
7			53	99
8			55	>99

Table 3. Mukaiyama's Substrate Scope for the Oxidative Cyclization

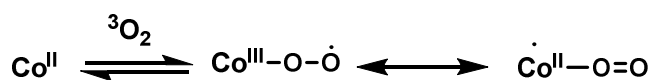
A mechanism was hypothesized by Mukaiyama in his original work, however, experimental validation of the proposed mechanism was absent.⁶ Mukaiyama hypothesized coordination of the cobalt catalyst to the alcohol and alkene sections of the pentenol (Scheme 27). An oxygen-centered radical (**I**) is formed and stereoselectivity guided towards the alkene via π -bond interaction with the cobalt centre. Due to steric factors, the cobalt complex resides opposite the R group (**II**) of the alkenol and forms a *trans*-THF junction. This leaves a cobalt-stabilized radical (**IV**), which can either be oxidized by molecular oxygen then terminated with solvent to form the major hydroxylated THF product (**2.08**) or quenched before oxidation to form the alkyl THF (**2.07**).



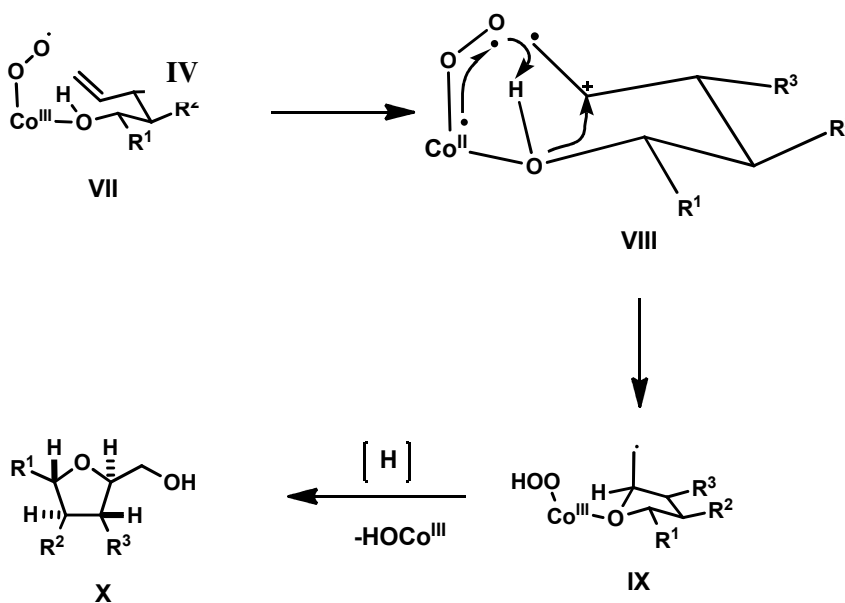
Scheme 25. Mukaiyama's Proposed Mechanism

2.2 Hartung's Mechanism of the Mukaiyama Cyclization

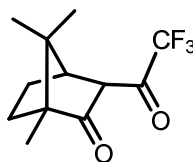
In a more recent work, the Hartung group has proposed an alternative mechanism,¹⁰ in which the coordination of dioxygen to the paramagnetic cobalt species forms a strong Lewis acid and metal oxidizing agent (Scheme 28). The O₂ cobalt species then coordinates to the alcohol in the starting material (Scheme 29). Hartung states that Co(acac)₂ complexes have the ability to oxidize alkenes to the radical cation. A single electron transfer occurs between the alkene and the Co(III) centre (VII). Without the restraint of the double bond, the former alkene carbons are free to rotate into a more suitable chair transition state that allows for hydroxyl attack onto the cation to form the *trans*-THF ring (IX). The reaction is terminated with quenching of the oxygen-centred radical to form the alcohol and loss of Co(III)OH (X).



Scheme 26. Cobalt Activation of O₂



Scheme 27. Hartung's Proposed Mechanism



2.09

Figure 3. Ligand Used in the Hartung Studies

Hartung was able to provide evidence for his mechanism through an extensive substrate scope using a cobalt complex of **2.09** (Figure 3). The proposed radical cation intermediate (**VIII**) was supported by the lack of diastereoselectivity when a non-terminal alkene was cyclized. A similar observation was also seen by Pagenkopf and co-workers in 2006 and is discussed in section 2.4.3 (Table 4). These observations preclude an epoxide intermediate as high selectivity would be expected for such an intermediate. A large substrate scope showed high diastereoselectivity towards 2,5-*trans*-configurations in the final product with 2,3 *trans* and 2,4 *cis* also giving moderate diastereoselectivity. The latter relationships can be overcome by a stronger influence by 2,5 *trans* diastereoselectivity. This is attributed to the chair transition state involving the radical cation intermediate.

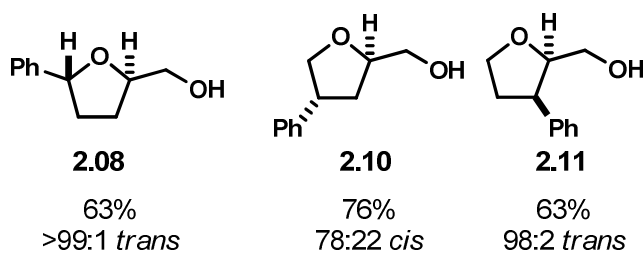
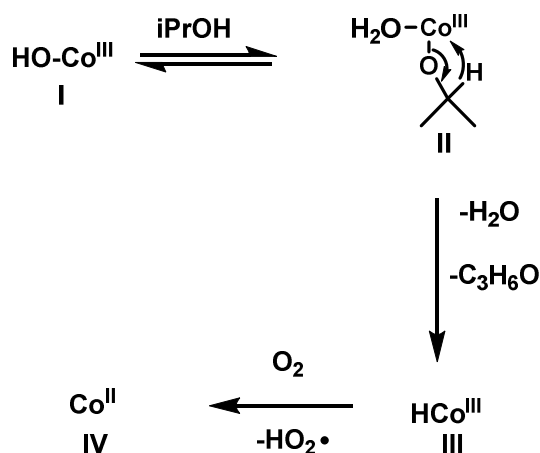


Figure 4. Diastereoselectivity of the Mukaiyama Cyclization

An important step in any catalytic sequence is regeneration of the catalyst. As it is apparent that Co(III)OH will not catalyze the cyclization, there must be a pathway for the

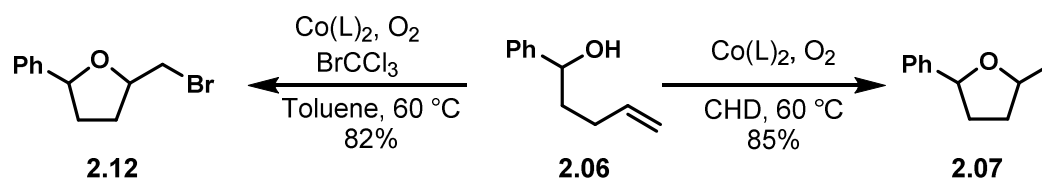
renewal of the original complex. The use of a suitable hydrogen donor proves vital to this sequence as the Co(III)OH (**I**, Scheme 30) by-product coordinates itself to a donor molecule (often *i*PrOH) and performs an oxidation to create the oxidized donor molecule and H₂O, which are lost leaving the hydridocobalt(III) complex (**III**). This is then reduced by abstraction by O₂ (**IV**). The production of acetone during mechanistic studies supported Hartung's pathway. During NMR studies using deuterated *isopropanol*-d₈, it was found that solvent was a major proton source for termination of the radical species.



Scheme 28. Catalyst Regeneration

Hartung noted several limitations including the inability to form 2,5-substituted THFs with bulky substitution patterns in appreciable yield and pyran ring formation being inaccessible using the same reaction conditions. Despite these limitations, increased utility for this chemistry was obtained by expanding the electrophiles that are capable of terminating the primary radical produced during the catalytic cycle. By utilizing alternative reaction conditions, a toluene/cyclohexadiene (CHD) solvent system with added BrCCl₃

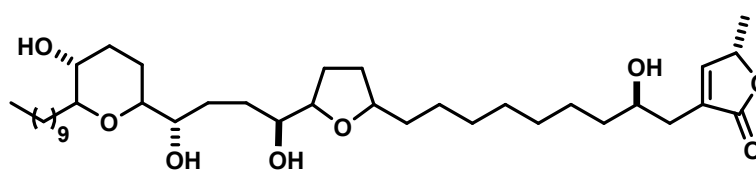
can produce the primary bromide product (**2.12**, Scheme 31).¹¹ Alternatively, CHD as the sole reaction solvent allows for reductive termination of the catalytic cycle to produce the fully reduced product (**2.07**).



Scheme 29. Hartung Reductive Termination of an Oxidative Cyclization

2.3 Applications

Given the Mukaiyama oxidative cyclization's inherent synthetic utility, several syntheses have been reported with the Co(II) catalyst as the THF-forming step. The first was the synthesis of gigantetrocin A by Wang and Shi followed by Evans' synthesis of mucocin (**2.13**).¹² The Mukaiyama oxidative cyclization was also utilized by the Pagenkopf group in the synthesis of aplysiallene (**2.24**)¹³ and bullatacin (**2.17**)¹⁴, which will be addressed later in section 2.4.0.

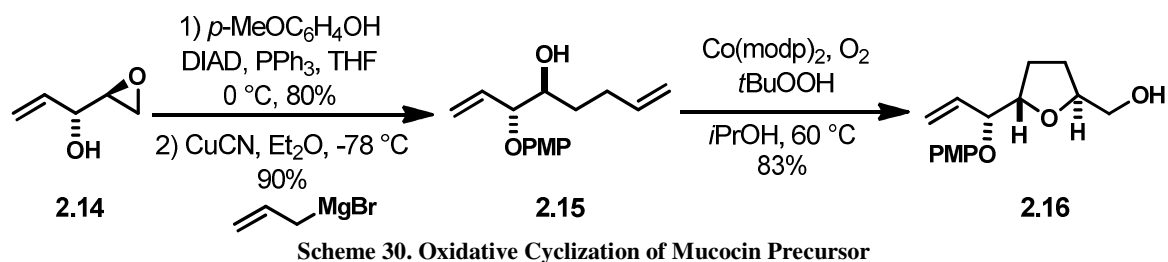


2.13

Figure 5. Mucocin

The synthesis of mucocin (**2.13**) shows how a rather simple starting material can very quickly be formed into a more complex molecule via oxidative cyclization of the appropriate precursor (Scheme 32). Sharpless epoxide **2.14** is treated with allyl Grignard reagent to afford THF precursor **2.15**. Application of the cobalt-catalyzed oxidative

cyclization conditions forms *trans*-THF ring **2.16**, generating a new stereocentre with a very high degree of diastereocontrol. This sequence demonstrates the convenience of the oxidative cyclization.



2.4 The Pagenkopf Group

2.4.0 Natural Product Synthesis – Bullatacin and Aplysiallene

A driving force for exploration of the Mukaiyama oxidative cyclization has been the pursuit of several natural product syntheses within the Pagenkopf group. Bullatacin¹⁴ and aplysiallene¹³ have unique structural complexities and the former displaying high bioactivity making it an interesting target and a more complex application of the THF cyclization.

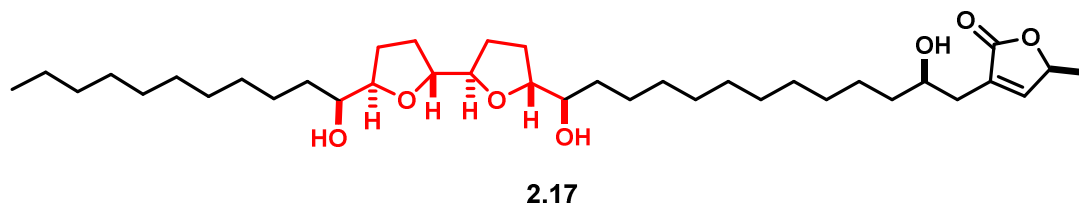
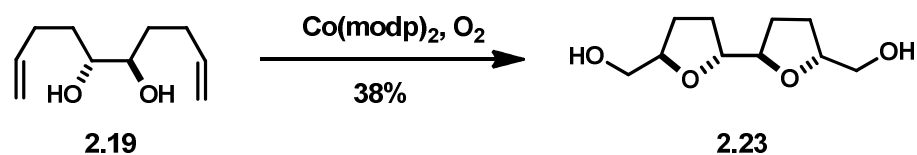
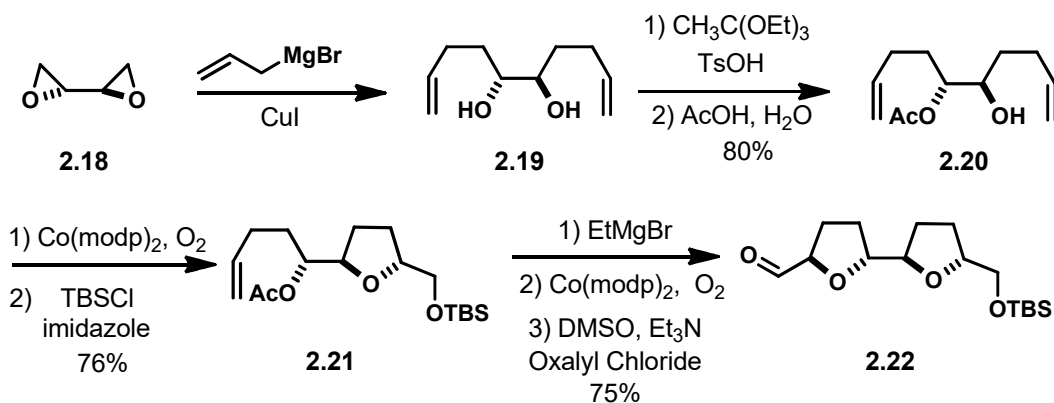


Figure 6. Bullatacin



Scheme 31. Unprotected Cyclization Attempt



Scheme 32. Key Steps in the Synthesis of Bullatacin

The synthesis of bullatacin (**2.17**), completed in 2006,¹⁵ utilized the Mukaiyama oxidation to create the central *bis*-THF core (**2.22**).¹⁴ The starting diepoxide was opened by allyl magnesium bromide to form dipentenol substrate **2.19**. From the dipentenol substrate, a cyclization reaction would have produced the core of bullatacin, but despite a published precedent, the reaction proceeded in an unacceptable yield (Scheme 33).¹² Monoprotection of diol and performing the THF cyclization in a stepwise fashion produced the finished core in 45% over 7 steps (Scheme 34).

Aplysiallene (**2.24**) contains an interesting fused *bis*-THF core, which under closer examination can be constructed in a similar manner to bullatacin (**2.17**).¹³ Unlike the synthesis of bullatacin, the THF core was successfully cyclized in good yield; however, attempts to desymmetrize the tetrahydrofuran core were unsuccessful. Wang and Pagenkopf were then able to apply a similar strategy to that of the bullatacin synthesis to

access the THF core. Initial desymmetrization of diol precursor **2.25** followed by two sequential cyclizations gave the THF core (**2.27**) of aplysiallene in good overall yield (Scheme 35).

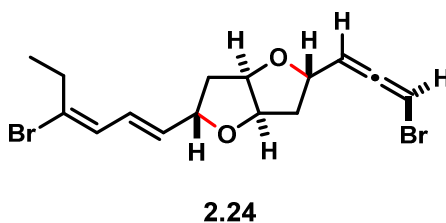
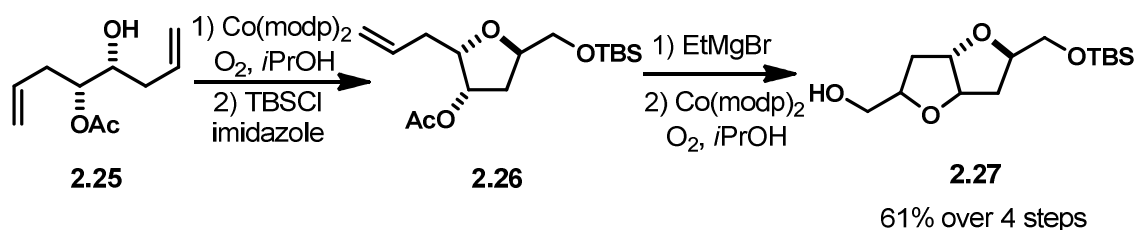


Figure 7. Aplysiallene

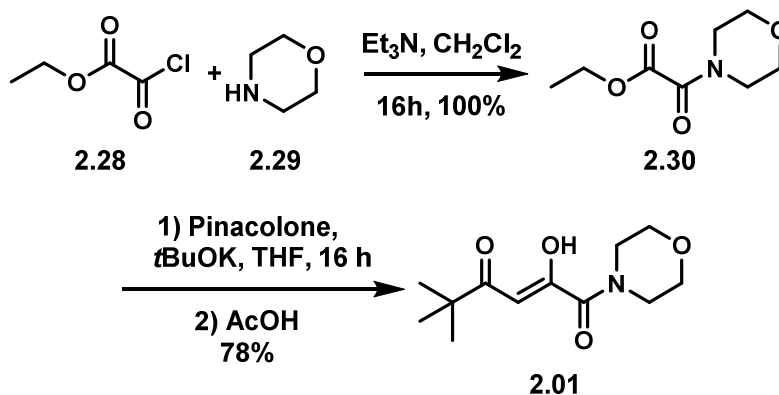


Scheme 33. Key Steps in the Synthesis of Aplysiallene

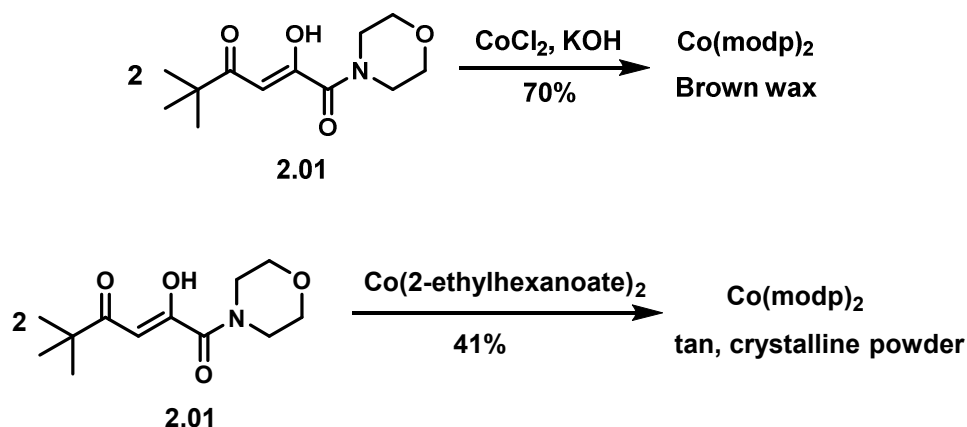
2.4.1 “Revamped” Synthesis of The Mukaiyama Ligands

While being an efficient method of obtaining THF rings, the Mukaiyama catalyst was not without drawbacks. The catalyst is prepared using CoCl₂ and KOH conditions in order to coordinate the morpholine derived ligand (modp) (Scheme 36). The catalyst also produced inconsistent yields in the cyclization of THF rings, and this is hypothesized to be due to low purity and decomposition of the catalyst. The Pagenkopf group was able to redesign the synthetic route to the catalyst by utilizing cobalt-2-(ethylhexanoate)₂ in place of CoCl₂, which allowed for the complexation to occur in consistently good yield (Scheme 37).¹⁶ Also, unlike the original procedure to produce the Mukaiyama catalyst, which was

a brown wax, the new method produced a crystalline powder allowing for convenient use in the laboratory setting.



Scheme 34. Modp Ligand Synthesis



Scheme 35. Synthesis of Co(modp)_2

2.4.2 Crystal Structures

Throughout the course of the previously described natural product synthesis projects, effort was directed to the refinement and expansion of the Mukaiyama methodology. Several variations of the cobalt catalysts were prepared in hopes of producing a catalyst with higher stability and overall performance in the oxidative cyclization. Conveniently, x-ray quality crystals were obtained during these studies and

the structure of the catalyst was found. At that point in time, very little structural information was known as the paramagnetic cobalt centre makes NMR experimentation near impossible. After the synthesis of a broad range of ligands with varying substitution patterns, one was successfully crystallized in both the Co(II) and Co(III) oxidation states.¹⁶ The Co(II) species was shown to be a bidentate structure with a single cobalt centre (Figure 8). The Co(III) species, however, was shown to contain two cobalt centres with bridging hydroxyl groups and two associated ligands (Figure 8).

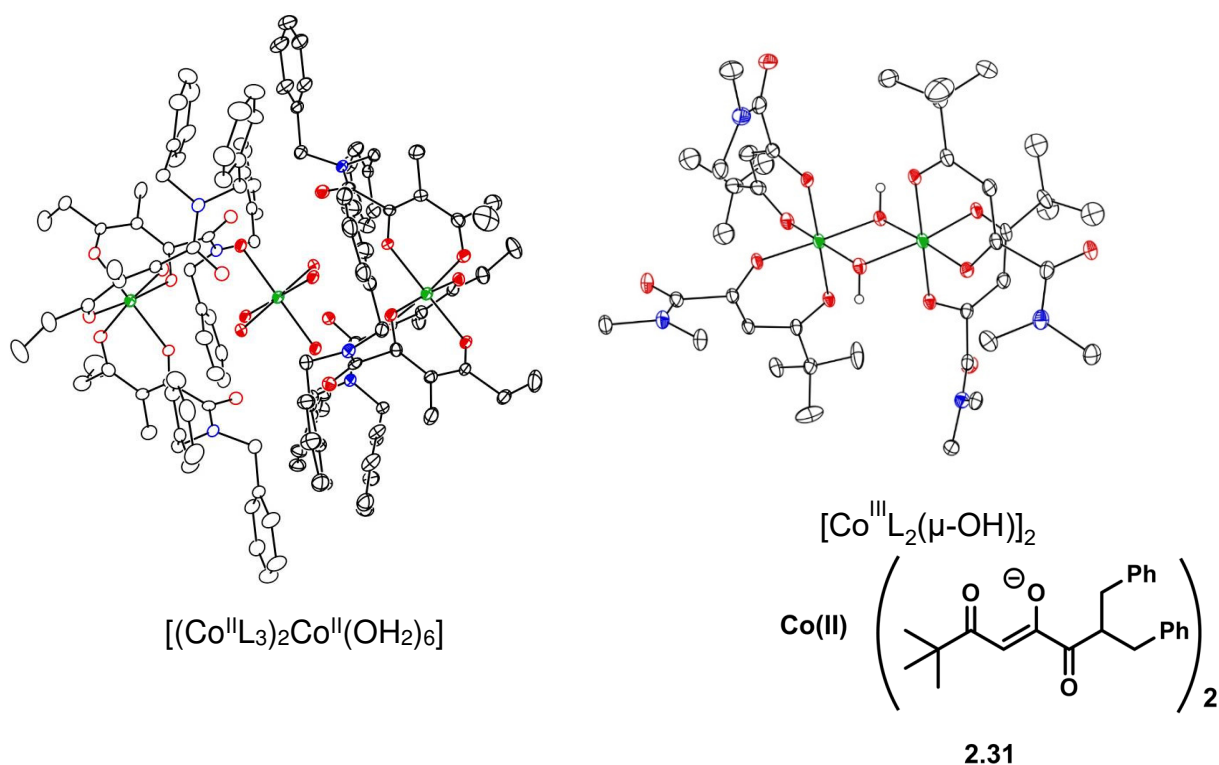
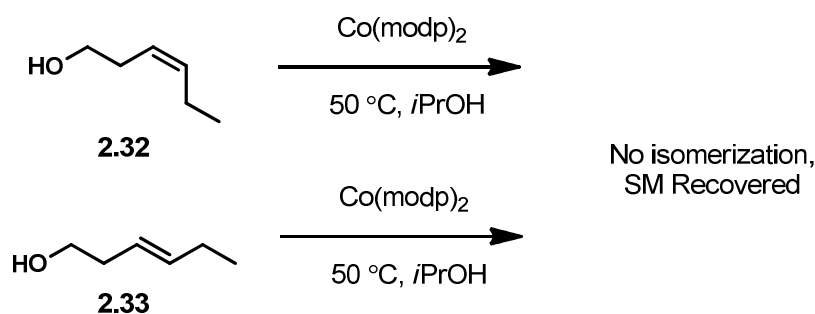


Figure 8. X-Ray Crystal structures of $\text{Co}(\text{DiBn})_2$

2.4.3 Substrate Scope Exploration

Through a series of experiments conducted in the Pagenkopf lab¹⁵ the general reactivity scope of the cobalt catalyzed cyclization was explored (Table 4). The reactivity

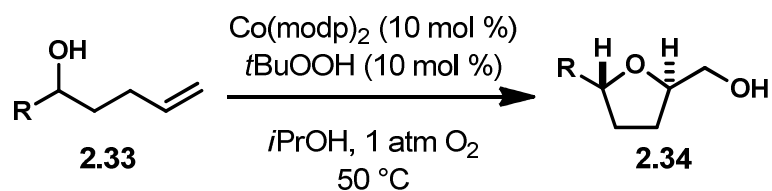
of the cobalt centre with various homoallylic alcohols was tested and it was found that they do not cyclize. It is also important to note that the *E/Z* configuration of the alkene substrate is not affected by the reaction conditions and this selectivity allows for an enhanced synthetic utility (Scheme 38). When both alkenes **2.32** and **2.33** were subjected to cyclization conditions, only the starting material was recovered. The chemoselectivity and lack of isomerization allows a greater tolerance for external functionality on a substrate molecule, increases this methodology's utility in synthesis.



Scheme 36. Isomerization Experiment

Cyclization precursors with an *exo*-methylene unit gave the desired methyl-substituted product in similar yield to the unsubstituted starting material (Entry 2, Table 4). Placing a geminal dimethyl group on the terminal end of the alkene resulted in the complete shutdown of reactivity, with only starting material obtained (Entry 3, Table 4). Substitution on the two position of the alcohol gave a good yield, but only a 1.7:1 *cis/trans* diastereoselectivity (Entry 4, Table 4). A pentanol with phenyl substitution at the three position was able to cyclize in good yield and produced an 8:1 (*trans:cis*) ratio at the 2,3 substitution. Similar results were also obtained by Hartung¹⁰, which assisted in elucidating the previously discussed mechanism (Scheme 29). An internal alkene could be cyclized

but without any selectivity towards the stereochemistry of the produced secondary alcohol. The internal alkene cyclization was performed using both *cis* and *trans* alkenes resulting in virtually the same product ratios, likely due to a common radical intermediate (Table 4, Entries 6-7).



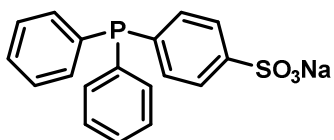
Scheme 37. Mukaiyama Oxidative Cyclization

Entry	Alcohol	Product	Yield
1			82
2			75
3			0
4			83 (1.7:1 <i>cis/trans</i>)
5			75 8:1 <i>trans:cis</i>)
6			71% (1.2:1 <i>syn:anti</i>)
7			53% (1.3:1 <i>syn:anti</i>)

Table 4. Substitution Effect on dr.

2.5 Objectives of the Current Research

Despite the high dr, simplicity of starting materials, and good yields of the Mukaiyama oxidative cyclization, there is great difficulty when attempting to remove the decomposed cobalt by-products while isolating the product. During the purification of cyclization products with flash column chromatography, the green cobalt residue will streak on silica and coelute with the desired THF product. Difficulty in obtaining purified products was amplified when attempting to scale-up reactions to produce large quantities of starting material for synthesis. Even after multiple purification attempts, cobalt species may still remain and contaminate the product. This is not only a problem because the product is impure but also because the paramagnetic cobalt species causes characterization



2.35

Figure 9. Sulphonated Phosphine

via NMR spectroscopy to be difficult or in some cases impossible. As this transformation played an integral part of many current synthetic projects within the Pagenkopf group, it was decided that dedication of resources to surmount this challenge was warranted. The first and seemingly simplest option was to modify the existing ligands. Many methods have been developed in order to overcome solubility problems in other catalytic reactions, these include but are not limited to sulfonated ligands and ionic liquids (Figure 9).¹⁷ These modifications aim to add functionality without affecting the desirable reactivity of the original ligand. The method envisioned to work the best with the Mukaiyama catalyst was to modify the morpholine ring of the modp (**2.01**) ligand by replacing morpholine with a 1-methyl piperazine unit (**2.37**). This would allow the ligand to be converted to the ammonium species and extracted via an acid workup.

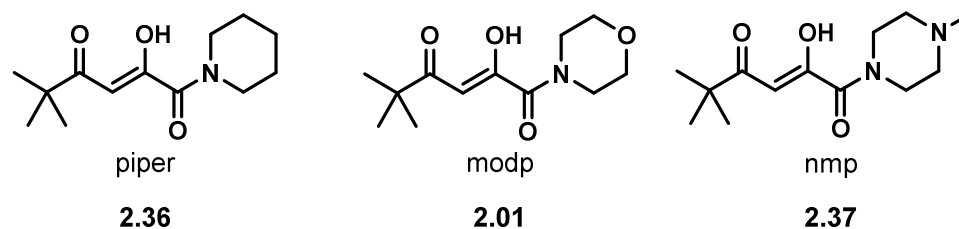


Figure 10. Several CoL₂ Ligands

2.6 Results & Discussion

With a (*Z*)-2-hydroxy-5,5-dimethyl-1-(4-methyl-1-piperazinyl)-2-hexene-1,4-dione ligand (nmp) target in mind, the synthesis of a highly polar or ideally aqueous-soluble Mukaiyama catalyst began.¹⁸ The synthesis began with condensation of 1-methylpiperazine with ethyloxalyl chloride (Scheme 40). A subsequent Claisen condensation with pinacolone afforded the ligand. Previously reported conditions called for the use of aqueous acetic acid to quench the reaction and form the enol product. When these conditions were used in the synthesis of **2.37**, poor yields were observed due to formation of the ammonium species and loss in the aqueous workup. This was solved by using two equivalents of acetic acid in CH₂Cl₂ and a simple filtration to remove the residual potassium acetate salt. Complexation of the ligand to the cobalt(II) centre was challenging as standard condition led to poor yields and a purple solid that performed poorly in the oxidative cyclization. A purple color is indicative of unreacted cobalt(II) ethylhexanoate species, which interferes with the desired cyclization reaction. Previous studies within the

Pagenkopf group have provided crystallographic evidence that showed adventitious water in the crystal structure and its importance in synthesizing the various cobalt catalysts.¹⁶

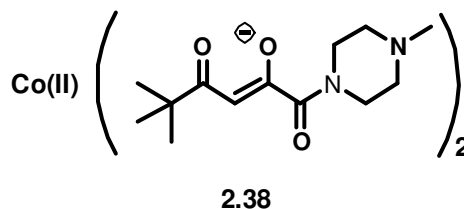
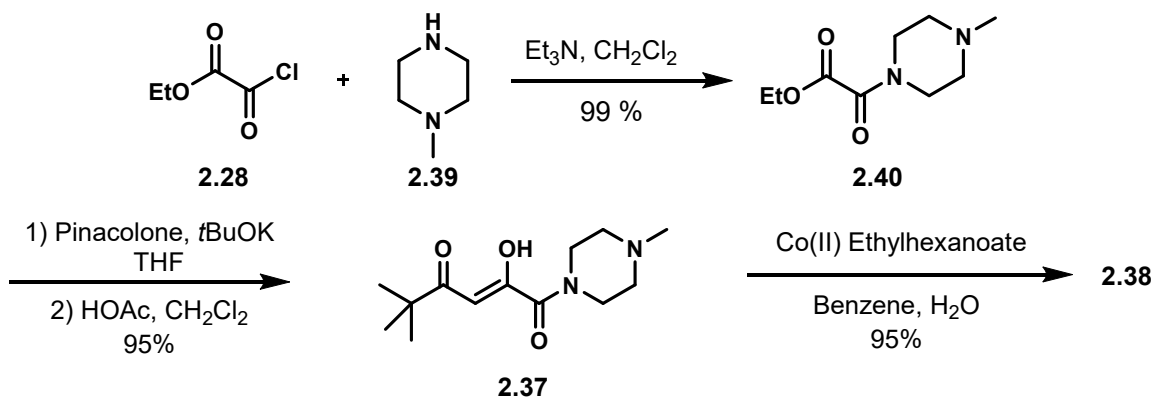


Figure 11. Cobalt NMP Catalyst

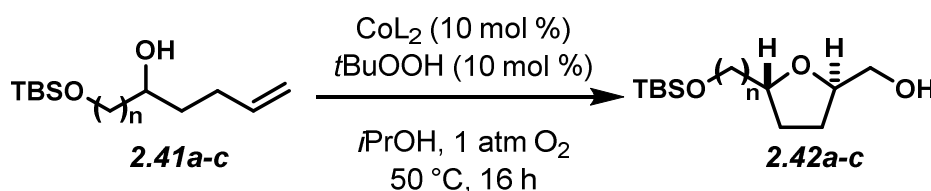
It was found that the addition of several equivalents of water into the complexation mixture afforded a tan powder, which is a typical appearance for previous catalysts.



Scheme 38. Synthesis of Co(nmp)₂

This powder was subsequently tested against the standard piper (**2.36**) and modp (**2.01**) catalyst systems (Figure 10) with several TBS protected pentenols of varying side chain length (Table 5). These were chosen due to their ease of separation from the standard cobalt complexes allowing a more accurate and reproducible yield of the desired catalyst. Comparing all three test substrates, the nmp catalyst (**2.38**) provided an efficient method of extraction and improved yields by up to 28%. It is important to note that three methods

of extraction were examined: an aqueous acid wash (1 M HCl), a phosphate buffer wash, and methylation. All three successfully removed the cobalt species from the reaction but the strong acid was abandoned in favour of the two milder options as strongly acidic conditions can cause decomposition of sensitive functionalities.



Scheme 39. Initial Co(nmp)₂ Reaction Conditions

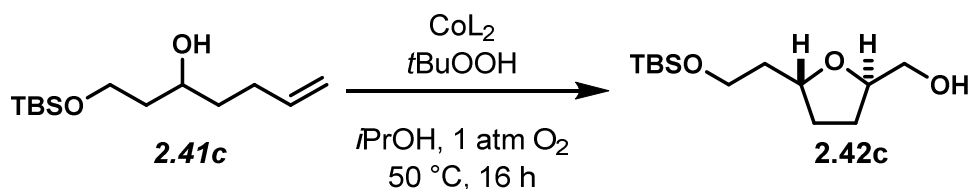
Entry	Starting Material	n	Yield %			
			modp (2.01)	piper (2.36)	nmp (2.37) ^a	nmp (2.37) ^b
1	2.41a	1	65	39	92	93
2	2.41b	2	68	75	90	90
3	2.41c	3	79	74	92	95

^a pH 4 phosphate buffer, ^b Methylation of the catalyst with MeI

Table 5. Preliminary catalyst comparison

After determining that the newly designed nmp catalyst (**2.37**) gave superior yields, experimentation into the optimal catalytic loading began (Table 6). The modp catalyst performed optimally at catalyst loadings as low as 10 mol %. Poor yields and by-product formation started to occur at low loadings using modp (**2.01**) and piper (**2.36**) ligands, along with complete consumption of the starting material. As the cobalt species produced product it began to degrade and the degradation products began to decompose the THF methanol products. In addition to decomposition pathways, the formation of reduction products could be observed as previously demonstrated by Mukaiyama. In contrast, the nmp catalyst (**2.38**) proved to be effective with catalyst loadings as low as 5 mol % and degraded harmlessly at loadings of 3 and 1 mol %. The lack of decomposition products

from the $\text{Co}(\text{nmp})_2$ allowed for the clean production of THF products and the absence of any observable THF methyl reduction products. The production of a single product in exceptional yield contributed significantly to the ease of purification and subsequently to the synthetic utility of the newly designed catalyst (**2.38**).



Scheme 40. $\text{Co}(\text{L})_2$ Catalyst and Catalytic Loading Conditions

Entry	Catalyst	Mol %	Yield (%)
1	$\text{Co}(\text{modp})_2$	15	68
2	$\text{Co}(\text{modp})_2$	10	65
3	$\text{Co}(\text{modp})_2$	5	47 ^a
4	$\text{Co}(\text{nmp})_2$	15	95
5	$\text{Co}(\text{nmp})_2$	10	97
6	$\text{Co}(\text{nmp})_2$	5	93
7	$\text{Co}(\text{nmp})_2$	3	57 (93) ^b
8	$\text{Co}(\text{nmp})_2$	1	10 (77) ^b

^a All starting material was consumed.

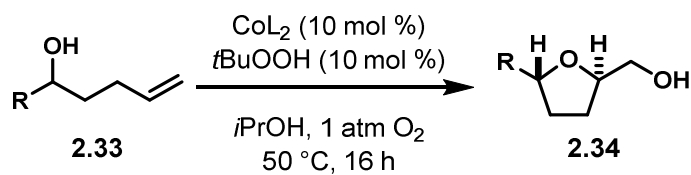
^b Yield based on recovered starting material.

^c Several examples were completed by Nick Morra and Barb Bajtos

Table 6. Catalyst Loading Studies

Initial $\text{Co}(\text{nmp})_2$ (**2.38**) results (Table 5 and 6) led to the examination of the versatility of the $\text{Co}(\text{nmp})_2$ catalyst and to determine if it was superior to the previous catalyst ($\text{Co}(\text{modp})_2$ (**2.38**) and $\text{Co}(\text{piper})_2$ (**2.36**)) across a wide variety of substrates. The

substrates were put through reaction conditions with all three catalysts and various purification methods were employed with the Co(nmp)₂ complex (**2.38**) (Table 7). The use of a buffer wash was effective but did not offer any improvement in yield as compared to the piper catalyst (**2.36**) (Table 7). These problems were also encountered initially with the methylation procedure but switching the extraction solvent from hexanes to dichloromethane allowed for an optimal extraction. In all cases, the purified product was obtained in over 80% yield with many instances over 90% (Table 7). In some cases, a thin pad of silica was used to filter the catalyst from the reaction mixture. While this method can be substrate-dependent it is by far the most efficient in those cases. Two enantiomerically pure examples were prepared using the Co(nmp)₂ catalyst. These examples represent the core structures of Aplysiallene and Bullatacin. The yields were either equal or superior to those reported in literature (Table 7, Entry 10-11).^{13,14}



Scheme 41. Substrate Scope Reaction Conditions

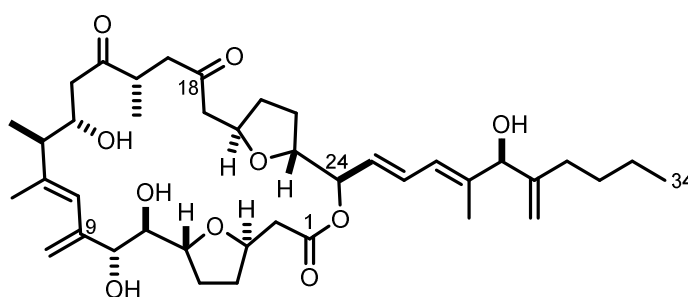
^a Entry	Product	Yield %			
		modp	piper	nmp MeI	nmp buffer
1		69 ^b	64 ^b	85	54
2		20	58	90	66
3		29	81 ^b	90	85
4		46	57	95	40
5		62	76	91	58
6		54	47	91	45
8		71	49	86	80
9		38	42	88	46
10 ^b		55 ^c	81	83	78
11 ^b		69 ^d	79	88	79

a) Typical reaction conditions: cyclization precursor (1 eq), $\text{Co}(\text{nmp})_2$ (10 mol %), $t\text{BuOOH}$ (10 mol %), $i\text{PrOH}$ (10 mL), O_2 (1 atm), 55 °C. *b*) This yield is a mixture of THF product contaminated with cobalt species that could not be removed by repeated chromatography. Thus, the yield is artificially elevated. *c*) See ref.¹³ *d*) See ref.¹⁴. *e*) Several examples were performed by Barb Bajtos, Andrew Stevens and Ben Machin.

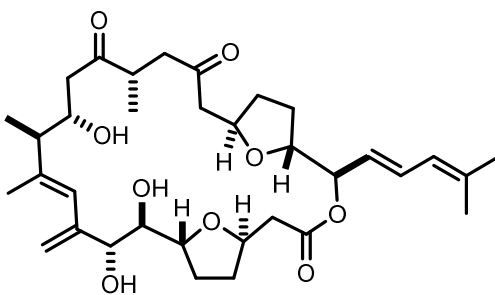
Table 7. Substrate Scope

2.7 Applications of $\text{Co}(\text{nmp})_2$ in Total Synthesis

Throughout the development of the $\text{Co}(\text{nmp})_2$ catalyst a major driving force for the research was the concurrent studies towards the total synthesis of amphidinolide C (**2.43**). While the synthesis of this molecule was possible with $\text{Co}(\text{modp})_2$, the newly developed nmp ligand allowed for a higher yielding step as well a simplified and more practical application in the laboratory.



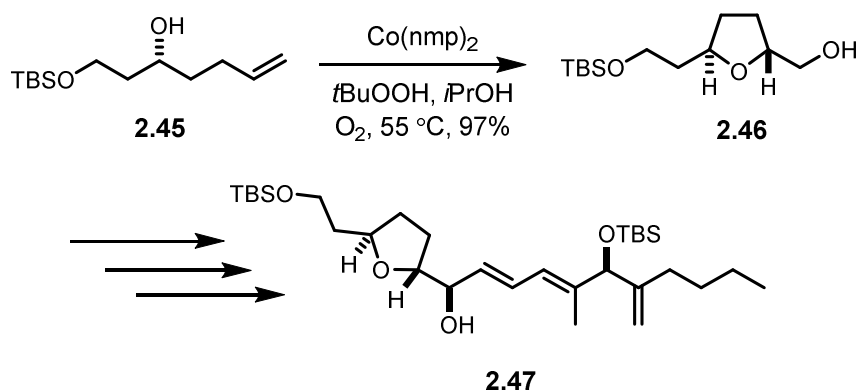
2.43



2.44

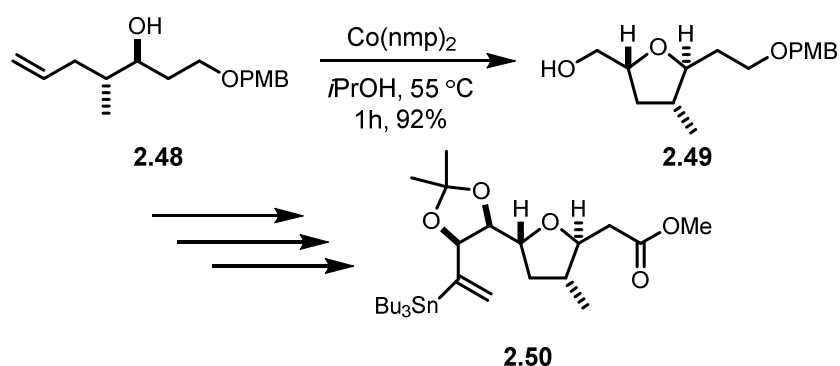
Figure 12. Amphidinolide C and F

The C(18) to C(34) fragment of amphidinolide C was prepared by Nick Morra via the Mukaiyama cyclization (Scheme 44).¹⁹ Sharpless epoxide derived pentenol **2.45** was cyclized to the corresponding THF methanol product in 97 % yield. The pendant alcohol serves as a functional handle for the construction of “tail” segment of the natural product (**2.43**). Fragment **2.47** was efficiently synthesized on gram scale in high yield.



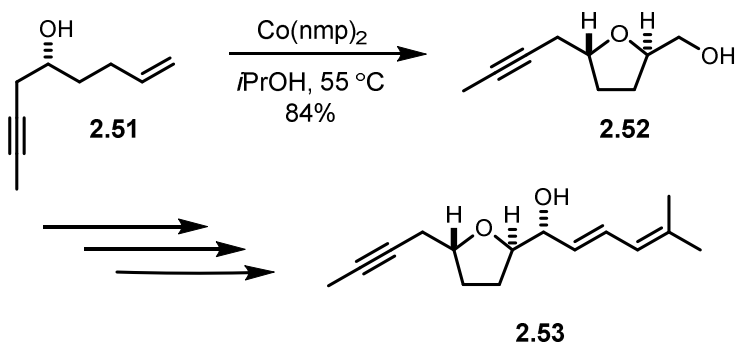
Scheme 42. The Gram Scale Synthesis of the C(18)-C(34) Fragment of Amphidinolide C

The C(1) – C(9) fragment of amphidinolide C was also constructed using the Mukaiyama cyclization to form the THF core (Scheme 45).²⁰ The cyclization precursor was derived from a Sharpless epoxide but, unlike the previously described fragment, it required a one carbon homology to give the required PMB ether. Cyclization unsurprisingly gave the desired THF product in 92% yield. Further functionalization was undertaken to prepare for an envisioned Stille coupling and macrolactonization. Despite the efficient synthesis of all sections of amphidinolide C, the total synthesis of the target was not realized using this route.



Scheme 43. The Gram Scale Synthesis of C(1) – C(9) Fragment of Amphidinolide C

In 2013, Furstner and co-workers completed the total synthesis of amphidinolide F using $\text{Co}(\text{nmp})_2$ catalyzed Mukaiyama oxidative cyclization (Scheme 46).²¹ An alkyne-substituted precursor **2.51** was cyclized to afford THF methanol **2.52**. Alkyne-substituted THF **2.52** would allow for Furstner's ring closing alkyne metathesis and esterification assembly steps. Furstner also completed the total synthesis of amphidinolide C in 2015, utilizing a similar strategy to form the core of the molecule.²²



Scheme 44. Furstner's Synthesis of the C(18)-C(28) fragment of Amphidinolide F

2.8 Summary and Conclusions

It has been over 25 years since the initial discovery of the Mukaiyama oxidative cyclization and in that time period it has been advanced to become an integral methodology in THF synthesis. Many had observed the possible applications of Mukaiyama's methodology and demonstrated its synthetic utility in total synthesis. Even with a great deal of attention, it took several years before a mechanism was proposed and experimentally elucidated. The Hartung group produced an important body of work in this field, allowing a great deal of development in the Mukaiyama methodology. While in

search of a convenient purification method for products of the oxidative cyclization, a new nmp ligand suitable for the Mukaiyama oxidative cyclization was designed and synthesized. The challenge of producing a catalyst with a simplified purification method was also met as it is now possible to remove the cobalt catalyst through acid extraction, methylation and ultimately a simple filtration. The greatest achievement of this process was that the newly designed Co (nmp)₂ catalyst was shown to produce a higher reactivity towards the pentanol substrates and more resistance to decomposition. The novel Co(nmp)₂ catalyst was subsequently applied in the synthesis of amphidinolide C and F, with replication of the previously observed high yields. This newly developed catalyst is a great advancement in the Mukaiyama oxidative cyclization, and higher yields accompanied by improved purification techniques will allow for a broad range of use.

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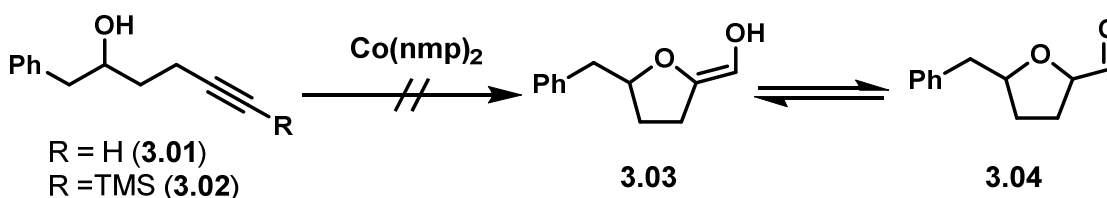
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3. Application of Co(NMP)₂ in Expanded THF Substitution Patterns

3.1 Initial Scope Expansion for Co(nmp)₂

Results from the initial Co(nmp)₂ (2.38) catalyst studies led to interesting questions about the reactivity of the catalyst. One of these was that an exo dig type cyclization could be possible, thus leading to the formation of an enol. This enol could subsequently tautomerize to generate an aldehyde. Unfortunately, after 6 days under standard cyclization conditions both the TMS-protected (3.02) and unprotected (3.01) alkynols showed no cyclization product (Scheme 47).



Scheme 45. Alkyne Oxidative Cyclization

Another area of exploration that was envisioned was the ability to perform enantioselective transformations with the oxidative cyclization. This could potentially be introduced by modification of the ligand, where a chiral functionality is appended to one of the ligand ends (Figure 13). The use of a chiral entity in place of the either the *t*Bu group or the piperazine ring could possibly invoke some enantioselectivity. Ideally, this catalyst would react specifically with a single enantiomer of the parent pentenol and produce an enantio-enriched THF product. Alternatively, this could facilitate the transformation of racemic pentenols to enantio-enriched substrate. To date, using camphor in place of pinacolone has been attempted but requires further investigation.

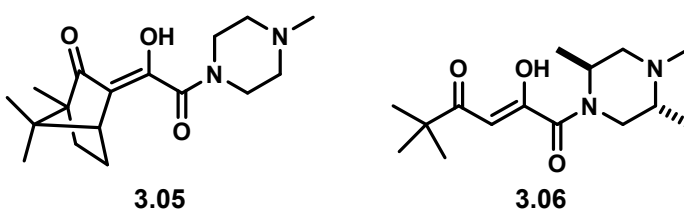
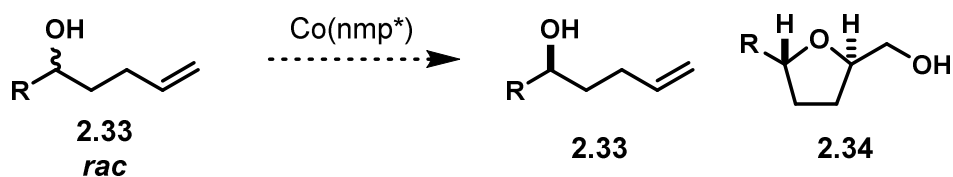


Figure 13. Proposed Chiral nmp Ligands

Scheme 46. Proposed Resolution using $\text{Co}(\text{nmp})_2$

3.2 Synthesis of 2,2,6 – Trisubstituted THF Methanols

There are many natural products in which oxygen heterocycles are substituted on the carbon atom adjacent the hetero atom (2,5 in the case of THFs). Examples include monensin (Figure 14)¹ and ionomycin (Figure 15).² Monensin and ionomycin are in a class of compounds known as ionophores. These molecules are able to coordinate to various ions from $\text{Ca}(\text{II})$ to $\text{Pb}(\text{II})$. Monensin is used in the dairy and beef industries as it has been shown to improve the ability of cattle to metabolize feed. This is due to the molecule's ability to facilitate ion transportation through lipid membranes as an antiporter.³ In dairy cattle increased production of milk is observed along with lowered rates of gastrointestinal disease.³

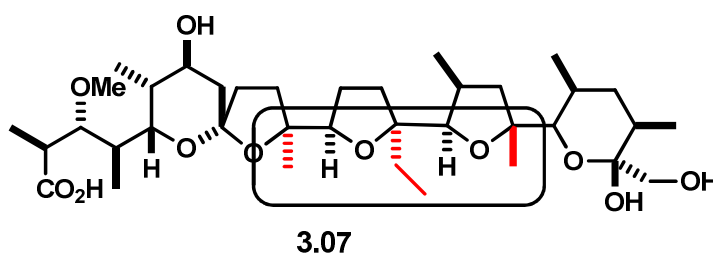


Figure 14. Monensin

Ionomycin is a Ca(II) ionophore, which like Monensin, shows a high binding affinity to metal ion centres. Ionophores have the ability to readily bind with calcium and facilitate its transport across lipid membranes, which has led to their application in biological studies of intracellular ion concentrations.

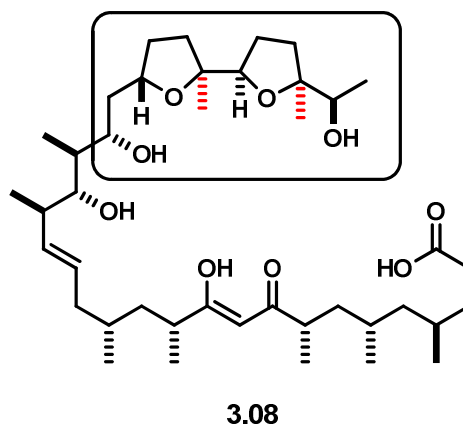
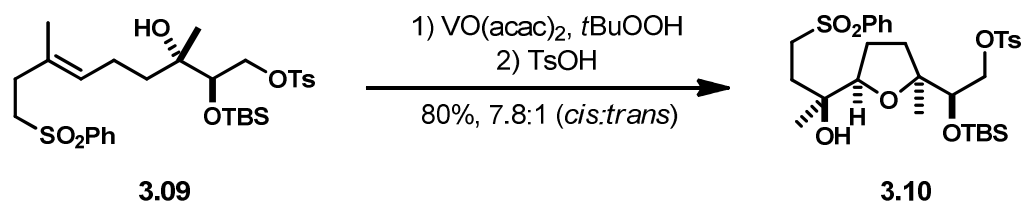


Figure 15. Ionomycin

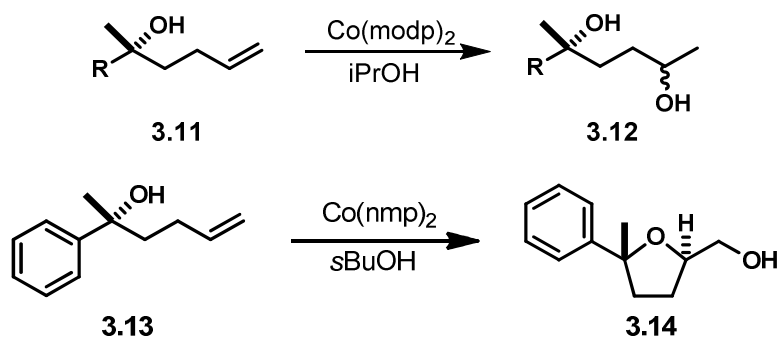
Due to the interesting biological activities of Ionomycin, and other polyether ionophores, it has been the subject of synthetic studies. Launtens and co-workers completed the synthesis of Ionomycin in 2002.² The synthetic strategy towards the methyl-substituted THF core was a simple epoxidation/ cyclization.⁴ The geraniol-derived starting material was obtained in 7 steps from the naturally occurring terpenoid. Using a vanadium catalyst and TBHP the trisubstituted alkene was epoxidized (Scheme 49). Subsequent treatment with TsOH allowed for the cyclization product to be formed in a 7.8:1 mixture of the desired *cis* product over the *trans*. Similar chemistry was subsequently used to create the second THF in the final natural product.



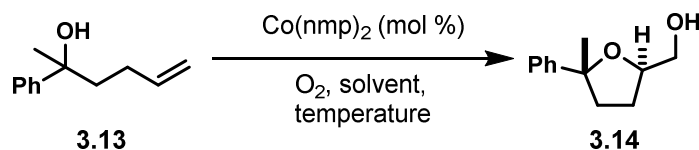
Scheme 47. Lautens THF Synthesis of Ionomycin

3.3 Initial Studies with Co(nmp)₂

With various natural products containing additional methyl functionality it was decided that functionality studies with the new Co(nmp)₂ catalyst would begin. Various substitution patterns have been tolerated by the oxidative cyclization on every position of the THF ring except trisubstitution in a 2,2,5 pattern. Hartung showed that, using traditional ligands, the cyclization was unable to occur or occurred in very poor yields.¹⁰ Preliminary experiments within the Pagenkopf lab found that Co(modp)₂ was also unable to produce the cyclized methyl-substituted THF product in substantial yield but also performs a competitive hydration of the alkene (Scheme 50). When Co(nmp)₂ was used, the result was an almost 100% mass recovery and a mixture of cyclized product and starting material.

Scheme 48. Methyl Substituted *trans*-THF Ring Formation

Initial studies carried out by Andrew Stevens⁵ gave trace amounts of the *trans*-THF product under the original NMP cyclization conditions but a simple increase in temperature from 50 °C to 80 °C afforded 72% yield of a mixture of starting material and desired product (Table 8). This gave an excellent starting point for further optimization. Increased catalyst loading was found to lower yields but increased the ratio of the desired product to starting material (Entries 2-4). A significant increase in yield was observed with an increase in reaction concentration (Entries 5-10). Solvent effects on the reaction were also manipulated in hopes of achieving higher yield. It was hypothesized that solvents capable of increased O₂ content would be beneficial to the transformation. Trifluoroethanol, benzene, and dichloroethane all produced poor results in yield and product ratio whereas *s*BuOH showed quantitative mass recovery of starting material and product was observed, with a 7:1 product to starting material ratio (Entries 11-14). The optimal catalyst loading was re-evaluated using *s*BuOH as the reaction solvent. An optimal catalyst loading of 30 % was found to give a quantitative yield of 9.7:1 product to starting material (Entries 15-16). The catalyst loading was found to be able to be reduced to 17.5 mol % without compromising the conversion, though lower loadings were unsuccessful (Entry 17).



Scheme 49. 2,2,5 Substituted THF Cyclization Conditions

Entry	Catalyst Loading (%)	Conversion (sm/pdt)	Yield (total) ^a	Temp	Solvent	mL
1	10	trace	-	55	<i>i</i> PrOH	8
2	10	2.5:1	72	80	<i>i</i> PrOH	8
3	15	1.9:1	76	80	<i>i</i> PrOH	8
4	20	1.3:1	69	80	<i>i</i> PrOH	8
5	10	1.0:1.0	77	80	<i>i</i> PrOH	4
6	20	1.0:5.2	81	80	<i>i</i> PrOH	4
7	10	1.0/3.6	79	80	<i>i</i> PrOH	2
8	20	1.0/5.2	80	80	<i>i</i> PrOH	2
9	20	1.0/2.6	75	80	<i>i</i> PrOH	1
10	20	1.0/1.8	77	80	<i>i</i> PrOH	0.5
11	20	-	-	70	CF ₃ CH ₂ OH	2
12	20	1.0:7.2	quant	80	<i>s</i> BuOH	2
13	20	1.0:2.6	-	70	C ₆ H ₆	2
14	20	1.0:1.4	-	70	C ₂ H ₄ Cl ₂	2
15	30	1.0:9.7	quant	80	<i>s</i> BuOH	2
16	15	1.0:4.7	quant	80	<i>s</i> BuOH	2
17	17.5	1.0:5.1	quant	80	<i>s</i> BuOH	2

^a Yield is a weighted average of starting material to product as the overall conversion produced little to no by-products.

^b This work was completed by Andrew Stevens. SM = Starting Material, PDT = Product.

Table 8. Optimization study on methyl substituted THFs

Although these initial findings were very promising, a serious problem was discovered by use of column chromatography to separate the starting material from the products. The recovered yields were significantly less than expected. A simple experiment was conducted in which a known concentration of mesitylene, as an internal standard, was added to the crude product in order to determine if contamination by a salt or other NMR-inactive compounds were the cause of the discrepancy between crude and purified yield.

The mesitylene peaks were integrated to known product peaks and the ratio was used to calculate the yield of product. It was determined that indeed the crude yields were reliable and that the composition of the crude mixture was causing decomposition of the product upon flash-column chromatography. Efforts were put towards an effective method for the purification of these THF products. It appears that these trisubstituted THFs are unstable on silica gel and require other means of purification. When an effective method of purification can be determined, a larger scope of substrates will be examined.

Several different substrates were examined in order to see the effects of steric and electronics on the reaction. Most reactions gave quantitative crude yields as a mixture of unconverted starting material and product (Table 9). Both methyl and ethyl substitution were shown to be capable substrates in the reaction (Table 9, Entries 1-2). Long-chain allyl and homo allyl substituents were also able to undergo the reaction although the allyl substrate performed poorly in the reaction. The use of bulky sterically hindering groups gave poor yields (Entry 5), as did the electron donating phenyl acetylene group (Entry 6). Finally, oxaspirocycles were formed in modest yield in both the [4.5] and [4.4] varieties (Entries 7-8).

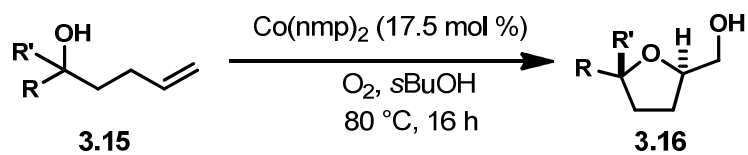


Figure 16. Conditions for methyl THF cyclization

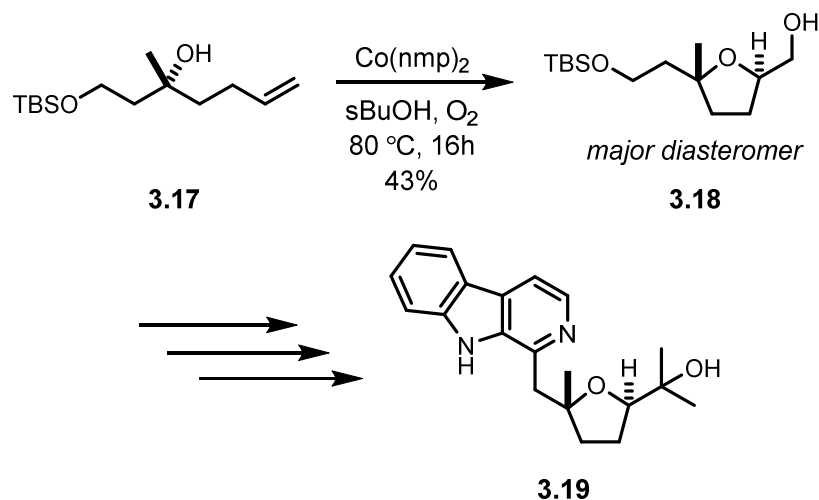
Entry	Product	Isolated Yield (%) brsm
1		42 (58)
2		56 (83)
3		55 (75)
4		20 (26)
5		25 (32)
6		19 (20)
7		41 (51)
8		39 (73)
9		0

^A Several examples were completed by Andrew Stevens.

Table 9. Preliminary substrate scope for methyl substituted THFs

3.4 Applications of Co(nmp)₂ in the Synthesis of Cyclocapitelline

The newly discovered capability of the Mukaiyama oxidative cyclization with Co(nmp)₂ to produce 2,2,5 substituted THF rings was utilized in the synthesis of cyclocapitelline (Scheme 52).⁵ Geoff Phillips used a geraniol-derived tertiary alcohol **3.17** was cyclized under the optimized reaction conditions developed in the previously described substrate exploration. The cyclization of **3.17** produced a mixture of diastereomers of **3.18** in a 3:1 (*trans:cis*) ratio. This mixture was used without separation to access cyclocapitelline (**3.19**) and *isocyclocapitelline* in 12 steps from geraniol.

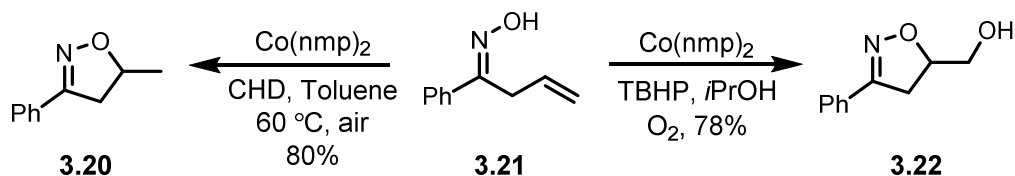


Scheme 50. The Synthesis of Cyclocapitelline

3.5 Oxime Synthesis with Co(nmp)₂

Yu and co-workers utilized the Co(nmp)₂ catalyst in their synthesis of β,γ -unsaturated oxazolines (Scheme 53).⁶ Yu determined the under standard Co(nmp)₂ cyclization conditions an oxime such as **3.21** can be cyclized to form 4,5 dihydroisooxazoles in good yield. Substitution on the α -carbon gave diastereoselectivity but with no example over 2:1. Alternatively, the Co(nmp)₂ catalyst can be subjected to Hartung's conditions using CHD in toluene to produce the reduced methyl product (**3.20**).⁷

The $\text{Co}(\text{nmp})_2$ catalyst gave good yields under these conditions, consistent with those under oxidative conditions.



Scheme 51. Yu Cyclization of Oximes

3.6 Summary and Conclusion

There has been significant progress towards expanding several new substitution patterns within the substrate scope. Developing a better understanding of product decomposition will be essential to fully understand the limits of this reaction and efforts are already underway to fully explore this. This will include the use of protecting groups or other derivatization to stabilize the molecule for purification and possibly the development of a different method of purification. The use of $\text{Co}(\text{nmp})_2$ to cyclize new varieties of compounds has greatly expanded the scope and future possibilities of these reactions in natural product synthesis. I have successfully examined 2,2,5-trisubstituted THFs in varying degrees of complexity. Subsequently, the synthesis of cyclocapitelline was accomplished using the $\text{Co}(\text{nmp})_2$ catalyst and the reaction conditions developed for trisubstituted. An interesting application to the synthesis of oximes was also undertaken by the Yu group. Overall, the $\text{Co}(\text{nmp})_2$ catalyst has allowed for the expansion of the Mukaiyama oxidative cyclization substrate scope and will be at the forefront of any further developments in this field.

References

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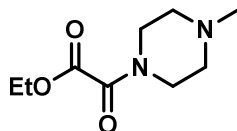
4. Experimental Procedures

All reactions were run under an argon atmosphere unless otherwise indicated. Flasks were oven-dried and cooled in a desiccator prior to use unless water was used in the reaction. Solvents and reagents were purified by standard methods.¹ Dichloromethane, diethyl ether, and tetrahydrofuran (THF) were purified by passing the solvents through activated alumina columns. *iso*-Propanol (99.5%, 0.2% H₂O) was used as received from Caledon Laboratory Chemicals. All other chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. The progress of reactions were monitored by thin layer chromatography (TLC) performed on F254 silica gel plates. The plates were visualized by staining with ceric ammonium molybdate (CAM)² or *p*-anisaldehyde. Column chromatography was performed with Silica Flash P60 60 Å silica gel from Silicycle according to the Still method.³ Centrifugations were conducted with an International Clinical Centrifuge model CL at approx. 8000 rpm for 10 min (International Equipment Company, USA).

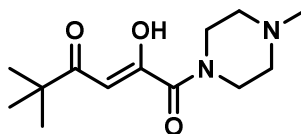
The ¹H and ¹³C NMR data were obtained on 400 or 600 MHz spectrometers. All spectra were obtained in deuterated chloroform and were referenced to residual chloroform at δ 7.25 ppm for ¹H spectra and the center peak of the triplet at δ 77.0 (t) for ¹³C spectra. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad; app, apparent. EI high resolution mass spectra were obtained using a spectrometer at an ionizing voltage of 70 eV. Melting points are uncorrected.

Synthesis of Co (nmp)₂

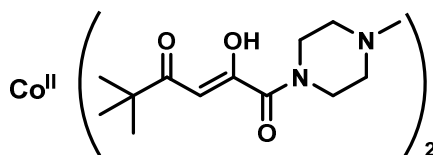
Ethyl 2-(4-methylpiperazin-1-yl)-2-oxoacetate (2.40)



To a solution of *N*-methylpiperazine (22.2 mL, 200 mmol, 1 eq) and triethyl amine (27.8 mL, 200 mmol, 1 eq) in CH₂Cl₂ (200 mL) at 0 °C was added ethyl oxalyl chloride (22.4 mL, 200 mmol, 1 eq). The reaction was warmed to room temperature and stirred for 16 h. The resulting heterogeneous mixture was quenched with NaHCO₃ solution (200 mL) and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (3 × 100 mL), the organic phases were combined and washed with brine (200 mL), dried over anhydrous MgSO₄ and concentrated under reduced pressure to afford an orange oil (39.6 g, 99%). The product was used without further purification. *R_f* 0.10 (66% EtOAc/Hex); ¹H NMR (400 MHz, CDCl₃) δ 4.30 (q, *J* = 7.2 Hz, 2H), 3.64-3.61 (m, 2H), 3.43-3.41 (m, 2H), 2.42-2.40 (m, 4H), 2.29 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 162.9, 160.3, 62.3, 55.1, 54.3, 46.2, 41.4, 14.2; HRMS *m/z* calcd for C₉H₁₆N₂O₃ [M+H⁺]: 200.1161, found: 200.1163.

(Z)-2-Hydroxy-5,5-dimethyl-1-(4-methylpiperazin-1-yl)hex-2-ene-1,4-dione (2.37)

A solution of *tert*-BuOK (4.48 g, 40 mmol, 2 eq) in THF (100 mL) was added to a solution of pinacolone (2.50 mL, 20 mmol, 1 eq) and glycoxyate **2.40** (4.00 g, 20 mmol, 1 eq) in THF (20 mL) at 0°C and warmed to rt (room temperature). The mixture was stirred at room temperature for 16 h and subsequently treated with 40 mL of 1M HOAc in CH₂Cl₂. After stirring for 0.5 h the slurry was filtered through celite and concentrated under reduced pressure to afford an orange syrup (4.32 g, 85%). The product was used without further purification. *R_f* 0.15 (5% MeOH/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 5.97 (s, 1H), 3.66-3.58 (m, 4H), 2.46-2.43 (m, 4H), 2.31 (s, 3H), 1.19 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 200.9, 185.3, 163.8, 95.3, 55.1, 54.3, 45.8, 41.6, 27.2; HRMS *m/z* calcd for C₁₃H₂₂N₂O₃ [M+H⁺]: 254.1630, found: 254.1644.

Co^{II}(nmp)₂ (2.38)

To a solution of NMP ligand **2.37** (2.54 g, 10 mmol, 2 eq) in benzene (50 mL) was added Co(II) ethylhexanoate (65 wt % solution, 1.88 M in mineral spirits, 5 mmol, 1 eq). The reaction was stirred for 10 min, water (0.36 mL, 20 mmol) was added and the reaction stirred for 16 h at rt. Hexanes (200 mL) was added and the brown solids were separated by centrifugation. The solids were triturated with hexanes and this was repeated an additional three times. The product was then transferred to a flask and the remaining

solvent was removed under reduced pressure to afford the $\text{Co}(\text{NMP})_2$ catalyst (2.69 g, 95%) as a beige solid. LRMS: m/z $[\text{M} + \text{Na}]^+$ calc. for $\text{C}_{78}\text{Co}_3\text{H}_{126}\text{N}_{12}\text{NaO}_{18}$: 1718.72; found: 1718.8; combustion analysis: calc. for $\text{Co}(\text{NMP})_2 \cdot (\text{H}_2\text{O})_{3.5}$, C 49.68, H 7.86, N 8.91; found: C 49.58%, H 7.53%, N 8.84%. Based on previously obtained crystal structures of related compounds,⁴ it is believed that the structure of the catalyst is similar, comprised of three cobalt atoms and six ligands per unit cell. Two outer cobalt atoms, each surrounded by three ligands, flank an inner cobalt atom. Inclusion of water in the crystal structure is likely, as elemental analysis of samples after prolonged drying over P_2O_5 in a drying pistol results in data that requires 3.5 water molecules per cobalt atom.

Synthesis of Pentenol substrates and products

General Grignard Procedure:

A 250 mL round bottom flask equipped with a reflux condenser was charged with allyl magnesium bromide (1.0 M solution in ether, 60 mL, 60 mmol, 1.3 eq) and cooled to 0 °C with a water-ice bath. The epoxide (46.1 mmol, 1 eq) was added through the reflux condenser manually via syringe at a rate that produced a steady reflux. Once the addition was complete, the condenser was washed with 10 mL of dry diethyl ether and the ice bath was removed. After 0.2 h excess allyl magnesium bromide was quenched with half saturated aqueous NH_4Cl and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried (MgSO_4), filtered through celite and concentrated under reduced pressure.

General Grignard Addition to Aldehydes Procedure: A 250 mL round bottom flask equipped with a reflux condenser was charged with homoallyl magnesium bromide (1.0 M

solution in ether, 60 mL, 60 mmol, 1.3 eq) and cooled to 0 °C with a water-ice bath. The aldehyde (46.1 mmol, 1 eq) was added through the reflux condenser manually via syringe at a rate that produced a steady reflux. Once the addition was complete the condenser was washed with 10 mL of dry diethyl ether and the ice bath was removed. After 0.2 h excess allyl magnesium bromide was quenched with half saturated NH₄Cl and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered through celite and concentrated under reduced pressure.

General Cyclization Procedure: The cyclization precursor (1.0 mmol, 1.0 eq) was added as a solution in 10 mL *i*PrOH to a flask charged with Co(L)₂ (0.10 mmol, 0.10 eq) under 1 atm of O₂ (balloon). At room temperature, *tert*-butyl hydroperoxide (5.33 M in isooctane, 19 μL, 0.1 mmol, 0.1 eq) was added in one portion, and the resulting solution was heated at 55 °C for 16 h. The crude reaction mixture was purified using one of the methods listed below.

Purification Procedure A (Co(modp)₂ and Co(piper)₂): The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel using EtOAc-hexanes for elution

Purification Procedure B (Co(NMP)₂ methylation): The reaction mixture was cooled to rt, purged of O₂ with argon and methyl iodide (62 μL, 1.0 mmol, 1.0 eq) was added. After 16 h the reaction mixture was concentrated under reduced pressure and the residue was dissolved in water (20 mL) and CH₂Cl₂ (20 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (4 × 20 mL). The combined organic layers were

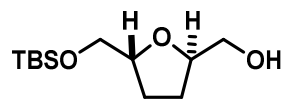
washed with brine, dried MgSO_4 , filtered through celite and concentrated under reduced pressure.

Purification Procedure C (Co(NMP)₂ buffer wash): The reaction mixture was concentrated under reduced pressure and the residue was dissolved in hexanes (20 mL) and buffer (20 mL, pH 5.5).

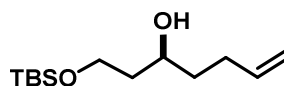
The heterogeneous mixture was separated and the aqueous layer was extracted with hexanes (4 × 20 mL). The combined organic layers were washed with buffer, brine, dried (MgSO_4), filtered through celite and concentrated under reduced pressure.

Purification Procedure D (Co(NMP)₂ acid wash): The reaction mixture was concentrated under reduced pressure and the residue was dissolved in hexanes (20 mL) and 1 M HCl (20 mL). The heterogeneous mixture was separated and the aqueous layer was extracted with hexanes (4 × 20 mL). The combined organic layers were washed with buffer, brine, dried with anhydrous MgSO_4 , filtered through celite and concentrated under reduced pressure.

Purification Procedure E (Silica Gel Filtration): The reaction mixture was filtered through a thin pad of silica layered on top of a thin pad of celite. The reaction flask and silica pad were washed with an additional 100 mL of EtOAc. The EtOAc filtrate solution was concentrated under reduced pressure.

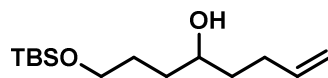
(5-((*tert*-Butyldimethylsilyloxy)methyl)tetrahydrofuran-2-yl)methanol (2.42a)

The title compound was prepared using the general cyclization procedure to afford a clear yellow oil (39 – 93%). R_f 0.33 (33 v/v % EtOAc/Hex); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 4.13-4.04 (m, 2H), 3.66-3.57 (m, 3H), 3.47 (dd, $J = 11.4, 6.2$ Hz, 1H), 2.01-1.93 (m, 2H), 1.89 (br s, 1H), 1.79-1.73 (m, 1H), 1.71-1.65 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 79.8, 79.7, 65.9, 64.9, 28.2, 27.3, 25.9, 18.4, -5.3; HRMS m/z calcd for $\text{C}_{12}\text{H}_{26}\text{O}_3\text{Si}$ [(M+H) $^+$]: 247.1729, found: 247.1729.

(S)-1-(*tert*-Butyl-dimethyl-silyloxy)-hept-6-en-3-ol (2.41a)

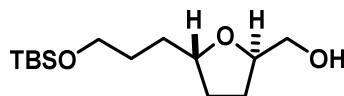
The title compound was prepared using the general Grignard procedure, to afford a clear colorless oil (99.6%, 11.24 g) which was used without further purification. R_f 0.60 (30 v/v % EtOAc/Hex); $^1\text{HNMR}$ (400 MHz, CDCl_3) δ 5.83 (ddd, $J = 17.1, 10.3, 6.6$ Hz, 1H), 5.08-4.92 (m, 2H), 3.92-3.78 (m, 3H), 3.45 (br s, 1H), 2.25-2.05 (m, 2H), 1.72-1.48 (m, 4H), 0.89 (s, 9H), 0.07 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 138.7, 114.5, 71.6, 62.8, 38.2, 36.6, 29.8, 25.8, 18.1, -5.5.

1-(*tert*-Butyldimethylsilyloxy)oct-7-en-4-ol (2.41c)

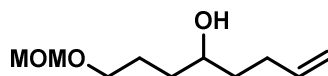


The title compound was prepared using the general Grignard procedure, to afford colorless oil (95%, 3.2 g). R_f 0.58 (30 v/v % EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 5.85-5.75 (m, 1H), 5.01 (dd, $J = 17.2, 1.2$ Hz), 4.91 (dd, $J = 10.2, 1.2$ Hz), 3.64-3.49 (m, 3H), 2.74 (br s, 1H), 2.20-2.06 (m, 2H), 1.65-1.33 (m, 6H), 0.86 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.7, 114.5, 70.8, 63.5, 36.4, 34.6, 30.1, 29.0, 25.9, 18.2, -5.4; HRMS m/z calcd for $\text{C}_{14}\text{H}_{30}\text{O}_2\text{Si}$ $[(\text{M}+\text{H})^+]$: 259.2093, found: 259.2089.

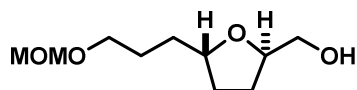
(5-(3(*tert*-Butyldimethylsilyloxy)-propyl)tetrahydrofuran-2-yl)methanol (2.42c)



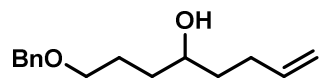
The title compound was prepared using the general cyclization procedure to afford a clear yellow oil (74 - 95%). R_f 0.30 (33 v/v % EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 4.09 (ddd, $J = 14.1, 6.6, 3.5$ Hz, 1H), 3.97-3.92 (m, 1H), 3.64-3.59 (m, 3H), 3.49-3.45 (m, 1H), 2.06-2.00 (m, 1H), 1.98-1.94 (m, 1H), 1.92-1.87 (m, 1H), 1.69-1.47 (m, 6H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 79.3, 78.8, 65.1, 63.1, 32.1, 32.0, 29.5, 27.5, 25.9, 18.3, -5.3; HRMS m/z calcd for $\text{C}_{14}\text{H}_{30}\text{O}_3\text{Si}$ $[(\text{M}+\text{H})^+]$: 275.2042, found: 275.2032.

1-(Methoxymethoxy)oct-7-en-4-ol (Table 7, Entry 1)

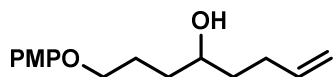
The title compound was prepared using the general Grignard procedure, to afford a colorless oil (44%, 0.592 g). R_f 0.32 (33 v/v % EtOAc/Hex); ^1H NMR (400MHz, CDCl_3) δ 5.84 (ddt, $J = 17.0, 10.3, 6.6$ Hz, 1H), 5.05 (ddd, $J = 17.2, 3.5, 1.6$ Hz, 1H), 4.97 (ddd, $J = 10.2, 3.3, 1.4$ Hz, 1H), 4.63 (s, 2H), 3.65 (br s, 1H), 3.57 (t, $J = 6.3$ Hz, 2H), 3.36 (s, 3H), 2.27-2.16 (m, 1H), 2.16-2.04 (m, 2H), 1.79-1.69 (m, 2H), 1.66-1.60 (m, 1H), 1.58-1.46 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.6, 114.7, 96.4, 71.0, 67.9, 55.2, 36.6, 34.5, 30.0, 26.0; HRMS m/z calcd for $\text{C}_{10}\text{H}_{20}\text{O}_3$ $[(\text{M}+\text{H})^+]$: 189.1491, found: 189.1506.

(5-(3-(Methoxymethoxy)propyl)tetrahydrofuran-2-yl)methanol (Table 7, Entry 1)

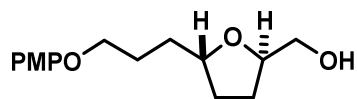
The title compound was prepared using the general cyclization procedure to afford a light yellow oil (54 – 85%). R_f 0.05 (30 v/v % EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 6.83 (s, 4H), 4.14-4.12 (m, 1H), 4.04-3.91 (m, 3H), 3.77 (s, 3H), 3.67-3.62 (m, 1H), 3.52-3.51 (m, 1H), 2.10-1.95 (m, 3H), 1.89-1.77 (m, 3H), 1.74-1.55 (m, H); ^{13}C NMR (100MHz, CDCl_3) δ 153.7, 153.1, 115.4, 114.6, 79.0, 78.9, 68.4, 65.0, 55.7, 32.1, 32.0, 27.5, 6.1; HRMS m/z calcd for $[(\text{M}+\text{H})^+]$: 205.1440, found: 205.1427.

1-(Benzyloxy)oct-7-en-4-ol (Table 7, Entry 2)

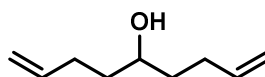
The title compound was prepared using the general Grignard procedure, to afford yellow oil (47%, 1.01 g) R_f 0.32 (33 v/v % EtOAc/Hex); ^1H NMR (400MHz, CDCl_3) δ 7.36-7.27 (m, 5H), 5.83 (ddt, $J = 17.1, 10.3, 6.6$ Hz, 1H), 5.03 (ddd, $J = 17.2, 3.5, 2.0$ Hz, 1H), 4.95 (ddd, $J = 10.2, 3.1, 1.2$ Hz, 1H), 4.51 (s, 2H), 3.65-3.59 (m, 1H), 3.55-3.46 (m, 3H), 2.25-2.16 (m, 1H), 2.14- 2.09 (m, 1H), 1.79 – 1.70 (m, 2H), 1.56-1.45 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.6, 128.4, 127.7, 114.6, 73.0, 70.48, 36.5, 34.7, 30.0, 26.1; HRMS m/z calcd for $[\text{M}^+]$: 234.1620, found: 234.1627.

1-(4-Methoxyphenoxy)oct-7-en-4-ol (Table 7, Entry 3)

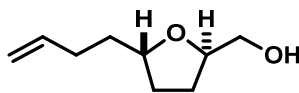
The title compound was prepared using the general Grignard procedure, to afford dark orange oil (82%, 1.514 g). R_f 0.32 (30 v/v % EtOAc/hex); ^1H NMR (400 MHz, CDCl_3) δ 6.80 (s, 4H), 5.82 (ddt, $J = 17.0, 10.1, 6.8$ Hz, 1H), 5.03 (d, $J = 16.0$ Hz, 1H), 4.96 (d, $J = 10.2$ Hz, 1H), 3.91-3.86 (m, 2H), 3.72 (s, 3H), 3.65-3.64(m, 1H), 2.49 (br s, 1H), 2.24-2.09 (m, 2H), 1.91-1.77 (m, 2H), 1.69-1.61 (m, 1H), 1.57-1.49 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.8, 152.83, 138.34, 116.0, 115.26, 114.43, 70.7, 68.46, 55.46, 36.35, 33.85, 29.85, 25.48; HRMS m/z calcd for $\text{C}_{15}\text{H}_{22}\text{O}_3$ $[\text{M}^+]$: 250.1569, found: 250.1568.

(5-(3-(4-Methoxyphenoxy)propyl)tetrahydrofuran-2-yl)methanol (Table 7, Entry 3)

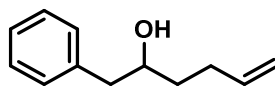
The title compound was prepared using the general cyclization procedure to afford a clear yellow oil (39 – 93%). R_f 0.24 (50 v/v % EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 6.83 (s, 4H), 4.14-4.12 (m, 1H), 4.04-3.91 (m, 3H), 3.77 (s, 3H), 0.77 (m, 1H), 3.52-3.51 (m, 1H), 2.08-1.98 (m, 3H), 1.89-1.77 (m, 3H), 1.74-1.55 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.7, 1.53.1, 115.4, 114.6, 78.9, 68.4, 65.0, 55.7, 32.1, 32.0, 27.5, 26.12; HRMS m/z calcd for $\text{C}_{15}\text{H}_{22}\text{O}_4$ [M^+]: 266.1518, found: 266.1509.

Nona-1,8-dien-5-ol (Table 7, Entry 4)

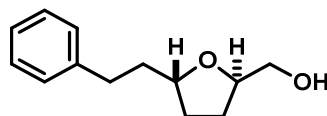
The title compound was prepared using the general Grignard procedure, to afford a clear colourless oil (81%, 1.59 g) R_f 0.35 (20 v/v % EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 5.88-5.78 (m, 2H), 5.04 (d, $J = 16.8$ Hz, 2H), 4.96 (d, $J = 10.2$ Hz, 2H), 3.64 (br s, 1H), 2.23-2.08 (m, 4H), 1.61-1.49 (m, 5H); ^{13}C NMR (100 Hz, CDCl_3) δ 138.5, 114.7, 70.9, 36.5, 30.0; HRMS m/z calcd for $\text{C}_9\text{H}_{16}\text{O}$ [M^+]: 140.1201, found: 140.1202.

(5-(But-3-enyl)tetrahydrofuran-2-yl)methanol (Table 7, Entry 4)

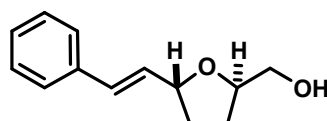
The title compound was prepared using the general cyclization procedure to afford a clear yellow oil (40 – 95%). R_f 0.2 (30 v/v % EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 5.84-5.78 (m, 1H), 5.04-4.93 (m, 2H), 4.09 (ddd, $J = 10.5, 6.4, 3.5$ Hz, 1H), 3.96-3.91 (m, 1H), 3.61 (dd, $J = 10.4, 3.2$ Hz, 1H), 3.47 (dd, $J = 11.4, 6.2$ Hz, 1H), .22- 2.00 (m, 4H), 1.98-1.92 (m, 1H), 1.72-1.62 (m, 2H), 1.56-1.49 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.3, 114.6, 78.8, 78.8, 64.9, 34.8, 31.9, 30.4, 27.5; HRMS m/z calcd for $\text{C}_9\text{H}_{16}\text{O}_2$ $[(\text{M}+\text{H})^+]$: 157.1229, found: 157.1232.

1-phenylhept-6-en-3-ol (Table 7, Entry 7)

The title compound was prepared according to the general Grignard addition to aldehydes procedure to afford a clear colourless oil (90%, 2.00 g). R_f 0.48 (30 v/v % EtOAc/hexanes); ^1H NMR (600 MHz, CDCl_3) δ 7.32-7.29 (m, 2H), 7.23-7.19 (m, 3H), 5.85 (ddt, $J = 17.0, 10.3, 6.6$ Hz, 1H), 5.06 (dq, $J = 17.0, 1.8$ Hz, 1H), 4.99 (dd, $J = 10.0, 1.2$ Hz, 1H), 3.68-3.64 (m, 1H), 2.81 (ddd, $J = 14.1, 10.0, 5.9$ Hz, 1H), 2.68 (ddd, $J = 13.8, 9.7, 7.0$ Hz, 1H), 2.25-2.19 (m, 1H), 2.17-2.11 (m, 1H), 1.83-1.73 (m, 2H), 1.64-1.54 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 142.0, 138.4, 128.3, 125.7, 114.7, 70.77, 39.0, 36.5, 32.0, 30.0; HRMS m/z calcd for $\text{C}_{13}\text{H}_{18}\text{O}$ $[\text{M}^+]$: 176.1201, found: 176.1195.

(5-phenethyltetrahydrofuran-2-yl)methanol (Table 7, Entry 8)

The title compound was prepared using the general cyclization procedure to afford a clear yellow oil (49 – 86%). R_f 0.23 (30 v/v % EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.18 (m, 5H), 4.18-4.12 (m, 1H), 4.00- 3.93 (m, 1H), 3.65 (ddd, $J = 11.3, 7.0, 3.1$ Hz, 1H), 3.50 (dt, $J = 11.5, 6.0$ Hz, 1H), 2.79-2.63 (m, 2H), 2.09-1.88 (m, 4H), 1.82-1.55 (m, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 141.9, 128.3, 128.2, 125.7, 78.9, 64.9, 37.3, 32.4, 31.9, 27.5; HRMS m/z calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$ [M^+]: 206.1307, found: 206.1309; combustion analysis: calc. for $\text{C}_{13}\text{H}_{18}\text{O}_2$, C 75.69, H 8.80; found: C 75.01%, H 8.62%.

(E)-(5-styryltetrahydrofuran-2-yl)methanol (Table 7, Entry 9)

The title compound was prepared using the general cyclization procedure to afford a clear yellow oil (38 - 88%). R_f 0.34 (40 v/v % EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.20 (m, 5H), 6.58 (d, $J = 16.0$ Hz, 1H), 6.19 (dd, $J = 16.0, 6.6$ Hz, 1H), 4.59 (q, $J = 6.6$ Hz, 1H), 4.26-4.20 (m, 1H), 3.70 (dd, $J = 11.7, 3.1$ Hz, 1H), 3.54 (dd, $J = 11.7, 5.9$ Hz, 1H), 2.21-2.13 (m, 1H), 2.07-2.00 (m, 1H), 1.83-1.72 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.7, 130.8, 130.1, 128.5, 127.6, 126.5, 80.0, 79.6, 65.1, 33.1, 27.6; HRMS m/z calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$ [M^+]: 204.1150, found: 204.1158.

The following compounds have been previously reported: Compounds 6a,⁵ 7b,⁶ Table 3, Entry 2, Product;⁷ Table 3, Entry 5, Starting Material;⁸ Table 3, Entry 5, Product;⁹ Table 3, Entry 6, Starting Material;¹⁰ Table 3, Entry 6, Product; Table 3, Entry 7, Starting Material;¹¹ Table 3, Entry 7, Product; Table 3, Entry 10, Starting Material; Table 3, Entry 9, Starting Material;¹² Table 3, Entry 10, Product; Table 3, Entry 11 Starting Material; Table 3, Entry 11, Product.

Synthesis of Hexenol substrates

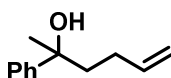
General Procedure for Cyclization: The cyclization precursor (1.0 mmol, 1.0 eq) was added to a solution of 2 mL *s*BuOH and preoxidized Co(L)₂ (0.10 mmol, 0.10 eq) under 1 atm of O₂ (balloon). The resulting solution was heated at 70 °C for 16 h. The crude reaction mixture was filtered through a thin pad of silica and washed with CH₂Cl₂. The crude product was purified by silica chromatography (gradient 10 v/v % to 40 v/v %, EtOAc/Hexanes).

General Procedure for Grignard Addition to Ketones:

A 250 mL round bottom flask equipped with a reflux condenser was charged with alkyl magnesium bromide 1.0 M solution in ether, 60 mL, 60 mmol, 1.3 eq) and cooled to 0 °C with a water-ice bath. The ketone (46.1 mmol, 1 eq) was added through the reflux condenser manually via syringe at a rate that produced a steady reflux. Once the addition was complete the condenser was washed with 10 mL of dry diethyl ether and the ice bath was removed. After 0.2 h excess alkyl magnesium bromide was quenched with half saturated NH₄Cl and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The

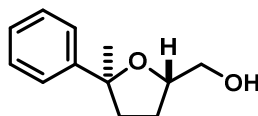
combined organic layers were washed with brine, dried over MgSO_4 , filtered through celite and concentrated under reduced pressure.

2-Phenylhex-5-en-ol (3.13)

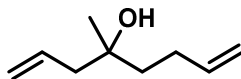


The title compound was prepared using the general Grignard addition to ketones procedure to afford a light yellow oil (85%, 1.72 g). R_f 0.44 (20 v/v % EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, $J = 7.0$ Hz, 1 H), 7.37 - 7.44 (m, 3 H), 7.31 (t, $J = 7.8$ Hz, 2 H), 7.18 - 7.25 (m, 2 H), 5.67 - 5.86 (m, 1 H), 4.85 - 4.98 (m, 2 H), 2.00 - 2.05 (m, 1 H), 1.83 - 1.94 (m, 3 H), 1.75 (s, 1 H), 1.51 - 1.56 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.7, 138.2, 128.6, 126.6, 124.7, 114.5, 74.7, 43.0, 30.4, 28.5; HRMS m/z calcd for $\text{C}_{12}\text{H}_{16}\text{O}$ [M^+] 176.1201, found: 176.1199.

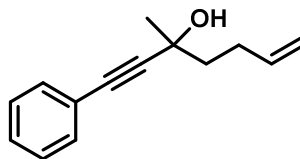
(2-Methyl-2-Phenyltetrahydrofuran-2-yl) methanol (3.14)



The title compound was prepared using the general cyclization procedure to afford a light yellow oil (42%, 40.4 mg). R_f 0.23 (20 v/v % EtOAc/hexanes); ^1H NMR (600 MHz, CDCl_3) δ 7.38 - 7.45 (m, 2 H), 7.30 - 7.35 (m, 2 H), 7.20 - 7.24 (m, 1 H), 4.13 - 4.24 (m, 1 H), 3.76 (d, $J = 11.7$ Hz, 1 H), 3.51 - 3.61 (m, 1 H), 2.21 - 2.30 (m, 1 H), 1.99 - 2.18 (m, 2 H), 1.75 - 1.89 (m, 2 H), 1.50 - 1.57 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.7, 128.0, 126.7, 124.6, 124.2, 85.2, 79.0, 65.7, 65.4, 39.4, 39.2, 30.4, 29.6, 29.6, 27.5, 27.3; HRMS m/z calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2$ [$(\text{M}+\text{H})^+$]: 193.1229, found: 193.1223.

4-Methylocta-1,7-diene-4-ol (Table 9, Entry 4)

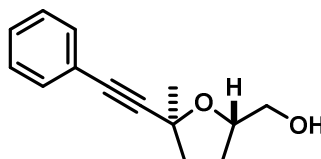
The title compound was prepared using the general addition of Grignard to ketones procedure to afford a yellow oil (99%, 1.40 g). R_f 0.29 (20 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 600MHz): δ 5.80 - 5.91 (m, 2 H), 5.09 - 5.20 (m, 2 H), 5.05 (d, $J = 17.6$ Hz, 1 H), 4.96 (d, $J = 10.5$ Hz, 1 H), 2.25 (d, $J = 6.4$ Hz, 2 H), 2.12 - 2.19 (m, 2 H), 1.51 - 1.61 (m, 3 H), 1.19 ppm (s, 3 H); ^{13}C NMR (CDCl_3 , 101MHz): δ 139.2, 134.2, 119.1, 114.7, 72.4, 46.7, 41.1, 28.6, 27.0 ppm; LRMS m/z calcd for $\text{C}_9\text{H}_{16}\text{O}$ [M^+] 140.1, found: 140.1.

3-Methyl-1-phenylhept-6-en-1-yn-3-ol (Table 9, Entry 6)

A 1 L round bottom flask was charged with phenylacetylene (4.39 mL, 40 mmol, 1 eq) in 400 ml THF under argon. The solution was cooled to -78 °C (CO_2 (s)/acetone) and BuLi (24 mL, 48 mmol, 1.2 eq) was added. The solution was stirred for 5 min. Hex-5-en-2-one was added to the flask at -78 °C and warmed to rt. The reaction was monitored by TLC (20 v/v % EtOAc:hexanes). When starting material was consumed the reaction mixture was quenched with half saturated aqueous NH_4Cl . The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organics were washed with brine, and dried over

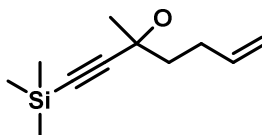
anhydrous MgSO_4 . The solution was filtered through a pad of celite and concentrated under reduced pressure. The resultant oil was purified by silica gel column chromatography (gradient 10:1 to 4:1 v/v % EtOAc:hexanes) to afford a clear colourless oil (71%, 5.71 g). R_f 0.40 (20 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 600 MHz): δ 7.40 - 7.48 (m, 2 H), 7.28 - 7.34 (m, 3 H), 5.85 - 5.99 (m, $J = 16.9, 10.2, 6.7, 6.7$ Hz, 1 H), 5.12 (d, $J = 17.0$ Hz, 1 H), 5.02 (d, $J = 11.7$ Hz, 1 H), 2.31 - 2.47 (m, 2 H), 2.11 (br. s., 1 H), 1.81 - 1.92 (m, 2 H), 1.61 ppm (s, 3 H); ^{13}C NMR (CDCl_3 , 151MHz): δ 138.4, 131.6, 128.2, 122.7, 114.9, 92.5, 83.7, 68.5, 42.7, 30.0, 29.3, 28.3 ppm; HRMS m/z calcd for $\text{C}_{14}\text{H}_{16}\text{O}$ [(M-H) $^+$] 199.1123, found 199.1125.

5-Phenylethynyltetrahydrofuran-2-methanol (Table 9, Entry 6)



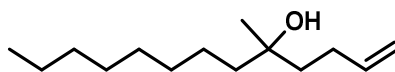
The title compound was prepared according to the general cyclization procedure to afford a light yellow oil (19%, 20.5 mg). R_f 0.21 (30 v/v % EtOAc/hexanes); ^1H NMR (400MHz, CDCl_3) δ 7.41 (dd, $J = 3.3, 6.4$ Hz, 2 H), 7.26 - 7.31 (m, 3 H), 4.22 - 4.38 (m, 1 H), 3.70 - 3.81 (m, 1 H), 3.54 (dt, $J = 5.4, 11.4$ Hz, 1 H), 2.08 - 2.38 (m, 2 H), 1.80 - 1.93 (m, 2 H), 1.64 (s, 3 H); ^{13}C NMR (101MHz, CDCl_3) δ 131.7, 131.6, 128.2, 128.2, 91.9, 83.0, 80.7, 79.2, 77.3, 77.2, 64.9, 41.0, 40.3, 28.0, 27.6, 27.1.

3-Methyl-1-(trimethylsilyl)hept-6-en-1-yn-3-ol



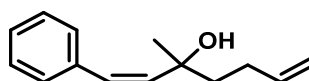
The title compound was prepared as per the synthesis of compound 3-Methyl-1-phenylhept-6-en-1-yn-3-ol (Table 9, Entry 6) to afford a clear colourless oil (39%, 168.5 mg). R_f 0.50 (20 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 400MHz): δ 5.87 (dd, $J = 16.8, 10.2$ Hz, 1 H), 5.06 (d, $J = 17.2$ Hz, 1 H), 4.97 (d, $J = 10.2$ Hz, 1 H), 2.18 - 2.34 (m, 2 H), 1.97 (br. s., 1 H), 1.73 (ddd, $J = 9.7, 6.5, 2.9$ Hz, 2 H), 1.46 (s, 3 H), 0.15 ppm (s, 6 H); ^{13}C NMR (CDCl_3 , 101MHz): δ 138.4, 114.8, 109.2, 87.8, 68.3, 42.5, 29.9, 29.3, -0.1 ppm; HRMS m/z calcd for $\text{C}_{11}\text{H}_{20}\text{OSi}$ [(M-H) $^+$] 19.1205, found 195.1213.

5-Methyltridec-1-en-5-ol



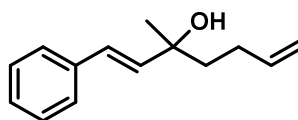
The title compound was prepared by the general Grignard addition to ketones procedure to afford a yellow oil (83%, 2.1 g). R_f 0.82 (30 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 400MHz): δ 5.73 - 5.94 (m, 1 H), 5.03 (d, $J = 17.2$ Hz, 1 H), 4.94 (d, $J = 10.2$ Hz, 1 H), 2.05 - 2.20 (m, 2 H), 1.51 - 1.58 (m, 2 H), 1.41 - 1.48 (m, 2 H), 1.24 - 1.34 (m, 14 H), 1.16 (s, 3 H), 0.80 - 0.92 ppm (m, 3 H); ^{13}C NMR (CDCl_3 , 101MHz): δ 139.1, 114.3, 72.7, 42.0, 40.8, 31.9, 30.2, 29.6, 29.3, 28.4, 26.9, 23.9, 22.7, 14.1 ppm; HRMS m/z calcd for $\text{C}_{11}\text{H}_{20}\text{OSi}$ [M $^+$] 212.2140, found 212.2136.

(Z) -4-Methyl-1-phenylocta-1,7-diene-4-ol



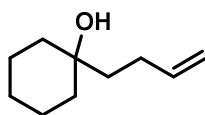
A 10 mL round bottom flask was charged with 3-methyl-1-phenylhept-6-en-1-yn-3-ol (502 mg, 2.5 mmol, 1 eq) in 3 mL of MeOH. Quinoline (100 mg, 0.75mmol, 0.28 eq) and Lindlar's Catalyst (104.5 mg, 0.25 mmol, 0.1 eq.) were added to the solution. H₂ (g) was bubbled through the solution for 2 min and then placed under H₂ using a balloon. The reaction was monitored by TLC (20 v/v % EtOAc:hexanes). When no alkyne was observed the reaction was filtered through a pad of celite and the solvent was removed by rotary evaporator. The crude product was purified by silica gel column chromatography (10 % EtOAc:hexanes) to afford a pale yellow oil (35%, 175 mg) R_f 0.47 (30 v/v % EtOAc/hexanes); ¹H NMR (CDCl₃, 600 MHz): δ 7.28 - 7.35 (m, 4 H), 7.22 - 7.25 (m, 1 H), 6.52 (d, *J* = 12.9 Hz, 1 H), 5.77 - 5.85 (m, 1 H), 5.66 (d, *J* = 12.9 Hz, 1 H), 5.00 (d, *J*=17.0 Hz, 1 H), 4.93 (d, *J*=8.2 Hz, 1 H), 2.13 - 2.19 (m, 2 H), 1.62 - 1.68 (m, 2 H), 1.54 - 1.58 (m, 1 H), 1.33 ppm (s, 3 H); ¹³C NMR (CDCl₃,151 MHz): δ 138.8, 138.2, 137.4, 128.8, 128.3, 128.1, 127.0, 114.4, 74.5, 42.7, 29.5, 28.6 ppm; HRMS *m/z* calcd for C₁₁H₂₀OSi [M+] 202.1358, found 202.1349.

(E)-3-Methyl-1-phenylhepta-1,6-dien-3-ol



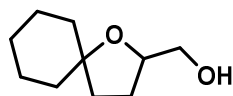
A 10 mL round bottom flask was charged with 3-Methyl-1-phenylhept-6-en-1-yn-3-ol (537.4 mg, 2.5 mmol, 1 eq) in 2 mL Ether. The solution was cooled to 0 °C and added Red-Al (1.27 g, 4.1 mmol, 1.6 mL) dropwise as a solution in toluene. The mixture was allowed to warm to rt and was monitored by TLC (20 v/v % EtOAc:hexanes). When the reaction was complete by TLC it was quenched by addition of 1M H₂SO₄. The aqueous layer was extracted with ether (3 x 5 mL). The organic layers were combined and washed with brine and dried over MgSO₄. Solvent was removed under reduced pressure. The crude product was purified via silica gel chromatography (10 v/v % EtOAc:hexanes) to afford a yellow oil (39%, 211.5 mg). *R_f* 0.39 (20 v/v % EtOAc/hexanes); ¹H NMR (CDCl₃, 400 MHz): δ 7.33 - 7.37 (m, 2 H), 7.29 (t, *J* = 7.6 Hz, 2 H), 7.15 - 7.24 (m, 1 H), 6.56 (d, *J* = 16.0 Hz, 1 H), 6.24 (dd, *J* = 16.0, 1.6 Hz, 1 H), 5.75 - 5.88 (m, 1 H), 4.96 - 5.06 (m, 1 H), 4.93 (d, *J* = 10.2 Hz, 1 H), 2.08 - 2.18 (m, 2 H), 1.66 - 1.73 (m, 2 H), 1.55 (s, 1 H), 1.37 ppm (d, *J* = 1.6 Hz, 3 H); ¹³C NMR (CDCl₃, 100 MHz): δ 138.8, 136.9, 136.4, 128.6, 127.4, 127.3, 126.4, 114.6, 73.3, 41.7, 28.5, 28.4.; HRMS *m/z* calcd for C₁₁H₂₀OSi [M⁺] 202.1358, found 202.1351.

1-(but-3-enyl)cyclohexanol (Table 9, Entry 10)



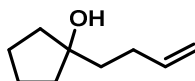
The title compound was prepared using the general addition of Grignards to ketones procedure to afford a clear colourless oil (69%, 798 mg). R_f 0.83 (30 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 5.78 - 5.91 (m, $J = 17.0, 10.3, 6.6, 6.6$ Hz, 1 H), 5.03 (d, $J = 17.2$ Hz, 1 H), 4.94 (d, $J = 10.2$ Hz, 1 H), 2.08 - 2.18 (m, 2 H), 1.36 - 1.64 (m, 13 H), 1.30 - 1.36 (m, 2 H), 1.18 - 1.30 ppm (m, 1 H); ^{13}C NMR (CDCl_3 , 101MHz): δ 139.3, 114.3, 71.4, 41.4, 37.5, 27.4, 25.8, 22.2 ppm; HRMS m/z calcd for $\text{C}_{10}\text{H}_{18}\text{O}$ $[\text{M}^+]$ 154.1356, found 154.1358.

Oxaspiro[4.5]decan-2-ylmethanol (Table 9, Entry 10)



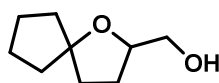
The title compound was prepared using the general cyclization procedure to afford a yellow oil (34%, 154.5 mg). R_f 0.19 (30 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 4.02 - 4.13 (m, 1 H), 3.66 (dd, $J = 11.3, 2.3$ Hz, 1 H), 3.44 (dd, $J = 11.1, 5.3$ Hz, 1 H), 2.10 (br. s., 1 H), 1.83 - 1.96 (m, 1 H), 1.59 - 1.81 (m, 5 H), 1.27 - 1.57 ppm (m, 8 H); ^{13}C NMR (CDCl_3 , 101MHz): δ 78.1, 65.2, 38.3, 37.3, 27.1, 25.6, 24.0, 23.7 ppm; HRMS m/z calcd for $\text{C}_{10}\text{H}_{18}\text{O}_2$ $[\text{M}^+]$ 170.1307, found 170.1306.

1-(but-3-enyl)cyclopentanol (Table 9, Entry 9)



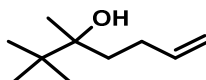
The title compound was prepared using the general Grignard addition to ketones procedure to afford a light yellow oil (42%, 441.7 mg). R_f 0.66 (30 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 400MHz): δ 5.76 - 5.99 (m, 1 H), 5.04 (d, $J = 17.2$ Hz, 1 H), 4.94 (d, $J = 10.2$ Hz, 1 H), 2.12 - 2.26 (m, 2 H), 1.72 - 1.87 (m, 3 H), 1.47 - 1.72 (m, 10 H), 1.36 ppm (d, $J = 2.3$ Hz, 2 H); ^{13}C NMR (CDCl_3 , 101MHz): δ 139.3, 114.3, 82.5, 40.5, 39.8, 29.3, 23.8 ppm; HRMS m/z calcd for $\text{C}_9\text{H}_{16}\text{O}[\text{M}^+]$ 140.1203, found 140.1198.

Oxaspiro[4.4]nonan-2-ylmethanol (Table 9, Entry 9)



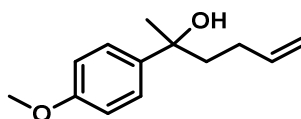
The title compound was prepared using the general cyclization procedure to afford a yellow oil (41%, 34.6 mg). R_f 0.15 (30 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 4.00 - 4.08 (m, 1 H), 3.66 (dd, $J = 11.3, 3.1$ Hz, 1 H), 3.46 (dd, $J = 11.3, 5.5$ Hz, 1 H), 1.87 - 2.00 (m, 2 H), 1.65 - 1.85 (m, 8 H), 1.49 - 1.63 ppm (m, 4 H); ^{13}C NMR (CDCl_3 , 101MHz): δ 78.3, 65.4, 38.9, 38.1, 36.6, 27.6, 24.0 ppm;

2,2,3-Trimethylhept-6-en-ol (Table 9, Entry 5)



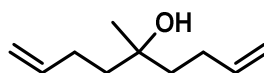
The title compound was prepared using the general Grignard addition to ketones procedure to afford a yellow oil (84%, 943.1 mg). R_f 0.50 (20 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 400 MHz): δ 5.79 - 5.92 (m, 1 H), 5.04 (d, $J = 17.2$ Hz, 1 H), 4.94 (d, $J = 10.2$ Hz, 1 H), 2.05 - 2.28 (m, 2 H), 1.46 - 1.68 (m, 2 H), 1.12 (s, 3 H), 0.93 ppm (d, $J = 2.0$ Hz, 9 H); ^{13}C NMR (CDCl_3 , 101MHz): δ 139.6, 114.3, 76.3, 38.1, 35.2, 28.5, 25.3, 20.8 ppm LRMS m/z calcd for $\text{C}_{10}\text{H}_{20}\text{O}$ [(M-CH₃)⁺]141.1279, found 141.1.

2-(4-methoxyphenyl)hex-5-en-2-ol



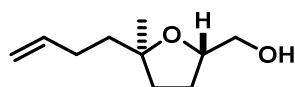
The title compound was prepared using the general Grignard addition to ketones procedure to afford a light orange oil. R_f 0.42 (30 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 400MHz): δ 7.30 - 7.37 (m, 2 H), 6.85 - 6.89 (m, 2 H), 5.71 - 5.85 (m, 1 H), 4.88 - 5.01 (m, 2 H), 3.80 (s, 3 H), 1.85 - 2.06 (m, 4 H), 1.74 - 1.79 (m, 1 H), 1.54 ppm (s, 3 H); ^{13}C NMR (CDCl_3 , 101MHz): δ 158.2, 139.9, 138.8, 125.9, 114.5, 113.4, 74.4, 55.2, 43.1, 30.3, 28.6 ppm; HRMS m/z calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$ [M⁺]206.1307, found 206.1313.

5-Methylona-1,8-dien-5-ol (Table 9, Entry 3)



The title compound was prepared by the general Grignard addition to ketones procedure to afford a clear colourless oil (99%, 1.80 g). R_f 0.45 (20 v/v % EtOAc/hexanes); ^1H NMR (CDCl_3 , 400MHz): δ 5.78 - 5.90 (m, 2 H), 5.04 (dd, $J = 17.2, 1.6$ Hz, 2 H), 4.95 (dd, $J = 10.2, 2.0$ Hz, 2 H), 2.07 - 2.17 (m, 5 H), 1.52 - 1.59 (m, 5 H), 1.27 (s, 1 H), 1.18 ppm (s, 3 H); ^{13}C NMR (CDCl_3 , 101MHz): δ 138.9, 114.4, 72.6, 40.9, 28.3, 26.8 ppm; HRMS m/z calcd for $\text{C}_{10}\text{H}_{18}\text{O}$ $[\text{M}^+]$ 154.1358, found 154.1353.

(5-(but-3-enyl)tetrahydrofuran-2-yl)methanol (Table 9, Entry 3)



The title compound was prepared using the general cyclization procedure to afford a light yellow oil (55%, 43 mg). R_f 0.17 (30 v/v % EtOAc/hexanes); ^1H NMR (600 MHz, CDCl_3) δ 5.83 (dd, $J = 10.5, 17.0$ Hz, 1 H), 5.02 (d, $J = 17.6$ Hz, 1 H), 4.93 (d, $J = 9.9$ Hz, 1 H), 3.67 (d, $J = 2.3$ Hz, 1 H), 3.44 - 3.49 (m, 1 H), 2.05 - 2.15 (m, 2 H), 1.87 - 1.98 (m, 2 H), 1.75 - 1.85 (m, 2 H), 1.67 - 1.75 (m, 1 H), 1.54 - 1.66 (m, 3 H), 1.19 - 1.32 (m, 3 H); ^{13}C NMR (101 MHz CDCl_3) δ 138.9, 114.1, 83.4, 79.1, 78.3, 65.3, 65.1, 40.9, 40.2, 37.1, 36.7.

Images of $\text{Co}(\text{modp})_2$ Column



Figure 17. The varying bands of decomposed cobalt catalyst (modp and piper ligands).

Bands are clearly shown to elute at widely varying R_f values during column chromatography. These bands in many cases overlap with the cyclized product and in several instances have been shown to make accurate characterization extremely difficult.

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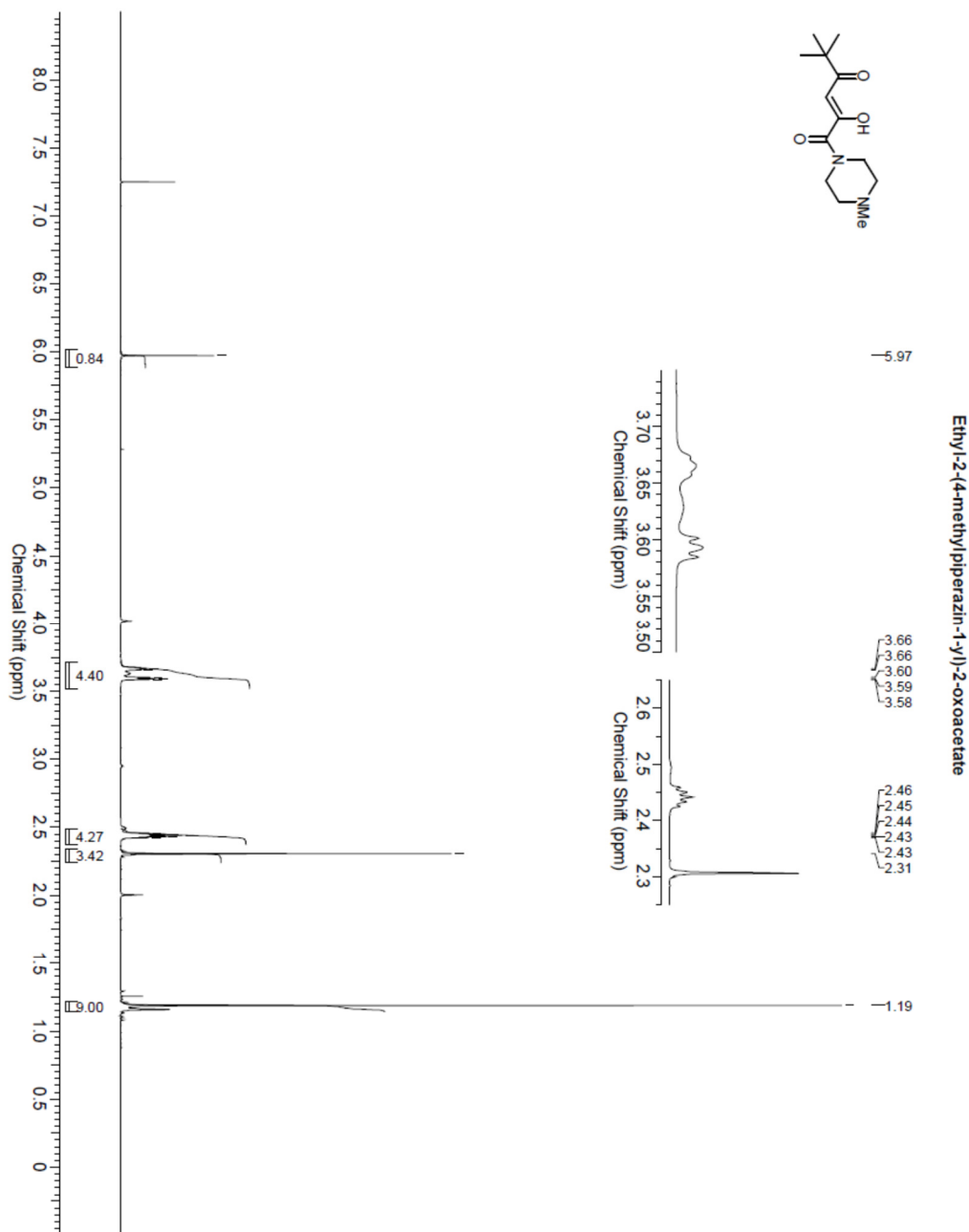
5. Appendices

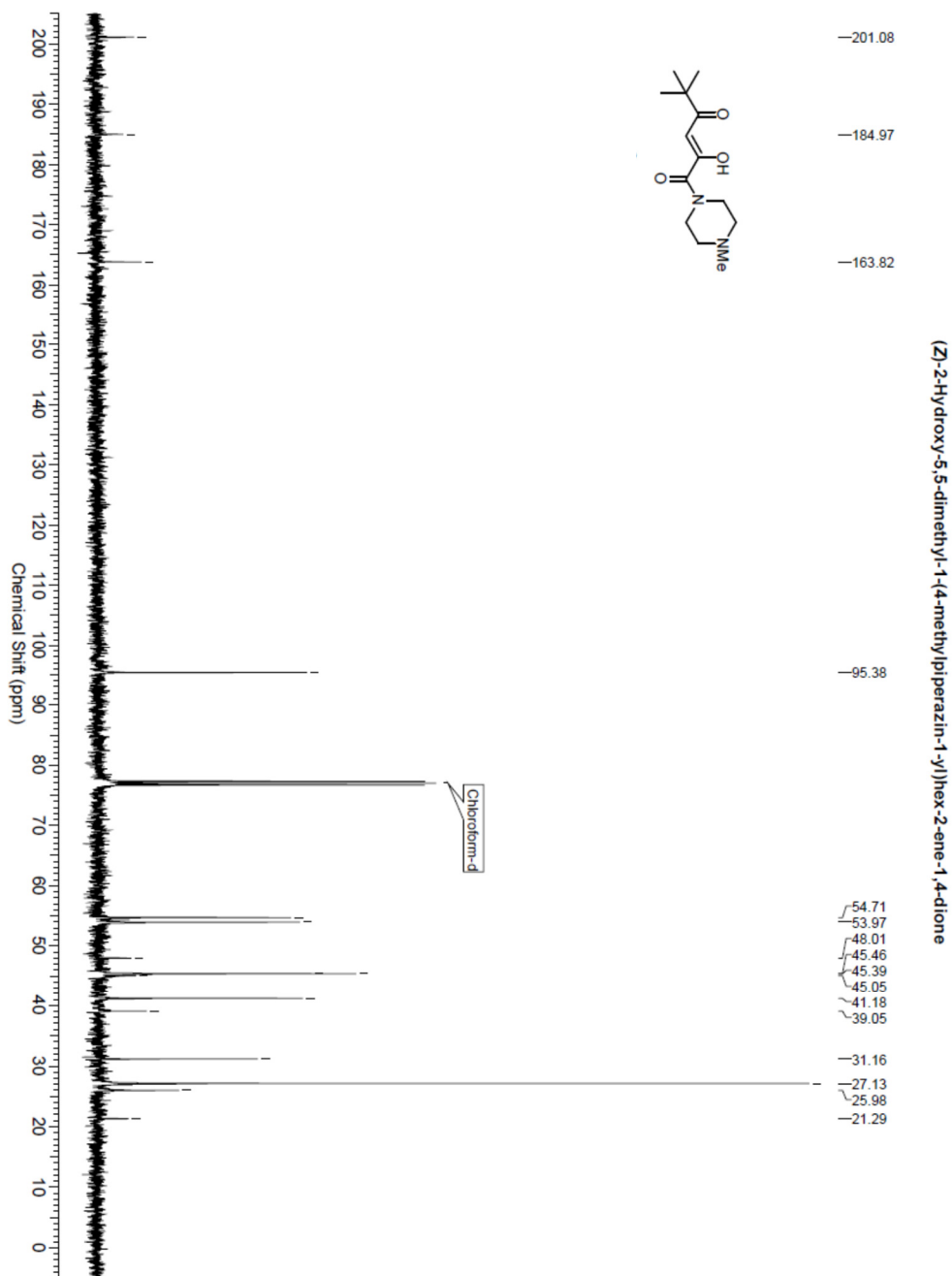
SPECTRA 1. ETHYL-2-(4-METHYLPIPERAZIN-1-YL)-2-OXOACETATE (2.37)	88
SPECTRA 2. ETHYL-2-(4-METHYLPIPERAZIN-1-YL)-2-OXOACTATE (2.40).....	90
SPECTRA 3. 1-(TERT-BUTYLDIMETHYLSILOXY)HEX-5-EN-2-OL (2.41A)	92
SPECTRA 4. 5-((TERT-BUTYLDIMETHYLSILOXYMETHYL)TETRAHYDROFURAN-2-YL)METHANOL (2.42A).....	94
SPECTRA 5. (S)-(TERT-BUTYLDIMETHYLSILANYOXY)HEPT-6-EN-3-OL (2.41B)	96
SPECTRA 6. [(2R, 5R)-5-[2-(TERT-BUTYL-DIMETHYL-SILANYLOXY)-ETHYL]- TETRAHYDROFURAN-2- YL]-METHANOL (2.42B)	98
SPECTRA 7. 1-(TERT-BUTYLDIMETHYLSILOXY)-OCT-7-EN-4-OL (2.41C)	100
SPECTRA 8. (5-(3-TERT-BUTYLDIMETHYLSILOXY)PROPYL)TETRAHYDROFURAN-2-YL) - METHANOL (2.42C).....	102
SPECTRA 9. 1-(METHOXYMETHYLOXY)-OCT-7-EN-4-OL	104
SPECTRA 10. (5-(3-METHOXYMETHOXY)PROPYL)TETRAHYDROFURAN-2-YL)METHANOL.....	106
SPECTRA 11. 1-(BENZOYLOXY)-OCT-7-EN-OL	108
SPECTRA 12. (5-(3-(BENZYLOXY)PROPYL)TETRAHYDROFURAN-2-YL) METHANOL	110
SPECTRA 13. 1-(4-METHOXYPHENYLOXY)OCT-7-EN-4-OL	112
SPECTRA 14. (5-(3-(4-METHOXYPHENOXY)PROPYL)TETRAHYDROFURAN-2-YL)-METHANOL	114
SPECTRA 15. NONA-1,8-DIEN-5-OL.....	116
SPECTRA 16. (5-(BUT-3-ENYL)-TETRAHYDRO-FURAN-2-YL)-METHANOL (TABLE 7, ENTRY 4).....	118
SPECTRA 17. 1-PHENYL-PENT-4-EN-OL	120
SPECTRA 18. (5-PHENYL-TETRAHYDRO-FURAN-2-YL)-METHANOL	122
SPECTRA 19. 1-PHENYL-HEX-5-EN-2-OL.....	124
SPECTRA 20. (5-BENZYL-TETRAHYDRO-FURAN-2-YL)-METHANOL (TABLE 7, ENTRY 7).....	126
SPECTRA 21. 1-PHENYL-HEPTA-1,6-DIEN-3-OL	127
SPECTRA 22. (5-STYRYL-TETRAHYDROFURAN-2-YL)-METHANOL	129
SPECTRA 23. (5-(BUT-3-ENYL)TETRAHYDROFURAN-2-YL)METHANOL	131
SPECTRA 24. 4-METHYLOCTA-1,7-DIENE-4-OL	133
SPECTRA 25. 3-METHYL-1-PHENYLHEPT-6-EN-1-YN-3-OL	133

SPECTRA 26. 3-METHYL-1-(TRIMETHYLSILYL)HEPT-6-EN-1-YN-3-OL	136
SPECTRA 27. 5-METHYLTRIDEC-1-EN-5-OL	138
SPECTRA 28. (E)-3-METHYL-1-PHENYLHEPTA-1,6-DIEN-3-OL	140
SPECTRA 29. (Z)-3-METHYL-1-PHENYLHEPTA-1,6-DIEN-3-OL	141
SPECTRA 30. 1-(BUT-3-ENYL)-CYCLOHEXANOL	143
SPECTRA 31. 1-(BUT-3-ENYL)-CYCLOPENTANOL	145
SPECTRA 32. 2,2,3-TRIMETHYLHEPT-6-EN-3-OL	147
SPECTRA 33. 1-OXASPIRO[4.4]NONAN-2-YLMETHANOL	149
SPECTRA 34. 1-OXASPIRO[4.5]DECAN-2-YLMETHANOL.....	151
SPECTRA 35. (5-PHENYL-5-METHYLTETRAHYDROFURAN-2-YL)METHANOL	153
SPECTRA 36. 2-PHENYLHEX-5-EN-2-OL	154
SPECTRA 375-PHENYLETHYNYLTETRAHYDROFURAN-2-METHANOL (TABLE 9, ENTRY 6)	155
SPECTRA 38. (5-(BUT-3-ENYL)TETRAHYDROFURAN-2-YL)METHANOL	156

Spectral Data

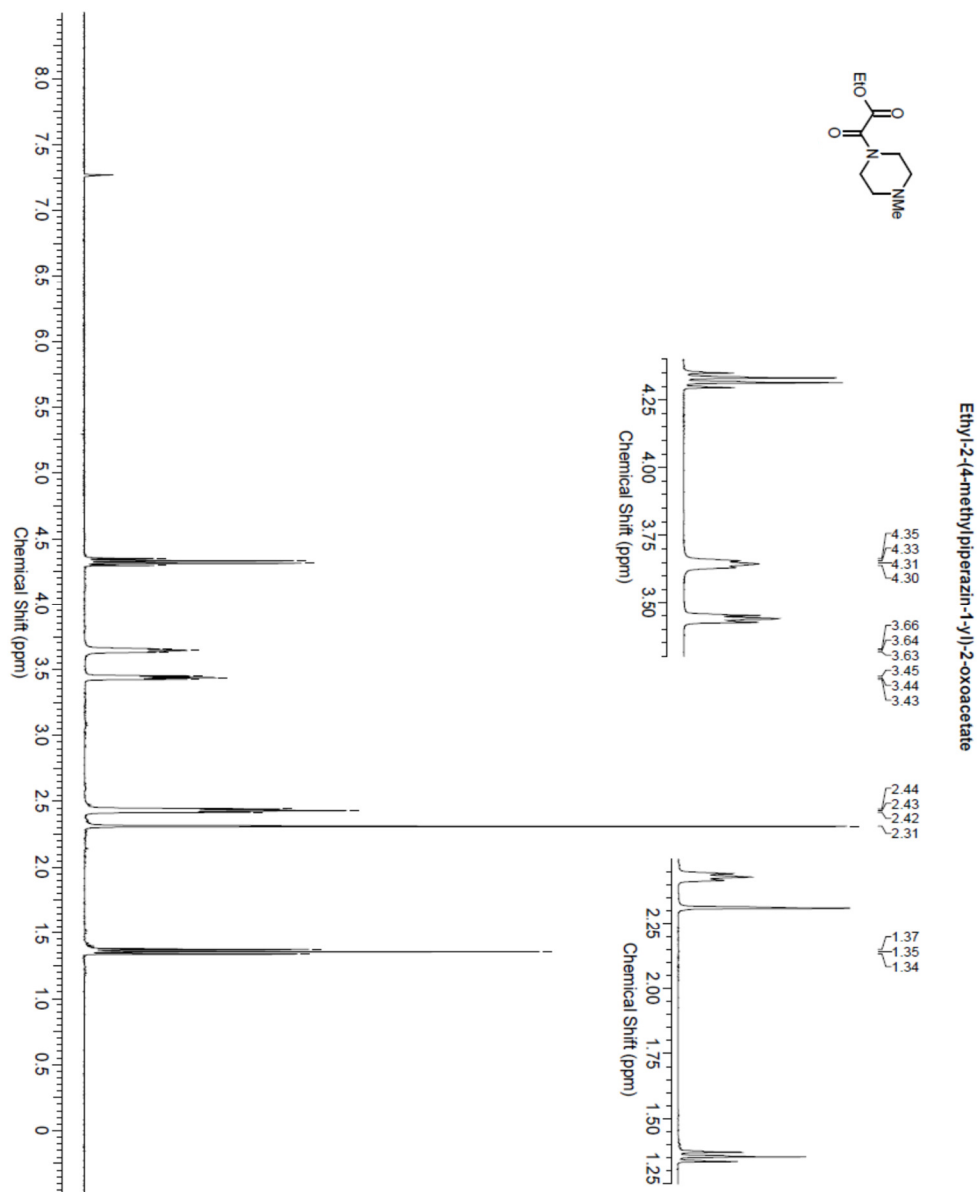
Spectra 1. Ethyl-2-(4-methylpiperazin-1-yl)-2-oxoacetate (2.37)

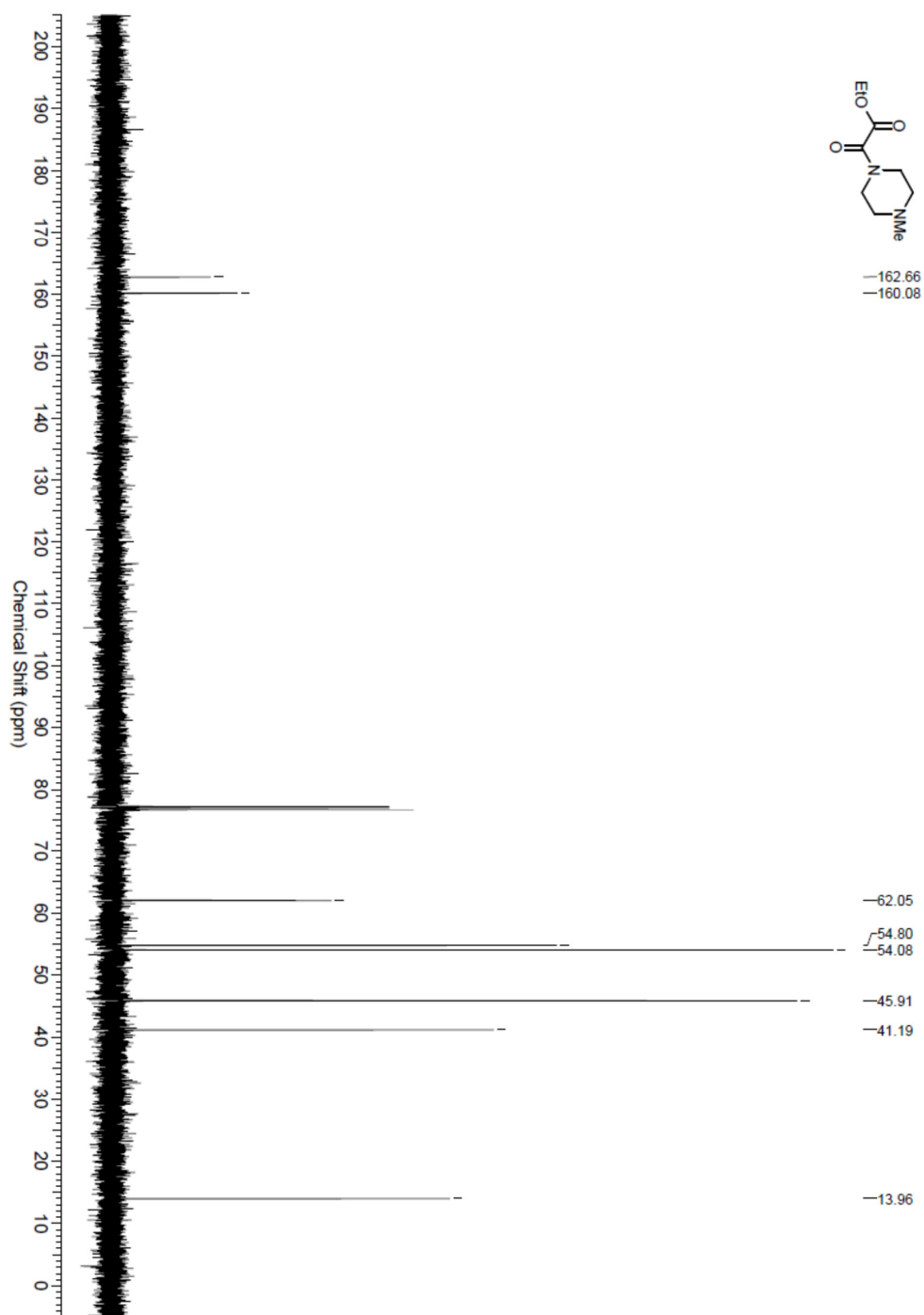
¹H NMR (CDCl₃, 400 MHz)



¹³C NMR (CDCl₃, 100 MHz)

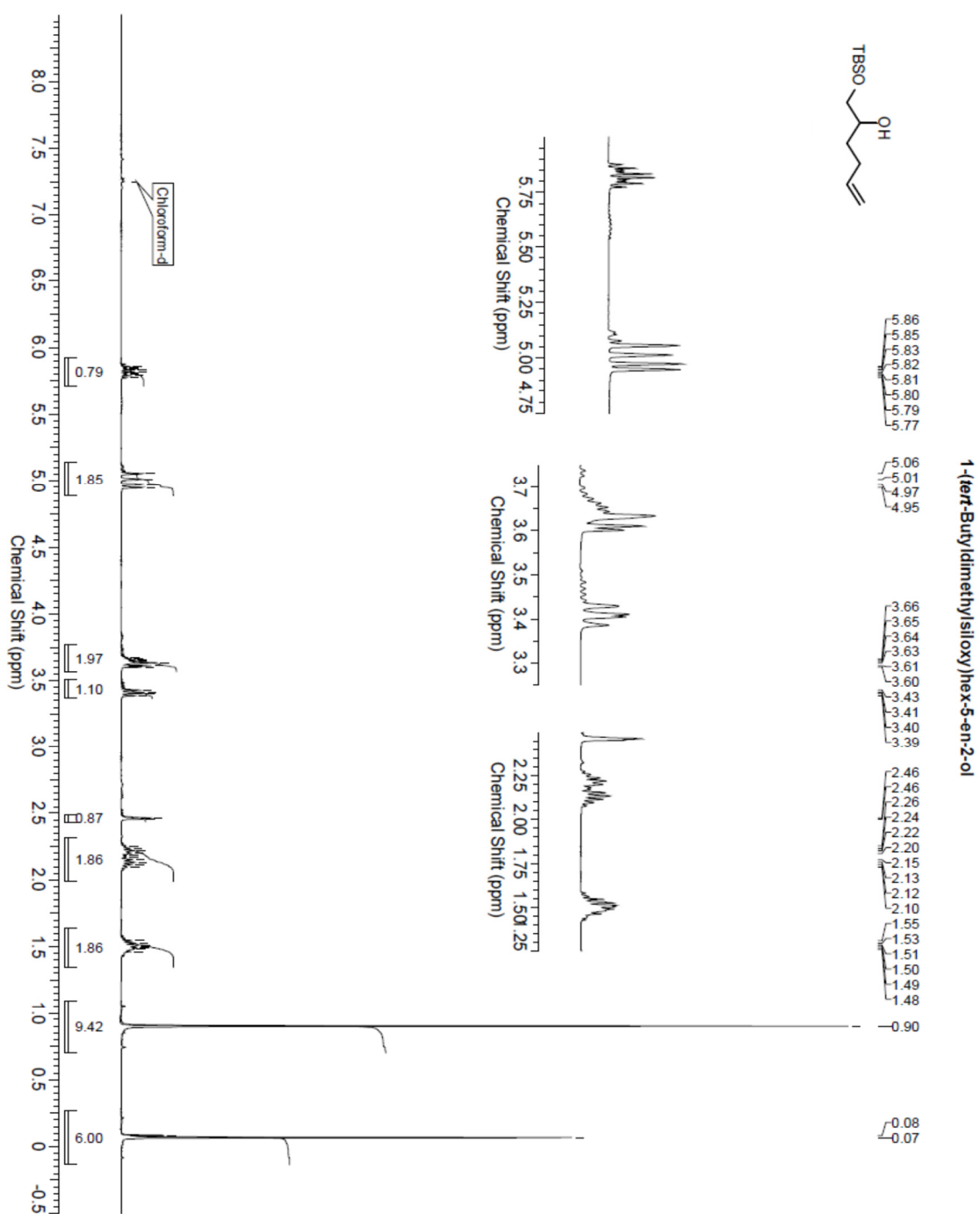
Spectra 2. Ethyl-2-(4-methylpiperazin-1-yl)-2-oxoacetate (2.40)

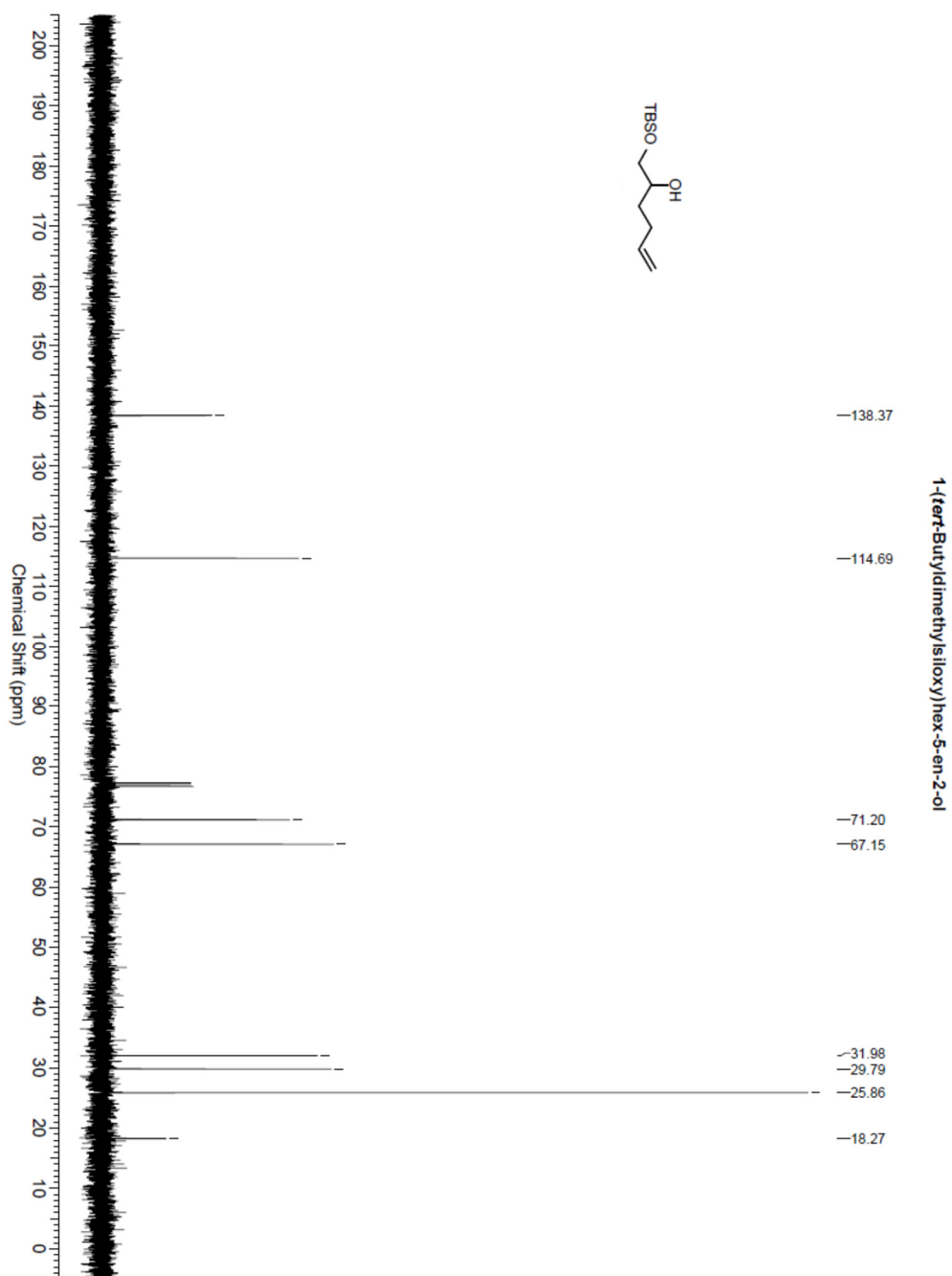
 ^1H NMR (CDCl_3 , 400 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)

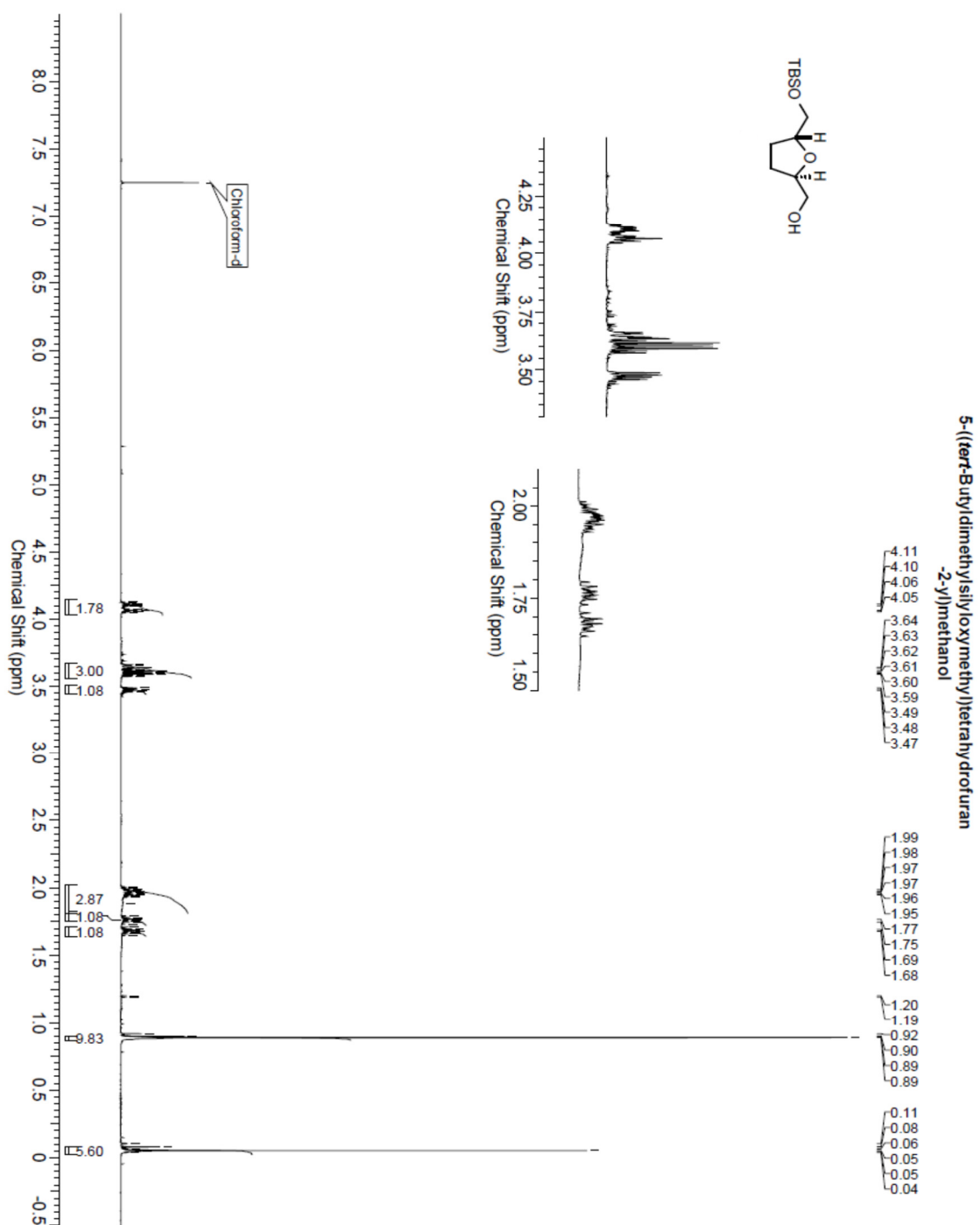
Spectra 3. 1-(tert-Butyldimethylsiloxy)hex-5-en-2-ol (2.41a)

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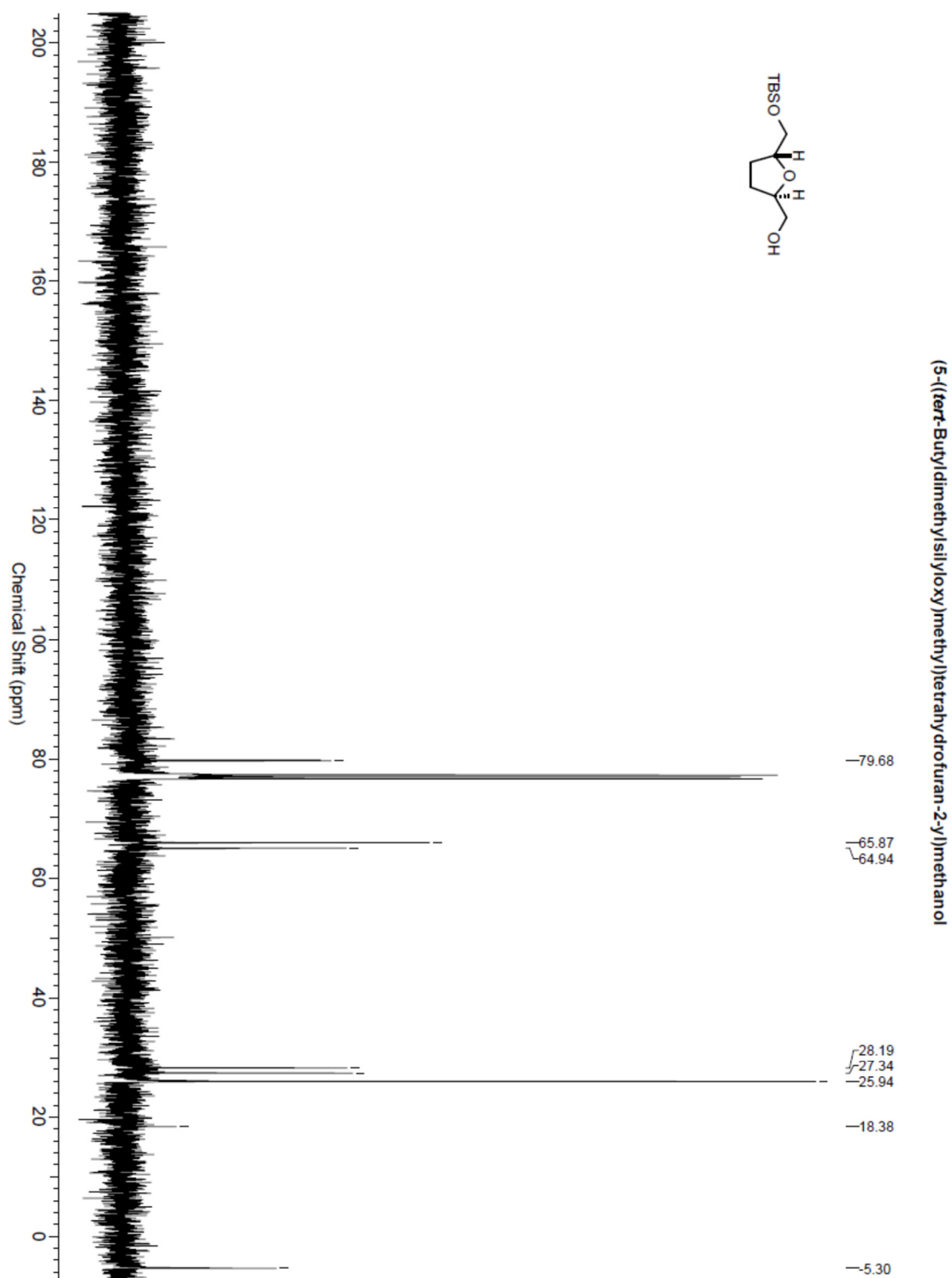


^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 4. 5-((tert-Butyldimethylsilyloxymethyl)tetrahydrofuran-2-yl)methanol
(2.42a)

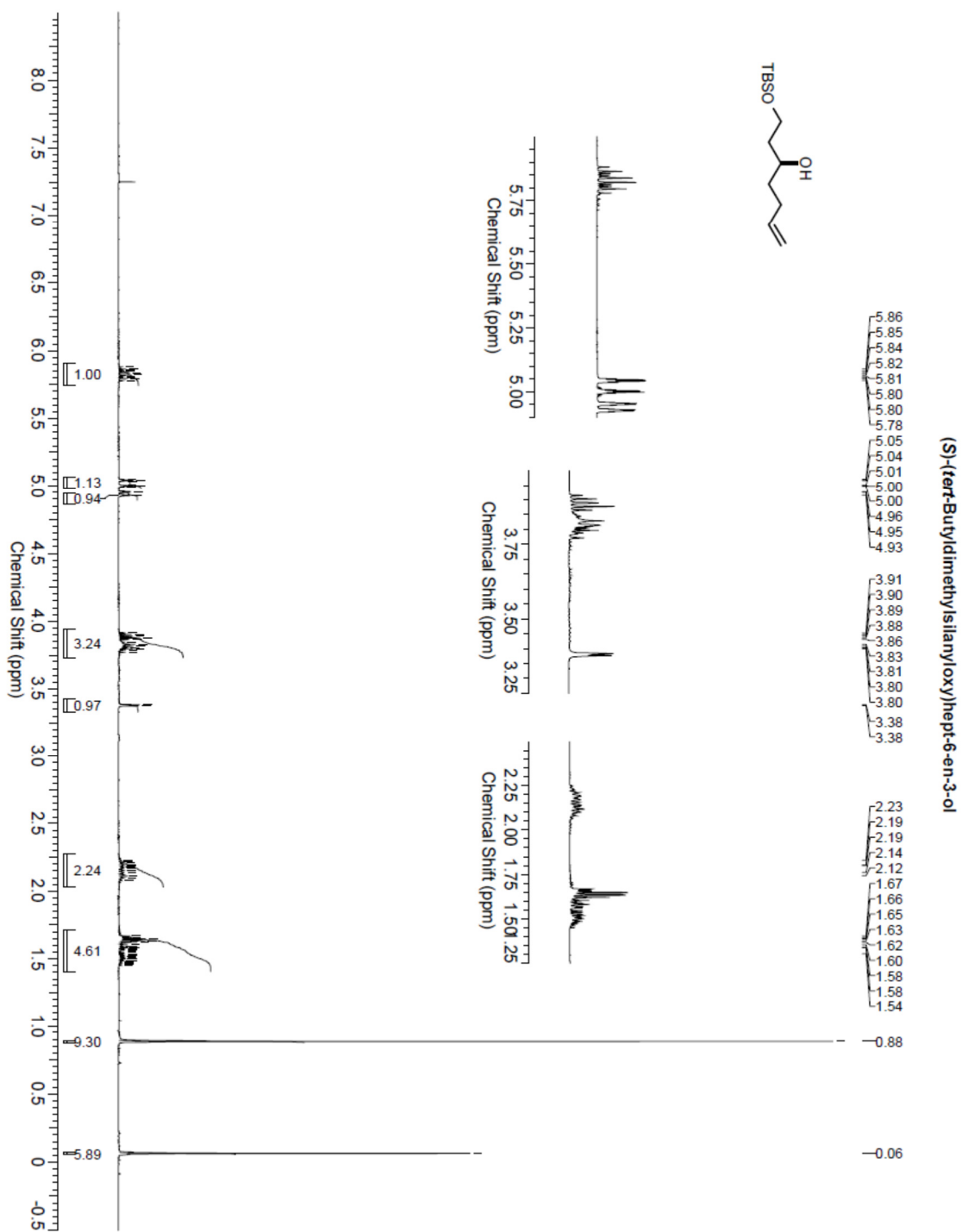


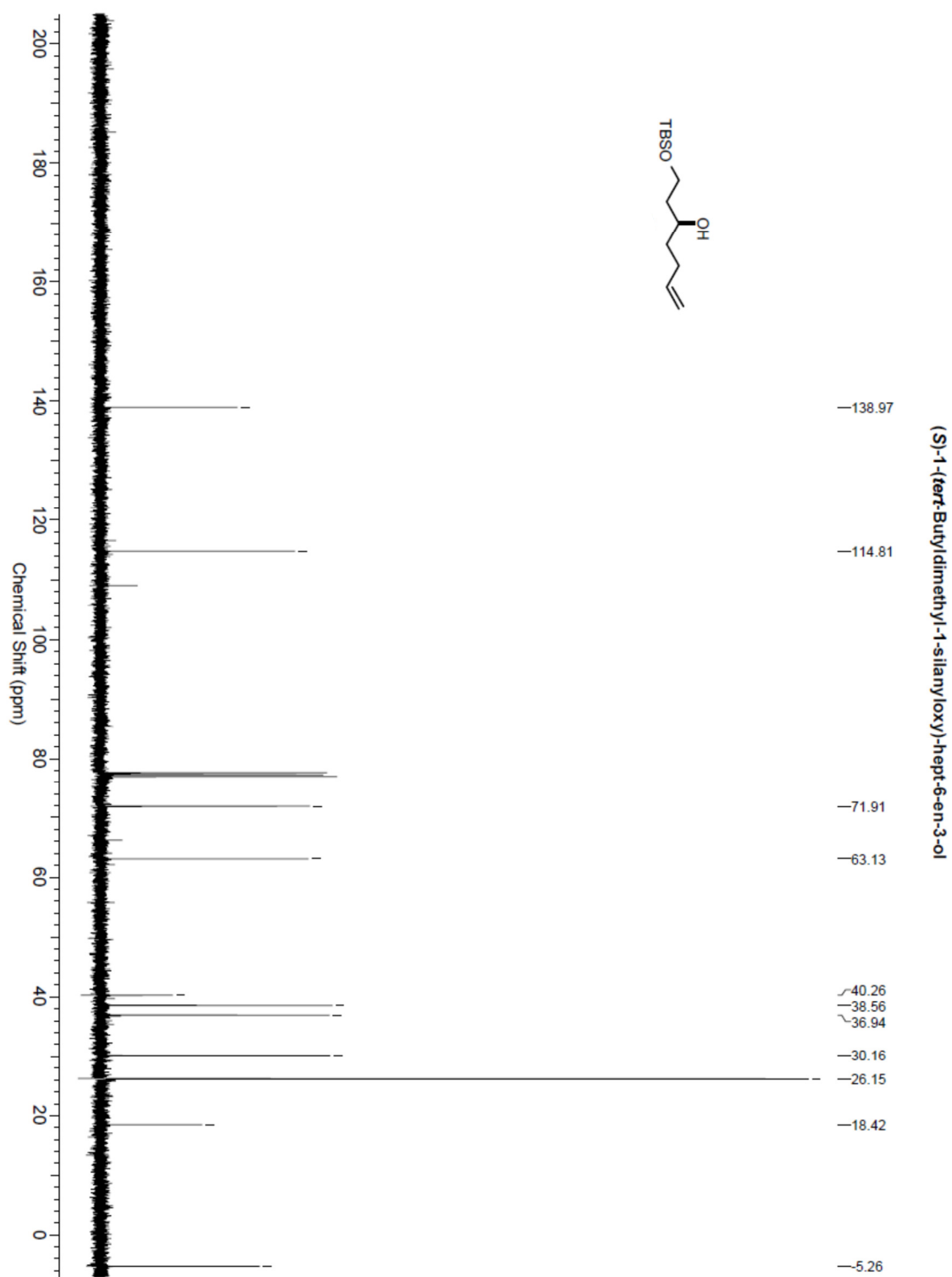
^1H NMR (CDCl_3 , 400 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)

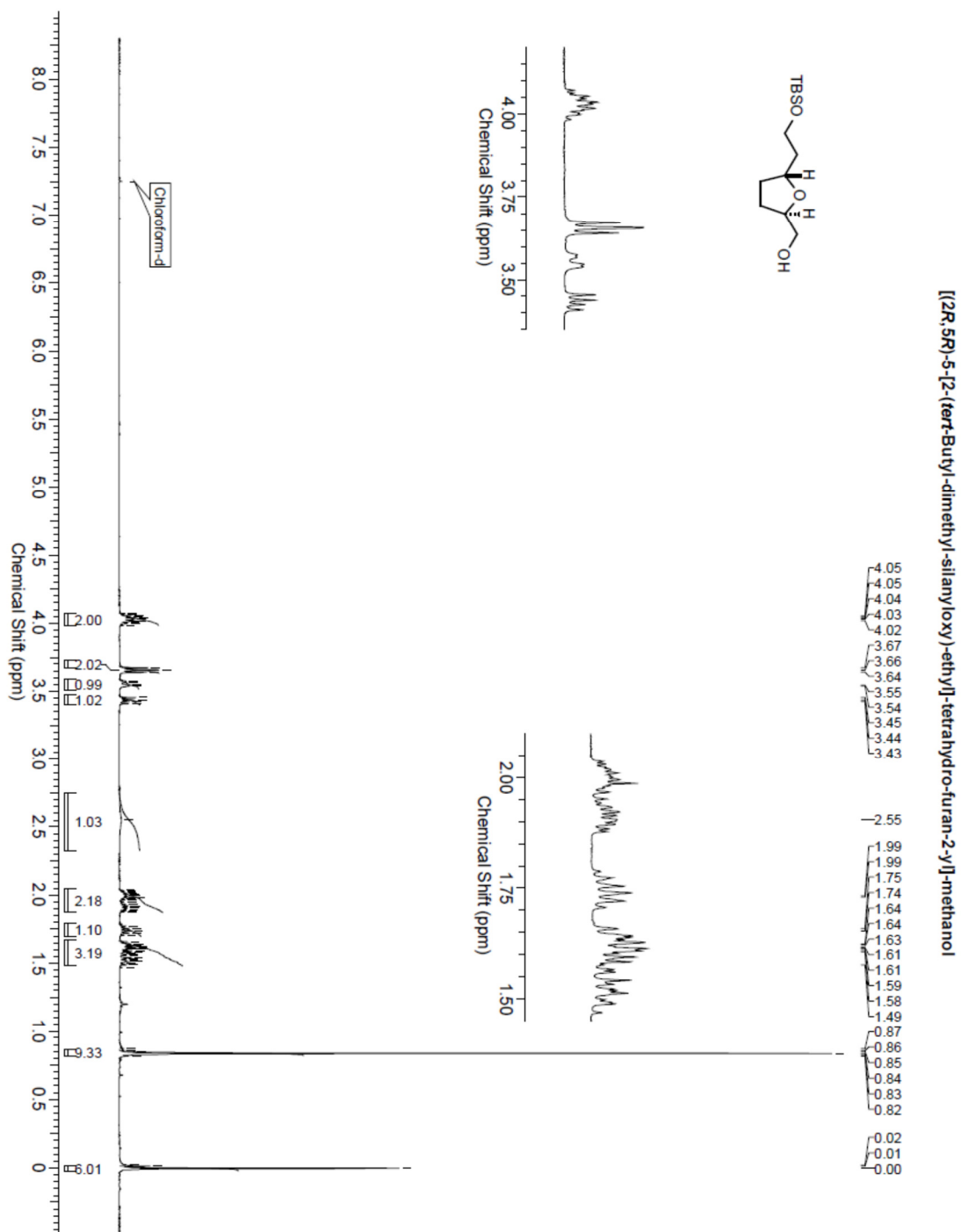
Spectra 5. (S)-(tert-Butyldimethylsilyloxy)hept-6-en-3-ol (2.41b)

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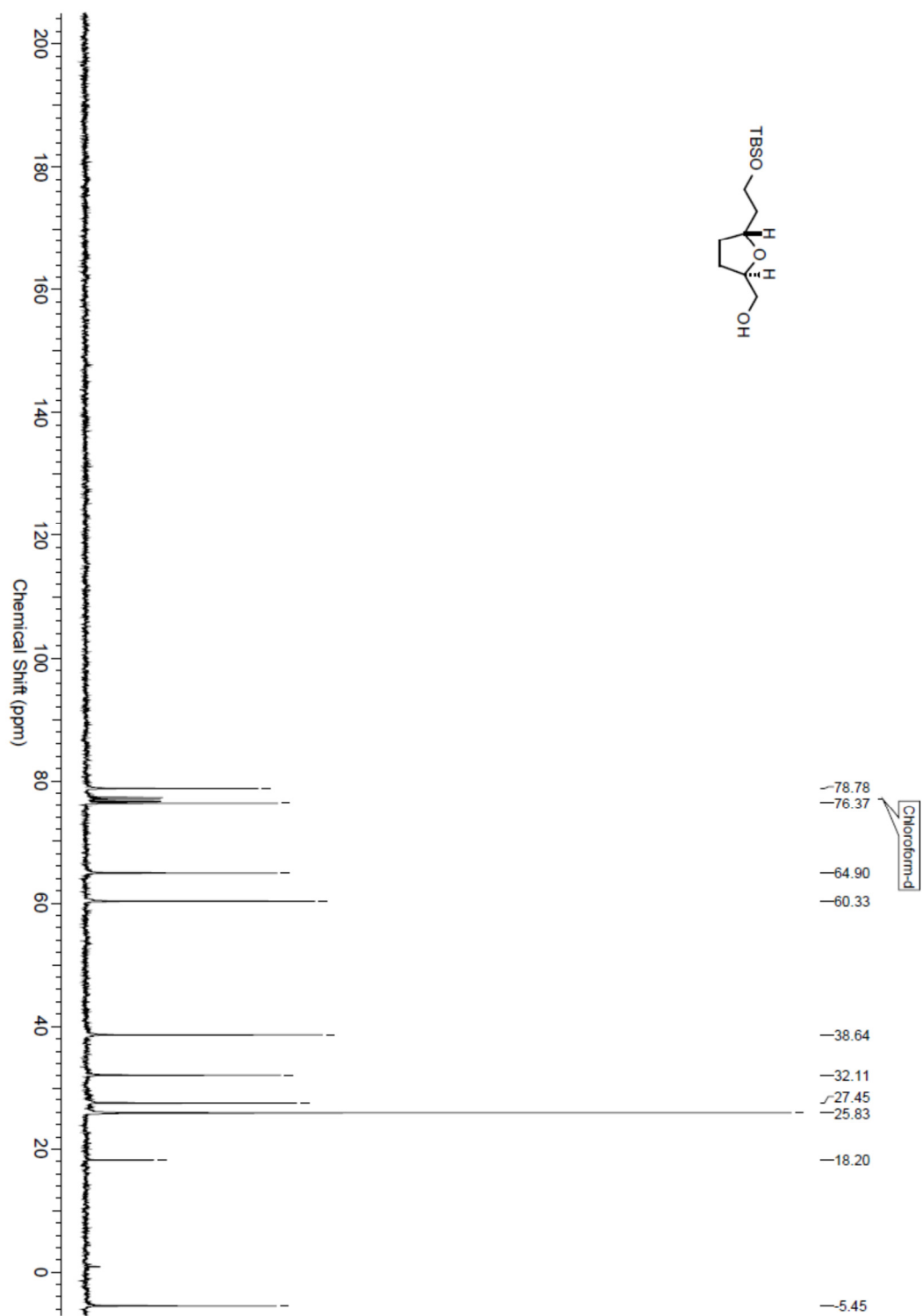


^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 6. [(2R, 5R)-5-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-tetrahydrofuran-2-yl]-methanol (2.42b)

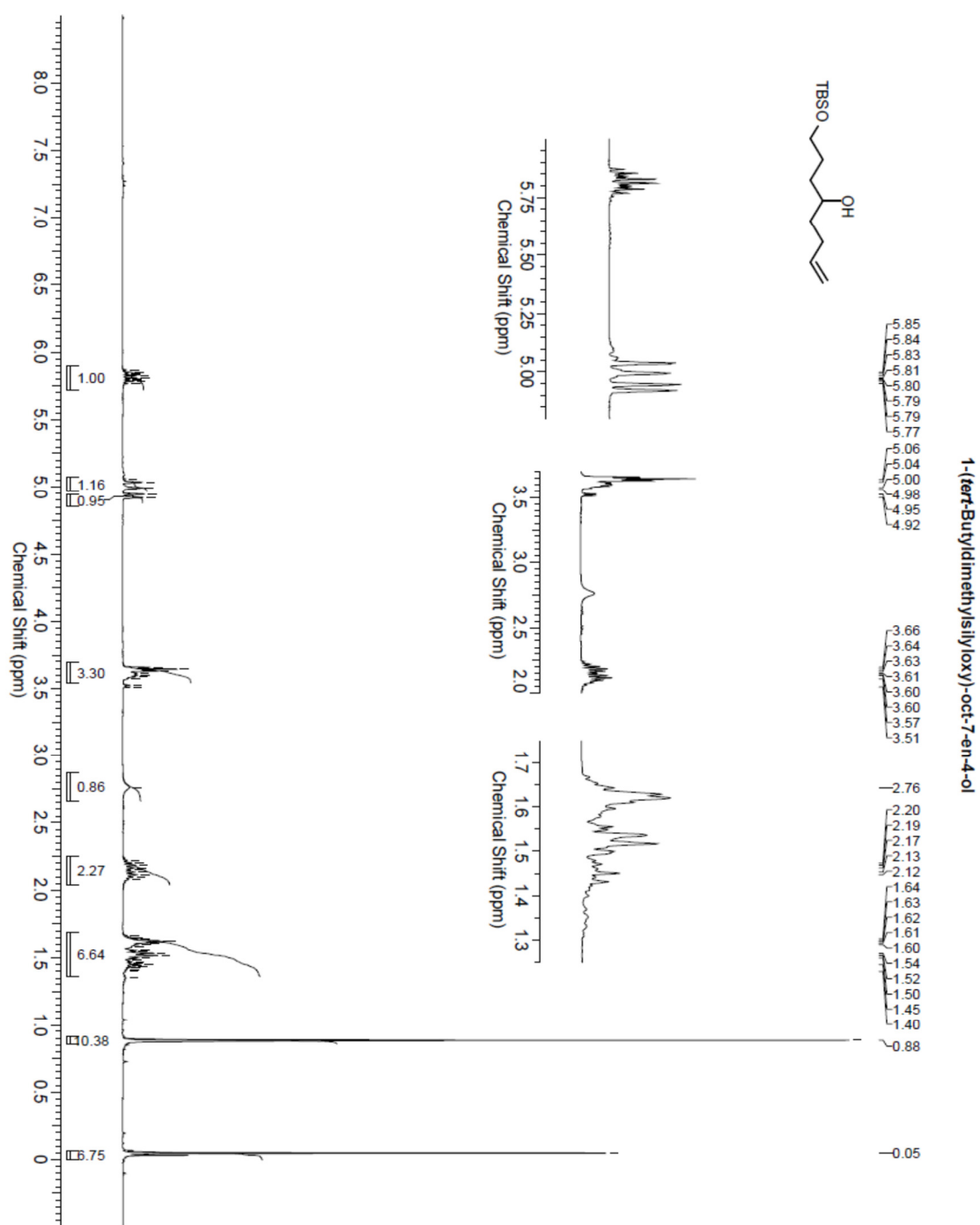


^1H NMR (CDCl_3 , 400 MHz)

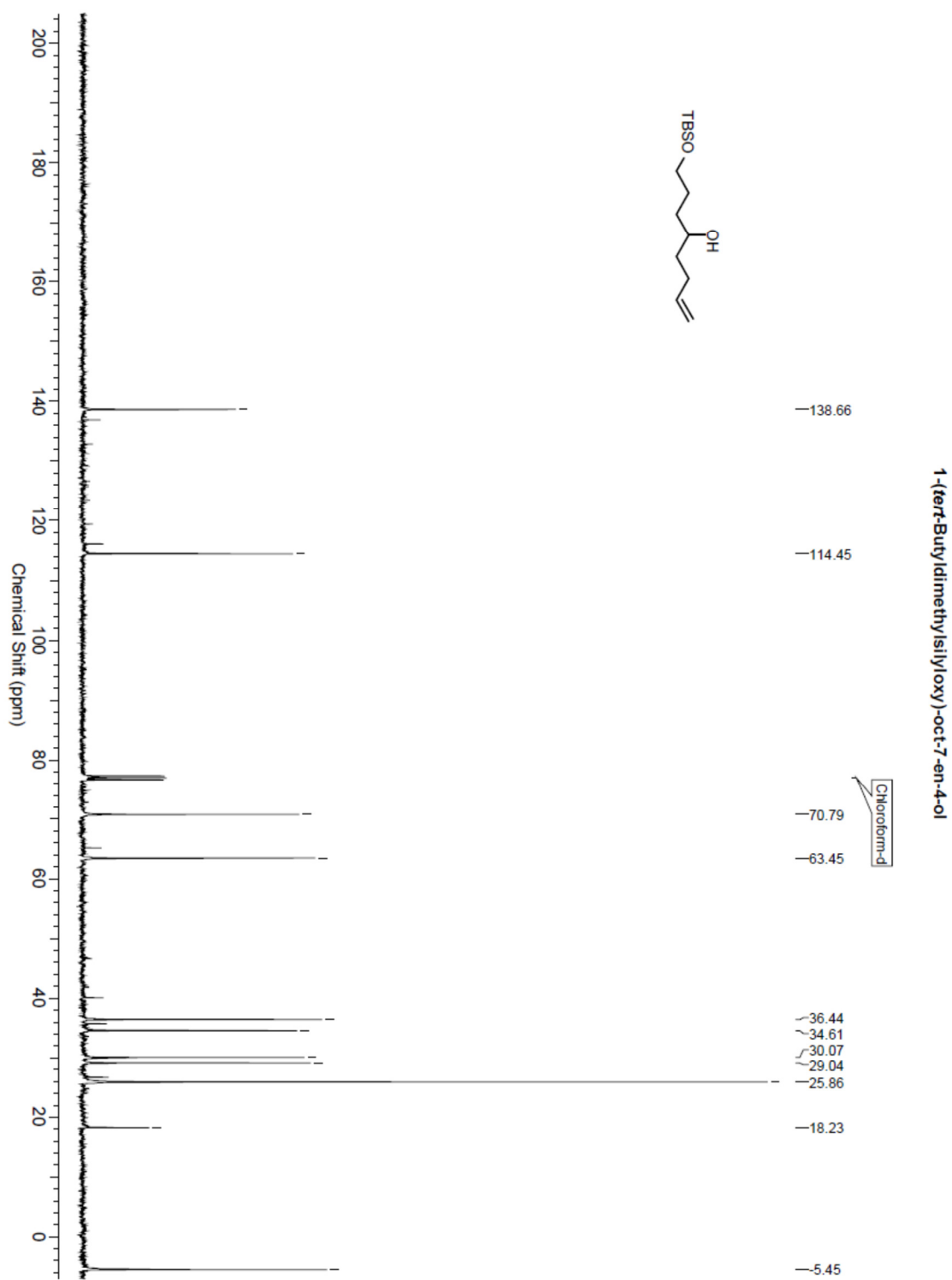
[(2*R*,5*R*)-5-[2-(*tert*-Butyldimethylsilyloxy)-ethyl]tetrahydrofuran-2-yl]-methanol

¹³C NMR (CDCl₃, 100 MHz)

Spectra 7. 1-(tert-butyldimethylsilyloxy)-oct-7-en-4-ol (2.41c)

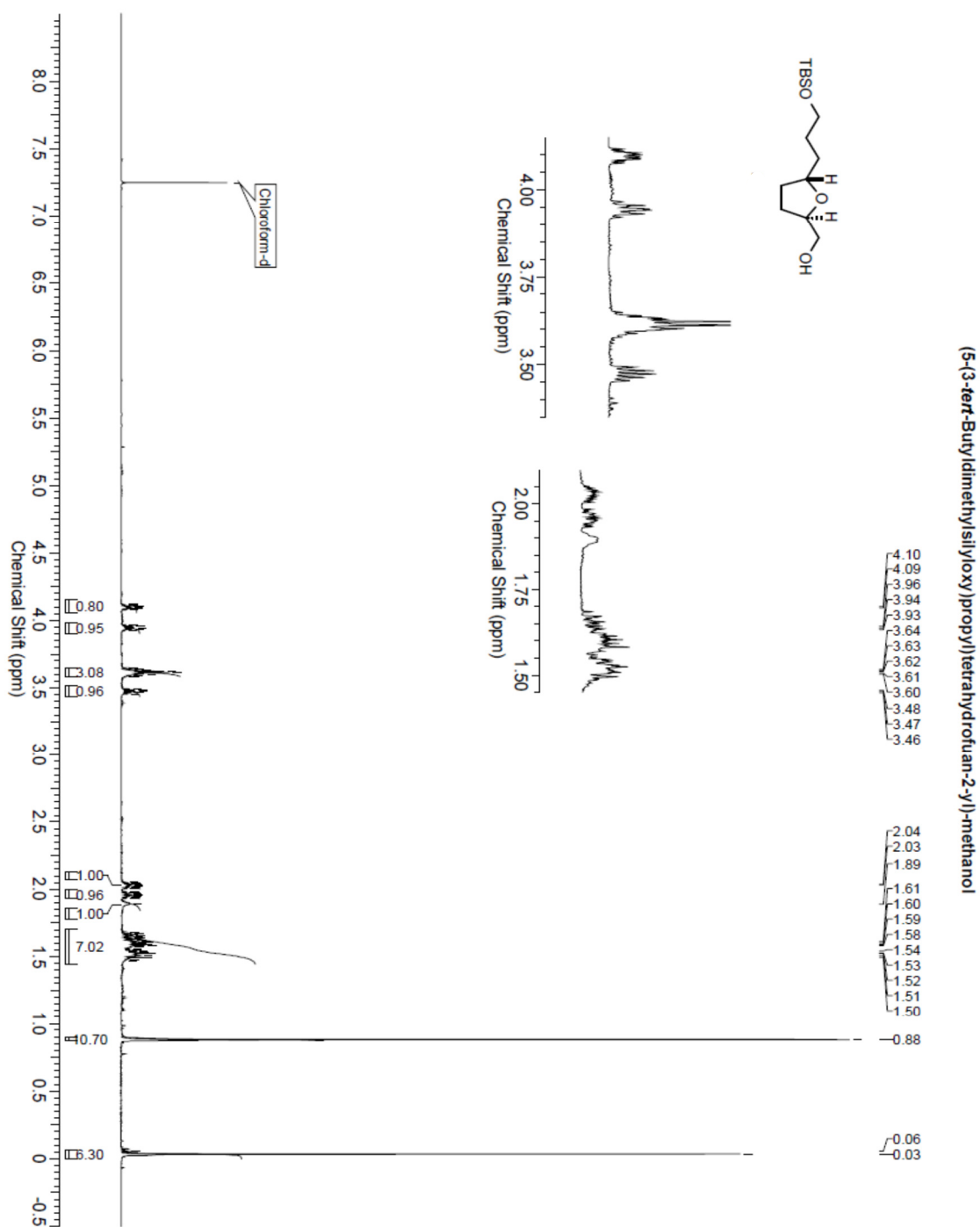


¹H NMR (CDCl₃, 400 MHz)

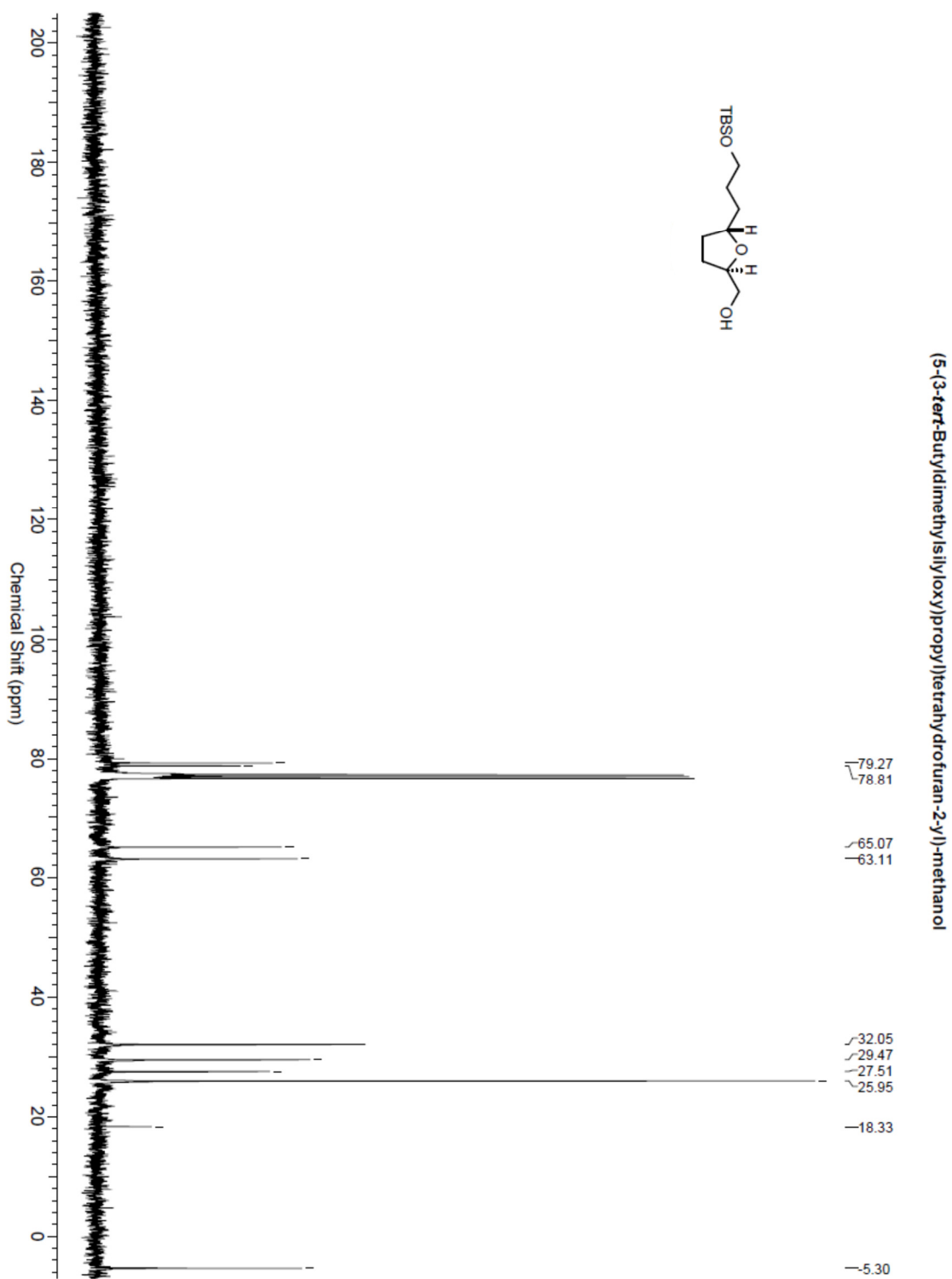


¹³C NMR (CDCl₃, 100 MHz)

**Spectra 8. (5-(3-tert-Butyldimethylsilyloxy)propyl)tetrahydrofuran-2-yl)-methanol
(2.42c)**

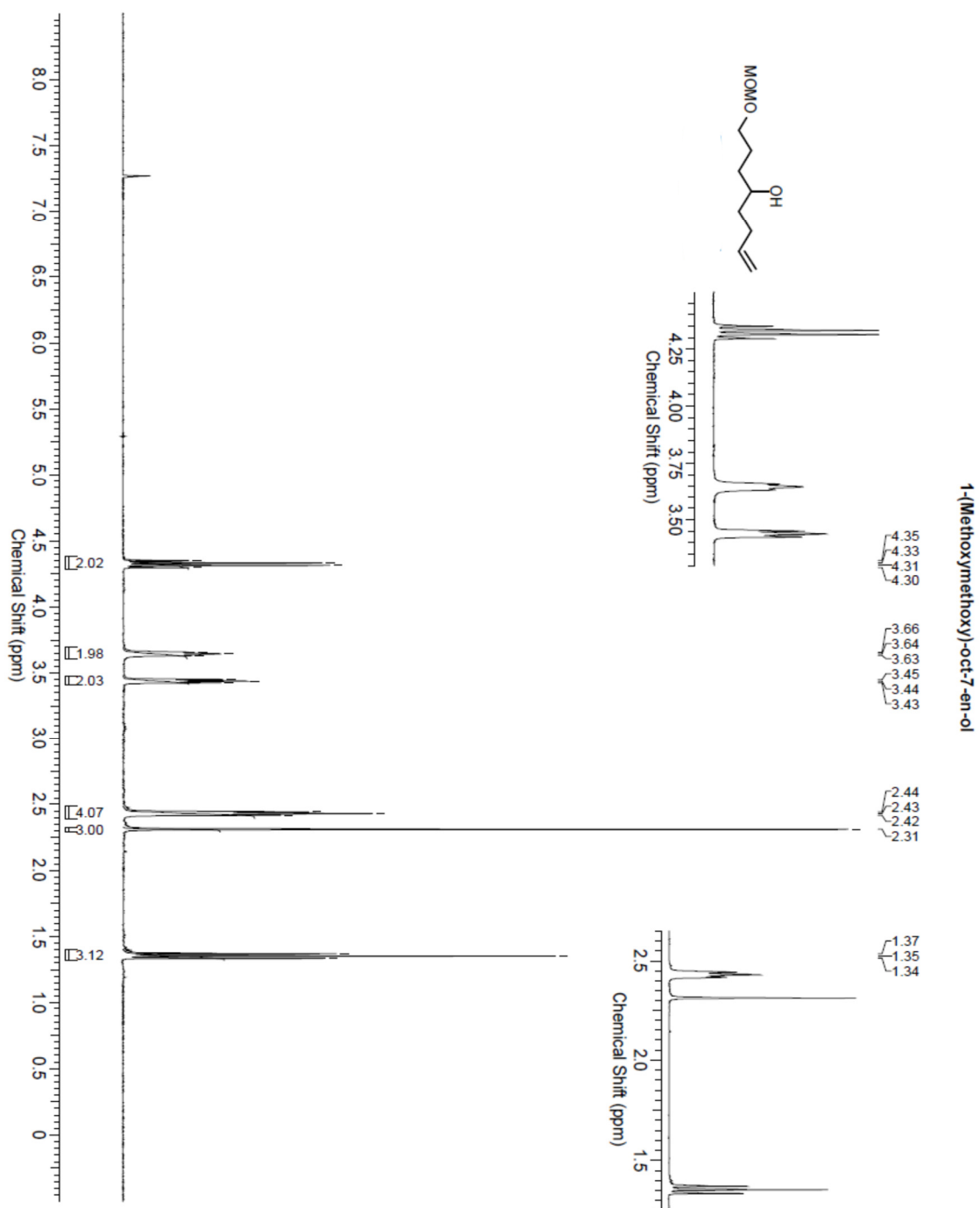


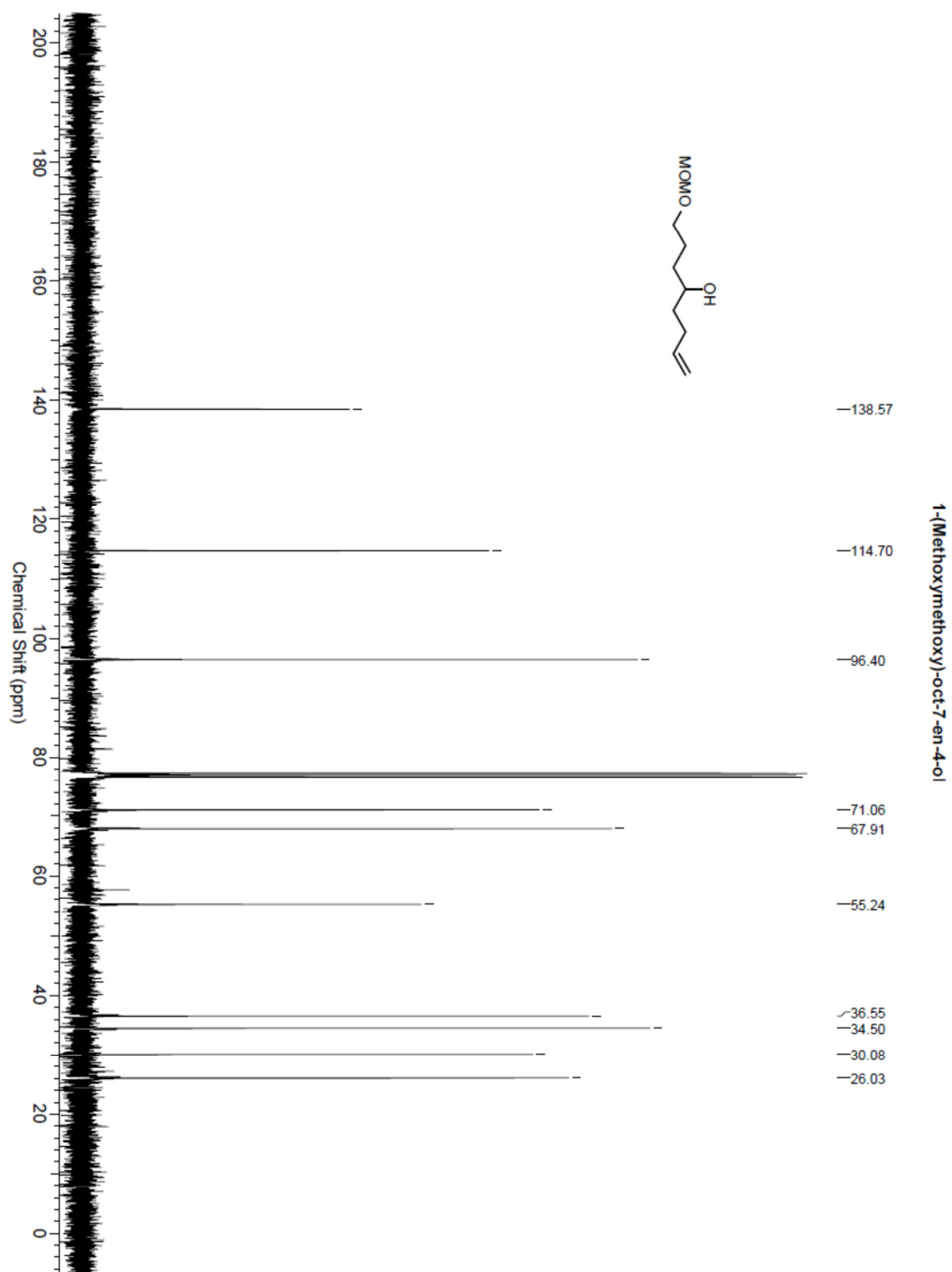
$^1\text{H NMR}$ (CDCl_3 , 400 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 9. 1-(Methoxymethoxy)-oct-7-en-4-ol

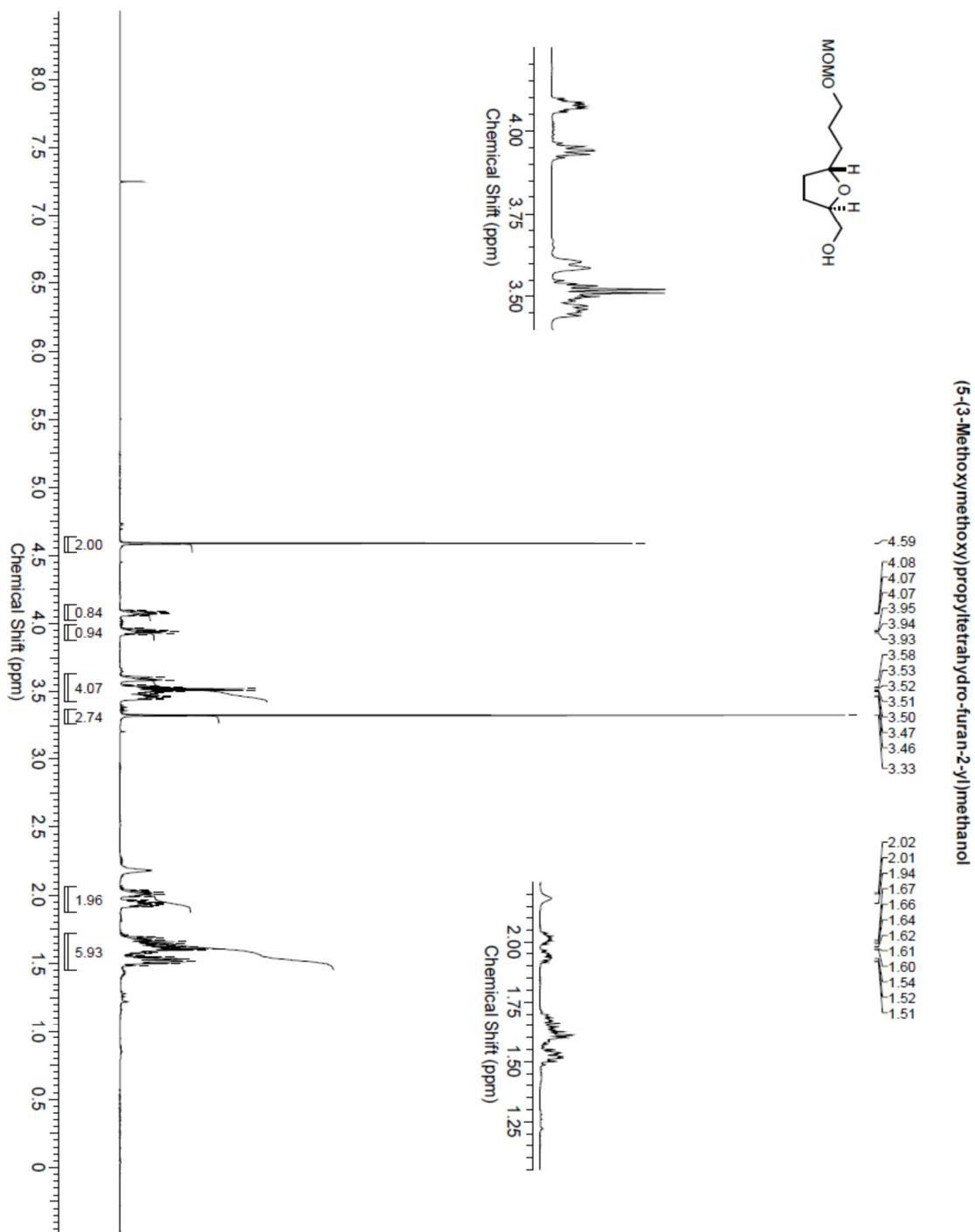
 ^1H NMR (CDCl_3 , 400 MHz)

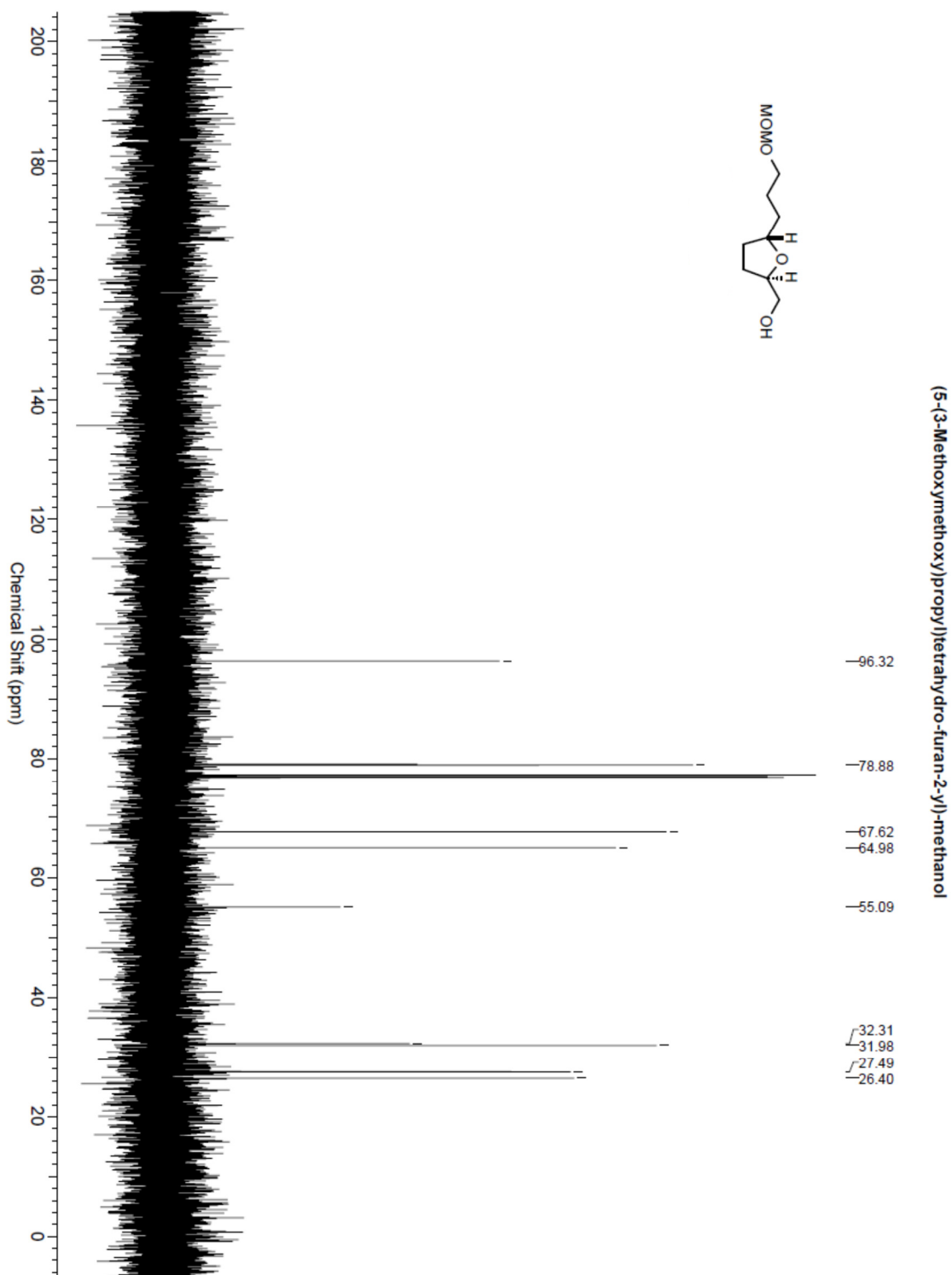


^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 10. (5-(3-Methoxymethoxy)propyltetrahydrofuran-2-yl)methanol

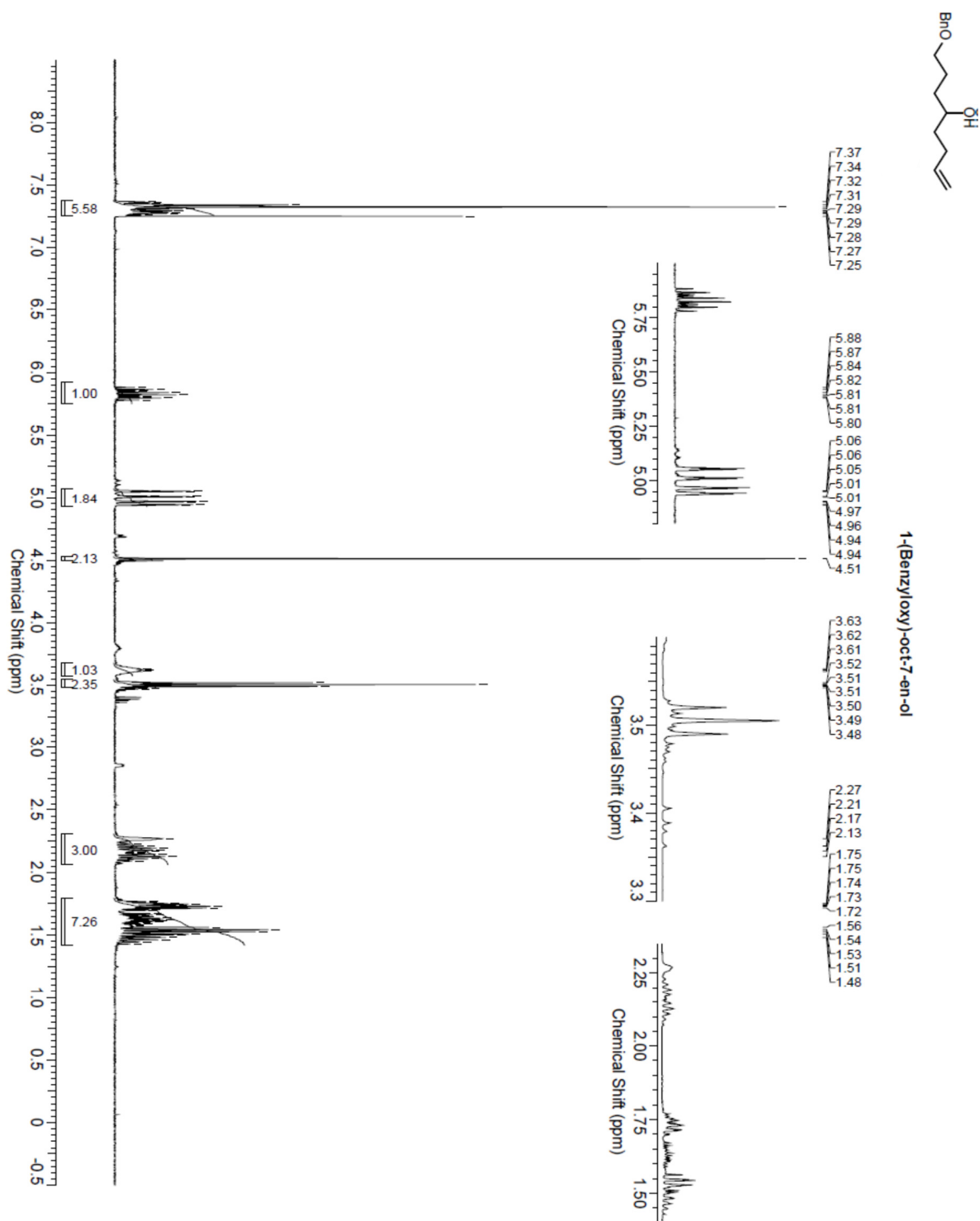
(Table 7, Entry 1)

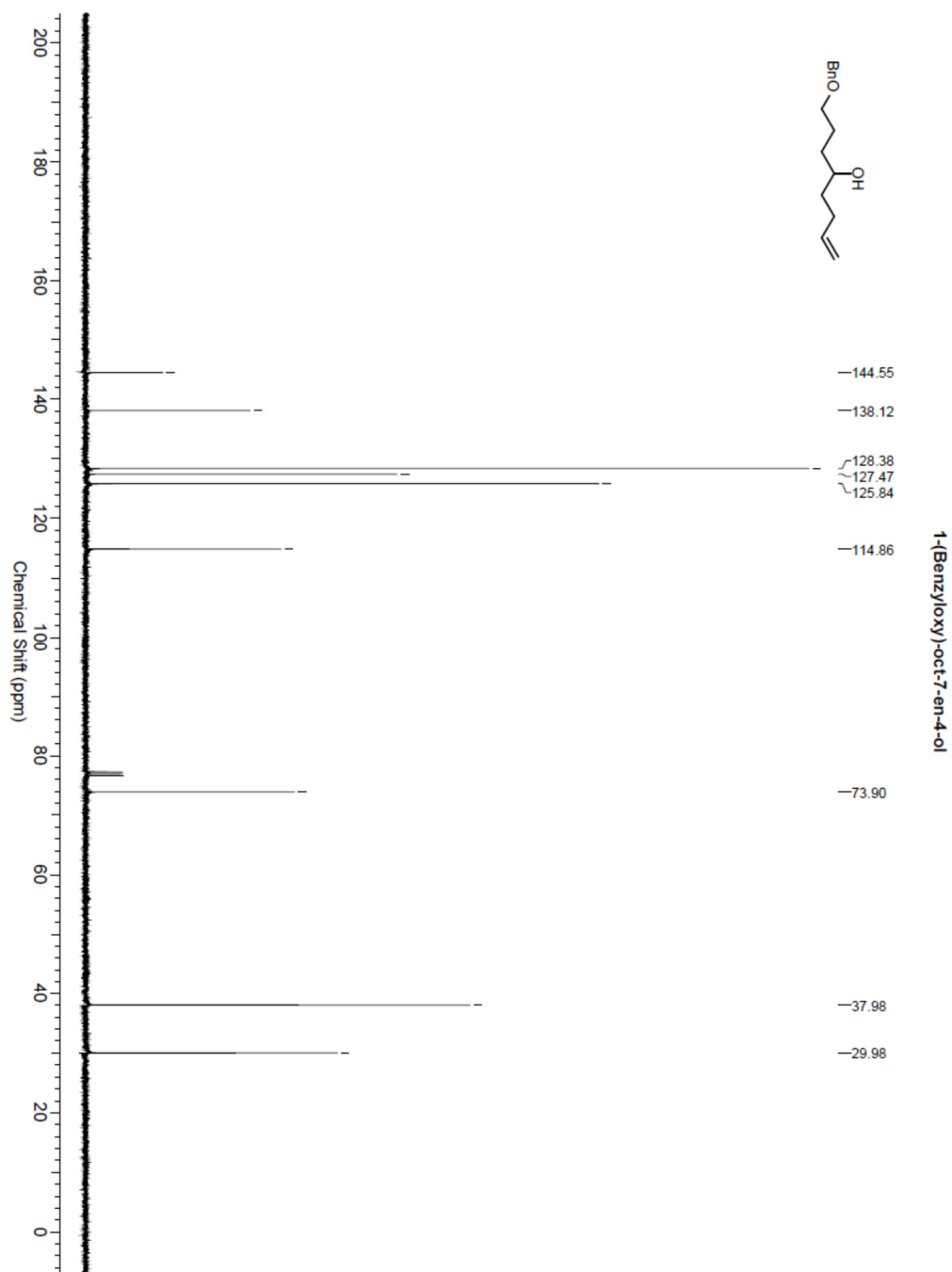
 ^1H NMR (CDCl_3 , 400 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)

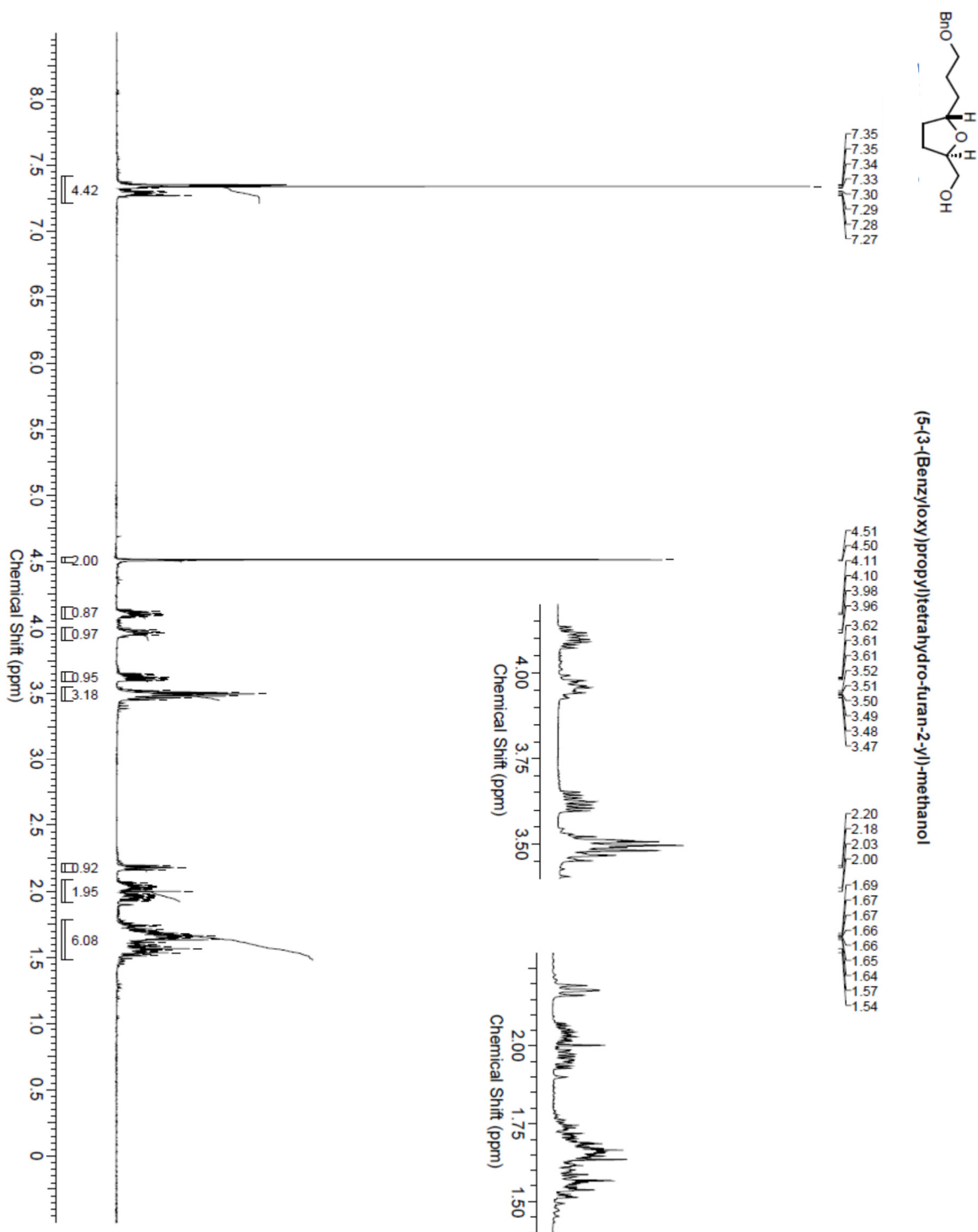
Spectra 11. 1-(Benzoyloxy)-oct-7-en-ol

 ^1H NMR (CDCl_3 , 400 MHz)

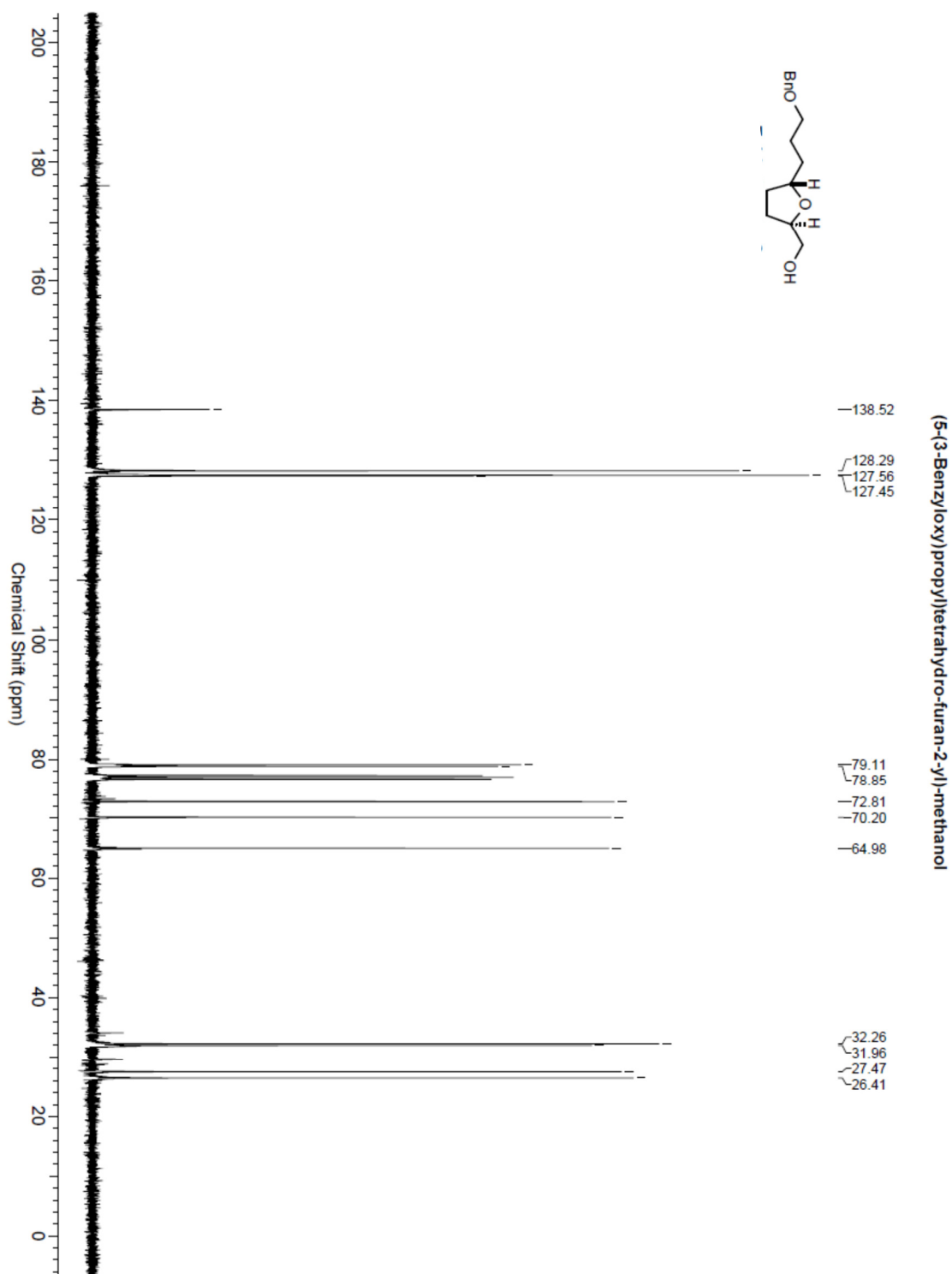


^{13}C NMR (CDCl₃, 100 MHz)

Spectra 12. (5-(3-(Benzyloxy)propyl)tetrahydrofuran-2-yl) methanol
 (Table 7, Entry 2)

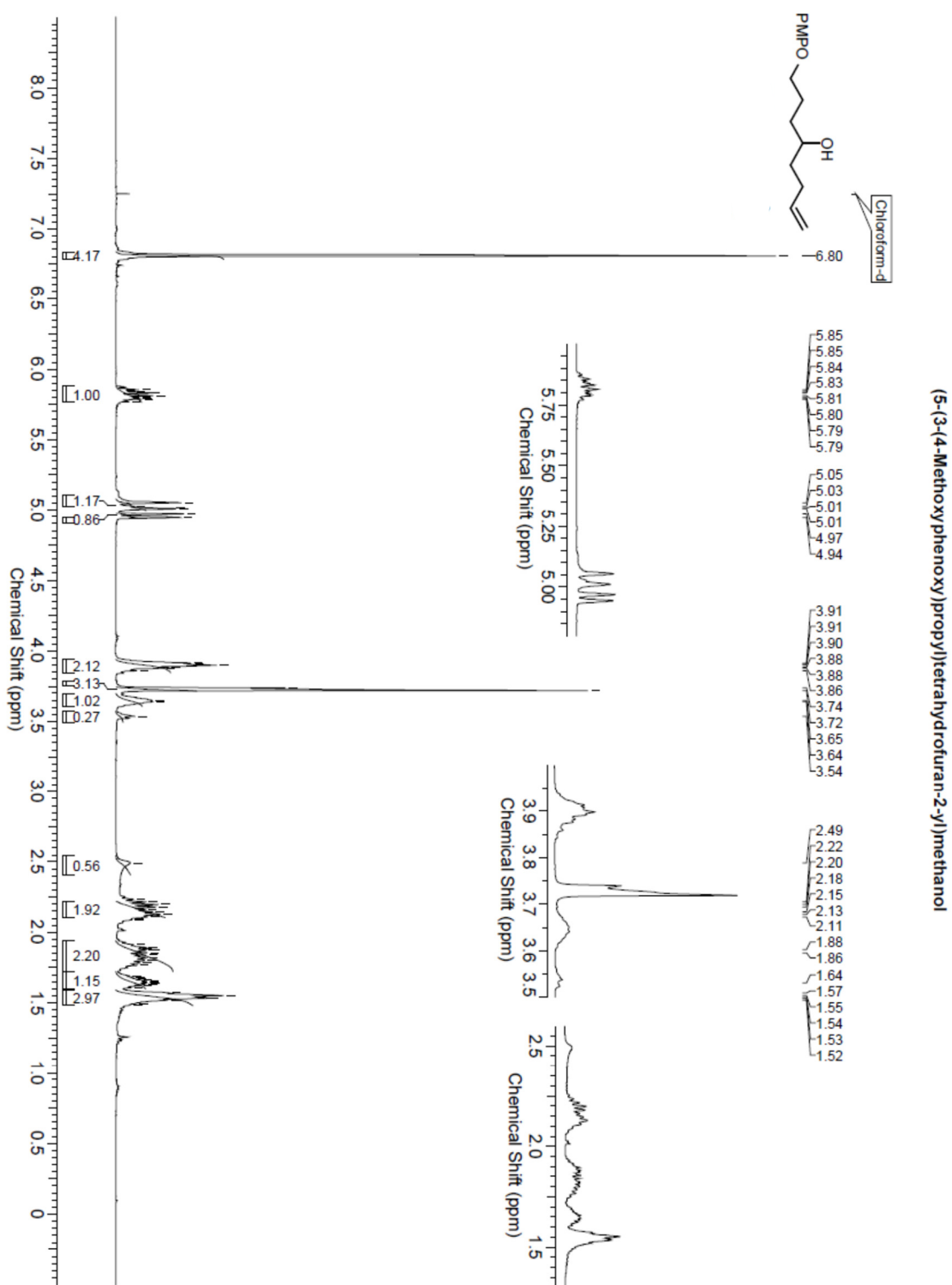


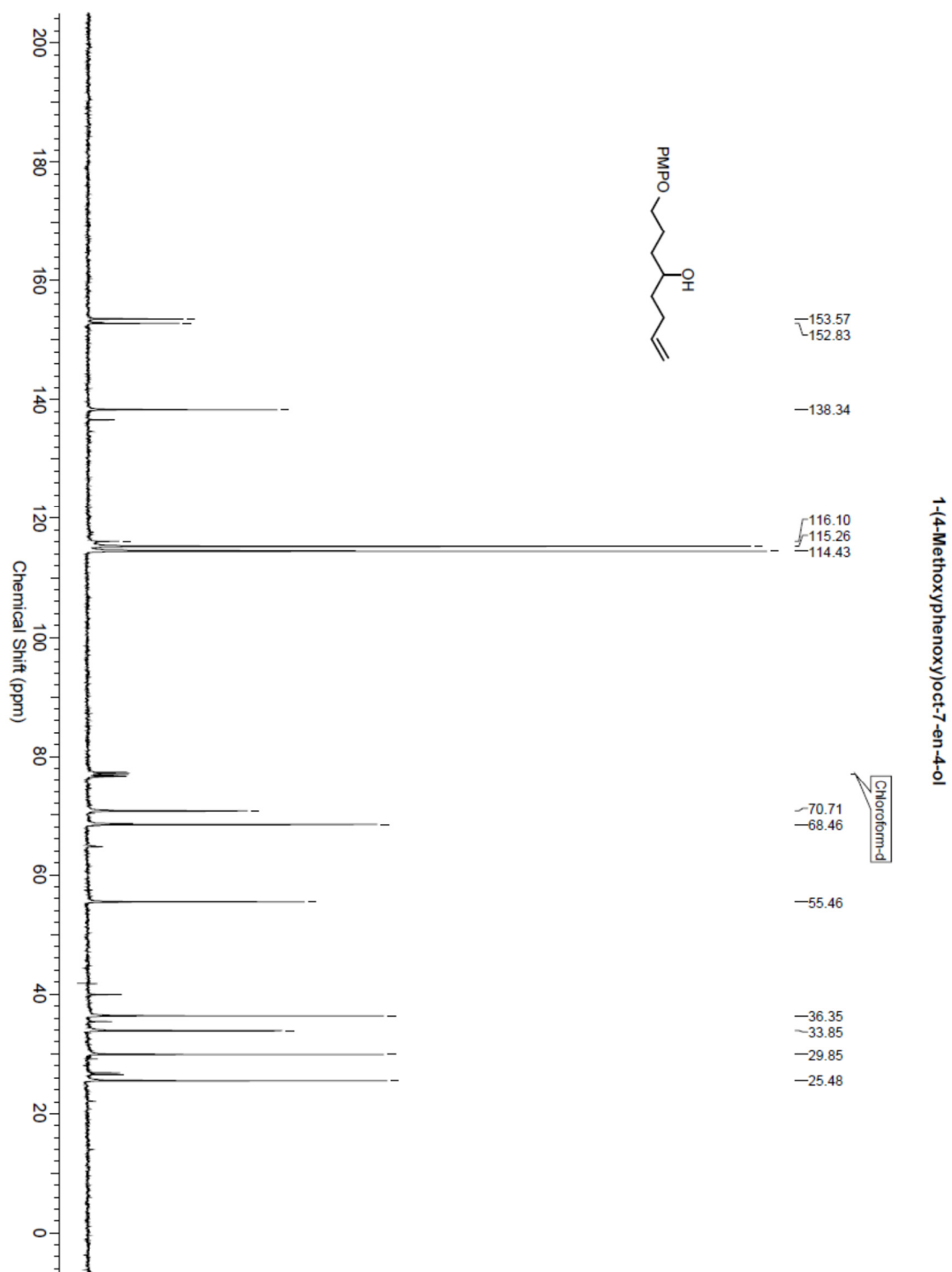
¹H NMR (CDCl₃, 400 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 13. 1-(4-Methoxyphenoxy)oct-7-en-4-ol

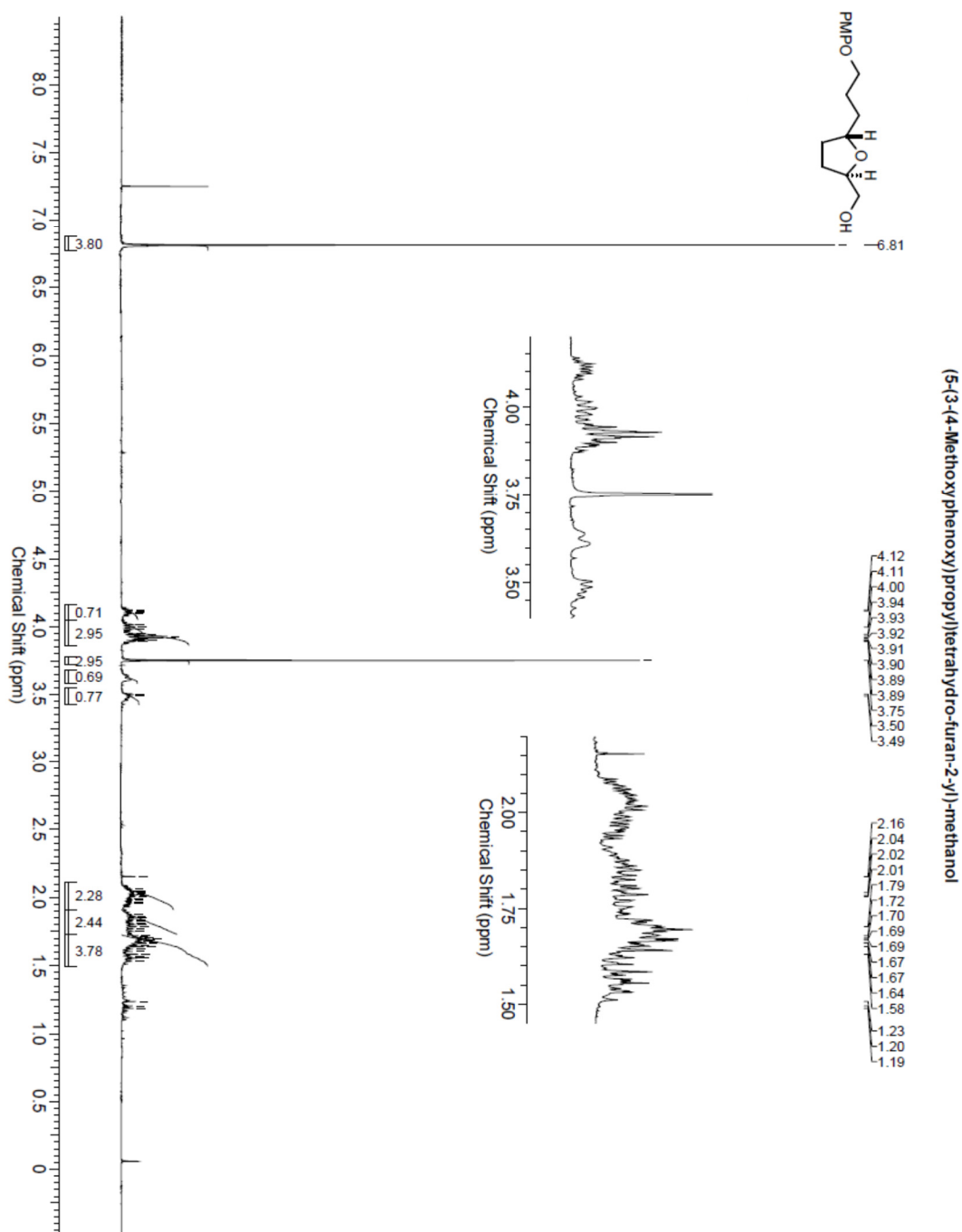
 ^1H NMR (CDCl_3 , 400 MHz)

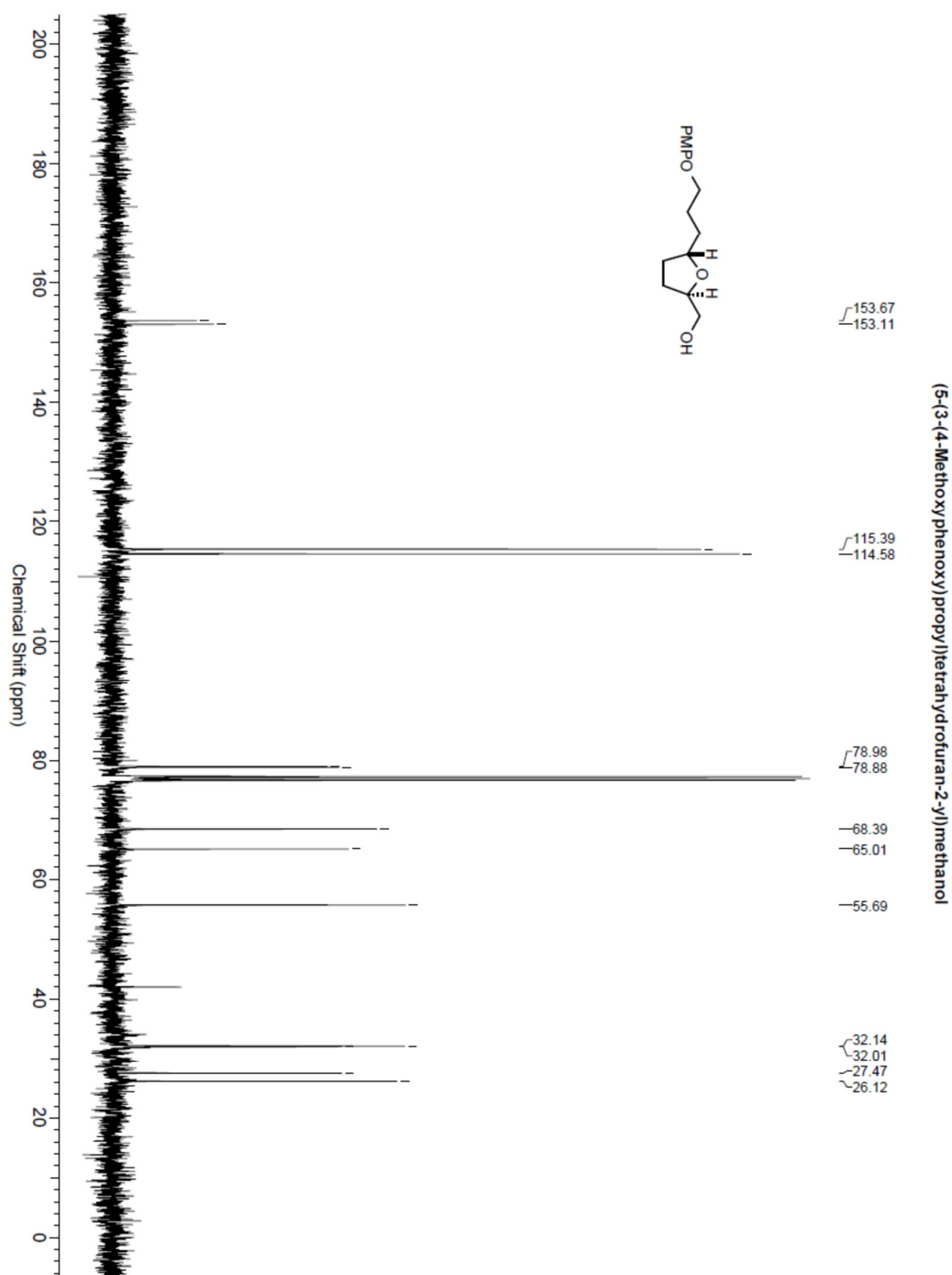


^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 14. (5-(3-(4-Methoxyphenoxy)propyl)tetrahydrofuran-2-yl)-methanol

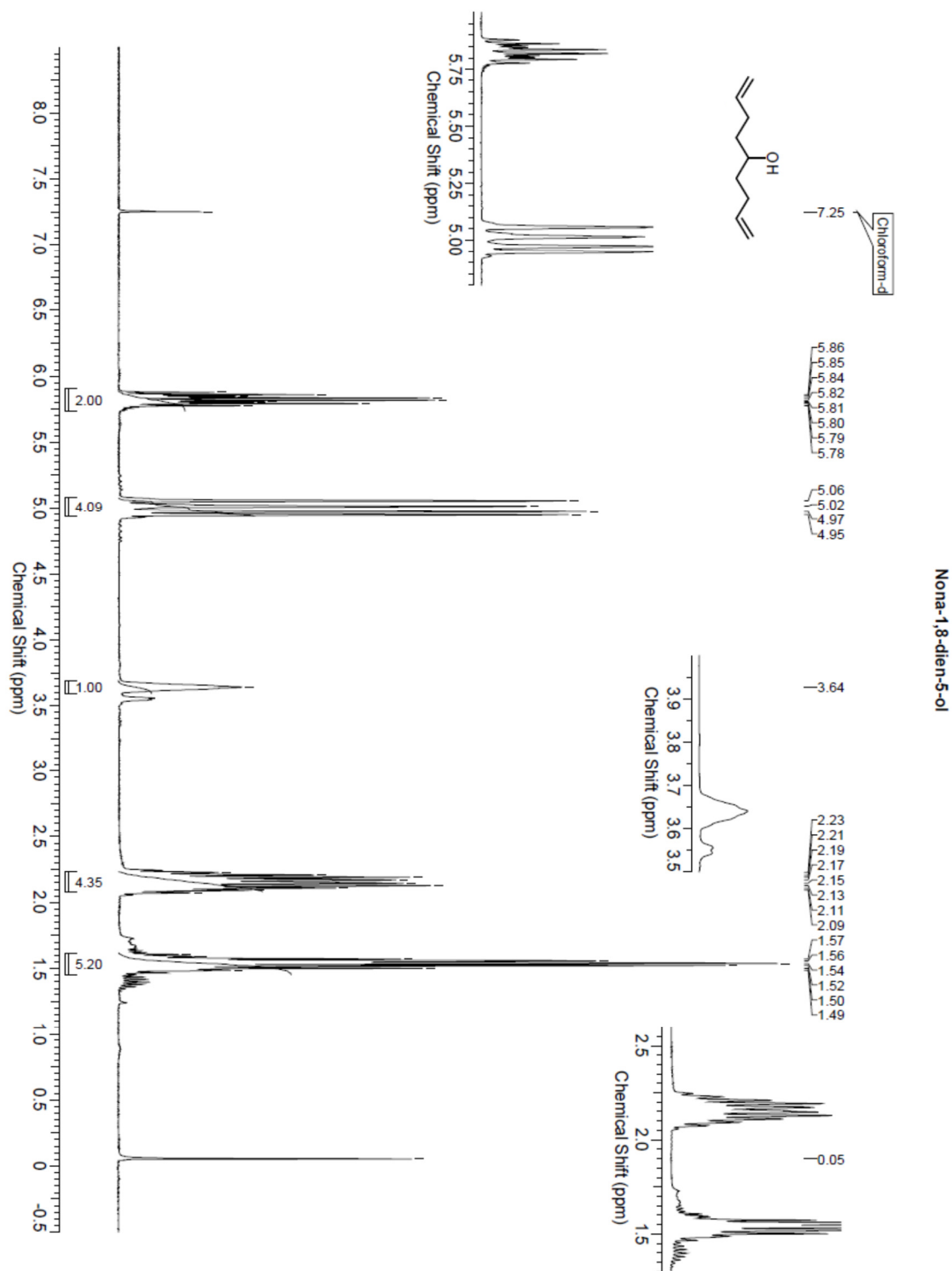
(Table 7, Entry 3)

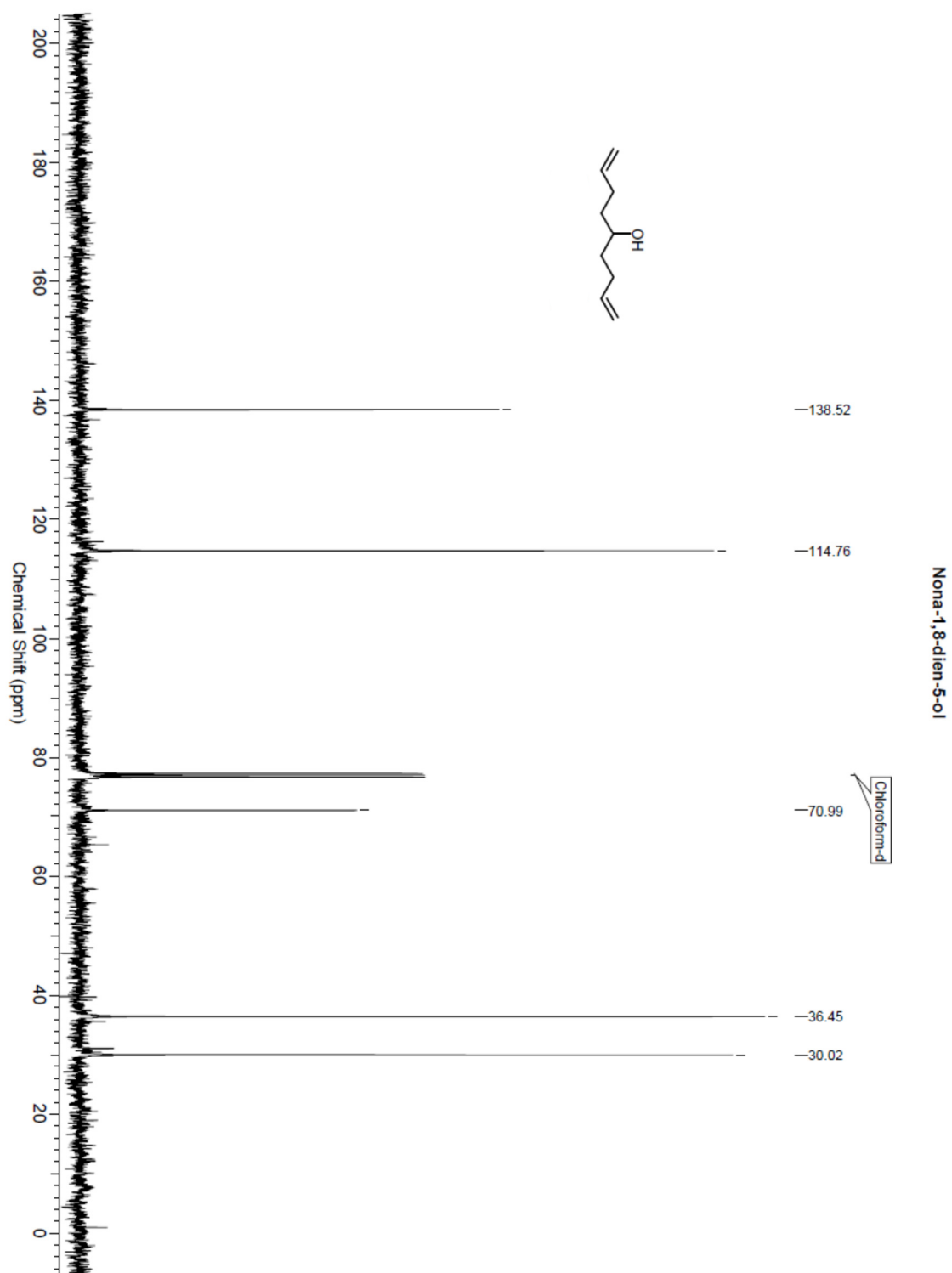
¹H NMR (CDCl₃, 400 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)

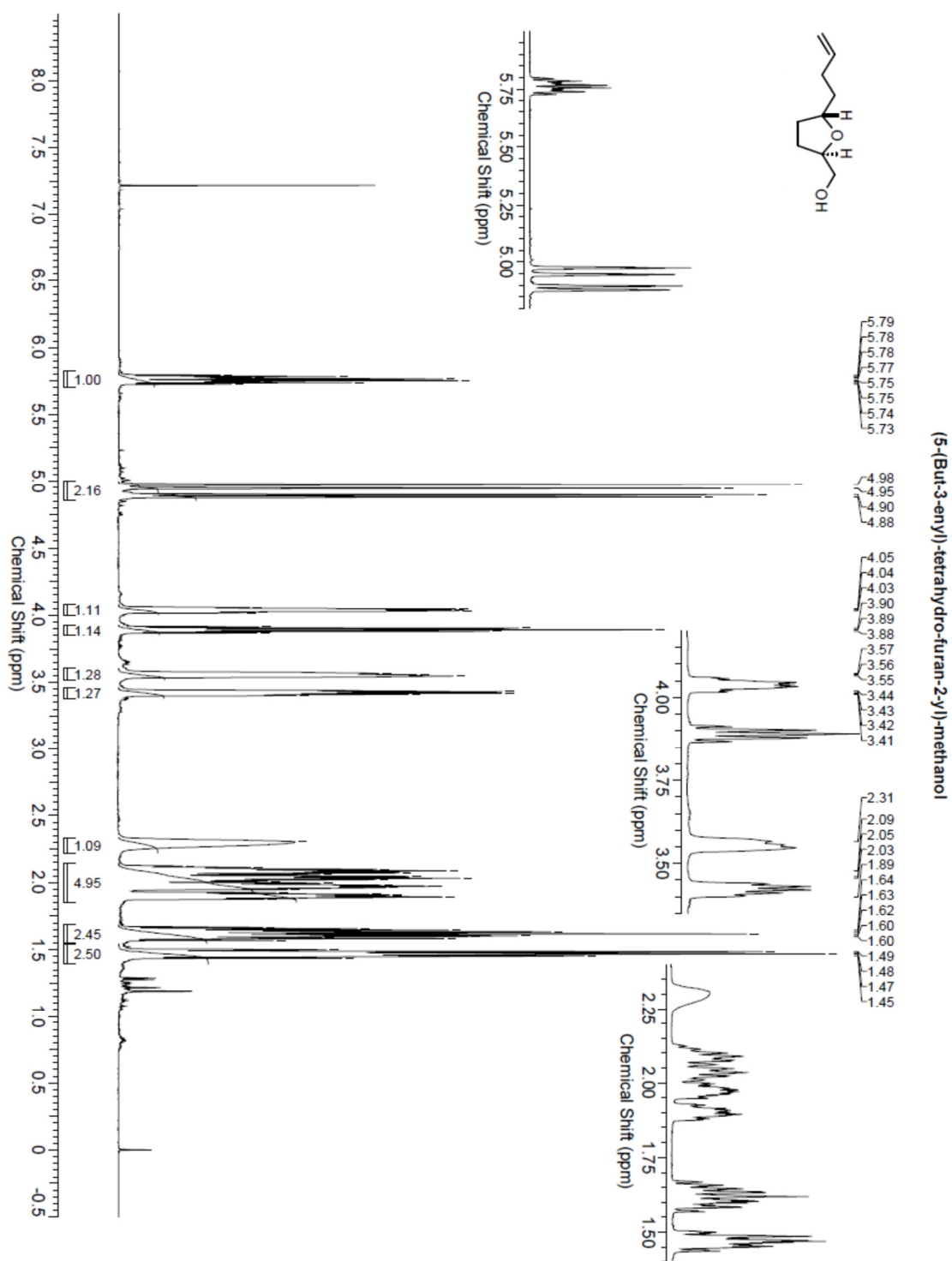
Spectra 15. Nona-1,8-dien-5-ol

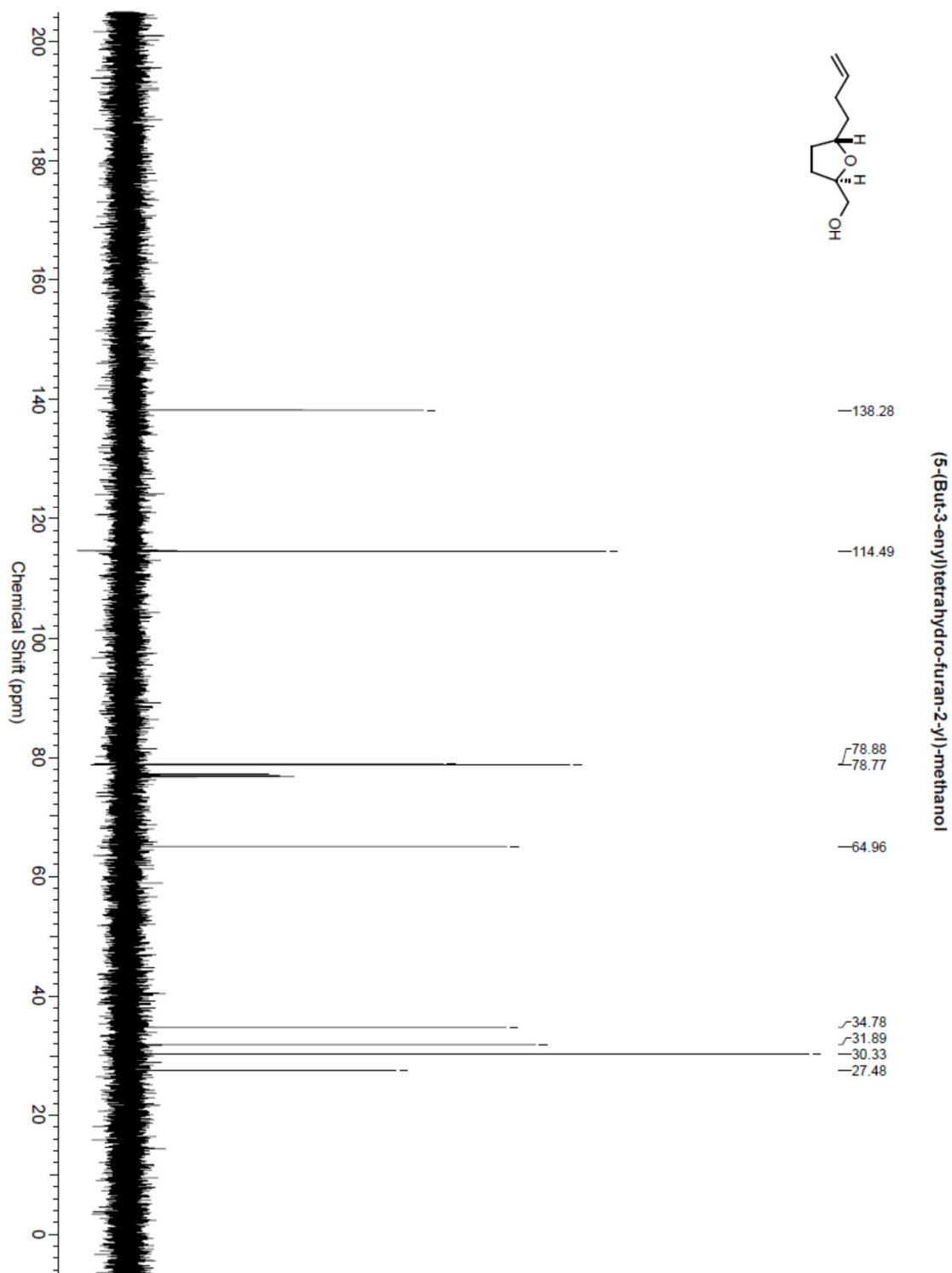
 ^1H NMR (CDCl_3 , 400 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)

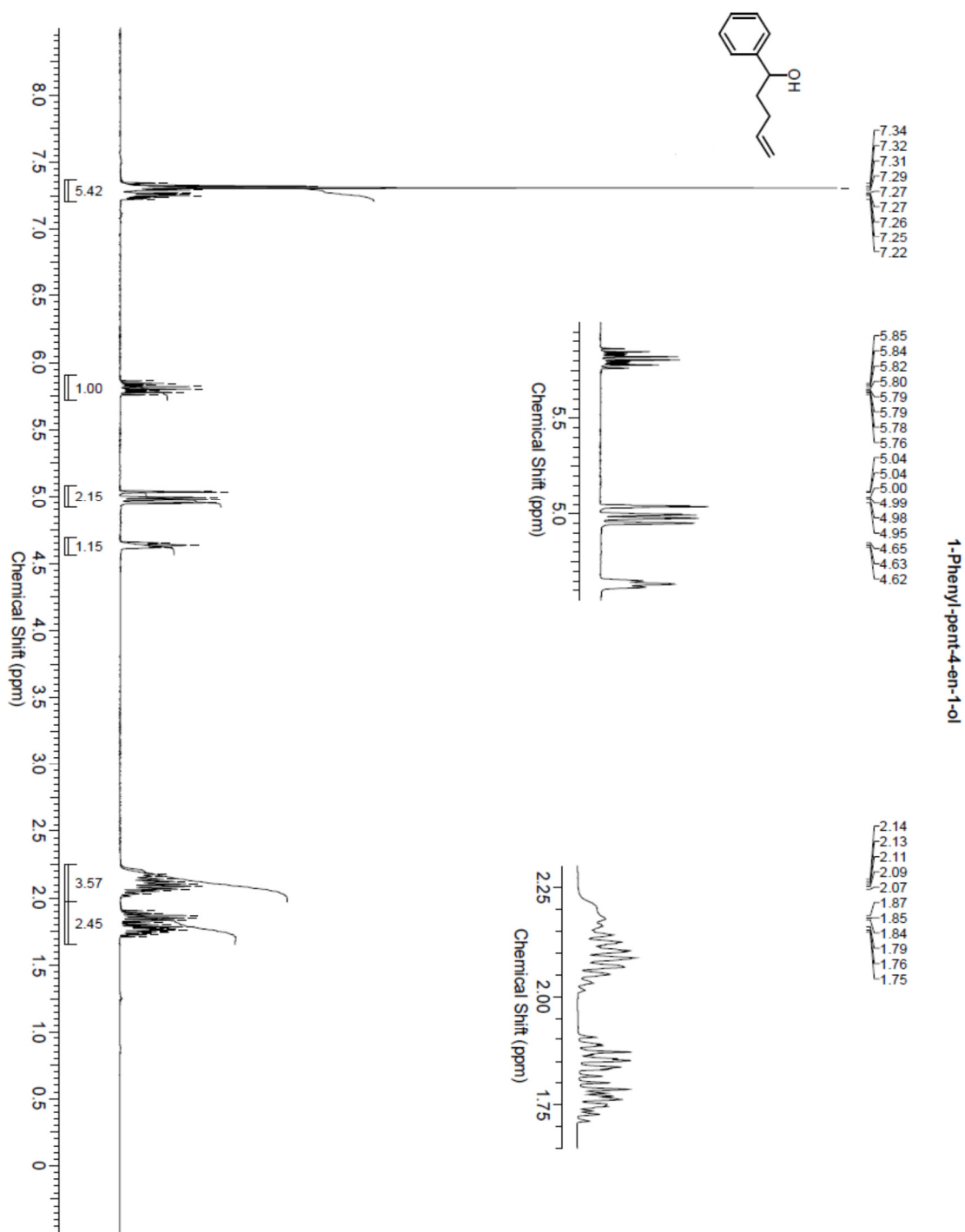
Spectra 16. (5-(But-3-enyl)-tetrahydro-furan-2-yl)-methanol (Table 7, Entry 4)

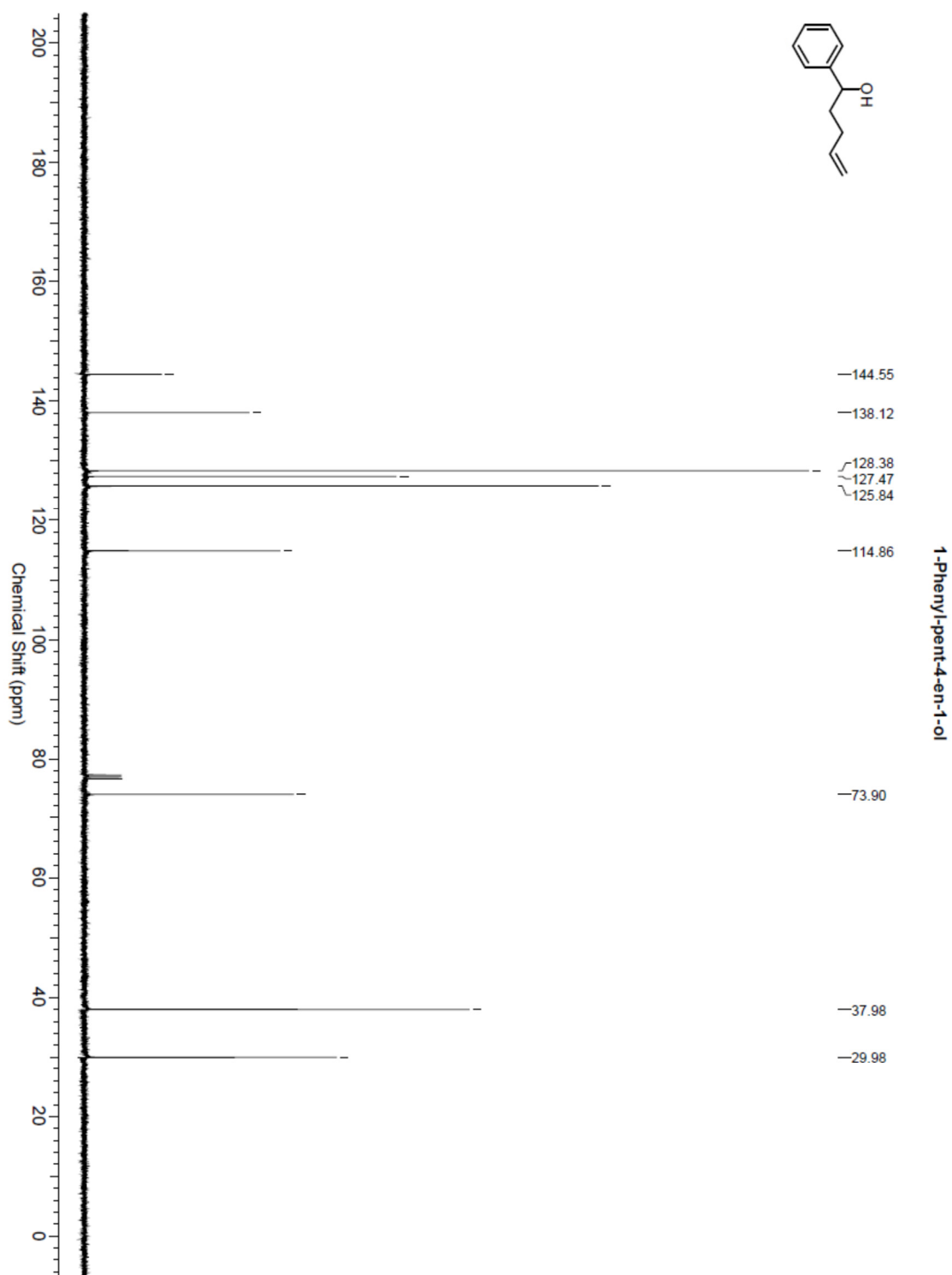
¹H NMR (CDCl₃, 400 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 17. 1-Phenyl-pent-4-en-ol

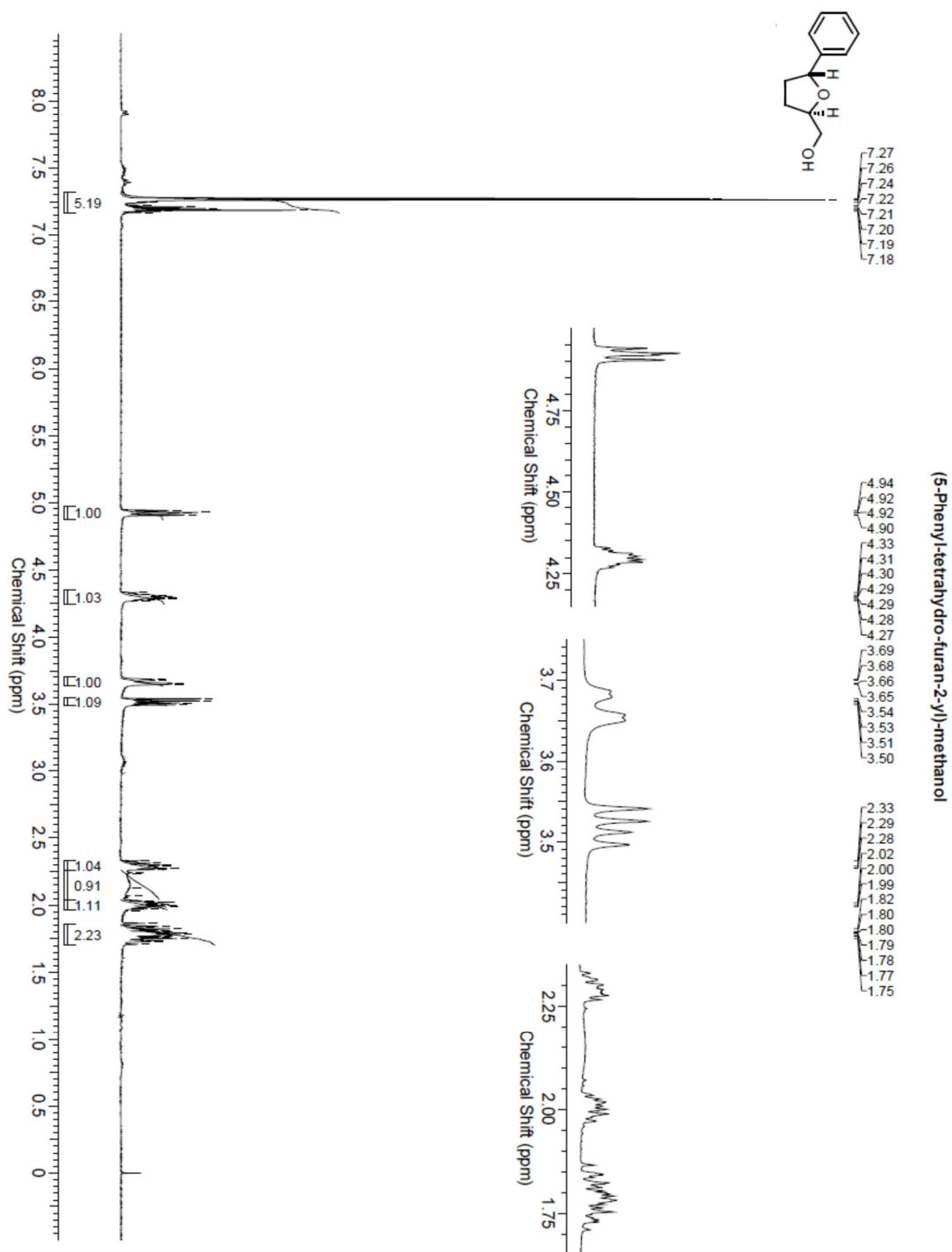
¹H NMR (CDCl₃, 400 MHz)

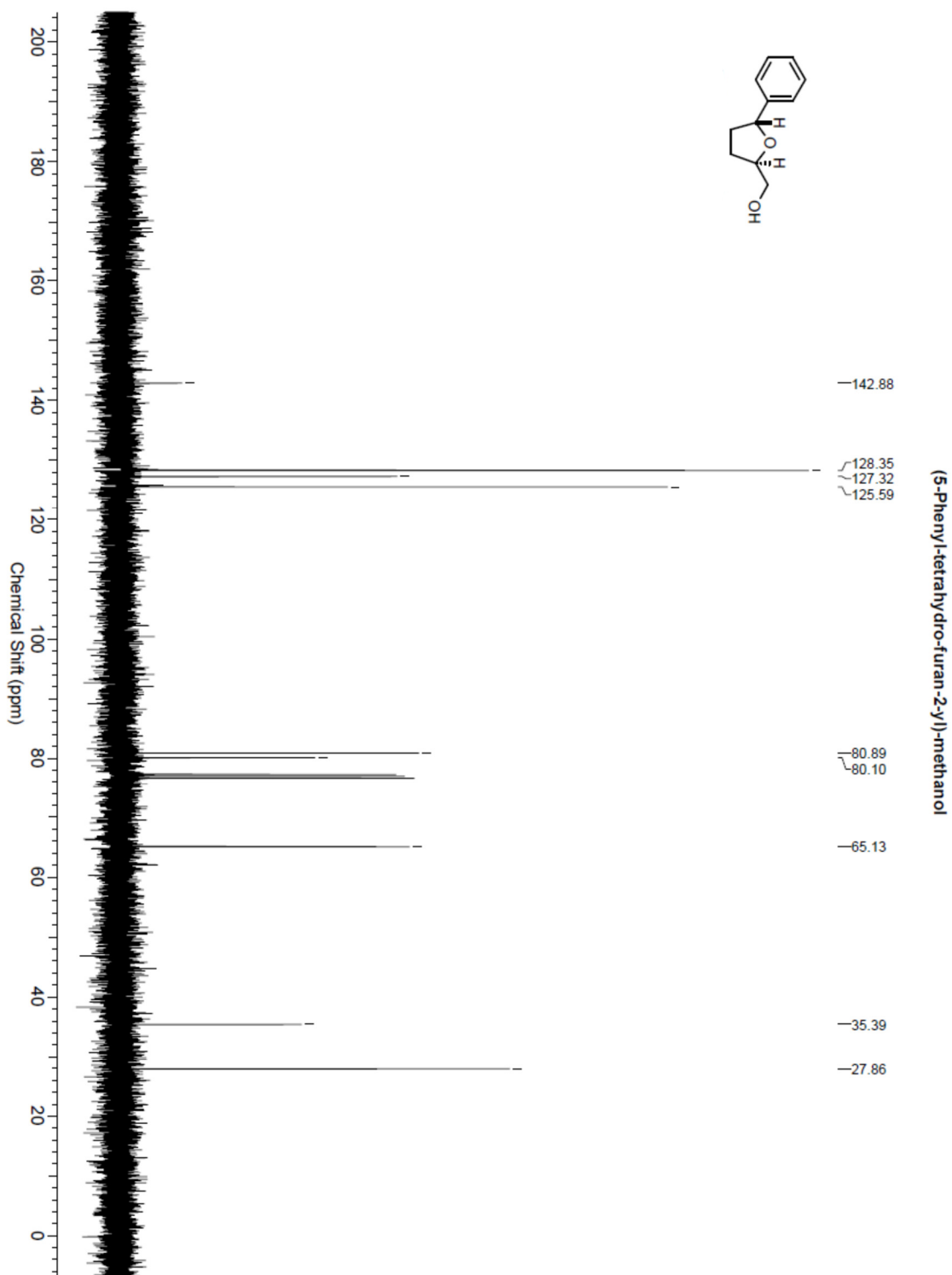


¹³C NMR (CDCl₃, 100 MHz)

Spectra 18. (5-Phenyl-tetrahydro-furan-2-yl)-methanol

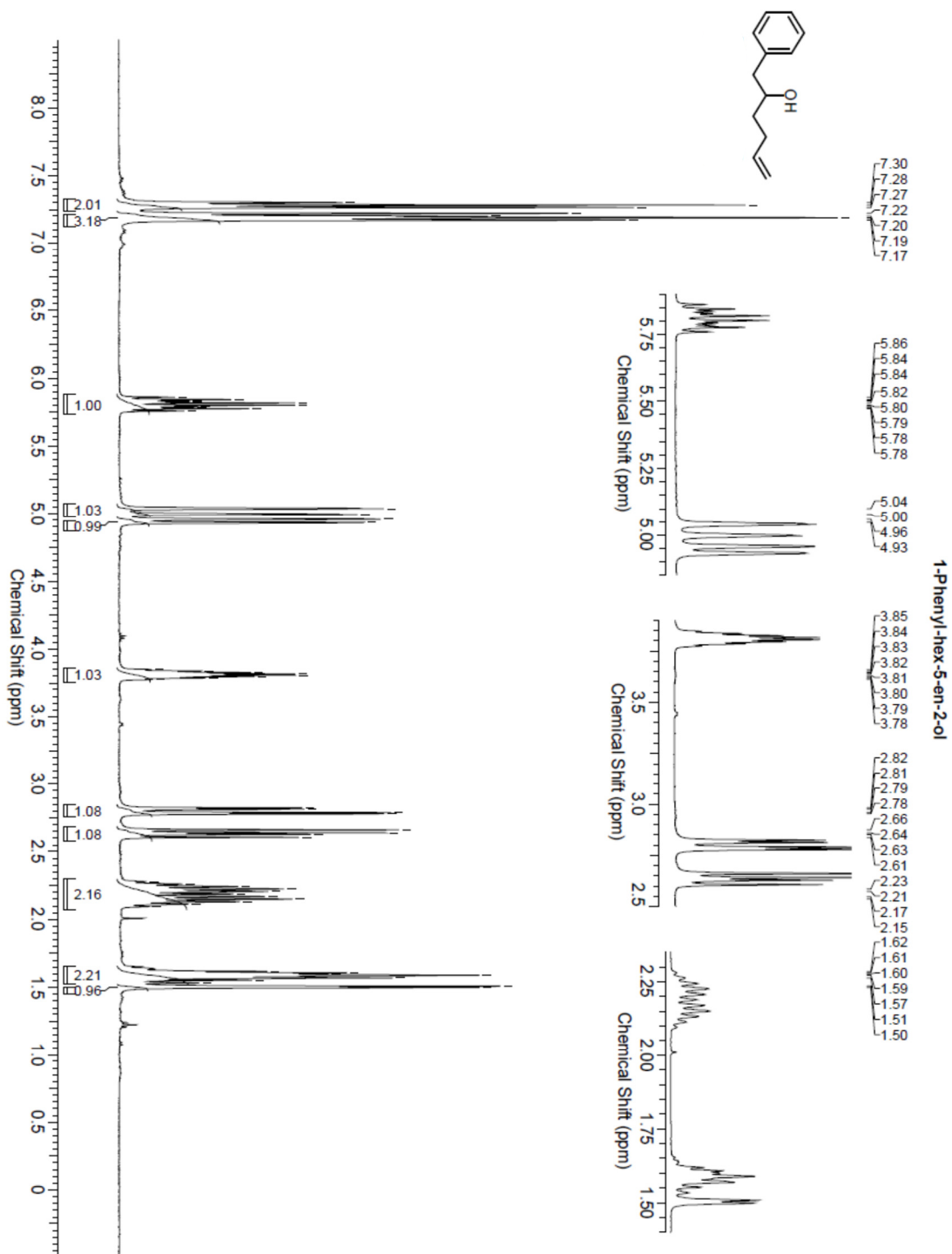
(Table 7, Entry 6)

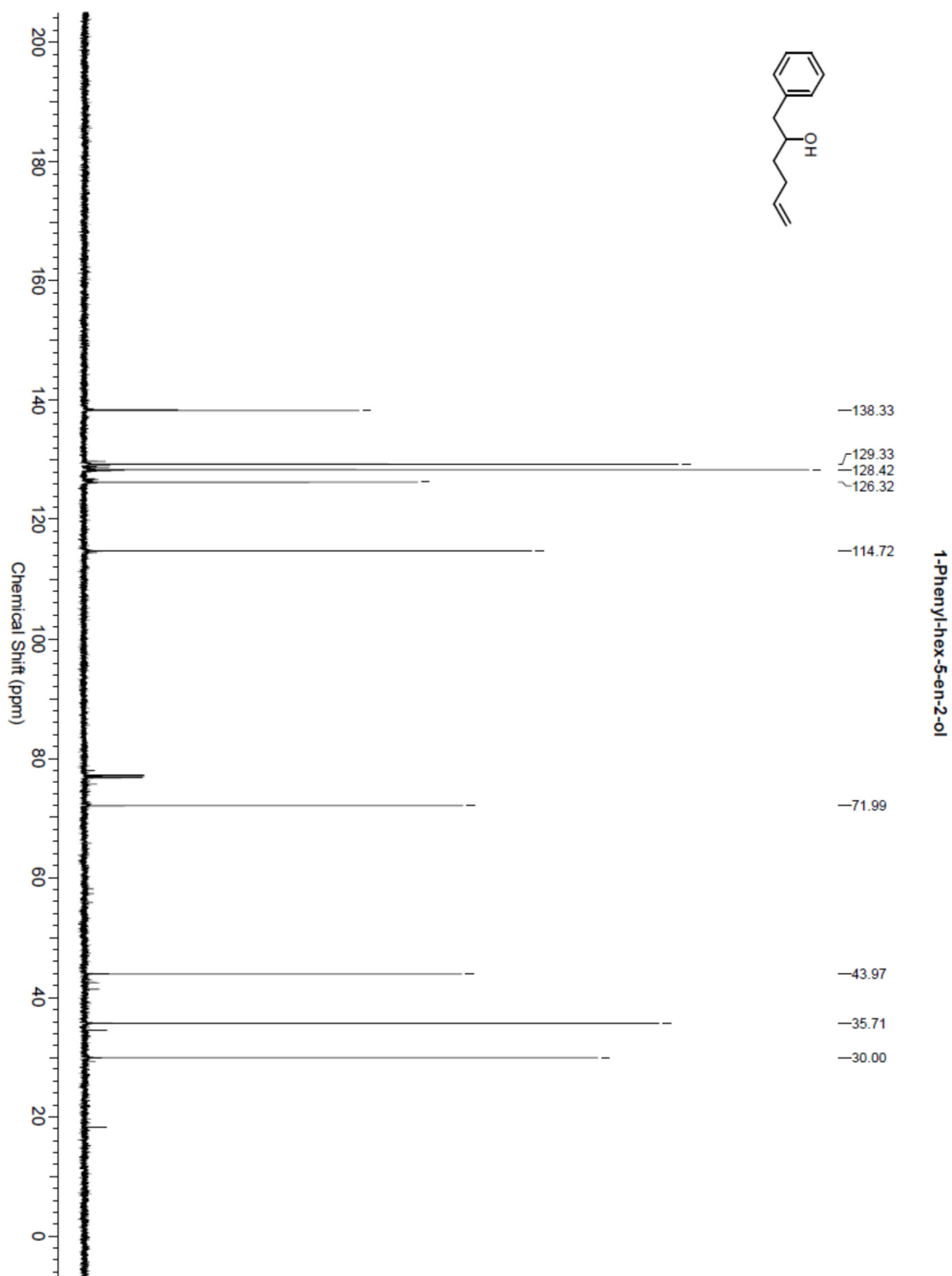
 ^1H NMR (CDCl_3 , 400 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)

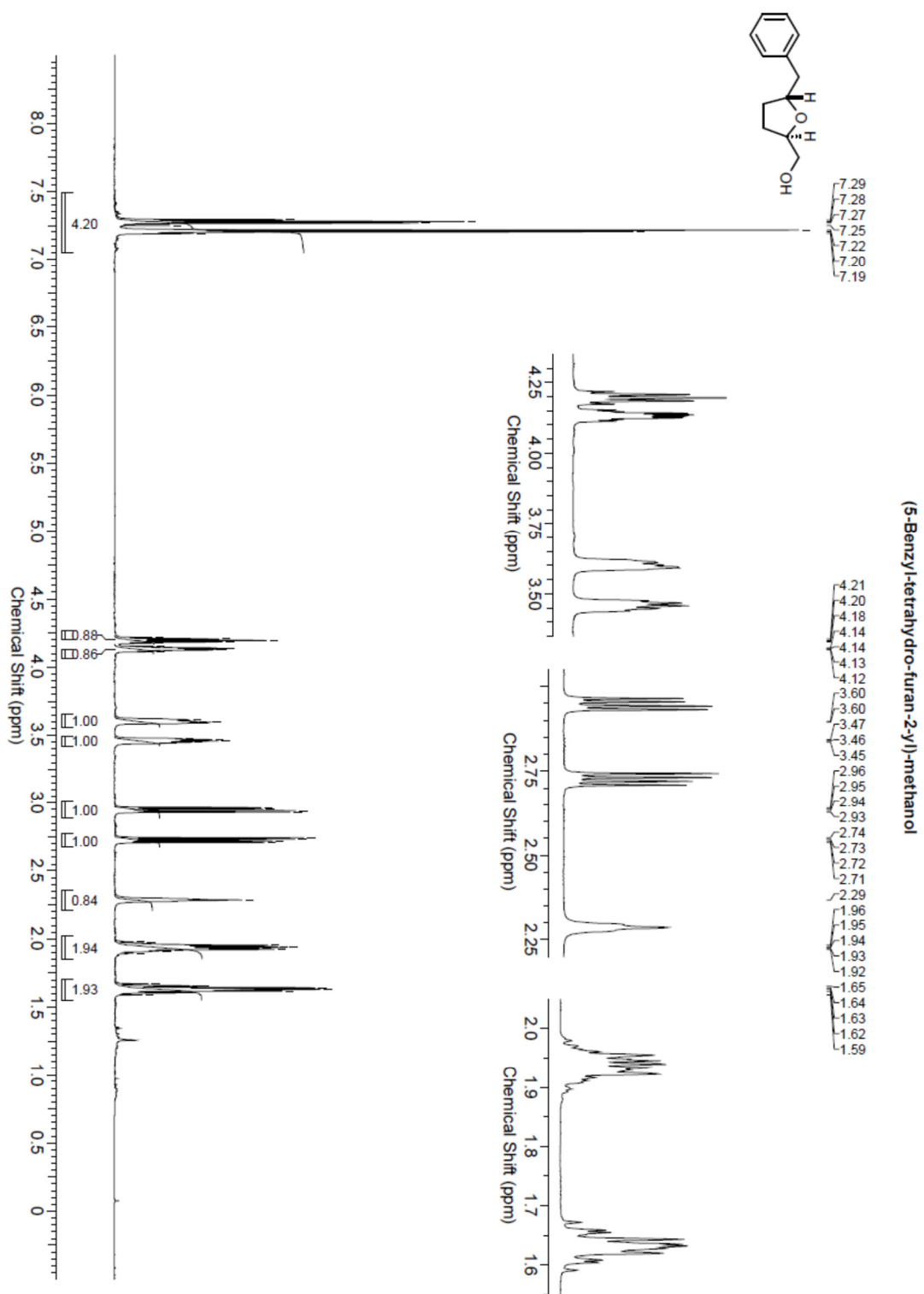
Spectra 19. 1-Phenyl-hex-5-en-2-ol

¹H NMR (CDCl₃, 400 MHz)

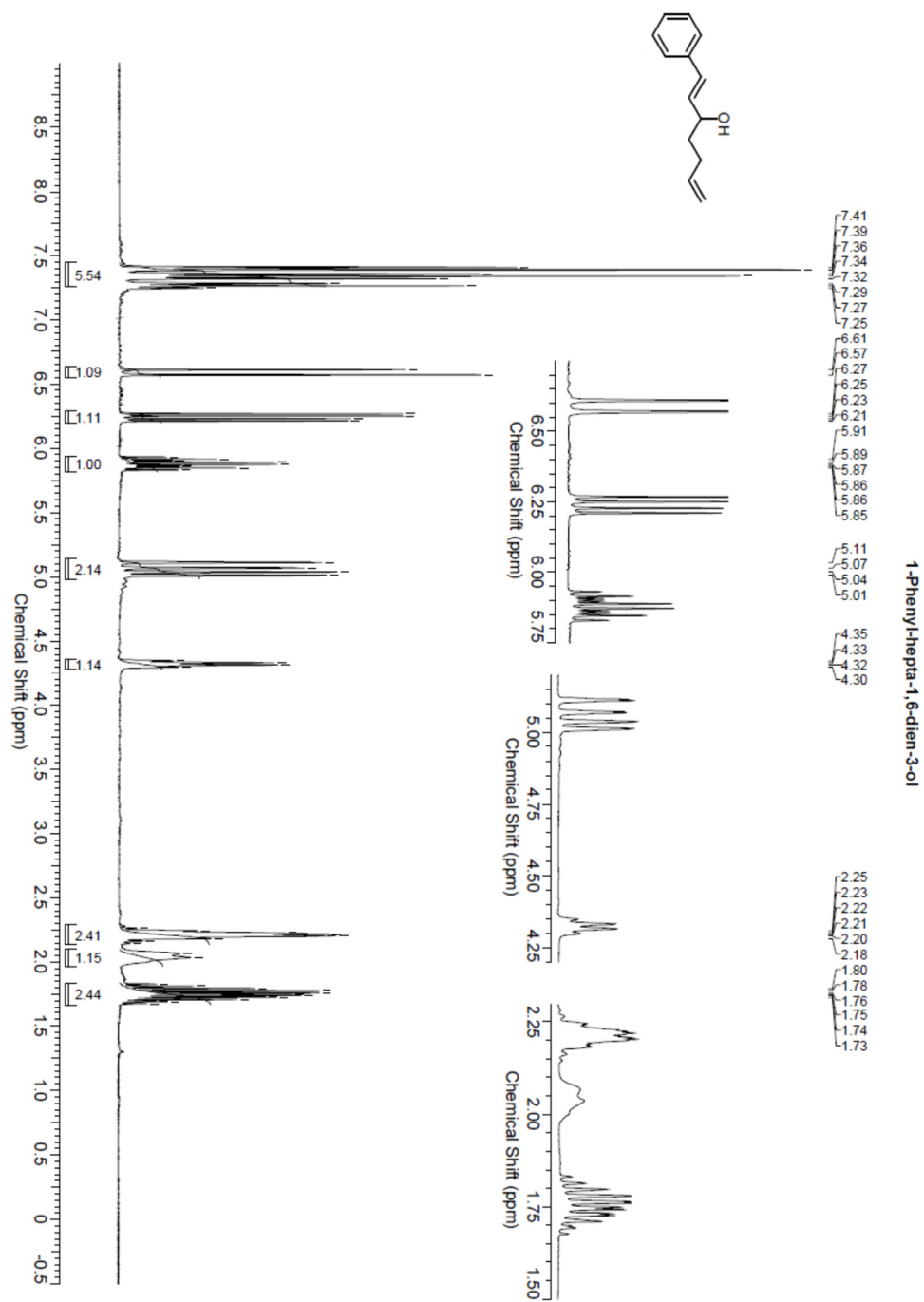


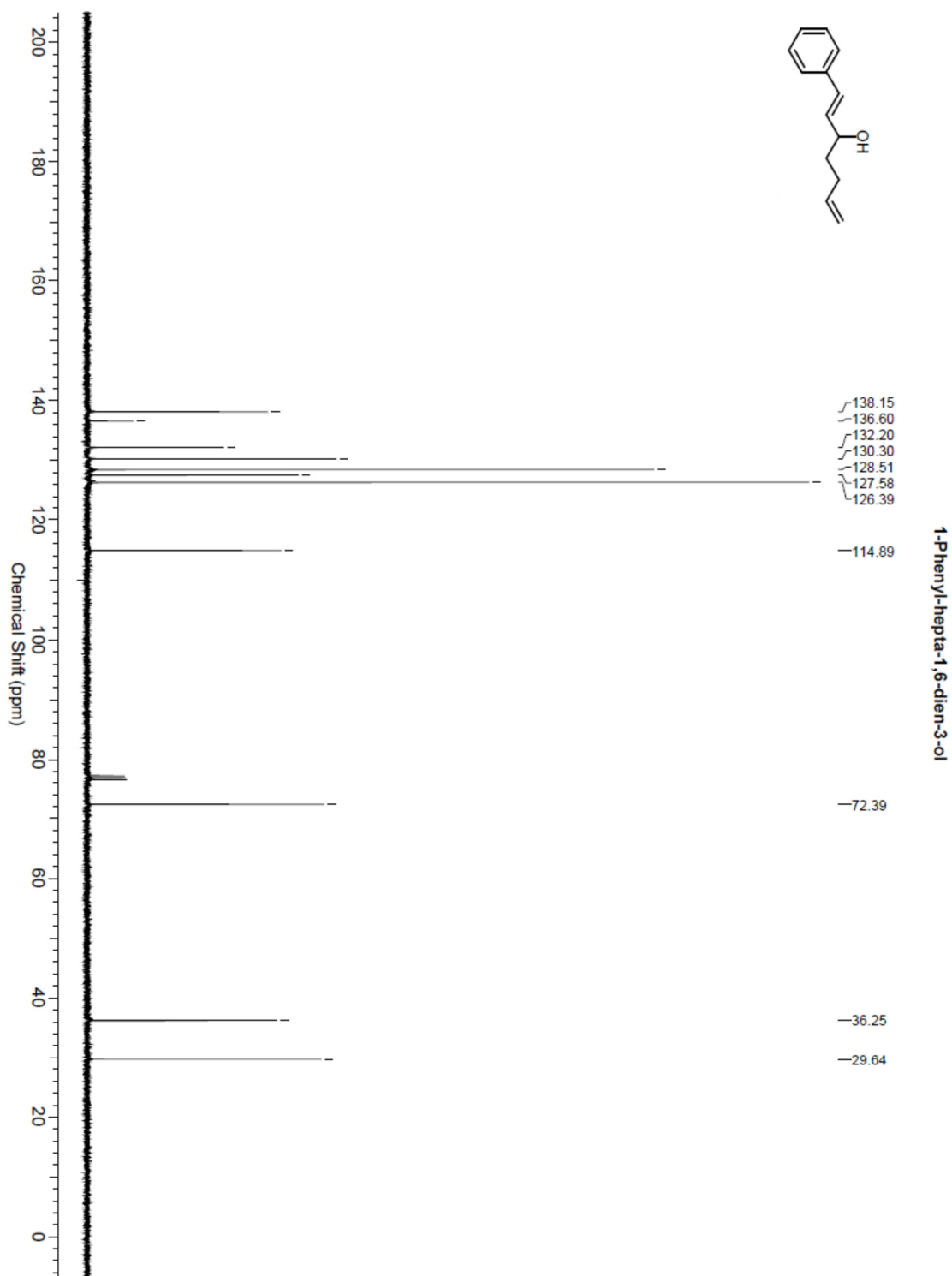
^{13}C NMR (CDCl_3 , 150 MHz)

Spectra 20. (5-Benzyl-tetrahydro-furan-2-yl)-methanol (Table 7, Entry 7)

¹H NMR (CDCl₃, 600 MHz)

Spectra 21. 1-Phenyl-hepta-1,6-dien-3-ol

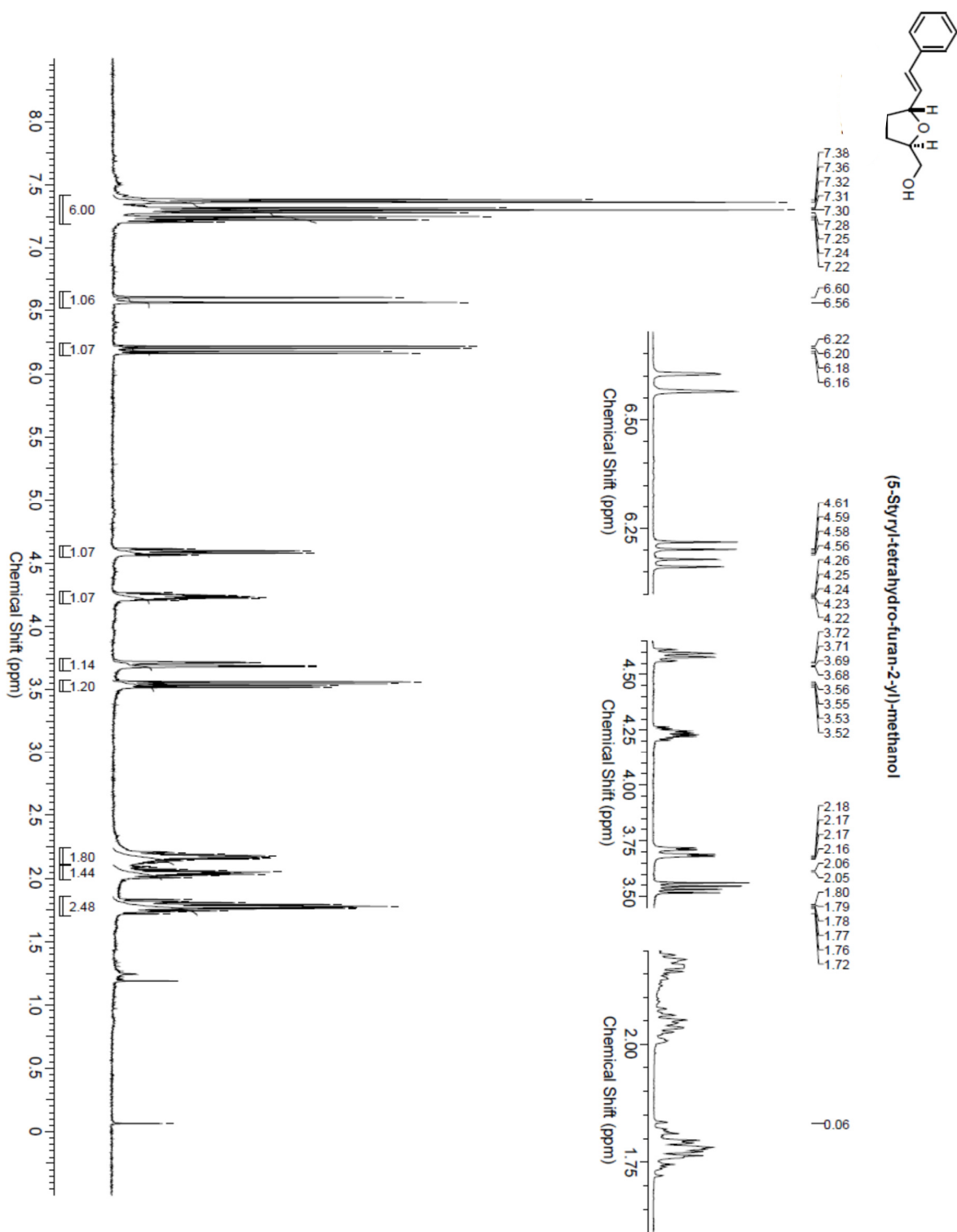
¹H NMR (CDCl₃, 400 MHz)

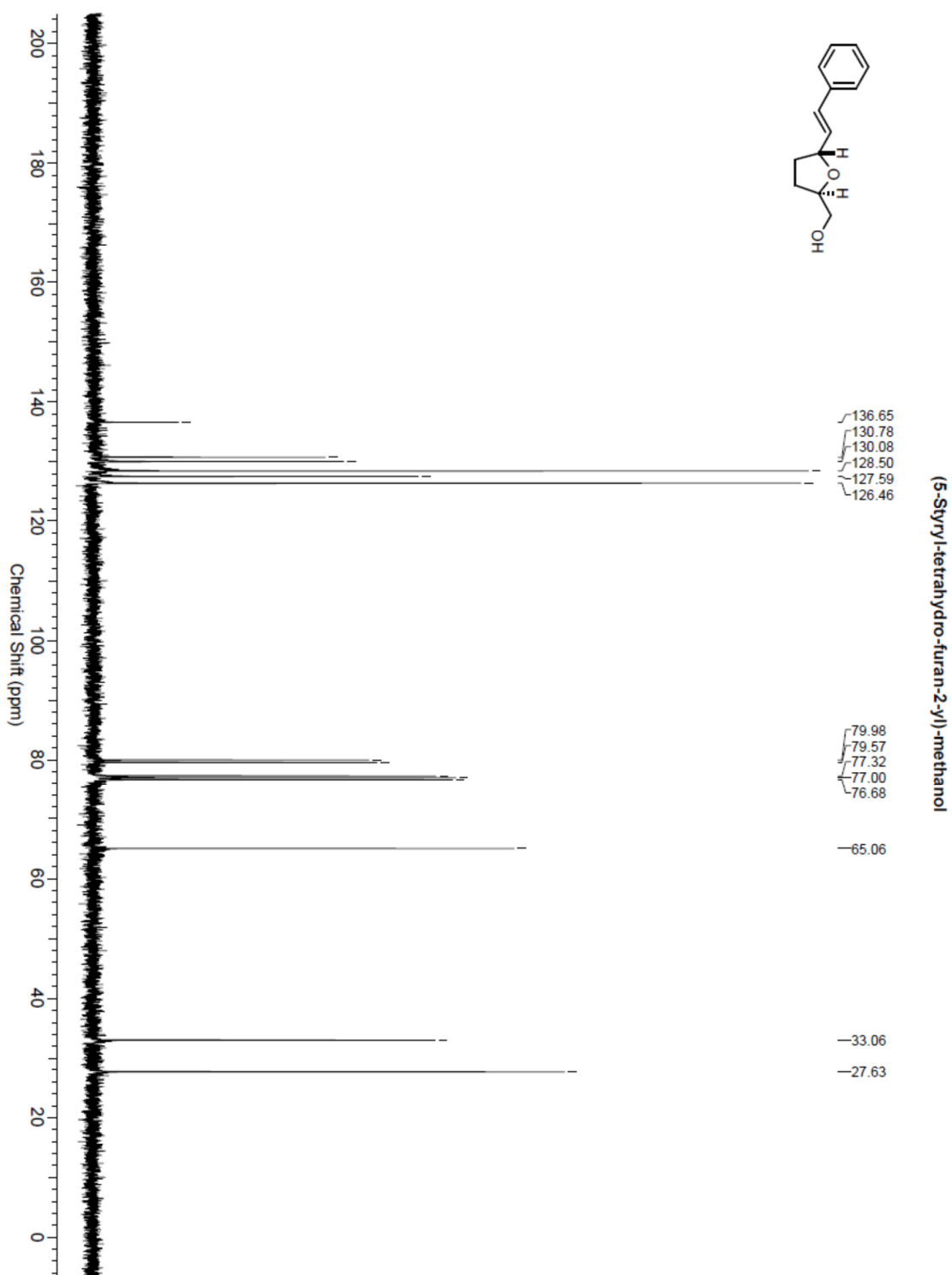


¹³C NMR (CDCl₃, 100 MHz)

Spectra 22. (5-Styryl-tetrahydrofuran-2-yl)-methanol

(Table 7, Entry 9)

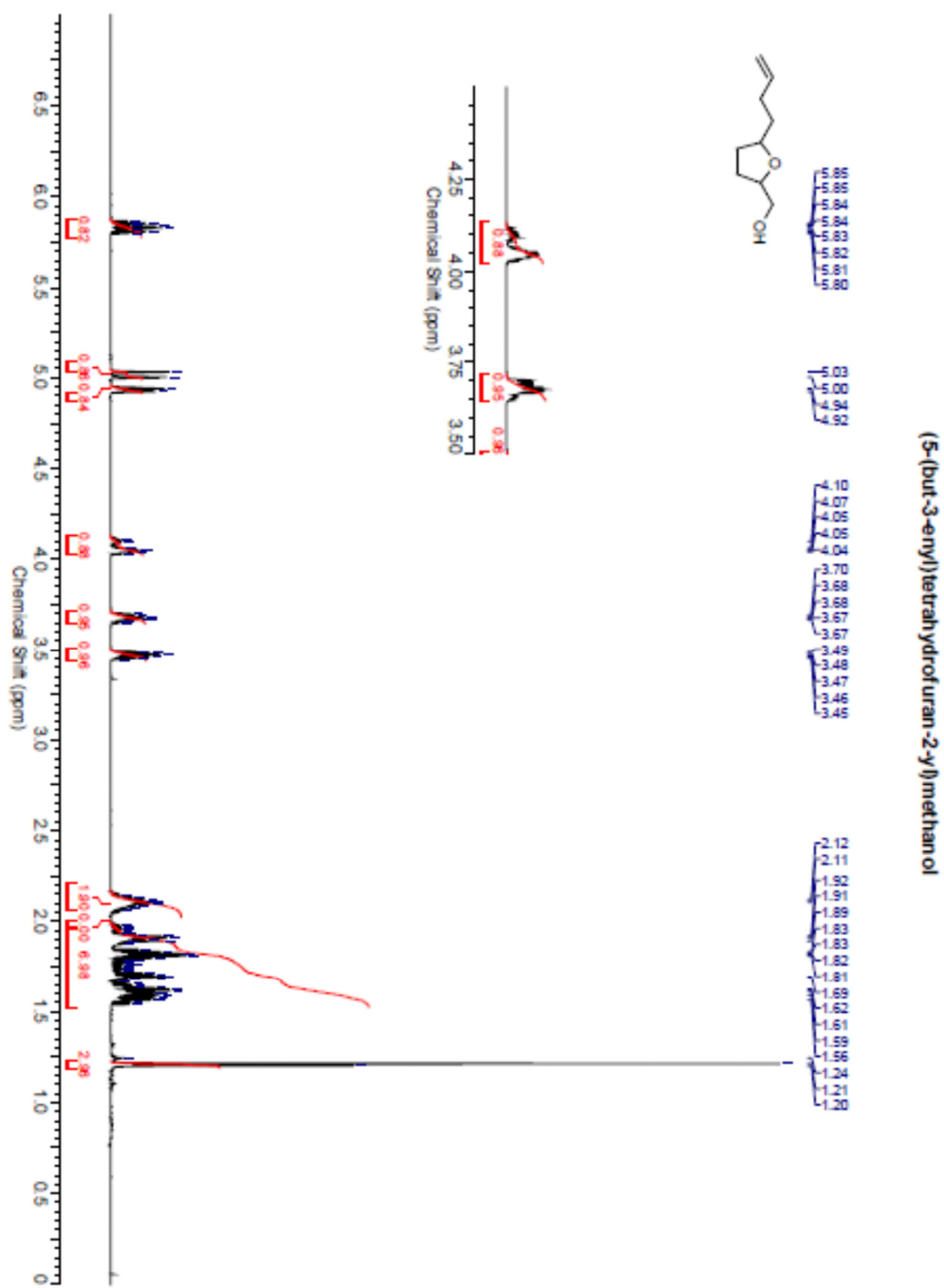
¹H NMR (CDCl₃, 400 MHz)

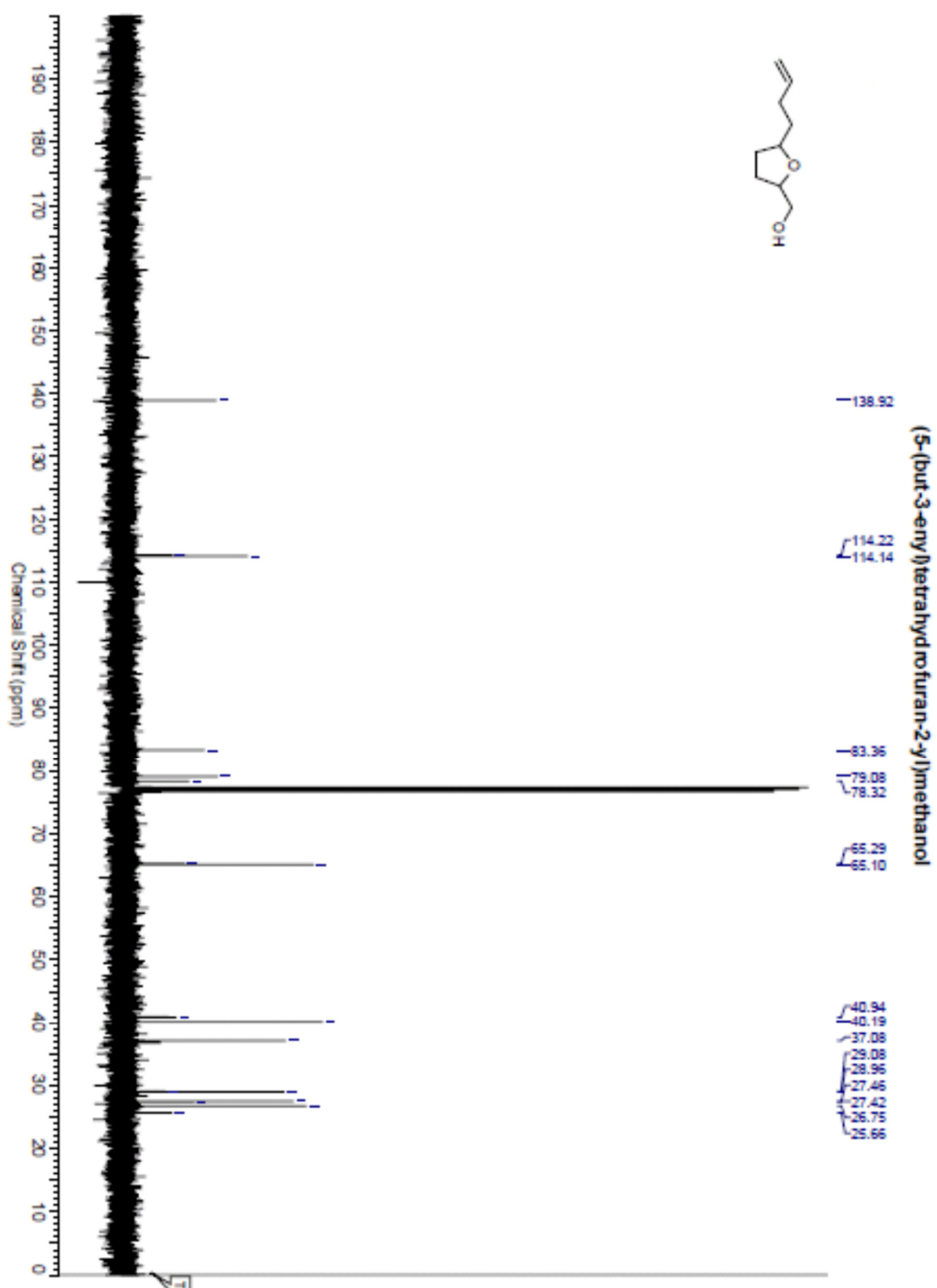


^{13}C NMR (CDCl_3 , 100 MHz)

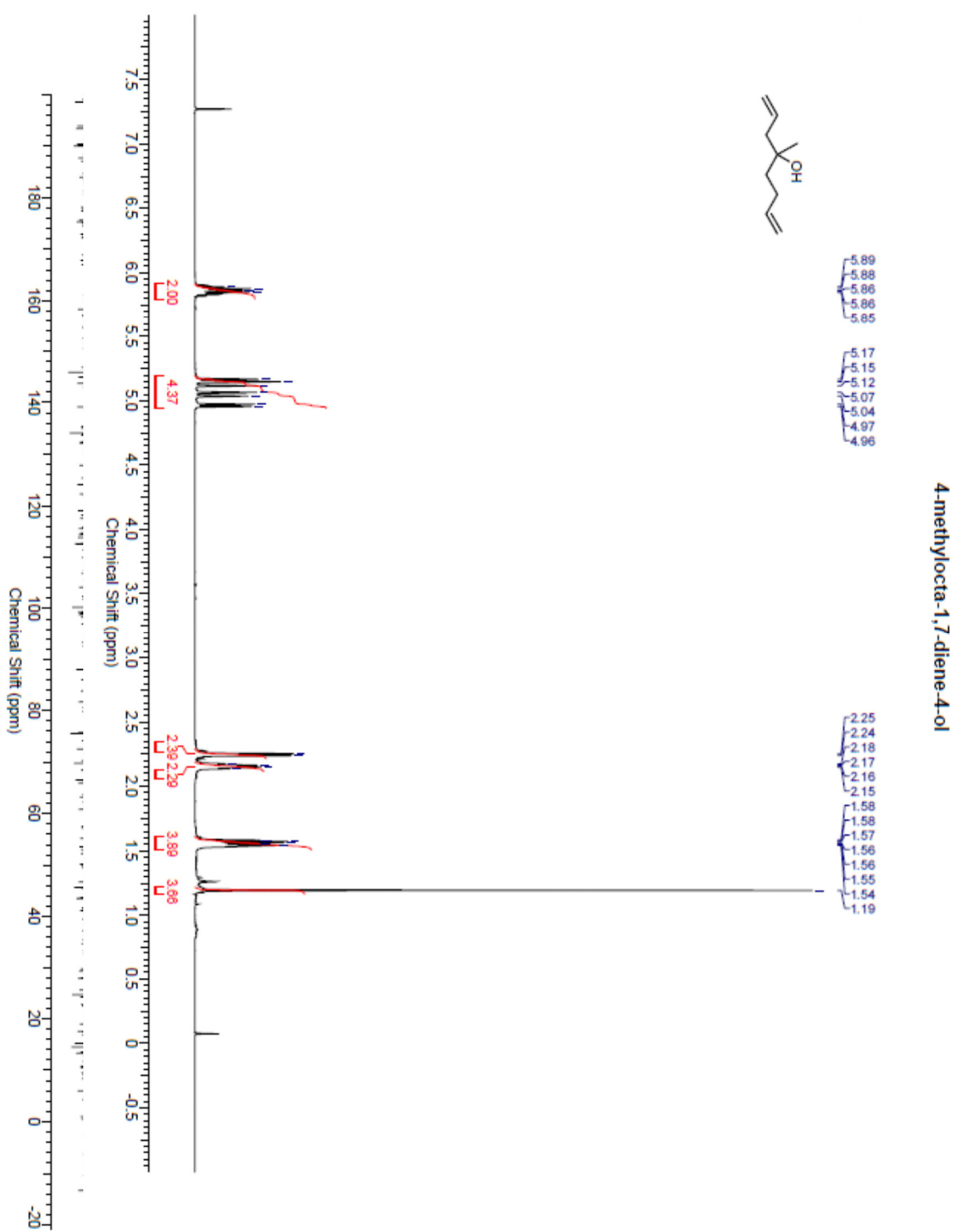
Spectra 23. (5-(but-3-enyl)tetrahydrofuran-2-yl)methanol

(Table 9, Entry 3)

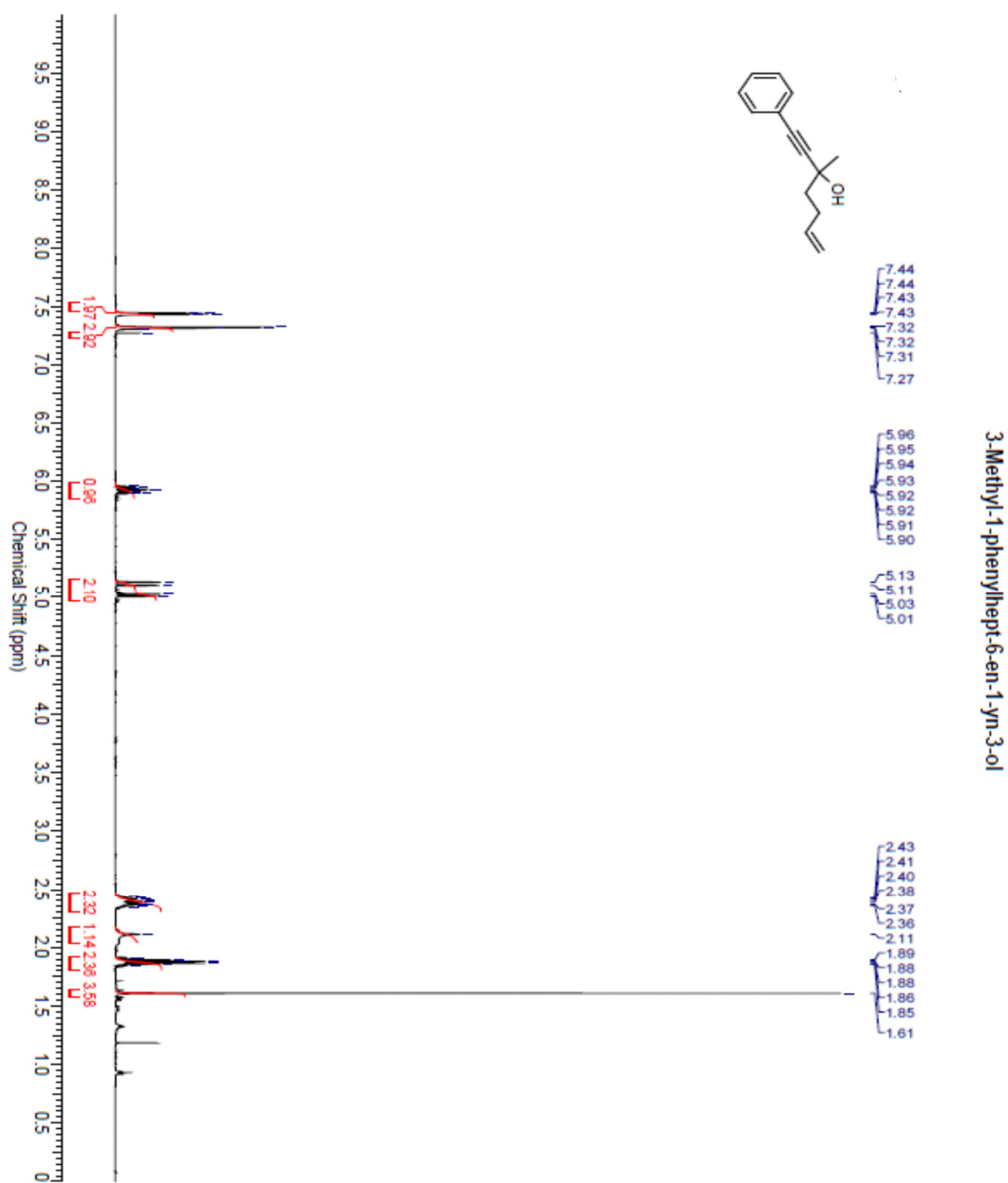
¹H NMR (CDCl₃, 400 MHz)

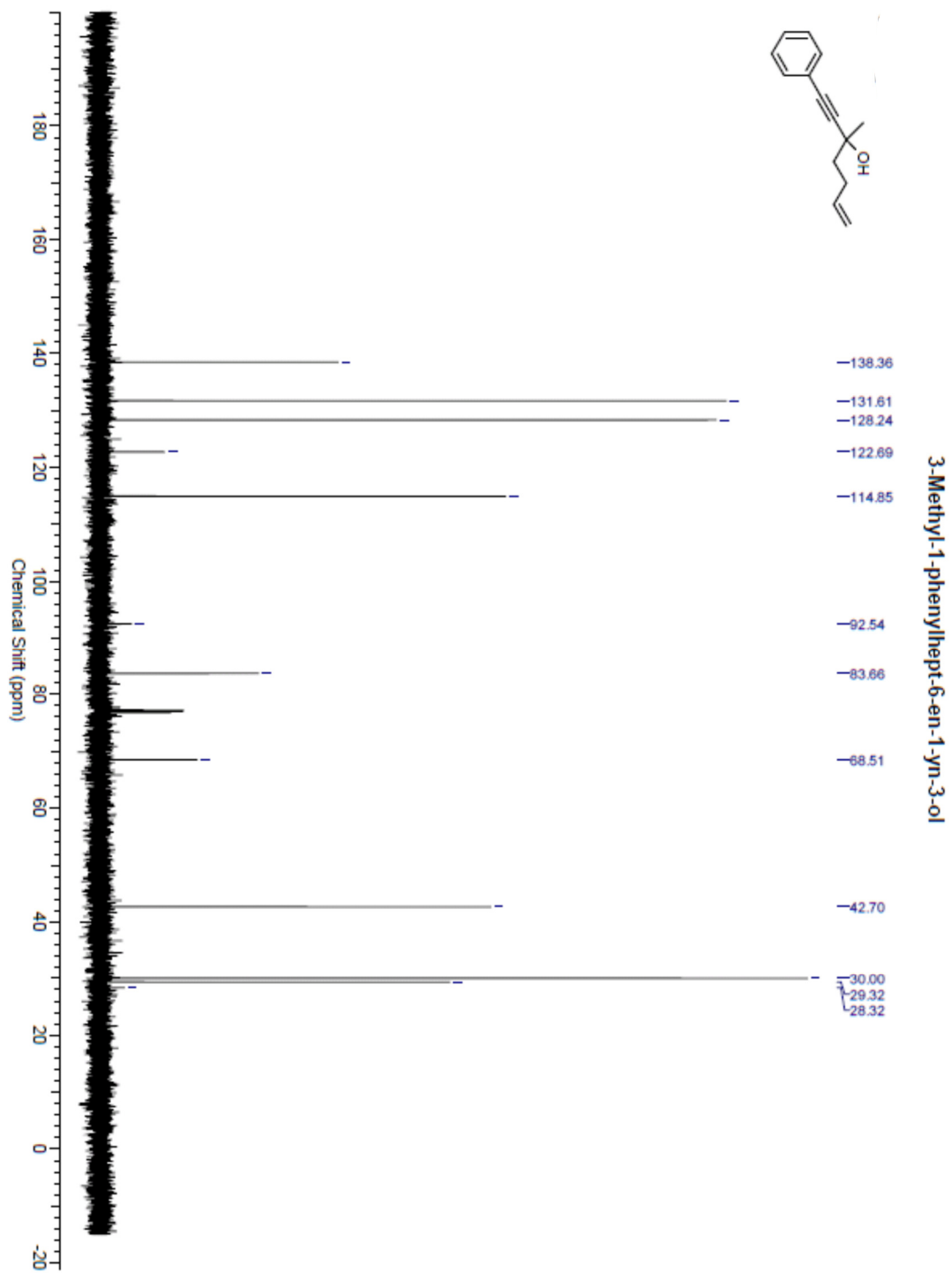


Spectra 24. 4-Methylocta-1,7-diene-4-ol

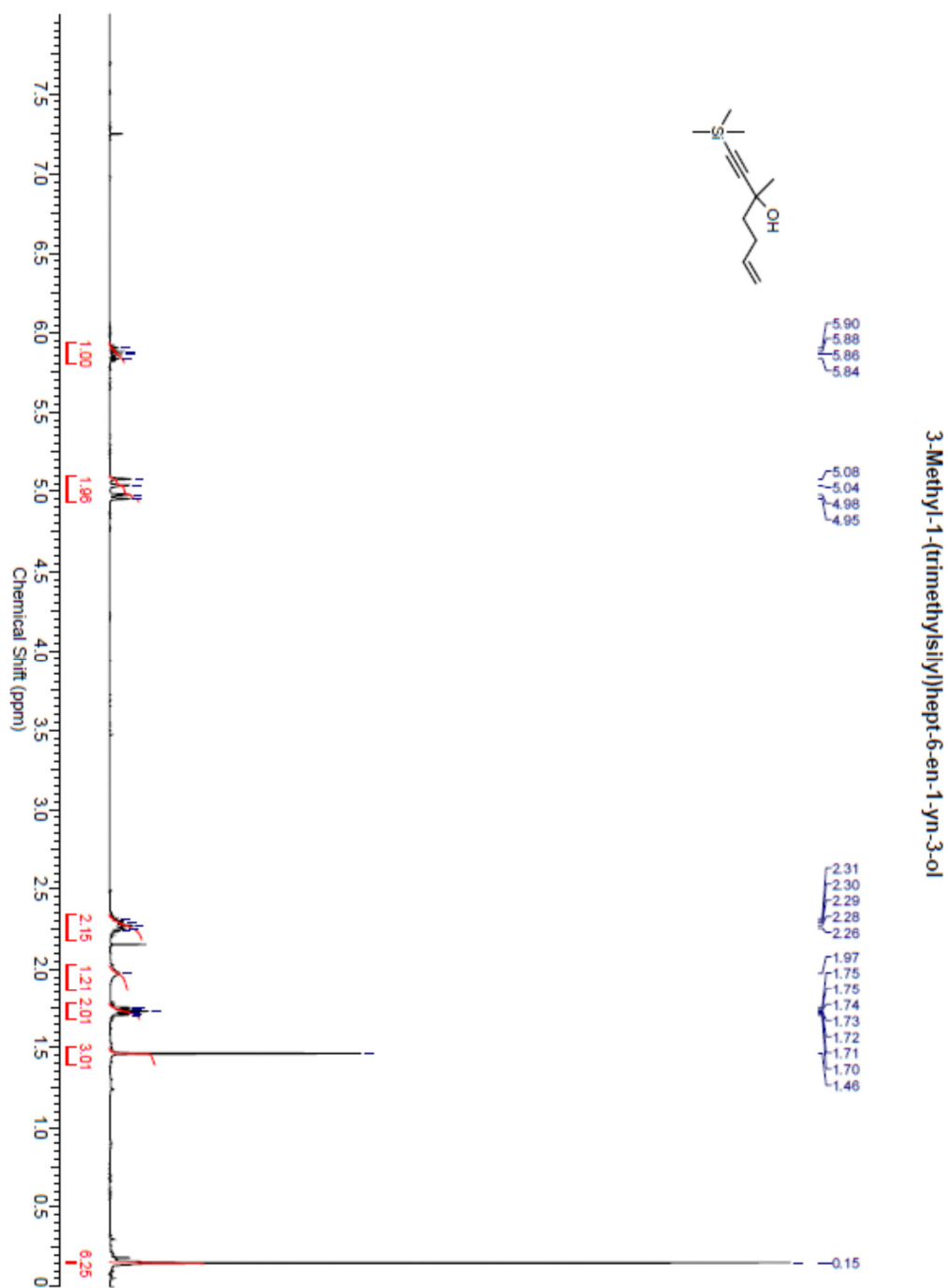
 ^1H NMR (CDCl_3 , 600 MHz)

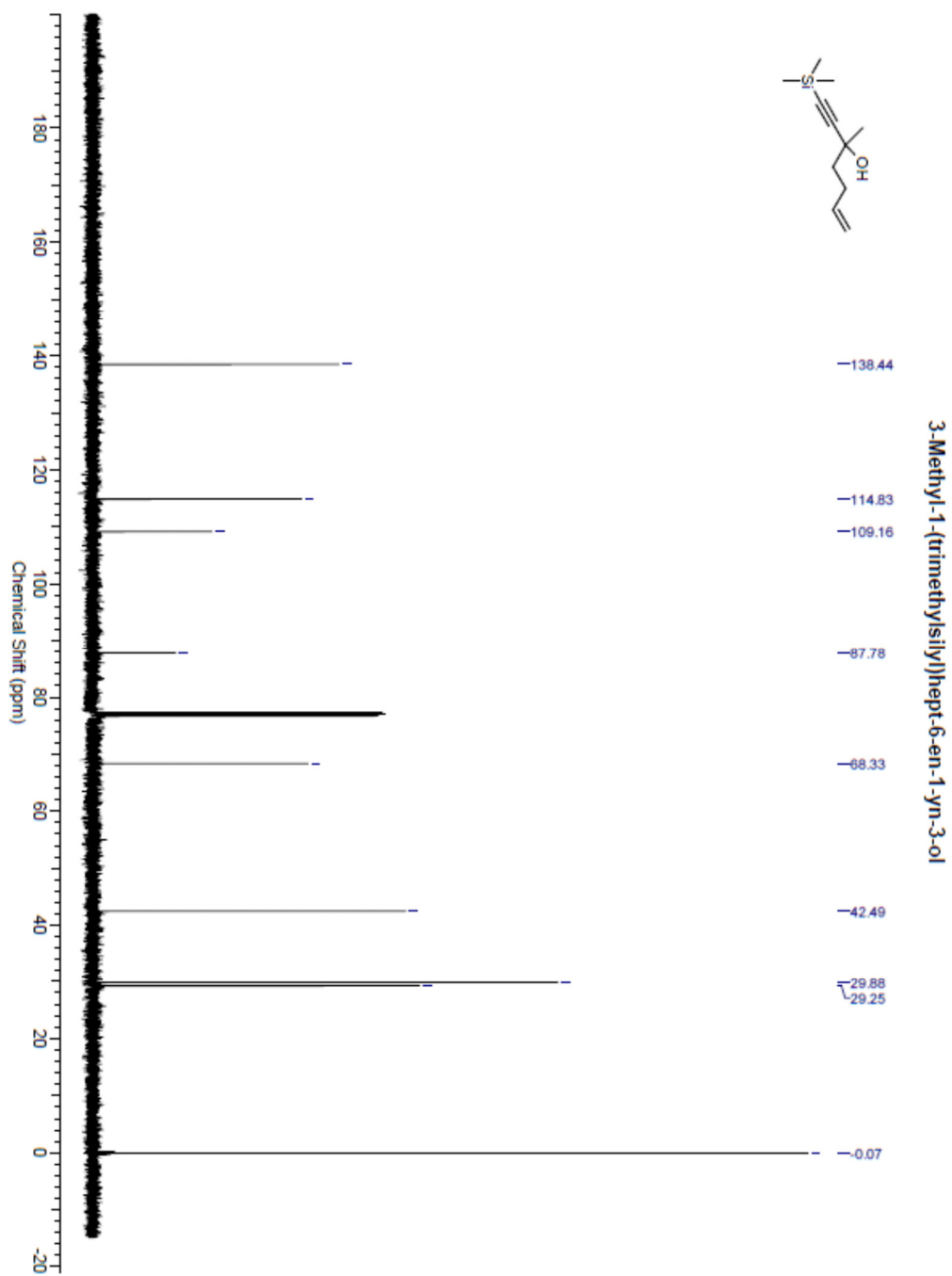
Spectra 25. 3-Methyl-1-phenylhept-6-en-1-yn-3-ol

 ^1H NMR (CDCl_3 , 600 MHz)



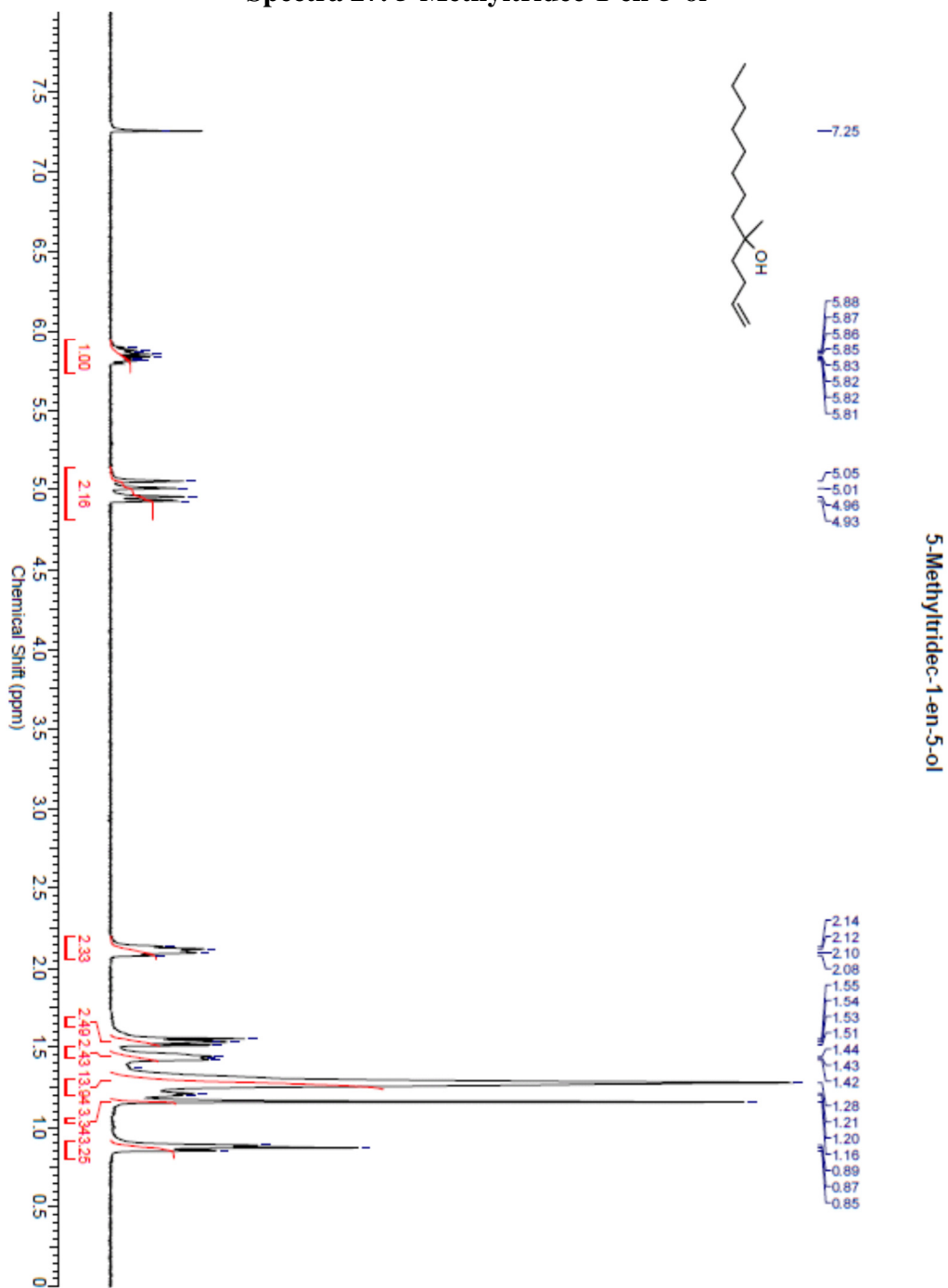
Spectra 26. 3-Methyl-1-(trimethylsilyl)hept-6-en-1-yn-3-ol

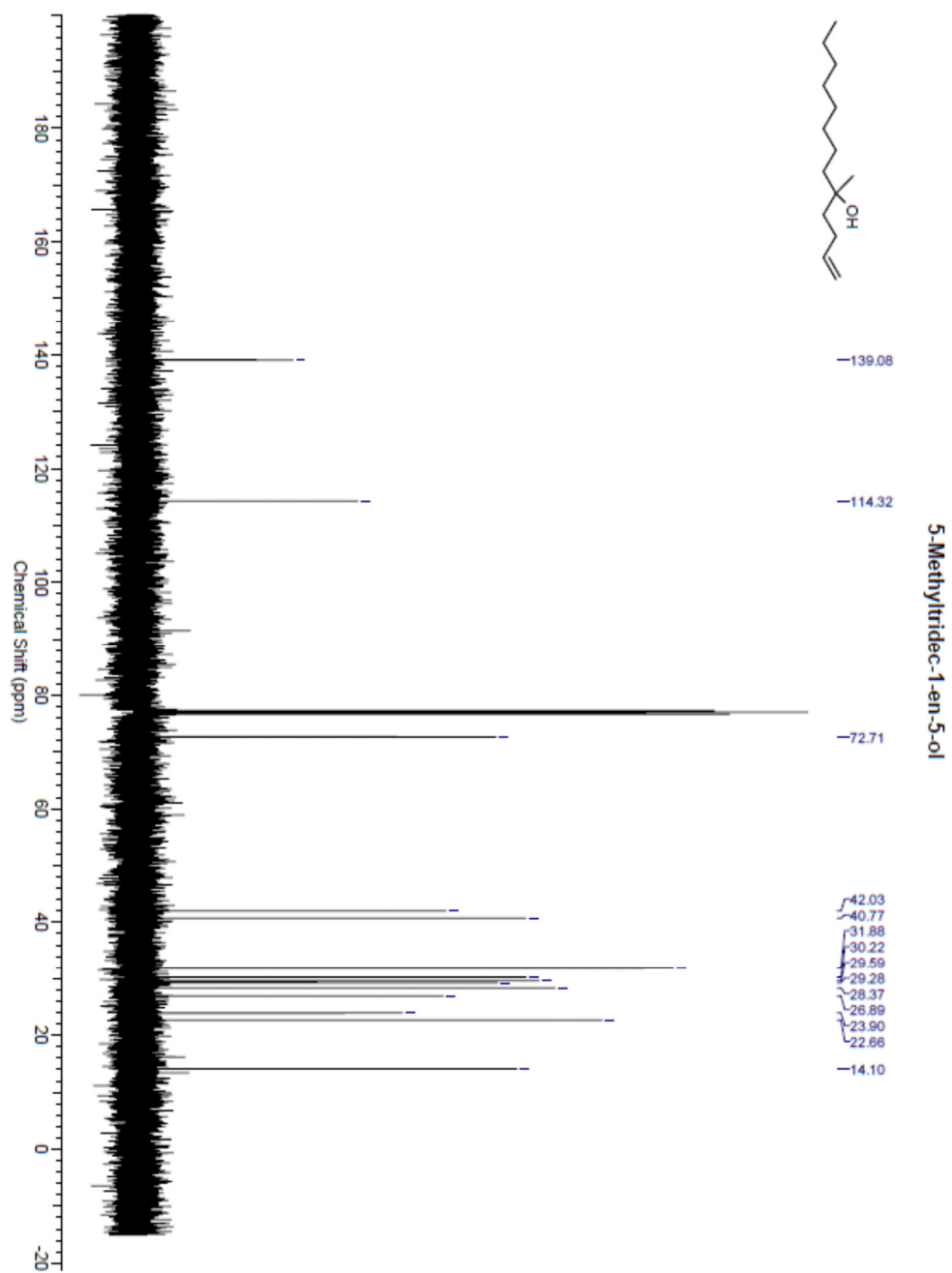
¹H NMR (CDCl₃, 600 MHz)



^{13}C NMR (CDCl_3 , 100 MHz)

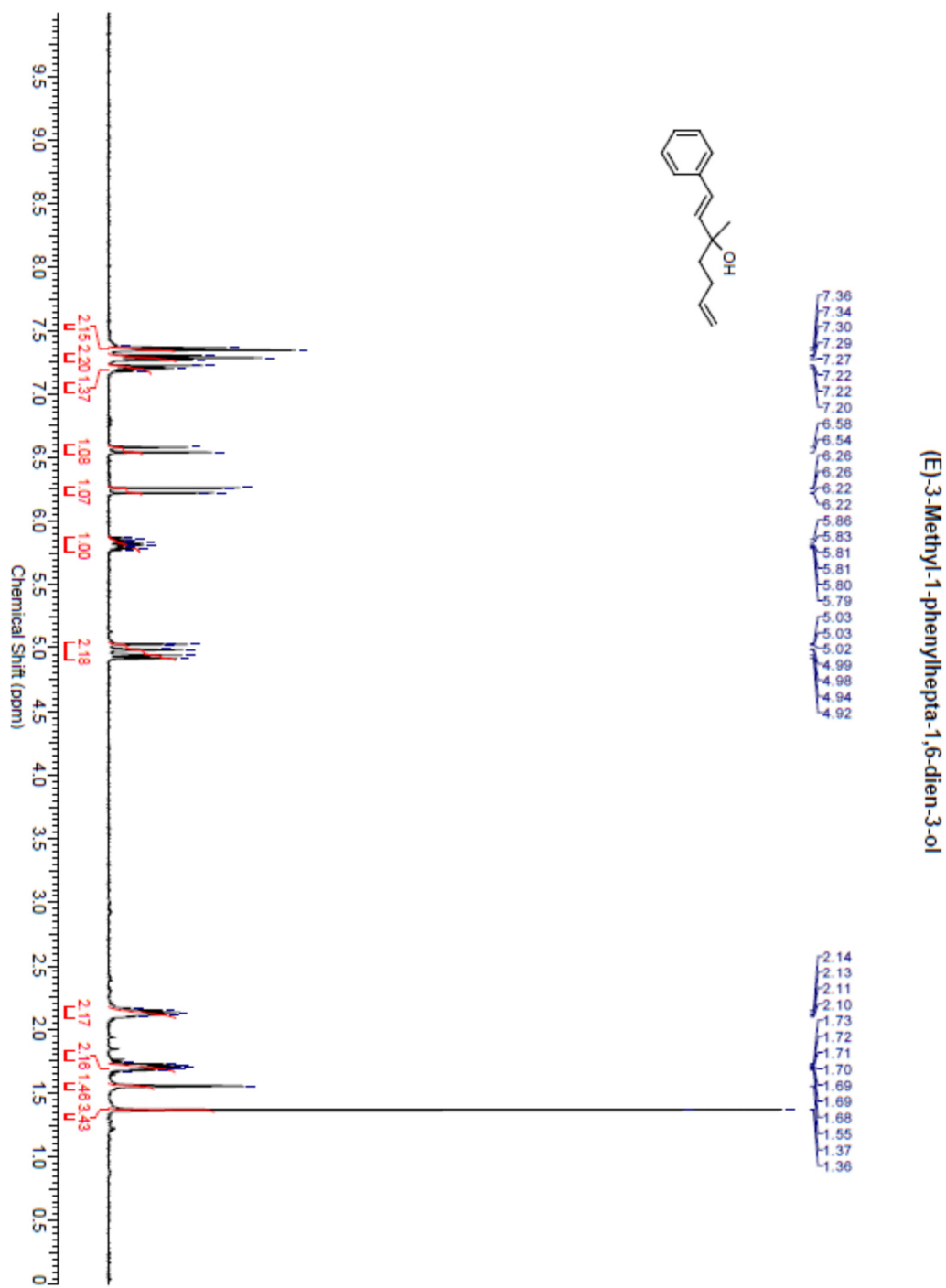
Spectra 27. 5-Methyltridec-1-en-5-ol

 ^1H NMR (CDCl_3 , 600 MHz)

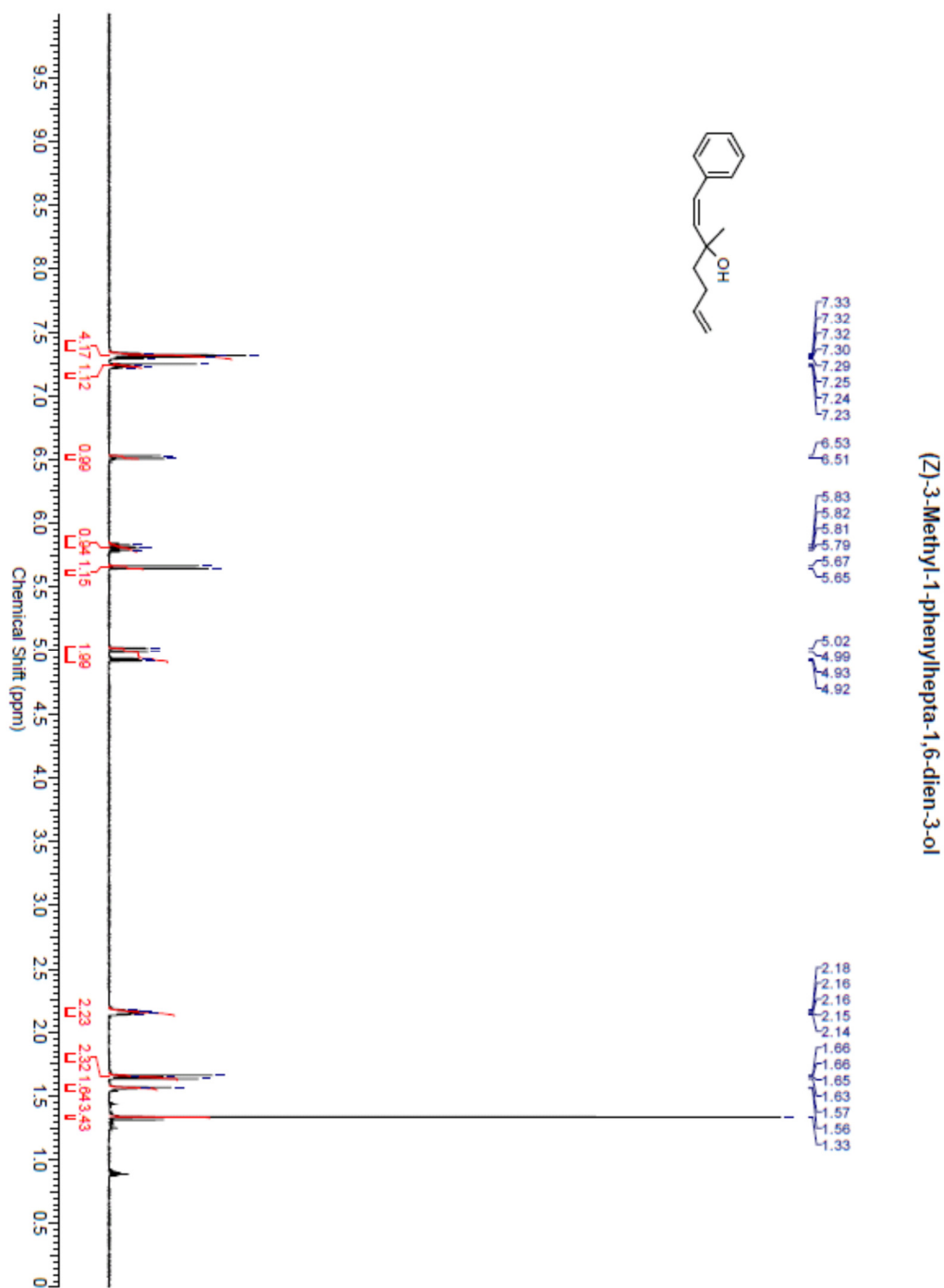


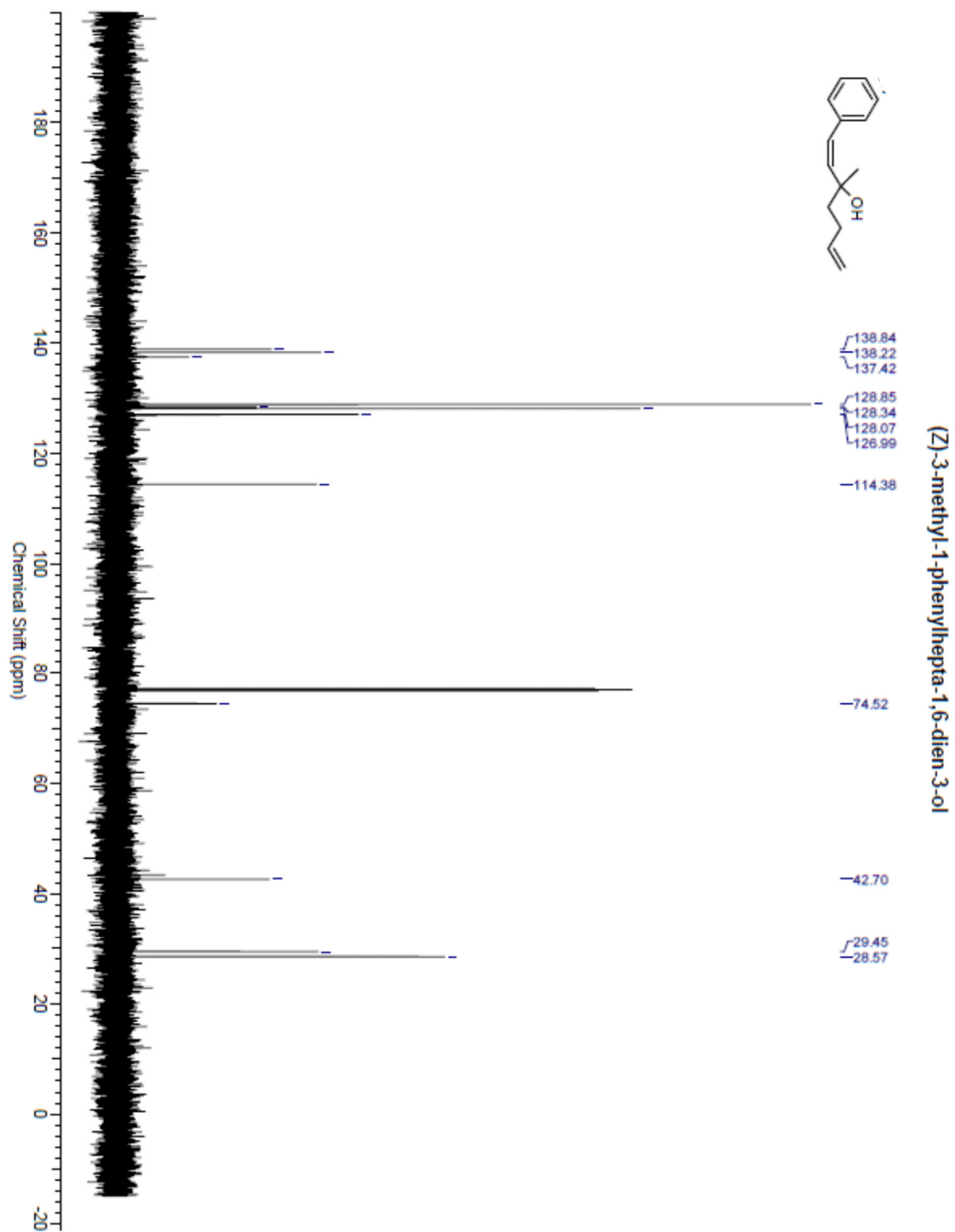
^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 28. (E)-3-Methyl-1-phenylhepta-1,6-dien-3-ol

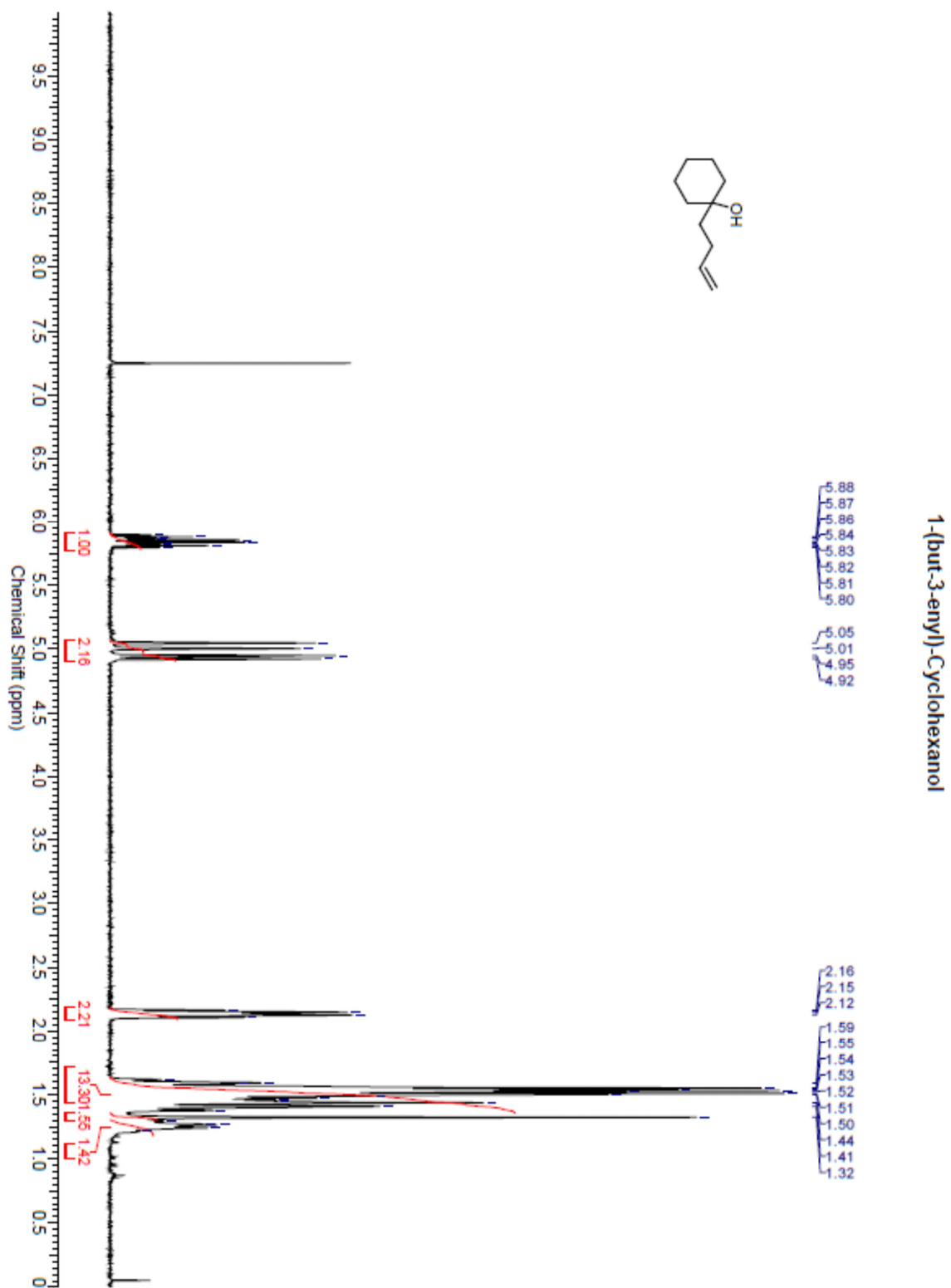


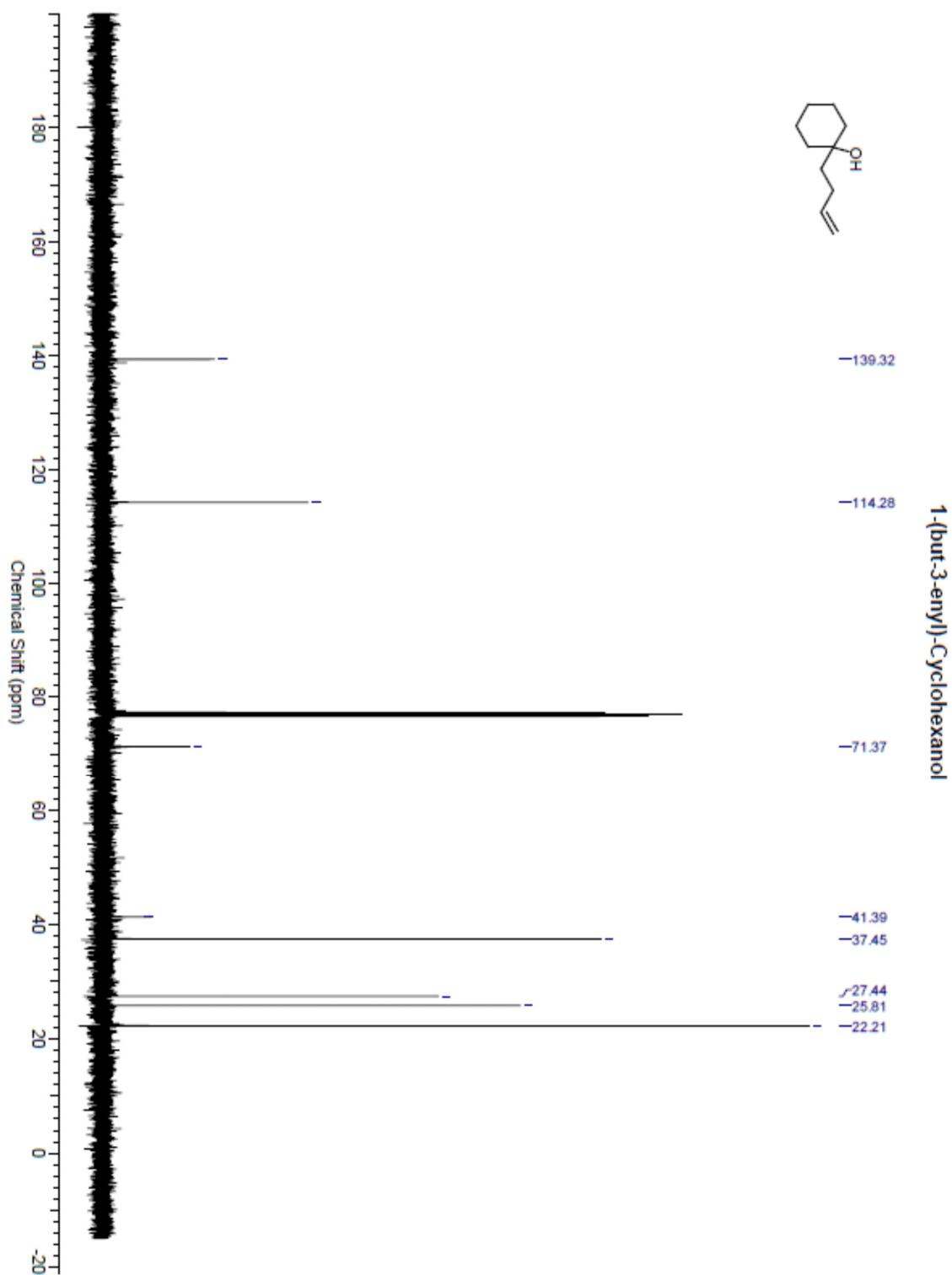
Spectra 29. (Z)-3-Methyl-1-phenylhepta-1,6-dien-3-ol

 ^1H NMR (CDCl_3 , 600 MHz)

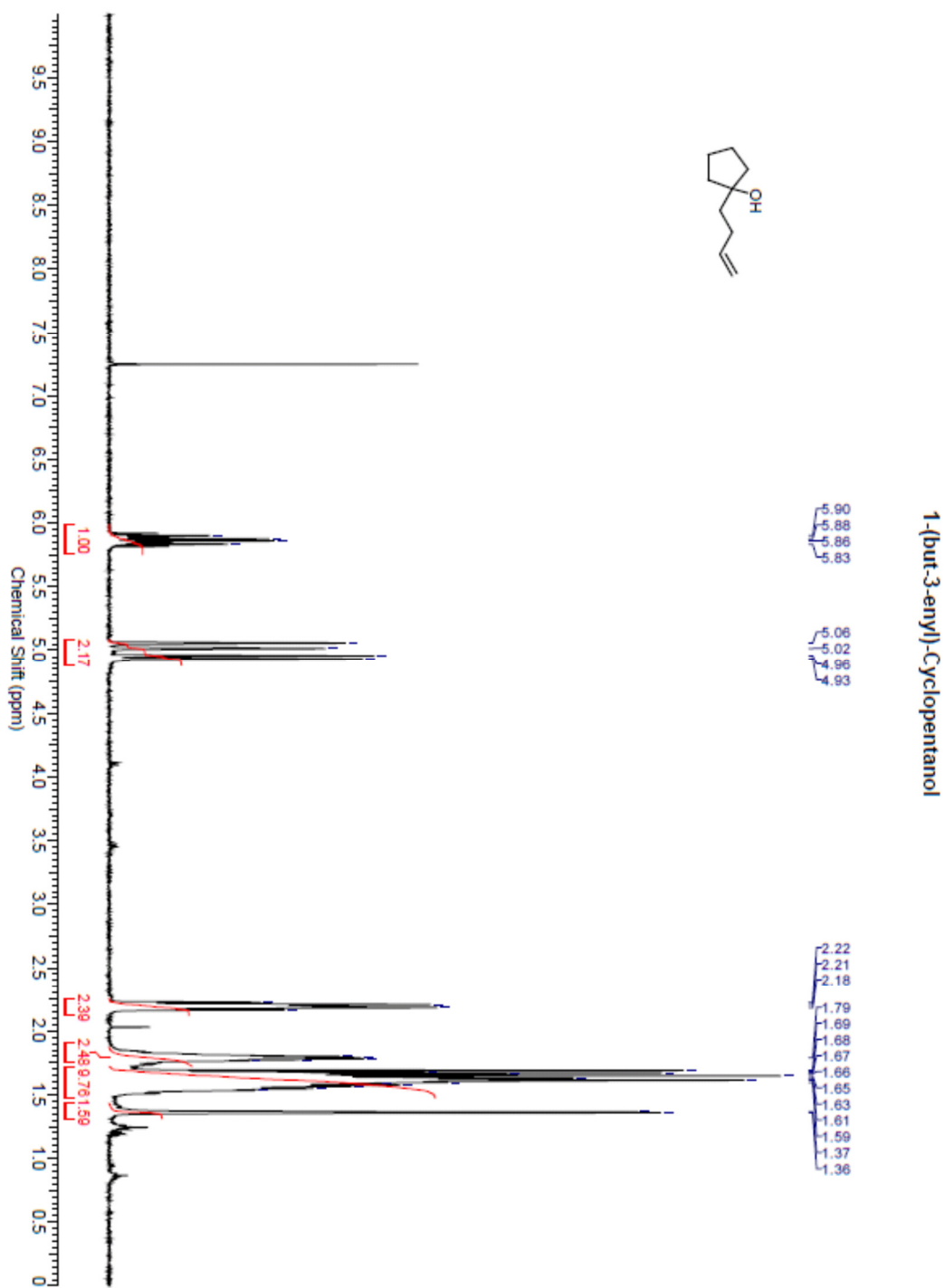
NMR (CDCl₃, 100 MHz)¹³C

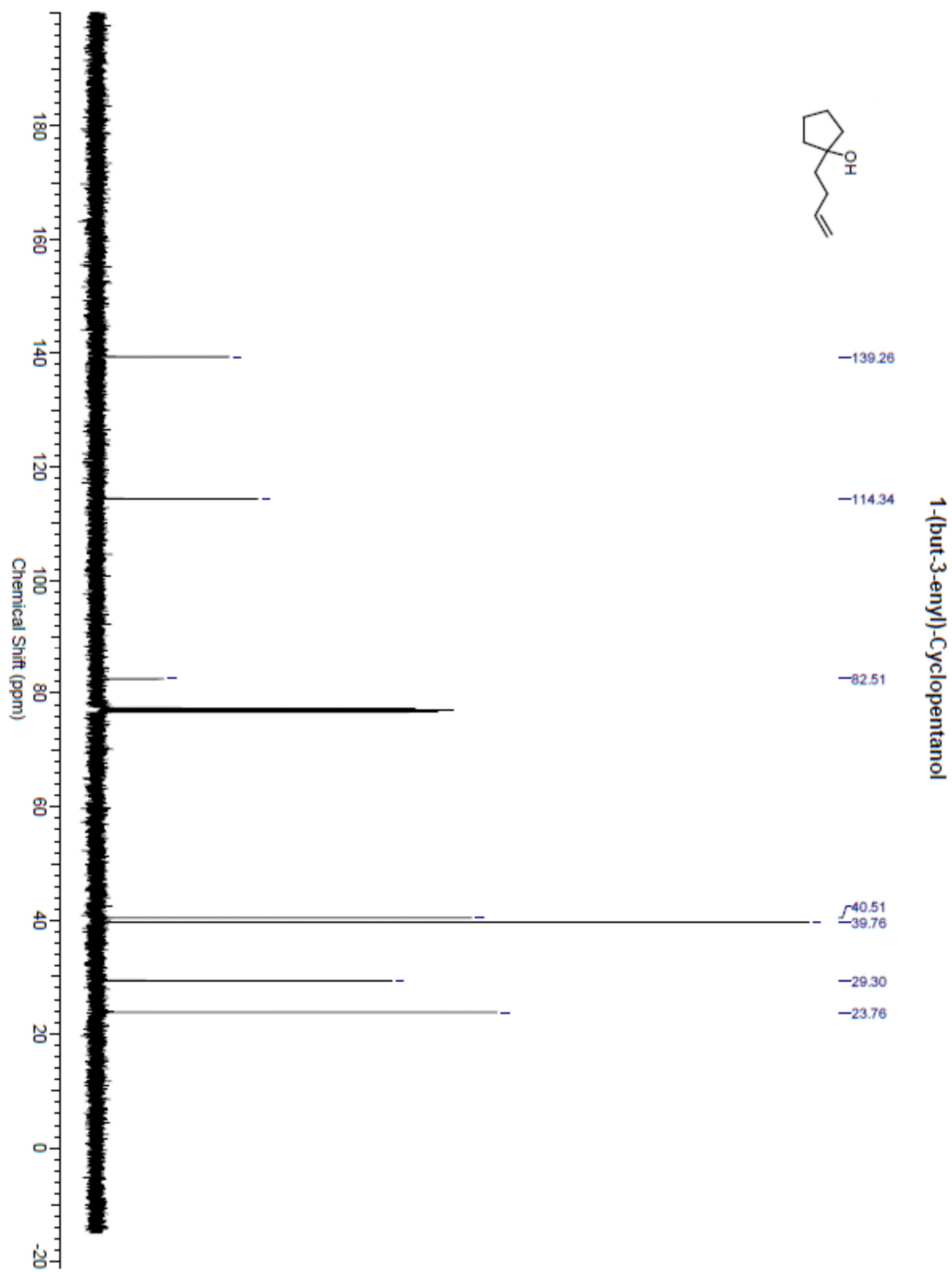
Spectra 30. 1-(but-3-enyl)-Cyclohexanol



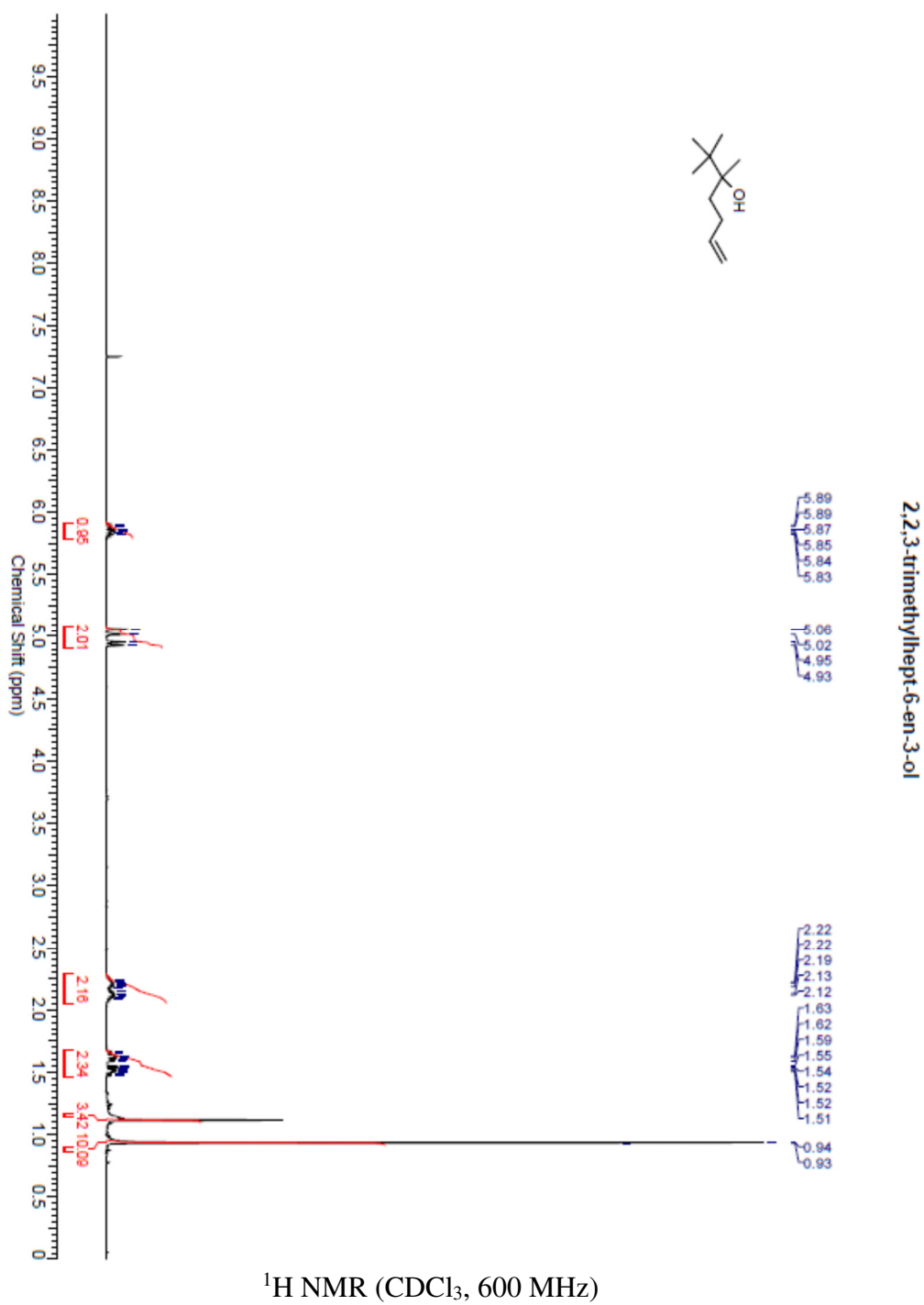


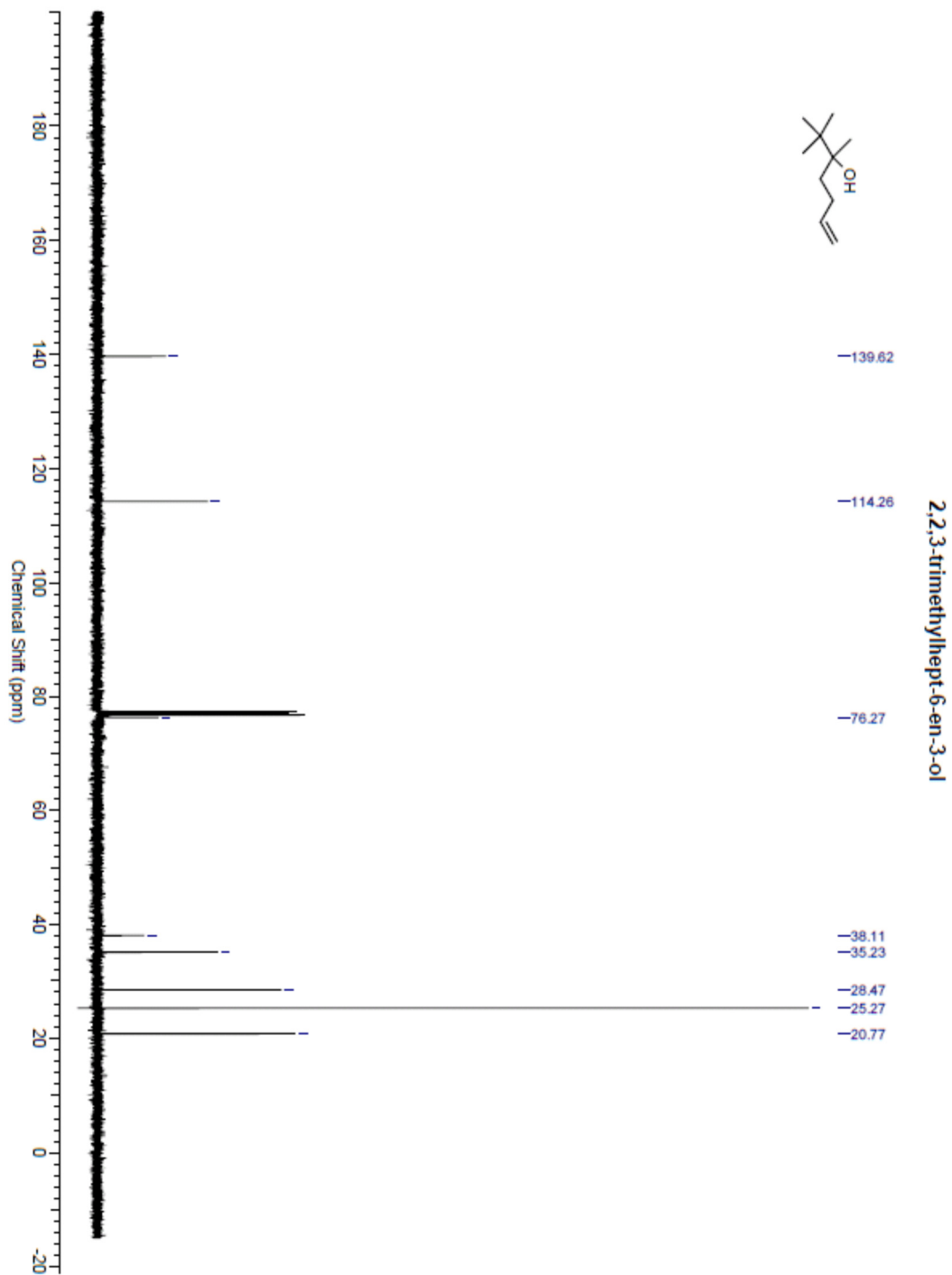
Spectra 31. 1-(but-3-enyl)-Cyclopentanol

 ^1H NMR (CDCl_3 , 600 MHz)



Spectra 32. 2,2,3-trimethylhept-6-en-3-ol

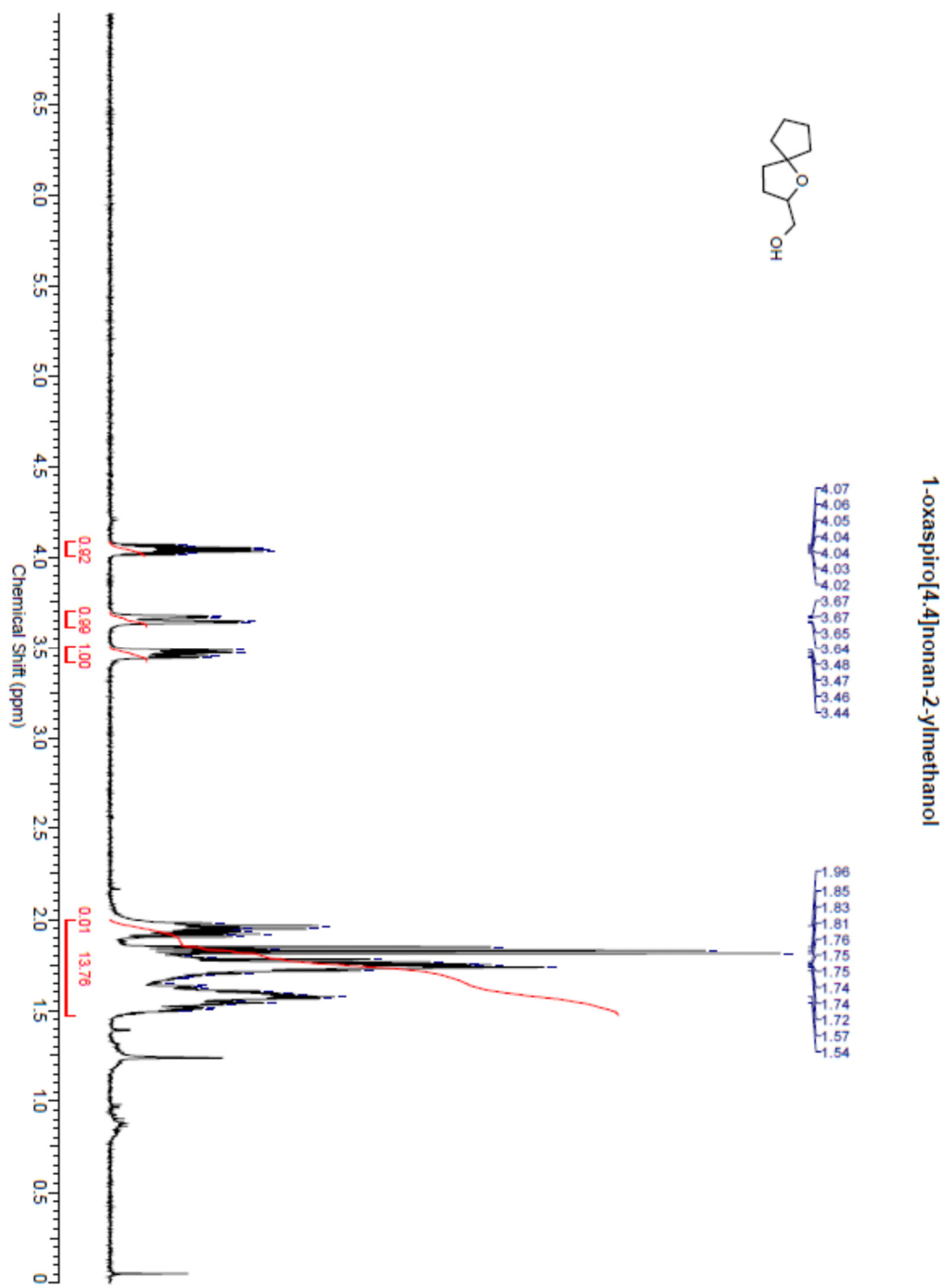


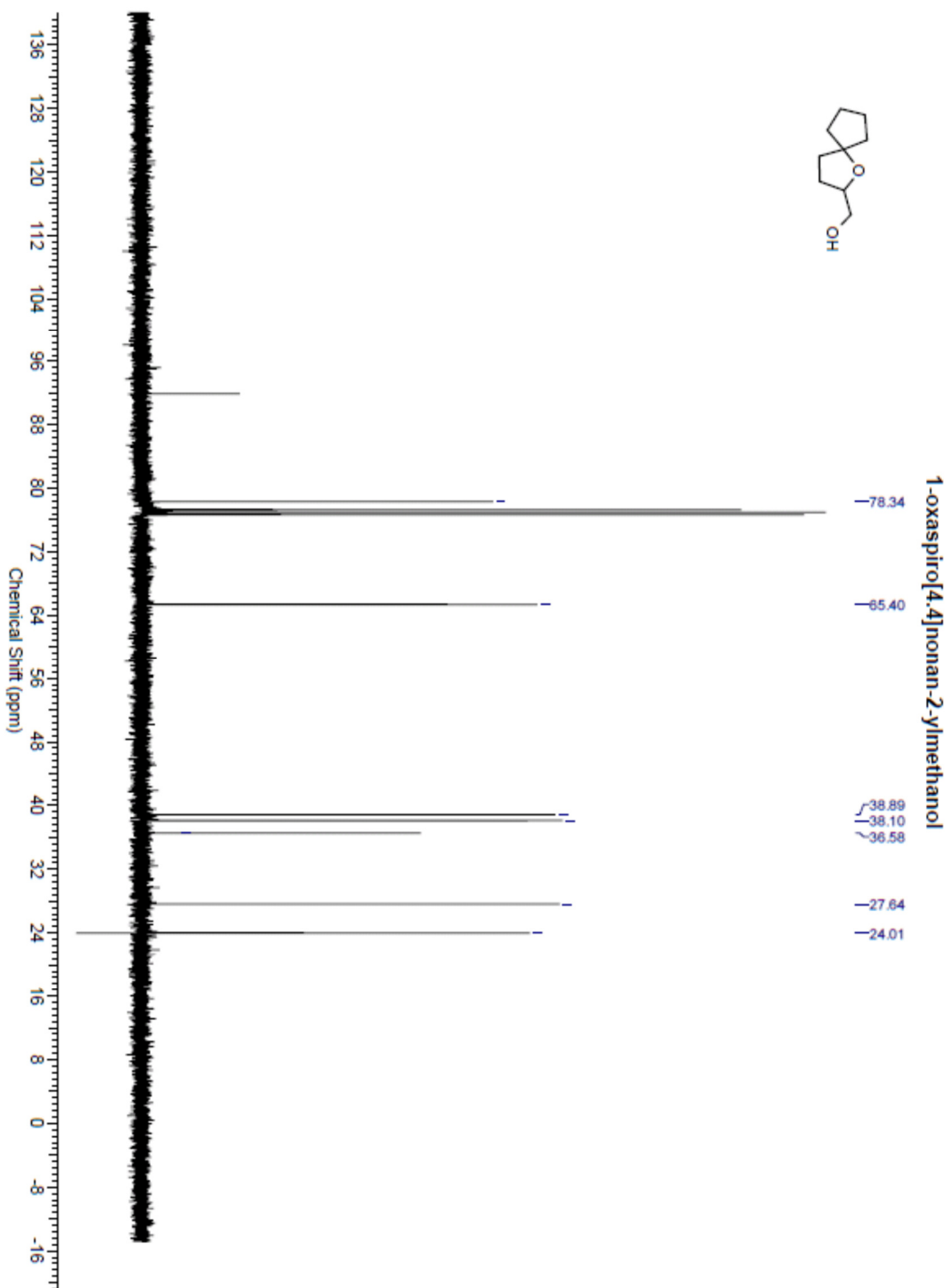


^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 33. 1-oxaspiro[4.4]nonan-2-ylmethanol

(Table 9, Entry 7)

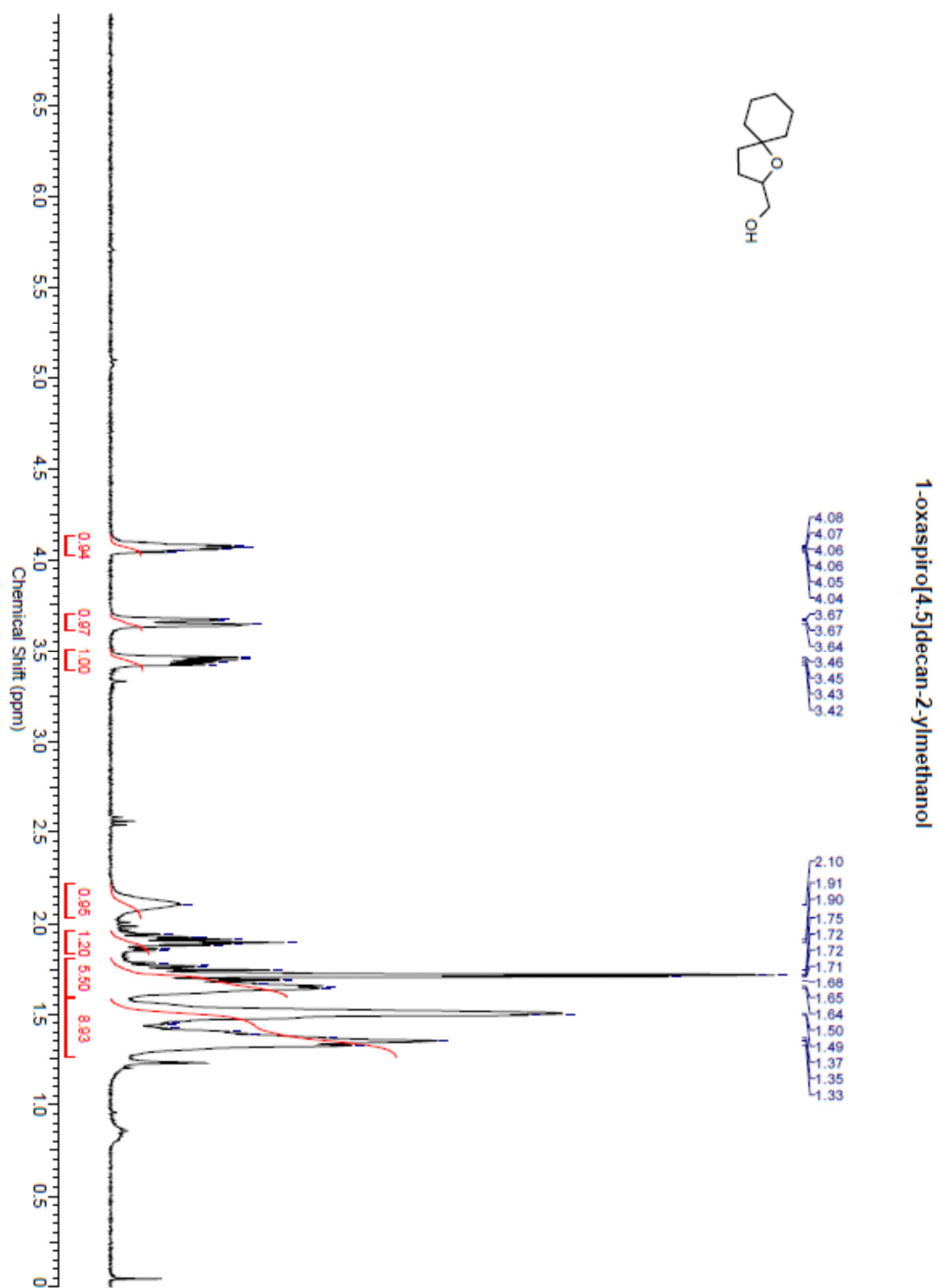
 ^1H NMR (CDCl_3 , 600 MHz)

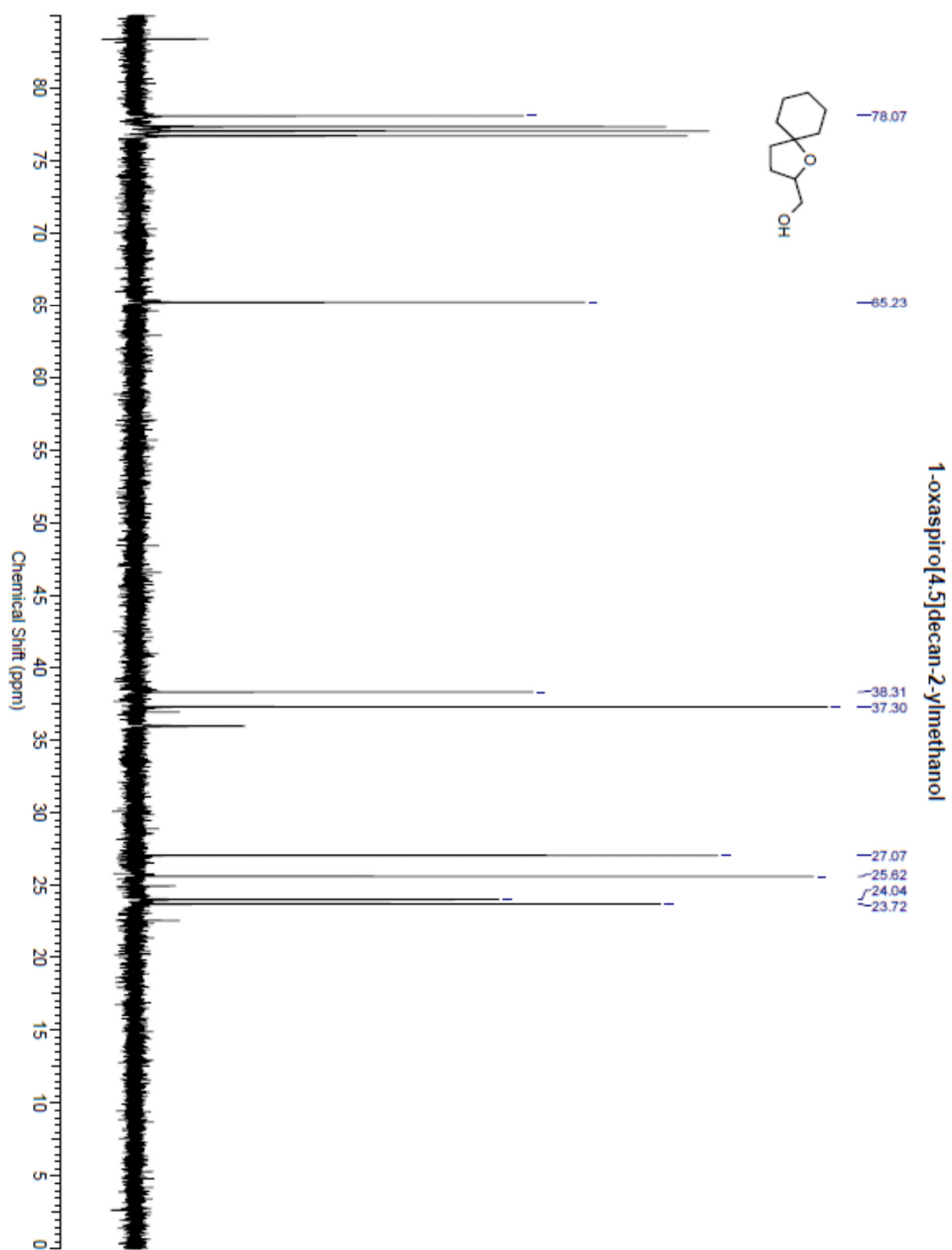


^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 34. 1-oxaspiro[4.5]decan-2-ylmethanol

(Table 9, Entry 8)

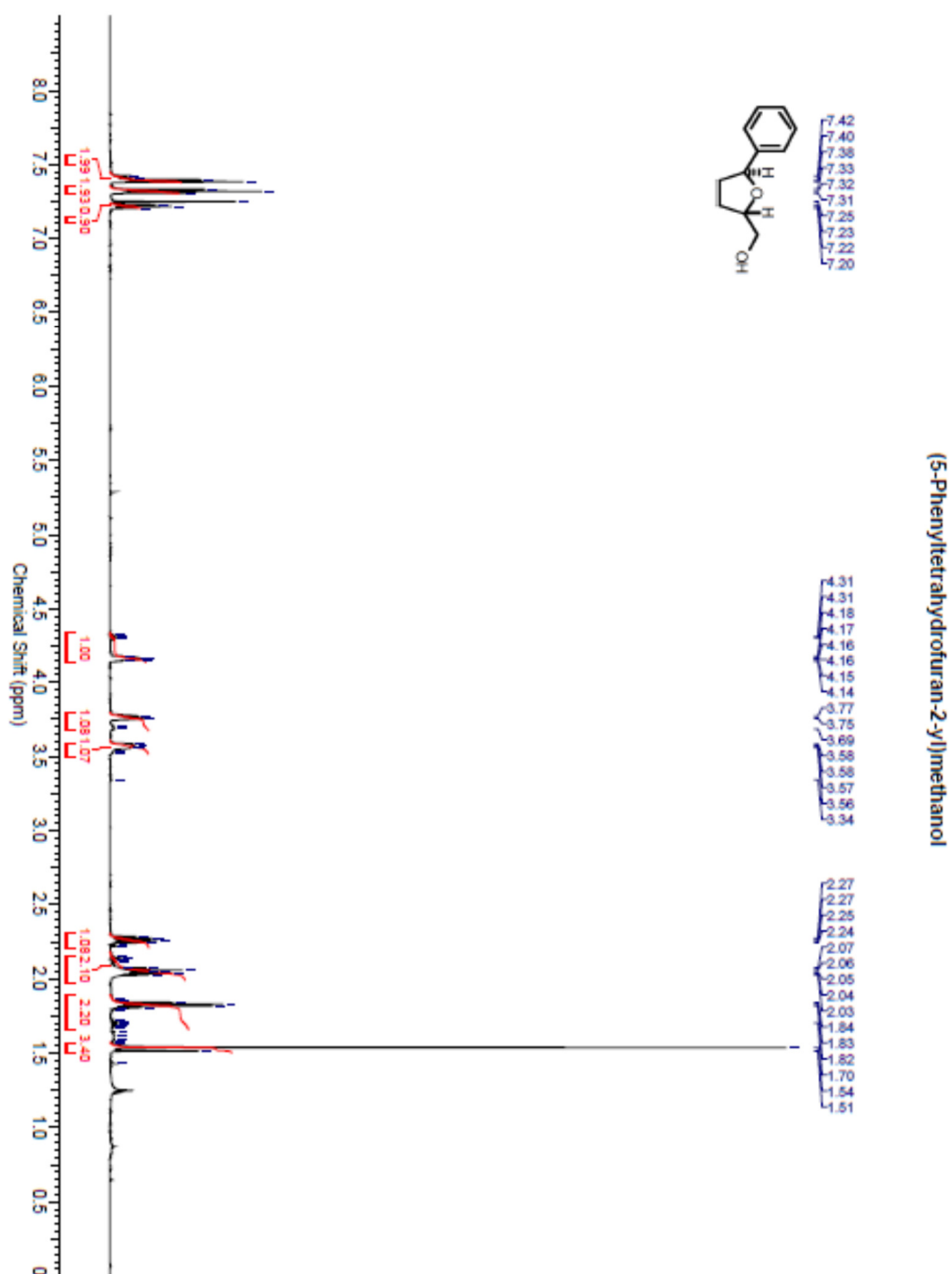
 ^1H NMR (CDCl_3 , 600 MHz)



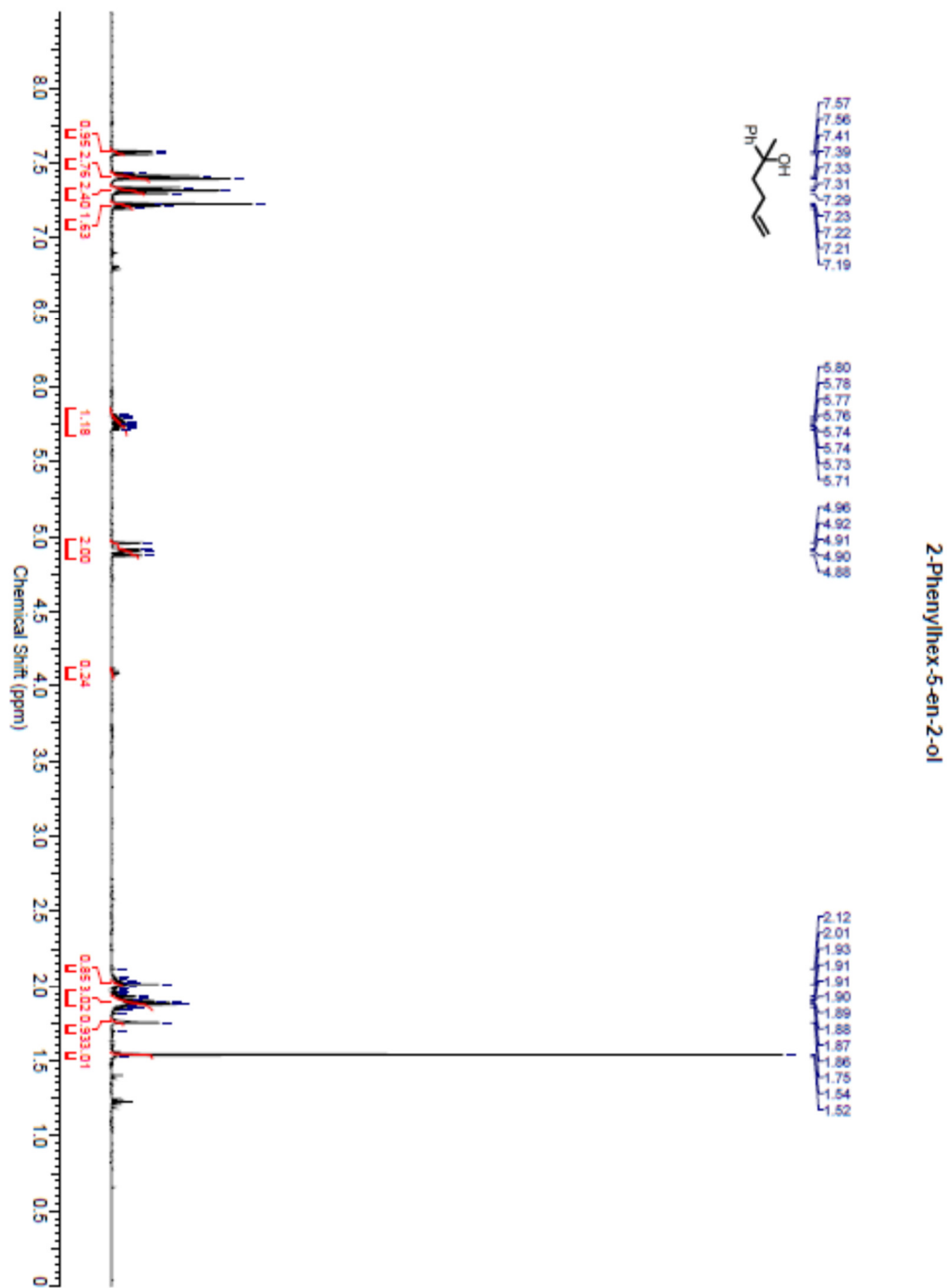
^{13}C NMR (CDCl_3 , 100 MHz)

Spectra 35. (5-Phenyl-5-methyltetrahydrofuran-2-yl)methanol

(Table 9, Entry 1)

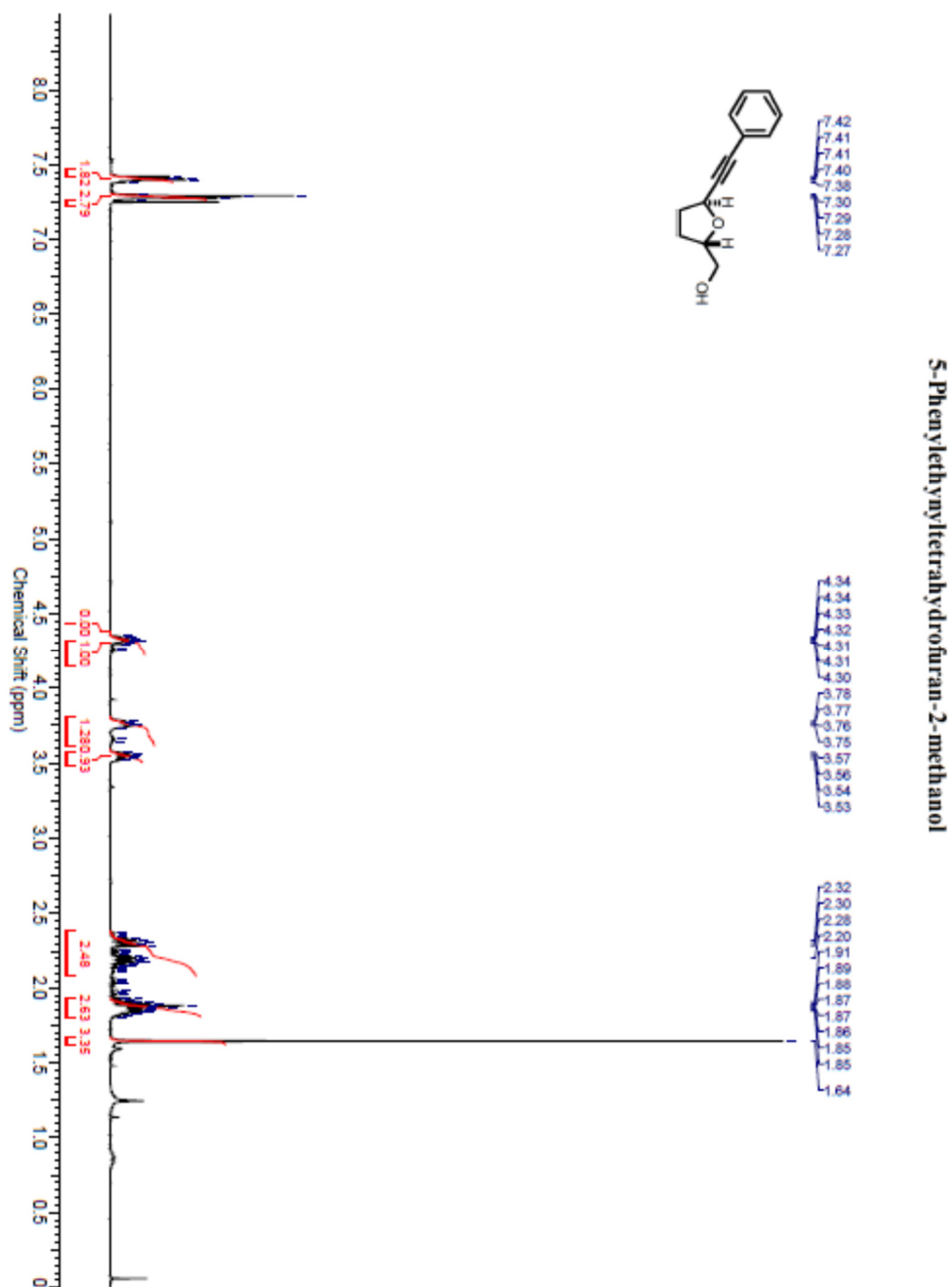
 ^1H NMR (CDCl_3 , 600 MHz)

Spectra 36. 2-Phenylhex-5-en-2-ol



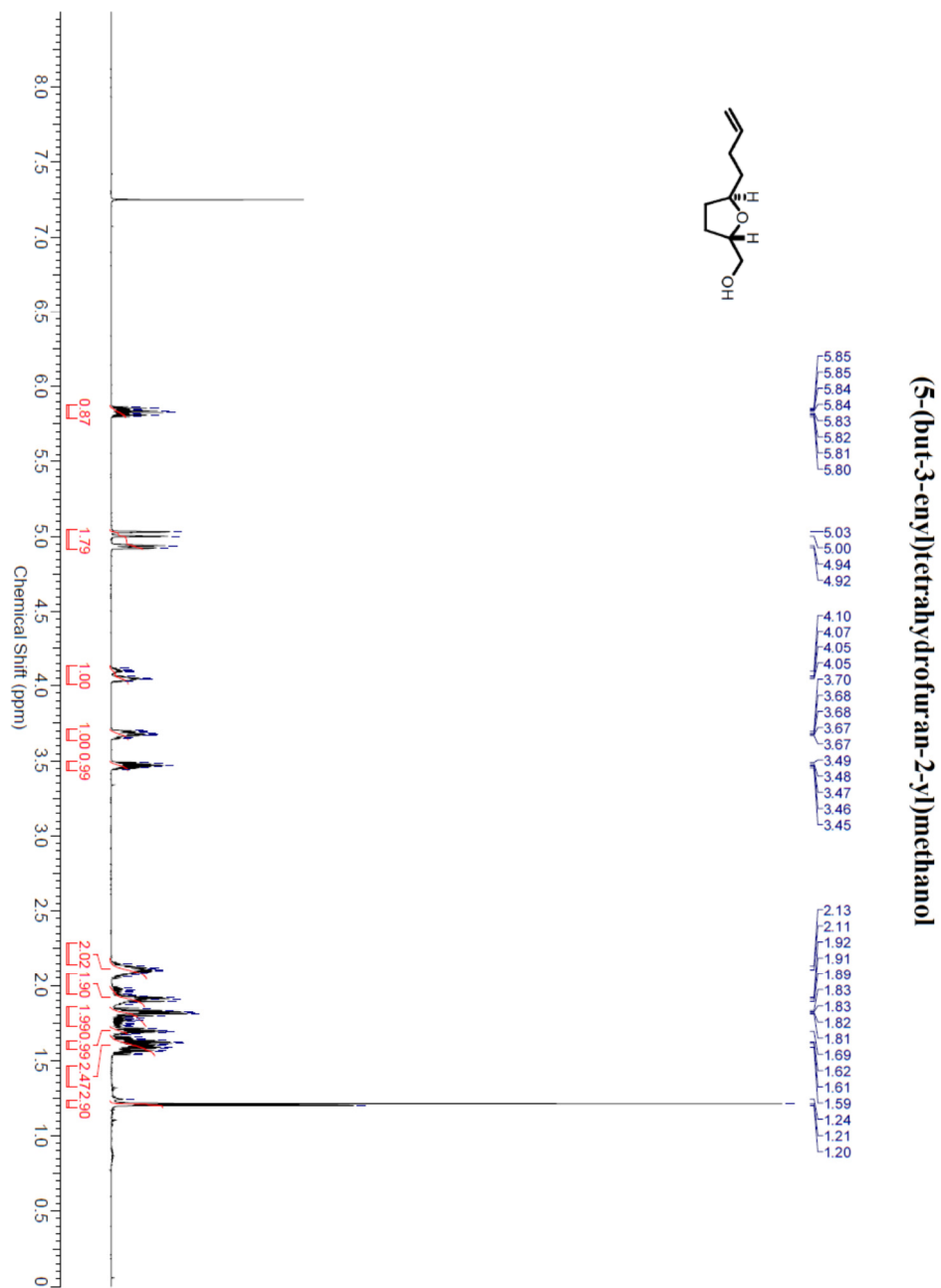
Spectra 375-Phenylethynyltetrahydrofuran-2-methanol

(Table 9, Entry 6)

 ^1H NMR (CDCl_3 , 600 MHz)

Spectra 38. (5-(but-3-enyl)tetrahydrofuran-2-yl)methanol

(Table 9, Entry 3)

¹H NMR (CDCl₃, 600 MHz)

6. Curriculum Vitae

Education

Master of Science (2016)

Synthetic Organic Chemistry
Western University, London, Ontario
Research Advisor: Professor Brian L. Pagenkopf

Bachelor of Science (2009)

Honors Specialization in Chemistry
Western University, London, Ontario
Research Advisor: Professor Brian L. Pagenkopf

Research and Relevant Work Experience

Graduate Research Associate September 2009 – July 2011

Western University, London, Ontario
Research Advisor: Professor Brian L. Pagenkopf
Project: Development of a second generation cobalt catalyst for the oxidative formation of *trans*-THF rings

Graduate Teaching Assistant September 2009 – April 2011

Western University, London, Ontario

Undergraduate Thesis Student September 2008 – April 2009

Western University, London, Ontario
Research Advisor: Professor Brian L. Pagenkopf
Project: The Synthesis of 1, 2 *anti*-hydroxymethyl functionality via asymmetric Shi epoxidation and Lewis acid mediated reductive epoxide opening

Publications

- (3) Oxidative Cyclization of Tertiary Pentanol Derivatives Forming 2,5,5-trisubstituted THF Rings and the Total Synthesis of Cyclopetalline. Geoffrey A. Phillips, Cory Palmer, Andrew C. Stevens, Mathew L. Piotrowski, Daryl S. R. Dekruyf, and Brian L. Pagenkopf,* *Tetrahedron Lett.* **2015**, *56*, 6052-6055.
- (2) The Formal [4 + 3] Cycloaddition Between Donor-Acceptor Cyclobutanes and Nitrones. Andrew C. Stevens, Cory Palmer, and Brian L. Pagenkopf, * *Organic Letters* **2011**, *13*, 1528 – 1531.
- (1) Improved Yields and Simplified Purification with a Second Generation Cobalt Catalyst for the Oxidative Formation of *trans*-THF Rings. Cory Palmer, Nicholas A. Morra, Andrew C. Stevens, Barbora Bajtos, Ben P. Machin and Brian L. Pagenkopf,* *Organic Letters* **2009** *11*, 5614 – 5617.

Conference Presentations

- (3) Improved Yields and Simplified Purification with a Second Generation Cobalt Catalyst for the Oxidative Formation of *trans*-THF Rings. **Cory Palmer**; Andrew

- C. Stevens; Nicholas A. Morra; Barbora Bajtos; Ben P. Machin; Brian L. Pagenkopf*. 93rd Canadian Chemistry Conference and Exhibiton, "Diversity in Chemistry". Toronto, Ontario.
- (2) Improved Yields and Simplified Purification with a Second Generation Cobalt Catalyst for the Oxidative Formation of *trans* -THF Rings. **Cory Palmer**; Andrew C. Stevens; Nicholas A. Morra; Barbora Bajtos; Ben P. Machin; Brian L. Pagenkopf*. The 20th Quebec Ontario Minisymposium in Synthetic and Bioorganic Chemistry. Québec City, Quebec.
- (1) The Synthesis of 1,2 - Anti Hydroxy Methyl Functional Groups from Unfunctionalized Trisubstituted Alkenes. **Cory Palmer**, Nick Morra and Brian L. Pagenkopf*. The 37th Southern Ontario Undergraduate Student Chemistry Conference. St.Catharines, Ontario.

Poster Presentations

- (1) Improved Yields and Simplified Purification with a Second Generation Cobalt Catalyst for the Oxidative Formation of *trans* -THF Rings. **Palmer, C.**; Stevens, A.C.; Morra, N.A.; Bajtos, B.; Machin, B.P.; Pagenkopf, B.L*, Latest Trends in Organic Synthesis. St. Catharines, Ontario.

Awards and Scholarship

Deans Honor List	2007-2008
Academic All-Canadian - Wrestling	2007-2008

Courses and Grades

Course	Instructor	Grade
Chem 4473	Dr. M. Kerr	92
Chem 9503	Dr. K.Baines	88
Chem 9563	Dr. B. Pagenkopf	78
Chem 9553	Dr. J. Wisner	96
Chem 9658	Seminar	75